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Research paper

Understanding agglomeration of indomethacin during the dissolution of micronised indomethacin mixtures through dissolution and de-agglomeration modeling approaches

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Abstract

The purpose of this research was to correlate the state of agglomeration determined by the modeling of dissolution and de-agglomeration profiles, using mixtures of micronised indomethacin designed to have different dissolution rates and extents of particle agglomeration in dissolution media. Dissolution profiles were determined using the USP paddle method. De-agglomeration profiles were obtained from laser diffraction particle sizing of mixtures of indomethacin in dissolution media under non-sink conditions. Data were modeled and key parameters estimated using a non-linear least squares estimation algorithm. The key parameters of initial apparent volume concentrations as dispersed and agglomerated particles, and dissolution rate constants (for dissolution modeling), and the apparent volume concentrations of dispersible and non-dispersible agglomerates and the de-agglomeration rate constant (for de-agglomeration modeling) were related to indomethacin and sodium lauryl sulphate concentrations in the lactose–povidone mixtures. Micronised sodium lauryl sulphate added to the mixture was more effective in de-agglomeration than equivalent concentrations in the dissolution media. An excellent correlation existed between the total initial apparent volume concentration of agglomerates determined by dissolution and de-agglomeration ($P = 0.98$). The use of key parameters estimated from the modeling of dissolution and de-agglomeration profiles provides a useful tool in dosage form development of formulations of poorly water soluble drugs.

Keywords: Dissolution modeling; De-agglomeration; Non-linear least squares parameter estimation; Laser diffraction particle sizing; Poorly water soluble drugs; Indomethacin

1. Introduction

Studies on the dissolution of micronised drugs in powder mixtures were conducted extensively during the period from the mid 1980s to the early 1990s. These studies addressed the influence of the physicochemical properties of the mixtures, especially those of the carriers and drugs on dissolution rates. Included in this research were studies addressing carrier solubility [1–5], carrier particle size [2,3], drug concentration [1,5–8], agitation rates [1,9], pH of dissolution medium [4,10] and added excipients [3,8,11,12]. More recently, dissolution studies of micronised drugs such as diazepam, nitrazepam, oxazepam and flunitrazepam in interactive mixtures have shown that dissolution rates were concentration dependent with increasing drug concentration decreasing the dissolution rate [13–15]. Drug agglomeration was observed during the dissolution of these benzodiazepine interactive mixtures [15–17]. Modeling of the dissolution data for diazepam and oxazepam indicated that dissolution occurred from dispersed drug particles and agglomerates and that the dissolution data could be fitted to bi-exponential equations [15–17]. The initial percentage of dispersed particles

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and agglomerates, and the dissolution rate constants were derived by non-linear, least squares parameter estimation algorithms. The incorporation of micronised surfactants into interactive mixtures improved the dissolution rate of benzodiazepines by decreasing agglomeration and increasing the dissolution rate constants [17]. Laser diffraction particle sizing used in the modeling studies clearly has demonstrated the existence of both dispersed and agglomerated particle distributions [15,17]. In addition, the agglomeration behaviour of benzodiazepine mixtures in dissolution media under non-sink conditions has been monitored by laser diffraction particle sizing [18]. Particle size measurements over a 60 min period demonstrated a decrease in the degree of agglomeration with time. A de-agglomeration profile was constructed using area under the relevant distributions and total particle concentration. Interactive mixtures with higher benzodiazepine concentrations displayed de-agglomeration with a greater degree of agglomeration. Addition of micronised surfactants like sodium lauryl sulfate and cetrimide to interactive mixtures dramatically decreased agglomeration. Modeling of the de-agglomeration profiles allowed the estimation of three important parameters: the concentration of dispersible and non-dispersible agglomerates, and the de-agglomeration rate constant. Since, for poorly water soluble compounds showing dissolution limited absorption, dissolution will be maximised when the drug is fully dispersed, the estimated parameters of concentration of non-dispersible agglomerates and the de-agglomeration rate constants provide key insight of the extent of longer term agglomeration of the drug in the dissolution media. Both of these parameters therefore should relate to dissolution rates and they might be suitable indicators of the rate and extent of dissolution of these drugs in solid formulations and also of their bioavailability.

The hypothesis that we wish to test in this research is that it may be possible to use the state of agglomeration or dispersion of very poorly water-soluble drugs determined using simple laser diffraction methodologies under non-sink conditions to predict the extent of agglomeration that might occur during dissolution of a drug under sink conditions. The use of such a tool would enhance the process of formulation development. The specific purpose of this research was to determine if the estimates of agglomeration obtained by particle sizing and de-agglomeration modeling under non-sink conditions correlated with those obtained through the modeling of dissolution data from paddle dissolution methods. Micronised indomethacin was chosen as a model drug since it possessed low water solubility, but had good permeability. Strategies to produce mixtures of the micronised indomethacin with lactose with differing degrees of agglomeration during dissolution utilised differing drug and micronised surfactant concentration incorporated within the mixture.

