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COMMUNICATION

Captopril Floating and/or Bioadhesive Tablets: Design and Release Kinetics

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ABSTRACT

Two viscosity grades of hydroxypropylmethylcellulose (HPMC 4000 and 15000 cps) and Carbopol 934P were used to prepare captopril floating tablets. In vitro dissolution was carried out in simulated gastric fluid (enzyme free) at 37°C ± 0.1°C using the USP apparatus 2 basket method. Compared to conventional tablets, release of captopril from these floating tablets was apparently prolonged; as a result, a 24-hr controlled-release dosage form for captopril was achieved. Drug release best fit both the Higuchi model and the Korsmeyer and Peppas equation, followed by first-order kinetics. While tablet hardness and stirring rate had no or little effect on the release kinetics, tablets hardness was found to be a determining factor with regard to the buoyancy of the tablets.

Key Words: *Bioadhesive; Captopril; Floating; Release kinetics; Tablets.*

INTRODUCTION

Captopril, (1-[(2S)-3-mercapto-2-methyl propionyl]-L-proline), an angiotensin-converting enzyme inhibitor, has been used widely for the treatment of hypertension and congestive heart failure (1). The drug is freely water soluble and has elimination half-life after an oral dose of 1.7 hr (2). It is stable at pH 1.2, and as the pH increases, the drug becomes unstable and undergoes a degradation reaction (3); moreover, the drug exhibits a prominent food interaction, and its bioavailability is markedly reduced when coadministered with food (4). Benefits of the controlled-release dosage form of the drug have been reported (5,6).

Various attempts have been made to develop floating systems to control drug release; among them is the so-called hydrodynamically balanced system (HBS™) (7,8). Such a system is useful for drugs acting locally in the proximal gastrointestinal (GI) tract or for drugs that degrade in the intestinal fluid; captopril is one drug from the latter category.

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The present study involved the design of captopril floating tablets and the investigation of the in vitro release pattern of the drug; moreover, it examined the effects of the tablet hardness and the stirring rate on the release kinetics.

EXPERIMENTAL

Materials

Captopril was obtained from Chang Zhou Pharmaceutical Company (Chang Zhou, China) and passed through 120-μm mesh before use; Methocel K4MCR and K15MCR (hydroxypropylmethylcellulose [HPMC] 4000 and 15000 cps, respectively) were obtained as gift samples from Colorcon Company (Shanghai, China) and were used as received; Carbopol 934P was obtained from B. F. Goodrich (Brecksville, OH). Immediate-release conventional tablets were capoten (12.5 mg captopril/tablet, Sino-American Shanghai Squibb Pharmaceutical Co., Shanghai, China). Other materials were pharmacopoeial grade.

Preparation of Floating Tablets

For each formulation (1–4, as listed in Table 1), captopril and lactose Methocel K4MCR and/or K15MCR were manually blended homogeneously with a mortar. The mixture was wetted using ethanol (95%), passed through a 12-mesh screen, and dried in a hot air oven at 40°C overnight. The 12/16 fraction granules were collected and blended with Carbopol 934P and magnesium stearate. The homogeneous blend was then compressed into tablets on a single-punch tablet press (Shanghai Pharmaceutical Factory 1 for Machineries, Shanghai, China) equipped with 12-mm diameter flat punches. The tablet hardness was in the range 3–4 kg/cm^2 on a Monsanto tablet hardness tester.

Buoyancy test

For formulations 1 and 4, different tablet hardness were adopted to form tablets of hardness 2.4 and 8 kg/cm^2. These tablets were subjected to the buoyancy test, and for each tablet hardness, 6 tablets were used. Except for the basket, USP apparatus 2 was used. The time between introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured.

In Vitro Dissolution Studies

The release of captopril from different floating tablets was determined using USP 23 apparatus 2 basket (ZRS-4 Intelligent dissolution tester, Tianjin University Co., Tianjin, China) under sink conditions. The dissolution medium was 900 ml 0.1 N HCl (pH 1.2, enzyme free) at 37°C ± 0.1°C with a stirring speed of 75 rpm. For each formulation, 6 tablets were maintained in the stainless steel baskets (36 × 20 mm, 40 mesh). Samples (4 ml) were withdrawn at intervals, filtered, and replaced by an equivalent volume of fresh solvent. Dissolution data were corrected for this dilution effect (9).

