Preparation and Characterization of Drug-Solution-Dropping Tablet

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ABSTRACT

This study is an attempt to improve dissolution rate of a poorly water-soluble drug from tablet by drug-solution-dropping technique. Diazepam was used as a model drug. Absolute alcohol and dichloromethane were used to prepare diazepam solution. The 50 μl solution (5 mg diazepam) was dropped on blank tablet by using microsyringe. Two kinds of blank tablets were prepared by direct compression (DC) and wet granulation (WG) methods, using dicalcium phosphate dihydrate and lactose as diluents, respectively, with 1000, 1400 or 1800 kg compression force. The surfaces of diazepam-solution-dropping tablets were characterized by Scanning electron microscope (SEM). Their morphologies revealed the smoother surface than that of blank tablet, particularly from wet granulation method of higher compression force but not being clear to point out diazepam particles on the surface. X-ray diffraction by monochromator (single crystal) mode was also used to point out the crystalline or amorphous form of the drug. X-ray monochromator analysis could not be used to confirm the crystallinity of diazepam on the surface of prepared tablet. Differential scanning calorimetry thermatogram showed the peak of diazepam only in the tablet prepared from wet granulaion blank tablet. Dissolution profiles of the prepared tablet from the two kinds of blank tablets were compared to diazepam tablet prepared by the conventional direct compression and wet granulation technique. The result profiles revealed that this drug-solution-dropping technique could be applied especially to poorly-water-soluble drug such as diazepam by using blank tablet at 1000 kg compression force. The dissolution rate of drug-solution-dropping tablet (DSDT) from blank tablet prepared by WG method was faster than that of DSDT from blank tablet prepared by DC method. Certainly, more uniformity of active ingredient is also an advantage of the drug-solution-dropping tablet prepared.

Key words: Diazepam, Drug-solution-dropping tablet

INTRODUCTION

The dissolution rate of drug from tablet is affected by its active ingredient's surface area and consequently, affects in oral bioavailability of the product. The development of formulations containing poorly-water-soluble drugs for oral delivery can be achieved by improving their dissolution. It has been found that increasing the available surface area by reducing the particle size can often markedly improve dissolution rates and lead to dramatic improvements in bioavailability. In some cases, the decreasing drug particle through micronized powder by milling tends to agglomerate (Westerberg, 1993) or accelerate the polymorphic conversion (Cheng et al., 2007). According to the differences of solubility and dissolution rates of polymorphs, the bioavailability of pharmaceuticals depends on polymorphous crystals (Miyazaki et al., 1974; Murphy et al., 2002; Rollinger et al., 2002). It has been shown that the polymorph in amorphous form of drug usually dissolves more rapidly than the corresponding crystalline form. Therefore the dissolution and bioavailability of formulation containing active ingredient in amorphous form (Hancock and Zografi, 1997; Ashford, 2002) including pseudopolymorphs form such as solvates would be increased (Shefter and Higuchi, 1963; Suleiman and Najib, 1989). On the other hand, the processes in making tablets, including blending, granulating, drying and especially compressing affected therapeutic property of the drug because polymorphic forms, crystal habit, size and surface area would be changed during these processes. (Chan and Doelker 1985; Koivisto et al., 2006).

A new technique of tablet preparation was patented, a chargeable pharmaceutical tablet which could solve the mentioned problems. The tablet was prepared by immersing or loading a blank tablet with liquid form of the active pharmaceutical ingredient (Lee and Lee, 2002; Holm et al., 2006). In this study, diazepam displays a poorly-water-soluble drug, which results in low and erratic oral bioavailability. Attempts were made to enhance the dissolution of diazepam using "a drug-solution-dropping" technique which had success for water-soluble drug, chlorpheniramine maleate (Chitvanich et al., 2008). The characterization of the preparation was compared to that of conventionally-prepared tablet. In vitro drug dissolution rate was used as main criteria for comparison between both kinds of blank tablet with dropping drug solution and also with conventional tablet prepared by DC and WG methods.

MATERIALS AND METHODS

Materials

Diazepam (Changzhou) as model drug was provided by Atlantic Laboratories. Absolute ethyl alcohol (AR grade, Merck) and dichloromethane (AR grade, Fisher scientific) were used to solubilize the model drug. Dibasic calcium phosphate dihydrate (DCP direct compression grade, USP 24 standard, Sudeep Pharma) and lactose monohydrate (Pharmatose®, DMV International) were used as the filler of direct compression and wet granulation tablet, respectively. Croscarmellose

sodium (Ac-Di-Sol®, FMC), polyvinyl pyrrolidone, (PVP K30 Serva, USA), magnesium stearate (Akcros chemicals), purified talcum BP (Haichen) were used as disintegrant, binder, lubricant and glidant of tablet, respectively.

MATERIAL AND METHODS

DC blank tablet

DCP as a water-insoluble filler and 2 percent by weight of Ac-Di-Sol® as a superdisintegrant were mixed thoroughly for five minutes. Subsequently, the homogeneous powder was combined with 0.75 percent by weight of magnesium stearate as lubricant for two minutes. The mixed powder was then compressed on instrumented single-stroke tableting machine (Fette® KO, Germany) with 1000, 1400 and 1800 kg compression force (CF). The obtained blank tablets had a flat surface with a diameter of 10 mm and 500 mg weight. The porosity of blank tablet was determined by measuring the amount of displaced helium gas into the tablet porosity, using Accupyc 1330 pycnometer (Micromeritics, USA).

