Dissolution improvement of poorly water-soluble drug by cogrinding method using jar mill

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Abstract: As a representative proton pump inhibitor, Lansoprazole was poorly soluble in water which caused the low oral bioavailability. The present study was carried out to enhance the dissolution of lansoprazole by cogrinding with some commonly used hydrophilic polymers (β-CD, PVP, HPMC, L-HPC, CS, PEG and PVPP) in the weight ratio of 1:1 for 2 h in the jar mill. Samples of coground mixture, micronised drug, and physical mixture were characterized by XRPD, and DSC, the results showed that the drug crystallinity reduced in the coground process. The amount of drug released from the coground mixtures in PBS (pH 6.8, 37°C) in 30 min was 100% approximately (except the coground mixtures prepared with VPP or PEG) while released from the micronised drug was just about 20%. Increasing the hydrophilicity and diminishing the size of drug particles by cogrinding were the main causes for enhancing the dissolution of the drug. The results of the stability study of lansoprazole in coground mixture showed that there were no significant changes in the drug content and dissolution characteristics 6 months later. It is clear that the cogrinding method described in the article is very effective for enhancing the dissolution of the poorly soluble drugs, and it is easy for industrialization, showing a strong potential for future applications.

Keywords: Dissolution improvement; lansoprazole; cogrinding; poorly water-soluble drug; jar mill.

INTRODUCTION

At present, about 40% of compounds arising from combinatorial screening were poorly water soluble, up to 60% of compounds coming directly from synthesis were poorly soluble (Lipinski, 2002). Poorly water-soluble compounds often show low bioavailability when administered orally, because the absorption of the drug in the gastrointestinal tract can usually be a rate-limiting step (Sugimoto *et al*., 1998). Therefore, it is important to improve the dissolution of such kind of drugs.

Lansoprazole(LSP),2-(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl) methyl sulfinyl benzimidazole, is a benzimidazole derivative which selectively inhibits the H^+/K^+-atpase of the parietal cell of the stomach(Nagaya *et al*., 1989; Gerloff *et al*., 1996). As a representative proton pump inhibitor, LSP has been clinically used in the therapy of gastric and duodenal ulcerative diseases (Bara-dell *et al*., 1992; Spence and Faults, 1994). Moreover, LSP is practically insoluble in water and has high lipophilicity (log P=2.875). Thus the dissolution rate of lansoprazole is expected to limit its absorption from the gastrointestinal tract (Amidon *et al.*, 1995). Attempts to increase the oral bioavailability of the drug have therefore chiefly centered on particle size reduction. Increasing the rate and extent of dissolution of LSP by micronization has been shown to lead to an increased oral bioavailability directly, which finally allows reduction in dosage (Thanos *et al.*, 2003).

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A much more direct way of increasing the dissolution velocity is by increasing the surface area of the drug powder, i.e. micronization often diminishes the mean particle size of the drug to 3-5 μm approximately. However, many of the new compounds showed the absolutely low solubility which micronization can't lead to a sufficient increase of the bioavailability in oral administration. Therefore, the next step to take was nanonisation, the drug powder was transferred to the nanocrystals, the typical size of which was about 200-600 nm (Hancock and Zografi, 1997; Grau *et al.,* 2000).

There are several methods to reduce the size of drug particles such as pulverization of large particles using a ball mill or jar mill (Liversidge *et al*., 1992; Bruno *et al.,* 1996). Particle engineering technology has drawn much attention as the method could enhance the solubility and bioavailability of the poorly water-soluble drugs significantly (Shabouri, 2002). Generally, fine drug particles could be prepared by spray drying, rapid expansion of the supercritical solution (RESS), grinding method and so on (Kayrak *et al*., 2003; Charoenchaitrakool *et al*., 2000; Nykamp *et al*., 2002). The grinding method shows several advantages such as being performed easily and environmental friendly since it requires no organic solvents (Tozuka *et al*., 2004).

