Preparation and Characterization of Chlorpheniramine Maleate-Solution-Dropping Tablet

Orawan Chitvanich[1], Busaban Sirithunyalug[2], Siriporn Okonogi[2], Sirivipa Piyamongkol[2] and Jakkapan Sirithunyalug[2*]

[1]Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Science, Huachiew Chalermprakiet University, Samutrprakarn 10540, Thailand

[2]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand

**Corresponding author. E-mail: jakkapan@pharmacy.cmu.ac.th*

ABSTRACT

This study is an attempt to design a novel method, drug-solution-dropping, in preparing tablets expected to release the drug faster than from conventional method. Chlorpheniramine maleate (CPM) was used as a model drug. Firstly, we prepared tablets containing no drug (blank tablets) by direct compression (DC) with dicalcium phosphate dihydrate, croscarmellose sodium and magnesium stearate as filler, super disintegrant and lubricant, respectively. Another kind of blank tablet was prepared by wet granulation (WG), using lactose as diluent. Absolute alcohol and dichloromethane were used to prepare CPM solution in a concentration of 100 micrograms per microliter. The prepared solution of 40 microliters (4 mg CPM) was dropped on each blank tablet by using microsyringe. A scanning electron microscope (SEM) was used to characterize both blank and CPM-solution-dropping tablet. Their morphology showed that the particle size of the dropped CPM in the tablet was reduced. X-ray monochromator (single crystal) analysis and differential scanning calorimetry (DSC) were used to examine the crystalline of CPM after dropping onto both kinds of blank tablets. Both techniques could not characterize powder or granule which was taken from the drug-solution-dropping tablet whether it was the drug particle or the excipients. Dissolution profiles of the CPM-solution-dropping tablet from DC and WG blank tablets were compared to CPM tablets prepared by conventional DC and WG method and also to commercial tablets. The results of the dissolution tests revealed that the drug-solution-dropping tablet could be considered a novel form to promote a faster drug release rate especially the drug-solution-dropping prepared from DC blank tablet with 1000 kg of compression force and WG blank tablet with 1800 kg of compression force. Having more uniformity of content is also an advantage of the drug-solution-dropping tablet prepared.

Key words: Chlorpheniramine maleate, Solution-dropping tablet

INTRODUCTION

The most widely used of all pharmaceutical dosage forms is tablet. When the absorption of drug from a tablet is dissolution rate-limited, a more soluble and faster dissolving form may be utilized to improve the rate and extent of bioavailability. Over the years, the dissolution of drugs in tablet form has been introduced with different degrees of success. The basic knowledge of crystal and dissolution properties of pharmaceutical solids could help solve many problems associated with dissolution and absorption characteristics of resultant tablets (Yamamoto and Piyarom, 2000). Many researchers studied the effect of different forms of crystal of drug, called polymorphism, on its bioavailability (Aguiar et al., 1967; Miyasaki et al., 1974). It showed that the amorphous form of drug usually dissolves more rapidly than the corresponding crystalline form. Several delivery technologies rely on stabilizing the drug in its amorphous form to increase its dissolution and bioavailability (Aulton, 2002). Thereby the particle size reduction was initially reported to enhance bioavailability of griseofulvin, digoxin, oxazepam and felodipin, especially when particle size is below 10 μm, it can increase the intrinsic dissolution rate drastically (Nyström, 1996). Some techniques of size reduction are grinding (Keneniwa et al., 1973) and rapid recrystallization from solution (Liversidge and Cundy, 1995). Nevertheless, the crystallization may occurr by grinding. Thereafter, solid solutions and eutectic mixtures have been used, at least in research laboratories, to increase the rate of dissolution of drugs, presumably by decreasing the particle size of the drug molecules. This is why soft gelatin elastic capsules containing solutions of such medications show higher bioavailability when compared to conventional oral solid dosage form (Elbert, 1977). The study of Liquisolid tablets demonstrated significantly higher drug release rates compared to tablets prepared by direct compression method (Spireas and Sadu, 1998).

In general, tablet dosage form is prepared by compaction of a formulation containing the solid drug substances and certain excipients selected to aid the processing and improve the properties of tablet. The compaction will affect therapeutic property of the drug. It is due to the effect of polymorphic forms, crystal habit, size and surface area changed during the processes (Berggren et al., 2004). A new technique of tablet preparation was patented, a chargeable pharmaceutical tablet which could solve this problem. The tablet was prepared by immersing a blank tablet in liquid form of the active pharmaceutical ingredient (Fang-Yu and Fang-Chen, 2002).

In this present work, CPM-solution-dropping tablet was prepared by dropping 40 microliters (4 mg CPM) of CPM solution on a blank tablet consisting of the same powder excipients of CPM tablet prepared by the direct compression (DC) and wet granulation (WG) method. The characterization of the preparation was compared to that of conventionally-prepared and commercial tablet. *In vitro* drug dissolution rate was used as main criteria for comparison.

MATERIALS AND METHODS

Materials

The following materials were used: Chlorpheniramine maleate (lot no. SC/C0304159, Supriya Chemicals, Mumbai, India), absolute ethyl alcohol (AR grade, Merck, Germany) and dichloromethane (AR grade, Fisher scientific, England). A direct compression tablet includes dibasic calcium phosphate dihydrate (DCP direct compression grade, USP 24 standard, lot no. T27B, Sudeep Pharma Ltd. India), Ac-Di-Sol® (Croscarmellose sodium, lot no. T651N, FMC, Belgium) and magnesium stearate (lot no. 1812, Akcros chemicals, Netherland). Pharmatose® (lactose monohydrate, lot no. 10025939, DMV International) and PVP K30 (polyvinyl pyrrolidone, Serva, USA) were used as a diluent and a binder, respectively, in a wet granulation tablet. SEA CHLOR® (SEA PHARM CO., LTD., Lot No. 5374C) was a commercial chlorpheniramine maleate, 4 mg tablet.

