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Research Paper

Development and Evaluation of Controlled Release Mucoadhesive Tablets of Captopril

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ABSTRACT

The present investigation focuses on the development of mucoadhesive tablets of captopril which are designed to prolong the gastric residence time after oral administration. Matrix tablets of captopril were formulated using four mucoadhesive polymers namely guar gum, xanthan gum, HPMC K4M and HPMC K15M and studied for parameters such as weight variation, thickness, hardness, content uniformity, swelling index, mucoadhesive force and in vitro drug release. Tablets formulated Xanthan gum or HPMC K4M with HPMC K15M provide slow release of captopril over period of 12 hr and were found suitable for maintenance portion of oral controlled release tablets. The cumulative % of drug release of formulation F9 and F10 were 90 and 92, respectively. In vitro release from these tablets was diffusion controlled and followed zero order kinetics. The 'n' values obtained from the pappas-karsemeyer equation suggested that all the formulation showed drug release by non-fickian diffusion mechanism. Tablets formulated Xanthan gum or HPMC K4M with HPMC K15M (1:1) were established to be the optimum formulation with optimum bioadhesive force, swelling index & desired invitro drug release. This product was further subjected to stability study, the results of which indicated no significant change with respect to Adhesive strength and in vitro drug release study.

KEYWORDS: Drug delivery; Controlled release; HPMC K4M; HPMC K15M; Xanthan gum.

Introduction

Several approaches have been suggested to increase GI transit time, addressing the issue of localized drug delivery. Both low and high-density drug delivery systems have been suggested as possible approaches to extend the transit time but the results of exploratory studies area equivocal. In another system in which particle size, relative to stomach retropulsion has been suggested as a means to delay stomach emptying and thereby prolong transit time. This phenomenon is also relatively short duration, particularly drug delivery system administered in absence of food. An alternative approach is to employ bioadhesive polymers that adhere to epithelial surface. Such polymer applied to any mucus membranes and perhaps non-mucus membrane as well. Thus, bioadhesive polymers would find application in the eye, nose vagina and GIT including the buccal cavity and rectum (Vyas and Khar, 2002). An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment (Bramhankar and Jaiswal, 2002). The controlled drug delivery system is one, which delivers the drug at a predetermined rate, locally or systemically for a predetermined period of time. The targeted drug delivery system is one, which delivers the drug only to its site of action and not to the non-target organs or tissues.

Despite the several advantages associated with oral controlled drug delivery systems, there are so many disadvantages. Such limitations of controlled release can be overcome by gastro-retentive system. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT), i.e. Gastro retentive Dosage Forms (GRDFs), will provide us with new and important therapeutic options. These efforts results in Gastro retentive dosage forms (GRDFs) that was designed in large part based on many approaches, like mucoadhesive drug delivery system (Patil et al., 2006), mucoadhesive polymers (Chowdary and Srinivas, 2000), mechanism of bioadhesion (Jasti et al., 2003) and bioadhesive polymers (Table 1) (Khanna et al., 1998; Singla et al., 2000). To over the relatively short GI time and improve localization for oral controlled release drug delivery system, bioadhesive polymers which adhere to the epithelial surface are effective and lead to significant improvement in oral drug delivery. Improvements are also expected for other mucus-covered sites of drug administration. Bioadhesive polymers find application in the eye, nose

and vaginal cavity as well as the GI tract including the buccal cavity and rectum.

TABLE 1

The mucoadhesive polymers reported in the literature.

Polymer	Mucoadhesive property
Carbopol 974 P	+ + +
Carbopol 971 P	+ + +
Carbopol 934 P	+ + +
Hydroxy propylmethyl cellulose	+ + +
Carboxymethyl cellulose	+ + +
Sodium alginate	+ + +
Xanthan gum	+ +
Guar gum	+ +
Polyvinyl pyrrolidone	+
Chitosan	+
Polyethylene glycol	+

NOTE: + + + Excellent; + + Fair; + Poor.

In this study we sought to design a controlled release mucoadhesive oral tablet to increase the residence time of the drug in to the stomach and release for extended period of time in order to increase bioavailability of the drug, reduce dosing frequency, and improve patient compliance.

Materials and Methods

The formulation development, evaluation and analysis were formulated as per previously published reports (Rowe et al., 2003; Goud et al., 2004; Owens et al., 2005; Singh et al., 2006; Achar and Peppas, 1994; Singh and Ahuja, 2002; Bredenberg and Nystrom, 2003; Noha et al., 2004; Ikeda and Kimura, 2000; Krishna and Thakur, 2006; Ceschel et al., 2006; Patel et al., 2004).

TABLE 2

Materials used in the Study.

S. No.	Materials	Grade	Manufactures / Suppliers
1.	Captopril	Pharma	Microlab
2.	HPMC K4M	Pharma	Colorcon Asia Pvt. Ltd.
3.	HPMC K15M	Pharma	Colorcon Asia Pvt. Ltd.
4	Xanthan gum	Pharma	C.P. kelco, U.S.A
5.	Guar gum	Pharma	Signet Chemical Corp.
6.	Avicel PH 102	Pharma	Signet Chemical Corp.
7.	Talc	A.R.	Loba Chemie
8.	Magnesium Stearate	A.R.	Loba Chemie
9.	Hydrochloric Acid	L.R.	S.D. Fine Chem. Ltd.
10.	Polyvinyl pyrolinedine	L.R	Nice Chemicals Laboratory

TABLE 3

Details of Instruments used in the Study.

S. No.	Instruments	Manufactures/ Suppliers
1.	Electronic Balance	Afcoset ER-120A
2.	Hardness Tester	Monsanto
3.	Friability test apparatus	Roche Friabilator
4.	Hydraulic Press	Kimaya Engineers
5.	Dial Caliper	Mitutoyo, Japan.
6.	Tablet Dissolution Tester (USPXX III)	Electro Lab
7.	Tap Density Tester	Electro Lab
8.	UV Spectrophotometer	Shimadzu, UV 1601
9.	IR Spectrophotometer	Thermo Nicolet

Preformulation Studies

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility, compatibility studies and physical properties.

Determination of melting point: Melting point of Captopril was determined by capillary method.

Solubility: Solubility of Captopril was determined in water, 0.1N HCL, practically insoluble in ethanol (95%), chloroform and ether.

Compatibility studies: Compatibility with excipients was confirmed by carried out IR studied. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Physical Properties

Bulk density: Bulk density is defined as a mass of a powder divided by the bulk volume.

Procedure: A sample powder of Captopril (5 g) was introduced in 100 mL graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below;

$$\text{Bulk density } (\rho_0) = M/V_o \qquad \text{.....(1)}$$

Where, M = mass of the powder

Vo = volume of the powder

Procedure: The powder sample under test was screened through sieve no. 18 and the weight of sample equivalent to 5 g was filled in 100 mL graduated cylinder. The mechanical tapping of the cylinder was carried out using at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume V_o was noted. Tapping was proceeding further for an additional tapping 750 times and tapped volume, V_b was noted. The difference between two tapping volume was less than 2%, so V_b was considered as a tapped volume V_F.

