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COMMUNICATION

Design and Evaluation of a Two-Layer Floating Tablet for Gastric Retention Using Cisapride as a Model Drug

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ABSTRACT

A new kind of two-layer floating tablet for gastric retention (TFTGR) with cisapride as a model drug was developed. The in vitro drug release was determined, and the resultant buoyancy and the time-buoyancy curve were plotted. Because of the sodium bicarbonate added to the floating layer, when immersed in simulated gastric fluid (SGF) the tablet expands and rises to the surface, where the drug is gradually released. The in vitro drug release of this kind of two-layer dosage was controlled by the amount of hydroxypropylmethylcellulose (HPMC) in the drug-loading layer. Generally, the more HPMC, the slower the drug releases. Because cisapride has greater solubility in SGF than simulated intestinal fluid (SIF), its in vitro drug dissolution in SGF is faster than in SIF. One of the distinguishing characteristics of this kind of tablet is the separate regulation of buoyancy and drug release. The idea developed in this experiment can be used as a general model for the design of other tablets for gastric retention.

Key Words: *Cisapride; Gastric retention; Two-layer floating tablet.*

INTRODUCTION

In recent years, peroral dosage forms for gastric retention have drawn more and more attention for their theoretical advantage in permitting control over the time and site of drug release. This would be particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine, dissolve better in the acidic environment of the stomach, or exhibit local treatment of the stomach or pylorus. Various approaches have been used to prepare dosages for gastric retention. These systems mainly consist of swelling and expanding systems

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(1,2), floating and inflating systems (3), bioadhesive systems (4), and magnetically directed systems (5,6).

In this article, a novel floating system using cisapride, an orally administered prokinetic agent that facilitates or restores motility throughout the length of the gastrointestinal tract (7), as a model drug for gastric retention was prepared. One of the purposes for making this kind of tablet was to maintain the resultant buoyancy stable for at least 6 h. The other is because this drug has better solubility in acidic medium. This system is a tablet that consists of two sections. One of the sections contains sodium bicarbonate, expands rapidly on contact with simulated gastric fluid (SGF), and maintains buoyancy. The other layer is for drug loading. After being immersed in SGF, the section containing sodium bicarbonate expands rapidly; the whole tablet rises to the surface in less than 10 min and stays there for the gradual release of the active ingredient. Since this drug has greater solubility in SGF than in simulated intestinal fluid (SIF), the in vitro drug release of the conventional slow-release tablet will be greatly retarded if SGF is replaced by SIF. It can be predicted that the bioavailability of the cisapride conventional slow-release tablet will be reduced because it cannot float on the surface of gastric fluid and will be expelled into the intestine with chyme in about 2 h.

EXPERIMENTAL

Materials

Materials used were cisapride (EP grade, content 99.62%, lot 990902, Chengdu Jin Chang Pharmaceutical Research Institute, Chengdu, China), hydroxypropylmethylcellulose (HPMC) (K15 M CR Premium EP, lot LA 06012 N01; K100 MCR Premium EP, lot MJ 18012 N01, Colorcon, Shanghai); microcrystalline cellulose (MCC; pharmaceutical grade, lot 990511, Jiangsu, China); starch 1500 (pharmaceutical grade, lot 990201, Zhejiang, China); maize starch (pharmaceutical grade, lot 990506, Shenyang, China). All other materials and agents used were pharmaceutical or analytical grade. The SGF (pH 1.2) and SIF (pH 6.8) were prepared according to the USP 22/NF 17 method. A single-punch press machine (type TDP, Shanghai, China) and UV-Vis spectrophotometer (type 9100, Beijing, China) were used.

Methods

Preparation of the Two-Layer Tablet

The preparation of the two-layer tablet had two steps. First, granules containing 10% $NaHCO_3$, 50% starch 1500, and 40% HPMC (K100 MCR) were prepared using 80% ethanol (v/v) as a wetting agent. The granules were dried at 60°C in an oven. Second, granules containing cisapride were prepared by mixing the drug with the excipients in formulation as shown in Table 1. The granules were then dried at the above conditions. Finally, 0.3 g floating granules and 0.2 g drug-loading granules were weighed and pressed with the single-punch machine into a flat two-layer tablet 12 mm in diameter and 4.5 mm high.