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. The obtained blank tablets had a flat surface with a diameter of 10 mm and 500 mg tablet weight.

WG blank tablet

Lactose as a water soluble diluent and polyvinyl pyrrolidone as a binder, in solution form with the concentration 5% in isopropyl alcohol, were wet-mixed and sieved through 14 mesh. The granule received was dried at 60°C in hot air oven (Binder, ED 240/E2, Germany) overnight and then passed through a 16 mesh-size sieve. The dried granule was mixed with 2% magnesium stearate as lubricant and 3% talcum as glidant for two minutes. The mixed granule was compressed to form 350 mg tablet, using the same compression forces as DC blank tablet.

CPM tablet by direct compression (CPM DC) and wet granulation (CPM WG)

The excipients and methods were the same as in the preparation of DC and WG blank tablets, except for having CPM incorporated during the dry-mixing.

CPM-solution-dropping tablet

CPM was dissolved in a mixed solvent of absolute alcohol and dichloromethane in a ratio of 1:3 by volume to obtain a solution concentration of 100 micrograms per microliter. A 40-µl portion of the prepared solution (4 mg CPM) 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 CPM solution. All of treated tablets were dried

at 50°C in hot air oven for one hour.

Tablet characterization

Scanning electron microscope, powder X-ray pattern and differential scanning calorimetry were used to characterize CPM and other ingredients of blank tablets and CPM-solution-dropping tablet. Particle morphology from tablet was revealed by SEM (Scanning Electron Microscope, JEOL, JSM-5910LV, Japan). The accelerating voltage of SEM 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 surface of DC blank tablet and WG blank tablet were also compared to the surface of CPM-solution dropping tablet. Powdered X-ray patterns were carried out to determine the sample 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 CPM and another excipient in the tablet, including the powder from surface of CPM-solution-dropping tablet. 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 the CPM-solution-dropping tablets prepared from DC and WG blank tablet were performed in dissolution tester (Hanson Research, USA) according to USP 28. The speed was 50 rpm and 500 ml of 0.01 N hydrochloric acid was used as medium. The samples were collected at 1, 3, 5, 7, 9, 15, 20, 25 and 30 minutes and analyzed for CPM by using a spectrophotometer (Spekol 1200 Germany) at the absorbance of 265 nm. CPM released was calculated from standard curve of CPM reference standard (Department of Medical Sciences, Ministry of Public Health, Thailand, control no. 247034).

The statistical significant differences in the result of dissolution tests of various CPM tablets in this study was performed by comparisons of two independent groups with unknown variance (Bolton, 1997).

RESULTS AND DISCUSSION

Morphology studies

The morphology of CPM powder in Figure 1 (a) using SEM, magnification 500X, shows the angular shape and smooth surface with 50 micron-size range. Each excipient used in DC and WG blank tablets such as dibasic calcium phosphate dihydrate (DCP dihydrate), Ac-Di-Sol®, lactose, magnesium stearate and talcum also was evaluated under the same condition and its 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 (Ainley and Weller, 1994).

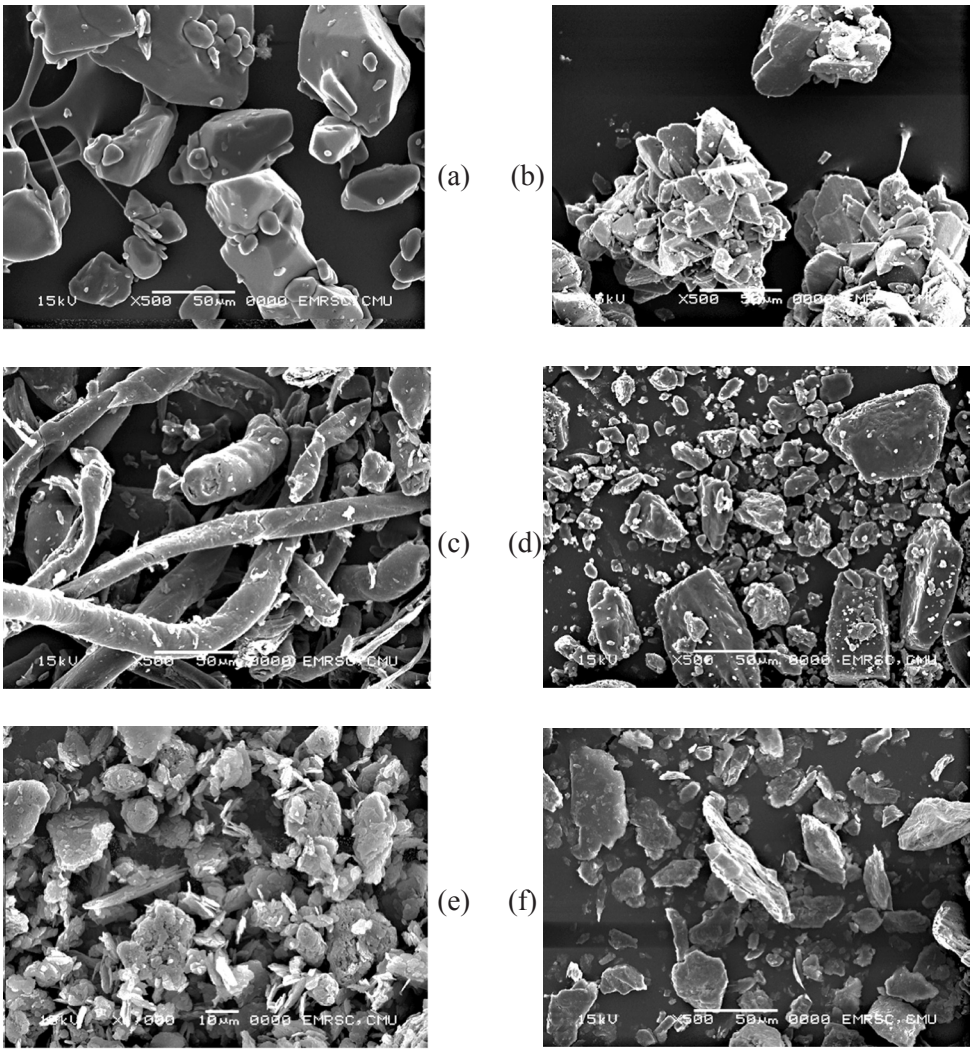


Figure 1. SEM micrographs (500X) of (a) CPM, (b) DCP dihydrate, (c) Ac-Di-Sol®, (d) Lactose, (e) Magnesium stearate and (f) Talcum.

