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Nanosuspensions of poorly soluble drugs: Preparation and development by wet milling

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ABSTRACT

Nanosizing techniques are important tools for improving the bioavailability of water insoluble drugs. Here, a rapid wet milling method was employed to prepare nanosuspensions: 4 types of stabilizers at 4 different concentrations were tested on 2 structurally different drug compounds: indomethacin and itraconazole. Photon correlation spectroscopy (PCS) results showed that the finest nanosuspensions were obtained when 80 wt% (to drug amount) pluronic F68 was the stabilizer for indomethacin and 60 wt% pluronic F127 for itraconazole. Compared to physical mixtures, dissolution rates of the nanosuspensions showed significant increases. The morphology of nanoparticles was observed by transmission electron microscopy (TEM). Crystalline state of the drugs before and after milling was confirmed using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). The physical and chemical stabilities of the nanosuspensions after storage for 2 months at room temperature and at 4 °C were investigated using PCS, TEM and HPLC. No obvious changes in particle size and morphology and no chemical degradation of the drug ingredients were seen.

1. Introduction

Poorly water-soluble drugs pose a great challenge in drug formulation development (Kipp, 2004; Keck and Müller, 2006; Dai et al., 2007). The low saturated solubility and dissolution velocity lead to poor bioavailability. With the increasing number of newly developed lipophilic drug compounds, many techniques have been proposed, such as solid dispersions, cosolvents, emulsions, liposomes and nanoparticles based on lipidic or polymer carriers. However, the use of large amounts of excipients or organic solvents is limited in pharmaceutical formulations due to possible toxicity of the compounds.

Nanosuspension is a sub-micron colloidal dispersion of drug particles which are stabilized by surfactants, polymers or a mixture of both (Chingunpituk, 2007). This formulation has a high drug loading, low incidence of side effects by the excipients, and low cost (Date and Patravale, 2004). Owing to the increased surface-to-volume ratio of the nanocrystals, an increase in saturated solubility and very fast dissolution rate can be seen, especially below particle sizes of 1 μm (Müller and Peters, 1998). Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of the drug and thereby enhancing its absorption (Kayser et al., 2003). Another pronounced advantage is that there are many administration routes for nanosuspensions, such as oral (Kesisoglou et al., 2007), parenteral (Xiong et al., 2008; Wong et al., 2008), pulmonary (Jacobs and Müller, 2002), dermal (Mishra et al., 2009) and ocular (Kassem et al., 2007).

Nanosuspensions can be obtained either by particle size reduction of larger crystals to nano-size (top-down approach) or by the precipitation of dissolved molecules into solid particles (bottom-up approach) (Van Eerdenbrugh et al., 2008). In wet milling technique, a typical top-down approach, the mechanical grinding by media milling pearls in water is used to obtain drug/stabilizer suspensions. Compared to other nanosizing techniques, wet milling avoids organic solvents and is easy to scale-up.

So far, four nanoformulations manufactured by wet milling are on the market (Van Eerdenbrugh et al., 2008). Another new formulation (INVEGA® SUSTENNA™) using the same technique has been approved by the FDA in 2009. Unfortunately, there are still some problems about the wet milling. Only a few effective stabilizers have been found. The efficacy testing and selection of the stabilizers are still made on a trial and error basis, because little systematic understanding is available on this research area (Van Eerdenbrugh et al., 2009; Peltonen and Hirvonen, 2010; Cerdeira et al., 2010). The published results using the same materials are sometimes based on different milling systems, which may make a difference for the

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process. Many potential influencing factors, including hardness, hydrophobicity and chemical structure of the drugs, and surface tension, viscosity, molecular weight and functional groups of the stabilizers, make the result analyses complicated. Moreover, the dissolution method and transformations of crystalline form of the nanoparticles during the milling should be taken into consideration.

In this study, nanosuspensions were prepared using the wet milling technique: 2 structurally different low solubility drug compounds (indomethacin and itraconazole) and 4 kinds of stabilizers at 4 different concentrations were investigated to reveal the relationships between the drugs and the stabilizers. Dissolution behaviors of the nanosuspensions and physical component mixtures were compared. Subsequently, the crystalline states were characterized before and after the size reduction. Finally, the physical and chemical stabilities of the nanosuspensions were determined for 2 months.

2. Materials and methods

2.1. Materials

Indomethacin (IND, Hawkins, MN, USA) and itraconazole (ITR, Orion Pharma, Espoo, Finland) were used as the model drugs. Poloxamer 188 (Pluronic F68) and Poloxamer 407 (Pluronic F127) from BASF Co. (Ludwigshafen, Germany), Polysorbate 80 (Tween® 80, Fluka Chemika, Buch, Switzerland) and polyethylene glycol (PEG, Sigma, St. Louis, MO, USA) of M_W 6000g/mol were used as stabilizers. Phosphoric acid (85%, Riedel-de Haën, Seelze, Germany), methanol and acetonitrile (HPLC grade, VWR International, Pennsylvania, USA), trifluoroacetic acid (TFA, Sigma, Aizu, Japan), ethanol (96%, v/v, Primalco, Rajamäki, Finland), potassium hydrogen phthalate (Sigma, St. Louis, MO, USA), sodium hydroxide (NaOH, Sweden), and hydrochloric acid (HCl, Merck KGaA, Darmstadt, Germany) were used for the characterization of nanosuspensions. In all the experiments the water was ultrapurified Millipore® water (Millipore, Molsheim, France).

