Drug Development and Industrial Pharmacy, 22(12), 1237–1241 (1996)

Effect of Grinding of β-Cyclodextrin and Glibenclamide on Tablet Properties. Part I. In Vitro

Ampol Mitrevej, Nuttanan Sinchaipanid, Varaporn Junyaprasert, and Ladda Warintornuwat

Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand

ABSTRACT

Physical properties including dissolution characteristics of glibenclamide (GB) tablets were studied. Directly compressed and wet-granulated GB tablets gave only 35% and 40% drug dissolved, respectively. Physical mixing, kneading, and grinding of β-cyclodextrin (CD) with GB were investigated. It was found that the grinding method could markedly enhance the release of drug from the tablets. The physical properties of these tablets were unchanged after they had been stored at 40°C and 75% RH for at least 3 months. The GB/CD mixture at a ratio of 1 to 4, ground for 24 or 48 hr, exhibited superior dissolution and chemical stability. Differential scanning calorimetry indicated that an inclusion complex was produced. Decreasing grinding time or CD concentration could result in incomplete formation of the inclusion complex. It was concluded that pretreatment of the drug with CD by the grinding method could significantly improve the dissolution and stability of GB tablets.

INTRODUCTION

Glibenclamide (GB), one of the most widely used hypoglycemic drugs in the sulfonylurea group, has a dissolution problem because of its poorly soluble characteristic. Several attempts have been made to improve the dissolution of the drug, for example, the use of amorphous form, soluble polymorphic forms (1,2), water-soluble salts with alkali hydroxide (3), solid dispersion techniques (4), and coprecipitation with linear polymer (5).

Current research shows that cyclodextrins possess an ability to encapsulate various molecules at molecular state, resulting in new physicochemical properties, including the increases in solubility and bioavailability, a greater stability, and a reduction of side effects (6). Sanghavi and coworkers (7) studied the solubilization of GB with β-cyclodextrin (CD) and its derivatives. They

found that kneading GB with an aqueous slurry of CD resulted in an inclusion complex which exhibited better solubility in comparison with untreated GB. The objective of this study was to investigate the effect of incorporation of CD into GB on the physical properties and aging of GB tablets.

MATERIALS

Glibenclamide (Lot No. 506/163, Italy) and β-cyclodextrin (Kleptose®, lot no. E0165, Roquette, France) were used as received. Other materials used were microcrystalline cellulose, MCC (Avicel® PH102, lot no. 2447, Asahi Chemical Industry, Japan), spray-dried lactose, SDL (Super-Tab®, lot no. 2031104, The Lactose Company of New Zealand Ltd., New Zealand), cornstarch (lot no. CQ 01, Holland), colloidal silica (Aerosil®, lot no. D-60287, Merck, Germany), and magnesium stearate (lot no. 1238, Volovskoyo, Yugoslavia).

METHODS

Preparation of Glibenclamide Tablets

Glibenclamide (GB) tablets were prepared by using three different methods, i.e., direct compression, wet granulation, and addition of CD. The first two methods are known as conventional methods. The tablets were compressed on a single-punch tablet press (Fette® type E1, Germany) using 8-mm punches to the hardness of 40 N. Each 100-mg tablet contained 5 mg of GB.

Conventional Tablets

With the direct compression method, GB was mixed with a filler, i.e., MCC or SDL, in a tumbling mixer for 10 min. Then 0.5% magnesium stearate was added and mixed for additional 3 min. The blend was then compressed into tablets.

With the wet granulation method, the formulation consisted of 10% cornstarch as a disintegrant, 2% cornstarch as a binder, 0.5% magnesium stearate as a lubricant, and lactose as a filler. GB was blended with half of the disintegrant and the lactose in a planetary mixer. Cornstarch as 10% paste was then added to the blend. The damp mass was passed through a 14-mesh sieve and dried at 50°C. The dried granulation was screened through the 14-mesh sieve and mixed with the second half of the disintegrant and magnesium stearate. The tablets were compressed in the same manner as previously described.

Addition of β-Cyclodextrin

CD was incorporated in GB by various methods, i.e., physical mixing, kneading, and grinding. The GB/CD mixture was mixed with 0.1% colloidal silica, 0.5% magnesium stearate, and 25% MCC. The amount of GB/CD mixture used was such that each 100-mg tablet contained 5 mg of GB. SDL was then added to make a tablet weight of 100 mg. The final mixture was compressed into tablets. As a control, GB was ground without CD for 24 hr. The ground GB was treated in the same manner as that described for ground mixture of GB and CD.