The SEM morphology of the surface of DC blank tablet at 1000, 1400 and 1800 kg of compression forces (CF) are shown in Figure 2 (a), (b) and (c), respectively. It showed the continuous surface in some area of surface of tablet. The porosity of tablet at lower CF was found to be higher than the tablet of higher CF. The shape and size of DCP dihydrate were different from the intact DCP dihydrate shown in Figure 1 (b). For CPM-solution-dropping tablets prepared from DC blank tablets, surfaces which are shown in Figure 2 (d), (e) and (f) were similar to the surface of DC blank tablets of all CF. It is not clear to point out which one is CPM particles on the tablet surface. It may be possible that the CPM solution dropped penetrated into the pores of the tablet.

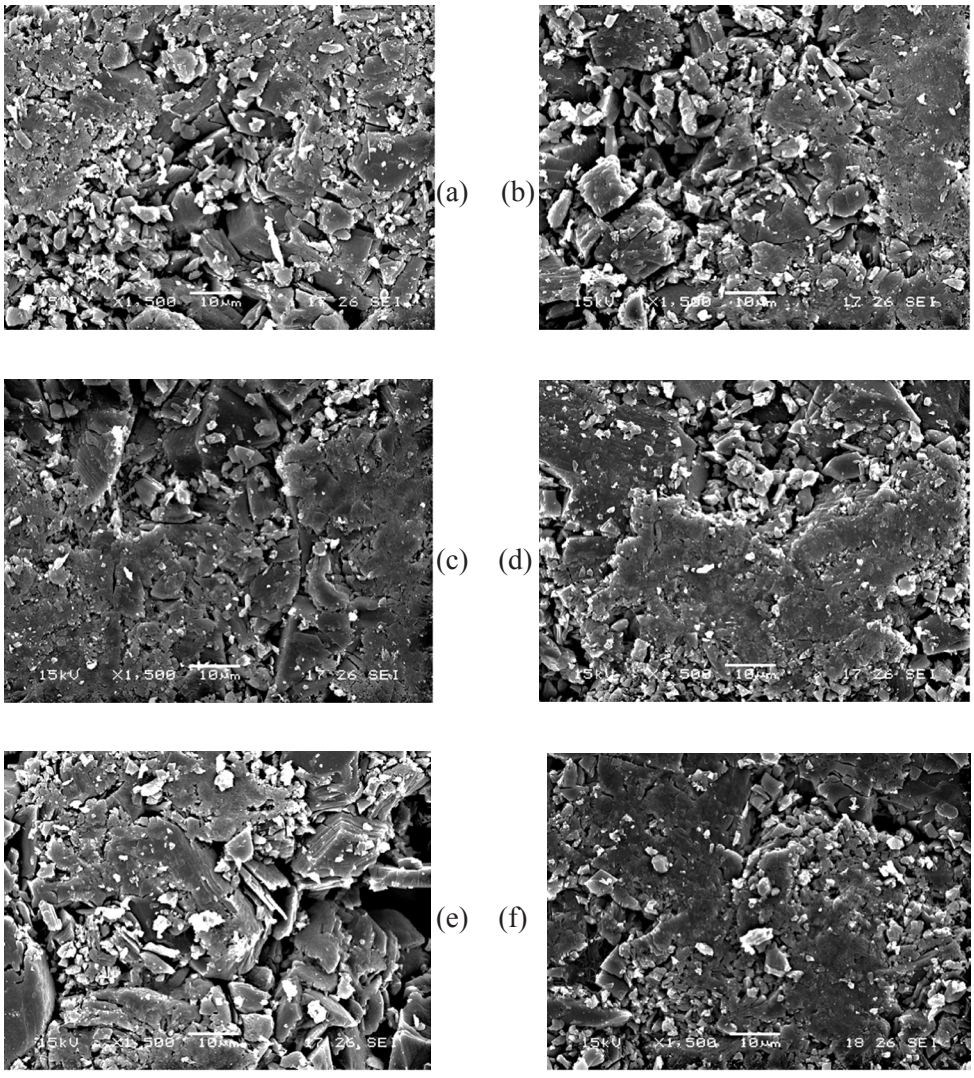


Figure 2. The surface morphologies by SEM (1,500X) of the DC blank tablets at CF of (a) 1000 kg, (b) 1400 kg and (c) 1800 kg and of CPM-solution-dropping tablet prepared from DC blank tablet at (d) 1000 kg, (e) 1400 kg and (f) 1800 kg of CF.

The SEM morphology of the surface of WG blank tablets and CPM-solution-dropping tablet prepared from WG blank tablet of all tested CF are shown in Figure 3. The surface of CPM-solution-dropping tablets looked similar to their blank tablets compressed at the same CF. Apparent porosity of WG blank tablet was lower than DC blank tablet because the soft granules from lactose adhered close together better than DC filler particles like DCP dihydrate. CPM particles may seemingly be found on the surface of the WG blank tablet dropped with CPM solution at all CF. The size of CPM particles found was in the range of 10 micron while the CPM particles before mixing in tablet was about 50 micron.