WG blank tablet

Lactose as a water-soluble diluent, 2 percent by weight of Ac-Di-Sol® as a superdisintegrant and polyvinyl pyrrolidone as a binder, concentration 5 percent in isopropyl alcohol, were thoroughly wet-mixed and sieved through 14 mesh. The granule was dried at 60°C in hot-air oven (Binder, Germany) overnight and then passed through a 16 mesh-size sieve. The dried granule was mixed with 2 percent by weight of magnesium stearate as lubricant and 3 percent by weight of talcum as glidant for two minutes. The mixed granule was compressed to form 350 mg tablet, using the same machine and CFs as DC blank tablet. The porosity of the obtained tablet was determined by using Accupyc 1330 pycnometer (Micromeritics, USA).

Diazepam tablet prepared by direct compression method (diazepam DC) and wet granulation method (diazepam WG)

The excipients and methods were the same as in the preparation of DC and WG blank tablets, except for diazeapm incorporation during the dry-mixing process.

Drug-solution-dropping tablet (DSDT)

DSDT were prepared by a method as described previously (Chitvanich et al., 2008). Exact amount of diazepam was dissolved in a mixed solvent of absolute alcohol and dichloromethane (1:3 by volume) to obtain a solution concentration of 100 micrograms per microliter. A 50-µl portion of the prepared solution (5 mg diazepam) was dropped on the surface of DC blank tablet by using 50 µl-microsyringe (Hamilton # 80500). WG blank tablet was treated in the same manner but using only dichloromethane as a solvent for preparing diazepam solution. All of treated tablets were dried at 50°C in hot-air oven for one hour.

Tablet characterization

Scanning electron microscopy, powder X-ray pattern and differential scanning calorimetry were used to characterize diazepam and other ingredients of blank tablets and DSDT. Particle morphology from tablet was revealed by SEM (Scanning Electron Microscope, JEOL, JSM-5910LV, Japan). The accelerating voltage was set at 20 kV and magnification at 100x – 1500x. The samples were in the aluminium stub with two-faced glue paper and coated with gold before SEM analysis. The surfaces of DSDT were also compared to the surface of DC and WG blank tablet. Powdered X-ray patterns were carried out to determine the drug crystalline behavior by using X-ray monochromator (single crystal) (modified JEOL, JDX 8030; Siemens D500). Samples were exposed to Cu Kα radiation 20 kv. The patterns were shown in the range of the diffraction angles (2-theta) 5° and 40°. The differential scanning calorimeter (DSC 7, Perkin Elmer, USA) was used to show the thermal behavior of diazepam, DCP dihydrate, lactose monohydrate and scratched powder from surface of DSDT. The powder sample 3-5 milligram was packed in a sealed aluminum pan, 40 microliter size. The running temperature was 75°C to 200°C with the heating rate of 10°C/min.

Dissolution Profiles

The dissolution profiles of DSDT prepared from DC and WG blank tablet were performed in dissolution tester (Hanson Research, USA). The tester was apparatus type 1 according to the USP monograph (USP 30). The speed was 100 rpm and 900 ml of 0.1 N hydrochloric acid was used as medium. The dissolved drug samples with six replicates were collected at 1, 3, 5, 7, 9, 15, 20, 25 and 30 minutes and analyzed for diazepam by using a spectrophotometer (Spekol 1200, Germany) at the absorbance of 242 nm. The dissolved drug was calculated from standard curve of diazepam reference standard.

The statistical significant differences in the result of dissolution tests of conventionally-prepared diazepam tablets and DSDT in this study was performed by comparisons of two independent groups with unknown variance (Bolton, 1997).

RESULTS AND DISCUSSION

Morphology studies

The morphology of diazepam powder in Figure 1 (a), magnification 500X, shows the size and shape that looked like lactose (d) with smoother surface. The size range was not more than 50 micron. Each excipient used in DC and WG blank tablets such as DCP dihydrate, Ac-Di-Sol®, lactose and talcum also was evaluated under the same condition except for magnesium stearate, the magnification: 1000X. Their micrographs are shown in Figure 1 (b), (c), (d), (e) and (f) respectively. The SEM images of such excipients powder correspond to the information stated in the literature (Raymond et al., 2006).

The SEM morphology of the surface of DC blank tablet at 1000, 1400 and 1800 kg of CFs are shown in Figure 2 (a), (b) and (c), respectively. It showed the

continuous surface in some area. The porosity of tablet at higher CF was found to be less than of the tablet of lower CF because of the increasing of bonding of the particles in tablet (Parrot, 1989). The pore size was not more than 10 microns under compression. The shape and size of DCP dihydrate were different from the intact DCP dihydrate which are shown in Figure 1 (b). The surface of DSDT prepared from DC blank tablet at 1000 kg CF in Figure 2 (d) was found to have higher porosity than DC blank tablet at the same CF.

