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**THE DISSOLUTION OF
ALPHA LACTOSE MONOHYDRATE.**

**A MATHEMATICAL MODEL FOR PREDICTING
DISSOLUTION TIMES.**

A thesis presented in partial fulfilment of the requirements

for the degree
of Masters in
Biotechnology and Bioprocess Engineering at
Massey University

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1993

Abstract

Commercially available lactose is generally available in the form of alpha lactose monohydrate. The dissolution of this is slow in comparison to other sugars due to lactose existing in solution as alpha and beta lactose. When alpha lactose monohydrate has dissolved up to the alpha lactose solubility limit, no more can dissolve until some of the alpha lactose in solution has mutarotated to beta lactose. This makes mutarotation and the solubility of alpha lactose the two main limiting factors in lactose dissolution.

A variety of factors can affect the mutarotation rate and solubility of lactose. Temperature and pH affect both significantly. The effect of carbohydrates in solution on the solubility of alpha lactose is particularly important as it has been found that beta lactose inhibits the solubility of alpha lactose.

Dissolution of alpha lactose may be considered to consist of three steps; surface disintegration from the crystal, dissolution into the bulk of solution, and mutarotation of alpha to beta in solution. Attempts to model this process have previously been unsuccessful.

For dissolution to total lactose concentrations above the alpha lactose solubility limit, it was found that the effect of beta lactose on the solubility of alpha lactose had a significant effect on the dissolution of lactose. For dissolution to total lactose concentrations below the alpha lactose solubility limit, it was found that the surface disintegration reaction was significant, particularly at low temperatures.

A model was developed for predicting the dissolution of alpha lactose. This was found to compare well to experimental results for both single size and mixed crystal size lactose. The model worked well in dissolutions with excess lactose, dissolution to total lactose concentrations above and dissolutions below the alpha lactose solubility limit.

Acknowledgements

I wish to thank the following people and organizations for their help and support;

The Lactose company of New Zealand, without whose financial support this work would not have been done.

My supervisor Dr. Tony Paterson, For his advice and constructive criticism which helped me to formulate my ideas of how to proceed and whose constant badgering helped me finish this thesis.

Wayne Mallet and John Alger for their technical assistance and knowhow in the experiments carried out in this investigation.

Prof. Andrew Cleland for his excellent notes on mathematical modelling.

Most of all, I am indebted to the two most important people in my life; Ruth Mabbitt (soon to be Ruth Lowe) for loving me and encouraging me to finish this work, and my Lord and Saviour Jesus Christ, for keeping me on the straight and narrow in life and helping me keep a clear perspective.

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CHAPTER 1

Introduction.

The dissolution of alpha lactose is of industrial importance to many organisations. Users and manufacturers of lactose often require that lactose be dissolved in water before use.

There are several processes involved in the dissolution of lactose crystals. These may be split into two distinct categories;

- (i) Surface Processes
- (ii) Bulk Fluid Processes

Processes involved at the crystal surface involve disintegration from the crystal lattice and mass transfer of lactose to the bulk of solution, whereas bulk fluid processes include the solubility effect of alpha lactose and mutarotation reactions.

1.1 Lactose

Lactose, commonly referred to as "milk sugar", is the characteristic carbohydrate of milk. The milk of mammals is the sole source of lactose on a commercial basis. Commercially, lactose is produced from whey utilising a crystallization process.

As described by its chemical name 4-O- β -D-galactopyranosyl-D-glucopyranose, lactose is a disaccharide consisting of D-glucose and D-galactose joined by a 1,4- β -glycosidic linkage. Lactose exists as two stereo-isomers, known as alpha lactose and beta lactose, which differ in steric configuration of -OH and -H groups (Figure 1.1).

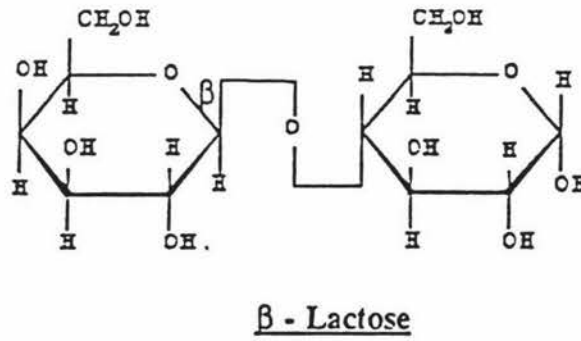
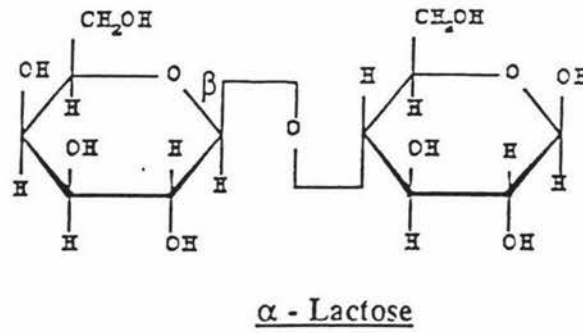


Figure 1.1 Chemical structure of alpha and beta lactose (Heimann 1980).

Lactose is commonly found in three different solid forms, alpha lactose monohydrate, beta lactose anhydride, and amorphous lactose. Alpha lactose monohydrate, or more simply α -hydrate, is the most common commercial form of crystalline lactose and is produced when lactose is crystallized from aqueous solutions at temperatures below 93.5°C. Beta lactose anhydride (beta anhydride) is another crystalline form which is produced when lactose is crystallized at temperatures above 93.5°C. Amorphous or "glass" lactose is a non-crystalline form of lactose consisting of both alpha and beta lactose and is produced as a result of rapid drying of lactose solutions (Eg. milk powder production).

1.1.1 Alpha Hydrate

The most common form of commercially available lactose is alpha hydrate. The crystalline structure of alpha hydrate can take a variety of shapes, depending on the conditions of crystallization. The principle factor governing the crystalline habit is the precipitation pressure, more commonly known as the degree of supersaturation, which is the ratio of concentration to the solubility of lactose (Herrington 1934A). Figure 1.2 shows the possible crystal forms that alpha lactose produces under different levels of supersaturation. The shape can vary from the "undeveloped" prism produced at high supersaturation values to the "fully developed" tomahawk produced at low supersaturation. Commercially available alpha hydrate most commonly demonstrates the tomahawk shape (Figure 1.3), with the angle $\beta=105^\circ$ (Visser and Bennema 1983).

1.1.2 Beta Anhydride

Another form of lactose crystals is beta lactose anhydride. This is sweeter and considerably more soluble than alpha hydrate, which has lead to an increase in the commercial production of beta anhydride. Beta anhydride can be produced by crystallizing at temperatures above 93.5°C, and also can be prepared from alpha lactose by refluxing with methanol containing small amounts of sodium hydroxide.

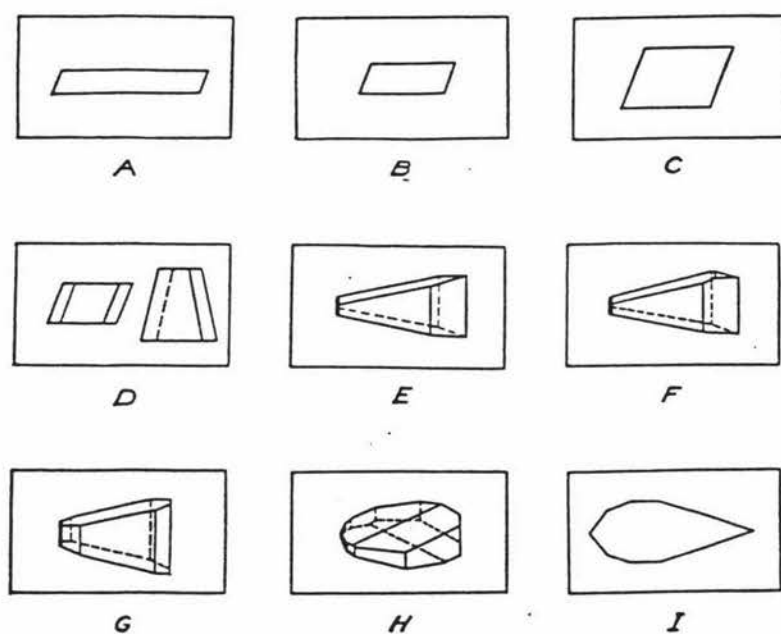


Figure 1.2 Crystalline habit of alpha lactose monohydrate under differing growth conditions from A = high growth rate to I = low growth rate (Herrington 1934A).

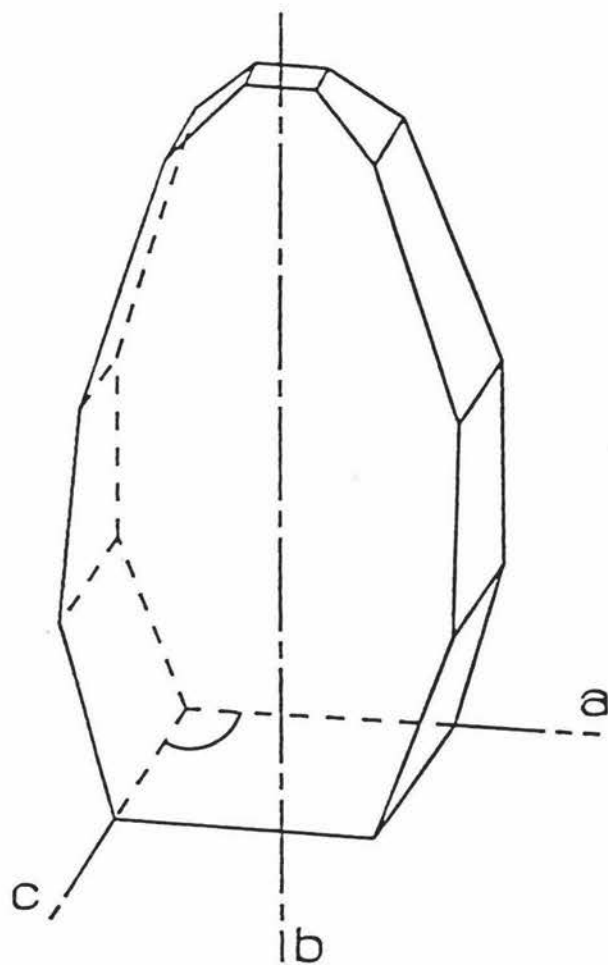


Figure 1.3 Fully developed "tomahawk" crystal of alpha lactose monohydrate (Kreveld and Michaels 1965).

1.1.3 Anhydrous Lactose

When a lactose solution is dried rapidly, its viscosity increases so quickly that crystallization cannot take place (Holsinger 1988). This leads to a dry lactose essentially in the same condition as it was in solution, except for the removed water. Lactose in milk powder is in this form and is very hygroscopic. This lactose is non-crystalline and exists in the same equilibrium mixture of alpha and beta lactose that existed prior to drying (Zadow 1984).

1.2 Physical Properties of Lactose

Physical properties of both alpha and beta lactose are well documented. Whittier (1944) gives a summary of these results.

1.2.1 Density

The density of alpha lactose monohydrate and beta anhydride crystals have been found to be 1540 kg/m^3 and 1589 kg/m^3 respectively (Wong *et al.* 1988). The densities of lactose solutions have been determined by McDonald and Turcotte (1948) and Buma (1980). McDonald and Turcotte developed equations for relating concentration on a percent weight to weight basis to the density of solution. Tables are available containing precise data on the density of lactose solutions (McDonald and Turcotte 1948, Buma 1980).

1.2.2 Viscosity of lactose solutions

The change in viscosity of lactose solution with concentration and time has been documented by Buma (1980). Tables of the effect of concentration and temperature on the viscosity of lactose solutions can be found in Buma (1980).

Table 1.1 Specific optical rotation values for lactose.

Temperature °C	$[\alpha_D]$	$[\alpha_F]$	$[\alpha_M]$
20	91.1	33.5	55.48
25	90.81	33.09	55.2
45	89.65	31.45	54.03

1.2.3 Optical rotation

The physical characteristic defining the difference between alpha and beta lactose is their optical rotating ability. This characteristic difference in the optical rotating ability of the isomers of lactose enables the relative amounts of alpha and beta lactose in solution to be determined by polarimetric measurement.

The most commonly quoted values for the optical rotation of alpha and beta lactose are those by Whittier (1944). However, a recent study by Buma and van der Veen (1980) has suggested these values were incorrect, possibly due to the presence of impurities in the initial experiments. The suggested values by Buma and van der Veen are shown in Table 1.1.

The specific optical rotations are determined from the observed optical rotations measured by a polarimeter by the following equation;

$$[\alpha] = \frac{100r}{lC} \quad (1.1)$$

where $[\alpha]$ = Specific optical rotation of lactose. (°)

r = Observed optical rotation (°m²/kg)

l = Length of column of solution (m)

C = Concentration of active substance (kg/m³)

The fraction of alpha lactose in solution (x) and hence beta lactose can be determined from the specific optical rotation using the equation below;

$$x = \frac{[\alpha] - [\alpha_\beta]}{[\alpha_\alpha] - [\alpha_\beta]} \quad (1.2)$$

where x = Mass fraction of alpha lactose in solution
 $[\alpha_\alpha]$ = Specific optical rotation of alpha lactose ($^\circ$)
 $[\alpha_\beta]$ = Specific optical rotation of beta lactose ($^\circ$)

To calculate the fraction of alpha lactose in solution either the specific optical rotations for alpha and beta lactose at the temperature at which the optical rotation must be known or the measured specific optical rotation must be converted to a known temperature using the following equation;

$$[\alpha]^{20} = \frac{[\alpha]^\theta}{(1 + k(\theta - 20))} \quad (1.3)$$

where $[\alpha]^\theta$ = Specific optical rotation at the temperature $\theta^\circ\text{C}$ ($^\circ$)
 k = Temperature coefficient

1.3 Mutarotation

As mentioned previously, lactose exists in two forms, alpha and beta lactose. In solution (and in some solids) an equilibrium exists between these two forms of lactose. The equilibrium reaction is known as mutarotation and can be represented by the following equation:



This reaction has been shown by Hudson (1904) to be a first order reaction. For a dilute solution at a constant temperature initially containing (a) moles of alpha and (b) moles of beta, then the rate at which beta is formed may be expressed as;

$$\frac{dx}{dt} = k_1(a - x) - k_2(b + x) \quad (1.5)$$

- where x = moles of beta lactose in solution (moles)
 a = moles of alpha lactose initially in solution (moles)
 b = moles of beta lactose initially in solution (moles)
 k_1 = rate of conversion of alpha lactose to beta lactose (s^{-1})
 k_2 = rate of conversion of beta lactose to alpha lactose (s^{-1})

This can be integrated and expressed in terms of optical rotations;

$$k_1 + k_2 = \frac{1}{t} \ln \left[\frac{r_0 - r_{\infty}}{r_t - r_{\infty}} \right] \quad (1.6)$$

- where t = time (s)
 r_0 = optical rotation at time $t = 0$. ($^{\circ}m^2/kg$)
 r_t = optical rotation at time $t = t$. ($^{\circ}m^2/kg$)
 r_{∞} = optical rotation at time $t = \infty$, ie at mutarotation equilibrium. ($^{\circ}m^2/kg$)

Values of $k_1 + k_2$ for the mutarotation of alpha lactose monohydrate at different temperatures determined by Herrington (1934B), Haase and Nickerson (1966A & B), Patel and Nickerson (1970) and van Kreveland (1969) are shown in Table 1.2 and also in Figure 1.4 in the form of an Arrhenius plot. From Figure 1.4 it is apparent that there is some discrepancy in the literature on the rate of mutarotation. Haase and Nickerson (1966) and Van Kreveland (1969) appear to have a somewhat faster mutarotation rate than that of Herrington (1934B), Isbell and Pigman (1937), and Patel and Nickerson (1970). The reason for this discrepancy is not clear, but may be due to the presence of impurities which altered the mutarotation rate during experiments.

Calculating arrhenius constants using all the rate data by the non-linear method suggested by Chen and Aris (1992), gives Arrhenius constants of $A_0 = 3.61584 \times 10^{10} s^{-1}$ and $E_a = 81539.98 \text{ kJ/kgmol}$ for $k_1 + k_2$.

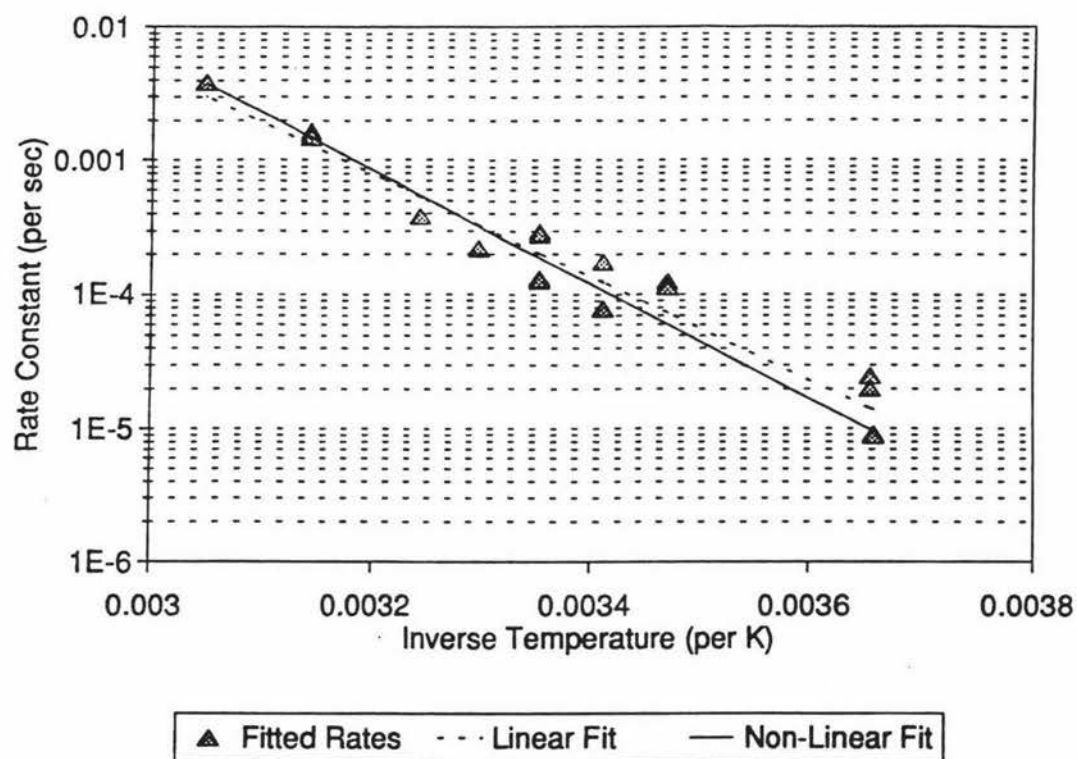


Figure 1.4 Arrhenius plot of mutarotation rates $k_1 + k_2$.

Table 1.2 Mutarotation reaction rate constants for lactose.

Temperature °C	k_1+k_2 sec ⁻¹ (x10 ⁻³)
0.2	0.00890 ^b
0.5	0.02228 ^c
15	0.11989 ^c
	0.11295 ^d
20	0.175 ^c
	0.7808 ^b
25	0.2860 ^c
	0.2807 ^d
	0.1320 ^a
	0.1265 ^f
30	0.2192 ^f
35	0.3812 ^f
45	1.6217 ^c
	1.4808 ^d
55	3.7592 ^c

^a Herrington (1934B), ^b Isbell and Pigman (1937), ^c Haase and Nickerson (1966A),

^d Haase and Nickerson (1966B), ^e Van Kreveld (1969), ^f Patel and Nickerson (1970).

1.3.1 Factors affecting Mutarotation

In order to convert alpha lactose to beta lactose, it is necessary only that there be a migration of one proton. Baker (1929) believed that this could take place directly. However, Lowery (1927) suggested that the transfer of a proton would take place in two or more stages. Initially, a proton is withdrawn from one part of the molecule while another is supplied to some other part, keeping the molecule electrically neutral. At a later stage the process is reversed, with the new proton not necessarily entering the position of the initially withdrawn proton. This results in the transformation of one isomer to the other as shown in Figure 1.5, which can only take place in the presence of both a donor and acceptor of protons. This suggests that many substances which act as proton acceptors and donors may influence the mutarotation of lactose.

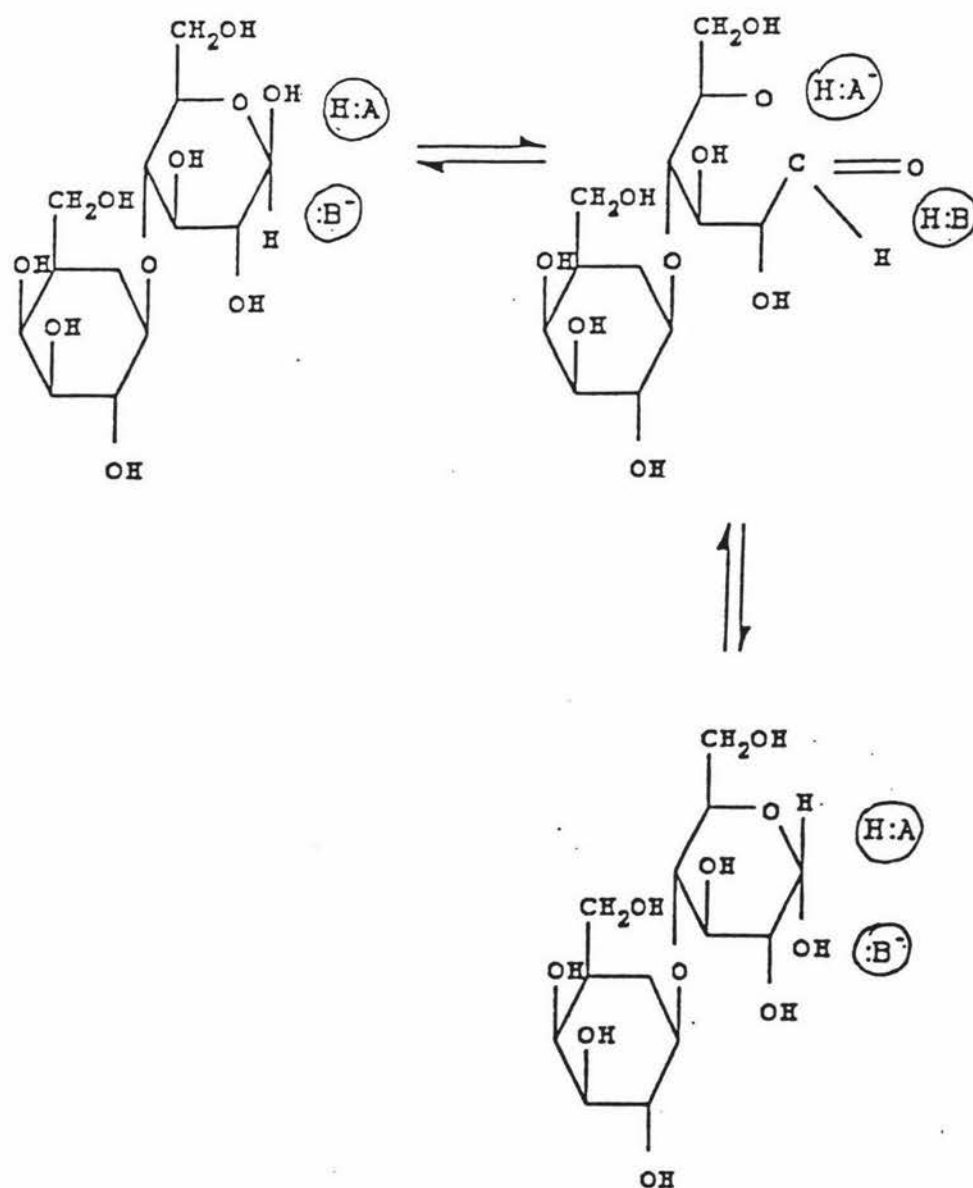


Figure 1.5 Mechanism for Acid/Base catalysis of mutarotation (Bocock 1992).

1.3.1.1 Acids and Alkalies

The actions of acids and alkalies has been shown to affect the rate of mutarotation. Hunziker (1926) found that the mutarotation rate increased rapidly if the pH dropped below 2 or increased above 7, with a minimum rate at pH 4.5 (Figure 1.6). However, results by Jelen and Coulter (1973) and Nickerson and Moore (1974) on lactose crystallization suggest that the presence of weak organic acids such as acetic and lactic acid has an inhibitory effect on mutarotation. This was most likely due to the weak acid reducing the pH from a neutral pH to a pH close to the minimum rate value of 4.5.

1.3.1.2 Salts

Salts have an effect on the mutarotation of lactose. This has often been attributed to hydrolysis, with a consequent rise in pH. However, Herrington (1934) examined the effect of four different salts independent of pH and found that all except for potassium chloride increased the rate of mutarotation (Table 1.3). Potassium chloride was found to decrease the rate of mutarotation. Patel and Nickerson (1970) confirms these results, with potassium phosphate, potassium citrate and sodium citrate catalyzing mutarotation, and potassium chloride, potassium sulphate and others retarding mutarotation. Haase and Nickerson (1966) found that a combination of salts equal to that present in milk nearly doubles the mutarotation rate. The catalysis of mutarotation by the salts can be explained in terms of proton acceptors and donors. However, the retardation of mutarotation by potassium chloride, potassium sulphate and other salts cannot be explained in this manner.

1.3.1.3 Carbohydrates

Patel and Nickerson (1970) found that the presence of sucrose inhibited mutarotation. This effect was only slight at concentrations below 40% (w/v), but as the concentration was increased above this level, mutarotation was rapidly decreased to half the normal rate.

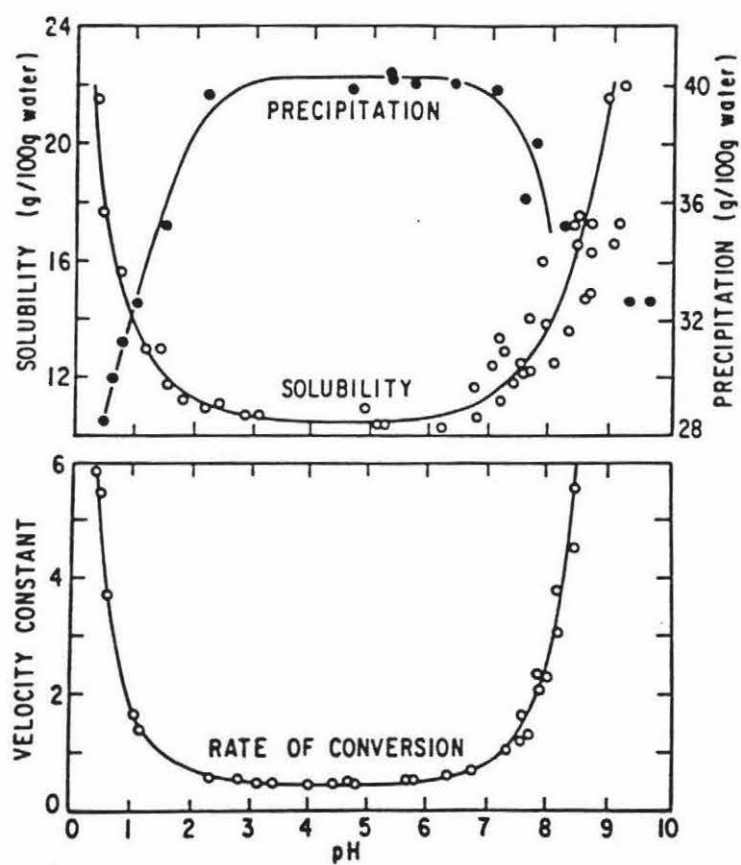


Figure 1.6 The effect of pH on the solubility and mutarotation rate of lactose.

Table 1.3 Influence of salts on the mutarotation rate of lactose.

Salt	k_1+k_2 (hr ⁻¹)
None	0.475
Potassium chloride	0.413
Ammonium chloride	0.501
Potassium acetate	2.8
Ammonium acetate	3.5

All solutions were adjusted by HCl to pH 5.0 and measured at 25°C.

Table 1.4 Influence of amino compounds on the mutarotation rate of lactose.

Additive	k_1+k_2 (hr ⁻¹)
None	0.630
Glycine	0.768
DL alanine	0.708
DL valine	0.738
DL glutamic acid	0.870
Ammonium chloride	0.666
Urea	0.618
Saccharine	0.648
Pyridine	1.698

All solutions adjusted with NaOH or HCl to pH 6.0 and measured at 20°C.

1.3.1.4 Amino compounds

Amino compounds have been shown to have an effect on the mutarotation of lactose. Table 1.4 shows the rate of mutarotation for different amino compounds, from van Kreveland (1969). pH was not a factor in these experiments as all solutions were standardised to pH 6.0. This shows that amino compounds such as glycine and pyridine increased the rate of mutarotation, with pyridine increasing the mutarotation rate by over two times.

1.4 Solubility of Lactose

The solubility behaviour of alpha and beta lactose is considerably different. When alpha lactose crystals are added to water, initially the solubility of lactose is limited. This slowly increases over time. This increasing solubility of lactose is due to the mutarotation of lactose from the alpha isomer to the beta isomer, with the initial solubility level being the solubility of α -lactose. Mutarotation then proceeds to convert alpha lactose to beta lactose, allowing more alpha lactose to dissolve. This process continues until the beta lactose equilibrium concentration is reached, preventing any further lactose from dissolving and producing a final solubility of lactose. If beta lactose, which has a higher solubility than alpha lactose, is added to water, a higher initial solubility is produced which then approaches the same total solubility concentration as alpha lactose.

At temperatures above 93.5°C, beta lactose becomes the limiting solubility component and the situation above is reversed. Consequently, if lactose is crystallized at temperatures below 93.5°C, alpha lactose is formed, where-as at temperatures above 93.5°C beta lactose is formed (Walstra and Jenness 1984).

The alpha and total solubility values of lactose are shown in Table 1.5 (Whittier 1944, Visser 1982). However, work by Burma and van der Veen (1974) and Roetman and Burma (1974) suggested that the β/α ratios used to calculate the alpha lactose solubility limit were incorrect, leading to incorrect estimations of the alpha lactose solubility limit. The corrected alpha lactose solubility limit and the previously reported solubility limits are shown in Table 1.5. It can be seen that the corrections do not change the alpha lactose solubility limit greatly.

1.4.1 Factors affecting Lactose solubility

Various factors have been found to affect the solubility of lactose. These range from factors as varied as temperature, solvent, pH of solution, presence of other sugars and the presence of salts.

1.4.1.1 Solvents

The solvent in which lactose is dissolved in has been shown to effect the solubility of lactose. Alcohols have been found to reduce the solubility of lactose (Majd and Nickerson 1976). The longer the length of the alcohol chain, the lower the solubility of lactose. Even the addition of alcohols to aqueous solutions will reduce the solubility of lactose (Singh *et al* 1991). Acetone also reduces the solubility of lactose, and a procedure to recover lactose from whey has been based on this (Kerckkonen *et al* 1963).

Table 1.5 Solubility of lactose in water.

Temperature (°C)	Reported C_{α} g/100g	Reported C_{β} g/100g	β/α	Estimated C_{α} g/100g
0	5.0	11.90	1.61	4.56
15	7.1	16.86	1.60	6.48
20		19.10	1.59	7.37
25	8.6	21.81	1.58	8.45
30		24.81	1.56	9.69
33		26.95		
39	12.6	31.60	(1.55)	12.39
40		32.75	(1.54)	12.89
48		41.09		
49	17.8	42.20	(1.52)	16.75
50		43.46	1.52	17.25
55		50.19		
60		58.40	1.50	23.36
64	26.2	65.80	(1.49)	26.43
65		67.72		
70		78.26	(1.47)	31.68
74	34.4	85.90	(1.46)	34.92
75		90.40	1.46	36.75
80		104.60	(1.45)	42.69

1.4.1.2 Acid and Alkalies

The pH of solution also has an effect on the solubility of lactose. Hunziker (1926) found that lactose solubility was a minimum at pH 4.5 and at pH's above 7 and below 2 the solubility of lactose rose dramatically (Figure 1.6).

1.4.1.3 Carbohydrates

Studies have been made into the effects of other sugars on the solubility of lactose. Talley and Hunter (1952) found that the presence of D-Glucose and D-Galactose had a solubility depressing effect on lactose which could be expressed in the form of the following equation;

$$La = 17.50 - 0.2452Gl - 0.2477Ga \quad (1.7)$$

where La = total solubility of lactose (g/100g)

Gl = concentration of D-Glucose in solution (g/100g)

Ga = concentration of D-Galactose in solution (g/100g)

Nickerson and Moore (1972) found that the presence of sucrose in solution also had a solubility depressing effect on lactose. Visser (1982) suggested that the presence of beta lactose in solution had a similar solubility depressing effect on alpha lactose as sucrose, and that the solubility values of alpha lactose should be more correctly quoted as the solubility of alpha lactose at mutarotation equilibrium with beta lactose. The alpha lactose solubility could then be expressed as;

$$C_{\alpha}^{\beta} = C_{\alpha}^{\beta eq} - F(C_{\beta} - C_{\beta}^{\alpha eq}) \quad (1.8)$$

where C_{α}^{β} = solubility of alpha lactose in the presence of beta lactose (kg/m³)

$C_{\alpha}^{\beta eq}$ = solubility of alpha lactose at mutarotation equilibrium (kg/m³)

C_{β} = concentration of beta lactose in solution (kg/m³)

$C_{\beta}^{\alpha eq}$ = concentration of beta lactose at mutarotation equilibrium (kg/m³)

F = solubility depressing effect of beta lactose.

Table 1.6 Values of F and $C_{\alpha}^{\beta=0}$ at various temperatures.

Temperature °C	C_l (kg/m ³ solution)	C_{α} (kg/m ³ solution)	$C_{\alpha}^{\beta=0}$ (kg/m ³ solution)	F
0	110.95	42.51	47.72	0.03232
10	138.46	53.25	57.71	0.05230
20	170.84	65.96	75.28	0.09086
30	213.93	83.57	98.28	0.11287
40	369.82	103.23	126.28	0.12256
50	338.04	134.14	167.41	0.16312
60	421.98	168.79	220.75	0.20522
70	512.30	207.41	277.85	0.23104
80	610.16	249.04	370.94	0.33755
90	708.02	291.37	483.88	0.46204

This equation can be simplified to;

$$C_{\alpha}^{\beta} = C_{\alpha}^{\beta=0} - FC_{\beta} \quad (1.9)$$

where $C_{\alpha}^{\beta=0}$ = solubility of alpha lactose in the absence of beta lactose (kg/m³)

Table 1.6 contains values of F and $C_{\alpha}^{\beta=0}$ in SI units estimated from Visser (1982).

1.4.1.4 Salts

The presence of salts in solution has been shown to affect the solubility of lactose. Several calcium salts, chloride, bromide, and nitrate increase the solubility of lactose (Herrington 1934). Other salts such as calcium oxide have the opposite effect. The use of calcium oxide for the extraction of lactose from whey has been proposed.

1.5 Surface Phenomena

There is little information on the possibility of surface reactions being involved in the dissolution process, other than suggesting that diffusion is the only significant process taking place at the surface (Thurlby 1976). However, preliminary dissolution work by Hodges (1992) at low lactose concentrations and temperatures suggests that dissolution alone cannot explain surface phenomena. Other mechanisms must be occurring.

The dissolution of alpha lactose monohydrate may be considered to be a reversal of the crystallization process. This suggests that a close study of factors that affect crystallization may reveal information on surface phenomena occurring in the dissolution process.

1.5.1 Crystallization

The crystallization of alpha lactose is generally understood to involve the following three processes (Visser 1980);

- (1) Mutarotation in the bulk solution.
- (2) Diffusion of alpha lactose to the surface of the crystal
- (3) Integration of alpha lactose into crystal surface.

Studying diffusion and the surface integration reaction of lactose crystallization should reveal information on dissolution surface phenomena. There is much literature investigating the role of various factors and additives in crystallization. However, there is also much discrepancy between the literature on the effects of various additives. This is often due to the conditions under which experiments are carried out, altering the controlling factor of crystallization, and hence giving differing effects.

1.5.1.1 Acids and Alkalies

Acids have been shown to have a variable effect on the crystallization of lactose. Michaels and Van Kreveld (1966) found that acids had only minimal effect on crystallization where-as Nickerson and Moore (1974) found that strong acids had a great effect on crystallization. This difference in the literature can be attributed to the differing conditions under which the experiments were carried out. Tweig and Nickerson (1968) found that mutarotation is the controlling factor when crystal surface area is high. The effect of acids found by Nickerson and Moore (1974) can be attributed to mutarotation as their experiments used high surface areas. The work by Michaels and van Kreveld (1966) utilized single crystals, with surface effects being the controlling factor. This indicates that acid has little effect on the surface phenomena taking place in crystallization.

1.5.1.2 Carbohydrates

Conflicts also exists on the effects of carbohydrates on crystallization. Michaels and van Kreveld (1966) and van Kreveld (1969) found in their experiments that carbohydrates with similar structures to alpha lactose, including beta lactose, inhibited crystallization of lactose. Nickerson and Moore (1974) found the reverse, with glucose and maltose having minimal or slightly increasing the rate of crystallization which was attributed to a decrease in solubility of lactose due to the presence of sugars. Nickerson suggested that the procedure used by van Kreveld et al does not apply to the growth of normal alpha lactose monohydrate crystals. However, work by Visser (1980, 1984) found that for surface limited crystallization a natural inhibitor appeared to be associated with the lactose crystals. This inhibitor was identified as a disaccharide phosphate and appeared to be incorporated with high preference in growing alpha lactose monohydrate, making ion exchange resins the only easy way to separate the growth inhibitor from lactose.

1.5.1.3 Crystal Faces

Van Kreveld and Michaels (1965) found that the crystal faces of alpha lactose monohydrate do not grow uniformly. The crystals were found to grow in one direction only, with the nucleus of the crystal at the apex of the tomahawk. The different habits of alpha hydrate due to different supersaturation were found to be equivalent to the tomahawk form and arise from the different relative growth rates between crystal faces. This may apply in the dissolution process if the same integration reaction is simply reversed.

1.5.2 Crystallization Kinetics

Attempts have been made to quantify the kinetics of lactose crystallization in terms of supersaturation. Tweig and Nickerson (1968) found that the rate of lactose crystallization could not be explained by first-order diffusion kinetics. This was due to mutarotation effects, with possibly some surface reaction having an influence as well. Thurlby (1976) conducted experiments with constantly replenished lactose solutions, hence excluding mutarotation as a variable, and found that the crystallization kinetics were from third and fourth order in relation to supersaturation. Table 1.7 gives a summary of Thurlby's results which were fitted to Equation 1.10. Thurlby suggested that these results could not be explained by diffusion.

$$\frac{dW}{d\tau} \cdot \frac{1}{A} = k_c (C_\alpha - C_\infty)^n \quad (1.10)$$

- where W = anhydrous mass of lactose (g)
 τ = crystallization time (hr)
 A = total crystal surface area (m²)
 k_c = overall crystallization rate constant (g.hr⁻¹.m⁻²(wt%)⁻ⁿ)
 C_α = concentration of lactose in solution (wt%)
 C_∞ = solubility of alpha lactose in solution (wt%)
 n = order of reaction for crystallization

Shi *et al* (1989) found the growth kinetics for contact nucleation. This was based on the relative supersaturation ($s - 1$), where s , the supersaturation ratio was defined by Visser (1982) as;

$$s = \frac{C_t}{C_s - FK_m(C_t - C_s)} \quad (1.11)$$

where C_t = total concentration of lactose in solution (g/100g)
 C_s = total solubility limit of lactose (g/100g)
 K_m = ratio of beta to alpha lactose concentrations at equilibrium.
 F = Solubility depressing effect of beta lactose.

The mean growth kinetics of alpha lactose contact nuclei were expressed as:

$$\frac{dD_c}{dt} = k_0 e^{\left(-\frac{E}{RT}\right)} [(s - 1) - 0.47]^n \quad (1.12)$$

where D_c = diameter of crystal (μm)
 k_0 = Frequency factor ($\mu\text{m}/\text{min}$)
 E = arrhenius constant (kcal/mol)
 R = universal gas constant (kcal/mol.K)
 T = temperature (K)

The value 0.47 represents the critical supersaturation below which crystal growth was not observed. Table 1.8 gives the values of k_0 , E , and n found by Shi *et al* (1989).

Table 1.7 Crystallization rate constants and order of reaction from Thurby (1976).

Temperature (°C)	Reaction Order, n	Rate Constant*, k_c $\text{g.hr}^{-1}.\text{m}^{-2} (\text{wt}\%)^{-n}$
15	3.0	0.107
25	2.9	0.197
35	3.1	0.156
40	3.4	0.106
50	4.1	0.073

* For alpha lactose supersaturation in wt%

Table 1.8 Kinetic growth parameters for equations developed by Shi *et al* (1989).

Parameter	k_o (Frequency Factor)	E (Activation energy)	n
	($\mu\text{m}/\text{min}$)	(kcal/mol)	
Estimate	1.2×10^6	9.8	2.2
Standard Error	...	0.5	0.1

1.6 Dissolution Modelling

Hodges (1992) developed a mathematical model for predicting the dissolution of lactose in solution. Dissolution was considered to be a two step process. Firstly, alpha lactose diffused from the surface of the crystal into the bulk of solution. Secondly, mutarotation of the alpha lactose to beta lactose in the bulk of solution occurred. The assumptions made in the model were:

- (i) No significant reaction occurred at the surface of the crystal.
- (ii) Lactose crystal geometry remained constant throughout dissolution.
- (iii) All crystal surface area was available for dissolution.
- (iv) Alpha lactose solubility was unaffected by other compounds.
- (v) Constant temperature throughout dissolution.
- (vi) Perfect mixing in system.
- (vii) Mutarotation can be described by a first order rate constant.
- (viii) Mass transfer coefficient remained constant with changing particle size.

In order to model the change in particle size with time, a simplified crystal shape was assumed. Figure 1.7 shows the shape used in Hodges (1992). The width, height, and depth of the crystal were measured experimentally to be 1:1.333:0.6. From this ratio, equations for the surface area (A_p) and volume (V_p) of the crystal in terms of the width (D_c) of the crystal were found to be;

$$V_c = 0.2667D_c^3 \quad (1.13)$$

$$A_c = 2.8211D_c^2 \quad (1.14)$$

where V_c = volume of crystal (m^3)
 A_c = surface area of crystal (m^2)
 D_c = width of crystal (m)

Three differential equations were required. These were for alpha lactose concentration (C_α), beta lactose concentration (C_β), and crystal size (D_c). Expressions for these were developed using unsteady state mass balances and are given below:

$$\frac{dM_\alpha}{dt} = k_L A (C_\alpha - C_\alpha) - k_1 M_\alpha + k_2 M_\beta \quad (1.15)$$

$$\frac{dM_\beta}{dt} = k_1 M_\alpha - k_2 M_\beta \quad (1.16)$$

$$\frac{dD_c}{dt} = \frac{3.52633 k_L (C_\alpha - C_\alpha)}{\rho_c} \quad (1.17)$$

where M_α = mass of alpha lactose in solution (kg)
 M_β = mass of beta lactose in solution (kg)
 k_L = mass transfer coefficient (m/s)
 ρ_c = density of alpha lactose monohydrate crystal (kg/m^3)
 and C_α and C_α have units of kg/m^3 .

The volume of solution was defined as mass of water + dissolved solid over the density of solution at the given concentration. Using the density data from McDonald and Turcotte (1948) and Buma (1980), regression equations for solution density were found for each temperature.

Mass transfer constants were evaluated using the conductance concept given by Clift *et al* (1978). This was calculated for the starting particle size using the formula given below:

$$k_L = \frac{Sh'_0 L'}{D} \quad (1.18)$$

where Sh'_0 = Sherwood number for diffusion into a stagnant medium.
 L' = characteristic length of lactose crystal (m)
 D = diffusivity of lactose solution (m^2/s)

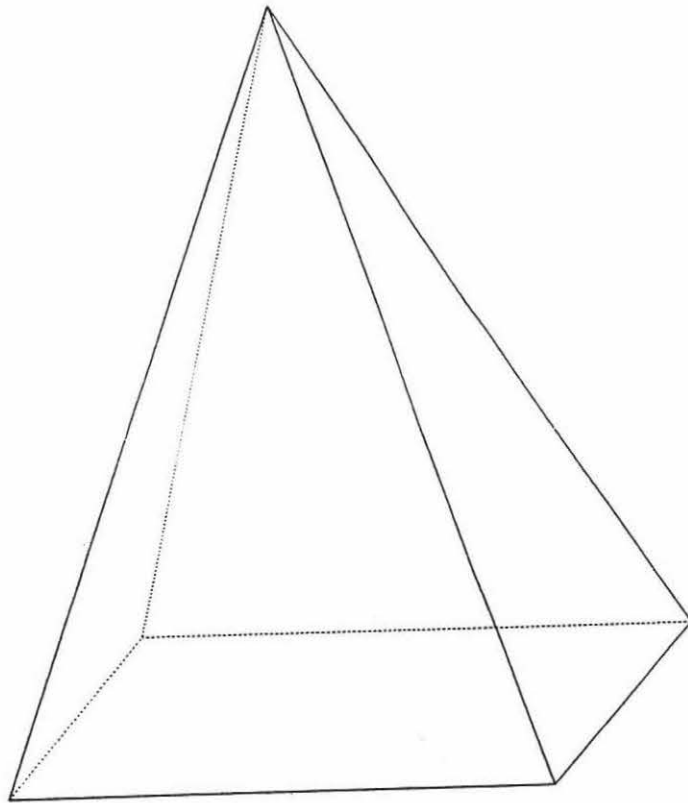


Figure 1.7 Simplified alpha lactose monohydrate crystal shape used by Hodges (1992).

Experiments were carried out by Hodges (1992) with three different masses of lactose. This enabled the testing of the model under three different regimes;

- (i) Final concentration at total solubility limit (saturated solutions).
- (ii) Final concentration between the alpha lactose solubility limit and the total solubility limit.
- (iii) Final concentration below the alpha lactose solubility limit.

In the first two regimes mutarotation controls dissolution, where-as in the third regime surface phenomena are controlling.

Figures 1.8 to 1.10 show a comparison of the model against experimental data. Figure 1.8 shows that the model agrees well with the experimental data in region (i). There does however appear to be a discrepancy in the alpha lactose concentration. The model predicts that alpha lactose will quickly reach its solubility limit and then remain at this value. However, what appears to happen is that alpha lactose overshoots its solubility limit and then asymptotically drops towards its solubility limit. A possible explanation for this is that as suggested by Visser (1982), the increasing presence of beta lactose may depress the solubility of alpha lactose.

In region (ii) where the final concentration is below the total solubility limit, Figure 1.9 shows that the model over-predicts the rate of dissolution for this case. This could be due to the beta lactose solubility depressing effect as above.

In the third region, Figure 1.10 shows that again the model over-predicts the rate of dissolution. In this region mass transfer was assumed to be controlling. An assumption was made that the mass transfer coefficient was constant during dissolution. This is not justifiable as a changing particle size would give a changing mass transfer coefficient.

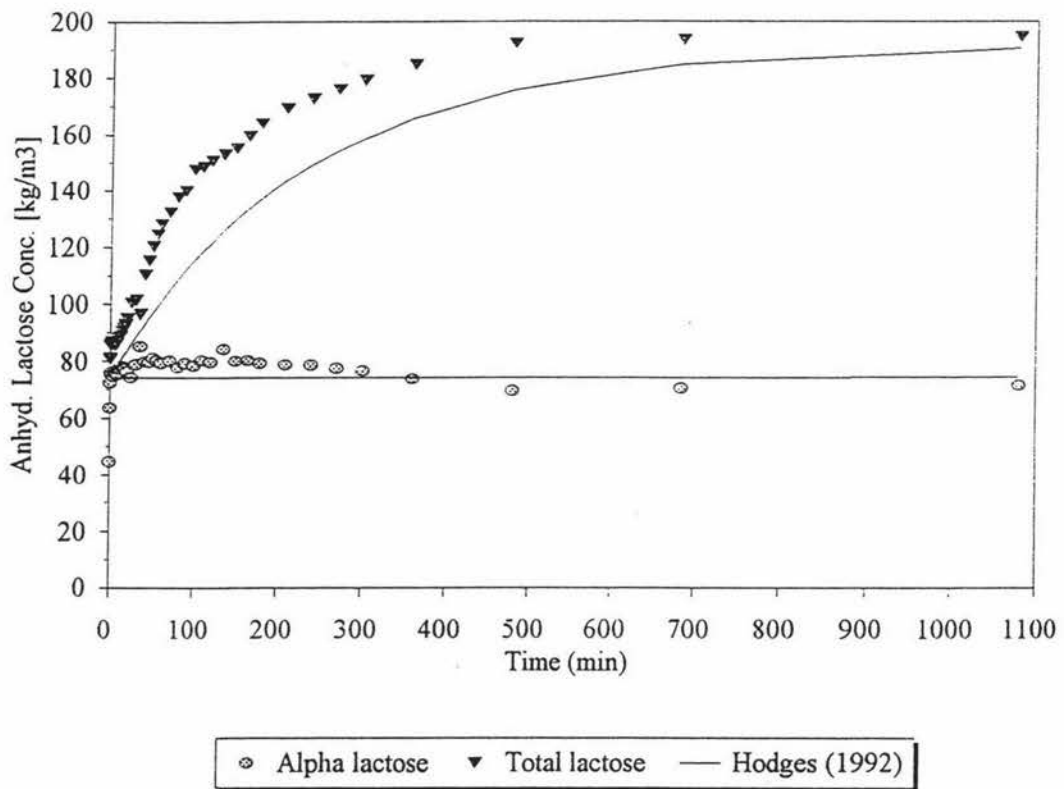


Figure 1.8 Dissolution of lactose with excess lactose in solution. Operation conditions: 25°C, Stirring speed 200 rpm.

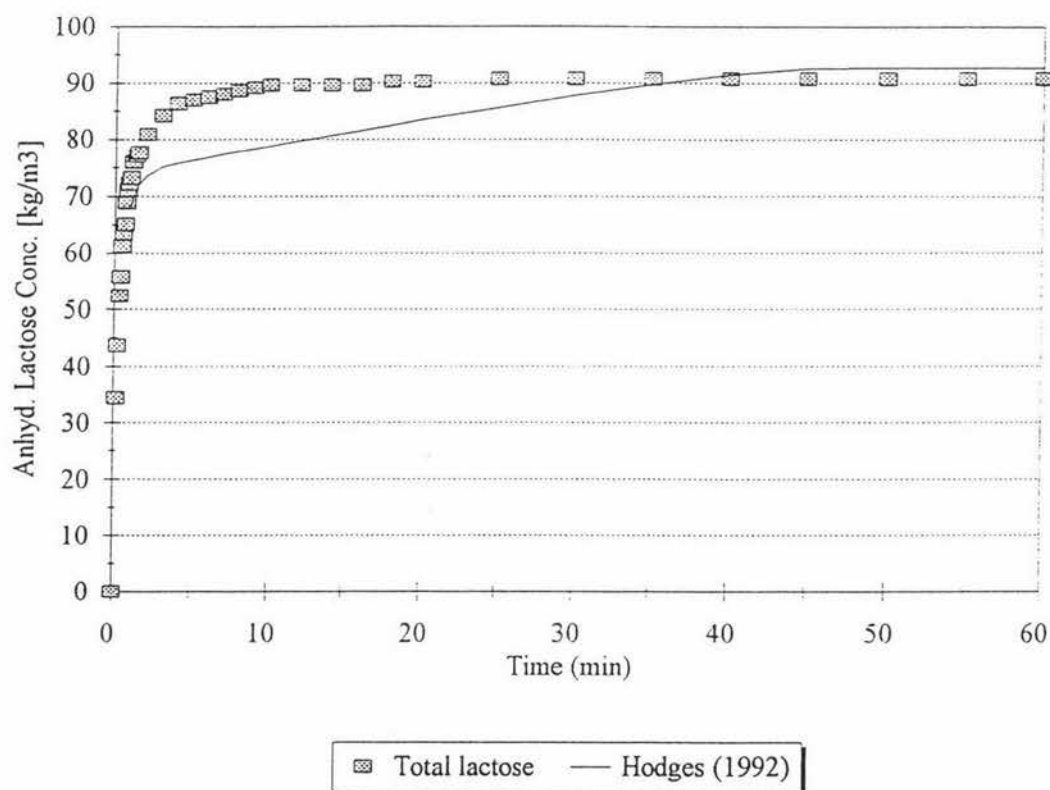


Figure 1.9 Dissolution of lactose below the total solubility limit. Operating conditions: 25°C, Final concentration 92.5 kg/m³, Stirring speed 200 rpm.

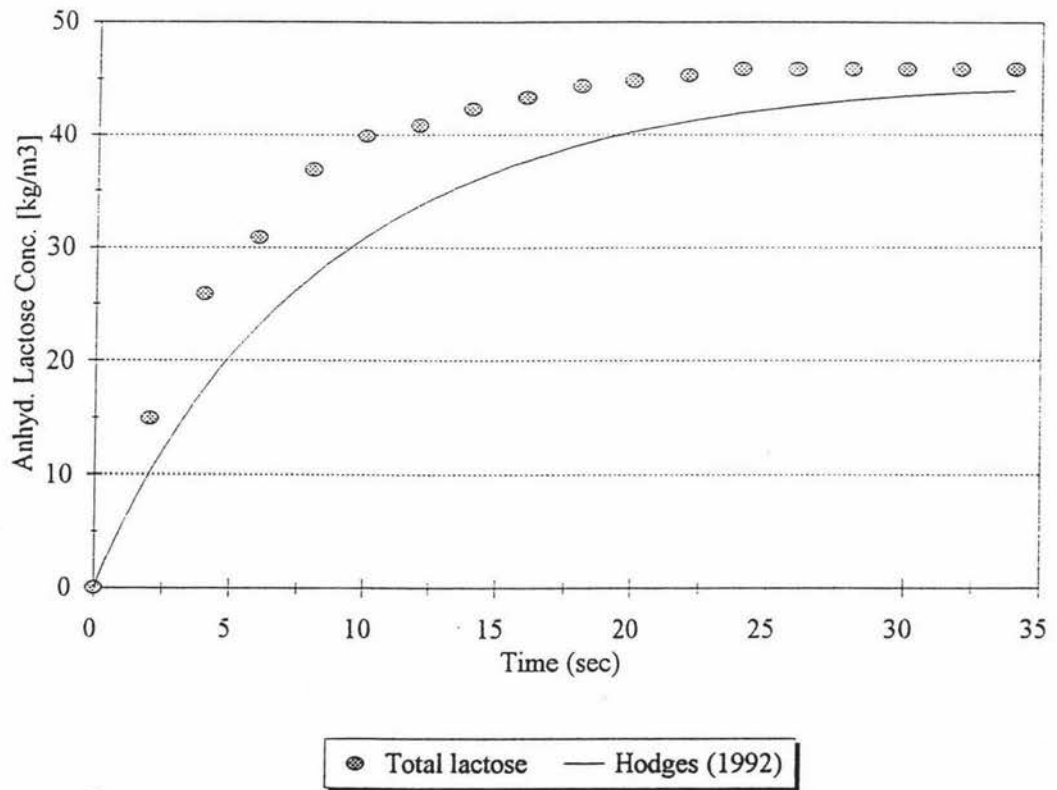


Figure 1.10 Dissolution of lactose below the alpha lactose solubility limit. Operating conditions: 25°C, Final concentration 44.5 kg/m³, Stirring speed 200 rpm.

1.7 Summary

Lactose commonly exists in either of two crystal forms, alpha lactose monohydrate or beta lactose anhydride, the most common commercially being alpha lactose monohydrate. The dissolution of alpha hydrate is slow in comparison to other sugars. This is due to the relatively insoluble nature of alpha lactose and the subsequent mutarotation of alpha lactose in solution to beta lactose.

Mutarotation of lactose is a first order reaction and can be affected by a variety of factors, the most important being temperature. Additives such as acids, salts, carbohydrates and amino acids also have been shown to have an effect on the rate of mutarotation.

The solubility of lactose is affected by a variety of factors, among them temperature, pH, and the presence of carbohydrates and other additives. The presence of other carbohydrates in solution is particularly important as it has been found that the presence of beta lactose affects the solubility of alpha lactose. This suggests that the values of the alpha lactose solubility limit quoted in the literature are in fact the solubility of alpha lactose at the equilibrium concentration of beta lactose.

Dissolution may be considered to consist of three steps, a surface disintegration step, a diffusion step, and a mutarotation step. Each of these steps must be carried out in sequence. Examining crystallization literature has produced conflicting information on what could affect the surface diffusion reaction.

A model has been developed for predicting lactose dissolution in solution. The model ignored any surface reaction phenomena and any possible effects by compounds on the alpha lactose solubility, considering only diffusion and mutarotation as processes in dissolution. This model was found to adequately predict the dissolution of lactose with excess lactose, but was found to depart from the experimental results when dissolution occurred without excess lactose and below the alpha lactose solubility limit.