2.2. Media milling

The nanosuspensions were prepared using a wet-milling technique. Stabilizer was dissolved in 5 ml water. 2 g of drug powder was dispersed in the aqueous stabilizer solution. The obtained suspensions were inserted in the milling bowl containing 70 g of milling pearls (zirconium oxide, diameter 1 mm). Additional of 5 ml water was used to collect the residual suspensions from the beaker to the milling bowl. Four types of stabilizers and stabilizer concentrations were used: F68, F127, Tween 80 and PEG 6000, with the concentrations of 10 wt%, 25 wt%, 60 wt% and 80 wt% (relative to the drug amount). Milling bowl was placed in a planetary ball mill (Pulverisette 7 Premium, Fritsch Co., Idar-Oberstein, Germany), and grinding was performed at 1100 rpm. One grinding cycle was 3 min. After each grinding cycle there was a 15 min pause and then the milling direction was reversed. Each formulation was prepared at least twice. After the milling, the nanosuspensions were separated from the grinding pearls by sieving and, if needed, dried using FTS Lyostar II freeze drying system (SP Industries Inc., Warminster, USA).

2.3. Particle size distribution

The mean particle sizes and polydispersity indexes (PIs) of the nanosuspensions were analyzed by photon correlation spectroscopy (PCS) with Malvern Zetasizer 3000HS (Malvern Instrument, Malvern, UK). PI means the width of the particle size distribution. The lower the PI value, the more monodisperse the particles are. If the PI lager than 0.7, the particles in suspensions are polydisperse. A part of the fresh nanosuspensions was diluted with saturated solution containing ca. 0.1 wt% of stabilizer, in order to achieve a suitable concentration for the measurements by PCS. The nanosuspensions were sonicated for 4 min before the size measurements. The analyses were performed with a dispersant refractive index of 1.33. The measurements were performed 3 times for each sample.

2.4. Dissolution studies

Dissolution behavior of fresh nanosuspensions was studied by paddle method according to the European Pharmacopoeia using dissolution system Erweka DT-06 (Heusentamm, Germany). Phthalate buffer (pH = 5.0) and 0.1 M HCl aqueous solution of 600 ml at 37 °C were used as the dissolution media for IND and ITR, respectively. Exact amounts of the nanosuspensions were transferred to the dissolution vessel and stirred at 100 rpm, and the same amounts of the nanosuspensions were collected for the measurements of the total drug amounts used in dissolution testings. Sink conditions were maintained during the dissolution tests. At predetermined time intervals, 5 ml of dissolution medium was withdrawn and the same volume of fresh medium was added. To remove any undissolved drug particles, the samples were centrifuged at 13,000 rpm for 8 min. Drug concentrations were quantified by HPLC. To measure the total drug amount of IND, the samples were dried in an oven and dissolved in ethanol. After diluting with water, the concentrations were measured by HPLC. For total drug amount of ITR, methanol was used to dissolve the samples and methanol: aqueous solution (1:1, v/v) was used for the dilution. Dissolution profiles of pure drugs and drug suspensions of the physical mixtures were also measured under the same conditions as controls. All these experiments were performed in triplicate.

2.5. HPLC assay

HPLC instrument (Agilent 1100 series, Agilent technologies, Germany) was used for quantification of the drug concentrations. For the analyses of IND, 20 μl of the samples was injected into a Luna 3 μ C18 100A (150 mm × 4.6 mm) column (Phenomenex Co., California, USA). The mobile phase, comprising of acetonitrile and 0.2% phosphoric acid in water (pH 2.0) (60:40, v/v) was used at a flow rate of 1.5 ml/min. The IND sample concentrations were quantified at a UV wavelength of 320 nm.

For the analyses of ITR, 20 μl of the samples was injected into a Gemini-NX 3 μ C18 110A (100 mm × 4.6 mm) column (Phenomenex Co., California, USA), and the mobile phase consisted of acetonitrile and 0.1% trifluoroacetic acid in water (55:45, v/v). The flow rate was set at 1 ml/min and UV-detection was performed at 261 nm.

2.6. Transmission electron microscopy (TEM)

The samples were pipetted on formvar film-coated copper grids with a mesh size 300 (Agar Scientific, Essex, UK) and dried at ambient conditions. The morphological evaluation of the particles in suspensions was performed by TEM (FEI Tecnai F12, Philips Electron optics, Holland).