2. Materials and methods

2.1. Materials

Indomethacin (Sigma Chemical Co., USA) was the adherent model drug. Indomethacin and sodium lauryl sulphate (sls) (Sigma, USA) were micronised and possessed a volume mean diameter of 8.9 μm by laser diffraction and projected area diameters less than 10 μm when examined using SEM, respectively. Micronisation was achieved by fluid energy milling (Chrispro Jetmill model 75P compressed air 5.8 atm at 12.7 l/s) and stored at room temperature in a closed container. Lactose–povidone granules (250–355 μm), used as the carrier, were prepared from nine parts of lactose (Wyndalle, New Zealand) and one part of povidone (Kollidon® 25, BASF, Germany) by wet granulation using 10% (w/w) povidone solution. The wet granules were tray dried in an incubator at 50 °C for 24 h and a 250–355 μm sieve fraction were obtained by sieve classification using standard sieves (Labotechnics, Australia) and a sieve shaker (Fritsch, Australia).

2.2. Interactive mixtures

Interactive mixtures were prepared using a previously validated mixing method; micronised drug (and surfactant) were placed between two layers of carrier in a glass vial and shaken vigorously by hand for 5 min [13,17,18]. Homogeneity of all mixtures were determined by removing 20×150 mg samples (or 20×15 mg when smaller samples were required), extracting into absolute alcohol (CSR, Australia), and assaying spectrophotometrically.

2.3. Particle size analysis

The particle size distribution of the micronized indomethacin was determined using laser diffraction (Malvern Mastersizer S, Malvern Instruments, England). Dispersion was achieved using a sonicator to break up the agglomerates in the indomethacin suspension in sls solution (0.5 mg ml^{-1}). The particle size distributions of the interactive mixtures containing indomethacin were determined under non-sink conditions. A suitable amount of the interactive mixture was added to 250 ml the purified water at 37 °C in the Small Volume Sample Dispersion Unit, and the speed was set to mid range and was constant for all the determinations. The obscuration of the sample was 10–30%. For each interactive mixture, distributions were taken at 2 min intervals for 1 h. Validation of the performance of the particle sizing process over the time of the experiments was undertaken [18].

2.4. Spectrophotometric analysis

Spectrophotometric analyses were performed using a scanning ultraviolet–visible spectrophotometer (Cecil 6000 series, model CE 6700, Cecil Instruments, England).

Beer's law calibration plots were obtained in absolute alcohol for the homogeneity studies (318 nm, 0.02–0.06 mg ml^{-1}) and in purified water for the dissolution studies (265 nm, 0.002–0.008 mg ml^{-1}). At least four concentrations and four replicates were used for the calibration. Linear regression analysis indicated no significant deviations from linearity and no significant deviations from a zero intercept. Absorbance of the lactose carrier was insignificant in the dissolution studies, and was small (<0.05) and accounted for in the homogeneity determinations. Correlation coefficients approached 1.000.

2.5. Dissolution studies

An automated dissolution system consisting of the dissolution apparatus (model DT 6, Erweka, Germany), auto-controlled multi-channel peristaltic pump (Watson Marlow Ltd 503 V/RL, England), an ultraviolet–visible spectrophotometer with 10 mm flow cells (Cecil Instrumentation Ltd, England, CE 6700), and controlled using Erweka software was employed in all of the dissolution studies according to the USP/NF paddle method. A 1000 ml volume of dissolution medium was introduced into the dissolution vessel, covered, and incubated to 37 °C. Samples of interactive mixture (34–150 mg) were sequentially added to the cells using the Erweka software count down. Sequential sampling using a filter probe occurred over 60 min at regular 2 min intervals using six replicates.

2.6. Data fitting

The Marquardt–Levenberg algorithm was used to find the coefficients (parameters) of the independent variable(s) that give the best fit between the equation and the data [18–21]. This algorithm seeks the values of the parameters that minimise the sum of the squared differences between the values of the observed and predicted values of the dependent variable. The following statistics were used to assess the goodness of the fit: coefficient of determination (Rsqr), the coefficient of variation (CV%), the dependency (defined as 1 − (variance of the parameter, other parameters constant)/(variance of the parameter, other parameters changing), and the norm which is square root of the sum of squares. The plot of residuals was used to see trends in the data fit. The residuals were tested for randomness using the residual analysis (runs test) [22]. The test is based on the order of consecutive occurrences, i.e. number of positive or negative deviations, either too may short runs or too few long runs indicative of non-randomness [22].

