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Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine

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Abstract

Poorly water-soluble drugs such as nifedipine (NIF) (∼20 μg/ml) offer challenging problems in drug formulation as poor solubility is generally associated to poor dissolution characteristics and thus to poor oral bioavailability. In order to enhance these characteristics, preparation of nifedipine nanoparticles has been achieved using high pressure homogenization. The homogenization procedure has first been optimized in regard to particle size and size distribution. Nanoparticles were characterized in terms of size, morphology and redispersion characteristics following water-removal. Saturation solubility and dissolution characteristics were investigated and compared to the un-milled commercial NIF to verify the theoretical hypothesis on the benefit of increased surface area. Crystalline state evaluation before and following particle size reduction was also conducted through differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to denote eventual transformation to amorphous state during the homogenization process. Through this study, it has been shown that initial crystalline state is maintained following particle size reduction and that the dissolution characteristics of nifedipine nanoparticles were significantly increased in regards to the commercial product. The method being simple and easily scaled up, this approach should have a general applicability to many poorly water-soluble drug entities.

Keywords: Nanoparticles; Drugs; High pressure homogenization; Dissolution; Crystalline state; Nifedipine

1. Introduction

Together with membrane permeability, the solubility/dissolution behaviour of a drug is a key determinant to its oral bioavailability, the latest frequently being the rate-limiting step to absorption of drugs from the gastrointestinal tract. Since an increasing number of newly developed drug candidates present poor water-solubility, approaches to overcome this factor are of great importance in drug formulation. Nifedipine (NIF) (Fig. 1), a highly potent calcium-channel blocker

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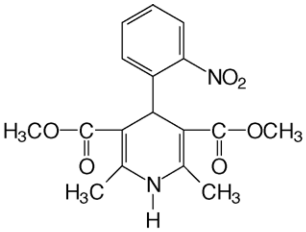

Fig. 1. Chemical structure of nifedipine (1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine-dicarboxylic acid dimethyl ester).

belonging to the group of 1,4-dihydropyridines widely used in the treatment of vascular diseases such as hypertension and angina pectoris, was used as a model drug.

Formulations approaches that have been reported, with mixed results, for dissolution rate enhancement of NIF include compaction with hydroxypropylmethylcellulose (HPMC) (Mitchell et al., 2003), cogrinding with HPMC (Sugimoto et al., 1998) or bile salts (Suzuki et al., 2001), formation of solid dispersions as coprecipitates or coevaporates with mannitol (Zajc et al., 2005), phosphatidylcholine esters (Yamamura and Rogers, 1996), HPMC (Cilurzo et al., 2002), chitosan derivatives (Portero et al., 1998), polyethylene glycols (Lin and Cham, 1996; Sencar-Bozic et al., 1997) and polyoxyethylene–polyoxypropylene copolymers (Vippagunta et al., 2002), and inclusion complexes with beta-cyclodextrins (Hirayama et al., 1994; Bayomi et al., 2002).

In addition to the general solubility enhancement techniques described above, drug particle size reduction has often been used, in regards to the Noyes–Whitney and Ostwald–Freundlich equations, to enhance dissolution and solubility characteristics of poorly water-soluble compounds (Hintz and Johnson, 1989; Lu et al., 1993; Kondo et al., 1993a,b; Mosharraf and Nyström, 1995). Although micronization of drugs to micrometer-range sizes has been shown insufficient in this purpose (Müller et al., 2001), formation of drug nanoparticles is actually a very promising approach. Particle size reduction to the nanometer-range can be achieved through high pressure homogenization (HPH). This technique has been extensively described relative to particle size reduction efficiency by Müller et al. in respect with reproducibility (Grau et al., 2000) and processing of highly concentrated suspensions (Krause and Müller, 2001). It presents various advantages over other milling techniques as it is very simple, time-saving and is a solvent-free process.

In this study, HPH was evaluated for NIF nanoparticle preparation. NIF nanoparticles were assayed for their dissolution and solubility behaviour to confirm theoretical enhancement predictions. NIF crystalline state was also evaluated before and following particle size reduction as another advantage of nanoparticulate systems relative to other dissolution rate-enhancing methods, such as solid dispersions, is that initial crystalline state shall be maintained; the method thus not relying on the presence of the amorphous form of the drug, which is characterized by long-term time instability, for the solubility/dissolution rate increase. Optimization of formulations has also been achieved through dispersion of nanoparticles in highly hydrophilic carriers such as mannitol to prevent particle agglomeration in powdered state and further increase dissolution characteristics. This agglomeration phenomenon, inherent to nanoparticulate systems, was thought in various in vivo studies, to limit the dissolution rate enhancement advantage procured by particle size reduction (Liversidge and Cundy, 1995).

2. Materials and methods

2.1. Materials

NIF was purchased from Indis (Aarteselaar, Belgium). Methocel E15 (hydroxy-propylmethyl-cellulose) was purchased from Colorcon (West Point, PA, USA). Mannitol was purchased from Roquette (Roquette Frères, Lestrem, France). Water used was obtained through a CFOF 01205 Milli-Q Water Purification System (Millipore Corporation, Bedford, MA, USA). The other materials were of analytical reagent grade.

