JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation and *in-vitro* Evaluation of Captopril Floating Matrix Tablets Using HPMC 50cps

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ABSTRACT:

In the present investigation a gas powered tablets (floating tablets) of Captopril were prepared to increase the gastric retention time in order to improve the therapeutic effect of the drug by increasing its bioavailability. Captopril is antihypertensive drug, it is soluble in water; its maximum absorption is from the stomach and upper part of the intestine. The Gas powered tablets were prepared by direct compression method. A present investigation comprises a drug Captopril, a gas generating agent 6 to 18% sodium bicarbonate, water soluble polymers 40 to 60% HPMC 50 cps to get the desired controlled release over a period of 10 hrs. The prepared tablets were subjected to post-compressional parameters such as hardness, friability, weight variation, thickness, drug content, lag time subsequently buoyancy time, and *in-vitro* dissolution studies. Drug compatibility with excipients was checked by FTIR and DSC studies. The formulations C3 was found to be promising, which shows an *in vitro* drug release of 91.32% in 10 hrs along with satisfactory floating lag time (2 min.27 sec.). All the formulations exhibited diffusion dominated drug release.

KEYWORDS: Captopril, HPMC 50 cps, gastro-retentive floating drug delivery systems, hydro dynamically balanced systems.

Article history:
Received 17 Feb 2012
Accepted 10 March 2012
Available online 13 Jun 2012

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Introduction:

Oral sustained release dosage forms have been developed for the past three decades due to their considerable therapeutic advantages[1]. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract, i.e. stomach and small intestine due to the relatively short transit time of the sustained release dosage forms in these anatomical segments. Thus, after only a short period (< 6 h), the sustained release dosage forms lefts the upper gastrointestinal tract and the drug is released in non-absorbing distal segments of the gastrointestinal tract. This results in a short absorption phase that is often accompanied by lesser bioavailability. It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a sustained manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of sustained release dosage forms for these drugs[2,3]. The need for gastroretentive dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems[4]. These efforts resulted in gastroretentive dosage that were designed in large part based on the approaches like: (a) low density form of the dosage form that causes buoyancy on the gastric fluid in the stomach[5]; (b) high density dosage form that is retained in the bottom of the stomach; (c) bio-adhesion to the stomach mucosa[6]; (d) lowered motility o the gastrointestinal tract by concomitant administration

of drugs or pharmaceutical excipients[7]; (e) expansion by swelling or unfolding to a large size which limits emptying of the dosage form through the pyloric sphincter[8].

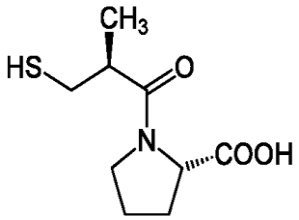

Figure. 1: Structure of Captopril

Captopril (Figure.1) an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. Captopril is rapidly absorbed and has bioavailability of about 75% and half life is approximately 2 hours.[9] It has been reported, however, that the duration of antihypertensive action after a single oral dose of Captopril is only 6-8 hours, so clinical use requires a daily dose of 37.5-75 mg to be taken three times .[10] It is most stable at pH 1.2 and as pH increases, it becomes unstable and undergoes a degradation reaction.[11] The virtue of the prolonged release dosage form of Captopril has been reviewed.[12]

The objective of this present investigation was to formulate floating matrix tablets of Captopril by using different polymers to prolong the gastric residence time and increase the drug bioavailability.

MATERIALS AND METHODS

Captopril was gift sample from Rajesh chemicals, Mumbai. HPMC 50 cps, talc, magnesium stearate, and all the other chemicals used were of pharmaceutical grade.

Drug-excipients Compatibility studies

Fourier transform infrared (FTIR) spectroscopy

Compatibility studies were carried out to know the possible interactions between Captopril and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FTIR spectroscopy.IR spectrum of pure drug and excipients was seen in between 500-4000 cm^{-1}.

