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Research paper

Counter-intuitive enhancement in the dissolution of indomethacin with the incorporation of cohesive poorly water-soluble inorganic salt additives

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ABSTRACT

The objective of this work was to investigate the influence of various micronized poorly water-soluble inorganic materials on the dissolution and de-agglomeration behaviour of a micronized, poorly water-soluble model drug, indomethacin, from lactose interactive mixtures. Dissolution of indomethacin was studied using the USP paddle method and the data were modelled with multi-exponential equations using a nonlinear least squares algorithm in order to obtain key parameter estimates. The dispersion of indomethacin mixtures was measured by laser diffraction. The addition of aluminium hydroxide and calcium phosphate to binary mixtures of indomethacin counter-intuitively improved the dissolution rate of indomethacin due to significant increases in both the estimated initial concentration and dissolution rate constant of dispersed particles of indomethacin. While some enhancement was due to pH changes in the dissolution medium, the presence of these poorly water-soluble inorganic salts caused de-agglomeration. Average particle size distributions indicated that the presence of aluminium hydroxide within the matrix of indomethacin had reduced the agglomerate concentration whilst increasing the dispersed particle concentration. These findings provide the first evidence of the ability of poorly water-soluble inorganic salts to enhance the de-agglomeration and dissolution of micronized powders, potentially translating to improved bioavailability of poorly water-soluble drugs.

1. Introduction

Poor water solubility represents one of the major causes of drug candidate failure in pharmaceutical product pipelines, whereby more than one-third of drugs listed in the United States Pharmacopoeia are poorly water-soluble [1]. For compounds that are poorly soluble in water and show dissolution-limited absorption, incomplete oral bioavailability can result. Dissolution is maximized only when the drug is fully dispersed in the gastrointestinal fluids.

Particle size reduction is often used to generate micron or submicron-sized drug particles with increased surface area for more rapid dissolution in the gastrointestinal tract; however, such fine particles are cohesive and agglomerate since at such sizes, the van der Waals attraction generally exceeds gravitational detachment [2,3]. Due to a reduced surface area available for dissolution, agglomerates of poorly water-soluble drugs are difficult to disperse and can experience poor dissolution rates.

Formulation strategies have been developed to enhance the dissolution of cohesive poorly water-soluble micronized drugs that agglomerate. Creation of interactive mixtures, which theoretically consist of fine drug particles adhered onto coarse carriers, has contributed to formulation optimization in several ways. Firstly, this approach increases the homogeneity of low dose drugs [4] and also enhances the bulk flow characteristics. Secondly, interactive mixtures have been shown to contribute to the improvement of drug dissolution and bioavailability [5]. As the cohesive drug adheres onto the coarse carrier surface, agglomeration is reduced and a larger drug surface area is exposed to the dissolution medium. Hence, an improved dissolution rate is achieved. The use of water-soluble carriers may further enhance drug dissolution because they dissolve rapidly in the dissolution medium and increase the dispersion state of the micronized powders [6]. In addition, other strategies to reduce agglomeration and its effects during drug dissolution in interactive mixtures include the incorporation of surfactants [7–10], as well as using both lower concentrations of the drug [11–13] and smaller carriers [6,14]. The latter two strategies can give rise to increased carrier surface areas available to the drug, therefore resulting in greater dispersion.

The formulation strategies described rely on the drug particles being fully dispersed on the carrier surface. While this can happen in some instances, it is more likely that powder mixing processes result in complex mixtures of interactive units and agglomerates.

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Mixture particulate composition will depend on processing conditions, and drug and formulation properties. Thus, in reality, some other de-agglomeration mechanism will be required for complete powder dispersion in the dissolution medium.

In parallel to dissolution studies, research into the use of interactive mixtures for dry powder inhalers has revealed the importance of the structure of agglomerates in affecting the extent of drug aerosolization [15–17]. These studies demonstrated that the incorporation of micronized lactose and other micronized materials in lactose carrier-based interactive mixtures had a positive impact on the aerosolization efficiency of drugs through improved de-agglomeration. The resultant mixed agglomerates of micronized drug and micronized lactose (or micronized drug and other micronized materials) were proposed to have reduced tensile strength, as the dispersion of agglomerates was related to the tensile strength [3].

The tensile strength (σ) of agglomerates is dependent on the particle size, work of adhesion and packing fraction of the agglomerates. Many mathematical models have been used to define tensile strength and one of the equations is as follows [18]:

$$\sigma = \frac{15.6\phi^4 W}{d} \quad (1)$$

where ϕ is the packing fraction, W is the work of adhesion and d is the particle diameter.

As the particle size of a drug is confined by its functionality, the ability to modify the strength of agglomerates can be achieved by either manipulating the particle surface composition or morphology to change the work of adhesion, or by changing the packing fraction of the agglomerate by, for example, adding materials that will modify the agglomerate structure.

Previous studies have shown that the presence of micronized lactose increased the dissolution rate of drugs through an "agglomerate modifying" mechanism [19]. The increased de-agglomeration and dispersion was attributed to the open packing structure of mixed agglomerates that had formed. Unexpectedly, preliminary findings during our research demonstrated that the presence of micronized poorly water-soluble materials also increased the dissolution rate of drugs. It is hypothesized that these micronized inorganic salts could lead to the formation of mixed additive-drug agglomerates that more readily de-agglomerate than pure drug agglomerates alone. Therefore, the aim of this project was to systematically test the effect of micronized poorly water-soluble inorganic salts in enhancing the dissolution of a poorly water-soluble model drug, indomethacin.

2. Materials and methods

2.1. Materials

Micronized indomethacin, IMC (Sigma–Aldrich, USA), was employed as the model drug (D_{10} = 1.7 μm, D_{50} = 4.8 μm, D_{90} = 14.5 μm). Two lactose carriers were used including lactose-povidone granules (D_{10} = 12.8 μm, D_{50} = 95.6 μm, D_{90} = 233.3 μm) and lactose spray-dried for direct compression (D_{10} = 68.9 μm, D_{50} = 149.3 μm, D_{90} = 244.3 μm) (The Lactose Company of New Zealand, New Zealand). The cohesive poorly water-soluble excipients used as ternary components in the mixtures were inorganic salts, including: aluminium hydroxide (AH) (Merck, Germany) (D_{10} = 2.0 μm, D_{50} = 7.0 μm, D_{90} = 37.6 μm), barium sulphate (BS) (Riedel-deHaën, Germany) (D_{10} = 2.4 μm, D_{50} = 5.2 μm, D_{90} = 9.7 μm), dibasic calcium phosphate dihydrate (CP) (Mendell, USA) (D_{10} = 2.8 μm, D_{50} = 7.4 μm, D_{90} = 15.6 μm) and calcium sulphate dihydrate (CS) (Fluka, Switzerland) (D_{10} = 3.2 μm, D_{50} = 7.1 μm, D_{90} = 16.8 μm). These inorganic materials are commonly used pharmaceutical excipients in oral dosage formulations [20–25] and are generally regarded as being nontoxic following oral administration [26].

