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Development and optimization of solid dispersion containing pellets of itraconazole prepared by high shear pelletization

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Abstract

This study investigated the solid dispersion containing pellets of itraconazole for enhanced drug dissolution rate. The influence of process parameters used during high shear pelletization on the pellet properties including pellet size and dissolution rate was also studied. Solid dispersions of itraconazole were prepared with Eudragit® E100, a hydrophilic polymer, by a simple fusion method followed by powdered and characterized by differential scanning calorimetry and X-ray powder diffraction. Solid dispersions containing pellets were consequently prepared using a lab-scale high shear mixer. In order to improve the product quality, a central composite design was applied to optimize the critical process variables, such as impeller speed and kneading time, and the results were modeled statistically. Itraconazole was presented as an amorphous state in the solid dispersion prepared at a drug to polymer ratio of 1:2. Both studied parameters had great effect on the responses. Powdered solid dispersion and pellets prepared using the optimal parameter settings showed approximately 30- and 70-fold increases in dissolution rate over the pure drug, respectively. Solid dispersion prepared by simple fusion method could be an option for itraconazole solubility enhancement. Pelletization process in high shear mixer can be optimized effectively by central composite design.

Keywords: Itraconazole; Solid dispersion; Dissolution enhancement; High shear pelletization; Pellet characteristics; Central composite design

1. Introduction

Itraconazole is a potent synthetic triazole antifungal drug with activities against broad spectrum of fungal species (Saag and Dismukes, 1998; Odds et al., 2000; Jain and Sehgal, 2001). It has a molecular formula $C_{35}H_{38}C_{l2}N_8O_4$ and molecular weight of 705.64, and is a weak basic drug, possessing extremely low water solubility ($S \sim 1$ ng/ml at neutral pH and $S \sim 6$ μg/ml at pH 1), and pK_a of 3.7 (Peeters et al., 2002; Heykants et al., 1989). The mechanism of action of this compound is similar to all other azole antifungals. It inhibits cytochrome P450 of the fungi and thus interferes in sterol biosynthesis in cell membrane, leading to cell death (Heykants et al., 1987). According to the biopharmaceutics classification system, itraconazole is an extreme example of a class II compound meaning that its oral bioavailability is determined by dissolution rate in the GI tract (Amidon et al., 1995; Dressman et al., 1998, 2001).

Today, 35–40% of all new chemical entities suffer from poor aqueous solubility. It is generally recognized that low solubility or dissolution rate often becomes a rate-limiting step in absorption of poorly water-soluble drugs from GI tract and compromises oral bioavailability because the driving force for absorption of most drugs across biological membranes is concentration of drug in solution (Maeda et al., 1979; Chiba et al., 1991). Therefore, the enhancement of the dissolution rate of poorly water-soluble drugs after oral administration is one of the most challenging aspects of modern pharmaceutics.

Some techniques, such as size reduction and solid dispersion, have been applied to increase the solubility and dissolution properties of poorly water-soluble drug. Solid dispersion is a system in which drug particles are distributed throughout a solid matrix. Particle size of drugs in this system may be reduced markedly, and the physical state of the drug may be transformed from the crystalline to partially amorphous in this system. Therefore, this system provides the possibility of enhancing the solubility or

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dissolution rate remarkably (Kislalioglu et al., 1991; Moyano et al., 1997; Van den Mooter et al., 2001; Gruenhagen, 1995).

Although the use of solid disperse technique for solubility enhancement of itraconazole has been reported by several authors (Leuner and Dressman, 2000; Jung et al., 1999; Verreck et al., 2003), there are only two main methods for the solid dispersion preparation: solvent casting and melt extrusion. However, these methods require either the application of organic solvent or specialized equipment. There is definitely a need to explore a simple method for itraconazole solid dispersion preparation.

Pellets are defined as the multiple-unit dosage form and believed to have many therapeutic advantages, such as effectiveness and safety, over the single-unit dosage forms. High shear granulation and pelletization have been widely used in the pharmaceutical industry and have many advantages over other techniques (Parikh, 1997). Different phases of growth were identified for high shear pelletization: nucleation, fragmentation, densification, exponential growth due to coalescence, and break up (Vonk et al., 1997). The pelletization is a multivariate process and the product properties are sensitive to the change of the process variables, such as impeller speed and kneading time. Hence it is important to optimize these critical parameters (Vonk et al., 1997; Voinovich et al., 2000, 2001; Hamdani et al., 2002; Ameye et al., 2002).