For the physical mixing method, GB was mixed with CD at the ratio of 1:4 by weight in the tumbling mixer for 10 min. The GB/CD mixture was further mixed with the other ingredients and then compressed. For the kneading method, CD was mixed with water in a mortar until a smooth paste was obtained. GB was added to the paste at the ratios of 1:2 and 1:4 by weight. The mixture was kneaded for 1 hr. The paste was dried in the hot air oven at 50°C. The dried mass was screened through a 60-mesh sieve. The kneaded GB/CD mixture was further processed in the same manner as described previously.

For the grinding method, GB and CD were mixed at the ratios of 1:2 and 1:4 by weight. Each mixture was ground in a ball mill at a speed of 120 rpm for 12, 24, or 48 hr, then screened through the 60-mesh sieve. The mixture was mixed with other ingredients and then compressed into tablets.

Evaluation of Tablet Properties

Tablet properties were determined after the tablets had been stored for 24 hr at 25°C and 45% RH. The hardness was measured with a hardness tester (Schleuniger 4M, Switzerland). The results reported were the averages of 10 tablets for each formulation. Tablet friability was determined using a Roche-type friabilator (8). Disintegration time was determined using USP XXII method; each value reported was the average reading of 6 tablets. Since there is no official dissolution test procedure for GB tablets, the method developed by Hassen et al. (1) was employed in this study. The absorbance was determined at a wavelength of 225 nm, at 5-min intervals for 30 min.

Differential Scanning Calorimetry (DSC) Study

Thermal analyses of GB, CD, and the mixtures were conducted using differential scanning calorimeter (model DSC7, Perkin–Elmer Corp., Norwalk, CT, USA) at a scanning rate of 10°C/min over the temperature range of 30°–230°C under nitrogen steam. Peak temperatures were determined after calibration with an idium standard.

Aging Effect

Selected formulations were stored at 40°C and 75% RH for 3 months. Effects of aging on dissolution, drug contents, and physical properties were evaluated.

RESULTS AND DISCUSSION

Properties of GB Tablets Prepared by Conventional Methods

All the three formulations gave tablets of good weight uniformity. The MCC-based tablets had the lowest value of disintegration time, 0.10 min, which could be due to disintegration property of MCC (9). The disintegration time of SDL-based tablets was approximately 4.32 min. Since the tablets were composed mainly of water-soluble excipient, the tablets would dissolve rather than disintegrate in the aqueous medium. The disintegration time of the tablets prepared by the wet granulation method was less than 1 min. It was found that the dissolution of these formulations was less than 40%. Therefore, simple formulations prepared by conventional methods are not suitable.

Properties of GB/CD Tablets

The GB/CD mixtures prepared by various methods were compressed to the hardness of 40 N. The friability values were found to be less than 0.1%. The disintegration times of all formulations were less than 30 sec. The dissolution profiles of the tablets are shown in Fig. 1. The dissolution of A serves as a control. It can be seen that B exhibited dissolution patterns similar to those A. Both of them released less than 40% of the drug at 30 min. The dissolution of A, however, was slightly better than that of B. This could be a result of the grinding, which produced smaller GB particles in comparison with B. Physical mixing of CD with GB was shown to have no effect on the dissolution.

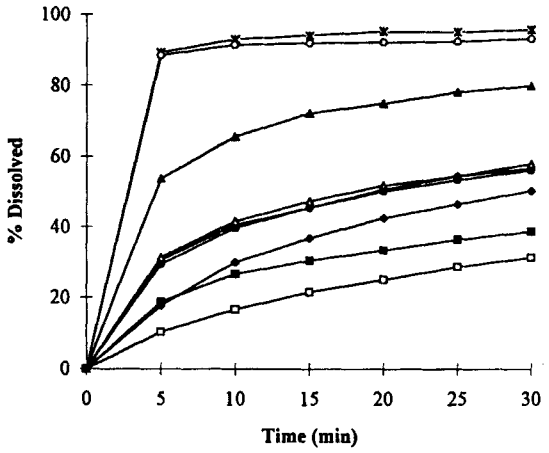

Figure 1. Dissolution profiles of various glibenclamide/β-cyclodextrin preparations: (■) A, Ground GB, 24 hr; (□) B, physical mixture; (◆) C, kneaded mixture 1:2; (●) D, kneaded mixture 1:4; (Δ) E, ground mixture 1:2, 24 hr; (◇) F, ground mixture 1:2, 48 hr; (▲) G, ground mixture 1:4, 12 hr; (○) H, ground mixture 1:4, 24 hr; (*) I, ground mixture 1:4, 48 hr.

