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RESEARCH PAPER

Cyclodextrin Complex Osmotic Tablet for Glipizide Delivery

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ABSTRACT

Poorly soluble glipizide was selected as the model drug to prepare osmotic pump tablets (OPT) with proper accessorial material after it was made an inclusion complex by kneading method in order to increase solubility. Polyethylene glycol 4000 (PEG4000) and cellulose acetate (CA) were selected as the coating materials, and acetone–water (95:5) co-solvent was employed as the coating medium. The effects of the osmotic promoting agent, diameter of the drug-releasing orifice, coating composition, and coat weight on the drug release profile were investigated. The drug release profile of the optimal formulation was compared with a commercialized push–pull osmotic tablet. The results indicated that glipizide–cyclodextrin inclusion complex OPT had excellent zero-order release characteristics in vitro.

Key Words: *β-Cyclodextrin; Glipizide; Inclusion complex; Osmotic pump*

INTRODUCTION

In the 1970s the elementary osmotic pump (EOP) was introduced by Theeuwes.[1] Since the EOP is very simple to prepare and can release drug in a controlled pattern over a long period, there has been increasing interest in the development of EOP in the past two decades. However, the generic EOP is only suitable for the delivery of moderate-solubility drugs. To overcome this limitation, a push–pull osmotic tablet (PPOT) was developed in the 1980s.[2] Both Adalat® (nifedipine) and Glucotrol XL® (glipizide) are commercialized PPOT products. Although the PPOT succeeds in delivering drug with either

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poor or high water solubility, it has some disadvantages. Firstly, the tablet core has two layers, so a complex technology that is bilayer tablet compressing technology is needed. Secondly, suspension formed in the drug layer of PPOT has more viscosity than that of EOP. To withstand the pressure within the tablets, the membrane of PPOT must be thicker than that of EOP. This can result in a long "lag time" before drug release. At last, after coating, a complicated laser-drilling technology should be employed to drill the orifice on the side of the drug layer. Owing to the complicated process of preparing PPOT, many modified methods were used to prepare an osmotic pump for insoluble drugs.[3–6] Although some were simple, most of them were just suitable for one or several drugs with specified characters and couldn't apply to all insoluble drugs. Since 1998, Okimoto has investigated OPT for poorly water-soluble drugs (testosterone, prednisolone, and chlorpromazine) utilizing $(SBE)_{7m}$-β-CD as both a solubilizer and osmotic agent.[7–9] Here, a simple EOP was prepared with glipizide (GLI) as the model drug and conventional beta-cyclodextrin(β-CD) as solubilizer. The factors responsible for controlling drug release through the osmotic pump were evaluated from release studies. The optimal formulation whose release profile was similar to that of commercialized product (Glucotrol XL, the PPOT product of Pfizer) was gained.

MATERIALS AND METHODS

Materials

Beta-cyclodextrin was purchased from Yu Nan Pharmaceutical Manufacturing (Guangdong, China). Glipizide was purchased from the Fifteenth Pharmaceutical Manufacturing of Shanghai (Shanghai, China). Polyethylene glycol 4000 (PEG4000, average molecular weight) was purchased from Shanghai Chemical Company (Shanghai, China). Cellulose acetate (CA-398-10) was a gift from Eastman Chemical Company (USA). The other chemicals used were analytical grade.

Phase-Solubility Study

The binding constants between GLI and β-CD were determined using the phase-solubility method. Excess GLI (0.2 g) was added to water, or lactose, or NaCl, or mannitol-saturated solution (20 mL) containing different concentrations of β-CD, and shaken at 37°C for 5 days. Then, the filtered solutions were analyzed by high-performance liquid chromatography (HPLC) after diluting with the mobile phase. The GLI was fractionated on a Hypersil ODS column (15 cm×4.6 mm, ID with 5 μm packing material) with detection at 275 nm using a mobile of methanol–water (60:40, with 0.2% acetate acid). The intrinsic solubility of GLI and the binding constants with β-CD were calculated using least squares regression analysis as suggested by Higuchi and Connors.[10]

Preparation of Inclusion Complexes

Solid complexes were prepared using different ratios of GLI and β-CD. The ratios were calculated on a molecular basis, and the following proportions were prepared: 1:2, 1:10, 1:20. The complexes were made by the kneading method and the effect of the kneading time on the complexation was also investigated. The results show that after 2 hr the kneading time has little effect on the complexation. So GLI and different molar quantities of β-CD were wetted in a mortar with 50% methanol until a paste was obtained and mixed for 2 hr. Then, these pastes were left to air dry for one night and finally mildly ground and stored under vacuum in a desiccator for 3 days. The product was sieved through a 0.247-mm mesh.