Central composite design (CCD) is a response surface design which provides information on direct effects, pairwise interaction effects and curvilinear variable effects and is widely used for formulation and process optimization in the field of pharmaceutics (Krogars et al., 2000; Vaithiyalingam and Khan, 2002). High shear manufacturing process of theophylline containing pellet has been evaluated successfully using a face-centered CCD (Dévay et al., 2006). It is very efficient and flexible, providing much information on experiment variable effects and overall experimental error in a minimal number of required runs. Therefore, circumscribed CCD is a very suitable tool for process optimization of high shear pelletization in this study.

The objectives of this present study are: (a) to investigate if it is possible to enhance the dissolution rate of itraconazole by using solid dispersions, which are produced by a simply fusion method, as the raw material to prepare pellets in a high shear mixer; (b) to optimize the process parameters which powerfully affect the characteristics of the resultant pellets by a central composite design.

2. Materials and methods

2.1. Materials

All the chemicals used in this research were of standard pharmaceutical grade. Itraconazole was purchased from Tianjin Lisheng Pharmaceutical Co. Ltd. (Tianjin, China), methacrylic acid copolymers (Eudragit® E100) from Röhm Pharma (Germany), and microcrystalline cellulose (MCC, Avicel PH 101) from Asahi Kasei (Japan). Methanol was HPLC grade and other reagents were analytical reagent grade. Purified water was used as the binder liquid.

2.2. Equipment

A laboratory-scale vertical high shear mixer (MicroGral®, Collette, Belgium) equipped with a transparent glass bowl of 1000 ml, which makes the entire process visible, a three-blade impeller with curved blade tips and a chopper was used for pelletization in this study. In this design of mixer-granulator, both impeller blades and chopper are mounted on vertical shaft fixed through the lip, so that the vessel is easily removable and changeable. The rotational speed of impeller and chopper can be varied between 0–1800 and 0–4000 rpm, respectively. Throughout the pelletization process, the product temperature (IR temperature probe), the torque (N m), the rotational speed of impeller and chopper were measured and record.

2.3. Preparation of solid dispersions of itraconazole

Solid dispersions of itraconazole were prepared by a fusion method. Initially, itraconazole and Eudragit® E100 were mixed thoroughly in a blender for 10 min. The mixture was spread out in a very thin layer on a stainless steel pan followed by gradual heating until it reached a molten state (the temperature was around 175 °C). This molten mixture was then cooled hastily by keeping the undersurface of the pan touching tightly with ice, resulting in rapid solidification of Eudragit® E100 and formation of solid dispersion of itraconazole. The resulting solid dispersions were collected after milling for 1 min with a laboratory mill and sieving to exclude particles which are larger than 250 μm.

2.4. Preparation of pellets

Itraconazole solid dispersion containing pellets were prepared in the laboratory scale high shear mixer. Purified water was used as the binder liquid. A powder mixture containing 30% itraconazole solid dispersion and 70% microcrystalline cellulose were used as raw material and the total mass for each batch is 100 g. The powders were filled into the vessel and premixed for 3 min using the same impeller speed which was applied in the following pelletization and the chopper was off during this stage. A precisely determined amount of binder liquid (55 ml) was then added to the powder mix using a titration device (Universal Titronic, Schott, Germany) in 5 min while the impeller and chopper were running, and the mass was kneaded for a preset period of time after the liquid addition. In order to remove the material adhering to the inner surface of the bowl, the pelletization process was interrupted every 60 s to scrap the bowl. Prior to standard analysis, the pellets produced were dried to constant weight in a tray dryer at 40 °C and then stored in sealed bags.

2.5. Experiment design

To reduce the number of trials needed to attain the highest amount of information on product properties, the screening was planned applying a circumscribed central composite design. The process variables including impeller speed and kneading time (processing time after the liquid addition) were defined

Table 1
Factors and levels of the circumscribed central composite design

Normalised levels	Experimental settings	
	x_1 impeller speed (rpm)	x_2 kneading time (s)
−1.414	400	120
−1	488	146
0	700	210
1	912	274
1.414	1000	300

as factors, the percentage yield and the dissolution rate of pellets ranging from 800 to 1000 μm and the medium diameter of the particles, which was defined as particle size corresponding to 50th weight percentile (X_{50}) of the cumulative particle size distribution, were used separately as the responses in the mathematical modeling. Therefore, a special polynomial equation, with six coefficients to estimate, was generated for the description of the measured responses as function of the process variables (Eq. (1)) and then the results were used to approximate the response surface:

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_1^2 + b_4x_2^2 + b_5x_1x_2 \quad (1)$$

where y is the response, b_0 the constant, and b_1, b_2, b_3, b_4, b_5 are the regression coefficient. x_1, x_2 represents the main effect, x_1^2, x_2^2 the quadratic effect and x_1x_2 is the interaction effect. The effects were evaluated statistically at 0.1 level ($\alpha = 0.1$).