2.7. Differential scanning calorimetry (DSC)

Thermal properties of dried samples were analyzed with a DSC 823e (Mettler Toledo Inc., Columbus, USA). The samples were placed in sealed aluminum pans perforated in the lid. The temperature range for the measurements was from 25 to 180 °C for IND and from 25 to 200 °C for ITR, with the heating rate of 10 °C/min. The

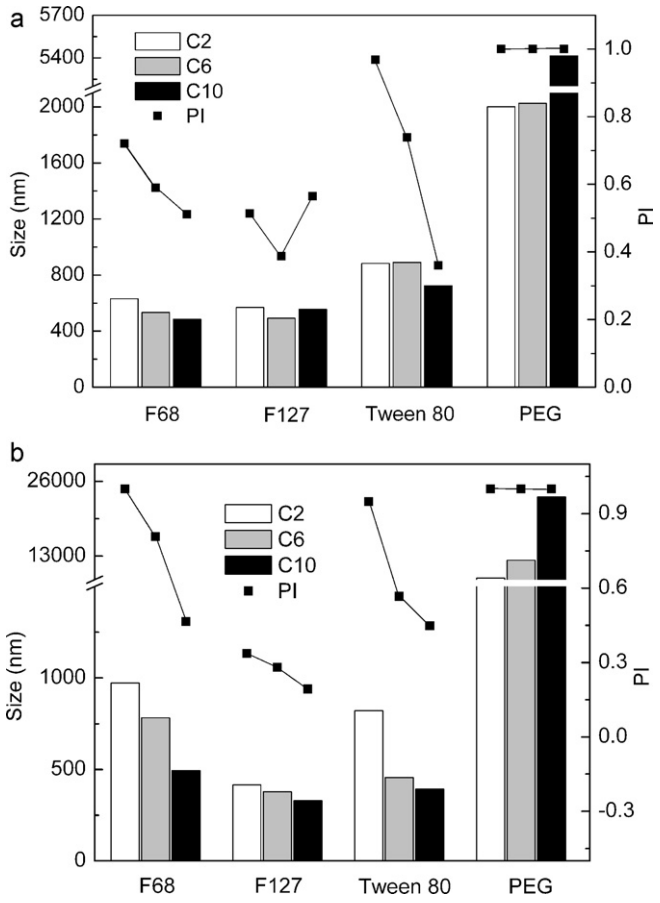

Fig. 1. Mean particle sizes and PIs of the suspensions with the same stabilizer concentration (25% drug content), as a function of milling cycle. IND suspensions (upper) and ITR suspensions (lower). C2, C6 and C10 in the figure mean after 2, 6 and 10 milling cycles of 3 min each.

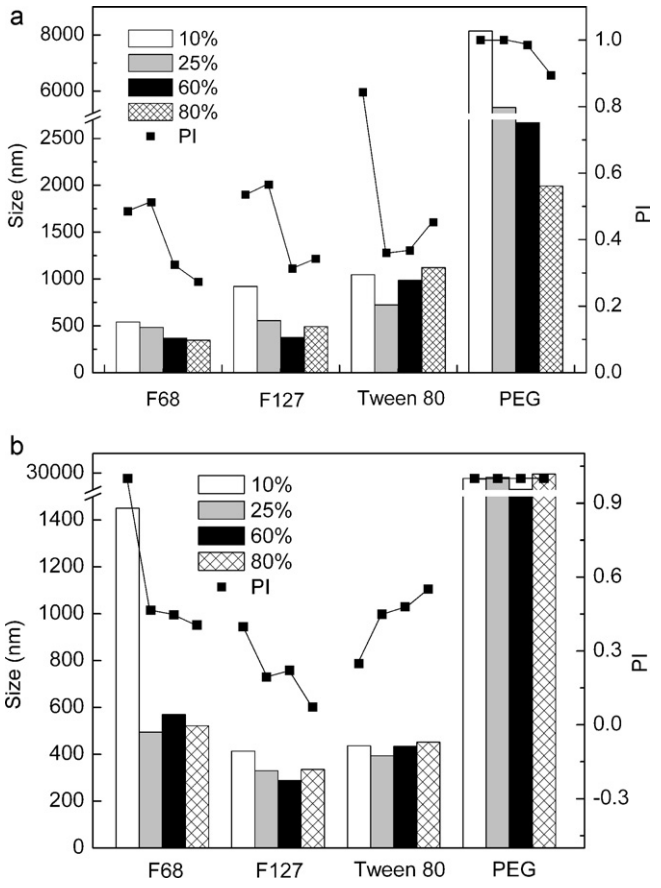

Fig. 2. Mean particle sizes and polydispersity indexes (PIs) of the suspensions with different stabilizers and stabilizer concentrations after milling for 10 cycles. IND suspensions (upper) and ITR suspensions (lower).

measurements were performed under nitrogen flow of 50 ml/min. Pure drugs and physical mixtures of the drugs and the stabilizers were tested as controls. The data were analyzed with STAR^e software (Mettler Toledo, Columbus, USA).

2.8. X-ray powder diffraction (XRPD)

XRPD patterns were determined from dried nano-formulations, pure drugs and physical mixtures of drugs and stabilizers by an X-ray diffractometer (Bruker AXS D8, Karlsruhe, Germany). The XRPD was performed in symmetrical reflection mode using Cu-Kα radiation with λ = 1.54 Å (40 kV and 40 mA). The sample was placed on a flat aluminum sample holder. Data were collected by scanning from 5° to 40° with 0.02° steps, and the measuring time per step was 0.5 s.