3. Results and discussion

3.1. Indomethacin mixtures

Binary mixtures of indomethacin and lactose–povidone granules were prepared using micronised indomethacin (5, 10, and 15%). Also, ternary mixtures of indomethacin, sls and lactose–povidone granules were prepared using micronised indomethacin (5, 10 and 15%) and micronised sodium lauryl suplhate (1, 2, 3, and 5%). The homogeneity of the mixtures was excellent with CV less than 2% for the 150 mg samples and less than 4.7% for the 20 mg samples.

3.2. Dissolution of indomethacin mixtures

The dissolution profiles of indomethacin binary mixtures and ternary mixtures with 1% sls were obtained by adding 100 mg of the 5% mixture, 50 mg of the 10% mixture and 34 mg of the 15% mixture to distilled water. The concentration of dissolved indomethacin was less than the solubility of indomethacin (0.0008%). The concentration was chosen to increase sensitivity of the UV spectrophotometric assay and, while not truly sink conditions at about 10% of saturation, preliminary studies demonstrated that all the indomethacin dissolved in the distilled water during dissolution. The dissolution profiles of the binary and ternary mixtures of indomethacin in distilled water are shown in Figs. 1 and 2. As seen in previous studies, the dissolution rate of binary mixtures was concentration

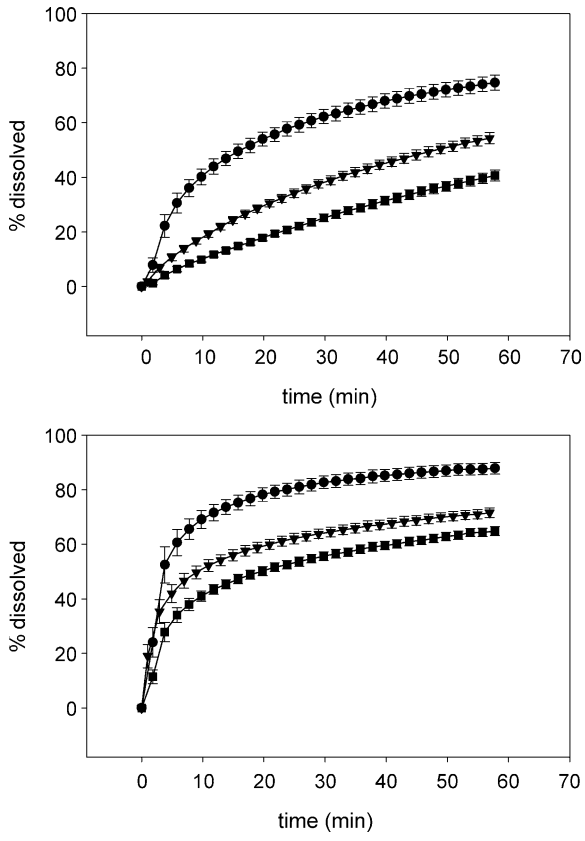

Fig. 1. Influence of indomethacin concentration on the dissolution of interactive mixtures of indomethacin in 1000 ml of purified water at 37.5 °C using the paddle method at 100 rpm. Top: binary mixtures of indomethacin and lactose–povidone granules; Bottom: ternary mixtures of indomethacin with lactose–povidone granules and with 1% sls. (●, 5%; ▼, 10%; ■, 15%).

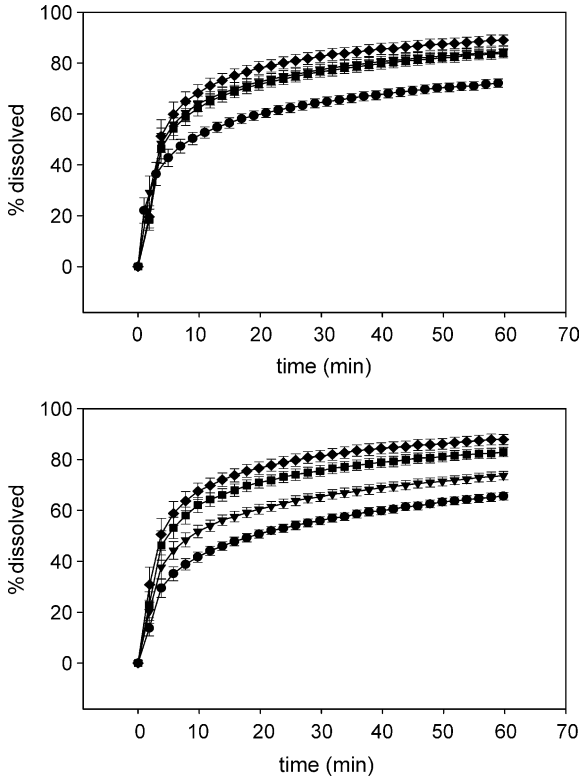

Fig. 2. Influence of sodium lauryl sulphate concentration on the dissolution of indomethacin interactive mixtures in 1000 ml of purified water at 37.5 °C using the USP paddle method at 100 rpm. Top: 10% indomethacin; Bottom: 15% indomethacin. (●, 1% sls; ▼, 2% sls; ■, 3% sls; ♦, 5% sls).

