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COMMUNICATION

Effect of Aging on the Dissolution Stability of Glibenclamide/ β-Cyclodextrin Complex

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ABSTRACT

The effect of aging on the physicochemical stability of glibenclamide (GB)/β-cyclodextrin (CD) systems and tablets made with CD-complexed GB was studied. Infrared (IR) spectrometry and X-ray diffraction analyses showed that the properties of the products were unaffected even after a storage period of 4 years, except that the crystallinity of GB/CD physical mixture was decreased with aging. The dissolution rate of the kneaded mixture, inclusion complex, and tablets made with the inclusion complex were unaffected on storage for 4 years. Thus, the age-related dissolution problems of GB can be overcome by utilizing the GB/CD complex in the tablet dosage form.

INTRODUCTION

During storage, a drug product may undergo changes in physicochemical characteristics that can affect the bioavailability of the dosage form. For a tablet dosage form, the product has to meet specifications on all physicochemical parameters, such as drug assay, hardness, disintegration time, and dissolution rate, during its shelf life. During storage, the excipients may interact with the drug and hence affect its dissolution characteristics. Hence, drug-excipient interactions are studied thoroughly by pharmaceutical manufacturers during the preformulation stage and during the entire shelf life. Stability data for the final product will be required to be given in the product license application, and inadequate stability data are one common reason for refusal of a license application (1,2).

Glibenclamide (GB), a widely used oral hypoglycemic drug of the sulfonyl urea group, is virtually insoluble in water (3), and hence its dissolution is considered to be

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a rate-limiting step for absorption. There are several reports of GB tablets showing marked variations in the dissolution and bioavailability of the drug (4–7), and also aging adversely affects the dissolution rate and bioavailability of GB tablets (8). The dissolution rate–limited bioavailability problems can be overcome by the use of solid dispersions (9–13) or surfactants (14,15) or by micronization (16).

In an earlier report (17), we demonstrated the improvement of dissolution rate and hypoglycemic activity of GB by β-cyclodextrin (CD). In the present study, we investigated the effect of aging on the physicochemical stability of GB/CD systems, as well as tablets made with CD-complexed GB, and the results are presented here.

EXPERIMENTAL

Materials

Glibenclamide, lactose anhydrous (direct-tableting grade), and sodium starch glycolate were obtained as gift samples, respectively, from Cadila Labs (Bombay), Humko Sheffield (Tennessee), and Generichem Corporation (New Jersey). The β-cyclodextrin, purchased from SD Fine Chemicals (Bombay, India), was recrystallized from double-distilled water. All other chemicals employed were analytical reagent grade.

Methods

Preparation of Glibenclamide/Cyclodextrin Compounds

The GB/CD inclusion complex, kneaded mixture, and physical mixture were prepared in a 1:2 molar ratio. The preparation of GB/CD compounds and their characterization has been reported elsewhere (17).

The moisture content of the products was approximately 4% as determined by thermogravimetric analysis (Linsies type 2045 TG analyzer). The GB content of GB/CD compounds was determined by a spectrophotometric assay after dissolving the product in a water/methanol mixture (50/50), with 28 mg of the GB/CD compound equivalent to 5 mg of GB. The powder samples were passed through a number 100 mesh sieve and stored in amber-colored vials plugged with absorbent cotton. The vials were placed in an oven maintained at 30°C and 50% relative humidity.

Characterization of Glibenclamide/Cyclodextrin Compounds

Infrared Spectroscopy

Infrared (IR) spectra of the physical mixture, kneaded mixture, and inclusion complex were recorded for both fresh products and products aged 4 years. The KBr disks containing the samples were prepared, and IR spectra were obtained on a Jasco IR report 100 spectrometer.

X-Ray Diffractometry

X-ray diffractometry of both fresh samples and samples aged 4 years were recorded on a Rigaku D-max III horizontal X-ray diffractometer. The following operating conditions were followed: nickel-filtered $CuK_{i\alpha}$ radiation; voltage 35 kV; current 25 mA; and scan speed $-1°2\theta$/min.