The SEM morphology of the surface of WG blank tablets and DSDT prepared from WG blank tablet of all tested CF are shown in Figure 3. The surface of WG blank tablets at 1800 kg CF was smoother than of 1400 and 1000 kg CF. For all DSDT, surface looked smoother than the WG blank tablet at the same CF. Especially at 1800 kg CF, the surface of DSDT looked like the multiple layer of sheet and diazepam particles had not been seen. In this case, only dichloromethane, rapidly evaporated was used as the single solvent for preparing of drug solution not like in the case of DC blank tablet which drug solution was prepared from the mixture of ethyl alcohol and dichloromethane. Then the drug solution will spread and evaporate rapidly, resulting in the multiple layer of dropped drug.

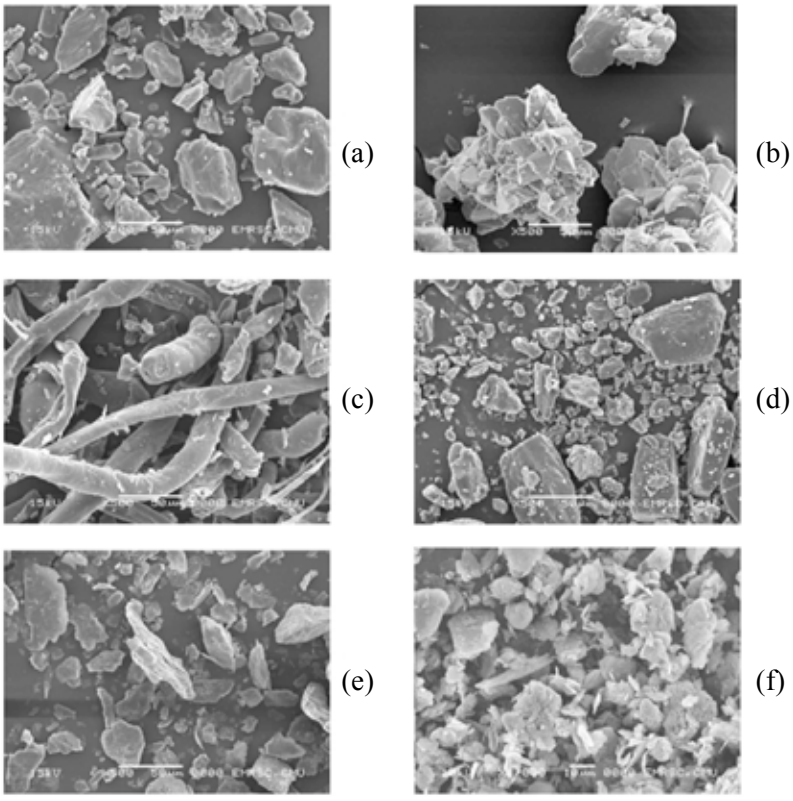


Figure 1. SEM morphologies (500X) of (a) Diazepam, (b) DCP dihydrate, (c) Ac-Di-Sol®, (d) Lactose (e) Talcum and (f) 1000X of Magnesium stearae.

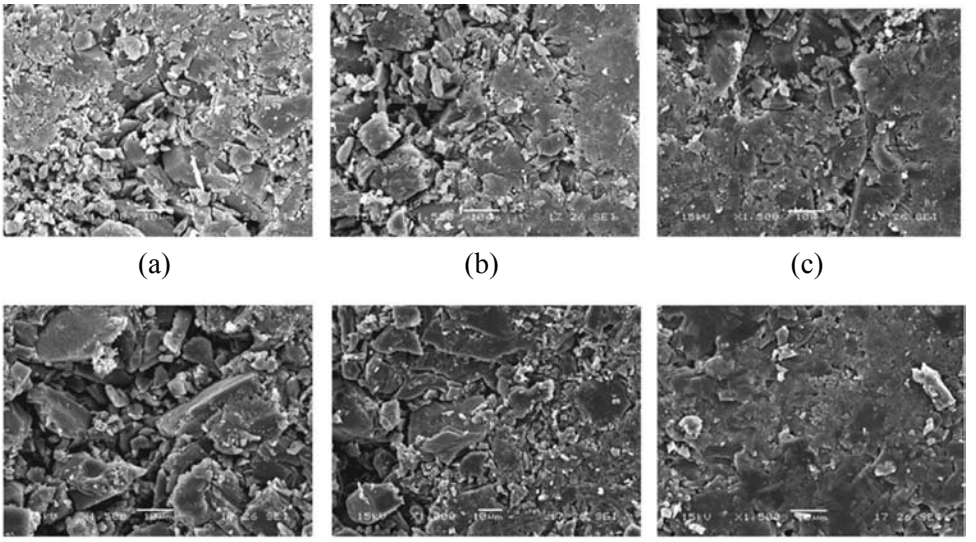


Figure 2. The surface morphologies by SEM (1,500X) of the DC blank tablets at CF of (a) 1000 kg, (b) 1400 kg and (c) 1800 kg and of DSDT prepared from DC blank tablet at (d) 1000 kg, (e) 1400 kg and (f) 1800 kg of CF.