The process variables with their relative experimental values are reported in Table 1.

Pellets were produced according to different levels of the factors (Table 1). Each experiment was performed in triplicate.

2.6. Differential scanning calorimetry (DSC)

Thermal analysis of itraconazole, the physical mixtures of itraconazole and Eudragit® E100, and the solid dispersions were carried out using differential scanning calorimetry method. Samples were examined using a Shimadzu TGA-50 DSC instrument (Shimadzu Corporation, Japan). Samples equivalent to approximately 8 mg itraconazole were placed in aluminum pans and heated from 25 to 200 °C with a heating rate of 10 °C/min.

2.7. Powder X-ray diffraction

Powder X-ray diffraction was performed using a Rigaku D/max-2500PC diffractometer (Rigaku, Tokyo, Japan), with monochromatic Cu Kα radiation (λ = 1.5407 Å), voltage 50 kV, current 100 mA and 2θ over a 2–45° range. Diffraction patterns of pure itraconazole, Eudragit® E100 and solid dispersion prepared at the drug-to-polymer ratio of 1:2 were determined.

2.8. In vitro dissolution testing

In vitro drug release was tested using an USP 24 Type2 dissolution testing apparatus (paddle method). Purified water (1000 ml) consisting of 4 ml HCl were used as the dissolution media. Other parameters include paddle speed of 100 rpm, 37 ± 0.5 °C.

For all the dissolution tests discussed in this study, samples equivalent 100 mg itraconazole were added directly into the dissolution medium. The dissolution process was monitored for 1 h and samples were taken at 5, 10, 20 30, 45, 60 min and replaced with an equal volume of the same fresh medium. An aliquot of 5 ml was filtered through a 0.45 μm filter. The sample solutions were diluted and drug released from pellets was determined spectrophotometrically at a wavelength of 254 nm. All experiments were performed in triplicate.

2.9. HPLC analysis

The exact drug content in the pellets was determined using an appropriate HPLC method. The analysis was performed using a Hitachi HPLC system (Hitachi, Japan). The column used was Luna 5u C18 (250 mm × 4.6 mm, Merck, Phenomenex, USA). The mobile phase consisted of methanol, water and 0.065 mol l^{-1} ammonium acetate (70:20:6 v:v:v). The flow rate was 0.8 ml min^{-1}, the injection volume is 20 μl and the UV detector was set at 261 nm.

A certain amount of pellets (10 g) was taken and milled to fine powder. Then about 50 mg powders was accurately weighed, added to a 100-ml volumetric flask containing 20 ml of methanol and sonicated for 10 min. After that a volume of 100 ml was attained by diluted the solution with mobile phase. Precisely 2 ml of the solution which was taken from the flask and then filtered through a 0.22 μm membrane was diluted by mobile phase to obtain a volume of 10 ml. The sample solution was then examined by HPLC method with the conditions described above.

2.10. Pellet size distribution

The pellet size and pellet size distribution were estimated by sieve analysis. Each batch of the pellets was sieved before the subsequent test in order to remove the lumps larger than 2000 μm. Samples of about 50 g was sieved using a set of standard sieves (1600, 1250, 1000, 800, 710, 630, 500 and 400 μm), vibrating at an amplitude of 2 mm for 5 min on a Retsch VE1000 shaker (Germany). The fraction remaining on each screen was weighed and expressed as a percentage of the total weight and medium diameter of pellets was obtained according to the cumulative size distribution. All results presented are the mean of 3 determinations. Pellets ranging between 800 and 1000 μm in size were selected for in vitro dissolution test so that the effect of particle size on dissolution rate is excluded.

