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Comminution of ibuprofen to produce nano-particles for rapid dissolution

S. Plakkot[a,*], M. de Matas[b], P. York[b], M. Saunders[c], B. Sulaiman[d]

[a] Lena Nanoceutics Ltd., Institute of Pharmaceutical Innovation, Bradford BD7 1DP, UK
[b] Institute of Pharmaceutical Innovation, University of Bradford, BD7 1DP, UK
[c] Kuecept Drug Delivery Technologies, Ystrad Mynach, Hengoed CF82 7FN, UK
[d] Dena Technology Ltd., Barnsley S71 1HN, UK

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ABSTRACT

A critical problem associated with poorly soluble drugs is low and variable bioavailability derived from slow dissolution and erratic absorption. The preparation of nano-formulations has been identified as an approach to enhance the rate and extent of drug absorption for compounds demonstrating limited aqueous solubility. A new technology for the production of nano-particles using high speed, high efficiency processes that can rapidly generate nano-particles with rapid dissolution rate has been developed. Size reduction of a low melting ductile model compound was achieved in periods less than 1 h. Particle size reduction of ibuprofen using this methodology resulted in production of crystalline particles with average diameter of approximately 270 nm. Physical stability studies showed that the nano-suspension remained homogeneous with slight increases in mean particle size, when stored at room temperature and under refrigerated storage conditions 2–8 °C for up to 2 days. Powder containing crystalline drug was prepared by spray-drying ibuprofen nano-suspensions with mannitol dissolved in the aqueous phase. Dissolution studies showed similar release rates for the nano-suspension and powder which were markedly improved compared to a commercially available drug product. Ibuprofen nano-particles could be produced rapidly with smaller sizes achieved at higher suspension concentrations. Particles produced in water with stabilisers demonstrated greatest physical stability, whilst rapid dissolution was observed for the nano-particles isolated in powder form.

1. Introduction

Recent trends in the research have shown that a disproportionate number of compounds identified through combinatorial screening programs have a tendency to suffer from low aqueous solubility with consequent impact on bioavailability by the oral route. These molecules are difficult to formulate using conventional approaches and are associated with innumerable formulation-related performance issues (Merisko-Liversidge and Liversidge, 2008).

Amongst the range of approaches used to address this issue, the use of nano-particles with vast surface area to volume ratio has been highlighted as a strategic platform. A nano-suspension is a sub micron colloidal dispersion of pharmaceutical active ingredients stabilized by surfactants (stabilizers) in a liquid phase (Chingunpituk, 2007). Nano-particles are defined as a discrete internal phase consisting of an active pharmaceutical ingredient having physical dimensions, less than 1 μm in an external phase (Merisko-Liversidge and Liversidge, 2008).

Techniques used for drug nano-particle preparation can be classified into two principle classes. Processes which reduce the size of larger drug particles to sub-micron levels through communition are considered to be "Top–down" methods. "Bottom–up" processes on the other hand involve the controlled precipitation of nano-particulates through non-solvent addition (Ali et al., 2009; Verma et al., 2009).

This study presents a new technology for producing sub-micron crystallites of drugs with challenging mechanical properties (Sulaiman, 2007). The size reduction system comprises a radially symmetrical sleeve having an axial passage way with an upstream inlet and a downstream outlet. A radially symmetrical rotor sits within the sleeve and rotates at high speed. Grinding media are located within the gap between the rotor and sleeve, which confer high energy impact and shear forces leading to rapid size reduction of particles in suspension. Methods for producing crystalline nano-suspensions and dispersions in powder form using this technology are described here with evidence of improved dissolution rates for a model compound. A process flow diagram for this technology and Lena DM 100 nano-particle production machine (Sulaiman, 2007) is shown in Fig. 1.

* Corresponding author. Tel.: +44 1274 236140; fax: +44 1274 234679.
E-mail addresses: splakkot@brad.ac.uk, smitha@lenanano.com, smithapnair@hotmail.com (S. Plakkot).

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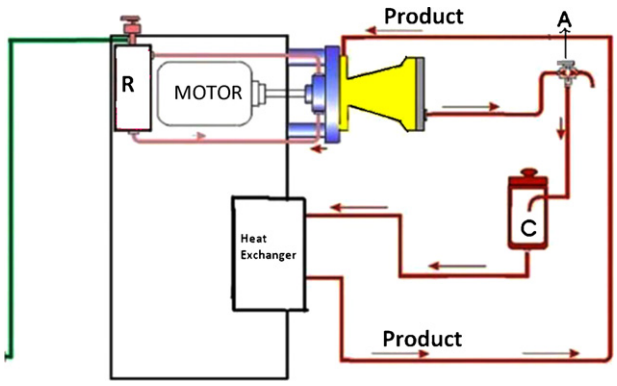

Fig. 1. Flow diagram depicting DM100 nano-particle production machine, where A = 3 way re-cycle/sample valve, C = Process vessel, R = Mechanical seal reservoir.

The mechanical properties of some pharmacological actives can often be inadequate for efficient size reduction. Ductile materials in particular have a tendency to deform rather than fragment, especially at sizes below the brittle-ductile transition (Larsson and Kristensen, 2000), whilst hard abrasive materials can also be problematic (Müller et al., 2001). The high surface energy and wide size distribution of resultant particulates can also lead to agglomeration and crystal growth. Samsonov et al. (2003) suggested that the stability of nano-particles may be treated as interplay between contributions from both volume and surface to the total free energy of the system. As particles are reduced in size from micron to nano scale, surface energy contributes increasingly to the total Gibb's free energy (Delogu, 2005). In an attempt to minimise this surface energy and form a stable colloidal system, particles will agglomerate, with consequent increase in particle size and reduction in surface area. Understanding and manipulating the forces governing nanoscale colloidal phenomena is therefore the key to controlling phase behaviour and the stability of nano-particulate systems (Morla and Meredith, 2005). The ability to produce a stable nano-suspension will therefore be determined using both means of process and composition of the formulation.

