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COMMUNICATION

# Studies of Hydroxypropyl Methylcellulose Donut-Shaped Tablets

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**ABSTRACT**

*Simple uncoated compressed tablets with a central hole (donut shape) or multihole tablets were prepared. Theophylline and diltiazem hydrochloride were used as model drugs to investigate in vitro drug release from donut-shaped tablets. The effects of hole size, the number of holes, drug solubility, and stirring rate on release kinetics were investigated. As for the donut-shaped tablets, the duration of zero-order drug release could be up to 80–90%. When the hole size was increased, the release rate increased, and the duration of linear drug release was longer. The durations of linear drug release of two-hole and three-hole tablets were longer than that of the single-hole tablets. As the drug solubility increased, the duration of linear drug release was shortened. However, three stirring rates (50 rpm, 100 rpm, 150 rpm) had little effect on the drug release.*

***Key Words:*** *Diltiazem hydrochloride; Donut-shaped tablets; Hydroxypropyl methylcellulose; Theophylline; Zero-order release.*

## INTRODUCTION

Controlled release of therapeutically active agent is highly desirable. There are a number of approaches for preparation of controlled-release dosage forms. Controlled matrix devices have been among the most widely used drug delivery systems; they represent a substantial part of controlled-release dosage forms and are com-

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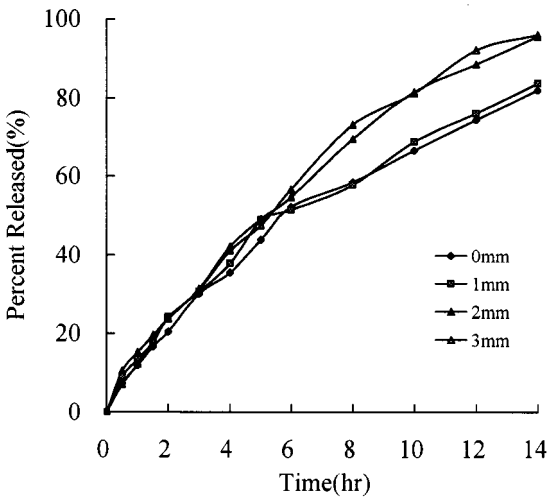


**Figure 1.** Effect of hole size on the release of theophylline from donut-shaped tablets.

monly manufactured (1–4). A variety of approaches exists for preparation of controlled-release matrix tablets, most of which involve addition of excipients that provide a matrix for diffusion of the active substance. A disadvantage frequently cited is their inability to achieve zero-order release kinetics. They always yield first-order kinetics or square-root-of-time-kinetics (3,5).

Since the main interest is to develop controlled tablets that follow zero-order release kinetics, many efforts have been made to achieve this. But, there are fewer methods that exist for preparing tablets that release drug at a constant rate. Among these are tablets coated with a porous rate-controlling membrane, osmotic pumps, or a gradient matrix system, which consists of a cylinder composed of a hydrophobic polymer that is characterized by a concentration gradient along its length (6–8). In addition, one possible means of altering release kinetics from matrix systems is to vary the matrix geometry, thus leading to pie-shaped (9), semihemisphere (1,10), multihole (11), and core-in-cup tablets (12). Not all these designs are suitable for large-scale manufacturing processes.

In 1965, J. P. Cleave proposed tablets with holes that could realize zero-order release. By optimization of the size and number of holes, a tablet that has a constant surface area as it dissolves can be proposed in theory, thus resulting in a constant release rate (13). Accordingly, some people developed perforated coated tablets with holes (3). Others developed perforated uncoated tablets with a central hole (14). In the present study, matrix tablets with one hole or multihole tablets were prepared to obtain zero-order release kinetics. Hydroxypropyl methylcellulose (HPMC) was selected as the excipient. Theophylline and diltiazem hydrochloride were used as model drugs to investigate in vitro drug release from donut-shaped tablets.

## MATERIALS AND METHODS

### Materials

Theophylline was purchased from the 16th Pharmaceutical Factory of Shanghai (Shanghai, China), and diltiazem hydrochloride was purchased from Huang Hai Pharmaceutical Factory of Shanghai. HPMC (Methocel K4M, K15M, K100M) and ethocel (20cp, lot KL 17013702) were obtained gratis from the Colocon Company (Shanghai, China). Magnesium stearate (Shanghai Reagent Factory No. 2, Shanghai, China), lactose (Shanghai Reagent Factory No. 2), and all other reagents used were analytical grade.

