Original Article

Drug Release Studies of Naproxen Agglomerates Produced by the Antisolvent Approach in the Presence of Hydroxypropyl Cellulose

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Abstract

In this study, the effect of recrystallization of naproxen in the presence of hydroxypropyl cellulose (HPC) on the release rate of drug was investigated. Crystals were generated by the anti-solvent approach using the HPC solution in water as the anti-solvent. The samples were subjected to various physicochemical evaluations such as crystal size, scanning electron microscopy, Fourier transform infrared (FT-IR) spectroscopy, solubility, wettability and dissolution studies. Results revealed that HPC play a key role in controlling the primary crystal size, morphology, size and surface properties of naproxen agglomerates. Crystallization of naproxen in the presence of HPC caused a marked modification of its dissolution. The particles obtained in the presence of HPC exhibited slower dissolution rate compared to those produced in the absence of HPC. This was attributed to the adsorption of HPC on the surface of the naproxen crystals. It was shown that the solubility of naproxen increased in solution containing HPC. Moreover, there was a significant difference between the solubility of untreated naproxen and that of samples crystallized in the presence of HPC in water. Contact angle measurements revealed that control crystals obtained in the absence of HPC have a greater contact angle than those produced in the presence of HPC. FT-IR spectroscopy results indicated the absence of any interaction between drug and HPC. This study highlights the influence of polymeric additive on the crystallization process leading to modified performance.

1. Introduction

The final purification of the Active Pharmaceutical Ingredient (API) is usually a crystallization step, in which the product properties like the crystal size distribution, crystal shape, degree of agglomeration, and agglomerate properties, depend on how the process is operated. A number of factors influence the crystallization process, like the nature of solvent, rate and extent of super-saturation, heating/cooling rate, stirring rate and the presence of additives [1]. One of the

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most common causes of habit modification is the presence of additives in the crystallizing solution. The presence of small amounts of an effective additive in the crystallization medium can dramatically change the crystal size and shape [2]. The additives used in crystallization procedures may be classified into several groups: surface active agents, low molecular weight organic or inorganic substances, long chain polymeric materials and proteinaceous substances [3]. Those additives which influence the crystallization processes are those that can be adsorbed on to the crystal surfaces [2]. The degree of adsorption between additives and the crystal surfaces depends on their chemical and structural properties such as the presence of anionic or cationic groups, or the possibility of the formation of hydrogen bonds [2, 4].

In the present study, the crystallization of naproxen was carried out by solvent- change approach in the presence of inert polymer hydroxypropyl cellulose (HPC) and the role of concentration of HPC was studied in the recrystallized product. HPC is a cellulose ether obtained by chemical reaction of the hydroxyl groups at positions 2, 3, and/or 6 of the glucose residues of cellulose and is a commonly used drug excipient [5]. In our previous study, it has been shown that the crystallization of naproxen in the presence of HPC significantly improved its compaction properties [6]. The aim of this study was to investigate the dissolution properties of naproxen crystallized in the presence of HPC in order to determine if they had been modified.

2. Materials and methods

Naproxen (Shasun Chemicals, India), HPC (Nisso HPC-H, Nippon Soda, Japan) and acetone (Merck, Germany) were used.

2.1. Crystallization procedure

The crystallization process used in this study was similar to method which was introduced in previous study as the spherical crystallization technique [6]. Naproxen (1 g) was dissolved in 4 ml of acetone at 50 °C, then the solution was added to 50 ml distilled water (20 °C) containing different concentrations of HPC (0.10, 0.25, 0.50 and 1.00% wt) under fixed stirring conditions (200 rpm, paddle type agitator with 4 blades). The precipitated crystals were collected after 10 min. by vacuum filtration onto a sintered glass filter and then were washed with cold water. The harvested crystals were evenly spread on an oversized petri dish and were dried for 12 h in an oven (60 °C). The dried crystals were stored in screw-capped jars at room temperature before use.

2.2. Yields of products

The yields of production were calculated as the weight percentage of the agglomerates after drying, with respect to the initial total amount of drug was used for the preparations.

