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FORMULATION AND BIOAVAILABILITY STUDY OF BIOADHESIVE GASTRORETENTIVE TABLETS OF CAPTOPRIL

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ABSTRACT:

The present study concerns the development of bioadhesive tablets of Captopril which were designed to prolong the gastric residence time after oral administration. Captopril is an angiotensin converting enzyme inhibitor; it has been widely used for the treatment of hypertension and congestive heart failure. Tablets of Captopril were prepared by direct compression method using bioadhesive polymers like Carbopol 934P, PVP K90 and CMC-Na in different ratios. Gastroretentive tablets were evaluated by different methods for parameters such as thickness, hardness, weight uniformity, disintegration time, friability, drug content uniformity, swelling index, matrix erosion, surface pH, bioadhesive strength and *in vitro* drug release. The tablets were evaluated for in vitro release in 0.1N HCl(pH 1.2) for 12hr in standard dissolution apparatus. In order to determine the mode of release, the data was subjected to Zero order, first order, Higuchi and Peppas diffusion model. Among all the formulations, F11 with the combination of Carbopol 934 and CMC-Na showed greater *in vitro* drug release (97.25% at the end of 12 hrs), good swelling and better bioadhesive strength than using single polymers and other polymers combinations. So, the formulation (F11) was selected as optimized. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism isfound to be non-Fickian/anomalous according to Korsmeyer–Peppas (n value is 0.91938). Furthermore, the pharmacokinetic parameters of the optimized formula (F11) were studied in six healthy human volunteers. While orally administrated Captopril tablets (marketed as Capoten®) was used as a reference. Bioavailability was estimated from plasma concentration which determined up to 12hrs, after drug administration. According to the in vivo absorption profile, a significant difference in the means of C_{max}, T_{max}, t1/2 and MRT was detected between the innovator and the reference preparation. Such data provides strong evidence that the formulated Captopril tablets have better therapeutic sustaining effects than the market product.

KEY WORDS:
Bioadhesive tablets, Captopril, Carbopol 934, swelling index.

INTRODUCTION:

Oral administration is always the preferred means of drug delivery to the systemic circulation due to low cost of therapy, ease of administration, patient compliance, etc. Many attempts have been made to develop sustained release oral dosage forms with better clinical effects and reduced dosing frequency. However, the success of these conventional sustained release dosage forms for oral use is limited due to the inability to increase their residence time in the stomach and proximal portion of the small intestine (Sriamornsak*et al.*, 2005). The variable and too rapid gastrointestinal transit can result incomplete drug release from the dosage form at the absorption site in the gastrointestinal tract (GIT) leading weaken efficacy of the administered dose. To overcome this restrictions, in various oral sustained release dosage forms have been designated to be retained in the gastric region for prolonged period and released incorporated drugs to increase their bioavailability (Nayak*et al*., 2010b). Many approaches have been reported in the literature for improved gastroretention for oral sustained release dosage forms, viz. floatation (Nayak and Malakar, 2011), bio- or mucoadhesion (Nayak*et al*., 2010a) and other delayed gastric empting devices.

Bioadhesion may be defining as the state in which two materials, at least one of which is biological in nature, are held together for extended period by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucous membrane the phenomenon is referred to as mucoadhesion (Smart*et a*l., 1984). Bioadhesive formulations use polymers as the adhesive component. These polymers are often water soluble and when used in a dry form, they attract water from the mucosal surface and this water transfer leads to strong interaction. These polymers also form viscous layers when hydrated with water, which increases the retention time over the mucosal surfaces leads to adhesive interactions (Batchelor, 2004). In addition to bioadhesivity, controlling the release of a drug from the dosage form is also desirable. Controlled drug delivery systems should provide a continuous delivery of drugs at predictable and reproducible kinetics for a predetermined period. The potential advantages of this concept include the minimization of drug-related sideeffects due to controlled therapeutic blood levelsinstead of oscillating blood levels and improved patientcompliance due to reduced frequency of dosing. It istherefore clear that the challenge in the formulation ofnovel systems for bioadhesive drug delivery is toidentify technologies and formulation excipients tosimultaneously optimize both the bioadhesivity anddrug release kinetics.

Captopril is an angiotensin converting enzyme inhibitor; it inhibits the conversion angiotensin I to angiotensin II. As angiotensin II is a vasoconstrictor and a negativefeedback mediator for renin activity, lower angiotensin II levels results in a decrease in blood pressure. It has been widely used for the treatment of hypertension and congestive heart failure. Captopril acts orally and the dosage used for the treatment of congestive heart failure ranges from 50 to 150 mg daily. After oral ingestion of a single dose the maximum hemodynamic effect is observed after 45–90 min. The drug is freely water-soluble and it has elimination half-life after an oral dose is 2-3 h. It is stable at pH 1.2, and as the pH increase, the drug becomes unstable and undergoes a degradation reaction. Captopril has been a drug of choice in hypertension management. However, after single oral dosing of the drug, the antihypertensive action is only effective for 6–8 hr. Development of a controlled delivery system for Captopril would bring many advantages for patients. The development of oral controlled release formulations for Captopril is difficult because of in vivo and in vitro instability. The drug also undergoes from dose dumping and burst phenomenon (being freely water soluble) when formulated as controlled

or sustained release formulation. So present investigation under taken todevelop a controlled release oral solid dosage form (Koner*et al*., 2007;Khan*et al*., 2000;Nur and Zhang, 2000a;Nur and Zhang 2000b and Martínez-González and Villafuerte-Robles, 2003).

