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NOVEL DRUG DELIVERY SYSTEM FOR CAPTOPRIL

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ABSTRACT

It is known that drug substances showing no difference in absorbance along the whole gastro-intestinal (GI) tract are suitable for SR-formulations with an extended release characteristic. However, a decrease in bioavailability from proximal to distal parts of the gut may be suited for a limited retard effect. In this investigation, attempts have been made to design a suitable delivery system for captopril which is poorly bio-available from the alkaline regions of the GI-tract. The principles of 'Bioadhesion' as well as 'Gastric Floating Systems' are utilized in this study.

INTRODUCTION

Captopril USP, an orally active inhibitor of the angiotensin converting enzyme (ACE)[1] has been widely used as a potent drug of

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first choice in antihypertensive therapy. The drug however, manifests two vital shortcommings viz. (i)The duration of action after a single oral dose being 6-8 hours requires a daily input of 37.5-75 mg in three divided doses for clinical use[2]. (ii)The bioavailability of the drug is markedly reduced when administered with food. Studies have indicated the degradation of captopril at higher pH conditions to be the main reason for the same[3].

Attendant benefits of controlled/sustained release therapy for this drug have been also been reported[4,5].

In this work, studies were carried out to design a controlled release system for captopril using easily available materials, bearing in mind the principal idea to retain the system as long as possible in the proximal region of the GI-tract. Simplicity of methods as well as ease of scale-up manufacture has been given prime importance in this investigation.

MATERIALS AND METHODS

Materials: Captopril was generously donated by the Squibb Inst.forMedical Research, NJ, USA.;HPMC 4000 and 15000 cps grades were obtained as gift samples from Dow Chemical Co.,USA;Carbopol 934P was kindly donated by BFGoodrich,USA; Ethyl cellulose (ds=2.42-2.53, ethoxy content=47.5-49.0),BDH Chemicals,UK; Eudragit RS 100, Rohm Pharma,Germany; Microcrystalline cellulose, Cellulose Products of India. All other materials conforming to pharmacopial standards were procured from Loba Chemie, Bombay.

Preparation of floating capsule system: All the ingredients listed in Table 1 for each formulation were separately screened and blended using a specially designed and fabricated blender (drum type, 30 g capacity) and filled into hard gelatin capsule shells (#1) using a hand-filling machine suitably modified to fill 50 capsules.

Preparation of Bioadhesive systems: For formulation No.8 (Table 2), ingredients were mixed and dry granulated using Erweka dry granulator.

TABLE 1: Formulations for Floating Capsule System

INGREDIENT (g) [For 50 capsules]	FORMULA NUMBER 1	2	3	4	5	6	7
Captopril	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Methocel*K4M	-	-	-	1.25	2.5	5.0	2.5
Methocel K15M	1.25	2.5	5.0	-	-	-	2.5
Lactose	5.57	4.95	3.7	5.57	4.95	3.7	3.7
MCC	5.57	4.95	3.7	5.57	4.95	3.7	3.7
Mag. stearate	0.35	0.35	0.35	0.35	0.35	0.35	0.35

* HPMC (K4M and K15M are the 4000 and 15000 cps grades respectively)

TABLE 2: Formulations for Bioadhesive System

INGREDIENT (g) [For 50 tablets]	FORMULA NUMBER 8	9	10	11	12	13	14
Captopril	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Lactose	2.15	5.0	5.0	5.0	5.0	5.0	5.0
Eudragit RS 100	-	0.25	0.5	1.0	-	-	-
Ethyl cellulose	-	-	-	-	0.25	0.5	1.0
Carbopol 934P	10.0	-	-	-	-	-	-
Mag. stearate	0.35	0.4	0.4	0.4	0.4	0.4	0.4
Bioadhesive polymer**	-	9.35	9.1	8.6	9.35	9.1	8.6

** Poly(acrylic acid) cross linked with 0.001 % ethylene glycol dimethacrylate [synthesized in this laboratory]

The granules were compressed into 10.5 mm dia.round. flat-bevelled edged tablets on a single stroke tablet press (Cadmach, India). The hardness of tablets was about 4 Kg/sq.cm. on a Monsanto tablet hardness tester. For Formulation No. 9 through 14, captopril and lactose were screened through 60 mesh and blended using the blender described earlier. The blend was granulated using a solution of the

retarding polymer (udragit/ethyl cellulose) in isopropyl alcohol. The mass was dried in a hot air oven at 37°C. Granules obtained by sifting through 16 mesh seive were blended with magnesium stearate and the bioadhesive polymer which was synthesized in this laboratory by a method reported by Robinson *et al*[6]. This blend was then compressed into 10.5 mm round flat-bevelled edge tablets with a hardness of 2-2.5 Kg/sq.cm (Monsanto units).