Table 1

Formulation of the Two-Layer Tablet of Cisapride for Gastric Retention

Composition	Floating Layer (%)	Drug-Loading Layer (%)			
		F_1	F_2	F_3	F_4
HPMC (K100 MCR)	40				
$NaHCO_3$	10				
Starch–1500	50	23	29	35	20
HPMC (K15 MCR)		5	10	15	20
MCC		9	16	7	14
Maize starch		58	40	43	41
Cisapride		5	5	5	5

Preparation of the Conventional Slow-Release Tablet

For the conventional slow-release tablet, 0.2 g drug-loading granules were weighed and pressed into a flat tablet 8 mm in diameter and 3.5 mm high. The density of this slow-release tablet was approximately 1.14 mg/cm^3.

Buoyancy Determination

Based on the mechanism described by Timmermans and Moes (8), a special apparatus for the determination of the buoyancy was developed as shown in Fig. 1. This device is composed of a Westphal balance (accuracy 1.0 mg) and a water bath maintained at 37°C.

In the measurement of the resultant buoyancy, the tablet was placed in the basket. When it contacted with test medium newly prepared from deaerated water (SGF, pH 1.2, 37°C), the tablet expanded, and the density decreased because of this expansion. The upward or downward force then was transmitted to the balance by the connecting line, which is always fastened. By adjusting the balance weight set, the resultant buoyancy could be deter-

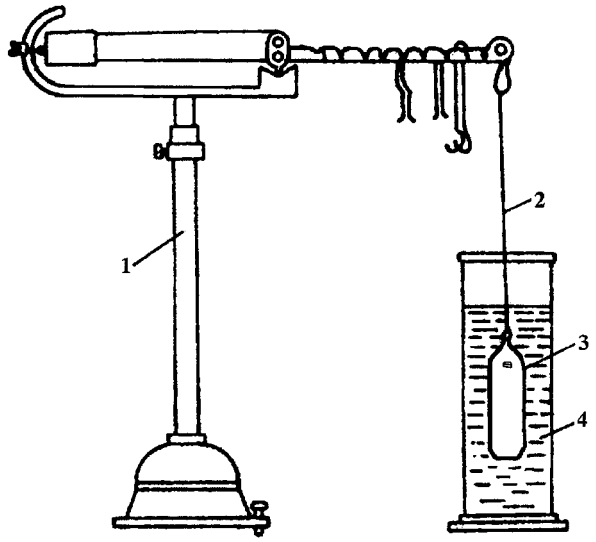

Figure 1. Apparatus for buoyancy determination of intragastric floating tablet: (1) Westphal balance; (2) connecting line; (3) basket; (4) test medium (SGF).

mined. The buoyancy-time curve was constructed as shown in Fig. 2. The buoyancy determination for the conventional slow-release tablet was carried out using the same method.

Dissolution

The USP 22/NF 17 dissolution method with apparatus II was used to study drug release. SGF (500 ml, pH 1.2, 37°C), prepared according to the procedure given in USP 22, was used as the dissolution medium. Rotating speeds of 50 and 100 rpm were used separately in the drug release test. Then, 5 ml of the dissolution medium was taken out at 0, 1, 2, 3, 4, 5, 6, and 8 h and determined at 272 nm. The withdrawn sample was replenished with 5 ml of the same fresh medium.

Both SGF and SIF were used in the in vitro dissolution of the conventional slow-release tablet. During the first 2 h, the drug dissolution was carried out in SGF (500 ml, pH 1.2, 37°C). A 5-ml sample was taken out at 0, 1, and 2 h. The withdrawn sample was replenished with the same amount of the same fresh medium. At the end of the second hour, the tablet was moved to 500 ml SIF (pH 6.8, 37°C). A 5-ml sample was taken out at 3, 4, 5, 6, and 8 h. The withdrawn sample was replenished with the same amount of same fresh medium. The amount of drug released was calculated from the equation $Y = 0.037x + 0.0057$.

Results are given as the mean ± standard deviation (SD) with $P < .05$ was considered as significant.

