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Research paper

Enhancement of the dissolution of indomethacin in interactive mixtures using added fine lactose

Ayman Allahham, Peter J. Stewart *

Victorian College of Pharmacy, Monash University, Parkville, Australia

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Abstract

The objective of the study was to investigate the effect of fine lactose on the *in vitro* dissolution of indomethacin in interactive mixtures containing spray-dried lactose and lactose monohydrate (106–250 μm). Dissolution of the indomethacin was measured using an automated dissolution apparatus following the USP paddle method at 100 rpm. The particle size distributions of indomethacin mixtures were measured using a Mastersizer S under non-sink conditions. Data fitted bi-exponential or tri-exponential dissolution models, representing dissolution from dispersed and agglomerated particle distributions. The addition of fine lactose (VMD 3.8 ± 0.4 μm) to 20% indomethacin-coarse lactose mixtures resulted in significantly increased rates of dissolution caused by increases in the estimated dissolution rate constants for dispersed particles (K_d) and by de-agglomeration. Agglomerates in the mixture showed little tendency to comminute under shear pressure. De-agglomeration in the dissolution medium was attributed to increased porosity of agglomerates, caused by dissolution of water soluble fine lactose in the agglomerate structure. The median particle size (D_{50}) of the dispersed particle distribution decreased with increasing concentrations of added fine lactose, indicating increasing extents of de-agglomeration, and a good correlation between K_d and $(D_{50})^2$ resulted for the coarse lactose-based mixtures ($R^2 > 0.984$).
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Keywords: Indomethacin interactive mixtures; *In vitro* dissolution; De-agglomeration; Poorly water-soluble drugs; Particle sizing; Mathematical models; Oral drug delivery; Milling and solid dosage form

1. Introduction

Studies on the dissolution of interactive mixtures containing micronised drugs dispersed on coarse carriers have been conducted extensively since the mid-1980s. The use of interactive mixtures was shown to result in improved dissolution rates for poorly water-soluble drugs [1]. When high concentrations of micronised drug particles were used and when coarse carrier surfaces were saturated, the micronised drug particles tended to agglomerate and hence retard dissolution [2,3]. Several strategies have been used to enhance the dissolution of poorly water-soluble drugs in interactive mixtures including: optimising drug concentration [4–6], optimising carrier particle size [7], using micronised surfactants [3] and adding excipients such as magnesium stearate and Emcompress [7], magnesium stearate and sodium stearyl fumarate [6], corn starch, pregelatinized starch and magnesium stearate [8]. Modelling of the dissolution data confirmed that the dissolution occurred from dispersed drug particles and agglomerates and that the dissolution data could be fitted to a bi-exponential equation [2]

$$C = C_d \exp(-K_d t) + C_a \exp(-K_a t) \quad (1)$$

where C is the concentration of the undissolved drug (%) at time t; C_d and C_a are the initial concentrations (%) of dispersed particles and agglomerates, respectively; K_d and K_a are the dissolution rate constants (min^{-1}) for the dispersed particles and agglomerates, respectively. The strategies

* Corresponding author. Victorian College of Pharmacy, Monash University, 381 Royale Parade, Parkville 3052, Australia. Tel.: +61 3 99039517; fax: +61 3 99039583.
E-mail address: peter.stewart@vcp.monash.edu.au (P.J. Stewart).

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used for optimisation of drug concentrations and carrier particle sizes and the inclusion of micronised surfactants enhanced de-agglomeration and thus resulted in more rapid dissolution [2,3].

Recently, the ability of agglomerated micronised salmeterol xinafoate (SX) particles to de-agglomerate and disperse as an aerosol in an air stream was shown to be related to the structure and strength of the agglomerates [9,10]. The presence of fine lactose in these coarse lactose-based powder mixtures resulted in enhanced dispersion due to the formation of mixed agglomerates of SX and fine lactose that were shown to have lower strength and subsequent increased de-agglomeration capability. The tensile strength of the agglomerates (σ) can be defined

$$\sigma = \frac{15.6\mathrm{PF}^4 W}{D} \quad (2)$$

where PF is the packing fraction, W is the work of adhesion and D is the particle diameter [11]. As shown in Eq. (2), the tensile strength depends on packing fraction of the agglomerate (PF^4), particle size of the micronised particles comprising the agglomerate (d) and the work of adhesion between the interacting particles in the agglomerate (W). Hence, while the diameter of micronised particles in the mixture is less likely to be changed to produce major changes in tensile strength, the porosity of the agglomerate and the interactive force between particles in the agglomerate can be manipulated by the physicochemical changes in the particle properties (e.g., shape, crystal face orientation, crystal structure) or by the addition of micronised excipients into the agglomerate.

Therefore, it is hypothesised that fine lactose associated with the coarse lactose carrier particles present in interactive mixtures or added as an agglomerate modifier might play a role in enhancing dissolution of micronised drugs through the formation of mixed agglomerates of drug and fine lactose that more readily de-agglomerate due to differing works of adhesion and/or packing fractions to those of the pure drug agglomerates. Such agglomerates are more likely to disperse under the hydrodynamic conductions present in dissolution media during the dissolution process.

The aim of this research was to examine the influence of adding fine lactose with or without the lactose carriers on the dissolution of a model drug, indomethacin. In order to study the effect of fine lactose as an agglomerate modifier, indomethacin was used at a concentration of 20% where substantial agglomeration was known to occur [12] and where the use of lower indomethacin concentrations will result in greater dispersion, less agglomeration and hence, would provide less discriminating conditions to test the effect of the addition of fine lactose. Lactose monohydrate and spray-dried lactose were chosen as model coarse lactose carriers because of their use within the pharmaceutical industry. The extent of agglomeration was determined using the previous modelling approach [2,3] and through laser diffraction particle sizing of the powder mixtures. The modelling approach applied the Marquardt–Levenberg non-linear least squares algorithm to fit the dissolution data to a multi-exponential equation, the exponential terms of which represented dissolution from dispersed particles and agglomerates. A bi-exponential equation usually provided the best fit of the dissolution data and the equation parameters of initial concentrations of agglomerates and dispersed particles and their respective dissolution rate constants were estimated. The key objective was to develop an understanding of the mechanism of dissolution enhancement by this novel formulation approach. While dissolution enhancement of poorly, water-soluble drugs can be achieved through the addition of surfactants to formulations, the use of more inert excipients such as micronised lactose is an attractive alternative to achieve dissolution enhancement.

2. Materials and methods

2.1. Materials

Indomethacin (Sigma, St. Louis, MO, USA) was the model drug. Two lactose carriers were used: lactose monohydrate and lactose spray-dried (sieve fraction of 106–250 μm) (Lactose New Zealand, Hawera, NZ). Milli-Q water with a resistivity of 18.2 MΩ cm at 25 °C and a Total Organic Carbon (TOC) of 5–10 ppb (Millipore Milli-Q water purification system, USA) containing sodium lauryl sulphate (0.005% w/v). (Sigma, Castle Hill, NSW, Australia) was used as the dissolution medium.