DSC Studies

Differential scanning calorimetry studies were carried out to study the changes in amorphous to crystalline or vice-versa or any polymorphic changes during formulation of tablets. Thermograms of drug, mixture of drug and polymer and mixture of drug and sodium bicarbonate were obtained using Dupont 2100 series thermal analysis system. Heating rate was 5° C min^{-1}.

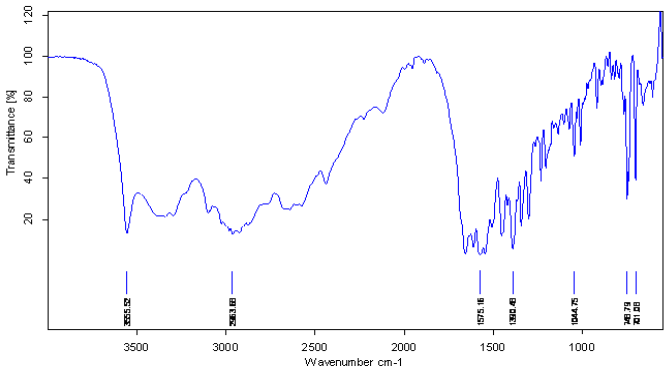

Figure. 2: IR spectra of plain Captopril

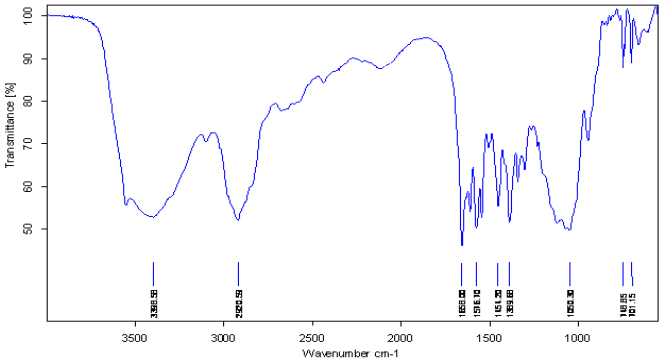

Figure. 3: IR spectra of drug with HPMC 50 cpsS

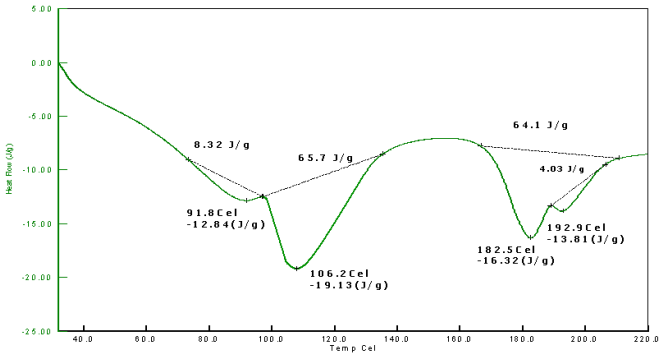

Figure 4: DSC spectra of Captopril

Table 1: Composition of Captopril floating matrix tablets

Ingredients (mg)	Batch code								
	C1	C2	C3	C4	C5	C6	C7	C8	C9
Captopril	50	50	50	50	50	50	50	50	50
HPMC 50 cps	100	100	100	125	125	125	150	150	150
Sodium bicarbonate	15	30	45	15	30	45	15	30	45
Mannitol	80	65	50	55	40	25	30	15	-
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total	250	250	250	250	250	250	250	250	250

Table 2: Precompressional parameters of all the Captopril floating matrix tablets

Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (degree)
C1	0.5237 ± 0.07	0.6119 ± 0.06	14.41 ± 1.29	1.16 ± 0.04	25.49 ± 0.43
C2	0.5309 ± 0.03	0.6213 ± 0.02	14.55 ± 1.35	1.17 ± 0.02	27.22 ± 0.97
C3	0.5188 ± 0.05	0.6128 ± 0.07	15.33 ± 1.19	1.18 ± 0.03	25.83 ± 1.81
C4	0.5412 ± 0.02	0.6307 ± 0.07	14.19 ± 1.42	1.16 ± 0.03	26.97 ± 1.09
C5	0.5405 ± 0.03	0.6313 ± 0.09	14.38 ± 1.05	1.16 ± 0.02	25.56 ± 1.53
C6	0.5337 ± 0.04	0.6220 ± 0.05	14.19 ± 1.09	1.16 ± 0.04	27.15 ± 1.67
C7	0.5241 ± 0.07	0.6115 ± 0.07	14.29 ± 1.25	1.16 ± 0.03	25.72 ± 1.36
C8	0.5124 ± 0.08	0.6089 ± 0.03	15.84 ± 1.13	1.18 ± 0.02	24.98 ± 1.10
C9	0.5193 ± 0.09	0.6108 ± 0.08	14.98 ± 1.07	1.17 ± 0.03	26.55 ± 1.27

All above reading are average ± SD, n=3

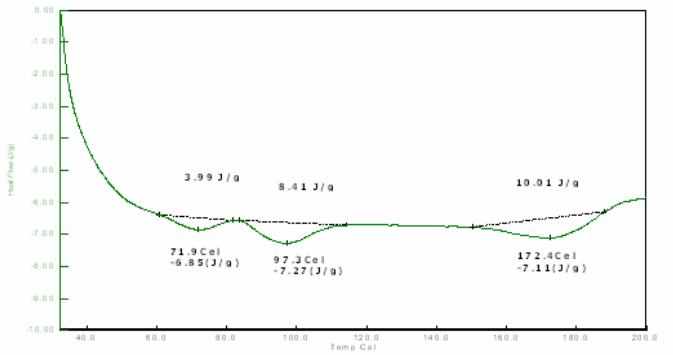

Figure 5: DSC spectra of drug with HPMC 50 cps

Preparation of floating matrix tablet of Captopril [10]

Floating matrix tablets were prepared by mixing the drug Captopril 50 mg with the gas generating component, sodium bicarbonate and other ingredients by geometric mixing in mortar and pestle for 10 min. The above powder was lubricated with magnesium stearate and talc in mortar and pestle for 2 min. The lubricated blend was compressed into tablets using 8 mm concave-face round tooling on Rimek Minipress II MT rotary tablet machine. Compression force was adjusted to obtain tablets of hardness 4-6 kg/cm^2 with 4.5 mmMinipress II MT rotary tablet machine. Compression force was adjusted to obtain tablets of hardness 4-6 kg/cm^2 with 4.5 mm tablet thickness; the details of composition are given in Table 1.

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Evaluation of tablets

Tablet was evaluated for hardness, friability, weight variation, thickness, drug content, *in vitro* buoyancy study, swelling