2.9. Stability of nanosuspensions

The physical and chemical stabilities of the nanosuspensions were investigated after storage for 2 months at room temperature (25 °C) and 4 °C, respectively. For physical stability, the size and morphology of the nanosuspensions were determined by PCS and TEM. The nanosuspensions were sonicated for 4 min before the PCS size measurements. HPLC was used to assess possible chemical degradation during storage. Any decrease in the area of the drug peak of the stored sample compared to the pre-storage sample was considered as degradation.

3. Results and discussion

3.1. Effect of milling time

Particle sizes and PIs of the micro/nanosuspensions with the same stabilizer concentration (25% stabilizer) but different milling times are shown in Fig. 1. Routinely, the mean diameters of bulk crystalline drug materials are tens of micrometers and the size distributions are broad. After only 2 cycles of milling (one milling cycle takes 3 min), the mean sizes of the two drugs were decreased dramatically below 1 μm, except with PEG as the stabilizer. With increasing milling times, both drugs showed almost identical results, i.e. the sizes and the PIs were decreased. Long milling time makes the big particles split into small ones and provide sufficient time for the stabilizers to absorb onto the drug surfaces. The size-decreasing trend was more obvious for ITR. Further prolonging in the milling times was not beneficial, because clearly decreased particle sizes and size distributions were not achieved. Oppositely, longer milling times could induce slight growth in particle size, as was the case with F127 as a stabilizer for IND. This phenomenon was also found in milling process using the high pressure homogenization (Pu et al., 2009).

3.2. Effect of stabilizer choice and concentration

To gain insight into the manufacture of nanosuspensions, four stabilizers including macromolecular polymers and a small molecular weight surfactant, were investigated at different concentration levels. As can be seen in Fig. 2, with fixed milling time of 10 cycles, the particle sizes and size distributions were affected not only by