dependent [13–15]. For the 10% binary mixture, less than 60% had dissolved within 60 min. When 1% sls was added to the interactive mixture, the dissiolution rate increased slightly with about 70% indomethacin dissolving in 60 min for the 10% indomethacin mixture. Concentration dependent dissolution was also seen for the ternary indomethacin mixtures containing 1% sls. The slow dissolution rates and concentration dependent behaviour were attributed to partial agglomeration of the micronised powder; such agglomeration had been previously shown in the concentration dependent dissolution of benzodiazepines interactive mixtures [13–15]. The slow dissolution rates also were consistent with the dissolution of larger 'particles'. For example, in recent studies in our laboratories, a powder mixture of indomethacin with a volume mean diameter of 55 μm showed only about 40% dissolution after 60 min in a 0.005% sls dissolution media. The influence of added micronised sls (1–5%) to the mixtures is seen in Fig. 2 for 10 and 15% ternary indomethacin mixtures. Increased sls in the mixture increased the dissolution rate and this was consistent with previously reported results for benzodiazepines [17,23]. The mechanism for increased dissolution rates was associated with the production of mixed agglomerates of indomethacin and sls during mixing due to competitive particle interactions and particle redistribution within the mixture, and the subsequent increased dispersion due to high dissolved sls concentrations in the agglomerate microenvironment during dissolution [23].The dissolution data were modelled using multi-exponential equations [15–17] as follows:

$$C = C_d \exp(-tk_d) + C_{a1} \exp(-tk_{a1}) + C_{a2} \exp(-tk_{a2}) + \cdots \quad (1)$$

where C was the percent of undissolved particles at time t, C_d, C_{a1} and C_{a2} were the initial apparent volume percentage as dispersed particles (d) and as agglomerated particles (a1, a2, …), respectively, and k_d, k_{a1} and k_{a2} were the dissolution rate constants for the dispersed (d) and aggregated particles (a1, a2, …), min^{-1}, respectively. Combined data from six replicate determinations were modelled using the nonlinear least squares curve fitting software package Sigmaplot® (Jandel Scientific) which utilised the Marquardt–Levenberg algorithm [19–21] to determine the absolute true minima for the sum of squared deviations. Data were unweighted and truncated when the mean of the dependent variable was not significantly different from the final data point. Residuals were shown to be randomly distributed using the runs test [22]. The modeling of dissolution data using this methodology has been previously described [15].

For the 5% binary mixture, the dissolution data were best fitted by a bi-exponential equation and the estimated parameter of initial apparent volume percentage as dispersed and agglomerated particles and the dissolution rate constants for dispersed and agglomerated particles for the indomethacin mixtures were obtained (Table 1). However, for the more concentrated binary mixtures, the extent of agglomeration approached 100% and the dissolution data were best fitted by a mono-exponential equation (Table 1). The half-lives for dissolution of the agglomerates ranged between about 46 and 77 min, while the dissolution of the dispersed particles was rapid with a half-life of the dispersed particles in the 5% binary mixture being 4.4 min. The results in Table 2 showed that the dissolution of ternary mixture containing a low concentration of sls was faster than that of binary mixture. The ternary mixture had a much lower

Table 1
Influence of indomethacin concentration on the estimated parameters of initial concentration of dispersed particles (C_d) and agglomerates (C_a), and on the dissolution rate constants for dispersed particles (k_d) and agglomerates (k_a) when indomethacin mixtures with lactose–povidone granules underwent dissolution in distilled water at 37.5 °C using the paddle method at 100 rpm

Estimated parameters	Indomethacin		
	5%	10%	15%
C_d (%)	42.5 (3.3%)[a]		
k_d (min^{-1})	0.159 (6.1%)		
C_a (%)	58.8 (2.4%)	95.3 (0.8%)	98.7 (0.2%)
k_a (min^{-1})	0.015 (4.0%)	0.014 (2.1%)	0.009 (0.9%)

[a] The numbers in parenthesis are the coefficients of variation determined through the non-linear least squares algorithm and are derived from the use of six replicates with 30 data points in each replicate.