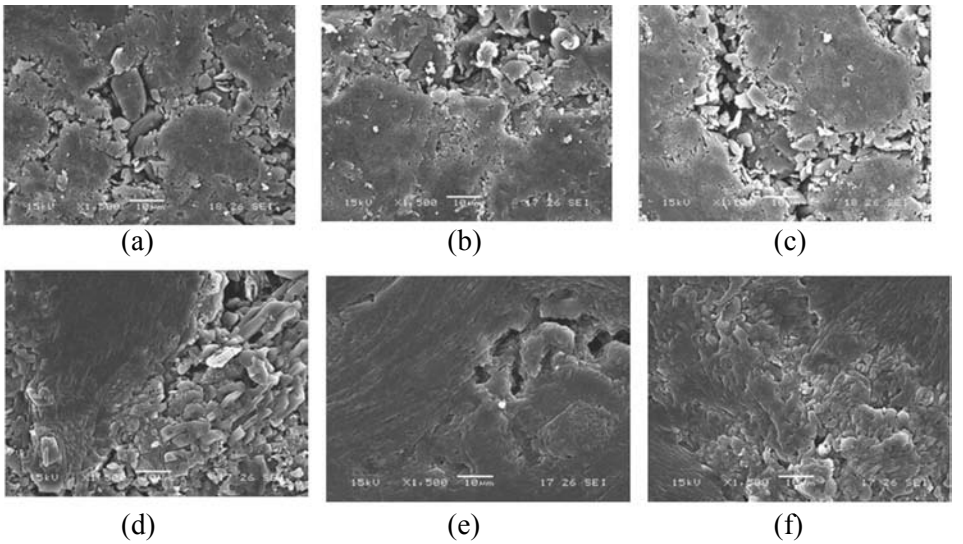
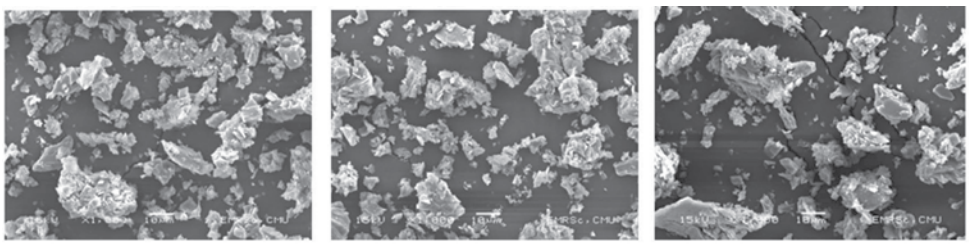


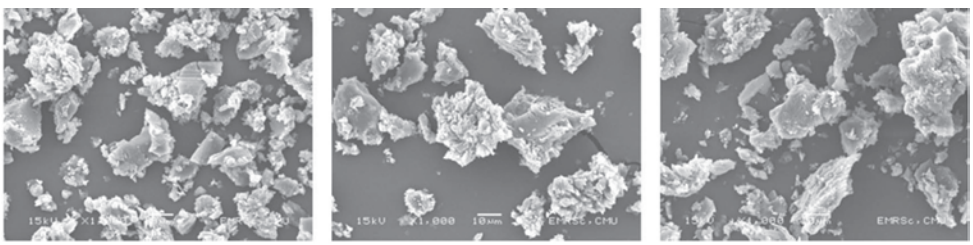
Figure 3. The surface morphologies by SEM (1,500X) of the WG blank tablets at CF of (a) 1000 kg, (b) 1400 kg and (c) 1800 kg and of DSDT prepared from WG blank tablet at (d) 1000 kg, (e) 1400 kg and (f) 1800 kg of CF.

The diazepam particles could not be found on the surface of DSDT by SEM. Subsequently, the SEM was used again to characterize particles scratched from superficial surface of tablet. It was not clear to point out which one is diazepam particle as shown in Figure 4 (a), (b), (c) for DSDT prepared from DC blank tablet and also in Figure 5 (a), (b), (c) for DSDT prepared from WG blank tablet of all tested CF. Diazepam particles might be of very small size and having extremely small amount.



(a) (b) (c)

Figure 4. SEM micrographs (1,000X) or particles scratched from superficial surface of DSDT prepared from DC blank tablet at (a) 1000 kg, (b) 1400 kg and (c) 1800 kg of CF.



(a) (b) (c)

Figure 5. SEM micrographs (1,000X) of particles scratched from superficial surface of DSDT prepared from WG blank tablet at (a) 1000 kg, (b) 1400 kg and (c) 1800 kg of CF.

