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Research Article

FAST DISSOLVING IBUPROFEN NANOCRYSTAL-LOADED SOLID DOSAGE FORMS

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ABSTRACT

Purpose: Many expensive formulation approaches are conducted to accelerate the dissolution velocity of ibuprofen for a faster performance. A very simple approach is the drug nanonization by high pressure homogenization (HPH), which leads to an accelerated dissolution velocity. In this study ibuprofen nanocrystals were produced by HPH incorporated into effervescent and pellet formulations. The properties of the final formulations have been tested with respect to redispersabilty, morphology and dissolution velocity.

Methods: A formulation screening was carried out to ascertain the most suitable formulation for further processing. A Micron LAB 40 (APV Homogenizers, Unna, Germany) was used for the HPH. Photon correlation spectroscopy (PCS) (Malvern Zetasizer IV) and laser diffraction (LD) (Coulter LS 230) were employed to determine the particle size. The pellets were formed by extrusion and spheronization using an extruder Caleva Model 10 (Caleva, Sturminster Newton, UK) and a spheronizer Caleva Model 120 (Caleva, Sturminster Newton, UK). Dissolution test was performed with a Pharmatest PTW SIII (Pharma Test, Hamburg, Germany). Drug concentrations were determined using HPLC.

Results: A suitable nanosuspension formulation could be found. After 40 homogenization cycles the size-average determined with PCS was 929 nm. A polydispersity index of 0.157, indicates a narrow size distribution. The volume size distribution showed that 50% (LD 50%) of the ibuprofen nanocrystals were smaller than 1.983 µm and 1.763 µm in diameter after redispersion. Pellets and effervescent powders were successfully produced. Ibuprofen nanocrystal could be redispersed completely from both formulations. Both formulations have shown a complete dissolution within 30 minutes in 0.1 N HCl-solution.

Keywords: Nanosuspension, Nanocrystals, Ibuprofen, Pellet, Effervescent, Solubility, Dissolution

INTRODUCTION

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) and belongs to the group of propionic acid derivatives (**Fig. 1**). It inhibits the enzyme cyclooxygenase (prostaglandin synthesis) which catalyzes the transformation of unsaturated fatty acids to prostaglandins. One assumes that the inhibition of the prostaglandin synthesis is the cause for the analgesic, antipyretic, and anti-inflammatory action of the drug. It is used to treat inflammatory rheumatoid diseases and to relieve acute pain[1,2,3,4].

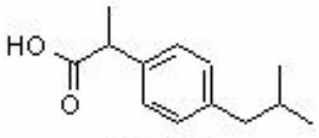

Fig. 1: Chemical structure of ibuprofen

In general, ibuprofen is suited for the treatment of pain, in particular for the treatment of pain being related to the musculoskeletal system, but also headaches, postoperative pain, dysmenorrheal, etc. Pain accompanying arthritis can be reduced and the mobility of the joints can be increased. In the case of chronic rheumatoid arthritis, ibuprofen not only reduces pain, but also joint swelling and morning stiffness. Ibuprofen has been used successfully for other rheumatoid diseases such as spondylitis ankylosans (Bechterew disease), juvenile rheumatoid arthritis, and acute gout seizures. However, nonsteroidal anti-inflammatory agents only have a symptomatic effect, but the development of the actual disease is not significantly influenced. There are even indications that a long-term treatment may have an unfavourable influence.

For soft tissue rheumatism (e.g. periarthropathy of the shoulder) NSAID can be beneficial; however, it has not been demonstrated whether they represent advantages in comparison with other methods of treatment [1,2].

Production of ibuprofen nanocrystals can improve physicochemical properties. After production by high pressure homogenization (HPH), ibuprofen nanocrystals can be incorporated into solid dosage forms. The release of ibuprofen nanocrystals can be evaluated.

Ibuprofen nanocrystals will be produced by HPH and incorporated into effervescent and pellet formulations. Then the physicochemical properties of the final formulations will be tested with respect to redispersabilty, saturation solubility, morphology and dissolution velocity.