The purpose of this study was to evaluate the effectiveness of a new comminution technology for reducing the particle size of a highly ductile active pharmaceutical ingredient (API) to sub-micron levels whilst acquiring an understanding of the factors influencing particle size stability. The intention of these studies was to reduce the size of a problematic ductile compound to sub-micron levels in order to improve the dissolution rate of the selected API.

2. Materials and methods

2.1. Materials

Ibuprofen USP, 2-[4-(2-methylpropyl) phenyl] propanoic acid was purchased from Albermarle Europe sprl, (Belgium). Hydroxypropyl methylcellulose (HPMC) was a gift from Shinetsu (Japan). Sodium lauryl sulphate (SLS) was purchased from Sigma–Aldrich, USA. Kollidon 30 (PVP K-30) was purchased from BASF (Aktiengesellschaft Ludwigshafen, Germany). Ibuprofen oral pediatric suspension 'BP' was purchased from Lloyd's pharmacy, UK. All other materials used were of analytical grade and purchased from established suppliers.

2.2. Preparation of nano-suspensions

Suspensions of ibuprofen were produced at solids loads of 2% (w/w) and 15% (w/w) in a medium comprising hydroxypropyl methylcellulose 6cPs (0.5%, w/w), polyvinylpyrrolidone K-30 (0.5%, w/w) and sodium lauryl sulphate (0.1%, w/w). A list of stabilizers and composition used in processing ibuprofen suspensions is given in Table 1. Suspensions of coarse ibuprofen were recycled through the size reduction chamber using a range of processing conditions described in Section 2.4. Ibuprofen was selected as the model compound owing to its challenging mechanical properties (Larsson and Kristensen, 2000). Additionally, ibuprofen is a compound with low intrinsic solubility and is considered a class II compound according to The Biopharmaceutics Classification System, for which the entire adult dose of 200 mg cannot be dissolved under acidic conditions pH 1.2–4.5 (Healy and Corrigana, 1992). At these pHs, any catastrophic aggregation of the formulation would reduce the potential for increased rates of absorption. Suspensions in acidic conditions were therefore produced in order to establish the potential for a stable colloidal system at pH values typical of the stomach. Ibuprofen is also a ductile material with low melting point for which comminution to ultrafine levels has previously been shown to be difficult (Larsson and Kristensen, 2000).

Table 1
List of stabilizers and its composition used for processing ibuprofen suspensions.

Suspensions prepared and processed	Compositions of the stabilizers used	Conditions in which the suspensions were processed
2% (w/w) ibuprofen	0.5% (w/v) PVP, 0.5% (w/v) HPMC and 0.1% (w/v) SLS	In water at neutral pH
2% (w/w) ibuprofen	0.5% (w/v) PVP, 0.5% (w/v) HPMC and 0.1% (w/v) SLS	pH 2.0
15% (w/w) ibuprofen	0.5% (w/v) PVP, 0.5% (w/v) HPMC and 0.1% (w/v) SLS	In water at neutral pH
15% (w/w) ibuprofen	0.5% (w/v) PVP, 0.5% (w/v) HPMC and 0.1% (w/v) SLS	pH 2.0

2.3. Effect of suspension medium

The 2% (w/w) and 15% (w/w) ibuprofen suspensions were processed in water and at pH 2.0. The standard solution contained purified water where the 0.5% (w/v) PVP, 0.5% (w/v) HPMC and 0.1% (w/v) SLS were firstly dissolved with subsequent dispersion and addition of ibuprofen. The acidic solution was adjusted to pH 2 using hydrochloric acid. The stabilizers were then dissolved in this solution and the ibuprofen was dispersed thereafter.

2.4. Effect of process time

Ibuprofen suspensions were dispensed into the processing system (Fig. 1), in which 150 mL of 0.2 mm yttrium stabilised zirconium beads (Glen mills, USA) had already been charged. The comminution system was then activated and the input materials recycled for 60 min.

5 mL aliquots of the resultant suspensions were collected at 5, 10, 15, 30, 45 and 60 min and the particle size was measured using photon correlation spectroscopy (PCS). At the conclusion of processing, the active content of the samples was determined by reverse phase HPLC. The particle size was evaluated further using transmission electron microscopy (TEM). Samples were then characterised using differential scanning calorimeter (DSC) and X-ray powder diffraction (XRD), after separation of solids by centrifugation.

2.5. Characterisation of nano-particles

2.5.1. Photon correlation spectroscopy (PCS)

The particle size distribution of the ibuprofen nano-suspension was determined by PCS using the Zetasizer Nano series, Model ZEN3600 (Malvern instruments, UK). Samples were diluted with water (1:4) for the 15% (w/w) suspension for which 1 mL of the sample was diluted with water. The 2% (w/w) suspension was used as prepared. Water was selected as the dispersant and temperature was 25 °C. Disposable sizing cuvettes were used and all measurements were made in triplicate with mean values and standard deviations being reported.

2.5.2. Zeta potential

The zeta potential for the suspensions was determined using Zetasizer Nano series, Model ZEN3600 (Malvern instruments, UK). The suspensions were diluted 1:10 for 2% (w/w) suspension with the dispersion medium and for 15% (w/w) 0.2 mL was diluted 10 times with the dispersion medium. Water was selected as the dispersant and temperature was set to 25 °C. Clear disposable zeta cells were used. Measurement duration was selected as automatic with minimum 10 runs and maximum 100 runs. All measurements were made in triplicate with mean values and standard deviations being reported. Automatic attenuation selection and automatic voltage selection was used, where the voltage is based on the measured conductivity of the sample.