CHAPTER 2

Experimental Procedures

2.1 Materials

The α -lactose monohydrate used in this work was "Wyndale" special dense grade hydrous lactose provided by The Lactose Company of New Zealand Ltd (Cyphers: 1102425 124, and 1093025 104). This was separated into different particle fractions by sieving in a test sieve shaker for 10 minutes. Sieves with apertures 420 μ m, 300 μ m, 210 μ m, 150 μ m, and 105 μ m were used with particle fractions between 300 μ m and 210 μ m, 210 μ m and 150 μ m, and 150 μ m and 105 μ m collected. Unsieved lactose samples were also used in some experiments.

Distilled water was used in all experiments.

2.2 Equipment

2.2.1 Equipment Layout

The experimental setup used for the differing mixing regimes can be found in Figure 2.1. This consisted of a New Brunswick Scientific Co. Ltd. 20 litre fermentation vessel placed into a temperature controlled waterbath. The contents of the vessel were continuously sampled via the pumping circuit, with a flow rate in the circuit of 1 l/min. A blue stone filter prevented the entry of lactose crystals into the pumping circuit and a sample point in the circuit enabled continuous collection of the vessel contents without entrained lactose crystals. The flow rate out of the sampling point was controlled via the tap to 20 ml/min.

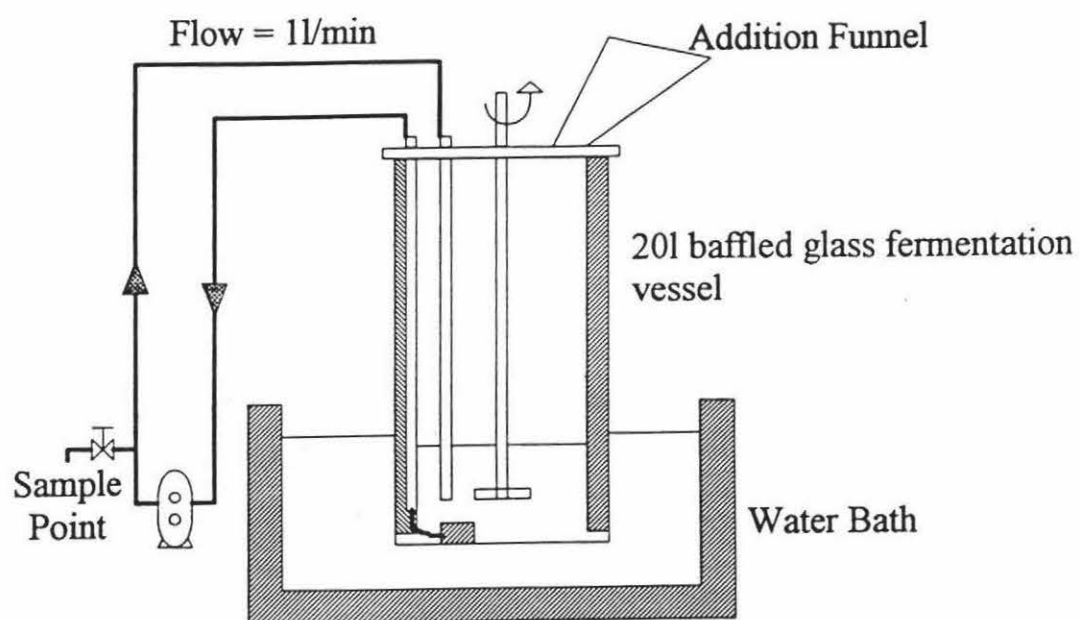


Figure 2.1 Experimental apparatus used in dissolution runs with changing stirring rates.

Figure 2.2 shows the experimental setup used in all other dissolution experiments. This consisted of a baffled stainless steel vessel with an overhead stirrer placed in a temperature controlled waterbath. As before, a filtered pumping circuit (flow rate 1 l/min) enabled the vessel's contents to be sampled continuously free of entrained lactose crystals. The sampling flow rate was, as before, 20 ml/min.

2.2.2 Equipment Details

Refractometer: Atago Optical Work Co. Ltd. Abbe Refractometer Type #302
(Serial Number: 94557).

Test Sieve Shaker: Endecotte test sieve shaker. EFL 1, Mk II. (Serial Number: 6192).

Positive Displacement Pump: Greylor Co. Positive Displacement Pump, Model PQM-1 (Serial Number: 90-01813).

Stirrer: Watson Victor Ltd "Caframo", Stirrer Type RZR1-64.

2.3 Methods

2.3.1 Standard curve for refractometer

The measurement of the total lactose content in solution was carried out using a Atago Abbe Refractometer, which measured the refractive index of the solution. The total lactose content was determined from this by preparing standard curves for lactose solutions at 20°C and 25°C.

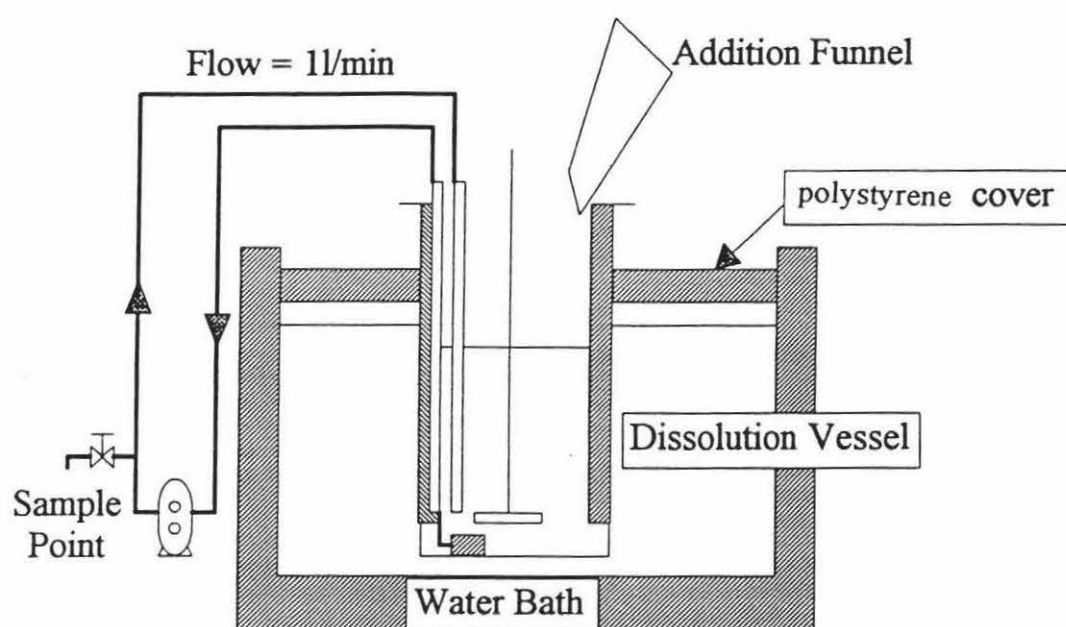


Figure 2.2 Experimental apparatus used in dissolution experiments.

2.3.1.1 Preparing standard solutions of lactose.

Known weights of sieved α -lactose monohydrate were added to 100ml or 250ml volumetric flasks and the flasks half filled with water. This was placed in either a 20°C or a 25°C waterbath, depending on the standard temperature required. To aid dissolution of the lactose, a drop of ammonia was added to each flask.

When the lactose was fully dissolved, water at the required temperature was added to the flasks to make up to the required 100ml (or 250ml).

The weight of monohydrate to be added and intended anhydrous lactose concentrations prepared for 20°C and 25°C standard curves are shown in Tables D1 and D2 in Appendix D. The weight of α -lactose monohydrate to be added was calculated in the following way:

Example: To get 30 kg/m³ anhydrous lactose in a 100ml volumetric flask;

$$\begin{aligned}\text{Required mass of anhydrous lactose} &= 30 \text{ kg/m}^3 \times 0.1 \times 10^{-3} \text{ m}^3 \\ &= 3.0 \text{ g anhydrous lactose.}\end{aligned}$$

The molar masses of α -lactose monohydrate ($\text{C}_{12}\text{H}_{22}\text{O}_{11} \cdot \text{H}_2\text{O}$) and anhydrous α -lactose ($\text{C}_{12}\text{H}_{22}\text{O}_{11}$) are 360.31 kg/kgmol and 342.3 kg/kgmol respectively. At a relative humidity of 40% α -lactose monohydrate has a moisture content of 0.4%. Therefore to convert from anhydrous lactose to α -lactose monohydrate:

$$\text{Mass of Monohydrate} = \frac{\text{Mass of Anhydrate}}{\left(1 - \frac{0.4}{100}\right)} \times \frac{342.3}{360.31} \quad (2.1)$$

To convert mass of lactose monohydrate to mass of anhydrous lactose the following equation is used:

$$\text{Anhydrate} = \text{Monohydrate} \times \left(1 - \frac{0.4}{100}\right) \times \frac{342.3}{360.31} \quad (2.2)$$

$$\begin{aligned} \therefore \text{The mass of monohydrate required} &= 3.0\text{g} / (0.996 \times 0.950015) \\ &= 3.1705\text{g } \alpha\text{-lactose monohydrate.} \end{aligned}$$

Upon measuring the α -lactose monohydrate, the actual anhydrous concentration was determined from the mass added.

Example: For the 30 kg/m^3 case above, 3.1729g of monohydrate was added to the 100ml volumetric flask, not 3.1705g.

$$\begin{aligned} \text{Mass of dry anhydrous lactose added} &= 3.1729\text{g} \times 0.996 \times 0.950015 \\ &= 3.0022\text{g anhydrous lactose.} \end{aligned}$$

$$\begin{aligned} \therefore \text{Concentration of lactose (anhydrous basis)} &= 3.0022 \times 10^{-3} \text{ kg} \div 0.1 \times 10^{-3} \text{ m}^3 \\ &= 30.02 \text{ kg/m}^3 \end{aligned}$$

2.3.1.2 Measurement of refractive index of standards.

The refractive index of the lactose solutions were measured at the given temperature (20°C or 25°C) with the refractometer. Measurements were carried out in triplicate and in a randomized order. The temperature of the refractometer was kept constant by passing water from a waterbath through jackets around the main prism. The refractometer measurements can be found in Tables D1 and D2 in Appendix D.

2.3.1.3 Data analysis.

A regression analysis was carried out using MINITAB v8.2 to produce a regression equation between anhydrous lactose concentration and refractive index. The equations generated were as follows:

$$C_i^{20} = -8641.83 + 6480.19 n^{20} \quad (2.3)$$

$$C_i^{25} = -8741.24 + 6555.86 n^{25} \quad (2.4)$$

with regression coefficients (R^2) of 100.0% and 100.0% respectively. Full details of the regression can be found in Tables E1 and E2 in Appendix E.

2.3.2 Dissolution experiments.

Dissolution experiments were carried out at a variety of temperatures, stirring conditions, final concentrations, and particle sizes. Details of the individual experimental conditions used can be found in each chapter.

For experiments requiring temperatures lower than 20°C, ice was added to the waterbath to bring the system to the required temperature, while at higher temperatures a heated waterbath was used.

2.3.2.1 Materials.

Lactose (sieved or unsieved)

2.3.2.2 Procedure.

Two litres of distilled water was measured into the dissolution vessel and with the stirrer and sampling circuit in operation, allowed to come to thermal equilibrium with the waterbath and the waterbath and vessel temperature recorded. The required mass of α -lactose monohydrate was weighed and placed in an oven to preheat (or cool) the lactose

to the required temperature. The sample tap was opened and the lactose quickly added via the funnel into the dissolution vessel. Timing was started as soon as the lactose hit the water. Samples were collected continuously at set sampling intervals, which depended on the time the dissolution took. At the end of dissolution the vessel temperature was taken again.

The total lactose content of each sample was determined by measuring the refractive index of the solution with the Atago refractometer, and using the regression equations 2.3 and 2.4. The refractometer was temperature controlled to either 20°C or 25°C by passing water from a waterbath through the jackets around the main prism.

2.3.2.3 Data analysis.

For runs carried out at the same temperature as the refractometer measurements the conversion of refractive index to anhydrous lactose concentrations is simple.

Example: For a run carried out at 25°C and measured in the refractometer at 25°C, a sample gives $n^{25} = 1.3360$.

Using equation 2.4;

$$\begin{aligned}\text{Lactose Concentration} &= -8741.24 + 6555.86 \times 1.3360 \\ &= -8741.24 + 8758.63 \\ &= 17.39 \text{ kg/m}^3 \text{ (anhydrous basis)}.\end{aligned}$$

For runs carried out at different temperatures than what they are measured at a correction is necessary due to the changing density of the lactose solution. Section 2.4 contains an analysis of the density data available. An example calculation is shown below.

Example: For a run carried out at 50°C and measured in the refractometer at 20°C, a sample gives $n^{20} = 1.3540$.

The conversion to anhydrous lactose concentration must take two steps. Firstly, the refractive index at 20°C is converted to a concentration at 20°C. This is then converted to the concentration at the required temperature.

Using equation 2.3;

$$\begin{aligned}\text{Lactose Concentration at } 20^{\circ}\text{C} &= -8641.83 + 6480.19 \times 1.3540. \\ &= -8641.83 + 8774.14 \\ &= 132.31 \text{ kg/m}^3 \text{ (anhydrous basis)}\end{aligned}$$

The anhydrous lactose concentration at 50°C is then given by:

$$C_i^{50} = C_i^{20} \times \frac{\rho^{50}}{\rho^{20}} \quad (2.5)$$

The values of ρ^{50} and ρ^{20} are dependant on the concentration of lactose at that temperature and are given by:

$$\rho^{20} = 998.246 + 0.39235 C_i^{20} \quad (2.6)$$

$$\rho^{50} = 991.605 + 0.36760 C_i^{50} \quad (2.7)$$

from Section 2.4, Table 2.1.

The calculation of ρ^{50} requires the concentration of lactose at 50°C, which is what is being calculated in equation 2.5. This involves the solution of three simultaneous equations above, giving

$$C_i^{50} = \frac{991.605 C_i^{20}}{\rho^{20} - 0.3676 C_i^{20}} \quad (2.8)$$

The value of ρ^{20} is

$$\begin{aligned}\rho^{20} &= 998.246 + 0.39253 \times 132.31 \text{ kg/m}^3 \\ &= 1050.29 \text{ kg/m}^3\end{aligned}$$

Substituting this and the value of C_i^{20} into equation 2.8 gives $C_i^{50} = 130.98 \text{ kg/m}^3$

2.4 Density Correlations

McDonald and Turcotte 1948, and Buma 1980 give data on the effect of temperature and concentration of lactose on the density of lactose solutions. Regression analysis on this data to produce a correlation for the density of solution at a given temperature against concentration of lactose was carried out using MINITAB v8.2. Table 2.1 contains a summary of this regression analysis, which can be found in detail in Tables E3 to E8 in Appendix E.

Table 2.1 Correlation summary of density to concentration of lactose solutions.

Temperature (°C)	Intercept (kg/m ³)	Slope (kg solution/kg anhyd. lactose)	R ²
20 ¹	998.246	0.39235	100.0%
25 ¹	997.124	0.38966	100.0%
30 ²	998.503	0.36310	99.8%
40 ²	995.266	0.36474	99.8%
50 ²	991.605	0.36760	99.8%
60 ²	987.782	0.37150	99.6%

¹ McDonald and Turcotte (1948), ² Buma (1980).

CHAPTER 3

Model 1: Inclusion of alpha lactose solubility effects.

3.1 Introduction

The dissolution model developed by Hodges (1992) predicted the general trend of the dissolution process when lactose was added above the alpha lactose solubility limit. However, there was an offset from the experimental data. Closer examination of the predictions showed that there was a lack of fit of the predicted alpha lactose concentration in solution when compared to the experimental values. The prediction assumed dissolution was mass transfer controlled up to the alpha lactose solubility limit, whereafter the alpha lactose concentration was assumed to remain constant. Experimentally it was found that the alpha lactose concentration reached a concentration higher than the reported alpha lactose solubility limit, and then asymptotically approached the solubility limit. This discrepancy in the alpha lactose prediction appeared to be the cause of the offset between the predicted total lactose concentration and the experimental values.

There are two possible reasons for this discrepancy in the alpha lactose concentration during dissolution

- (i) In the region where mutarotation is controlling (above the α -lactose solubility limit) β -lactose is having a solubility depressing effect on α -lactose.
- (ii) In the region where surface effects (eg mass transfer) are controlling (below the α -lactose solubility limit) it was assumed by Hodges (1992) that the mass transfer coefficient was constant. This assumption is not valid due to the changing size of the lactose crystals during dissolution.

Section 1.4.1 in Chapter 1 discussed the factors which effect the solubility of alpha lactose in solution. Visser (1982) suggested that the presence of beta lactose reduces the solubility of alpha lactose and that the values of the alpha lactose solubility limit quoted in the literature should be more precisely called the solubility of alpha lactose at the beta lactose equilibrium concentration. This suggests that at the early stages of dissolution when the beta lactose concentration is low, the solubility limit of alpha lactose will be higher than that reported by the literature.

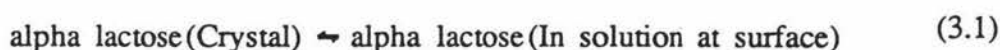
3.2 Model Formulation

3.2.1 Physical System.

The dissolution of lactose can be considered to be a reversal of the crystallization process. This suggests that dissolution involves the following three steps

- (i) Surface disintegration of alpha lactose monohydrate at the surface.
- (ii) Diffusion of alpha lactose from the surface of the crystal to bulk of the solution.
- (iii) Mutarotation of alpha lactose to beta lactose in the bulk solution.

This can be represented in the form of equations.



Each step is assumed to take place in sequence.

The diffusion of alpha lactose from the surface of the crystal to the bulk of solution cannot take place if alpha lactose is at the solubility limit in the bulk of solution. This suggests that when the alpha lactose solubility limit is reached, the only way that dissolution can proceed is for alpha lactose to mutarotate to beta lactose, with the diffusion process maintaining the alpha lactose concentration in the bulk solution

making mutarotation the rate limiting step when the total concentration is above the alpha lactose solubility limit.

3.2.1.1 Model assumptions

Mass transfer from the surface of the crystal to the bulk of solution was considered to be mass transfer by diffusion into a stagnant liquid. This was assumed as the lactose particle can be considered to be moving at its terminal velocity in relation to the fluid, which is sufficiently small for these sized particles to enable the solution to be considered a stagnant liquid. This allows a constant Sherwood number to be assumed, enabling the mass transfer coefficient to be estimated with changing particle size.

The surface disintegration reaction was considered to be sufficiently fast to be able to be ignored in the model formulation.

The assumptions made in the formulation of the model can be summarised as follows

- (i) The surface disintegration step occurs instantaneously and has no effect on dissolution.
- (ii) Lactose crystal geometry remains constant throughout dissolution.
- (iii) All crystal surface area is available for dissolution.
- (iv) Constant temperature throughout dissolution.
- (v) Perfectly mixed system
- (vi) The mutarotation reaction can be described as a first order reaction with rate constants given in section 1.3.
- (vii) Constant particle Sherwood number throughout dissolution.
- (viii) Alpha lactose solubility is affected by beta lactose in the manner suggested by Visser (1982).
- (ix) Single particle size used for dissolution.

3.2.2 Differential Equations.

In order to follow the dissolution of lactose, there are three time dependant variables that must be determined. These are the size of the lactose crystal (D_c), the concentration of alpha lactose in solution (C_α), and the concentration of beta lactose in solution (C_β). For each of these variables a differential equation must be derived.

3.2.2.1 Lactose crystal size.

To model the reduction in crystal size as dissolution proceeds, the shape of the lactose crystal must be known. Figure 1.3 in section 1.1 of the introduction shows the common form of alpha lactose monohydrate crystals. A simplified shape was used in the development of this model (Figure 3.1). As mentioned in the assumptions, the relative dimensions of the lactose crystals were assumed to be constant with changing particle size. The length of the crystal was used as the characteristic dimension for dissolution (D_c).

The basis for the lactose crystal size equation was determined by performing a mass balance across a single crystal. This can be worded as follows

$$\left[\begin{array}{c} \text{Rate of decrease of} \\ \text{Lactose Crystal Mass} \end{array} \right] = \left[\begin{array}{c} \text{Rate of Transport of} \\ \text{Lactose from Crystal Surface} \end{array} \right] \quad (3.4)$$

Expressing this in terms of an ordinary differential equation gives

$$-\frac{dM_c}{dt} = k_L A_c (C_\alpha^\beta - C_\alpha) \quad (3.5)$$

where M_c = Mass of lactose crystal (kg)

k_L = Mass transfer coefficient (m/s)

A_c = Surface area of lactose crystal (m^2)

C_α^β = Alpha lactose solubility limit in the presence of beta lactose (kg/m^3)

C_α = Alpha lactose concentration in bulk of solution. (kg/m^3)

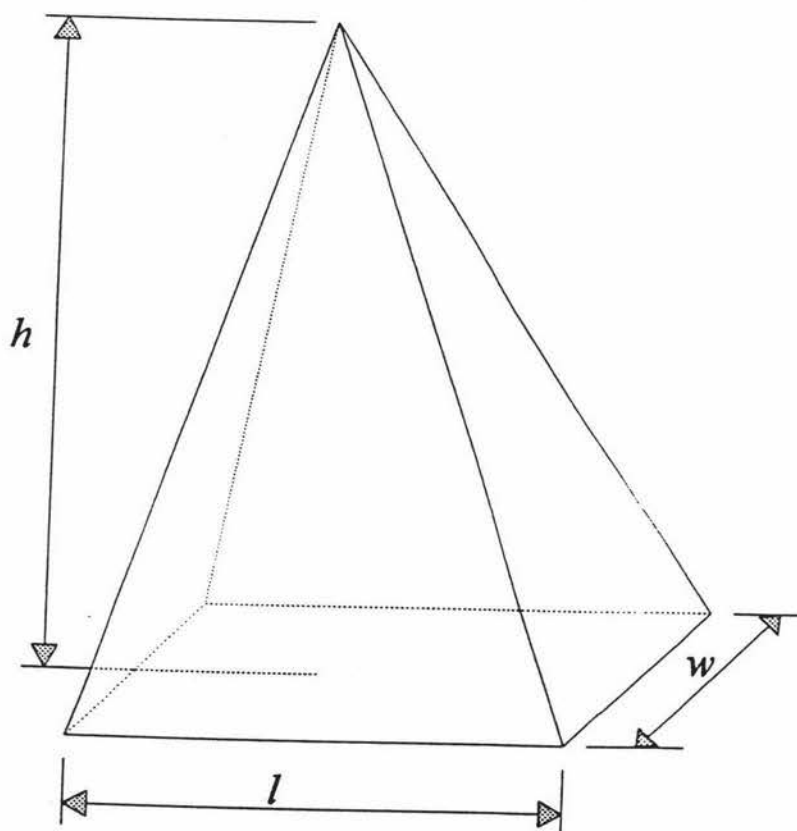


Figure 3.1 Simplified alpha lactose monohydrate crystal shape used in model formulation.

The mass of lactose in crystal form is given by

$$M_c = V_c \times \rho_c \quad (3.6)$$

where V_c = Volume of lactose crystal (m^3)

ρ_c = Density of lactose crystal (kg/m^3)

Assuming that the crystal density is constant, the reduction in mass can be expressed as a reduction in volume:

$$\frac{dM_c}{dt} = \rho_c \frac{dV_c}{dt} \quad (3.7)$$

The volume and area of the lactose crystal can be expressed in terms of the characteristic dimension of the lactose crystal.

$$A_c = a_1 D_c^2 \quad (3.8)$$

$$V_c = v_1 D_c^3 \quad (3.9)$$

where v_1 = volume conversion factor.

a_1 = area conversion factor.

This enables the reduction in volume to be expressed in terms of the characteristic dimension, assuming that the relative dimensions of the particle is constant for all sizes.

Using the product rule gives

$$\rho_c \frac{dV_c}{dt} = \rho_c \frac{dV_c}{dD_c} \times \frac{dD_c}{dt} \quad (3.10)$$

$$\rho_c \frac{dV_c}{dt} = 3v_1 \rho_c D_c^2 \frac{dD_c}{dt} \quad (3.11)$$

Substituting this and equation (3.8) into equation (3.5) and rearranging gives:

$$-\frac{dD_c}{dt} = \frac{k_L a_1 (C_{\infty}^B - C_{\alpha})}{3v_1 \rho_c} \quad (3.12)$$

which gives an ordinary differential equation for D_c , the characteristic dimension of the crystal.

3.2.2.2 Alpha lactose concentration.

The alpha lactose concentration was determined by performing a mass balance of alpha lactose over the whole system. This was worded as follows

$$\begin{aligned} \left[\begin{array}{c} \text{Rate of accumulation} \\ \text{of alpha lactose in} \\ \text{bulk solution.} \end{array} \right] &= \left[\begin{array}{c} \text{Rate of mass transfer} \\ \text{of alpha lactose from} \\ \text{crystal surface} \end{array} \right] + \\ &\left[\begin{array}{c} \text{Rate of production of} \\ \alpha\text{-lactose from } \beta\text{-lactose} \\ \text{by mutarotation} \end{array} \right] - \left[\begin{array}{c} \text{Rate of production of} \\ \beta\text{-lactose from } \alpha\text{-lactose} \\ \text{by mutarotation} \end{array} \right] \end{aligned} \quad (3.13)$$

Expressing this in terms of an ordinary differential equation gives:

$$\frac{dM_{\alpha}}{dt} = k_L n A_c (C_{\alpha}^{\beta} - C_{\alpha}) + k_2 C_{\beta} V_s - k_1 C_{\alpha} V_s \quad (3.14)$$

- where M_{α} = Mass of alpha lactose in bulk of solution (kg)
 C_{β} = Concentration of beta lactose in bulk of solution (kg/m³)
 V_s = Volume of solution (m³)
 n = Number of lactose crystals in solution
 k_1 = Reaction constant for conversion of alpha lactose to beta lactose (s⁻¹)
 k_2 = Reaction constant for conversion of beta lactose to alpha lactose (s⁻¹)

This can be simplified to

$$\frac{dM_{\alpha}}{dt} = k_L n A_c (C_{\alpha}^{\beta} - C_{\alpha}) + k_2 M_{\beta} - k_1 M_{\alpha} \quad (3.15)$$

where M_{β} = Mass of beta lactose in solution (kg).

The mass of alpha and beta lactose is determined from the concentrations as follows

$$M_{\alpha} = C_{\alpha} V_s \quad (3.16)$$

$$M_{\beta} = C_{\beta} V_s \quad (3.17)$$

This cannot be substituted into the differential equation and easily simplified to give a differential equation for dC_α/dt as the volume of solution varies with time. This necessitates the solution of the differential equation in terms of the mass of alpha lactose in solution, not the concentration of alpha lactose.

3.2.2.3 Beta lactose concentration.

The beta lactose concentration was determined by performing a mass balance of beta lactose around the whole system. This was worded as follows

$$\left[\begin{array}{c} \text{Rate of accumulation} \\ \text{of beta lactose in} \\ \text{bulk solution.} \end{array} \right] = \left[\begin{array}{c} \text{Rate of production of} \\ \beta\text{-lactose from } \alpha\text{-lactose} \\ \text{by mutarotation} \end{array} \right] - \left[\begin{array}{c} \text{Rate of production of} \\ \alpha\text{-lactose from } \beta\text{-lactose} \\ \text{by mutarotation} \end{array} \right] \quad (3.18)$$

Expressing this in terms of an ordinary differential equation gives

$$\frac{dM_\beta}{dt} = k_1 C_\alpha \cdot V_s - k_2 C_\beta \cdot V_s \quad (3.19)$$

which as in the alpha lactose case can be simplified to

$$\frac{dM_\beta}{dt} = k_1 M_\alpha - k_2 M_\beta \quad (3.20)$$

As in section 3.2.2.2 for alpha lactose the non-constant nature of the volume of solution necessitates that the equation be solved in this form, with the concentration of beta lactose determined from Equation (3.17).

3.2.3 Algebraic Equations.

3.2.3.1 Volume of solution.

The volume of solution is dependant on both the mass of lactose in solution, which increases as dissolution proceeds, and the density of solution, which is dependant on the concentration of lactose in solution. Expressing this in terms of a word equation gives

$$\left[\begin{array}{c} \text{Volume of solution} \\ \text{in vessel} \end{array} \right] = \frac{\left[\begin{array}{c} \text{Initial mass of} \\ \text{fluid in tank} \end{array} \right] + \left[\begin{array}{c} \text{Mass of} \\ \text{dissolved lactose} \end{array} \right]}{\left[\begin{array}{c} \text{Density of} \\ \text{solution} \end{array} \right]} \quad (3.21)$$

The mass of dissolved lactose is expressed in the model in terms of anhydrous lactose. However lactose is dissolved as alpha lactose monohydrate. This suggests that the mass of dissolved anhydrous lactose must be converted to hydrous lactose to give the actual mass dissolved. This is done the following way

$$\left[\begin{array}{c} \text{Mass of dissolved} \\ \text{lactose monohydrate} \end{array} \right] = \frac{\left[\begin{array}{c} \text{Molecular wt.} \\ \text{of monohydrate} \end{array} \right]}{\left[\begin{array}{c} \text{Molecular wt.} \\ \text{of anhydrate} \end{array} \right]} \times \left[\begin{array}{c} \text{Mass of dissolved} \\ \text{anhydrous lactose} \end{array} \right] \quad (3.22)$$

Anhydrous lactose has the form $C_{12}H_{22}O_{11}$, where as lactose monohydrate has the form $C_{12}H_{22}O_{11} \cdot 1H_2O$. This gives anhydrous lactose and lactose monohydrate molecular weights of 342.30 and 360.31 kg/kgmol respectively.

A correction must also be made for the free moisture contained in the lactose. Alpha lactose monohydrate will absorb 0.4% moisture at a relative humidity of 40%. The wet lactose monohydrate is then calculated by

$$\left[\begin{array}{c} \text{Mass of wet} \\ \text{monohydrate} \end{array} \right] = \left[\begin{array}{c} \text{Mass of dry} \\ \text{monohydrate} \end{array} \right] \div \left(1 - \frac{0.4}{100} \right) \quad (3.23)$$

Converting word equations (3.21) to (3.23) to a mathematical equation gives;

$$V_s = \frac{\left(M_i + \frac{360.31 \times (M_\alpha + M_\beta)}{342.30 \times \left(1 - \frac{0.4}{100} \right)} \right)}{\rho_s} \quad (3.24)$$

which simplifies to

$$V_s = \frac{(M_i + 1.05684(M_\alpha + M_\beta))}{\rho_s} \quad (3.25)$$

where M_i = initial mass of fluid in tank (kg)
 ρ_s = density of lactose solution (kg/m³)

3.2.3.2 Density of lactose solution.

The density of lactose solutions are dependant on the concentration of lactose in solution. Work by McDonald and Turcotte (1948) and Buma (1980) have produced density data for given temperatures and concentrations. A linear regression analysis has been performed (appendix A) to fit the data to the following equation

$$\rho_s = m_l C_l + c_l \quad (3.26)$$

where C_l = Total lactose concentration (kg/m³)
 m_l = Slope of regression line (kg solution/kg anhydrous lactose)
 c_l = Intercept of regression line (kg/m³)

Values of m_l and c_l at different temperatures can be found in Table 2.3 in the experimental section.

3.2.3.3 Alpha lactose solubility.

In section 1.4.1 in the introduction, it was shown that the solubility of alpha lactose is affected by the presence of other sugars in solution, particularly beta lactose. The solubility effect of beta lactose on alpha lactose is given in Equation (1.9)

$$C_{\alpha}^{\beta} = C_{\alpha}^{\beta=0} - F C_{\beta} \quad (3.27)$$

Table 1.6 in the introduction gives values for $C_{\alpha}^{\beta=0}$ and F at various temperatures.

3.2.3.4 Mass transfer coefficient.

In this model, the assumption made is that the Sherwood number is constant. The definition of the Sherwood Number is as follows

$$Sh' = \frac{k_L l'}{D} \quad (3.28)$$

where D = Diffusivity of lactose in water (m^2/s)

l' = Characteristic length of crystal (m)

The characteristic length is defined in terms of the surface area of the particle and the perimeter of the particle.

$$l' = \frac{A_c}{\left[\begin{array}{c} \text{Maximum perimeter of crystal} \\ \text{projected normal to flow} \end{array} \right]} \quad (3.29)$$

This can be related to the characteristic dimension (D_c) in the following manner

$$l' = d_1 D_c \quad (3.30)$$

where d_1 = length conversion factor.

Combining the above equations to give an expression for the mass transfer coefficient gives

$$k_L = \frac{Sh' D}{d_1 D_c} \quad (3.31)$$

3.2.3.5 Lactose concentrations.

The differential equations developed to determine the concentration of lactose in solution give a value for the mass of lactose in solution. These are converted to lactose concentration by rearranging equations (3.16) and (3.17) to give

$$C_{\alpha} = \frac{M_{\alpha}}{V_s} \quad (3.32)$$

$$C_{\beta} = \frac{M_{\beta}}{V_s} \quad (3.33)$$

The total concentration of lactose is calculated by

$$C_t = \frac{M_{\alpha} + M_{\beta}}{V_s} \quad (3.34)$$

3.2.4 Definition of system inputs.

3.2.4.1 Crystal dimensions.

Figure 3.1 shows the simplified crystal shape used in this model, with a height h , width w , and length l . The length of the crystal has been defined previously as the characteristic dimension of the crystal (D_c). Experimental measurements of the height and length of alpha lactose monohydrate crystals were carried out and can be found in Table C1 in Appendix C. These give a ratio of the length of the crystal to the height of the crystal of 1:1.6795. The width of the crystal cannot be easily measured. However, the angle at the apex of an alpha lactose monohydrate crystal is known to be 23° (van Kreveland and Michaels, 1965). From the sine of this angle the ratio of the width w to the length l was determined to be 1:0.6035. Stating the height and width in terms of the characteristic dimension then gives

$$h = 1.6795 D_c \quad (3.35)$$

$$w = 0.6035 D_c \quad (3.36)$$

3.2.4.2 Volume of crystal.

The crystal geometry assumed is a trapezium. The formula for the volume of a trapezium is

$$V_c = \frac{lwh}{3} \quad (3.37)$$

Substituting for l , w , and h , to give the equation in terms of D_c gives

$$V_c = 0.3379D_c^3 \quad (3.38)$$

ie $v_l = 0.3379$.

3.2.4.3 Surface area of crystal.

The surface area of the crystal can be found by summing the individual face areas of the trapezium.

$$A_c = lw + 2 \left(\frac{l}{2} \times \sqrt{h^2 + \left(\frac{w}{2} \right)^2} \right) + 2 \left(\frac{w}{2} \times \sqrt{h^2 + \left(\frac{l}{2} \right)^2} \right) \quad (3.39)$$

Substituting for l , w , and h , to give the equation in terms of D_c gives

$$A_c = 3.3674D_c^2 \quad (3.40)$$

ie $a_l = 3.3674$.

3.2.4.4 Characteristic length.

The characteristic length of the lactose crystal is defined by equation (3.29) in terms of the area of the crystal and the maximum perimeter of the crystal projected normal to flow. Assuming that the crystal orientates itself to present the minimum area normal to the flow, the perimeter will be $2l + 2w$. Substituting this into equation (3.29) gives

$$l' = \frac{A_c}{2l + 2w} \quad (3.41)$$

Substituting for surface area, l and w gives

$$l' = 1.0500D_c \quad (3.42)$$

ie $d_l = 1.0500$.

3.2.4.5 Sherwood number.

The Sherwood number was calculated assuming the diffusion of lactose into a stagnant medium. This will give the slowest reasonable mass transfer constant. The calculation methodology is based on the conductance concept from Cliff *et al* (1978).

The definition of conductance is

$$\text{Conductance} = \frac{k_L A_c}{D} \quad (3.43)$$

For a sphere of radius r_{sp} , the conductance is given by Cliff *et al* (1978, p89) as

$$\left[\begin{array}{c} \text{Conductance} \\ \text{of sphere} \end{array} \right] = 4\pi r_{sp} \quad (3.44)$$

The conductance of particles can be approximated by using a "conductance factor". This is defined as

$$\Delta' = \frac{\text{conductance of particle}}{\text{conductance of equivalent sphere}} \quad (3.45)$$

The formula for the conductance of a particle is then

$$\left[\begin{array}{c} \text{conductance} \\ \text{of particle} \end{array} \right] = 4\Delta'\pi r_{sp} \quad (3.46)$$

Figure 4.13 in Cliff *et al* (1978, p90) presents a graphical correlation for the conductance factor in terms of the perimeter equivalent factor (Σ), which is defined as

$$\Sigma = \frac{\text{surface area of particle}}{\text{surface area of perimeter equivalent sphere}} \quad (3.47)$$

The perimeter of the crystal was defined previously as $2l + 2w$. This enables the radius of the perimeter equivalent to be calculated as

$$r_{sp} = \frac{2l + 2w}{2\pi} \quad (3.48)$$

which on substitution for l and w simplifies to

$$r_{sp} = 0.5104D_c \quad (3.49)$$

The surface area can then be calculated by

$$A_{sp} = 4\pi(0.5104D_c)^2 \quad (3.50)$$

or

$$A_{sp} = 3.2737D_c^2 \quad (3.51)$$

Substituting this equation and the equation for the surface area of the particle (equation 3.40) gives $\Sigma = 1.029$, independent of particle size. Using Figure 4.13 in Cliff *et al* (1978, p90), the value of Δ' was found to be 1.02. Substituting this and equation (3.48) into equation (3.46) and substituting for l and w gives

$$\left[\begin{array}{c} \text{conductance} \\ \text{of particle} \end{array} \right] = 6.5423D_c \quad (3.52)$$

The definition of the Sherwood number is given by equation (3.28). By multiplying the conductance by l' and dividing by A_c , the Sherwood number for diffusion into a stagnant medium is produced, ie

$$Sh' = \frac{[\text{conductance}] \times l'}{A_c} \quad (3.53)$$

Substituting equations for conductance, l' , and A_c into the above equation gives $Sh' = 2.034$, independent of particle size, which can be rounded to 2, the usual limiting Sherwood number for diffusion into a stagnant medium for small particles.

3.2.4.6 Diffusivity

The diffusivity of lactose solutions are given in the International Critical Tables, Volume V, p 63. Table 3.1 contains a summary of these results.

Table 3.1 Measured diffusion coefficients of lactose.

Temperature (°C)	Diffusivity (m ² /s)
10	3.2 × 10 ⁻⁹
15	3.8 × 10 ⁻⁹
20	4.2 × 10 ⁻⁹

To estimate diffusivity at higher temperatures, the following relationship suggested by Perry and Green (1984) was used

$$\frac{D\mu}{T} = \text{Constant} \quad (3.54)$$

where μ = Viscosity of solution (Pa.s)

T = Temperature of solution (K)

Table 3.2 contains estimated values of the Diffusion coefficient D from 0°C to 70°C using this method, along with the solution viscosities used.

Table 3.2 Estimated diffusion coefficients for lactose solutions.

Temperature (°C)	Viscosity of water (Pa.s) (×10 ⁻⁶)	Diffusivity of Lactose (D) (m ² /s) (×10 ⁻⁹)
0	1753.0	2.3
5	1502.0	2.7
10	1300.0	3.2
15	1136.5	3.8
20	1002.0	4.2
25	933.0	4.7
30	797.0	5.6
35	718.5	6.3
40	651.0	7.1
45	594.0	7.9
50	544.0	8.7
60	463.0	10.6
70	400.0	12.6

3.2.4.7 Mutarotation rate constants.

Table 1.2 in section 1.3 lists values of $k_1 + k_2$ for the mutarotation reaction. These can be fitted to the Arrhenius equation form

$$k_1 + k_2 = A_0 e^{-\left(\frac{E_a}{RT}\right)} \quad (3.55)$$

where A_0 = Frequency factor (s^{-1}).

E_a = Activation energy (kJ/kgmol)

Analysis of this data by non-linear regression using the method of Chen and Aris (1992) to give Arrhenius constants A_0 and E_a of $3.61584 \times 10^{10} s^{-1}$ and 81539.98 kJ/kgmol respectively. The values of k_1 and k_2 are determined from the value of $k_1 + k_2$, using the beta to alpha solubility ratio from Table 1.5 in the following way

The rate of change of beta lactose is given by equation (3.19). At steady state (mutarotation equilibrium) this reduces to

$$k_1 C_\alpha = k_2 C_\beta \quad (3.56)$$

Rearranging gives

$$k_1 = k_2 \frac{C_\beta}{C_\alpha} \quad (3.57)$$

Defining K_m as the ratio of the beta to alpha lactose concentrations at equilibrium, the equation above can be rearranged to give

$$k_2 = \frac{k_1 + k_2}{(1 + K_m)} \quad (3.58)$$

The value of k_1 is then determined by back substitution.

Example: Determining the values of k_1 and k_2 at 25°C.

Knowing the Arrhenius constants A_0 and E_a are $3.61584 \times 10^{10} s^{-1}$ and 81539.98 kJ/kgmol respectively, the value of $k_1 + k_2$ is

$$\begin{aligned}
&= 3.61584 \times 10^{10} \times \exp(-81539.98 \div (8.314 \times (25 + 273.15))) \\
&= 3.61584 \times 10^{10} \times \exp(-32.895) \\
&= 0.00018717 \text{ s}^{-1}
\end{aligned}$$

From Table 1.5 at a temperature of 25°C, $K_m = 1.58$.

$$\begin{aligned}
\therefore k_2 &= 0.00018717 \div (1 + 1.58) \\
&= 7.2547 \times 10^{-5} \text{ s}^{-1}
\end{aligned}$$

Back substitution gives

$$\begin{aligned}
k_1 &= 1.8717 \times 10^{-4} - 7.2547 \times 10^{-5} \\
&= 1.1462 \times 10^{-4} \text{ s}^{-1}
\end{aligned}$$

3.2.4.8 Number of crystals in solution.

The number of lactose crystals is determined simply by dividing the mass of alpha lactose added to the solution by the mass of a single crystal. Expressing this in terms of an equation gives

$$n = \frac{M_L}{0.3379 \rho_c D_c^3}$$

where ρ_c = Density of lactose crystal.

3.2.5 Initial conditions.

For the model, it is necessary for each dependant variable to have an initial condition. The concentration initial conditions are simple as the concentration of lactose in solution is initially zero. However, the initial particle size is not zero.

3.2.5.1 Initial particle size.

The initial particle size of the lactose crystal must be related to some experimental measurement to enable the model to be of any practical use. A particle size analysis can be carried on lactose samples using a Malvern Instruments MASTER Particle Sizer M6.10. This returns a particle size (D_p) based on the particle projected area (A_p) as follows

$$D_p = \sqrt{\frac{4A_p}{\pi}} \quad (3.60)$$

The projected area of the particle depends on the orientation of the particle. For powder sample measurements, the sample is blown across the measurement chamber, presenting the maximum length for measurement. This gives a projected area maximum and minimum for the alpha lactose monohydrate crystal of

$$A_{p \max} = \frac{1}{2}l \sqrt{h^2 + \left(\frac{w}{2}\right)^2} \quad (3.61)$$

$$A_{p \min} = \frac{1}{2}w \sqrt{h^2 + \left(\frac{l}{2}\right)^2} \quad (3.62)$$

Rearranging each equation in terms of the characteristic dimension of the crystal gives

$$A_{p \max} = 0.8532D_c^2 \quad (3.63)$$

$$A_{p \min} = 0.5288D_c^2 \quad (3.64)$$

The average value of the projected area will be

$$A_{p \text{ av}} = 0.6910D_c^2 \quad (3.65)$$

Substituting this into equation (3.59) and solving for D_c gives

$$D_c = \sqrt{\frac{\pi D_p^2}{2.764}} \quad (3.66)$$

which simplifies to

$$D_c = 1.0661D_p \quad (3.67)$$

3.2.6 Summary of model.

The model can be summarized into the following equations

- (i) Ordinary Differential Equations.(with values of v_i and a_i substituted)

$$-\frac{dD_c}{dt} = \frac{3.3219 k_L (C_{\alpha}^{\beta} - C_{\alpha})}{\rho_c} \quad (3.68)$$

$$\frac{dM_{\alpha}}{dt} = 3.3674 k_L n D_c^2 (C_{\alpha}^{\beta} - C_{\alpha}) + k_2 M_{\beta} - k_1 M_{\alpha} \quad (3.69)$$

$$\frac{dM_{\beta}}{dt} = k_1 M_{\alpha} - k_2 M_{\beta} \quad (3.70)$$

- (ii) Algebraic Equations.

$$V_s = \frac{(M_i + 1.05684 (M_{\alpha} + M_{\beta}))}{\rho_s} \quad (3.71)$$

$$\rho_s = m_1 C_i + c_1 \quad (3.72)$$

$$C_{\alpha}^{\beta} = C_{\alpha}^{\beta=0} - F C_{\beta} \quad (3.73)$$

$$k_L = \frac{1.9048 D}{D_c} \quad (3.74)$$

$$C_{\alpha} = \frac{M_{\alpha}}{V_s} \quad (3.75)$$

$$C_{\beta} = \frac{M_{\beta}}{V_s} \quad (3.76)$$

$$C_i = \frac{M_{\alpha} + M_{\beta}}{V_s} \quad (3.77)$$

(iii) System Inputs

- (a) Sherwood number = 2.
- (b) $C_{\alpha}^{\beta=0}$ and F values Given in Table 1.6.
- (c) Diffusivity Given in Table 3.1.
- (d) Mutarotation rate constants E_a , A_0 and K_m given in section 1.3.
- (e) Density coefficients m_i and c_i given in Table 2.3.

3.2.7 Solution of model.

No analytical solution to the above model was attempted due to the changing nature of k_L with D_c . Instead, the model was solved numerically using ESL, an advanced simulation language (Hay *et al* 1988) on an IBM compatible 386DX personal computer with a numeric maths coprocessor. Appendix A (Model 1) contains a listing of the program used.

3.3 Validation of Model

After the model has been formulated, it is necessary to test the validity of the model. This is done by comparing the predictions the model makes against experimental results.

3.3.1 Effect of stirring.

In the modelling of mass transfer in this system, it was assumed that the Sherwood number was constant, which is equivalent to saying that mass transfer occurred by diffusion, with no convection effects occurring. To test the validity of this assumption, a series of experiments at different stirring rates were carried out. If convection has a large effect on mass transfer, then changing the stirring regime should effect the rate of dissolution under conditions when mass transfer is controlling the rate of dissolution.

3.3.1.1 Experimental.

Experiments were carried out using the procedure given in section 2.3 in replicate at 25°C, with four different stirring speeds

- (i) 200 rpm
- (ii) 400 rpm
- (iii) 600 rpm
- (iv) 800 rpm

109.32 grams of alpha lactose monohydrate (sieve fraction 150-210 μ m) was used in each dissolution run to give a final anhydrous concentration of 50 kg/m³, which is below the alpha lactose solubility limit where dissolution was expected to be mass transfer controlled. Measurements of the refractive index were carried out at 25°C.

3.3.1.2 Results and Discussion.

Tables F9 and F10 in Appendix F contains the results of the dissolution experiments carried out at different stirring speeds, consisting of the measured refractive index at different time intervals. The data analysis of the refractive indices was carried out as in section 2.3.2.3 to produce concentrations in kg anhydrous lactose per m³ of solution.

Measurements of the particle sizes for the crystal can be found in Table C3 in Appendix C, giving a mean particle size of 202.9 μ m, which when converted to the characteristic dimension of the crystal gives 216.3 μ m.

Figure 3.2 shows a plot of the four different stirring regimes. Experimental points are averages from the duplicate runs. The plot has been normalized to adjust for experimental variations in the final concentrations reached. Table 3.3 shows the concentrations reached for each run.

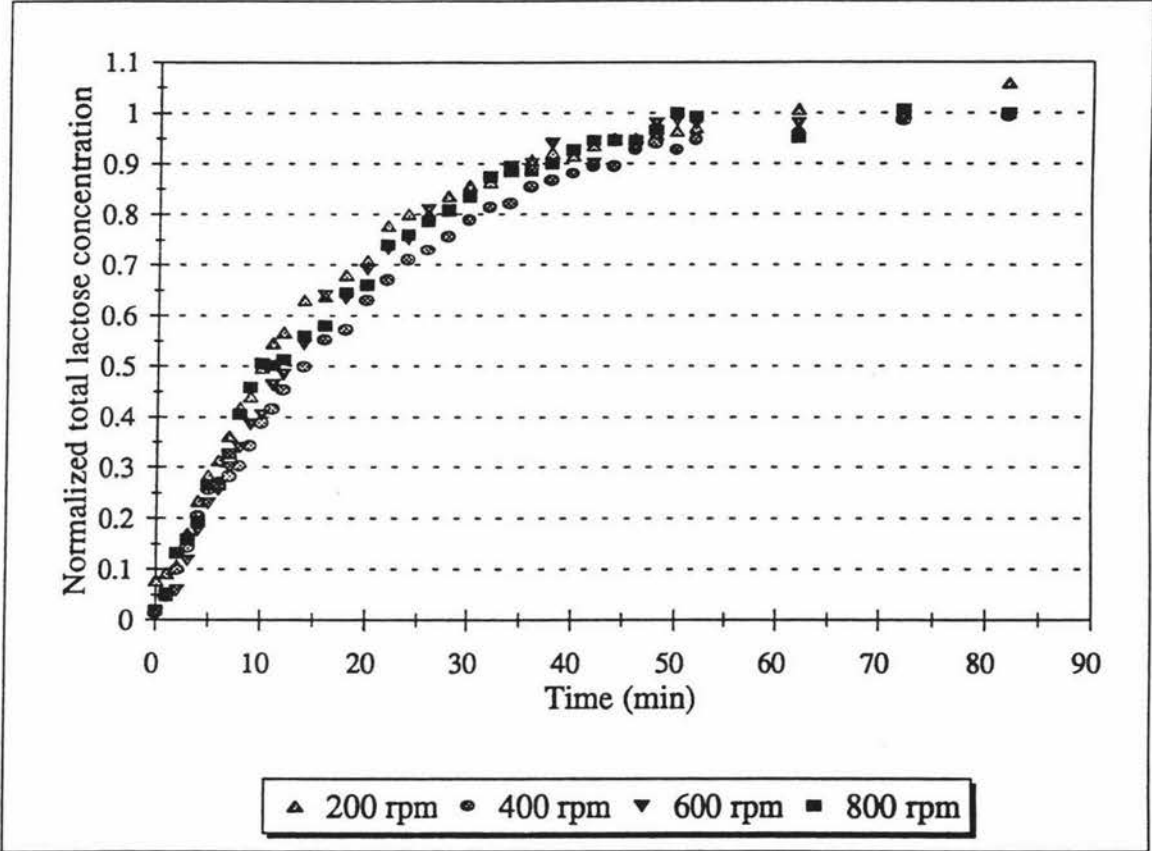


Figure 3.2 Effect of stirring rate on lactose dissolution. Operating conditions: 25°C, Final concentration 50 kg/m³ anhydrous lactose.

Examination of the final concentrations reached (Table 3.3) shows that in some runs the target concentration of 50 kg/m^3 was not reached. This was due to problems with the early experimental apparatus where lactose adhering to the sides and baffles of the vessel, showing that not all the lactose entered solution. The modified dissolution apparatus used in later experiments overcame this problem by using an open top vessel and a large funnel to direct the lactose into solution without any adhering to the sides or the baffles of the vessel.

A comparison of the dissolution of lactose at different stirring speeds in Figure 3.2 shows that there is no apparent differences in dissolution between the stirring rates. Higher stirring speeds do not appear to increase the rate of dissolution, indicating that the constant Sherwood number assumption is reasonable. The only requirements for stirring that do exist are that the stirring speed is sufficient to retain all crystals in suspension, presenting their full area for dissolution.

Table 3.3 Final concentrations reached in dissolution at different stirring speeds.

Stirring Speed (rpm)	Final Concentration (kg/m^3)	Run Order
200	47.5	1
200	44.9	2
400	50.8	4
400	48.9	6
600	50.2	3
600	50.2	7
800	48.2	5
800	50.2	8

3.3.2 Comparison of model to dissolution above the alpha lactose solubility limit.

In the dissolution region above the alpha solubility limit, the controlling factors for dissolution should be the solubility limit of alpha lactose and the rate at which the alpha lactose mutarotates to beta lactose. A comparison of the model predictions to experimental results in this region would indicate whether or not these processes are being correctly modeled.

3.3.2.1 Experimental.

Experimental work carried out by Hodges (1992) demonstrated the dissolution of lactose above the alpha lactose solubility limit. Experiments were carried out with and without excess lactose at 25°C and 45°C. Particle size fractions 210-300 μm and 105-150 μm were used in the dissolutions. The concentrations aimed for below the total solubility limit were 92.5 kg/m^3 for 25°C and 246 kg/m^3 for 45°C, with 0.1976 kg and 0.5933 kg of anhydrous lactose added to 2 litres of water for the 25°C and 45°C runs respectively. For experiments carried out with excess lactose, 0.473 kg and 0.946 kg of anhydrous lactose were used for the 25°C and 45°C runs respectively.

3.3.2.2 Results and discussion.

The results obtained by Hodges (1992) can be found in Tables F1 to F4 in Appendix F. Results consist of anhydrous alpha, beta and total lactose concentration with time for runs with excess lactose and total anhydrous lactose concentrations only for the runs carried out below the total lactose solubility limit.

Measurements of the particle sizes for the crystals can be found in Table C2 and C4 in Appendix C, giving a mean particle sizes of 116.1 and 221.0 μm for particle fractions 105-150 and 210-300 respectively. This gives characteristic dimensions for the crystal of 123.8 and 235.6 μm .

The developed model was run at 25°C and 45°C. The system inputs used can be found in Tables B1 and B2 in Appendix B, and the resulting concentrations found in Tables F1 to F4 in Appendix F.

Figures 3.3 and 3.4 show a comparison of the experimental runs with excess lactose against the model for 25°C and 45°C respectively, along with the predictions from Hodges (1992). An improvement in fit is apparent between the previous model by Hodges (1992) and the model developed, noticeably the alpha lactose concentration is more closely predicted, which affects the overall total lactose concentration.

Figures 3.5 and 3.6 show a comparison of experiments carried out below the total solubility limit with the model developed here and the model of Hodges (1992). The figures show that the model developed gives a greatly improved fit. For both the 25°C and 45°C experiments not only the shape of the dissolution curve but the approximate dissolution finishing time has been more closely predicted.

Table 3.4 shows the predicted times of dissolution for both with excess lactose and below excess lactose along with the experimentally observed dissolution times. Here the improvements made by the model are apparent, with the apparently small correction in the shape and position of the dissolution curves having a large effect on the predicted dissolution time.

Table 3.4 Predicted verses experimental dissolution times above the alpha lactose solubility limit.

Operating Conditions.	Dissolution Times (min)		
	Observed Dissolution Time	Predicted. (Hodges, 1991)	Predicted. (This report)
25°C, Target Conc = 92.5 kg/m ³ .	10	47.7	17.0
45°C, Target Conc = 246 kg/m ³ .	25	37.4	24.9

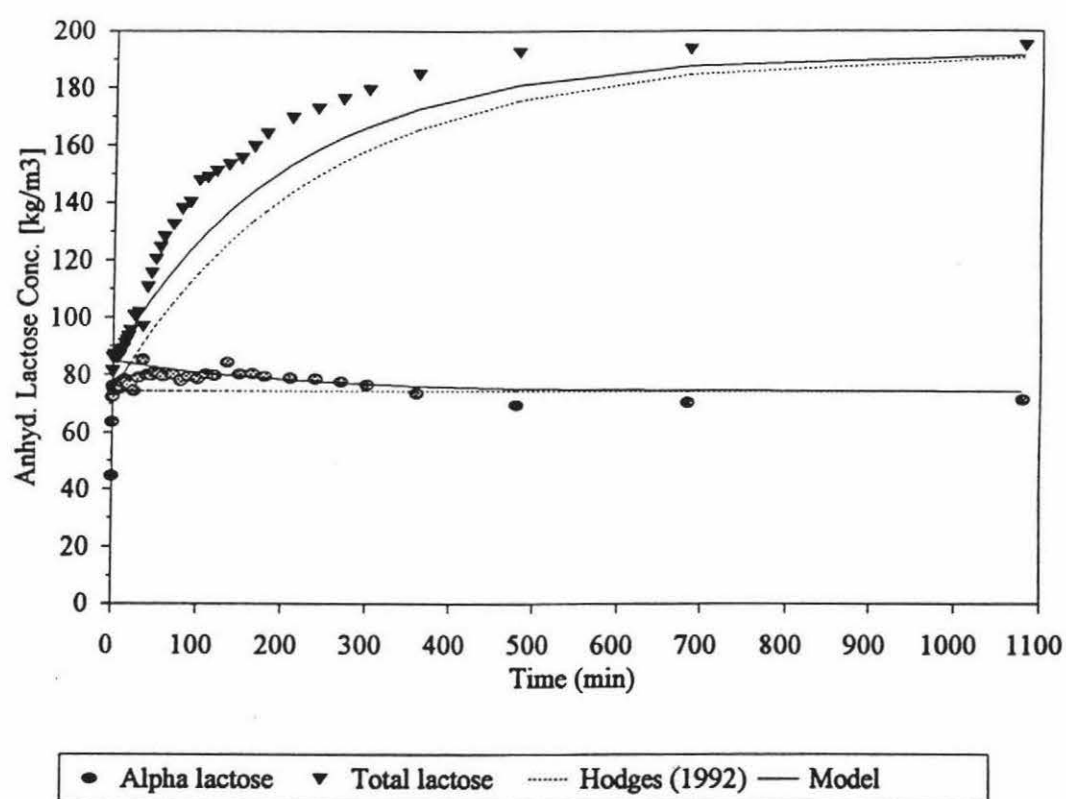


Figure 3.3 Dissolution of lactose with excess lactose in solution. Operating conditions: 25°C, Stirring speed 400rpm.