MATERIAL AND METHODS

Materials

Ibuprofen was provided from BASF Aktiengesellschaft GmbH (Ludwighafen, Germany). Sodium dodecyl sulfate (Fluka Chemie GmbH, Germany), Tween® 80 (Uniqema, Berlgium), Poloxamer®188 (BASF Aktiengesellschaft GmbH, Ludwighafen, Germany) and Polyvinyl Alcohol (PVA) Wt. 90.000 (Sigma Aldrich GmbH, Deisenhofen, Germany) were used to stabilize nansuspensions. Double-distillated water was used as dispersion media and other chemicals were of analytical reagent grade.

Methods

Production of ibuprofen nanosuspensions by high pressure homogenization (HPH)

Ibuprofen nanosuspensions were produced by HPH using A Micron LAB 40 (APV Homogenizers, Unna, Germany). Micronized ibuprofen was first dispersed into stabilizer solution and mixed using an Ultra-Turrax T25 (Janke & Kunkel GmbH, Staufen, Germany) at 8000 rpm for 10 seconds. Immediately pre-suspension was transferred into Micron LAB 40 and then passed through the homogenizer to obtain nanosuspensions. Regarding to hard crystalline of ibuprofen, homogenization has taken place using 40 cycles of 1500 bars at 5°C. To construct particle size reduction profile, samples were withdrawn after each five cycles. The particle sizes were analyzed by laser diffractometry (LD) and Photon correlation spectrophotometry.

Particle size analyses of ibuprofen nanosuspensions

Photon correlation spectroscopy (PCS) (Malvern Zetasizer IV, Malvern Instrument, UK) and laser diffraction (LD) (Coulter LS 230) were employed to determine the particle size of the drug nanocrystals. Coulter LS 230 (Beckman Coulter, Krefeld, Germany),

yielding volume weighted diameters d50%, d95%, d99%, Mie theory, real refractive (rf) index: 1.46, imaginary rf index: 0.01. Zetasizer IV (Malvern Instruments, Malvern, UK), yielding PCS mean diameter (z-average) and Polydispersity Index (PI).

Polarized light microscopy

Morphology of the ibuprofen nanocrystals were observed by a Leitz microscope (Leitz, Wetzlar, Germany), magnification: 1000 fold (oil immersion). 3 times of observations were made for each sample.

DSC

DSC 821e (Mettler Toledo AG, Gießen, Germany) was employed to analyze melting points and thermal analyzing, measuring range: 25°C - 90°C, heating rate: 5K/min, peak onset and melting enthalpy calculated with Star software Version 6.0 also from Mettler Toledo (Mettler Toledo AG, Gießen, Germany).

Lyophilization of ibuprofen nanosuspension

Ibuprofen nanosuspension was lyophilized without a cryoprotective agent. Firstly, ibuprofen nanosuspensions were rapid cooled down to -70°C for 2 hours followed by primary drying at 0.03 mbar and secondary dry at 0.001 mbar for 48 hours.

Spray drying process (SD)

A Büchi 190 Mini Spray Dryer (Büchi, Flawil, Switzerland) equipped with a 0.5 mm two fluid nozzle was used. The peristaltic pump was set at number 2, the aspirator was set to number 10 (-30 mbar). The atomizing airflow was set at 800 Ln/h and the heating was set to number 10. This combination of parameters yielded an inlet temperature of 150 ± 2 °C and an outlet temperature of 100 ± 2 °C. Samples were placed after collection in a vacuum desiccator over silica gel at room temperature at least one day before characterization.

Extruding and Spheronizing of Pellets

The extrusion-spheronization process is a multiple step procedure, involving mixing, wet granulation, extrution, spheronization and drying. The first step was dry mixing of ibuprofen nanocrystal and lactose (mixing ratio 1:2). The water was poured to dry mass of them (final ratio ibuprofen : lactose : water = 1:2:1) and followed by wet granulation using a coating pan, which converted the ibuprofen and lactose into a plastic mass that can be easily extruded by a basket *extruder* (*Caleva Model 10*, Sturminster Newton, UK). The coating pan was rotated at 25 rpm within certain time until a plastic mass (pellet mass) formed.

The extruded strands were transferred into a *spheronizer* (*Caleva Model 120*, Sturminster Newton, UK) where, when upon contact with the rotating friction plate, they were instantaneously broken into short cylindrical rods and were pushed towards and up the stationary wall of the processing chamber by centrifugal force.