3. Result and discussion

3.1. Differential scanning calorimetry (DSC)

In order to investigate the effect of the amount of Eudragit® E100 on the formation of products, different drug/polymer complexes were prepared at drug-to-polymer composition ratios

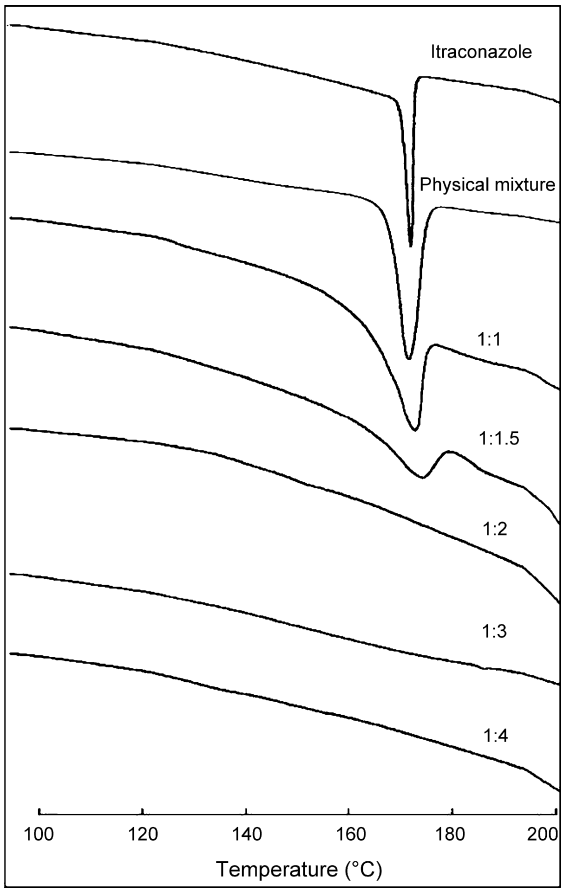

Fig. 1. DSC curves of itraconazole, physical mixture mixed at the itraconazole-to-Eudragit® E100 ratio of 1:2 and solid dispersions prepared by fusion method. The numbers represent the drug-to-polymer ratio (w/w).

(w/w) of 1:1, 1:1.5, 1:2, 1:3 and 1:4 and their thermal characteristics and dissolution profiles were studied by DSC method and dissolution determination, respectively. Fig. 1 shows DSC result of pure itraconazole with a sharp endothermic peak at 175 °C that corresponds to the melting point of itraconazole. The physical mixture of itraconazole and Eudragit® E100 at the ratio of 1:2 also showed an endothermic peak of itraconazole at about 175 °C, which indicated that itraconazole was still present as a crystalline state. On the other hand, as the amounts of Eudragit® E100 were increased, the endothermic peak of itraconazole disappeared gradually. At the ratio of 1:2 and above, the DSC curves without melting peak of itraconazole indicate the absence of crystalline itraconazole and the formation of solid dispersions. However, an X-ray diffraction study would be needed to confirm this. Dissolution profiles of these products are showed in Fig. 2. After the solid dispersions were formed (at the ratios of 1:2, 1:3 and 1:4), improved dissolution profiles with more than 30% of drug of released over pure itraconazole powder were observed, however, no significant difference between the dissolution profiles of these solid dispersions was found (Fig. 2). Therefore, we selected the lowest drug/polymer ratio system (1:2) which gave adequate dissolution and physicochemical properties for the further analysis and development.

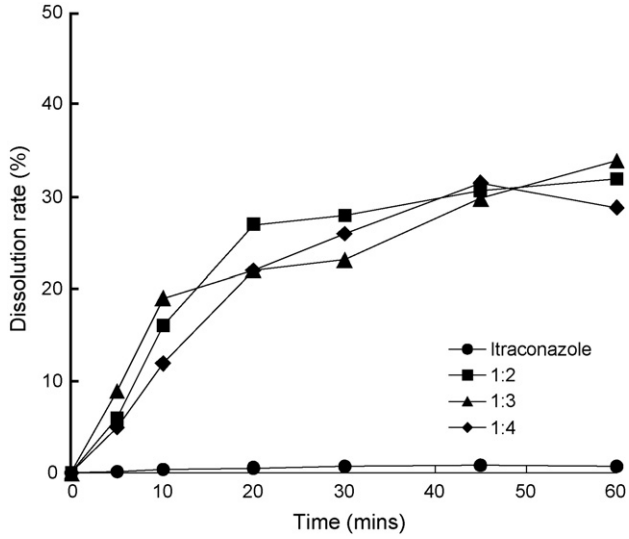

Fig. 2. Drug release profiles of itraconazole and solid dispersions. The numbers represent the drug-to-polymer ratio (w/w).