However, grinding hydrophobic drugs usually caused the aggregation of drug particles (Fukami *et al*., 2006) and consequently resulted in the limitation of size reduction and low enhancement for oral bioavailability. Cogrinding

of the poorly water-soluble drug with hydrophilic polymers has been found to be a simple and effective method to make the drug particles being smaller and in a more stable state (Yamada *et al*., 1999; Wongmekiat *et al*., 2002; Wongmekiat *et al*., 2003), and the method is environment friendly comparing to other techniques, it does not require organ solvents and sophisticated equipments. Therefore, it is suitable for industrial manufacture on a large scale (Toshio *et al*., 1995; Masaaki *et al*., 1996; Hideaki *et al*., 1997; Fumihiko and Yoshiharu, 1997). In this research, we cogrinded LSP with some commonly used hydrophilic polymers such as Polyvinylpyrrolidone (PVP), β-cyclodextrin (β-CD), Hydroxypropyl Methyl Cellulose (HPMC), low substitution Hydroxypropyl celllusose (L-HPC), Polyethy-lene glycol (PEG), Cross linking Polyvinyl-pyrrolidone (PVPP) and Chitosan (CS) in the jar mill with the weight ratio of 1:1 to improve the dissolution of LSP, accordingly improving its oral bioavailability. The 1:1 w: w ratio was selected to maximize the likelihood of observing any interaction(Mura *et al*., 1998). The main focus of the research was on identifying which one of the polymers could enhance the dissolution of lansoprazole and studying the storage stability of the cogrinding samples, expecting to maintain the crystalline structure of the drug to meet the stability problems which often associated with the amorphous form.

MATERIALS AND METHODS

Materials and reagents

Lansoprazole was purchased from Avilive pharmaceuticals Co. Ltd (Zhejiang, China). PVP (Polyvinylpyrrolidone, Plasdone®K29/32) was kindly gifted from ISP Chemicals Co. Ltd. (Shanghai, China). β-CD (Betacyclodextrin)was kindly supplied by Nihon Shokuhin Kako Co. Ltd.(Japan). HPMC (hydroxypropyl methyl cellulose) and L-HPC (low substituted hydroxyprepyl cellulose) were kindly gifted from Shinetsu (Japan). PEG 6000 (polyethylene glycol 6000) and PVPP (Crospovidone) were purchased from BASF Co. Ltd. (Gamany). CS (Chitosan) was obtained from Gollden Shell Biochemical Co. Ltd. (Zhe-jiang, China). All other reagents were of analytical grade.

Preparation of coground and physical samples

The cylindrical jar of the rolling jar mill (WL-21, Abbe Inc., Chongqing, China) was filled with zirconia balls up to 600 ml which gave the ball charge of about 40% of its total internal volume (V/V), the diameter of the zirconia balls was 1 mm. The gasket between the lid and the jar ensured a well-sealed system during cogrinding. The rotation speed of the cylindrical jar was 85 rpm. 48 g of powder mixture (LSP and hydrophilic polymers include β-CD, PVP, HPMC, L-HPC, CS, PEG or PVPP) was added to the jar in each batch experiment. This jar milling process was much less energy intensive compared to the ball milling with high energy. No increase in the temperature was noted within the sensitivity of ±1°C during the cogrinding process. Coground mixtures (GM): The powder mixture comprised of LSP and hydrophilic polymer (β-CD, PVP, HPMC, L-HPC, CS, PEG or PVPP) in the weight ratio of 1:1 was milled at 25°C in the jar mill for 2 h, and the milled powder was sieved with the mesh size of 100 and stored in the glass vials at room temperature for further analysis.

Physical mixtures (PM): LSP and hydrophilic polymer (β-CD, PVP, HPMC, L-HPC, CS, PEG or PVPP) was respectively milled at 25°C in the jar mill for 2 h, and mixed in the weight ratio of 1:1 for 15 min. The milled powder was sieved as described above.

Assay of the drug content

The total concentration of LSP in samples was determined using HPLC (SHIMADZU, LC-20AT, Japan) system equipped with an UV detector, a quaternary pump, a degasser, an auto-sampler, a column heater. LSP was separated by a C18 column (Diamonsil, 5 μm, 4.6 mm ×250 mm, SHIMADZU, Japan) guarded with a refillable pre-column (C18, 2.0 mm × 20 mm, Alltech, USA) at 40 °C. The wavelength was set at 284 nm. The mobile phase was the mixture of acetonitrile/water/n-triethylamine/ phosphoric acid (700/300/5/1.5, V/V), adjusted the pH to 7.3 with phosphoric acid, pumped at the flow rate of 1.0 ml/min. A set of seven calibration standards was run with each series of the samples. All experiments were performed in triplicate. The inter-day variations were less than 7.0%. Linear calibrations were obtained between 0 and 10 μg/mL, the coefficient correlation was greater than 0.99, and the limit of quantification was 10 ng/mL.