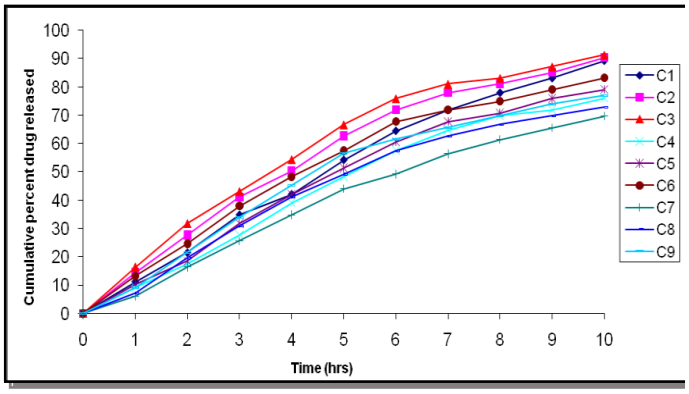

Figure 6: *In-vitro* drug release profile of formulations C1-C9

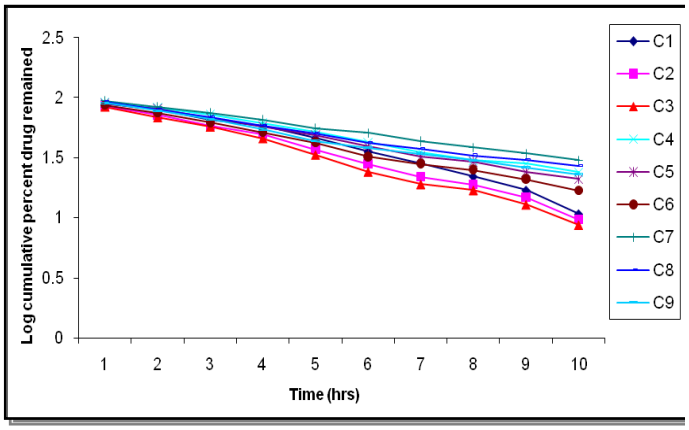

Figure 7: Log cumulative percent drug remained vs. time plots (first order) of formulations C1-C9

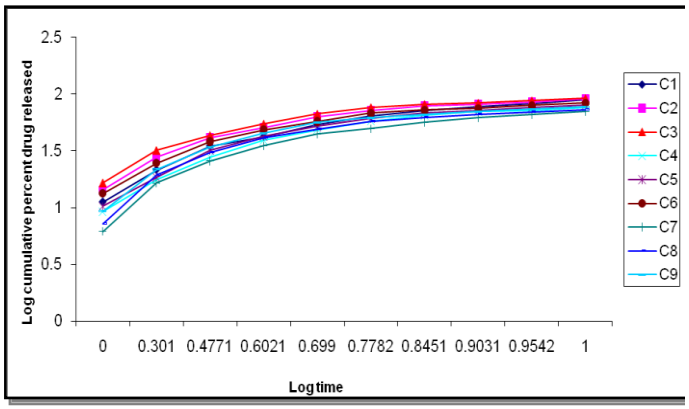

Figure 8: Log cumulative percent drug released vs log time plots (Peppas plots) of formulations C1-C9

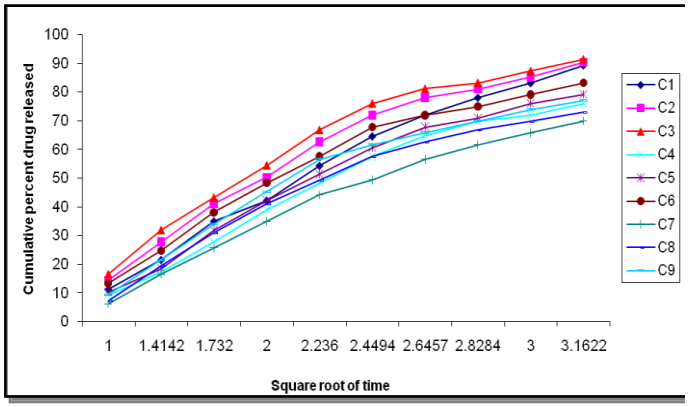

Figure 9: Cumulative percent drug released vs square root of time plots (Higuchi plots) of formulations C1-C9

Table 3: Post compressional properties of Captopril floating matrix tablets

Batch code	Weight variation of tablets (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
C1	251 ± 1.14	4.55 ± 0.08	5.0 ± 0.85	0.32 ± 0.02
C2	249 ± 0.92	4.57 ± 0.07	5.1 ± 0.43	0.48 ± 0.09
C3	248 ± 0.87	4.55 ± 0.05	5.2 ± 0.38	0.68 ± 0.08
C4	250 ± 0.62	4.56 ± 0.03	5.0 ± 0.90	0.36 ± 0.03
C5	248 ± 0.29	4.57 ± 0.10	4.6 ± 0.53	0.56 ± 0.02
C6	249 ± 0.43	4.57 ± 0.04	5.3 ± 0.60	0.64 ± 0.07
C7	251 ± 0.59	4.55 ± 0.01	5.6 ± 0.87	0.44 ± 0.04
C8	249 ± 0.91	4.56 ± 0.10	5.1 ± 0.45	0.60 ± 0.03
C9	248 ± 0.75	4.57 ± 0.05	5.2 ± 0.61	0.76 ± 0.02

index, *In vitro* dissolution studies and stability study. The Pfizer hardness tester and Roche friabilator were used to test hardness and friability loss respectively. In weight variation test, 20 tablets were selected at random and average weight was determined using electronic balance. Tablets were weighed individually and compared with average weight. Thickness of tablets was determined by using dial caliper. For drug content analysis, a total 10 tablets were weighed and powdered. The powder equivalent to 10 mg of Captopril was taken and dissolved in 0.1 N HCl. After that an aliquot of the