Inclusion Complex Investigation

Differential scanning calorimetry analysis was performed with a Perkin Elmer DSC7. Samples were prepared by placing about 7 mg of sample into an aluminum pan, which was covered and crimped for analysis. The resulting thermogram was analyzed qualitatively by examining the peak temperature of the melt of glipizide and the transition contour and quantitatively by calculating the enthalpy of the melt of glipizide associated with the cyclodextrin–cavity dehydration from about 50°C to 300°C. The heating rate was 10°C/min; the analysis range was from 50°C to 300°C; nitrogen flow rate was 50 mL/min.

Preparing the Tablet Core

The basic tablet formulation and the varying range of all chemicals are listed in Table 1, unless otherwise noted. In each formulation, the effect of

Table 1

The Basic Tablet Formulation and Varying Range of All Chemicals

Chemicals	Basic Amount (mg)	Varying Range (mg)	Osmotic Pressure of Saturated Solution (37°C, $\times 10^6$ Pa)
Glipizide	5	5	—
β-CD	125	60–250	—
Lactose	400	300–500	10.17
Mannitol	400	400	3.85
NaCl	400	400	36.07
Calcium sulfate	130	5–195	~0.001

calcium sulfate on drug release was assumed to be minor. Thus, the amount of calcium sulfate was variable to maintain the total weight of each tablet fixed at 660 mg, in order to maintain the volume and surface area relatively constant. For the preparation of core tablets, inclusion complexes of GLI with β-CD mixture of lactose each containing 5 mg GLI were compressed with an 11-mm round (concave) punch under a pressure of 7×10^6 Pa.

Coating and Drilling

Tablets were coated using a pan coater. Cellulose acetate (CA, 3% w/v) in acetone containing known levels of plasticizer was used as coating solution. The amount of plasticizer together with the membrane thickness from formulations A1 to A5 is listed in Table 2. The coating conditions were outlined as follows: pan specification, stainless steel, spherical, 230-mm diameter; pan rotating rate, 40 rpm; spray rate, 10 mL/min; drying, using a heat gun. The coated tablet was dried overnight at 50°C to remove residual solvent before a 0.5 mm orifice was drilled by laser on one side of the tablet. The coat weight was the mean value of tablet weight gain for 50 tablets.

Dissolution Test

The dissolution tests were carried out using a paddle method. The amount of GLI released in 200 mL of 0.1 M pH 7.4 phosphate was measured at a paddle rotation speed of 50 rpm at 37°C. The amount of GLI was determined by measuring the absorbance at 275 nm using a UV-260 ultraviolet spectrophotometer (Shimadzu Co., Tokyo, Japan). All the tests were performed with six tablets.

RESULTS AND DISCUSSION

Phase Solubility of GLI with β-CD

The intrinsic solubility of GLI, a poorly water-soluble drug, is 1.82 μg/mL at 37°C in water, 0.69 μg/mL in lactose-saturated solution, 2.24 μg/mL in mannitol-saturated solution, and 1.56 μg/mL in NaCl-saturated solution. The plots in Fig. 1 show the phase solubility diagrams of GLI with β-CD in the four different kinds of solution. The solubility of GLI increased linearly with increasing concentration through 0.025 M for β-CD in all four kinds of solution. This suggested 1:1 complexation in this concentration range. Table 3 summarizes the values of GLI in different media. The values in Table 3 show that the stability constants of the complex are different in the four kinds of solution. This may be explained by the "enthalpy effect."[11]

Differential Scanning Calorimetry Data and Complexation Percentages

Except for the sample of drug–cyclodextrin in molar ratio 1:20, all the complex powders prepared by kneading present the GLI melting peak. But compared to the physical mixture with same drug–cyclodextrin molar ratio, the area of the GLI melting peak of the complex decreased with drug–cyclodextrin decreasing molar ratio. This suggests that a lower drug–cyclodextrin molar ratio is helpful to increase complexation percentages. Table 4 summarizes the values of the different prepared

Table 2

Coating Formulation and Membrane Thickness

Coating Formulation No.	Amount of PEG4000 (CA, w/w %)	Coat Weight (mg)
A1	5	20
A2	10	20
A3	15	20
A4	15	13
A5	15	27