2.5.3. Transmission electron microscope (TEM)

The TEM used was an FEI Tecnai 12, (FEI Company, Netherlands) which was operated at 120 kV. The software version on the SIS Megaview III camera was Analysis 3.2. 1 μL of the 15% (w/w) and 2% (w/w) ibuprofen suspensions were diluted to 1 mL with water. Approximately 7 μL of these samples were then placed on the surface of a copper grid (200 mesh) coated with formvar/carbon, using a micropipette. The grid was then allowed to dry thoroughly before viewing.

2.5.4. Scanning electron microscopy (SEM)

Surface morphology of ibuprofen and spray dried nano ibuprofen powder were examined using a scanning electron microscope (FEI Quanta 400, Netherlands). Ibuprofen particles were fixed on an aluminium stub with a conductive double sided carbon tape. An accelerating voltage of 20 kV was used and the images were taken at a range of magnifications.

2.5.5. Differential scanning calorimetry (DSC)

The sample suspensions were centrifuged at 14,800 rpm for 30 min and the dried sample residue was taken for analysis. DSC analysis was conducted using the DSC module of the TA instruments Q2000 series thermal analysis system (TA Instruments Ltd, Crawley, UK). Samples of approximately 5 mg were analysed in triplicate using a heating rate of 10 °C/min between 25 °C and 125 °C.

2.5.6. X-ray powder diffraction (XRPD)

X-ray powder diffraction was performed using dried residue obtained by centrifugation of the suspensions and then dried in air oven. The XRPD data were obtained using the Bruker D8 powder diffractometer (Bruker, Karlsruhe, Germany). Samples were scanned using a copper Kα radiation source over the 2θ range 5–50° with a step size of 0.01 per minute and scan time of 1 s per step.

2.6. High pressure liquid chromatography (HPLC)

The concentration in samples of ibuprofen was determined using the modified USP method. A Waters Alliance (Water Systems, UK) 2695 separations module with 2487 dual wavelength

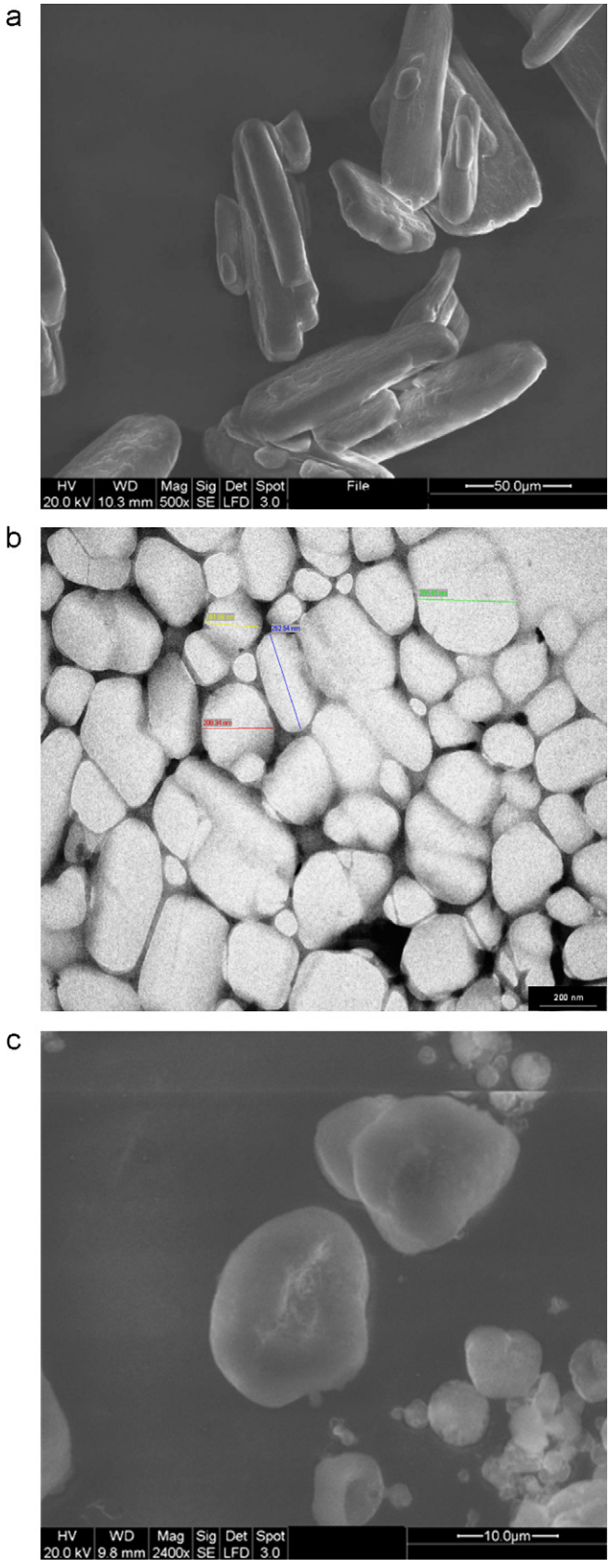

Fig. 2. (a) SEM Image of the initial particle size of Ibuprofen. (b) TEM image showing the particle size of 15% (w/w) ibuprofen after processing. (c) SEM image of spray dried powder.

