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**Original Article**

# Design and evaluation of a Sustained Release Gastroretentive Dosage form of Captopril

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Sustained drug delivery system, Tablet, Captopril, HPMC, Gastro-intestinal tract, Bioavailability

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**Abstract:** Sustained drug delivery means not only prolonged duration of drug delivery but also implies predictability and reproducibility of drug release kinetics. In the present study gastroretentive dosage form (tablet) was selected as a method to design sustained release dosage forms because it is a rapidly expanding technology. The objective of the work was to design sustained release tablets of Captopril as gastroretentive drug delivery dosage form of a drug meant for management of treat high blood pressure (hypertension), congestive heart failure, kidney problems caused by diabetes, and to improve survival after a heart attack. Formulation of gastroretentive drug delivery dosage forms are done based on optimization under factorial design of formula and classed formulation batches in which concentration of polymer HPMC of various grades (HPMC K15 M, HPMC K100M and HPMC K4M) varied with the ration of sodium bi carbonate and microcrystalline cellulose. Therefore, the Aim of the present work is design to formulate and evaluate gastroretentive dosage form (tablets) of Captopril for efficient sustained release after oral administration in case of congestive heart failure, kidney problems caused by diabetes.

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## Introduction

Sustained drug delivery means not only prolonged duration of drug delivery but also implies predictability and reproducibility of drug release kinetics. Sustained release dosage forms are gaining increased acceptance over conventional dosage forms in the treatment of several acute and chronic conditions. In addition to better patient compliance, they reduce the incidence and severity of side effects. They have proved particularly valuable in ensuring continuous therapeutic-c effects in the treatment of arthritis, angina pectoris, and hypertension etc. [1-3]

The objective of the work was to design sustained release tablets as gastroretentive drug delivery dosage form of Captopril. The drug is considered as a drug of choice for the treatment of hypertension and congestive heart failure. The bioavailability of captopril is approximately 60-75% and it has elimination half-life after an oral dose is 2-3 h. It is stable at acidic pH (1.2) and is specifically absorbed from the stomach. As the pH increases, the drug becomes unstable and undergoes a pseudo first order degradation reaction. There is a strong prerequisite to localize the developed captopril formulation at the target area of the gastrointestinal tract.

To overcome the above drawbacks the present study is aimed at developing a floating dosage form to be remained buoyant in the stomach, thereby, increasing the gastric residence time, stability, patient's compliance and enhancing the bioavailability of drug through sustained release. [4-8]

## Materials and Methods

### Materials

Captopril was obtained as a gift sample from Torent Pharmaceutical Pvt. limited, Ahmedabad, HPMC (All Grades), Sodium bicarbonate, Citric acid, Microcrystalline cellulose, Magnesium stearate, Talc were obtained from Loba Chemical Pvt. limited, Mumbai. All other ingredients obtained were of Pharmaceutical Grade.

### Methods

### Conformation and authentication of Drug [9-11]

### Infrared spectroscopy:

Infrared spectrum of any compound given information about the functional group present in the compound. An Infrared spectrum of drug was taken using KBr pellet method. Various peaks in IR spectrum were interpreted for presence of different group in the structure of drug. The IR spectrum was recorded on Shimadzu 8400-S FTIR spectrophotometer Japan.

### Ultra-Violet (UV) spectroscopy

Organic molecules when exposed to light in UV region they absorb light of wavelength depending on the type of electron transition associated with the absorption. The absorption maximum of drug was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.10 mg of drug was weighed accurately and dissolved in 10 ml of 0.1 N HCL in 10 ml of volumetric flask and suitable stock solution was prepared. The spectrum of this stock solution was run in 200-400 nm range in ultra-visible Spectrophotometer (Shimadzu 1700, Japan).

### Quantitative estimation

### Calibration curve in 0.1 N HCl

10 mg drug was weighed accurately and transferred to 10 ml volumetric flask. Drug was dissolved in sufficient quantity of *0.1 N* HCl and volume up to 10 ml was done with *0.1 N* HCl. Thus, the stock solution of drug in *0.1 N* HCl was prepared.

### Preparation of standard calibration curve of Captopril in 0.1 N HCL

From above stock solution, various dilutions were prepared to get concentration, 5-50 g/ml. The graph of concentration v/s peak area was plotted and data was subjected to linear regression analysis on the maximum absorbance ($\lambda_{max}$) 203nm.