Solid-state characterization

It is important to study the polymorphic changes of diazepam on the surface of DSDT. X-ray monochromator was used to examine the scratched powder from the surface of DC and WG blank tablet prepared at 1000, 1400 and 1800 kg CF which are shown in Figures 6 (a), (c), (e) and 7 (a), (c), (e), respectively. After dropping diazepam solution on the surface of blank tablets, the patterns of diffracted x-ray of the scratched powder from the surface were determined and shown in Figures 6 (b), (d), (f) for DC tablet and 7 (b), (d), (f) for WG tablet. Their major peaks of scratched powder from DSDT prepared from DC blank

tablets showing at a scattering angle (2Θ) were of about 11.6, 20.9 and 29.2. Their patterns looked similar to the patterns from blank tablets at 1000 and 1800 kg of CF with the same intensity peaks as shown in Figures 6 (b), (f) and 6 (a), (e), respectively. It was found more peaks i.e. at 17.6, 25.2 and 27.2 of scratched powder from DSDT prepared from 1400 kg CF of DC blank tablets as shown in Figure 6 (d). It suggested that the crystal habit of diazepam may be different from DSDT of 1000 and 1800 kg CF.

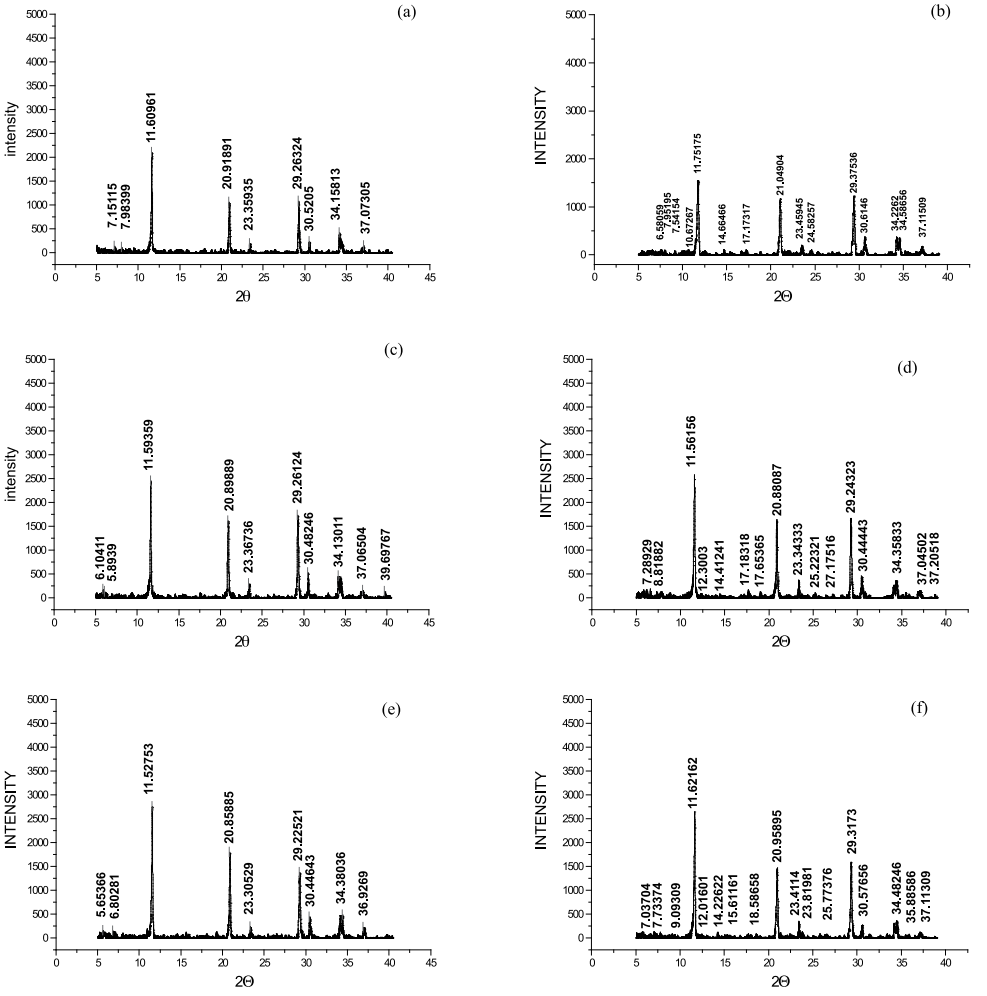


Figure 6. XRD patterns by X-ray monochromater of the powder scratched from the surface of DC blank tablet of 1000, 1400 and 1800 kg CF before dropping diazepam solution (a, c, e) and after dropping diazepam solution (b, d, f) of the same CF.

Scratched powder from DSDT prepared from WG blank tablets and their blank tablet at 1000 and 1400 kg CF had the same diffraction patterns as shown in Figures 7 (b), (d) and 7 (a), (c) respectively. It can be concluded that this method could not be utilized to characterize because of very small amount of diazepam on surface tablet. But for 1800 kg CF of DSDT, it was found peak additionally at angle 2Θ about 24.6 which was different from which of blank tablet as shown in Figure 7 (f) and (c), respectively.