Table 2
Influence of sodium lauryl sulphate (sls) concentration on the estimated parameters of initial concentration of dispersed particles (C_d) and agglomerates (C_a), and on the dissolution rate constants for dispersed particles (k_d) and agglomerates (k_a) when indomethacin (5.0, 10.0 and 15.0%) mixtures with lactose-povidone granules and micronised sls (1.0, 3.0 and 5.0%) underwent dissolution in distilled water at 37.5 °C using the paddle method at 100 rpm

Indomethacin concentration (%)	Estimated parameters	sls		
		1.0%	3.0%	5.0%
5.0	C_d (%)	70.0 (2.1%)[a]	75.5 (2.0%)	81.1 (3.7%)
	k_d (min^{-1})	0.324 (4.4%)	0.324 (4.2%)	0.279 (7.9%)
	C_a (%)	30.6 (3.4%)	25.3 (4.4%)	21.8 (10.4%)
	k_a (min^{-1})	0.018 (5.9%)	0.020 (7.0%)	0.014 (20.7%)
10.0	C_d (%)	46.1 (3.4%)	64.4 (3.1%)	71.3 (3.5%)
	k_d (min^{-1})	0.400 (8.2%)	0.273 (6.6%)	0.275 (7.3%)
	C_a (%)	51.5 (1.9%)	37.4 (4.1%)	31.0 (6.4%)
	k_a (min^{-1})	0.011 (5.1%)	0.015 (7.9%)	0.018 (10.5%)
15.0	C_d (%)	41.4 (2.3%)	62.0 (2.1%)	65.4 (1.6%)
	k_d (min^{-1})	0.249 (5.1%)	0.287 (4.6%)	0.321 (3.4%)
	C_a (%)	59.0 (1.2%)	38.6 (2.5%)	34.4 (2.2%)
	k_a (min^{-1})	0.009 (3.4%)	0.015 (5.0%)	0.019 (3.7%)

[a] The numbers in parenthesis are the coefficients of variation determined through the non-linear least squares algorithm and are derived from the use of six replicates with 30 data points in each replicate.

initial apparent volume percentage as agglomerates and thus a higher initial apparent volume percentage as dispersed particles. Interestingly, the dissolution rate constants of the dispersed particles in the ternary mixtures were slightly greater than those of the binary mixtures. Since the particle size distribution of dispersed particles of indomethacin did not change for binary or ternary sls mixtures, the increased dissolution rate was likely to be caused to the presence of significant concentrations of sls in the diffusion layer, thereby increasing the dissolution rate due to increased solubility of the indomethacin in this diffusion layer. These effects were also seen for the dissolution of benzodiazepines [17,23]. The half-lives of dissolution from dispersed particles and agglomerates were between 1.7 and 2.8 min and between 34.5 and 77.0 min, respectively. The results were consistent with previous studies of effect of surfactants on the dissolution of drug in interactive mixtures [13–17].

3.3. Particle size distributions of the interactive mixtures

When the indomethacin (5.0–15.0%)–lactose binary and indomethacin (5.0–15.0%)–sls (1.0–5.0%)–lactose ternary interactive mixtures were added to the distilled water at concentrations giving non-sink conditions, the lactose carrier dissolved rapidly leaving fully dispersed particles and agglomerates of indomethacin. Some of the indomethacin dissolved from both dispersed particles and agglomerates to yield a saturated solution. The particle size distribution of the remaining dispersion showed distributions representing the dispersed micronised particles (up to about 20 μm) and agglomerates (around 100 μm), respectively. The dispersed particle and agglomerate distributions identified for indomethacin were consistent with those seen in previous dissolution modeling studies [15,17] and de-agglomeration studies [18] on the benzodiazepines undertaken in the our laboratory.

3.4. Monitoring the state of agglomeration of indomethacin

The information present in the particle size distribution of the indomethacin dispersions can be used to determine the state of agglomeration of the indomethacin after its addition to dissolution media from powder mixtures. In this study, the dispersed and agglomerated particle volume concentrations (C_{dpv} and C_{apv} %) were obtained using the area under the dispersed and agglomerated particle distributions.Using the total volume concentration (C_{tpv}), then the percent of agglomerated particles can be determined at any time, t as follows [18]:

$$\text{apparent volume percentage as agglomerates} = (C_{apv}/C_{tpv})100 \quad (2)$$

The apparent volume percentage as agglomerates can be used to monitor changes in the state of particle dispersion with time. The packing arrangement in these agglomerates is unknown, but is likely to contain some void space and the degree of agglomeration from particle size distributions may be overestimated. However, agglomeration arises from particulate interactions during the preparation of the powder mixture and SEMs of mixtures show a close network of particles in multi-layers and discrete agglomerates within the mixture. Particles are likely to be tightly packed within the agglomerates, but there is no way to determine or prove this. The terminology ‘apparent volume percentage as agglomerates’ has been used in this paper to address this issue.