The tapped density was calculated in g/ cm^3 by the formula,

$$\text{Tapped density } (\rho_t) = M/V_f \qquad \text{.....(2)}$$

Where, M = weight of sample powder taken

V_f = tapped volume

Compressibility Index

Procedure: The bulk density and tapped density was measured and compressibility index was calculated using the formula,

$$\text{C.I.} = \{(\rho_t - \rho_o)/ \rho_t\} \times 100 \qquad \text{.....(3)}$$

Where, ρ_t = tapped density

ρ_o = bulk density

Hausner Ratio

Procedure: Tapped density and bulk density were measured and the Hausner ratio was calculated using the formula,

$$\text{Hausner ratio} = \rho_t/\rho_o \qquad \text{.....(4)}$$

Where, ρ_t = tapped density

ρ_o = bulk density

Preparation of Standard Curve of Captopril

100 mg of captopril was dissolved in 100 mL calibrated volumetric flask and completing to volume with 0.1 N Hydrochloric acids. From this 10 mL pipette out in 100 ml calibrated volumetric flask and dilution was made with 0.1 N HCl. From this stock solution 10 mL pipette out in 100 mL calibrated volumetric flask and dilution was made with 0.1 NHCl. From this solution 1 mL, 2 mL, 3 mL, 4 mL and to 10 mL was pipette out in different 10 mL volumetric flask and this was finally diluted with 0.1 NHCl. The absorbance was noted at 209 nm.

Preparation of Calibration Curve

TABLE 4

Standard Curve of Captopril at 209 nm by UV Spectrometry.

S. No.	Concentration µg/mL	Absorbance
0	0	0
1	1	0.0834
2	2	0.1533
3	3	0.2010
4	4	0.2905
5	5	0.3447
6	6	0.4229
7	7	0.4850
8	8	0.5669
9	9	0.6270
10	10	0.7137

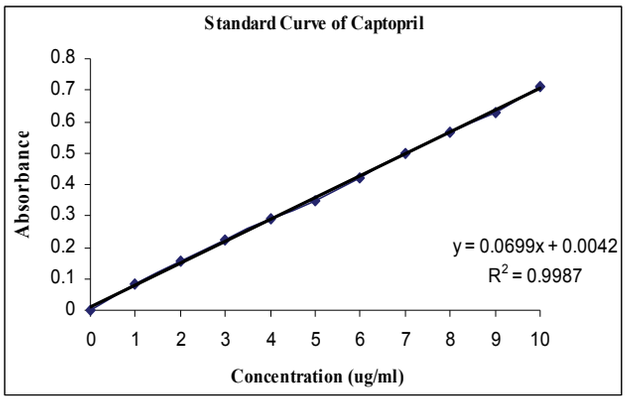

Fig. 1. Standard Curve of Captopril.

TABLE 5

Composition of Mucoadhesive Tablets of Captopril (in mgs).

S. No.	Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Captopril	100	100	100	100	100	100	100	100	100	100	100
2	Guar gum	50	100		--	--	--	--	--	--	--	--
3	Xanthan gum	--	--	50	100	--	--	--	--	---	50	50
4	HPMC K4M	--	--	--	--	50	100	--	--	50	--	50
5	HPMC K15M	--	--	--	--	--	--	50	100	50	50	--
6	PVP K-30	24	24	24	24	24	24	24	24	24	24	24
7	IAP	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8	Avicel PH 102	60	10	60	10	60	10	60	10	10	10	10
9	Talc	3	3	3	3	3	3	3	3	3	3	3
10	Mg. stearat	3	3	3	3	3	3	3	3	3	3	3

Formulation of Mucoadhesive Tablet

Mucoadhesive matrix tablets containing Captopril were prepared by wet granulation technique using variable concentrations of HPMC K4M, HPMC K15M, Xanthan gum, Guar gum.

All the ingredients except Avicel PH 102, magnesium stearate and talc were blended in glass mortar uniformly. Mixed all the ingredients and passed through sieve no 60. Granulation was done with sufficient solution of PVP K30 and isopropyl alcohol. Wet mass was passed through sieve no 12 and dried at 45-55 °C for 2 hrs. Dried granules were sized by sieve no. 18 and mixed with Avicel PH 102, magnesium stearate and talc. Granules obtained were compressed with 9 mm punch. The weights of the tablets were kept constant for formulations F1 to F11. The formulations were shown Table 1.

Evaluation of Mucoadhesive Tablet

All the prepared mucoadhesive tablets were evaluated for following official unofficial parameters.

Hardness: Hardness was measured using Pfizer hardness tester. For each batch three tablets were tested.

Friability: Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(W_o/W)\} \times 100 \quad \text{.....(5)}$$

Where, % F = friability in percentage

W_o = Initial weight of tablet

W = weight of tablets after revolution

Weight variation: Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table 6. They showed little deviation by more than twice the percentage shown.

TABLE 6

Percentage Deviation Allowed under Weight Variation Test.

Average weight of tablet (mg)	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

Thickness: Three tablets were selected randomly from each batch and thickness was measured by using screw gauge.

Drug content: Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 100 mg Captopril was shaken with 100 mL of 0.1 N Hydrochloric acid in 100 mL volumetric flask and from this 5 mL is pipette out and then dilute up to 100 mL. From standard solution again 5 mL pipette out and diluted up to 100 mL in 100 mL volumetric flask. Resulting solution was filtered and assayed at 206 nm and content of Captopril was calculated. Results are shown in Table 11 to 20.

Bioadhesive Strength

Bioadhesive strength of the tablet was measured on the modified physical balance. The design used for measuring the bioadhesive strength was shown in Fig. 3. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward potrution of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media 0.1N HCl pH 1.2, which was then placed below right side of the balance.

Goat or rat stomach mucosa was used as a model membrane and buffer media 0.1N HCl pH 1.2 was used as moistening fluid. The goat or rat stomach mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The underlying mucous membrane was separated using surgical blade and wash thoroughly with buffer media 0.1N HCl pH 1.2. It was then tied over the potrusion in the Teflon block using a thread. The block was then kept in glass beaker. The beaker was filled with phosphate buffer media 0.1N HCl pH 1.2 up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments.