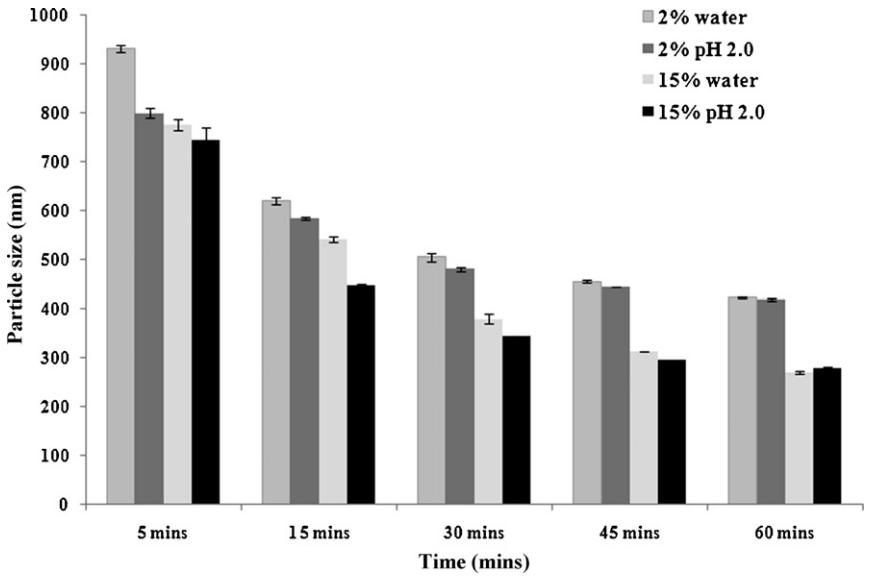

Fig. 3. Average particle size plot for 2% and 15% (w/w) ibuprofen nano-suspension measured by PCS.

absorbance detector at 214 nm was used with C-18 silica based 25 cm × 4.6 mm × 5 μm column (Vydac Technology Ltd., UK). The mobile phase was acetonitrile:water (50:50), with pH adjusted to 2.5 using ortho phosphoric acid. The flow rate was set to 1.0 mL/min, column temperature to 30 ± 2 °C and the sample temperature to 20 ± 2 °C. The method was shown to be suitably linear, accurate, sensitive and selective. Products formed at the end of processing were sampled in triplicate from the top, middle and bottom of the sample container.

2.7. Stability of the nano-suspensions

The particle size and the active content of the nano-suspensions after manufacture were measured at 0, 1 and 2 days for both the 2% and 15% (w/w) suspensions after storage at 2–8 °C and at room temperature. The particle size was measured using the Zetasizer Nano and the active content was measured by HPLC.

2.8. Spray drying of ibuprofen nano-suspensions

Spray-drying was carried out using a Büchi 190 Mini Spray Dryer (Buchi Labortechnik AG, Flawil, Switzerland) fitted with a two-fluid nozzle and peristaltic pump. The processing parameters comprised an inlet temperature of 130 °C, an atomizing air flow rate of 700 L/h, a liquid feed rate of 3 mL/min and an aspirator vacuum of approximately 38 mbar. A resulting outlet temperature of 65 °C was observed.

The 15% (w/w) nano-suspensions in water and pH 2.0 were spray dried using the Buchi B-190 mini spray dryer. An equivalent mass of mannitol (15%, (w/w)) was added to the ibuprofen nano-suspension and dissolved. The resultant suspension was then spray dried to produce a free flowing powder, which was analysed for active content, particle size and solid state characteristics by XRPD and DSC.

2.9. Dissolution of ibuprofen nano-suspensions and spray dried powder

The dissolution characteristics of nano-suspension, spray-dried powders and as supplied API were compared at pH 7.2 using USP II apparatus (paddle method) with paddle speed of 50 rpm. Phosphate buffer pH 7.2 (British Pharmacopoeia Volume IV, 2008. Appendix I D. Buffer solutions) was used as the dissolution media at a volume of 900 mL with the temperature of the dissolution bath

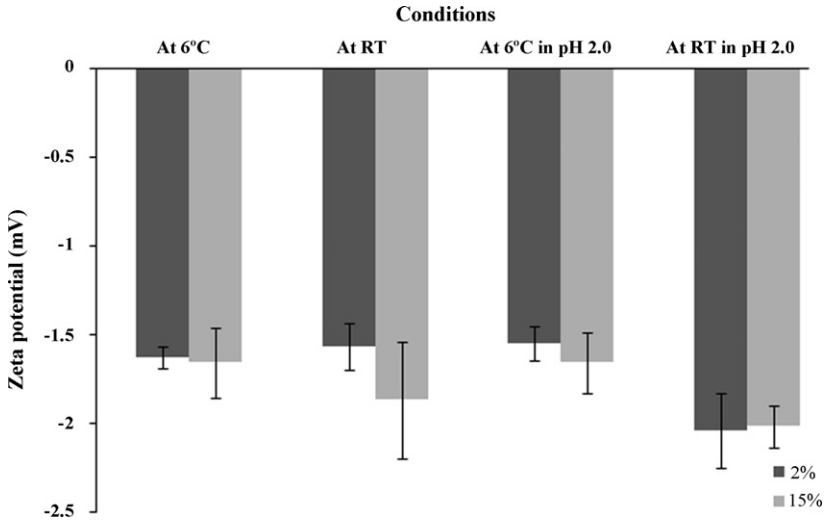

Fig. 4. Zeta potential values for 2% and 15% (w/w) ibuprofen suspensions at various conditions with 0.5% (w/v) PVP, 0.5% (w/v) HPMC and 0.1% (w/v) SLS as diluting medium.

Table 2
Average particle size distribution data for 2% (w/w) ibuprofen suspensions in water and at pH 2.0.

Conditions	Day 0		Day 1				Day 2			
	PS (nm)	SD	PS at 2–8 °C (nm)	SD	PS at RT (nm)	SD	PS at 2–8 °C (nm)	SD	PS at RT (nm)	SD
Water	424	0.96	482	19.36	458	1.63	477	13.40	449	4.32
pH 2.0	420	3.55	454	6.97	438	7.59	441	9.81	449	2.36

PS, average particle size; SD, standard deviation; RT, room temperature 20–25 °C.

Table 3
Active content as % of nominal for 2% (w/w) ibuprofen suspensions in water and at pH 2.0.