Nifedipine being a highly photolabile compound, all experiments were performed under subdued light; the photodegradation rate constant being indeed found to increase with decreasing particle size when NIF is in powder state (Teraoka et al., 1999).

2.2. Preparation of samples

The steps in the preparation of drug nanoparticles were as follows.

2.2.1. Formation of drug nanosuspensions

Nifedipine powder was poured in an aqueous surfactant solution (5% NIF, w/v, suspensions) under magnetic stirring (500 rpm). After dispersion, a first size-reduction step using an Ultra-Turrax T25 Basic homogenizer (IKA-Werke, Staufen, Germany) at 24,000 rpm (10 min for a 50 ml sample) was conducted on the suspension (in an ice bath to prevent sample temperature increase). Nanosuspensions were then prepared using an EmulsiFlex-C5 high pressure homogenizer (Avestin Inc., Ottawa, Canada). Pre-milling low pressure homogenization cycles (C) were first conducted on the NIF suspension to further decrease particle size (15C 7000 PSI–10C 12,000 PSI). High pressure homogenization was then finally applied for 20 cycles at 24,000 PSI. Since HPH causes sample temperature increase (increase of 30 °C following 20C at 24,000 PSI), all operations were carried out using an heat exchanger, placed ahead of the homogenizing valve, with sample temperature maintained at 10 ± 1 °C. Samples were withdrawn after the different size reduction steps for size distribution analysis.

2.2.2. Water-removal

Spray-drying using a Büchi B191a Mini Spray-Dryer (Büchi, Flawil, Switzerland) was applied in order to retrieve nanoparticles in dried-powder state from the nanosuspensions described above. Suspensions were passed at a spray rate of 3.5 ml/min. The drying temperature was set at 115 °C. Spray airflow was set at 800 l/h and drying airflow was set at 35 m^3/h.

2.3. Particle size and shape characterization

Size and size distribution of the particles in suspension following the different homogenization steps and in dried state following water redispersion were determined through laser diffraction (LD), with a wet sampling system (MasterSizer 2000, Malvern Instruments, Worcestershire, UK) and the diameters reported were calculated using volume distribution (three sets of five measurements). The median volume particle size, $d(v;\,0.5)$ (size of the particles for which 50% of the sample volume contains particles smaller than "*d* 0.5", the other particles being larger than "*d* 0.5"), $d(v;\,0.1)$ and $d(v;\,0.9)$ were used as characterization parameters. Estimated specific surface areas of dispersed particles (m^2/g) were also retrieved from LD data. A refractive index of 1.54 was used for measurements. Morphological evaluation of nanoparticles was conducted through scanning electron microscopy (SEM) (JSM-6100, JEOL, Tokyo, Japan) following platinum coating.

2.4. Dissolution

A Distek 2100C USP dissolution apparatus (Distek Inc., North Brunswick, NJ, USA) Type II (paddle method) at rotation speed of 60 rpm was used for in vitro testing of drug dissolution from the various formulations. Dissolution was carried out on an equivalent of 10 mg of nifedipine (in powder state). Deionized water (0.05% polysorbate 20) was used as the dissolution medium. The volume, pH and temperature of the dissolution medium were 900 ml, 7.0 and 37.0 ± 0.2 °C, respectively. Automatic withdrawals at fixed times were filtered in-line and assayed through ultraviolet absorbance determination at 235 nm using an Agilent 8453 UV/vis Dissolution Testing System (Agilent, USA). The mean results of triplicate measurements and the standard deviation were reported.

2.5. Solubility

Saturation solubility measurements were assayed through ultraviolet absorbance determination at 235 nm using an Agilent 8453 UV/vis Spectrophotometer (Agilent). Fifty millilitres of suspensions (water pH 7.0–0.05% polysorbate 20) (nifedipine content = 2 mg/ml) prepared from NIF in powder state, was placed at a temperature of 37 ± 0.1 °C and shaked at 150 min^{-1} using a GFL 1086 shaker—thermostatic cabinet (Labortechnik, Burgwedel, Germany). Both micro- and nanosuspensions were filtered using 0.1 μm Millex-VV PVDF filters (Millipore Corporation) prior to analysis. The mean results of triplicate measurements and the standard deviation were reported.

2.6. Crystalline state evaluation of dried samples

2.6.1. Differential scanning calorimetry (DSC)

Thermal properties of the powder samples were investigated with a Perkin-Elmer DSC-7 differential scanning calorimeter/TAC-7 thermal analysis controller with a intracooler-2 cooling system (Perkin-Elmer Instruments, USA). The amount of product to be analyzed shall range from 3 to 5 mg and be placed in perforated aluminium sealed 50 μl pans. Heat runs for each sample has been set from 40 to 200 °C at 5 °C/min, using nitrogen as blanket gas. The apparatus is indium/cyclohexane calibrated.

2.6.2. *Powder X-ray diffraction (PXRD)*

PXRD diffractograms of each of the excipients, and all of the un-milled and milled nifedipine formulations were recorded using a Siemens Diffractometer D5000 (Siemens, Germany) with a Cu line as the source of radiation. Standard runs using a 40 kV voltage, a 40 mA current and a scanning rate of 0.02° min^{-1} over a 2θ range of 3–40° were used.