Due to gravity, the particles fall back to the friction plate and the cycle was repeated until the desired sphericity is achieved. Finally, they are dried either on trays or in a fluid bed-dryer prior to the further processing [5].

Fusion method of the effervescent granule

In the fusion method, the one molecule of water present in each molecule of citric acid acts as the binding agent for the powder mixture. Just before mixing the powder, the acid source were powdered and then mixed with the other powders (previously passed through a number 60 sieve) to ensure uniformity the mixture. The sieves and the mixing equipment should be made from stainless steel or other material resistant to the effect of the acids.

The mixing of the powder was performed as rapidly as is practical, preferably in an environment of low humidity to avoid the adsorption of moisture from the air leading for premature chemical reaction. After mixing the powder was placed in a glass or a suitable dish in an oven previously heated to between 93° and 104°C. During the heating process, a spatula was used to turn over the powder. The heat causes the release of the crystallization water from the citric acid, which in turn dissolves a portion of the powder mixture, setting off the chemical reaction and consequently release of some carbon dioxide. This causes the softened mass of the powder to become somewhat spongy, and when of the proper consistency, it was removed from the oven and rubbed to a sieve to produce granules of the desired size. A no. 84 sieve was used to produce medium granules. When all of the mass had passed through the sieve, the granules were immediately dried at a temperature not exceeding 54°C and immediately transferred to containers which are the promptly and tightly sealed [6].

HPLC condition for Ibuprofen

The amount of released ibuprofen in the collected medium was determined by high performance liquid chromatography (HPLC; Thermo Separation Product, USA). The HPLC conditions were as following: column, Spherisorb ODS 5 mm (diameter), 20 cm (length); mobile phase: methanol/Na_2HPO4 0.01 M (25%); flow rate, 1.0 mL/min; UV/Vis detector; λ max. at 220nm [7].

Saturation solubility

Excess of ibuprofen was placed into 40 ml vials containing dispersion media and covered by aluminum foil to avoid chemical degradation while exposure by light from outside. After sonicating in a water bath (Bandelin RK 514, Berlin, Germany) for 30 second, the vials were placed in a shaker (Innova™ 4230, New Brunswick Scientific Edision, NJ-USA) with controlled temperature at 25°C. The shaker was moved at 100 rpm for 1 week. At certain time samples were withdrawn for measuring dissolved ibuprofen. Aliquots were filtered using a Sartorius (Sartorius AG, Goettingen Germany) filter 0.1 µm and transferred into 1.5 ml eppendorf tube. Concentration of dissolved ibuprofen was analyzed by high performance liquid chromatography (HPLC).

Dissolution velocity

Dissolution testing had been done according to USP XXIV using rotating paddle with speed of 100 rpm at 37°C. A Pharmatest PTW SIII (Pharma Test Apparatebau GmbH, Hainburg, Germany) was employed and pellets and effervescent granule containing of 50 mg ibuprofen were located into 900 ml media-contained chamber. Dissolution was performed for 2 hours and at certain time samples were withdrawn and filtered using 0.1 µm filters (Sartorius AG, Goettingen Germany). The aliquots were transferred into effendorf tube. Furthermore dissolved ibuprofen was determined by HPLC.

RESULT AND DISCUSSION

Dried ibuprofen nanocrystals

A suitable nanosuspensions formulation could be found. After 40 homogenization cycles the size-average determined with PCS was 929 nm. A polydispersity index of 0.157 indicates a narrow size distribution.

Drying directly after production is one method for inhibiting the aggregation or growth of ibuprofen nanocrystals [8,9]. **Fig. 2** shows a microscopic picture of re-dispersed spray-dried ibuprofen nanocrystals compared to homogenized ibuprofen nanosuspensions. In general, spray-dried nanocrystals had a larger particle size compared to ibuprofen nanosuspensions. Despite the larger particle size, the ibuprofen nanocrystals were clearly homogeneously distributed. Hardly any agglomerated or aggregated particles were found.

No difference was found between re-dispersed spray-dried ibuprofen nanocrystals and lyophilized ibuprofen. Both nanocrystals were bigger compared to those of the original nanosuspensions. Particle size distribution of the lyophilized ibuprofen nanocrystals, while exceeding the nanocrystals range, was relatively narrow with homogeneous distribution (**Fig. 2** and **Fig. 3**). Lyophilized ibuprofen nanocrystals could be admixed with other excipients to produce effervescent granule. In next section, the particle size distribution of the ibuprofen nanocrystals was analyzed after re-dispersion from effervescent granule in water.