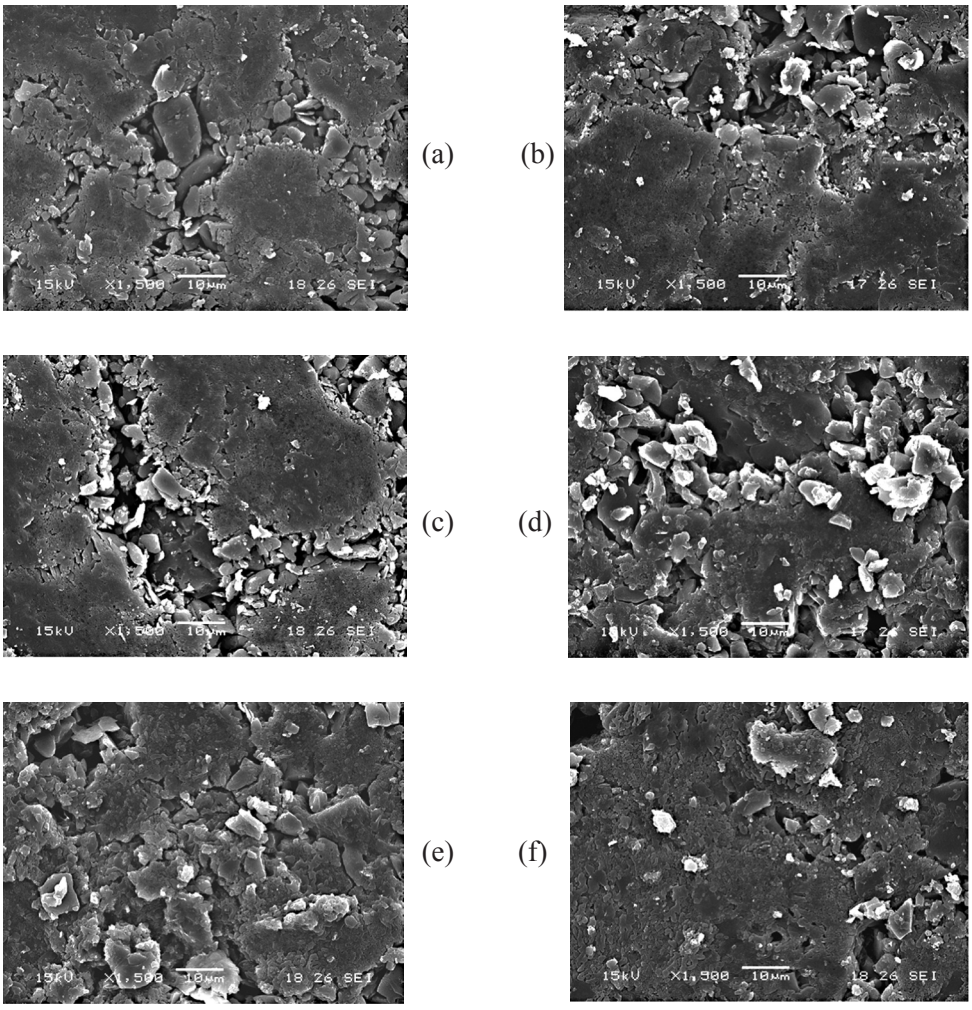


Figure 3. SEM micrographs (1,500X) of the WG blank tablets at CF of (a) 1000 kg, (b) 1400 kg and (c) 1800 kg and of CPM-solution-dropping tablet prepared from WG blank tablet at (d) 1000 kg, (e) 1400 kg and (f) 1800 kg of CF.

Solid-state characterization

The scratched surface powder from DC and WG blank tablet prepared at 1000, 1400 and 1800 kg of CF were examined by X-ray monochromator shown in Figure 4 (a), (b), (c) and 5 (a), (b), (c), respectively. After CPM solution was dropped on the surface of blank tablets, the patterns of diffracted x-ray of the scratched powder from the surface of tablet which possibly was found to have high quantity of CPM are shown in Figure 4 (d), (e), (f) for DC and 5 (d), (e), (f) for WG. Their prominent peaks of scratched powder from CPM-solution-dropping prepared from DC blank tablets at angle 2θ were of about 11.5, 20.8 and 29.2 and for WG blank tablets at

angle 2θ were of about 19.1, 20.0 and 21.2. Their patterns from all kinds of tablet look similar to their blank tablets at all tested CF with the same intensity peaks. Their patterns could not be differentiated between the drug-solution-dropping and blank tablet because CPM solution dropped after solvent evaporation may not be changed to crystal form or too small quantity to be detected.