***Table 1***

*Comparison of the Duration of Linear Drug Release by Tablets with Different Hole Sizes*

| 0 mm | | 1 mm | | 2 mm | | 3 mm | |
|---|---|---|---|---|---|---|---|
| $M_t/M$ (%) | Correlation Coefficient (±SD, $n = 3$) | $M_t/M$ (%) | Correlation Coefficient (±SD, $n = 3$) | $M_t/M$ (%) | Correlation Coefficient (±SD, $n = 3$) | $M_t/M$ (%) | Correlation Coefficient (±SD, $n = 3$) |
| 52.32 | 0.996 (0.020) | 51.53 | 0.991 (0.020) | 54.77 | 0.991 (0.016) | 56.72 | 0.996 (0.009) |
| 58.58 | 0.988 (0.039) | 57.85 | 0.983 (0.036) | 69.64 | 0.992 (0.023) | 73.31 | 0.997 (0.021) |
| 66.43 | 0.983 (0.027) | 68.95 | 0.984 (0.038) | 81.71 | 0.992 (0.017) | 81.40 | 0.993 (0.008) |
| 74.59 | 0.981 (0.034) | 76.26 | 0.983 (0.039) | 88.79 | 0.989 (0.009) | 92.35 | 0.991 (0.008) |
| 82.17 | 0.981 (0.054) | 83.96 | 0.983 (0.038) | 95.80 | 0.985 (0.013) | 96.20 | 0.985 (0.015) |

The fit used is $M_t/M_\infty = kt + b$.

***Table 2***

*Comparison of the Duration of Linear Drug Release by Tablets with Different Numbers of Holes*

| 2 mm | | 2 mm * 2 | | 2 mm * 3 | |
|---|---|---|---|---|---|
| $M_t/M$ (%) | Correlation Coefficient (±SD, $n = 3$) | $M_t/M$ (%) | Correlation Coefficient (±SD, $n = 3$) | $M_t/M$ (%) | Correlation Coefficient (±SD, $n = 3$) |
| 42.00 | 0.983 (0.017) | 44.33 | 0.986 (0.003) | 50.31 | 0.991 (0.006) |
| 52.67 | 0.987 (0.026) | 56.02 | 0.990 (0.007) | 64.43 | 0.993 (0.027) |
| 58.95 | 0.986 (0.016) | 68.56 | 0.993 (0.003) | 77.46 | 0.995 (0.024) |
| 68.89 | 0.988 (0.019) | 77.70 | 0.995 (0.008) | 87.10 | 0.995 (0.015) |
| 78.47 | 0.991 (0.019) | 83.22 | 0.993 (0.003) | 90.80 | 0.996 (0.021) |

The fit used is $M_t/M_\infty = kt + b$.

### Preparation of Tablets

The 400-mg tablets, containing 100 mg model drug, were formulated at different ratios of HPMC to diluent (ethocel or lactose). Magnesium stearate (1% w/w) was used as a lubricating agent throughout the formulations. All the ingredients (model drug, HPMC, diluent, magnesium stearate) were mixed and then directly compressed on a single-punch machine (model TDP, Shanghai, China) using a 12-mm diameter flat-faced punch. The hardnesses of the tablets were in the range 8–9 kg and 4–5 kg for theophylline and diltiazem · HCl, respectively. Holes were bored with a drill bit (Φ1 mm, Φ2 mm, Φ3 mm).

### Dissolution Studies

Dissolution tests were performed in triplicate using an Intelligent Dissolution Tester (model ZRS-4, Tianjin University Radio Factory, Tianjin, China) at a rotation speed of 100 rpm and at 37°C in 900 ml distilled water. Theophylline and diltiazem HCl were chosen as model drugs. The drug release was determined by an ultraviolet (UV) spectrophotometer at 272 nm for theophylline and 236 nm for diltiazem · HCl.