The media used for the dissolution studies included deionized water (Milli-Q water purification system, Millipore Corporation, USA), phosphate buffer pH 5.0 and acetate buffer pH 5.0 (British Pharmacopoeia, 2009). IMC has a pK_a of 4.5 [27,28], and its solubility will change significantly with change in pH. The pH condition of pH 5.0 was chosen to balance the ability to achieve a solubility which would provide sink conditions with analytical capability using ultraviolet (UV) analysis and discrimination for testing small differences in dissolution rate [29,30]. Note at pH 7.0, the rate of dissolution was very rapid due to the high solubility. The buffer solutions were prepared using deionized water, potassium dihydrogen phosphate (Merck, Germany), potassium hydroxide (Merck, Germany), sodium acetate trihydrate (Merck, Germany) and glacial acetic acid (Scharlab, Spain). Sodium lauryl sulphate (SLS) (Sigma, Australia) was added to the dissolution medium (0.1% w/v) to improve the wettability of IMC.

The following solvents were used as the dispersion media for the particle size measurements of the various materials: deionized water and 0.01% w/v SLS solution for IMC and all inorganic salts, and propan-2-ol (Merck, Australia) for lactose.

2.2. Particle size analysis of powders

Particle size distributions (PSD) of the raw materials were determined by laser diffraction using the Malvern Mastersizer S (Malvern Instruments Ltd., UK). A reverse Fourier lens with a 300 mm focal length and an active beam length of 2.4 mm was attached to a small volume dispersion cell (MSX1) containing a stirrer (set to half the maximum speed), in order to measure particle sizes ranging from 0.05 to 900 μm.

Specific presentations were created for each material analyzed and these included their refractive index (RI) values in order to account for the different optical characteristics of the particles and dispersing liquids listed in Section 2.1. Prior to performing particle size measurements, a slurry of each sample was first prepared and sonicated for 5 min. An adequate amount of each material was then added to 50 ml of the dispersion medium contained within the dispersion unit to achieve an obscuration range between 10% and 30%.

Analysis of micronized IMC and all inorganic excipients were determined in water and slurries of each sample were prepared using a few drops of 0.01% (w/v) SLS solution. The reference RIs for IMC, AH, BS, CP, CS and water were 1.74, 1.69, 1.64, 1.63, 1.60 and 1.33, respectively, with an estimated imaginary RI of 0.01 for all samples. Measurement of spray-dried lactose was performed using propan-2-ol as the dispersant with the reference RIs for lactose and propan-2-ol as 1.533 and 1.378, respectively, and an imaginary RI of 0.001. Drops of the dispersant were used to prepare a slurry of the lactose before addition to the dispersion unit.

Average PSDs were derived from five replicates for all samples and log-normal graphs of frequency by volume (%) versus particle size were then constructed. These were further characterized by the D_{10}, D_{50}, D_{90} cumulative particle undersize values and volume mean diameter (VMD).

2.3. Dispersion of mixtures by the Spraytec

To assess the extent of dispersion in air, *in situ*, real-time PSDs of the IMC mixtures were measured by laser diffraction using the Spraytec particle sizer (Malvern Instruments Ltd., UK), equipped with an inhalation cell attachment. Analysis was undertaken with a Rotahaler® inhaler device (GlaxoSmithKline, UK) at a flow rate of 60 l/min, calibrated with a TSI 4000 series flow meter (TSI Instru-

ments Ltd., UK). Measurements for each mixture were made on five replicates for a duration of 4 s, with triggering, noise and background levels of 50, 0 and 100 light energy units, respectively. Default RI values of 1.72 and 1.00 were used for the particulate and dispersant materials, respectively. The PSDs of the aerosolized mixtures were analyzed using RTsizer software V5.51 (Malvern Instruments Ltd., UK).

2.4. Preparation of powder formulations

2.4.1. Micronization

Micronization of IMC, BS, CP and CS was conducted by fluid energy milling in a 75 mm stainless steel jet mill (Model 75P Chrispro jet mill; Micro-Macinazione SA, Switzerland), fed via a DR40 vibratory feeding channel with S/S hopper tray under compressed filtered air of 620 kPa.

2.4.2. Preparation of lactose-povidone carrier

The lactose-povidone granules were prepared from lactose and povidone in a 9:1 ratio by wet granulation using a 10% w/w aqueous povidone solution. The wet granules were tray-dried in an oven at 50 °C for 24 h. Dry granules were lightly comminuted and then sieved to obtain particles in the 106–250 μm size range.

2.4.3. Preparation of interactive mixtures

This study was conducted in two separate phases of work where several differences in relation to the preparation of the interactive mixtures are detailed below.

In our preliminary work, the concentration of drug (IMC) was maintained at 20% w/w and lactose-povidone granules were used as the carrier material for all mixtures. Binary mixtures (control) were prepared by placing the drug (20% w/w) between two equal layers of the carrier material (80% w/w), made up to a total weight of 5 g in a glass vial. The mixture was initially inverted several times to prevent the micronized drug particles from adhering to the sides of the vial and then shaken vigorously for 5 min by hand. This method was selected from a number of methods and had been previously validated [8,10]. Ternary mixtures were prepared as described above, where the ternary additive (1% or 10% w/w) was placed together with the drug (20% w/w) between the carrier material (79% or 70% w/w).

In our second phase of work, all mixtures were comprised of 10% w/w IMC and spray-dried lactose was used as the carrier material. Binary (10% w/w drug and 90% w/w carrier) and ternary (10% w/w drug, 10% w/w ternary additive and 80% w/w carrier) interactive mixtures were arranged into 30 ml glass jars as described above and mixed in a Turbula® mixer (Model T2F; Willy A. Bachofen Maschinenfabrik, Switzerland) for 20 min at the instrument's maximum speed of 101 rpm. All mixtures were prepared in duplicate.