### Drug-Excipient interaction [9]

Compatibility of the drug with excipients was determined by differential scanning calorimetry (DSC) analysis. This study was carried out to detect any change on chemical constitution of the drug after combination with the excipients in the ration (1:1).

### Preparation of Gastroretentive Dosage form [12-16]

For the preparation of Gastroretentive tablets of captopril**,** wet granulation method was adopted. The formulation composition of different batch is shown in **table 2**. All the powders passed through 40 mesh sieve. The required quantity of captopril, fillers and other ingredients were mixed thoroughly. Magnesium stearate and talc were finally added as a lubricant and glidant respectively. The dry blends were tested for various pre-compression parameters like bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio etc. Wet granulation method was used for the preparation of tablets. Accurately measured quantities of drug and excipients were taken as shown in **Table 1**. Isopropyl alcohol (IPA) was used as granulating mixture of drug and excipients were taken for granulation.

IPA was added until wet mass was formed and passed through 20# to get the required granules, Granules formed through wet granulation were dried in oven till the moisture content was below 1%. Then the above dried granules were taken in to 'v' cone blender and magnesium state and talc was added to it and blend for 15 min. The tablets were punched using Rotary compression machine of 8 mm concave-face round tooling. Compression force was adjusted to obtain tablets of hardness 4-6 kg/cm$^2$.

**Table 1 Formula for gastroretentive tablet**

| Ingredients (mg) | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Captopril | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| HPMC K15 M | 100 | 100 | 100 | - | - | - | - | - | - |
| HPMC K100M | - | - | - | 100 | 100 | 100 | - | - | - |
| HPMC K4M | - | - | - | - | - | - | 100 | 100 | 100 |
| Sodium bicarbonate | 15 | 30 | 45 | 15 | 30 | 45 | 15 | 30 | 45 |
| Citric acid | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Microcrystalline cellulose | 80 | 65 | 50 | 80 | 65 | 50 | 80 | 65 | 50 |
| 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** | **255** | **255** | **255** | **255** | **255** | **255** | **255** | **255** | **255** |

**Evaluation of pre-compression parameters of dry blend powders** [17-22]

**Bulk density (g/cm$^3$)**

To measure bulk density, the powder blend was filled in a 100ml capacity measuring cylinder up to at least 1/4$^{th}$ height and tapped for 3-4 times. Bulk density is the quotient of weight to the volume of the sample. It is usually expressed in (g/cm$^3$).

$$\text{Bulk density} = (M) / (Vo)$$

Where M = mass of the power blend, Vo = Volume of the power blend

**Tapped density (g/cm$^3$)**

To measure Tapped density, the powder blend was filled in a 100ml capacity graduated measuring cylinder up to at least 1/4$^{th}$ height as filled to determine the bulk density. As tapped density is the quotient of weight of the sample to the volume and it is usually measure after taping a measuring cylinder at least upto 1000 times from a height of ~ 1.5 inch. It is also expressed in (g/cm$^3$). It was the resultant of three successive experiments.

$$\text{Tapped density} = (M) / (Vt)$$

Where M = mass of the power blend, Vt = Tapped volume of the power blend

**Angle of repose**

The friction force in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It can be defined as the maximum angle possible among the surface of the powder heap and the straight plane. Angle of repose is establishing by use funnel method. A funnel was kept upright in a stand at a height above a paper located on a straight plane. The funnel underneath is blocked and 10 gm of sample powder is crammed in funnel. Then funnel be opened to release the powder on the paper to form a smooth conical heap. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula;

$$\tan Ø = h/r \; ; \; Ø = \tan^{-1} h/r$$

Where, h- height of the heap and r- Radius of the heap

**Powder compressibility**

It designates powder flow characteristics. The Hausner's ratio and compressibility index are deals with the flow behavior of powder to be compressed. It represents the relative importance of inter particulate interactions among the powder. In case of free-flowing powder, such behavior is generally less and tapped densities will be very closer in assessment. For poor flowing characteristics, there are often greater inter particle interactions, and a greater variation between bulk and tapped densities will be observed.

**a. Carr's index (or) % compressibility**

It signifies powder flow properties. It is expressed in percentage and is give

$$I = 100 \times (D_t - D_b) / D_t$$

Where, $D_t$ is the tapped density of the powder and $D_b$ is the bulk density of the powder

**b. Hausner's ratio**

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula:

$$\text{Hausner's ratio} = D_t / D_b$$

Where, $D_t$ is the tapped density, $D_b$ is the bulk density

**Evaluation of Gastroretentive Tablets**

Evaluation was performed to assess the physiochemical properties and release characteristics of developed formulation.

