

PREPARATION AND *IN-VITRO* EVALUATION OF FLOATING SUSTAINED-RELEASE CAPTOPRIL TABLETS AND CAPSULES

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تم في هذا البحث تحضير أقراص وكبسولات الكابتوبريل ممتدة الإنطلاق باستخدام مبدأ "الطفو" وذلك لإحتجاز العقار في المعدة لمدة طويلة. وقد تم استخدام بوليمر الهيدروكسي بروبيل ميثيل سليولوز ٤,٠٠٠ ، ١٥,٠٠٠ مع العقار بنسبة ١:١ ، ٣:٢ لتحضير الأقراص والكبسولات بطريقة التحبيب الرطب وباستعمال ايدراجيت رس ١٠٠ ، رس بى م كعوامل محببة بنسب ١٠% ، ٢٥% وزن/وزن للعقار. كذلك تم استخدام بيكروبونات الصوديوم بنسبة ٣% من صياغة القرص أو الكبسولة كمولد لغاز ثاني أكسيد الكربون للتأكيد وللحفاظة على خواص الطفو للصياغة المحضرة. وقد تم تقييم الأقراص والكبسولات بالنسبة لخاصية الطفو وللخواص الطبيعية والإنطلاق. وقد أظهرت النتائج أن الكبسولات تطفو في الحال بينما تبدأ الأقراص في الطفو بعد ٢٠ دقيقة في محاكى العصارة المعدية. كما أن هذه الأقراص والكبسولات قد أحتفظت بخاصية الطفو فى هذا الوسط طول فترة دراسة الإنطلاق (ثمان ساعات) ووجد أن الأقراص لها خواص طبيعية جيدة وأن الزيادة فى نسبة البوليمر ينتج عنها زيادة وقت الإنطلاق وأن طريقة الإنطلاق تتبع نموذج هيجوشى.

Sustained-release captopril tablets and capsules were prepared using the principle of gastric floating approach in order to retain the drug in the stomach for an extended period of time, thus increasing the residence time in the proximal region of the GI tract. Hydroxypropylmethylcellulose (HPMC) 4,000 and 15,000 at a drug:polymer ratios 1:1 and 2:3 were used for the preparation of the tablets and the capsules by the wet granulation method employing Eudragits RS100 and RSPM as granulating agents in a 10 and 25 % w/w ratio of the drug. Sodium bicarbonate at a 3 % w/w ratio of the tablet or capsule formula was used as CO₂ generating agent. A single station tablet press was used for making the tablets. The tablets and capsules were evaluated with regard to their floating as well as their physical and in-vitro release properties. The results showed that the capsules have an immediate floating, while the onset time for the tablets to float was about 20 minutes in simulated gastric fluid (SGF). The tablets and the capsules maintained their floating characteristics during the release study (8 hours) in the SGF. The tablets were found to have good physical characteristics. An increase in the polymer ratio resulted in a prolongation in the release time. The release profile from the different batches was found to follow Higuchi model with a correlation coefficient > 0.990

INTRODUCTION

Floating dosage forms may be designed based on the hydro-dynamically balanced controlled release delivery system (HBS). This system is a formulation essentially composed of a drug intimately mixed with gel-forming hydrocolloids that swells after oral ingestion. If

formulated in a dosage form, whether capsule, tablet or beadlets, the product acquires a bulk density less than one, and upon contact with the gastric fluid, it remains buoyant in the stomach while the drug is slowly released by diffusion through the gelatinous barrier as the stomach fluid permeates through the matrix.¹ The buoyancy and the release characteristics of the

dosage forms are achieved by the use of specific excipients. A carbon dioxide generating mechanism can be incorporated into the gel containing matrix. The liberated carbon dioxide is entrapped in the jellified hydrocolloid producing an upward motion of the dosage form and maintaining its buoyancy.^{2,3}

Captopril is an orally active angiotensin converting enzyme inhibitor (ACEI) used for the treatment of hypertension. It has a very short duration of action and is administered two to three times daily. Once daily dosing of such a drug is important for patient compliance. Captopril has a rapid degradation rate in the alkaline region of the GIT⁴ therefore, increasing the residence time of the drug in the stomach would be an appropriate method to prepare sustained-release dosage form. The aim of this work was to prepare captopril sustained-release floating tablets and capsules using a wet granulation technique. The floating and release characteristics of these dosage forms were studied.