3.2. Powder X-ray diffraction

The X-ray diffraction patterns for the pure itraconazole, Eudragit® E100 and the solid dispersion are depicted in Fig. 3. Pure itraconazole gave a diffraction peak corresponded to a separate crystalline drug phase. Solid dispersion prepared by fusion method showed the absence of diffraction peak of itraconazole pointing to a transition of itraconazole from a crystalline to an amorphous state as a consequence of the preparation procedure. Both the DSC and X-ray results confirm that itraconazole is present as an amorphous state in solid dispersion and milling did not induce re-crystallization.

3.3. Drug content in pellets

Drug content in prepared pellets was measured by HPLC analysis. The results appear drug content range from 98.6 to 103.6% (Table 2), indicating all pellets prepared according to each designed experiment obtained a high content uniformity.

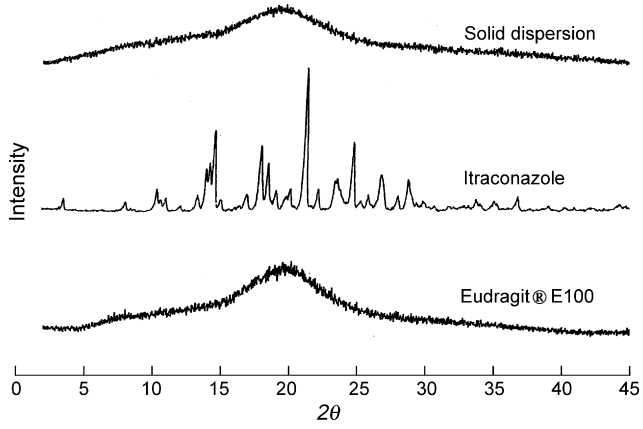

Fig. 3. X-ray powder diffraction results of pure itraconazole, Eudragit® E100 and solid dispersion prepared at the drug-to-polymer ratio of 1:2.

Table 2
Experimental plan, observed response values and drug content in pellets[a,b]

Experiment	Normalised levels of factors		Responses			Drug content
	x_1 impeller speed	x_2 kneading time	y_1 (%)	y_2 (μm)	y_3 (%)	
1	−1	−1	72.9 ± 2.08	679.3 ± 23.12	32.4 ± 1.14	102.8 ± 0.4
2	−1	1	77.6 ± 2.14	842.7 ± 28.43	42.3 ± 0.70	103.6 ± 0.9
3	1	−1	78.4 ± 2.62	814.0 ± 23.52	50.6 ± 0.79	99.4 ± 0.2
4	1	1	80.4 ± 4.65	887.7 ± 19.35	67.1 ± 1.86	100.7 ± 1.0
5	−1.414	0	71.4 ± 0.56	764.7 ± 21.08	36.2 ± 2.42	100.9 ± 0.7
6	1.414	0	81.9 ± 3.02	831.3 ± 21.96	56.7 ± 1.11	98.6 ± 1.1
7	0	−1.414	78.6 ± 0.46	793.7 ± 28.54	40.1 ± 0.92	102.9 ± 0.5
8	0	1.414	84.3 ± 2.87	904.3 ± 34.96	66.8 ± 2.15	101.9 ± 0.3
9	0	0	84.4 ± 0.83	922.7 ± 17.01	62.1 ± 1.37	102.4 ± 0.4
10	0	0	82.6 ± 2.35	899.7 ± 39.55	66.9 ± 1.76	100.6 ± 0.5
11	0	0	80.9 ± 1.10	890.6 ± 12.34	70.8 ± 0.55	99.9 ± 0.8
12	0	0	88.1 ± 1.31	841.1 ± 27.28	67.4 ± 1.64	100.1 ± 0.7
13	0	0	83.6 ± 1.66	913.5 ± 27.78	72.9 ± 1.41	99.5 ± 0.4

[a] Measure responses—y_1: drug dissolved within 45 min (%); y_2: medium diameter (μm); y_3: percentage yield (w/w) between 800 and 1000 μm (%).
[b] Observed values: mean ± S.D., $n = 3$.