In the other study, ibuprofen nanosuspensions was directly incorporated into lactose to produce ibuprofen pellets. Production of pellets and effervescent granules will be explained in detail in next section.

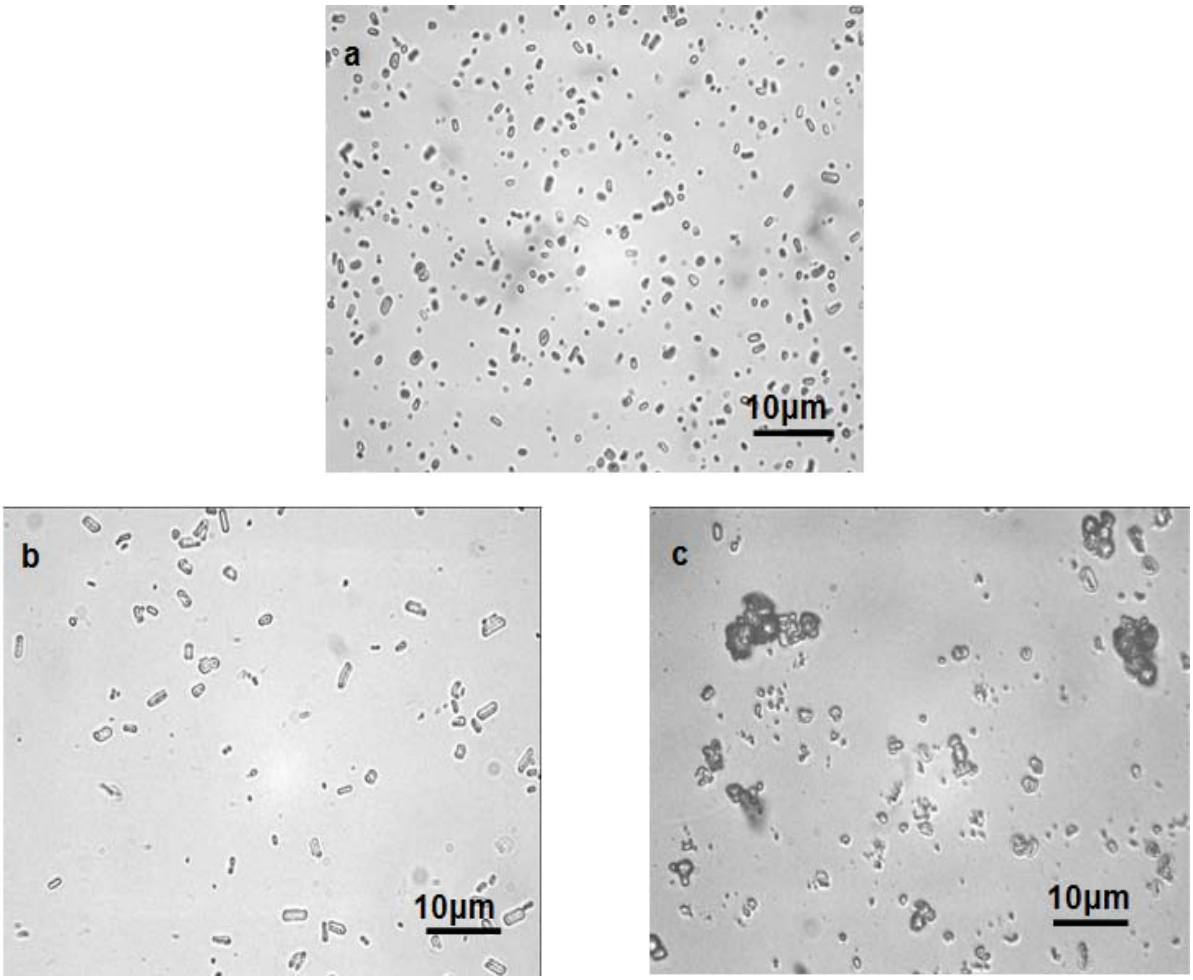

Fig. 2: Light microscopic pictures of ibuprofen nanosuspension after production (a), re-dispersed ibuprofen nanocrystals after lyophilization (b) and re-dispersed ibuprofen nanocrystals after spray drying (c)