The aim of this study was to identify optimal formulation parameters for Captopril preparation using Carbopol 934p, Sodium carboxymethyl cellulose and PVP K90 as bioadhesive polymers. The effect of different polymers on the drug release from bioadhesive tablets was studied. The bioadhesive tablets were evaluated in terms of weight variation, thickness, hardness, friability, surface pH, swelling index, matrix erosion, mucoadhesive strength, in vitro drug release as well as bioavailability study.

MATERIALS AND METHODS

Materials:

Captopril powder was kindly supplied by Egyptian International Pharmaceutical Industries Company (EPICO), Egypt. Carbopol 934, Sodium carboxymethylcellulose, and PVP K_{90}, were kindly supplied by El-Nile PharmaceuticalChemical Company, Cairo, Egypt. All other chemicals were commercially available products of analytical grade and used as received.

Method of Preparation of bioadhesive tablets

Twelve formulae containing 50 mg Captopril each were prepared by conventional wet granulation method employing Carbopol 934, Sodium carboxymethyl cellulose, and PVP K_{90}, as mucoadhesive materials. At first the required quantity of drug, diluent and polymer taken in a motor and pestle for trituration. Then the solvent blend of water and ethyl alcohol (1:1) is added drop wise with continuous stirring until the wet mass is formed. Then the wet masses were passed through 12 mesh sieve and wet granules were dried at 60 ^{0}C for 4 hours. The dried granules (20 mesh) after blending with talc and magnesium stearate in a laboratory cubic mixer for 10 minutes were compressed using Erweka tableting machine. The tablets were then considered for further study (Chowdary*et al*.,2003). The details of composition are given in Table (1).

Table 1: Formulation codes of different Captopril bioadhesive tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Captopril	50	50	50	50	50	50	50	50	50	50	50	50
Carbopol 934	50	100	200	-	-	-	-	-	-	100	100	-
PVP K_{90}	-	-	-	50	100	200	-	-	-	100	-	100
*CMC-Na	-	-	-	-	-	-	50	100	200	-	100	100
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Mg stearate	5	5	5	5	5	5	5	5	5	5	5	5
Avicel 101	390	340	240	390	340	240	390	340	240	240	240	240

*CMC-Na: Sodium carboxymethyl cellulose, all the quantities are in mg.

Evaluation of Bioadhesive Tablets (Lachman*et al*., 1992):

Physical parameters

Hardness:

The tablet was placed between two anvils of hardness tester (Pharmatest PTB 301) and force

(kg) was gradually increases in order to get exact reading. The reading at the marked scale was recorded for the pressure, which is required to break the tablet.

Friability:

In this test tablets were weighed and placed in a Roche friabilator test apparatus, the friabilator was operated at 25 rpm for 100 revolutions. After 100 revolutions the tablets were removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of tablets (Lachman*et al*., 1992). The observed value should not be more than 1%. The percentage friability was measured using thefollowing formula:

$$F(\%) = \{1-(Wt/W)\} \times 100$$

Where, % F = friability in percentage, W = Initialweight of tablet, Wt = weight of tablets afterrevolution.

Drug content (Jimenez murinez and quirino-barreela,2008):

Five tablets for each batch were taken and triturated. Powder equivalent to 100mg of drug was weighed and transferred to beaker and then 0.01N HCL was added and it was then shaken for 10 minutes and finally 0.01N HCL was added to make the volume up to 100ml and solution was then sonicated for 15 minutes and filtered through Whatman filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 209 nm using UV/Visible spectrophotometer.

Weight variation (Indian Pharmacopeia, 1996):

Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance. The average weight and standard deviation of 20 tablets was calculated. Average and SD were calculated and reported in Table (2).

SWELLING STUDY OF FORMULATION:

The swelling of the polymers can be measuredby their ability to absorb water and swell. The swellingproperty of the formulation was done using USPdissolutionapparatus I(Agarwal and Mishra, 1999 and Mohammed and Khedr, 2003). The medium used was 900 ml of 0.1N HCl which is maintained at 37±0.5°C, rotated at 50 rpm.Weight of individual tablet was taken prior to the swelling study (W1). The tablet was removed every one hourinterval up to 8 hour and excess water removed carefully using filter paper. The swollen tablets were re-weighed (W2); Percent hydration (swelling index) was calculated as shown in Table (3).Using following formula:

Swelling Index (%) = {(W2) – (W1)/ (W1)} x 100; where W1- initial weight of tablet, W2- weight of the swollen tablet (Gerogianniset al., 1993).

MATRIX EROSION:

After swelling study, the swollen tablets were dried at 600 C for 24 hours in a hot air oven and kept in a desiccator for 48 hrs and reweighed again (W3). The Matrix erosion was calculated according to AgaiahGoud*et al*. (2011).