Dissolution study

The dissolution study was performed using a dissolution tester (ZRS-8G, Tianjin, China) based on the method Ⅱ in Pharmacopoeia of China (paddle method). The samples containing 15 mg of lasoprazole were added 1000 ml of phosphate buffer (pH 6.8), and maintained at 37±0.5°C with the paddle rotation speed of 100 rpm. At each predetermined sampling time, 10 ml of the sample was withdrawn and filtered through the Millipore membrane (Millex® AP, 0.45 μm). The concentrations of lasoprazole which dissolved from the samples (micronised LSP, PM and GM) in the filtrate were determined using the spectrophotometer (UV-160, Shimadzu, Kyoto, Japan). All experiments were performed in triplicate.

Differential Scanning Calorimetry (DSC)

Thermal analysis of the samples (micronised LSP, hydrophilic polymers, PM and GM) were carried out using the Differential Scanning Calorimeter (DSC, 204A/G phoenix® instrument, Netzsch, Germany). Accurately weighed samples (10 mg) were placed in the sealed Luminal pans with pierced lid and scanned at the

heating rate of 10°C/min over the temperature range of 30-300 °C. The instrument was calibrated with indium and zinc prior to analyze of samples under the nitrogen atmosphere, the nitrogen flow rate was at a rate of 100 ml/min.

X-ray powder diffractometry (XRPD)

XRPD of the samples (micronised LSP, hydrophilic polymers, PM and GM) was performed with the X-ray diffractometer (X′pert PRO, Panalytical, Holland) over the 2-40°2θ range at the scan rate of 1°/min, where the tube anode was Cu with Kα equal to 0.154 nm monochromatized with a graphite crystal. The pattern was collected with 40 kV of tube voltage and 40 mA of tube current in the step scan mode (step size 0.05, counting time 1 s/step).

Storage stability studies

Samples (micronised LSP, PM and GM) were stored in the watch-glass in an air-conditioned room, maintaining at the temperature of 23-25°C, and relative humidity (R.H.) of 75%. 6 months later, the drug content and dissolution characteristics were studied to evaluate the storage physical stability of the samples.

Statistical evaluation and presentation

Results from the solubility and the dissolution studies were presented as mean values with standard deviations.

RESULTS

Assay of the drug content

The results of the stability studies for LSP showed that the total concentrations of LSP in the samples were almost the same. It showed that the process of cogrinding could keep LSP quite stable, which indicated that cogrinding