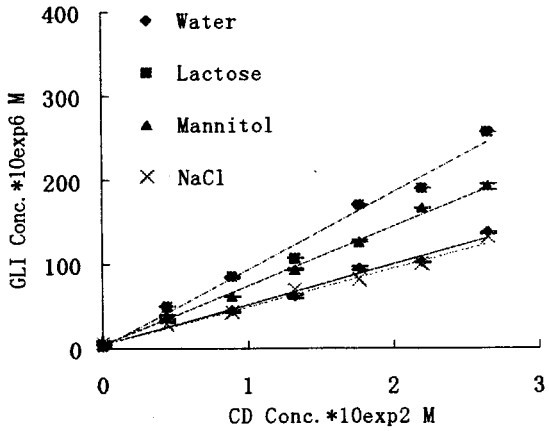

Figure 1. Phase solubility diagram of GLI with β-CD.

powders. From these values the theoretical complexation percentages have been calculated, comparing the melting enthalpy of pure drug with peak enthalpies of processed powders and, at the same time, taking into account the real quantity of drug in the powder. There was good linearity between the enthalpy of fusion and the weight ratio of GLI in the physical mixture ($r^2 = 0.998$).

Influences of Tablet Formulation Variables on Drug Release

To study the influences of tablet formulation variables on drug release, tablets with various formulations were prepared, subsequently coated with the same coating formulation, A3 in Table 2, and a 0.5-mm diameter orifice was drilled on one side of the surface.

Figure 2 shows that different osmotic promoting agents had a different influence on the drug release profile. The basic formulation of the core is GLI (5 mg), β-CD (125 mg), osmotic promoting agent (400 mg), and calcium sulfate (130 mg). With variance of osmotic promoting agent, both drug release rate and amount of drug release in 14 hr were different. On the one hand, in different osmotic promoting agent-saturated solutions the solubility of GLI increased by β-CD was different; on the other hand, different osmotic promoting agents had different osmotic pressure. These two reasons led to a marked difference in drug release profile among the three formulations. The formulation with lactose as osmotic promoting agent shows the best zero-order release pattern in 14 hr.

Based on the above result, lactose was adopted as osmotic agent in the following studies. Figure 3 shows that the amount of lactose had some influence on GLI release. The rate of drug delivery is constant as long as excess lactose is present inside the device, but the rate declines toward zero once the concentration of lactose falls below saturation. So the amount of lactose influenced the amount of GLI released in 14 hr but didn't have a marked effect on the release rate. The amount of GLI released in 14 hr increased as the amount of lactose increased. The more lactose incorporated into the tablet, the more core formulation could be liquified and, as a consequence, the more GLI was released in 14 hr.

Based on the above results, 500 mg lactose was adopted as osmotic agent in the following studies. Figure 4 shows the release profiles to study the influence of amount of β-CD. It can be observed that the amount of β-CD had a pronounced influence on the release profile. It acts as a solubilizer, and increases the solubility of GLI. However, complexation of drug molecules to cyclodextrin is a dynamic process, whereby the guest molecule continuously associates and dissociates from the host

Table 3

Phase-Solubility Data of GLI in Different Media

Medium	r^2	Slope$\times 10^3$	Intercept$\times 10^6$	Binding Constant (M^{-1})
Water	0.984	4.8	5.0	965
Lactose	0.989	9.2	1.8	5159
NaCl	0.991	4.6	5.0	924
Mannitol	0.997	7.1	4.7	1521

Table 4

Differential Scanning Calorimetry Data of β-CD Complex and Physical Mixture

Molar Ratio		Complex		Physical Mixture	
Drug	β-CD	J/g	% Complex	J/g	% Complex
Glipizide		307.87	0	307.87	0
1:2		47.21	34.6	72.24	0
1:10		3.721	85.9	26.35	0
1:20		0	100	11.51	0

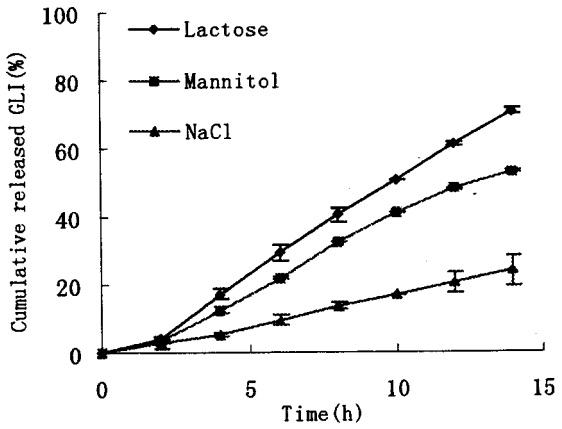

Figure 2. Influence of different osmotic promoting agent on drug release.