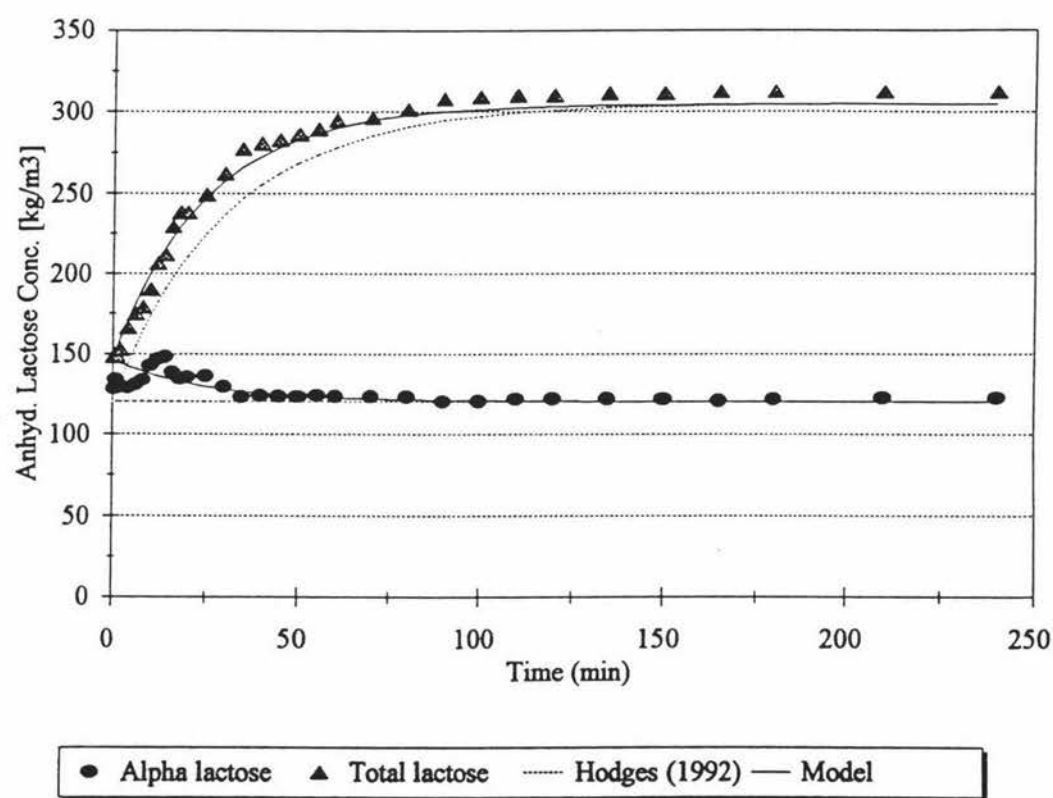


Figure 3.4 Dissolution of lactose with excess lactose in solution. Operating conditions: 45°C, Stirring speed 400rpm.

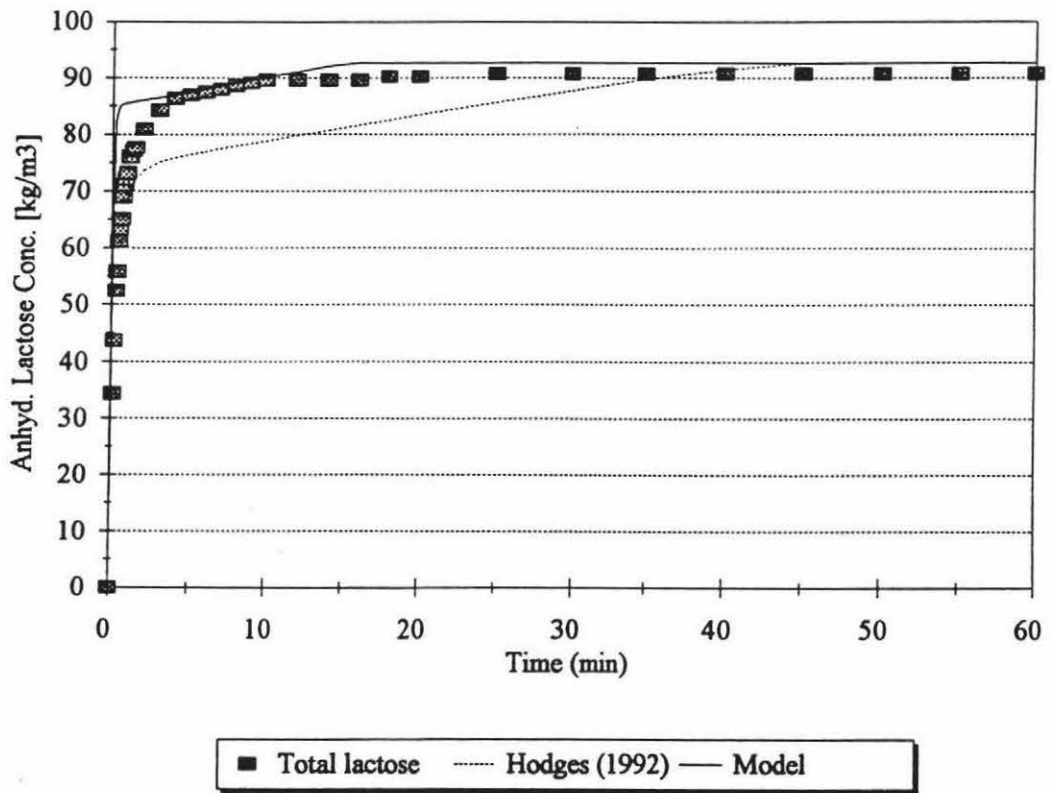


Figure 3.5 Dissolution of lactose above the alpha lactose solubility limit. Operating conditions: 25°C, Final concentration 92.5 kg/m³, Stirring speed 400rpm.

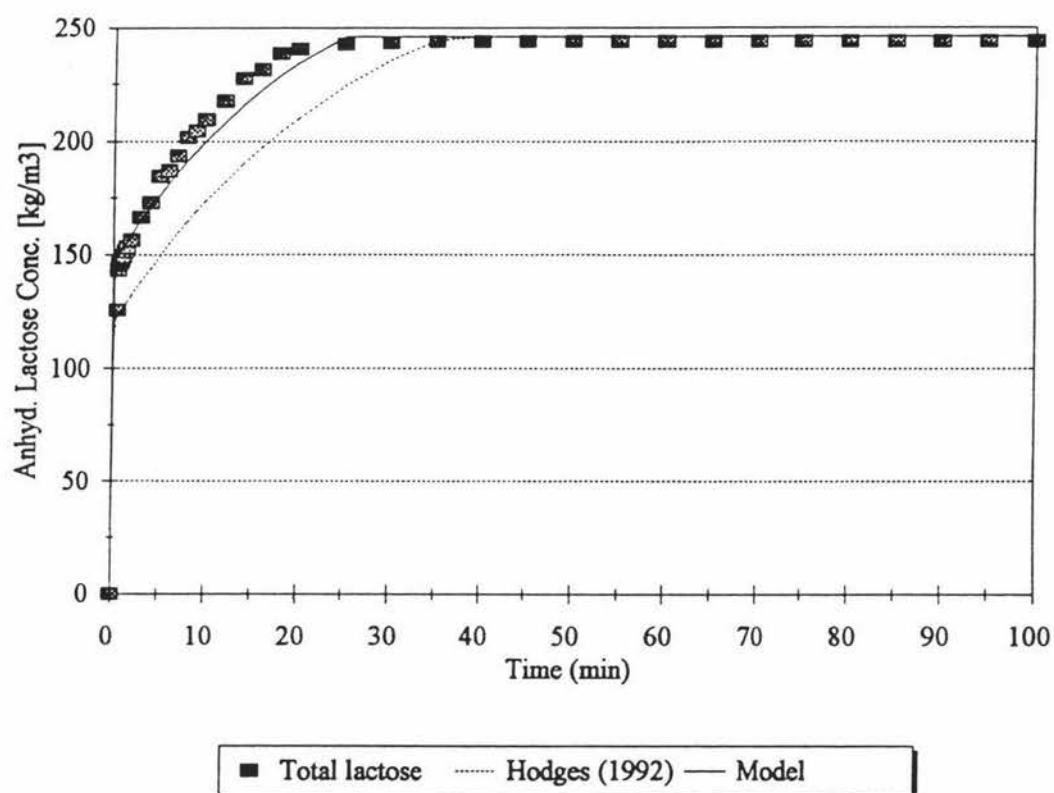


Figure 3.6 Dissolution of lactose above the alpha lactose solubility limit. Operating conditions: 45°C, Final concentration 246 kg/m³, Stirring speed 400rpm.

3.3.3 Comparison of model to dissolution below the alpha lactose solubility limit.

In the dissolution region below the alpha lactose solubility limit, the model predicts that the controlling factor for dissolution will be the mass transfer of alpha lactose from the surface of the crystal to the bulk of solution. Mutarotation should not be a limiting factor as the alpha lactose solubility limit has not been reached, and any surface disintegration reactions have been neglected.

3.3.3.1 Experimental.

Experimental work was carried out by Hodges (1992) demonstrating the dissolution of lactose below the alpha lactose solubility limit. Experiments were carried out at 25°C and 45°C with particle size fractions 105-150 μm and 210-300 μm . Target concentrations of 44.5 kg/m^3 using 0.0914 kg of anhydrous lactose and 92.5 kg/m^3 using 0.1976 kg of anhydrous lactose added to 2 litres of water for 25°C and 45°C respectively were used. Further details of the experimental procedure and apparatus used can be found in Hodges (1992).

3.3.3.2 Results and discussion.

The results obtained by Hodges (1992) can be found in Tables F5 to F8' in Appendix F. Results consist of the variation of the lactose concentration with time during dissolution.

The particle sizes are the same as those used in the previous experiment, giving characteristic crystal dimensions of 123.8 μm and 235.6 μm .

The developed model was run at 25°C and 45°C. The system inputs used can be found in Tables B1 and B2 in Appendix B, and the resulting total lactose concentrations found in Tables F5 to F8 in Appendix F. The model developed by Hodges (1992) utilizing a constant mass transfer coefficient was also solved using the same system inputs as the model developed in this report.

Figures 3.7 and 3.8 show a comparison of the experimental results and the results predicted from the two models at 25°C and 45°C respectively, and Table 3.5 shows a comparison of the predicted and experimentally observed dissolution times. It is immediately apparent that the dissolution predictions from the model do not fit the experimental results. The model predictions suggest that dissolution should occur much faster than what is actually occurring. It must be noted that the constant mass transfer model gives closer predictions than the constant Sherwood model. This is due to the constant mass transfer model not taking into account the increasing mass transfer value as the particle size decreases, which is not realistic. The discrepancies between the predicted and observed dissolution rates could instead be caused by the mass transfer coefficient being calculated incorrectly, or some surface effect that has not been modeled is taking place.

It is not feasible to suggest that a smaller mass transfer coefficient be used as the Sherwood number calculated is based on the diffusion of lactose from the crystal surface to a stagnant medium giving the smallest reasonable mass transfer coefficient possible for a given particle size. It is possible that the diffusion coefficients of lactose in water are in error, and this will be investigated by a sensitivity analysis.

Table 3.5 Predicted verses experimental dissolution times below the alpha lactose solubility limit.

Operating Conditions.	Dissolution Times (sec)		
	Observed Dissolution Time	Predicted. (Hodges 1992)	Predicted. (This report)
25°C, Target Conc = 44.5 kg/m ³ .	25	45.12	7.16
45°C, Target Conc = 92.5 kg/m ³ .	25	24.16	2.86

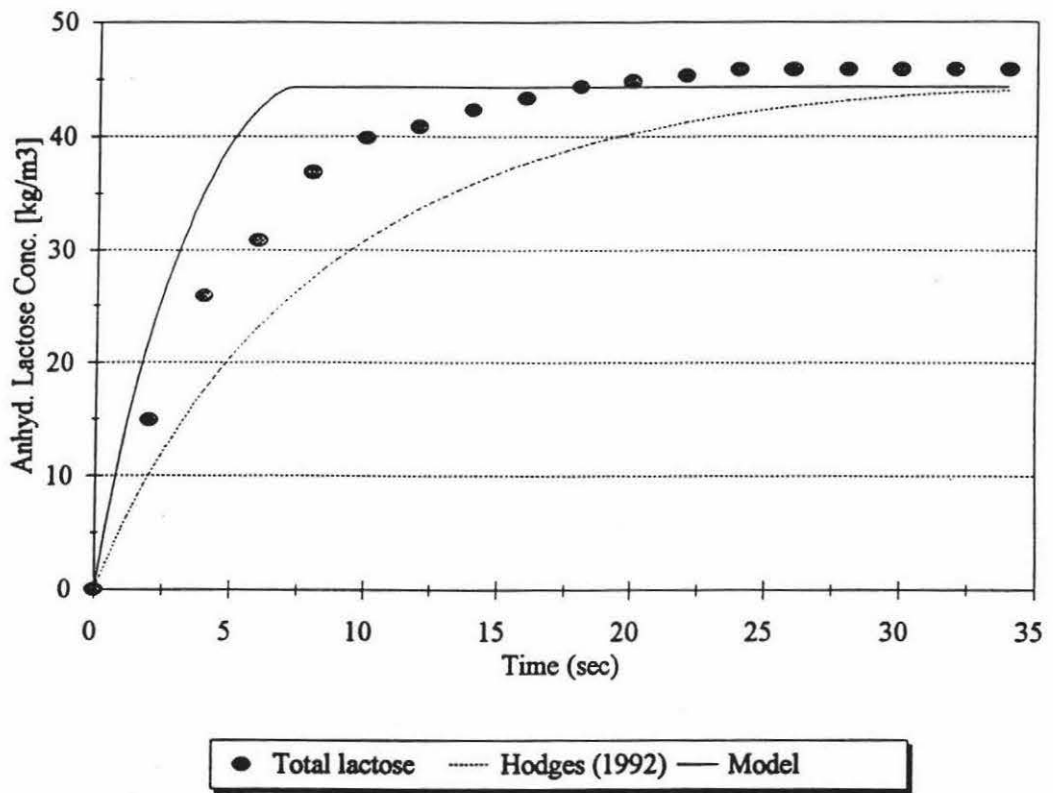


Figure 3.7 Dissolution of lactose below the alpha lactose solubility limit. Operating conditions: 25°C, Final concentration 44.5 kg/m³, Stirring speed 400 rpm.

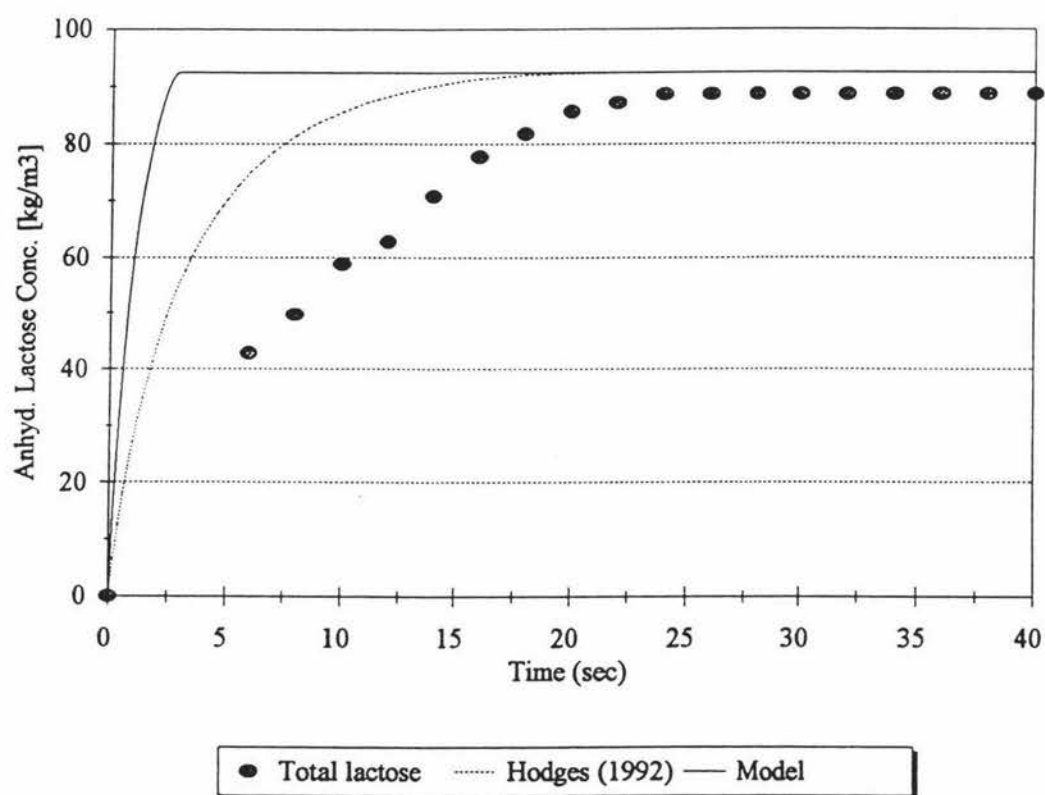


Figure 3.8 Dissolution of lactose below the alpha lactose solubility limit. Operating conditions: 45°C, Final concentration 92.5 kg/m³, Stirring speed 400 rpm.

There are several possibilities for processes that may be slowing the dissolution process below the alpha lactose solubility limit. These are

- (i) Surface disintegration reaction. It is possible that the removal of alpha lactose from the crystalline lattice into solution may not be instantaneous as assumed and could be a rate limiting step.
- (ii) Active Surfaces. In section 1.5.1 of the introduction it was suggested that during crystallization not all surfaces actively participate, with some growing at much slower rates than others. It is possible that this may also occur during dissolution, which would lead to a smaller area participating in dissolution.

3.4 Sensitivity Analysis

In the predictions of the dissolution model, many variables are used as system inputs and initial conditions. Each of these variables will have some degree of error. However, not all of these variables will be critical in predicting dissolution times.

It has been found that there is a large discrepancy between the experimental results and the model below the alpha lactose solubility limit. Whether this difference is due to errors mentioned above or due to an un-modeled process must be determined.

Error in the variables can come from two particular sources

- (i) Experimental errors. These are the errors possible in experimental conditions which the model uses, e.g. Temperature, Mass of lactose added, particle size, and volume of solution. These may have a compound effect on the system inputs.

- (ii) Model errors. These are errors in the estimated system inputs, ie. mutarotation rate, Sherwood number, Diffusivity, and alpha lactose solubility. These were determined independently of the system being studied. The true values of these may not be known and in some cases correlations have been used to estimate these values.

By altering these values by ± 10 or 20% , the significance of any possible experimental or model errors can be determined.

3.4.1 Experimental errors.

There are four main variables which could be effected during experiments. These are

- (i) Temperature
- (ii) Mass of lactose added
- (iii) Particle Size
- (iv) Volume of Solution

3.4.1.1 Temperature changes.

Changing the temperature has a wide effect on the system inputs in the model. Variables affected by temperature are alpha lactose solubility, mutarotation reaction rate, solution density, the alpha to beta equilibrium value, and the diffusivity of solution. Table 3.6 shows the temperature run of $25 \pm 2^\circ\text{C}$ and the effect on each of these system inputs.

Figures 3.9 to 3.11 show the effect of altering temperature by $\pm 10\%$ on the regions with excess alpha lactose, above the alpha lactose solubility limit and below the alpha lactose solubility limit respectively. From Figures 3.9 and 3.10 where dissolution occurs above the alpha lactose solubility limit, it is apparent that changing the temperature by $\pm 10\%$ has a very large effect on dissolution. The model predicts that in these regions mutarotation is the controlling process in dissolution. Examining Table 3.6 shows that

temperature has had a large effect on the mutarotation rates k_1 and k_2 . The other major factor that appears to have altered dissolution is the altered solubility of alpha lactose. This has affected the concentration at which mutarotation, which is slower than mass transfer becomes the controlling factor in dissolution. The effect of this is very apparent in Figure 3.10, where the dissolution process changes from being mutarotation controlled to mass transfer controlled by the changed alpha solubility limit at higher temperatures. Experimentally, the temperature is not likely to vary by more than $\pm 1^\circ\text{C}$, and the changes will not be as dramatic as those shown here.

Figure 3.11 shows the effect of temperature on the dissolution of alpha lactose below the alpha lactose solubility limit. The effect of temperature here is not as large as that of dissolution above the alpha lactose solubility limit. This is because mutarotation and solubility effects, which were the major causes of change above the alpha lactose solubility limit, are not a factor in this region of dissolution. Instead, the diffusion coefficient is the major system input which alters with temperature which has an effect below the alpha lactose solubility limit. This does not change as dramatically as the mutarotation rate, as can be seen in Table 3.6. Comparing against the experimental results, the change in temperature does not account for the difference between the experimental and predicted dissolution times for dissolution of lactose in solutions below the alpha lactose solubility limit.

Table 3.6 Effect of changing temperature on system inputs.

System Inputs	Temperature	
	22.5°C	27.5°C
$C_{\alpha}^{p=0}$	80.456 kg/m ³	91.892 kg/m ³
F	0.07101	0.08265
k_1	$8.7000 \times 10^{-5} \text{ s}^{-1}$	$1.5031 \times 10^{-4} \text{ s}^{-1}$
k_2	$5.4172 \times 10^{-5} \text{ s}^{-1}$	$9.5738 \times 10^{-5} \text{ s}^{-1}$
K_m	1.59	1.57
D	$4.45 \times 10^{-9} \text{ m}^2/\text{s}$	$5.15 \times 10^{-9} \text{ m}^2/\text{s}$
c_i	997.685 kg/m ³	997.814 kg/m ³
m_i	0.39101	0.37638

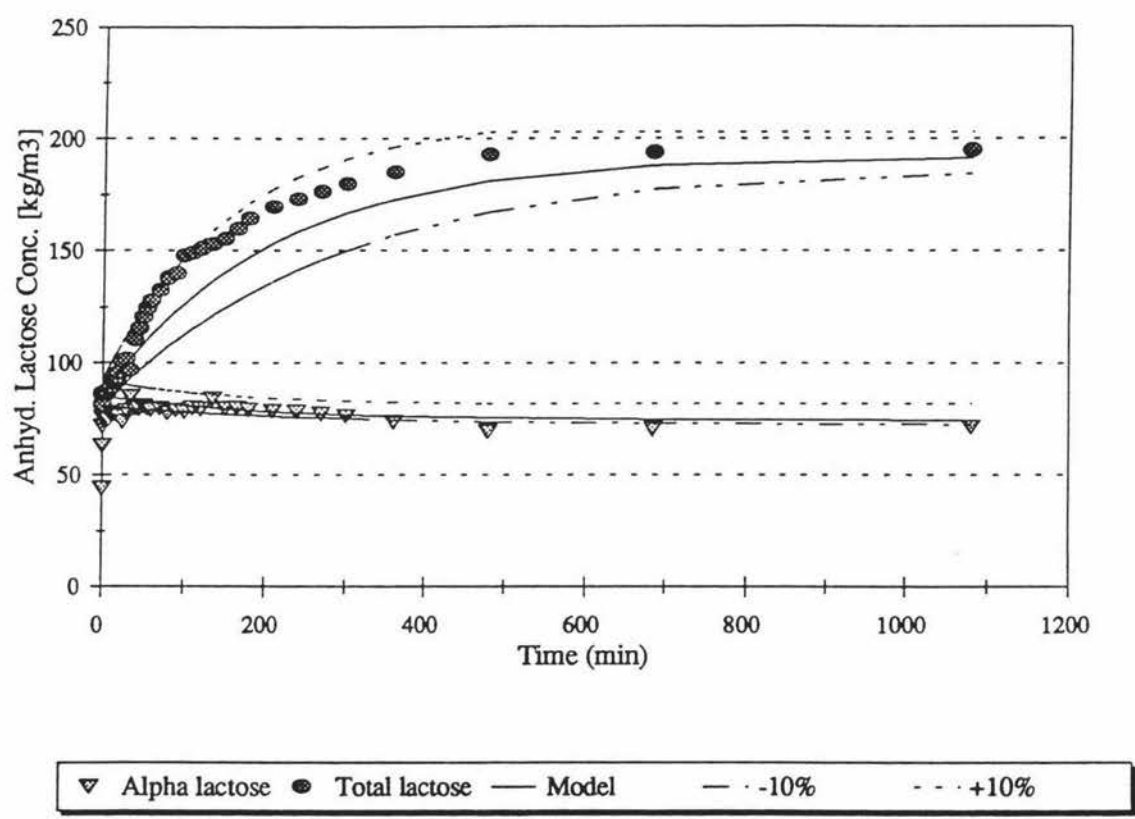


Figure 3.9 Effect of changing temperature with excess lactose in solution.

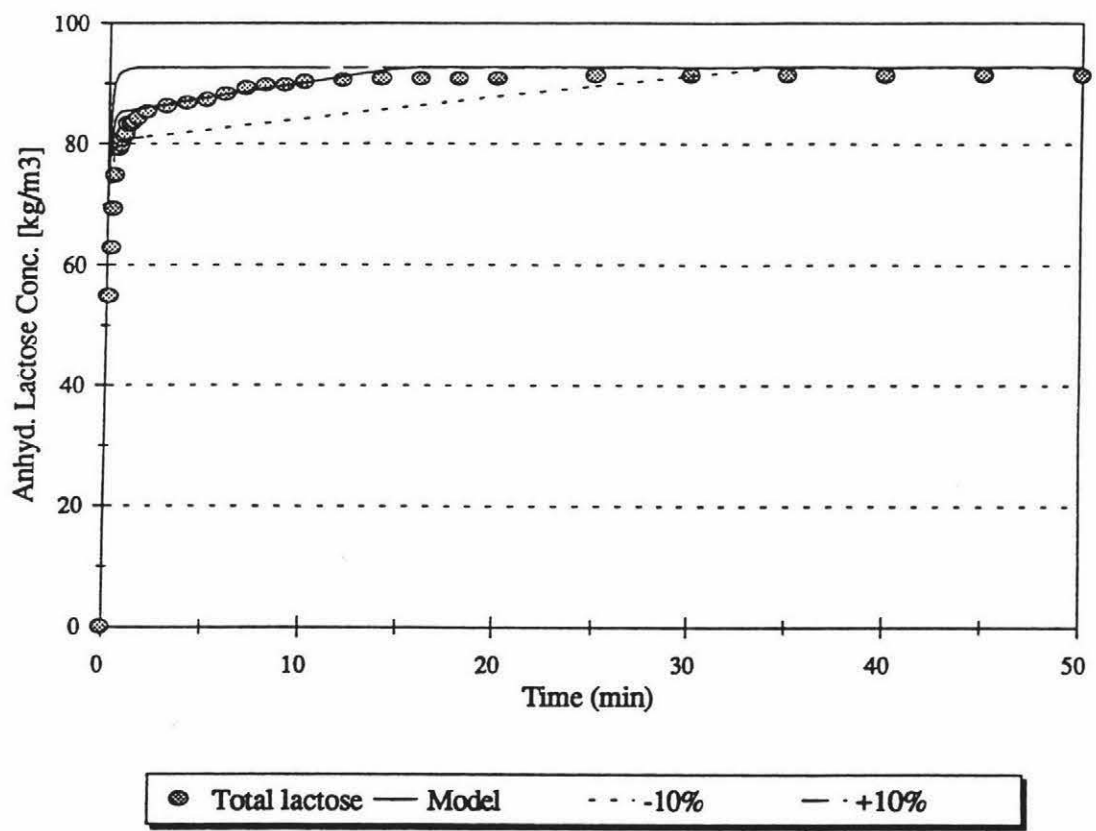


Figure 3.10 Effect of changing temperature below the total solubility limit.

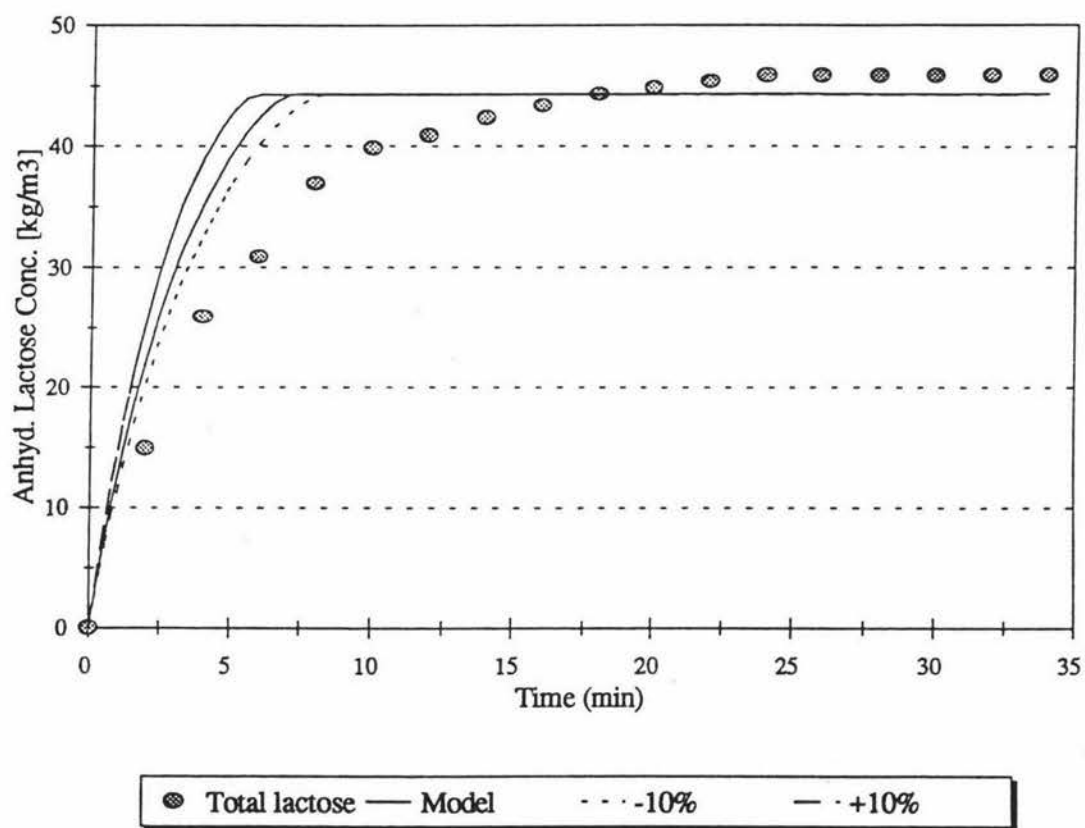


Figure 3.11 Effect of changing temperature below the alpha lactose solubility limit.

3.4.1.2 Mass of lactose added and volume of solution.

Experimentally, the mass of lactose added and the volume of solution will vary for a variety of reasons. Errors may occur during weighing, or while the lactose is being added to solution some lactose may be lost. The volume of solution may be altered by measurement errors, or at high temperature dissolutions, evaporation of solution may become significant.

Table 3.7 shows the changes in initial mass $\pm 10\%$. The model was run with these changes.

Figures 3.12 to 3.14 show the effect of mass changing for the three different regions of dissolution. Where alpha lactose is added in excess (Figure 3.12), altering the lactose only had an effect when the mass added was below the amount required to reach the total solubility limit.

For dissolution of lactose above the alpha lactose solubility limit but below the total solubility limit (Figure 3.13), changing the mass added has a significant effect on the dissolution time as more or less alpha lactose must mutarotate. However, for dissolution below the alpha lactose solubility limit (Figure 3.14), changing the mass added is predicted to have a minimal effect on the dissolution of lactose, apart from changing the final concentration reached. This is because according to the model, reducing the mass added decreases the driving force for mass transfer and the available area for dissolution, compensating for the less mass added to give similar dissolution times.

Table 3.7 Changing lactose mass by $\pm 10\%$.

Mass added normally (g anhydrous lactose)	-10%	+10%
473.0	425.7	520.3
197.6	159.84	217.36
91.4	82.26	100.54

The volume of solution has a similar effect as the mass of lactose on dissolution, but in reverse. Reducing the volume of solution is equivalent to increasing the mass of lactose being added to solution.

3.4.1.3 Particle size.

The variation in initial particle size may come from either experimental sources or system input sources. It is possible (and in fact most probable) that the lactose crystals used are not of one single particle size. It is also possible that the way in which measured particle sizes are expressed in terms of the particle dimensions may be in error.

The characteristic dimension of the crystal used was 123.8 μm . This may vary considerably due to the uncertainty of the particle separation and the correlation between the measured particle size and particle dimensions. A variation of $\pm 20\%$ was used to examine the effect of the variability in particle sizes, giving high and low bounds of 148.6 μm and 99.04 μm respectively.

For dissolution above the alpha lactose solubility limit, changing the particle size was predicted by the model to have no effect on the dissolution of lactose. This is due to mutarotation being the controlling factor of dissolution at this point.

Figure 3.15 shows the predicted effect of particle size error on dissolution below the alpha lactose solubility limit. Here particle size does have some effect on dissolution. This is due to mass transfer being assumed to be the controlling effect, which is dependant on particle size. However, it must be noted that the variation of the particle size by 20% still does not account for the discrepancy between the model and the experimental results.

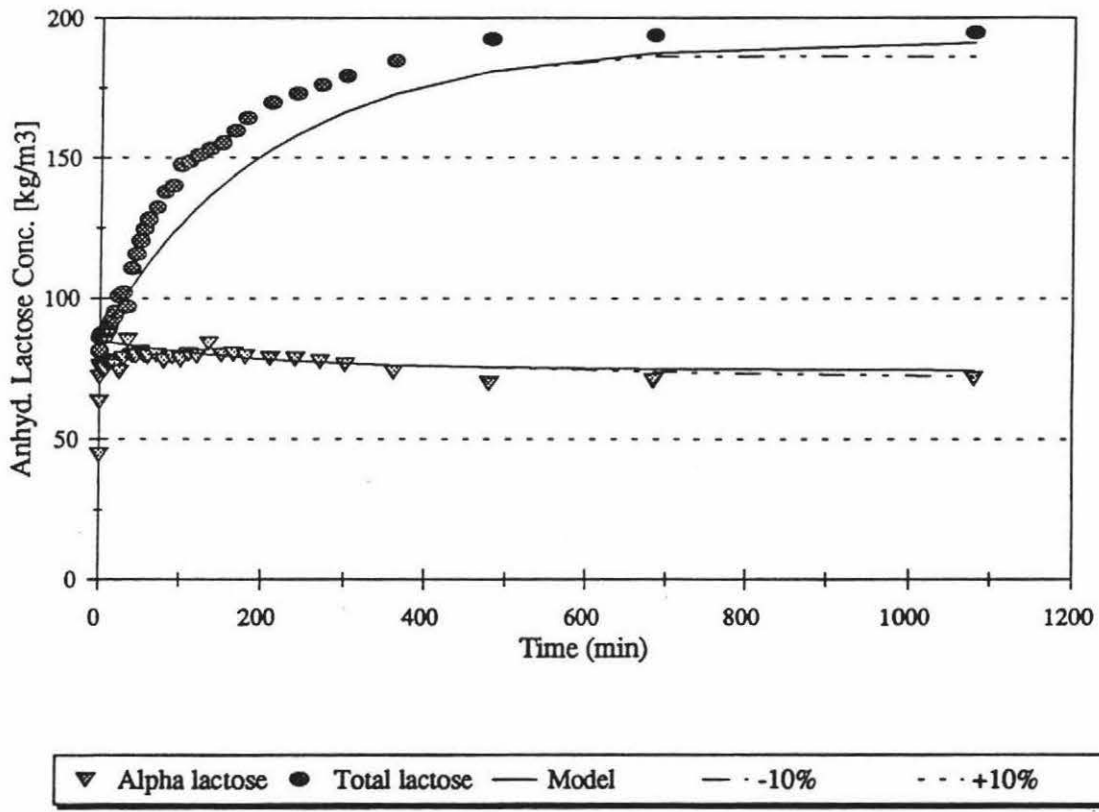


Figure 3.12 Effect of changing mass added with excess lactose.

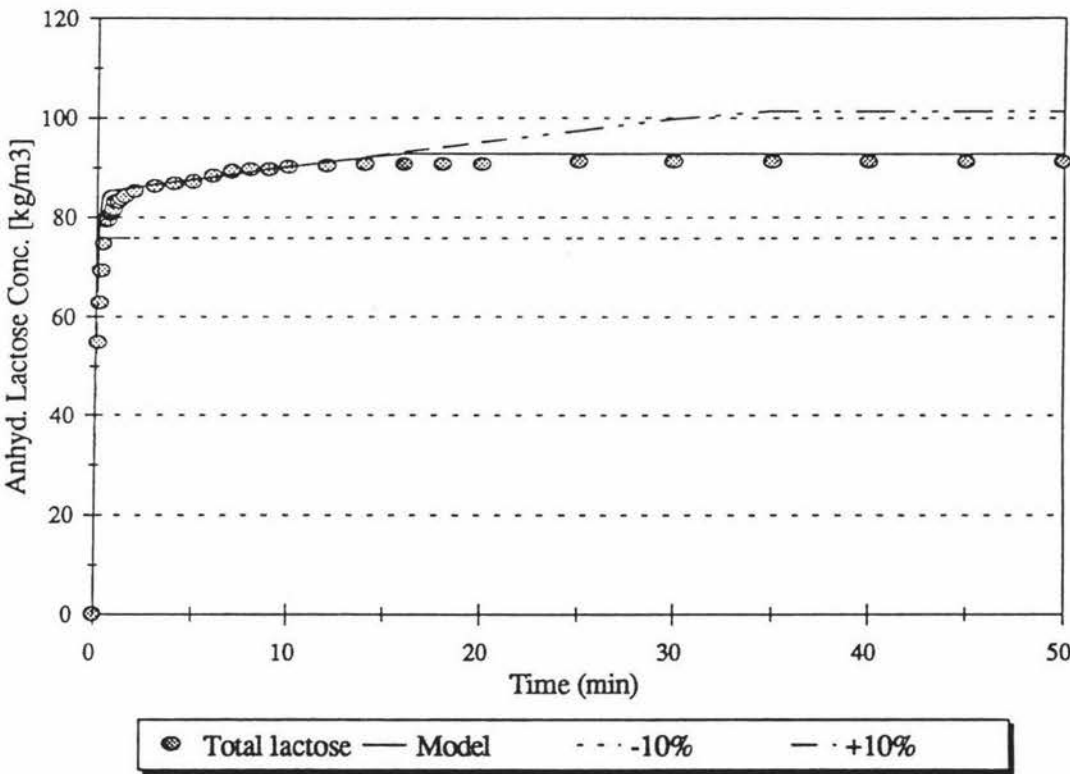


Figure 3.13 Effect of changing mass added below the total solubility limit.

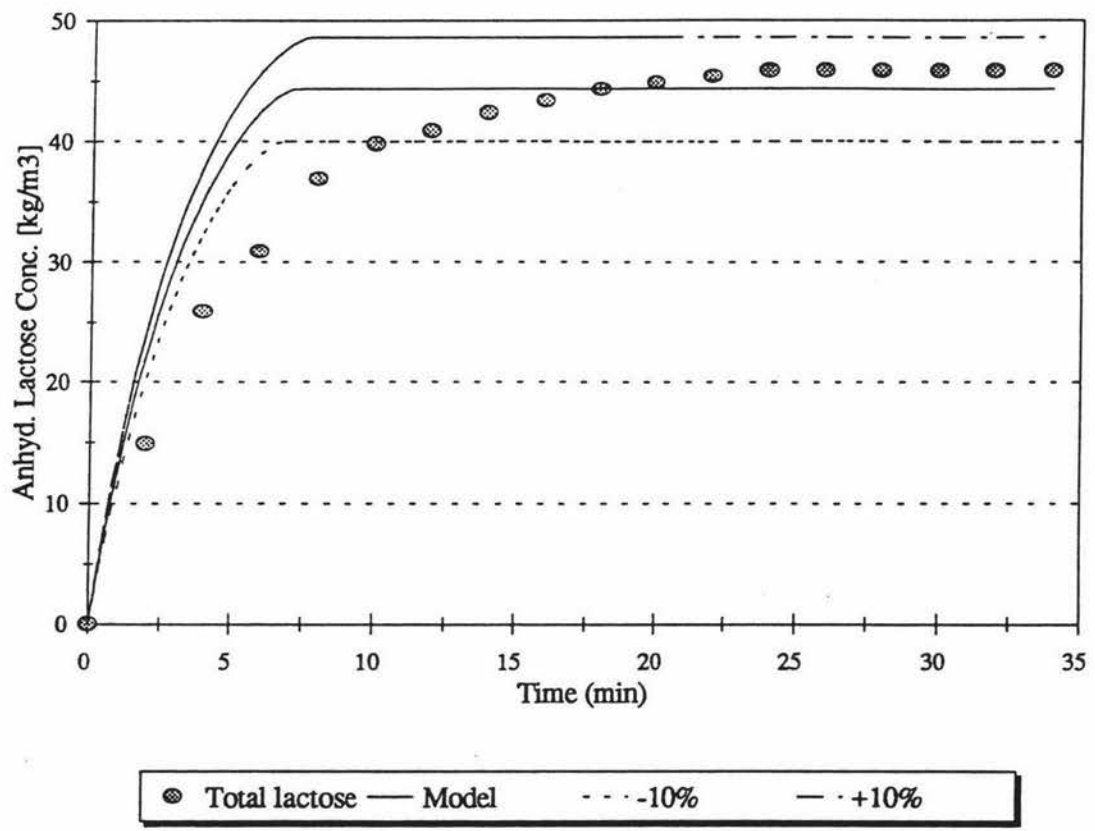


Figure 3.14 Effect of changing mass added below the alpha lactose solubility limit.

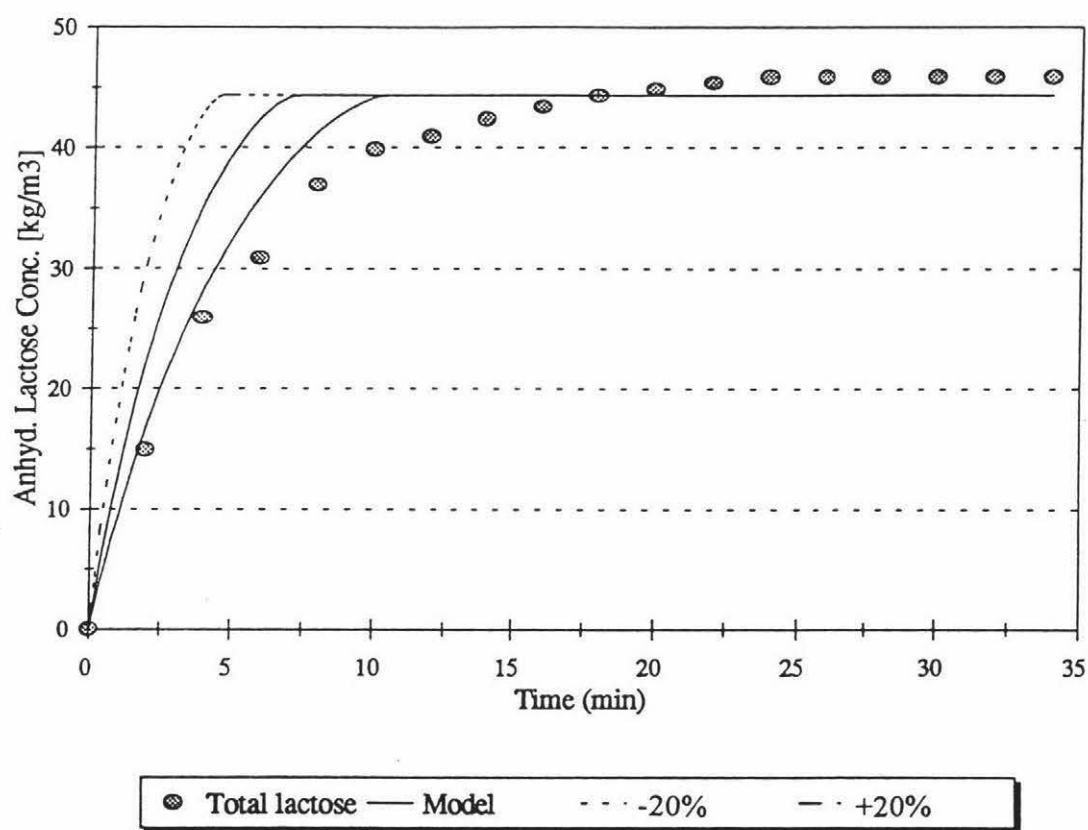


Figure 3.15 Effect of changing particle size below the alpha lactose solubility limit.

3.4.2 Model errors.

In the determination of this model, a variety of values were estimated from the literature and from first principles. Not all of these are well defined at the operating conditions used in the experimental work.

3.4.2.1 Mutarotation rate.

Section 1.3 in the introduction gave values of the mutarotation constants for a variety of temperatures. However, there was some discrepancy in the literature. It is important to examine the effect of altering the mutarotation constants on dissolution to determine the importance of these discrepancies.

In the literature, the mutarotation constants are given in terms of $k_1 + k_2$. Reported values of $k_1 + k_2$ at 25°C vary from $2.860 \times 10^{-4} \text{ s}^{-1}$ to $1.265 \times 10^{-4} \text{ s}^{-1}$, with the Arrhenius analysis performed in section 1.3 giving a value of $1.8717 \times 10^{-4} \text{ s}^{-1}$. The effect of these upper and lower bounds on dissolution will be examined.

Figures 3.16 and 3.17 show the effect of changing the mutarotation constants above the alpha lactose solubility limit. In both cases, altering the mutarotation rate significantly affected the way in which dissolution was predicted, with the final dissolution times being significantly affected. It is apparent that using the reported high values of $k_1 + k_2$ gives a significantly improved fit to the model. The low values of the mutarotation rate reported may be caused by the presence of inhibitors in solution. Performing a non-linear arrhenius analysis without these low values of the mutarotation rate gives values of A_0 and E_a of $1.9943 \times 10^9 \text{ s}^{-1}$ and 73664.05 kJ/kgmol respectively. This gives values of $k_1 + k_2$ at 25°C and 45°C of $2.473 \times 10^{-4} \text{ s}^{-1}$ and $1.603 \times 10^{-3} \text{ s}^{-1}$ respectively. The effect of using these mutarotation rates on the predicted dissolution times is shown in Table 3.8, along with the previous predictions and the experimentally observed times. The prediction of dissolution time has markedly improved, for the 25°C case with the difference between the predicted and observed results falling from 70% to 20%. However, the 45°C case has gone from 0.4% to 10%.

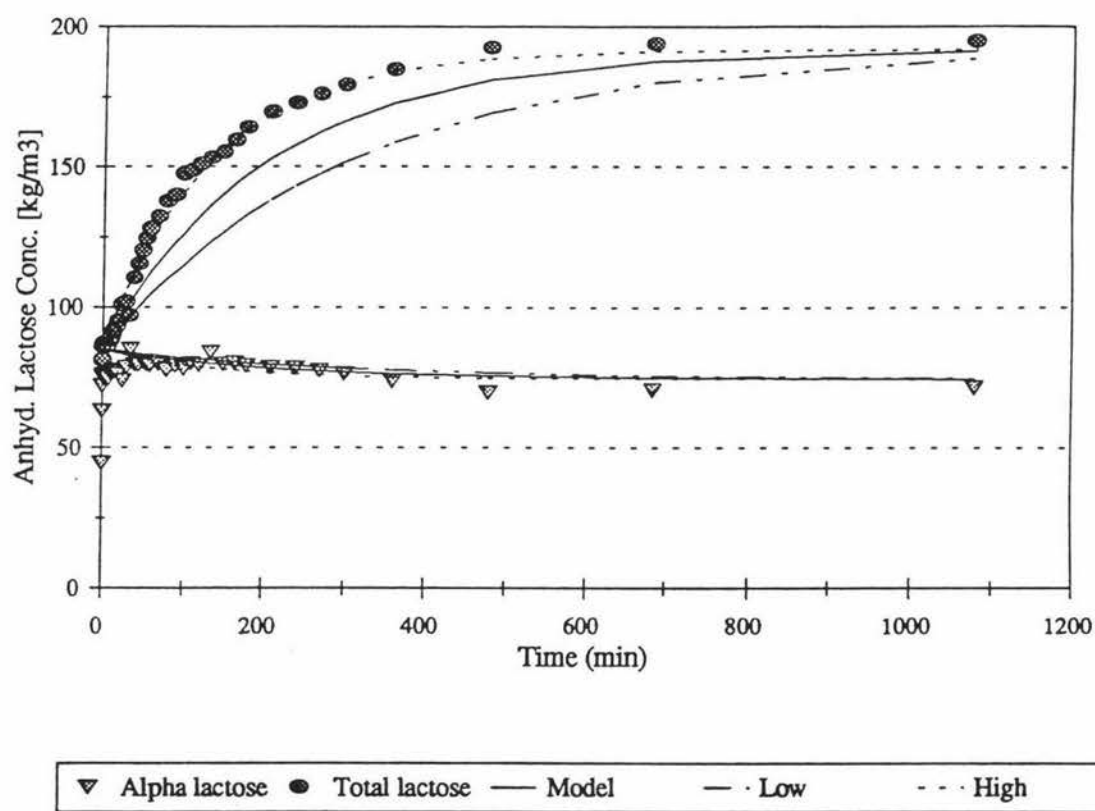


Figure 3.16 Effect of mutarotation rate on dissolution with excess lactose.

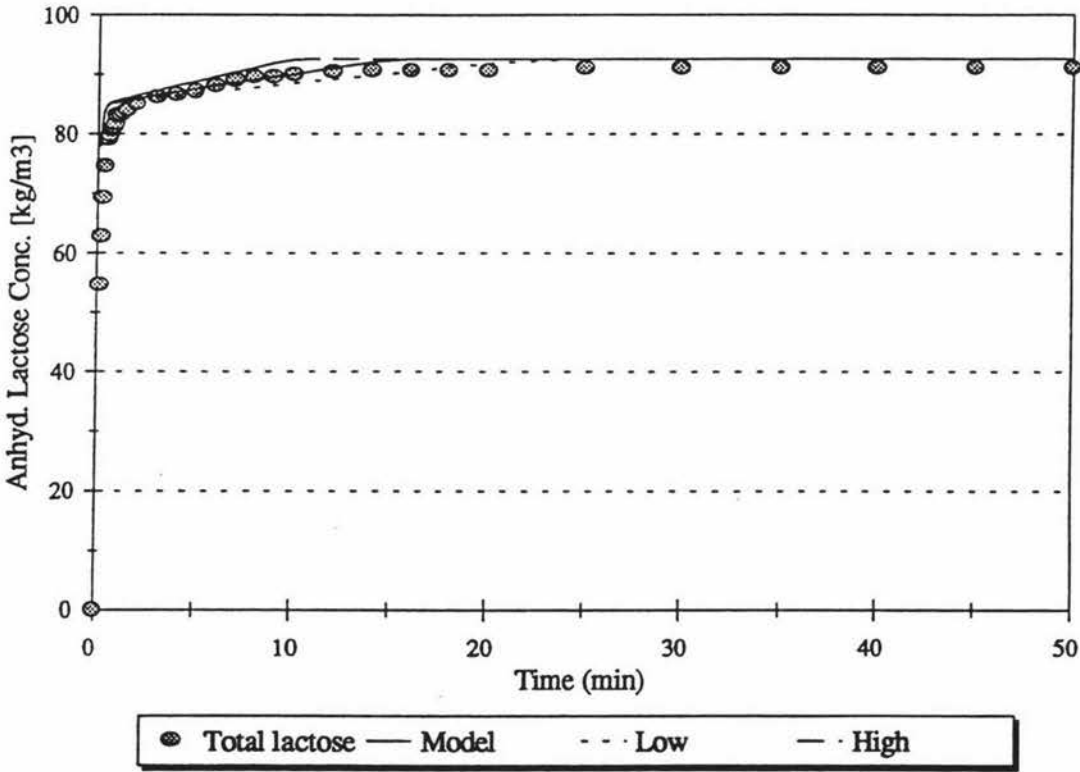


Figure 3.17 Effect of mutarotation rate on dissolution below the total solubility limit.

Table 3.8 Predicted dissolution times with corrected mutarotation rates.

Operating Conditions.	Dissolution Times (min)		
	Observed Dissolution	Predicted.	Predicted.
	Time	(Old mutarotation rates)	(New mutarotation rates)
25°C, Target Conc = 92.5 kg/m ³ .	10	17.0	11.8
45°C, Target Conc = 246 kg/m ³ .	25	24.9	22.5

Altering the mutarotation constants was predicted to have no effect on dissolutions below the alpha lactose solubility limit. This is because mutarotation is not a controlling factor in these dissolutions as the solubility limit of alpha lactose is not reached.

3.4.2.2 Sherwood number.

The Sherwood number has been estimated using the conductance equivalence principle of Cliff *et al* (1978) for the diffusion of lactose into a stagnant medium. The calculation methodology for this is long, involving many assumptions. The effect of altering the Sherwood number by $\pm 20\%$ will show if this can account for the discrepancy between the experimental and predicted results below the alpha lactose solubility limit.

The estimated Sherwood number found by the conductance concept was 2. Varying this by $\pm 20\%$ gives Sherwood numbers of 1.6 to 2.4. A Sherwood number below two cannot be justified but is included for completeness.

Figure 3.18 shows the effect of altering the Sherwood number on the rate of dissolution of lactose. Altering the Sherwood number does have a significant effect on dissolution below the alpha lactose solubility limit. However the change in Sherwood number, even reducing the Sherwood number below what is generally considered reasonable, has not brought the prediction in line with the results generated by experiment. Some other effect apart from diffusion is occurring which further slows the dissolution process.

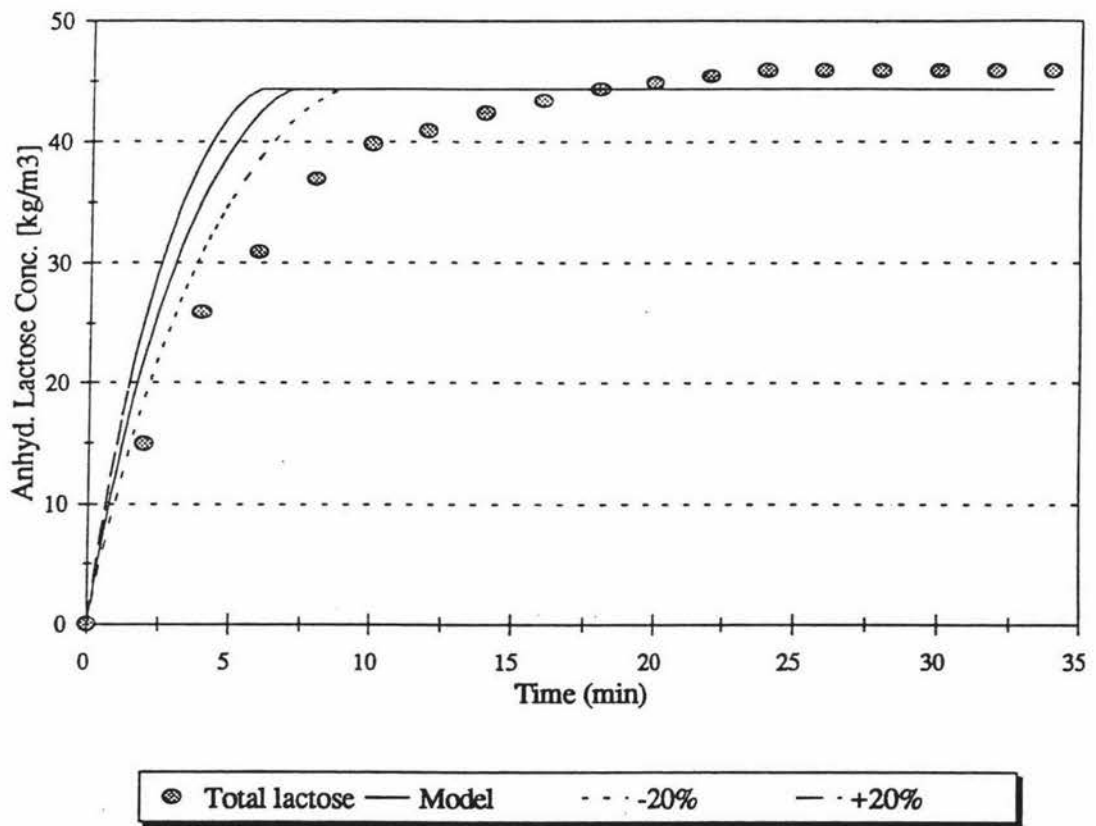


Figure 3.18 Effect of Sherwood number on dissolution below the alpha lactose solubility limit.