The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established. A preload of 10 mg was placed on the slide for 5 min (preload time) to established adhesion bonding between mucoadhesive tablet and goat or rat stomach mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when mucoadhesive tablet was detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive tablet from stomach mucosa was noted as bioadhesive strength in grams. From the bioadhesive strength following parameter was calculated.

$$\text{Force of adhesion (N)} = \frac{\text{Bioadhesive strength}}{1000} \times 9.81 \quad \text{.....(6)}$$

$$\text{Bond strength (N/m}^2\text{)} = \frac{\text{Force of adhesion (N)}}{\text{Surface area of tablet (m}^2\text{)}} \quad \text{.....(7)}$$

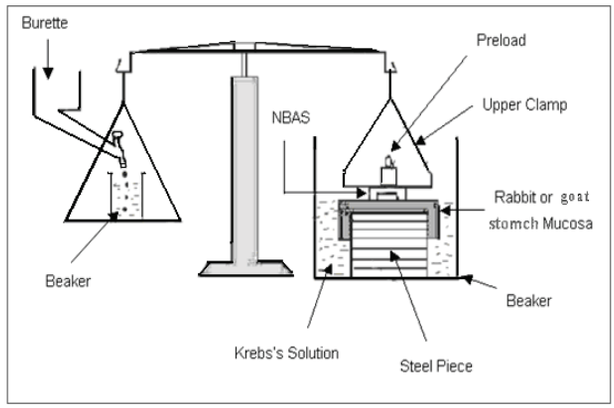

Fig. 2. Mucoadhesion Test Assembly.

Swelling index: Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet.

Method: For each formulation batch, one tablet was weighed and placed in a beaker containing 200 mL of buffer media. After each interval the tablet was removed from beaker and weighed again up to 8 hours. The swelling index was calculated using following formula.

$$\text{Swelling Index (S.I.)} = (W_t - W_o)/W_o \quad \text{.....(8)}$$

Where, S.I. = Swelling index

W_t = Weight of tablet at time t

W_o = Weight of tablet before placing in the beaker

In Vitro release study: Standard USP or IP dissolution apparatus have been used to study *in vitro* release profile using both basket and rotating paddle.

In vitro release rate study of mucoadhesive tablet of Captopril was carried out using the Apparatus 2 (Basket apparatus) method. Place the tablet in a dry basket at the beginning of each test. Lower the Basket before rotation operates the apparatus immediately at 50 rpm. Medium used for release rate study was 900 mL 0.1 N HCl during the course of study whole assembly was maintained at 37 $\pm$ 0.5 °C. Withdraw a 5 mL of sample at

time interval 1,2,3,4, ---up to 12 hr and replaced with 5 mL of fresh dissolution medium.

The withdrawn samples dilute with dissolution medium and then filter it with Whatman filter paper and assayed at 209 nm.

The % release of Captopril was calculated. The observations for different batches are shown in succeeding tables. The percentage release of Captopril with respect to time for each batch, are graphically shown below.

Data Analysis

The release data obtained from various batches was studied with respect to effect of drug: polymer ratio, diluents ratio. To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches was fitted to zero order, first-order, Higuchi, Hixon-Crowell, Korsemeyer and Peppas, and Weibull models to ascertain the kinetic modeling of drug release. The method of Bamba et al was adopted for deciding the most appropriate model.

- ***Zero order:*** In many of the modified release dosage form particularly controlled or sustained release dosage form (those dosage forms that release the drug in planned, predictable and slower than normal manner) is zero order kinetics.

$$Q = K_o t \quad \text{.....(9)}$$

Where, Q is the amount of drug release at time, t and Ko is the release rate constant.

- ***First order:*** Most conventional dosage form exhibits this dissolution mechanism some modified release preparations, particularly prolonged release formulation adhere to this type of dissolution pattern.

$$\text{Log } Q = K_1 t \quad \text{.....(10)}$$

Where Q is the percent of drug release at time, t and K1is the release rate constant.

- ***Higuchi equation:*** A Large number of modified release dosage form contain some sort of matrix system is such instances the drug dissolves from this matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion control) and thus the following relationship applies.

$$Q = Kt_1/2 \quad \text{.....(11)}$$

Where, Q is the percentage of drug release at time, t and K is the diffusion rate constant.

- ***Peppas equation:***

$$Q = Kt_n \quad \text{.....(12)}$$

Where, Q is the percent of drug release at time, t and K is the diffusion rate constant and n is diffusional exponent. If n is equal to one the release is zero order. If n is equal to 0.5 the release is best explained by fickian diffusion and if $0.5 < n < 1$ then the release is through anomalous diffusion or case II diffusion in this model a plot of % drug released versus log time is linear.

- ***Hixson crowell model:*** Some specialized dosage forms contain many drug particles of the same size and shape of their agglomerates that dissolve evenly in such instances the dissolution process can be expressed by the Cube–root law.

If the dissolution pattern of the drug is dictated by the actual dissolution of drug molecules, then the following relationship applies.

$$M = [(100) \times ((1/3) - k \times t)^3] \quad \text{.....(13)}$$

Where k is Hixon Crowell Constant (Mass / time) $^{1/3}$

In this model the % drug unreleased versus cube root of time is linear.

TABLE 7

Percentage Deviation Allowed under Weight Variation Test.

N	Mechanism
0.5	Fickian diffusion
0.5 < n < 1	Non- fickian diffusion
1	Class II transport

Stability Studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile

The prepared Mucoadhesive tablets (F1 to F11) of captopril were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, oven temperature (40 ± 2 ºC) and refrigerator (2-8 ºC) for a period of 30 days.

Results and Discussion

Mucoadhesive GRDDS tablets of captopril were prepared and evaluated to increase its local action and bioavailability.

Melting point determination: Melting point of captopril was found to be in the range 104-110 ºC, which complied with IP standards, indicating purity of the drug sample.

Solubility: Captopril was found to be soluble in water, 0.1NHCL, chloroform and ether.

Compatibility study: Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of captopril were obtained at 1035.8 cm^{-1}, 1049.3 cm^{-1}, 1471.7 cm^{-1}, 1747.5 cm^{-1}, 2980.0 cm^{-1}, 2873.9 cm^{-1}.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. Interparticulate interactions that influence the bulking properties of a powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder; such a comparison is often used as an index of the ability of the powder to flow. The bulk density and tapped density was found to be 0.543 and 0.806 gm/cm^3 respectively.

A simple indication of ease with which a material can be induced to flow is given by application of a compressibility index. The value for compressibility index of Captopril was found to be 32.612 that reflect the

poor flow property of Captopril, which was supported by the Hausner ratio of 1.483.

The physical characterization of the Polymer was done by evaluating them for the physical characteristics such as bulk density, tapped density, compressibility index, and Hauser's ratio. All the excipients were found to have desirable physical characteristics.

Physical properties:

TABLE 8

Physical Properties of Tablets of Batch F1 to F11.