The rationale for using a different drug concentration, lactose carrier type and mixing method in the later stages of this study was based on recent studies conducted in our laboratories. Firstly, in considering the known effects of concentration dependent dissolution whereby higher drug concentrations in interactive mixtures result in decreased dissolution rates [31], the use of a lower concentration of drug (10% w/w) would provide better conditions for testing where substantial agglomeration is known to still occur [32]. Secondly, investigation into the effect of using different lactose carrier types on drug dissolution demonstrated faster dissolution of the drug from ternary mixtures containing spray-dried lactose, compared with those of lactose-povidone [30]. Thirdly, the use of a higher shear Turbula® mixer with long mixing times and faster speeds was found to produce greater extents of deagglomeration [32] and therefore provided the basis for the mixing conditions used in the later phases of the current study.

The binary formulations analyzed by the Spraytec were a 1:1 composition of IMC and AH (5 g total), where each material was arranged layer-by-layer in 30ml glass jars prior to mixing in the Turbula® under the same conditions as detailed earlier.

2.5. Dissolution studies

Dissolution of the different mixtures was conducted using an automated dissolution apparatus (Erweka DT6; Erweka, Germany) equipped with an online UV spectrophotometer containing six 10 mm UV-grade flow through cells (Cecil CE 3021; Cecil Instruments Ltd., UK) and multi-channel peristaltic pump (IPC 8 Ismatec® pump; Ismatec SA, Switzerland). The USP Dissolution Apparatus 2 paddle method (United States Pharmacopeia 32/National Formulary 27, 2009) was used at a rotational speed of 100 rpm. The dissolution medium (1000 ml) comprised either deionized water or the buffer solution (995 ml) and 0.1% w/v SLS solution (5 ml) to improve drug wettability. All dissolution media were filtered and freshly degassed through a 0.45 μm membrane (Millipore Corporation, USA) and equilibrated to 37.0 ± 0.5 °C in the dissolution bath. Samples of interactive mixtures ($n = 6$) were then added to the dissolution vessels in series, yielding a theoretical drug concentration of 3 μg/l in each vessel to give sink conditions. Upon automatic sampling, absorbance readings (six replicates) for IMC were recorded at the wavelength of maximum absorption at 2-min intervals over a period of 60 or 120 min.

The amount of IMC dissolved (%) at each time point was calculated from the mean drug content using a validated UV assay (Section 2.6), which was based on five replicates per mixture.

2.6. UV analysis of indomethacin

The IMC content from the dissolution studies was determined by a validated UV spectrophotometric assay using a single beam UV–visible spectrophotometer (Cecil CE 3021; Cecil Instruments Ltd., UK). The UV spectra of IMC in all dissolution media were obtained over a wavelength range of 200–500 nm at a sufficient concentration of 5.0 μg/ml. The wavelengths of maximum absorption (λ_{max}) were determined at 265.7, 265.4 and 263.7 nm in phosphate buffer pH 5.0, acetate buffer pH 5.0 and water, respectively. The Beer's law calibration plots for IMC in the different media at the corresponding wavelengths were constructed using three replicates over six concentrations (from 0.5 to 3.0 μg/ml), which was within the solubility range of the drug to achieve sink conditions. The regression coefficient (R^2) was $\geqslant 0.9999$ showing good linearity, and there was no significant deviation from the zero intercept ($P > 0.05$). The accuracy ranged from 97.3% to 101.0%, and the coefficient of variation (CV) for precision ranged from 1.0% to 3.6% for representative low, medium and high concentrations along the calibration plot.

2.7. Scanning Electron Microscopy (SEM)

The surface and particle morphologies of the raw materials and interactive mixtures were examined at several magnifications under a Phenom scanning electron microscope (FEI Company, The Netherlands), operated at 5 kV. Powder samples were mounted on aluminium stubs using carbon-coated adhesive tabs and then gold coated with a sputter coater (Emitech K550X sputter coater, UK and Edwards RV3 vacuum pump, UK) at 20 nm thickness prior to analysis.

2.8. Statistical modelling and analysis

Dissolution data were modelled using a nonlinear least squares regression analysis based on the Levenberg–Marquardt algorithm

[33,34] in order to estimate the coefficients or parameters of the independent variables that provide the best fit between the equation and the data (SigmaPlot® 11.0; Systat Software Inc., USA) [7]. The average undissolved concentrations (%) of IMC versus time data were modelled using multi-exponential single (2 parameter), double (4 parameter) and triple (6 parameter) decay equations. Discrimination between these models in order to assess the goodness of fit was performed on the basis of several statistical parameters, including the correlation coefficient (R^2) (a measure of the degree of correlation), dependency values (an indication of model complexity), Norm value (an index of the closeness of fit), F-statistic (assesses the improved fit with the use of additional parameters) and Akaike Information Criterion (AIC) (provides a measure of goodness of fit based on maximum likelihood by relating the weighted residual sum of squares (WRSS) to the number of parameters that were required to obtain the fit).

Comparison between groups of values obtained from the dissolution profiles, estimated modelling parameters and particle size distributions was performed using one-way analysis of variance (ANOVA) with a post-hoc Tukey's test (PASW Statistics 17.0; IBM Corporation, USA). Probability values (P) of less than 0.05 were considered as statistically significant.

3. Results and discussion

3.1. The effect of a poorly water-soluble inorganic salt, calcium phosphate, on the dissolution of indomethacin (20%) interactive mixtures

Dissolution profiles of the binary mixture (control) containing 20% micronized IMC and lactose-povidone granules, as well as ternary mixtures containing 20% micronized IMC, lactose-povidone granules and either 1% or 10% of micronized CP, were determined in water over 120 min (Fig. 1). The results demonstrated a marked improvement in the dissolution profile, concentration dependent with the addition of poorly water-soluble micronized CP. The extent of improvement in dissolution rate was counter-intuitive since the addition of poorly water-soluble excipients to the powder formulations might be expected to decrease dissolution rate, especially where a micronized particle of CP might adhere to the granule surface producing an insoluble/hydrophobic barrier to the dissolution medium.