2.3. Crystal size and shape analysis

To determine the primary crystal size, the agglomerates obtained in the presence of HPC were disintegrated in an aqueous solution of Tween 80 (0.05%) using ultrasonicator (VC 130, Sonics and Materials Inc., USA) for 30 sec at 100 W before determining the crystal size. A small amount of obtained powder (about 20 mg) was suspended in mineral oil (Sigma Chemical Co., St. Louis, USA) and the suspension was spread onto a microscope slide. A cover slip was applied, allowing the suspension to settle homogeneously between the two glass surfaces. Crystal size was assessed by an optical microscope (Nikon Labophot, Tokyo, Japan) via a miniature video camera. One hundred of crystals were measured in each sample and the surface volume mean diameter was recorded.

The agglomerates shape was also assessed by optical microscope. One hundred of particles were measured in each sample and

shape factor were recorded. The shape factor (SF) is defined as the smoothness of the particle, if the value is close to 0 the particle is elongated and/or irregular, if it is close to 1, then it is smooth and rounded.

Shape factor (S) was calculated using the following equation.

$$S = \frac{P^2}{4\pi A} \qquad \_Eq.1$$

where A and P are the area and the perimeter of the particle, respectively. The surface topography of the agglomerates were observed using a scanning electron microscope (LEO 440I, Cambridge, UK).

2.4. Determination of naproxen solubility

The solubility of the samples was determined in water, by following procedure. The samples (100 mg) were dispersed in 10 ml of freshly distilled water bath at 25 °C until such time as the UV absorbance reading of a filtered sample was the same on three successive days. In order to determine the aqueous solubility of naproxen in the presence of HPC, the same procedure was carried out, but the pure drug powder was dispersed in 10 ml freshly distilled water containing various concentrations of HPC. The mean of three determinations was used to calculate the solubility of drug in the aqueous media.

2.5. Contact angle determination

Dry powder was compressed at 1000 kg compression force using a hydraulic press (Riken Seiki Co., Japan) with 8 mm diameter flat faced punches. A droplet of water (3 μl) was placed onto the surface of the compact and observed using a low power microscope. The contact angle was determined by measuring the tangent to the curve of the droplet on the surface of the compact.

2.6. In vitro release studies

The *in vitro* dissolution of ibuprofen samples was determined with a USP rotating paddle method. Samples (100 mg) were dispersed in dissolution vessel containing 900 ml distilled water maintained at 37±0.5 °C and stirred at 50 rpm. At the preset time intervals, aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain a constant volume. After suitable dilution, the samples were analyzed spectrophotometrically at 272 nm.

2.7. Statistical evaluation of data

Quantitative data were reported as mean±standard deviation (SD). Statistical analysis was performed using the analysis of variance (ANOVA). Comparison between the two means was determined using the Tukey's test with statistical significance evaluated at
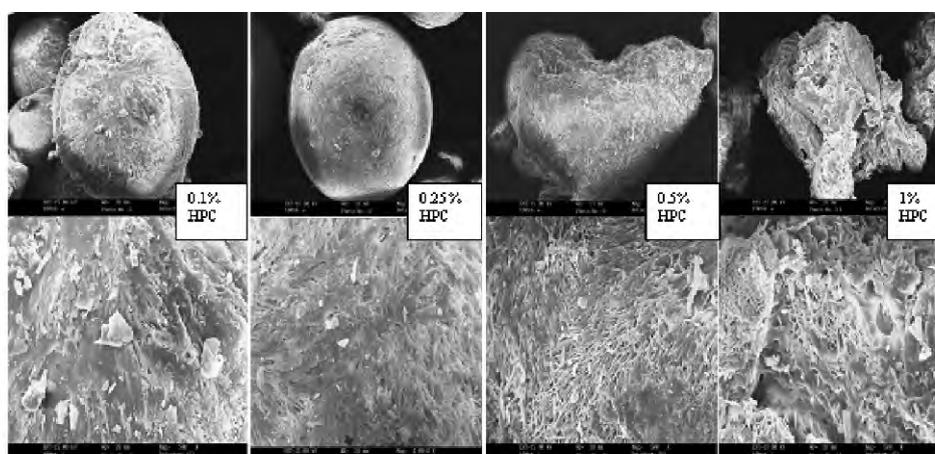

Figure 1. SEM photomicrographs of naproxen particles recrystallized in the presence of different concentration of HPC.

p< 0.05. Statistical analysis of the dissolution data using the percentage of drug released with time as the quantitative parameter was undertaken.