Fig. 3 shows a representative de-agglomeration profile of the percentage of agglomerates (apparent volume percentage as agglomerates) versus time for a indomethacin (10%) binary interactive mixture and for a indomethacin (10%) ternary interactive mixtures with 3% sls. In general, the de-agglomeration profiles showed that the apparent volume

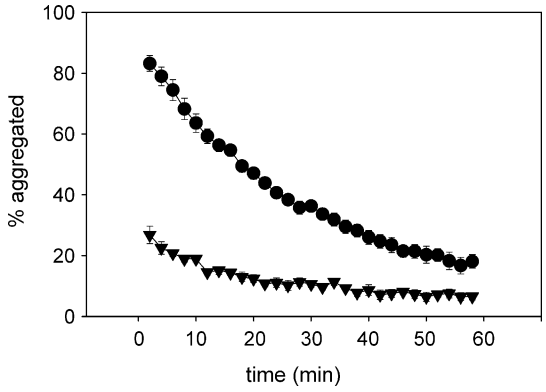

Fig. 3. De-agglomeration profile of percentage of agglomerates (mean ± SD) for 10% indomethacin interactive mixtures in 250 ml of purified water at 37.5 °C (●, binary mixture; ▼, ternary mixture with 3% sls).

percentage as agglomerates in the ternary mixtures were lower than those of binary mixtures. The initial apparent volume percentage as agglomerates in indomethacin ternary mixture (i.e. $C_0 + C_{0a}$) was around 30%, and was significantly lower than that of the binary mixtures (around 85%). Incorporation of micronised sls into interactive mixture improved particle dispersion and therefore was consistent with the outcomes of the dissolution studies for these mixtures. Fig. 3 also demonstrated that the degree of agglomeration decreased with time in an exponential-like manner.

3.5. Modeling the deagglomeration profile

The modeling of de-agglomeration profiles has been described previously [24]. The de-agglomeration profiles for the indomethacin mixtures were fitted to the following exponential equations:

$$C_a = C_{0a}\exp(-K_a t) \quad (3)$$

$$C_a = C_0 + C_{0a}\exp(-K_a t) \quad (4)$$

$$C_a = C_{0a}\exp(-K_a t) + C_{0b}\exp(-K_b t) \quad (5)$$

where C_a was the apparent volume percentage as agglomerates at time t; C_0 was the apparent volume percentage as non-dispersible agglomerates, which did not de-agglomerate during the dissolution time; C_{0a} was the initial apparent volume percentage as dispersible agglomerates, which de-agglomerated during dissolution time; K_a was the de-agglomeration rate constant. C_{0b} represented the percentage of agglomerates, which de-agglomerated according to the rate constant (K_b).

The de-agglomeration curves were best modelled by using the three parameter single exponential decay equation (Eq. (4) and the estimated parameters are shown in Table 3. The assessment of goodness of the fit showed that the R^2 values of the binary and ternary mixtures were 0.998 and 0.973, respectively. The norm values (norm value = $(SS)^{0.5}$) of binary and ternary mixtures were 4.1 and 4.6, respectively. The value of CV (%) were generally relatively small and the dependency values were not close to 1 indicating that the equation used was not over-parameterised. These statistics indicated a good fit of the data to the three-parameter exponential equation.

Table 3
Influence of indomethacin concentration (5.0–15.0%) on the estimated parameters of concentration of non-dispersed agglomerates (C_0), concentration of dispersible agglomerates (C_{0a}), and on the de-agglomeration rate constants (K_a) when indomethacin mixtures with lactose-povidone granules were added to distilled water at 37.5 °C

Estimated parameters	Indomethacin		
	5.0%	10.0%	15.0%
C_0 (%)	6.8 (7.4%)[a]	7.1 (14.3%)	10.7 (10.9%)
C_{0a} (%)	48.5 (1.0%)	82.4 (1.0%)	87.2 (1.8%)
K_a (min^{-1})	0.048 (3.3%)	0.036 (3.1%)	0.058 (5.1%)

[a] The numbers in parenthesis are the coefficients of variation determined through the non-linear least squares algorithm and are derived from the use of six replicates with 30 data points in each replicate.

The results in Tables 3 and 4 show the influence of indomethacin concentration on the estimated parameters of C_0, C_{0a} and k_a for binary mixtures and the effect of sls concentrations on the estimated parameters in ternary mixtures of indomethacin, sls and lactose–povidone granules. Increasing the concentration of the micronised indomethacin in the binary mixture increased both the apparent volume percentage as dispersible and non-dispersible agglomerates, but was more significant for the dispersible agglomerates. At the highest concentration (15%), the apparent volume percentage as dispersible agglomerates was nearly 90%, however, non-dispersible agglomerates were only about 10%. The de-agglomeration process for the binary mixture was relatively rapid with de-agglomeration half-lives between about 12 and 19 min. The apparent volume percentage as dispersible agglomerates (C_{0a}) of binary mixtures were much higher than those of ternary mixtures. Ternary mixtures also demonstrated concentration dependent agglomeration particularly for the apparent volume percentage as dispersible agglomerates (C_{0a}). Increasing sls concentrations in the interactive mixture caused greater dispersion shown in the apparent volume percentage as dispersible agglomerates (C_{0a}) values in Table 4. Both indomethacin and sls concentration had little influence on the apparent volume percentages as non-dispersible agglomerates (C_0) in the ternary mixtures with this parameter being less than 6.6%. The apparent volume percentages as non-dispersible agglomerates (C_0) for binary mixtures were only slightly higher than those of the ternary mixtures.