This significant increase in dissolution rate with the addition of micronized CP was considered to result from two possible mechanisms. Firstly, the presence of a micronized ternary component has been demonstrated to increase the rate of dissolution of IMC [19], although this occurred when water-soluble lactose (not poorly water-soluble inorganic salts) was added to mixtures. The mechanism of improvement seen in Fig. 1 could be related to an increased extent of de-agglomeration of the cohesive IMC powder, associated with possible changes in the tensile strength of the agglomerates. Secondly, a pH change during the dissolution of these mixtures in the aqueous unbuffered medium might be expected due to dissolution of IMC and possibly some of the added micronized CP. To test this second proposition, the pH of the unbuffered dissolution media was monitored during the dissolution of these mixtures.

The pH changes over 120 min in water for the binary lactose-povidone mixture containing 20% IMC and ternary mixtures containing 20% IMC with either 1% or 10% of micronized CP are shown in Fig. 2. The dissolution media of all mixtures showed a gradual decrease in pH with time. For both the binary and 10% ternary mixtures, the pH decreased from an initial value of 5.6 ± 0.3 before addition of the mixture to 5.2 ± 0.3 after 10 min. The pH of the dissolution media containing the binary and 1% ternary mixtures decreased to about 4.5 after 2 h of the dissolution, while the pH of the dissolution medium containing the 10% ternary mixture increased gradually to a final value of 5.4 ± 0.1 after 2 h. This higher pH in the dissolution medium containing 10% CP might be attributed to its partial dissolution with time and stirring at 37 °C.

There was no significant difference in the pH of the media for the binary and the two ternary mixtures (1% and 10%) during the first 10 min. The saturation solubility of IMC can be calculated as follows [35]:

$$pH_b = pK_a + \log\frac{S - S_o}{S_o} \quad (2)$$

where pH_b is the pH below which the drug separates from solution as the undissociated acid, pK_a is the negative logarithm of the acid–base equilibrium constant, S is the solubility at any time and S_o is the concentration of the unionized form of the drug in solution. Using a pK_a value of 4.5 and assuming that the solubility of IMC in buffer of pH 1.0 represents S_o, the solubility of IMC can be shown to change from 41.4 mg/l to 1.7 mg/l by changing the pH from 6.0 to 4.0. As the rate of dissolution is directly linked to the saturation solubility, the dissolution rate constant is therefore likely to decrease as the dissolution proceeded; however, since the pH of the dissolution media was not significantly different for all mixtures in the first 10 min, the unexpected large increase in dissolution rate for the IMC mixture containing CP (10%) was not pH related. The slower dissolution behaviour for the binary mixture and to some extent the 1% ternary mixture where the pH decreased to about 4.5 was attributed (at least to some extent) to the pH decrease with time.

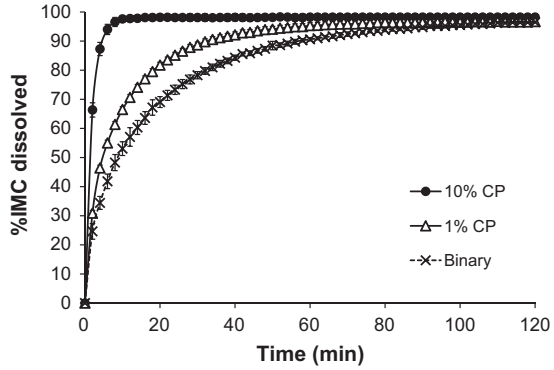

Fig. 1. Dissolution profiles of the binary mixture containing indomethacin (IMC; 20%) and lactose-povidone carrier, and ternary mixtures with added 1% or 10% of micronized calcium phosphate (CP), determined in water using the USP paddle method at 100 rpm and 37 °C (n = 6 for each mixture).

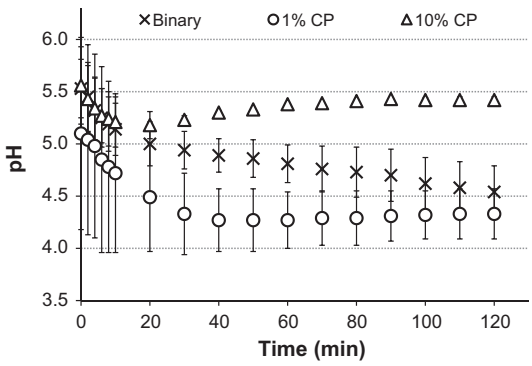

Fig. 2. pH changes in water during the dissolution of indomethacin from binary and ternary (1% and 10% micronized calcium phosphate, CP) mixtures, measured at 37 °C.

3.2. Understanding the dissolution through nonlinear least squares modelling

As in previous studies, a multi-exponential equation can be used to fit dissolution data for micronized drugs with dissolution considered to be occurring essentially from dispersed particles and agglomerates [7,8]. A bi-exponential equation has been most often used and represents dissolution from a dispersed particle and agglomerate bi-modal distribution of the IMC in the dissolution medium:

$$C = C_d \exp(-k_d t) + C_a \exp(-k_a t) \quad (3)$$

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, with their corresponding dissolution rate constants (min^{-1}) k_d and k_a. Sometimes, more than one agglomerate distribution occurs and a tri-exponential equation involves two agglomerate size populations designated $a1$ and $a2$ which can be expressed as follows:

$$C = C_d \exp(-k_d t) + C_{a1} \exp(-k_{a1} t) + C_{a2} \exp(-k_{a2} t) \quad (4)$$

Dissolution data of the IMC binary and ternary (1% and 10% CP) mixtures conducted in water were modelled using the multi-exponential equations. The statistical decisions around the selection of the best model have been discussed previously [7,19] and will not be repeated in this paper. For this dissolution, the tri-exponential model provided the best fit since it produced higher F and R^2 values and lower Norm and AIC for the three mixtures (except for the 1% ternary mixture where the AIC value was the most critical value for the selection of the tri-exponential model).

Since the pH of the unbuffered medium was changing with time, it was necessary to test the effect of dissolution time on the dissolution data modelling for these mixtures. The binary and the 1% micronized CP ternary mixtures were selected for this experiment because of their slow dissolution rate. Dissolution data at different time intervals (30, 60, 90 and 120 min) were modelled using the exponential equations and were best fitted with the tri-exponential model. The estimated initial concentration of dispersed particles (C_d) and their dissolution rate constants (k_d) modelled at different dissolution times are shown in Fig. 3. Comparison between C_d or k_d for either the binary mixture or the 1% CP mixture demonstrated no significant difference with time ($P > 0.91$). This result supported the view that the pH decrease with time for mixtures with slow dissolution rate had no effect on either the type of the model fit or the estimated parameters from this equation at different times.