3. Results and discussion

When the acetone solution of the drug was poured into water, quasi emulsion droplets formed immediately. This observation suggested that phase separation occurred and the agglomerates were produced by solidification of the quasi emulsion droplets. At a certain temperature, a mixture of two solvents is homogeneous when these solvents are pure. In the presence of a third compound with a solubility that is higher in one of two solvents, phase separation occurs. It is assumable that cooling of the solvent and instant local mixing of acetone and water at the interface of the droplet induced precipitation of the drug, thus forming a shell enclosing the acetone and the dissolved drug. Counter diffusion of acetone and water through the shell promoted further crystallization of the drug in the droplet from the surface inwards. According to the mechanism proposed, we suppose that any factor which could modify the time needed to form the shell will be critical in the process, because the drug crystallization might also be affected. This process is nearly the quasi emulsion solvent diffusion of Kawashima *et al.* [7]. In order to investigate the contribution of HPC in this method, the agglomerates prepared with various HPC concentrations in the aqueous phase. In the absence of the HPC, crystallization occurred without the stable formation of acetone droplets and the acetone droplets collided and adhered. On the basis of these finding, it was considered that HPC in the aqueous medium acted as a protector against coalescence at the initial stage.

However, as indicated in Table 1, the recovery percentage of naproxen agglomerates decreased as the concentration of HPC in the aqueous phase increased. The percentage of recovery in the absence of HPC was 92% whilst in the presence of 1% (w/v) of HPC it was 60%. This result can be explained as follows. Increasing HPC concentration in the aqueous phase can lead to increased viscosity (68 cps for 0.1% to 2455 cps for 1%) (6), beyond which, the time taken to form shell boundary is delayed. In this case, more solvent could diffuse from the droplets carrying dissolved drug. A longer time for membrane solidification of the particles obtained in higher concentration of HPC results in a greater amount of drug passing into the aqueous phase. The result may be a great amount of drug powder with few spherical agglomerates and consequently decreasing yield of the agglomerates by increasing HPC concentration.

Figure 1 presents the SEM images of the particles obtained in the presence of HPC. The particles precipitated from 0.1 or 0.25% (wt) HPC aqueous solution had nearly spherical shape and contained packed crystals. Figure 1 displays the distortion of agglomerates obtained in the presence of higher concentrations of HPC. This fact is also confirmed by comparing shape factor of the agglomerates obtained in the presence of 0.1 or 0.25% (wt) HPC, which is close to 1 (>0.9), with the shape factor of the agglomerates obtained in the presence of 1% (wt) HPC (0.76) (Table 1). The above results indicate that HPC plays a key role in controlling the
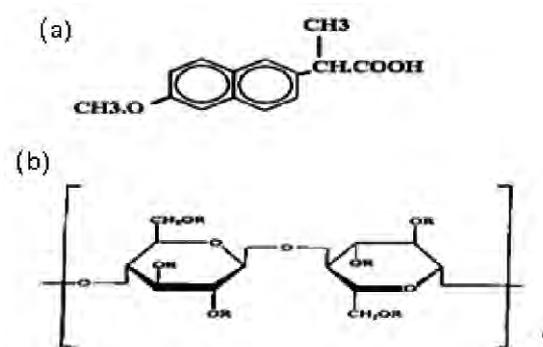

Figure 2. Molecular structure of: a) naproxen, and b) HPC recrystallized in the presence of different concentration of HPC.