Batch no.	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content uniformity (mg)
F1	240.3 ± 5.12	6.83 ± 0.289	3.033 ± 0.11	0.57	98.56
F2	240.8 ± 3.95	6.63 ± 0.321	2.80 ± 0.05	0.58	99.43
F3	239.9 ± 4.09	6.57 ± 0.40	2.76 ± 0.05	0.55	97.12
F4	239.8 ± 4.23	7.20 ± 0.26	2.70 ± 0.15	0.39	98.76
F5	240.2 ± 2.89	6.77 ± 0.25	2.66 ± 0.05	0.41	99.96
F6	240.1 ± 2.78	7.53 ± 0.451	2.93 ± 0.15	0.49	98.51
F7	240.3 ± 2.05	6.43 ± 0.49	2.55 ± 0.08	0.61	99.84
F8	239.9 ± 2.22	7.07 ± 0.50	2.62 ± 0.05	0.76	98.39
F9	240 ± 2.10	7.10 ± 0.458	2.53 ± 0.052	0.67	99.78
F10	239.8 ± 2.39	6.60 ± 0.173	2.81 ± 0.076	0.48	97.01
F11	240.5 ± 2.11	6.70 ± 0.200	2.76 ± 0.115	0.39	98.45

Each reading is an average of three determinations (Avg.± S.D)

Swelling study: Swelling study was performed on all the batches (F1 to F11) for 8 hr. The results of swelling index were shown in Table 9. Swelling index against time (hr) was plotted in Fig. 4.

The batch F7, F8 contains HPMC K15M had more swelling because its high viscosity grade polymer than F5, F6 contains HPMC K4M.

From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found for tablets of batch F9 containing HPMC K15M having nominal viscosity of 15,000 cps. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as adhesion capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

TABLE 9

Swelling Index of Tablets of Batch F1 to F11.

Batch no.	Time (hrs)								
	0	1	2	3	4	5	6	7	8
F1	0	0.625	0.854	1.042	1.167	1.250	1.250	--	--
F2	0	0.559	0.862	1.045	1.186	1.065	1.024	--	--
F3	0	0.673	0.918	1.122	1.245	1.327	1.347	1.306	--
F4	0	0.618	0.950	1.116	1.241	1.324	1.344	1.386	--
F5	0	0.111	0.399	0.605	0.852	0.934	1.140	1.181	1.058
F6	0	0.118	0.224	0.477	0.646	0.857	0.983	1.025	1.152
F7	0	0.106	0.532	0.660	0.830	0.915	1.000	1.043	1.085
F8	0	0.157	0.570	0.674	0.736	0.860	0.901	0.942	0.983
F9	0	0.560	0.880	1.160	1.380	1.460	1.480	1.520	1.540
F10	0	0.687	0.934	1.016	1.119	1.140	1.222	1.305	1.222
F11	0	0.598	0.803	0.926	1.008	1.131	1.172	1.254	1.295

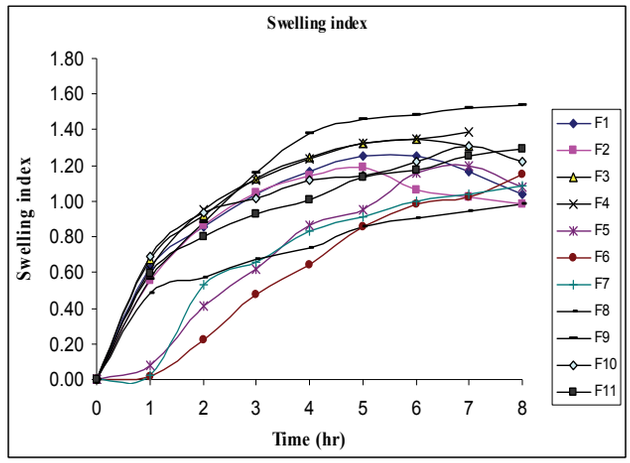

Fig. 3. Swelling Study from Select Batches.

Bioadhesive strength: The mucoadhesive property of tablet of Captopril containing varying proportion of polymers was determined with a view to develop a good adhesiveness without any problems. The bioadhesion characteristics were affected by the type and concentration of the bioadhesive polymers (Table 10). The highest adhesion force i.e. highest strength of the mucoadhesive bond (0.3098) was proposed by F10 containing HPMC K15M and Xanthan gum (1: 1) in combination with total polymer concentration is 40%. In batch F1, and F2 concentration of Guar gum increases. The mucoadhesive strength of formulation was increased.

F3, F4, concentration of Xanthan gum increases. The mucoadhesive strength of formulation was increased.

F5, F6 containing HPMC K15 M and F7, F8, containing HPMC K4 M in same concentration showed, good mucoadhesive strength. HPMC K15 M showed more mucoadhesive strength than HPMC K4 M.

From the observation concluded that with increasing concentration of polymer mucoadhesive strength increases and viscosity of polymer also affect the mucoadhesive strength.

TABLE 10

In vitro Mucoadhesive Strength and Force of Batch F1 to F11.

Batch code	Mucoadhesive strength (g)	Mucoadhesion force (N)
F1	7.225 ± 0.035	0.0708 ± 0.0004
F2	9.24 ± 0.07	0.0906 ± 0.0009
F3	14.15 ± 0.115	0.1388 ± 0.0015
F4	18.745 ± 0.065	0.1838 ± 0.0009

TABLE 10 *Contd...*

Batch code	Mucoadhesive strength (g)	Mucoadhesion force (N)
F5	16.425 ± 0.114	0.1611 ± 0.0015
F6	20.15 ± 0.11	0.1976 ± 0.0015
F7	21.57 ± 0.03	0.2116 ± 0.0004
F8	27.52 ± 0.1	0.2699 ± 0.0013
F9	29.38 ± 0.1	0.2882 ± 0.0013
F10	31.59 ± 0.05	0.3098 ± 0.0006
F11	29.96 ± 0.293	0.2939 ± 0.0017

Each reading is an average of three determinations (Avg.± S.D)

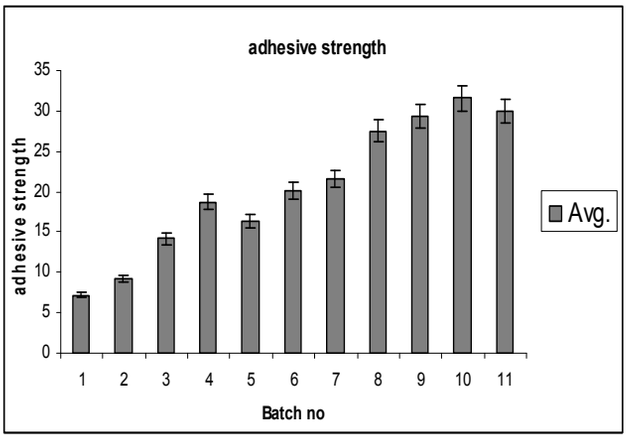

Fig. 5. Column Graph of the Adhesive Force.

In-vitro dissolution study: The results obtaining in vitro release studies were plotted in different model of data treatment as follows

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation)
5. (percentage retained)$^{1/3}$ Vs time (Hixson –Crowell Erosion Equation)

In vitro release obtained for formulations F1 to F11 were tabulated in Table's 11, 12, 13, 14 and 15 Figs. 9, 10, 11, 12, and 13 shows the plot of cumulative % drug released as a function of time.

The *in vitro* dissolution was carried out on all the batches. The release of Captopril from mucoadhesive tablet varied according to the type and concentration of polymer. Batch F1, F2, had % cumulative release 97.61% in 5 hrs, 96.22% in 7 hr. From above observation concluded that polymer concentration increases duration of release increases.