3. Results and discussion

Commercial nifedipine used for this study was characterized by relatively large particles ($d(v;\ 0.5)$ about 100 μm as reported in Table 1) and had to follow preliminary size reduction steps prior to high pressure homogenization operation as the homogenizing gaps of the homogenizer are too small at the homogenizing pressures used (i.e. 25 μm at 22,000 PSI; Müller et al., 2001). Table 1 shows the results of size analysis following the different size reduction steps and indicate that the low pressure pre-milling homogenization cycles are not sufficient for adequate particle size reduction achievement as they only yield a small percentage of sub-micrometer sized particles (18% in volume below 1 μm). High pressure homogenization cycles were found necessary in that regard; yielding a nanoparticle population with a $d(v;\ 0.5)$ around 300 nm and 86% (in volume) of the particles below 1 μm. The small fraction of microparticles left after the HPH cycles, responsible for a bimodal size distribution curve, indicate the limitations of the apparatus. These microparticles can eventually be eliminated by simple centrifugation.

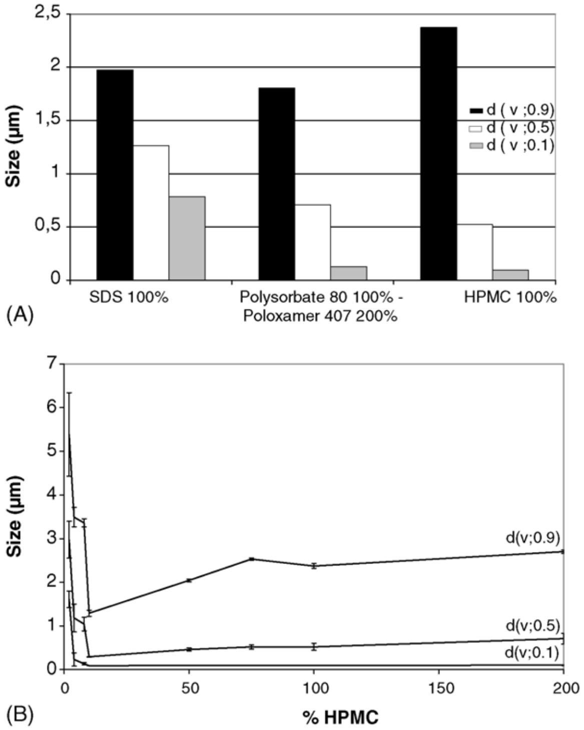

Fig. 2. (A) Influence of type of surfactant and (B) influence of HPMC % on NIF particle size reduction efficiency (all % expressed relative to NIF content, w/w).

HPMC of low viscosity grade was used for the suspension's stabilization as this water-soluble polymer offers adequate surface active properties when compared to other commonly used surfactants such as sodium dodecyl sulphate, polysorbates and poloxamers (ethylene oxide/propylene oxide copolymer). Indeed, a surfactant being necessary for nanoparticle stabilization after the homogenization operation, HPMC was found to yield the best results in regards to NIF particle size reduction efficiency (Fig. 2A). Furthermore, HPMC also has the advantage of having a high melting point when compared to polysorbates and poloxam-

Table 1
LD results following successive size reduction steps for a nifedipine 5%–HPMC 0.5% (w/w) suspension

Milling operation	$d(v;\ 0.5) \pm$ S.D. (μm)	$d(v;\ 0.1) \pm$ S.D. (μm)	$d(v;\ 0.9) \pm$ S.D. (μm)
No milling	98.7 ± 0.4	21.9 ± 0.2	267.2 ± 0.5
Turrax® milling	15.7 ± 0.3	3.07 ± 0.17	51.6 ± 0.4
Pre-milling HPH	2.43 ± 0.09	0.509 ± 0.017	5.20 ± 0.25
HPH 24,000 PSI	0.291 ± 0.006	0.089 ± 0.003	1.29 ± 0.07

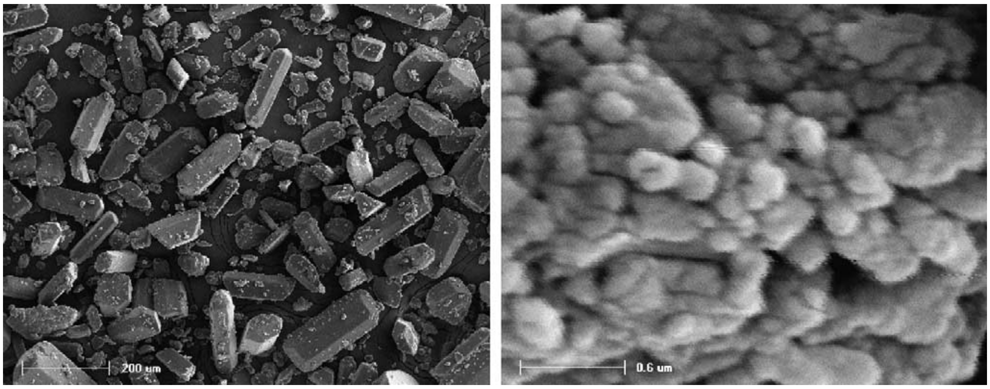

Fig. 3. SEM micrographs of un-milled commercial nifedipine (left) (magnification 100×; scale = 200 μm); spray-dried nifedipine nanosuspension (right) (magnification 40,000×; scale = 0.6 μm).

ers; a low melting point being problematic during the spray-drying operation (particle agglomeration) particularly if no carriers are used. An HPMC concentration of 10% (w/w) relative to nifedipine content was found optimal (Fig. 2B), over a range of 2–200%, in regards to particle size reduction and to suspension processing (i.e. increase in sample viscosity with increasing HPMC %).