Table 1. Production yield, primary crystal size, shape factor, contact angle and solubility of the samples (mean± SD, n=3).

Materials	Yield (%)	Primary mean crystal size (μm)	Shape factor	Contact angle (o)	Solubility (mg/l)
Untreated naproxen	-	9.05	0.60±0.35	-	36.5±1.8
Crystallized in presence of: 0% HPC	92±0.4	9.34	0.71±0.32	75±1.5	37.9±1.5
0.1% HPC	87±0.2	8.90	0.93±0.13	62±1.1	47.6±1.3
0.25% HPC	84±0.14	7.85	0.99±0.13	60±0.9	46.7±1.2
0.5% HPC	67±0.14	7.35	0.84±0.16	61±1.0	48.0±1.3
1% HPC	60±0.39	7.14	0.76±0.15	60±1.2	47.9±1.1

morphology of naproxen particles. As can be seen in SEMs with higher magnification the surface of the agglomerates obtained with different concentration of HPC also showed significant differences. The surface of the agglomerates obtained in 0.1% HPC did not show separate crystals and its surface was more closely compacted. With increasing concentration of HPC in the crystallization medium, the resultant agglomerates became more porous and its surface was rougher than those obtained with lower concentration of HPC.

As discussed above, increasing the amount of HPC incorporated in the aqueous phase can lead to increase viscosity, beyond which the hardening of the agglomerates delayed and consequently counter diffusion of acetone and water increased. Due to this fact, more water could diffuse into the droplets before their solidification, thus forming more water pockets (pores). Therefore, agglomerates structure can be modified by a greater amount of water uptake, which may induce the creation of a more porous structure or the appearance of some defects on the particle.

As indicated in Table 1, the size of the individual crystallite comprising the agglomerate obtained in the presence of HPC was significantly less than those obtained in the absence of HPC. This may be because polymer create or prolong supersaturation and increase the viscosity of the medium for controlling crystallization [8]. Reported studies have suggested that adsorption of polymers on the surface of nuclei leads to the formation of a diffusional boundary layer, which inhibits nucleation and growth, resulting in finer crystal yield [2, 9]. As can be seen in Figure 2, HPC contains hydroxypropyl groups, which can form hydrogen bonds between the drug molecule
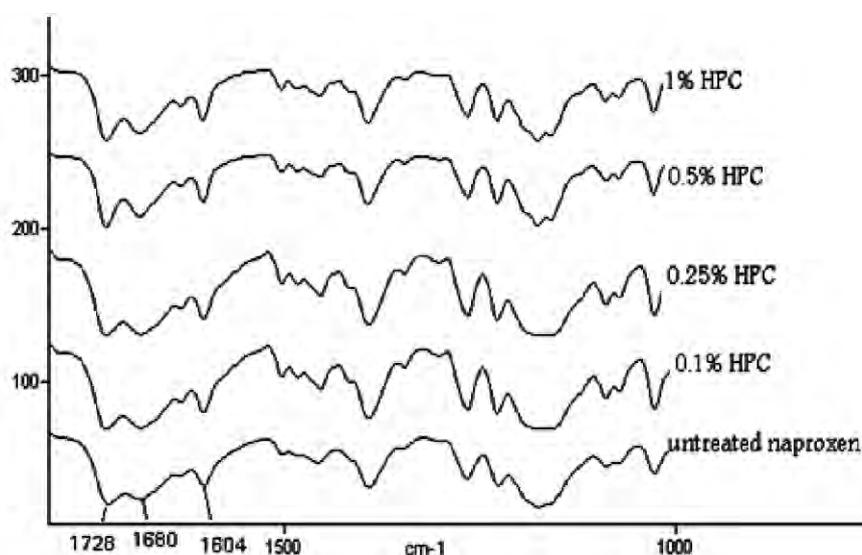
Figure 3. FT-IR spectra of untreated naproxen and recrystallized naproxen in presence of different concentrations of HPC.

and polymer. Therefore, it can be expected the polymer presented in the aqueous solution is absorbed on the surface of the formed hydrophobic drug particles to inhibit crystal growth [10-13].