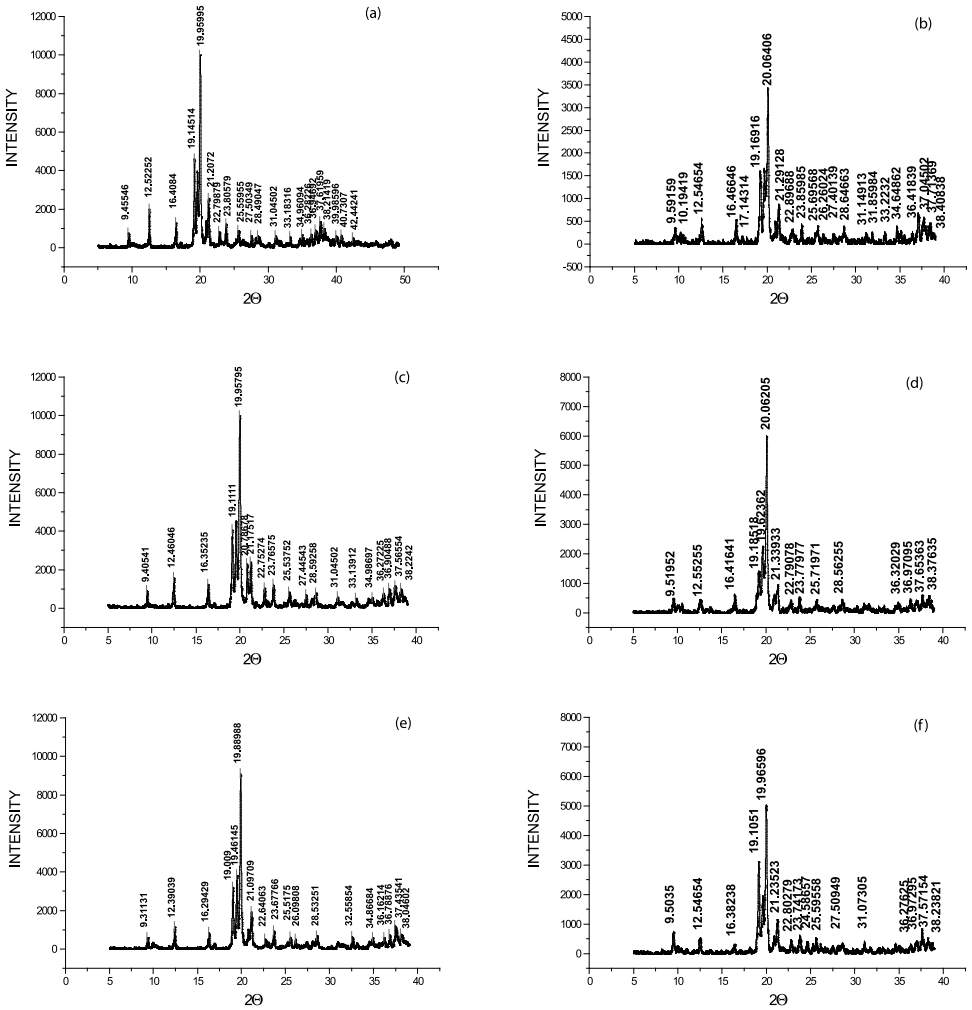


Figure 7. XRD patterns by X-ray monochromater of the powder scratched from the surface of WG blank tablet of 1000, 1400 and 1800 kg CF before dropping diazepam solution (a, c, e) and after dropping diazepam solution (d, b, f) of the same CF.

It might be the crystalline of diazepam on the tablet surface resulting from not penetrating deeply via pore as in 1000 and 1400 kg CF tablet. It may contribute to enhancement of dissolution of the drug if the crystallinity of diazepam is reduced or behaved amorphous form in tablets (Shah et al., 2007). However, it could not be convinced that the habits of diazepam particles after solvent evaporation were amorphous or crystalline form. The reason may be drug content in sample having a very small amount.

For a study of polymorphism by DSC, the thermal behavior of the powder scratched from the surface of DSDT prepared from DC blank tablet of 1000 kg CF is shown in Figure 8 (c) which displayed the endothermic peaks at 110.7, 116.8 and 154.8?C. The mentioned peaks did not correspond to the range of melting point of diazepam, 132.3°C, and DCP dihydrate at 138.9°C as shown in Figure 8 (a) and (b). Interaction between diazepam and DCP dihydrate might occur.

According to the Figure 9 (a) and (b), intact diazepam and lactose showed endothermic peaks at 132.3 and 147.8°C, respectively. DSC thermogram of the scratched powder from the surface of DSDT prepared from WG blank tablet of 1000 kg CF showed the same peaks in this area, at 130.4 and 144.5°C in Figure 9 (c) which indicated that there was no interaction between drug and excipients or change in crystalline form.