Captopril Assay

Dissolution samples were reacted with 0.002 M solution of 2,2′-dipyridyl disulfide (Tokyo Kasei Co., Tokyo, Japan) in phosphate buffer (pH 8.0). The mercapto group (–SH) in the captopril molecule reacts completely with 2,2′-dipyridyl disulfide to form 2-thiopyridone quantitatively (10). The concentration of the 2-thiopyridone

Table 1

Formulations for Captopril Floating Tablets

Ingredients (g) (for 20 tablets)	Formula			
	1	2	3	4
Captopril	0.250	0.250	0.250	0.250
Methocel K4MCR[a]	2.700	4.063	—	1.875
Methocel K15MCR[a]	—	—	4.063	1.875
Carbopol 934P	0.750	0.938	0.938	0.938
Lactose	1.250	0.938	0.938	1.250
Magnesium stearate	0.050	0.063	0.063	0.063

[a] Methocel K4MCR and K15MCR are the 4000 and 15,000 cps grades of HPMC, respectively.

formed at 340 nm (UV-752 double-beam spectrophotometer, Analytical Instruments Co., Shanghai, China) is an indication of the captopril concentration in the dissolution samples.

Effect of Tablet Hardness on the Drug Release

In addition to the tablets of 4 kg/cm^2 hardness, another two sets of 6 tablets each of formulation 1 with different hardnesses (2 and 8 kg/cm^2) were subjected to the in vitro release test described above to study the effects of tablet hardness on the drug release profile.

Effect of Stirring Rate

Tablets of formulations 1 and 4, 6 tablets each, with tablet hardnesses of 3–4 kg/cm^2 were subjected to the dissolution test at 75, 100, and 150 rpm to examine the effect of the stirring rate on the drug release pattern.

RESULTS AND DISCUSSION

Figure 1 shows the captopril cumulative percentage released graphed versus time for the different captopril floating tablet formulations (8). Compared to conventional tablets, all formulations tested showed a sustained-release pattern of captopril over 24 hr with varying cumulative percentage released; moreover, tablets of all formulations (1–4) remained floating and appeared swollen until the end of the dissolution test. As expected, the drug release rate was dependent on the viscosity grade and the concentration of the polymer used. Tablets of formulation 1 (drug to HPMC 4000cps ratio was 1:10.8) showed the highest drug release rate, whereas formulation 3 tablets (drug to HPMC 15000 cps ratio was 1:16.2) exhibited the lowest release rate. The HPMC and Carbopol combination to control the swelling rate has been mentioned before in the literature (11), and a 16-hr sustained-release formulation for captopril has also been patented (12). However, a 24-hr sustained-release formulation of captopril has not been reported.

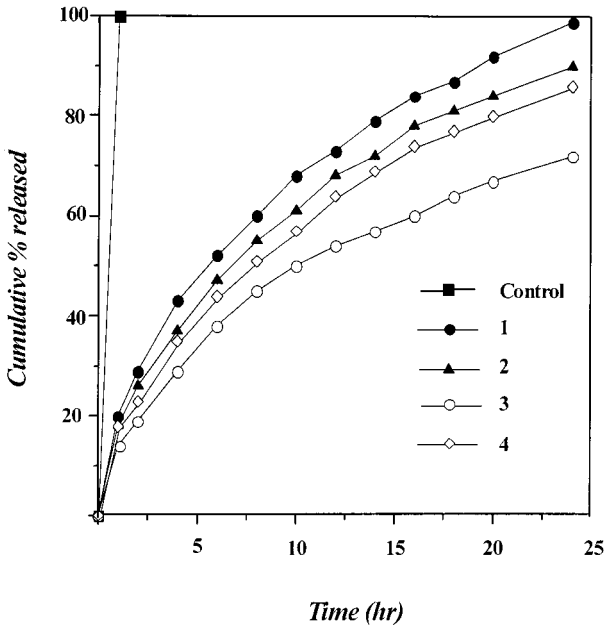

Figure 1. In vitro release of captopril from floating tablet formulations 1–4 compared to release from immediate conventional tablet. Each data point represents the average of six determinations.