Matrix Erosion (%) = {(W1) – (W1)/ (W1)} x 100

Surface pH:

The surface pH was determined to investigate the possible in vivo side effects of the formulation. An acidic or alkaline formulation causes irritation of the mucosal membrane and hence, this is an important parameter in developing a bio- ormucoadhesive dosage form. A combined glass electrode was used for determination of surface pH. The tablets were kept in contact with 10 ml distilled water pH 6.5 ± 0.5 for 2 h in 25 ml beakers. The tablets swell up and pH was noted by bringing the electrode near the surface of the formulation after equilibrating for 1 minute (Boltenberg*et al*., 1991).

In vitro Bioadhesion strength:

In vitro tablet bioadhesion studies were done using rabbit stomach tissue (Betageri*et al.*, 2001). The force required for separating the tablet from the tissue surface was determined by a modified physical balance previously applied (Parodiet al., 1996). As illustrated in Fig. (1),the device was composed mainly of two arms balance. The left arm of the balance was replaced by a tablet holder composed of small platinum lamina (L), which was vertically suspended through a wire. At the same side a movable platform (P) was maintained in the bottom in order to fix the rabbit stomach tissue (M). A glass beaker (B) was placed on the right pan of the balance. A burette (b) was fixed near the right arm to allow water to fall in the beaker at constant rate. The tablet (T) was glued to the platinum lamina (L). At the lower plate surface, rabbit stomach tissue was stuck with the glue and on the upper plate tablet was stuck, and. pH 1.2 buffer solution was used as a moistening fluid and 20 µl was spread on the surface of contact of the tissue. Then the upper jaw with tablet stuck on the plate was lowered slowly so that it just touched the tissue surface. A preload of 50 gm was placed over the platinum lamina for 5 minutes as the initial pressure. The preloads removed and water was allowed to fall in the beaker at constant rate. The increasing weight of water added would gradually stretch the tablet from the tissue till complete detachment of the adhesive bond. The water in the beaker was weighed and the bioadhesive force was calculated per unit area of the tablet as follows:

F = (Ww × g) /A where: F is the bioadhesion force dyne/cm^2; Ww is the weight of collected water in gm; g is the acceleration due to gravity 981 cm/sec^2; A is the surface area of the tablet cm^2. The rabbit stomach tissue was changed for each experiment. All the experiments were done in triplicate.

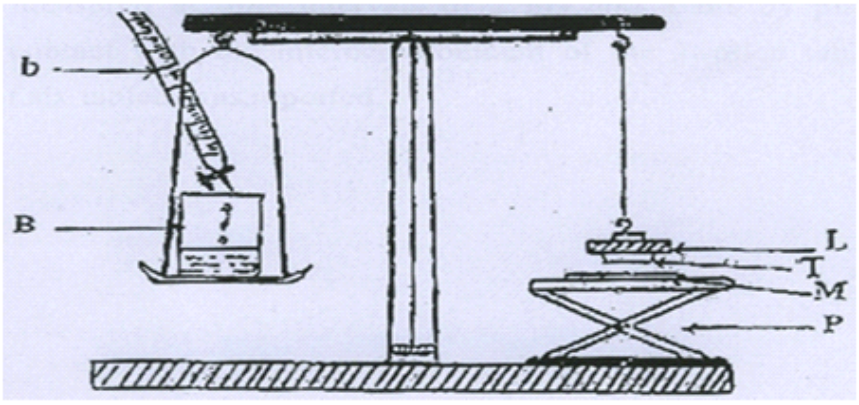

Fig. 1: Schematic representation of the apparatus used for the in vitro determination of bioadhesion force.

IN VITRO DRUG RELEASE STUDY:

The dissolution test was performed using standard USP apparatus I.Three tablets from each formula were tested. Thedissolution medium was 900 ml 0.1N HCl (pH 1.2).The temperature was maintained at 37 ± 0.5°C. Therotation speed was 50 rpm.Aliquots of 5 ml were withdrawn at predetermined time intervals of 1, 2, 4, 6, 8, 10, 12 hrs. and the volume was replaced with fresh dissolution medium. Above 5 ml samples were filtered through Whatman filter paper and analyzed for Captopril after appropriate dilution by measuring the absorbance at 209 nm. The study was performed in triplicate.

DRUG RELEASE KINETICS (CURVE FITTING ANALYSIS):

To analyze the mechanism of the drug release rate kinetics of thedosage form, the data obtained were fitted into zero order, firstorder Higuchi model and Korsmeyer's equation release models (Gupta *et al*., 1993 andAli*et al*., 2002).