Test Methods:

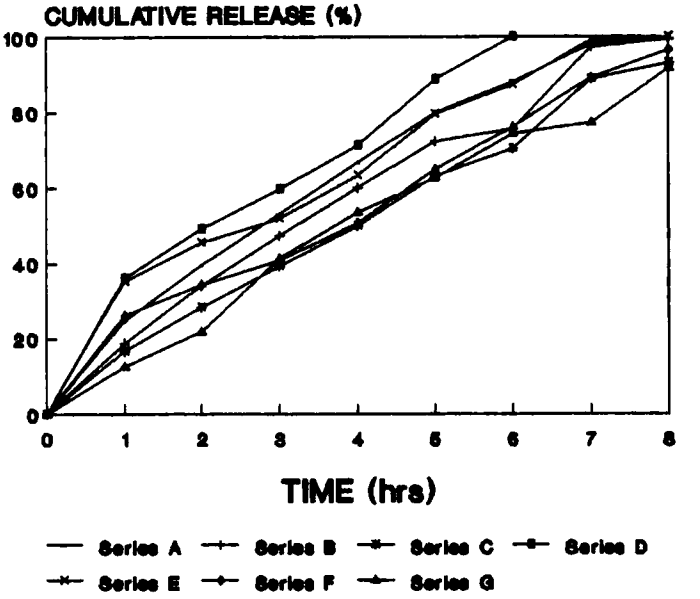
The floating behaviour of the capsules was determined by placing one capsule over artificial gastric fluid[7,8]. Dissolution studies (4 replicates), were performed on the floating capsules using the USP/NF dissolution apparatus at the basket rotation of 50 rpm. Distilled water (900 ml at 37°C) was used as the dissolution medium. Analysis was carried out by a very sensitive colorimetric method developed in this laboratory[9]. For the bioadhesive tablets, dissolution was carried as above except, the basket was replaced by paddle and the drug analysed spectrophotometrically at 205 nm.

RESULTS AND DISCUSSION

The floating capsule system for captopril was successfully prepared using the simple techniques described herein. Similar systems have been reported for drugs with restricted absorption from the lower ileum for e.g. riboflavin[8,10]. All the capsule blends were well within the limits for content uniformity and fill weight variation implying the usage of regular conventional methods of capsule manufacture for these novel delivery systems. The use of carbopol 934P as a bioadhesive as well as a rate controlling polymer has been enumerated several times in literature[11-16]. A 16 hour controlled release formulation for captopril has also been patented[17]. The bioadhesive tablets could also be prepared with as much ease as observed for conventional tablets. However, the relative humidity had to be maintained less than 30% to avoid sticking.

Drug Release:

The capsule formulations, probably due to the gelatin shell, were found to show interference in the UV method of estimation. A colorimetric method using diazotisation and complexation with N-1-naphthyl-ethylenediamine dihydrochloride was developed to analyse



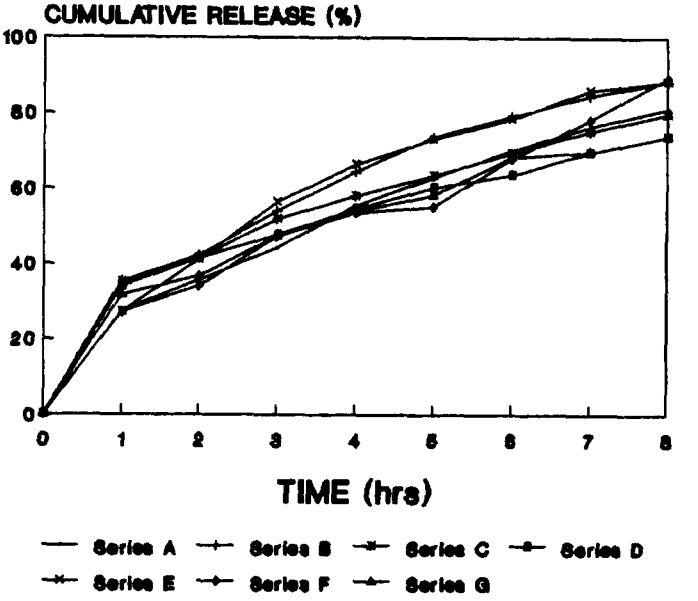
Key: Series A to G sequentially represent formulations 1 through 7 in Table - 1

FIGURE - 1

In-vitro captopril release from floating capsule systems

captopril at concentrations of 0.1 - 4.0 mcg/ml[9]. No interference was observed in the case of bioadhesive tablets which were analysed at 205 nm. The regression coefficient and the slope of the standard curve were found to be 0.99989 and 0.04345 respectively.

For both the systems, the study was designed to investigate the effects of different grades of the retarding polymers with varying ratios to standard excipients on the *in-vitro* dissolution profiles. A considerable emphasis however, is laid on the ease and convenience of large scale manufacture of the systems. As can be seen from Figures 1 and 2, the *in-vitro* release of almost all systems studied was as anticipated. The release rate was directly proportional to the viscosity and concentration of the polymer used. In comparison to Eudragit RS 100, ethyl cellulose was observed to be a stronger retardant.