Table 4: Physico-chemical properties of Captopril floating matrix tablets

Batch code	Drug content (%)	Swelling index (%)
C1	98.67 ± 1.08	33.20 ± 0.49
C2	99.11 ± 0.95	37.84 ± 0.56
C3	98.89 ± 1.44	41.76 ± 0.43
C4	98.26 ± 1.27	44.97 ± 0.70
C5	98.53 ± 0.86	51.20 ± 0.26
C6	98.78 ± 0.69	57.20 ± 0.12
C7	98.19 ± 1.49	48.20 ± 0.92
C8	99.23 ± 1.25	58.16 ± 0.19
C9	98.49 ± 0.88	65.06 ± 0.71

Table 5: Floating ability of various Captopril floating matrix tablets

Batch Code	Floating Lag time (min:sec)	Floating duration (hrs)	Integrity
C1	31:47	>12	Intact
C2	04:21	>12	Intact
C3	02:27	>12	Intact
C4	36:31	>12	Intact
C5	05:21	>12	Intact
C6	05:02	>12	Intact
C7	41:23	>12	Intact
C8	06:18	>12	Intact
C9	04:43	>12	Intact

All values are expressed as mean ± SD, n=3.

filtrate was diluted and analyzed spectrophotometrically at 211 nm. Using 900 ml of 0.1 N HCl monitored *in vitro* dissolution of Captopril from tablets at 37 ± 0.5^{0}C at 50 rpm using programmable dissolution tester. Aliquots were withdrawn at 1 hour time intervals. Aliquots, following suitable dilution were assayed spectrophotometrically at 211 nm. The stability study of the tablets were carried out according to ICH guidelines by storing tablets in stability chamber at 40 ± 2^0 C / 75 ± 5% RH for 3 months.

Table 6: *In vitro* drug release parameters ($t_{50\%}$, $t_{70\%}$, $t_{90\%}$) of Captopril floating matrix tablets of HPMC 50 cps

Formulation code	$t_{50\%}$ (hrs)	$t_{70\%}$ (hrs)	$t_{90\%}$ (hrs)	Cumulative % drug release in 10 hrs
C1	**4.60**	**6.82**	**-**	**89.27**
C2	**3.97**	**5.84**	**9.96**	**90.29**
C3	**3.67**	**5.53**	**9.85**	**91.32**
C4	**5.22**	**8.77**	**-**	**75.93**
C5	**4.87**	**7.90**	**-**	**79.00**
C6	**4.35**	**6.82**	**-**	**83.11**
C7	**6.20**	**-**	**-**	**69.77**
C8	**5.22**	**9.60**	**-**	**72.85**
C9	**4.43**	**8.52**	**-**	**76.95**

Table 7: *In-vitro* drug release data of the stability formulation C3

Sr. No.	Time (hrs)	Cumulative % drug released ± S.D at 40 ± 1°C			
		1st day	30th day	60th day	90th day
1	1	13.33 ± 0.72	12.89 ± 0.52	13.23 ± 0.55	13.29 ± 0.79
2	2	28.73 ± 0.92	29.92 ± 0.39	29.09 ± 0.43	28.64 ± 0.82
3	3	43.09 ± 0.81	42.67 ± 0.76	43.26 ± 0.69	43.02 ± 0.66
4	4	56.43 ± 0.32	55.09 ± 0.92	55.82 ± 0.77	56.68 ± 0.73
5	5	69.77 ± 0.72	70.27 ± 0.67	69.47 ± 0.75	70.12 ± 0.58
6	6	81.06 ± 1.15	80.57 ± 0.87	79.91 ± 0.82	80.23 ± 0.41
7	7	87.21 ± 1.23	86.29 ± 0.42	87.13 ± 0.95	87.25 ± 0.39
8	8	91.26 ± 1.56	90.42 ± 0.85	90.40 ± 0.66	89.98 ± 0.76
9	9	94.40 ± 1.85	95.66 ± 0.59	93.87 ± 0.49	94.18 ± 0.85
10	10	97.47 ± 1.47	98.21 ± 0.93	96.62 ± 0.88	97.30 ± 0.44