NIF nanoparticles being prepared in a suspension state, water needs to be removed after the homogenization operation in order retrieve particles in a powder state for storage purpose and for the various assays conducted. As expected, nanoparticle agglomeration following the water-removal operation is clearly observed on SEM micrographs of Fig. 3 and represented through particle size analysis after redispersion (Fig. 4; Table 2) where the nanoparticle population has completely disappeared (% of particles in volume below 1 μm < 1%) leaving a population with a $d(v; 0.5)$ around 4 μm. This agglomeration leading to a decrease in specific surface area (Table 2) and thus to a predicted decrease in dissolution rate, a water-soluble carrier was used to prevent this phenomenon; its role being to recrystallize around NIF nanoparticles during the water-removal operation, thus preventing particle interaction and agglomeration. The carrier used was mannitol, added at 100% (w/w) relative to nifedipine content (Table 3) prior to the spray-drying operation. Fig. 4 and Table 2 show the results of size analysis following water-redispersion (magnetic stirring 300 rpm for 10 min) for mannitol and mannitol-less formulations. The influence of the carrier was clearly shown to be beneficial and critical regarding prevention of nanoparticle agglomeration as original particle size is restored. Mannitol, being a highly water-soluble compound, shall also procure the advantage of creating a highly hydrophilic environment around NIF nanoparticles.

Dissolution profiles for nifedipine un-milled crystals and nifedipine nanoparticles for mannitol-less and mannitol-added formulations are shown in Fig. 5. Comparison of the profiles obtained for the mannitol-less formulation and un-milled NIF clearly shows the dissolution rate enhancement obtained with nano-sized systems as 95% of the drug is dissolved following 60 min to 5% for the un-milled drug. Complete dissolution coming after about 90 min for nifedipine nanoparticles.

Table 2
LD results following water-redispersion of spray-dried formulations A and B

Formulation	$d(v; 0.5) \pm$ S.D. (μm)	$d(v; 0.1) \pm$ S.D. (μm)	$d(v; 0.9) \pm$ S.D. (μm)	Below 1 μm (%)	Estimated specific surface area (m^2/g)
Before spray-drying	0.291 ± 0.006	0.089 ± 0.003	1.29 ± 0.07	86	29.9
Spray-dried formulation A	3.70 ± 0.09	1.73 ± 0.04	8.60 ± 0.33	<1	1.88
Spray-dried formulation B	0.339 ± 0.006	0.093 ± 0.002	1.60 ± 0.04	80	27.5

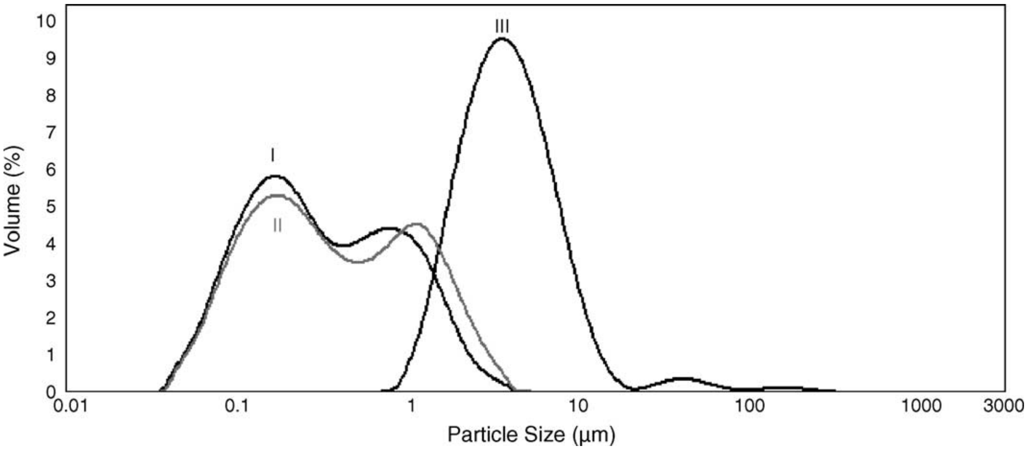

Fig. 4. LD volume size distribution curves prior to spray-drying (I) and after water-redispersion (magnetic stirring: 300 rpm for 10 min) of spray-dried formulations A (II) and B (III).

