Drug Development and Industrial Pharmacy, 26(10), 1125–1128 (2000)

COMMUNICATION

The Influence of Diluent on the Release of Theophylline from Hydrophilic Matrix Tablets

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ABSTRACT

The role of β-cyclodextrin (β-CD) on the apparent solubility of theophylline was investigated by the solubility method. Binary systems of theophylline and β-CD were prepared using the dry co-grinding method. Their characterization was performed by differential scanning calorimetry (DSC). The dissolution rate of theophylline and theophylline/β-CD and dissolution studies of matrix tablets prepared from mixtures containing theophylline and ground theophylline were carried out. It can be concluded that β-CD is related to an increase in the apparent solubility and dissolution rate of the drug, promoting improvement on the release of theophylline from matrices manufactured with hydroxypropylmethylcellulose (HPMC). This can be attributed to the amorphous state and the increased wettability of the drug.
Key Words: *Controlled release; β-Cyclodextrin; Matrix tablets; Theophylline.*

INTRODUCTION

There are a number of good reasons for controlling the release of drugs, not the least of which is the fact that often safety, efficacy, and patient compliance can be improved over conventional dosage forms (1,2). Hydroxypropylmethylcellulose (HPMC) is often used to prepare controlled-release dosage forms because of its important characteristics (2–7). The potential use of natural cyclodextrins (CDs) and their synthetic derivatives has been extensively studied to improve certain properties of the drugs, such as solubility, stability, and/or bioavailability (8–10).

On the other hand, grinding is often used as a technique to reduce the particle size of powders to enhance the solubility, dissolution rate, and bioavailability of poorly water soluble drugs. This treatment is a simple technique, is easy to carry out, and may increase the mo-

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lecular interaction in the ground mixtures, often providing complex formation and changes in crystalline state of the drug into the amorphous state, with improvements of the dissolution properties (11–13).

Recently, Roselli et al. (14) demonstrated that the dissolution rate of a poorly water soluble drug can be enhanced markedly by a simple and low-cost formulation process involving only a ground mixture of drug/hydrophilic cyclodextrins and suitable excipients before compaction.

In our previous studies, the effect of diluent on the release of theophylline from matrix tablets was investigated, but not observed (15). Paying attention to the described considerations, the aim of this work was to study the influence of the diluent β-CD co-ground with theophylline on the in vitro characteristic release of drug from matrices manufactured with HPMC. For this purpose, the effect of β-CD on the dissolution of theophylline was studied by the solubility method. Binary systems of theophylline and β-CD were prepared using the dry co-grinding method, and their characterization was performed by differential scanning calorimetry (DSC). The dissolution rates of theophylline and the ground mixture contained in gelatin capsules were determined in water. Dissolution studies of matrix tablets prepared with theophylline and theophylline/β-CD were carried out according to USP 23 at pH 1.2, 6.5, and 7.5 (16).

EXPERIMENTAL

Materials

The following materials were used: theophylline anhydrous (TPH), Boehringer; HPMC, Methocel K 15M, Colorcon, Spain; β-CD, Roquette, Lestrem, France; lactose, Tablettose; talc and magnesium stearate, reagent grade.

Solubility Studies

The solubility studies were performed according to the method described by Higuchi and Connors (17). Increasing amounts of β-CD (0–40 $\times$ 10^3 M) were added to a suspension of 5 g TPH in 100 ml of distilled water. The systems were shaken at 20°C ± 0.5°C. After equilibrium was attained, aliquots were filtered, diluted with water, and analyzed spectrophotometrically at 264 nm for TPH against a calibration curve (correlation coefficient = 0.9996).

Preparation of the Ground Mixture

A ground mixture of TPH:β-CD (100:44) g was prepared by co-grinding in a ceramic ball mill for 12 hr.

Characterization of the Ground Mixture

The characterization of the ground mixture was carried out by DSC. The measurements were recorded on a Shimadzu model 50 (Kyoto, Japan). Indium (99.99%, mp 157.6°C) was used to calibrate the apparatus. All samples (2–4 mg) were placed in aluminum pans and sealed before being heated under a nitrogen stream at a scanning rate of 10°C/min from 25°C to 400°C.