2.2. Particle classification and measurement

Classification of particle fractions was achieved using standard stainless steel test sieves (Labtechnics, Kilkenny, SA, Australia) and an automatic sieve shaker (Fritsch, Idar-oberstein, Germany). Micronisation of indomethacin (VMD 6.9 ± 1.6 μm) and lactose (VMD 3.8 ± 0.4 μm) was conducted by fluid energy milling (Chrispro Jetmill, Molinazzo di Monteggio, Switzerland (75P), compressed air 5.8 atm at 12.7 L s^{-1}).

Particle size distributions were determined using a Malvern Mastersizer S (Malvern Instruments, Malvern, Worcestershire, UK). A lens (with a laser range of 300R mm and a beam length of 2.4 mm) was attached to a measuring cell (MSX1) containing a stirrer with a capacity of 150 mL. Approximately 500 mg of lactose powder was dispersed in 5 mL of absolute ethanol with the aid of sonication in a water bath for 3 min. Particle size analysis for lactose was analysed with the refractive index of lactose (1.533) and ethanol (1.36) and an estimated imaginary refractive index of 0.1. For micronised indomethacin, agglomerates were broken using a flat spatula and very small amount of water before loading it into the same sample cell. Particle size analysis for indomethacin was analysed with the refractive index of indomethacin (1.74) and water (1.33) and an estimated imaginary refractive index

of 0.1. The obscuration value was kept between 10 and 30 and residual values were less than 1.0% for each distribution. Five replicates were taken for each sample. Repeatability and accuracy was verified in accordance with the procedures of ISO 13320.

The particle size distributions of interactive mixtures were determined using laser diffraction particle sizing (Mastersizer S, Malvern Instruments, Malvern, Worcestershire, UK) at 2 min after the addition of the mixture to 100 mL of water in the sample cell at 23.0 ± 0.5 °C to allow dissolution of the lactose.

2.3. Interactive mixture preparation

Binary interactive mixtures (5 g) containing 20% indomethacin as a drug and either lactose monohydrate or lactose spray-dried as coarse carriers and ternary interactive mixtures containing in addition FL in concentrations ranging from 5% to 20% were prepared using a laboratory method that had been previously validated [13]. Binary mixtures containing indomethacin and fine lactose only (without the coarse carrier) in different ratios (indomethacin-fine lactose 4:1, 2:1, 1:1, 1:2 and 1:4) were prepared by mixing the two materials using the same mixing method. Homogeneity of the interactive mixtures was assessed using 20 samples of 50 mg powder samples selected systematically from identified areas over the whole powder mixture which had to be emptied from the mixing container to enable sampling. The indomethacin content in the mixtures ranged from 95.6% to 100.2% with coefficients of variations (CV%) from 1.7% to 2.6%.

2.4. Dissolution

Dissolution studies were conducted using an automated dissolution apparatus (Erweka, DT6, Heusenstamm, Germany) equipped with a 3021-Cecil UV spectrophotometer containing 10 mm UV flow cells (Cecil, Cambridge, UK) and an ISM1-B peristaltic pump (Ismatec Ltd., Zurich, Switzerland). A USP/NF paddle method was used at a rotational speed of 100 rpm. Milli-Q water (Millipore Milli-Q water purification system, USA) was filtered and degassed through a 0.45 μm Millipore membrane (Millipore, Bedford, MA, Ireland). Dissolution medium (1000 mL), freshly degassed prior to use, was equilibrated to 37.0 ± 0.5 °C. Different weights of interactive mixtures ($n = 4$–6) were added to the dissolution apparatus to maintain an indomethacin concentration of 5 mg L^{-1} in each vessel in series (from vessel 1 to vessel 6 over 20 s in accordance with the sample loading time allowed in the dissolution software). Indomethacin concentrations were determined using the UV spectrophotometer at 2 min intervals over 120 min and dissolution data analysed using a Pharmatest dissolution software (V: 5.025-5b, Pharmatest, Hainburg, Germany).

Dissolution data were modelled using SigmaPlot 8.0 software (SPSS Inc., Point Richmond, CA, USA) which uses a Marquardt–Levenberg algorithm to find the coefficients (parameters) of the independent variables that give the best fit of the equation to the data [14]. The average of the undissolved concentrations (%) collected from all the vessels was tested against time using a mono-exponential (two parameters), bi-exponential (four parameters) or tri-exponential (six parameters) equation. When estimating the initial concentrations and rate constants at the differing conditions, the curve fitting and parameter estimation using the specific exponential model was applied to individual data from each vessel. Discrimination between these models was conducted mainly using the Akaike Information Criterion (AIC) which is an approximately unbiased estimator of the expected Kullback–Leibler information of a fitted model, which can be used as a discrepancy measure between the actual and the fitted model [15], the norm value which is square root of the sums of squares when weighting is used and is an index of the closeness of fit and the F value which gauges the contribution of the independent variables in predicting the dependent variables. Other statistical parameters used to assess the goodness of fit were the coefficients of determination, R^2, the parameter of dependencies which is an indication of model complexity and the coefficients of variations for the estimated parameters (CV%) which is the normalised standard error of each parameter.

2.5. UV-spectroscopy

Indomethacin concentration was determined using a validated ultraviolet spectrophotometric assay using a UV spectrophotometer containing a 10 mm UV flow cells (Cecil, Cambridge, UK). Calibration curves for indomethacin were constructed using four concentrations with four replicates of each at the wavelength of maximum absorbance in water and ethanol (263.7 and 318.2 nm, respectively). Curves were linear ($R^2 > 0.999$) and intercepts were not significantly different from zero ($P > 0.06$). The accuracy of assay at low, medium and high concentrations was within 98.4–102.0% with a precision (CV) of less than 6.3%. The absorbance of lactose was negligible and no significant interference was noticed (<0.010 AU).

2.6. Solubility determination

The solubility of indomethacin in water was determined by immersing a 50 mg sample of the drug in a filled 50-mL plastic vial. Three samples were shaken at 125 strokes/min in a controlled-temperature water bath at 23.0 ± 0.5°C and 37.0 ± 0.5°C (Grant, Cambridge, England). Samples (3 mL) were then filtered using a 25 mm ID nylon filter membrane (0.45 μm, Scientific Products Company PTY Lt., Australia), dissolved in ethanol, diluted and assayed using the UV spectrophotometer (3021-Cecil UV, Cecil Instruments, Cambridge, England) at the maximum wavelength of the drug in each medium. Sampling was taken

after 2, 10, 24 h and then each day until the solubility calculated was within a 5% standard deviation (six replicates).