All values are expressed as mean ± SD

Table 7: Drug content data of stability formulation C3

Sr. No.	Batch code	1st day (%)	30th day (%)	60th day (%)	90th day (%)
1	**C3**	99.95 ± 1.12	99.73 ± 1.19	99.71 ± 1.02	99.70 ± 1.32

All values are expressed as mean ± SD

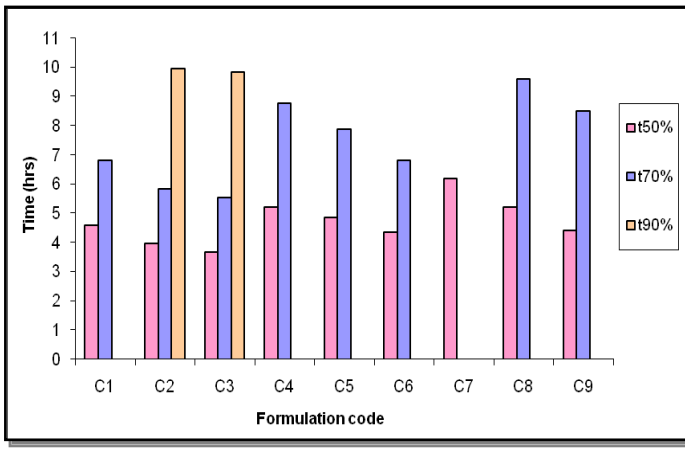

Figure 10: Comparison of dissolution parameters ($t_{50\%}$, $t_{70\%}$, $t_{90\%}$) of Captopril floating matrix tablets of HPMC 50 cps

RESULTS AND DISCUSSION

The compatibility of drug with other ingredients was checked by FTIR and DSC studies, these results revealed that there was no interaction between drug and other excipients, the results are shown in Fig. 2 to 6. The flow properties of the powder mixture are important for the uniformity of mass of tablets; the flow of powder mixture was before compression of tablets. The values of pre-compressional parameters were

within prescribed limit as per USP XXVII and indicate good flow properties. The results are shown in table 2. The post-compressional parameters results are shown in tables 3 to 5 and Fig.6 to 10. In all the formulations the hardness test indicates good mechanical strength. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be uniform in all formulations. The tablet thickness was found to be 4.55 to 4.57 mm. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5%, which provide good uniformity in all formulations. The *in-vitro* drug release results suggest that, the drug was released by mixed order kinetics. To ascertain, the drug release mechanism the *in-vitro* release data were also subjected to Higuchi's diffusion and Peppa's plots by taking log cumulative percent drug released versus log time. Results of these kinetic plots and n values, suggest that the drug was released by Fickian control with swelling. The swelling index for the formulations from C1 to C9 was found to be in the range of 33.20 to 65.06 %. The *in-vitro* buoyancy of formulations from C1 to C9 containing HPMC 50 cps was >12 hrs. Short-term stability studies of the promising formulation C3 indicated that there are no significant changes in drug content and dissolution parameter values after 3 months at 40 ± 2°C / 75 ± 5% RH, are shown in table 7 and 8.

ACKNOWLEDGEMENTS

The authors are thankful to Rajesh chemicals, Mumbai, for providing gift sample and also very much thankful to Prof. Kishoresingh K.Chatrapathi President, R.M.E.S's College of Pharmacy Gulbarga, for his valuable support and providing necessary facilities to carry out the research work.

Conclusion

In the present study gas powered controlled drug delivery systems of Captopril were successfully developed in the form of tablets to improve the local action and its bioavailability, which reduces the wastage of drug and ultimately improves the solubility for drugs that are less soluble in high pH environment.

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