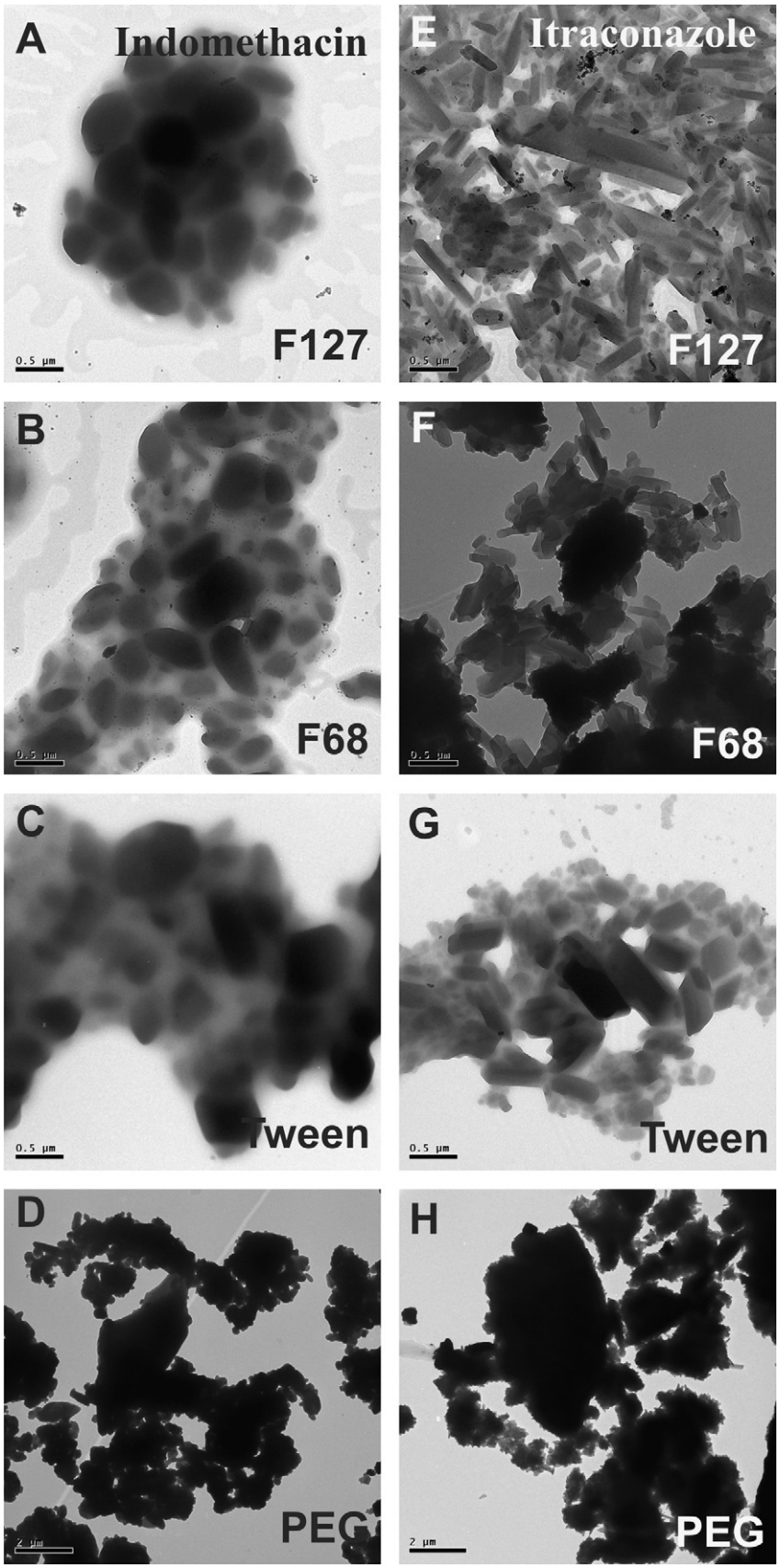

Fig. 3. TEM images of suspensions: (A–D) IND stabilized by the F127 (80%), F68 (25%), Tween 80 (25%) and PEG (60%); (E–H) ITR stabilized by the F127 (25%), F68 (25%), Tween 80 (25%) and PEG (25%).

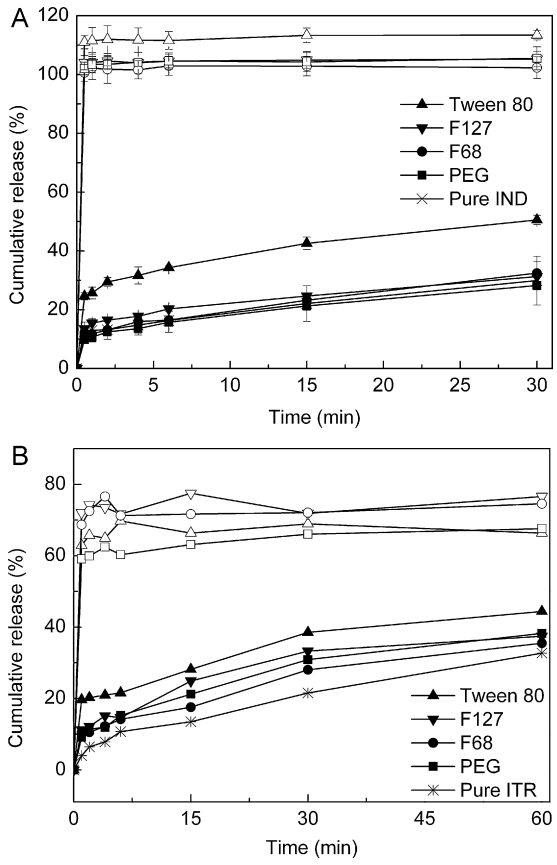

Fig. 4. The dissolution profiles of IND (A) and ITR (B) from nanosuspensions (open symbols), physical mixtures and pure drug (solid symbols) with 25% stabilizer.

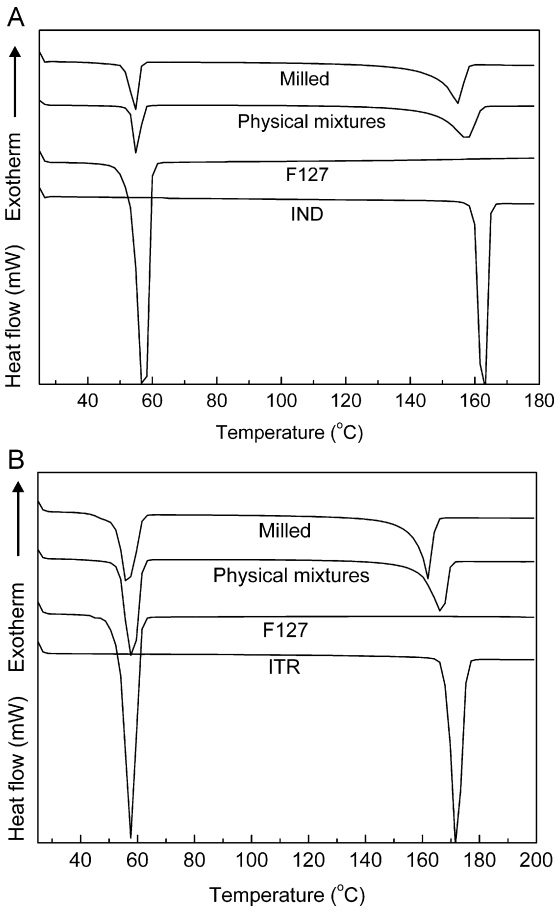

Fig. 5. The DSC patterns of IND (A) and ITR (B), from up to down: milled sample, physical mixtures, pure F127 and bulk drug.

the type of stabilizer but also by the stabilizer concentration. These results confirm the different roles of stabilizer in wet-milling as compared to high pressure homogenization technique, where the final nanocrystal size was found to be independent on the stabilizers used and the role of the surfactants is to stabilize and protect the nanocrystals from aggregation (Mishra et al., 2009; Jacobs et al., 2001).