As the incorporation of 10% CP to the mixtures produced a more dramatic increase in IMC dissolution compared to that of 1% CP, the modelling parameters of the tri-exponential equation that provided the best fit were then estimated for the 10% CP ternary mixture (Table 1). A number of outcomes result from the modelling. Firstly, the initial concentration of dispersed particles, C_d, estimated for the dissolution of IMC from the ternary mixture was significantly greater than that of the binary mixture in water ($P < 0.05$). This outcome clearly supported the fact that the presence of CP facilitated de-agglomeration of the cohesive IMC. Secondly, the dissolution rate constant for the dispersed particle distribution, k_d, was around 0.5 min^{-1} for the binary mixture and increased slightly with added CP (10%). The data in the early times of the dissolution profile largely contributed to the estimation of the dissolution rate constant of the dispersed particles; during these early dissolution times, the pH of the water changed from about 5.6 to 5.2. The dissolution rate constants for the dispersed particles, therefore, were average dissolution rate constants for dissolution in this pH range. However, as the dissolution proceeded and the pH of the medium changed to some extent, the dissolution rate constants for the agglomerates represented some average value over a pH range and were lower than might be expected if the dissolution media were buffered. More importantly, a significant increase in k_{a1} ($P < 0.001$) between the binary and ternary mixtures inferred a transformation of the primary distribution of agglomerates ($a1$) into more dispersible particles upon the addition of 10% CP; the k_{a1} of the ternary mixture was in turn also similar to that of its k_d ($P = 0.044$). Thus, the total dispersed particle concentration resulting from the 10% CP ternary mixture was around 98%, with the remaining 2% of particles existing as agglomerates (C_{a2}) due to the infinitesimally small k_{a2} value. This was in comparison with the binary mixture with only 28% of initially dispersed particles.

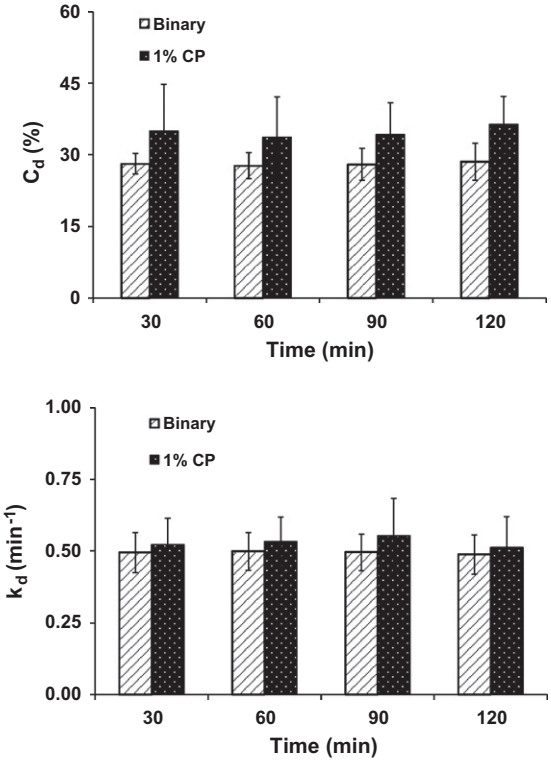

Fig. 3. Effect of dissolution time on the estimated dispersed particle concentrations (C_d in %) and corresponding dissolution rate constants (k_d in min^{-1}) for indomethacin (20%) binary and 1% micronized calcium phosphate (CP) ternary mixtures with lactose-povidone carrier in water.

Table 1
Estimated tri-exponential modeling parameters of initial concentrations of dispersed particles (C_d) and agglomerates (C_{a1} and C_{a2}), and the corresponding dissolution rate constants (k_d, k_{a1} and k_{a2}) for dissolution of indomethacin (20%) binary and 10% micronized calcium phosphate (CP) ternary mixtures with lactose-povidone carrier in water.

	Binary	10% CP
C_d (%)	28.6 ± 3.8	53.1 ± 6.1
k_d (min^{-1})	0.488 ± 0.067	0.603 ± 0.123
C_{a1} (%)	57.2 ± 3.3	44.7 ± 7.3
k_{a1} (min^{-1})	0.060 ± 0.008	0.577 ± 0.122
C_{a2} (%)	19.6 ± 8.0	2.2 ± 1.2
k_{a2} (min^{-1})	0.015 ± 0.005	0.001 ± 4.2E-04

3.3. Effect of poorly water-soluble inorganic additives on indomethacin dissolution in buffered media

A further series of studies were conducted to examine a range of poorly water-soluble inorganic additives. In order to eliminate any influence of pH change due to the presence of the inorganic salts on

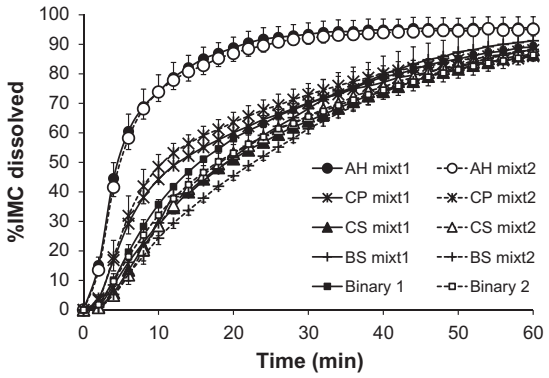

Fig. 4. Dissolution profiles of binary mixtures containing indomethacin (IMC; 10%) and spray-dried lactose carrier, and ternary mixtures with added inorganic excipients (10% each of aluminium hydroxide, AH; barium sulphate, BS; calcium phosphate, CP; calcium sulphate, CS), determined in phosphate buffer pH 5.0 using the USP paddle method at 100 rpm and 37 °C ($n = 6$ for two replicate mixtures).

the dissolution rate of IMC, the dissolution profiles of IMC (10%) from ternary interactive mixtures containing several types of cohesive fine poorly water-soluble inorganic materials (aluminium hydroxide, AH; barium sulphate, BS; calcium phosphate, CP; calcium sulphate, CS) (10% each) and spray-dried lactose carrier were obtained in phosphate buffer at pH 5.0 over 60 min (Fig. 4). All powder mixtures were prepared and tested in duplicate in order to demonstrate the reproducibility of each system.