**Hardness**

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

**Friability**

Roche friabilator was used for testing the friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

**Weight variation**

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. Deviation should not exceed the values given in **table 2**.

**Table 2: Standard limit value in weight variation test**

| Average weight of a tablet | Percentage Deviation |
|---|---|
| 80 mg or less | ±10 |
| >80 and <250mg | ±7.5 |
| 250mg or more | ±5 |

**Drug content**

Ten tablets were weighed and powdered and 255 mg equivalent weight of captopril was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with 0.1N HCL pH 1.2. Subsequently the solution in volumetric flask was filtered and suitable dilutions were made and analyzed at 203 nm using UV-Visible spectrophotometer. The drug content of each sample was estimated from standard curve of drug using 0.1N HCl, pH 1.2.

**Floating lag time and floating duration**

Floating lag time is the time required by tablets to emerge at the surface when introduced in the dissolution medium and floating duration is the duration for which it remained buoyant. It was determined using a 0.1 N HCl filled (250 ml) in glass beaker.

***In-vitro* floating studies**

The *in-vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP dissolution apparatus type-II (basket) using 900 ml of 0.1 N HCl buffer solution at 100 rpm at 37±0.5°C. The time required for the formulation to rise to the surface of the dissolution medium and the duration for which the formulation constantly floated on the dissolution medium were noted as floating lag time and total time, respectively.

***In-vitro* buoyancy studies**

To study the *in-vitro* buoyancy, an effervescent approach was adopted. Sodium bicarbonate was added as a gas-generating agent. As the dissolution medium (0.1 N HCl) got imbibed into the tablet matrix, the acidic fluid interacted with Sodium bicarbonate resulting in the generation of $CO_2$. The generated gas was entrapped and protected within the gel, formed by the hydration of polymer and gum acacia, and thereby decreased the density of the tablet. As the density of the tablet fell below 1g/ml, the tablet became buoyant. Tablets containing HPMC shows good gel strength, entrapping $CO_2$ gas within and thereby imparting stable and persistent buoyancy. The system need to float in a few minutes after contact with gastric fluid, to prevent the dosage form from being pushed into the small intestine together with food. The higher amount of effervescent agent caused faster and higher $CO_2$ generation. Thus, Sodium bicarbonate was essential to achieve optimum buoyancy. In general, gastric emptying time was 4 h. Moreover, during formation of the floating tablets, evolving gas permeated through the matrix leaving gas bubbles or pores, which also increased the release rate of the active ingredient from the matrix. The amount of sodium bicarbonate also played an important role in floating lag time of tablets, the higher the amount the lesser the floating lag time, and *vice versa*.

**Water uptake studies**

The swelling of the polymers was measured by their ability to absorb water and swell. The water uptake study of the tablet was done using a USP dissolution apparatus type-II (basket) in 900 ml of pH 1.2 Hydrochloric acid buffer at 100 rpm. The medium was maintained at 37±0.5°C throughout the study. At regular time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as:

$$WU\ (\%) = \frac{\text{Weight of Swollen tablet- Initial weight of tablet}}{\text{Initial weight of tablet}} X\ 100$$

The swelling of the polymers used could be determined by water uptake of the tablet. The percent swelling of the tablet was determined at different time intervals. The complete swelling was achieved by the end of 8 h, so percent swelling was determined at the end of 8 h for all the developed formulations.

***In-vitro* release profile**

Release of the prepared tablets was determined up to 12 hrs. using U.S.P. II (type II) dissolution rate test apparatus. Nine hundred ml of 0.1 N HCl was used as dissolution medium. The rotation of paddle was fixed at 75 r.p.m. and the temperature of 37+0.5ºC was maintained throughout the experiment. Samples of 1 ml were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analyzed spectrophotometrically for drug contents on double beam UV/Visible spectrophotometer at λ max 203 nm. The results in the form of percent cumulative drug released.

**Mathematical model fitting of obtained drug release data**

The *in vitro* drug dissolution profiles were fitted to various models and release data was analyzed based on Korsmeyer-Peppas equation and Higuchi kinetics.