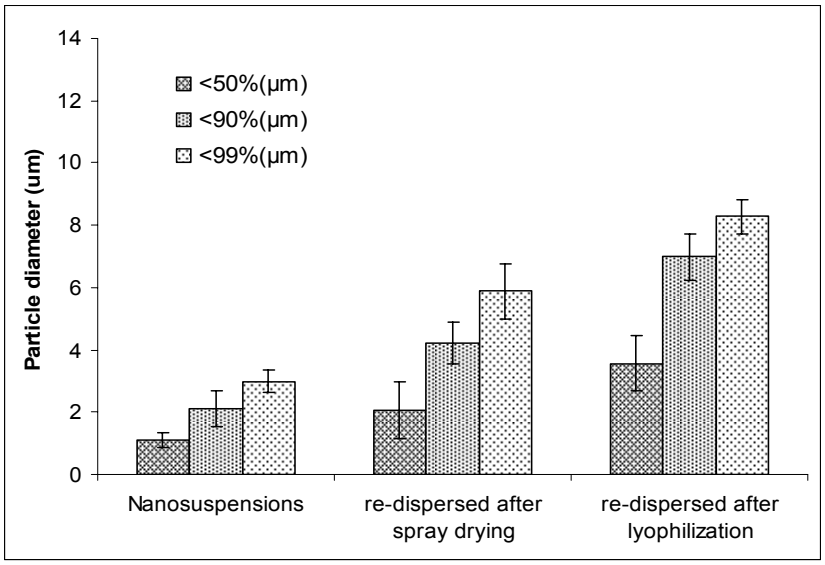

Fig. 3: LD particle sizes of ibuprofen nanosuspension and re-dispersed ibuprofen after spray drying and lyophilization

Thermal Analysis

Thermal analyses of lyophilized and spray-dried ibuprofen nanocrystals were performed. According to the DSC data, the spray drying and lyophilization have almost no influence on the crystallinity of the ibuprofen nanocrystals. The melting point of all nanocrystals was similar to that of the raw material (between 74°C to 76°C). The slight difference in melting point might be explained by the presence of stabilizer (**Fig. 4**) [9, 10].

Due to the presence of poloxamer 188 in the nanosusupensions, temperature peaked at around 40°C in either lyophilized or spray-dried, indicating that poloxamer 188 melted at around 40°C. In contrast, other stabilizers did not reveal a peak because of their very low concentration such as only 0.2% for SDS or liquid state at room temperature, such as Tween 80.

Saturation solubility and dissolution velocity of nanocrystals

Solubility of ibuprofen nanocrystals was also evaluated in three different media. As shown in **Fig. 6,** the saturation solubility of ibuprofen nanocrystals increased slightly but not to a significant extent at pH of 6.8. At steady state (after 3 days) ibuprofen nanocrystals showed similar saturation solubility to ibuprofen microcrystals.

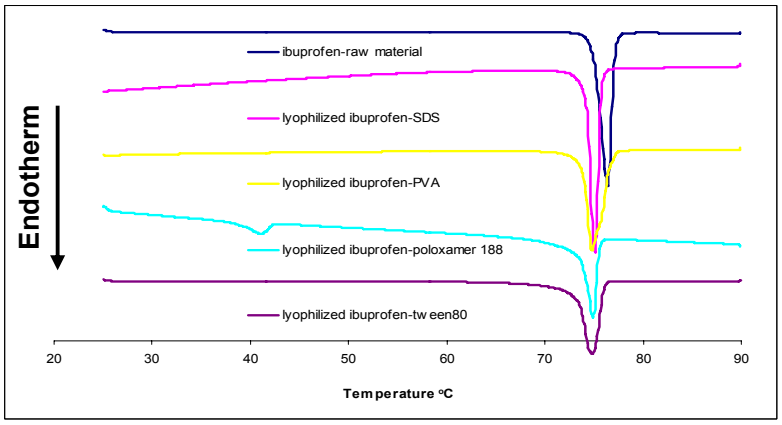

Fig. 4: Influence of stabilizers on fusion temperature and crystallinity of lyophilized ibuprofen nanocrystals