Conditions	Day 0		Day 1				Day 2			
	%AC	SD	%AC at 2–8 °C	SD	%AC at RT	SD	%AC at 2–8 °C	SD	%AC at RT	SD
Water	79.07	0.31	75.51	0.17	75.38	0.01	75.64	0.42	75.14	0.04
pH 2.0	77.24	0.36	73.08	0.02	75.20	0.19	74.61	0.07	75.84	0.06

%AC, percentage active agent content; SD, standard deviation; RT, room temperature 20–25 °C.

Table 4
Average particle size data for 15% (w/w) ibuprofen suspensions in water and at pH 2.0.

Conditions	Day 0		Day 1				Day 2			
	PS (nm)	SD	PS at 2–8 °C (nm)	SD	PS at RT (nm)	SD	PS at 2–8 °C (nm)	SD	PS at RT (nm)	SD
Water	271	2.52	277	1.63	280	4.19	286	2.94	285	2.06
pH 2.0	279	2.16	352	5.35	379	5.65	373	1.89	401	3.30

PS, average particle size; SD, standard deviation; RT, room temperature 20–25 °C.

set to 37 °C. 5 mL aliquots of the dissolution media were collected at 0, 2, 6, 10, 15, 30, 45 and 60 min and were replaced with equivalent volumes of fresh media. Aliquots were then centrifuged at 14,800 rpm for 30 min to separate undissolved drug. The supernatant was collected and analysed for levels of drug using the HPLC method specified in Section 2.6.

3. Results and discussion

3.1. Particle size reduction

The initial size of elongated particles of ibuprofen with aspect ratios of 4–6 was approximately in the range 20–30 μm by 80–120 μm as determined by SEM (Fig. 2(a)). These coarse particles were shown to be subject to rapid size reduction with sub-micron levels achieved within 5 min (see Fig. 3).

Ibuprofen suspensions processed for 5 min using the size reduction system reduced the particle size to less than 1000 nm. Further reduction in particle size was observed when processed for 60 min (Fig. 3). TEM showed a notable number of particles at sizes less than 500 nm (see Fig. 2(b)) suggesting that this size reduction method has the potential to achieve further comminution at prolonged processing times. The achievement of a plateau in size reduction however suggests that comminution in the latter stages of the experiment occurs by abrasion rather than fragmentation.

Concentrated suspensions containing sub-micron particles show non-Newtonian flow behaviour including phenomena like shear thinning, shear thickening and yielding. These phenomena are closely related to particle–particle interactions. The shear stress of the processed suspensions increases with decreasing particle size and processing time (Stenger and Peukert, 2003) which leads to further size reduction.

Greater concentration of particles leads to a greater number of stress events with some self attrition leading to smaller particle size. It is clear from the trends in size reduction that comminution is most effective for the higher concentration suspensions where interactions with the grinding media are likely to occur more frequently and where some self-attrition is also likely to occur. There is no evidence of particles with sizes exceeding 1000 nm for the pH 2.0 suspensions at time points up to 60 min.

The results from this study can be compared favorably with those obtained using the RESS (rapid expansion of supercritical solutions) method (Cristini et al., 2003), where particles of average size 1–3 μm were obtained. Also, in the study by Larsson and Kristensen (2000), particles produced by wet milling demonstrated diameters in the range 8–10 μm. Using the new rapid high shear approach, however, transition from coarse particulates to sub-micron levels occurs rapidly using a single processing step.

3.2. Stability studies, particle size distribution and zeta potential measurements

The particle size and drug content (as percentage of nominal) of samples with nominal concentration of 2% (w/w) ibuprofen stored at 2–8 °C and room temperature for periods up to 2 days are given in Tables 2 and 3 respectively.

Table 5
Active content as % of nominal for 15% (w/w) ibuprofen suspensions in water and at pH 2.0.

Conditions	Day 0		Day 1				Day 2			
	%AC	SD	%AC at 2–8 °C	SD	%AC at RT	SD	%AC at 2–8 °C	SD	%AC at RT	SD
Water	83.69	0.77	77.91	0.38	82.14	0.08	81.08	0.27	81.53	0.42
pH 2.0	78.07	0.03	77.09	0.02	77.79	0.49	77.20	0.79	77.95	0.03

%AC, percentage active agent content; SD, standard deviation; RT, room temperature 20–25 °C.

It was observed that the particle size increased slightly from day 0 to day 2 at both room temperature (20–25 °C) and 2–8 °C for the 2% (w/w) ibuprofen suspensions under normal and pH 2.0 conditions. No evidence of sedimentation was observed for any of the samples tested.

The average particle size and active agent content (as percentage of nominal) of samples with nominal concentration of 15% (w/w) ibuprofen stored at 2–8 °C and room temperature for periods up to 2 days are given in Tables 4 and 5 respectively.

Tables 4 and 5 show particle size and active content data respectively for formulations containing ibuprofen at a concentration of 15% (w/w). These data indicate that the water based formulation demonstrated negligible growth at both conditions over the 2 day period. Preparations produced in water showed no marked sign of particle growth, degradation or sedimentation. However, although the pH 2 sample also showed no signs of loss of active agent or sedimentation, some particle growth did occur which was more pronounced at room temperature. Despite particle growth over 2 days, it is probable that the particles will remain in nano-particulate form during transit through the stomach, where residence times in the fasted state are less than 30 min. This will enable ibuprofen to be maintained in a suitable form for rapid dissolution in the small intestine.

According to the DLVO theory, a system can be regarded as stable if electrostatic repulsion dominates the attractive Van der Waals forces (Lagaly, 1984). The particles must overcome an energy barrier of electrostatic repulsion to approach one another and form agglomerates. If their velocity or kinetic energy is sufficiently high, they will collide. Higher temperatures are likely to increase the kinetic energy of the system still further, and so greater levels of agglomeration are expected. This principle suggests trends towards better stability under storage conditions of 2–8 °C (Freitas and Muller, 1998a,b).