**RESULT AND DISCUSSION**

**Conformation and authentication of drug**

**Infrared spectroscopy:**

Identification and authentication of drug sample was done by infrared spectroscopy. The IR spectra showed the presence of principal groups like at 3398 $cm^{-1}$ OH stretching, 3104 C-C stretching; 3006 $cm^{-1}$ C-H stretching, 1707 $cm^{-1}$ C=O stretching and 1136 $cm^{-1}$ SH Bending. The principal groups of infrared spectroscopy showed that the drug sample was authentic.

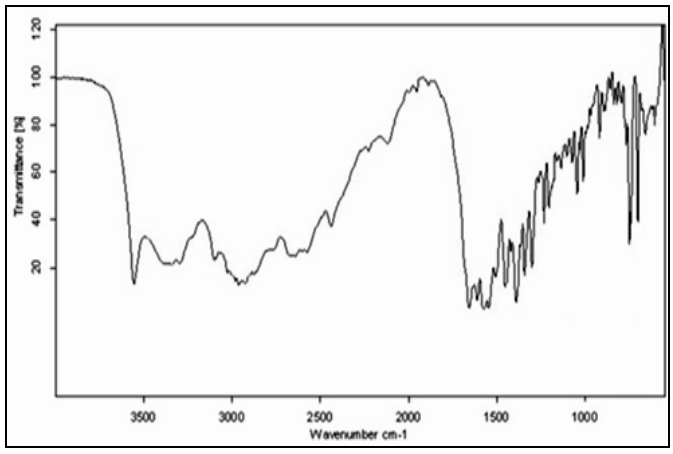


**Figure 1: Infrared spectrum of Drug sample**

**Table 3: Characteristic IR peaks of drug**

| S. No. | Wave Number ($cm^1$) | Characteristic absorption |
|---|---|---|
| 1. | 3398 | OH stretching |
| 2. | 3104 | C-C stretching |
| 3. | 3006 | C-H stretching |
| 4. | 1707 | C=O stretching |
| 5. | 1136 | SH Bending |

**Ultra-Violet (UV) spectroscopy**

Identification and authentication of drug sample was done by ultraviolet spectroscopy and it was scanned in the range of 200-400 nm. Drug absorption maximum $\lambda_{max}$ was found to be at 203 nm in 0.1 N HCl. Absorption maximum showed that drug sample was authenticated.

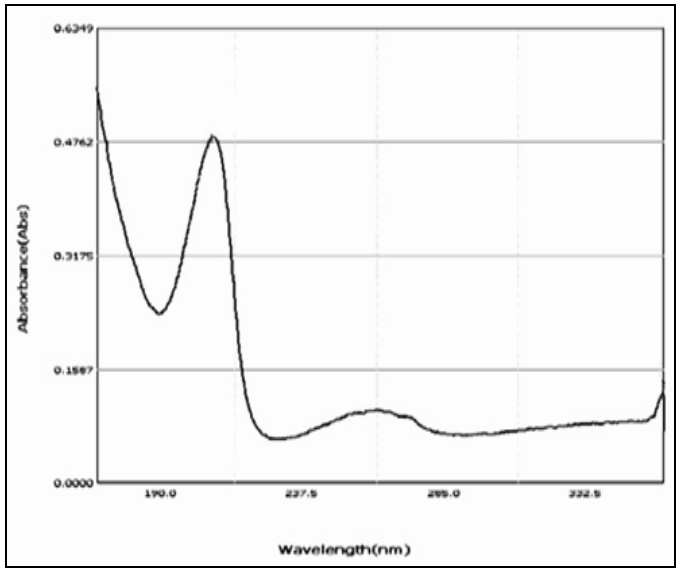


**Figure 2: Absorption maximum of drug sample**

**Quantitative estimation**

Quantitative estimation of drug sample was done by different calibration curves which were prepared in *0.1N* HCl, phosphate buffer solution pH 6.8 in concentration range of 5-50 g/ml and the $R^2$ value was found to be 0.9979 and 0.9991 respectively which indicated the linearity of the graph.