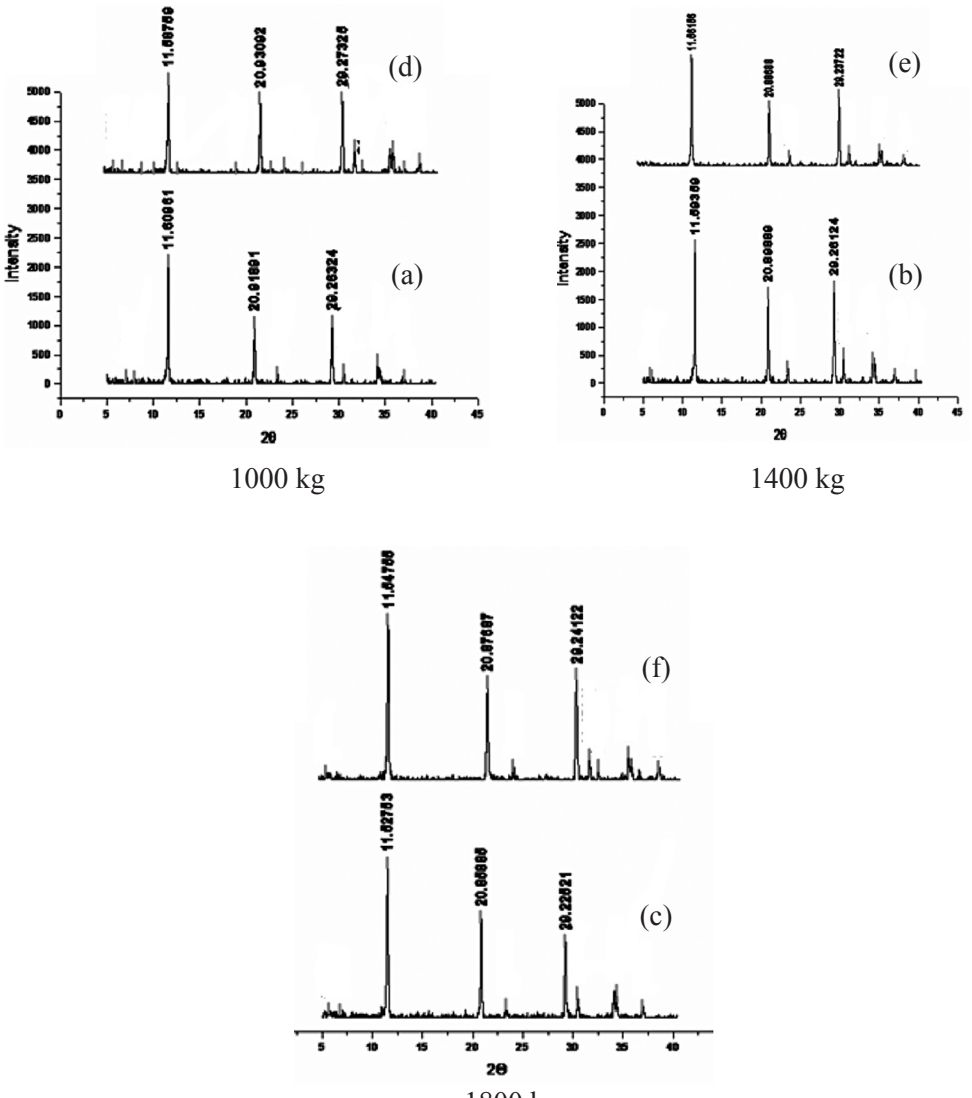


Figure 4. XRD pattern by X-ray monochromator of the powder from the surface of DC blank tablet before dropping CPM solution of 1000, 1400, 1800 kg CF (a, b, c) and after dropping CPM solution of 1000, 1400, 1800 kg CF (d, e, f). The curves have been separated in the y-axis to aid visualization.

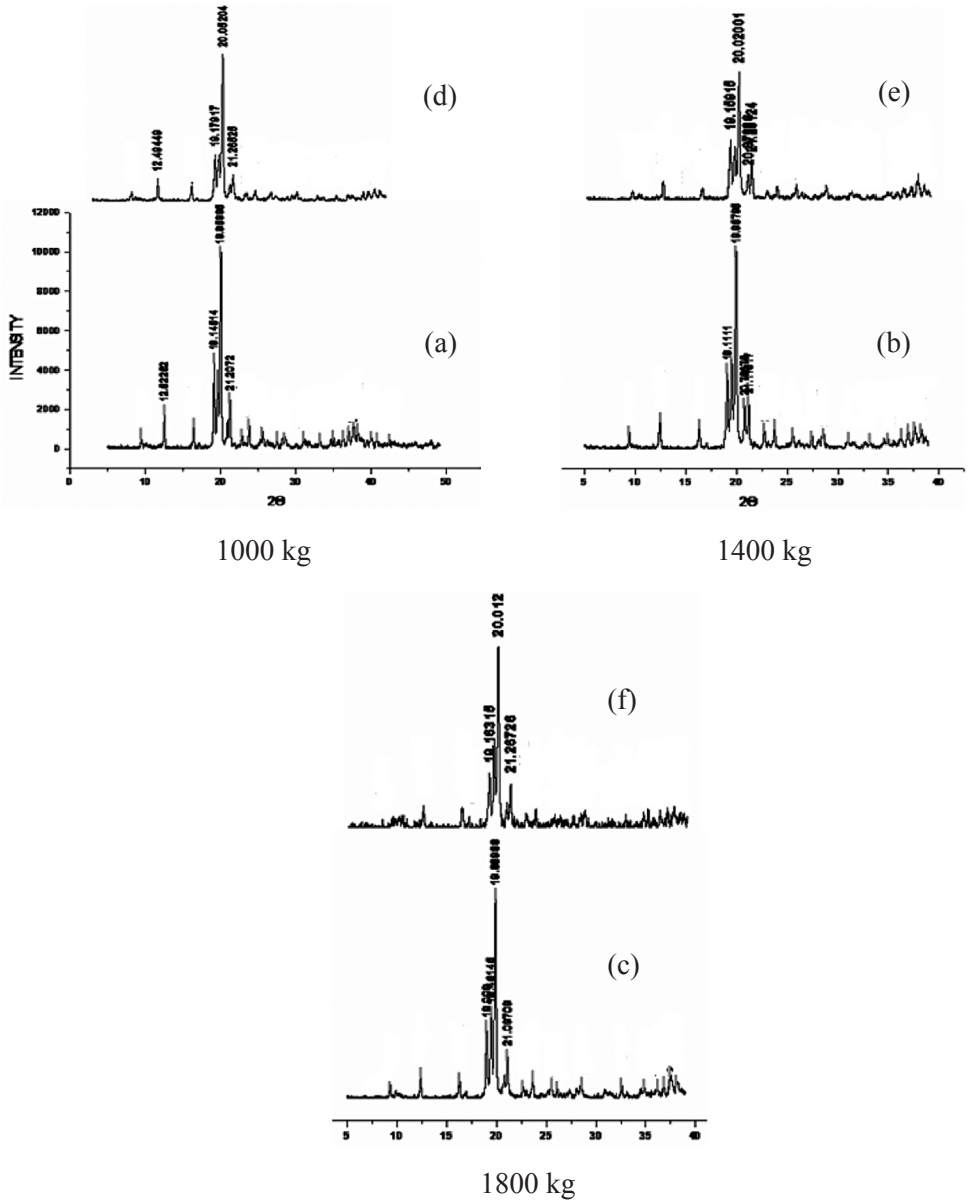


Figure 5. XRD pattern by X-ray monochromator of the powder from the surface of WG blank tablet before dropping CPM solution of 1000, 1400, 1800 kg CF (a, b, c) and after dropping CPM solution of 1000, 1400, 1800 kg CF (d, e, f). The curves have been separated in the y-axis to aid visualization.