2.7. Aerodynamic particle size analysis by Aerosizer

The particle size of the indomethacin-fine lactose mixtures was measured by an Aerosizer (Amherst Process Instruments Inc., Amherst, MA, USA) using dry powder dispersion system (aerodisperser). A small amount of powder (about 5 mg) was placed in the sample cup of the aerodisperser and measurement was carried out at a medium feed rate and sample run time of 300 s. Different shear pressures were applied to study the effect of increasing shear on the agglomerate strength of the powder (3.4, 10.3, 20.7 and 27.6 kPa). The particle size of the mixture was analysed using API Aerosizer software (LD Version 7.04) and the average particle size of five replicates was calculated for each sample.

2.8. Scanning electron microscopy

The particles were examined at several magnifications under an S-570 scanning electron microscope (SEM) (Hitachi, Tokyo, Japan) operating at 15 kV. Powder samples were mounted on metal sample plates. The samples were gold coated with a sputter coater (BAL-TEC SCD 005, Balzers, Liechtenstein).

3. Results and discussion

3.1. Preliminary experiments

Summaries of the particle size distributions of micronised indomethacin, lactose monohydrate and spray-dried carriers (sieved fraction 106–250 μm) and fine lactose were determined using the Mastersizer S (Table 1). The results indicated that the lactose monohydrate carrier contained a higher percentage of inherent fines less than 5 μm ($3.6 \pm 0.3\%$) compared with the lactose spray-dried lactose ($0.5 \pm 0.1\%$). The volume mean diameter ($D[4,3]$) of indomethacin was almost double that of the fine lactose, i.e., ($D[4,3]$ was 6.9 ± 1.6 μm and 3.8 ± 0.4 μm for indomethacin and fine lactose, respectively).

Interactive mixtures of 20% indomethacin were selected to ensure over-saturation of the adhesion surface sites and levels of indomethacin agglomeration sufficiently high to test the influence of fine lactose on de-agglomeration during dissolution. Initial concentrations of agglomerated particles were greater than 77% [12]. The Scanning Electron Micrographs (SEMs) of indomethacin-coarse lactose mixtures demonstrated the multi-particulate complexity of the mixtures with evidence of indomethacin adhesion on the coarse lactose carriers and agglomeration both on and off the coarse lactose surface (Fig. 1).

3.2. Effect of added fine lactose on the dissolution of the indomethacin-coarse lactose-based mixtures

The dissolution profiles of 20% indomethacin-coarse lactose mixtures (binary) and the 20% indomethacin-coarse lactose mixtures with added fine lactose 5–20% (ternary) containing either lactose monohydrate or spray-dried lactose as the coarse lactose carrier are shown in Fig. 2. The results demonstrated that the dissolution rate of indometh-

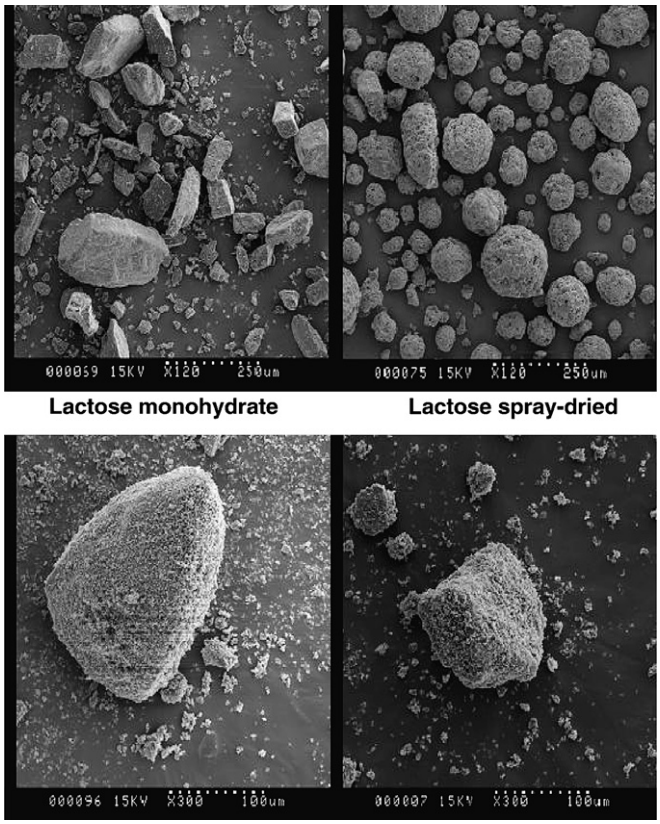

Fig. 1. Scanning Electron Micrographs of coarse lactose (top) and indomethacin mixtures (20% w/w) (bottom) containing lactose monohydrate carrier (left) lactose spray-dried carrier (right).

Table 1
Particle size data for the materials in the indomethacin interactive mixtures

Material name	$D(4,3)$		$D(v,0.1)$		$D(v,0.5)$		$D(v,0.9)$		<5 μm		<10 μm	
	Av.	SD	Av.	SD	Av.	SD	Av.	SD	Av.	SD	Av.	SD
Lactose monohydrate	135.7	1.4	16.8	1.2	123.3	1.4	272.5	3.6	3.6	0.3	6.6	0.5
Lactose spray-dried	135.1	1.4	68.9	1.0	149.3	1.1	244.3	3.3	0.5	0.1	0.7	0.1
Indomethacin	6.9	1.6	1.1	0.2	3.8	0.6	9.6	2.0	64.6	7.5	91.1	4.0
Fine lactose	3.8	0.4	6.3	0.6	3.4	0.3	2.1	0.2	80.1	4.8	99.6	0.5

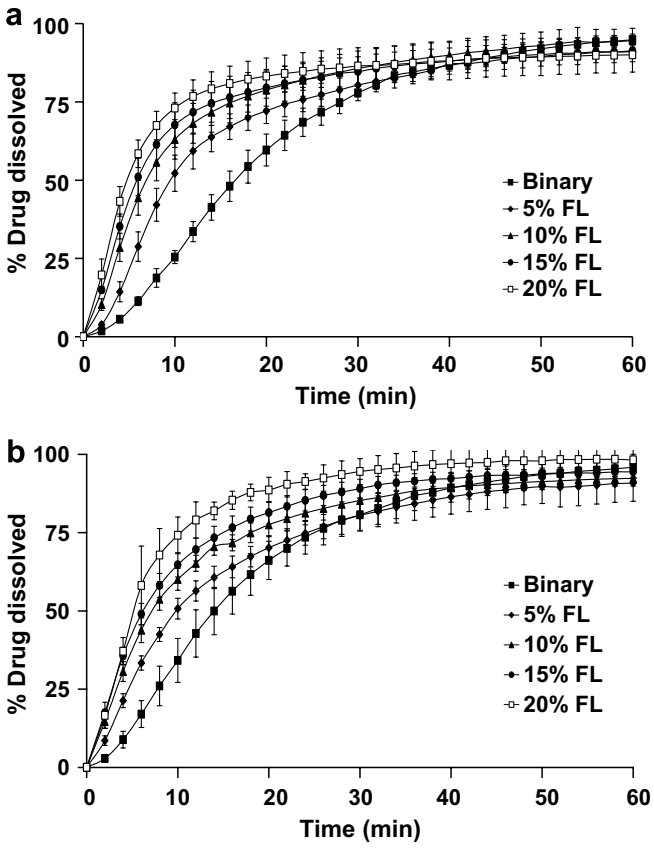

Fig. 2. Influence of added fine lactose on the dissolution of indomethacin (20%) mixtures containing (a) lactose spray-dried and (b) lactose monohydrate, determined using the USP Paddle Method at 100 rpm measured in degassed water containing 0.005% SLS at 37 °C.