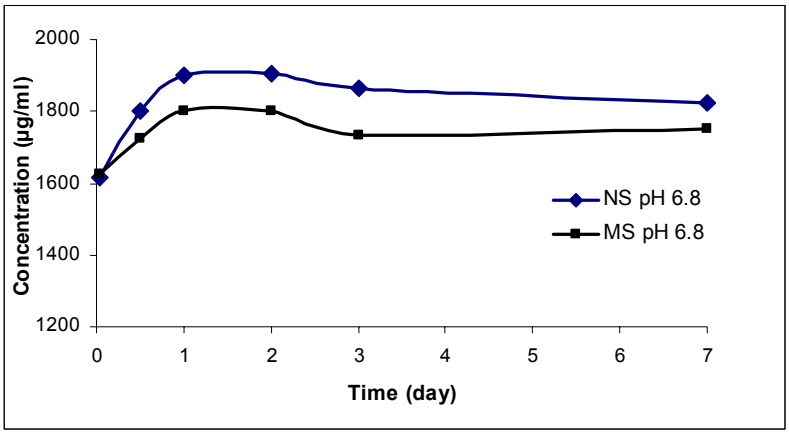

Fig. 5: Saturation solubility of ibuprofen nanocrystals and raw materials in buffer having a pH of 6.8 at 25°C

Similar to the saturation solubility in water, saturation solubility of ibuprofen nanocrystals in buffer at pH 1.2 was also evaluated. In buffer at pH 1.2, solubility was slightly enhanced at day 3 (at steady state conditions) compared to microcrystals. Unlike the saturation solubility in water, the saturation solubility of ibuprofen nanocrystals was initially lower than that of microcrystals. However after 3 days, saturation solubility increased for the nanocrystals and was slightly higher than for microcrystal suspension.

Again, saturation solubility at the early stages (before equilibrium reached) of the study clearly fluctuated due to presence of fine nanocrystals and potentially amorphous fractions of dried ibuprofen as mentioned before.

Chemically structure of ibuprofen is weak acid. Therefore, in a basic solution it will form salts and the solubility will be increased. Solubility of the ibuprofen nanocrystals was compared with ibuprofen microcrystals in buffer solution having a pH of 6.8. In this solution, both ibuprofens will form the salt of ibuprofen and solubility will be increased.

The particle size reduction influenced the saturation solubility of ibuprofen in buffer at pH 6.8. **Fig. 5** shows the enhanced solubility of ibuprofen nanocrystals in comparison to ibuprofen microcrystals. In this medium, the saturation solubility of ibuprofen nanocrystals was 1824±8.4 µg/ml, only slightly higher than the solubility of ibuprofen microcrystals. In the same condition solubility of ibuprofen microcrystals was only 1751±6 µg/ml. The difference in saturation solubility between ibuprofen nanocrystals and microcrystals was assumed by the difference in particle size of both ibuprofens. This result indicates that superiority of drug nanocrystals compared to drug microcrystals points to better physicochemical properties in the drug nanocrystals.

In general it can be concluded that in case of ibuprofen there was not solubility enhancement (water, at buffer pH 1.2) or very little (at buffer pH 6.8). This is well in agreement with the theory, because ibuprofen is not a poorly soluble drug, with solubility up to almost 2000 µg/ml. According to Buckton and other authors, a pronounced increase can only be found for sparingly soluble drugs [10,11,12,13,14,15].

In addition, powder of ibuprofen nanocrystals could completely dissolve in water in a period of 10 minutes. This result was superior to the dissolution velocity of micronized raw material (drug dissolved 62% within 10 minutes). **Fig. 6** reveals superiority of dissolution velocity of ibuprofen nanocrystals in comparison to micronized raw material.