Fig. 5 also reports the influence of HPMC, a hydrophilic polymer, on un-milled drug dissolution characteristics. HPMC was shown to only slightly enhance the dissolution of un-milled nifedipine when both were physically mixed; the effect being more pronounced following hydrophylization of the drug particles (spray-dried formulation A prior to size reduction operations), as these are now homogeneously coated with the water-soluble polymer.

NIF micrometer-sized particles, obtained after Turrax® milling ($d(v; 0.5) = 15\ \mu m$), were also assayed for their dissolution behaviour (Fig. 5). The approximate 10-fold decrease in particle size from the un-milled commercial NIF, accompanied by a surface area increasing from 0.134 to 0.758 m^2/g, yielded a 19-fold increase in dissolution rate (DR) at the beginning of dissolution (0.019–0.366 mg/min). Although the DR enhancement is clearly shown, it is still limited and smaller than the one obtained with NIF nanoparticles (1.09 and 3.77 mg/min for formulations A and B, respectively), this mainly due to higher specific surface area achievement with the latest (1.88 and 27.5 m^2/g for formulations A and B, respectively; Table 2).

Dissolution profiles for mannitol-less and mannitol-added NIF formulations are also compared on Fig. 5. This water-soluble additive is shown to further increase the NIF nanoparticle DR as 75% of the drug is already dissolved after 2 min versus 20% for formulation A. Complete dissolution being reached after only 10 min versus 90 min for formulation A. The difference observed between formulations A and B shall be attributed to the fact that mannitol acts as a carrier preventing particle agglomeration during the spray-drying operation (Fig. 4; Table 2) and that it creates a highly hydrophilic environment around NIF nanoparticles beneficial for drug dissolution. No correlations can be made between surface areas and DR for both systems as surface areas have been estimated through LD data and that, for formulation A, it is not representative of the effective surface area directly in contact with the dissolution medium. Formulation A is in fact represented by agglomerates of nanoparticles thought to show high porosity and thus having an effective surface area greater than the 1.88 m^2/g value found. Direct correlations will only be found when agglomeration is limited as in the case of formulation B versus un-milled NIF, where an approximate 200-fold increase in surface results in a 200-fold increase in DR.

Table 3
Nifedipine formulations A and B

Formulation A	
Nifedipine	5%
Methocel E15	0.5%
H_2O	Ad 100%
Formulation B	
Nifedipine	5%
Methocel E15	0.5%
Mannitol	5%
H_2O	Ad 100%

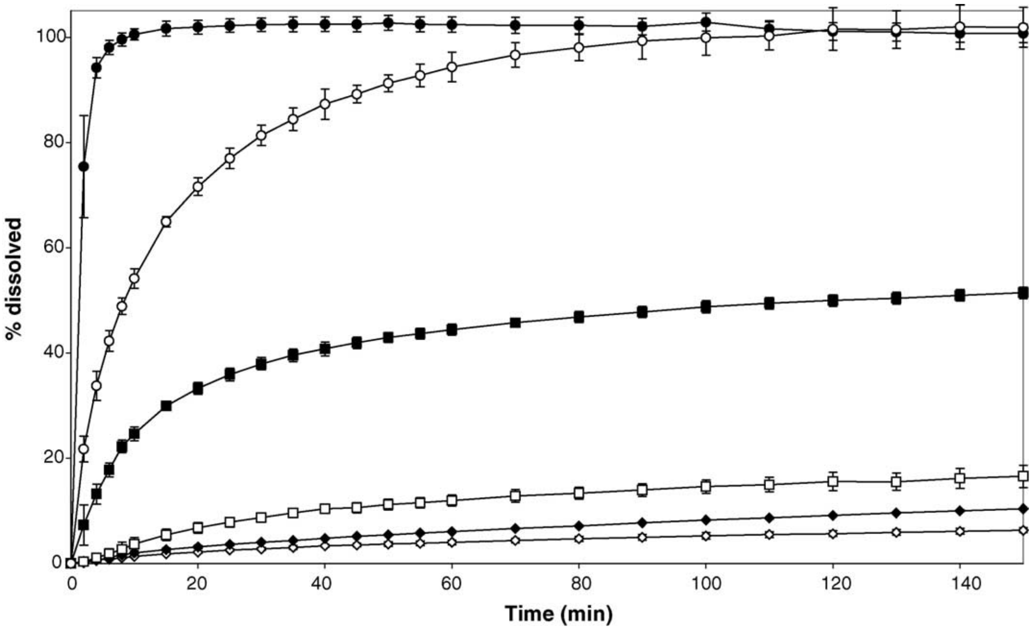

Fig. 5. Dissolution profiles for: (◊) un-milled commercial NIF; (⧫) NIF/HPMC, 10:1 (w/w) physical mixture (mortar); (□) spray-dried formulation A (no milling); (■) spray-dried formulation A (Turrax® milling); (○) spray-dried formulation A (HPH milling); (●) spray-dried formulation B (HPH milling).