Effect of β-Cyclodextrin on the Dissolution Rate of Theophylline Anhydrous

The typical dissolution curves obtained for TPH or its equivalent weight of TPH/β-CD ground mixture contained in gelatin capsules were determined according to the following method: Gelatin capsules (attached with a few turns of wire helix that would otherwise float) were tested using a dissolution apparatus with a rotating paddle (Hanson Research). The dissolution medium was 1000 ml of distilled water maintained at 37°C, and the speed used was 100 rpm. Samples were withdrawn, filtered, and analyzed spectrophotometrically (λ = 264 nm) at regular intervals. The studies were carried out in triplicate.

Formulations

According to previous studies (15,18), the composition of individual matrix tablets is shown in Table 1.

Preparation of Matrix Tablets

The preparation of matrices was carried out as described in previous work (18).

Table 1

Composition of Theophylline Anhydrous Matrix Tablets

Composition	Formulation A (mg)	Formulation B (mg)
TPH	100	100
β-CD	—	44
HPMC	50	50
Lactose	44	—
Talc	4	4
Magnesium stearate	2	2

Determination of Theophylline Anhydrous in the Matrix Tablets

TPH content of matrix tablets was determined by spectrophotometric analysis at 264 nm following the previous method (15).

Disintegration Studies

The disintegration tests were carried out as described previously (15).

Dissolution Studies

The dissolution studies of matrix tablets were carried out according to the USP 23 paddle method (16). It was an automatic procedure with a Hanson Research model at a speed of 100 rpm and a Shimadzu UV 160 spectrophotometer. The samples were analyzed every 15 min for 8 hr. Buffer solutions adjusted to pH values of 1.2, 6.5, and 7.5 were used as dissolution media. The amount of theophylline in solution was determined by spectrophotometry (λ = 264 nm). The studies were carried out in triplicate.

RESULTS AND DISCUSSION

Solubility Studies

The solubility diagram for TPH in the presence of several concentrations of β-CD is presented in Fig. 1. This plot shows that the aqueous solubility of the drug increases in the presence of β-CD, which agrees with a previous deduction (19).

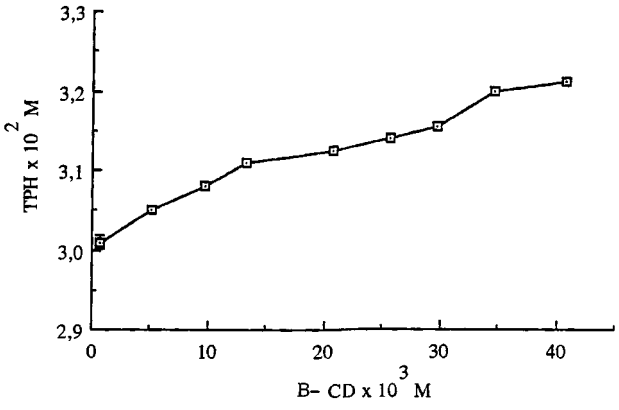

Figure 1. Effect of β-CD on the solubility of TPH in water at 20°C.

An apparent stability constant K_c was calculated considering all data of the curve (1.62 M^{-1}) from the slope of the phase solubility line (Fig. 1) as follows: K_c = slope/S_0 (1 − Slope) = 1.62 M^{-1}, where S_0 is the solubility of the pure drug at the same temperature ($S_0 = 3.00 \times 10^2$ M). This low value of K_c is not included in the range 200 to 5000 M^{-1}, considered by various authors appropriate for the formation of an inclusion complex (20).

Characterization of the Ground Mixture

DSC curves presented in Fig. 2 show a different thermogram for the ground mixture compared to that of either the drug or β-CD; this was taken as an indication that TPH is dispersed in or complexed with β-CD in some way, leading to a reduction in the overall crystallinity of the system. These results are in accordance with those of other researchers (19,21).

Dissolution Studies

Figure 3 demonstrates that the gelatin capsules without β-CD led to a dissolution of the drug; however, comparing the two release profiles, it is undeniable that β-CD played a key role in the dissolution of TPH.