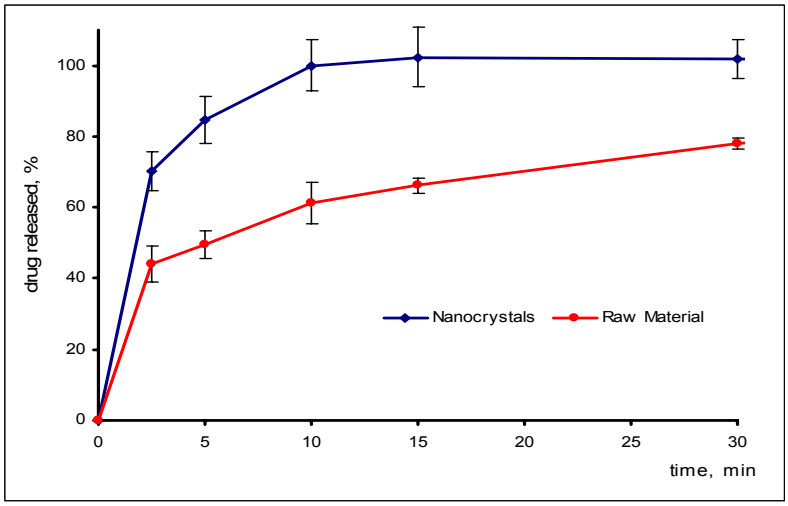

Fig. 6: Dissolution velocity profile of raw material (mean size d50%: 56 µm, LD) and ibuprofen nanocrystals (mean size: 929 nm, PCS) in water

Oral formulations: pellets and effervescent granules

The nanosuspensions were further investigated by incorporation into pellet and effervescent powders. Ibuprofen nanocrystals loaded pellet and effervescent granul were successfully produced. Formulation C of the effervescent formulation has shown the fastest redispersion time (**Table 1**) [10, 16].

Ibuprofen nanocrystals were also incorporated into a pellet formulation. In this formulation, ibuprofen nanosuspension was directly admixed with lactose to form the pellet mass using a mixing pan. In the next step of the process, an extruder and a spheronization were used to generate pellets [10, 16].

Considering the drying process, ibuprofen nanocrystals were agglomerated after spray drying as revealed in **Fig 7**. For this reason, liquid aqueous nanosuspension was directly admixed to lactose to avoid agglomeration of particles. This technique was effective as it enabled the nanosuspension to remain properly re-dispersed as fine particles in water, be incorporated non-aggregated into the pellets and finally be released as fine nanocrystals after dissolution of the pellets, as illustrated in **Fig. 8** (d).

Table 1: Ibuprofen nanocrystal-loaded effervescent granule formulations

Formulation	Composition	
Effervescent A	Nanocrystals	28%
	Mannitol	11 %
	Citric acid	26 %
	Sod Bicarbonat	35 %
Effervescent B	Nanocrystals	28%
	Mannitol	11 %
	Citric acid	22 %
	Sod Bicarbonat	33 %
	Fum. Acid	6 %
Effervescent C	Nanocrystals	28%
	Mannitol	10 %
	Citric acid	24 %
	Sod Bicarbonat	38 %
Effervescent D	Nanocrystals	28%
	Mannitol	16 %
	Citric acid	10 %
	Sod Bicarbonat	30 %
	Tartaric Acid	16 %
Pellet	Nanocrystals	33.3%
	Lactose	66.7%

Effervescent granule is one of the solid dosage forms in which nanocrystals can be incorporated. Theoretically, effervescent formulations consist of an acid source and a gas source. In this research, simple effervescent formulations were chosen for ease of preparation in a laboratory. There are many methods for producing effervescent granule, in this study the fusion method was employed to produce the final product. The composition of the effervescent granule formulations can be seen in **Table 1** [10, 16].