F3, F4, had % cumulative release 93.34% in 9 hr, F4 is 94.32%hr in 9 hr. From above observation concluded that polymer concentration increases duration of release increases.

The batch F5, F6 had concentration range 20%, 40%, (total tablet weight) showed % cumulative release 94.894% in 8hr, 98.07% in 10 hr but release is less as compare to Xanthan gum polymer because it's a high viscosity grade polymer.

The batch F7, F8 had same concentration which released 96.65% in 9hr, 97.79% in 11 hr.

From the result it was concluded that the increasing polymer concentration of HPMC the release of drug might be slower which also supported by Xu and Sunada who reported that HPMC content was predominant controlling factor, as the concentration of polymer increased, drug release rates decreased and Vice Versa

The batch F9, F10, F11 contain total polymer concentration 40% with concentration range (20:20 %), (20:20%) in combination of HPMC K15M with HPMC K4M, Xanthan gum and (20:20%) in HPMC K4M with Xanthan gum had % cumulative release 90.20%, 91.85%, and 94.46%. The batch F9, F10 release is too much retarded.

TABLE 11

Comparative Dissolution Profile of Trial Batches.

Time (hrs)	Cum. % drug release										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0.0	0	0	0	0	0.00	0.00	0.00
1	41.64	35.25	29.68	28.24	23.41	21.24	18.14	15.06	13.74	14.51	18.24
2	59.02	52.60	45.45	37.81	35.82	30.04	32.03	26.69	22.57	23.87	34.01
3	72.65	64.74	57.003	51.46	45.91	39.51	39.06	35.47	34.22	30.52	51.16
4	84.77	76.09	66.75	64.25	57.07	51.63	51.15	42.88	43.89	36.12	58.33
5	97.61	83.79	79.05	71.47	69.06	60.96	64.15	49.07	51.51	42.82	61.84
6	--	90.18	86.34	77.23	79.90	69.30	75.77	61.67	57.79	51.55	67.22
7	--	96.22	93.34	83.94	89.74	74.97	81.97	67.96	62.57	58.73	73.64
8	--	--	--	91.68	94.89	80.88	88.85	80.07	68.40	65.53	78.56
9	--	--	--	95.32	--	89.57	96.65	88.08	73.33	72.57	84.34
10	--	--	--	--	--	98.07	--	93.07	77.75	78.36	90.85
11	--	--	--	--	--	--	--	97.79	85.13	84.33	94.46
12	--	--	--	--	--	--	--	--	90.20	91.85	--

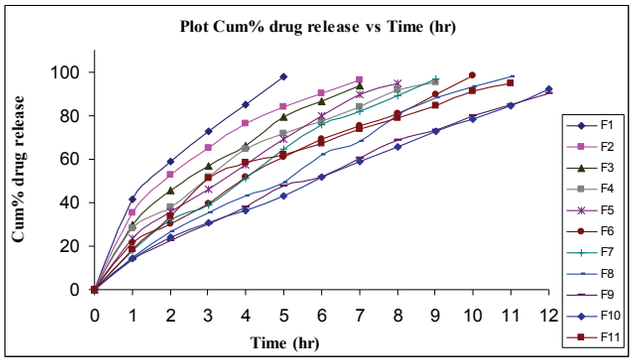

Fig.5. Comparative Dissolution Profile of Trial Batches.

TABLE 12

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F1 Formulation.

Time (hr)	Root T	Log T	Cum % drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum % drug release	(% retained)$^{1/3}$
1	1	0	41.64	58.36	1.6195	1.7661	3.878
2	1.4142	0.3010	59.02	40.98	1.7709	1.6125	3.447
3	1.7321	0.4771	72.65	27.35	1.8612	1.4369	3.013
4	2	0.6020	84.77	15.22	1.9282	1.1824	2.478
5	2.236	0.6989	97.61	2.39	1.9894	0.3784	1.337

TABLE 13

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F2 Formulation.

Time (hr)	Root T	Log T	Cum % drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum % drug release	(% retained)$^{1/3}$
1	1	0	35.25	64.747	1.547	1.811	4.015
2	1.414	0.3010	52.60	47.397	1.721	1.676	3.618
3	1.732	0.4771	64.75	35.252	1.811	1.547	3.278
4	2	0.6020	76.09	23.911	1.881	1.379	2.881
5	2.236	0.6989	83.79	16.208	1.923	1.210	2.531
6	2.449	0.7782	90.19	9.814	1.955	0.992	2.141
7	2.646	0.8451	96.22	3.777	1.983	0.577	1.557

TABLE 14

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F3 Formulation.

Time (hr)	Root T	Log T	Cum % drug release	Cum.% drug retained	Log Cum. % drug release	Log Cum % drug release	(% retained)$^{1/3}$
1	1	0	29.68	70.32	1.472	1.847	4.127
2	1.414	0.3010	45.45	54.55	1.658	1.737	3.745
3	1.732	0.4771	57.01	42.99	1.756	1.633	3.503
4	2	0.6020	65.75	34.24	1.818	1.535	3.247
5	2.236	0.6989	79.04	20.95	1.898	1.321	2.757
6	2.449	0.7782	86.34	13.65	1.936	1.135	2.39
7	2.646	0.8451	93.80	6.193	1.972	0.792	1.836

TABLE 15

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F4 Formulation.

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	28.24	71.764	1.451	1.856	4.155
2	1.414	0.3010	37.81	62.195	1.578	1.794	3.962
3	1.732	0.4771	51.46	48.538	1.711	1.686	3.647
4	2.000	0.6021	64.25	35.750	1.808	1.553	3.294
5	2.236	0.6990	71.47	28.530	1.854	1.455	3.055
6	2.449	0.7782	77.23	22.774	1.888	1.357	2.834
7	2.646	0.8451	83.94	16.061	1.924	1.206	2.523
8	2.828	0.9031	91.68	8.315	1.962	0.920	2.025
9	3.000	0.9542	95.32	4.685	1.979	0.671	1.673

TABLE 16

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F5 Formulation.

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	23.42	76.579	1.370	1.884	4.246
2	1.414	0.3010	35.82	64.180	1.554	1.807	4.003
3	1.732	0.4771	45.91	54.092	1.662	1.733	3.781
4	2.000	0.6021	57.07	42.929	1.756	1.633	3.501
5	2.236	0.6990	69.06	30.936	1.839	1.490	3.139
6	2.449	0.7782	79.91	20.095	1.903	1.303	2.718
7	2.646	0.8451	89.75	10.252	1.953	1.011	2.172
8	2.828	0.9031	94.90	5.104	1.977	0.708	1.721

TABLE 17

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F6 Formulation.