IN VIVO STUDIES:

Protocol

Captopril bioadhesive tablet which is considered as an optimized formulation (F11). As it gave best drug release at the end of 12 hour and showing better Bioadhesive property was subjected to in vivo study. Also one market product, Capoten® 50 mg tablets (GalaxoSmithklin- Pharmaceutical Co., Egypt) was orally administered to six healthy human male volunteers in order to identify the pharmacokinetic properties and relative bioavailability of Captopril for all the formulations. *In vivo* experiments were carried out on six human volunteers of healthy Egyptian male ranging 25–40 (mean± standard error (S.E.): 30.5±4.4) years old and weighing 65–100 kg (85.5 ± 3.3)in two groups. The volunteers were fully informed of the nature of the study and the procedures involved. The participants did not suffer from any disease and were not on any medication at the time of the study. On the first day of the study, immediately, after taken the initial blood sample, each volunteer received a 50 mg single dose of selected F11 formula and Capoten® 50 mg tablets in a cross over manner. The respective dose of the drug was given with 150 mL of water and the participants were instructed to rinse the mouth during drinking.

Heparinized venous blood samples were drawn just before administration and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hr. thenplaced in dry stoppered glass tubes. Plasma was separated and frozen prior to assay for Captopril by HPLC. All volunteers fasted until 3 hrs. after drug administration. A washout period of 1 week was included between the administrations of each product. In the second phase, the test (F11) and reference Capoten® tabletswere crossed between the two groups of volunteers.

Drug Analysis:

Captopril plasma level was simultaneously determined by using an HPLC method (Amini*et al*., 1999) with slight modification in which Lorazepam (AmounPharmaceutical Co., Egypt) was used as internal standard. The method included 0.5 ml of plasma, 0.01 ml of internal standard (Lorazepam 20µg/ml), and 0.5 ml NaOH 1M. These components were mixed together in a 2.0 ml conical tube and vortexes (Vortex mixer, Medtronic, P-selecta, 246539, Switzerland) for 1 minute. The tube was cooled in a freezer (-75oC ± 5oC) (General Electric, 500 123,USA) for 1.5 minutes and then centrifuged at 1440g (Centrifuge Janetzk T30, Germany) for 12 minutes at room temperature (25oC). The supernatant was separated and injected into the chromatographic system (model HP 1100, Hewlett-Packard, Les, ULis,

UK). Captopril concentration was determined using analytical column LICHrospher 100RP18 (Sum Putiele size, 125 x 4 cm) and eluted with a mobile phase consisting of a mixture of 100% acetonitrile and 0.1% formic acid. The column temperature was 25oC. Flow rate was maintained at 1.0 ml/min and Captopril was detected by UV detector (Agilent Technologies) set at a wavelength of 209 nm. Typical retention times for Captopril and the internal standard were 5 and 4 minutes, respectively. Captopril peak areas were used for its quantification. Under these conditions, the method was linear in the range of 10 – 80 ng/ml (10, 20, 25, 50, 65 and 80 ng/ml).

Quality control (QC) samples were included in every analytical run (during both method of validation and analysis of the study samples) to verify performance.

Calculation of the pharmacokinetic Parameters and Statistical Analysis:

The pharmacokinetic parameters representing area under the curve from zero to infinity ($AUC_{0-\infty}$) was calculated using trapezoidal rule from the time interval 0 to the last measurable point, 12 hr. The maximum peak plasma concentration (C_{max}) and the time corresponding to maximum concentration (T_{max}) were determined from visual inspection of the concentration – time plots. The mean residence time (MRT) was calculated also.Relative bioavailability of bioadhesive Captopril tablet formulation (F11), compared to Capoten ® tablet, wascalculated according to the following equation:

Relative bioavailability % = {[AUC] T / $[AUC]_R$} X 100, where $[AUC]_T$ is the area under the curve for Captopril bioadhesive formulation (F11), and $[AUC]_R$ is the area under the curve for Capoten ® tablet.All the data represents the mean ± S.D. The differences were considered to be significant at a level of $p < 0.05$, using paired T test.

RESULTS AND DISCUSSION

Bioadhesive tablets of Captopril were developed in order to increase the gastric residence time of drug, so that they can be retained in stomach for longer time and help in controlled release of drug up to 12 hr. The tablets were prepared by direct compression method using different bioadhesive polymers such as carbopol 934, PVP K_{90} and sodium–carboxymethyl cellulose in different ratios

Evaluation of Bioadhesive Tablets:

The prepared bioadhesive tablets were evaluated for various physical parameters such as weight variation, hardness, friability, thickness, disintegration time and drug content. All formulations were produced under the same conditions to avoiding processing variables.The general appearance of tablets, its visual identity and overall “elegance” is essential for acceptability, the shape of all the formulation remained white, smooth, flat faced circular and no visible cracks. The hardness was in the range of 5 to 7 kg/cm^2, hardness value increases with increasing polymer ratio, this was significantly observed in F1, F2 and F3. Friability was in the range of 0.34 to 0.72% less than 1% indicates good mechanical strength to withstand the handling and transportations. Drug content was in the range of 97.24 % to 100.07 % and thickness was in the range of 5.3 to 5.8 mm. Weight of the prepared bioadhesive tablets were found to be in the range of 498 to 503 mg. The results are summarized in Table (2).

Table 2: Post compression properties of Captopril bioadhesive tablets.