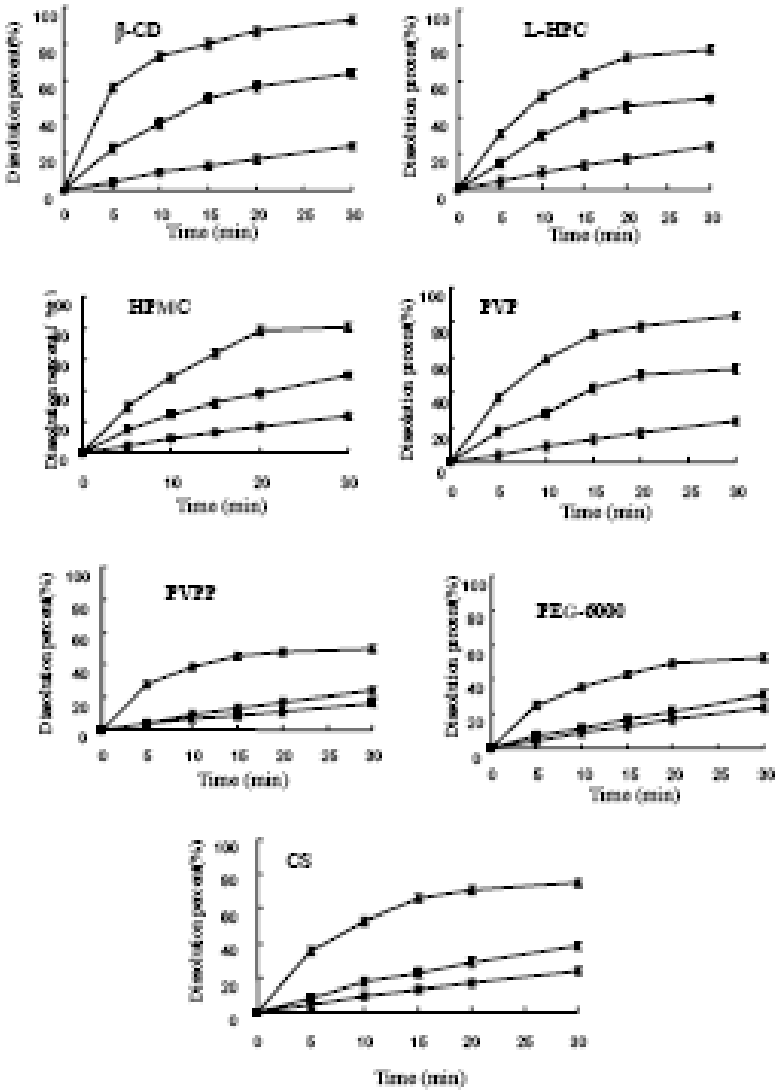

Fig. 1: Dissolution profiles of 15 mg lansoprazole in PBS (pH 6.8, 37±0.5°C, n = 3, ±SD). (◆) indicates micronised lansoprazole. (■) indicates micronised lansoprazole in a physical mixture with the polymer (1:1). (▲) indicates a binary co-ground mixture with the polymer (1:1).

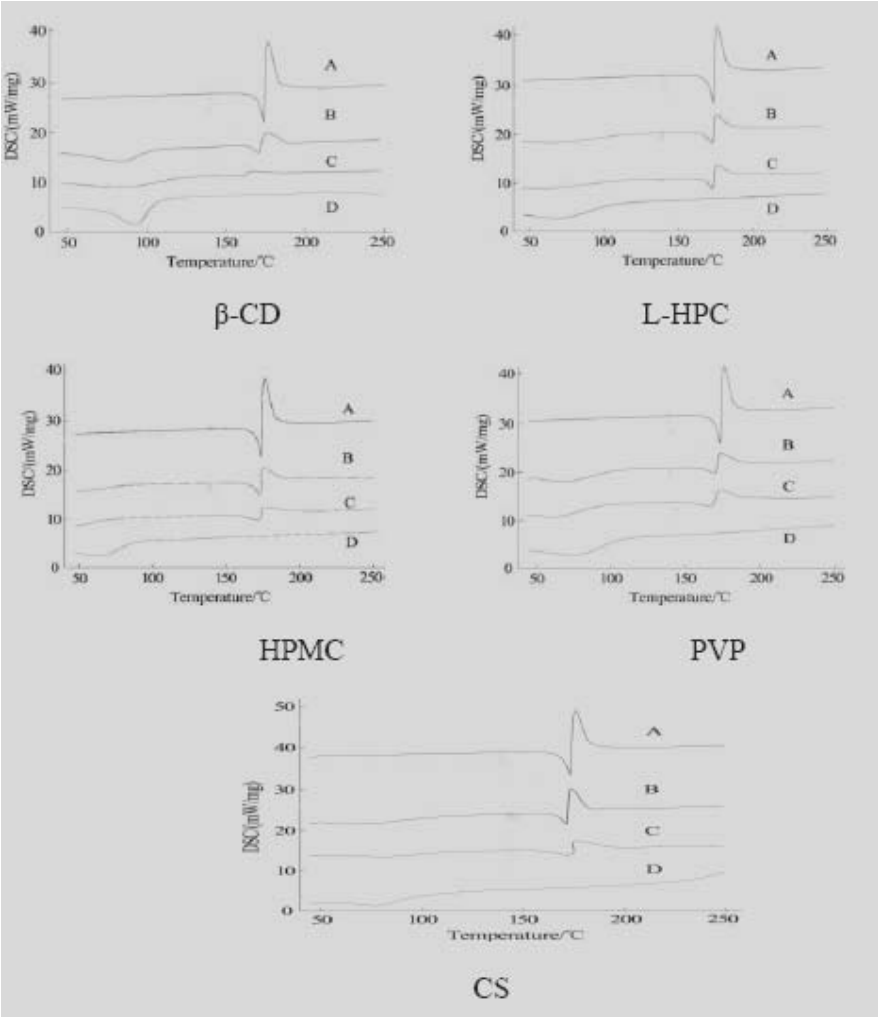

Fig. 2: DSC thermo-grams of pure drug Lansoprazole (A), micronised lansoprazole in a physical mixture with the polymer (1:1, B). Co-ground mixtures of the drug with the polymer (1:1, C), and hydrophilic polymer (D).

method could be made full use of to improve the dissolution rate of the poorly hydrophilic drugs such as lansoprazole.