The results demonstrated a marked improvement in IMC dissolution with the addition of several of the poorly water-soluble inorganic excipients to the mixtures. This was particularly evident with AH, in comparison with the binary mixture comprised of IMC and spray-dried lactose alone, i.e. the amount of IMC dissolved after 20 min was 88.8 ± 3.6% for the ternary mixture with added AH, compared with 53.1 ± 2.8% for the binary mixture ($P = 0.001$). The addition of CP as a ternary component to the mixtures also produced some improvement (63.6 ± 3.7%), although to a lesser extent than AH. Dissolution performance for the ternary mixtures containing BS, CP and CS was observed to be less effective than that with added AH ($P \leqslant 0.002$).

3.4. pH effects of inorganic additives in the diffusion layer

The basis of using a buffered medium to conduct the dissolution experiments described in Section 3.3 was such that it would provide sufficient capacity to maintain the bulk solution at pH 5.0 over the duration of the dissolution study. However, in order to assign the dissolution changes to the intrinsic influence of the inorganic salts on the powder structure, other effects such as pH changes in the microenvironment of the diffusion layer needed to be discounted. For weakly acidic drugs such as IMC ($pK_a \sim 4.5$), the pH of the diffusion layer solution will be critical in determining its dissolution rate. Close to the surface of the dissolving particle/agglomerate, the concentration of IMC will be saturated. Because the IMC and inorganic salt particles are closely associated, the concentration of the inorganic salt is also likely to be saturated. The buffer in the diffusion layer will therefore require sufficient buffering capacity to maintain its pH in the presence of the saturation concentration of the inorganic salt, as any pH changes in the diffusion layer close to the dissolving particle will change the saturation concentration of IMC and thus its dissolution rate constant.

Although the use of a buffered medium maintained a constant pH in the bulk solution throughout the dissolution study, there is some possibility that the alkaline inorganic salts might cause transient pH changes in the diffusion layer. To determine whether this had occurred, the pH of the dissolution media containing the inorganic salts at concentrations exceeding their solubility was studied.

The pH of a saturated solution for each inorganic compound in phosphate buffer at pH 5.0 was monitored over a 180 min period and is shown in Fig. 5A. For AH, the results indicated a distinct increase in the initial pH of 4.96 to 5.14 upon addition of the excipient to the buffered medium to form a saturated solution; the pH subsequently continued to increase slightly before stabilizing to a final value of 5.26. A similar trend was observed for a saturated solution of CP, whereby the pH ascended more dramatically from 5.00 to 5.26 and reached a plateau within 30 min to a pH of 5.35. Contrastingly, CS produced a reduction in the pH, levelling off to a final value of 4.62. BS was the only excipient which did not alter the solution pH at its saturated concentration, remaining close to the original buffer pH of 5.0 throughout the entire period. These changes in pH demonstrated that firstly, small amounts of the inorganic salts were dissolving in the diffusion layer and secondly, the phosphate buffer did not provide sufficient buffering capacity.

To further assess whether there was a relationship between changes in the diffusion layer pH for each of the inorganic compounds and the dissolution of IMC, the data from Fig. 5A were extrapolated at the 20 min time point and regressed against the corresponding amount of dissolved IMC. There was no indication of any direct correlation between the two parameters; hence, the improvements in dissolution performance seen in the presence of some of the inorganic additives were not expected to be entirely due to a pH effect. To confirm this finding, changes in the saturated solution pH for all inorganic compounds were once again monitored in a buffer that would provide much stronger capacity to resist any changes in the diffusion layer pH. The use of an acetate buffer at pH 5.0 demonstrated more stringent control of the pH with all values remaining close to the original buffer pH (Fig. 5B).

Dissolution tests for the binary and ternary mixtures containing AH were then repeated in duplicate in acetate buffer pH 5.0 (Fig. 6).

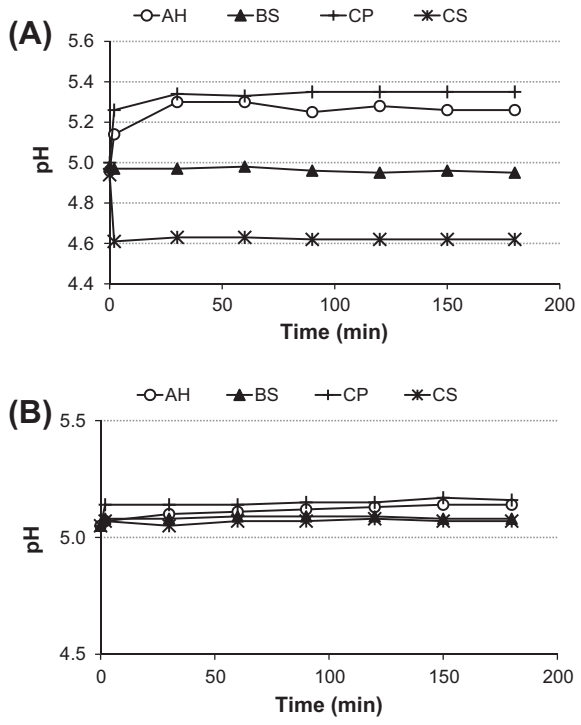

Fig. 5. pH changes over time in saturated solutions of each inorganic excipient, aluminium hydroxide (AH), barium sulphate (BS), calcium phosphate (CP) and calcium sulphate (CS) in: (A) phosphate buffer pH 5.0 and (B) acetate buffer pH 5.0.

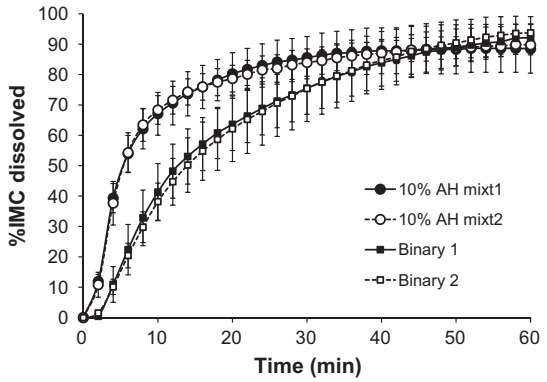

Fig. 6. Dissolution profiles of binary mixtures containing indomethacin (IMC; 10%) and spray-dried lactose carrier, and ternary mixtures with added 10% aluminium hydroxide (AH), determined in acetate buffer pH 5.0 using the USP paddle method at 100 rpm and 37.0 °C (n = 6 for two replicate mixtures).