Some investigators had shown that kneading poorly soluble drug with CD could improve the dissolution of the drug (7,10). In the present study, GB was kneaded with CD at two proportions, i.e., 1:2 (C) and 1:4 (D). The dissolution of C was found to be slightly better than A and B but slightly less than D. Higher concentration of CD could have improved the dissolution of GB; however, at 30 min only 56.16% of the drug was released. It is of interest that this finding did not agree with those reported by Sanghavi and coworkers (7). They reported that the kneaded GB/CD mixture and pure GB gave 94–99% and 43% drug release at 45 min, respectively, whereas in the present study, only 56.16% and 38.67% were obtained with kneaded mixture (C) and ground GB (A) at 30 min. The available information suggests that the discrepancy was due to the difference in the test procedures.

It had been reported that grinding of a certain drug with CD yielded an inclusion complex which exhibited better drug dissolution (11). However, grinding GB with CD at the ratio of 1:2 for either 24 (E) or 48 (F) hr could not improve the dissolution. Figure 1 indicates that E and F have dissolution patterns similar to D. The similarity could be due to the possibility that the amount of CD was not sufficient to form inclusion complex with GB.

The increase in the amount of CD to 1:4 ratio could substantially improve the dissolution. The results at 30

min show that grinding GB with CD for 12 hr (G) increased the dissolution to 79.86%. The increase in the grinding time to 24 (H) and 48 (I) hr further improved the drug release, i.e., 93.19% and 95.72%, respectively. In fact, more than 90% of the drug dissolved could be obtained even at 10 min. These findings suggested that grinding GB with CD at the ratio of 1:4 for 24 and 48 hr would produce comparable degrees of inclusion, whereas grinding for only 12 hr produced unsatisfactory result.

Differential Scanning Calorimetric Study

Thermal analyses of GB/CD and selected mixtures of GB and CD at the ratio of 1:4 were conducted using a different scanning calorimeter. Figure 2(a) is a typical DSC curve of GB showing the endothermic peak at 174°C. This peak was attributed to the melting of GB, which coincided with the value given in the literature (4). The peak of ground GB [Fig. 2(b)] remained unchanged at 174°C; therefore, grinding did not alter the crystallinity of GB. The DSC curve of CD [Fig. 2(c)] exhibited a broad endothermic peak at about 80°C, which was the dehydration peak of crystal water of CD (12,13). The mixture of GB and CD prepared by physical blending exhibited a DSC curve [Fig. 2(d)] with two endothermic peaks resembling the combination of curves A and C.

It can be seen that grinding GB alone and physical mixing GB with CD did not alter the crystallinity of GB. However, grinding the mixture of GB and CD at the ratio of 1:4 for 12 hr caused the broadening of CD peak and diminishing GB peak intensity [Fig. 2(e)]. The changes in both peaks became more evident with increasing grinding time [Figs. 2(f) and 2(g)]. Grinding the mixture for 48 hr [Fig. 2(g)] resulted in the disappearance of endothermic peak of GB. This finding suggested that GB could form an inclusion complex with CD (11). The formation of inclusion complex was a result of grinding and was enhanced by the increased grinding time, which resulted in the improved dissolution.

The effect of grinding GB with CD at the ratio of 1:2 on the DSC curve is illustrated by Fig. 2(h). Broadening of the CD peak and diminishing in the GB peak intensity were observed. Nevertheless, the degree of change was less as compared with those of the 24- and 48-hr ground mixtures at the ratio of 1:4. The result could be due to incomplete complex formation when less CD was used.

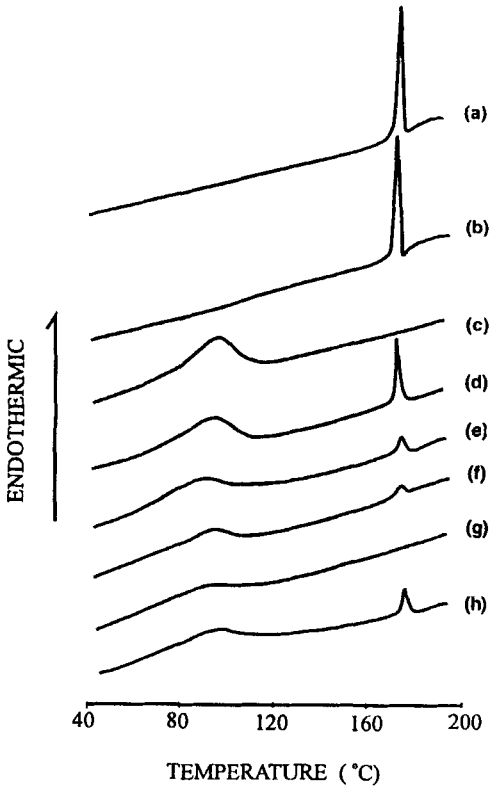

Figure 2. DSC thermograms of various glibenclamide preparations: (a) crystalline glibenclamide; (b) ground glibenclamide; (c) β-cyclodextrin; (d) physical mixture; (e) ground mixture 1:4, 12 hr; (f) ground mixture 1:4, 24 hr; (g) ground mixture 1:4, 48 hr; (h) ground mixture 1:2, 48 hr.