The thermal behavior of the powder scratched from surface of CPM-solution-dropping tablet prepared from DC blank tablet of 1000 kg CF is shown in Figure 6 (c) which displayed the peaks at 132.4 and 139.3°C. The mentioned peaks were in the range of melting point of CPM, 135.7°C, and DCP dihydrate at 138.9°C as shown in Figure 6 (a) and (b).

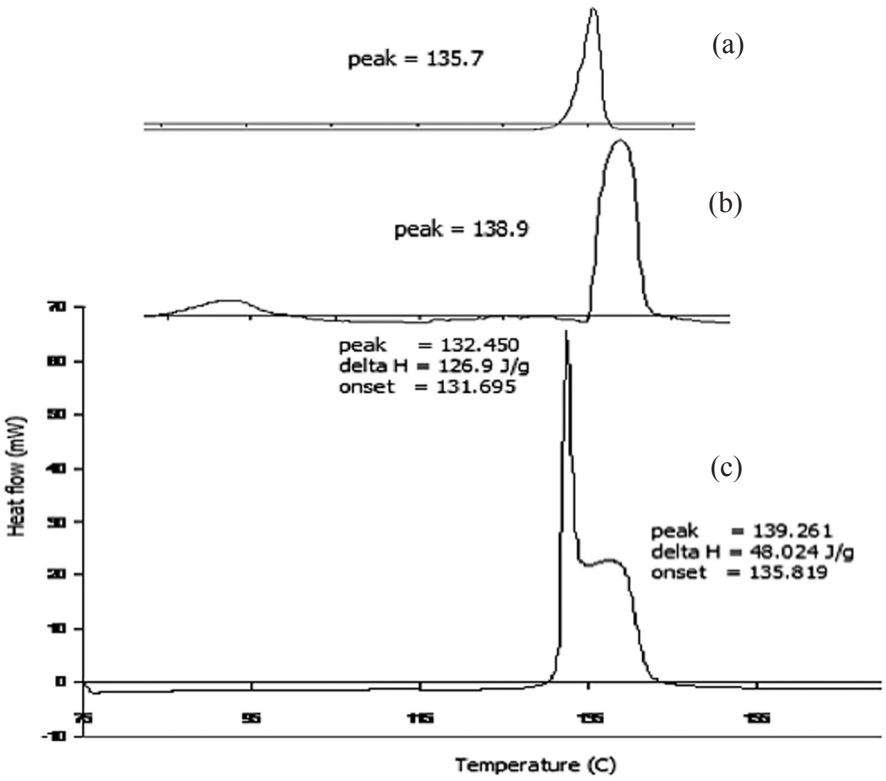


Figure 6. DSC thermograms of (a) CPM, (b) DCP dihydrate and (c) powder scratched from surface of CPM-solution-dropping tablet prepared from DC blank tablet. The curves have been separated in the y-axis to aid comparison.

The thermogram of the scratched powder near the surface of CPM-solution-dropping tablet prepared from WG blank tablet showed two distinct peaks at 142.6 and 170.6°C in Figure 7 (c) which corresponded to endothermic peak of lactose at 147.8 – 161.3°C as shown in Figure 7 (b). DSC thermogram pointed out clearly at DCP dihydrate and lactose which were the major ingredients in the CPM-solution-dropping tablets prepared from the blank tablets. The thermal peak of CPM could not be found clearly in Figure 8 (c) because of too small amount of CPM in the powder sample.

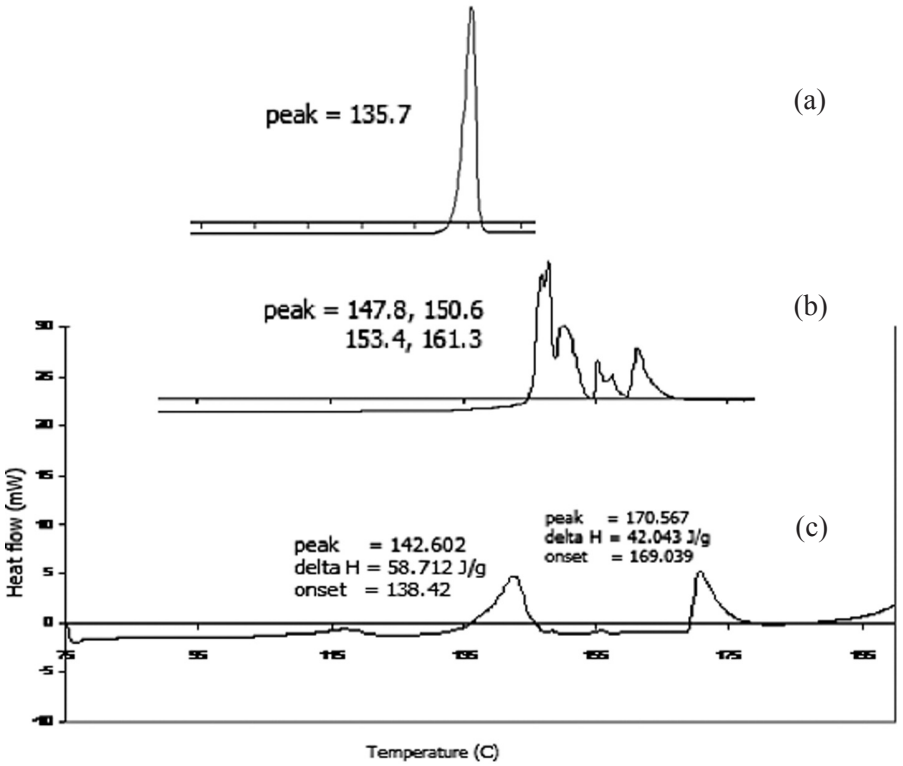


Figure 7. DSC thermograms of (a) CPM (b) lactose and (c) powder scratched from surface of CPM-solution-dropping tablet prepared from WG blank tablet. The curves have been separated in the y-axis to aid comparison.