As reported in our previous study, the mean particle size of the agglomerates also was a function of HPC concentration in the external aqueous phase. The mean particle size decreased from 515 to 468 with an increase in the HPC concentration from 0.1 to 1% (wt) [6]. This drop in the particle size with the increase in HPC concentration is probably due to the differences in the stability of the emulsions formulated with different concentrations of HPC. Increasing the viscosity of HPC solution due to increasing HPC concentration could result in the formation of a stable emulsion with smaller droplet size, leading to the formation of smaller sized agglomerates.

The FT-IR spectra of untreated naproxen and agglomerates are presented in Figure 3. FT-IR spectra recorded in the 1000-1800 cm^{-1} spectral region. The typical bands of naproxen carbonyl stretching between 1728 cm^{-1} and 1604 cm^{-1} [14], was still discernable and did not show any shift in the agglomerates. It is obvious that the principle absorption bands for the samples are similar suggesting that there were no differences between the internal structure and conformation of these samples. FT-IR spectroscopic analysis which did not detect any change of the crystalline form of drug, or any interaction with HPC confirmed that HPC could be incorporated physically into the agglomerates by the adhesion to the surface of the crystals. X-ray powder diffraction patterns [6] identical to naproxen for crystals generated using HPC suggested that this additive is not within the crystal lattice but only adsorbed on the surface. Moreover, the results of differential scanning calorimetry [6] in agreement with FT-IR spectroscopic analysis and X-ray powder diffraction studies indicated that the naproxen crystallized in the presence of HPC did not exhibit any structural differences compared to untreated naproxen crystals and also showed no sign of interaction between the drug and HPC.

The aqueous solubility of naproxen in the presence of different amounts of HPC is illustrated in Table 2. According to this Table HPC in concentrations above 0.05 wt% had a marked effect on the solubility of the naproxen; however, at lower concentration (0.02% (wt)) it had no significant effect ($p > 0.05$). The aqueous solubility of samples
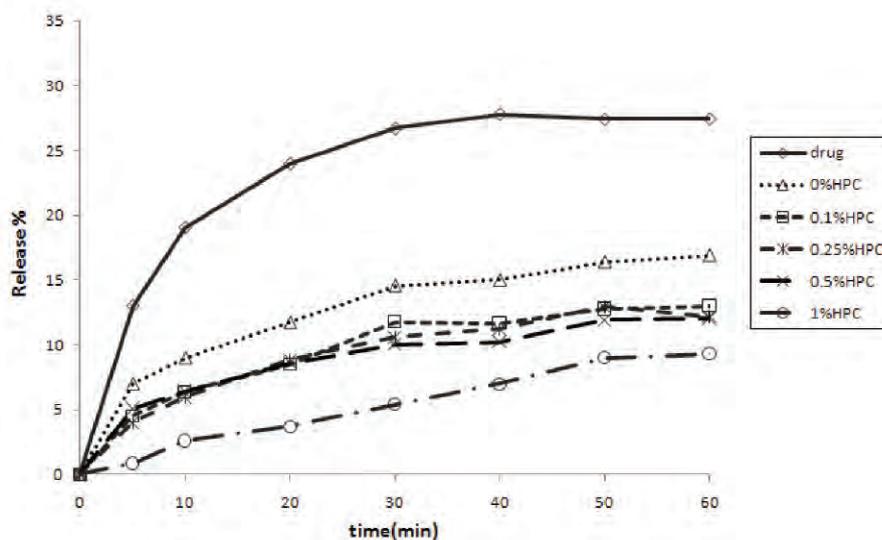

Figure 4. Dissolution profile of untreated naproxen and recrystallized naproxen in presence of different concentrations of HPC.

crystallized in the absence and presence of different concentration of HPC are listed in Tabel 1. These results showed that HPC in crystallization medium had a significant effect on the solubility of naproxen.