Similar increases in the dissolution of IMC were evident as were previously observed with the use of phosphate buffer; for example the amount of dissolved IMC after 20 min was 80.3 ± 6.9% for the ternary 10% AH mixture, compared with 63.6 ± 8.6% for the binary mixture ($P < 0.001$). At 60 min, the amounts of dissolved IMC between all mixtures were not significantly different ($P > 0.05$). Thus, the effect of pH could be eliminated as a major contributor towards the enhanced dissolution performance.

3.5. Modelling of dissolution data for indomethacin-inorganic additive mixtures in buffered media

Dissolution data for the IMC ternary (10% AH, BS, CP and CS) mixtures conducted in phosphate buffer pH 5.0 (Fig. 4) were modelled using multi-exponential equations, whereby the bi-exponential model was found to give the best fit with higher F and slightly lower AIC values for all mixtures. The reason(s) for this difference in data fit compared with the tri-exponential model obtained in the preliminary study are unknown, but may be due to the use of different dissolution media or the possibility of a pH effect causing variations in the resulting agglomerate distribution. The estimated parameters for the initial concentrations of dispersed (C_d) and agglomerated particles (C_a), as well as their corresponding dissolution rate constants (k_d and k_a), are summarized in Table 2. Comparison of C_d values across all ternary mixtures demonstrated that only the addition of 10% AH produced a significant increase from the binary mixture ($P < 0.05$) and was also significantly greater than those mixtures containing 10% BS and CP ($P \leqslant 0.03$). In contrast, the k_d values of the ternary mixtures were either significantly lower for those containing BS and CS, or higher for those containing AH and CP from that of the binary mixture ($P \leqslant 0.001$). The differences in k_d between all ternary mixtures were statistically different ($P < 0.001$), except between those containing BS and CS ($P = 0.16$).

Table 2
Estimated bi-exponential modeling parameters of initial concentrations of dispersed particles (C_d) and agglomerates (C_a), and the corresponding dissolution rate constants (k_d and k_a) for dissolution of indomethacin (10%) binary and 10% ternary (aluminium hydroxide, AH; barium sulphate, BS; calcium phosphate, CP; calcium sulphate, CS) mixtures with spray-dried lactose carrier in phosphate buffer pH 5.0.

	C_d (%)	k_d (min^{-1})	C_a (%)	k_a (min^{-1})
Binary	48.5 ± 8.2	0.071 ± 0.000	55.7 ± 7.8	0.026 ± 0.001
10% AH	93.1 ± 1.4	0.166 ± 0.000	10.7 ± 1.9	0.015 ± 0.001
10% BS	53.4 ± 0.2	0.037 ± 0.004	52.4 ± 0.5	0.037 ± 0.004
10% CP	50.0 ± 4.8	0.133 ± 0.003	54.6 ± 4.1	0.024 ± 0.000
10% CS	85.2 ± 16.7	0.045 ± 0.003	20.2 ± 15.9	0.015 ± 0.008

Therefore, these outcomes provided evidence to suggest that the incorporation of both AH and CP in particular had promoted the formation of more dispersible particles of IMC due to the dissolution rate constants which were 1.9–2.3-fold higher than that of the binary mixture.

3.6. Mechanisms of enhanced indomethacin dispersion and dissolution

Micrographic (SEM) images of the various mixtures were obtained to visualize and understand the particle interactions occurring within each mixture containing the different inorganic excipients (Fig. 7). The binary mixture (containing 10% IMC and spray-dried lactose) showed the carriers heavily saturated with multi-layers of drug particles adhered to their surfaces and complete dispersion is not achieved due to the high drug load (Figs. 7A and B). With the addition of 10% CP, cohesive agglomerates of IMC were partially stripped away from the surfaces of the carrier (Figs. 7C and D). Detachment of a significant amount of drug particles from the carrier surfaces occurred in the presence of AH; this also led to the formation of loose mixed agglomerates of IMC and AH off the carrier surface which more readily de-agglomerated than the pure drug agglomerates due to the presence of AH within the matrix of IMC (Figs. 7E and F).

To develop a more profound understanding of the underlying mechanism(s) reflecting the observed changes in dissolution performance for the 10% AH ternary mixture that demonstrated the most significant improvement, laser diffraction particle sizing of an aerosolized plume of IMC and AH was performed using an *in situ* particle size analyzer (Spraytec). As seen in Fig. 8, the PSDs of pure IMC and AH alone were both bimodal in shape, with the two distributions representing some larger agglomerates in addition to finer particles at the lower end of the spectrum. In contrast, the PSD of a binary formulation composed of a 1:1 blend of IMC and AH (corresponding to the 10% AH ternary mixture) showed that the presence of AH had shifted the IMC distribution to lower values and the size of the fine particle distribution had dramatically increased; for example, analysis of the PSD characteristics revealed a significantly increased proportion of fine particles <5 μm from 6.5 ± 0.3% and 3.6 ± 0.1% for IMC and AH, respectively, to 17.0 ± 0.5% for the IMC-AH binary formulation ($P < 0.001$). The larger size of the fine particle distribution associated with the binary formulation suggested that when AH is mixed with IMC which is off the surface of the carrier, the presence of AH enhanced particle dispersion by detaching some of the finely agglomerated IMC particles. The SEM images and particle sizing data are consistent with the enhanced dissolution performance of IMC observed in the profiles (Fig. 4).

Addition of ternary components to powder formulations has previously been shown to improve the dispersion and de-agglomeration of drugs during aerosolization. In particular, those studies which have focused on the use of fine lactose have proposed that the enhanced performance was related to the structure of the resultant agglomerates. A range of underlying mechanistic effects were postulated, including the presence of mixed drug and fine particle multi-layers that allowed greater drug detachment from the carrier surface due to the adherence of fine lactose onto the carrier particles [15,16,36]; the ability of fine lactose to produce a drug agglomerate structure with much greater porosity and propensity to disperse [19]; and the formation of an open-packed, agglomerate structure that more readily dispersed due to the lower packing fraction and hence decreased tensile strength [17].