Dissolution studies

Figure 8 showed the drug dissolution profiles of the CPM-solution-dropping tablets prepared from DC blank tablets in comparison with the profile from CPM DC tablets at the same three CF, 1000, 1400, 1800 kg and also of the commercial CPM tablet. All of them meet the requirement in monograph of USP that not less than 80% of 4 mg of CPM is released within 30 minutes. At 1000 kg of CF, 90% of CPM was released from the CPM-solution-dropping tablet within 5 minutes and significantly faster than CPM DC tablet ($p<0.01$). It could be explained by a higher porosity and more irregular surface prepared at lower CF. CPM solution could possibly penetrate into the DC blank tablets and CPM transforms to amorphous form after solvent evaporation and then from this form it increases dissolution rate. At 1400 and 1800 kg CF, the dissolution rate was not significantly different between the profile from the CPM DC tablet and the CPM-solution-dropping tablet ($p>0.01$). CPM released from commercial tablet studied was shown to be slower than CPM DC and CPM-solution-dropping tablet.

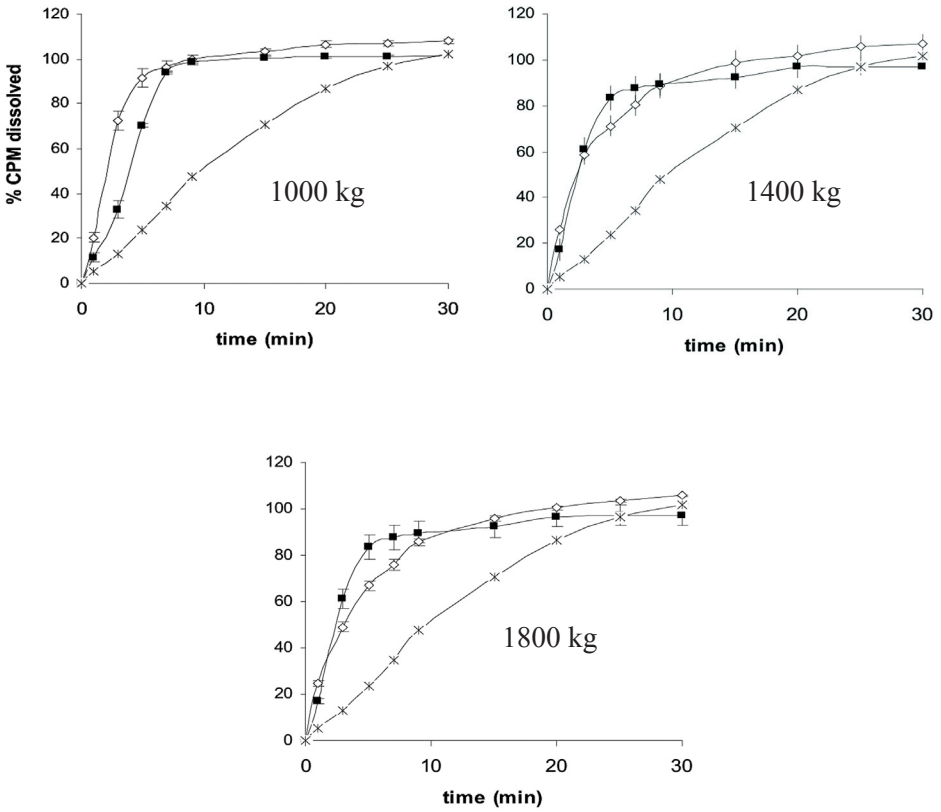
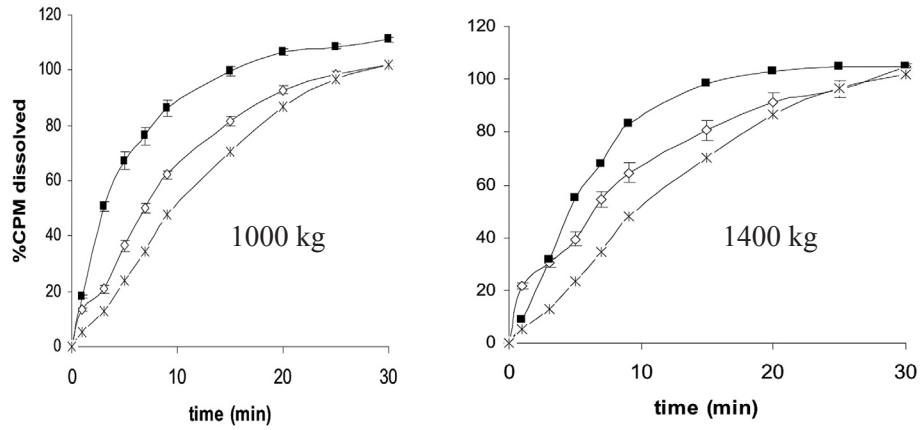


Figure 8. CPM dissolution profiles of the CPM-solution-dropping tablet prepared from DC blank tablet ◇, CPM DC tablet ■, at three compression forces (1000, 1400, 1800 Kg) and commercial CPM tablet ✳.