3.4.2.3 Diffusion coefficient.

The diffusion coefficients used have been derived from data at 0, 15 and 20°C, with a correlation used to find diffusion coefficients at higher temperatures. It is possible that large errors may be generated by this, which warrants investigating the effect of altering the diffusion coefficient by $\pm 20\%$.

At 25°C the diffusion coefficient has been estimated to be $4.7 \times 10^{-9} \text{ m}^2/\text{s}$. This gives 20% bounds of 3.8×10^{-9} and $5.6 \times 10^{-9} \text{ m}^2/\text{s}$.

Figure 3.19 shows the effect of altering the diffusion coefficient below the alpha lactose solubility limit. Changing the diffusion coefficient does have a significant effect on the rate of dissolution. However, the effect of altering the diffusion coefficient is not large enough to account for the difference between the predicted and experimental results.

Above the alpha lactose solubility limit changing the diffusion coefficient has no effect on dissolution as mass transfer is not a controlling factor in this region.

3.4.2.4 Alpha lactose solubility.

The values of $C_{\alpha}^{\beta=0}$ and F , which determine the alpha lactose solubility limit, were based on the values determined by Visser (1982). The accuracy of these values is not known.

The values of $C_{\alpha}^{\beta=0}$ and F are not independent of one another but together at the equilibrium concentration of beta lactose must give the alpha lactose solubility at equilibrium. Table 3.9 gives values of $C_{\alpha}^{\beta=0} \pm 10\%$, with the corresponding F values to give an alpha lactose solubility limit of 74.39 kg/m^3 .

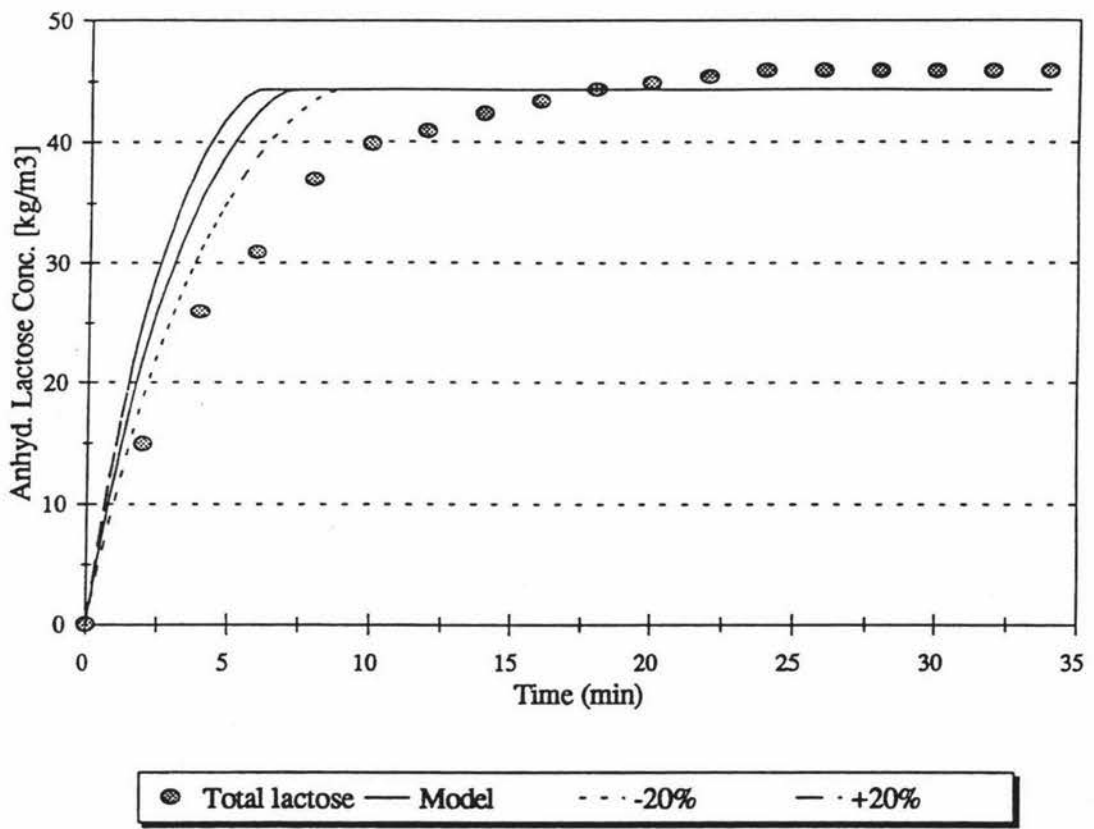


Figure 3.19 Effect of diffusion coefficient on dissolution below the alpha lactose solubility limit.

Table 3.9 Changing alpha lactose solubility.

Variable	-10%	+10%
$C_{\alpha}^{\beta=0}$	76.563 kg/m ³	93.577 kg/m ³
F	0.018493	0.163249

Figures 3.20 and 3.21 show the effect of the alpha lactose solubility with and without excess lactose respectively. In the case of excess lactose (Figure 3.20) although the shape of the curve has been altered, the time taken to reach equilibrium concentrations have not changed dramatically. However, for dissolution without excess lactose (Figure 3.21), the effect of altering the alpha lactose solubility is dramatic. This is due to the change in the concentration at which mutarotation becomes the controlling process. In the given example, by increasing the value of $C_{\alpha}^{\beta=0}$, the dissolution has been shifted from a largely mutarotation controlled dissolution to a mass transfer controlled dissolution, with a dramatic decrease in dissolution time.

For dissolution below the alpha lactose solubility limit (Figure 3.22), it was predicted that the changing alpha lactose solubility would change the rate of dissolution. This is because altering the solubility limit alters the predicted driving force for mass transfer.

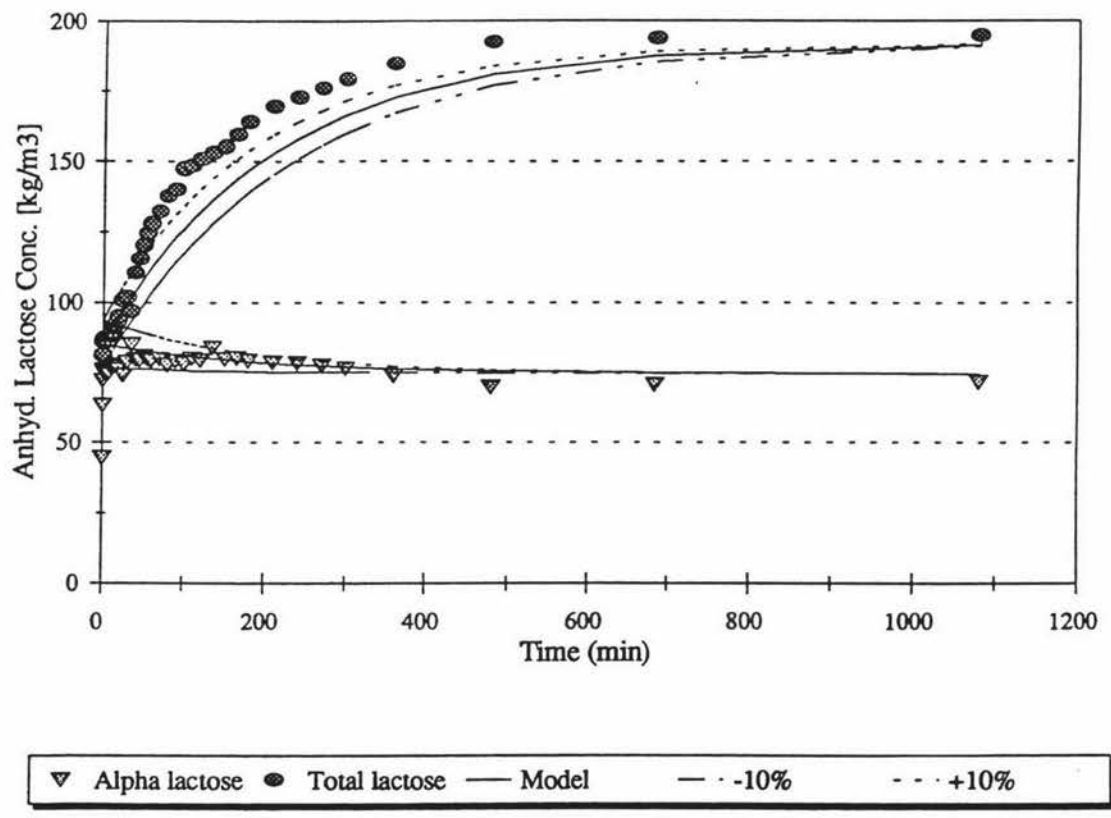


Figure 3.20 Effect of alpha lactose solubility on dissolution with excess lactose.

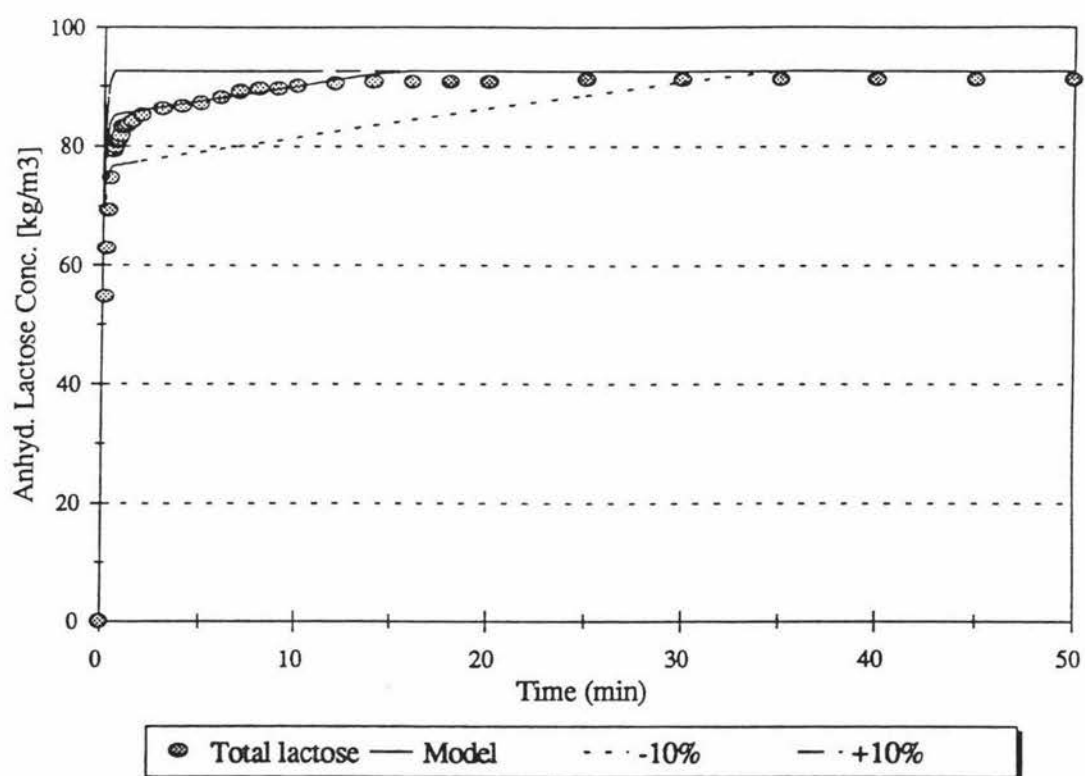


Figure 3.21 Effect of alpha lactose solubility on dissolution below the total solubility limit.

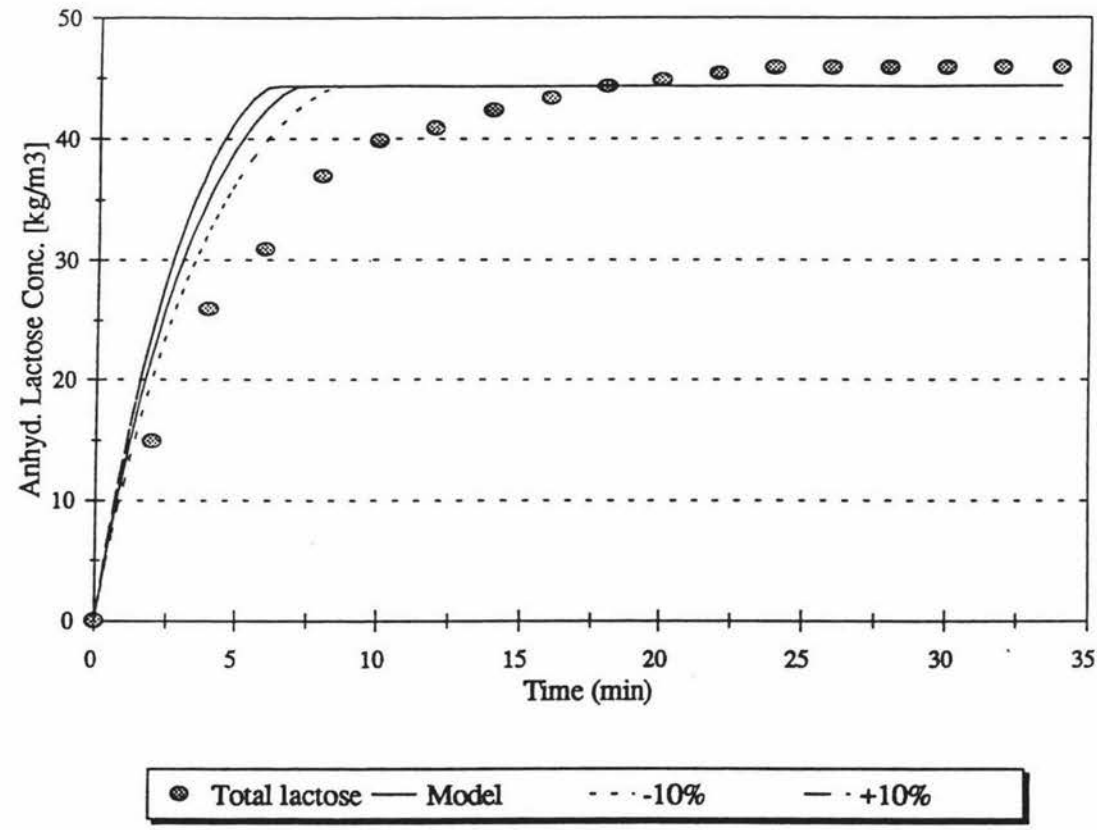


Figure 3.22 Effect of lactose solubility on dissolution below the alpha lactose solubility limit.

3.4.3 Sensitivity analysis summary.

Experimental factors were predicted to have a significant effect on the dissolution rate when dissolving above the alpha lactose solubility limit, particularly the temperature of dissolution. However, comparison of the model predictions with experimental results above the alpha lactose solubility limit has shown in this study that if care is taken these can be eliminated. Below the alpha lactose solubility limit experimental factors were predicted to have less of an effect.

Depending on the region in which dissolution was occurring, different model factors were shown to have significant effects on the predicted dissolution rates. Above the alpha lactose solubility limit, mutarotation rate and alpha lactose solubility limit were shown to have a large effect on the predicted dissolution rates. The values of $C_{\alpha}^{\beta=0}$ and F chosen were found to fit well with the experimental data. However, the mutarotation rate constants $k_1 + k_2$ were found to be in error. An examination of the literature showed that discrepancies existed, possibly due to inhibitory compounds present in some experiments. Below the alpha lactose solubility limit the Sherwood number and diffusion coefficient were predicted to effect dissolution.

For dissolution below the alpha lactose solubility limit, neither experimental nor model errors could account for the discrepancy between the predicted and experimental dissolution rates. It must be concluded that some other process is occurring which currently is not being modeled.

3.5 Conclusions

The model developed by Hodges (1992) was improved to include the effect of beta lactose on the solubility of the alpha lactose and diffusion controlled mass transfer. This produced a model with three ordinary differential equations and seven algebraic equations which were solved simultaneously using a numerical simulation package.

The addition of the effect of beta lactose on the solubility of alpha lactose was found to improve dissolution predictions above the alpha lactose solubility limit, especially in the case where lactose was not added in excess.

When dissolution occurred below the alpha lactose solubility limit, a marked discrepancy was found to exist between the experimental results and the results predicted by the model. Experimental results showed that dissolution in this region occurred three to four times slower than that predicted by the model. A sensitivity analysis showed that this could not be accounted for by errors in experimental conditions or the estimated system inputs. Possible reasons for the discrepancies are

- (i) The surface disintegration reaction is not instantaneous as assumed.
- (ii) Not all surface area active for dissolution.

Chapter 4 investigates the possibility of a surface disintegration reaction being the rate controlling factor in dissolution for solutions below the alpha lactose solubility limit.

CHAPTER 4

Model 2: Inclusion of Surface Reaction Effect.

4.1 Introduction

The dissolution model developed in Chapter 3 was found to predict the dissolution of lactose above the alpha lactose solubility limit accurately. However, the model predictions for dissolution below the alpha lactose solubility limit were considerably different from the experimental results. In these cases, the dissolution rate was over-predicted by the model by 3 to 4 times. A postulated reason for this discrepancy was the presence of a surface disintegration reaction which occurs before diffusion takes place, limiting the rate of dissolution. The previous model assumed that this reaction occurred sufficiently fast to have no effect on dissolution. This assumption may not be valid.

For any surface reaction that takes place, the way in which the reaction rate changes with temperature will most likely follow an Arrhenius type relationship. This can be expressed in the form

$$k_r = A_s e^{-\left(\frac{E_s}{RT}\right)} \quad (4.1)$$

where k_r = Overall surface reaction rate (m/s)

A_s = Frequency Factor for surface reaction (m/s)

E_s = Activation Energy for surface reaction (kJ/kgmol)

By determining the surface reaction rate at different temperatures, the conformity of the rates to Arrhenius law can be determined.

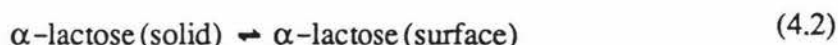
4.2 Model Formulation

4.2.1 Physical system

The physical system is the same as that in Chapter 3, section 3.2.1. However, different assumptions have been made in the formulation of the model.

4.2.1.1 Model assumptions

As in the previous model, mass transfer from the crystal surface was considered to be mass transfer by diffusion into a stagnant medium, leading to the constant Sherwood number assumption. However, when the surface reaction is taken into consideration, diffusion cannot proceed until the surface disintegration reaction has taken place. The surface disintegration reaction was assumed to be a first order reaction of the form



The assumptions made in the model can be summarized as follows

- (i) The surface disintegration step occurred as a first order chemical reaction.
- (ii) Lactose crystal geometry remained constant throughout dissolution.
- (iii) All crystal surface area was available for dissolution.
- (iv) Constant temperature occurred throughout dissolution.
- (v) Perfectly mixed system.
- (vi) Mutarotation can be described by a first order rate constants.
- (vii) Constant Sherwood number throughout dissolution.
- (viii) Alpha lactose solubility affected by beta lactose in a linear manner.
- (ix) Single crystal size used during dissolution.

4.2.2 Differential equations

As in the previous model, there were three time dependant variables that must be determined. This necessitated three ordinary differential equations.

4.2.2.1 Lactose crystal size

The simplified shape for lactose used in the previous model was used for this model, with the characteristic length of the crystal D_c .

The basis for the lactose crystal size differential was determined as before by a mass balance around a single lactose crystal, giving

$$\left[\begin{array}{c} \text{Rate of decrease of} \\ \text{Lactose Crystal Mass} \end{array} \right] = \left[\begin{array}{c} \text{Rate of Transport of Lactose} \\ \text{from Crystal Surface} \end{array} \right] \quad (4.3)$$

Expressing this in terms of the mass transfer flux gives

$$-\frac{dM_c}{dt} = NA_c \quad (4.4)$$

where N = Mass transfer flux of alpha lactose ($\text{kg/m}^2\cdot\text{s}$).

The mass transfer flux is defined as

$$N = k_L(C_{\alpha} - C_{\alpha c}) \quad (4.5)$$

where $C_{\alpha c}$ = Concentration of dissolved alpha lactose at crystal surface (kg/m^3).

However, the rate of transport of lactose from the lactose surface is dependant on the availability of lactose from the surface disintegration reaction. The production of alpha lactose available for dissolution can be found by a mass balance of alpha lactose around the crystal surface, giving

$$\left[\begin{array}{c} \text{Rate of accumulation of} \\ \text{alpha lactose at crystal} \\ \text{surface (per unit area).} \end{array} \right] = \left[\begin{array}{c} \text{Rate of disintegration} \\ \text{of alpha lactose from} \\ \text{crystal surface} \end{array} \right] - \left[\begin{array}{c} \text{Rate of integration} \\ \text{of alpha lactose into} \\ \text{crystal surface} \end{array} \right] \quad (4.6)$$

Note that the word equation is expressed in terms of per unit area. Assuming that the reaction is first order and converting to a differential equation gives

$$r_1 = k_3 C_{\alpha c} - k_4 C_{\alpha} \quad (4.7)$$

- where r_1 = Rate of accumulation of alpha lactose at crystal surface ($\text{kg/m}^2\cdot\text{s}$).
 $C_{\alpha c}$ = Concentration of alpha lactose in solid (kg/m^3).
 k_3 = Rate of disintegration of alpha lactose from crystal surface (m/s).
 k_4 = Rate of integration of alpha lactose into crystal surface (m/s).

At mutarotation equilibrium, the rate of accumulation of alpha lactose at the surface is zero and the liquid surface concentration is the alpha lactose equilibrium concentration. Expressing this in terms of an equation gives

$$k_3 C_{\alpha c} = k_4 C_{\alpha}^{\beta} \quad (4.8)$$

The solid alpha lactose concentration can be assumed to be constant and by substituting the above equation into equation (4.7) can be eliminated, giving the following equation for the rate of accumulation of alpha lactose at the surface

$$r_1 = k_r (C_{\alpha}^{\beta} - C_{\alpha}) \quad (4.9)$$

At steady state, the rate of formation of alpha lactose at the crystal surface is equal to the mass transfer flux. ie $N = r_1$. Combining this result with equations (4.8) and (4.4) enables $C_{\alpha c}$ to be eliminated from the mass transfer flux equation. ie

$$N = \frac{1}{\frac{1}{k_r} + \frac{1}{k_L}} (C_{\alpha}^{\beta} - C_{\alpha}) \quad (4.10)$$

Substituting this into equation (4.4) gives

$$-\frac{dM_c}{dt} = \frac{A_c}{\frac{1}{k_r} + \frac{1}{k_L}} (C_{\alpha}^{\beta} - C_{\alpha}) \quad (4.11)$$

As in Chapter 3, section 3.2.2.1, this equation can be expressed in terms of the characteristic dimension of the crystal

$$-3v_1 \rho_c D_c^2 \frac{dD_c}{dt} = \frac{a_1 D_c^2}{\frac{1}{k_r} + \frac{1}{k_L}} (C_{\alpha}^{\beta} - C_{\alpha}) \quad (4.12)$$

which rearranges to give

$$-\frac{dD_c}{dt} = \frac{a_1(C_{\alpha}^{\beta} - C_{\alpha})}{3v_1\rho_c\left(\frac{1}{k_r} + \frac{1}{k_L}\right)} \quad (4.13)$$

One thing to note from the above model is that if k_r is much greater than k_L , ie if the surface reaction is significantly fast, then the equation reverts to the equation developed for the previous model.

4.2.2.2 Alpha lactose concentration

The alpha lactose concentration in the bulk of solution was determined as before by performing a mass balance of alpha lactose around the whole system. This can be worded as follows

$$\left[\begin{array}{c} \text{Rate of accumulation} \\ \text{of alpha lactose in} \\ \text{bulk solution.} \end{array} \right] = \left[\begin{array}{c} \text{Rate of mass transfer} \\ \text{of alpha lactose from} \\ \text{crystal surface} \end{array} \right] + \left[\begin{array}{c} \text{Rate of mutarotation} \\ \text{of beta lactose to} \\ \text{alpha lactose} \end{array} \right] - \left[\begin{array}{c} \text{Rate of mutarotation} \\ \text{of alpha lactose to} \\ \text{beta lactose} \end{array} \right] \quad (4.14)$$

Expressing this in terms of a differential equation gives

$$\frac{dM_{\alpha}}{dt} = nA_c n_1 + k_2 C_{\beta} V_s - k_1 C_{\alpha} V_s \quad (4.15)$$

Substituting for the mass flux n_1 gives

$$\frac{dM_{\alpha}}{dt} = \frac{nA_c}{\frac{1}{k_r} + \frac{1}{k_L}} (C_{\alpha}^{\beta} - C_{\alpha}) + k_2 M_{\beta} - k_1 M_{\alpha} \quad (4.16)$$

As in the previous model, this must be solved in this form due to the changing nature of the volume of solution.

4.2.2.3 Beta lactose concentration

The beta lactose is determined with exactly the same equation as in the previous model. This gives a differential equation of

$$\frac{dM_{\beta}}{dt} = k_1 C_{\alpha} V_s - k_2 C_{\beta} V_s \quad (4.17)$$

4.2.3 Algebraic equations

All of the algebraic equations derived for the previous model apply for this model and can be found in section 3.2.3. These are for

- (i) Volume of solution
- (ii) Density of solution
- (iii) Alpha lactose solubility
- (iv) Mass transfer coefficient
- (v) Lactose concentrations.

4.2.4 System Inputs

All of the system inputs for the previous model apply to this model and can be found in section 3.2.4. These are

- (i) Crystal dimensions
- (ii) Volume of crystal
- (iii) Surface area of crystal
- (iv) Characteristic length
- (v) Sherwood Number
- (vi) Diffusivity
- (vii) Mutarotation rate constants
- (viii) Number of crystals in solution.

One additional system input has been added to the model. This is the surface disintegration reaction rate k_r . This system input is an empirical value and independent estimates of this at different temperatures could not be found from the literature. Instead, values of the surface disintegration reaction rate will be fitted to the experimental data using a least squares optimization procedure.

4.2.5 Initial Conditions

The initial conditions are the same as the previous model (section 3.2.5).

4.2.6 Summary of Model

The model can be summarized into the following equations

- (i) Ordinary Differential Equations.

$$-\frac{dD_c}{dt} = \frac{3.3219(C_{\alpha}^{\beta} - C_{\alpha})}{\rho_c \left(\frac{1}{k_r} + \frac{1}{k_L} \right)} \quad (4.18)$$

$$\frac{dM_{\alpha}}{dt} = \frac{3.3674nD_c^2}{\frac{1}{k_r} + \frac{1}{k_L}} (C_{\alpha}^{\beta} - C_{\alpha}) + k_2 M_{\beta} - k_1 M_{\alpha} \quad (4.19)$$

$$\frac{dM_{\beta}}{dt} = k_1 M_{\alpha} - k_2 M_{\beta} \quad (4.20)$$

- (ii) Algebraic Equations.

$$V_s = \frac{(M_i + 1.05684(M_{\alpha} + M_{\beta}))}{\rho_s} \quad (4.21)$$

$$\rho_s = m_1 C_i + c_1 \quad (4.22)$$

$$C_{\alpha}^{\beta} = C_{\alpha}^{\beta=0} - FC_{\beta} \quad (4.23)$$

$$k_L = \frac{Sh'D}{1.0500D_c} \quad (4.24)$$

$$C_\alpha = \frac{M_\alpha}{V_s} \quad (4.25)$$

$$C_\beta = \frac{M_\beta}{V_s} \quad (4.26)$$

$$C_i = \frac{M_\alpha + M_\beta}{V_s} \quad (4.27)$$

(iii) System Inputs.

- (a) Sherwood Number = 2.
- (b) $C_{\alpha}^{\beta=0}$ and F values Given in Table 1.6
- (c) Diffusivity Given in Table 3.1
- (d) Mutarotation rate E_a and A_0 given in Chapter 1, section 1.3.
- (e) Density coefficients m_i and c_i given in Table 2.3.

4.2.7 Solution of Model.

No analytical solution to the above model was attempted due to the changing nature of k_L with D_c . Instead, as in the previous model, the model was solved numerically using ESL, (Hay *et al* 1988) on an IBM compatible 386DX personal computer with a numeric maths coprocessor. Appendix A (Model 2a-2c) contains a listing of the programs used.

4.3 Surface Reaction Effect

The region where the previous model had shown discrepancies with experiential results was where mass transfer was assumed to be controlling, ie when the target concentration was below the alpha lactose solubility limit. This is the region where the modification to the model will be apparent, and all experiments to fit values of the surface reaction rate will be conducted in this region.

4.3.1 Experimental

It was required that the surface reaction rate be determined for a variety of temperatures to enable an Arrhenius plot to be produced and to determine where the surface reaction no longer has an effect on dissolution.

Experiments were carried out using the procedure given in section 2.3 in replicate at four different temperatures with the particle size fraction 150-210 μm and at six different temperatures with the particle size fraction 210-300 μm . Table 4.1 lists the experimental conditions for each run.

Table 4.1 Experimental conditions for surface reaction runs.

Temperature (°C)	Particle Size Fractions (μm)	Target Concentration (kg/m^3)	Lactose Added (kg anhydrous)
0	210-300	25.0	0.05085
15	150-210, 210-300	24.9	0.05074
25	150-210, 210-300	50.0	0.10377
37	210-300	100.0	0.21583
50	150-210, 210-300	123.9	0.27358
70	150-210, 210-300	201.3	0.47737

Measurements of the refractive index was carried out initially at one second intervals and after twenty seconds were carried out at two second intervals. The refractive index of the samples were measured at 25°C.

Data analysis on the results was carried out by the method given in section 2.3.2.3, giving total anhydrous lactose concentrations in kg/m^3 .

The crystal sizes were measured using a Malvern particle size analyser, v6.1. Tables C6 to C8 in Appendix C give the results of this.

4.3.2 Least squares fit to model

In order to evaluate the surface reaction rate constant at a given temperature, a method had to be derived to objectively estimate the surface reaction constant from the experimental data. A least squares fit of the model to the experimental data, involving calculating the residual sum of squares of the fit was decided upon. For the final fit achieved, the coefficient of determination R^2 was calculated for comparison to other fits.

The least squares fit involved the calculation of two statistical variables. These were

- (i) Residual Sum of Squares.
- (ii) Coefficient of Determination.

The sum of squares can be divided into two categories. These are the sum of squares due to the model, and the sum of squares due to errors or residues. Together these make up the total sum of squares.

The total sum of squares is defined as the sum of squares corrected for the mean. Expressing this in terms of an equation gives

$$\text{Total SS} = \sum_{i=1}^n (x_i - \bar{x})^2 \quad (4.28)$$

where n = Number of experimental points.

x_i = Measured experimental points.

$\bar{x}$ = Mean of experimental points.

The residual sum of squares is defined in terms of the difference between the estimated and measured values of the data. Expressing this in terms of an equation gives

$$\text{Residual SS} = \sum_{i=1}^n (x_i - \hat{x})^2 \quad (4.29)$$

where $\hat{x}$ = Estimated value of experimental points.

The sum of squares due to the model can be found from the difference between the Residual sum of squares and the Total sum of squares, ie

$$\text{Model SS} = \text{Total SS} - \text{Residual SS} \quad (4.30)$$

The coefficient of determination R^2 is commonly used to show how well the prediction agrees with the data. This is defined as follows

$$R^2 = \frac{\text{Model SS}}{\text{Total SS}} \quad (4.31)$$

Substituting for the Model sum of squares gives

$$R^2 = 1 - \frac{\text{Residual SS}}{\text{Total SS}} \quad (4.32)$$

4.3.2.1 Program

The least squares fit program developed involved an iterative approach to calculating the best fit value of the surface reaction rate k_r . High and low bounds for the reaction rate were used, with the calculations finishing when the difference between the upper and lower bounds were sufficiently small.

Figure 4.1 shows a structure diagram of the program. The variables shown on the figure and their definitions are as follows

k_r	Value of surface reaction rate used for calculation by the model.
HIGH_ k_r	Upper bound for the surface reaction rate.
LOW_ k_r	Lower bound for the surface reaction rate.
RESIDUAL_SS	Residual sum of squares calculated by the model.
HIGH_SS	Residual sum of squares for upper bound value of k_r .
LOW_SS	Residual sum of squares for lower bound value of k_r .
FLAG	Logical variable indicating which bound is being calculated in the current iteration.
ERROR	Finishing criteria for the least squares fit.

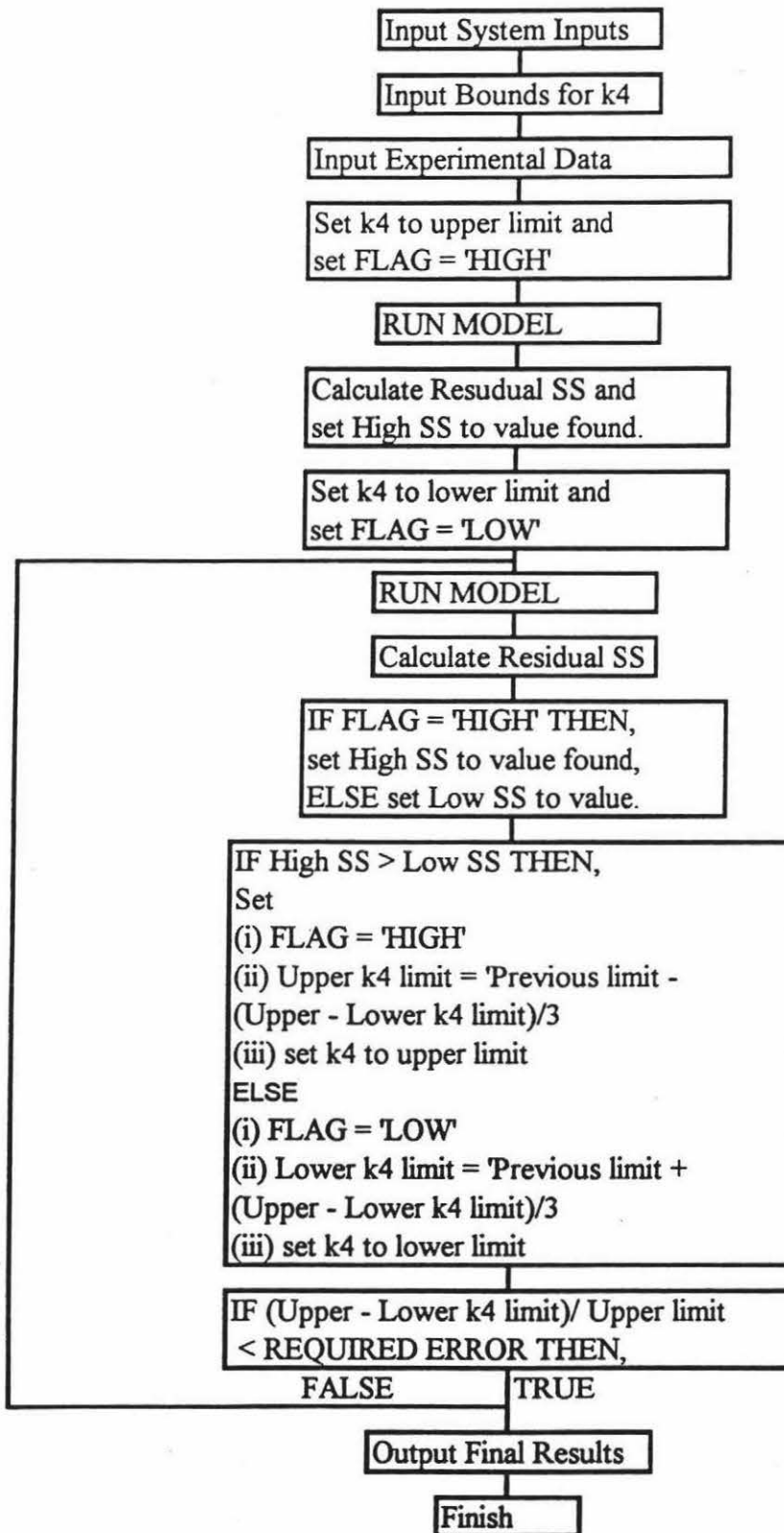


Figure 4.1 Structure diagram of ESL simulation program.

The program works by determining the residual sum of squares at the upper and lower bounds of k_r and depending on which is closer to the optimal value of k_r , the upper bound is decreased or the lower bound is increased. This process continues until the upper and lower bounds are within acceptable error bounds. The ESL program which does this can be found in Appendix A.

4.3.3 Determining Arrhenius Constants for Model

The experimental results for the runs from Table 4.1 can be found in Tables G1 to G10 in Appendix G. These consist of the measured refractive index along with the calculated total anhydrous lactose concentration in kg/m^3 .

Figures 4.2 and 4.3 show a comparison of the previous model to the experimental results at 70°C with two different particle sizes. It can be seen that the previous model fits the data well, indicating that any surface reaction that is occurring is sufficiently fast at this temperature to have no effect.

For each of the runs below 70°C , the least squares analysis was carried out to determine the best fit value of the surface reaction rate. Tables B3 to B8 in Appendix B give the system inputs used. Table 4.2 contains the results of this analysis, along with the coefficient of determination R^2 . A point to note from Table 4.2 is that the differing particle size does not significantly effect the fitted value of the surface reaction rate, indicating that as the particle size changes, the surface reaction rate does not change.

Figures 4.4 to 4.8 give examples of the effect of the surface reaction in comparison to the previous model for 0, 15, 25, 37, and 50°C using the average value of the surface reaction determined for each temperature. Here it is apparent that the addition of the surface reaction term, especially at low temperatures has greatly improved the fit of the model to the experimental data. At 37°C the duplicate run was unable to produce a surface reaction rate as the difference between the model without the surface reaction and with the surface reaction was small, as is apparent in Figure 4.7. This also occurred with the 50°C experiments.

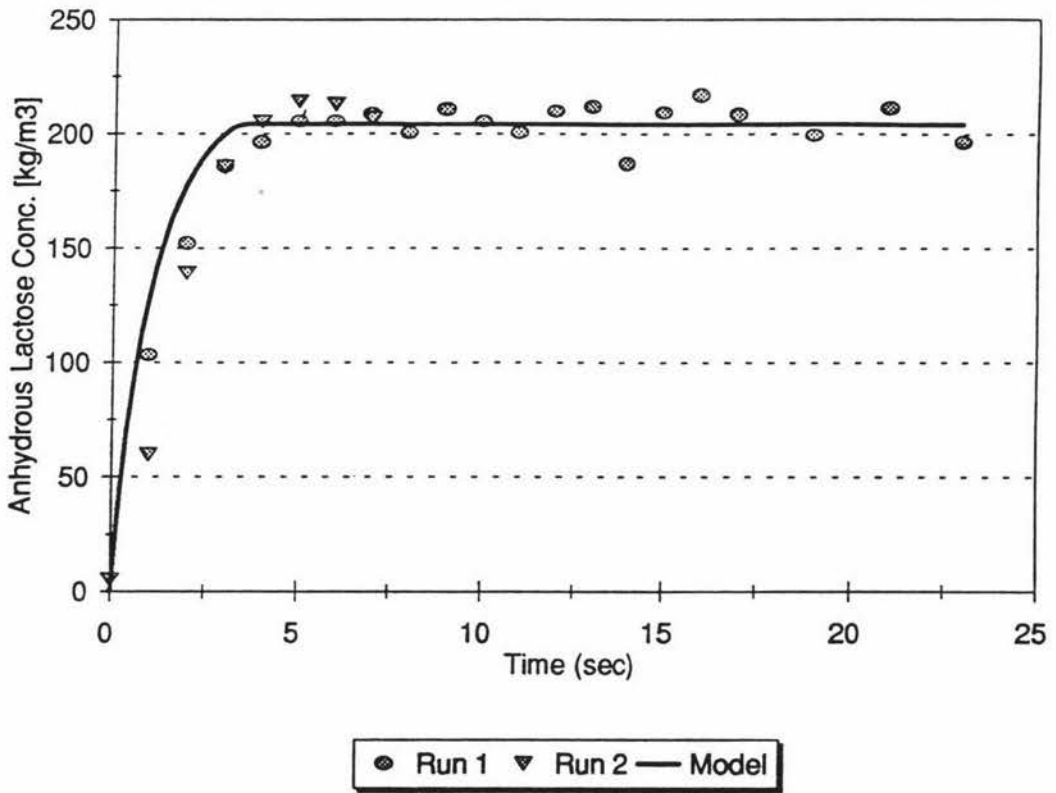


Figure 4.2 Dissolution of alpha lactose below the alpha lactose solubility limit. Operating conditions: 70°C, Final Concentration 205 kg/m³, Particle Size 150-210 µm.

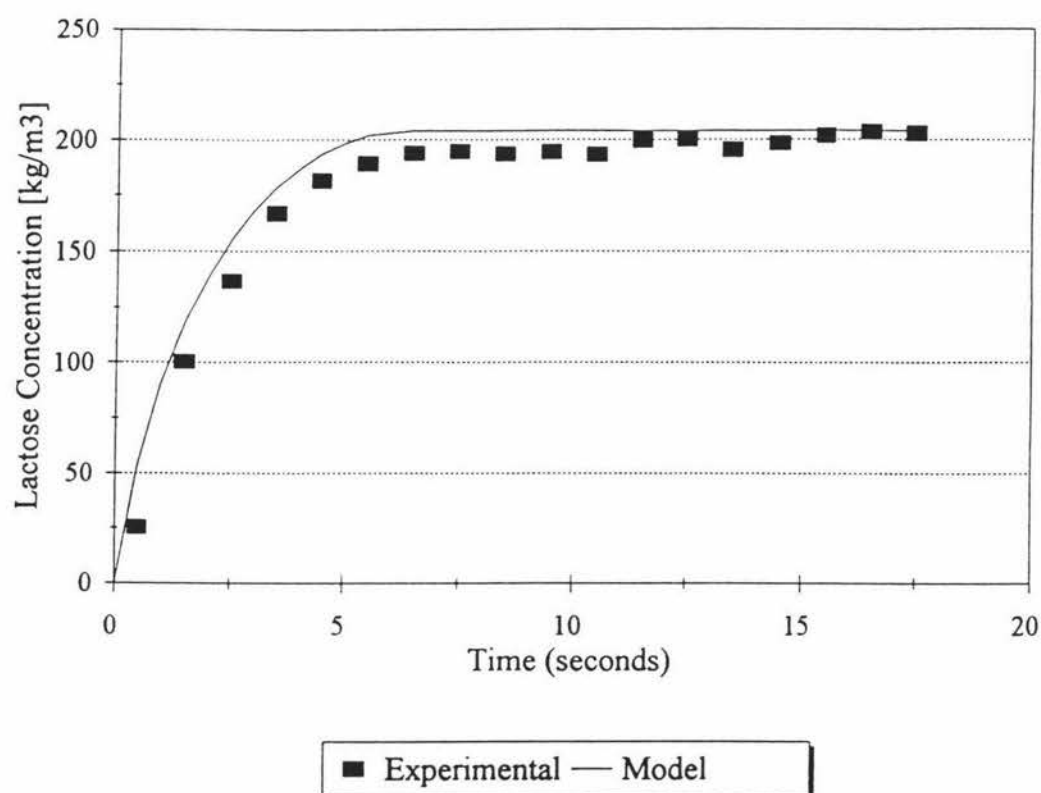


Figure 4.3 Dissolution of alpha lactose below the alpha lactose solubility limit. Operating conditions: 70°C, Final Concentration 205 kg/m³, Particle Size 210-300 μ m.

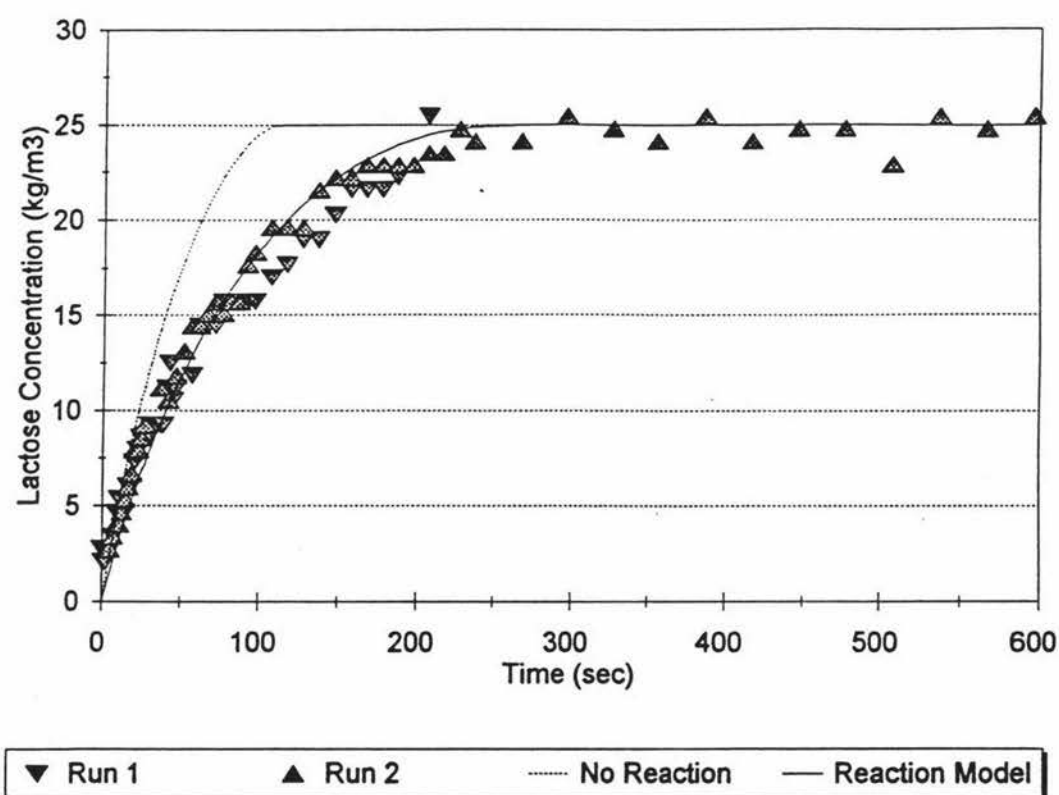


Figure 4.4 Comparison of surface reaction model prediction to experimental data for dissolution below the alpha lactose solubility limit. Operating conditions: 4°C, Final concentration 25 kg/m³, Particle size 210-300.

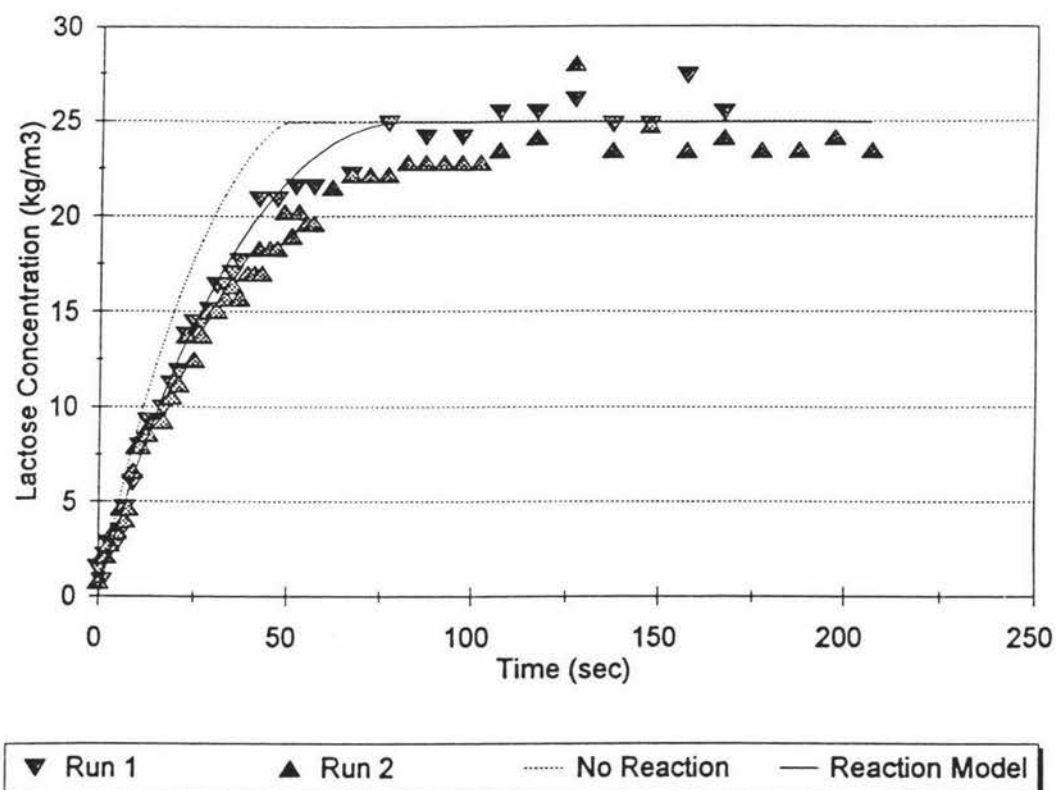


Figure 4.5 Comparison of surface reaction model prediction to experimental data for dissolution below the alpha lactose solubility limit. Operating conditions: 15°C, Final concentration 25 kg/m³, Particle size 210-300.

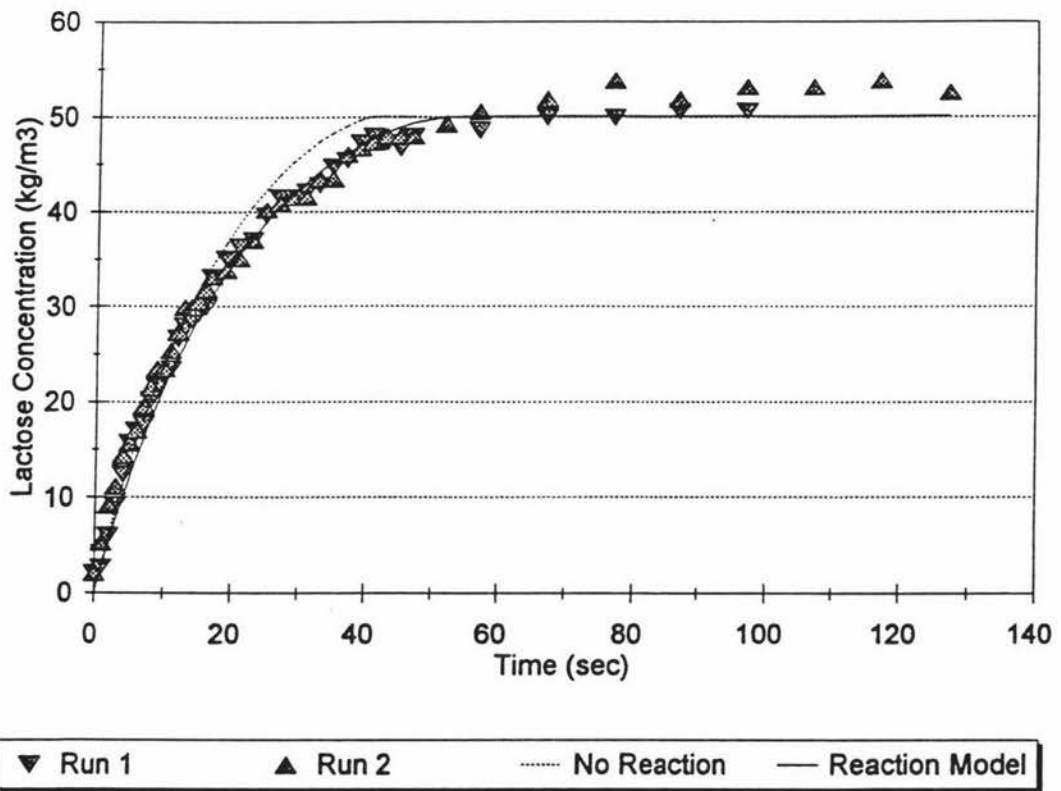


Figure 4.6 Comparison of surface reaction model prediction to experimental data for dissolution below the alpha lactose solubility limit. Operating conditions: 25°C, Final concentration 50 kg/m³, Particle size 210-300.

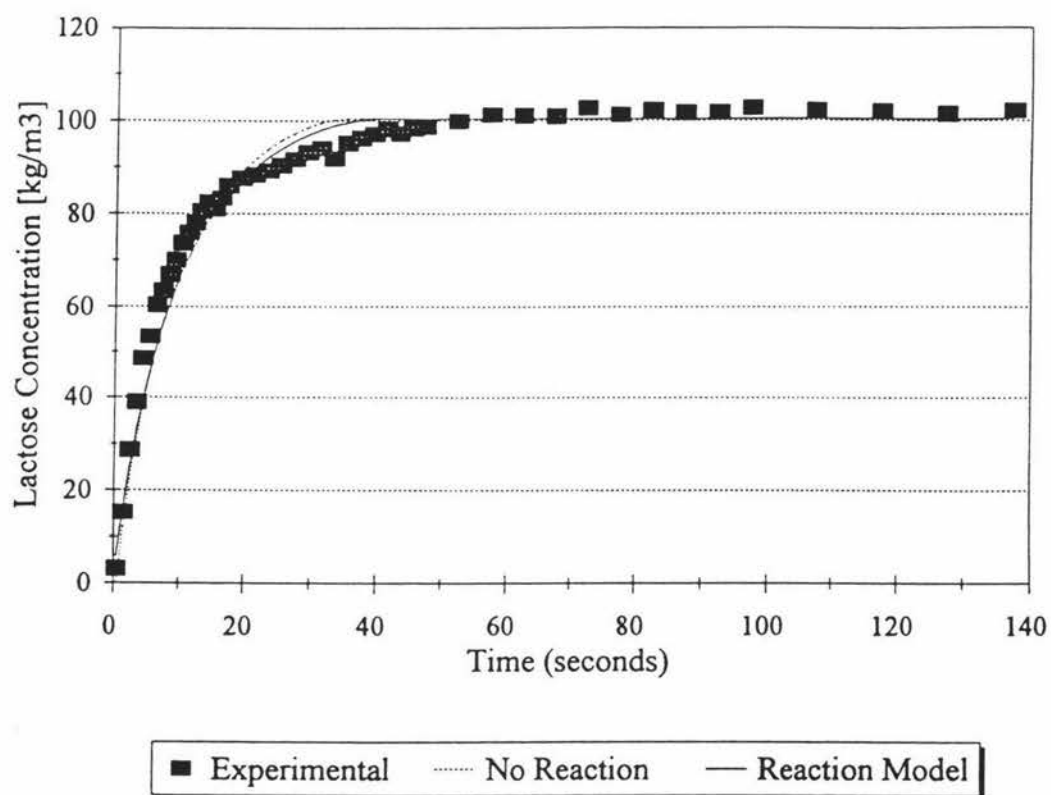


Figure 4.7 Comparison of surface reaction model prediction to experimental data for dissolution below the alpha lactose solubility limit. Operating conditions: 37°C, Final concentration 100 kg/m³, Particle size 210-300.

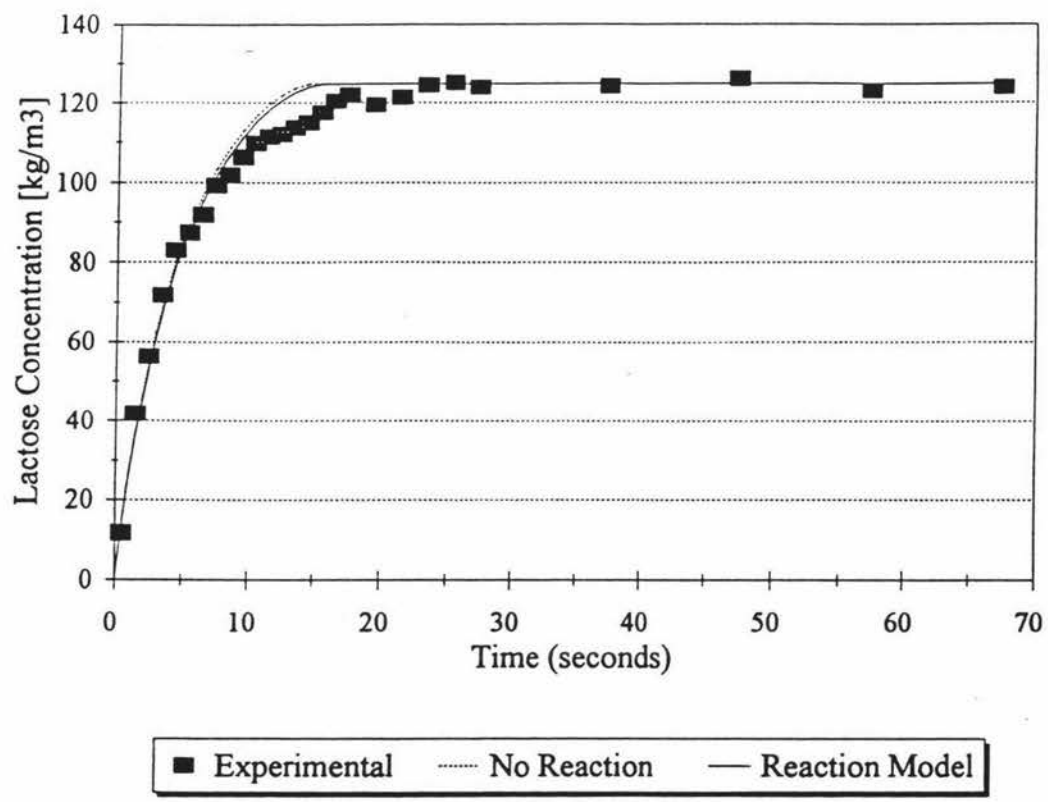


Figure 4.8 Comparison of surface reaction model prediction to experimental data for dissolution below the alpha lactose solubility limit. Operating conditions: 50°C, Final concentration 125 kg/m³, Particle size 210-300.