Dissolution studies

The dissolution curves of micronised LSP, physical mixtures and coground mixtures were shown in fig. 1. As can be noted, cogrinding made the significant improvement of the dissolution characteristics of LSP, the dissolution rate of coground mixtures were faster than the micronised drug and the physical mixture samples. In addition, β-CD made the most obvious solubilization effect and PVPP made the worst effect. The sequence of polymer which made solubilization effect on LSP in the coground mixture was: β-CD> PVP> HPMC> L-HPC> CS> PEG> PVPP.

Solid-state studies

DSC was carried out to investigate the effect of cogrinding on the thermal behavior of the samples (micronised LSP, hydrophilic polymers, PM and GM). The DSC thermograms, enthalpy and melting point data of the samples were shown in fig 2. The DSC curve of LSP was typically a crystalline anhydrous substance, with a sharp fusion endotherm peaked at 151.0~169.0^{o}C, and a sharp fusion exothermic peaked at 168.0~179.0^{o}C. The characterristic melting peak of LSP appeared practically unchanged in all the examined binary systems, but they appeared to be reduced in intensity. This indicated that the milling for the drug in the jar mill didn't induce any amorphous-ness in the samples but made the drug being microcrystalline. In addition, the peak in the ß-CD coground mixture disappeared totally indicating that the drug conversed to the amorphous state. In binary mixtures of drug and carrier (either PM or GM samples), the significant reduction in melting point and enthalpy was observed.

The XRPD (X-ray powder diffractometry) analysis were carried out for the samples (micronised LSP, hydrophilic polymers, PM and GM), and the XRPD pattern were shown in fig. 3. The XRPD of pure LSP showed the