3.4. Pellets characterization

Itraconazole solid dispersion containing pellets were prepared according to the circumscribed central composite design. Table 2 gives an overview of the characteristics of these pellets. From the results reported in Table 2, it can be noticed a faster dissolution rate for the pellets: more than 70% of the drug was dissolved within 45 min as compared to less than 1% determined for the pure itraconazole powder. This could be attributed to the presence of the polymer. Eudragit® E100 is a hydrophilic polymer with tertiary amine functional groups. This kind of polymer is soluble at pH < 5 and reported recently for increasing solubility of water-insoluble drugs (Susuki et al., 1996; Jung et al., 1999). In addition, the highly dispersing condition of the drug in the carrier or the transition of the physical state of itraconazole from crystalline to amorphous would help improving the dissolution rate significantly. Another interesting phenomenon must be paid attention to is that pellets prepared in all designed experiments showed dramatically improved dissolution profiles over the raw solid dispersion powder. Similar observation has also been reported but no reason has been presented (Jung et al., 1999). In this study, that may be explained by the fact that the pellets obtained a sufficient wetting as they stayed at the bottom of the testing cup during the entire test process whereas powdered solid dispersion kept afloat as a hydrophobic powder resulting in a lower dissolution rate.

The model equation generated to fit the data and reflected the influence of process parameters on dissolution rate of the drug is as follow:

$$y_1 = 83.92 + 2.894x_1 + 1.845x_2 - 4.067x_1^2$$
$$(r^2 = 0.8456, \quad p < \alpha = 0.1) \tag{2}$$

It can be noted that the coefficients b_4 and b_5 of Eq. (2) had no statistic significance for response y_1, since the statistic p-values of the two coefficients are 0.11 and 0.59, respectively.

With respect to the pellet size characteristics, both responses, y_2 (X_{50}) and y_3 (percent yield between 800 and 1000 μm) were affected remarkably by the investigated process variables. The equations generated are as follow:

$$y_2 = 893.52 + 34.239x_1 + 49.193x_2 - 52.165x_1^2 - 26.658x_2^2$$
$$(r^2 = 0.8963, \quad p < \alpha = 0.1) \tag{3}$$

The coefficient b_5 has no statistical significance ($p = 0.18$):

$$y_3 = 68.02 + 9.000x_1 + 8.020x_2 - 11.250x_1^2 - 7.748x_2^2$$
$$(r^2 = 0.9527, \quad p < \alpha = 0.1) \tag{4}$$

The coefficient b_5 has no statistical significance ($p = 0.44$).

Fig. 4 demonstrates the changes in drug dissolution rate caused by the variation of the process parameter. It was observed that the maximum dissolution rate was near the central region. Taken together with Eq. (2), surface maximum may be reached when the levels of x_1 and x_2 are 0.315 and 0.490, respectively.

Figs. 5 and 6 illustrate the relationship between the corresponding responses and factors. It was found that extending

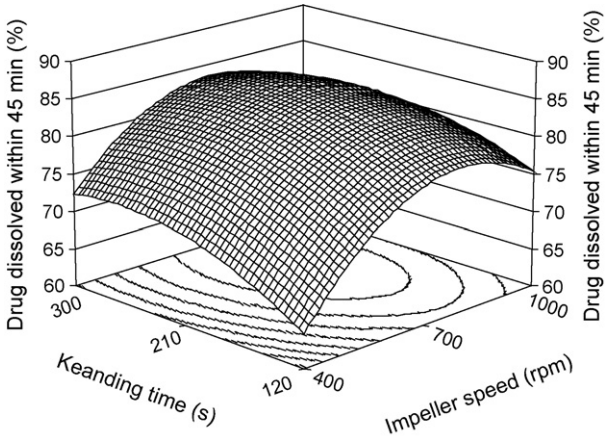

Fig. 4. Influence of impeller speed and kneading time on the dissolution rate of itraconazole.