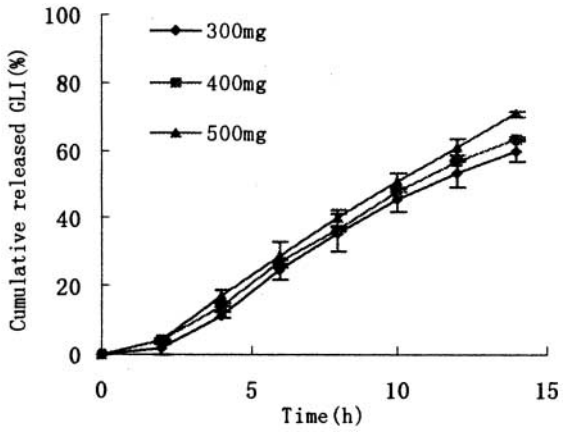

Figure 3. Influence of amount of lactose on drug release.

cyclodextrin. From the point of view of kinetics, the larger the amount of β-CD in a solution, the less the amount of free drug is in the solution. So the larger the amount of β-CD used, the more the amount of GLI would be released. However, in 14 hr more GLI was released in the formulation of GLI to β-CD (1:10) than in the formulation of GLI to β-CD (1:20). Up to 24 hr, slightly more GLI was released in the formulation of GLI to β-CD (1:20) than in the formulation of GLI to β-CD (1:10). A large amount of β-CD will decrease the rate of drug release. This may be the reason that drug released in the formulation of GLI to β-CD (1:20) is less and has poor zero-order characterstics at 14 hr. In Fig. 4, only little of the drug was released in the case of 0 mg β-CD. Zero-order drug release was observed to increase with increasing amount of β-CD. The rate of drug delivery is constant as long as excess complex is present inside the device, but

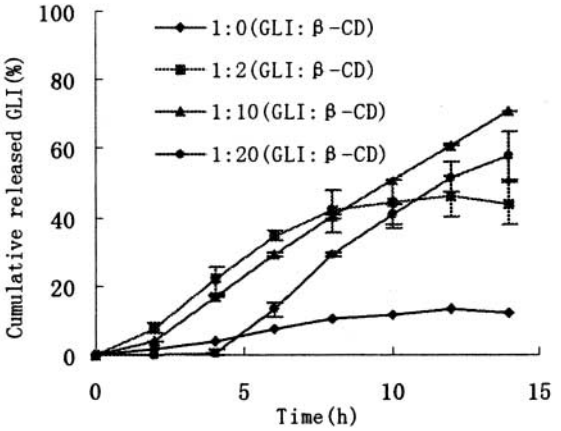

Figure 4. Influence of amount of β-CD on drug release.

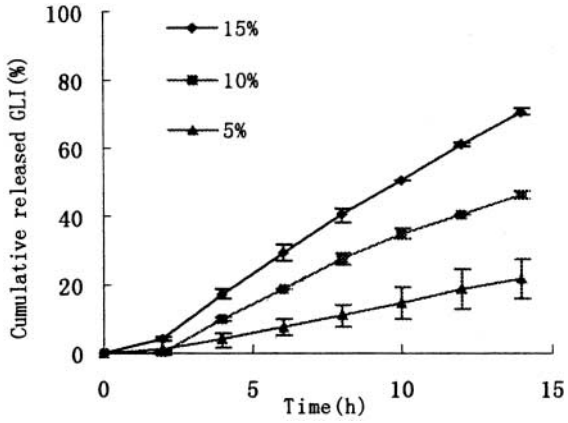

Figure 5. Influence of PEG level on drug release.

the rate declines toward zero once the concentration of complex falls below saturation.

Based on the above results, the optimal formulation of the tablet core is molar ratio of drug–cyclodextrin 1:10, with amount of lactose 500 mg. This formulation was used in the following studies.

Influence of Membrane Variables on Drug Release Profile

The membrane is a key factor with relation to the release profile of EOP. The release profiles of the optimal tablet core coated by a CA membrane with 5%, 10%, 15% of PEG4000 are compared in Fig. 5 to study the influence of amount of PEG level leading to an increase of drug release rate. The more PEG incorporated into the CA membrane, the more void space formed after leaching and, in turn, the higher the permeability of the membrane, the higher the drug release rate obtained.

To study the influence of membrane thickness on drug release profiles, the optimal tablets were coated to different coat weight of 13 mg, 20 mg, 27 mg, respectively, using a coating solution with a PEG level of 15%. Figure 6 shows that the release rate decreased as the membrane thickness increased. As the thickness increased, the resistance of the membrane to water diffusion increased and the rate of imbibing water decreased; resulting in turn in the drug release rate decreasing. It was found that a zero-order release pattern and release rate up to 14 hr was obtained in the case of the 15% coating.