It is also well known that increases in intensity of light radiation and temperature lead to accelerated particle growth (Freitas and Muller, 1998a,b). A high film rigidity of the stabilizers (microviscosity) avoids fusion of the film layers after particle contact, where microviscosity is a temperature dependent factor. Temperature increase causes a microviscosity decrease leading to destabilization (Schuhmann, 1995) and higher values of zeta potential. The slight increases in zeta potential observed in this study (see Fig. 4) are therefore probably linked to the slight growth in particle size that was observed over the storage period.

Zeta potential values for the 2% (w/v) and 15% (w/v) ibuprofen suspensions in water and at pH 2.0, stored at room temperature and at 2–8 °C were in the ranges given in Fig. 4. No marked differences in zeta potential were observed between the formulations, although a trend towards higher zeta potential was observed for samples stored at room temperature. Owing to the relatively low levels of zeta potential observed in this study (−1.5 to −2.5 mV) it is probable that stabilisation of these nano-particles is by steric stabilisation rather than electrostatic repulsion. Lindfors et al. (2008) previously showed that PVP absorbs on to the surfaces of crystals. The presence of this polymer on particle surfaces has the potential to retard crystal growth and agglomeration through decreased integration of molecular layers on to the crystal surface and potentially through reduced interparticulate interaction and diminished potential for agglomeration.

3.3. SEM for the spray dried powder

Evaluation of the spray dried powder showed particles with size in the range 5–10 μm (Fig. 2(c)) with spherical morphology. It is probable that one or more nano-particles of ibuprofen have been immobilised in this matrix which provides reduced potential for particle agglomeration.

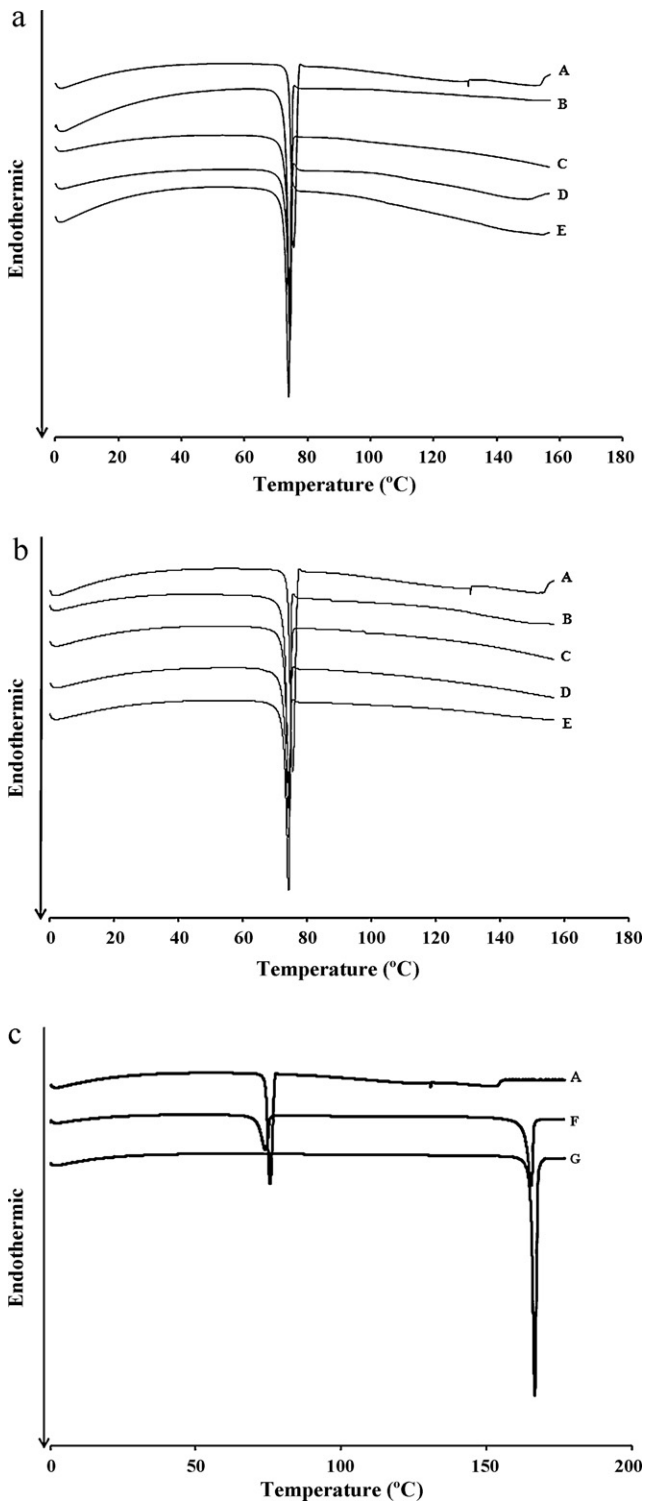

Fig. 5. DSC profiles for: (a) processed 2% (w/w) ibuprofen nano-suspension, (b) processed 15% (w/w) ibuprofen nano-suspension and (c) ibuprofen spray dried powder, where (A), ibuprofen starting material; (B), nano-suspension stored for 2 days at RT (pH 2); (C), nano-suspension stored for 2 days at 2–8 °C (pH 2); (D), nano-suspension stored for 2 days at RT (water); (E), nano-suspension stored for 2 days at 2–8 °C (water), (F), spray dried nano ibuprofen powder and (G), mannitol.

3.4. Physical form characterisation

DSC showed that ibuprofen had maintained its crystallinity and physical form following size reduction and spray drying respectively. The DSC thermal profile for particles isolated from suspension by centrifugation and in the spray dried form (Figs. 5(a)–(c)), show a sharp endothermic melting transition at similar melting temperature to the parent drug ibuprofen (70–80 °C). The endothermic transition observed at temperatures above 160 °C is related to the fusion and decomposition of the water soluble carrier mannitol. After processing and spray drying, XRPD patterns (Figs. 6(a) and (b)) showed peaks at similar 2θ positions to those of the starting material suggesting that nano-crystalline drug had been encapsulated in particles alongside the inert carrier. All other peaks shown are related to the crystalline structure of the water soluble carrier mannitol.