**Calibration curve in 0.1N HCl**

**Table 4: Calibration curve of drug in *0.1N HCl***

| S. No. | Concentration ( g/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.114 |
| 3 | 10 | 0.210 |
| 4 | 15 | 0.318 |
| 5 | 20 | 0.431 |
| 6 | 25 | 0.510 |
| 7 | 30 | 0.620 |
| 8 | 35 | 0.711 |
| 9 | 40 | 0.826 |
| 10 | 45 | 0.900 |
| 11 | 50 | 0.972 |

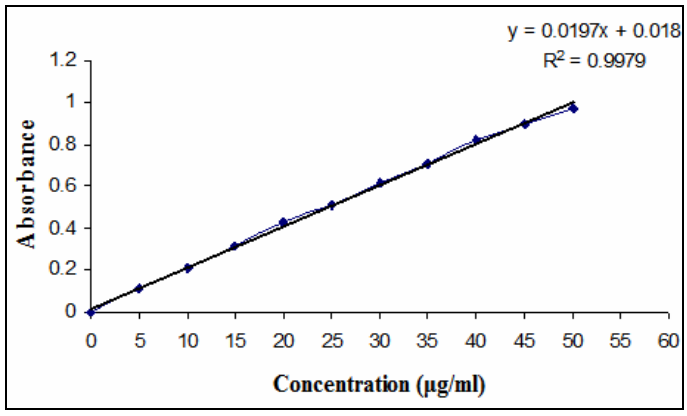


**Figure 3: Standard curve of drug in *0.1N HCl***

**Compatibility studies**

**Drug Excipients Interaction**

DSC thermogram showed endothermic and exothermic peaks. Drug and polymer displayed their characteristic individual melting trends without any appreciable deviation. From this it is observed that there is no interaction between drug and polymer. The compatibility study was also done by physical observation and observing the results of drug-excipients compatibility study (physical), it was concluded that there is no incompatibility between drug and selected excipients. Hence, the excipients selected can be used with drug as they are compatible with each other.