3.6. Influence of intra- or extra-agglomerate sls on de-agglomeration parameters

A study was undertaken to compare the de-agglomeration behaviour of binary mixtures of indomethacin in

Table 4
Influence of indomethacin concentration (5.0–15.0%) on the estimated parameters of concentration of non-dispersed agglomerates (C_0), concentration of dispersible agglomerates (C_{0a}), and on the de-agglomeration rate constants (K_a) when indomethacin mixtures with lactose-povidone granules were added to distilled water at 37.5 °C

Indomethacin concentration (%)	Estimated parameters	sls		
		1.0%	3.0%	5.0%
10.0	C_0 (%)	6.2 (5.5%)[a]	6.6 (6.8%)	3.8 (9.9%)
	C_{0a} (%)	30.8 (1.9%)	21.6 (3.5%)	17.7 (2.7%)
	K_a (min^{-1})	0.066 (4.7%)	0.065 (8.8%)	0.056 (7.9%)
15.0	C_0 (%)	5.6 (5.2%)	4.0 (8.4%)	5.9 (10.0%)
	C_{0a} (%)	48.9 (1.6%)	24.7 (3.2%)	18.7 (5.9%)
	K_a (min^{-1})	0.084 (3.2%)	0.078 (6.8%)	0.069 (14.1%)

[a] The numbers in parenthesis are the coefficients of variation determined through the non-linear least squares algorithm and are derived from the use of six replicates with 30 data points in each replicate.

dissolution media containing an equivalent concentration of sls to that in the ternary mixtures (extra-agglomerate) with ternary indomethacin mixtures containing micronised sls (intra-agglomerate). The de-agglomeration profiles for 10 and 15% indomethacin with lactose–povidone granules were obtained in aqueous sls solutions (ranging from 0.8 to 6.0 mg ml^{-1}); these higher indomethacin concentration mixtures of 10 and 15% were chosen because they showed greater agglomeration than the 5% mixture and would provide a better test for determining the difference between intra- and extra- agglomerate effects. These concentrations were equivalent to the amount of sls that would be present when 10 and 15% indomethacin ternary mixtures containing 1.0, 3.0 and 5.0% sls were added to 250 ml of distilled water during laser diffraction particle sizing of the mixtures. The de-agglomeration profiles of the ternary indomethacin mixtures containing 1.0, 3.0 and 5.0% sls also were determined in distilled water. All the de-agglomeration profiles were fitted to the three-parameter exponential equation and the estimated parameters of C_0, C_{0a} and k_a determined. The results in Fig. 4 show the differences in total and non-dispersible agglomeration for the de-agglomeration of indomethacin in intra-agglomerate and extra-agglomerate systems. The results indicate that the mixtures containing micronised surfactant de-agglomerated much more efficiently than binary mixtures in sls solutions. Both the total apparent volume percentages as agglomerates and the apparent volume percentages as non-dispersible agglomerates were smaller for the ternary indomethacin mixture in water. The presence of sls within the micro-environment of the agglomerate has a powerful effect on deagglomeration.

3.7. Correlation between the initial extent of agglomeration estimated from dissolution and from the de-agglomeration profile modeling

The correlation between the initial apparent volume percentage as agglomerates of indomethacin in binary and ternary interactive mixtures estimated from the de-aggregation data and dissolution data modeling is shown in Fig. 5. The data represents the modeling results from a range of indomethacin and sls concentrations in the mixtures. Given that the estimates of agglomeration were obtained from very different methodologies, i.e. particle sizing under non-sink