Table 1 gives the mean contact angle values of water droplets on the sample surface. The results for naproxen crystallized in presence of HPC indicated improved wettability of these samples by water compared to the sample obtained in the absence of HPC. A high contact angle ($\theta=75°$) for the agglomerates obtained in absence of HPC indicated the poor wettability of this sample by water. The contact angle was reduced to about 60° when HPC was incorporated in the agglomerates, but was independent of HPC content. Incorporation of HPC in the agglomerates would undoubtly increase the wettability of these particles.

Figure 4 shows the dissolution profiles of naproxen crystallized in presence of 0.1, 0.25, 0.5 or 1 wt% of HPC. The dissolution profiles of untreated naproxen and samples crystallized in the absence of HPC are also included in this Figure. The percentage of drug dissolved within the first 30 min. was used to compare dissolution rate of various samples. To assess the differences between pure drug and the generated samples, water was chosen as a discriminatory dissolution medium. This Figure indicates that there is a marked reduction in the dissolution rate of naproxen from the agglomerates obtained in the absence of HPC in comparison with the untreated naproxen. Decreasing dissolution rate of drug from the agglomerates may be attributed to the increase of the particle size compared to untreated naproxen crystals. It should be noted that the agglomerates did not disintegrate to primary crystals during dissolution time. According to Figure 4, the release rate of the drug from the agglomerates obtained in the presence of HPC was decreased compared to the agglomerates obtained in the absence of HPC. To explain

Table 2. Effect of concentration of HPC on the aqueous solubility of naproxen.

Conc. of HPC (wt%)	Solubility of naproxen (mg/l)
0	36.5±1.8
0.02	38.0±1.5
0.05	47.9±1.3
0.1	47.7±1.4
0.25	49.0±1.4
0.5	48.8±1.3
1	49.0±1.5

this result, the dissolution processes and factors involving dissolution rate would be considered. In general, dissolution may be described by two rate processes: the rate of the interfacial or solid-solvent reaction leading to solubilization of the molecule, and the rate associated with the diffusional or transport process of the solvated molecule to bulk of the dissolution medium. During the process of solubilization, a stagnant layer which surrounds the particle is saturated with dissolved HPC and drug molecules. HPC as a water-soluble polymer do not show saturation solubility as such, but rather swell and absorb water to produce a continuum of concentration between the solid surface and the bulk medium which resulting in increasing the thickness of the diffusion layer [15, 16]. Although the solubilization process can occur fast for the agglomerates obtained in presence of HPC as a consequence of improving wettability (Table 1), in the diffusion layer, the viscosity is sufficiently high to render diffusion through the concentrated layer slow, thereby impeding dissolution. In other words, the solubilization process might be neutralized by the diffusion process by increasing the viscosity of the solution around the solid particle as discussed above. No significant differences ($p>0.05$) could be observed in the drug release behavior of the agglomerates by increasing HPC concentration from 0.1 to 0.5% (wt) in crystallization medium. As discussed previously, increasing HPC concentration in crystallization medium delays drug crystal precipitation and solid crust

formation at the droplet surface which consequently causes forming more pores in the agglomerates as shown in Figure 1. Porous structures of the agglomerates obtained in presence of high concentrations of HPC are probably able to facilitate the penetration of the dissolution medium into the agglomerates, explaining the not effective delay of drug release due to increasing HPC concentration from 0.1 to 0.5% (wt) in crystallization medium.

According to solubility results, modifying dissolution rate of naproxen from the agglomerates as a consequence of improving solubility of drug in the presence of HPC may be ruled out. As reported in a previous study [6], the naproxen particles crystallized in the presence of 1% of HPC consisted of about 5.5% (w/w) HPC. Therefore, by dispersing 100 mg of these particles in 900 ml of water, the concentration of HPC in the medium would be about 0.0006% (wt). The results of Table 2 indicate that this concentration is far below that required to affect the naproxen solubility. Similar results have been reported by Chiou et al. [17], who showed that although surfactants can increase the solubility of poorly soluble compounds, the amounts of surfactant adsorbed onto the drug particles crystallized in the presence of surfactants are probably too small to affect the solubility of the drug in bulk solution.