Nanoparticles with narrow size distributions were obtained successfully in all cases except with PEG as the stabilizer. The mean size of IND particles decreased to 345 nm stabilized by F68 (80%), 375 nm stabilized by F127 (60%), and 723 nm stabilized by Tween (25%) (Fig. 2). F68 was the most effective stabilizer for IND, followed by F127 and Tween 80. Both the polymeric stabilizers are poloxamers and have the same overall molecular structure: linear ABA triblock polymer chain (A stands for hydrophilic polyethylene oxide (PEO) segment and B stands for hydrophobic polypropylene oxide (PPO) segment). The hydrophobic PPO chains can drive the polymer to adsorb on the surface of drug particles, while the hydrophilic PEO chains surround the drug particles providing steric hindrance against aggregation. IND nanosuspension stabilized by the F68 seemed a little better than by the F127, especially at low stabilizer concentrations. The F68 has a lower molecular weight than the F127 (8400 g/mol vs. 12,600 g/mol), which may exert less kinetic restriction in the adsorption process and faster diffusion (Lee et al., 2008). For the surfactant, Tween 80, the yielded particle sizes were larger than in the drug samples stabilized by the polymers. The mean diameters of the IND/Tween nanosuspensions measured by PCS were larger than those observed by TEM. Tween 80 is a small molecule, which forms a thin adsorption layer and, thus, offers less effective steric stabilization upon approaching the particles than the higher molecular weight polymers (Sepassi et al., 2007).

For ITR (Fig. 2), the smallest particles were milled when 60% of F127 was used as a stabilizer, then followed by 25% Tween, 25% F68 and PEG. Here, F68 was less effective than Tween because of high viscosity of suspensions. Different from the IND, drug suspensions with high viscosity were achieved when F68 and ITR were mixed. Comparing the results of the two drugs, differences appeared, mainly caused by the different natures of drug compounds, e.g. hardness and hydrophobicity. However, for both the drugs, good nanosuspensions were always obtained at high concentrations of the poloxamers, but at low concentrations of the Tween 80, obviously reflecting the different molecular weights of the stabilizers.

Compared to other stabilizers, PEG was not successful in producing nanosuspensions at many concentrations for both the model drugs. The PEG molecules do not have any hydrophobic groups, which are needed to drive the adsorption of polymer chain towards the hydrophobic drug particles. Instead, the long hydrophilic chain of PEG can capture the water molecules through hydrogen bonding, which are formed between the hydroxyl group and ether bond of PEG and water molecules. Because of this, the slurry consisting of the drug, PEG and water for milling is in paste form and displays a very high viscosity. In wet milling, transfer of mechanical energy is one of the major parameters for the formation of nanocrystals, which involves the slurry viscosity, the size and density of milling medium and energy input (Lee et al., 2008). High viscosity of the slurry yields large intrinsic resistance against the moving of milling pearls, which makes the milling less efficient and only micron-sized particles are generated (Cerdeira et al., 2010). Thereby, PEG, or most likely any other very hydrophilic polymer, will not be an effective stabilizer in wet milling of hydrophobic drugs (Lee et al., 2010).

Table 1
The size distribution of IND nanosuspensions after storage for 2 months.

	F68		F127		Tween 80	
	Size (nm)	PI	Size (nm)	PI	Size (nm)	PI
0 days	394	0.34	393	0.42	986	0.37
60 days (4 °C)	392	0.34	384	0.29	756	0.68
60 days (25 °C)	395	0.35	389	0.30	736	0.62

3.3. Morphology of suspensions

The morphology of drug suspensions was observed using TEM (Fig. 3). Before milling, raw drug materials in surfactant solutions consisted of large crystals, which were visible to the naked eye. After milling, the large IND crystals in the presence of the stabilizers (except PEG) were transformed into nano-particles (Fig. 3A–C). The angular surfaces of the crystals were now much smoother. The gray areas around the nano-crystals in the TEM images are considered to be due to the polymer or surfactant. The image of suspensions in the presence of PEG is shown in Fig. 3D. A large number of clusters were found, although there were also some smaller particles around the large clusters. Low energy input and agglomeration are the key problems resulting in the micron-sized particles measured. All the milled IND samples not only exhibited the crystalline state, but also kept the same original shape, which was independent on the different types of stabilizers.

Fig. 3E–H shows the ITR crystals after milling. It is evident that the particles are nano-scale except with the PEG as stabilizer. Surprisingly, the different stabilizers lead to different shapes, i.e. rod-like crystals were generated by the F127 and F68, while cubic crystals were generated by the Tween. This could be related to the different interaction mechanisms of the stabilizers. In contrast, Jacobs et al. (2001) have shown that the shape of nanocrystal made by high pressure homogenization technique was not dependent on the type of stabilizer used. Here, for the two model drugs, the particle sizes shown in the TEM figures are well in accordance with the results measured by PCS, except for the case of Tween as stated above.