Table 4.2 Determined values of the surface reaction coefficient.

Temperature (°C)	Particle Size (µm)	Surface Reaction Rate (m/s) (×10 ⁻⁴)	R ²
4	210-300	0.2753	98.3%
4	210-300	0.2271	95.3%
15	150-210	0.5765	99.2%
15	150-210	0.8461	98.5%
15	210-300	0.6848	99.2%
15	210-300	0.4591	97.7%
25	150-210	4.760	99.4%
25	150-210	3.539	98.4%
25	210-300	2.877	99.2%
25	210-300	3.765	98.0%
37	210-300	3.467	98.5%
37	210-300	-	-
50	150-210	-	-
50	150-210	-	-
50	210-300	31.23	94.6%
50	210-300	9.696	97.6%

An Arrhenius plot of log of the surface reaction rate verses the inverse of the absolute temperature was prepared (Figure 4.9). A regression analysis was carried out on this using MINITAB v8.2 to examine for linearity. Table 4.3 gives a summary of this regression with full details of the regression analysis found in Table E9 in Appendix E. The results of this regression analysis indicate that a straight line can fit the Arrhenius plot, indicating that an Arrhenius type relationship in the discrepancy between the experimental results and the diffusion model does exist.

Using the values of the slope and intercept determined in the regression, the values of the Arrhenius constants E_a and A_a were determined to be

$$\begin{aligned}
 E_a &= 70,088.7 \text{ kJ/kgmol} \\
 A_a &= 4.19259 \times 10^8 \text{ m/s}
 \end{aligned}$$

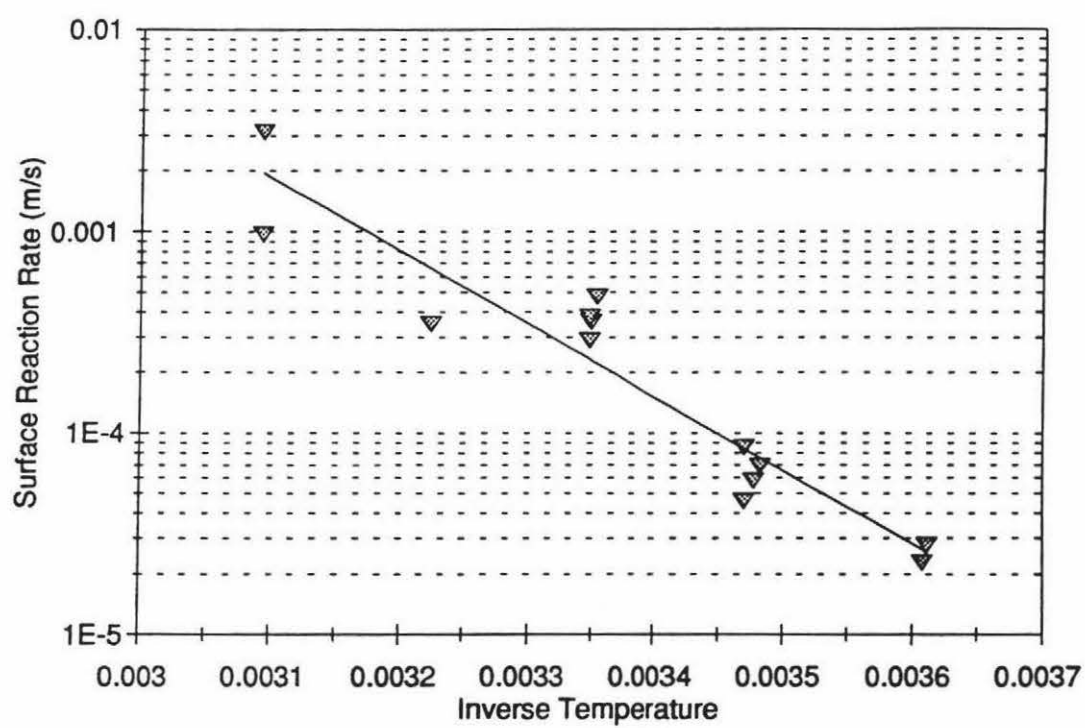


Figure 4.9 Arrhenius plot of fitted surface reaction rates.

Table 4.3 Summary of regression analysis for surface reaction.

Statistic	Value
Slope	-8430.2
Intercept	19.854
R^2	89.1%
$R^2(\text{adj})$	88.1%
Regression Sum of Squares	23.221
Error Sum of Squares	2.831
Total Sum of Squares	26.051

The effect of these Arrhenius constants on the predicted dissolution times can be seen in Table 4.4, along with the previous model predictions and the experimental results. At temperatures between 4 and 50 °C, the inclusion of the surface reaction rate has improved the prediction of the dissolution time. At 70°C, the surface reaction rate has no effect on the predicted rate of dissolution in comparison to the previous model as the reaction is sufficiently fast to be of no effect on dissolution.

Table 4.4 Predicted and experimental dissolution times at different temperatures and crystal sizes.

Temperature	Particle Size	Dissolution Time (sec)		
		Experimental	Surface Reaction Model	Dissolution Model
4	210-300	300	270.7	108.4
15	150-210	50	53.8	28.7
	210-300	85	82.6	49.7
25	150-210	35	34.1	23.8
	210-300	60	54.7	41.2
37	210-300	45	40.1	34.0
50	150-210	12	9.3	8.5
	210-300	25	15.7	14.7
70	150-210	5	3.5	3.5
	210-300	5	6.0	6.0

4.3.4 Surface Reaction versus Reduced Available Surface Area

A postulated reason for the discrepancy between the experimental and predicted results was a reduced available surface area for dissolution. This model is simply developed by including an available surface area factor f into the model developed in the previous chapter. This alters the differential equations for the crystal size and the alpha lactose concentration, giving the following differential equations

$$-\frac{dD_c}{dt} = \frac{k_L f a_1 (C_{\alpha}^{\beta} - C_{\alpha})}{3v_1\rho_c} \quad (4.33)$$

and

$$\frac{dM_{\alpha}}{dt} = k_L n f a_1 D_c^2 (C_{\alpha}^{\beta} - C_{\alpha}) + k_2 M_{\beta} - k_1 M_{\alpha} \quad (4.34)$$

where f = Available surface area fraction.

The differential equation for beta lactose concentration is unchanged from the equation developed in section 3.2.2.3. All algebraic equations developed in section 3.2.3 and system inputs developed in section 3.2.4 apply to this model.

Values of f can be fitted to the experimental data in the same manner in which surface reaction rates were fitted to the data in section 4.3.2. The program developed to find values of the available surface area can be found in Appendix A (Model 2c). Table 4.5 shows the results of this analysis with the fitted values of f at different temperatures and particle sizes. As with the model with the surface reaction rate included, this model shows consistency between different particle sizes in the fitted constant determined.

Figure 4.10 shows how the available surface area fraction changes with temperature. There is no simple explanation as to why the available surface area would change in this manner with temperature. This difficulty in explaining why and in what manner the available surface area factor increases with temperature places doubt on this model as a true representation of the physical system.

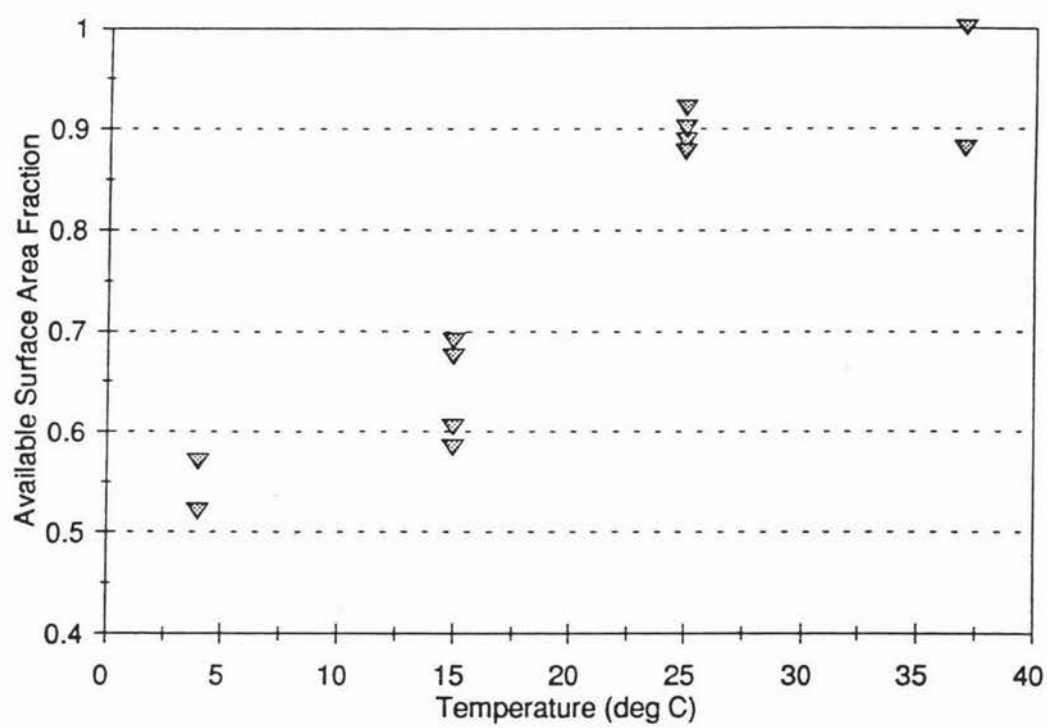


Figure 4.10 Effect of temperature on the fitted available surface area fraction.

Table 4.5 Fitted values of the available surface area coefficient.

Temperature (°C)	Particle Size (μm)	Available Surface Area Fraction.	R^2
4	210-300	0.5210	93.34%
4	210-300	0.5703	97.39%
15	150-210	0.6906	99.03%
15	150-210	0.6046	96.77%
15	210-300	0.5843	98.71%
15	210-300	0.6746	97.88%
25	150-210	0.8880	98.99%
25	150-210	0.9205	97.76%
25	210-300	0.9008	99.38%
25	210-300	0.8773	97.92%
37	210-300	0.8802	98.19%
37	210-300	1.0	96.30%

The fit provided by the available surface area fraction is not an improvement on the surface reaction model, making the added complexity of the available surface area model unnecessary to explain the difference between the experimental and predicted results.

4.3.5 Nomograph

It is possible to express the predicted dissolution times under different operating conditions in the form of a nomograph. The operating conditions that affect the dissolution times are temperature, final lactose concentration, and particle size.

Figures 4.13 to 4.18 show nomographs of lactose dissolution with temperature and final concentration at the particle sizes 50, 100, 150, 200, 300 and $400 \times 10^{-6}\text{m}$. This was generated using Model 2d in Appendix A, using the system inputs in Table B9 in Appendix B.

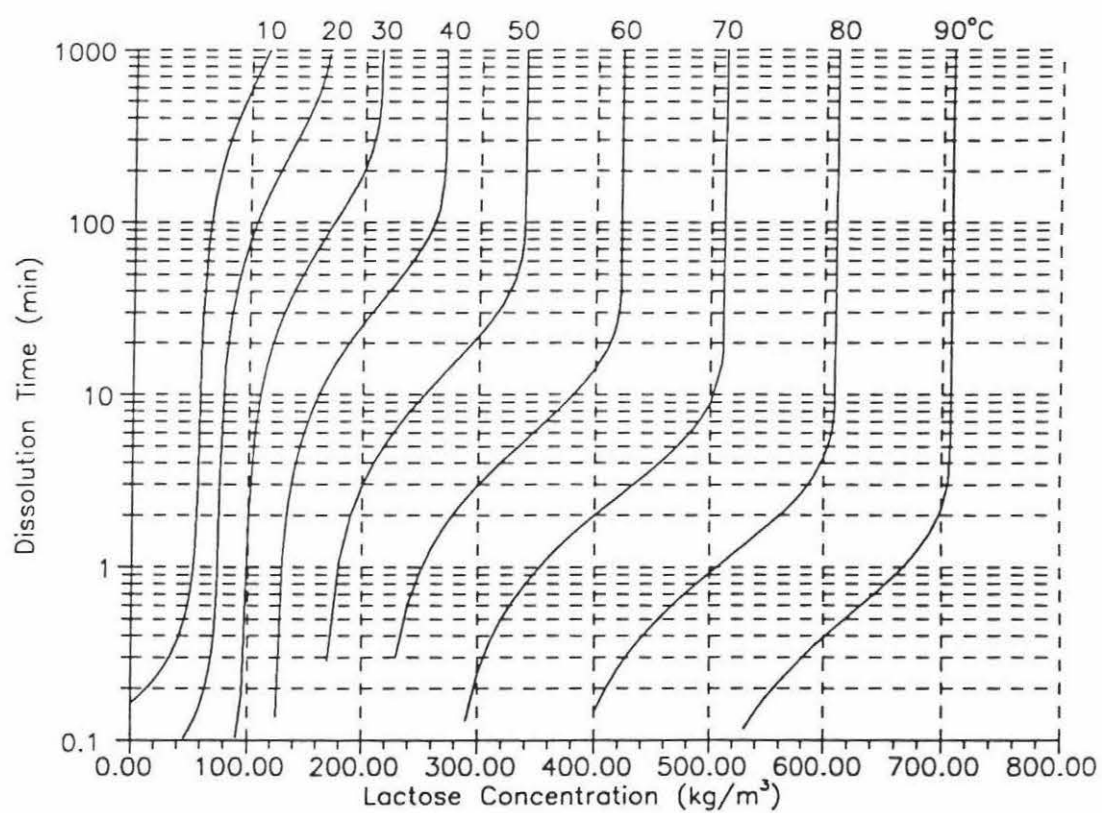


Figure 4.11 Nomograph of lactose dissolution times in distilled water with particle size $50 \times 10^{-6} \text{ m}$.

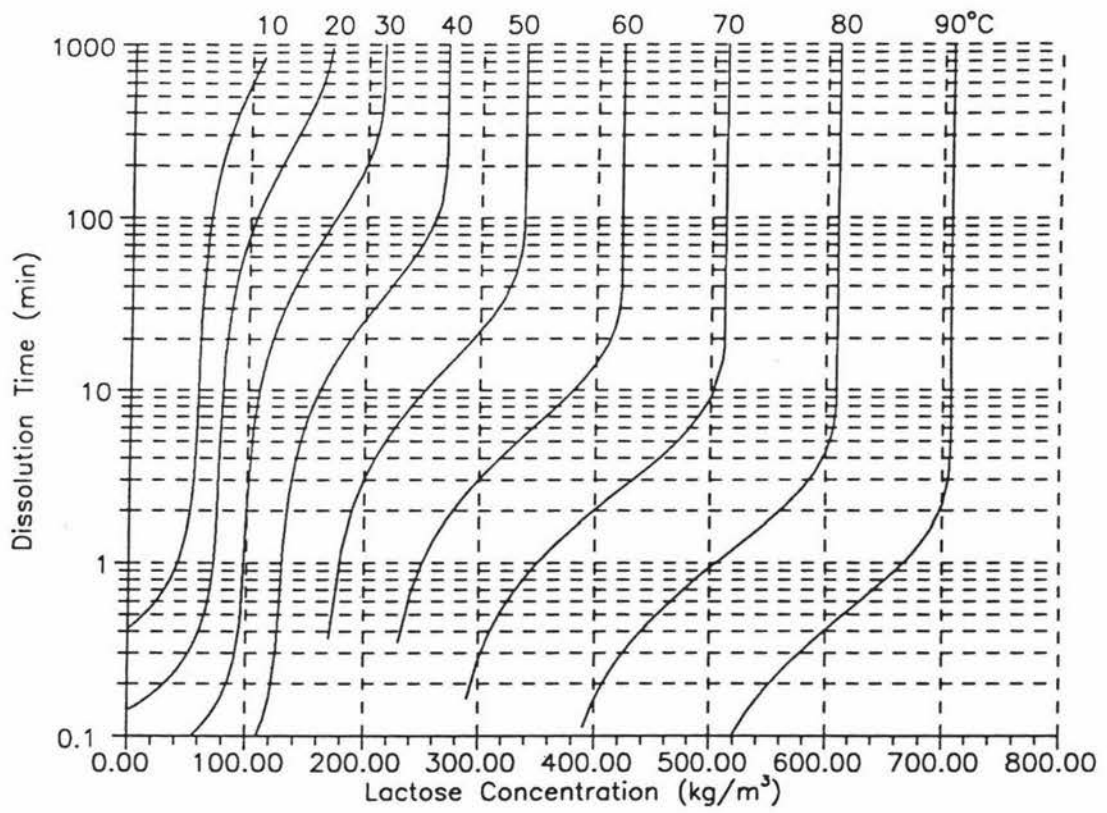


Figure 4.12 Nomograph of lactose dissolution times in distilled water with particle size $100 \times 10^{-6} \text{m}$.

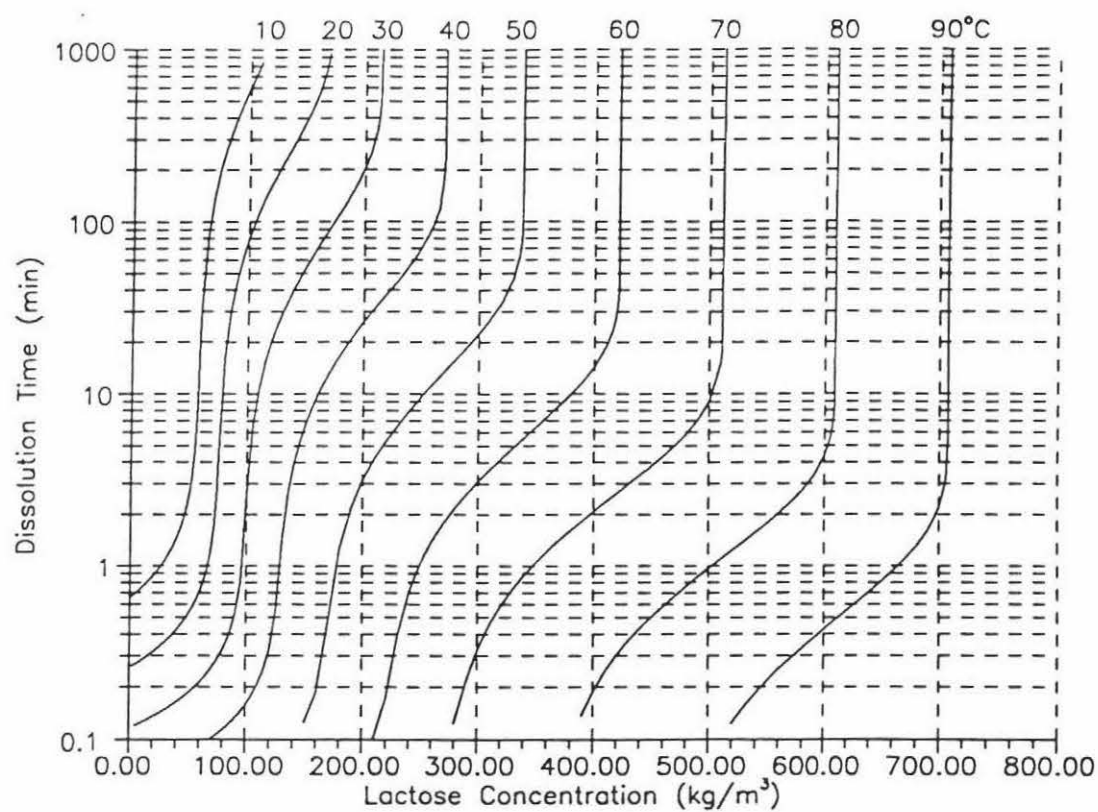


Figure 4.13 Nomograph of lactose dissolution times in distilled water with particle size $150 \times 10^{-6} \text{ m}$.

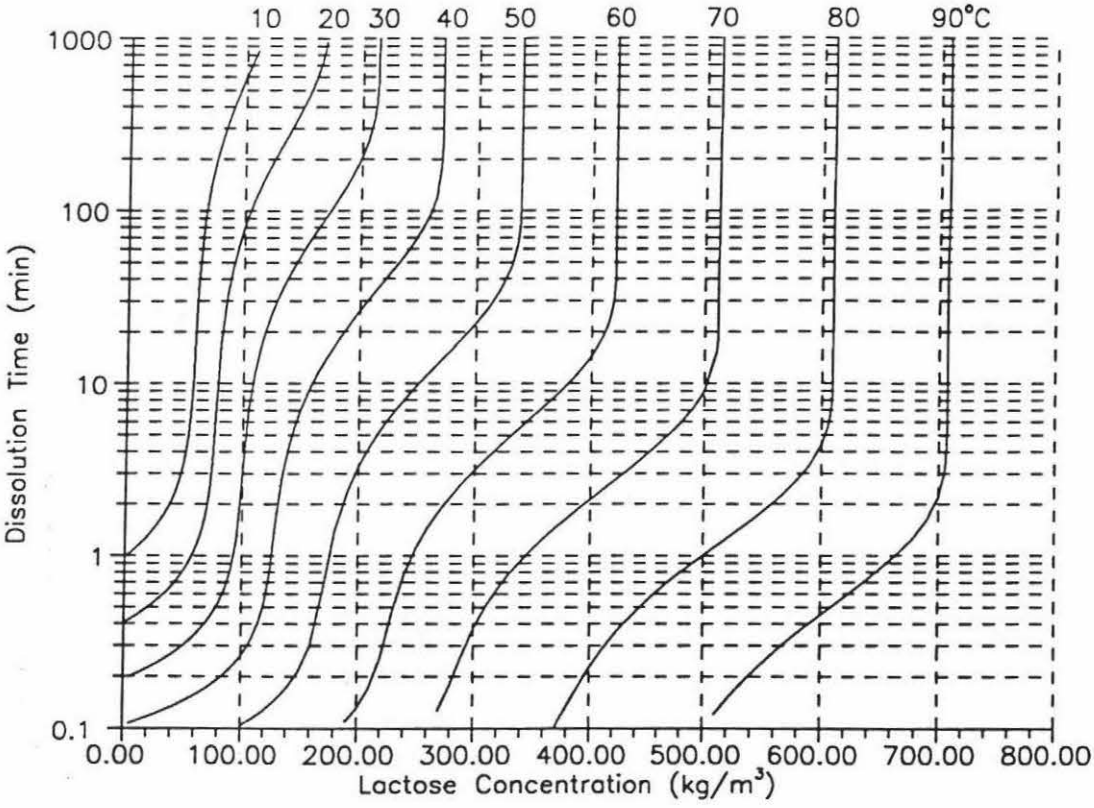


Figure 4.14 Nomograph of lactose dissolution times in distilled water with particle size $200 \times 10^{-6} \text{m}$.

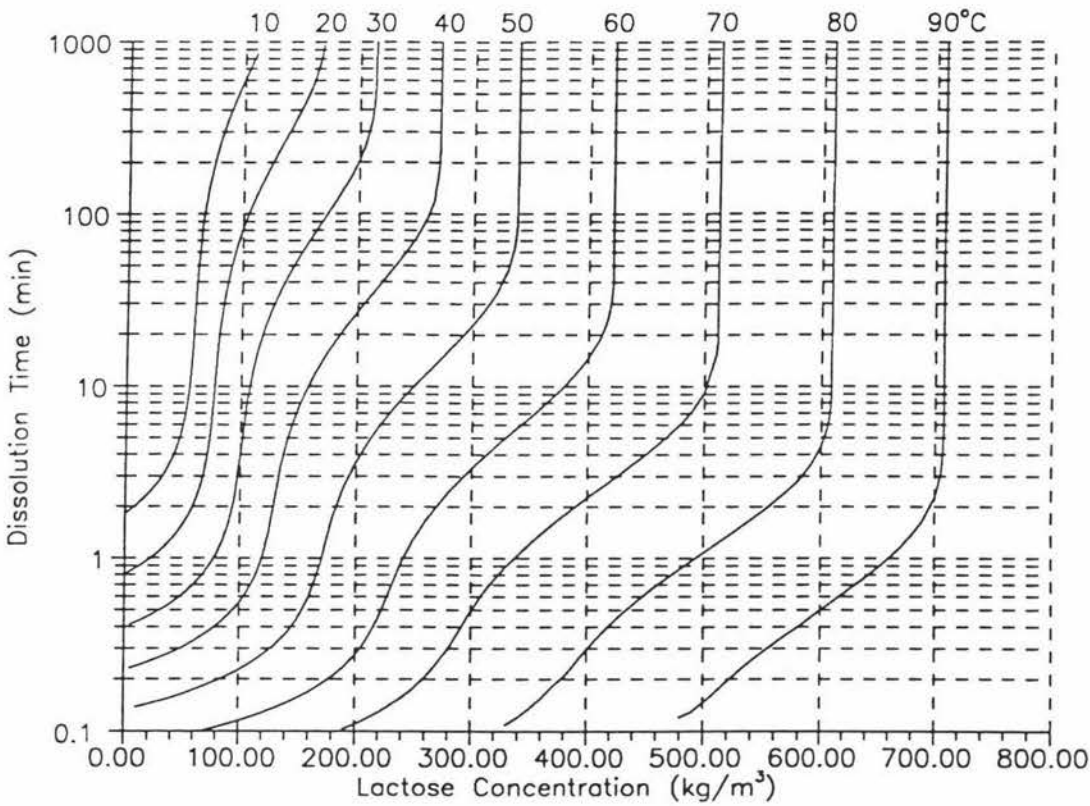


Figure 4.15 Nomograph of lactose dissolution times in distilled water with particle size $300 \times 10^{-6} \text{m}$.

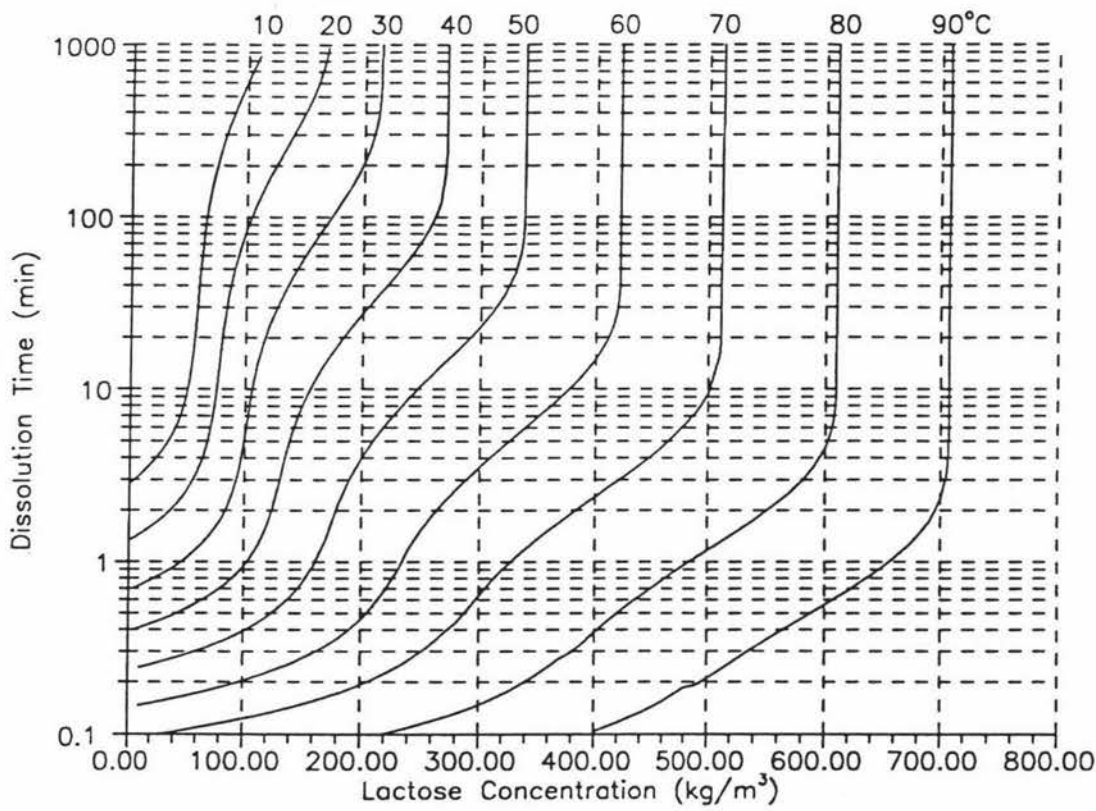


Figure 4.16 Nomograph of lactose dissolution times in distilled water with particle size $400 \times 10^{-6} \text{m}$.

4.4 Conclusions

The model developed in Chapter 3 was improved by adding to the model a first order surface disintegration reaction. The rates of the surface reaction could not be determined from the literature or by first principles. Instead, the surface reaction rates were determined by a least squares fitting procedure.

Surface reaction rates were evaluated for a variety of temperatures and at two particle sizes to determine whether an Arrhenius relationship was followed by the rates and to see if particle size affected the predicted rates. The initial particle size was found to have no effect on the fitted surface reaction rate, showing that the rates determined were not dependant on particle size. The surface reaction rates obtained followed an Arrhenius relationship, giving Arrhenius constants of

$$E_s = 70,088.7 \text{ kJ/kgmol}$$

$$A_s = 4.19259 \times 10^8 \text{ m/s}$$

The model was expressed in nomograph form to enable quick estimates of dissolution times to be made.

In conclusion the model including the first order surface disintegration reaction explained the discrepancy between the experimental and predicted results below the alpha lactose solubility limit. The nomographs produced enable predictions of the dissolution of single particle fractions of alpha lactose to be made for all regions of dissolution.

CHAPTER 5

Model 3: Effect of crystal size mixtures on dissolution

5.1 Introduction

The previous model developed in Chapter 4 was found to predict the dissolution of lactose in all regions with a fair degree of accuracy. However, the model was based on the assumption that dissolution occurred with one single crystal size. With the sieved fractions used in earlier experiments this did not appear to be a problem. However, commercial grade lactose is not sieved before it is dissolved and may consist of a wide range of crystal sizes. The effect of this on the predicted dissolution times is not known and in these cases it may be necessary to model dissolution with several different crystal sizes.

The previous model predicted that the initial crystal size only affects dissolution below the alpha lactose solubility limit, suggesting that crystal mixtures will only have effect on dissolution below the alpha lactose solubility limit. This assumption needs to be verified.

5.2 Model Formulation

5.2.1 Physical system

The physical system for dissolution in this model is the same as that for Chapters 3 and 4. However, different assumptions have been made in the formulation of the model.

5.2.1.1 Model assumptions

As in the previous models, mass transfer from the surface of the crystal was considered to be diffusion into a stagnant medium. The surface disintegration reaction was included into the model.

The previous models assumed that only one single crystal size was added to the solution. This assumption will not be made in this case, and the general form for dissolution will be derived.

The assumptions made can be summarized as follows

- (i) The surface disintegration step occurred as a first order chemical reaction.
- (ii) Lactose crystal geometry remained constant throughout dissolution.
- (iii) All crystal surface area was available for dissolution.
- (iv) Constant temperature occurred throughout dissolution.
- (v) Perfectly mixed system.
- (vi) Mutarotation can be described by a first order rate constants.
- (vii) Constant Sherwood number throughout dissolution.
- (viii) Alpha lactose solubility affected by beta lactose in a linear manner.

5.2.2 Differential Equations

5.2.2.1 Lactose crystal size

The formulation for the lactose crystal size for this model is very similar to that developed for the previous model in section 4.2.2.1, the difference being that the equation will be generalized for many crystal sizes.

The basis of the lactose crystal size reduction equation was determined by performing as in section 4.2.2.1 a mass balance around a single lactose crystal. Expressing this in terms of a differential equation gives

$$-\frac{dM_{ci}}{dt} = N_i A_{ci} \quad (5.1)$$

where M_{ci} = Mass of lactose crystal i (kg)

N_i = Mass transfer flux for crystal i (kg/m².s)

A_{ci} = Surface area of crystal i (m²)

The mass transfer flux can be defined in terms of the surface reaction rate and the mass transfer rate giving

$$N_i = \frac{1}{\frac{1}{k_r} + \frac{1}{k_{Li}}} (C_{\alpha}^{\beta} - C_{\alpha}) \quad (5.2)$$

where k_{Li} = Mass transfer coefficient for crystal i (m/s)

Substituted the above equation into the overall equation gives

$$-\frac{dM_{ci}}{dt} = \frac{A_{ci}}{\frac{1}{k_r} + \frac{1}{k_{Li}}} (C_{\alpha}^{\beta} - C_{\alpha}) \quad (5.3)$$

Expressing this in terms of the characteristic dimension of the crystal gives

$$-3v_1\rho_c D_{ci}^2 \frac{dD_{ci}}{dt} = \frac{a_1 D_{ci}^2}{\frac{1}{k_r} + \frac{1}{k_{Li}}} (C_{\alpha}^{\beta} - C_{\alpha}) \quad (5.4)$$

which can be rearranged to give

$$-\frac{dD_{ci}}{dt} = \frac{a_1 (C_{\alpha}^{\beta} - C_{\alpha})}{3v_1\rho_c \left(\frac{1}{k_r} + \frac{1}{k_{Li}} \right)} \quad (5.5)$$

where D_{ci} = Characteristic dimension of lactose crystal i (m)

For each different crystal size used in the model, a differential equation of the form above must be used to predict the change in crystal size with time.

5.2.2.2 Alpha lactose concentration

The alpha lactose concentration in the bulk solution was determined, as before, by performing a mass balance of alpha lactose around the system, which can be worded as follows

$$\left[\begin{array}{c} \text{Rate of accumulation} \\ \text{of alpha lactose in} \\ \text{bulk solution.} \end{array} \right] = \left[\begin{array}{c} \text{Rate of mass transfer} \\ \text{of alpha lactose from} \\ \text{crystal surface} \end{array} \right] + \left[\begin{array}{c} \text{Rate of mutarotation} \\ \text{of beta lactose to} \\ \text{alpha lactose} \end{array} \right] - \left[\begin{array}{c} \text{Rate of mutarotation} \\ \text{of alpha lactose to} \\ \text{beta lactose} \end{array} \right] \quad (5.6)$$

Expressing this in terms of a differential equation is made complex by the different crystal sizes as the total area for dissolution is the sum of all crystal sizes. This gives a differential equation of the form

$$\frac{dM_{\alpha}}{dt} = \int_{D_{i=1}}^{D_{i=N}} (nA_i N_i) dD_i + k_2 C_{\beta} - k_1 C_{\alpha} V_s \quad (5.7)$$

Expressing the integral in a discrete form gives

$$\frac{dM_\alpha}{dt} = \sum_{i=1}^m (n_i A_{ci} N_i) + k_2 C_\beta - k_1 C_\alpha V_s \quad (5.8)$$

where m = Number of different crystal sizes.

n_i = Number of crystals at size D_{ci} .

Substituting for the mass transfer flux gives

$$\frac{dM_\alpha}{dt} = \sum_{i=1}^m \left(\frac{n_i A_{ci}}{\frac{1}{k_r} + \frac{1}{k_{Li}}} \right) (C_{\alpha s}^\beta - C_\alpha) + k_2 C_\beta - k_1 C_\alpha V_s \quad (5.9)$$

5.2.2.3 Beta lactose concentration

The beta lactose is determined with exactly the same equation as in the previous model. This gives a differential equation of

$$\frac{dM_\beta}{dt} = k_1 C_\alpha V_s - k_2 C_\beta V_s \quad (5.10)$$

5.2.3 Algebraic equations

All of the algebraic equations derived for the previous model apply for this model and can be found in section 3.2.3. These are for

- (i) Volume of solution
- (ii) Density of solution
- (iii) Alpha lactose solubility
- (iv) Mass transfer coefficient
- (v) Lactose concentrations.

A mass transfer coefficient must be determined for each separate crystal size.

5.2.4 System Inputs

All of the system inputs for the previous models apply to this model and can be found in section 3.2.4. These are

- (i) Crystal dimensions
- (ii) Volume of crystal
- (iii) Surface area of crystal
- (iv) Characteristic length
- (v) Sherwood Number
- (vi) Diffusivity
- (vii) Mutarotation rate constants

The arrhenius constants for the surface reaction can be found in section 4.3.3.

The number of lactose crystals at the start of dissolution is defined depending on how the different crystal fractions reported. The number of crystals at a particular size can be defined in two ways

- (i) Percent of mass of lactose.
- (ii) Percentage of the total number of crystals.

5.2.4.1 Number of crystal (fraction of total mass)

The number of crystals at a particular crystal size is defined by the following equation when the mass fraction of lactose at each size is known

$$n_i = \frac{x_i \bar{M}_c}{\rho_c V_{ci}} \quad (5.11)$$

where x_i = Mass fraction of lactose at crystal size D_{ci} .

This is of use when a sieve analysis has been carried out.

5.2.4.2 Number of crystals (fraction of total number)

The number of crystals at a particular size is defined by the following equation when the total number fraction at each size is known

$$n_i = \frac{p_i M_c}{\sum_{i=1}^m (p_i \rho_c V_{ci})} \quad (5.12)$$

p_i = Number fraction of lactose at crystal size D_{ci} .

5.2.5 Initial Conditions

The initial conditions are the same as the previous model (section 3.2.5).

5.2.6 Summary of Model

The model is summarized by the following equations

(i) Ordinary Differential Equations.

$$-\frac{dD_{ci}}{dt} = \frac{a_1 (C_{\alpha}^{\beta} - C_{\alpha})}{3v_1 \rho_c \left(\frac{1}{k_r} + \frac{1}{k_{Li}} \right)} \quad (5.13)$$

where i = 1 to m

m = Number of crystal sizes in lactose added.

$$\frac{dM_{\alpha}}{dt} = \sum_{i=1}^m \left(\frac{n_i A_{ci}}{\frac{1}{k_r} + \frac{1}{k_{Li}}} \right) (C_{\alpha}^{\beta} - C_{\alpha}) + k_2 C_{\beta} V_s - k_1 C_{\alpha} V_s \quad (5.14)$$

$$\frac{dM_{\beta}}{dt} = k_1 M_{\alpha} - k_2 M_{\beta} \quad (5.15)$$

(ii) Algebraic Equations.

$$V_s = \frac{(M_i + 1.05684(M_\alpha + M_\beta))}{\rho_s} \quad (5.16)$$

$$\rho_s = m_1 C_i + c_1 \quad (5.17)$$

$$C_{\alpha}^{\beta} = C_{\alpha}^{\beta=0} - F C_{\beta} \quad (5.18)$$

$$k_{Li} = \frac{Sh'D}{1.0500D_{ci}} \quad (5.19)$$

$$C_{\alpha} = \frac{M_{\alpha}}{V_s} \quad (5.20)$$

$$C_{\beta} = \frac{M_{\beta}}{V_s} \quad (5.21)$$

$$C_i = \frac{M_{\alpha} + M_{\beta}}{V_s} \quad (5.22)$$

(iii) System Inputs.

(a) Sherwood Number = 2.

(b) $C_{\alpha}^{\beta=0}$ and F values; Given in Table 1.6

(c) Diffusivity; Given in Table 3.1

(d) Mutarotation rate; E_a and A_0 given in Chapter 1, section 1.3

(e) Density coefficients m_i and c_i given in Table 2.3.

(f) Surface Reaction rate; E_s and A_s given in Chapter 4, section 4.3.3

5.2.7 Solution of Model

No analytical solution to the above model was attempted due to the changing nature of k_L with D_c . Instead, as in the previous model, the model was solved numerically using ESL, (Hay *et al* 1988) on an IBM compatible 386DX personal computer with a numeric maths coprocessor operating at 25 MHz. Appendix A (Models 3a and 3b) contains a listing of the program used.

5.3 Validation of Model

After the model has been formulated, it is necessary to test the validity of the model. This is done by comparing the predictions of the model against experimental results. By constructing an artificial mixture of lactose where the lactose crystal size distribution is accurately known, the model predictions can be easily verified.

5.3.1 Dissolution of mixtures below the alpha solubility limit

In the previous model it was found that below the alpha lactose solubility limit the crystal size had a significant effect on the dissolution of alpha lactose. It is expected that if any effect of mixtures occurs, it will be present below the alpha lactose solubility limit.

5.3.1.1 Experimental

Two different lactose mixtures were constructed, consisting of mixtures from three different sieve fractions; 105-150 μm , 150-210 μm , and 210-300 μm , to give a final concentration of 50 kg/m³ at 25°C. The two mixtures consisted of;

- (i) Equal masses of each fraction.
- (ii) Equal initial surface area for each fraction.

Table 5.1 shows the mass of each fraction required to give the above mixtures.

Experiments were carried out using the procedure given in section 2.3 of the methods in replicate at 25°C. Measurement of the refractive index was carried out at 20°C at time intervals of one second for the first twenty seconds, and then two seconds until dissolution was finished. Data analysis of the results was carried out by the method given in section 2.3.2.3 in the methods, giving total anhydrous lactose concentration in kg/m³.

The crystal size for each fraction was determined using a Malvern particle size analyser v6.1. Tables C6 to C8 in Appendix C show the results of this analysis.

Table 5.1 Fractions required for mixture dissolution experiment below the alpha lactose solubility limit.

Crystal Fraction	Crystal Size (μm)	Equal Mass Mixture (kg monohydrate)	Equal Surface Area Mixture (kg monohydrate)
105-150	144.14	0.036447	0.025786
150-210	216.31	0.036447	0.034486
210-300	284.54	0.036447	0.049069
Total		0.109342	0.109342

The average crystal size for each mixture was calculated knowing the volume occupied by each crystal and the density of the crystals. This gave the following average crystal sizes;

- (i) Equal Mass Mixture = 171.9 μm
- (ii) Equal Area Mixture = 182.6 μm

5.3.1.2 Results and Discussion

Tables H3 to H4 in Appendix H contain the results of the experiments carried out and consist of the measured refractive index and the corresponding calculated total lactose concentration in kg of anhydrous lactose per m³ of solution. The data analysis of the refractive indices was carried out by the method given in section 2.3.2.3, giving total

anhydrous lactose concentrations in kg lactose per m³ of solution. The model developed in section 5.2 was run at 25°C with the system inputs found in Tables B10 and B11 (Appendix B). The resulting lactose concentrations can be found in Tables H3 and H4 (Appendix H).

Figures 5.1 and 5.2 show a comparison of the experimental runs below the alpha lactose solubility limit to the model predictions. An average crystal size comparison using the previous model is also shown. The figures show that there is good agreement between the experimental results and the prediction using the multiple crystal size model.

The average crystal size using the previous model does not produce as good an agreement with the experimental results as the multiple crystal size model and appears to over predict the rate of dissolution. This is most apparent in the predicted dissolution times in Table 5.2. This is due to the dominating effect of the large crystals at the latter stage of dissolution, which indicates that a single crystal size model may not give an accurate prediction for mixed crystal fractions below the alpha lactose solubility limit.

Table 5.2 Dissolution times for dissolution below the alpha lactose solubility limit.

	Dissolution Times	
	Constant Mass	Constant Area
Observed dissolution Time	35.0 sec	45.0 sec
Predicted (Average crystal size)	26.8 sec	29.7 sec
Predicted (multiple crystal size)	72.9 sec	71.0 sec

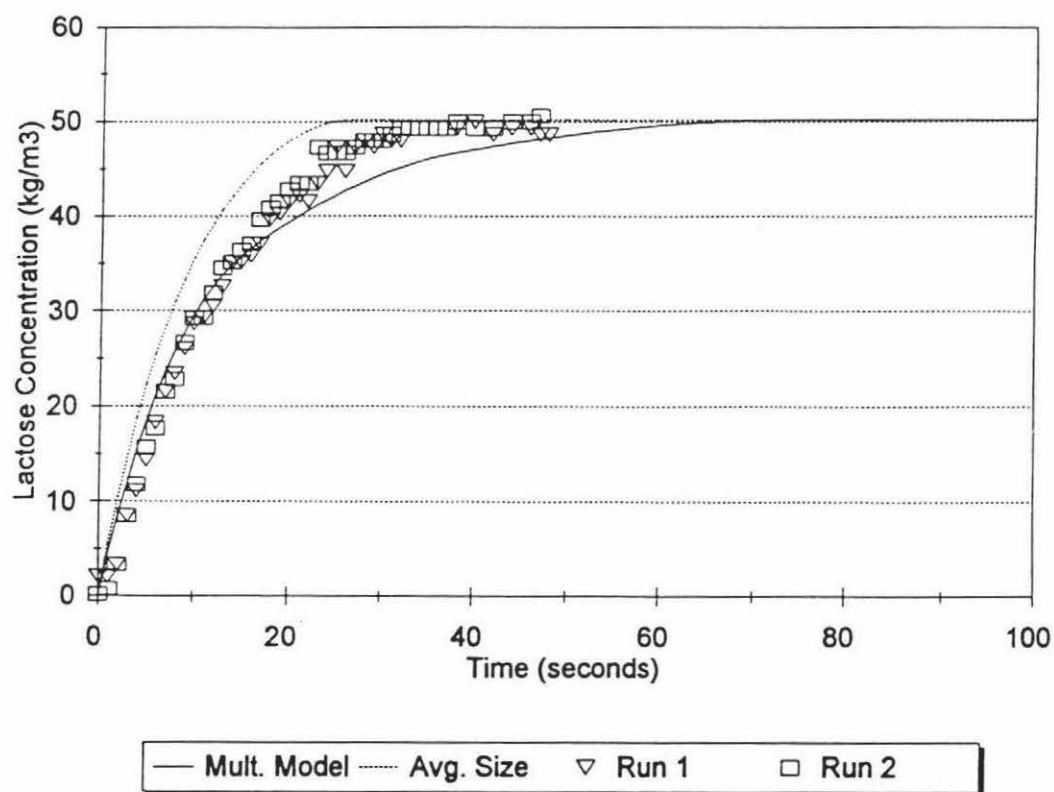


Figure 5.1 Comparison of multiple crystal size and average crystal size models to experimental data for dissolution of alpha lactose below the alpha lactose solubility limit with equal mass fractions. Operating Conditions: 25°C, Final concentration 50 kg/m³ (anhydrous), Fraction 105-150 μm - 0.036447 kg monohydrate, Fraction 150-210 μm - 0.036447 kg monohydrate, Fraction 210-300 μm - 0.036447 kg monohydrate.

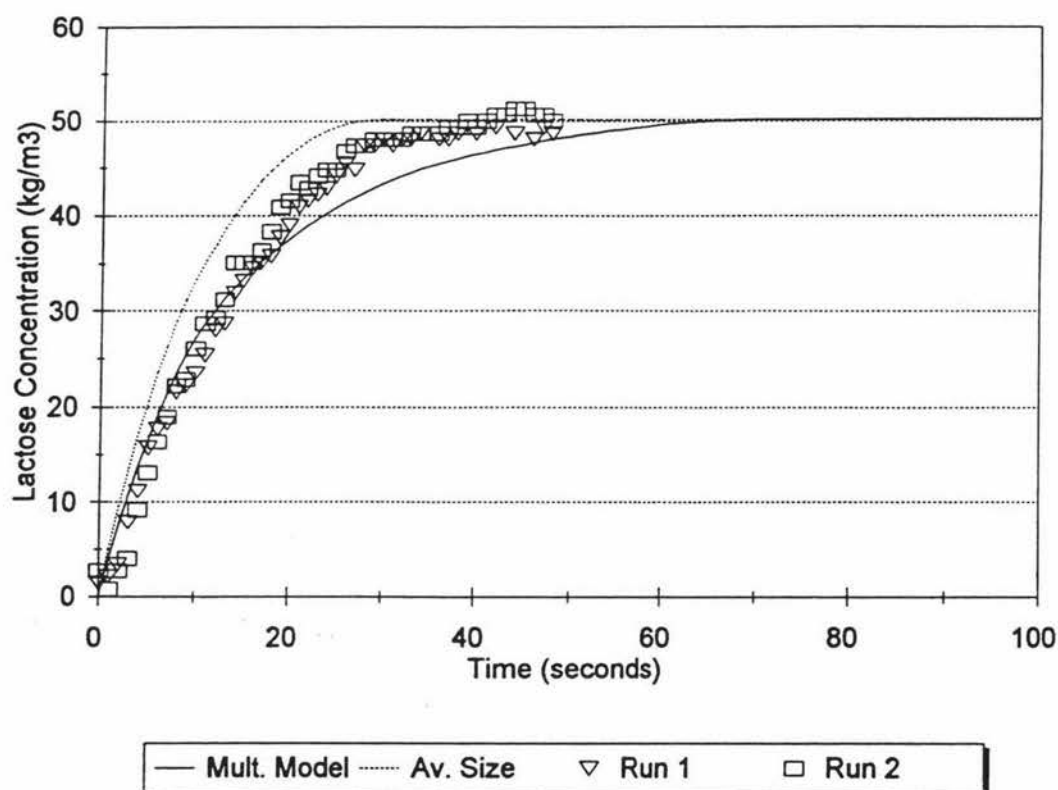


Figure 5.2 Comparison of multiple crystal size and average crystal size models to experimental data for dissolution of alpha lactose below the alpha lactose solubility limit with equal area fractions. Operating Conditions: 25°C, Final concentration 50 kg/m³ (anhydrous), Fraction 105-150 μm - 0.024401 kg monohydrate, Fraction 150-210 μm - 0.032634 kg monohydrate, Fraction 210-300 μm - 0.046433 kg monohydrate.

5.3.2 Dissolution of mixtures above the alpha solubility limit

For dissolution above the alpha lactose solubility limit, it is expected that the crystal size should not have a significant effect on the dissolution time. A single crystal size model should therefore produce as good a prediction as a multiple crystal size model in this region.

5.3.2.1 Experimental

As in the previous experiment, two different lactose mixtures were constructed. These consisted of mixtures from three different sieve fractions; 105-150 μm , 150-210 μm , and 210-300 μm , to give a final concentration of 150 kg/m^3 at 25°C which is above the alpha lactose solubility limit. The two mixtures consisted of equal masses and equal surface area of each fraction. Table 5.3 shows the mass of each fraction required to give the above mixtures.

Experiments were carried out using the procedure given in section 2.3 of the methods in replicate at 25°C. Measurement of the refractive index was carried out at 20°C at time intervals of five seconds for the first minute, ten seconds for the next minute then at one, two and finally at five minute intervals until dissolution was finished.

Table 5.3 Fractions required for mixture dissolution experiment above the alpha lactose solubility limit.

Crystal Fraction	Crystal Size (μm)	Equal Mass Mixture (kg monohydrate)	Equal Surface Area Mixture (kg monohydrate)
105-150	144.14	0.117474	0.08311
150-210	216.31	0.117474	0.11115
210-300	284.54	0.117474	0.15816
Total		0.352423	0.352423

Data analysis of the results was carried out by the method given in section 2.3.2.3 in the methods, giving total anhydrous lactose concentration in kg/m^3 .

5.3.2.2 Results and Discussion

Tables H1 and H2 in Appendix H contain the results of the experiments carried out and consist of the measured refractive index and the corresponding calculated total lactose concentration in kg of anhydrous lactose per m³ of solution. The data analysis of the refractive indices was carried out by the method given in section 2.3.2.3, giving total anhydrous lactose concentrations in kg lactose per m³ of solution. The model developed in section 5.2 was run at 25°C with the system inputs found in Tables B10 and B12 in Appendix B. The resulting lactose concentrations can be found in Tables H1 and H2 (Appendix H).

Figures 5.3 and 5.4 show a comparison of the experimental runs above the alpha lactose solubility limit to the dissolution model, along with an average size model prediction. It is apparent from these figures that there is little difference between the two models in the predictions. Both predict the dissolution curve well.

Table 5.4 shows a comparison of the predicted dissolution times from the models and the observed dissolution time above the solubility limit, highlighting the similarity of the two models in this area. This suggests that for dissolution above the alpha lactose solubility limit, an average crystal size model is adequate for predicting the dissolution process.

Table 5.4 Dissolution times for dissolution above the alpha lactose solubility limit.

	Dissolution Times	
	Constant Mass	Constant Area
Observed dissolution Time	160.0 min	170.0 min
Predicted (Average crystal size)	151.2 min	151.4 min
Predicted (multiple crystal size)	154.0 min	154.0 min

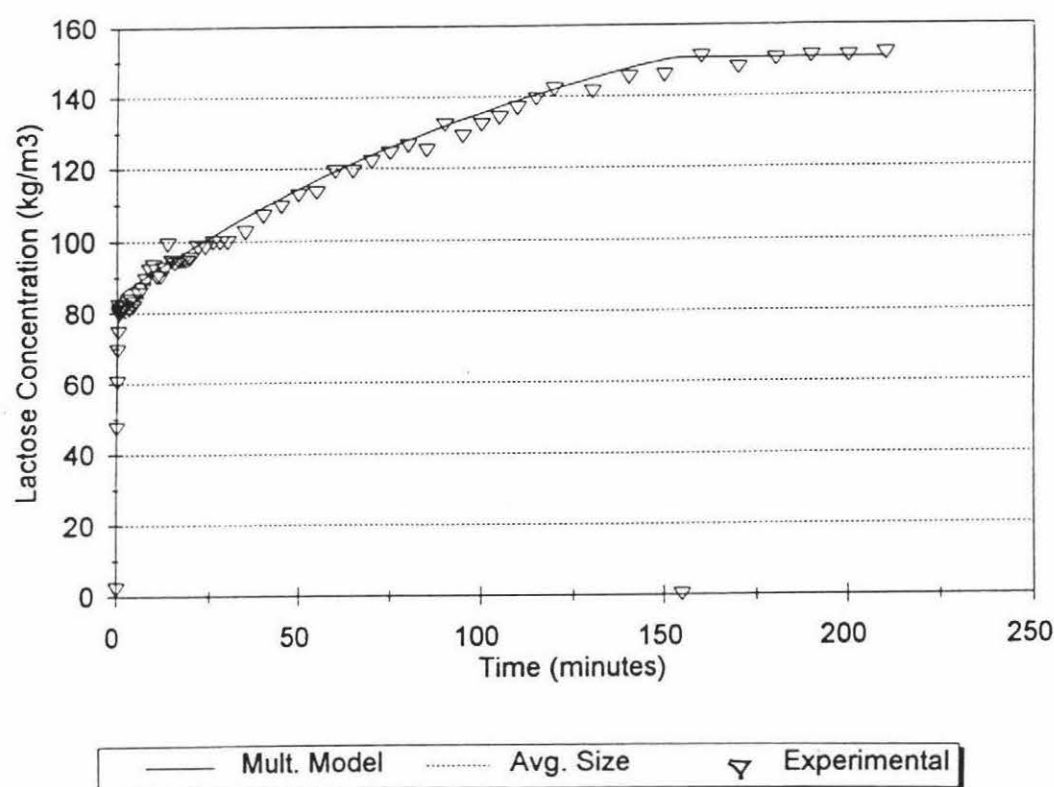


Figure 5.3 Comparison of multiple crystal size and average crystal size models to experimental data for dissolution of alpha lactose above the alpha lactose solubility limit with equal mass fraction. Operating Conditions: 25°C, Final concentration 150 kg/m³ (anhydrous), Fraction 105-150 μm - 0.117474 kg monohydrate, Fraction 150-210 μm - 0.117474 kg monohydrate, Fraction 210-300 μm - 0.117474 kg monohydrate.