Code	Weight (mg)*	Drug content (%) **	Hardness (Kg/cm_2) **	Friability (%) **	Disintegration time (min)**	Thickness (mm)*
F1	498 ± 2.52	97.24 ± 0.25	5.1 ± 0.15	0.42 ± 0.03	Swell	5.8 ± 0.05
F2	503 ± 2.08	100.07 ± 0.08	5.5 ± 0.06	0.39 ± 0.01	Swell	5.4 ± 0.06
F3	503 ± 1.53	99.37 ± 0.08	5.8 ± 0.06	0.36 ± 0.04	Swell	5.8 ± 0.01
F4	503 ± 1.53	98.06 ± 0.05	7.1 ± 0.10	0.62 ± 0.03	Swell	5.4 ± 0.05
F5	498 ± 3.61	100.04 ± 0.04	6.3 ± 0.15	0.65 ± 0.04	Swell	5.6 ± 0.06
F6	501 ± 2.08	98.70 ± 0.05	5.8 ± 0.06	0.72 ± 0.03	Swell	5.3 ± 0.05
F7	498 ± 3.51	97.24 ± 0.11	4.0 ± 0.10	0.47 ± 0.05	Swell	5.3 ± 0.08
F8	498 ± 1.53	99.49 ± 0.49	3.9 ± 0.10	0.55 ± 0.03	Swell	5.4 ± 0.05
F9	498 ± 2.89	98.41 ± 0.04	4.4 ± 0.10	0.34 ± 0.02	Swell	5.8 ± 0.01
F10	499 ± 1.53	97.35 ± 0.10	2.9 ± 0.10	0.65 ± 0.05	Swell	5.6 ± 0.03
F11	499 ± 3.51	99.90 ± 0.10	3.1 ± 0.10	0.55 ± 0.03	Swell	5.3 ± 0.08
F12	501 ± 3.06	99.12 ± 0.07	6.3 ± 015	0.42 ± 0.03	Swell	5.6 ± 0.06

All values are expressed as Average + SD, n (*) = 20, (**) = 03

SWELLING STUDY:

Swelling index was performed for all the formulations (F1-F12) up to 8 hrs. The results were shown in Table (3). It was found that swelling index are directly proportional to the concentration of the polymer used, as the polymer concentration increases there is increase in swelling index except with formulations containing PVP k_{90}. As formulations prepared with high concentrations of PVP showed less swelling index between all prepared formulae.The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer was not very strong. The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface. It was observed also that the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as adhesion property. When the tablets were examined for their swelling behavior F2, F3, F9, F11 formulations swelled more than 80% increase in the volume within 4th and F11 provides the highest swelling ratio with a 90% in dist. water at the end of the 4th while F6 shows the lowest swelling ratio with 42% in dist. water after four hours. Graphicalrepresentation swelling index of all the batches were shown in Fig.(2).

Table 3: Swelling Index of bioadhesive tablets.

	Formula Code											
Time (hr.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	24	29	32	14	10	9	17	19	24	20	35	23
2	43	55	60	23	20	18	39	52	59	41	69	45
4	67	82	89	48	45	42	69	73	88	76	90	65
6	126	137	145	91	88	75	80	94	110	127	151	105
8	181	206	220	116	105	94	133	121	180	185	236	145

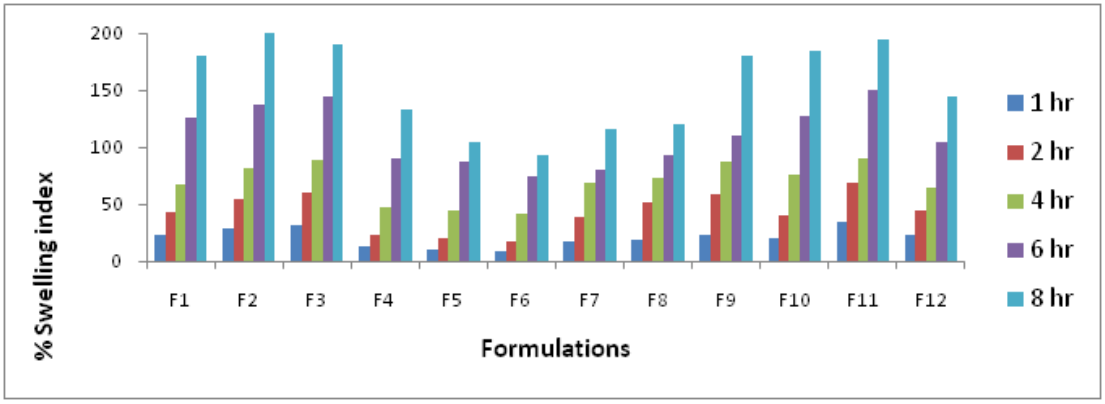

Fig. 2: Swelling index of Captopril bioadhesive tablets F1-F12.

Matrix Erosion:

The matrix erosion of formula which contains Carbopol 934: CMC-Na (F11) as bioadhesive polymers was found to exhibit least matrix erosion 8.1 %. This is because the presence of water that balanced the weight loss due to erosion (Fig.3).

Table 4: Matrix Erosion of Bioadhesive Tablet of Captopril.

Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Matrix Erosion (%)	10.02	9.25	8.30	12.40	12.95	13.30	11.05	11.15	8.90	9.60	8.10	9.85

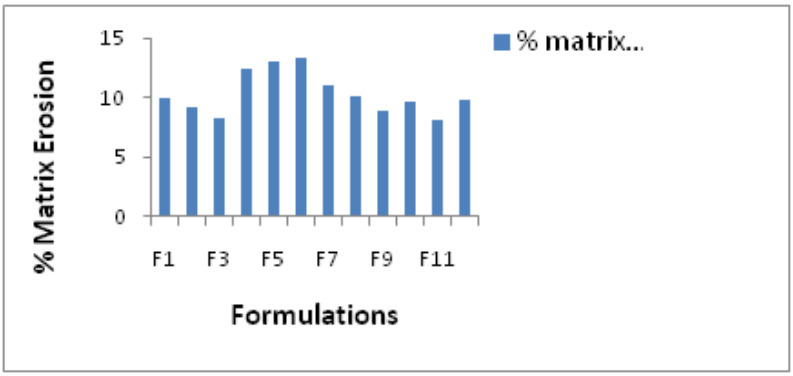

Fig. 3: Matrix Erosion of Bioadhesive Tablet of Captopril.

Surface pH:

The surface pH was determined in order to investigate the possibility of any side effects, in the gastrointestinal tract as acidic or alkaline pH was bound to cause irritation to the gastric mucosa. Surface pH of all formulations was found to be in the range of 3.3 to 4.5 so it was assumed that these formulations do not cause any irritation to the mucosal membrane(Table 5).

In vitro Bioadhesion strength:

The bioadhesive tendency could be an important property for gastroretentive drug delivery. The bioadhesion of all the Captopril tablets of varying ratios of polymers were tested and the force required to pull off the formulation from the mucous tissue was recorded as bioadhesion strength in (dyne/cm^2). The bioadhesion strength was found to be maximum in case of formulation F11, F3, F10, F2 and F1 i.e. 14358.52, 13163.42, 12121.91, 10800.33 and 9450.85 dyne/cm^2 respectively. This may be due to the fact that positive charges on surface of carbopol could give rise to strong electrostatic interaction with negatively charged mucus membrane (Vaishali*et al*., 2014).As the bioadhesion was mainly due to the bioadhesive nature of the polymer used, it was found from data in Table 5 that the bioadhesion strength for tablet formulae containing PVP are directly decreased with the increase in the polymer ratio in the tablet formula. F6 showed lowest bioadhesion at all. Carbopol 934 and CMC-Na is employed in bioadhesive formulations and delivery systems, when they were used together in F11 formula, the bioadhesive strength of the tablet reached the highest adhesion forces to rabbit stomach mucosa.

Table 5: Surface pH and in-vitro bioadhesion strength exhibited by different formulation of Captopril tablets.

Code	Surface pH *Avg ± S.D	Bioadhesion strength (dyne/cm^2) *Avg ± S.D
F1	3.3 ± 0.1	9450.85 ± 312.3
F2	3.5 ± 0.06	10800.33 ± 746.5
F3	3.6 ± 0.10	13163.42 ± 690.3
F4	3.8 ± 0.06	4362.49 ± 217.2
F5	4.1 ± 0.15	2717.05 ± 161.6
F6	4.5 ± 0.06	1677.96 ± 128.3
F7	3.4 ± 0.10	2432.95 ± 287.2
F8	3.6 ± 0.10	4823.45 ± 145.6
F9	3.6 ± 0.10	6670.52 ± 115.2
F10	3.4 ± 0.10	12121.91 ± 74.7
F11	3.9 ± 0.15	14358.52 ± 377.9
F12	4.2 ± 0.10	8798.53 ± 143.4

Each reading is an average of three determinations

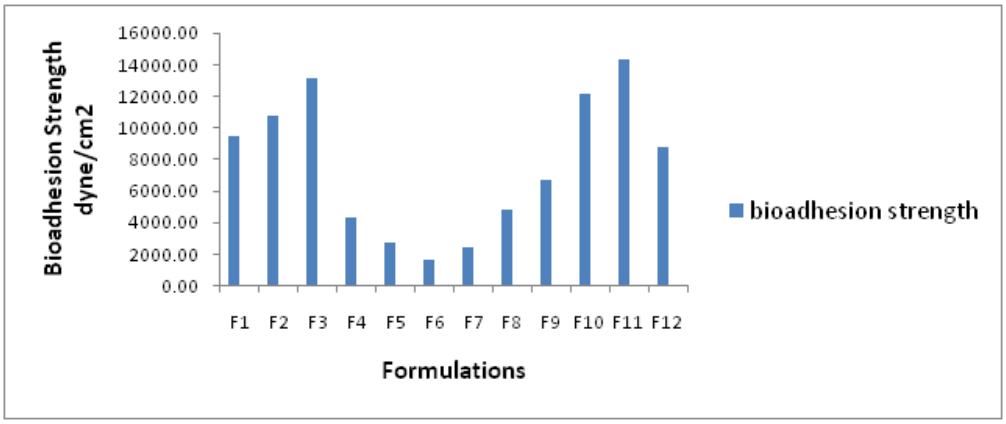

Fig. 4: *In vitro* bioadhesion strength exhibited by different formulation of Captopril tablets.