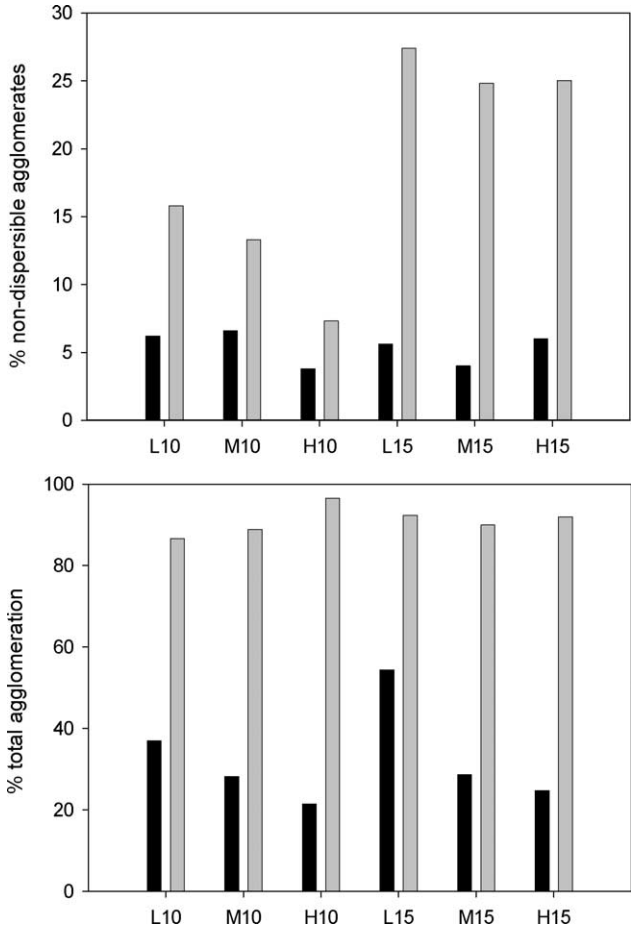

Fig. 4. Comparison of the effect of sodium lauryl sulphate present in the interactive mixture (black) or present in the dissolution medium (grey) on the apparent percentage of non-dispersible and total agglomerates ($C_0 + C_{0a}$) for differing concentrations of sls and indomethacin. *L*, *M* and *H* refer to the concentration of sls and are 1.0, 3.0 and 5.0% in the interactive mixture, respectively and are 1.2, 3.6 and 6.0 mg ml^{-1} in the dissolution media for the 10% indomethacin mixture and 0.8. 2.4 and 4.0 mg ml^{-1} in the dissolution media for the 15% indomethacin mixture. The number in the code on the *x*-axis refers to the percentage of indomethacin.

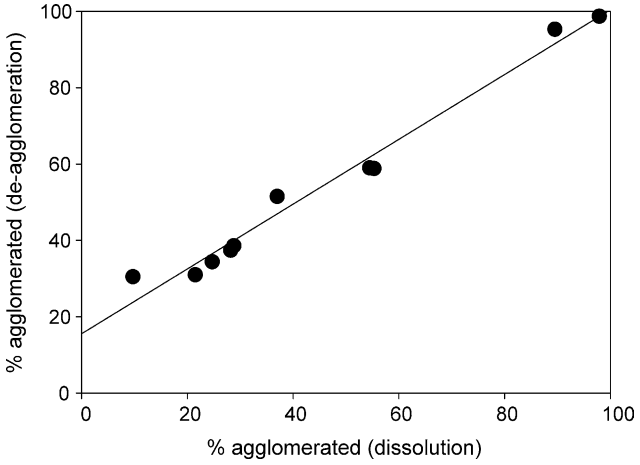

Fig. 5. Correlation between the initial percentage of agglomerated particles from dissolution data modeling (C_a) and the apparent initial percentage of agglomerated particles from de-aggregation data modeling ($C_0 + C_{0a}$) for indomethacin binary and ternary mixtures.

conditions and dissolution rate studies under sink conditions, the correlation was excellent with a coefficient (R^2) of 0.98. The good correlation provides evidence of the robustness of the methodologies in treating dissolution and de-agglomeration data. In addition, the good correlation reinforces the appropriateness of the use of laser diffraction particle sizing methodology in obtaining estimates of agglomeration during drug dissolution. Provided that the individual solid components of a formulation could be identified in the particle sizing, a relatively simple methodology, involving rapid particle sizing over time and subsequent data treatment, and without the need for drug assay, could be established as a screening process in formulation development.

4. Conclusion

Both modeling approaches (i.e. particle sizing under non-sink conditions and dissolution rate studies under sink conditions) may be useful in understanding the dissolution behaviour of formulations. Knowledge of relative extents of agglomeration or dispersion and the dissolution rate constants may explain the cause for poor dissolution of some formulations and may provide feedback to the formulator about formulation and processing strategies. However, the particle sizing approach may be more informative because it is able to determine the rate of de-agglomeration and the concentration of non-dispersible agglomerates. High initial agglomeration, slow de-agglomeration rates and high non-dispersible agglomeration would indicate significant potential formulation problems with dissolution and perhaps bioavailability of poorly water soluble drugs in a formulation. In addition, the total initial agglomeration from particle sizing approaches can be correlated well with agglomeration from dissolution modeling. The modeling tools described in this manuscript and previously may be valuable to the formulator in developing robust formulations and identifying causes for poor dissolution. The use of the dissolution modeling can be universally applied to any dissolution process provided the dissolution profile contains enough data points to allow for reliable modeling. The de-agglomeration profile approach will depend on the ability to identify the distributions of dispersed particles and agglomerates; this may sometimes be difficult with formulations containing insoluble excipients. However, it is a powerful tool in identifying the key parameters of de-agglomeration rate constants and apparent volume percentage as non-dispersible agglomerates.

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