3.4. Dissolution tests

Dissolution methods for water insoluble nanocrystals have attracted more and more attention (Crisp et al., 2007; Dolenc et al., 2009). For instance, it is typically difficult to measure the dissolution curve at the very first minutes because of the rapid dissolution rate. To remove the undissolved drug particles from the samples, two common methods are used: filtration and centrifugation. Nanoparticles smaller than the filter pore size can pass through the filter. On the other hand, hydrophobic drug molecules can easily interact with the filter membrane. Therefore, it is possible to misinterpret the dissolution rate results. For a high-speed centrifugation, the long separation time and possible high temperature can lead to further dissolution of particles. After comparing these two methods in pretests, centrifugation was chosen for the separation in this study.

For the dissolution of IND, the solubility was determined preliminarily at 37 °C in buffers with different pH. Because of the acidic nature of IND (pK_a = 4.5), the dissolution rate decreases as the pH of dissolution medium is lowered. To confirm the sink conditions during the dissolution process and to enhance the differences in dissolution rates between the nanosuspensions and controls, phthalate buffer at pH 5.0 was selected as the medium. As shown in Fig. 4A, the nanosuspensions exhibited a dramatic increase in drug release rate compared with the un-milled IND suspensions with the same stabilizer and stabilizer concentration. Immediately after the 1 min of the dissolution tests, all the drugs from the nano-formulations were released. The same behavior is typical for

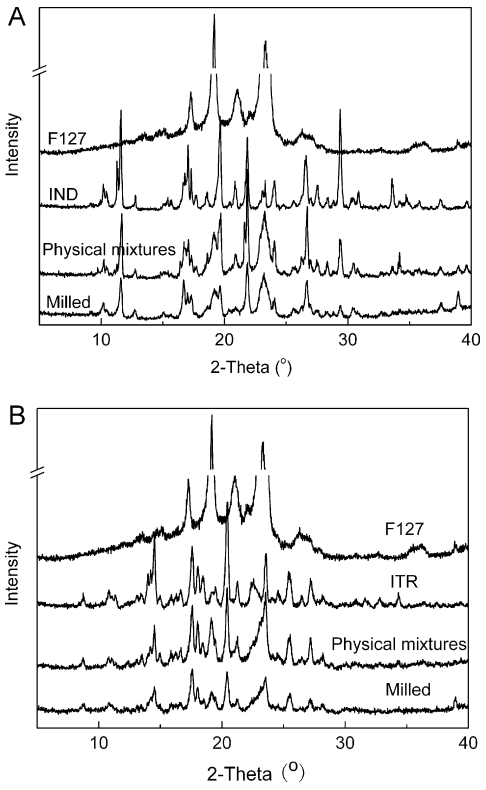

Fig. 6. X-ray analyses of IND (A) and ITR (B), from up to down: F127, bulk drug, physical mixtures and milled sample.

nanosuspensions milled by NanoCrystal® technology (Jinno et al., 2006). In contrast, less than 50% of IND was dissolved in 30 min from the micro suspensions.

It is worth noting here that although the suspensions stabilized by PEG were in micro-scale (5 μm), the dissolution rates were still as fast as from the nanosuspensions. This indicates that at least part of the primary particles was nanosized, although they were aggregated to larger clusters. The aggregated particles supposedly disintegrate into dispersed nanosized ones without time lag, resulting in a fast drug release rate like in the case of the nanosuspensions (Lee, 2003; Chaubal and Popescu, 2008). On the other hand, the hydrophilic PEG surrounding the IND particles may improve the dissolution rate to some extent also by a wetting effect. As for the physical mixtures, the dissolution rates with Tween 80 appeared to be at higher levels compared with the other stabilizers. This was obviously caused by Tween's excellent solubilizing and wetting properties.

For the water insoluble ITR, acidic environment and surfactant SDS are usually considered to improve the solubility and ensure the sink conditions for the dissolution experiments. Given to the fast dissolution rate of control samples in the presence of SDS, 0.1 M HCl without SDS was chosen as a more distinctive medium.

As shown in Fig. 4B, the ITR dissolution profiles were quite similar to those of IND. However, for the nanosuspensions, the dissolution rates were clearly increased at the beginning and remained unchanged with time. Incomplete release (60–80%) was possibly caused by some reasons. The hydrophobic nanoparticles are likely to adhere to the dissolution vessel because of its high adhesiveness (Müller et al., 2001), or ITR molecules were captured by other containers during the analysis steps.

3.5. Crystalline state evaluation

Changes in the crystalline form can occur during the milling and lyophilization (Savolainen et al., 2007). Amorphous material and