Key: Series A to G sequentially represent formulations 8 through 14 in Table - 2

FIGURE - 2

In-vitro captopril release from bioadhesive tablets

Although it would have been interesting to study the release rate kinetics and different transport mechanisms, the authors however, appreciate the significance and importance of the simple, "% Dissolved against Time" curve as a practical approach to develop a CR/SR dosage form. Incidently, this simple methodology happens to be most widely used by the industry today. However, from morphological point of view, all the capsule formulations appeared swollen at the end of the dissolution test. The bioadhesive tablets had disintegrated into tiny lumps of the resin coated granules adhered to the bioadhesive polymer as illustrated in Figure-3. The authors had prepared and investigated a similar ibuprofen bioadhesive system for pellets in capsules. The results of these from the *in-vivo* transit studies in rabbits were found to be highly encouraging[18].

Although, unlike riboflavin, cephalexin, hydrochlorothiazide etc., captopril does not exhibit the "window-effect", significant decrease in

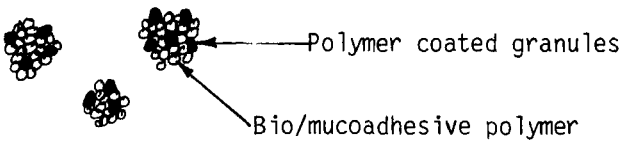


FIGURE-3: Bioadhesive tablets during dissolution testing

the bioavailability of the drug has been reported when coadministered with meals[3]. Therefore, the systems investigated herein, could possibly protect captopril from attack by food components by disallowing a proper contact with the latter[19].

SUMMARY AND CONCLUSIONS

A simple and practical approach to designing a peroral CR system that could be retained in the proximal GI tract for longer duration when compared to conventional systems has been presented. Both the types of systems developed for captopril possess potential for large scale manufacture without requiring any specialized machinery/equipments. Similar systems could also be tried for other drugs exhibiting bioavailability/stability problems in the distal GI tract. Although such advantages could arguably be denied on the basis of inadequate *in-vivo* validation, atleast no disadvantage with respect to the ease of manufacture and performance could be visualized for these systems.

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REFERENCES

1. M.A.Ondentti, B.Rubin, D.W.Cushman, *Science* ,196:441-444 (1977)
2. M.Miyazi *et al*,*Nipp.Jinzo Gakk.Shi*24:421-427 (1982)
3. S.M.Singhvi, D.M.McKinstry, J.M.Shaw, D.A.Willard, B.H.Migdalof, *J.Clin.Pharmacol.*, 22:135-140 (1982)

4. Y.Seta, T.Otsuka, H.Tokiwa, H.Naganuma, Y.Kawahara, K.Nishimura, R.Okada, *Int.J.Pharm.*, 41:263-269 (1988)
5. D.H.Robinson, J.Singh, *Drug Dev.Ind.Pharm.*, 14(4):545-560 (1988)
6. H.S.Ch'ng, H.Park, P.Kelly, J.R.Robinson, *J.Pharm.Sci.*, 74:399-405(1985)
7. X.D.Tu, Z.Y.Hua, *5th Int.Congr.Pharm.Tech., Paris* (1989)
8. J.L.Tossounian, W.J.Mergens, P.R.Seth, *Drug Dev.Ind.Pharm.*, 11(5):1019-1050 (1985)
9. N.M.Sanghavi, R.S.Matharu, M.M.Samarth, *Indian Drugs*, in press (1990)
10. J.Timmermans, B.V.Gansbeke, A.J.Moes, *5th Int.Congr. Pharm. Tech.*, Paris, (1989)
11. T.Nagai, Y.Machida, Y.Suzuki, H.Ikura, *US PATENTS*, 4226843 (1980) and 4250163 (1981)
12. Teijin Ltd., *JAPAN PATENT*, 8062012 (1980)
13. J.D.Smart, I.W.Kellaway, H.E.C.Worthington, *J.Pharm.Pharmacol.*, 36:295-299 (1984)
14. G.Hunt, P.Kearney, I.W.Kellaway, in "Drug Delivery Systems - Fundamentals and Techniques", eds. P.Johnson and J.G.Lloyd-Jones, Ellis Horwood Ltd., U.K., 180 - 199 (1987)
15. G.Ponchel, F.Touchard, D.Duchene, N.A.Peppas, *J.Controlled Release*, 5:129 - 141 (1987)
16. J.T.Fell, H.Harris, H.C.Sharma, D.C.Taylor, *Polym.Prepn.(Amer.Chem.Soc. Div.Polym.Chem.)*, 28(1):145 (1987)
17. M.T.Decrosta, N.B.Jain, E.Rudnik, *US PATENT*, 4666705 (1987)
18. N.M.Sanghavi, R.S.Matharu, presented at the "B.V.Patel International Symposium on Innovations in Pharmaceutical Sciences and Technology", at Ahmedabad, INDIA, October 27-29 (1990)
19. Y.Seta, F.Higuchi, Y.Kawahara, K.Nishimura, R.Okada, *Int.J.Pharm.*, 41:245-254 (1988)