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	21.24	78.755	1.327	1.896	4.286
2	1.414	0.3010	30.04	69.962	1.478	1.845	4.120
3	1.732	0.4771	39.52	60.482	1.597	1.782	3.925
4	2.000	0.6021	51.63	48.370	1.713	1.685	3.643
5	2.236	0.6990	60.97	39.033	1.785	1.591	3.392
6	2.449	0.7782	69.31	30.694	1.841	1.487	3.131
7	2.646	0.8451	74.97	25.029	1.875	1.398	2.925
8	2.828	0.9031	80.88	19.116	1.908	1.281	2.673
9	3.000	0.9542	89.58	10.419	1.952	1.018	2.184
10	3.162	1.0000	98.08	1.923	1.992	0.284	1.243

TABLE 18

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F7 Formulation.

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	18.14	81.858	1.259	1.913	4.341
2	1.414	0.3010	32.03	67.968	1.506	1.832	4.081
3	1.732	0.4771	39.07	60.934	1.592	1.785	3.935
4	2.000	0.6021	51.15	48.847	1.709	1.689	3.655
5	2.236	0.6990	64.62	35.377	1.810	1.549	3.282
6	2.449	0.7782	75.77	24.230	1.879	1.384	2.893
7	2.646	0.8451	81.97	18.033	1.914	1.256	2.622
8	2.828	0.9031	88.85	11.151	1.949	1.047	2.234
9	3.000	0.9542	96.65	3.350	1.985	0.525	1.496

TABLE 19

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F8 Formulation.

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	15.06	84.936	1.178	1.929	4.395
2	1.414	0.3010	26.69	73.314	1.426	1.865	4.185

TABLE 19 *Contd...*

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
3	1.732	0.4771	35.47	64.530	1.550	1.810	4.011
4	2.000	0.6021	42.88	57.120	1.632	1.757	3.851
5	2.236	0.6990	49.07	50.929	1.691	1.707	3.706
6	2.449	0.7782	61.68	38.322	1.790	1.583	3.371
7	2.646	0.8451	67.97	32.031	1.832	1.506	3.175
8	2.828	0.9031	80.07	19.929	1.903	1.299	2.711
9	3.000	0.9542	88.09	11.914	1.945	1.076	2.284
10	3.162	1.0000	93.08	6.921	1.969	0.840	1.905
11	3.317	1.0414	97.79	2.209	1.990	0.344	1.302

TABLE 20

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F9 Formulation.

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	13.74	86.262	1.138	1.936	4.418
2	1.414	0.3010	22.57	77.434	1.353	1.889	4.262
3	1.732	0.4771	30.43	69.570	1.483	1.842	4.112
4	2.000	0.6021	37.82	62.180	1.578	1.794	3.961
5	2.236	0.6990	47.64	52.360	1.678	1.719	3.741
6	2.449	0.7782	51.43	48.570	1.711	1.686	3.648
7	2.646	0.8451	60.17	39.830	1.779	1.600	3.415
8	2.828	0.9031	68.34	31.660	1.835	1.501	3.163
9	3.000	0.9542	73.25	26.750	1.865	1.427	2.990
10	3.162	1.0000	79.83	20.170	1.902	1.305	2.722
11	3.317	1.0414	85.13	14.870	1.930	1.172	2.459
12.00	3.464	1.0792	90.24	9.760	1.955	0.989	2.137

TABLE 21

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F10 Formulation.

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	14.51	85.490	1.162	1.932	4.405
2	1.414	0.3010	23.87	76.130	1.378	1.882	4.238
3	1.732	0.4771	30.52	69.480	1.485	1.842	4.111
4	2.000	0.6021	36.12	63.880	1.558	1.805	3.997
5	2.236	0.6990	42.82	57.180	1.632	1.757	3.852
6	2.449	0.7782	51.55	48.450	1.712	1.685	3.645
7	2.646	0.8451	58.73	41.270	1.769	1.616	3.455
8	2.828	0.9031	65.53	34.470	1.816	1.537	3.254
9	3.000	0.9542	72.57	27.430	1.861	1.438	3.015
10	3.162	1.0000	78.36	21.640	1.894	1.335	2.786
11	3.317	1.0414	84.33	15.670	1.926	1.195	2.502
12.00	3.464	1.0792	91.85	8.150	1.963	0.911	2.012

TABLE 22

In Vitro Release Profile of Captopril Mucoadhesive Tablets of F11 Formulation.

Time (hr)	Root T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1/3}$
1	1.000	0.0000	18.24	81.760	1.261	1.913	4.340
2	1.414	0.3010	34.01	65.990	1.532	1.819	4.041
3	1.732	0.4771	51.16	48.840	1.709	1.689	3.655
4	2.000	0.6021	58.33	41.670	1.766	1.620	3.467
5	2.236	0.6990	61.84	38.160	1.791	1.582	3.366
6	2.449	0.7782	67.22	32.780	1.827	1.516	3.200
7	2.646	0.8451	73.64	26.360	1.867	1.421	2.976
8	2.828	0.9031	78.56	21.440	1.895	1.331	2.778
9	3.000	0.9542	84.34	15.660	1.926	1.195	2.501
10	3.162	1.0000	90.85	9.150	1.958	0.961	2.091
11	3.317	1.0414	94.46	5.540	1.975	0.744	1.769

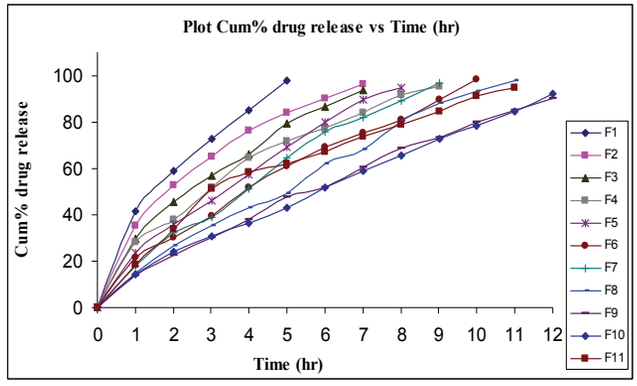

Fig. 6. *In Vitro* Cumulative Percent Drug Released Vs. Time for Formulation F1 to F11.

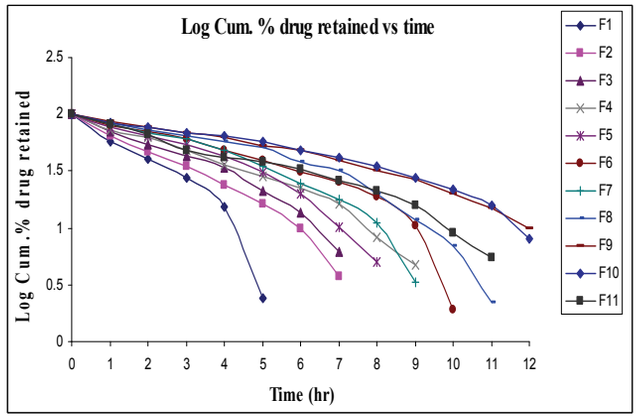

Fig. 7. Log Cumulative Percent Drug Retained Vs. Time for Formulation F1 to F11.