4. Conclusion

In the present study, the observed changes in size and morphology of naproxen particles and reduction in the yield are indicative that HPC is an effective additive during the crystallization of naproxen. In previous studies, it has been shown that crystallization of naproxen in the presence of HPC improved its compaction properties. The results of this study indicate that this crystallization process also caused a marked modification in the dissolution rate of the obtained particles. It was shown that the dissolution rate of naproxen from the agglomerates could be easily modulated with adjusting the concentration of HPC in the crystallization medium.

References

[1] Brittan HG, Vippagunta SR, Grant D J W. Crystalline solids. *Adv Drug Delev Rev* 2001; 48: 3-26.

[2] Davey JR. *The role of additives in precipitation processes*. In: Janic, S.J., De Jong, E.S. (Eds.), Industrial Crystallization. North Holland, The Netherlands, 1982; pp. 123-35.

[3] Mullin JW. *Crystallization*, third ed. Butterworths, Oxford. 1993.

[4] Khamskii EV. *Some problems of crystal habit modification*. In: Mullin, J.W. (Ed.), Industrial Crystallization. Plenum, New York. 1976; pp. 215-21.

[5] Kibbe AH, Wade A, Weller PJ (Eds.), *Handbook of Pharmaceutical Excipients*, second ed., American Pharmaceutical Association, 1988; pp. 223-8.

[6] Maghsoodi M, Hassan-Zadeh D, Barzegar-Jalali M, Martin G, Nokhodchi A. Improved compaction and packing properties of naproxen agglomerated crystals obtained by spherical crystallization technique. *Drug Dev Ind Pharm* 2007; 33: 1216-24.

[7] Kawashima Y, Takenchi H, Niwa T, hino T, Yamakoshi M, Kihara K. Preparation of spherically agglomerated crystals of an antibacterial drug for direct tabletting by a novel spherical crystallization technique. *Proc. 5th Int Conf Pharm Technol* 1989; 3: 228-34.

[8] Lu GW, Hawley M, Smith M, Geiger BM, Pfund W. Characterization of a novel polymorphic form of celecoxib. *J Pharm Sci* 2006; 95: 305-17.

[9] Raghavan SL, Trividic A, Davis A F, Hadgraft J. Crystallization of hydrocortisone acetate: influence of polymers. *Int J Pharm* 2001; 212: 213-21.

[10] Daniels R, Barta A. Pharmacopoeial cellulose ethers as oil-in water emulsifiers. I. interfacial properties. *Eur J Pharm Biopharm* 1994; 40: 128-33.

[11] Raghavan SL, Schuessel K, Davis A, Hadgraft J. Formation and stabilization of triclosan colloidal suspensions using supersaturated systems. *Int J Pharm* 2003; 261: 153-8.

[12] Rasenack N, Steckel H, Müller BW. Preparation of microcrystals by in situ micronization. *Powder Technol* 2004; 143: 291-6.

[13] Li XS, Wang JX, Shen ZG, Zhang PY, Chen JF,

Yun J. Preparation of uniform prednisolone microcrystals by a controlled microprecipitation method. *Int J Pharm* 2007; 342: 26-32.

[14] Mura P, Bettinetti GP, Cirri M, Maestrelli F, Sorrenti M, Catenacci L. Solid-state characterization and dissolution properties of naproxen-arginine-hydroxypropyl-β-cyclodextrin ternary system. *Eur J Pharm Biopharm* 2005; 59: 99-106.

[15] Craig DQ. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int J Pharm* 2002; 231: 131-44.

[16] Corrigan OI. Mechanisms of dissolution of fast release solid dispersions. *Drug Dev Ind Pharm* 1985; 11: 697-724.

[17] Chiou W L, Chen SJ, Athanikar N. Enhancement of dissolution rates of poorly water soluble drugs by crystallization in aqueous surfactant solution. 1. sulfathiazole, prednisolone and chloramphenicol. *J Pharm Sci* 1976; 65: 1702-4.

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