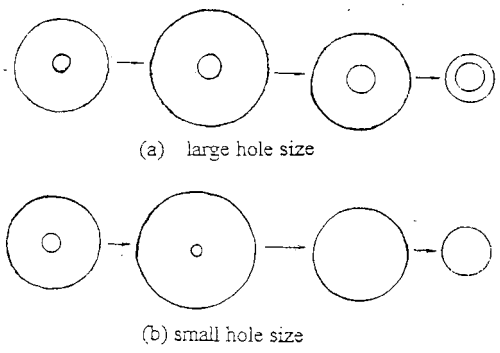


**Figure 2.** Schematic diagram of overall shape change with respect to the hole size.

## RESULTS AND DISCUSSION

The purpose of this study was to evaluate how various parameters such as the hole size, number of holes, drug

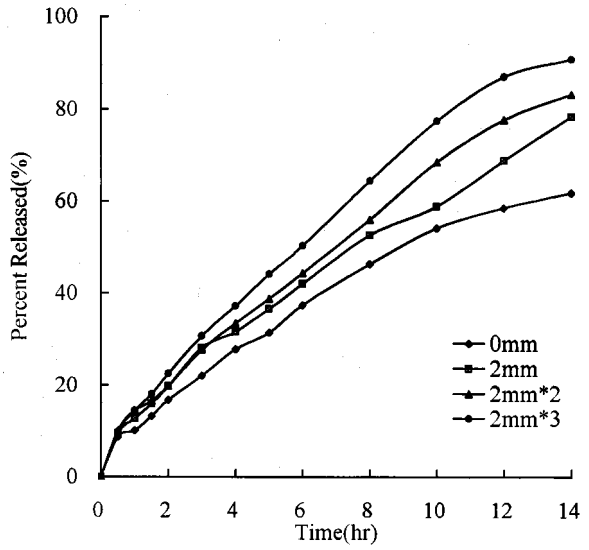


**Figure 3.** Effect of the number of holes on the release of theophylline from donut-shaped tablets.

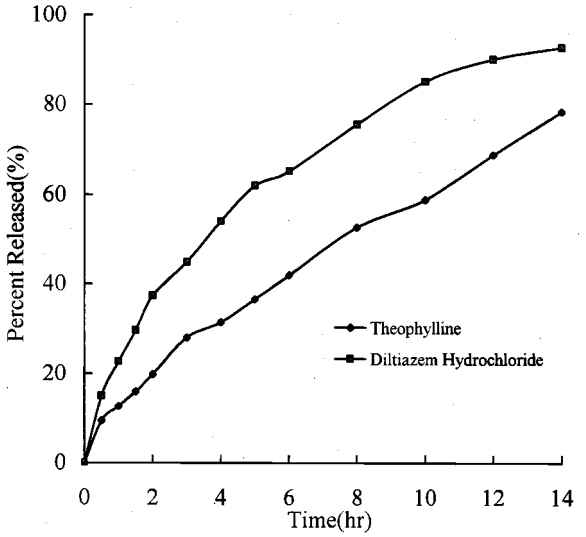


**Figure 4.** Effect of drug solubility on the release of drugs from donut-shaped tablets with a 2-mm hole.

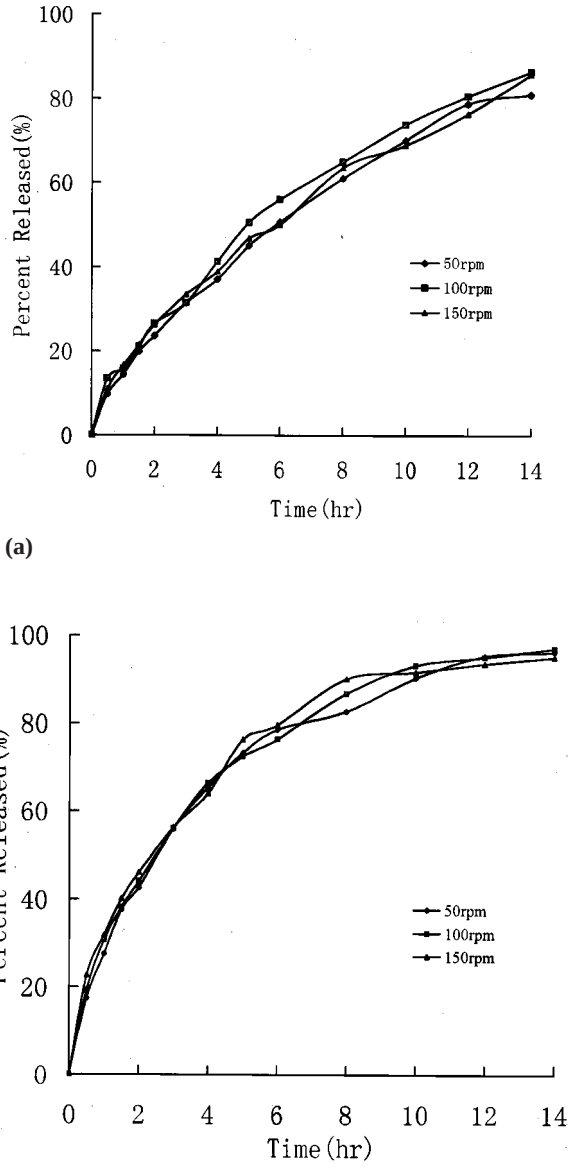


**Figure 5.** Effect of stirring rate on the release of drugs from donut-shaped tablets with a 2-mm hole: (a) from theophylline; (b) from diltiazem hydrochloride.

solubility, and stirring rate affect drug release from donut tablets.

Figure 1 and Table 1 demonstrate the effect of the hole size on the theophylline release from tablets of the perforated design. Release profiles show that the drug release from the tablets with the 2-mm and 3-mm hole is more rapid than from the tablets without holes. The liner release percentage of donut tablets is up to 80–90%. In contrast, the liner release percentage of tablets without holes is only about 50%. The most important reason for this difference is the releasing surface area. As to the tablets without holes, the releasing surface area decreases with time, thus leading to the anomalous release kinetics, while the donut tablets release drug through the outer surface and through the inner surface of the hole. During the release process, the increase of the inner surface area of the hole could compensate for the decrease of the outer surface area, thus providing a relatively constant surface area to release drug. On the other hand, the larger the hole size is, the longer the liner release will be. However, the release profile of the tablet with the 1-mm hole is similar to the tablet without holes. This could be explained by the shape change of the tablet during the drug release process (Fig. 2). Since HPMC is a hydrophilic polymer, the tablet is swollen in the early stage of the drug release process, so if the hole size is too small, the hole will be stemmed by the swollen polymer, thus leading to the release profiles similar to the tablet without holes.

The reports published about perforated tablets always deal with the tablets only with one hole and do not mention the multihole tablets. However, in 1965, Cleave's research paper investigated the tablets with one hole and