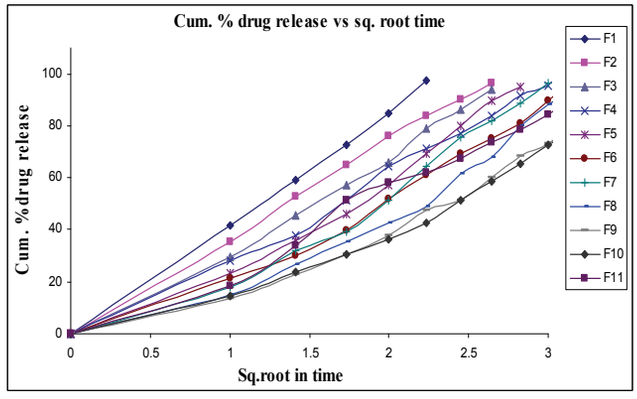

Fig. 8. Cumulative Percent Drug Retained Vs. Root Time for Formulation F1 to F11.

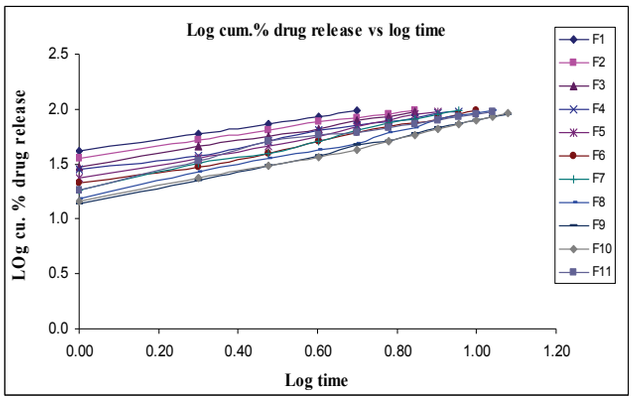

Fig. 9. Log Cumulative Percent Drug Retained Vs. Time for Formulation F1 to F11 of Captopril [PEPPAS].

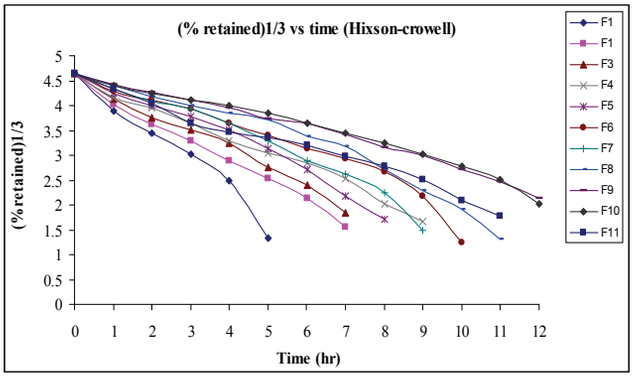

Fig. 10. Cube Root of Percent Drug Retained Vs. Time for Formulation F1 to F11 of Captopril [HIXSON-CROWELL].

The kinetic values obtained for different formulation were shown in Table 27, 28. The values of *in vitro* release were attempted to fit into various mathematical models. Plots of first order, zero order, Higuchi matrix, Peppas and Hixson-crowell were depicted in Fig. 14, 15, 16, 17, and 18. The regression coefficients for formulations F1, F2, F3 and F4 zero order plots were found to be 0.9948, 0.9632, 0.9865, and 0.9713 respectively. And formulations F5, F6, F7 and F8 were found to be 0.9939, 0.9913, 0.9901 and 0.9931 respectively. And formulations F9, F10, and F11 were found to be 0.9945, 0.9985 and respectively. The regression value for formulation F1 to F4 of first order plots were found to be 0.9609, 0.8928, 0.9257, and 0.9001 respectively. And formulations F5, F6, F7 and F8 were found to be 0.9401, 0.9220, 0.9092, and 0.9118 respectively. And formulations F9, F10, and F11 were found to be 0.9021, 0.9274, and 0.9621 respectively. Fig. 16 shows the graphical representation of cumulative drug released as a function of square root of time. This Higuchi plot was almost linear with regression coefficient values of 0.9977, 0.9959, 0.9969, 0.9940, 0.9892, 0.9909, 0.9894, 0.9824, 0.9903, 0.9811 and 0.9862 for formulation F1 to F11 respectively.

The linearity suggests that the release of captopril from Guar gum, Xanthan gum, HPMC K15M and HPMC K4M was diffusion controlled Plot of log cumulative percent drug released vs. log time is shown in Fig. 17

TABLE 23

Kinetic Values Obtained from *In Vitro* Released Data of Different Captopril Mucoadhesive Tablets Formulations.

	Plot of log cum % drug retained vs time (first order plot)			Plot of cum % release vs time (zero order plot)		
Formulation	Slope	First order rate constant k = slope × 2.303	Regression coefficient	Slope	Rate constant K=-slope	Regression coefficient
F1	0.0897	0.2066	0.9609	13.77	-13.77	0.9948
F2	0.0674	0.1552	0.8928	9.923	-9.923	0.9632
F3	0.0785	0.1808	0.9257	10.57	-10.57	0.9865
F4	0.0629	0.1449	0.9001	8.465	-8.465	0.9713
F5	0.084	0.1935	0.9401	10.52	-10.52	0.9939
F6	0.0691	0.1591	0.9220	8.445	-8.445	0.9913
F7	0.0842	0.1939	0.9092	9.921	-9.921	0.9901
F8	0.0736	0.1695	0.9118	8.457	-8.457	0.9931
F9	0.0667	0.1536	0.9021	6.987	-6.987	0.9945
F10	0.0655	0.1508	0.9274	6.948	-6.948	0.9985
F11	0.0569	0.1310	0.9621	6.912	-6.912	0.944

TABLE 24

Kinetic Values Obtained from *In Vitro* Released Data of Different Captopril Mucoadhesive Tablets Formulations.

	Plot of cum % drug released vs time in sq. root (Higuch matrix)		Plot of log cum % drug released vs log time (log T) (pappas)		Plot of (% retained)$^{1/3}$ vs time (Hixson- crowell)	
Formulation	Slope	Regression coefficient	Slope	Regression coefficient	Slope	Regression coefficient
F1	44.805	0.9977	0.5241	0.9987	-0.6053	0.9473
F2	37.282	0.9959	0.5188	0.9965	-0.3955	0.9941
F3	39.295	0.9969	0.5923	0.9984	-0.3689	0.9838
F4	35.025	0.9940	0.5787	0.9920	-0.3075	0.9896
F5	40.922	0.9892	0.6929	0.9958	-0.3617	0.9751
F6	36.083	0.9909	0.682	0.9938	-0.3007	0.9345
F7	40.588	0.9894	0.7719	0.995	-0.3385	0.9696
F8	37.42	0.9824	0.789	0.9962	-0.2962	0.9538
F9	32.202	0.9903	0.7713	0.9986	-0.2023	0.9858
F10	31.801	0.9811	0.7456	0.9951	-0.2032	0.9676
F11	31.42	0.9862	0.645	0.9691	-0.2353	0.9803