acin was dependent on the fine lactose concentration with an increase in dissolution rate occurring with an increase in fine lactose concentration for both carriers. For example, for lactose monohydrate mixtures, the percentage dissolved after 20 min was $66.1 \pm 6.1\%$, $70.1 \pm 3.5\%$, $77.5 \pm 3.5\%$, $81.3 \pm 3.6\%$ and $88.6 \pm 4.1\%$ for the binary and the ternary mixtures with added 5%, 10%, 15% and 20% fine lactose, respectively. The binary mixture containing coarse lactose monohydrate had a slightly faster dissolution rate compared with the one containing the lactose spray-dried carrier especially during the first 20 min (for example, after 10 min, the percentage dissolved for the lactose monohydrate binary mixture was $35.0 \pm 3.9\%$ compared to $25.4 \pm 2.1\%$ for the lactose spray-dried binary mixture). Given the influence of fine lactose observed in Fig. 2, the faster dissolution of the monohydrate binary mixture might have been associated with the higher inherent concentration of fine lactose (Table 1).

While the presence of fine lactose has a dramatic effect on the indomethacin dissolution rate, the mechanism for this increase was not clear. Therefore, to further understand this interaction and the role of fine lactose in this process, the dissolution data were modelled and the estimated dissolution parameters of initial concentration of dispersed particles and agglomerates and the dissolution rate constants for these species estimated.

3.3. Modelling of dissolution data for the binary and ternary indomethacin-lactose mixtures

Dissolution data were modelled using multi-exponential equations shown in Eq. (1) and the parameters of initial concentration of dispersed and agglomerated particles and the dissolution rate constants estimated by non-linear least squares parameter estimation algorithm [2]. Table 2 summarises the fitting results for the spray-dried lactose-based mixtures and was representative of the dissolution modelling for mixtures using both coarse lactose carriers. The dissolution data for the binary mixtures were best fitted by the mono-exponential equations with critical fitting parameters of AIC, norm and R^2 showing no improvement for higher order fits. In addition, the dependencies approached 1.0 for the higher order fits indicating over-parameterisation. The bi-exponential equation was chosen to represent the dissolution data for all ternary mixtures. For these data, the mono-exponential fit produced high AIC, high norm and small F values for all the mixtures using both coarse lactose carriers. For the ternary mixtures containing 5% and 10% fine lactose, the tri-exponential equation did not provide a better fit for the dissolution data because it gave higher AIC values and smaller F values. For ternary mixtures containing 15% and 20% fine lactose, some modelling indicators suggested that a tri-exponential equation might provide the best fit; however, the dependencies approached 1.0 suggesting over-parameterisation and examination of the estimated parameters revealed a relatively small third particulate population (<6%) with very small dissolution rate constants. Therefore, the bi-exponential equation was selected as the best fit equation for all the ternary mixtures for both coarse lactose carriers.

The modelling parameters of concentration of dispersed particles and dissolution rate constants were estimated from the best fit equations for all binary and ternary mixtures (Fig. 3). The parameters estimated for the dissolution of the binary mixtures were derived from the dissolution of a broad distribution of poorly differentiated dispersed and agglomerated particles (clearly seen in the particle size distributions of the binary mixtures seen in Fig. 4a and to a slightly lesser extent in Fig. 4b) and represent some composite of the estimated values of concentration and rate constants based on the whole of these distributions. The parameters cannot be said to represent "dispersed" or "agglomerated" particles and thus the initial concentration and the rate constant estimated from the mono-exponential fit of the dissolution data cannot be compared with the estimated parameters from the bi-exponential fit. The estimated concentration of particles shown in Fig. 3 is greater than 100% due to fact that the dissolution data were not normalised and some dissolution profiles showed values greater than the target concentration due to mixture

Table 2
The dissolution modelling statistics for different indomethacin-spray-dried lactose interactive mixtures (binary and ternary with addition of 5%, 10%, 15% and 20% fine lactose) for the mono-, bi- and tri-exponential fits

Modelling equation	Mixture	CV (%)[a]	Dependencies[a]	F^a	Norm[a]	R^{2a}	AIC[a]
Mono-exponential	Binary	1.3	0.450	6886	20.0	0.992	369.5
	Added 5% FL	3.0	0.447	1135	38.1	0.951	448.2
	Added 10% FL	3.0	0.432	1323	32.4	0.957	428.3
	Added 15% FL	5.0	0.440	331	54.0	0.849	490.7
	Added 20% FL	7.0	0.427	151	66.7	0.719	516.5
Bi-exponential	Binary	265.7	1.000	2217	20.0	0.992	373.5
	Added 5% FL	3.4	0.868	2788	14.1	0.993	330.9
	Added 10% FL	3.1	0.861	4460	10.2	0.996	291.4
	Added 15% FL	1.8	0.559	2939	11.1	0.994	301.9
	Added 20% FL	1.3	0.422	3997	8.7	0.995	271.3
Tri-exponential	Binary	469.7	1.000	1284	20.0	0.992	377.5
	Added 5% FL	331.6	1.000	1614	14.1	0.993	334.9
	Added 10% FL	42040000.0	1.000	2582	10.2	0.996	295.4
	Added 15% FL	9.6	0.983	2728	8.8	0.996	277.3
	Added 20% FL	28.7	0.992	3166	7.4	0.997	256.2

[a] Where CV% (coefficients of variations for the estimated parameters) and dependencies (an indication of model complexity) are shown only for the estimated parameter related to the initial concentration of ''dispersed'' particles or the distribution with the highest dissolution rate constant. F is a parameter which gauges the contribution of the independent variables in predicting the dependent variables. The norm is the square root of the sums of squares when weighting is used and is an index of the closeness of fit. R^2 is the coefficients of determination and AIC is an approximately unbiased estimator of the expected Kullback–Leibler information of a fitted model, which can be used as a discrepancy measure between the actual and the fitted model.