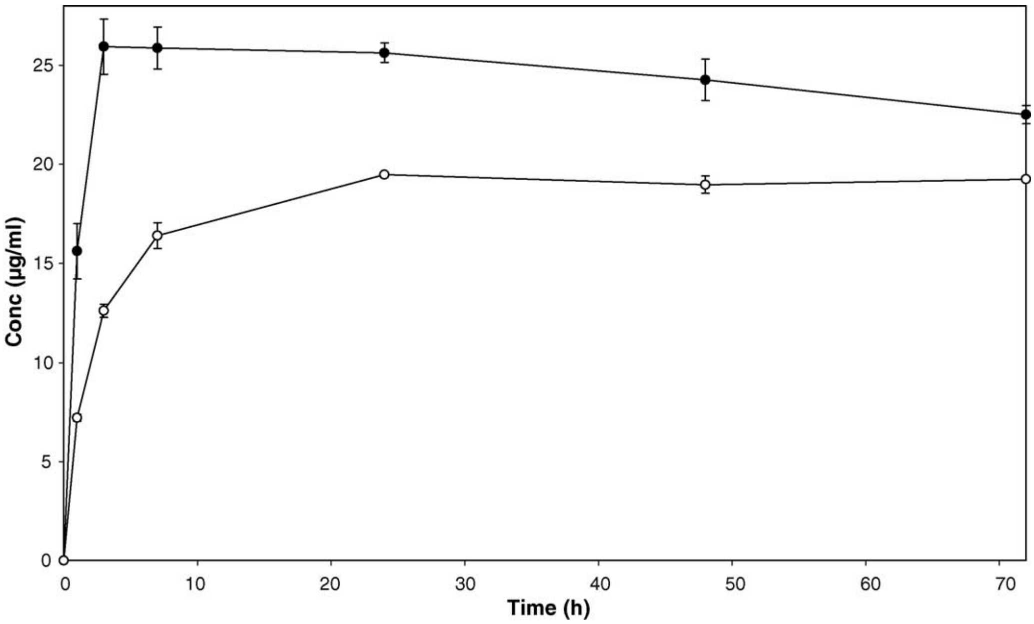

Fig. 6. Kinetics to saturation solubility achievement (37 °C) for: (○) un-milled commercial NIF and (●) and spray-dried formulation B (HPH milling).

Besides the obvious DR enhancement characteristics, NIF nanoparticles also show, to a lesser extent, increased saturation solubility when compared to the un-milled commercial drug (Fig. 6). At 37 °C, commercial NIF shows a water-solubility of 19.5 ± 0.1 μg/ml; concentration reached after 24 h. For NIF nanoparticles, a concentration of 25.9 ± 1.4 μg/ml was reached after 3 h. This concentration was, however, further shown to decrease slowly with time indicating achievement of a super-saturated NIF media.

In order to verify that this dissolution rate/solubility enhancement is not due to the presence of NIF