multihole tablets in theory by a mathematical model. His conclusion was that the two-hole tablet is basically better than the others in view of the liner release. In our study, we developed tablets with one hole, two holes, and three holes. Figure 3 and Table 2 show the effect of the number of holes on the release of theophylline from perforated tablets. Release profiles show that as the number of holes increased, the more rapid the drug release became. As for the liner release properties, the two-hole and three-hole tablets were obviously better than the one-hole tablet, but the three-hole tablet is slightly better than the two-hole tablet. This was not in complete accordance with Cleave's results. One reason could be the difference in the shape of the tablets. In Cleave's mathematical model, the tablet was rectangular, but the tablet we developed is a cylinder.

Many reports illustrate that the solubility of a drug will affect the release mechanism. We selected theophylline (an insoluble drug) and diltiazem hydrochloride (a soluble drug) as model drugs to investigate the effect of drug solubility on the drug release from donut-shaped tablets with a 2-mm hole. Figure 4 shows that, as drug solubility increases from theophylline to diltiazem hydrochloride, the release rate of the drug increases. But, the liner release percentage of theophylline is longer than that of diltiazem hydrochloride. This results from the difference of the release mechanisms. The release of highly soluble drug from HPMC tablets is controlled by the diffusion of the drug in the tablet, and the release of insoluble drug from HPMC tablets is controlled by erosion of the matrix. So, the release rate of highly soluble drug does not pertain to the release surface area of the tablet, which brings no modification of the liner release properties, in contrast with tablets without a hole.

Figure 5 illustrates the effect of stirring rate on the release of theophylline and diltiazem hydrochloride from the donut-shaped tablets with a 2-mm hole. As the stirring rate increases from 50 to 150 rpm, there are no obvious changes in the release profiles of both theophylline and diltiazem hydrochloride. This means that the hydrodynamic environment of the tablet does not significantly influence the drug release from donut tablets.

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