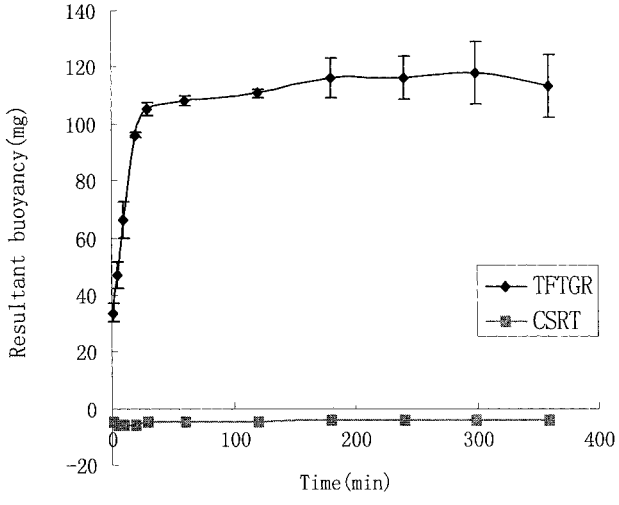

Figure 2. Time-buoyancy kinetics curve of cisapride two-layer floating tablet for gastric retention.

RESULTS AND DISCUSSION

In Vitro Buoyancy

On contact with the dissolution medium, hydrochloride in the test medium reacted with sodium bicarbonate in the floating layer of the two-layer tablet, inducing CO_2 formation in the floating section. Because the gas generated is trapped in and protected by the gel formed by the hydration of HPMC, the expansion of the floating section keeps the whole tablet buoyant on the surface of the test medium for as long as 6 h, as shown in Fig. 2. In the formulation of the floating section, HPMC K100 MCR was used to obtain a stickier gel to prevent the air bubble from rapture.

By using this type of HPMC, a great and stable persistent buoyancy was obtained. As shown in the floating kinetic curve, the two-layer tablet generated buoyancy as great as 110 mg in less than 10 min. Such buoyancy is strong enough for the whole tablet to go up to the surface and maintain the tablet on the surface for as long as 6 h and prevent the tablet from being expelled to the intestine. Because all four formulations had the same composition in the floating section, F_2 was selected for the buoyancy kinetics determination. Since the density of the conventional slow-release tablet was greater than that of SGF, a downward force or negative buoyancy was found in the resultant weight determination (Fig. 2).

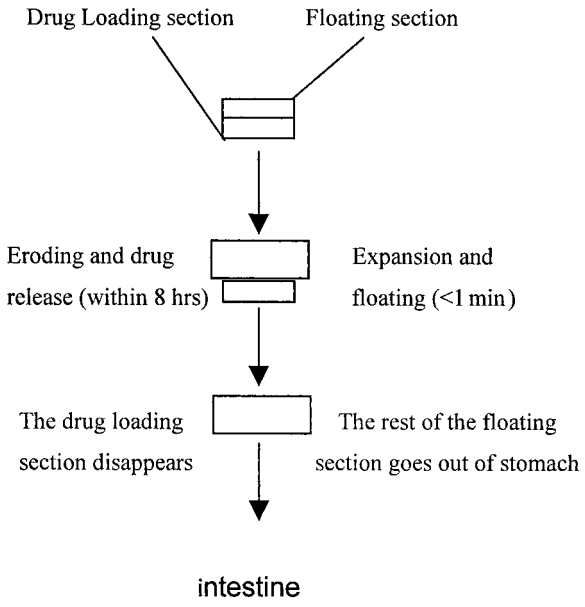

Figure 3. Schematic representation of the mechanism for a two-layer floating tablet for gastric retention.

Drug Dissolution

Cisapride is a water-insoluble drug; its release from the matrix is largely dependent on the erosion of the drug-loading section (Fig. 3). The ratio of HPMC in the drug-loading section was a key factor in controlling the drug release. As seen from Fig. 4, the higher the ratio of HPMC, the slower the drug released at 100 rpm. Unlike the water-soluble drug-loaded hydrophilic matrix, for which the addition of lactose accelerated the drug diffusion and release (9), the release of the water-insoluble drug cisapride was largely dependent on the erosion of the tablet.

Since the MCC usually used as a disintegrant improved the drug release from the matrix, there seemed a compromise between HPMC and MCC for the drug release. It is understandable that the drug release from F_4 (20% HPMC, 14% MCC) was even faster than that from F_3 (15% HPMC, 7% MCC) at 50 rpm. This can be explained as follows: The erosion leading to drug release came more from disintegrants than rotating force at a lower rotating speed. The drug release kinetics can be designed by adjusting the composition of the drug-loading section. For the tablets containing 5%, 10%, 15%, and 20% HPMC, the drug release profiles are shown in Fig. 4. For F_1, which contained the least HPMC in the drug-loading section, its drug release complies with a zero order only during the first 5 h when a rotating speed of 100 rpm was used. However, for F_2 and F_3, the drug release profiles comply with a zero order within 8 h. The ratio of HPMC in the drug release section controls the drug release by means of tablet erosion.