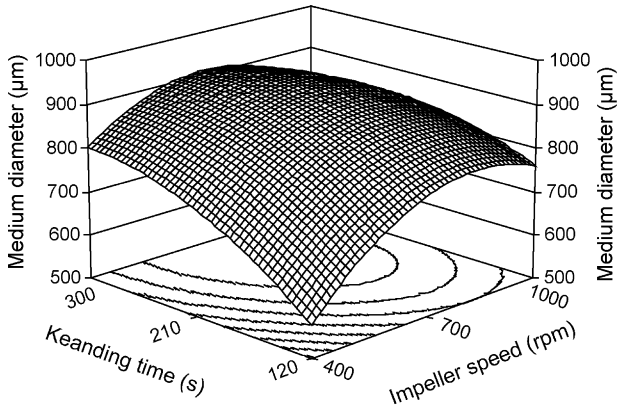

Fig. 5. Influence of impeller speed and kneading time on the medium diameter of pellets.

kneading time caused a shift in particle size distribution towards coarser particles, which can be observed from Table 2 that the X_{50} value grew from 679 μm (experiment no. 1) to 842 μm (experiment no. 2). Generally speaking, prolonging kneading time also increased the percentage yield in the 800–1000 μm size fraction (see experiment nos. 1–4). The observed thoroughly positive effect of kneading time is assumed to be a result of the fact that a long kneading period offers more colliding chances which are necessary for the granule growth. Another reason for this may be the improved wetting of the wet mass during the pelletization process. On the other hand, the influence of kneading time at low levels was more pronounced than that at high levels. This can be reflected by the surface plot as the slope of curve leveled off when high kneading time level was applied. This phenomenon results probably from the equilibrium between the granule growth and breakage. When the kneading time is shorter than 210 s, prolonging kneading time induced the densification of granules as well as offered more colliding chances to the particles. Consequently, the liquid kept inside granules would be squeezed out to the surfaces, which may make the mass wet and adhesive and led to the fast growth of particles. However, at the high levels (>210 s), the closed system was near its growth equilibrium state and the amount of the liquid squeezed out decreased sharply. Therefore, prolonging the kneading time during this stage cannot promote the growth rate significantly.

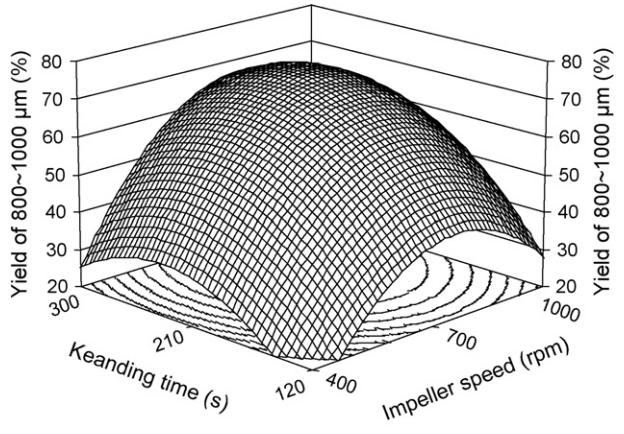

Fig. 6. Influence of impeller speed and kneading time on the percentage yield between 800 and 1000 μm.

With respect to the medium particle size, the impeller speed showed complicated effects. The effects of the impeller speed are similar to those of the kneading time as they can also be divided into two parts; however, there was something different between the influences of these two process variables. Unlike the effect of kneading time, the impeller speed did not cause a constant increasing but a bifacial effect on the particle size. That means there is a positive effect in the first phase while a negative one in the second on the particle size. This is consistent with the results reported by other researchers (Dévay et al., 2006). Fig. 6 demonstrates this relationship.

As shown in Fig. 6, a high value of the speed provoked the formation of large pellets and great percentage yield of the desired size fraction when the impeller speed is below 700 rpm. Other researchers have given the similar results (Zhou et al., 1997; Bock and Krass, 2001). This positive effect could also be probably attributed to the opportunistic collisions provided by the rotation at a high speed. However, when the impeller speed exceeded 700 rpm, a negative effect was found and the result showed a decrease of the pellet medium diameter. The shift of particle size to a smaller medium diameter can be explained by the higher destructive forces of the impeller (Dévay et al., 2006). When the destructive forces resulting from a high speed exceeded the bonding force, breakup of pellets became more important compared to growth of pellets. Although the intensive agitation led to an increasing number of collisions, the chance of successful collisions which is essential for pellet growth is decreased (Ramaker et al., 1998). That means the equilibrium between growth and break-up breaks and the latter is preferred. Therefore, high impeller speed in the second phase retarded the further growth and favored smaller particle medium diameter.

As predicted by the models generated, maximum of percentage yield of the desired size fraction (surface maximum) will appear when the levels of the investigated variables are 0.441 (x_1) and 0.564 (x_2), respectively.