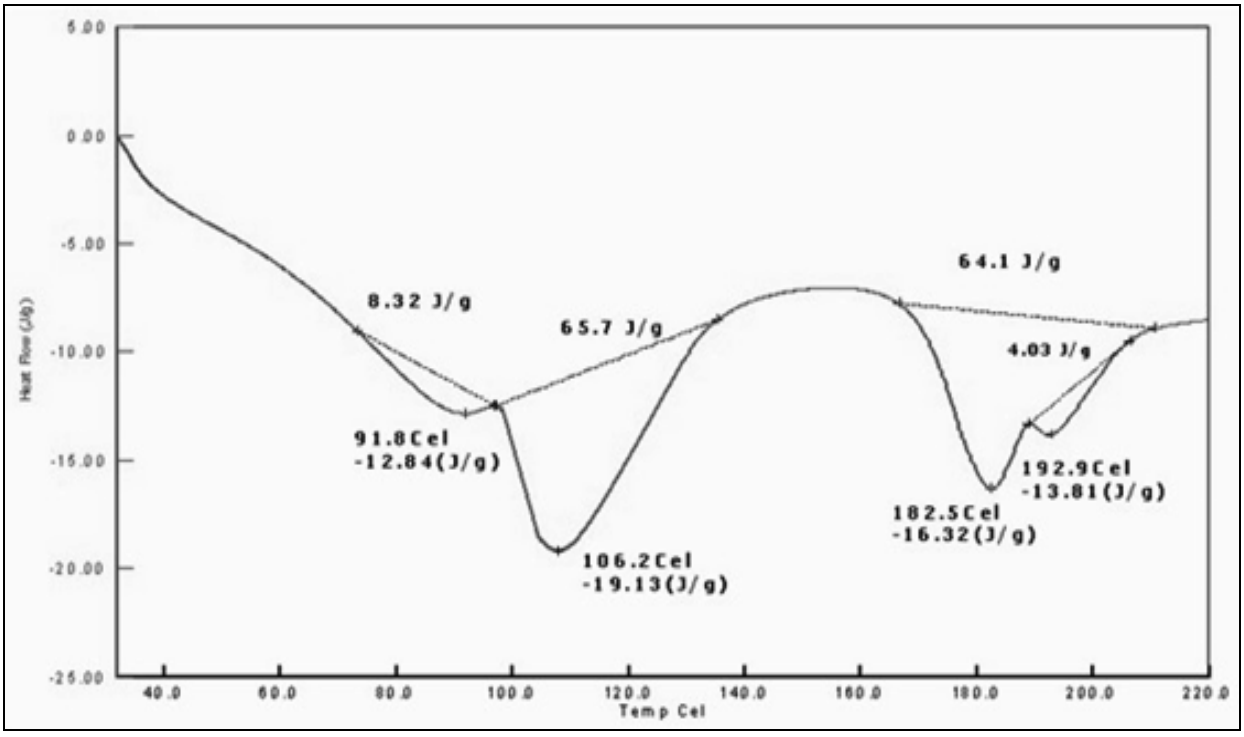


**Figure 4: DSC Thermogram of drug sample**

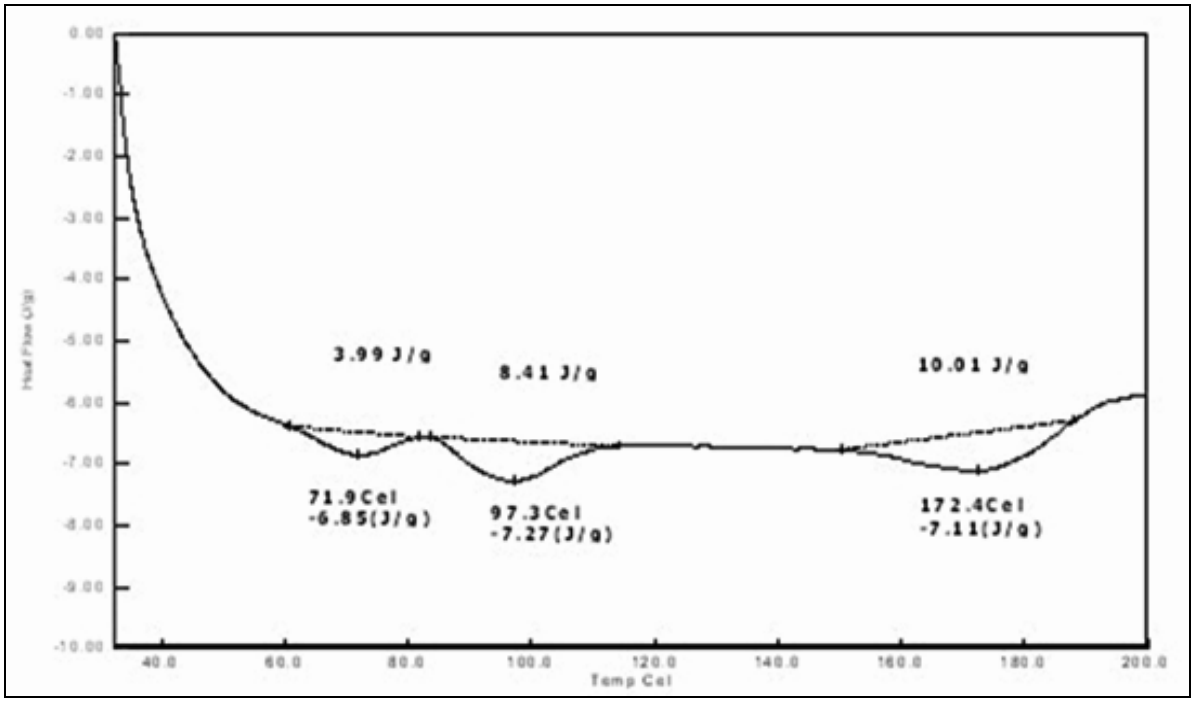


**Figure 5: DSC Thermogram of drug sample with HPMC Polymer**

The present study was carried out to perform the preformulation study of captopril pure drug. Organoleptic properties study, solubility study, identification and authentication of drug, partition coefficient, quantitative estimation of drug and compatibility study were carried out during preformulation study. Organoleptic properties study was carried out by physical observation. The IR spectroscopy, melting point and UV spectroscopy were performed for the identification of drug. Solubility analysis was done in different projected solvents. Partition coefficient was determined by using shake flask method. Quantitative estimation of drug was carried out by calibration curve in different solvents. Based on preformulation study it was concluded that the drug sample was found to be pure and authentic and there was no variation found in the drug sample and the drug was found to be suitable for the further formulation and optimization study.

**Evaluation of pre-compression parameters of dry blend powders of captopril tablet formulations**

Based on result revealed from experimented data pre-compression study for all formulation batches following crucial factors like: angle of repose **(θ)** was in the range of $23\text{-}26^0$ shows excellent flow behavior; Bulk and tapped density were found in the range of 0.41 to 0.54 gm/ml and 0.44 to 0.56 gm/ml respectively. Carr's index were studied and found in range of 14.15 to 16.29 %showing good flowability but needs some flow promoters. Values of Hausner's ratio shows good flowability.