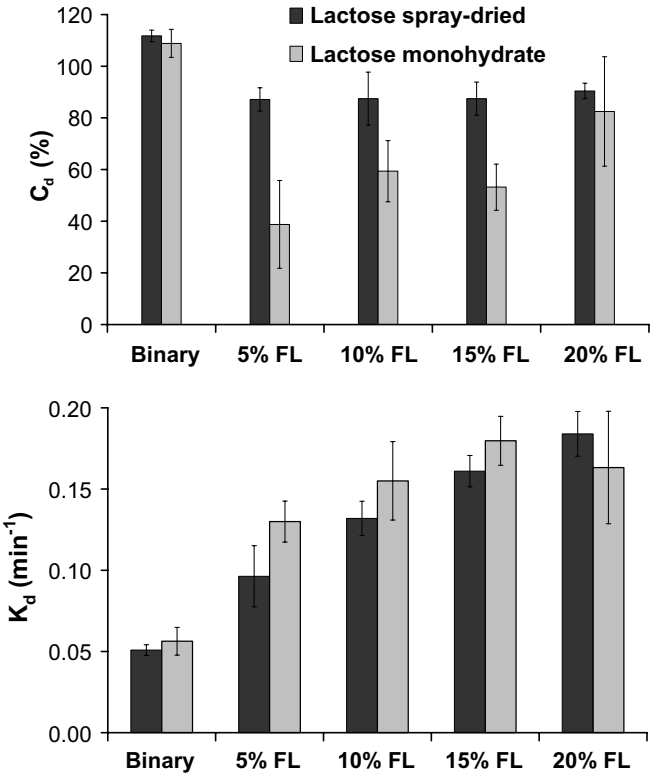

Fig. 3. Influence of added fine lactose (5–20%) on the estimated dispersed particle concentrations (C_d) and their dissolution rate constants (K_d) for binary and ternary indomethacin (20%) mixtures using ■ lactose spray-dried (106–250 μm) and ■ lactose monohydrate (106–250 μm) as the carriers.

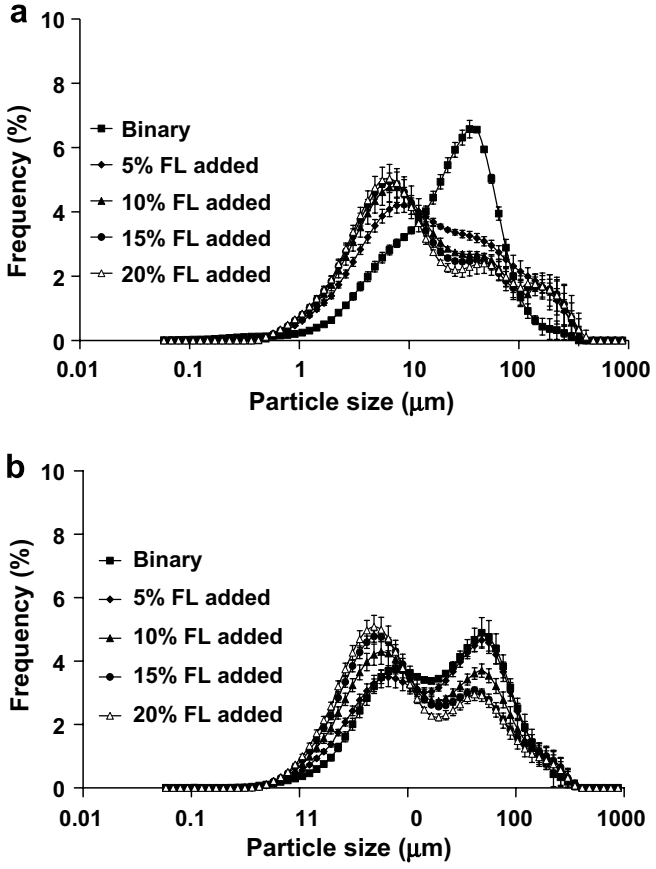

Fig. 4. Particle size distributions of indomethacin resulting from the addition of binary and ternary mixtures containing (a) lactose spray-dried and (b) lactose monohydrate as the carrier to degassed water. The particle size distribution was determined after 2 min to allow the dissolution of lactose.

and sampling variability. In spite of the slightly different dissolution rates during the first 20 min, comparison of these estimated parameters between the lactose monohydrate and spray-dried lactose binary mixtures did not reveal any significant difference in either estimated concentration or rate constant (t test, $P > 0.302$ and $P > 0.220$, respectively). Therefore, the small difference in the percentages of inherent fine lactose contained in these carriers (Table 1) did not result in any difference in the estimated parameters for these mixtures.

For the ternary mixtures, where dissolution data were fitted by the bi-exponential equation, comparison between the estimated C_d values across the different added fine lactose concentrations did not show any significant increase with the addition of fine lactose for both the lactose monohydrate and spray-dried lactose mixtures (one way ANOVA, $P > 0.894$ and >0.08 for the difference in C_d between the lactose spray-dried ternary mixtures and the lactose monohydrate ternary mixtures, respectively) except between the added 5% fine lactose and the added 20% fine lactose for the lactose monohydrate mixture where there was a significant increase in C_d ($P = 0.008$).

Comparison of estimated K_d across all the mixtures containing lactose spray-dried carrier found that there was a significant increase (one way ANOVA, $P < 0.031$) in K_d with increasing fine lactose concentration (except between the added 15% and the added 20% fine lactose ternary mixtures with $P = 0.114$) (Fig. 2b). For the lactose monohydrate mixtures, a similar trend of increasing K_d with the addition of increasing fine lactose was observed; however, the increase was not statistically significant due to the higher variability of the estimated parameters.

Based on diffusion controlled dissolution theory [16], dissolution rate constant can be related to parameters such as the volume of dissolution media, diffusion coefficient of the drug in the diffusion layer, thickness of diffusion layer, the saturation concentration of the drug in the dissolution media and the surface area of the particles. For truly dispersed particles of the same drug, these parameters should remain constant and there should be no change in the dissolution rate constant, K_d. The change in the dissolution rate observed in Fig. 3 is most likely associated with systematic surface area changes due to incomplete dispersion of the indomethacin during dissolution. To further understand this difference in K_d, the particle size distributions of the indomethacin in the binary and ternary mixtures were determined.

3.4. Particle size distributions of 20% indomethacin binary mixtures and ternary mixtures with added fine lactose

The particle size distributions of the binary (20% indomethacin) and ternary mixtures with added fine lactose (5%, 10%, 15% and 20%) in the dissolution medium, water, under non-sink conditions are shown in Fig. 4. The measurement was conducted after 2 min to give enough time for the lactose to dissolve leaving the indomethacin present as dispersed particles and agglomerates.