MATERIALS AND METHODS

Materials

Captopril was kindly supplied by Bristol-Myers Squibb (Cairo, Egypt, lot #496215), hydroxypropylmethylcellulose (HPMC) grades 4000 and 15000 cps (Aldrich Chemical Co., Milwaukee, WI, USA), Eudragit RS100 and RSPM (Rohm Pharma, GmbH, Darmstadt, Germany), lactose monohydrate (Merck, Darmstadt, Germany), magnesium stearate (Alba Chemical Co., USA), potassium iodide (BDH, Chemical Ltd., Pool, England), sodium bicarbonate and iodine (El-Nasr Pharmaceutical Chemical Co., Cairo, Egypt), all other chemicals and reagents were of analytical grades. Materials were used as received.

Formulation of the floating dosage forms

The following general formula was used for the preparation of captopril floating capsules and tablets:

<u>Ingredient</u>	<u>% w/w</u>
Captopril	33.3
HPMC	33.3 and 50.0
Eudragit	0.0, 3.3 and 8.3
Sodium bicarbonate	3.0
Magnesium stearate	1.0
Lactose to	100.0

Preparation of captopril granules

Calculated amounts of captopril powder and HPMC in different ratios were thoroughly mixed. The homogenous mixture was kneaded with acetonetic solution of either Eudragit RS100 or RSPM. The dough mass formed was passed through a 1600 μm screen. The granules thus obtained were dried at 50° for 2 hours. The dried granules were kept in a desiccator until complete drying (24 hours), then they were passed through 1250 μm screen. The bulk density of the granules as well as that of captopril powder was determined before and after tapping using a 100 ml graduated cylinder.

Preparation of captopril tablets

The dried granules were mixed with sodium bicarbonate and lactose for 15 minutes, then mixed with 1.0% w/w magnesium stearate for 5 minutes. The mixture was compressed into tablets using a single station tablet machine equipped with a flat-faced 8 mm diameter punches (Korsch-Berlin, EK/O Frankfurt, Germany). The machine was adjusted to produce tablets weighing approximately 150 mg and containing about 50.0 mg captopril.

Preparation of captopril capsules

Calculated amounts of granules with the required additives for each formula were blended and filled into hard gelatin capsules, size 0, manually as non-compressed powder.

Evaluation of captopril tablets

The prepared tablets were evaluated with regard to their weight and thickness uniformity (20 tablets), hardness (10 tablets) using an Erweka hardness tester (type TBT, GmbH, Germany), and friability using an Erweka friabilator (type TBA, GmbH, Germany).

Floating properties of captopril tablets and capsules

The USP dissolution apparatus was used. Each of the six vessels was filled with 500 ml 0.1 N HCl, kept at $37^{\circ} \pm 0.5$. One tablet or capsule was placed in each of the six vessels and the time for the dosage form to start floating and to remain buoyant over the solution was determined. The behavior of each formula was also observed.

Average drug content

Ten tablets or capsules were ground, mixed in a mortar and a sample equivalent to the weight of the tablet or capsule was weighed out. Captopril was extracted with 0.1 N HCl. The same procedure was carried out on blank tablets or capsule containing the same ingredients without captopril and the extract was used as a blank for the spectrophotometric determination of captopril at 351 nm using the standard iodine solution method.⁵

In-vitro release studies

The release profile of captopril from both floating dosage forms was determined using USP XXIII rotating basket method (SR 6D Dissolution test station, Hanson Research Corp., Chatsworth, CA, USA). The dissolution media was 500 ml of 0.1 N HCl maintained at $37^{\circ} \pm 0.5$. One tablet or capsule was placed in each of the five baskets and a blank tablet or capsule was placed in the sixth basket. The baskets were rotated at 50 rpm and at predetermined time intervals 5 ml samples were withdrawn, filtered off and immediately replaced with 5 ml of fresh dissolution solution equilibrated at 37° . The clear solution was assayed spectrophotometrically at 351 nm⁵ against the obtained blank solution that was run. The average of five readings was calculated after a correction was applied for the dilution effect.

RESULTS AND DISCUSSION

In the design of the captopril floating dosage form, HPMC high viscosity grade was used as a floating enhancer and a drug release retarder.⁶ Eudragit (RS100 or RSPM) was used in this formula to serve as a binder and coat for captopril and to render the matrix hydrophobic

thus decreasing the release rate of the drug even further.⁷ Sodium bicarbonate was added to liberate carbon dioxide by the acidity of the gastric content and produce an upward motion of the dosage form for maintaining and confirming its buoyancy.

The results of bulk density determination showed a significant lowering in the bulk density of the granules when prepared using either HPMC 4,000 or 15,000 compared to captopril powder. The bulk density of captopril powder was 0.5 and 0.8 g/cm³ before and after tapping, while in case of the granules average values of 0.21 and 0.25 g/cm³ were found, respectively. These values are far below the specific gravity of the gastric contents (reported value is 1.004 to 1.01). This is necessary to impart the floating properties to captopril dosage forms.