Previous studies have suggested that amorphization of poorly water-soluble drugs by milling has the potential to provide improvements in bioavailability (Mallick et al., 2008). Although enhancements in solubility may be beneficial, the unstable nature of amorphous materials, reduce their attractiveness to pharmaceutical manufacturers. The DSC and the XRPD data, given in Figs. 5(a)–(c) and 6(a) and (b) show that notable crystallinity of ibuprofen has been maintained for the size reduced ibuprofen suspension and spray dried powders.

The formulations developed in this study therefore have the potential to demonstrate greater physical stability than the dosage forms previously reported in the literature which contained drug in a predominantly amorphous form (Mallick et al., 2008).

3.5. Dissolution studies

The dissolution rate of the spray-dried powder was similar to that of the nano-suspension (pH 2 and water), with release being almost complete after 2 min (Fig. 7). This suggests that no marked particle growth or agglomeration had occurred during spray drying. The dissolution of both liquid and solid nano-formulations was markedly more rapid than that of the starting material and a marketed suspension, which can be explained by the substantial increases in particle surface area for the processed preparations.

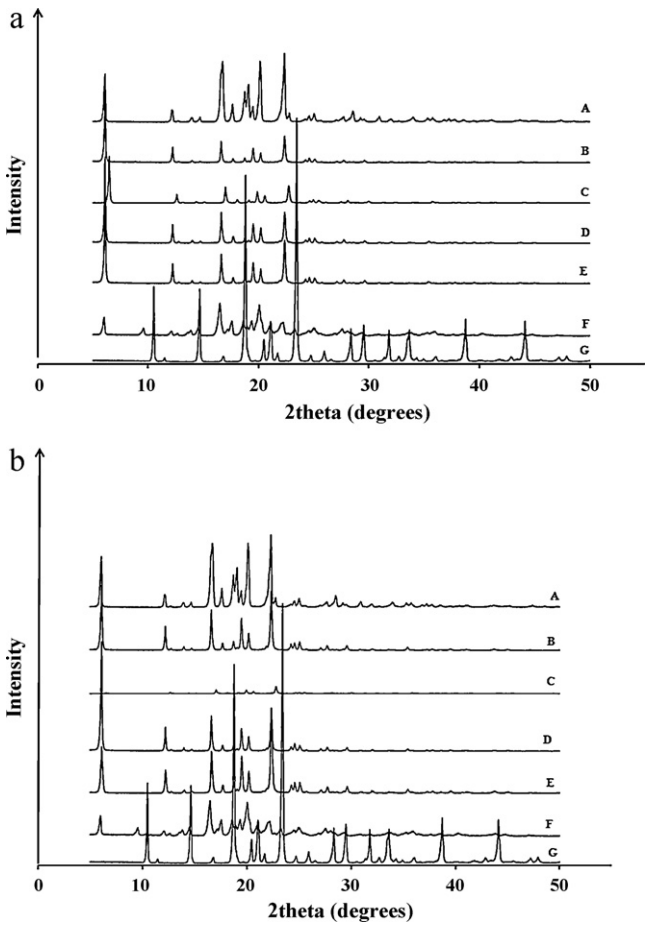

Fig. 6. X-ray powder diffraction patterns for (a) processed 2% (w/w) ibuprofen nano-suspension (b) processed 15% (w/w) ibuprofen nano-suspension, where (A), ibuprofen starting material; (B), processed nano-suspension in water stored for 2 days at 2–8 °C; (C), processed nano-suspension in water stored for 2 days at RT; (D), processed nano-suspension in pH 2.0 stored for 2 days at RT; (E), processed nano-suspension in pH 2.0 stored for 2 days at 2–8 °C; (F), spray dried nano ibuprofen powder and (G) mannitol.

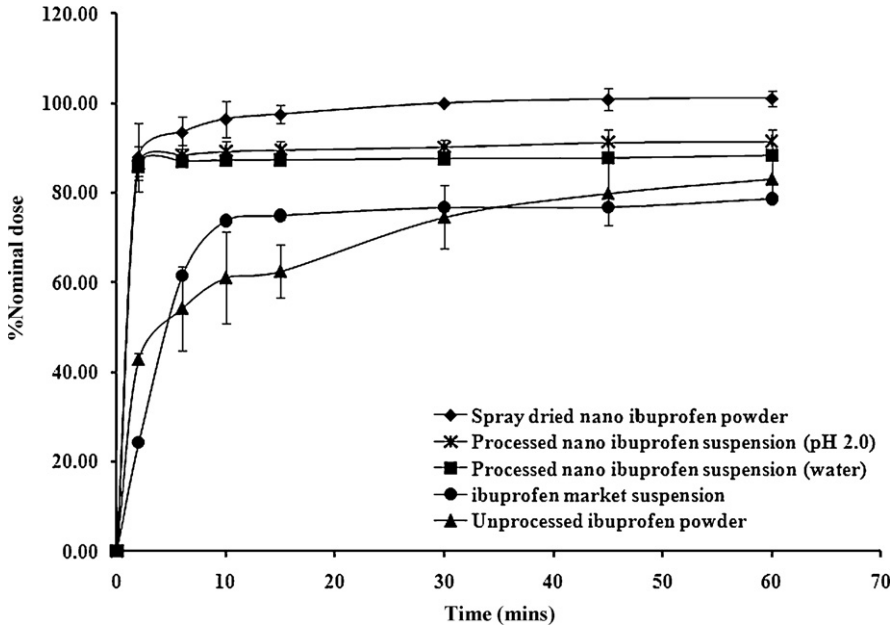

Fig. 7. Comparative dissolution of spray dried nano ibuprofen powder, nano ibuprofen suspension in pH 2 and water, ibuprofen market suspension, unprocessed ibuprofen powder.