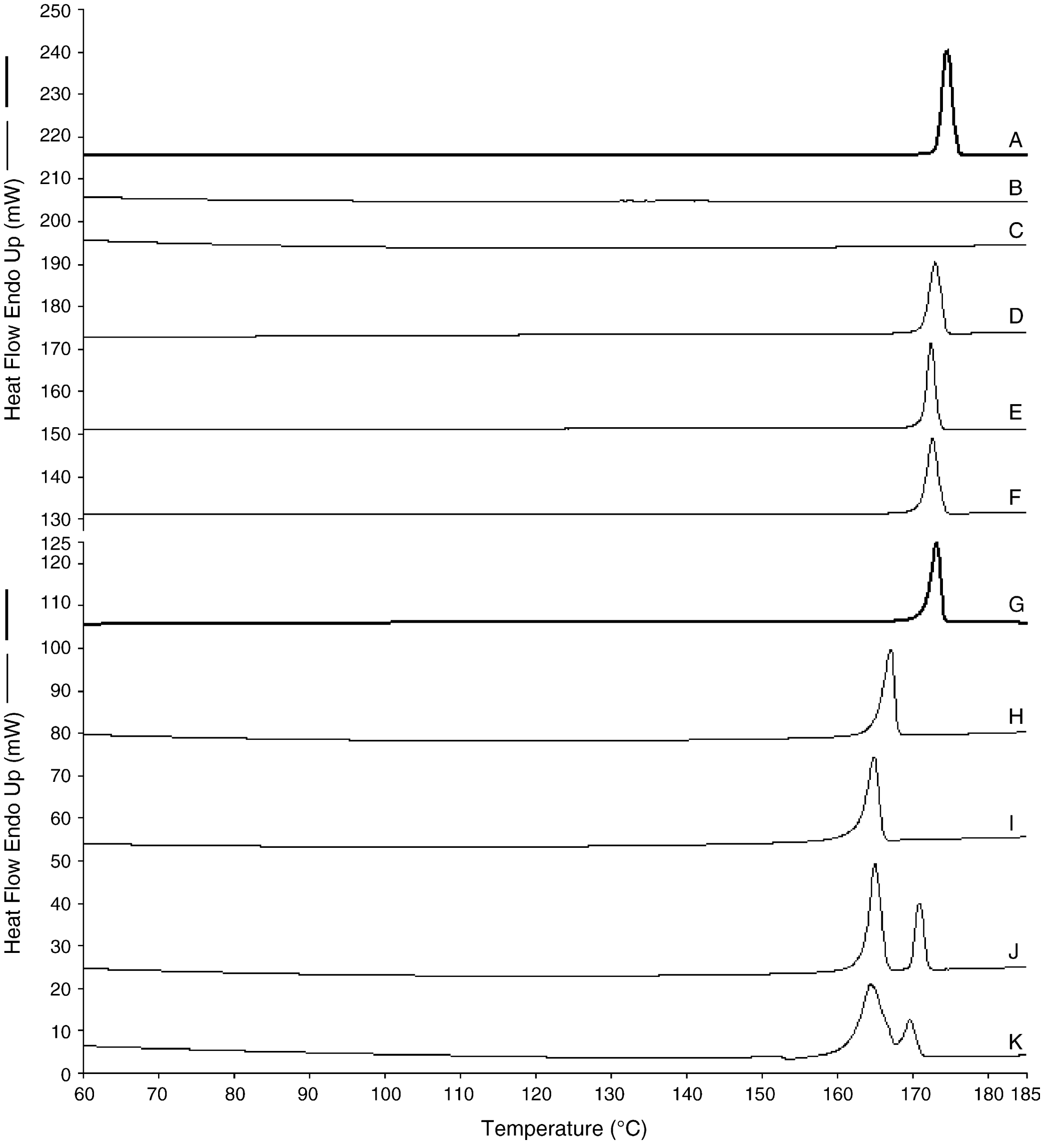

Fig. 7. DSC thermograms for: (A) un-milled commercial NIF; (B) HPMC; (C) spray-dried HPMC; (D) NIF/HPMC, 10:1 (w/w) physical mixture (mortar); (E) spray-dried formulation A (no-milling); (F) spray-dried formulation A (Turrax® milling); (G) spray-dried formulation A (nanoparticles); (H) mannitol; (I) spray-dried mannitol; (J) NIF/HPMC/mannitol, 10:1:10 (w/w) physical mixture (mortar); (K) spray-dried formulation B (nanoparticles).