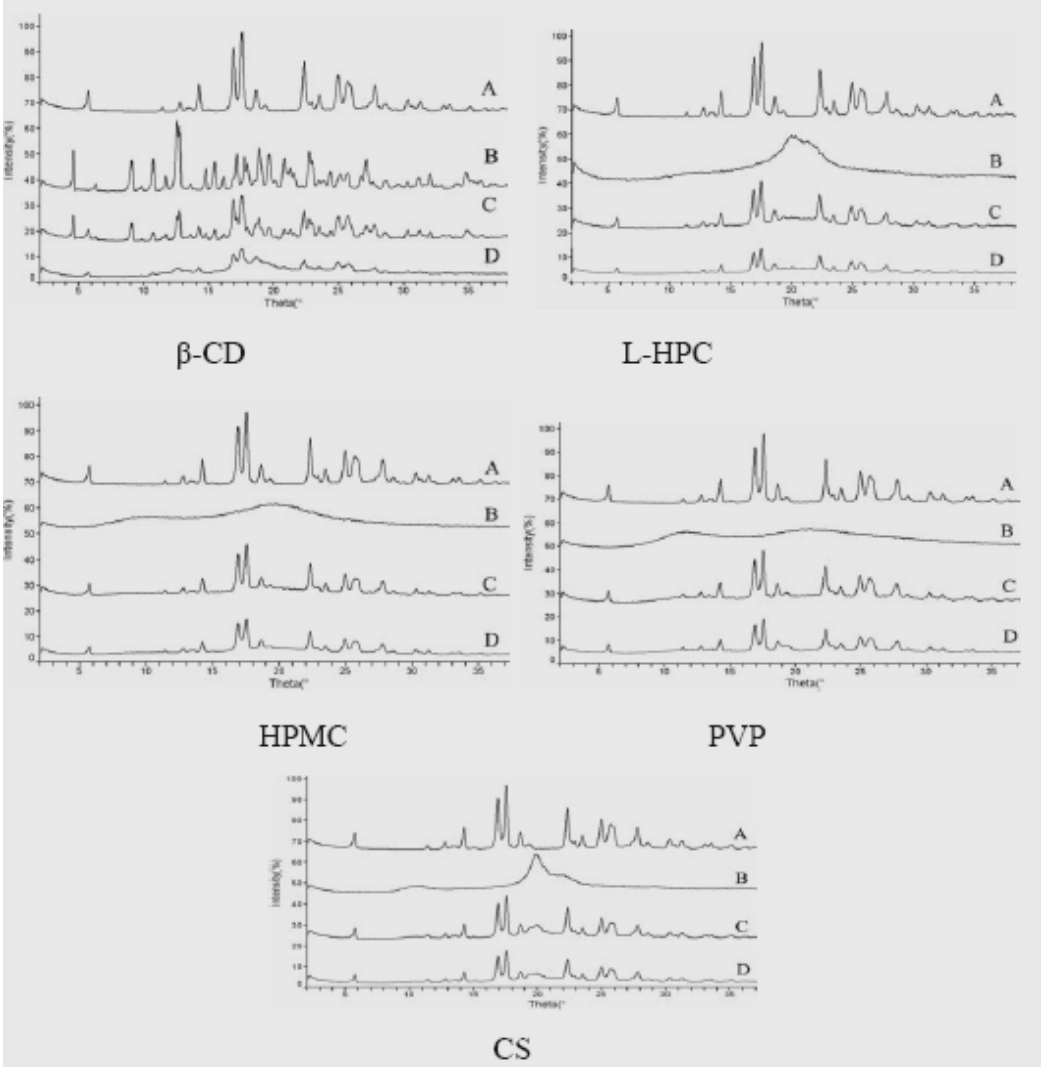

Fig. 3: X-ray analysis of pure drug Lansoprazole (A), hydrophilic polymer (B), micronised lansoprazole in a physical mixture with the polymer (1:1, C) and co-ground mixtures of the drug with the polymer (1:1, D).

characteristics peaks at 14°～28° at (2 θ). As shown in fig 3, the peaks of LSP disappeared after cogrinding with β-CD. On the other hand, the XRPD peaks for LSP persisted with a decrease in their intensity in physical mixtures and other coground mixtures samples. This indicated that the interaction between LSP and β-CD was the reason of rapid amorphization for LSP by cogrinding, but the other polymers just turned LSP into microcrystalline.

Stability of Stored Samples

The data collected from the samples (micronised LSP, hydrophilic polymers, PM and GM), which stored in the watch-glass in an air-conditioned room, maintaining at the temperature of 23-25^{o}C for 6-months were compared with those from the samples just prepared then. The results of assaying of the drug content showed that there was little reduction in the total concentration of LSP in the samples. For GM samples, the dissolution results which shown in fig 4 had no significant changes 6 months later, which indicated that the GM had good stability in 6 months, but for PM samples, the dissolution degraded significantly 6 months later due to the aggregation of the drug particles which resulted in the increasement of the particles size, since the reduction of particles size could enhance the dissolution of the drug.

DISCUSSION

With respect to the processing considerations, the homogeneity of the coground mixtures was extremely high. Cogrinding thus could be considered one of the most suitable methods to improve the content uniformity, especially for low dose formulations of high potency compounds.

At the surface of the drug crystal, the concentration of drug resulted from a balance of dissolution of the solid