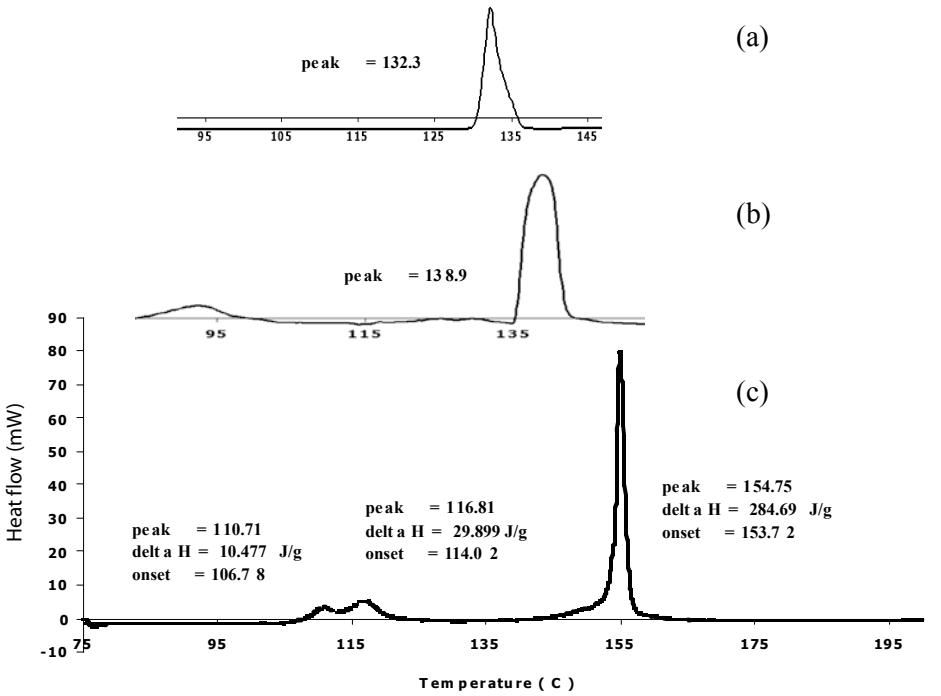


Figure 8. DSC thermograms of (a) diazepam, (b) DCP dihydrate and (c) powder scratched from the surface of DSDT prepared from DC blank tablet of 1000 kg CF. The curves have been separated in the y-axis to aid comparison.

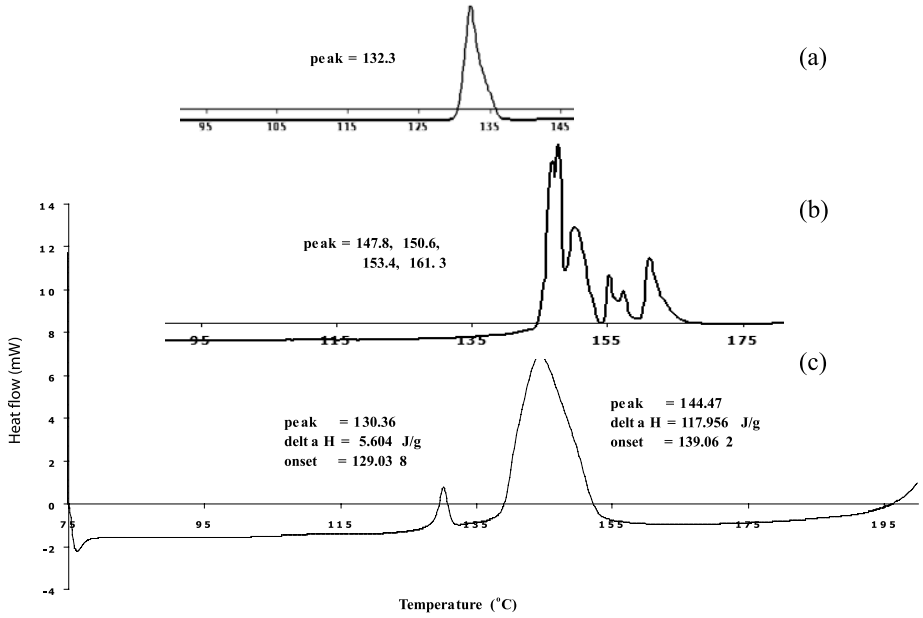


Figure 9. DSC thermograms of (a) diazepam, (b) lactose and (c) powder scratched from the surface of DSDT prepared from WG blank tablet of 1000 kg CF. The curves have been separated in the y-axis to aid comparison.

Dissolution studies

The drug dissolution profiles of DSDTs prepared from DC and WG blank tablets in comparison with the profiles from diazepam tablets prepared by conventional DC and WG methods at all tested CF are shown in Figure 10. All of them meet the requirement in monograph of USP 30 that not less than 85 percent of 5 mg of diazepam is dissolved within 30 minutes.

Dissolution rate of DSDTs prepared from DC blank tablet diazepam was significantly faster than that of the diazepam DC tablets at 3 and 5 minutes of 1000 kg CF tablet and at 3 minutes 1800 kg CF tablet ($p<0.01$). It could be explained by a higher porosity and more irregular surface prepared at lower CF. Diazepam solution could possibly penetrate into the DC blank tablets and after drying, diazepam appearance in small particle eventually transformed to amorphous form and then increased the dissolution rate (Holm et al, 2006; Shanbhag et al, 2008). Of 1400 kg CF tablet, the dissolution rate of DSDT was significantly slower than of diazepam DC tablet at all points ($p<0.01$). However, from the performance in 1800 kg CF, the dissolution rate of DSDT was not significantly different from diazepam DC tablet ($p>0.01$). The dissolution rate of DSDT prepared from DC tablets of 1000, 1800 kg CF were faster than of 1400 kg CF. This phenomenon corresponded to the X-ray diffractogram of DSDT prepared from DC tablet of 1400 kg CF.