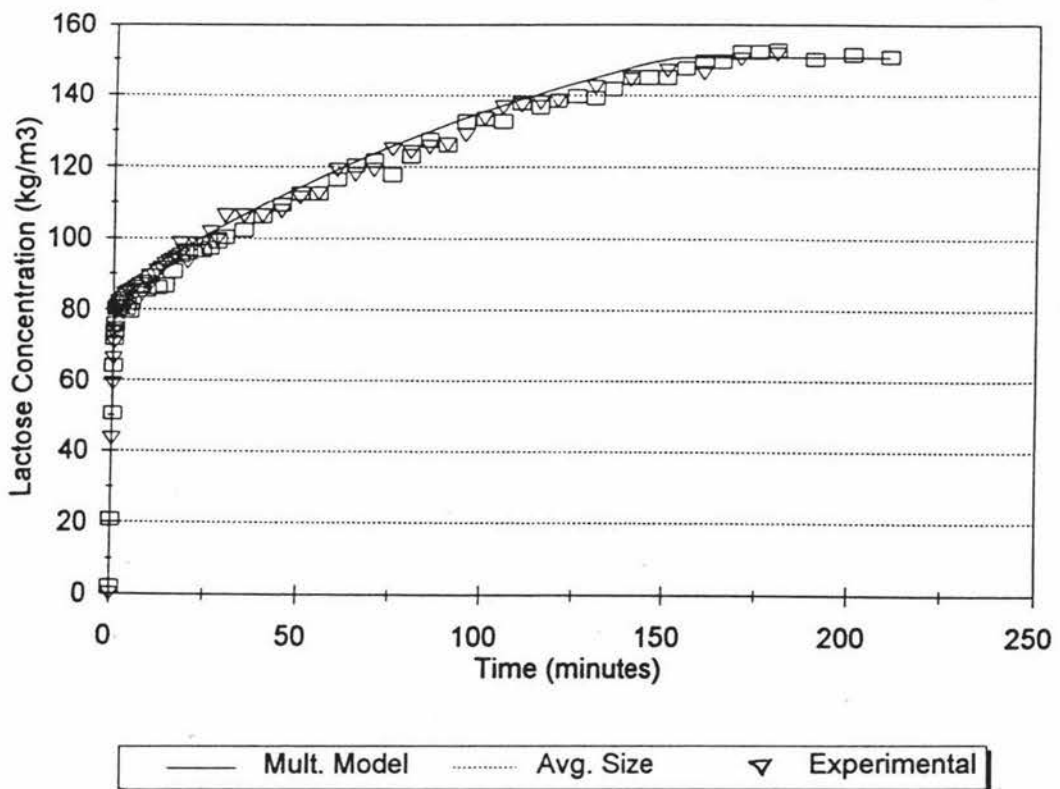


Figure 5.4 Comparison of multiple crystal size and average crystal size models to experimental data for dissolution of alpha lactose above the alpha lactose solubility limit with equal area fractions. Operating Conditions: 25°C, Final concentration 150 kg/m³ (anhydrous), Fraction 105-150 μm - 0.08311 kg monohydrate, Fraction 150-210 μm - 0.11115 kg monohydrate, Fraction 210-300 μm - 0.15816 kg monohydrate.

5.4 Dissolution predictions for unsieved commercial lactose

In industry, lactose does not often have such a simple predefined crystal size as that used in the experiments carried out in previous sections. A bag of lactose may have a large crystal distribution, varying from large crystals to very fine crystals.

In this situation, it would be necessary to measure the crystal size distribution of the lactose and then use one of two methods to predict the dissolution time.

- (i) Single crystal size model using the largest crystal size in the lactose sample as the initial crystal size.
- (ii) Multiple crystal size model using the measured crystal size distribution as a predictor for the initial crystal sizes.

The first method should provide the longest possible dissolution time. This may be of use in situations where undissolved lactose may cause complications in downstream processing. Using the multiple crystal size model should give a more accurate prediction of dissolution time, as well as follow the dissolution profile more carefully.

5.4.1 Comparison of model predictions on unsieved lactose

To test the suitability of either of the two methods, it is necessary to compare the predictions of the models on an unsieved sample of lactose.

The effect of unsieved lactose on dissolution time was only examined below the alpha lactose solubility limit. Previous experiments have shown that crystal size has a minimal effect on the dissolution rate above the alpha lactose solubility limit.

5.4.1.1 Experimental

A sample of lactose was taken from a bag of Wyndale Super Dense grade lactose and analyzed for crystal size distribution using a Malvern crystal size analyzer. Table C9 in Appendix C gives the results of this analysis.

An experiment was carried out using the procedure given in section 2.3 at 25°C with sufficient lactose to give a final concentration of 50 kg/m³. Measurements of refractive index were carried out at 20°C at time intervals of 1 seconds for the first 20 seconds, and then 2 seconds until dissolution was complete.

Data analysis of the results was carried out using the method given in section 2.3.2.3, giving total anhydrous lactose concentration in kg/m³.

For the maximum crystal size model, the largest crystal size in the Malvern analysis in Appendix C was 564.0 µm. Using equation 3.66, this gives a value for the maximum initial crystal size of 601.3 µm.

The multiple crystal size model requires that the crystal size distribution be split into discrete crystal sizes. Table 5.5 shows a cumulative frequency distribution of the crystal size analysis. This is shown in Figure 5.5. Using this, a crystal size distribution consisting of eleven crystal size intervals with an interval width of 50 µm were determined (Table 5.6).

5.4.1.2 Results and Discussions

Table H5 in Appendix H contain the results of the experiments carried out and consist of the measured refractive index and the corresponding calculated total lactose concentration in kg of anhydrous lactose per m³ of solution. The model developed in section 5.2 was run at 25°C to give a final lactose concentration of 50 kg/m³ (Tables B10 and B14 in Appendix B) and using the crystal size distribution from Table 5.5. The resulting lactose concentrations can be found in Table H5 in Appendix H.

Table 5.5 Cumulative frequency distribution of unsieved lactose.

Crystal size range. (μm)	Percent of crystals in range	Cumulative Frequency
0-25	2.0 %	2.0 %
25-50	2.6 %	4.6 %
50-75	3.1 %	7.7 %
75-100	7.8 %	15.5 %
100-125	10.1 %	25.6 %
125-150	9.8 %	35.4 %
150-175	11.1 %	46.5 %
175-200	11.3 %	57.8 %
200-225	10.2 %	68.0 %
225-250	8.4 %	76.4 %
250-275	6.5 %	82.9 %
275-300	4.8 %	87.7 %
300-325	3.6 %	91.3 %
325-350	2.6 %	93.9 %
350-375	1.9 %	95.8 %
375-400	1.4 %	97.2 %
400-425	1.0 %	98.2 %
425-450	0.7 %	98.9 %
450-475	0.5 %	99.4 %
475-500	0.3 %	99.7 %
500-525	0.2 %	99.9 %
525-550	0.1 %	100.0 %
550-575	0.0 %	100.0 %

Table 5.6 Average crystal sizes for eleven (11) crystal size model.

Mid-point crystal size (μm)	Converted crystal size (μm)	Percent of crystals at crystal size
25	26.7	4.5 %
75	80.0	10.9 %
125	133.3	19.9 %
175	186.6	22.5 %
225	239.9	18.6 %
275	293.2	11.3 %
325	346.5	6.2 %
375	399.8	3.4 %
425	453.1	1.7 %
475	506.4	0.7 %
525	559.7	0.1 %

Figure 5.6 shown a comparison between the multiple crystal size and two single crystal size models to the experimental results. The two single crystal size models consisted of the average size of the distribution of 204.3 μm (adj.), and the maximum size of the distribution of 601.3 μm (adj.). The average size model follows the dissolution curve well initially but deviates from the experimental results as dissolution nears completion, leading to an under-prediction of the dissolution time. The multiple particle size model follows the shape of the dissolution curve, but over-predicts the dissolution time. The dissolution prediction from the largest particle size model was not close to the experimental results, which suggested that using this value in the model did not give a good estimate of the progress of dissolution.

It must be noted that the model should be the maximum dissolution time possible as the diffusion coefficient is based on the smallest possible for the system (Sherwood number of 2.0).

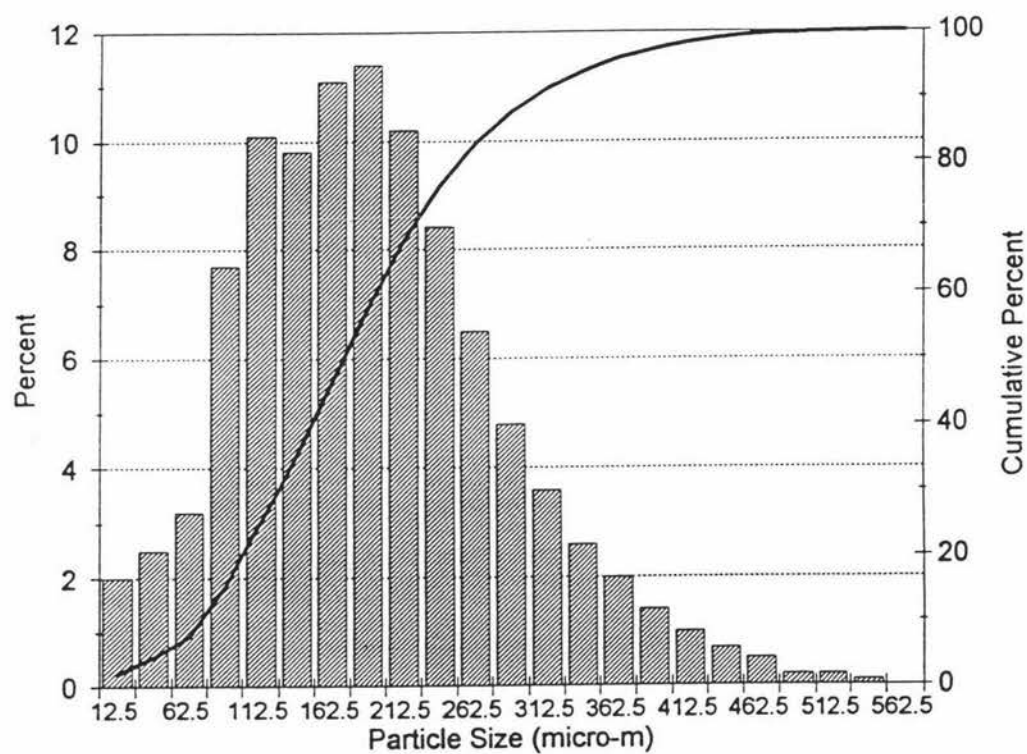


Figure 5.5 Frequency distribution of crystal sizes in unsieved lactose measured using a Malvern Crystal size analyzer.

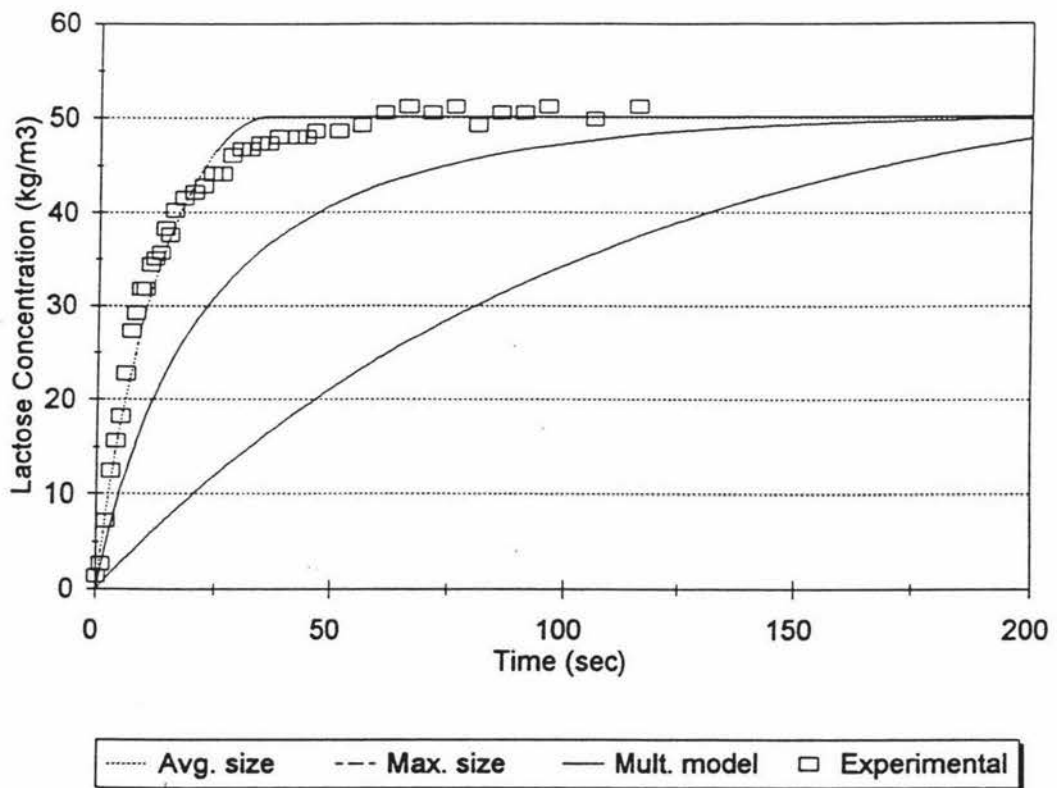


Figure 5.6 Comparison of multiple crystal size (eleven sizes) and average crystal size models to experimental data for dissolution of alpha lactose. Operating Conditions: 25°C. Mass monohydrate: 0.109342 kg.

Table 5.7 Summary of frequency distributions for different number of size intervals.

Number of size intervals in distribution	Interval width (μm)	Average size (μm)	Adjusted average (μm)
Twenty three (23)	25	191.5	204.3
Eleven (11)	50	191.5	204.3
Six (6)	100	192.1	204.9
Three (3)	200	189.8	202.5
Two (2)	300	186.9	199.4

To see if the prediction of the multiple crystal size model was affected by the number of crystal sizes, the model was rerun with different numbers of particle sizes. Table 5.7 gives a summary of the distributions with size intervals of 25, 50, 100, 200, and 300 μm (number of crystal sizes of 23, 11, 6, 3, and 2). Tables B10 and B13 to B17 in Appendix B gives the crystal sizes and system inputs used. From the variation of average crystal size at larger size intervals, it is apparent that size intervals larger than 100 μm (six crystal sizes) gives poorer approximations of the actual particle distribution present.

Figure 5.7 shows the comparisons between the model predictions with differing crystal sizes. There is very little difference between the twenty three and eleven particle size models, with the six crystal size model also being very similar to these two. The two and three crystal size models show the effects of the poor approximation of the distribution, giving dissolution curves of different shape to the experimental results. These results show that six to eleven crystal sizes (size interval width of 50-100 μm) are sufficient to model the distribution of lactose crystals.

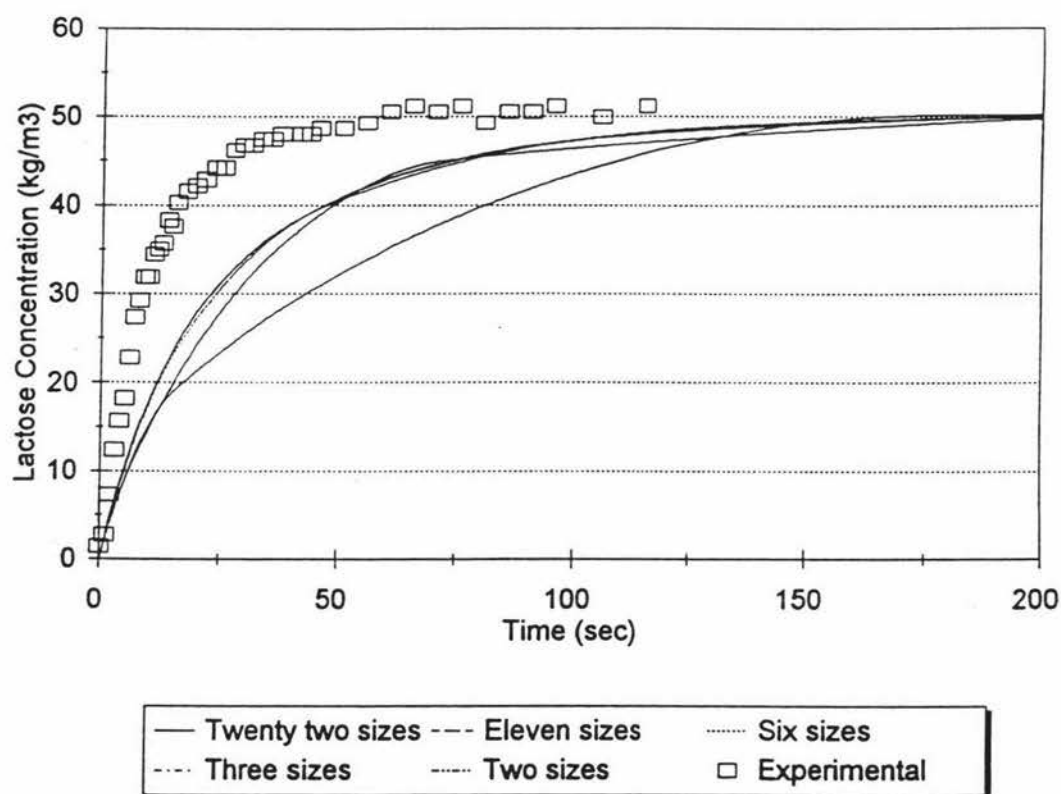


Figure 5.7 The effect of the number of crystal sizes on the multiple crystal size model. Operating Conditions: 25°C. Mass monohydrate: 0.109342 kg.

5.5 Conclusions

The models developed in the previous chapters assumed that only one crystal size existed in solution. For dissolving industrial lactose, this will not be the case. To account for this a generalized form of the models developed in chapters 3 and 4 was developed which could be applied to any particle distribution.

Comparison of the multiple model developed and the single crystal size model of chapter 4 to the experimental dissolution of an artificial mixture of crystal sizes above and below the alpha lactose solubility limit shows that;

- (i) The single crystal size model does not predict the dissolution of mixtures well.
- (ii) The multiple crystal size model predicts the dissolution profile of lactose mixtures.
- (iii) Above the alpha lactose solubility limit there is minimal difference between the two models, indicating that crystal size is not important in this regime.

This indicates that to obtain an accurate prediction of the dissolution of multiple crystal size mixtures below the alpha lactose solubility limit, multiple crystal size model is necessary.

The crystal size distribution of commercial grade lactose was measured and modeled using a model with eleven (11) crystal sizes. This predicted the dissolution profile well although the dissolution time was over-predicted. However, predictions using a single average crystal size model gave an under-prediction of the dissolution time. The model should give the maximum possible dissolution time as the slowest possible mass transfer was assumed.

CHAPTER 6

Summary

Hodges (1992) developed a model to predict the dissolution of alpha lactose in water. However, this model was inaccurate for dissolution where there is not excess lactose. This study intended to improve on the model developed by Hodges (1992) by identifying what is not being modeled correctly and to modify the model accordingly.

The following improvements on the model were made;

- (i) Inclusion of the effect of beta lactose on the solubility of alpha lactose.

This was found to improve the model prediction above the alpha lactose solubility limit. However, predictions below the alpha lactose solubility limit did not line up with experimental results.

- (ii) Inclusion of surface disintegration reaction.

This had a marked improvement on the dissolution predictions below the alpha lactose solubility limit. The values of the surface reaction rate were found at a variety of temperatures and followed an Arrhenius type relationship, suggesting that this assumption is valid.

- (iii) Inclusion of multiple crystal sizes.

The above two models predicted the dissolution of lactose of a single defined crystal size well. However, in the industrial case mixtures of crystal sizes are used. For dissolution above the alpha lactose solubility limit, this has no effect. For dissolution below the alpha lactose solubility limit with crystal mixtures, the single size model underpredicts the dissolution time. The model was modified to allow modelling of crystals of different sizes dissolving simultaneously. This was found to give an improved prediction.

To summarize what model is necessary for each situation;

- (i) For dissolution above the alpha lactose solubility limit, no matter what particle sizes, Model 1 is sufficient.
- (ii) For dissolution below the alpha lactose solubility limit with a single crystal size, Model 2 is necessary.
- (iii) For dissolution below the alpha lactose solubility limit with crystal size mixes, Model 3 is necessary.

Nomenclature

a	Moles of alpha lactose initially in solution.	[moles]
a_l	Area conversion factor	
A	Total crystal surface area	[m ²]
A_c	Surface area of single lactose crystal	[m ²]
A_{ci}	Surface area of crystal i	[m ²]
A_p	Partical projected area	[m ²]
$A_{p\ av}$	Average particle projected area	[m ²]
$A_{p\ max}$	Maximum partical projected area	[m ²]
$A_{p\ min}$	Minimum particle projected area	[m ²]
A_s	Frequency factor for surface reaction	[m/s]
A_{sp}	Surface area of parimeter equilivant sphere	[m ²]
A_0	Frequency factor for $(k_1 + k_2)$.	[s ⁻¹]
b	Moles of beta lactose initially in solution.	[moles]
c_l	Intercept for density correlation	[kg/m ³]
C	Concentration of active substance	[kg/m ³]
C_t	Total concentration of lactose in solution	[kg/m ³]
C_s	Total solubility limit of lactose	[kg/m ³]
C_α	Concentration of α -lactose in solution	[kg/m ³]
$C_{\alpha c}$	Concentration of α -lactose in crystal	[kg/m ³]
$C_{\alpha l}$	Concentration of α -lactose at crystal surface	[kg/m ³]
$C_{\alpha s}$	Solubility of α -lactose	[kg/m ³]
$C_{\alpha s}^\beta$	Solubility of α -lactose with a β -lactose concentration of C_β	[kg/m ³]
$C_{\alpha s}^{\beta eq}$	Solubility of α -lactose at mutarotation equilibrium	[kg/m ³]
$C_{\alpha s}^{\beta=0}$	Solubility of α -lactose in the absence of β -lactose	[kg/m ³]
$C_\beta^{\alpha eq}$	Concentration of β -lactose at mutarotation equilibrium	[kg/m ³]
C_β	Concentration of β -lactose in solution.	[kg/m ³]
d_l	Length conversion factor	
D	Diffusivity of lactose in water	[m ² /s]
D_c	Diameter of crystal	[m]

D_{ci}	Diameter of crystal i	[m]
D_i	Initial crystal diameter	[m]
D_{max}	Maximum crystal size in lactose	[m]
D_{min}	Minimum crystal size in lactose	[m]
D_p	Diameter of particle measured by Malvern	[m]
D_p	Diameter of particle crystalizing	[μ m]
E	Arrhenius constant	[kcal/mol]
E_a	Arrhenius constant for ($k_1 + k_2$).	[kJ/kmol]
E_s	Arrhenius constant for surface reaction	[kJ/kmol]
f	Available surface area fraction	
F	Solubility depressing Factor	
G	Crystal growth rate	[μ m/min]
Ga	Concentration of D-galactose in solution	[g/100g]
Gl	Concentration of D-glucose in solution	[g/100g]
h	Height of lactose crystal	[m]
k	Temperature Coefficient (= -0.0014)	
k_c	Overall crystallization rate constant	[g.h ⁻¹ .m ⁻² (wt%) ⁻ⁿ]
k_L	Liquid side mass transfer coefficient	[m/s]
k_{Li}	Mass transfer coefficient for crystal i	[m/s]
k_r	Overall surface reaction rate	[m/s]
k_o	Frequency factor for crystal growth.	[μ m/min]
k_1	Mutarotation reaction rate constant for α -lactose to β -lactose	[s ⁻¹]
k_2	Mutarotation reaction rate constant for β -lactose to α -lactose	[s ⁻¹]
k_3	Rate of disintegration of alpha lactose from crystal surface	[m/s]
k_4	Rate of integration of alpha lactose into crystal surface	[m/s]
k	Temperature Coefficient (= -0.0014)	
K_m	β/α ratio of lactose solution at mutarotation equilibrium	
l	Length of column of solution	[m]
l	Length of lactose crystal	[m]
l'	Characteristic length of crystal	
	= $A_c / (\text{maximum perimeter projected on a plane normal to the flow})$	[m]
La	Total solubility of lactose	[g/100g]

m	Number of crystal sizes in model	
m_l	Slope of density correlation	[kg solution/kg anhydrous lactose]
M_c	Mass of lactose crystals	[kg]
M_{ci}	Mass of lactose crystal i	[kg]
M_i	Initial mass of fluid in dissolution vessel	[kg]
M_α	Mass of alpha lactose in solution	[kg]
M_β	Mass of beta lactose in solution	[kg]
n	Number of lactose crystals in solution	
n	Order of crystallization reaction	
n	Number of experimental points	
n^{20}	Refractive index of Lactose Solution at 20°C	
N	Mass transfer flux	[kg/m ² .s]
N_i	Mass transfer flux for crystal i	[kg/m ² .s]
R	Universal Gas Constant	[kJ/kgmol.K]
r	Optical rotation	[°m ² /kg]
r_{sp}	Radius of perimeter equilivant sphere	[m]
r_t	Optical rotation at time $t = t$.	[°m ² /kg]
r_0	Optical rotation at time $t = 0$.	[°m ² /kg]
r_l	Rate of accumulation of alpha lactose at crystal surface	[kg/m ² .s]
r_∞	Optical rotation at time $t = \infty$. (mutarotation equilibrium)	[°m ² /kg]
s	Supersaturation Ratio	
Sh'	Sherwood Number ($Sh' = k_t L' / D$)	
t	Time	[s]
T	Temperature	[K]
v_l	volume conversion factor	
V_c	Volume of single lactose crystal	[m ³]
V_{ci}	Volume of crystal i	[m ³]
V_s	Volume of solution	[m ³]
W	Anhydrous mass of crystals	[g]
w	Width of lactose crystal	[m]
x	Moles of β -lactose in solution	[moles]
x_e	Estimated value of experimental point	

x_i	Mass fraction of lactose at crystal size D_{ci} .
x_i	Measured experimental point
$\bar{x}$	Meanb of experimental points
X	Fraction of α -lactose in solution

Greek Letters

$[\alpha]$	Specific optical rotation	[°]
$[\alpha_\alpha]$	Specific optical rotation of α -lactose	[°]
$[\alpha_\beta]$	Specific optical rotation of β -lactose	[°]
$[\alpha_\infty]$	Specific optical rotation of lactose solution at equilibrium	[°]
$[\alpha]^\theta$	Specific optical rotation at temperature $\theta^\circ\text{C}$	[°]
Δ'	Conductance Factor	
θ	Temperature of lactose solution	[°C]
μ	Viscosity of lactose solution	[Pa.s]
ρ_s	Density of lactose solution	[kg/m ³]
ρ_c	Density of alpha lactose monohydrate crystal.	[kg/m ³]
Σ	Perimeter equilivant factor	
τ	Crystallization time	[hr]

Added Letters

n_i	Number of crystals in solution at crystal size D_{ci} .
p_i	Fraction of number of lactose crystals at size D_{ci} .

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APPENDIX A

Numerical programs for solving differential equations

Model 1:Dissolution of lactose with one crystal size, and alpha lactose solubility effects.

```

--
-- Version 1.0
-- Date 17/11/92
--
STUDY
--
MODEL Dissolve(REAL: Finish:= REAL: Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,D,c1,m1);
--
-- Definition of variables and constants.
--
REAL: n;
REAL: Dc,Ma,Mb,Ca,Cb,Ct;
REAL: Cas,Rhos,Vs,kl;
LOGICAL: Not_Finished;
--
-- Definitions of initial conditions.
--
INITIAL
  Ma:=0.0;
  Mb:=0.0;
  Dc:=Di;
  --
  Finish:=0.0;
  n:=Ml/(Rhoc*0.3379*(Di**3));
  Vs:=Vi;
  Rhos:=c1;
  Not_Finished:=TRUE;
--
-- Dynamic Modelling Section
--
DYNAMIC
  Ca:=Ma/Vs;
  Cb:=Mb/Vs;
  Ct:=(Ma+Mb)/Vs;
  Cas:=Cas0-F*Cb;
  kl:=if Dc>0 Then Sh*D/(1.05*Dc)
      else 0;
  --
  Ma':=3.3674*kl*n*(Dc**2)*(Cas-Ca)+k2*Mb-k1*Ma;
  Mb':=k1*Ma-k2*Mb;
  Dc':=-3.3219*kl*(Cas-Ca)/Rhoc;
  --
  When Dc<=0.0 And Not_Finished Then
    Finish:=t;
    Not_Finished:=False;
  End_When;
STEP
  Rhos:=m1*Ct+c1;

```



```

Vs:=(Vi*c1+1.05684*(Ma+Mb))/Rhos;
COMMUNICATION
  Prepare "lact1",t,Ca,Cb,Ct,Dc;
  Tabulate t,Ca,Cb,Ct,Dc,Vs;
End Dissolve;
--
-- Experimental Section
--
REAL: Temp;
REAL: Cas0,F,k1,k2,k1_k2,Km;
REAL: D,m1,c1;
REAL: Sh,Vi/0.002/,Rhoc/1540.0/;
REAL: MI,Di;
REAL: Finish;
--
PRINT "Input System Conditions";
PRINT;
READ Temp,k1_k2;
READ Cas0,F,Km;
READ c1,m1;
READ D;
READ Sh;
--
k2:=k1_k2/(1+Km);
k1:=k1_k2-k2;
--
PRINT;
PRINT "Input Run Conditions";
PRINT;
READ MI,Di;
READ Algo,Cint,Nstep;
READ Tfin;
--
Dissolve(Finish := Sh,Vi,Rhoc,Di,MI,Cas0,F,k1,k2,D,c1,m1);
--
PRINT;
PRINT "Dissolution time was ",Finish," sec.";
--
END_STUDY

```

Model 2a: Dissolution of lactose with one crystal size, alpha lactose solubility effects, and surface reaction.

```
--
-- Version 3.0
-- Date 6/1/93
--
STUDY
--
MODEL Dissolve(REAL: Finish := Real: Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,kr,D,c1,m1);
--
-- Constants and Variables
REAL: Dc,Ma,Mb,Ca,Cb,Ct,Cas;
REAL: Rhos,Vs,n,kl;
LOGICAL: Not_Finished;
--
INITIAL
--
Ma:=0.0;
Mb:=0.0;
Dc:=Di;
n:=Ml/(Rhoc*0.3379*Di**3);
Vs:=Vi;
Rhos:=c1;
Not_Finished := TRUE;
--
DYNAMIC
--
Ca:=Ma/Vs;
Cb:=Mb/Vs;
Ct:=(Ma+Mb)/Vs;
Cas:=Cas0-F*Cb;
kl := if Dc>0 Then Sh*D/(1.05*Dc)
      else 1;
--
Ma':= if Dc>0 Then 3.3674*(Dc**2)*n*(Cas-Ca)/(1/kr+1/kl)-k1*Ma+k2*Mb
      else k2*Mb-k1*Ma;
Mb':= k1*Ma-k2*Mb;
Dc':= if Dc > 0 then -3.3219*(Cas-Ca)/((1/Kr+1/kl)*Rhoc)
      else 0.0;
--
When Dc <= 0 And Not_Finished Then
  Finish:=t;
  Not_Finished:=FALSE;
End_When;
--
STEP
--
Rhos:=c1+m1*Ct;
Vs:=(Vi*c1+1.05684*(Ma+Mb))/Rhos;
--
COMMUNICATION
--
Prepare "lact3",t,Ca,Cb,Ct;
Tabulate t,Ca,Cb,Ct,Dc;
--
```

```

END Dissolve;
--
-- Experimental Section
--
REAL: Temp;
REAL: Cas0,F,k1,k2,k1_k2,kr,Km;
REAL: R/8.314/,A/4.19259E8/,E/70088.7/;
REAL: A1/1.9943e9/,E1/73664.05/;
REAL: D,m1,c1;
REAL: Sh/2.0/,Vi/0.002/,Rhoc/1540.0/;
REAL: MI,Di;
REAL: Finish;
--
PRINT "Input System Conditions";
PRINT;
READ Temp;
IF Temp = 25 THEN
  Cas0:=85.07; F:=0.090857; Km:=1.58;
  c1:=997.124; m1:=0.398662; D:=3.8E-9;
ELSE
  READ Cas0,F,Km;
  READ c1,m1,D;
END_IF;
--
kr:=A*exp(-E/(R*(Temp+273.15)));
k1_k2:=A1*exp(-E1/(R*(Temp+273.15)));
k2:=k1_k2/(1+Km);
k1:=k1_k2-k2;
--
PRINT;
PRINT "Input Run Conditions";
PRINT;
READ MI,Di;
READ Algo,Cint,Nstep;
READ Tfin;
--
Dissolve(Finish := Sh,Vi,Rhoc,Di,MI,Cas0,F,k1,k2,kr,D,c1,m1);
--
PRINT;
PRINT "Dissolution time was ",Finish," sec.";
--
END_STUDY

```

Model 2b: Iterative dissolution of lactose with one crystal size, alpha lactose solubility effects, and surface reaction for calculating surface reaction rate.

```
--
-- 21/12/92 (Version 2.0)
--
STUDY
--
PACKAGE GLOBAL;
  REAL: MODL(0..1500),DATA(1500,2);
  INTEGER: Num_Data;
END;
--
PROCEDURE RESID(REAL:Kr)RETURN REAL;
  USE GLOBAL;
  REAL: Rsum,Val;
  INTEGER: Z;
  --
  Rsum:=0.0;
  For Z:=1..Num_Data
  Loop
    Val := (DATA(Z,2)-MODL(DATA(Z,1)))**2;
    Rsum := Rsum+Val;
  End_Loop;
  RETURN Rsum;
END RESID;
--
PROCEDURE RSQUARE(REAL:RSUM,AVERAGE)RETURN REAL;
  USE GLOBAL;
  REAL: TSum,Val,RSqu;
  INTEGER: Z;
  --
  TSum:=0.0;
  For Z:=1..Num_Data
  Loop
    Val := (DATA(Z,2)-AVERAGE)**2;
    TSum:= TSum+Val;
  End_Loop;
  RSqu:=(1-RSUM/TSum);
  RETURN RSqu;
END RSQUARE;
--
-- Model for dissolution of lactose.
--
MODEL Dissolutuion(:= Real: Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,kr,D,c1,m1);
  USE GLOBAL;
  --
  -- Constants and Variables
  REAL: Dc,Ma,Mb,Ca,Cb,Ct,Cas;
  REAL: Rhos,Vs,n,kl;
  --
  INITIAL
    Ma:=0.0;
    Mb:=0.0;
    Dc:=Di;
```

```

n:=Ml/(Rhoc*0.3379*Di**3);
Vs:=Vi;
Rhos:=c1;
DYNAMIC
Ca:=Ma/Vs;
Cb:=Mb/Vs;
Ct:=(Ma+Mb)/Vs;
Cas:=Cas0-F*Cb;
kl := if Dc>0 Then Sh*D/(1.05*Dc)
      else 1;
--
Ma':= if Dc>0 Then 3.3674*(Dc**2)*n*(Cas-Ca)/((1/Kr+1/kl)-k1*Ma+k2*Mb
      else k2*Mb-k1*Ma;
Mb':= k1*Ma-k2*Mb;
Dc':= if Dc > 0 then -3.3219*(Cas-Ca)/((1/Kr+1/kl)*Rhoc)
      else 0.0;
STEP
Rhos:=c1+m1*Ct;
Vs:=(Vi*c1+1.05684*(Ma+Mb))/Rhos;
COMMUNICATION
MODL(t):=Ct;
END Dissolution;

--
-- Experimental Section
USE GLOBAL;
REAL: Temp;
REAL: Cas0,F,k1,k2,k1_k2,Kr,Km;
REAL: D,c1,m1;
REAL: Sh/2.0/, Vi/0.002/,Rhoc/1540.0/;
REAL: Ml,Di;
REAL: Finish;
REAL: Kr_High,Kr_Low,Error;
CHARACTER: Question;
CHARACTER: Filename(40);
FILE: Infile;
REAL: Resid_Hi, Resid_Lo,RSqu_Hi,RSqu_Lo,Average;
INTEGER: Err,Count;
LOGICAL: HIGH;
--
PRINT;
PRINT "Input System Conditions";
PRINT;
READ Temp,k1_k2;
READ Cas0,F,Km;
READ c1,m1;
READ D;
--
k2:=k1_k2/(Km+1);
k1:=k1_k2-k2;
--
PRINT;
PRINT "Input Run Conditions";
PRINT;
READ Ml,Di;
READ Nstep;

```

```

PRINT;
Algo:=2;Cint:=1;
--
PRINT;
PRINT "Input Experimental Data";
err:=3;
While err = 3
Loop
  READ "Type in filename >",filename;
  OPEN Infile, filename,IOSTAT=err;
  If err=3 then PRINT; PRINT "Invalid file name! Please reenter file."; End_if;
End_Loop;
Num_Data:=0;
err:=0;
Finish:=0;
Average:=0;
While err = 0
Loop
  Num_Data:=Num_Data+1;
  READ infile, DATA(Num_Data,1),DATA(Num_Data,2),IOSTAT=err;
  Average:=Average+DATA(Num_Data,2);
  If DATA(Num_Data,1)>Finish then
    Finish:=DATA(Num_Data,1);
  End_if;
End_Loop;
Average:=Average/Num_Data;
Tfin:=Finish;
--
Question:="N";
While NOT Question = "Y"
Loop
  PRINT;
  PRINT "Input High and Low Bounds for analysis.";
  PRINT;
  READ "High Value for Kr >",kr_High;
  READ "Low Value for Kr >",kr_Low;
  READ "Error Condition >",Error;
  PRINT;
  READ "Is the above correct? (Y/N)",Question;
End_Loop;
PRINT;
PRINT;
PRINT "-- ITERATIONS --";
PRINT;
--
--Iterative evaluation of kr
--
Kr:=Kr_High;
Dissolution(:=Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,kr,D,c1,m1);
Resid_Hi:=Resid(Kr);
RSqu_Hi:=RSQUARE(Resid_Hi,Average);
PRINT " 1: HIGH: Kr =",Kr," Residual =",Resid_Hi:9.3," R^2 =",RSqu_Hi;
--
High:=False; Kr:=Kr_Low;
Count:=1;
While Count < 50

```

```

Loop
Count:=Count+1;
Dissolution(:=Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,kr,D,c1,m1);
If High Then
    Resid_Hi:=Resid(kr);
    RSqu_Hi:=RSQUARE(Resid_Hi,Average);
    PRINT Count:3.0," : HIGH: Kr =",Kr,
        ", Residual =",Resid_Hi:9.3," , R^2 =",RSqu_Hi;
Else
    Resid_Lo:=Resid(kr);
    RSqu_Lo:=RSQUARE(Resid_Lo,Average);
    PRINT Count:3.0," : LOW: Kr =",Kr,
        ", Residual =",Resid_Lo:9.3," , R^2 =",RSqu_Lo;
End_if;
TERMINATE ((Kr_High-Kr_Low)/2)/Kr_High < Error;
If Resid_Hi>Resid_Lo Then
    High:=True;
Else
    High:=False;
End_if;
If HIGH Then
    Kr_High:=Kr_High-(Kr_High-Kr_Low)/3;
    Kr:=Kr_High;
Else
    Kr_Low:=Kr_Low+(Kr_High-Kr_Low)/3;
    Kr:=Kr_Low;
End_if;
End_Loop;
--
PRINT;
PRINT "System Conditions:";
PRINT "Temperature = ",Temp," C";
PRINT "Cas = ",Cas0," kg/m3, F = ",F," , b/a ratio = ",Km;
PRINT;
PRINT "Run Conditions";
PRINT "Mass Added = ",Ml," kg, Initial Part. Size = ",Di;
PRINT;
PRINT "Fitted Values of Reaction Rate Constant.";
PRINT "High Value =",Kr_High," ,Sum of Squares =",Resid_Hi," ,R^2 =",RSqu_Hi;
PRINT "Low Value =",Kr_Low," ,Sum of Squares =",Resid_Lo," ,R^2 =",RSqu_Lo;
END_STUDY

```

Model 2c: Iterative dissolution of lactose with one crystal size, alpha lactose solubility effects, and available surface area for calculating surface area factor.

```
--
-- Started 5/1/93 (Version 4.0)
--
STUDY
--
PACKAGE GLOBAL;
  REAL: MODL(0..1500),DATA(1500,2);
  INTEGER: Num_Data;
END;
--
PROCEDURE RESID(REAL:SAF)RETURN REAL;
  USE GLOBAL;
  REAL: Rsum,Val;
  INTEGER: Z;
  --
  Rsum:=0.0;
  For Z:=1..Num_Data
  Loop
    Val := (DATA(Z,2)-MODL(DATA(Z,1)))**2;
    Rsum := Rsum+Val;
  End_Loop;
  RETURN Rsum;
END RESID;
--
PROCEDURE RSQUARE(REAL:RSUM,AVERAGE)RETURN REAL;
  USE GLOBAL;
  REAL: TSum,Val,RSqu;
  INTEGER: Z;
  --
  TSum:=0.0;
  For Z:=1..Num_Data
  Loop
    Val := (DATA(Z,2)-AVERAGE)**2;
    TSum:= TSum+Val;
  End_Loop;
  RSqu:=(1-RSUM/TSum);
  RETURN RSqu;
END RSQUARE;
--
MODEL Dissolutuion(:= Real: Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,SAF,D,c1,m1);
  USE GLOBAL;
  --
  -- Constants and Variables
  REAL: Dc,Ma,Mb,Ca,Cb,Ct,Cas;
  REAL: Rhos,Vs,n,kl;
  --
  INITIAL
    Ma:=0.0;
    Mb:=0.0;
    Dc:=Di;
    n:=Ml/(Rhoc*0.3379*Di**3);
    Vs:=Vi;
```



```

    Rhos:=c1;
DYNAMIC
    Ca:=Ma/Vs;
    Cb:=Mb/Vs;
    Ct:=(Ma+Mb)/Vs;
    Cas:=Cas0-F*Cb;
    k1 := if Dc>0 Then Sh*D/(1.05*Dc)
          else 1;
    --
    Ma' := if Dc>0 Then 3.3674*k1*SAF*(Dc**2)*n*(Cas-Ca)-k1*Ma+k2*Mb
           else k2*Mb-k1*Ma;
    Mb' := k1*Ma-k2*Mb;
    Dc' := if Dc > 0 then -3.3219*k1*SAF*(Cas-Ca)/Rhoc
           else 0.0;
STEP
    Rhos:=c1+m1*Ct;
    Vs:=(Vi*c1+1.05684*(Ma+Mb))/Rhos;
COMMUNICATION
    MODL(t):=Ct;
END Dissolution;
--
-- Experimental Section
USE GLOBAL;
REAL: Temp;
REAL: Cas0,F,k1,k2,k1_k2,SAF,Km;
REAL: D,c1,m1;
REAL: Sh/2.0/, Vi/0.002/,Rhoc/1540.0/;
REAL: MI,Di;
REAL: Finish;
REAL: SAF_High,SAF_Low,Error;
CHARACTER: Question;
CHARACTER: Filename(40);
FILE: Infile;
REAL: Resid_Hi, Resid_Lo,RSqu_Hi,RSqu_Lo,Average;
INTEGER: Err,Count;
LOGICAL: HIGH;
--
PRINT;
PRINT "Input System Conditions";
PRINT;
READ Temp,k1_k2;
READ Cas0,F,Km;
READ c1,m1;
READ D;
--
k2:=k1_k2/(Km+1);
k1:=k1_k2-k2;
--
PRINT;
PRINT "Input Run Conditions";
PRINT;
READ MI,Di;
READ Nstep;
PRINT;
Algo:=2;Cint:=1;
--

```

```

PRINT;
PRINT "Input Experimental Data";
err:=3;
While err = 3
Loop
  READ "Type in filename >",filename;
  OPEN Infile, filename,IOSTAT=err;
  If err=3 then PRINT; PRINT "Invalid file name! Please reenter file."; End_if;
End_Loop;
Num_Data:=0;
err:=0;
Finish:=0;
Average:=0;
While err = 0
Loop
  Num_Data:=Num_Data+1;
  READ infile, DATA(Num_Data,1),DATA(Num_Data,2),IOSTAT=err;
  Average:=Average+DATA(Num_Data,2);
  If DATA(Num_Data,1)>Finish then
    Finish:=DATA(Num_Data,1);
  End_if;
End_Loop;
Average:=Average/Num_Data;
Tfin:=Finish;
--
Question:="N";
While NOT Question = "Y"
Loop
  PRINT;
  PRINT "Input High and Low Bounds for analysis.";
  PRINT;
  READ "High Value for SAF >",SAF_High;
  READ "Low Value for SAF >",SAF_Low;
  READ "Error Condition >",Error;
  PRINT;
  READ "Is the above correct? (Y/N)",Question;
End_Loop;
PRINT;
PRINT;
PRINT "-- ITERATIONS --";
PRINT;
--
--Iterative evaluation of SAF
--
SAF:=SAF_High;
Dissolution(:=Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,SAF,D,c1,m1);
Resid_Hi:=Resid(SAF);
RSqu_Hi:=RSQUARE(Resid_Hi,Average);
PRINT " 1: HIGH: =",SAF," , Residual =",Resid_Hi:9.3," , R^2 =",RSqu_Hi;
--
High:=False; SAF:=SAF_Low;
Count:=1;
While Count < 50
Loop
  Count:=Count+1;
  Dissolution(:=Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,SAF,D,c1,m1);

```

```

If High Then
  Resid_Hi:=Resid(SAF);
  RSqu_Hi:=RSQUARE(Resid_Hi,Average);
  PRINT Count:3.0," : HIGH: =",SAF,
    ", Residual =",Resid_Hi:9.3," , R^2 =",RSqu_Hi;
Else
  Resid_Lo:=Resid(SAF);
  RSqu_Lo:=RSQUARE(Resid_Lo,Average);
  PRINT Count:3.0," : LOW: =",SAF,
    ", Residual =",Resid_Lo:9.3," , R^2 =",RSqu_Lo;
End_if;
TERMINATE ((SAF_High-SAF_Low)/2)/SAF_High < Error;
If Resid_Hi>Resid_Lo Then
  High:=True;
Else
  High:=False;
End_if;
If HIGH Then
  SAF_High:=SAF_High-(SAF_High-SAF_Low)/3;
  SAF:=SAF_High;
Else
  SAF_Low:=SAF_Low+(SAF_High-SAF_Low)/3;
  SAF:=SAF_Low;
End_if;
End_Loop;
--
PRINT;
PRINT "System Conditions:";
PRINT "Temperature = ",Temp," C";
PRINT "Cas = ",Cas0," kg/m3, F = ",F," , b/a ratio = ",Km;
PRINT;
PRINT "Run Conditions";
PRINT "Mass Added = ",Ml," kg, Initial Part. Size = ",Di;
PRINT;
PRINT "Fitted Values of Available Surface Area Factor.";
PRINT "High Value =",SAF_High," ,Sum of Squares =",Resid_Hi," ,R^2 =",RSqu_Hi;
PRINT "Low Value =",SAF_Low," ,Sum of Squares =",Resid_Lo," ,R^2 =",RSqu_Lo;
PRINT "Average =",(SAF_High+SAF_Low)/2;
END_STUDY

```

Model 2d: Iterative dissolution of lactose with one crystal size, alpha lactose solubility effects, and surface reaction rate for generating nomograph.

```
--
-- Version 5.1
-- Date 6/1/93
--
STUDY
--
MODEL Dissolve(REAL: Finish := Real: Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,kr,D,c1,m1);
--
-- Constants and Variables
REAL: Dc,Ma,Mb,Ca,Cb,Ct,Cas;
REAL: Rhos,Vs,n,kl;
LOGICAL: Not_Finished;
--
INITIAL
--
Ma:=0.0;
Mb:=0.0;
Dc:=Di;
n:=Ml/(Rhoc*0.3379*Di**3);
Vs:=Vi;
Rhos:=c1;
Not_Finished := TRUE;
--
DYNAMIC
--
Ca:=Ma/Vs;
Cb:=Mb/Vs;
Ct:=(Ma+Mb)/Vs;
Cas:=Cas0-F*Cb;
kl := if Dc>0 Then Sh*D/(1.05*Dc)
      else 1;
--
Ma':= if Dc>0 Then 3.3674*(Dc**2)*n*(Cas-Ca)/(1/kr+1/kl)-k1*Ma+k2*Mb
      else k2*Mb-k1*Ma;
Mb':= k1*Ma-k2*Mb;
Dc':= if Dc > 0 then -3.3219*(Cas-Ca)/((1/Kr+1/kl)*Rhoc)
      else 0.0;
--
When Dc <= 0 And Not_Finished Then
  Finish:=t;
  Not_Finished:=FALSE;
End_When;
--

STEP
--
Rhos:=c1+m1*Ct;
Vs:=(Vi*c1+1.05684*(Ma+Mb))/Rhos;
```

```

--
COMMUNICATION
--
    TERMINATE NOT Not_Finished;
--
END Dissolve;

--
-- Experimental Section
--
REAL: Temp;
REAL: Cas0,F,k1,k2,k1_k2,kr,Km;
REAL: R/8.314/,A/4.19259E8/,E/70088.7/;
REAL: A1/1.9943e9/,E1/73664.05/;
REAL: D,m1,c1;
REAL: Sh/2.0/,Vi/0.002/,Rhoc/1540.0/;
REAL: C_Start,C_Finish,C_Step;
REAL: C_Target,Ml,Di;
REAL: Finish;
FILE: Outfile;
CHARACTER: Filename(12),Repeat;
--
PRINT "Input System Conditions";
PRINT;
READ Temp;
IF Temp = 25 THEN
    Cas0:=85.07; F:=0.090857; Km:=1.58;
    c1:=997.124; m1:=0.398662; D:=3.8E-9;
ELSE
    READ Cas0,F,Km;
    READ c1,m1,D;
END_IF;
--
kr:=A*exp(-E/(R*(Temp+273.15)));
k1_k2:=A1*exp(-E1/(R*(Temp+273.15)));
k2:=k1_k2/(1+Km);
k1:=k1_k2-k2;
--
PRINT;
PRINT "Input Run Conditions";
PRINT;
READ C_Start,C_Finish,C_Step;
READ Algo,Cint,Nstep;
--

Repeat:="Y";
While Repeat = "Y"
LOOP
    READ Di;
    READ "Output Filename > ",Filename;
    Tfin:=100000.0;
    PRINT;
--

```

```

REWRITE Outfile,Filename;
PRINT Outfile,"Temperature =",Temp;
PRINT Outfile,"Particle Size =",Di;
PRINT Outfile,"Concentration  Finish Time";
--
FOR C_Target:=C_Start..C_Finish STEP C_Step
LOOP
  Ml:=(Vi*c1*C_Target)/(c1+m1*C_Target-1.0584*C_Target);
  Dissolve(Finish := Sh,Vi,Rhoc,Di,Ml,Cas0,F,k1,k2,kr,D,c1,m1);
  PRINT "Conc =",C_Target," Disolution =",Finish," sec.";
  PRINT Outfile,C_Target,Finish;
END_LOOP;
CLOSE Outfile;
PRINT;
READ "Repeat at same temperature? (Y/N) ",Repeat;
END_LOOP;
--
END_STUDY

```

Model 3a: Dissolution of lactose with three crystal sizes, alpha lactose solubility effects, and surface reaction.

```
--
-- Date 14/1/93
--
STUDY
--
Model Dissolve(REAL:Finish :=
REAL: D1,D2,D3,M1,M2,M3,Cas0,F,Km,Temp,D,c,m);
--
-- Constants and variables
--
REAL: Dc1,Dc2,Dc3;
REAL: Ma,Mb,Ca,Cb,Ct,Cas;
REAL: Sum1,Sum2,Sum3,SumTot;
REAL: Val,Rhos,Vs,n1,n2,n3;
REAL: K11,K12,K13;
REAL: Sh/2.0,Vi/0.002/,Rhoc/1540.0/;
REAL: R/8.314/,A/4.19259E8/,E/70088.7/,A1/1.9943E9/,E1/73664.05/;
REAL: kr,k1_k2,k1,k2;
LOGICAL: NotFin1,NotFin2,NotFin3,Fin;
--
INITIAL
--
kr:=A*exp(-E/(R*(Temp+273.15)));
k1_k2:=A1*exp(-E1/(R*(Temp+273.15)));
k2:=k1_k2/(1+Km);
k1:=k1_k2-k2;
Finish:=0.0;
--
Ma:=0.0;
Mb:=0.0;
Dc1:=D1;
Dc2:=D2;
Dc3:=D3;
--
n1:=M1/(Rhoc*0.3379*D1**3);
n2:=M2/(Rhoc*0.3379*D2**3);
n3:=M3/(Rhoc*0.3379*D3**3);
Vs:=Vi;
Rhos:=c;
NotFin1:= TRUE;
NotFin2:= TRUE;
NotFin3:= TRUE;
Fin:=FALSE;
--
DYNAMIC
Ca:=Ma/Vs;
Cb:=Mb/Vs;
Ct:=(Ma+Mb)/Vs;
Cas:=Cas0-F*Cb;
--
k11:=IF Dc1>0 THEN Sh*D/(1.05*Dc1)
      ELSE 1;
k12:=IF Dc2>0 THEN Sh*D/(1.05*Dc2)
```

```

ELSE 1;
kl3:=IF Dc3>0 THEN Sh*D/(1.05*Dc3)
      ELSE 1;
--
Sum1:=IF Dc1>0 THEN (3.3674*(Dc1**2)*n1)/(1/kr+1/kl1)
      ELSE 0;
Sum2:=IF Dc2>0 THEN (3.3674*(Dc2**2)*n2)/(1/kr+1/kl2)
      ELSE 0;
Sum3:=IF Dc3>0 THEN (3.3674*(Dc3**2)*n3)/(1/kr+1/kl3)
      ELSE 0;
SumTot:=Sum1+Sum2+Sum3;
--
Ma':=SumTot*(Cas-Ca)-k1*Ma+k2*Mb;
Mb':=k1*Ma-k2*Mb;
Dc1':=IF Dc1>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/kl1)*Rhoc)
      ELSE 0;
Dc2':=IF Dc2>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/kl2)*Rhoc)
      ELSE 0;
Dc3':=IF Dc3>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/kl3)*Rhoc)
      ELSE 0;
--
WHEN Dc1 <= 0 AND NotFin1 THEN
  NotFin1:=FALSE;
END_WHEN;
WHEN Dc2 <= 0 AND NotFin2 THEN
  NotFin2:=FALSE;
END_WHEN;
WHEN Dc3 <= 0 AND NotFin3 THEN
  NotFin3:=FALSE;
END_WHEN;
WHEN NOT Fin AND NOT NotFin1 AND NOT NotFin2 AND NOT NotFin3 THEN
  Finish := t;
  Fin := TRUE;
END_WHEN;
--
STEP
--
Rhos:=c+m*Ct;
Vs:=(Vi*c+1.05684*(Ma+Mb))/Rhos;
--
COMMUNICATION
--
PREPARE "lact6",t,Ca,Cb,Ct;
TABULATE t,Ca,Cb,Ct;
--
END Dissolve;
--
-- Experimental Section
--
REAL: Temp;
REAL: Cas0,F,Km;
REAL: C,M,D;
REAL: M1,M2,M3,D1,D2,D3;
REAL: Finish;
--
PRINT "Dissolution Model with three particle sizes";

```



```

PRINT;
PRINT "Input System Conditions";
PRINT;
READ Temp;
IF Temp = 25 THEN
  Cas0:=85.07; F:=0.090857; Km:=1.58;
  c:=997.124; m:=0.398662; D:=3.8E-9;
ELSE
  READ Cas0,F,Km;
  READ c,m,D;
END_IF;
--
PRINT;
PRINT "Input Run Conditions";
PRINT;
READ M1,D1;
READ M2,D2;
READ M3,D3;
PRINT;
PRINT "Input Integration Conditions";
READ Algo,Cint,Nstep;
READ " Finishing Time (sec) > ",Tfin;
--
Disolve(Finish := D1,D2,D3,M1,M2,M3,Cas0,F,Km,Temp,D,c,m);
--
PRINT;
PRINT "Dissolution time was ",Finish,"sec.";
--
END_STUDY