In addition to the ratio of HPMC in the drug-loading layer, the rotating speed also influences drug release. The higher the ratio of HPMC in the drug-loading layer, the smaller the difference in the drug release between 100 and 50 rpm (Fig. 5). There was a significant difference in drug release for F_1, F_2, and F_3 at the two different rotating speeds. However, for F_4, which contained the most HPMC in the drug-loading section, there was no significant difference for drug release at two different rotating

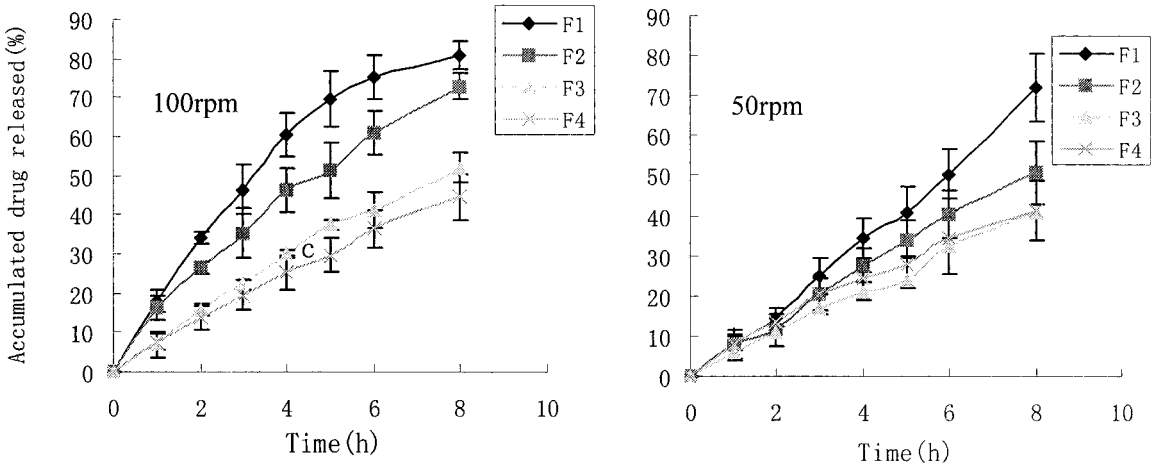

Figure 4. The influence of HPMC content in the formulation on drug release.