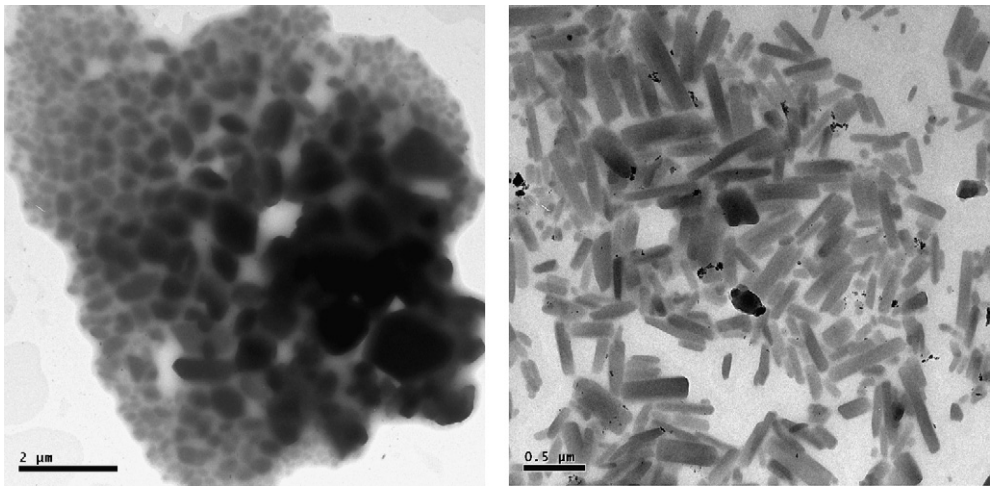

Fig. 7. TEM images of suspensions stabilized by the F127 after 2 months: IND nanosuspensions (left) and ITR nanosuspensions (right).

instable crystalline polymorphs can make controlling the quality of formulations problematic. Thereby, the crystalline states were examined by DSC and XRPD.

The DSC thermograms are shown in Fig. 5. The extrapolated onset temperature was used to define the melting point (T_m). Polymer F127 had a melting peak at approximately 54 °C. Pure IND showed a sharp endothermic melting peak at 160 °C, while T_m of pure ITR was 168 °C. Comparing the curves of physical mixtures and milled samples, no significant differences were found and no new peaks corresponding to glass transition or recrystallization appeared, implying that no amorphous forms were produced during milling. The shifts of IND and ITR peaks in the physical mixtures and the milled samples to lower melting temperatures were observed simultaneously. This could be due to the presence of the stabilizers in the samples (Teeranachaideekul et al., 2008; Sharmaa et al., 2009). The shift in the milled samples was more noticeable, because higher amounts of the stabilizer could be captured on the surfaces of the nanocrystals and also due to the smaller particle size.

The X-ray diffractograms are shown in Fig. 6. Physical mixtures of bulk drug and F127 were used as controls. The differences between pure drugs and physical mixtures were induced by the stabilizer F127. No apparent differences were found between the physical mixtures and milled samples. Low peak intensities in nanoformulations were observed, owing to the dilution of the particles with the stabilizer (Hecq et al., 2005). Combining the results of DSC and XRPD, it was demonstrated that the milling does not interfere with the crystalline states of the drug compounds.

3.6. Stability of suspensions

To investigate the physical and chemical stabilities, particle size, morphology and chemical degradation of the nanosuspensions were monitored for a period of 2 months at room temperature and at 4 °C. Nanosuspensions with 60% of stabilizers were used for this study.

As shown in Table 1, no big changes were seen in sizes and size distributions after the storage at room temperature and 4 °C, especially when F68 and F127 were used as the stabilizers. Good physical stability is related to the protection by the stabilizers and homogeneous sizes of the nanocrystals. Long swinging hydrophilic PEO chains on the particle surface provide an excellent steric hindrance, which prevents the particles from aggregating. Moreover, the poorly soluble drugs and homogeneous particles hinder the dissolution of smaller particles and growth of larger particles, i.e. Ostwald ripening.

The TEM micrographs of IND and ITR nanosuspensions after storage are shown in Fig. 7. The morphology of the crystals after 2 months was similar to the fresh samples. HPLC analyses showed that no extra peaks in the chromatograms and no changes in the drug concentrations were observed (data not shown), indicating that no chemical degradation of the drugs occurred during the storage. Theoretically, drug compounds exposed to aqueous solutions are relatively unstable. Good chemical stability of the nanosuspensions is explained by two effects: stabilizers on the surfaces of drug particles protect the drugs from the outer aqueous environment and, thus, reduce the chance of hydrolysis of the drug (Pu et al., 2009). Suleiman and Najib (1990) reported that indomethacin in the presence of Tween 80 produced a 7-fold increase in the stability against alkaline degradation (Suleiman and Najib, 1990). Secondly, the crystalline structures of the drugs result in high drug stabilities (Möschwitzer et al., 2004). In conclusion, the nanocrystal suspensions showed high long-term stability, indicating good shelf-life characteristic.

4. Conclusions

Nanosuspensions were successful prepared by a rapid wet milling technique. The study was performed with 4 types of stabilizers at 4 different concentrations for 2 drug compounds. In general, different drugs require their different optimal stabilizers. The amphiphilic block copolymers (F127 and F68) appeared to be more efficient than the low molecular weight surfactant (Tween 80). The stabilizer solutions owing high viscosity had a negative effect on size reduction and stability, such as F68 for ITR and PEG for IND and ITR. The nanosuspensions exhibited very fast dissolution rates in contrast to the bulk materials. Crystalline state of IND and ITR was not altered through particles size reduction. Furthermore, the nanosuspensions showed good long-term (two months) physical and chemical stabilities. The results show that the nanosuspensions produced by wet milling are potential drug formulations.

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