Previous reports of dissolution studies for enabling formulations of ibuprofen have shown marked increases in release rates such as the amorphous solid dispersions developed by Mallick et al. (2008), in which 83.5% of ibuprofen was released at 120 min. However the dissolution rates observed in these studies at the early time points were greater using the spray dried powder and nano-suspension investigated in this study which showed a release of drug at 2 min exceeding 85% of the nominal dose. Although some formulations of amorphous ibuprofen (Rajanikant et al., 2010) showed release rates equivalent to the preparations study explored in this paper, it is likely that amorphous systems will be less stable on storage than crystalline products owing to the notable propensity to crystallise.

The nano-systems showed improved faster dissolution characteristics over the commercial product which also demonstrated incomplete dissolution after 60 min.

4. Conclusions

The particle size of ibuprofen was reduced when processed at concentration of 15% (w/w) when suspended either in water or at pH 2, from a starting size of 20 μm × 120 μm to an average size of to <300 nm using the DM 100 processing system. The final particle sizes achieved were markedly lower than those previously reported in the literature for ibuprofen. With a relatively short processing time, it was possible to produce nano-particles which demonstrated more rapid dissolution than the unprocessed material. These particles were isolated as a fast dissolving solid form, which maintained a high level of crystallinity after processing whether processed in water or in acidic media. The stability of nano-particles at 15% (w/w) was however greatest when produced in non pH adjusted media. Nano-formulations subjected to spray drying gave free flowing powders which maintained an enhancement in the dissolution rate compared to conventional API. Further studies are planned to evaluate the effects of nano-processing on the rate and extent of ibuprofen absorption when administered via the oral route.

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References

Ali, H.S.M., York, P., Blagden, N., 2009. Preparation of hydrocortisone nanosuspension through a bottom-up nanoprecipitation technique using microfluidic reactors. Int. J. Pharm. 375, 107–113.

British Pharmacopoeia, Volume IV, 2008. Appendix I D. Buffer solutions.

Chingunpituk, J., 2007. Nanosuspension technology for drug delivery. Walailak J. Sci. Technol. 4, 139–153.

Cristini, F., Delalonde, M., Joussot-Dubien, C., Bataille, B., 2003. Elaboration of ibuprofen microcomposites in supercritical CO_2. In: Brunner, G., Kikic, I., Perrut, M. (Eds.), Proceedings of the 6th International Symposium on Supercritical Fluids, 1917–1922.

Delogu, F., 2005. Thermodynamics of the nanoscale. J. Phys. Chem. B 109, 21938–21942.

Freitas, C., Muller, R.H., 1998a. Effect of light and temperature on zeta potential and physical stability in solid lipid nanoparticle (SLN™) dispersions. Int. J. Pharm. 168, 221–229.

Freitas, C., Muller, R.H., 1998b. Spray-drying of solid lipid nanoparticles. Eur. J. Pharm. Biopharm. 46, 145–151.

Healy, A.M., Corrigana, O.I., 1992. Predicting the dissolution rate of ibuprofen-acidic excipient compressed mixtures in reactive media. Int. J. Pharm. 84, 167–173.

Lagaly, G., 1984. Energetische wechselwirkungen in dispersionen und emulsionen. In: Asche, H., Essig, D., Schmidt, P.C. (Eds.), Technologie von Salben, Suspensionen und Emulsionen, APV Paperback Series, vol. 10. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp. 32–61.

Larsson, I., Kristensen, H.G., 2000. Comminution of a brittle ductile material in a micros Ring Mill. Powder Technol. 107, 175–178.

Lindfors, L., Forssén, S., Westergren, J., Olsson, U., 2008. Nucleation and crystal growth in supersaturated solutions of a model drug. J. Colloid Interface Sci. 325, 404–413.

Mallick, S., Pattnaika, S., Swaina, K., Deb, P.K., Sahab, A., Ghoshalb, G., Mondalb, A., 2008. Formation of physically stable amorphous phase of ibuprofen by solid state milling with kaolin. Eur. J. Pharm. Biopharm. 68, 346–351.

Merisko-Liversidge, Liversidge, 2008. Drug nanoparticles: formulating poorly water-soluble compounds. Toxicol. Pathol. 36, 43–48.

Morla, T.K., Meredith, J.C., 2005. Simulation of interaction forces between nanoparticles in the presence of Lennard-Jones polymers: freely adsorbing homopolymer modifiers. Langmuir 21, 487–497.

Müller, R.H., Jacobs, C., Kayser, O., 2001. Nanosuspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the future. Adv. Drug Deliv. Rev. 47, 3–19.

Rajanikant, P., Nirav, P., Patel, N.M., Patel, M.M., 2010. A novel approach for dissolution enhancement of Ibuprofen by preparing floating granules. Int. J. Res. Pharm. Sci. 1, 57–64.

Samsonov, N.V.M., Solobnyakov, N.Y., Bazulev, A.N., 2003. Thermodynamic stability conditions for nanosized particles. Surf. Sci. 532–535, 526–530.

Schuhmann, R., 1995. Physikalische Stabilität parenteraler Fettemulsionen—Entwicklung eines Untersuchungsschemas unter besonderem Aspekt analytischer Möglichkeiten. Ph.D. thesis. Freie Universität Berlin, Berlin.

Stenger, F., Peukert, W., 2003. The role of particle interactions on suspension rheology-application to submicron grinding in stirred ball mills. Chem. Eng. Technol. 26.

Sulaiman, B., 2007. "The Milling System". Patent no.:WO/2007/020407.

Verma, S., Gokhaleb, R., Burgessa, D.J., 2009. A comparative study of top–down and bottom–up approaches for the preparation of micro/nanosuspensions. Int. J. Pharm. 380, 216–222.