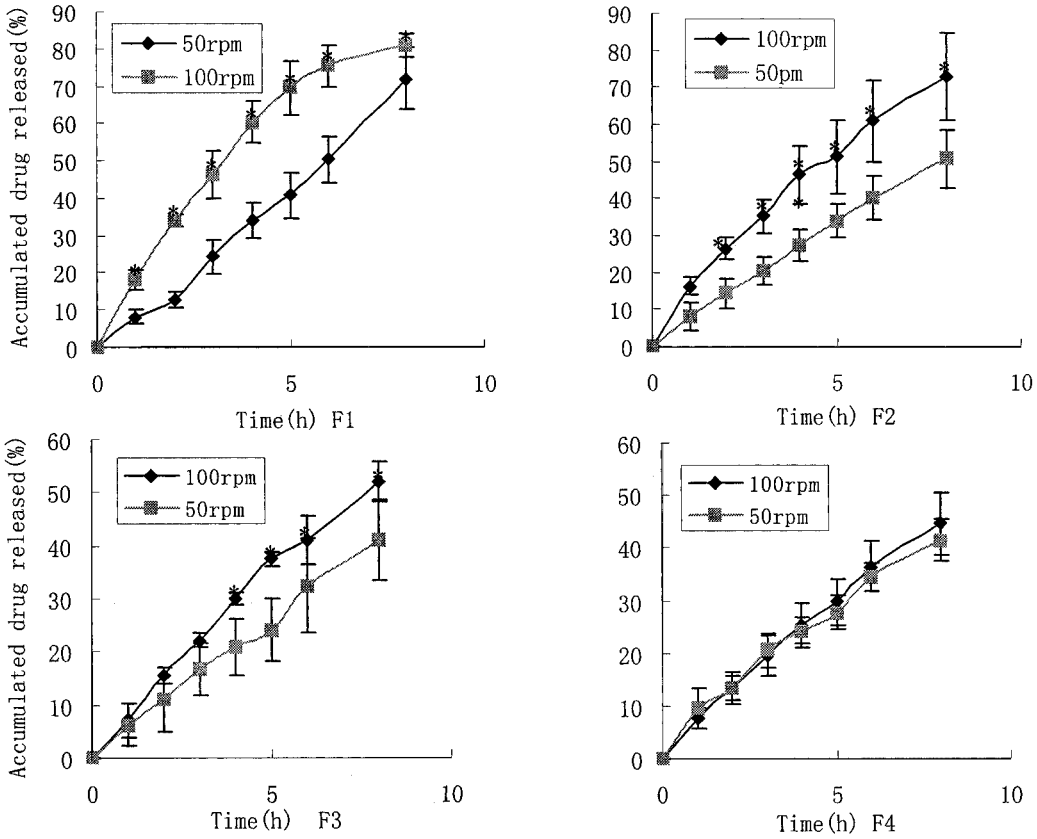

Figure 5. The influence of rotating speed on drug release.

speeds. This in turn can be explained by the fact that the ratio of HPMC was the key factor determining the in vitro drug release. As to the type of the in vitro drug release, all the profiles fit either a zero order or Higuchi type, except for F_1 at 100 rpm, which was more Higuchi model than zero-order release (Table 2).

The in vitro dissolution of the conventional slow-release tablet F_2 was compared with the floating two-layer tablet F_2 at 50 rpm (Fig. 6). Since cisapride has

Table 2

Fitting of the Drug Release Style

	Fitted by Zero Order (r)		Fitted by Higuchi's Plot (r)	
Formulations	50 rpm	100 rpm	50 rpm	100 rpm
F_1	0.9965	0.9582	0.9777	0.9875
F_2	0.9988	0.9943	0.9938	0.9965
F_3	0.9964	0.9939	0.9837	0.9974
F_4	0.9956	0.9978	0.9976	0.9939

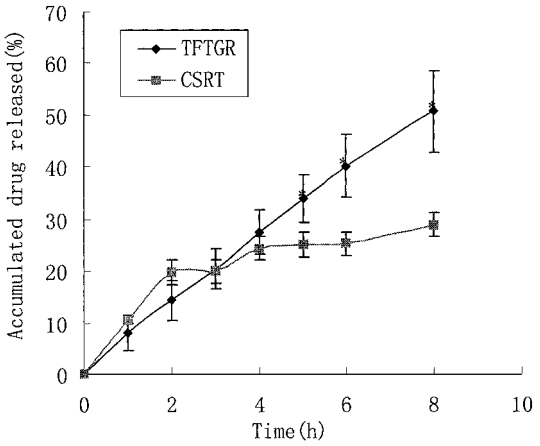

Figure 6. The in vitro drug release comparison between a two-layer floating tablet for gastric retention (TFTGR) and conventional slow-release tablet (CSRT).

better solubility in SGF than in SIF, it is understandable that its in vitro drug release would be retarded when SGF was replaced by SIF at the end of the second hour in the in vitro drug release test. As seen from Fig. 6, there was a significant difference at 5, 6, and 8 h in the drug release. Because the in vitro release of the water insoluble drug mainly takes place at the outer surface of the tablet, it is also understandable why the conventional slow-release tablet showed faster drug release during the first 2 h than the two-layer floating tablet.

CONCLUSION

Stable and persistent buoyancy was achieved by trapping the gas in the gel formed by the hydration of high-viscosity HPMC. This study showed that there is potential for this novel intragastric, floating, two-layer tablet to remain in the stomach for a longer time and to have a better in vivo drug release compared with the conventional slow-release tablet. Moreover, the two distinct layers allow separate regulation of the floating ability and drug release kinetics. Since cisapride has better solubility in SGF than in SIF, it is understandable that improved bioavailability may be obtained when it is incorporated in this gastric retention dosage.

The comparison of the bioavailability between the cisapride two-layer floating tablet and its conventional slow-release dosage is now being undertaken in our laboratory. This two-layer tablet construction for gastric retention could be used as a general model for the design of other gastric retention systems. There is also a great possibility for other drugs with better solubility in acidic medium than basic medium to have better bioavailability when incorporated in floating gastric retention dosages.

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