Data of the in vitro release were fitted to different equations and kinetic models to explain the release kinetics of captopril from these floating tablets. The kinetic models used were a zero-order equation (13) and first-order (14), Higuchi release (15), and Korsmeyer and Peppas models (16). The best fit with the highest correlation r and determination r^2 coefficients was shown by both the Higuchi ($r = .998 \pm .001$, $r^2 = .996 \pm .002$) and first-order ($r = .990 \pm 0.01$, $r^2 = .981 \pm .02$) models followed by the zero-order equation. The test reported by Schwartz et al. (17), based on the use of the differential forms of the first-order and square-root-of-time equations, was used to differentiate between the two models (Higuchi and first order) since both of the models showed similar high values of r and r^2 with acceptable linearity. Plots of the rate of the drug release versus 1/percentage drug released were linear, whereas those of rates versus percentage drug released were curved (Fig. 2). This clearly indicates that the release followed the Higuchi model rather than the first-order equation. Furthermore, plots of log percentage drug released versus log time revealed a high level of linearity ($r = .998 \pm .002$), with a calculated average slope of $0.522 \pm .008$ (figure not shown), which in turn is another confirmation that captopril release from these tablets is matrix (or diffusion) controlled release.

To explore the kinetics behavior further, results of the in vitro release corresponding to the fraction released equal to or more than 0.6 and less than or equal to 1.0 were fitted to the Korsmeyer and Peppas equation in a search for the value of the diffusional exponent n that characterizes the drug transport mechanism (18). The values of n were in the range 0.416–0.510 ($r = .998 \pm .001$, $r^2 = .996 \pm .001$), indicating the Fickian release gov-

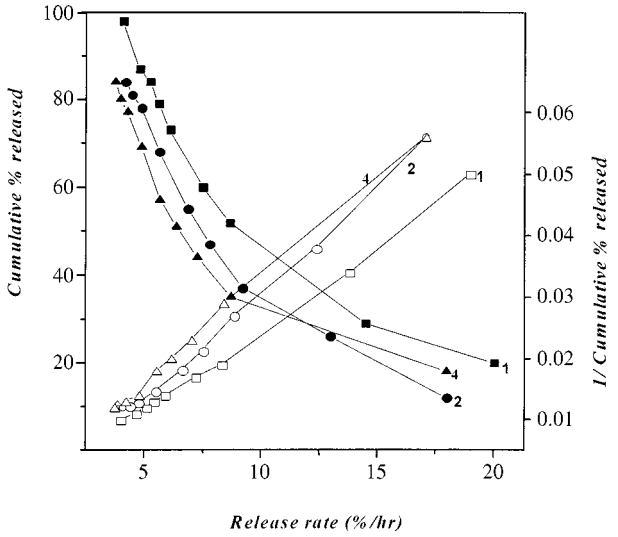

Figure 2. Plots of release rate of captopril against percentage (solid symbols) and reciprocal of the percentage (open symbols) of drug released from the floating tablets of formulations 1, 2, and 4. Each data point represents the average of six determinations.

erned by the drug diffusion. However, as indicated by the values of r and r^2, both of the models (Higuchi and Korsmeyer and Peppas) were found to be efficient in describing the release of captopril from the floating tablets, with drug release being proportional to the square root of release time in both of the release models.

It is evident from Fig. 1 that the rate of drug release decreased with time, which could be due to an increase in the diffusional path length for the drug to follow in the dissolution medium.

Buoyancy Time Measurements

On immersion in 0.1 N HCl solution (pH 1.2) at 37°C, tablets of hardness 2 kg/cm^2 float immediately and of 4 Kg/cm^2 sink for 3–4 min, then come up to the surface, and both remain buoyant up to 24 hr without disintegration. Tablets of hardness 8 kg/cm^2 show no floating capability until the end of the test period. In fact, buoyancy of the tablet is governed by both the swelling (hydration) of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids, which in turn results in an increase in the bulk volume, and the presence of internal voids in the dry center of the tablet (porosity). These two factors are essential for the tablet to acquire bulk density less than 1 and so remain buoyant on the gastric fluid (7). Therefore, compression of these tablets to high-degree hardness may result in reduction of the porosity of the tablets, and moreover, the compacted hydrocolloid particles on the surface of the tablets cannot hydrate rapidly when the tablet contacts the gastric fluids, and as a result of this, the capability of the tablet to float is significantly reduced. However, there is an optimum hardness for these tablets to remain buoyant and to meet the pharmacopoeial requirements of stability.