3.5. Validation of model optimization

In order to evaluate the optimization capability of the models generated according to the results of the circumscribed central composite design, pellets including the same formulation were prepared using the optimal process variable settings.

In vitro dissolution and yield comparisons of the results obtained from prepared pellets with that predicted by models are shown in Table 3. The results showed good agreement on product properties with theoretical predictions. The in vitro drug release was also evaluated from pellets which were prepared with the optimal settings after storage in 25 ± 2 °C, 60% RH for 6 months. Dissolution comparisons of initial pellets with those stored for 6 months are shown in Fig. 7. It can be noticed that dissolution rate of the drug after storage for 6 months appeared to be much similar to that obtained at initial time, which indicated pellets were stable under the storage condition.

Table 3
Result of experiments for confirming optimization capability[a]

	Factors			Responses		
	x_1 (rpm)	x_2 (s)		y_1 (%)	y_2 (μm)	y_3 (%)
Trial 1						
Normalised level of factors	0.315	0.490	Model predicted values	84.83	913.37	72.06
Experimental settings	767	241	Observed values	83.5 ± 1.90	930.6 ± 14.06	73.2 ± 1.18
Trial 2						
Normalised level of factors	0.441	0.564	Model predicted values	84.75	912.16	72.27
Experimental settings	794	246	Observed values	85.6 ± 1.35	922.4 ± 13.70	71.8 ± 0.85

[a] Observed values: mean ± S.D., $n = 3$.

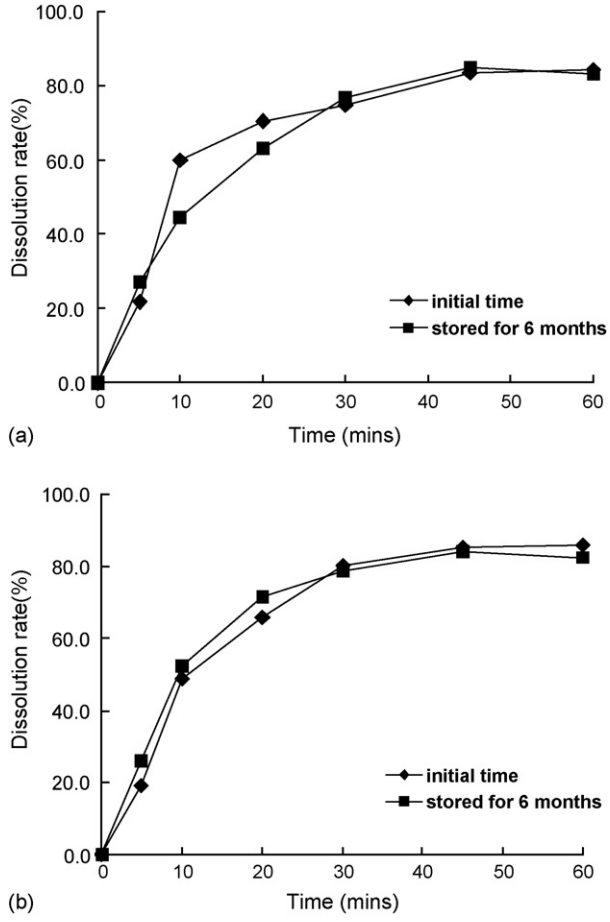

Fig. 7. Drug release from initial pellets and that stored for 6 months. The impeller speed and kneading time used for preparing pellets were (a) 767 rpm and 241 s; (b) 794 rpm and 246 s.

4. Conclusion

Successful dissolution rate improvement of itraconazole was obtained using solid dispersion prepared with Eudragit® E100 by a simple fusion method. Itraconazole was presented as an amorphous state in the solid dispersion at the drug-to-polymer composition ratio of 1:2 (w/w) according to the results of DSC and X-ray diffraction and was released almost 30 times faster than pure drug. Solid dispersion containing pellets showed high content uniformity and greater improvement of dissolution rate with approximately 70% of drug released within 45 min. Product properties including dissolution rate and percentage yield of desired size fraction were improved by using the optimal parameter settings and the results showed a good agreement with the prediction of the models. The method used to prepared solid dispersion of itraconazole in this study is relatively simple and safe because of the absence of specialized equipment and organic solvent. Impeller speed and kneading time are important parameters which affect the pellet characteristics complicatedly during high pelletization process. These parameters could be optimized effectively by a circumscribed central composite design.

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