The particle size analysis of the mixtures showed multimodal distributions which represented dispersed and agglomerated particulate populations. These data show similar distribution behaviour to that seen with benzodiazepine mixtures used in other studies [17,18]. Most of the distributions were bi-modal; however, there was some slight evidence of tri-modal behaviour for the indomethacin-spray dried lactose mixtures containing 10%, 15% and 20% of fine lactose with a shoulder on the agglomerate distribution. While this might prompt consideration of tri-exponential modelling, the dissolution data for these mixtures were better fitted using the bi-exponential equation rather than the tri-exponential equation. This could be seen from the statistical comparison in Table 2, where in these mixtures, the bi-exponential equation resulted in a smaller AIC and larger F values compared to the tri-exponential equation. Careful examination of the particle size distribution of mixtures containing both coarse lactose carriers showed that (a) the ratio of dispersed to agglomerated particles increased and (b) the distribution mode representing the dispersed indomethacin particles moved to lower particle sizes when the concentration of fine lactose increased.

Therefore, as the concentration of fine lactose in the mixture increased, de-agglomeration occurred, giving rise to an increased population of dispersed particles. However, the extent of dispersion caused by the fine lactose increased with increasing concentration of fine lactose, i.e., the presence of fine lactose produced a dispersed fraction with a higher proportion of fully dispersed particles. This behaviour is in contrast to that of previous studies undertaken in our laboratories concerned with studying drug loading [2] and influence of surface active agents [3] where changes in the relative ratio of dispersed to agglomerated particles were seen, but the dispersed particle size distribution did not change. The change in dispersed particle size distribution will also mean that comparisons between the initial concentrations of dispersed particles shown in Fig. 3 were not able to be performed.

To quantify this shift in the particle size distributions, the D_{50} for each ''dispersed'' distribution was calculated after removing data for the ''agglomerate'' distribution. The minima between the dispersed and agglomerated particle distributions were used to define the cut-off particle size and the median particle sizes (D_{50}) were calculated for the dispersed distribution for each mixture, except for the binary containing lactose spray-dried carrier where the dispersed distribution could not be identified within a broad, almost monomodal, distribution of dispersed particles and agglomerates (Fig. 5). Fig. 5 clearly confirms the subjective observations of the particle size distributions in Fig. 4 which were that the D_{50} decreased with added fine lactose in the mixture. The results also show a difference in the D_{50} of the dispersed indomethacin distribution between mixtures containing lactose monohydrate and spray-dried lactose mixtures with the same fine lactose

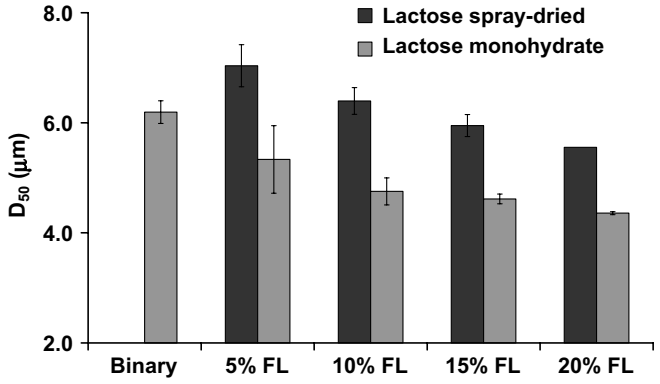

Fig. 5. The D_{50} of the dispersed indomethacin particle distribution obtained from ternary mixtures containing different percentages of added fine lactose with either lactose spray-dried or lactose monohydrate as the carrier (except for the binary containing lactose spray-dried carrier where the dispersed distribution could not be identified within a broad, almost monomodal distribution of dispersed particles and agglomerates).

concentration. This decrease in D_{50} might explain the increase in the estimated dissolution rate constant (K_d) with increased added fine lactose in the ternary mixtures shown in Fig. 2. To test this finding, the K_d (from the dissolution study) was regressed against the $(D_{50})^2$ (from the particle sizing study) for all mixtures (Fig. 6). The parameter $(D_{50})^2$ was selected instead of D_{50} because of the direct proportional relationship between the dissolution rate and the surface area of the sphere which is related to D^2 and not D (surface area of the sphere $= \pi D^2$). The two plots gave a good correlation ($R^2 > 0.986$) indicating an inverse relationship between K_d and $(D_{50})^2$. Thus, the presence of fine lactose in the coarse lactose-based indomethacin interactive mixtures results in differing dispersed particle distributions of truly dispersed particles and small agglomerates during dissolution and dissolution rates that were dependent on particle size.

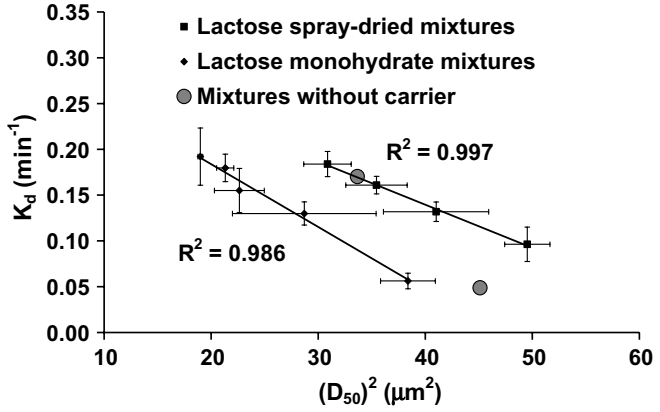

Fig. 6. Regression of K_d (estimated from modelling the dissolution data) versus $(D_{50})^2$ for the dispersed particles (from dispersion measured in water after 2 min) for binary (20% indomethacin) and ternary mixtures with added fine lactose (5–20%).

3.5. Effect of Indomethacin-FL ratio without carrier

In order to understand the mechanism of the increased dissolution rate with added fine lactose, the dissolution of binary mixtures containing indomethacin and fine lactose only in different ratios (indomethacin-fine lactose 4:1, 2:1, 1:1, 1:2 and 1:4) was performed in water containing 0.005% SLS over 2 h. The dissolution profiles (Fig. 7a) showed a similar trend to that of the coarse lactose ternary mixtures with an increased dissolution rate observed with an increase in fine lactose in the indomethacin-fine lactose mixtures, e.g., the following percentages of dissolved indomethacin were measured at 20 min: $24.6 \pm 1.6\%$, $29.4 \pm 2.9\%$, $39.3 \pm 2.2\%$, $77.0 \pm 3.7\%$ and $96.0 \pm 2.6\%$ for the indomethacin-fine lactose of 4:1, 2:1, 1:1, 1:2 and 1:4 mixtures, respectively.