Fabrication of Glibenclamide/Cyclodextrin Tablets

Each tablet contained 28 mg of GB/CD complex (equivalent to 5 mg of GB), 113 mg of lactose (direct-compression grade), 4.5 mg of sodium starch glycolate, 3 mg of zinc stearate, and 1.5 mg of talc. The batch size for the tablets was 500. Tablets were made by direct compression. All the ingredients were thoroughly mixed by a tumble mixer. Compression was done on a Manesty E-2-type single-punch tableting machine. Tablets thus obtained were stored as described for powder samples. Tablets were evaluated while fresh, after 1 year, and after 4 years for hardness, weight variation, friability, drug content, disintegration time, and dissolution rate according to the USP.

Dissolution Rate Studies

Dissolution rate studies of the fresh and aged GB/CD compounds and tablets were conducted on a USP standard dissolution apparatus. The dissolution medium was pH 7.4 phosphate buffer maintained at 37°C ± 0.5°C and stirred at 100 rpm by means of an adjustable constant-speed motor. A tablet or powder containing 5 mg of drug was introduced, and the time was recorded (time 0). Then, 5-ml samples were withdrawn at intervals, and the same volume of fresh dissolution medium, maintained at 37°C ± 0.5°C was added to the flask to maintain constant volume. The samples were assayed using an ultraviolet/visible (UV/Vis) spectrophotometer (Jasco 7800, Tokyo, Japan) at 229 nm. Dissolution studies for each formula-

tion were carried out in triplicate. The dissolution data are represented as the cumulative amount dissolved at 5 min (D 5), 30 min (D 30), and 60 minutes (D 60).

RESULTS AND DISCUSSION

Properties of Glibenclamide/Cyclodextrin Compounds

The IR spectra of both fresh and aged samples are shown in Fig. 1. Glibenclamide shows absorption peaks of the urea carbonyl group and amide carbonyl group at 1618 cm^{-1} and 1715 cm^{-1}, respectively. The absorption peak at 1521 cm^{-1} is due to urea NH bending and amide II bond (18). The characteristic carbonyl peaks observed in both drug and physical mixture at 1618 cm^{-1} and 1715 cm^{-1} are absent in the inclusion complex, whereas these peaks are evident in the kneaded mixture. Also, in the inclusion complex, the peak at 1521 cm^{-1} shifts to 1535 cm^{-1}. A comparison of IR spectra of fresh physical mixture, kneaded mixture, and inclusion complex with respectively aged samples indicates no noticeable change in the spectra of the samples on aging. This indicates that the product is stable during the entire storage period.

The effect of aging on the X-ray diffraction pattern of GB/CD compounds is shown in Fig. 2. The fresh kneaded mixture and inclusion complex show broader peaks of lower intensity compared with the fresh physical mixture. This indicates the less crystalline nature of both kneaded mixture and inclusion complex. The physical mixture, on storage for 4 years, showed substantial reduction in crystallinity, as indicated by broader peaks of lower intensity. Similarly, the kneaded mixture and inclusion complex also exhibited marked reduction in the peak intensity on storage for 4 years, indicating strong interaction of GB with CD during long-time storage.

The drug content of GB/CD systems was determined for fresh products and after 1 and 4 years storage. The assay values of the products aged 1 and 4 years were similar to those of fresh products. This indicates stabilization of GB against chemical decomposition during storage (19). The dissolution rate of drug from various GB/

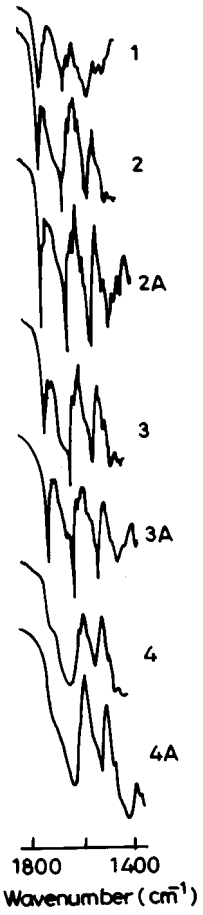

Figure 1. Infrared spectra of glibenclamide (1), GB/CD physical mixture (2, fresh; 2A, aged), kneaded mixture (3, fresh; 3A, aged), and inclusion complex (4, fresh; 4A, aged).