In vitro drug release study

In vitro dissolution studies of all the formulations of bioadhesive tablets were carried out in 0.1N HCl (pH 1.2). The study was performed for 12 hrs. The variation in drug release was due to different concentrations of polymer in all the 12 formulations. When % drug release was plotted versus time (Figs. 5& 6), it was observed that the increase in polymer concentration usually accompanied by decrease in the release rate. This might be due to increase in diffusional path length, which the drug molecule may have to travel and also it might attributed to the different diffusion and swelling behavior of the polymer. Among all the formulations, batch F11 showing greater drug release 97.25% at the end of 12 hour also it showing better Bioadhesive property thus it was considered as an optimized formulation.

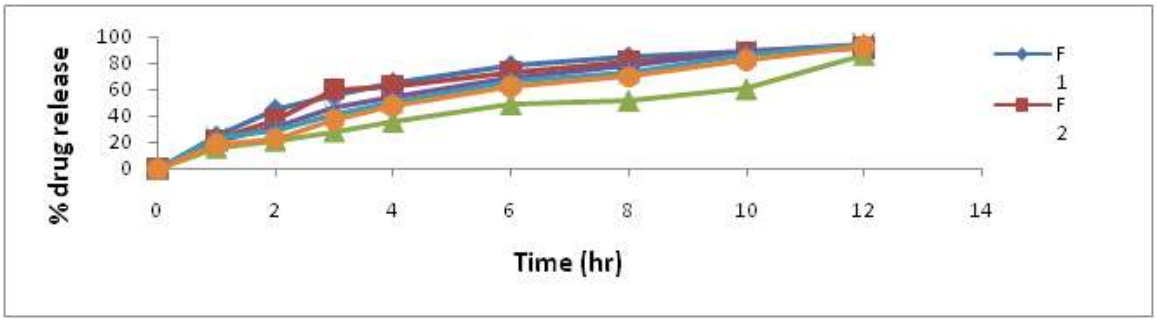

Fig. 5: Dissolution profile of Captopril bioadhesive tablets formulations (F1-F6).

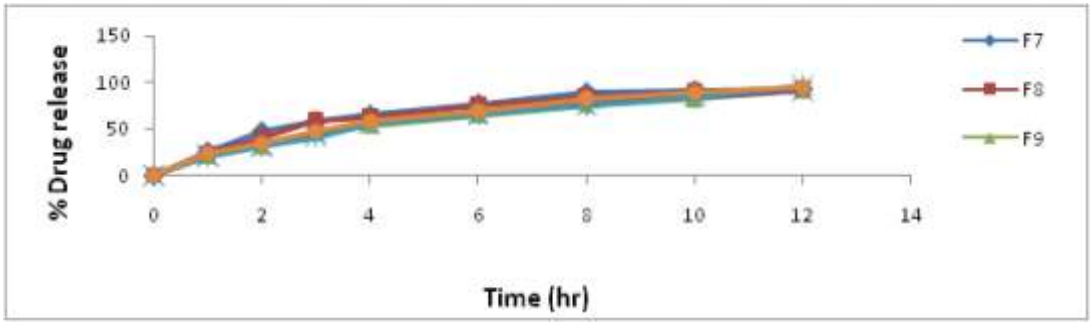

Fig. 6: Dissolution profile of Captopril bioadhesive tablets formulations (F7-F12)

Drug release kinetics (Curve fitting analysis).

The drug release data were fitted to models representing zero order (cumulative amount of drug released vs. time), first order (log percentage of drug unreleased vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), and Korsmeyer's equation (log cumulative percentage of drug released vs. time) kinetics to know the release mechanisms. All the formulations in this investigation could be best expressed by Higuchi's classical diffusion equation, as the plots showed high linearity (R2:0.979861 to 0.998628) indicates that the drug release follows diffusion mechanism. To confirm the diffusion mechanism, the data were fitted into Korsmeyer–Peppas equation. All the formulations showed(n) values ranging from 0.843675 to 0.925339, indicating that non-Fickian/anomalous diffusion (If the exponent n=0.5, then the drug release follows the Fickian diffusion, and if 0.5< n <1, then it is said to be non-Fickian or anomalous release). The results wereshown in Table (6).

Table 6: Kinetic values obtained from different plots of formulations F1 to F12.

Formulation Code	Zero order plots?	First order plots*	Higuchi's plots?	Korsmeyer et al's plots **	
	R^2	R^2	R^2	R^2	Slope (n)
F1	0.930243	- 0.974898	0.99747	0.851898	0.925339
F2	0.925378	-0.968597	0.99372	0.85469	0.914156
F3	0.90684	- 0.965711	0.979861	0.87275	0.843675
F4	0.976181	-0.98953	0.996678	0.853461	0.921385
F5	0.98929	-0.97454	0.996361	0.855357	0.914603
F6	0.987405	-0.97122	0.994847	0.857665	0.906051
F7	0.928362	-0.972969	0.99068	0.851898	0.925339
F8	0.932108	-0.975015	0.99374	0.85297	0.919711
F9	0.975121	-0.98963	0.995991	0.859328	0.898194
F10	0.967283	-0.992422	0.99577	0.856387	0.909051
F11	0.982561	-0.93783	0.996668	0.854875	0.919388
F12	0.970031	-0.99348	0.998628	0.852798	0.923987

?Zero order equation, $C=K_0 t$, *First order equation, Log C=logC-Kt/2.303, ●Higuchi's equation, Q= Kt½, **Korsmeyer et al's equation, $Mt/M \alpha Kt^n$.