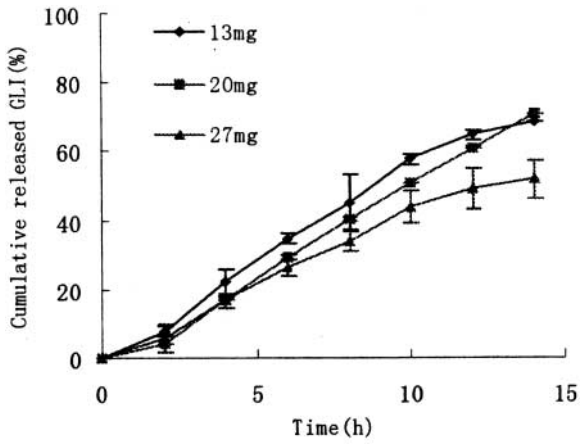

Figure 6. Influence of membrane weight on drug release.

Influence of Orifice Size on Drug Release

It was reported that there was an appropriate range of orifice sizes for EOP; these must be smaller than the maximum limit to minimize the contribution to the delivery rate made by diffusion through the orifice. Also, they must be larger than the minimum limit to minimize hydrostatic pressure inside the system. The optimal tablets were coated with A3 (Table 2), and subsequently a circular orifice with the same diameter was drilled on one side of the surface. Figure 7 shows the influence of orifice size on release profile. The results were in accordance with those of EOP. No significant difference existed in the release profiles for orifice diameters ranging from 0.3 to 0.8 mm. In the following

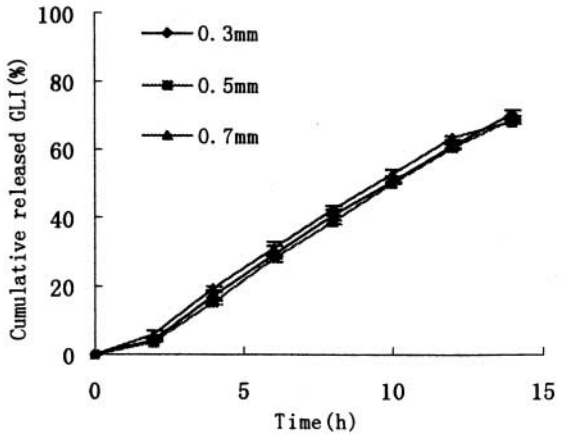

Figure 7. Influence of orifice size on drug release.

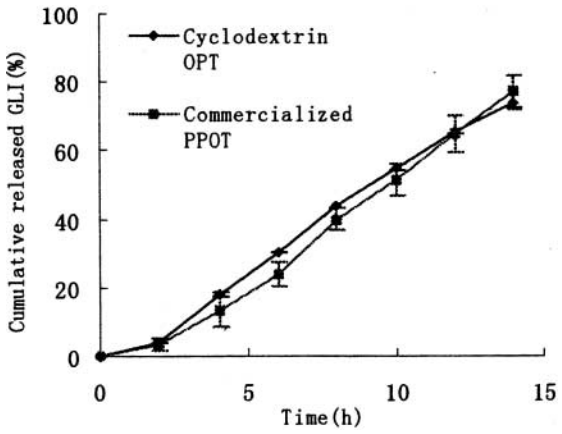

Figure 8. Glipizide release profile comparison of cyclodextrin OPT with commercialized PPOT.

studies, an orifice diameter of 0.5 mm, which was within the optimal range, was adopted.

Comparison with PPOT

The release rates of PPOT and cyclodextrin EOP tablets were obtained from their release profiles by numeric differential processing and are plotted in Fig. 8. It was found that constant rates both in PPOT and in cyclodextrin EOP tablets were observed up to 14 hr. The similarity factor (f_2) calculated for the two kinds of OPT was 59.9. So the release profile of cyclodextrin EOP tablets in this study was found to be very similar to that of the commercialized product.

CONCLUSION

The solubility studies indicated that β-CD was more effective in increasing the solubility of GLI in saturated lactose solution than in the other three solutions. It was found that the stability constant between drug and β-CD had profoundly positive effects on drug release, and complexation percentages also had a marked influence on the amount of drug released at the end of 14 hr. The optimal tablet formulation with good zero-order release pattern from 2 to 14 hr had been prepared. The release profile of the optimal tablet was found to be very similar to that of commercialized PPOT.

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