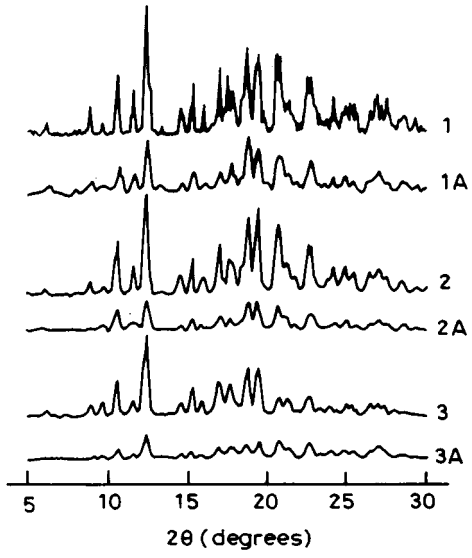

Figure 2. X-ray diffraction patterns of GB/CD physical mixture (1, fresh; 1A, aged), kneaded mixture (2, fresh; 2A, aged), and inclusion complex (3, fresh; 3A, aged).

Table 1

Dissolution of Glibenclamide after 5 min (D 5), 30 min (D 30), and 60 min (D 60) from Various GB/CD Systems

Product		D 5	D 30	D 60
Physical mixture	Fresh	26.88 ± 4.58	39.51 ± 4.00	43.58 ± 5.00
	1 year	27.80 ± 5.60	43.40 ± 5.84	49.40 ± 4.00
	4 years	25.09 ± 3.82	46.81 ± 4.90	57.58 ± 4.86
Kneaded mixture	Fresh	49.20 ± 5.42	81.47 ± 6.00	89.44 ± 3.89
	1 year	46.52 ± 6.00	77.33 ± 5.12	85.29 ± 5.16
	4 years	49.28 ± 5.49	81.64 ± 4.88	87.62 ± 6.19
Inclusion complex	Fresh	67.83 ± 4.49	96.91 ± 5.00	100.00 ± 5.60
	1 year	68.09 ± 4.48	95.92 ± 4.66	99.80 ± 4.90
	4 years	66.80 ± 5.00	95.26 ± 4.88	98.76 ± 4.00
Inclusion complex tablets	Fresh	44.10 ± 3.69	80.85 ± 4.62	92.46 ± 4.11
	1 year	46.00 ± 3.68	81.48 ± 4.56	90.84 ± 5.00
	4 years	45.56 ± 5.66	79.53 ± 4.66	91.31 ± 3.89

Values represent mean ± SD; $n = 3$.

CD systems is shown in Table 1. The dissolution rate of GB from the kneaded mixture and inclusion complex is significantly higher than that for the physical mixture. While the dissolution rate of the inclusion complex (D 60) is complete, for the kneaded mixture, the corresponding value is about 90%. The D 5 and D 30 values reveal that the inclusion complex dissolves at a faster rate than the kneaded mixture. However, the dissolution rate of kneaded mixture at 30 min (D 30) is significantly increased, but still to a lesser extent than that of inclusion complex.

A comparison of dissolution rates of fresh and aged products shows that the kneaded mixture and inclusion complex were unaffected even after 4 years of aging. Both the rate and extent of dissolution of the kneaded mixture and inclusion complex were unaffected during the storage periods, as indicated by the D 5 and D 60 values of both fresh and aged products. Reduced crystallinity, improved wettability, and molecular dispersion of GB due to CD are responsible for the observed effects.

The dissolution rate of the physical mixture is significantly increased with the aging of the sample. While the fresh product showed a D 60 of 43%, for products aged 1 and 4 years, the corresponding values were 49% and 57%, respectively. The higher dissolution rate of the physical mixture due to aging can be explained by the decrease in crystallinity of the product during storage, as evidenced from X-ray diffraction studies.

Properties of Glibenclamide/Cyclodextrin Tablets

The GB/CD tablets were made by direct compression. The hardness of the tablets was set at 5 units (monsanto). The friability of the tablets was 0.3%; disintegration time was 1.5 min. The above parameters did not change appreciably during the storage period of 4 years. The drug content of tablets aged 4 years was around 96% of the initial values. The stability of GB in the formulation is due to complexation with CD (19). The dissolution profiles of GB/CD tablets are shown in Table 1. It was found that about 90% of drug dissolved in 1 hr, and the dissolution rate remained unaffected even after a storage period of 4 years.

The results of the present study indicate that GB/CD complex can be incorporated into tablet formulations dissolution that is better and uniform. In light of the reports on dissolution-related bioavailability problems with several brands of GB tablets, as well as aging problems on the dissolution rate of solid dosage forms, there is a distinct advantage of utilizing the GB/CD complex in the tablet dosage form.

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