PHARMACOKINETIC ANALYSIS

Captopril was measurable in plasma at the first sampling time (30 min) in all six subjects after administration of the test and reference formulations. The mean plasma Captopril concentrations versus time for the 2 formulations are depicted in Fig.(7). Table (7)displays the pharmacokinetic parameters obtained for the reference and test formulations for Captopril. The mean values for C_{max}, T_{max}, and $AUC_{0-\infty}$ with the test formulation of Captopril were 303.78ng/mL, 4 h and1991.63 ng/mL.hrespectively; for reference, the values were 360.05ng/mL, 1.5 h and 725.50ng/mL.h.The area under the plasma concentration versus time curve AUC_{0-t} was calculated by the linear trapezoidal method. The AUC_{0-t} was extrapolated to infinity ($AUC_{0-\infty}$)by adding the equation of C_{last}/K_e, where Clast represents the last measured concentration. The MRT was calculated by the ratio of AUMC/ $AUC_{0-\infty}$ where AUMC is the area under the first moment curve (Shannon,2000).

There was a significant difference between F11 formulated tablets and Capoten® tablet in both C_{max} and T_{max} which both represent the absorption rate. Capoten ® tablets have shown the highest C_{max} and the shortest T_{max} values. F 11 tablets had a significantly higher MRT values than reference indicating more sustained drug release ability of such formula for oral controlled release systems.

Table 7: Pharmacokinetic parameters for F11 tablets and reference Capoten®50 mg tablet.

Pharmacokinetic parameters	F 11	Capoten ®50mg
C_{max} (ng/ml)	303.78 ± 61.11	360.05 ± 94.35
*T_{max}(hr.)	4 hr. ± 0.6	1.5 hr. ± 0.4
$AUC_{0-?}$ (ng.hr/ml)	1991.63 ± 4.5	725.50 ± 6.5
MRT (hr.)	5 ± 1.2	3.6 ± 0.8
Bioavailability %	------	103.30

Each data representing the mean ± S.D (n=6)
*Significant difference between F11 tablets and Capoten® 50 mg tablets at P<0.05.

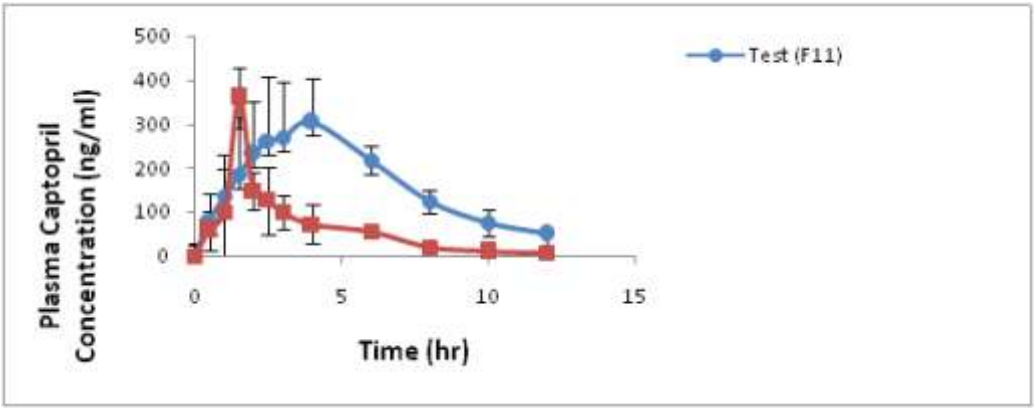

Fig. 7: Plasma Captopril concentrations against time for F-11 tablets and reference Capoten ® tablet. Each data represents mean ± S.D. (n=6).

CONCLUSION

From the present study, the following conclusions can be drawn: Bioadhesivegastroretentive tablets of Captopril can be prepared by direct compression method using CMC- Sodium, PVP K_{90} and carbopol 934 as bioadhesive polymers in different ratios. All the prepared tablet formulations were found to be good without capping and chipping. Tablets were subjected to various evaluation parameters such as Weight variation, Hardness, Friability, Drug content, swelling index, *in vitro* drug release study, *in vitro* bioadhesive strength study. It was revealed that tablets of all batches had acceptable physical parameters.

It was found that increase in the polymer concentration will increase swelling index, bioadhesive strength but decrease drug release. Tablets of batch F11 combination of CMC- Sodium and carbopol 934 have better *in vitro* drug release after 12 hrs. than the other formulations, and also showing good bioadhesive strength. The drug release kineticsfollows Higuchi model and the mechanism was found to be non Fickian/anomalous.Finally, comparing the selected formula F11 to the

commercially available Captopril product has revealed that the test formula had better in vivo sustaining effects that the reference.

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