Modelling of the dissolution data in Fig. 7 revealed that the bi-exponential and the tri-exponential equations provided the best fit. For the 4:1, 2:1 and the 1:4 indomethacin-fine lactose mixtures, the bi-exponential equation provided the best fit, while, for the 1:1 and the 1:2 indomethacin-fine lactose mixtures, data were best fitted by a tri-exponential equation. The dissolution parameters of the initial concentration of dispersed particles (C_d) and the dissolution rate constant for dispersed particle distribution (K_d) were estimated. The C_d values are not shown but ranged between about 19% and 72%. Comparison of C_d

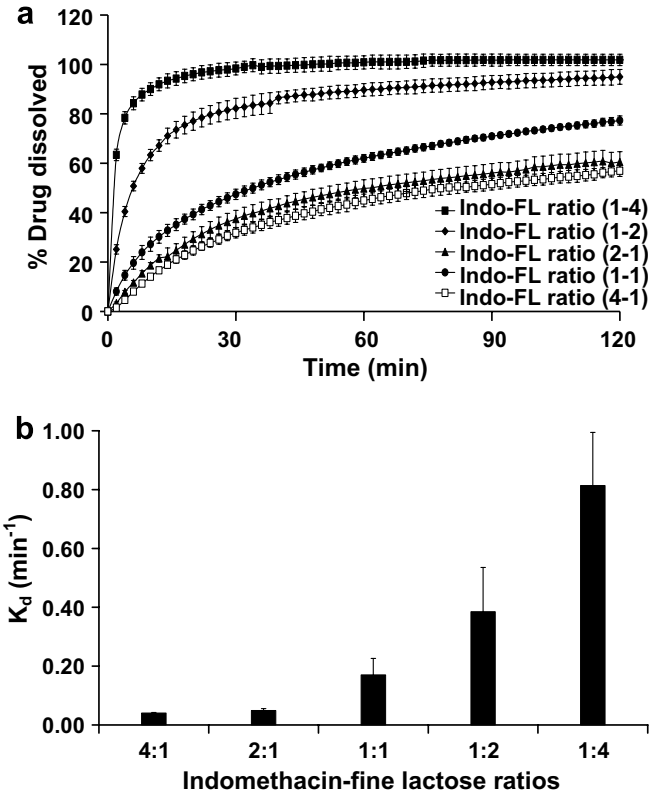

Fig. 7. Influence of indomethacin-fine lactose ratios in coarse lactose-free mixtures on (a) dissolution, measured in water with 0.005% SLS at 37 °C and (b) the estimated dissolution rate constants for the dispersed particles (K_d).

between the different mixtures revealed that there was little trend with increasing fine lactose concentrations. For example, the C_d for the 1:4 indomethacin-fine lactose mixture was significantly larger than all other mixtures (one way ANOVA, $P < 0.001$); however, the 4:1, 2:1 and the 1:2 indomethacin-fine lactose mixtures showed no significant difference in C_d (one way ANOVA, $P > 0.297$). Also, the C_d for the 1:1 indomethacin-fine lactose mixture was significantly smaller than both the 4:1 and 2:1 mixtures (one way ANOVA, $P < 0.016$). These results are not unexpected since the particle size distributions of the dispersed fraction may differ and are not able to be compared.

A clear trend was evident in the K_d values for the different mixtures (Fig. 7b), with a significant increase of K_d with increasing fine lactose in the mixture (one way ANOVA, $P < 0.001$). The trend in K_d for the binary mixtures was similar to that of the K_d in the coarse lactose-based ternary mixtures. The 1:2 and 1:4 indomethacin-fine lactose binary mixtures showed relatively high values of K_d compared with the coarse lactose-based ternary mixtures; however, these data extended beyond the indomethacin-fine lactose ratio studied in Fig. 3 where the maximum ratio was 1:1.

The particle sizing study for the mixtures with different ratios of indomethacin and fine lactose was conducted in water using the Mastersizer S. The particle size distributions for the different mixtures were plotted after 2 min to ensure dissolution of the lactose (Fig. 8a). The particle size distributions were multi-modal for all mixtures indicating distributions of dispersed and agglomerated particles. The dispersed particle distribution showed a gradual shift to decreasing particle sizes with the increase of the fine lactose fraction in the mixtures. In addition, a decrease in the agglomerate distribution was accompanied by an increase in the dispersed particle distribution. This shift was quantified by determining D_{50} which decreased with increasing fine lactose concentration in the mixture (Fig. 8b). The full regression between the estimated K_d from the dissolution data and the $(D_{50})^2$ is not shown, but resulted in a non-linear inverse relationship. The general trend was consistent with the outcome resulting from the addition of increased fine lactose to the 20% indomethacin-coarse lactose-based mixtures shown in Fig. 6. However, only the indomethacin-fine lactose ratios of 4:1 and 2:1 were comparable with the ratios of indomethacin to fine lactose in the coarse lactose-based mixtures and these data are plotted in Fig. 6. The two data points sit in the same space embraced by the two linear regressions. Given the difference in the regressions of the two coarse lactose-based mixtures and the lack of data points in this space for the coarse lactose-free mixtures, it is difficult to be dogmatic about comparative performance of all mixtures. However, the coarse lactose-free mixture showed similar trends to those of the coarse lactose-based mixtures in relation to changes in dispersion.

The finding in this study indicated that adding more fine lactose to micronised indomethacin with or without the coarse carrier resulted in the formation of smaller dispersed particles with higher dissolution rate constants.

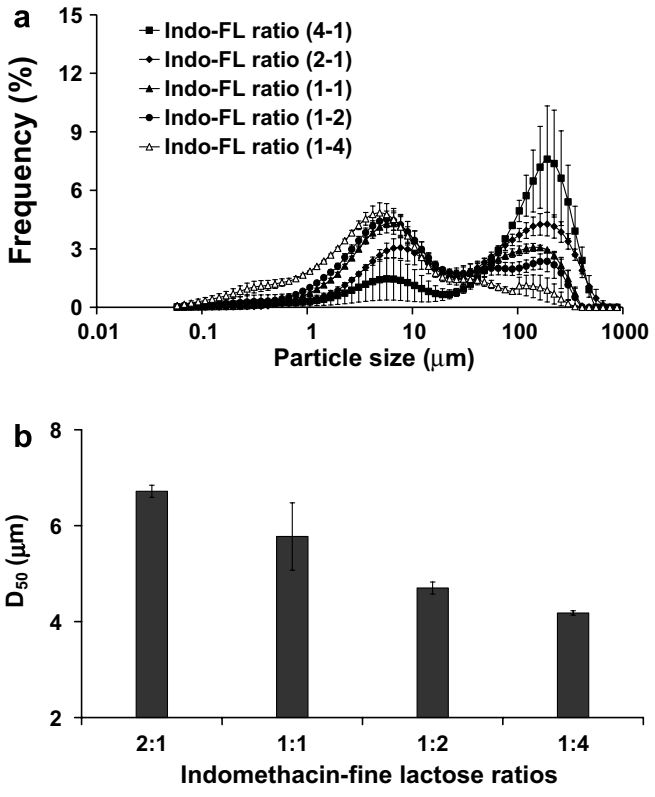

Fig. 8. Effect of fine lactose on the dispersion of indomethacin mixtures containing different ratios of indomethacin to fine lactose in water at 25 °C using the Mastersizer S. (a) Particle size distributions, (b) D_{50} for the dispersed particle distribution of the different mixtures.