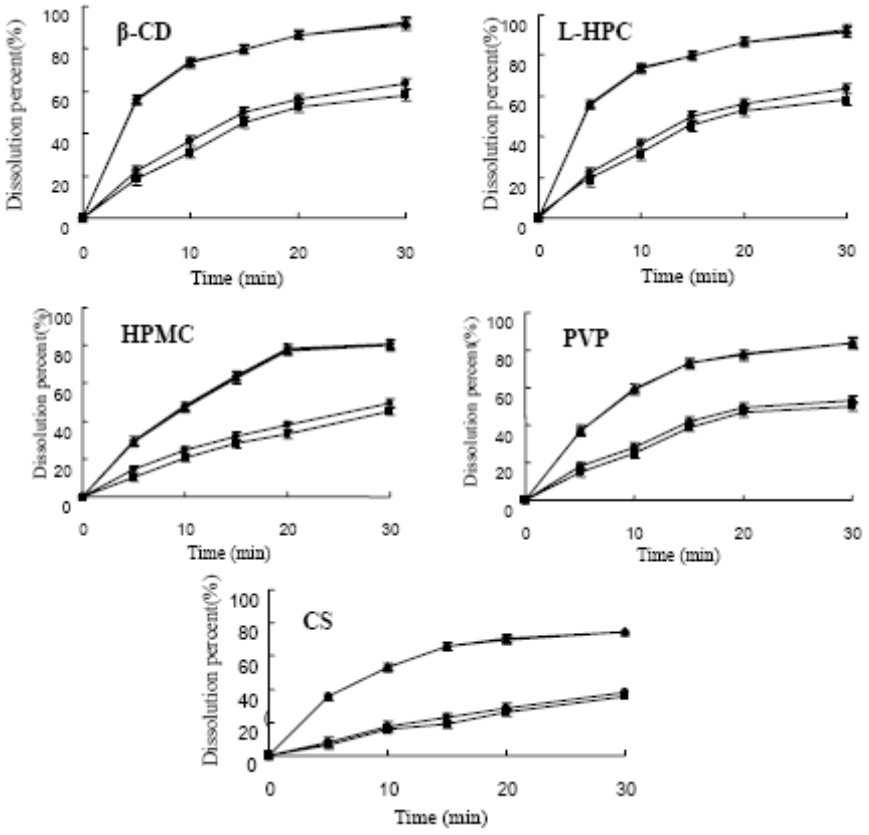

Fig. 4: Dissolution profiles of 15 mg lansoprazole in PBS (pH 6.8, 37±0.5°C, n=3, ±SD)(◆) indicates a binary coground mixture with the polymer (1:1) (▲) indicates a binary co-ground mixture with the polymer (1:1) stored at 25°C and 75% RH for 6 months.(●) indicates micronised lansoprazole in a physical mixture with the polymer (1:1)(■) indicates micronised lansoprazole in a physical mixture with the polymer (1:1) stored at 25°C and 75% RH for 6 months.

drug and deposition of crystals from the surrounding solution. Presence of a polymer at the surface slowed down the process of down the diffusion of the drug molecules to the solid surface and by reducing the surface area available for nucleation on the particle surface. On the other hand, presence of a polymer at the dissolving surface restricted the access of water molecules to the crystal surface (Sekikawa *et al*., 1978; Simonelli *et al*., 1970; Ziller and Rupprecht, 1988), thus slowing the dissolution of LSP. In the Lansoprazole dissolution studies, the polymers PVP, L-HPC and HPMC, were able to substantially decrease the rate of recrystallization but the diffusion barrier resulted in a lower rate of dissolution than observed for the β-CD cogrind sample.

As shown in fig. 1, the cogrinding of LSP with β-CD, PVP, HPMC, L-HPC, or CS could be an effective method to improve the dissolution rate of LSP. The results also proved that the physical mixtures of drug and hydrophilic polymer had solubilization effect on the poorly water-soluble drug to some extent.

When grinding the drug alone, the specific surface area of the particles increased when the particle size diminished, and consequently, the dissolution of the drug enhanced to some extent. Nevertheless, the Gibbs free energy would just be major when the particle size over diminished, and the drug particle would aggregate to be larger which would degrade the dissolution of the drug. When cogrind the drug with the hydrophilic polymers, the entropy value of the binary system would increase, the Gibbs free energy would diminish as shown by the second law of thermodynamics ($\Delta G=\Delta H-T\times\Delta S$), and the particles size could diminish further which resulted in enhancement of the dissolution of the drug. In addition, the hydrophilic polymers in the coground mixtures played a role of stabilizer, the strand like polymer which adhered to the small drug particles made the ruleless movement, educed the steric effect and consequently delay or forbid the agglomeration, grow-up and recrystallization of the drug (Lee *et al.* 2005). Meanwhile, the hydrophilicity of the polymers enhanced the wettability of the drug, and facilitated the dispersion and dissolution of the drug

particles. Thus, cogrinding could improve the dissolubility and dissolution rate of the drug.

CONCLUSION

The present study showed the cogrinding of hydrophilic polymers such as β-CD, PVP, HPMC, L-HPC, CS with the poorly water-soluble drug, lansoprazole, compared the dissolution characteristics between the cogrinding samples and physical mixtures, and studied the stability of the cogrinding samples. In conclusion, the cogrinding technique could be usefully applied in improving the dissolution characteristics of lansoprazole, even if much smaller amount of hydrophilic polymers were used (LSP/hydrophilic polymers=1:1, w/w). The results indicated that the hydrophilic polymers improved the dissolution crystallization by slowing characteristics of LPS and showed the perfect physical stability by preventing reversion of drug from the crystalline state to the amorphous state after cogrinding. This simple method could be further extended for the dissolution enhancement of the other poorly water-soluble drugs. The cogrinding technique, unlike the other solid dispersion techniques, was economically and environmentally desirable. In cogrinding approach, the use of toxic organic solvents could be easily avoided. Therefore, it was suitable for industrial manufacture on a large scale.

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