Investigating the floating properties of captopril capsules, it was found that upon placing the capsules in the test solution, they immediately float on the surface. The ratio of drug to polymer (HPMC) (D:P) has a significant effect on the floating properties of captopril capsules. At 1:1 (D:P) ratio, there was a definite floating time (approximately 40 minutes) after which the capsules ruptured, lost their shapes and the contents were dispersed with most of them floating in the media. At 2:3 (D:P) ratio, the capsules kept floating for the time of the experiment (8 hours) and did not rupture in the solution. This may be attributed to the higher ratio of HPMC which is responsible for the floating properties of the dosage form. In case of captopril tablets, once they were placed in the solution, they first sunk, moved up and down for approximately 20 minutes, then remained buoyant for all the remaining time of the experiment. During this time, they swelled but kept their general shape. The type of HPMC did not significantly affect the floating onset time of the tablets. This may be due to the similar rate of hydration of different HPMC grades.⁸

Physical properties of captopril tablets

Granulation of captopril formula improved the flowability and compressibility of the drug and made it possible to be compressed into tablets. These tablets were found to possess good physical properties, Table 1.

Table 1: Physical properties of captopril tablets

Property	Value
Weight uniformity	C.V. %, Range: 3.97 - 5.89
Thickness uniniformity	C.V. %, Range: 1.28 - 2.83
Hardness (Kg)	Mean (\pm S.D.), Range: 6.4 (\pm 0.83)-9.1 (\pm 0.59)
Friability	% loss, Range: 0.521 - 0.891
Hardness / Friability index	Range: 7.71 - 16.92
T _{50%} (hours)	Range: Capsules: 0.98 - 2.10 Tablets : 1.57 - 3.22

T_{50%}: Time for 50% of the drug to be released.

C.V. %: Coefficient of variation percent.

Range: represents the lower and the upper values of a given parameter for different formulations.

Release studies

Before running the drug release studies, the average drug content for all batches was determined. The results showed that this average was within the range of 95.6 to 102.2 % of the claimed amount.

The effect of (D:P) ratio on the rate of release of captopril from the floating dosage forms was studied. It was found that by increasing the polymer ratio, a decrease in the release rate was observed from both capsules and tablets. This is can be explained by the fact that higher amounts of HPMC absorb more water and cause a greater degree of swelling, this in turn, increases the tortuosity and the length of the drug diffusion path, hence, decreasing the rate of drug release. This is in agreement with the results of Wan *et al.*⁹ and Suwannee *et al.*¹⁰ On the other hand, increasing the Eudragit content in the formula resulted in slower release rate of captopril, Figs. 1 and 2. Eudragit RS100 is known to have low permeability to the gastric fluid due to its lower content of quaternary ammonium groups and Eudragit RSPM is a water insoluble polymer

with release retarding properties.^{7,11} The results also showed that there is no significant difference in captopril release from formulae containing different HPMC grades (4,000 and 15,000) at the same drug to polymer ratio, Fig. 3. The release of captopril from capsule and tablet dosage forms was compared. In general, tablets have longer release time than the corresponding capsule formula, Fig. 4. This was confirmed from the T_{50%} values, (time for 50% of the drug to be released), Table 1. This is due to the fact that compressed tablets have fewer pores for the dissolution media to penetrate than in case of capsules.¹²

The mechanism of captopril release from different systems was investigated by applying the release data to various kinetic models (zero, first and Higuchi). The Higuchi equation gave consistently higher values for the correlation coefficient than did the other models. Therefore, it was assumed that the release kinetics of captopril from the floating formulae are by diffusion through the gelatinous barrier formed by the HPMC polymers.¹

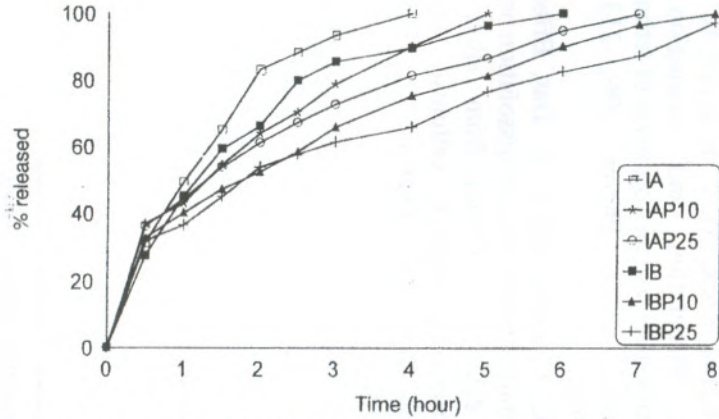


Fig. 1. Percent captopril released from capsules containing 1:1 (A) and 2:3 (B) captopril:HPMC 4000 (I) using Eudragit RSPM (P) in concentrations: 0% (IA and IB), 10% (IAP10 and IBP10), 25% (IAP25 and IBP25) w/w of captopril.