Effect of Tablet Hardness on the Release Profile

Figure 3 shows the release profile on a Higuchi plot of captopril from floating tablets of formulation 1 of different hardnesses. The release rate constants were 21.335%, 20.796%, and 20.072% hr$^{-1/2}$, corresponding to the tablet hardness values of 2, 4, and 8 kg/cm^2, respectively. Statistical analysis revealed no significant difference in the release rate constants ($p > .05$). A difference in tablet hardness reflects differences in tablet density and porosity, which are supposed to result in different release patterns of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet and formation of the gel barrier. Therefore, such an effect is expected to be prominent during the initial phase of the dissolution curve. However, results showed that tablet

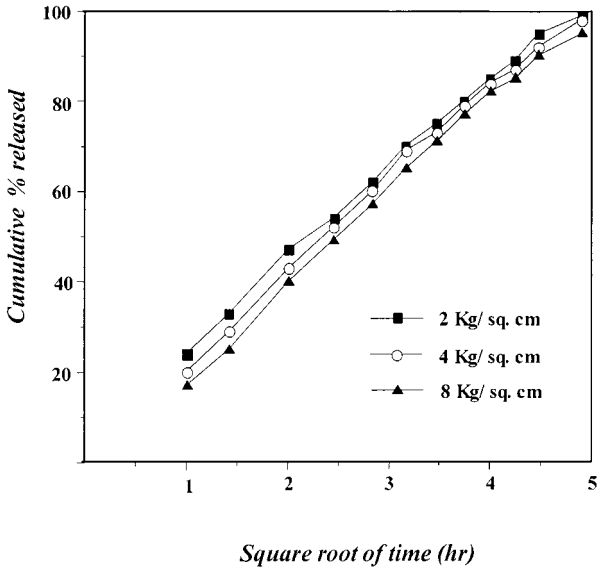

Figure 3. Captopril percentage released versus square root of time for the various hardness tablets (2, 4, and 8 kg/cm^2) of formulation 1. Each data point represents the average of six determinations.

Table 2

Time (hr) for 25% and 75% Captopril Release ($t_{25\%}$ and $t_{75\%}$, Respectively) from Floating Tablets of Formulations 1 and 4

Formula	Stirring Rate (rpm)	$t_{25\%}$ (hr)	$t_{75\%}$ (hr)
1	75	1.5	12.7
	100	1.5	12.5
	150	1.3	12.4
4	75	2.5	16.5
	100	2.2	16.5
	150	2.2	16.3

hardness had no (or little) effect on the release profile; this can be attributed to the fact that variations in the release pattern as a result of differences in tablets density and porosity during the initial period of dissolution could possibly be diminished by the high affinity of the polymer (HPMC) to the aqueous solution. The results are in agreement with a published work on theophylline matrix tablets (19).

Effect of the Stirring Speed

As summarized in Table 2, time for 25% and 75 % of captopril to be released was calculated as a function of the stirring rates 75, 100, and 150 rpm in two formulations (1 and 4). No significant effect on the dissolution rate of captopril from the floating tablets tested on application of different stirring rates ($p > .05$). From a theoretical point of view, increasing the rate of agitation of the dissolution fluid resulted in an increase of the dissolution rate of the drug. However, it is not the case with captopril, a freely water-soluble drug. In fact, the high solubility of captopril in water could possibly overcome any influence that can be exerted by changing the agitation rate during the dissolution test, as the result implies.

It is of interest to mention that, provided that the tablet remains buoyant on the gastric fluid, the presence of Carbopol could possibly aid in retaining the tablet, on oral ingestion, within the stomach by assisting in the adhesion of the dosage form on the gastric wall, which may add ease in enhancing the tablet gastric residence time. Moreover, incorporation of Carbopol within these formulations may assist in the protection of the drug from being attacked by food components when the dosage form is coadministered with food by minimizing drug-food contact (20), which in turn could possibly result in enhancement of the drug bioavailability. These formulations need to be examined in vivo for their floating and bioadhesive capabilities and, moreover, to optimize the drug release. However, such types of studies are now in progress.

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