In the current study, the structural arrangement of the agglomerates that formed was also found to be important in determining the extent of powder dispersibility. As seen from the SEM images, the lower degree of surface area coverage on the carrier unit revealed that particles of CP and AH had interacted with IMC and

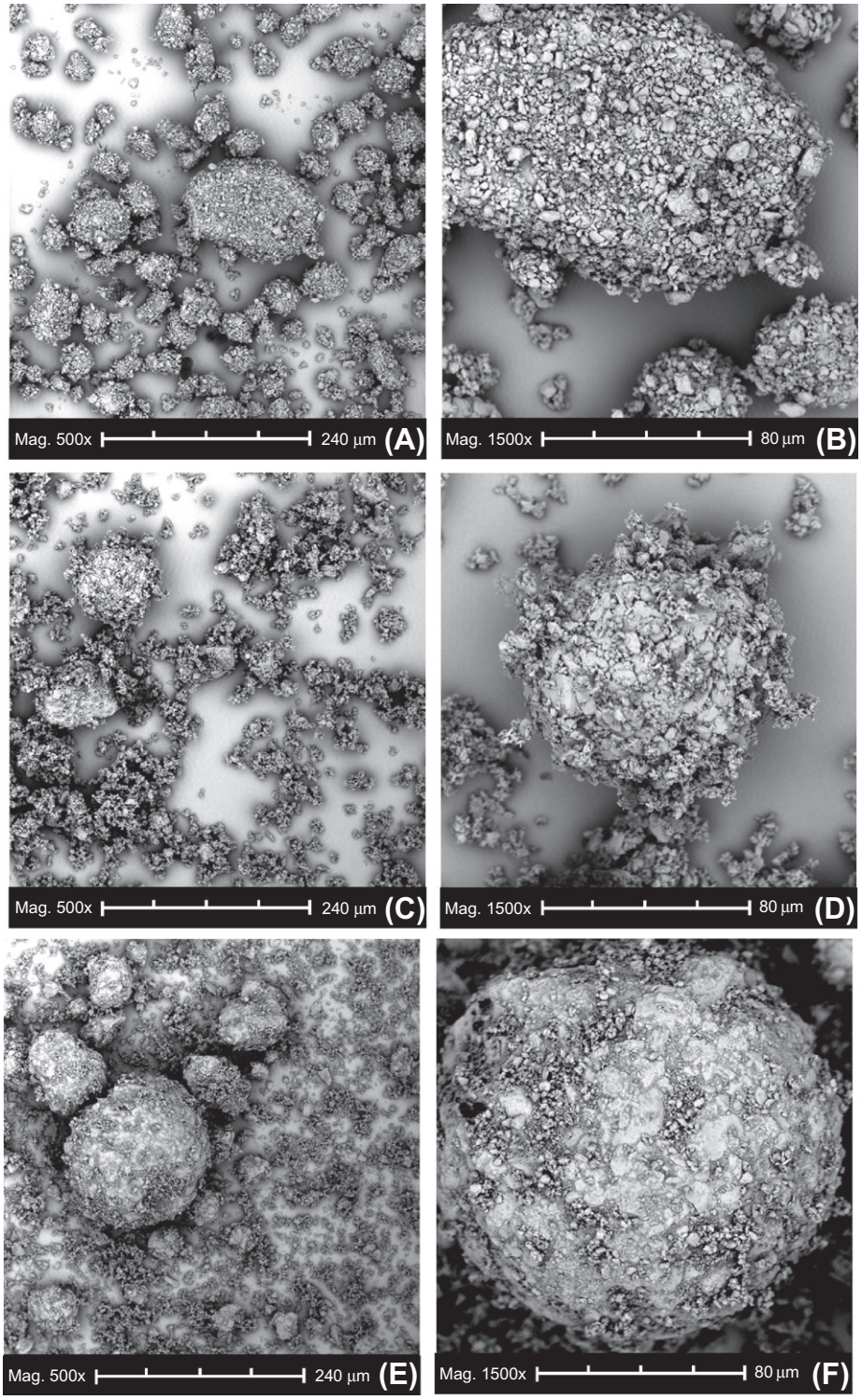

Fig. 7. Scanning electron micrographs of the indomethacin binary mixture (A, B), and ternary mixtures with added 10% each of calcium phosphate (C, D) and aluminium hydroxide (E, F).

formed a complex IMC-inorganic additive mixture off the carrier surface. The resultant mixed agglomerates were then able to disperse more readily than the cohesive agglomerates of IMC alone; this was corroborated by the particle sizing data which demonstrated increased dispersion of the binary IMC-AH formulation and thus the ability of AH to facilitate de-agglomeration. Henceforth, it was postulated that this mechanistic phenomenon would lead to the observed enhancements in dissolution performance with the incorporation of such inorganic materials. A discussion of these underlying mechanisms of dissolution has been detailed in our subsequent publication [37]. Further investigation into assessing the differing packing fractions and adhesional properties of the resultant mixed IMC-inorganic agglomerates would be necessary to substantiate the above findings.

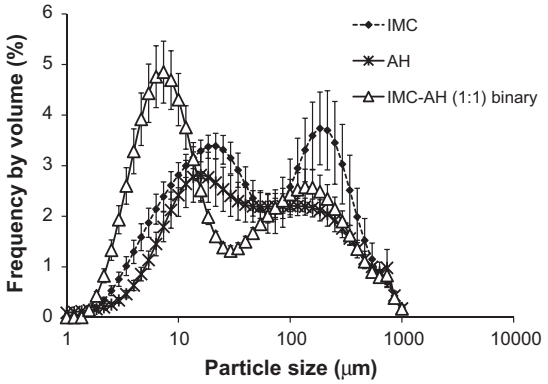

Fig. 8. Particle size distributions of pure micronized indomethacin (IMC) and aluminium hydroxide (AH) and a binary formulation of IMC-AH (1:1), measured by the Spraytec at an airflow rate of 60 l/min (n = 5).

4. Conclusion

The addition of two types of cohesive poorly water-soluble inorganic salts, aluminium hydroxide and calcium phosphate to mixtures of a poorly water-soluble micronized drug, indomethacin, has been found to counter-intuitively and significantly increase its rate of dissolution. The underlying mechanism of improved dissolution was primarily related to the ability of these poorly water-soluble inorganic materials to facilitate de-agglomeration of the highly cohesive micronized drug powders through modifying the mixture structure.

This novel and innovative strategy for dissolution improvement could be applied to the majority of current and newly formulated drugs on the market that are notoriously poorly water-soluble. Moreover, the proposed method is simple, practical, nontoxic, cost effective and scaleable for the pharmaceutical industry.

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