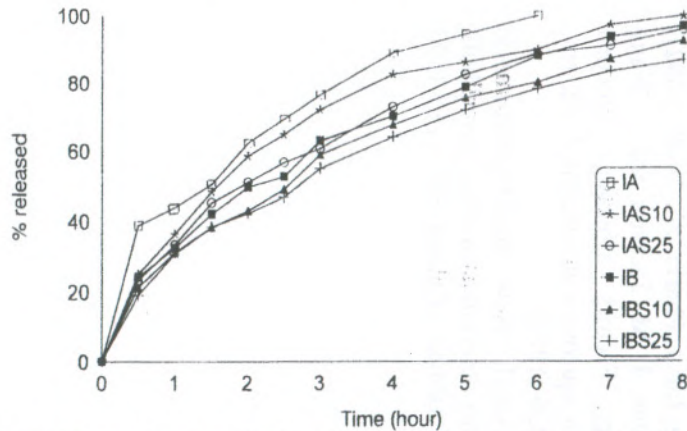


Fig. 2. Percent captopril released from tablets containing 1:1 (A) and 2:3 (B) captopril:HPMC 4000 (I) using Eudragit RS100 (S) in concentrations: 0% (IA and IB), 10% (IAS10 and IBS10), 25% (IAS25 and IBS25) w/w of captopril.

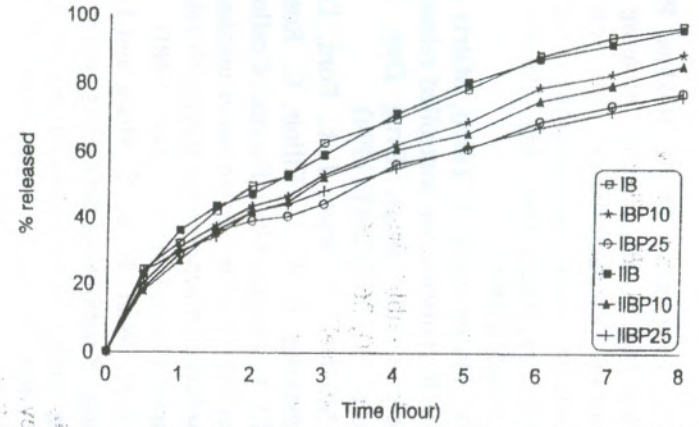


Fig. 3. Percent captopril released from tablets containing 2:3 (B) captopril:HPMC 4000 (I) or 15000 (II) using Eudragit RSPM (P) in concentrations: 0% (IB and IIB), 10% (IBP10 and IIBP10), 25% (IBP25 and IIBP25) w/w of captopril.

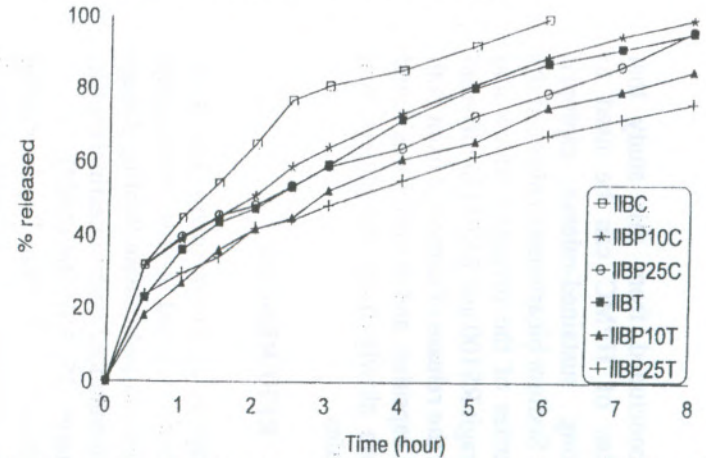


Fig. 4. Percent captopril released from capsules "C" and tablets "T" containing 2:3 (B) captopril:HPMC 15000 (II) using Eudragit RSPM (P) in concentrations: 0% (IIBC and IIBT), 10% (IIBP10C and IIBP10T), 25% (IIBP25C and IIBP25T) w/w of captopril.

Conclusion

It was concluded from this study that different grades of HPMC can be used to prepare floating sustained-release captopril dosage forms. Sodium bicarbonate enhanced the floating properties of the prepared tablets and capsules. Eudragit RS100 and RSPM in different ratios retarded the release of captopril from both the tablets and capsules, and the drug was found to release more slowly from the tablets than from the capsules.

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