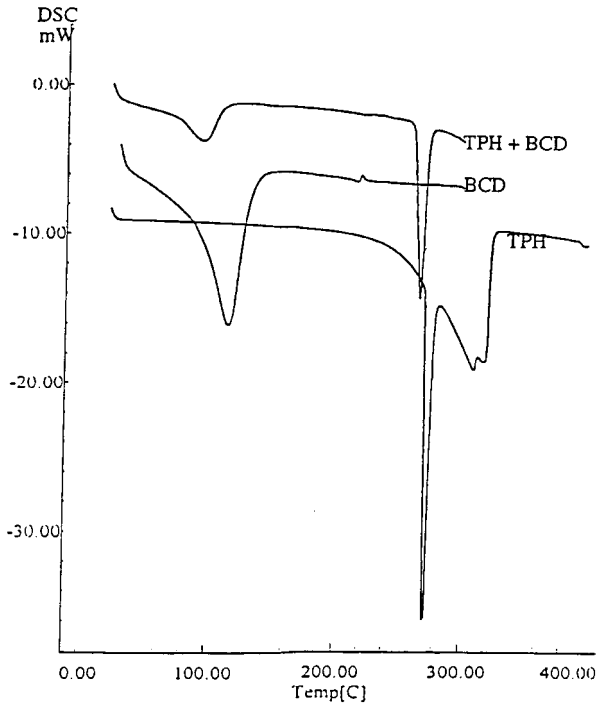

Figure 2. DSC curves for the TPH/β-CD system.

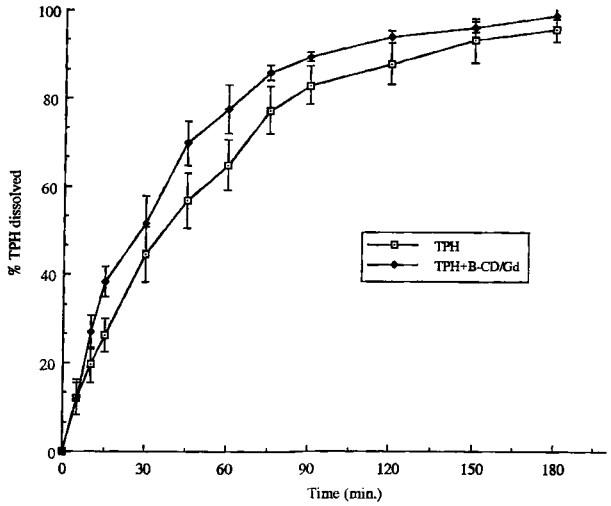

Figure 3. Effect of β-CD on the dissolution of TPH.

Concerning the effect of β-CD on the release of TPH from matrix tablets (Fig. 4), the observed increase in dissolution from matrices prepared with the ground mixture may be explained on the basis of the solubility of the drug in aqueous β-CD solutions and dissolution rate studies. It can be assumed that the β-CD molecule will operate locally on the hydrodynamic layer surrounding the particles of the drug, which produces a rapid increase of the amount of the dissolved drug. This enhancement in the dissolution can be attributed to the dispersion of TPH in the β-CD after grinding, but also to the nearly amorphous state of the system.

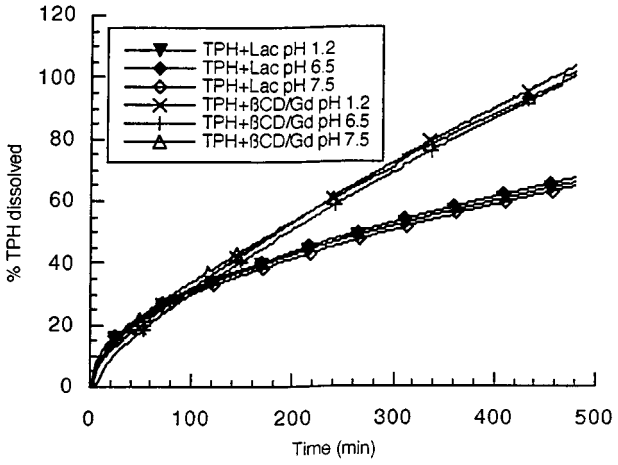

Figure 4. Dissolution profiles of TPH and its β-CD ground mixture from matrices.

CONCLUSIONS

The results allow us to conclude that, by a simple and low-cost formulation process involving only a ground mixture of drug/β-CD before compaction, it is possible to enhance both the apparent solubility and the dissolution of the drug in aqueous media, as well as the release of TPH from hydrophilic matrix tablets, maintaining the controlled-release properties for the drug.

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