This model is widely used when the release mechanism is not well know or when more than one type of release phenomenon was involved. The 'n' values can be used to characterize diffusion release mechanism as The 'n' value for F1 to F11 which is less than 0.789 this indicates that the release approximates non-fickian diffusion mechanism Hixson- crowell plot of the formulation were shown in Fig. 18. The regression coefficients of formulations F1 to F4 were found to be 0.9473, 0.9941, 0.9838, and 0.9896, respectively, formulation F5 to F8 were found to be 0.9751, 0.9345, 0.9696 and 0.9538, respectively, and formulation F9 to F11 were found to be 0.9858, 0.9676, and 0.9803. These results indicated that the release rate was limited by the drug particles dissolution rate and erosion of the polymer matrix. The *in vitro* drug release profile of tablet from each batch (F1 to F5) was carried out and results shown in Table 8. % cumulative drug release V/s time (hr) was plotted and shown in Fig. 16. From the overall dissolution profiles it was concluded that the drug release rate was decreased as the concentration of polymer increases and also affect the type of polymer used. This can probably be attributed to the different diffusion and swelling behaviors of the polymer. With the increasing macromolecular weight, the degree of entanglement of the polymer chains increases. Thus the mobility of the macromolecule in the fully swollen systems decreases. According to free volume of theory of diffusion, the probability for a diffusing molecule to jump form one cavity into another, hence, decreases. This leads to decreased drug diffusion coefficient and decreased release rates with increasing molecular weight ultimately the increasing in viscosity of the polymer.

It was also observed that the release rate was decreased when the viscosity and/or concentration of the polymer was increased. The linear relationship was found between the viscosity of the polymer and release rate of drug from the drug delivery system.

Stability Studies

TABLE 25

Stability studies of formulation stored at 2-8 °C.

Batch code	Mucoadhesive strength (g)	Mucoadhesion force (N)
F9	29.36 ± 0.057	0.2880 ± 0.0005
F10	31.57 ± 0.085	0.3097 ± 0.0008

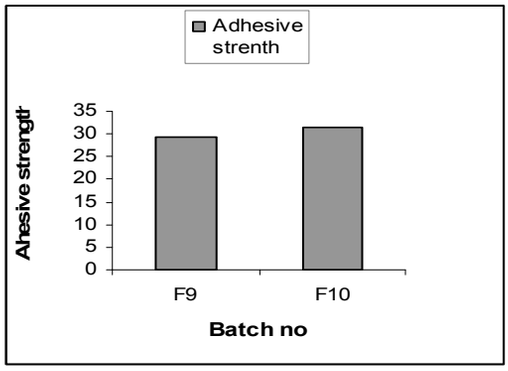

Fig. 11. Column graph of the adhesive force.

TABLE 26

Stability studies of formulation stored at Room temperature.

Batch code	Mucoadhesive strength (g)	Mucoadhesion force (N)
F9	29.375 ± 0.021	0.2880 ± 0.0002
F10	31.585 ± 0.049	0.3098 ± 0.0004

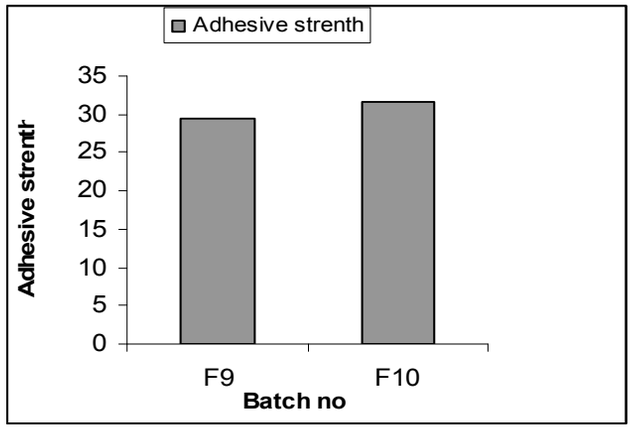

Fig. 12. Column graph of the adhesive force.

TABLE 27

Stability studies of formulation stored at 40 °C.

Batch code	Mucoadhesive strength (g)	Mucoadhesion force (N)
F9	29.33 ± 0.023	0.2878 ± 0.0002
F10	31.55 ± 0.049	0.3095 ± 0.0004

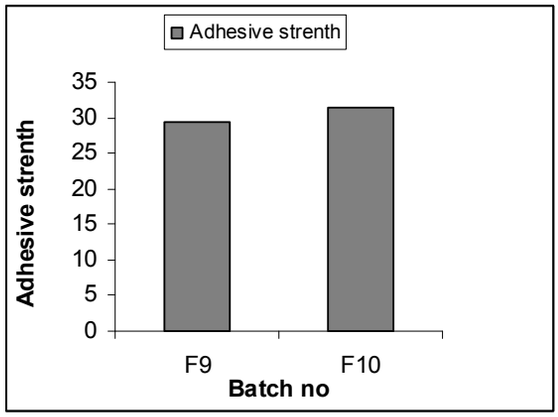

Fig. 13. Column graph of the adhesive force.

TABLE 28

Dissolution profile of stability batch of F9.

Time (hr)	Storage condition		
	Controlled	Room temperature	40 °C
0	0.00	0.00	0.00
1	13.74	12.82	13.08
2	22.57	23.20	22.52
3	34.22	33.99	33.50
4	43.89	43.60	43.11
5	51.51	52.06	51.14
6	57.79	57.67	56.85
7	62.57	62.46	61.97
8	68.40	68.16	67.84
9	73.33	73.00	72.73
10	77.75	77.79	77.39
11	85.13	84.84	84.05
12	90.20	89.86	89.15

TABLE 29

Dissolution profile of stability batch of F10.

Time (hr)	Storage condition		
	Controlled	Room temperature	40 °C
0	0.00	0	0.00
1	14.51	14.51	14.11
2	23.87	23.47	23.94
3	30.52	30.76	30.48
4	36.12	37.48	36.01
5	42.82	43.8	42.52
6	51.55	51.32	51.39
7	58.73	59.01	58.44
8	65.53	65.48	65.36
9	72.57	73.16	72.36
10	78.36	78.4	78.14
11	84.33	84.06	84.18
12	91.85	91.65	91.31

Conclusions

The formulation F9 containing 50 mg HPMCK15M and 50 mg HPMC K4M and Formulation F10 containing 50 mg HPMC K15M and Xanthan gum were consider as a best product with respect to adhesive strength, *in vitro* drug release. The bioadhesive strength of this formulation was found to be 30.21 gm and tablets of this formulation were able to adhere more than 8 hr. The drug release pattern of this formulation was found to be non-fickian and approaching zero order kinetics. Stability study of the optimized formulation was carried out and there was not any significant change with respect to Adhesive strength, *in vitro* residence time, *in vitro* drug release and *in vitro* permeation study.

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