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 redispersability, 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 Caliva Model 10 (Caleva, Sturminster Newton, UK) and a spherizer Caliva Model 120 (Caleva, Sturminster Newton, UK). Dissolution test was performed with a Pharmatest PTW III (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.¹⁻⁴

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, dysmenorrhea, 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 (Bechtereeve 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. periarticular spasm of the shoulder) NSAID can be beneficial; however, it has not been demonstrated whether they represent advantages in comparison with other methods of treatment.¹⁻⁴

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 redispersability, 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, Belgium), Poloxamer™ 188 (BASF Aktiengesellschaft GmbH, Ludwighafen, Germany) and Polyvinyl Alcohol (PVA) (Wt. 90.000 (Sigma Aldrich GmbH, Deisenhofen, Germany) were used to stabilize nanosuspensions. Double-distilled 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 bar at 5°C. To construct particle size reduction profile, samples were withdrawn after each five cycles. The particle sizes were analyzed by laser diffractionmetry (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 (r) index: 1.46, imaginary r 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 drying 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 to number 2, the aspirator was set to number 10 (-30 mbar). The atomizing airflow was set at 800 L/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 dioxide. This causes the softened mass of the powder to become promptly and tightly sealed.

**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, Spherosorb ODS 5 mm (dimension), 20 cm (length); mobile phase: methanol/Na,HPO4 0.01 M (25%); flow rate, 1.0 mL/min; UV/Vis detector; λmax at 220nm.

**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. 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).

Due to the presence of poloxamer 188 in the nanosuspensions, 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.

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](image)

**Oral formulations: pellets and effervescent granules**

The nanosuspensions were further investigated by incorporation into pellet and effervescent powders. Ibuprofen nanocrystals loaded pellet and effervescent granular 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 in 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 granules formulations**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Composition</th>
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<tbody>
<tr>
<td>Effervescent A</td>
<td>Nanocrystals 28%</td>
</tr>
<tr>
<td></td>
<td>Mannitol 11%</td>
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<tr>
<td></td>
<td>Citric acid 26%</td>
</tr>
<tr>
<td></td>
<td>Sod Bicarbonat 35%</td>
</tr>
<tr>
<td>Effervescent B</td>
<td>Nanocrystals 28%</td>
</tr>
<tr>
<td></td>
<td>Mannitol 11%</td>
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<td></td>
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<tr>
<td></td>
<td>Fum. Acid 6%</td>
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<tr>
<td>Effervescent C</td>
<td>Nanocrystals 28%</td>
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<tr>
<td></td>
<td>Mannitol 10%</td>
</tr>
<tr>
<td></td>
<td>Citric acid 24%</td>
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<tr>
<td></td>
<td>Sod Bicarbonat 38%</td>
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<tr>
<td>Effervescent D</td>
<td>Nanocrystals 28%</td>
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<tr>
<td></td>
<td>Mannitol 16%</td>
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<tr>
<td></td>
<td>Citric acid 10%</td>
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<tr>
<td></td>
<td>Sod Bicarbonat 30%</td>
</tr>
<tr>
<td>Pellet</td>
<td>Nanocrystals 33.3%</td>
</tr>
<tr>
<td></td>
<td>Lactose 66.7%</td>
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</tbody>
</table>

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.
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.\textsuperscript{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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