```

Model 3b: Dissolution of lactose with up to twenty three crystal sizes, alpha lactose solubility effects, and surface reaction.

```
--
-- Version 8.0
-- Date 5/10/93
--
STUDY
--
Model Dissolve(REAL:Finish :=
REAL: Pi(1..23),Di(1..23),Mi,Cas0,F,Km,Temp,D,c,m);
--
-- Constants and variables
--
REAL: Dc1,Dc2,Dc3,Dc4,Dc5,Dc6,Dc7,Dc8,Dc9,Dc10,Dc11;
REAL: Dc12,Dc13,Dc14,Dc15,Dc16,Dc17,Dc18,Dc19,Dc20,Dc21,Dc22,Dc23;
REAL: Ma,Mb,Ca,Cb,Ct,Cas;
REAL: Sum1,Sum2,Sum3,Sum4,Sum5,Sum6,Sum7,Sum8,Sum9,Sum10,Sum11,Sum12,Sum13;
REAL: Sum14,Sum15,Sum16,Sum17,Sum18,Sum19,Sum20,Sum21,Sum22,Sum23,SumTot;
REAL: Val,Rhos,Vs,n(1..23);
REAL: K11,K12,K13,k14,k15,k16,k17,k18,k19,k110,k111,k112,k113;
REAL: k114,k115,k116,k117,k118,k119,k120,k121,k122,k123;
REAL: Sh/2.0/,Vi/0.002/,Rhoc/1540.0/;
REAL: R/8.314/,A/4.19259E8/,E/70088.7/,A1/1.9943E9/,E1/73664.05/;
REAL: kr,k1_k2,k1,k2;
INTEGER: I;
LOGICAL: Fin(1..23),FinAll;
--
INITIAL
--
kr:=A*exp(-E/(R*(Temp+273.15)));
k1_k2:=A1*exp(-E1/(R*(Temp+273.15)));
k2:=k1_k2/(1+Km);
k1:=k1_k2-k2;
--
Ma:=0.0;
Mb:=0.0;
Dc1:=Di(1);
Dc2:=Di(2);
Dc3:=Di(3);
Dc4:=Di(4);
Dc5:=Di(5);
Dc6:=Di(6);
Dc7:=Di(7);
Dc8:=Di(8);
Dc9:=Di(9);
Dc10:=Di(10);
Dc11:=Di(11);
Dc12:=Di(12);
Dc13:=Di(13);
Dc14:=Di(14);
Dc15:=Di(15);
Dc16:=Di(16);
Dc17:=Di(17);
Dc18:=Di(18);
Dc19:=Di(19);
```

```

Dc20:=Di(20);
Dc21:=Di(21);
Dc22:=Di(22);
Dc23:=Di(23);
--
Val:=0.0;
FOR I := 1..23
LOOP
  Val := Val + Pi(I)*Rhoc*0.3379*Di(I)**3;
END_LOOP;
--
FOR I := 1..23
LOOP
  n(I):=Pi(I)*Mi/Val;
  Fin(I):=FALSE;
END_LOOP;
--
Vs:=Vi;
Rhos:=c;
FinAll:=FALSE;
--
DYNAMIC
Ca:=Ma/Vs;
Cb:=Mb/Vs;
Ct:=(Ma+Mb)/Vs;
Cas:=Cas0-F*Cb;
--
kl1:=IF Dc1>0 THEN Sh*D/(1.05*Dc1)
      ELSE 1;
kl2:=IF Dc2>0 THEN Sh*D/(1.05*Dc2)
      ELSE 1;
kl3:=IF Dc3>0 THEN Sh*D/(1.05*Dc3)
      ELSE 1;
kl4:=IF Dc4>0 THEN Sh*D/(1.05*Dc4)
      ELSE 1;
kl5:=IF Dc5>0 THEN Sh*D/(1.05*Dc5)
      ELSE 1;
kl6:=IF Dc6>0 THEN Sh*D/(1.05*Dc6)
      ELSE 1;
kl7:=IF Dc7>0 THEN Sh*D/(1.05*Dc7)
      ELSE 1;
kl8:=IF Dc8>0 THEN Sh*D/(1.05*Dc8)
      ELSE 1;
kl9:=IF Dc9>0 THEN Sh*D/(1.05*Dc9)
      ELSE 1;
kl10:=IF Dc10>0 THEN Sh*D/(1.05*Dc10)
      ELSE 1;
kl11:=IF Dc11>0 THEN Sh*D/(1.05*Dc11)
      ELSE 1;
kl12:=IF Dc12>0 THEN Sh*D/(1.05*Dc12)
      ELSE 1;
kl13:=IF Dc13>0 THEN Sh*D/(1.05*Dc13)
      ELSE 1;
kl14:=IF Dc14>0 THEN Sh*D/(1.05*Dc14)
      ELSE 1;
kl15:=IF Dc15>0 THEN Sh*D/(1.05*Dc15)

```

```

ELSE 1;
kl16:=IF Dc16>0 THEN Sh*D/(1.05*Dc16)
ELSE 1;
kl17:=IF Dc17>0 THEN Sh*D/(1.05*Dc17)
ELSE 1;
kl18:=IF Dc18>0 THEN Sh*D/(1.05*Dc18)
ELSE 1;
kl19:=IF Dc19>0 THEN Sh*D/(1.05*Dc19)
ELSE 1;
kl20:=IF Dc20>0 THEN Sh*D/(1.05*Dc20)
ELSE 1;
kl21:=IF Dc21>0 THEN Sh*D/(1.05*Dc21)
ELSE 1;
kl22:=IF Dc22>0 THEN Sh*D/(1.05*Dc22)
ELSE 1;
kl23:=IF Dc23>0 THEN Sh*D/(1.05*Dc23)
ELSE 1;
--
Sum1:=IF Dc1>0 THEN (3.3674*(Dc1**2)*n(1))/(1/kr+1/kl1)
ELSE 0;
Sum2:=IF Dc2>0 THEN (3.3674*(Dc2**2)*n(2))/(1/kr+1/kl2)
ELSE 0;
Sum3:=IF Dc3>0 THEN (3.3674*(Dc3**2)*n(3))/(1/kr+1/kl3)
ELSE 0;
Sum4:=IF Dc4>0 THEN (3.3674*(Dc4**2)*n(4))/(1/kr+1/kl4)
ELSE 0;
Sum5:=IF Dc5>0 THEN (3.3674*(Dc5**2)*n(5))/(1/kr+1/kl5)
ELSE 0;
Sum6:=IF Dc6>0 THEN (3.3674*(Dc6**2)*n(6))/(1/kr+1/kl6)
ELSE 0;
Sum7:=IF Dc7>0 THEN (3.3674*(Dc7**2)*n(7))/(1/kr+1/kl7)
ELSE 0;
Sum8:=IF Dc8>0 THEN (3.3674*(Dc8**2)*n(8))/(1/kr+1/kl8)
ELSE 0;
Sum9:=IF Dc9>0 THEN (3.3674*(Dc9**2)*n(9))/(1/kr+1/kl9)
ELSE 0;
Sum10:=IF Dc10>0 THEN (3.3674*(Dc10**2)*n(10))/(1/kr+1/kl10)
ELSE 0;
Sum11:=IF Dc11>0 THEN (3.3674*(Dc11**2)*n(11))/(1/kr+1/kl11)
ELSE 0;
Sum12:=IF Dc12>0 THEN (3.3674*(Dc12**2)*n(12))/(1/kr+1/kl12)
ELSE 0;
Sum13:=IF Dc13>0 THEN (3.3674*(Dc13**2)*n(13))/(1/kr+1/kl13)
ELSE 0;
Sum14:=IF Dc14>0 THEN (3.3674*(Dc14**2)*n(14))/(1/kr+1/kl14)
ELSE 0;
Sum15:=IF Dc15>0 THEN (3.3674*(Dc15**2)*n(15))/(1/kr+1/kl15)
ELSE 0;
Sum16:=IF Dc16>0 THEN (3.3674*(Dc16**2)*n(16))/(1/kr+1/kl16)
ELSE 0;
Sum17:=IF Dc17>0 THEN (3.3674*(Dc17**2)*n(17))/(1/kr+1/kl17)
ELSE 0;
Sum18:=IF Dc18>0 THEN (3.3674*(Dc18**2)*n(18))/(1/kr+1/kl18)
ELSE 0;
Sum19:=IF Dc19>0 THEN (3.3674*(Dc19**2)*n(19))/(1/kr+1/kl19)
ELSE 0;

```

```

Sum20:=IF Dc20>0 THEN (3.3674*(Dc20**2)*n(20))/(1/Kr+1/Kl20)
      ELSE 0;
Sum21:=IF Dc21>0 THEN (3.3674*(Dc21**2)*n(21))/(1/Kr+1/Kl21)
      ELSE 0;
Sum22:=IF Dc22>0 THEN (3.3674*(Dc22**2)*n(22))/(1/Kr+1/Kl22)
      ELSE 0;
Sum23:=IF Dc23>0 THEN (3.3674*(Dc23**2)*n(23))/(1/Kr+1/Kl23)
      ELSE 0;
SumTot:=Sum1+Sum2+Sum3+Sum4+Sum5+Sum6+Sum7+Sum8+Sum9+Sum10+Sum11+Sum12
      +Sum13+Sum14+Sum15+Sum16+Sum17+Sum18+Sum19+Sum20+Sum21+Sum22+Sum23;
--
Ma':=SumTot*(Cas-Ca)-k1*Ma+k2*Mb;
Mb':=k1*Ma-k2*Mb;
Dc1':=IF Dc1>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl1)*Rhoc)
      ELSE 0;
Dc2':=IF Dc2>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl2)*Rhoc)
      ELSE 0;
Dc3':=IF Dc3>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl3)*Rhoc)
      ELSE 0;
Dc4':=IF Dc4>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl4)*Rhoc)
      ELSE 0;
Dc5':=IF Dc5>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl5)*Rhoc)
      ELSE 0;
Dc6':=IF Dc6>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl6)*Rhoc)
      ELSE 0;
Dc7':=IF Dc7>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl7)*Rhoc)
      ELSE 0;
Dc8':=IF Dc8>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl8)*Rhoc)
      ELSE 0;
Dc9':=IF Dc9>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl9)*Rhoc)
      ELSE 0;
Dc10':=IF Dc10>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl10)*Rhoc)
      ELSE 0;
Dc11':=IF Dc11>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl11)*Rhoc)
      ELSE 0;
Dc12':=IF Dc12>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl12)*Rhoc)
      ELSE 0;
Dc13':=IF Dc13>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl13)*Rhoc)
      ELSE 0;
Dc14':=IF Dc14>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl14)*Rhoc)
      ELSE 0;
Dc15':=IF Dc15>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl15)*Rhoc)
      ELSE 0;
Dc16':=IF Dc16>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl16)*Rhoc)
      ELSE 0;
Dc17':=IF Dc17>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl17)*Rhoc)
      ELSE 0;
Dc18':=IF Dc18>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl18)*Rhoc)
      ELSE 0;
Dc19':=IF Dc19>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl19)*Rhoc)
      ELSE 0;
Dc20':=IF Dc20>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl20)*Rhoc)
      ELSE 0;
Dc21':=IF Dc21>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl21)*Rhoc)
      ELSE 0;
Dc22':=IF Dc22>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/Kl22)*Rhoc)

```

```

ELSE 0;
Dc23':=IF Dc23>0 THEN -3.3219*(Cas-Ca)/((1/Kr+1/kl23)*Rhoc)
ELSE 0;
WHEN Dc1 <= 0 AND NOT Fin(1) THEN
  Fin(1):=TRUE;
END_WHEN;
WHEN Dc2 <= 0 AND NOT Fin(2) THEN
  Fin(2):=TRUE;
END_WHEN;
WHEN Dc3 <= 0 AND NOT Fin(3) THEN
  Fin(3):=TRUE;
END_WHEN;
WHEN Dc4 <= 0 AND NOT Fin(4) THEN
  Fin(4):=TRUE;
END_WHEN;
WHEN Dc5 <= 0 AND NOT Fin(5) THEN
  Fin(5):=TRUE;
END_WHEN;
WHEN Dc6 <= 0 AND NOT Fin(6) THEN
  Fin(6):=TRUE;
END_WHEN;
WHEN Dc7 <= 0 AND NOT Fin(7) THEN
  Fin(7):=TRUE;
END_WHEN;
WHEN Dc8 <= 0 AND NOT Fin(8) THEN
  Fin(8):=TRUE;
END_WHEN;
WHEN Dc9 <= 0 AND NOT Fin(9) THEN
  Fin(9):=TRUE;
END_WHEN;
WHEN Dc10 <= 0 AND NOT Fin(10) THEN
  Fin(10):=TRUE;
END_WHEN;
WHEN Dc11 <= 0 AND NOT Fin(11) THEN
  Fin(11):=TRUE;
END_WHEN;
WHEN Dc12 <= 0 AND NOT Fin(12) THEN
  Fin(12):=TRUE;
END_WHEN;
WHEN Dc13 <= 0 AND NOT Fin(13) THEN
  Fin(13):=TRUE;
END_WHEN;
WHEN Dc14 <= 0 AND NOT Fin(14) THEN
  Fin(14):=TRUE;
END_WHEN;
WHEN Dc15 <= 0 AND NOT Fin(15) THEN
  Fin(15):=TRUE;
END_WHEN;
WHEN Dc16 <= 0 AND NOT Fin(16) THEN
  Fin(16):=TRUE;
END_WHEN;
WHEN Dc17 <= 0 AND NOT Fin(17) THEN
  Fin(17):=TRUE;
END_WHEN;
WHEN Dc18 <= 0 AND NOT Fin(18) THEN
  Fin(18):=TRUE;

```

```

END_WHEN;
WHEN Dc19 <= 0 AND NOT Fin(19) THEN
  Fin(19):=TRUE;
END_WHEN;
WHEN Dc20 <= 0 AND NOT Fin(20) THEN
  Fin(20):=TRUE;
END_WHEN;
WHEN Dc21 <= 0 AND NOT Fin(21) THEN
  Fin(21):=TRUE;
END_WHEN;
WHEN Dc22 <= 0 AND NOT Fin(22) THEN
  Fin(22):=TRUE;
END_WHEN;
WHEN Dc23 <= 0 AND NOT Fin(23) THEN
  Fin(23):=TRUE;
END_WHEN;
--
WHEN NOT FinAll AND Fin(1) AND Fin(2) AND Fin(3) AND Fin(4) AND Fin(5) AND
  Fin(6) AND Fin(7) AND Fin(8) AND Fin(9) AND Fin(10) AND Fin(11) AND
  Fin(12) AND Fin(13) AND Fin(14) AND Fin(15) AND Fin(16) AND Fin(17) AND
  Fin(19) AND Fin(20) AND Fin(21) AND Fin(22) AND Fin(23) THEN
  Finish:=t;
  FinAll:=TRUE;
END_WHEN;
--
STEP
--
Rhos:=c+m*Ct;
Vs:=(Vi*c+1.05684*(Ma+Mb))/Rhos;
--
COMMUNICATION
--
PREPARE "lact8",t,Ca,Cb,Ct;
TABULATE t,Ca,Cb,Ct;
--
END Dissolve;
--
-- Experimental Section
--
REAL: Temp;
REAL: Cas0,F,Km;
REAL: C,M,D;
REAL: Mi;
REAL: Pi(1..23),Di(1..23);
REAL: Finish;
INTEGER: I;
--
PRINT "Dissolution Model with twenty-three particle sizes";
PRINT;
PRINT "Input System Conditions";
PRINT;
READ Temp;
IF Temp = 25 THEN
  Cas0:=85.07; F:=0.090857; Km:=1.58;
  c:=997.124; m:=0.398662; D:=3.8E-9;
ELSE

```

```

READ Cas0,F,Km;
READ c,m,D;
END_IF;
--
PRINT;
PRINT "Input Run Conditions";
PRINT;
READ Mi;
Di(1):=0.00001334; Pi(1):=0.020;
Di(2):=0.00004001; Pi(2):=0.026;
Di(3):=0.00006669; Pi(3):=0.031;
Di(4):=0.00009336; Pi(4):=0.078;
Di(5):=0.00012004; Pi(5):=0.101;
Di(6):=0.00014671; Pi(6):=0.098;
Di(7):=0.00017339; Pi(7):=0.111;
Di(8):=0.00020006; Pi(8):=0.113;
Di(9):=0.00022674; Pi(9):=0.102;
Di(10):=0.00025341; Pi(10):=0.084;
Di(11):=0.00028009; Pi(11):=0.065;
Di(12):=0.00030676; Pi(12):=0.048;
Di(13):=0.00033344; Pi(13):=0.036;
Di(14):=0.00036011; Pi(14):=0.026;
Di(15):=0.00038679; Pi(15):=0.019;
Di(16):=0.00041346; Pi(16):=0.014;
Di(17):=0.00044014; Pi(17):=0.010;
Di(18):=0.00046681; Pi(18):=0.007;
Di(19):=0.00049349; Pi(19):=0.005;
Di(20):=0.00052016; Pi(20):=0.003;
Di(21):=0.00054684; Pi(21):=0.002;
Di(22):=0.00057351; Pi(22):=0.001;
Di(23):=0.00060019; Pi(23):=0.000;
PRINT;
PRINT "Input Integration Conditions";
READ Algo,Cint,Nstep;
READ " Finishing Time (sec) > ",Tfin;
--
Dissolve(Finish := Pi,Di,Mi,Cas0,F,Km,Temp,D,c,m);
--
PRINT;
PRINT "Dissolution time was ",Finish,"sec.";
--
END_STUDY

```


APPENDIX B

System inputs for lactose dissolution models

Table B1: System inputs for Model 1 at 25 deg C.

<u>Physical Conditions</u>			
Temperature	25.0 °C		
Diffisivity	4.7×10^{-9}		
Mutarotation			
$k_1 + k_2 =$	$1.8717 \times 10^{-4} \text{ s}^{-1}$	$K_m =$	1.58
Alpha lactose solubility			
$C_{\infty} =$	85.07 kg/m^3	$F =$	0.090807
Density correlation			
Slope =	0.38966	Intercept =	997.124 kg/m^3
<u>Process Conditions</u>			
Initial Mass =	0.473 or 0.1976 or 0.0914 kg		
Initial Volume =	2.0 litres		
Initial Diameter =	$284.5 \times 10^{-6} \text{ m}$ or $144.1 \times 10^{-6} \text{ m}$		

Table B2: System inputs for Model 1 at 45 deg C.

<u>Physical Conditions</u>			
Temperature	45.0 °C		
Diffisivity	7.9×10^{-9}		
Mutarotation			
$k_1 + k_2 =$	$1.4801 \times 10^{-3} \text{ s}^{-1}$	$K_m =$	1.53
Alpha lactose solubility			
$C_{\infty} =$	146.85 kg/m^3	$F =$	0.142843
Density correlation			
Slope =	0.36617	Intercept =	993.436 kg/m^3
<u>Process Conditions</u>			
Initial Mass =	0.946 or 0.5933 or 0.1976 kg		
Initial Volume =	2.0 litres		
Initial Diameter =	$284.54 \times 10^{-6} \text{ m}$		

Table B3: System inputs for Model 2. Fitting surface reaction rates.

<u>Physical Conditions</u>			
Temperature	4.0 °C		
Diffusivity	2.6×10^{-9}		
Mutarotation			
$k_1 + k_2 =$	$2.6049 \times 10^{-5} \text{ s}^{-1}$	$K_m =$	1.61
Alpha lactose solubility			
$C_{\alpha} =$	51.47 kg/m ³	$F =$	0.04044
Density correlation			
Slope =	0.3916	Intercept =	999.69 kg/m ³
<u>Process Conditions</u>			
Initial Mass =	0.05085 kg		
Initial Volume =	2.0 litres		
Initial Diameter =	$284.54 \times 10^{-6} \text{ m}$		

Table B4: System inputs for Model 2. Fitting surface reaction rates.

<u>Physical Conditions</u>			
Temperature	15.0 °C		
Diffusivity	3.8×10^{-9}		
Mutarotation			
$k_1 + k_2 =$	$8.8266 \times 10^{-5} \text{ s}^{-1}$	$K_m =$	1.60
Alpha lactose solubility			
$C_{\alpha} =$	68.170 kg/m ³	$F =$	0.05684
Density correlation			
Slope =	0.3861	Intercept =	999.30 kg/m ³
<u>Process Conditions</u>			
Initial Mass =	0.05074 kg		
Initial Volume =	2.0 litres		
Initial Diameter =	$216.3 \times 10^{-6} \text{ m}$	or	$284.54 \times 10^{-6} \text{ m}$

Table B5: System inputs for Model 2. Fitting surface reaction rates.

<u>Physical Conditions</u>			
Temperature	25.0 °C		
Diffusivity	4.7×10^{-9}		
Mutarotation			
$k_1 + k_2 =$	$1.8717 \times 10^{-4} \text{ s}^{-1}$	$K_m =$	1.58
Alpha lactose solubility			
$C_{\alpha} =$	85.07 kg/m ³	$F =$	0.090857
Density correlation			
Slope =	0.389662	Intercept =	997.124 kg/m ³
<u>Process Conditions</u>			
Initial Mass =	0.10377 kg		
Initial Volume =	2.0 litres		
Initial Diameter =	$216.3 \times 10^{-6} \text{ m}$	or	$284.54 \times 10^{-6} \text{ m}$

Table B6: System inputs for Model 2. Fitting surface reaction rates.

<u>Physical Conditions</u>			
Temperature	37.0 °C		
Diffusivity	6.6×10^{-9}		
Mutarotation			
$k_1 + k_2 =$	$7.8170 \times 10^{-4} \text{ s}^{-1}$	$K_m =$	1.55
Alpha lactose solubility			
$C_{\alpha} =$	119.586 kg/m ³	$F =$	0.11030
Density correlation			
Slope =	0.36425	Intercept =	996.24 kg/m ³
<u>Process Conditions</u>			
Initial Mass =	0.21583 kg		
Initial Volume =	2.0 litres		
Initial Diameter =	$216.3 \times 10^{-6} \text{ m}$	or	$284.54 \times 10^{-6} \text{ m}$

Table B7: System inputs for Model 2. Fitting surface reaction rates.

<u>Physical Conditions</u>			
Temperature	50.0 °C		
Diffusivity	8.7×10^{-9}		
Mutarotation			
$k_1 + k_2 =$	$2.4669 \times 10^{-3} \text{ s}^{-1}$	$K_m =$	1.52
Alpha lactose solubility			
$C_{\alpha} =$	167.41 kg/m ³	$F =$	0.16312
Density correlation			
Slope =	0.3676	Intercept =	991.605 kg/m ³
<u>Process Conditions</u>			
Initial Mass =	0.27358 kg		
Initial Volume =	2.0 litres		
Initial Diameter =	$216.3 \times 10^{-6} \text{ m}$	or	$284.54 \times 10^{-6} \text{ m}$

Table B8: System inputs for Model 2. Fitting surface reaction rates.

<u>Physical Conditions</u>			
Temperature	70.0 °C		
Diffusivity	12.6×10^{-9}		
Mutarotation			
$k_1 + k_2 =$	$6.887 \times 10^{-3} \text{ s}^{-1}$	$K_m =$	1.47
Alpha lactose solubility			
$C_{\alpha} =$	277.85 kg/m ³	$F =$	0.3005
Density correlation			
Slope =	0.35855	Intercept =	983.22 kg/m ³
<u>Process Conditions</u>			
Initial Mass =	0.47737 kg		
Initial Volume =	2.0 litres		
Initial Diameter =	$216.3 \times 10^{-6} \text{ m}$	or	$284.54 \times 10^{-6} \text{ m}$

Table B9: System inputs for dissolution time nomograph.

Temp. (°C)	D ($\times 10^{-9}$)	Mutarotation		Solubility		Density		Surface Reaction ($\times 10^{-3}$)
		$k_1 + k_2$ ($\times 10^{-3}$)	K_m	C_{∞}	F	Slope	Intcpt	
10	3.2	0.032	1.60	57.71	0.0523	0.3886	999.59	0.0492
20	4.2	0.107	1.59	75.28	0.0889	0.3924	998.25	0.1359
30	5.6	0.322	1.56	98.21	0.1129	0.3631	998.50	0.3510
40	7.1	0.905	1.54	126.28	0.1226	0.3647	995.27	0.8531
50	8.7	2.385	1.52	167.41	0.1631	0.3676	991.61	1.962
60	10.6	5.930	1.50	220.75	0.2052	0.3715	987.78	4.294
70	12.6	13.99	1.47	277.85	0.2340	0.3586	983.22	8.976
80	14.8	31.42	1.45	370.94	0.3376	0.3536	977.77	18.00
90	17.1	67.49	1.43	483.88	0.4620	0.3485	971.88	34.73

Table B10: Physical system inputs for Model 3.

Temperature	25.0 °C			
Diffusivity	4.7×10^{-9}			
Mutarotation				
	$k_1 + k_2 =$	$1.8717 \times 10^{-4} \text{ s}^{-1}$	$K_m =$	1.58
Alpha lactose solubility				
	$C_{\infty} =$	85.07 kg/m ³	$F =$	0.090857
Density correlation				
	Slope =	0.389662	Intercept =	997.124 kg/m ³
Surface Reaction Rate =				
Initial Total Mass =	0.109342	or 0.352423 kg		
Initial Volume =	2.0 litres			

Table B11: Lactose addition inputs for dissolution below the alpha solubility limit.

Crystal Size (μm)	Equal Mass Mixture (kg monohydrate)	Equal Surface Area Mixture (kg monohydrate)
144.1	0.036447	0.025786
216.3	0.036447	0.034486
284.5	0.036447	0.049069
Total	0.109342	0.109342

Table B12: Lactose addition inputs for dissolution above the alpha solubility limit.

Crystal Size (μm)	Equal Mass Mixture (kg monohydrate)	Equal Surface Area Mixture (kg monohydrate)
144.1	0.117474	0.08311
216.3	0.117474	0.11115
284.5	0.117474	0.15816
Total	0.352423	0.352423

Table B13: Lactose size distribution inputs (23 sizes) for dissolution of unsieved lactose.

Midpoint crystal size (μm)	Percent of crystals at crystal size
13.3	2.0 %
40.0	2.5 %
66.6	3.2 %
93.3	7.7 %
119.9	10.1 %
146.6	9.8 %
173.2	11.1 %
199.9	11.4 %
226.5	10.2 %
253.2	8.4 %
279.9	6.5 %
306.5	4.8 %
333.2	3.6 %
359.8	2.6 %
386.5	2.0 %
413.1	1.4 %
439.8	1.0 %
466.4	0.7 %
493.1	0.5 %
519.7	0.2 %
546.4	0.2 %
573.0	0.1 %
204.3 (Average)	100.0 %

Table B14: Lactose size distribution inputs (11 sizes) for dissolution of unsieved lactose.

Midpoint crystal size (μm)	Percent of crystals at crystal size
26.7	4.5 %
80.0	10.9 %
133.3	19.9 %
186.6	22.5 %
239.9	18.6 %
293.2	11.3 %
346.5	6.2 %
399.8	3.4 %
453.1	1.7 %
506.4	0.7 %
559.7	0.1 %
204.3 (Average)	100.0 %

Table B15: Lactose size distribution inputs (6 sizes) for dissolution of unsieved lactose.

Midpoint crystal size (μm)	Percent of crystals at crystal size
53.3	15.4 %
159.9	42.4 %
266.5	29.9 %
373.1	9.6 %
479.7	2.4 %
586.4	0.3 %
204.9 (Average)	100.0 %

Table B16: Lactose size distribution inputs (3 sizes) for dissolution of unsieved lactose.

Midpoint crystal size (μm)	Percent of crystals at crystal size
106.6	57.8 %
319.8	39.5 %
533.1	2.7 %
202.5 (Average)	100.0 %

Table B17: Lactose size distribution inputs (2 sizes) for dissolution of unsieved lactose.

Midpoint crystal size (μm)	Percent of crystals at crystal size
159.9	87.7 %
479.7	12.3 %
199.4 (Average)	100.0 %

APPENDIX C

Measurement of Crystal Dimensions

Table C1 Width and height of lactose crystals

Width (ocular units)	Height (ocular units)	Ratio
40	70	1.75
45	79	1.7556
60	86	1.433
40	66	1.65
40	59	1.475
13	21	1.61
13	22	1.692
8	15	1.875
8	15	1.875
		1.6795

Table C2 Measurement of Crystal size distribution of crystals used by Hodges (1992), Size Fraction 210-300 μm .

System number 2386 Diode #00065 * ALARMS SET A B C D *

Malvern Instruments MASTER Particle Sizer M6.10 Date 17-06-91 Time 10-15

Size microns	% under	Size band microns	%	Result source= Averaged
564.0	100.0	564.0	261.7	18.2
261.7	81.8	261.7	160.4	76.7
160.4	5.1	160.4	112.8	1.7
112.8	3.4	112.8	84.3	1.9
84.3	1.5	84.3	64.6	1.0
64.6	0.5	64.6	50.2	0.0
50.2	0.5	50.2	39.0	0.0
39.0	0.5	39.0	30.3	0.0
30.3	0.5	30.3	23.7	0.0
23.7	0.5	23.7	18.5	0.1
18.5	0.4	18.5	14.5	0.1
14.5	0.3	14.5	11.4	0.0
11.4	0.3	11.4	9.0	0.1
9.0	0.2	9.0	7.2	0.1
7.2	0.1	7.2	5.8	0.1
5.8	0.1			

System number 2386 Diode #00065 * ALARMS SET A B C D *

Table C3 Measurement of Crystal size distribution of crystals used by Hodges (1992), Size Fraction 150-210 μm .

System number 2386 Diode #00065 * ALARMS SET B D *

Malvern Instruments MASTER Particle Sizer M6.10 Date 17-06-91 Time 11-08

Size microns	% under	:	Size band microns	%	:	Result source= Averaged
564.0	100.0	:			:	Record No. = 3
261.7	97.1	:	564.0	261.7	2.9	Focal length = 300 mm.
160.4	55.6	:	261.7	160.4	41.5	Experiment type pia
112.8	4.8	:	160.4	112.8	50.8	Volume distribution
84.3	3.0	:	112.8	84.3	1.8	Beam length = 22.0 mm.
64.6	2.9	:	84.3	64.6	0.1	Obscuration = 0.1610
50.2	1.2	:	64.6	50.2	1.7	Volume Conc. = 0.0362 %
39.0	0.7	:	50.2	39.0	0.5	Log. Diff. = 4.56
30.3	0.7	:	39.0	30.3	0.0	Model indp
23.7	0.7	:	30.3	23.7	0.0	D(v,0.5) = 155.3 μm
18.5	0.7	:	23.7	18.5	0.0	D(v,0.9) = 220.3 μm
14.5	0.6	:	18.5	14.5	0.1	D(v,0.1) = 122.5 μm
11.4	0.5	:	14.5	11.4	0.1	D(4,3) = 162.0 μm
9.0	0.4	:	11.4	9.0	0.1	D(3,2) = 153.7 μm
7.2	0.3	:	9.0	7.2	0.1	Span = 0.6
5.8	0.2	:	7.2	5.8	0.1	Spec. surf. area
						0.0455 sq. m. /cc.

System number 2386 Diode #00065 * ALARMS SET B D *

Table C4 Measurement of Crystal size distribution of crystals used by Hodges (1992), Size Fraction 105-150 μm .

System number 2386 Diode #00065 * ALARMS SET B D *

Malvern Instruments MASTER Particle Sizer M6.10 Date 17-06-91 Time 11-17

Size microns	% under	:	Size band microns	%	:	Result source= Averaged
564.0	100.0	:			:	Record No. = 4
261.7	99.3	:	564.0	261.7	0.7	Focal length = 300 mm.
160.4	91.3	:	261.7	160.4	8.0	Experiment type pia
112.8	45.6	:	160.4	112.8	45.8	Volume distribution
84.3	9.4	:	112.8	84.3	36.1	Beam length = 22.0 mm.
64.6	4.5	:	84.3	64.6	5.0	Obscuration = 0.2208
50.2	3.8	:	64.6	50.2	0.7	Volume Conc. = 0.0353 %
39.0	2.0	:	50.2	39.0	1.8	Log. Diff. = 3.68
30.3	1.3	:	39.0	30.3	0.7	Model indp
23.7	1.3	:	30.3	23.7	0.0	D(v,0.5) = 116.1 μm
18.5	1.3	:	23.7	18.5	0.0	D(v,0.9) = 157.8 μm
14.5	1.1	:	18.5	14.5	0.2	D(v,0.1) = 85.0 μm
11.4	0.7	:	14.5	11.4	0.4	D(4,3) = 115.3 μm
9.0	0.6	:	11.4	9.0	0.1	D(3,2) = 108.7 μm
7.2	0.5	:	9.0	7.2	0.1	Span = 0.6
5.8	0.4	:	7.2	5.8	0.1	Spec. surf. area
						0.0664 sq. m. /cc.

System number 2386 Diode #00065 * ALARMS SET B D *

Table C5 Measurement of Crystal size distribution of crystals used by Hodges (1992), Unsieved Fraction.

System number 2386 Diode #00065 * ALARMS SET B D *

Malvern Instruments MASTER Particle Sizer M6.10 Date 17-06-91 Time 12-40

Size microns	% under	:	Size band microns	%	:	Result source= Averaged
564.0	100.0	:			:	Record No. = 5
261.7	71.4	:	564.0 261.7	28.6	:	Focal length = 300 mm.
160.4	22.9	:	261.7 160.4	48.6	:	Experiment type pia
112.8	10.6	:	160.4 112.8	12.3	:	Volume distribution
84.3	4.2	:	112.8 84.3	6.4	:	Beam length = 22.0 mm.
64.6	3.0	:	84.3 64.6	1.2	:	Obscuration = 0.2072
50.2	2.3	:	64.6 50.2	0.6	:	Volume Conc. = 0.0534 %
39.0	1.6	:	50.2 39.0	0.7	:	Log. Diff. = 4.08
30.3	1.4	:	39.0 30.3	0.2	:	Model indp
23.7	1.3	:	30.3 23.7	0.1	:	D(v,0.5) = 213.3 um
18.5	1.0	:	23.7 18.5	0.2	:	D(v,0.9) = 342.5 um
14.5	0.8	:	18.5 14.5	0.2	:	D(v,0.1) = 110.2 um
11.4	0.7	:	14.5 11.4	0.1	:	D(4,3) = 220.7 um
9.0	0.5	:	11.4 9.0	0.1	:	D(3,2) = 188.3 um
7.2	0.4	:	9.0 7.2	0.2	:	Span = 1.1
5.8	0.2	:	7.2 5.8	0.1	:	Spec. surf. area
					:	0.0413 sq. m./cc.

System number 2386 Diode #00065 * ALARMS SET B D *

Table C6 Measurement of Crystal size distribution of crystals used in this investigation, Size Fraction 105-150 µm.

System number 2386 Diode #00065 * ALARMS SET D *

Malvern Instruments MASTER Particle Sizer M6.10 Date 04-01-84 Time 23-55

Size microns	% under	:	Size band microns	%	:	Result source= Averaged
564.0	100.0	:			:	Record No. = 1
261.7	97.5	:	564.0 261.7	2.5	:	Focal length = 300 mm.
160.4	72.9	:	261.7 160.4	24.6	:	Experiment type pia
112.8	26.6	:	160.4 112.8	46.4	:	Volume distribution
84.3	10.9	:	112.8 84.3	15.6	:	Beam length = 22.0 mm.
64.6	7.6	:	84.3 64.6	3.3	:	Obscuration = 0.2499
50.2	4.4	:	64.6 50.2	3.2	:	Volume Conc. = 0.0445 %
39.0	2.5	:	50.2 39.0	1.9	:	Log. Diff. = 4.10
30.3	2.0	:	39.0 30.3	0.5	:	Model indp
23.7	1.7	:	30.3 23.7	0.3	:	D(v,0.5) = 135.2 um
18.5	1.4	:	23.7 18.5	0.3	:	D(v,0.9) = 198.8 um
14.5	1.0	:	18.5 14.5	0.4	:	D(v,0.1) = 80.1 um
11.4	0.8	:	14.5 11.4	0.2	:	D(4,3) = 137.6 um
9.0	0.6	:	11.4 9.0	0.2	:	D(3,2) = 120.8 um
7.2	0.4	:	9.0 7.2	0.2	:	Span = 0.9
5.8	0.3	:	7.2 5.8	0.2	:	Spec. surf. area
					:	0.0606 sq. m./cc.

System number 2386 Diode #00065 * ALARMS SET D *

Table C7 Measurement of Crystal size distribution of crystals used in this investigation, Size Fraction 150-210 μm .

System number 2386 Diode #00065 * ALARMS SET D *

Malvern Instruments MASTER Particle Sizer M6.10 Date 04-01-84 Time 00-24

Size microns	% under	:	Size band microns	%	:	Result source= Averaged
564.0	100.0	:			:	Record No. = 2
261.7	87.2	:	564.0	261.7	12.8	Focal length = 300 mm.
160.4	18.0	:	261.7	160.4	69.2	Experiment type pia
112.8	5.7	:	160.4	112.8	12.3	Volume distribution
84.3	2.2	:	112.8	84.3	3.5	Beam length = 22.0 mm.
64.6	1.7	:	84.3	64.6	0.5	Obscuration = 0.1870
50.2	1.0	:	64.6	50.2	0.7	Volume Conc. = 0.0527 %
39.0	0.9	:	50.2	39.0	0.1	Log. Diff. = 3.95
30.3	0.9	:	39.0	30.3	0.0	Model indp
23.7	0.8	:	30.3	23.7	0.0	D(v,0.5) = 202.9 μm
18.5	0.6	:	23.7	18.5	0.2	D(v,0.9) = 268.7 μm
14.5	0.5	:	18.5	14.5	0.1	D(v,0.1) = 141.4 μm
11.4	0.4	:	14.5	11.4	0.1	D(4,3) = 201.2 μm
9.0	0.3	:	11.4	9.0	0.1	D(3,2) = 189.4 μm
7.2	0.2	:	9.0	7.2	0.1	Span = 0.6
5.8	0.1	:	7.2	5.8	0.1	Spec. surf. area
						0.0369 sq. m./cc.

System number 2386 Diode #00065 * ALARMS SET D *

Table C8 Measurement of Crystal size distribution of crystals used in this investigation, Size Fraction 210-300 μm .

System number 2386 Diode #00065 * ALARMS SET D *

Malvern Instruments MASTER Particle Sizer M6.10 Date 04-01-84 Time 00-40

Size microns	% under	:	Size band microns	%	:	Result source= Averaged
564.0	100.0	:			:	Record No. = 3
261.7	47.6	:	564.0	261.7	52.4	Focal length = 300 mm.
160.4	3.8	:	261.7	160.4	43.9	Experiment type pia
112.8	3.8	:	160.4	112.8	0.0	Volume distribution
84.3	1.5	:	112.8	84.3	2.2	Beam length = 22.0 mm.
64.6	0.6	:	84.3	64.6	0.9	Obscuration = 0.2705
50.2	0.6	:	64.6	50.2	0.0	Volume Conc. = 0.1119 %
39.0	0.6	:	50.2	39.0	0.0	Log. Diff. = 4.95
30.3	0.5	:	39.0	30.3	0.0	Model indp
23.7	0.5	:	30.3	23.7	0.0	D(v,0.5) = 266.9 μm
18.5	0.4	:	23.7	18.5	0.1	D(v,0.9) = 411.5 μm
14.5	0.3	:	18.5	14.5	0.1	D(v,0.1) = 186.4 μm
11.4	0.3	:	14.5	11.4	0.0	D(4,3) = 281.3 μm
9.0	0.2	:	11.4	9.0	0.1	D(3,2) = 258.8 μm
7.2	0.1	:	9.0	7.2	0.1	Span = 0.8
5.8	0.1	:	7.2	5.8	0.0	Spec. surf. area
						0.0268 sq. m./cc.

System number 2386 Diode #00065 * ALARMS SET D *

Table C9 Measurement of Crystal size distribution of crystals used in this investigation, Unsieved Fraction.

System number 2386 Diode #00065

Malvern Instruments MASTER Particle Sizer Mk.10 Date 06-10-84 Time 08-20

Size : microns : under	% : in band	Size : microns : under	% : in band	Result source = 2709
564.0 : 100.0	0.0	375.0 : 95.0	1.0	Record No. = 5
562.0 : 100.0	0.0	350.0 : 85.0	0.0	Focal length = 300 mm.
560.0 : 100.0	0.0	325.0 : 91.0	0.0	Exposure type pla
558.0 : 100.0	0.0	300.0 : 87.7	4.0	Volume distribution
556.0 : 100.0	0.0	275.0 : 82.9	5.0	Beam length = 25.0 mm.
555.0 : 100.0	0.0	250.0 : 75.4	8.4	Obscuration = 0.2082
554.0 : 100.0	0.0	225.0 : 68.0	10.0	Volume Conc. = 0.0422 %
552.0 : 100.0	0.0	200.0 : 57.8	11.0	Log. Diff. = 0.00
551.0 : 100.0	0.0	175.0 : 46.4	11.1	Model index
550.0 : 100.0	0.1	150.0 : 35.3	9.0	D(v,0.5) = 132.7 um
525.0 : 99.9	0.2	125.0 : 25.0	10.1	D(v,0.9) = 315.1 um
500.0 : 99.7	0.3	100.0 : 15.4	7.0	D(v,0.1) = 85.0 um
475.0 : 99.5	0.5	75.0 : 7.7	3.1	D(4.3) = 139.5 um
450.0 : 99.0	0.7	50.0 : 4.5	0.6	D(2.2) = 146.0 um
425.0 : 98.3	1.0	25.0 : 2.0	1.0	Span = 1.2
400.0 : 97.2	1.4	5.0 : 0.0	0.0	Spec. surf. area
				0.0522 sq. m./cc.

System number 2386 Diode #00065

APPENDIX D

Data for standard curves

Table D1: Concentrations used and refractive index results for lactose standard solutions at 20°C

Intended Concentration (kg/m ³) anhydrous basis.	Wt. Monohydrate added (grams)	Actual Concentration (kg/m ³) anhydrous basis	Average Refractive index.
5	0.5265	4.982	1.3344
10	1.1071	10.475	1.3351
15	1.5720	14.874	1.3359
20	2.1153	20.015	1.3367
30	3.1729	30.022	1.3382
40	4.2764	40.463	1.3399
50	5.2640	49.808	1.3412
60	6.2994	59.605	1.3429
70	7.2975	69.049	1.3441
80	8.4963	80.392	1.3461
90	9.5262	90.137	1.3474
100	10.5811	100.118	1.3490
120	12.6894	120.067	1.3524
140	14.8371	140.389	1.3551

Table D2: Concentrations used and refractive index results for standard lactose solutions at 25°C

Intended Concentration (kg/m ³) anhydrous basis.	Wt. Monohydrate added (grams)	Actual Concentration (kg/m ³) anhydrous basis	Average Refractive index
5	0.5456	5.16	1.3340
10	1.0550	9.98	1.3348
15	1.5412	14.58	1.3356
30	3.1442	29.75	1.3379
45	4.7669	45.10	1.3403
60	6.3308	59.90	1.3425
80	8.4893	80.33	1.3459
100	10.5529	99.85	1.3488
120	12.7138	120.30	1.3514
140	14.8462	140.47	1.3547

APPENDIX E

Details of regression analysis performed.

Table E1: Regression of Refractive index vs lactose concentration at 20°C

MTB> Regress C2 1 C1

The regression equation is

conc = -8642 + 6480 ref

Predictor	Coef	Stdev	t-ratio	p
Constant	-8641.83	47.00	-183.88	0.000
ref	6480.19	35.00	185.15	0.000

s = 0.8292 R-sq = 100.0% R-sq(adj) = 100.0%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	23571	23578	34278.68	0.000
Error	12	8	1		
Total	13	23579			

Unusual Observations

Obs.	ref	conc	Fit	Stdev.Fit	Residual	St.Resid
13	1.35	120.067	121.977	0.405	-1.910	-2.64R

R denotes a obs. with a large st. resid.

Table E2: Regression of Refractive index vs lactose concentration at 25°C

MTB> Regress C2 1 C1

The regression equation is

conc = -8739 + 6554 ref

Predictor	Coef	Stdev	t-ratio	p
Constant	-8739.17	72.14	-120.69	0.000
ref	6554.28	53.93	121.53	0.000

s = 1.187 R-sq = 99.9% R-sq(adj) = 99.9%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	20808	20808	14768.43	0.000
Error	8	11	1		
Total	9	20819			

Table E3: Regression of density of solution vs lactose concentration at 20°C

MTB> Regress C2 1 C1

The regression equation is

dens = 998 + 0.392 conc

Predictor	Coef	Stdev	t-ratio	p
Constant	998.246	0.150	6662.81	0.000
conc	0.392350	0.001264	310.40	0.000

s = 0.2777 R-sq = 100.0% R-sq(adj) = 100.0%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	7430.0	7430.0	96349.46	0.000
Error	8	0.6	0.1		
Total	9	7430.6			

Unusual Observations

Obs.	conc	dens	Fit	Stdev.Fit	Residual	St.Resid
10	190	1073.57	1072.93	0.15	0.64	2.73R

R denotes a obs. with a large st. resid.

Table E4: Regression of density of solution vs lactose concentration at 25°C

MTB> Regress C2 1 C1

The regression equation is

dens = 997 + 0.390 conc

Predictor	Coef	Stdev	t-ratio	p
Constant	997.124	0.030	33075.38	0.000
conc	0.389662	0.000391	995.50	0.000

s = 0.05584 R-sq = 100.0% R-sq(adj) = 100.0%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	3089.6	3089.6	991013.94	0.000
Error	6	0.0	0.0		
Total	7	3089.6			

Table E5: Regression of density of solution vs lactose concentration at 30°C

MTB> Regress C2 1 C1

The regression equation is

dens = 999 + 0.363 conc

Predictor	Coef	Stdev	t-ratio	p
Constant	998.503	2.146	465.32	0.000
conc	0.363101	0.007614	47.69	0.000

s = 2.843 R-sq = 99.9% R-sq(adj) = 99.8%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	18388	18388	2273.21	0.000
Error	3	24	8		
Total	4	18412			

Table E6: Regression of density of solution vs lactose concentration at 40°C

MTB> Regress C2 1 C1

The regression equation is

dens = 995 + 0.365 conc

Predictor	Coef	Stdev	t-ratio	p
Constant	995.266	2.259	440.57	0.000
conc	0.364738	0.008037	45.38	0.000

s = 2.994 R-sq = 99.9% R-sq(adj) = 99.8%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	18459	18459	2059.62	0.000
Error	3	27	9		
Total	4	18486			

Table E7: Regression of density of solution vs lactose concentration at 50°C

MTB> Regress C2 1 C1

The regression equation is

$$\text{dens} = 992 + 0.368 \text{ conc}$$

Predictor	Coef	Stdev	t-ratio	p
Constant	991.605	2.570	385.89	0.000
conc	0.367600	0.009166	40.10	0.000

s = 3.406 R-sq =99.8% R-sq(adj) = 99.8%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	18654	18654	1608.33	0.000
Error	3	35	12		
Total	4	18689			

Table E8: Regression of density of solution vs lactose concentration at 60°C

MTB> Regress C2 1 C1

The regression equation is

$$\text{dens} = 988 + 0.372 \text{ conc}$$

Predictor	Coef	Stdev	t-ratio	p
Constant	987.782	3.217	307.07	0.000
conc	0.37150	0.01151	32.29	0.000

s = 4.264 R-sq =99.7% R-sq(adj) = 99.6%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	18953	18953	1042.64	0.000
Error	3	55			
Total	4	19008			

Table E9: Regression for determining constants for Surface Reaction.

MTB> Regress C2 1 C1

The regression equation is

$$c2 = 19.9 - 8430 c1$$

Predictor	Coef	Stdev	t-ratio	p
Constant	19.854	3.002	6.61	0.000
c1	-8430.2	887.5	-9.50	0.000

s = 0.5073 R-sq = 89.1%

R-sq(adj) = 88.1%

Analysis of Variance

SOURCE	DF	SS	MS	F	p
Regression	1	23.221	23.221	90.23	0.000
Error	11	2.831	0.257		
Total	12	26.051			

APPENDIX F

Dissolution data for Chapter 3: Data from Hodges (1992)

Table F1: Dissolution above the alpha lactose solubility limit at 25°C and with small crystal size.

Time (min)	Experimental		Hodges	Model
	(%Sucr.)	[kg/m ³]	[kg/m ³]	[kg/m ³]
0	0.00	0.00	0.00	0.00
0.1667	5.20	54.80	66.80	71.80
0.25	6.00	62.77	70.94	73.66
0.3333	6.65	69.25	72.60	74.18
0.4167	7.20	74.73	73.33	74.37
0.5	7.65	79.22	73.68	74.47
0.5833	7.65	79.22	73.87	74.54
0.6667	7.70	79.71	73.99	74.68
0.75	7.80	80.71	74.08	74.61
0.8333	7.85	81.21	74.16	74.75
0.9167	7.90	81.71	74.23	74.81
1	8.05	83.20	74.30	74.88
1.1667	8.05	83.20	74.43	75.01
1.3333	8.10	83.70	74.57	75.14
1.5	8.15	84.20	74.70	75.28
2	8.25	85.20	75.09	75.67
3	8.35	86.19	75.88	76.59
4	8.40	86.69	76.66	77.38
5	8.45	87.19	77.43	78.15
6	8.55	88.19	78.20	78.92
7	8.65	89.18	78.96	79.69
8	8.70	89.68	79.71	80.45
9	8.70	89.68	80.46	81.21
10	8.75	90.18	81.21	81.95
12	8.78	90.48	82.68	83.43
14	8.80	90.68	84.13	84.89
16	8.80	90.68	85.56	86.33
18	8.80	90.68	86.96	87.74
20	8.80	90.68	88.34	89.13
25	8.85	91.18	91.68	92.20
30	8.85	91.18	91.68	92.20
35	8.85	91.18	91.68	92.20
40	8.85	91.18	91.68	92.20
45	8.85	91.18	91.68	92.20
50	8.85	91.18	91.68	92.20

Table F2: Dissolution above the alpha lactose solubility limit at 25°C and with large crystal size.

Time (min)	Experimental		Hodges	Model
	(%Sucr.)	[kg/m ³]	[kg/m ³]	[kg/m ³]
0	0.00	0.00	0.00	0.00
0.1667	3.75	40.34	48.56	48.78
0.25	4.60	48.82	57.04	57.87
0.3333	5.40	56.79	62.22	63.38
0.4167	5.70	59.78	65.60	66.90
0.5	6.20	64.76	67.90	69.22
0.5833	6.40	66.76	69.53	70.81
0.6667	6.55	68.25	70.70	71.91
0.75	6.90	71.74	71.56	72.70
0.8333	7.10	73.73	72.21	73.26
0.9167	7.20	74.73	72.71	73.68
1	7.30	75.73	73.09	74.00
1.1667	7.55	78.22	73.64	74.44
1.3333	7.65	79.22	74.00	74.72
1.5	7.70	79.71	74.27	74.93
2	8.00	82.70	74.80	75.40
3	8.30	85.69	75.62	76.33
4	8.50	87.69	76.40	77.11
5	8.55	88.19	77.17	77.89
6	8.60	88.68	77.93	78.66
7	8.65	89.18	78.69	79.42
8	8.70	89.68	79.44	80.18
9	8.75	90.18	80.18	80.93
10	8.80	90.68	80.92	81.67
12	8.80	90.68	82.38	83.14
14	8.80	90.68	83.82	84.59
16	8.80	90.68	85.23	86.01
18	8.85	91.18	86.62	87.41
20	8.85	91.18	87.98	88.78
25	8.90	91.67	91.22	91.94
30	8.90	91.67	91.22	92.21
35	8.90	91.67	91.22	92.21
40	8.90	91.67	91.22	92.21
45	8.90	91.67	91.22	92.21
50	8.90	91.67	91.22	92.21

Table F3: Dissolution above the alpha lactose solubility limit at 45°C and with large crystal size.

Time (min)	Experimental		Hodges	Model
	(%Sucr.)	[kg/m3]	[kg/m3]	[kg/m3]
0	0.00	0.00	0.00	0.00
0.5	12.10	123.57	123.34	121.69
0.5833	13.70	139.52	123.95	122.29
0.6667	13.90	141.51	124.55	123.45
0.75	14.00	142.51	125.13	122.87
0.8333	14.05	143.00	125.72	124.03
0.9167	14.10	143.50	126.30	124.60
1	14.20	144.50	126.88	125.18
1.1667	14.25	145.00	128.04	126.32
1.3333	14.45	146.99	129.19	127.45
1.5	14.60	148.49	130.33	128.57
2	14.90	151.48	133.70	131.89
3	15.80	160.45	140.26	139.36
4	16.40	166.43	146.50	145.46
5	17.45	176.89	152.48	151.31
6	17.70	179.38	158.21	156.91
7	18.30	185.36	163.70	162.27
8	19.05	192.84	168.97	167.41
9	19.30	195.33	174.02	172.34
10	19.75	199.82	178.86	177.07
12	20.50	207.29	187.96	185.96
14	21.40	216.26	196.35	194.15
16	21.75	219.75	204.09	201.70
18	22.40	226.23	211.24	208.67
20	22.60	228.22	217.83	215.11
25	22.80	230.22	232.21	229.16
30	22.85	230.71	243.97	240.64
35	22.90	231.21	253.45	243.84
40	22.90	231.21	253.45	243.84
45	22.90	231.21	253.45	243.84
50	22.90	231.21	253.45	243.84
55	22.90	231.21	253.45	243.84
60	22.90	231.21	253.45	243.84
65	22.90	231.21	253.45	243.84
70	22.90	231.21	253.45	243.84
75	22.90	231.21	253.45	243.84
80	22.90	231.21	253.45	243.84
85	22.90	231.21	253.45	243.84
90	22.90	231.21	253.45	243.84
95	22.90	231.21	253.45	243.84
100	22.90	231.21	253.45	243.84

Table F4: Dissolution above the alpha lactose solubility limit at 45°C and with small crystal size.

Time	Experimental		Hodges	Model
(min)	(%Sucr.)	[kg/m3]	[kg/m3]	[kg/m3]
0	0.00	0.00	0.00	0.00
0.6667	13.90	141.51	125.05	124.03
0.75	14.40	146.49	125.64	123.45
0.8333	14.55	147.99	126.22	124.61
0.9167	14.65	148.98	126.81	125.18
1	14.80	150.48	127.39	125.76
1.1667	14.25	145.00	128.55	126.90
1.3333	14.50	147.49	129.70	128.03
1.5	14.60	148.49	130.84	129.15
2	14.95	151.97	134.21	132.48
3	16.10	163.44	140.79	139.95
4	16.40	166.43	147.03	146.05
5	17.30	175.40	153.02	151.90
6	17.80	180.38	158.75	157.50
7	18.75	189.85	164.24	162.86
8	18.95	191.84	169.51	168.00
9	19.65	198.82	174.57	172.93
10	20.20	204.30	179.41	177.66
12	20.65	208.79	188.53	186.55
14	21.40	216.26	196.93	194.74
16	22.15	223.74	204.68	202.29
18	22.50	227.23	211.84	209.27
20	22.60	228.22	218.45	215.71
25	22.70	229.22	232.87	229.77
30	22.80	230.22	244.75	241.35
35	22.90	231.21	251.25	243.81
40	22.90	231.21	251.25	243.81
45	22.90	231.21	251.25	243.81
50	22.90	231.21	251.25	243.81
55	22.90	231.21	251.25	243.81
60	22.90	231.21	251.25	243.81
65	22.90	231.21	251.25	243.81
70	22.90	231.21	251.25	243.81
75	22.90	231.21	251.25	243.81
80	22.90	231.21	251.25	243.81
85	22.90	231.21	251.25	243.81
90	22.90	231.21	251.25	243.81

Table F5: Dissolution below the alpha lactose solubility limit at 25°C and with large crystal size.

Time [sec]	Experimental		Hodges	Model
	[%Sucr.]	[kg/m3]	[kg/m3]	[kg/m3]
0	0	0.00	0.00	0.00
2	0.35	6.46	8.03	19.17
4	0.50	7.95	14.41	29.60
6	0.90	11.94	19.58	35.83
8	1.20	14.93	23.82	39.70
10	1.60	18.91	27.36	42.11
12	1.90	21.90	30.33	43.52
14	2.30	25.89	32.84	44.18
16	2.50	27.89	34.99	44.24
18	2.70	29.88	36.82	44.24
20	2.95	32.37	38.40	44.24
22	3.15	34.36	39.74	44.24
24	3.35	36.36	40.90	44.24
26	3.45	37.35	41.88	44.24
28	3.55	38.35	42.70	44.24
30	3.65	39.35	43.38	44.24
32	3.75	40.34	43.92	44.24
34	3.85	41.34	44.33	44.24
36	3.95	42.34	44.58	44.24
38	4.00	42.84	44.58	44.24
40	4.04	43.23	44.58	44.24
42	4.10	43.83	44.58	44.24
44	4.15	44.33	44.58	44.24
46	4.20	44.83	44.58	44.24
48	4.25	45.33	44.58	44.24
50	4.30	45.83	44.58	44.24
52	4.30	45.83	44.58	44.24
54	4.30	45.83	44.58	44.24

Table F6: Dissolution below the alpha lactose solubility limit at 25°C and with small crystal size.

Time [sec]	Experimental		Hodges	Model
	[%Sucr.]	[kg/m3]	[kg/m3]	[kg/m3]
0	0	0.00	0.00	0.00
2	1.20	14.93	18.40	31.08
4	2.30	25.89	29.45	41.57
6	2.80	30.88	36.48	44.24
8	3.40	36.86	41.00	44.24
10	3.70	39.85	43.74	44.24
12	3.80	40.84	43.74	44.24
14	3.95	42.34	43.74	44.24
16	4.05	43.33	43.74	44.24
18	4.15	44.33	43.74	44.24
20	4.20	44.83	43.74	44.24
22	4.25	45.33	43.74	44.24
24	4.30	45.83	43.74	44.24
26	4.30	45.83	43.74	44.24
28	4.30	45.83	43.74	44.24
30	4.30	45.83	43.74	44.24
32	4.30	45.83	43.74	44.24
34	4.30	45.83	43.74	44.24

Table F7: Dissolution below the alpha lactose solubility limit at 45°C and with large crystal size.

Time [sec]	Experimental		Hodges	Model
	[%Sucr.]	[kg/m3]	[kg/m3]	[kg/m3]
0	0	0.00	0.00	0.00
6	2.30	25.89	58.62	89.56
8	3.10	33.87	67.41	92.37
10	4.00	42.84	73.95	92.50
12	4.55	48.32	78.96	92.50
14	5.20	54.80	82.85	92.50
16	5.60	58.78	85.92	92.50
18	6.20	64.76	88.34	92.50
20	6.50	67.75	90.23	92.50
22	6.95	72.24	91.68	92.50
24	7.20	74.73	92.71	92.50
26	7.40	76.72	93.29	92.50
28	7.75	80.21	93.29	92.50
30	7.90	81.71	93.29	92.50
32	8.05	83.20	93.29	92.50
34	8.10	83.70	93.29	92.50
36	8.30	85.69	93.29	92.50
38	8.40	86.69	93.29	92.50
40	8.50	87.69	93.29	92.50
42	8.60	88.68	93.29	92.50
44	8.60	88.68	93.29	92.50
46	8.60	88.68	93.29	92.50

Table F8: Dissolution below the alpha lactose solubility limit at 45°C and with small crystal size.