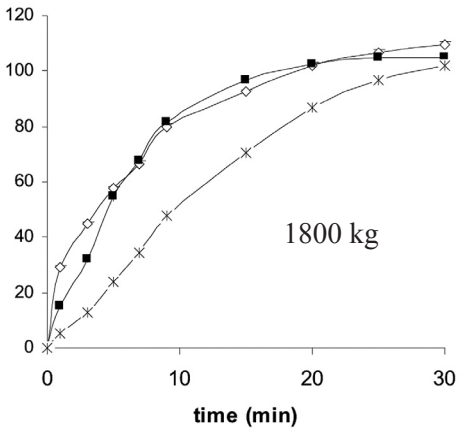


Figure 9. CPM dissolution profile of the CPM-solution-dropping tablet prepared from WG blank tablet ◇, CPM WG tablet ■, at three compression forces (1000, 1400, 1800 Kg) and commercial CPM tablet ✳.

The drug dissolution profiles of the CPM-solution-dropping tablets prepared from WG blank tablets and the CPM WG tablets as illustrated in Figure 9 all met the requirement in monograph of USP. The dissolution rates were not significantly different except that of the tablet at 1000 kg of CF which the CPM release rate from CPM-solution-dropping tablets were significantly slower than that of the CPM WG tablets, especially at 3 and 5 minutes ($p<0.01$). The CPM solution dropped may be unable to penetrate the smooth surface of the tablet and then CPM crystallized on the surface after solvent evaporation. And at 1800 kg of CF, the CPM released from CPM-solution-dropping tablets were significantly faster than that of the CPM WG tablets at 1 minutes ($p<0.01$). It pointed out that the dissolution rate of the CPM-solution-dropping tablets is not dependent on disintegration as CPM WG tablet when CF is increased. In comparison to the commercial CPM tablets, the dissolution rates only at 1, 3 and 5 minutes of the CPM-solution-dropping-tablets at 1000 and 1400 kg CF were faster than the commercial CPM tablets ($p<0.01$). But for CPM-solution-dropping tablets of 1800 kg compression force, it released the drug faster than the commercial CPM tablets at all times of study which could be explained by the same previously-mentioned, reason.

CONCLUSION

The novel preparation method of drug-solution-dropping tablet appears to be an alternative method for the rapid release preparation by using both DC and WG blank tablet. The SEM method could not point out the CPM particle on the surface from the other excipients. The intensity of single-crystal X-ray diffraction peak of the powder scratched from the surface of CPM-solution-dropping tablets prepared from DC and WG blank tablets seems to be of the same pattern as powder from the DC and WG blank tablets of all CF. The thermal peak of CPM in CPM-solution-dropping

tablets prepared from DC and WG blank tablets could not be found clearly. It could be concluded that, the SEM, XRD and DSC method could not clearly characterize the CPM in powder at the surface from the CPM-solution-dropping tablets because of too small amount of CPM. Anyway, the dissolution profile may be introduced to show the advantage, i.e., dissolution profile of CPM-solution-dropping tablet in comparison with tablet from the conventional methods, CPM DC and CPM WG, especially when using DC blank tablet at 1000 kg of CF and WG blank tablet at 1800 kg of CF.

ACKNOWLEDGEMENTS

Faculty of Pharmacy, Chiang Mai University was an important institute to provide an opportunity for this study. Parts of this work were financially supported by National Research Council of Thailand (NRCT).

REFERENCES

Ainley, W., and P.J. Weller. 1994. Handbook of pharmaceutical excipients, second edition. The Pharmaceutical Press, London.

Aguiar, A.J., J. Krc. Jr., A. W. Kinkel, and J. C. Samyn. 1967. Effect of polymorphism on the absorption of chloramphenicol from chloramphenicol palmitate. J. Pharm. Sci. 56: 847-853.

Aulton, M.E. 2002. Bioavailability-physicochemical and dosage form factors. p.239. In Pharmaceutics (second edition) The Science of Dosage Form Design. Churchill Livingstone, UK.

Berggren, J., G. Frenning, and G. Alderborn. 2004. Compression behaviour and tablet-forming ability of spray-dried amorphous composite particles. Eur. J. Pharm. Sci. 22: 191-200.

Bolton, S., 1997. Statistical inference. p.148-158. In Pharmaceutical statistics: Practical and clinical applications (3rd ed.). Dekker, New York.

Nyström, C. 1996. How to formulate a tablet for instant dissolution of practically insoluble drugs, S64. In Invited Lecture 05-Material Science. Eur. J. Pharm. Sci. 4 Suppl.

Elbert, W.R. 1977. Soft elastic gelatin capsules: unique dosage form. Pharm. Technol. 1: 44-50.

Fang-Yu Lee, and F.-C. Lee. 2002. United States Patent: 6,399,591.

Keneniwa, N., A. Ikekawa, and K. Hashimoto. 1973. Influence of operational variables on ball-milling of sulfadimethoxine and white alundum. Chem Pharm.Bull. 21: 676-681.

Liversidge, G. G. and C. K. Cundy. 1995. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int. J. Pharm. 125: 91-97.

Miyazaki, S., T. Artist, R. Hori, and K. Ito. 1974. Effect of polymorphism on the dissolution behavior and gastrointestinal absorption of chlortetracycline hydrochloride. Chem. Pharm. Bull. 22: 638-642.

Rochville, Md. 2005. The United States of Pharmacopeia. 28th Asian Edition. The United States of Pharmacopeia Convention Inc., Rockville, MD.

Spireas, S., and S. Sadu. 1998. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int. J. Pharm. 166: 177-188.

Yamamoto, K., and S. Piyarom. 2000. Method used of improving dissolution and absorption characteristics of poorly-soluble drugs. Srinakharinwirot Bhesajsarn 5: 84-100.

none