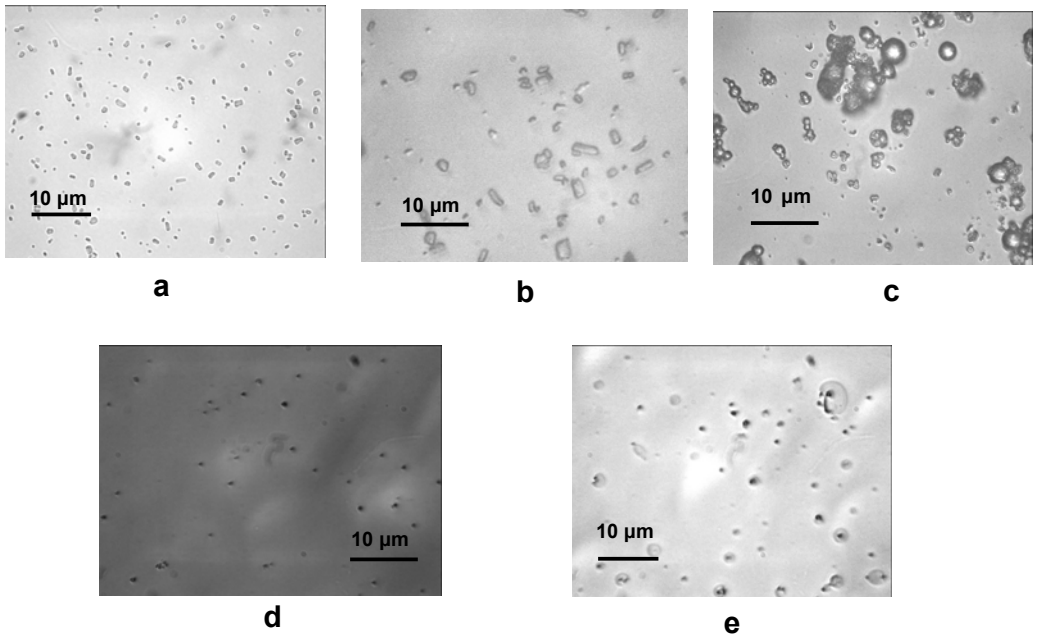

Fig. 7: Light microscopic pictures of ibuprofen nanosuspension (a), dried nanocrystals after spray-drying (b), dried nanocrystals after lyophilization (c), re-dispersed nanocrystals from pellets (d) and re-dispersed nanocrystals from effervescent granule (e)

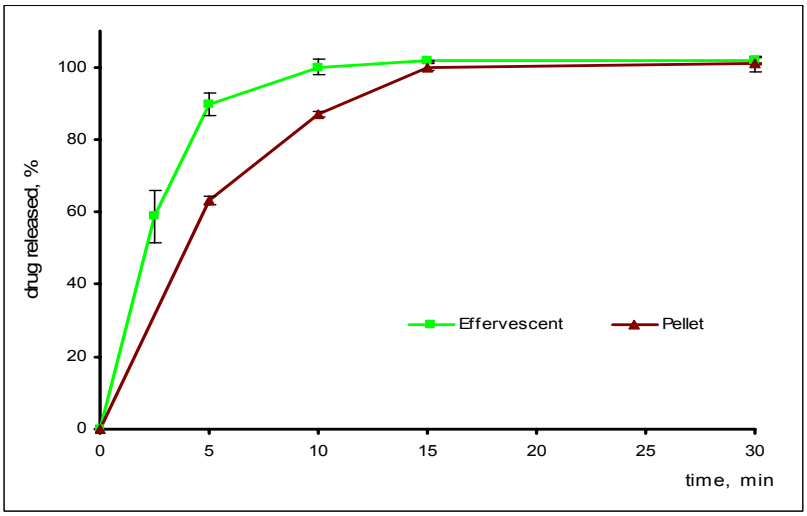

Fig. 8: Dissolution velocity profile of ibuprofen nanocrystals from effervescent formulation C and pellet formulations in water (detailed compositions of the effervescent formulations are given in Table 1)

Under the same condition, releasing ibuprofen nanocrystals from effervescent or pellets dosage form was also investigated. Ibuprofen nanocrystals were dissolved completely from the effervescent and pellet formulation. Within 15 minutes 100% of the ibuprofen nanocrystals could be dissolved from the pellet formulation (**Fig. 8**). This was a little slower than the dissolution velocity of the effervescent formulation. However, dissolution of the effervescent formulation was superior even compared to the dissolution of the raw material **(Fig. 8).** Accordingly, incorporation of ibuprofen nanocrystals into pellet and effervescent formulations does not delay the release of ibuprofen from these dosage forms [10, 16].

CONCLUSION

Stable ibuprofen nanocrystals can be produced by high pressure homogenization. Ibuprofen nanocrystals was not solubility enhancement (water and buffer pH of 1.2) or very little (buffer pH of 6.8). The incorporation of these nanocrystal into effervescent and pellet formulations lead to very little size increase after redispersion. The ibuprofen nanocrystals dissolved completely within 15 min from both dosage forms.

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