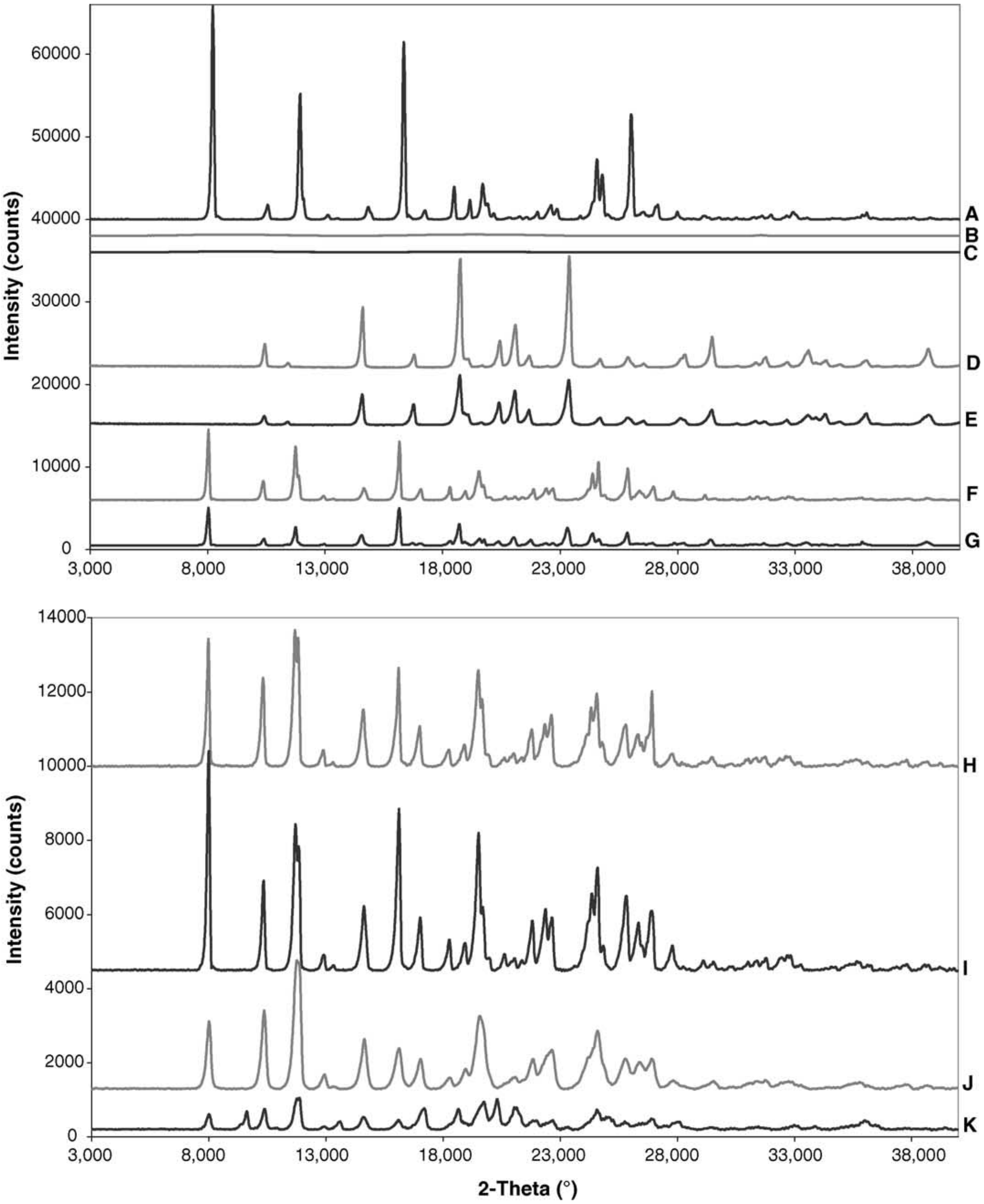

Fig. 8. PXRD diffractograms for: (A) un-milled commercial NIF; (B) HPMC; (C) spray-dried HPMC; (D) mannitol; (E) spray-dried mannitol; (F) NIF/HPMC, 10:1 (w/w) physical mixture (mortar); (G) NIF/HPMC/mannitol, 10:1:10 (w/w) physical mixture (mortar); (H) spray-dried formulation A (no-milling); (I) spray-dried formulation A (Turrax® milling); (J) spray-dried formulation A (nanoparticles); (K) spray-dried formulation B (nanoparticles).

Table 4
Influence of HPMC % (w/w, relative to NIF content) on PXRD peak intensity (counts–height) of NIF nanoparticles for given diffraction angles (2θ)

HPMC (%)	8.00°	10.34°	11.72°	14.62°	16.04°	19.58°	22.62°	24.60°
2	3171	3581	5586	2216	1703	3301	1888	2703
10	2783	2976	4950	1873	1319	3049	1600	2354
20	2687	2963	4528	1806	1294	2600	1462	2171
40	2428	2542	4144	1586	1174	2455	1278	1957

amorphous form, crystalline state evaluation of NIF nanoparticles was carried out. Three polymorphic forms of NIF have been identified through thermal analysis (Keymolen et al., 2002) and confirmed in our laboratory. Polymorphic form I present a melting peak at 172 °C, form II at 163 °C and form III at 140 °C; form I being the most stable polymorphic form, which is generally characterized by the lowest solubility. As it is shown on the DSC thermograms of Fig. 7, both NIF un-milled commercial product and NIF nanoparticles are present as polymorphic form I. The peaks were found to be nearly identical, with a calculated ΔH around 110 J/g for both un-milled NIF and NIF nanoparticles. The only difference observed was a slight shift in fusion temperature (174–173 °C) and a broadening of the peaks. These modifications were attributed to the presence of HPMC as we can clearly see on the other thermograms (Fig. 7D and E); decrease in particle size not showed to influence (Fig. 7F and G). These differences were further enhanced in the presence of mannitol (Fig. 7J and K), where the dilution of NIF particles is even higher.

PXRD diffractograms of Fig. 8 confirm that the high pressure homogenization operation does not interfere with NIF crystalline state as the diffraction pattern for NIF is conserved for nanoparticles. The only difference observed between un-milled NIF and NIF nanoparticles lies in peaks intensities, which was found smaller for nanoparticles. Here again, this difference was attributed to the presence of HPMC in the formulation. As we can see on Fig. 8, peaks intensities are in fact reduced for a NIF/HPMC physical mixture (Fig. 8F) and even further reduced for a spray-dried NIF/HPMC suspension prior to milling operations (Fig. 8H), where HPMC is thought to be more evenly distributed around NIF particles. The diffraction pattern and indeed the peak intensity for the latest were found similar for the spray-dried NIF nanoparticles (formulation A). Particle size, as observed for Turrax®-milled NIF, was not shown to alter peak intensity. Table 4 shows the influence of HPMC % relative to NIF in regards to peak intensity, which is clearly shown to decrease with increasing HPMC %. As expected from the observations presented above, spray-dried NIF nanoparticles (formulation B) show further decrease in peak intensity as dilution of the particles in mannitol is even higher than with HPMC. These results confirm that the reduction in peak intensity is essentially due to dilution of the particles in the additives (i.e. surfactant, carrier) rather than from particle size reduction or any change of the polymorphic form of the active ingredient.

Another interesting feature represented by the DSC thermograms of Fig. 7H and I and PXRD diffractograms of Fig. 8D and E is that mannitol is found to be crystalline which shall be of relevant importance when considering stability of formulation B NIF nanoparticles.

4. Conclusions

Through this study, it has been shown that formulation of nifedipine as nanoparticles has met great success in regards to dissolution rate and saturation solubility enhancement. High pressure homogenization was shown to be a simple and adequate operation for particle size reduction and is a technique that shall have general applicability depending on hardness of drug and adequate stabilizer utilization. Furthermore, crystalline state of NIF was shown not to be altered through particle size reduction, and shall be of great importance when considering long-term time stability of NIF formulations. Future work shall consist in permeation studies on cell lines and in the evaluation of in vivo pharmacokinetic properties of NIF nanoparticulate systems. Study of bioadhesive properties of these systems shall also be carried out.

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