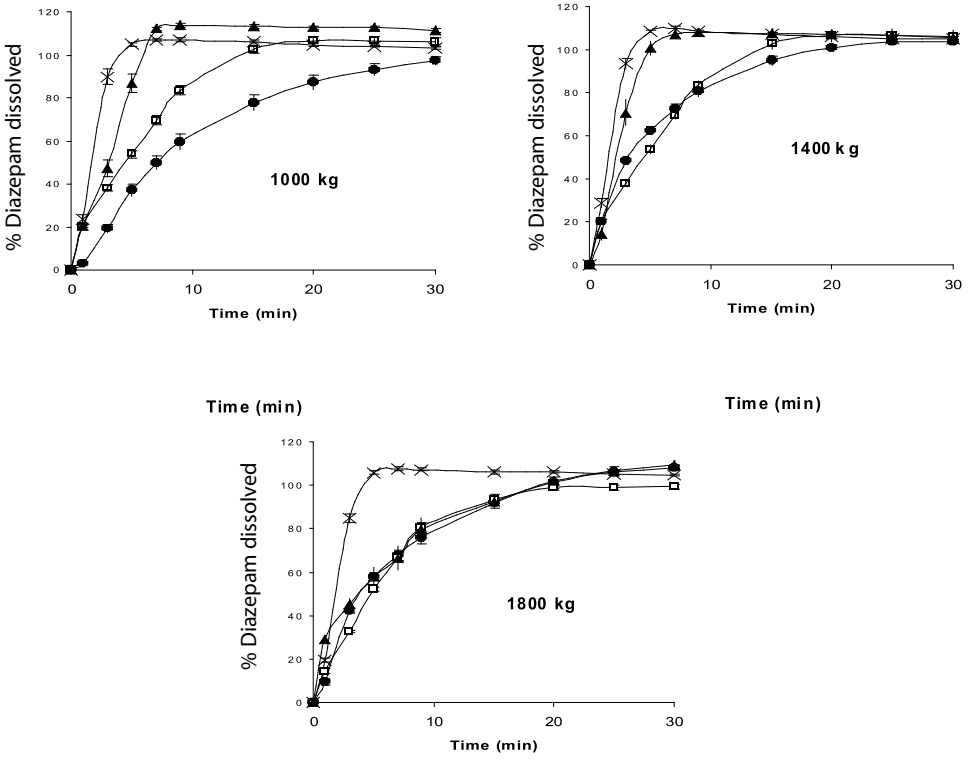


Figure 10. Diazepam dissolution profiles of the DSDT prepared from DC blank tablet●, DSDT prepared from WG blank tablet▲, diazepam DC tablet □ and diazepam WG tablet × of 1000, 1400 and 1800 kg CF.

For WG method, the DSDT of 1000 kg CF, the dissolution rate after 3 minutes was not significantly different comparing to diazepam WG tablet ($p>0.01$). Of 1800 kg CF, the dissolution rate of DSDT was clearly lower than of diazepam WG tablet. This pattern corresponded to X-ray diffractogram which showed the different peak of diazepam from the DSDT. This could be due to the smoother surface which the diazepam solution dropped may be unable to penetrate the smooth surface of the tablet and then diazepam crystallized on the surface after solvent evaporation.

Of DSDT from both blank tablets, the dissolution rate of DSDT prepared from WG blank tablets was faster than of DSDT prepared from DC blank tablets at 1000 and 1400 kg CF. The reason was that lactose monohydrate in WG blank tablet is freely albeit slowly soluble in water and as such it is a suitable diluent for active ingredients of low water solubility such as DZP (Armstrong, 2007). However, at 1800 kg CF, the dissolution rate exhibit no significant difference between the DSDT prepared from WG and DC blank tablet. It might be the same reason due to the very smoothness of both tablet surfaces and less porosity of the tablet.

CONCLUSION

This new method presented evidence that it is possible to prepare DSDT for the poorly-water-soluble drug, diazepam, similar to a soluble drug, chlorpheniramine maleate (Chitvanich et al., 2008). The SEM method could not clearly point out the diazepam particle on the tablet surface and under tablet surface of DSDT from the other excipients. X-ray diffractogram of the powder scratched from the tablet surface of DSDT prepared from DC blank tablet was apparently of the same pattern as powder scratched from the DC blank tablet at 1000 and 1800 kg. Also, the DSDT from WG blank tablet showed patterns in the same way as WG blank tablet did at 1000 and 1400 kg CF. It might be the cause of the small amount of diazepam on tablet surface of DSDT. The DSC peak of diazepam in DSDT prepared from DC and WG blank tablets at 1000 kg CF could not be found clearly. However, the dissolution profiles of DSDT prepared from DC blank tablet at 1000 kg CF showed the dissolution rate faster than that of diazepam DC tablets at 3 and 5 minutes and no difference between DSDT prepared from WG blank tablet and diazepam WG tablet at 1000 kg CF. It could be concluded that this novel preparation method appears to be an alternative method for a poorly-water-soluble drug or other therapeutic substance which is destroyed under compression force by using DC blank tablet and WG blank tablet, especially blank tablet of 1000 kg CF.

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