Time [sec]	Experimental		Hodges	Model
	[%Sucr.]	[kg/m3]	[kg/m3]	[kg/m3]
0	0	0.00	0.00	0.00
6	4.00	42.84	87.56	92.50
8	4.70	49.81	92.64	92.50
10	5.60	58.78	92.64	92.50
12	6.00	62.77	92.64	92.50
14	6.80	70.74	92.64	92.50
16	7.50	77.72	92.64	92.50
18	7.90	81.71	92.64	92.50
20	8.30	85.69	92.64	92.50
22	8.45	87.19	92.64	92.50
24	8.60	88.68	92.64	92.50
26	8.60	88.68	92.64	92.50
28	8.60	88.68	92.64	92.50
30	8.60	88.68	92.64	92.50
32	8.60	88.68	92.64	92.50
34	8.60	88.68	92.64	92.50
36	8.60	88.68	92.64	92.50
38	8.60	88.68	92.64	92.50
40	8.60	88.68	92.64	92.50

Table F9: Dissolution of lactose at 25°C at stirring speeds 200 and 400 rpm.

Time (sec)	Stirring Speed 200 rpm				Stirring Speed 400 rpm			
	ref. ind.	[kg/m ³]	ref. ind.	[kg/m ³]	ref. ind.	[kg/m ³]	ref. ind.	[kg/m ³]
0	1.334	4.27	1.3338	2.96	1.3336	1.65	1.3333	-0.32
1	1.334	4.27	1.334	4.27	1.334	4.27	1.3334	0.34
2	1.334	4.27	1.3342	5.58	1.3344	6.90	1.3338	2.96
3	1.3345	7.55	1.3346	8.21	1.335	10.83	1.3339	3.62
4	1.335	10.83	1.335	10.83	1.3357	15.42	1.3341	4.93
5	1.3355	14.11	1.3352	12.14	1.336	17.38	1.3346	8.21
6	1.3355	14.11	1.3356	14.76	1.336	17.38	1.3348	9.52
7	1.336	17.38	1.3358	16.07	1.336	17.38	1.335	10.83
8	1.3365	20.66	1.3361	18.04	1.3363	19.35	1.335	10.83
9	1.3365	20.66	1.3364	20.01	1.3364	20.01	1.3355	14.11
10	1.3369	23.28	1.3368	22.63	1.3368	22.63	1.3358	16.07
11	1.3374	26.56	1.337	23.94	1.3368	22.63	1.3362	18.70
12	1.3376	27.87	1.3371	24.60	1.3372	25.25	1.3364	20.01
14	1.338	30.50	1.3376	27.87	1.3375	27.22	1.3368	22.63
16	1.338	30.50	1.3377	28.53	1.338	30.50	1.3371	24.60
18	1.3384	33.12	1.3379	29.84	1.3381	31.15	1.3373	25.91
20	1.3387	35.09	1.338	30.50	1.3386	34.43	1.3377	28.53
22	1.3394	39.67	1.3383	32.46	1.339	37.05	1.3379	29.84
24	1.3393	39.02	1.3387	35.09	1.339	37.05	1.3385	33.77
26	1.3393	39.02	1.3387	35.09	1.3395	40.33	1.3383	32.46
28	1.3395	40.33	1.339	37.05	1.3395	40.33	1.3387	35.09
30	1.3397	41.64	1.3391	37.71	1.3397	41.64	1.339	37.05
32	1.3398	42.30	1.3391	37.71	1.3402	44.92	1.3389	36.40
34	1.34	43.61	1.3392	38.36	1.34	43.61	1.3392	38.36
36	1.34	43.61	1.3395	40.33	1.3402	44.92	1.3395	40.33
38	1.3401	44.26	1.3396	40.99	1.3404	46.23	1.3395	40.33
40	1.3399	42.95	1.3397	41.64	1.3405	46.89	1.3396	40.99
42	1.3401	44.26	1.3398	42.30	1.3404	46.23	1.3399	42.95
44	1.3402	44.92	1.3399	42.95	1.3405	46.89	1.3398	42.30
46	1.3401	44.26	1.34	43.61	1.3408	48.85	1.34	43.61
48	1.3403	45.57	1.3399	42.95	1.3409	49.51	1.3401	44.26
50	1.3403	45.57	1.34	43.61	1.3406	47.54	1.3402	44.92
52	1.3404	46.23	1.34	43.61	1.3408	48.85	1.3403	45.57
62	1.3407	48.20	1.3402	44.92	1.3409	49.51	1.3404	46.23
72	1.3406	47.54	1.3402	44.92	1.341	50.16	1.3407	48.20
82			1.3406	47.54	1.341	50.16	1.3408	48.85
Final Conc:		47.5		44.9		50.8		48.9

Table F10: Dissolution of lactose at 25°C at stirring speeds 600 and 800 rpm.

Time (sec)	Stirring Speed 600 rpm				Stirring Speed 800 rpm			
	ref. ind.	[kg/m3]	ref. ind.	[kg/m3]	ref. ind.	[kg/m3]	ref. ind.	[kg/m3]
0	1.3336	1.65	1.3333	-0.32	1.3335	0.99		
1	1.3336	1.65	1.3339	3.62	1.3337	2.31		
2	1.3338	2.96	1.3338	2.96	1.3339	3.62	1.3348	9.52
3	1.3344	6.90	1.3341	4.93	1.334	4.27	1.3351	11.48
4	1.3349	10.17	1.3345	7.55	1.3344	6.90	1.3352	12.14
5	1.3352	12.14	1.335	10.83	1.3349	10.17	1.3358	16.07
6	1.3356	14.76	1.335	10.83	1.3353	12.80		
7	1.3358	16.07	1.3355	14.11	1.3355	14.11	1.3361	18.04
8	1.3361	18.04	1.3358	16.07	1.336	17.38	1.3368	22.63
9	1.3365	20.66	1.3361	18.04	1.3363	19.35	1.3373	25.91
10	1.3366	21.32	1.3363	19.35	1.3367	21.97	1.3376	27.87
11	1.337	23.94	1.3368	22.63	1.3368	22.63	1.33743	26.76
12	1.3371	24.60	1.337	23.94	1.3371	24.60	1.3373	25.91
14	1.3378	29.19	1.3372	25.25	1.3375	27.22	1.3376	27.87
16	1.3385	33.77	1.338	30.50	1.3378	29.19	1.3376	27.87
18	1.3382	31.81	1.3382	31.81	1.3381	31.15	1.3383	32.46
20	1.3385	33.77	1.3388	35.74	1.3384	33.12	1.3382	31.81
22	1.3389	36.40	1.339	37.05	1.3389	36.40	1.3389	36.40
24	1.3392	38.36	1.339	37.05	1.3391	37.71	1.339	37.05
26	1.3397	41.64	1.3394	39.67	1.3393	39.02	1.3392	38.36
28	1.3395	40.33	1.3396	40.99	1.3395	40.33	1.3393	39.02
30	1.3397	41.64	1.3398	42.30	1.3397	41.64	1.3395	40.33
32	1.34	43.61	1.3401	44.26	1.34	43.61	1.3398	42.30
34	1.3403	45.57	1.3401	44.26	1.34	43.61	1.34	43.61
36	1.3403	45.57	1.3402	44.92	1.34	43.61	1.34	43.61
38	1.3406	47.54	1.3405	46.89	1.3402	44.92	1.34	43.61
40	1.3405	46.89	1.3404	46.23	1.3401	44.26	1.3405	46.89
42	1.3403	45.57	1.3402	44.92	1.3403	45.57	1.3406	47.54
44	1.3406	47.54	1.3406	47.54	1.3403	45.57	1.3406	47.54
46	1.3405	46.89	1.3405	46.89	1.3404	46.23	1.3405	46.89
48	1.341	50.16	1.3407	48.20	1.3405	46.89	1.3407	48.20
50	1.3409	49.51	1.3409	49.51	1.3407	48.20	1.341	50.16
52	1.3408	48.85	1.3409	49.51	1.3405	46.89	1.3411	50.82
62	1.3409	49.51	1.3408	48.85	1.34	43.61	1.341	50.16
72	1.3408	48.85	1.3411	50.82	1.3408	48.85	1.341	50.16
82	1.341	50.16	1.341	50.16	1.3406	47.54	1.3411	50.82
Final Conc:		50.2		50.2		48.2		50.2

APPENDIX G

Dissolution data for Chapter 4: Fitting surface reaction rate.

Table G1: Dissolution data for large particle sizes at 4 deg C.

Time (sec)	Experimental Data				Model	
	Ref index	[kg/m ³]	Ref index	[kg/m ³]	No Reaction	Reaction
0					0	0
3	1.334	2.75			1.5144	0.91215
4	1.3339	2.10			2.0019	1.209
5	1.3339	2.10			2.481	1.5022
6	1.334	2.75	1.334	2.75	2.952	1.792
7	1.334	2.75			3.4148	2.0783
8	1.334	2.75	1.334	2.75	3.8699	2.3613
9	1.334	2.75			4.3172	2.6409
10	1.3341	3.40	1.3341	3.40	4.7569	2.9173
12	1.3343	4.69	1.3342	4.04	5.6143	3.4603
14	1.3344	5.34	1.3342	4.04	6.4431	3.9907
16	1.3343	4.69	1.3343	4.69	7.2446	4.5088
18	1.3343	4.69	1.3344	5.34	8.0196	5.0151
20	1.3345	5.99	1.3345	5.99	8.7692	5.5098
22	1.3345	5.99	1.3346	6.64	9.4943	5.9932
24	1.3347	7.29	1.3348	7.94	10.196	6.4656
26	1.3348	7.94	1.3348	7.94	10.874	6.9274
28	1.3349	8.59	1.3349	8.59	11.531	7.3788
30	1.3349	8.59	1.335	9.24	12.167	7.8201
32	1.3349	8.59			12.782	8.2516
34	1.335	9.24			13.377	8.6734
35			1.3351	9.89	13.667	8.8808
36	1.335	9.24			13.953	9.086
38	1.335	9.24			14.51	9.4894
40	1.335	9.24	1.3353	11.18	15.049	9.8839
42	1.335	9.24			15.571	10.27
44	1.3353	11.18			16.076	10.647
45			1.3352	10.53	16.322	10.833
46	1.3355	12.48			16.564	11.016
48	1.3352	10.53			17.037	11.378
50	1.3353	11.18	1.3354	11.83	17.494	11.731
55			1.3356	13.13	18.571	12.581
60	1.3354	11.83	1.3358	14.43	19.559	13.386
65	1.3358	14.43	1.3358	14.43	20.463	14.149
70	1.3358	14.43	1.3359	15.08	21.288	14.871
75	1.3358	14.43	1.336	15.73	22.036	15.556
80	1.336	15.73	1.3359	15.08	22.709	16.204
85	1.336	15.73	1.336	15.73	23.309	16.818
90	1.336	15.73	1.336	15.73	23.835	17.4
95	1.336	15.73	1.3363	17.67	24.284	17.951
100	1.336	15.73	1.3364	18.32	24.648	18.473
110	1.3362	17.02	1.3366	19.62	25.002	19.434
120	1.3363	17.67	1.3366	19.62	25.002	20.293
130	1.3365	18.97	1.3366	19.62	25.002	21.059
140	1.3365	18.97	1.3369	21.57	25.002	21.738
150	1.3367	20.27	1.337	22.21	25.002	22.338
160	1.3369	21.57	1.337	22.21	25.002	22.865
170	1.3369	21.57	1.3371	22.86	25.002	23.322

Table G1: Cont

Time (sec)	Experimental Data				Model	
	Ref index	[kg/m ³]	Ref index	[kg/m ³]	No Reactio	Reaction
180	1.3369	21.57	1.3371	22.86	25.002	23.715
190	1.337	22.21	1.3371	22.86	25.002	24.047
200			1.3371	22.86	25.002	24.322
210			1.3372	23.51	25.002	24.544
220			1.3372	23.51	25.002	24.717
230			1.3374	24.81	25.002	24.843
240			1.3373	24.16	25.002	24.928
270			1.3373	24.16	25.002	25.002
300			1.3375	25.46	25.002	25.002
330			1.3374	24.81	25.002	25.002
360			1.3373	24.16	25.002	25.002
390			1.3375	25.46	25.002	25.002
420			1.3373	24.16	25.002	25.002
450			1.3374	24.81	25.002	25.002
480			1.3374	24.81	25.002	25.002
510			1.3371	22.86	25.002	25.002
540			1.3375	25.46	25.002	25.002
570			1.3374	24.81	25.002	25.002

Table G2: Dissolution data for large particle sizes at 15 deg C.

Time (sec)	Experimental Data				Model	
	Ref index	[kg/m ³]	Ref index	[kg/m ³]	No Reactio	Reaction
0	1.3338	1.45			0	0
3	1.3338	1.45	1.3337	0.80	2.8746	2.212
4	1.3337	0.80	1.3339	2.10	3.7786	2.9139
5	1.3339	2.10	1.3339	2.10	4.6569	3.5989
6	1.334	2.75	1.334	2.75	5.5102	4.2674
7	1.334	2.75	1.3341	3.39	6.3393	4.9199
8	1.334	2.75	1.3341	3.39	7.1449	5.5567
9	1.3341	3.39	1.3343	4.69	7.9277	6.1782
10	1.3343	4.69	1.3342	4.04	8.6882	6.7849
11			1.3343	4.69	9.4271	7.3771
12	1.3345	5.99	1.3346	6.64	10.145	7.9551
13			1.3348	7.94	10.843	8.5193
14	1.3348	7.94	1.3348	7.94	11.52	9.07
15			1.3349	8.58	12.178	9.6076
16	1.335	9.23	1.3349	8.58	12.817	10.132
17			1.335	9.23	13.438	10.644
18	1.335	9.23	1.335	9.23	14.04	11.144
19			1.335	9.23	14.625	11.632
20	1.3351	9.88	1.335	9.23	15.193	12.108
22	1.3353	11.18	1.3352	10.53	16.277	13.026
24	1.3354	11.83	1.3353	11.18	17.297	13.899
26	1.3357	13.77	1.3357	13.77	18.254	14.731
28	1.3358	14.42	1.3355	12.48	19.15	15.521
30	1.3358	14.42	1.3357	13.77	19.986	16.273
32	1.3359	15.07	1.3359	15.07	20.765	16.986
34	1.3361	16.37	1.3359	15.07	21.486	17.663
36	1.3361	16.37	1.336	15.72	22.15	18.305
38	1.3362	17.02	1.3361	16.37	22.757	18.913
40	1.3363	17.66	1.336	15.72	23.305	19.488

Table G2: Cont.

Time (sec)	Experimental Data				Model	
	Ref index	[kg/m ³]	Ref index	[kg/m ³]	No Reactio	Reaction
42			1.3362	17.02	23.792	20.03
44			1.3362	17.02	24.214	20.541
45	1.3368	20.91	1.3364	18.31	24.399	20.785
46			1.3362	17.02	24.564	21.022
48			1.3364	18.31	24.826	21.473
50	1.3368	20.91	1.3364	18.31	24.945	21.894
52			1.3367	20.26	24.945	22.287
54			1.3365	18.96	24.945	22.651
55	1.3369	21.56			24.945	22.823
56			1.3367	20.26	24.945	22.987
58			1.3366	19.61	24.945	23.296
60	1.3369	21.56	1.3366	19.61	24.945	23.578
65			1.3369	21.56	24.945	24.165
70	1.337	22.20	1.337	22.20	24.945	24.584
75			1.337	22.20	24.945	24.838
80	1.33741	24.86	1.337	22.20	24.945	24.939
85			1.3371	22.85	24.945	24.945
90	1.3373	24.15	1.3371	22.85	24.945	24.945
95			1.3371	22.85	24.945	24.945
100	1.3373	24.15	1.3371	22.85	24.945	24.945
105			1.3371	22.85	24.945	24.945
110	1.3375	25.45	1.3372	23.50	24.945	24.945
120	1.3375	25.45	1.3373	24.15	24.945	24.945
130	1.3376	26.10	1.3379	28.04	24.945	24.945
140	1.3374	24.80	1.3372	23.50	24.945	24.945
150	1.3374	24.80	1.3374	24.80	24.945	24.945
160	1.3378	27.39	1.3372	23.50	24.945	24.945
170	1.3375	25.45	1.3373	24.15	24.945	24.945
180			1.3372	23.50	24.945	24.945
190			1.3372	23.50	24.945	24.945
200			1.3373	24.15	24.945	24.945
210			1.3372	23.50	24.945	24.945

Table G3: Dissolution data for large particle sizes at 25 deg C.

Time (sec)	Experimental Data				Model	
	Ref index	[kg/m3]	Ref index	[kg/m3]	No Reactio	Reaction
0			1.3338	1.45	0	0
2			1.3338	1.45	5.9464	5.2317
3	1.3339	2.09	1.3339	2.10	8.662	7.6405
4	1.334	2.74	1.3344	5.34	11.223	9.9235
5	1.3345	5.98	1.335	9.22	13.639	12.089
6	1.335	9.21	1.3353	11.17	15.921	14.144
7	1.3355	12.45	1.3358	14.41	18.078	16.096
8	1.336	15.69	1.336	15.70	20.119	17.952
9	1.3362	16.98	1.3362	17.00	22.05	19.716
10	1.3363	17.63	1.3366	19.59	23.88	21.395
11	1.3367	20.22	1.3369	21.54	25.613	22.993
12	1.3369	21.51	1.3372	23.48	27.256	24.515
13	1.3371	22.80	1.3372	23.48	28.815	25.965
14	1.3372	23.45	1.3375	25.42	30.294	27.347
15	1.3377	26.69	1.3378	27.37	31.697	28.665
16	1.3379	27.98	1.3382	29.96	33.03	29.923
17	1.338	28.63	1.3382	29.96	34.295	31.122
18	1.3381	29.28	1.3383	30.61	35.496	32.266
19	1.3382	29.92	1.3385	31.90	36.637	33.359
20	1.3387	33.16	1.3387	33.20	37.72	34.401
22	1.339	35.10	1.3388	33.85	39.725	36.347
24	1.3392	36.40	1.339	35.14	41.529	38.12
26	1.3393	37.04	1.3393	37.09	43.149	39.736
28	1.3397	39.63	1.3398	40.33	44.597	41.206
30	1.34	41.57	1.3399	40.98	45.883	42.541
32	1.34	41.57	1.34	41.62	47.014	43.751
34	1.3401	42.22	1.34	41.62	47.993	44.844
36	1.3402	42.87	1.3403	43.57	48.818	45.827
38	1.3405	44.81	1.3403	43.57	49.477	46.703
40	1.3406	45.46	1.3407	46.16	49.94	47.479
42	1.3409	47.40	1.3408	46.81	50.069	48.156
44	1.341	48.04	1.3409	47.46	50.069	48.737
46	1.3409	47.40	1.341	48.10	50.069	49.221
48	1.3408	46.75	1.341	48.10	50.069	49.607
50	1.341	48.04	1.341	48.10	50.069	49.892
55			1.3412	49.40	50.069	50.144
60	1.3411	48.69	1.3414	50.70	50.069	50.144
70	1.3413	49.99	1.3416	51.99	50.069	50.144
80	1.3413	49.99	1.3419	53.94	50.069	50.144
90	1.3414	50.63	1.3416	51.99	50.069	50.144
100	1.3414	50.63	1.3418	53.29	50.069	50.144
110			1.3418	53.29	50.069	50.144
120			1.3419	53.94	50.069	50.144
130			1.3417	52.64	50.069	50.144

Table G4: Dissolution data for large particle sizes at 37 deg C.

Time (sec)	Experimental Data								Model	
	Ref ind.	[kg/m ³]	Ref ind.	[kg/m ³]	Ref ind.	[kg/m ³]	Ref ind.	[kg/m ³]	No Rea.	Reaction
0			1.3337	0.80			1.334	2.74	0.00	0.00
3	1.334	2.74	1.3339	2.09	1.3342	4.03	1.3342	4.03	31.02	29.36
4	1.3359	15.01	1.335	9.20	1.3369	21.47	1.336	15.66	38.66	36.70
5	1.3375	25.35	1.3375	25.35	1.3385	31.81	1.3386	32.45	45.35	43.15
6	1.3386	32.45	1.34	41.49	1.34	41.49	1.3399	40.84	51.22	48.85
7	1.34	41.49	1.3416	51.81	1.341	47.94	1.3418	53.10	56.40	53.91
8	1.3406	45.36	1.3422	55.68	1.3417	52.46	1.3429	60.20	61.00	58.42
9	1.3417	52.46	1.3438	66.00	1.3424	56.97	1.3438	66.00	65.10	62.45
10	1.3423	56.33	1.3442	68.58	1.343	60.84	1.3441	67.94	68.76	66.08
11	1.3428	59.55	1.3446	71.16	1.3432	62.13	1.3452	75.03	72.05	69.34
12	1.3434	63.42	1.3448	72.45	1.3441	67.94	1.3454	76.32	75.01	72.30
13	1.3439	66.65	1.3451	74.39	1.3449	73.10	1.3461	80.83	77.68	74.97
14	1.3442	68.58	1.3456	77.61	1.3448	72.45	1.3468	85.34	80.10	77.41
15	1.3447	71.81	1.3456	77.61	1.3454	76.32	1.347	86.63	82.29	79.62
16	1.3449	73.10	1.3468	85.34	1.3458	78.90	1.3468	85.34	84.29	81.64
17	1.3452	75.03	1.3472	87.92	1.3463	82.12	1.3468	85.34	86.10	83.49
18	1.3455	76.97	1.3469	85.99	1.346	80.19	1.3462	81.48	87.75	85.18
19	1.3456	77.61	1.3472	87.92	1.3462	81.48	1.347	86.63	89.26	86.73
20	1.346	80.19	1.3473	88.57	1.3464	82.77	1.348	93.08	90.64	88.15
22	1.3465	83.41	1.3473	88.57	1.347	86.63	1.3479	92.43	93.05	90.66
24	1.3467	84.70	1.348	93.08	1.347	86.63	1.3474	89.21	95.06	92.79
26	1.347	86.63	1.3483	95.01	1.3471	87.28	1.3473	88.57	96.73	94.58
28	1.3474	89.21	1.3484	95.65	1.3474	89.21	1.3472	87.92	98.09	96.09
30	1.3473	88.57	1.3485	96.30	1.3474	89.21	1.348	93.08	99.17	97.35
32	1.3475	89.86	1.3486	96.94	1.3478	91.79	1.3482	94.37	99.97	98.39
34	1.348	93.08	1.3492	100.81	1.3479	92.43	1.3476	90.50	100.38	99.22
36	1.348	93.08	1.3482	94.37	1.3472	87.92	1.3479	92.43	100.38	99.84
38	1.348	93.08	1.3489	98.87	1.3482	94.37	1.3482	94.37	100.38	100.24
40	1.348	93.08	1.3489	98.87	1.3486	96.94	1.3485	96.30	100.38	100.38
42	1.3484	95.65	1.349	99.52	1.3487	97.59	1.3484	95.65	100.38	100.38
44	1.3487	97.59	1.349	99.52	1.3485	96.30	1.349	99.52	100.38	100.38
46	1.3485	96.30	1.3486	96.94	1.3483	95.01	1.3492	100.81	100.38	100.38
48	1.3485	96.30	1.349	99.52	1.3486	96.94	1.3492	100.81	100.38	100.38
50	1.3485	96.30	1.3491	100.16	1.3489	98.87	1.349	99.52	100.38	100.38
55			1.3493	101.45	1.3489	98.87	1.349	99.52	100.38	100.38
60	1.3489	98.87	1.3495	102.74	1.3492	100.81	1.3495	102.74	100.38	100.38
65	1.3496	103.38	1.3493	101.45	1.3491	100.16	1.349	99.52	100.38	100.38
70	1.3493	101.45	1.3495	102.74	1.3491	100.16	1.349	99.52	100.38	100.38
75	1.3495	102.74	1.3494	102.10	1.3493	101.45	1.3498	104.67	100.38	100.38
80	1.3493	101.45	1.349	99.52	1.3494	102.10	1.3494	102.10	100.38	100.38
85	1.3493	101.45	1.3495	102.74	1.3495	102.74			100.38	100.38
90	1.3492	100.81	1.349	99.52	1.3495	102.74	1.3497	104.03	100.38	100.38
95	1.3494	102.10	1.3492	100.81	1.3495	102.74			100.38	100.38
100	1.3493	101.45	1.3497	104.03	1.3492	100.81	1.3498	104.67	100.38	100.38
110	1.3495	102.74	1.349	99.52	1.3497	104.03	1.3495	102.74	100.38	100.38
120			1.3494	102.10	1.3495	102.74	1.3493	101.45	100.38	100.38
130			1.349	99.52	1.3495	102.74	1.3494	102.10	100.38	100.38
140					1.3494	102.10			100.38	100.38

Table G5: Dissolution data for large particle sizes at 50 deg C.

Time (sec)	Experimental Data				Model	
	Ref inde	[kg/m3]	Ref inde	[kg/m3]	No Reac	Reaction
0					0	0
3	1.3367	20.10	1.3341	3.37	62.388	61.025
4	1.3418	52.86	1.3384	31.02	75.004	73.486
5	1.3427	58.64	1.342	54.15	85.22	83.614
6	1.3448	72.12	1.3447	71.47	93.588	91.939
7	1.3468	84.94	1.3462	81.09	100.5	98.84
8	1.3472	87.50	1.3472	87.50	106.24	104.6
9	1.3478	91.35	1.348	92.63	111.02	109.41
10	1.3491	99.68	1.349	99.04	115	113.44
11	1.3497	103.52	1.3492	100.32	118.28	116.8
12	1.3502	106.72	1.3501	106.08	120.94	119.56
13	1.351	111.84	1.3504	108.00	123.01	121.78
14	1.351	111.84	1.3509	111.20	124.45	123.47
15	1.3508	110.56	1.3513	113.76	124.91	124.59
16	1.3518	116.96	1.3508	110.56	124.91	124.91
17	1.3519	117.60	1.3511	112.48	124.91	124.91
18	1.352	118.24	1.3518	116.96	124.91	124.91
19	1.3527	122.72	1.352	118.24	124.91	124.91
20	1.353	124.64	1.3522	119.52	124.91	124.91
22			1.3522	119.52	124.91	124.91
24			1.3525	121.44	124.91	124.91
26			1.353	124.64	124.91	124.91
28			1.3531	125.28	124.91	124.91
30	1.3526	122.08	1.3532	125.92	124.91	124.91
40	1.3529	124.00	1.353	124.64	124.91	124.91
50	1.353	124.64	1.3535	127.84	124.91	124.91
60	1.3526	122.08	1.3529	124.00	124.91	124.91
70	1.3528	123.36	1.353	124.64	124.91	124.91

Table G6: Dissolution data for large particle sizes at 70 deg C.

Time (sec)	Experimental Data				Experimental Data				Model
	Ref inde	[kg/m3]	Ref inde	[kg/m3]	Ref inde	[kg/m3]	Ref inde	[kg/m3]	
0	1.3336	0.15			1.334	2.70	1.3338	1.43	0
3	1.3398	39.67	1.3398	39.67	1.3363	17.37	1.3345	5.89	168.16
4	1.356	142.42	1.3338	1.43	1.3498	103.18	1.358	155.06	186.7
5	1.363	186.60	1.336	15.46	1.3593	163.26	1.3623	182.18	198.36
6	1.3645	196.04	1.349	98.11	1.3619	179.66	1.364	192.89	204.09
7	1.3639	192.26	1.36	167.68	1.3625	183.44	1.3623	182.18	204.09
8	1.3645	196.04	1.3625	183.44	1.364	192.89	1.3626	184.07	204.09
9	1.3651	199.82	1.3636	190.38	1.3652	200.45	1.3627	184.70	204.09
10	1.365	199.19	1.363	186.60	1.3655	202.34	1.3636	190.38	204.09
11			1.3631	187.23	1.3657	203.60	1.3635	189.75	204.09
12			1.3636	190.38	1.3654	201.71	1.3638	191.64	204.09
13			1.3635	189.75	1.3653	201.08	1.3634	189.12	204.09
14			1.3659	204.86			1.3643	194.78	204.09
15			1.3655	202.34			1.3648	197.93	204.09
16			1.3528	122.18			1.3644	195.41	204.09
17			1.3638	191.64			1.366	205.49	204.09
18			1.365	199.19			1.3658	204.23	204.09
19					1.3658	204.23	1.3656	202.97	204.09
20							1.3656	202.97	204.09

Table G7: Dissolution data for medium particle sizes at 15 deg C.

Time (sec)	Experimental Data			
	Ref index	[kg/m ³]	Ref index	[kg/m ³]
0				
3	1.3339	2.10	1.334	2.75
4	1.3338	1.45	1.334	2.75
5	1.3339	2.10	1.334	2.75
6	1.334	2.75	1.3342	4.04
7	1.3342	4.04	1.3343	4.69
8	1.3342	4.04	1.3344	5.34
9	1.3345	5.99	1.3346	6.64
10	1.3347	7.29	1.3348	7.94
11	1.3349	8.58	1.335	9.23
12	1.335	9.23	1.335	9.23
13	1.335	9.23	1.3351	9.88
14	1.3351	9.88	1.3353	11.18
15	1.3351	9.88	1.3355	12.48
16	1.3355	12.48	1.3358	14.42
17	1.3354	11.83	1.336	15.72
18	1.3355	12.48	1.3359	15.07
19	1.3355	12.48	1.3359	15.07
20	1.3358	14.42	1.336	15.72
22	1.3359	15.07	1.3362	17.02
24	1.3361	16.37	1.3362	17.02
26	1.3365	18.96	1.3364	18.31
28	1.3363	17.66	1.3365	18.96
30	1.3364	18.31	1.3365	18.96
32	1.3367	20.26	1.3368	20.91
34	1.3366	19.61	1.3368	20.91
36	1.3368	20.91	1.3369	21.56
38	1.3368	20.91	1.337	22.20
40	1.3369	21.56	1.3371	22.85
42	1.3371	22.85	1.3371	22.85
44	1.337	22.20	1.3372	23.50
46	1.3372	23.50	1.3373	24.15
48	1.3371	22.85	1.3373	24.15
50	1.3372	23.50	1.3375	25.45
60	1.3373	24.15	1.3376	26.10
70	1.3373	24.15	1.3375	25.45
80	1.3375	25.45	1.3376	26.10
90	1.3373	24.15	1.3377	26.74
100	1.3373	24.15		

Table G8: Dissolution data for medium particle sizes at 25 deg C.

Time (sec)	Experimental Data			
	Ref index	[kg/m3]	Ref index	[kg/m3]
0				
3	1.3337	0.80	1.334	2.74
4	1.3342	4.03	1.3345	5.98
5	1.3349	8.57	1.3352	10.51
6	1.3355	12.45	1.3358	14.39
7	1.3361	16.33	1.3361	16.33
8	1.3367	20.22	1.3367	20.22
9	1.3371	22.80	1.337	22.16
10	1.3377	26.69	1.3377	26.69
11	1.3383	30.57	1.3381	29.28
12	1.3384	31.22	1.3385	31.87
13	1.3385	31.87	1.3387	33.16
14	1.339	35.10	1.3389	34.45
15	1.3392	36.40	1.3392	36.40
16	1.3395	38.34	1.3392	36.40
17	1.3397	39.63	1.3396	38.98
18	1.3397	39.63	1.3398	40.28
19	1.34	41.57	1.34	41.57
20	1.3402	42.87	1.34	41.57
22	1.3405	44.81	1.3402	42.87
24	1.3408	46.75	1.3404	44.16
26	1.3412	49.34	1.3407	46.10
28	1.3412	49.34	1.341	48.04
30	1.3413	49.99	1.3412	49.34
32	1.3414	50.63	1.3412	49.34
34	1.3417	52.57	1.3413	49.99
36	1.3415	51.28	1.3413	49.99
38	1.3417	52.57	1.3415	51.28
40	1.3415	51.28	1.3415	51.28
42	1.3416	51.93		
44	1.342	54.52		
46	1.3417	52.57		
48	1.3414	50.63		
50	1.3414	50.63	1.3416	51.93
60	1.3413	49.99	1.3414	50.63
70	1.3412	49.34	1.3414	50.63
80	1.3412	49.34	1.3415	51.28
90	1.3414	50.63	1.3413	49.99
100	1.3412	49.34		

Table G9: Dissolution data for medium particle sizes at 50 deg C.

Time (sec)	Experimental Data					
	Ref index	[kg/m3]	Ref index	[kg/m3]	Ref index	[kg/m3]
0						
3	1.3342	4.01	1.3392	36.17	1.3387	32.95
4	1.342	54.15	1.345	73.40	1.3457	77.89
5	1.3473	88.14	1.3474	88.78	1.3489	98.40
6	1.3505	108.64	1.3483	94.55	1.3501	106.08
7	1.351	111.84	1.3499	104.80	1.3508	110.56
8	1.3525	121.44	1.3509	111.20	1.3515	115.04
9	1.353	124.64	1.3512	113.12	1.352	118.24
10	1.3535	127.84	1.352	118.24	1.3528	123.36
11	1.3536	128.48	1.3527	122.72	1.3529	124.00
12			1.3534	127.20	1.353	124.64
13			1.3536	128.48	1.3533	126.56
14			1.3537	129.12	1.3532	125.92
15			1.3538	129.76	1.3535	127.84
16			1.3543	132.96	1.3532	125.92
17			1.3533	126.56	1.3535	127.84
18			1.3541	131.68	1.3537	129.12
19			1.3538	129.76	1.3535	127.84
20			1.3532	125.92	1.3534	127.20
22			1.3532	125.92		
24			1.3539	130.19		
26			1.3533	126.53		
28			1.353	124.70		
30			1.3528	123.36	1.352	118.24
40			1.353	124.64	1.353	124.64
50			1.3535	127.84	1.3525	121.44
60			1.3535	127.84	1.3526	122.08
70					1.352	118.24
80					1.352	118.24
90					1.352	118.24

Table G10: Dissolution data for medium particle sizes at 70 deg C.

Time (sec)	Experimental Data			
	Ref inde	[kg/m3]	Ref inde	[kg/m3]
0				
3			1.3344	5.25
4	1.3498	103.18	1.343	60.02
5	1.3575	151.90	1.3555	139.26
6	1.3628	185.33	1.3628	185.33
7	1.3645	196.04	1.366	205.49
8	1.366	205.49	1.3674	214.29
9	1.366	205.49	1.3672	213.04
10	1.3665	208.63	1.3662	206.74
11	1.3652	200.45		
12	1.3668	210.52		
13	1.366	205.49		
14	1.3652	200.45		
15	1.3667	209.89		
16	1.367	211.78		
17	1.363	186.60		
18	1.3666	209.26		
19	1.3678	216.81		
20	1.3665	208.63		
22	1.365	199.19		
24	1.3669	211.15		
26	1.3645	196.04		

APPENDIX H

Dissolution data for Chapter 5: Multiple crystal sizes.

Table H1: Dissolution data for dissolving above the alpha lactose solubility limit

Time		Constant Area Experimental Data				Model	
(sec)	(min)	Ref. Inde	[kg/m3]	Ref. Inde	[kg/m3]	Multiple	Avg
0				1.3339	2.09	0.00	0.00
5	0.0833	1.3403	43.51	1.3368	20.86	42.69	50.08
10	0.1667	1.3427	59.05	1.3414	50.63	61.62	68.91
15	0.25	1.3438	66.16	1.3435	64.22	71.34	77.11
20	0.3333	1.3445	70.69	1.3447	71.99	76.59	81.19
25	0.4167	1.3449	73.28	1.345	73.93	79.74	83.15
30	0.5	1.3451	74.57	1.345	73.93	81.70	84.19
35	0.5833	1.3459	79.75			82.97	84.75
40	0.6667	1.3459	79.75	1.3453	75.87	83.81	85.08
45	0.75	1.3458	79.10			84.38	85.28
50	0.8333	1.346	80.40	1.346	80.40	84.77	85.41
55	0.9167	1.346	80.40			85.04	85.51
60	1	1.346	80.40	1.346	80.40	85.25	85.59
70	1.1667	1.3461	81.04	1.3461	81.04	85.52	85.72
80	1.3333	1.3461	81.04	1.3461	81.04	85.71	85.84
90	1.5	1.3463	82.34	1.346	80.40	85.85	85.96
100	1.6667	1.3462	81.69	1.3462	81.69	85.98	86.07
110	1.8333	1.3463	82.34	1.346	80.40	86.11	86.19
120	2	1.346	80.40	1.346	80.40	86.22	86.31
150	2.5	1.3458	79.10	1.3464	82.99	86.57	86.65
180	3	1.3466	84.28	1.3464	82.99	86.92	87.00
210	3.5	1.3465	83.63	1.346	80.40	87.26	87.34
240	4	1.3467	84.93	1.3462	81.69	87.60	87.68
270	4.5	1.3466	84.28	1.3459	79.75	87.94	88.02
300	5	1.3468	85.57	1.3462	81.69	88.28	88.36
360	6	1.3469	86.22	1.3469	86.22	88.96	89.04
420	7	1.3464	82.99	1.347	86.87	89.63	89.71
480	8	1.3466	84.28	1.347	86.87	90.29	90.38
540	9	1.3471	87.51	1.3468	85.57	90.95	91.04
600	10	1.347	86.87	1.3474	89.46	91.61	91.70
660	11	1.3474	89.46			92.26	92.35
720	12	1.3476	90.75	1.3469	86.22	92.91	93.00
780	13	1.3477	91.40			93.55	93.65
840	14	1.3479	92.69	1.347	86.87	94.19	94.29
900	15	1.348	93.34			94.82	94.92
960	16	1.3481	93.98	1.3476	90.75	95.45	95.55
1020	17	1.3482	94.63			96.08	96.18
1080	18	1.3488	98.51	1.3483	95.28	96.70	96.80
1140	19	1.3485	96.57			97.31	97.42
1200	20	1.348	93.34	1.3484	95.93	97.92	98.03
1320	22	1.3488	98.51	1.3485	96.57	99.13	99.25
1435	23.917	1.3488	98.51	1.3485	96.57	100.27	100.40
1560	26	1.3493	101.75	1.3486	97.22	101.50	101.63
1680	28	1.349	99.81	1.3489	99.16	102.66	102.79
1800	30	1.35	106.28	1.3491	100.45	103.80	103.94

Table H1: Cont.

Time		Constant Area Experimental Data				Model	
(sec)	(min)	Ref. Inde	[kg/m ³]	Ref. Inde	[kg/m ³]	Multiple	Avg
2100	35	1.35	106.28	1.3494	102.39	106.60	106.74
2400	40	1.35	106.28	1.35	106.28	109.31	109.45
2700	45	1.3502	107.57	1.3505	109.51	111.93	112.07
3000	50	1.3508	111.45	1.351	112.75	114.45	114.60
3300	55	1.351	112.75	1.351	112.75	116.89	117.05
3600	60	1.352	119.21	1.3516	116.63	119.25	119.41
3900	65	1.3518	117.92	1.3522	120.51	121.53	121.70
4200	70	1.352	119.21	1.3524	121.80	123.74	123.90
4500	75	1.3529	125.04	1.3518	117.92	125.87	126.04
4800	80	1.3528	124.39	1.3526	123.10	127.93	128.11
5100	85	1.353	125.68	1.3533	127.62	129.92	130.10
5400	90	1.3531	126.33	1.3531	126.33	131.84	132.04
5700	95	1.3535	128.92	1.3541	132.80	133.69	133.90
6000	100	1.3542	133.45	1.3542	133.45	135.48	135.71
6300	105	1.3547	136.68	1.3541	132.80	137.19	137.46
6600	110	1.3548	137.33	1.3549	137.97	138.84	139.15
6900	115	1.3549	137.97	1.3547	136.68	140.46	140.78
7200	120	1.355	138.62	1.355	138.62	142.03	142.36
7500	125			1.3552	139.91	143.55	143.89
7800	130	1.3556	142.50	1.3551	139.27	145.00	145.37
8100	135			1.3555	141.85	146.40	146.79
8400	140	1.3559	144.44	1.356	145.09	147.74	148.16
9000	150	1.3563	147.03	1.356	145.09	150.12	150.55
9600	160	1.3562	146.38	1.3567	149.61	150.64	150.65
10200	170	1.3568	150.26	1.3571	152.20	150.64	150.65
10800	180	1.357	151.56	1.3572	152.85	150.64	150.65
11400	190			1.3568	150.26	150.64	150.65
12000	200			1.357	151.56	150.64	150.65
12600	210			1.3569	150.91	150.64	150.65

Table H2: Dissolution data for dissolving above the alpha lactose solubility limit

Time		Constant Mass Data		Model	
(sec)	(min)	Ref. Index	[kg/m3]	Multiple	Avg
0		1.3339	2.09	0.00	0.00
5	0.0833	1.3409	47.40	46.50	53.35
10	0.1667	1.3429	60.34	65.18	71.44
15	0.25	1.3443	69.40	74.21	78.82
20	0.3333	1.3451	74.57	78.80	82.27
25	0.4167	1.3463	82.34	81.40	83.82
30	0.5	1.346	80.40	82.95	84.59
35	0.5833	1.3459	79.75	83.90	85.00
40	0.6667	1.3459	79.75	84.49	85.23
45	0.75	1.346	80.40	84.88	85.37
50	0.8333	1.3461	81.04	85.13	85.47
55	0.9167	1.3461	81.04	85.31	85.55
60	1	1.346	80.40	85.45	85.62
70	1.1667	1.3461	81.04	85.64	85.74
80	1.3333	1.346	80.40	85.78	85.86
90	1.5	1.3462	81.69	85.91	85.98
100	1.6667	1.3462	81.69	86.03	86.09
110	1.8333	1.3463	82.34	86.15	86.21
120	2	1.3461	81.04	86.26	86.32
150	2.5	1.346	80.40	86.61	86.67
180	3	1.3464	82.99	86.95	87.01
210	3.5	1.3461	81.04	87.30	87.36
240	4	1.3465	83.63	87.64	87.70
270	4.5	1.3462	81.69	87.98	88.04
300	5	1.3464	82.99	88.32	88.38
360	6	1.3468	85.57	88.99	89.06
420	7	1.347	86.87	89.67	89.73
480	8	1.3474	89.46	90.33	90.40
540	9	1.3478	92.04	90.99	91.06
600	10	1.348	93.34	91.65	91.72
660	11	1.3475	90.10	92.30	92.37
720	12	1.3475	90.10	92.95	93.02
780	13	1.3479	92.69	93.60	93.66
840	14	1.3489	99.16	94.23	94.30
900	15	1.3482	94.63	94.87	94.94
960	16	1.3481	93.98	95.50	95.57
1020	17	1.3482	94.63	96.12	96.20
1080	18	1.3482	94.63	96.74	96.82
1140	19	1.3482	94.63	97.36	97.44
1200	20	1.3483	95.28	97.97	98.05
1320	22	1.3488	98.51	99.18	99.27
1435	23.917	1.3488	98.51	100.33	100.41
1560	26	1.349	99.81	101.56	101.64
1680	28	1.349	99.81	102.72	102.81
1800	30	1.349	99.81	103.86	103.96
2100	35	1.3494	102.39	106.65	106.76
2400	40	1.3501	106.92	109.34	109.47
2700	45	1.3505	109.51	111.94	112.09
3000	50	1.351	112.75	114.47	114.62

Table H2: Cont

Time		Constant Mass Data		Model	
(sec)	(min)	Ref. Index	[kg/m3]	Multiple	Avg
3300	55	1.3511	113.39	116.91	117.06
3600	60	1.352	119.21	119.27	119.43
3900	65	1.352	119.21	121.55	121.71
4200	70	1.3524	121.80	123.75	123.92
4500	75	1.3528	124.39	125.88	126.06
4800	80	1.3531	126.33	127.94	128.12
5100	85	1.3529	125.04	129.93	130.12
5400	90	1.354	132.15	131.86	132.05
5700	95	1.3535	128.92	133.72	133.92
6000	100	1.354	132.15	135.51	135.73
6300	105	1.3543	134.09	137.24	137.48
6600	110	1.3547	136.68	138.90	139.17
6900	115	1.3551	139.27	140.48	140.80
7200	120	1.3555	141.85	141.99	142.38
7500	125			143.49	143.91
7800	130	1.3554	141.21	144.95	145.39
8100	135			146.34	146.81
8400	140	1.356	145.09	147.67	148.18
9000	150	1.3561	145.73	150.04	150.57
9600	160	1.3569	150.91	150.64	150.65
10200	170	1.3564	147.67	150.64	150.65
10800	180	1.3568	150.26	150.64	150.65
11400	190	1.3569	150.91	150.64	150.65
12000	200	1.3569	150.91	150.64	150.65
12600	210	1.357	151.56	150.64	150.65

Table H3: Dissolution of lactose mixtures below the solubility limit

Time (sec)	Constant Area Experimental Data				Model	
	Ref. index	[kg/m3]	Ref. index	[kg/m3]	Three Size	Av
0	1.3338	1.45	1.334	2.74	0.00	0.00
1	1.3339	2.09	1.3337	0.80	3.97	4.99
2	1.3341	3.39	1.334	2.74	7.58	9.49
3	1.3348	7.92	1.3342	4.03	10.88	13.55
4	1.3353	11.15	1.335	9.21	13.88	17.22
5	1.336	15.69	1.3356	13.10	16.63	20.56
6	1.3363	17.63	1.3361	16.33	19.13	23.60
7	1.3364	18.27	1.3365	18.92	21.42	26.36
8	1.3369	21.51	1.337	22.16	23.51	28.88
9	1.337	22.16	1.3371	22.80	25.41	31.19
10	1.3372	23.45	1.3376	26.04	27.13	33.29
11	1.3375	25.39	1.338	28.63	28.69	35.22
12	1.3379	27.98	1.3381	29.28	30.09	36.98
13	1.338	28.63	1.3384	31.22	31.34	38.60
14	1.3385	31.87	1.339	35.10	32.45	40.07
15	1.3387	33.16	1.339	35.10	33.42	41.42
16	1.3389	34.45	1.339	35.10	34.31	42.65
17	1.339	35.10	1.3392	36.40	35.18	43.77
18	1.339	35.75	1.3392	38.34	36.01	44.79
19	1.3391	37.69	1.3395	40.93	36.79	45.71
20	1.3391	38.98	1.3395	41.57	37.55	46.53
21	1.3394	40.93	1.3399	43.51	38.27	47.27
22	1.3394	41.57	1.3399	42.87	38.95	47.92
23	1.3396	42.22	1.34	44.16	39.61	48.49
24	1.3396	42.87	1.34	44.81	40.23	48.97
25	1.3399	44.16	1.3403	44.81	40.82	49.38
26	1.3399	45.46	1.3403	46.75	41.39	49.70
27	1.34	44.81	1.3402	47.40	41.92	49.94
28	1.34	47.40	1.3402	47.40	42.43	50.09
29	1.3401	47.40	1.3404	48.04	42.91	50.16
30	1.3401	48.04	1.3404	48.04	43.36	50.17
31	1.3402	47.40	1.3405	48.04	43.78	50.17
32	1.3402	48.04	1.3405	48.04	44.18	50.17
33	1.3404	48.04	1.3405	48.69	44.55	50.17
34	1.3404	48.69	1.3405	48.69	44.89	50.17
36	1.3406	48.04	1.3408	48.69	45.48	50.17
37	1.3405	48.04	1.3409	49.34	45.74	50.17
38	1.3405	48.69	1.3409	49.34	45.98	50.17
40	1.3409	48.69	1.3409	49.34	46.45	50.17
42	1.3409	49.34	1.341	50.63	46.89	50.17
44	1.341	48.69	1.341	51.28	47.30	50.17
46	1.3409	48.04	1.341	50.63	47.68	50.17
47	1.341	49.34	1.341	50.63	47.87	50.17
48	1.341	48.69	1.341	49.99	48.04	50.17
50					48.38	50.17
55					49.09	50.17
60					49.65	50.17
65					50.01	50.17
70					50.17	50.17
75					50.17	50.17
80					50.17	50.17

Table H4: Dissolution of lactose mixtures below the solubility limit

Time (sec)	Constant Mass Experimental Data				Model	
	Ref. index	[kg/m ³]	Ref. index	[kg/m ³]	Three Size	Av
0	1.3339	2.09	1.3336	0.15	0.00	0.00
1	1.3339	2.09	1.3337	0.80	4.51	5.55
2	1.3341	3.39	1.3341	3.39	8.57	10.48
3	1.3349	8.57	1.3349	8.57	12.23	14.88
4	1.3353	11.15	1.3354	11.80	15.53	18.83
5	1.3358	14.39	1.336	15.69	18.51	22.37
6	1.3364	18.27	1.3363	17.63	21.21	25.56
7	1.3369	21.51	1.3369	21.51	23.64	28.44
8	1.3372	23.45	1.3371	22.80	25.84	31.03
9	1.3376	26.04	1.3377	26.69	27.82	33.39
10	1.338	28.63	1.3381	29.28	29.59	35.51
11	1.3381	29.28	1.3381	29.28	31.18	37.44
12	1.3383	30.57	1.3385	31.87	32.58	39.18
13	1.3386	32.51	1.3389	34.45	33.82	40.76
14	1.339	35.10	1.339	35.10	34.89	42.19
15	1.339	35.10	1.3392	36.40	35.80	43.47
16	1.3391	35.75	1.3393	37.04	36.57	44.62
17	1.3393	37.04	1.3397	39.63	37.33	45.65
18	1.3393	39.63	1.3397	40.93	38.05	46.57
19	1.3397	40.28	1.3399	41.57	38.73	47.38
20	1.3397	41.57	1.3399	42.87	39.39	48.08
21	1.3398	42.22	1.34	43.51	40.01	48.67
22	1.3398	41.57	1.34	43.51	40.61	49.17
23	1.34	43.51	1.3402	47.40	41.18	49.57
24	1.34	44.81	1.3402	46.75	41.73	49.86
25	1.3401	47.40	1.3403	46.75	42.25	50.06
26	1.3401	44.81	1.3403	46.75	42.74	50.15
27	1.34	47.40	1.3403	47.40	43.21	50.17
28	1.34	48.04	1.3403	48.04	43.66	50.17
29	1.3403	47.40	1.3409	48.04	44.08	50.17
30	1.3403	48.69	1.3409	48.04	44.47	50.17
31	1.3405	48.04	1.3408	48.69	44.85	50.17
32	1.3405	48.04	1.3408	49.34	45.19	50.17
33			1.3408	49.34	45.52	50.17
34			1.3408	49.34	45.82	50.17
36			1.3408	49.34	46.35	50.17
37			1.3409	49.34	46.58	50.17
38	1.3409	49.34	1.3409	49.99	46.78	50.17
40	1.341	49.99	1.341	49.34	47.13	50.17
42	1.3409	48.69	1.341	49.34	47.46	50.17
44	1.3411	49.34	1.341	49.99	47.78	50.17
46	1.341	49.34	1.3411	49.99	48.07	50.17
47	1.341	48.69	1.3412	50.63	48.21	50.17
48	1.341	48.69			48.35	50.17
50					48.61	50.17
55					49.18	50.17
60					49.64	50.17
65					49.97	50.17
70					50.14	50.17
75					50.17	50.17
80					50.17	50.17

Table H5: Dissolution below the alpha lactose solubility limit for unsieved lactose.

Time (sec)	Experimental				Multiple crystal size Model					Single size Mode	
	Ref. ind	[kg/m ³	Ref. ind	[kg/m ³]	23	11	6	3	2	(avg)	(max)
0	1.334	2.74	1.3338	1.45	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	1.3341	3.39	1.334	2.74	2.34	2.33	2.27	1.98	2.00	4.06	0.54
2	1.335	9.21	1.3347	7.27	4.53	4.52	4.39	3.83	3.88	7.80	1.07
3	1.3358	14.39	1.3355	12.45	6.58	6.56	6.37	5.56	5.65	11.24	1.60
4	1.3364	18.27	1.336	15.69	8.49	8.48	8.24	7.17	7.30	14.41	2.12
5	1.337	22.16	1.3364	18.27	10.30	10.27	10.02	8.66	8.84	17.34	2.64
6	1.3372	23.45	1.3371	22.80	11.98	11.96	11.69	10.04	10.28	20.05	3.15
7	1.3378	27.34	1.3378	27.34	13.57	13.56	13.27	11.29	11.62	22.57	3.66
8	1.338	28.63	1.3381	29.28	15.06	15.06	14.77	12.45	12.86	24.89	4.16
9	1.3382	29.92	1.3385	31.87	16.46	16.47	16.18	13.58	14.01	27.06	4.65
10	1.3388	33.81	1.3385	31.87	17.78	17.80	17.51	14.67	15.06	29.07	5.14
11	1.339	35.10	1.3389	34.45	19.04	19.04	18.76	15.73	16.02	30.94	5.63
12	1.3389	34.45	1.339	35.10	20.22	20.21	19.93	16.76	16.89	32.68	6.11
13	1.3391	35.75	1.3391	35.75	21.34	21.32	21.03	17.76	17.66	34.29	6.58
14	1.3394	37.69	1.3395	38.34	22.40	22.39	22.06	18.73	18.34	35.80	7.06
15	1.3399	40.93	1.3394	37.69	23.41	23.40	23.01	19.68	18.91	37.20	7.52
16	1.3396	38.98	1.3398	40.28	24.37	24.37	23.88	20.60	19.38	38.51	7.98
18	1.3402	42.87	1.34	41.57	26.14	26.16	25.51	22.36	20.29	40.86	8.89
20	1.3402	42.87	1.3401	42.22	27.74	27.77	27.04	24.02	21.18	42.89	9.78
22	1.3404	44.16	1.3402	42.87	29.20	29.21	28.47	25.60	22.04	44.63	10.65
24	1.3405	44.81	1.3404	44.16	30.53	30.50	29.82	27.09	22.88	46.11	11.50
26	1.3407	46.10	1.3404	44.16	31.73	31.71	31.08	28.49	23.70	47.35	12.34
28	1.3408	46.75	1.3407	46.10	32.84	32.84	32.26	29.83	24.50	48.36	13.16
30	1.341	48.04	1.3408	46.75	33.87	33.88	33.37	31.09	25.28	49.15	13.97
32	1.341	48.04	1.3408	46.75	34.81	34.85	34.40	32.28	26.04	49.72	14.75
34	1.341	48.04	1.3409	47.40	35.68	35.74	35.36	33.40	26.79	50.06	15.53
36	1.341	48.04	1.3409	47.40	36.48	36.55	36.25	34.47	27.51	50.17	16.29
38	1.341	48.04	1.341	48.04	37.22	37.28	37.07	35.48	28.22	50.17	17.03
42	1.341	48.04	1.341	48.04	38.57	38.57	38.51	37.32	29.59	50.17	18.47
44	1.341	48.04	1.341	48.04	39.17	39.17	39.13	38.16	30.24	50.17	19.17
46	1.3411	48.69	1.3411	48.69	39.73	39.74	39.68	38.95	30.89	50.17	19.86
51			1.3411	48.69	41.00	41.04	40.75	40.72	32.43	50.17	21.53
56	1.3411	48.69	1.3412	49.34	42.07	42.16	41.70	42.20	33.88	50.17	23.12
61			1.3414	50.63	43.00	43.08	42.58	43.39	35.24	50.17	24.63
66	1.3411	48.69	1.3415	51.28	43.82	43.85	43.39	44.30	36.53	50.17	26.08
71			1.3414	50.63	44.52	44.56	44.14	44.88	37.74	50.17	27.46
76	1.3413	49.99	1.3415	51.28	45.15	45.20	44.83	45.17	38.88	50.17	28.78
81			1.3412	49.34	45.70	45.77	45.46	45.43	39.96	50.17	30.04
86	1.3412	49.34	1.3414	50.63	46.19	46.27	46.03	45.69	40.97	50.17	31.25
91			1.3414	50.63	46.62	46.69	46.54	45.93	41.92	50.17	32.40
96	1.3412	49.34	1.3415	51.28	47.01	47.06	46.98	46.18	42.81	50.17	33.50
106	1.3411	48.69	1.3413	49.99	47.66	47.70	47.63	46.64	44.44	50.17	35.56
116			1.3415	51.28	48.19	48.24	48.03	47.08	45.85	50.17	37.45
120					48.36	48.43	48.18	47.24	46.36	50.17	38.16
130					48.75	48.79	48.53	47.65	47.51	50.17	39.82
140					49.06	49.08	48.85	48.02	48.47	50.17	41.34
150					49.31	49.33	49.13	48.37	49.24	50.17	42.72
160					49.51	49.53	49.38	48.70	49.80	50.17	43.98
170					49.67	49.69	49.58	49.00	50.12	50.17	45.12
180					49.80	49.79	49.75	49.27	50.17	50.17	46.15
190					49.89	49.89	49.85	49.51	50.17	50.17	47.06
200					49.97	49.97	49.90	49.72	50.17	50.17	47.87