Aging Effect on Glibenclamide Tablets

Selected formulations including ground GB (A), physical mixture (B), and ground GB/CD mixtures (E, F, H, and I) had been stored at 40°C and 75% RH for 3 months. Tablet weight, hardness, friability, and disintegration characteristics were not significantly affected by these storage conditions.

Chemical stability of GB tablets stored at 40°C and 75% RH are presented in Fig. 3. A appeared to degrade faster than did the others. This observation could be due to the fact that grinding creates new surfaces which are prone to degradation. B, E, and F seemed to decompose to the same extent, i.e., approximately 94% remaining at 3 months. The protection of GB against decomposition could be obtained with the ground mixture at the ratio of 1 to 4. Figure 3 indicates that both H and I did not show any decomposition after storage for 3 months.

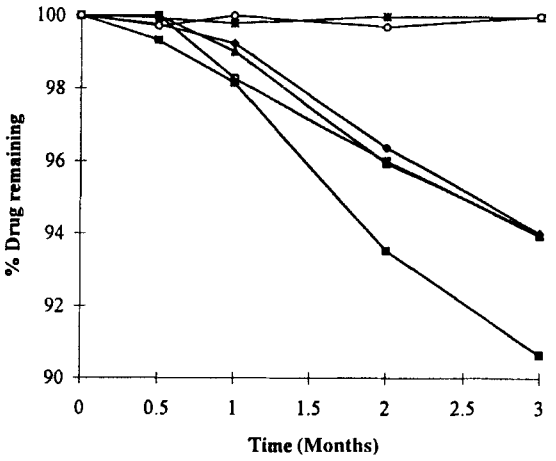

Figure 3. Chemical stability of various glibenclamide tablets stored at 45°C and 75% RH: (■) A, ground GB; (□) B, physical mixture; (Δ) E, ground mixture 1:2, 24 hr; (◇) F, ground mixture 1:2, 48 hr; (○) H, ground mixture 1:4, 24 hr; (∗) I, ground mixture 1:4, 48 hr.

The results suggested that inclusion complex formation had not only enhanced the dissolution of GB but also stabilized GB against chemical decomposition at the elevated temperature and humidity studied. It was found that dissolution of these tablets remained unchanged over a 3-month period. Therefore, CD did not have any unwanted effect on the dissolution of the inclusion complex after prolonged storage at high temperature and humidity.

CONCLUSIONS

Glibenclamide tablets were found to show a dissolution problem. The objective of this study was to minimize the problem by inclusion of GB into CD. Physical mixing and kneading of CD and GB did not improve the drug release. It was found that treatment of GB with CD by grinding at the ratio of 1 to 4 for 24 or 48 hr produced tablets with good physical properties including drug dissolution, i.e., more than 90% released at 30 min, as well as good chemical stability. The grinding of GB and CD seemed to be a simple and cost-effective method for preparing glibenclamide tablets.

REFERENCES

1. M. A. Hassen, N. M. Najib, and M. S. Sulieman, Int. J. Pharm., 67, 13 (1991).
2. M. S. Sulieman and N. M. Najip, Int. J. Pharm., 50, 103 (1989).
3. P. G. Tiakla, in *Analytical Profiles of Drug Substances* (K. Florey, ed), Academic Press, New York, 1981, Vol. 10, p. 338.
4. A. S. Geneidi, M. S. Adel, and E. Shehata, Canad. J. Pharm. Sci., 15, 7 (1980).
5. A. S. Geneidi, M. S. Adel, and E. Shehata, Canad. J. Pharm. Sci., 15, 81 (1980).
6. D. Duchene and D. Wouessidjewe, Pharm. Tech., 14(6), 30 (1990).
7. N. M. Sanghavi, H. Venkatesh, and V. Tandel, Drug Dev. Ind. Pharm., 20, 1275 (1994).
8. E. G. E. Shafer, E. G. Wollish, and C. E. Engel, J. Am. Pharm. Assoc. Sci. Ed., 45, 114 (1956).
9. G. E. Reier and R. F. Shangraw, J. Pharm. Sci., 55, 510 (1966).
10. N. M. Sanghavi, R. Mayekar, and M. Fruitwala, Drug Dev. Ind. Pharm., 21, 375 (1995).
11. S. Y. Lin, Y. H. Kao, and J. C. Yang, Drug Dev. Ind. Pharm., 14, 99 (1988).
12. Y. Nakai, Drug Dev. Ind. Pharm., 12, 1017 (1986).
13. J. Szejtli, *Cyclodextrins and Their Inclusion Complexes*, Akademiai Kiado, Budapest, 1982.