3.6. Estimation of agglomerate strength in the indomethacin-fine lactose mixtures using the Aerosizer

In order to test the hypothesis that the addition of fine lactose to indomethacin results in the formation of mixed agglomerates (indomethacin-fine lactose) with different agglomerate strengths due to different structures, the particle sizes of samples of indomethacin-fine lactose (without the coarse carrier) were tested in the Aerosizer using different shear pressures (3.4, 10.3, 20.7 and 27.6 kPa). The volume mean diameters of the agglomerates were plotted against the shear pressures (Fig. 9). In general, those mixtures with the highest concentration of fine lactose produced the largest agglomerates. For all mixtures, the study revealed that there was little change in particle size with increasing shear pressure. The change in particle size was not significant with either shear pressure (two way ANOVA, $P = 0.499$) or with the ratio of indomethacin-FL in the mixture (two way ANOVA, $P = 0.275$). There was also no evidence of interaction between these two factors (two way ANOVA, $P = 0.672$).

The Aerosizer study indicated that adding fine lactose to micronised indomethacin resulted in the formation of agglomerates (likely to be indomethacin-fine lactose agglomerates) that showed little propensity to fully

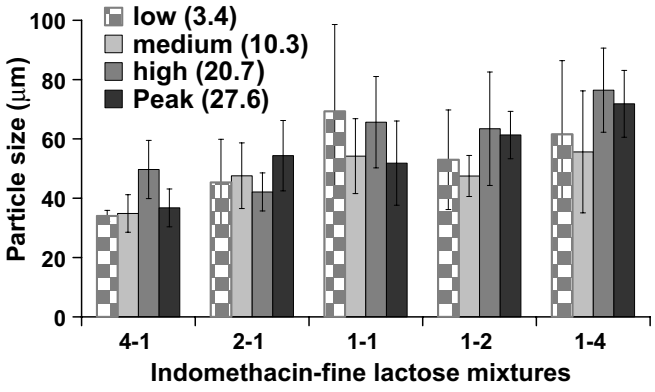

Fig. 9. Influence of shear pressure on the dispersion of agglomerates in indomethacin-fine lactose mixtures containing different fractions of fine lactose using the Aerosizer.

de-agglomerate with increasing shear pressure. Thus, while the size of the agglomerates was dependent on the fine lactose concentration, all agglomerates in the powder mixtures were relatively strong even under the highest shear pressures in the Aerosizer. It is difficult to determine the shear pressures generated under the dissolution conditions using the paddle method with a stirring rate of 100 rpm; intuitively, one would think that the shear conditions during dissolution were considerably less than a particle dispersion device on the Aerosizer and that these agglomerates would be unlikely to disperse during the hydrodynamic condition during dissolution. However, the behaviour in the dissolution medium, supported by the results of the dissolution modelling and particle sizing, suggested that de-agglomeration did occur as the concentration of the fine lactose increased. Thus, the de-agglomeration during dissolution was not related to the strength of the agglomerate that might be dependent on the factors such as packing fraction and particle interaction within the agglomerate, but is more likely to be connected with the agglomerate changes caused by dissolution of the fine lactose in the indomethacin-fine lactose agglomerates giving rise to open structures and agglomerate break-up. The extent of agglomerate structural change during dissolution is likely to be dependent on the ratio of indomethacin to fine lactose. Such conclusions on the mechanism of de-agglomeration remain speculative; however, the influence of fine lactose in the interactive indomethacin mixture is clear.

4. Conclusion

The addition of fine lactose to micronised indomethacin particles, with or without the coarse carrier, increased its rate of dissolution. Modelling the dissolution data using the multi-exponential equations proved to be useful in understanding the mechanism of dissolution of the particulate species of indomethacin in the interactive mixtures. When the dissolution data were modelled, the increased rate of dissolution was attributed mainly to an increase in the dissolution rate constant (K_d) and this was seen in both the ternary indomethacin-coarse lactose-fine lactose mixtures (Fig. 3) and binary indomethacin-fine lactose mixtures (Fig. 7). The observed dissolution rate increases showed little relationship to changes in the estimated parameter of initial concentration of dispersed particles (C_d). These findings from the modelling of the dissolution data were supported by the particle sizing studies of the indomethacin in the ternary and binary mixtures after dissolution of the lactose. The particle size distributions of dispersed particles were related to the concentration of fine lactose in the mixture and, for both the ternary and binary mixtures, there was a good inverse correlation between the K_d (from the dissolution data) and the $(D_{50})^2$ (from the particle sizing study).

The study demonstrated that the dispersed indomethacin particle distribution was not fully dispersed and contained a proportion of agglomerates. The results from the particle sizing experiment showed that the D_{50} of the dispersed particle distribution for the indomethacin ternary mixtures decreased from about 7.0 to 5.5 μm for the mixture containing the spray-dried lactose and from about 6.25 to 4.25 μm for the mixture containing lactose monohydrate. The D_{50} for fully dispersed indomethacin was 3.8 ± 0.6 μm (Table 1) indicating that the indomethacin in the ternary mixtures approached, but not quite achieved, full dispersion. The fact that the dissolution rate changes and the relationship between dissolution rate constant and dispersed distribution particle size behaved in a similar manner in both the ternary and binary mixtures indicated that the mechanisms controlling dissolution in both mixtures must have been similar. The extent of dispersion increased as the concentration of fine lactose in the mixtures increased indicating that the fine lactose played a role in the dispersion process. The mechanism by which this happened remains speculative and requires further study; however, the Aerosizer experiment indicated that it may not be related to the differing strengths of the agglomerates with different proportions of fine lactose and thus to their propensity to de-agglomerate and disperse. Further evidence of the relative magnitudes of shear produced with the Aerosizer compared with the hydrodynamic shear encountered in the dissolution vessel would be necessary to confirm this. When the mixtures were placed in the dissolution media, lactose was likely to dissolve rapidly. As the presence of fine lactose in the mixtures increased, it is probable that the dissolved lactose left an agglomerate structure of indomethacin with a much greater porosity and ability to disperse, with the resultant dispersed particle distribution dependent on the proportion of lactose.

In conclusion, the study gave evidence for the first time about the role of the fine lactose in enhancing the dissolution rate of a model drug, indomethacin. However, the outcomes from this study are fundamentally related to the mixing conditions used to prepare the indomethacin powder mixtures. Changes to mixing conditions may influence the particulate species present in the powder mixture and in

during dissolution. Care needs to be taken in interpreting dissolution data at other mixing conditions.

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