**Table 5: Micrometric study of dry blend powders of gastroretentive tablets**

| Formula code | Angle of repose (θ) | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index % | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | 23.50±1.41 | 0.4717±0.014 | 0.5124±0.052 | 15.15±0.87 | 1.08 ±0.12 |
| **F2** | 23.62±1.42 | 0.4218±0.033 | 0.5633±0.027 | 14.15±0.79 | 1.33±0.13 |
| **F3** | 25.32±1.51 | 0.4314±0.031 | 0.5491±0.047 | 16.29±1.32 | 1.25±0.23 |
| **F4** | 25.03±1.25 | 0.4653±0.026 | 0.5547±0.053 | 15.81±0.43 | 1.19±0.45 |
| **F5** | 24.07±1.51 | 0.4252±0.052 | 0.5156±0.045 | 15.43±0.41 | 1.21±0.24 |
| **F6** | 25.30±1.08 | 0.4537±0.042 | 0.5502±0.010 | 17.53±1.37 | 1.21±0.42 |
| **F7** | 24.03±1.25 | 0.4129±0.062 | 0.4457±0.035 | 15.81±0.43 | 1.08±0.56 |
| **F8** | 25.07±1.25 | 0.4652±0.042 | 0.5156±0.045 | 15.43±0.41 | 1.11±0.16 |
| **F9** | 26.30±1.31 | 0.5437±0.025 | 0.5502±0.010 | 14.59±1.37 | 1.01±0.42 |

All values are mean of three readings ± standard deviation

**Evaluation of Gastro-Retentive tablets**

Formulation of gastroretentive drug delivery dosage forms are done based on optimization under factorial design of formula and classed formulation batches as F1-F9 in which concentration of polymer HPMC of various grades (HPMC K15 M, HPMC K100M and HPMC K4M) varied with the ration of sodium bi carbonate and microcrystalline cellulose.

After pre-compression test the powder blend was compressed into tablets and it was evaluated based on post-compression analysis for various factors which includes hardness, friability, weight variation, dispersion time, *in-vitro* drug release after dispersion, wetting time, disintegration time, drug content and drug release.

Hardness was measured using Monsanto tablet hardness tester and it was found to be in range for batches F1-F9, 4.6±18 to 6.5 ± 0.72 Kg/cm$^2$ which showed that tablet could maintain its physical integrity up to ultimate user.

Friability was determined using Roche friabilator and it was found to be 0.20 to 0.78 ± 0.34% which indicates that tablet possess sufficient mechanical strength which can resist the shock and abrasion and maintain its physical integrity.

Weight variation was determined using twenty tablets and it was found to be 2.5% indicate content uniformity and showed that there was minimum variation in weight of the prepared tablets.

Drug content of formulation was determined and tablet showed drug content 98.33 ± 0.67% indicating the content uniformity and homogeneity in preparation.

Floating lag time was found to be between 35-98 seconds indicates that the tablets can be delay release the drug which can be then available for dissolution.

Maximum swelling percentage ranges between 223-425% which can be utilize for extended release property from formulated tablets.

**Table 6: Evaluation of formulated gastroretentive tablets**

| Batch | Weight Variation | Hardness* (Kg) | Friability * (%) | Content Uniformity* | Thickness* (mm) | Floating lag* | Max swelling* |
|---|---|---|---|---|---|---|---|
| **F1** | 255.25± 0.83 | 4.6±0.18 | 0.57±0.17 | 99.35±0.93 | 4.0±0.48 | 62±1.3 | 316±6.5 |
| **F2** | 255.76± 0.19 | 6.1±0.30 | 0.34±0.37 | 98.45±0.53 | 4.1±0.56 | 66±2.2 | 226±5.9 |
| **F3** | 255.78± 0.64 | 5.5±0.62 | 0.30±0.06 | 99.21±0.76 | 4.1±0.68 | 90±1.7 | 223±4.6 |
| **F4** | 255.39± 0.36 | 5.8±0.23 | 0.38±0.34 | 96.53±0.36 | 4.1±0.77 | 35±1.5 | 325±5.8 |
| **F5** | 255.38± 0.59 | 4.8±0.64 | 0.55±0.86 | 100.01±0.64 | 4.0±0.68 | 89±1.6 | 265±8.6 |
| **F6** | 255.34± 0.49 | 4.6±0.76 | 0.59±0.76 | 101.03±0.52 | 4.2±0.59 | 95±2.7 | 311±9.5 |
| **F7** | 255.45± 0.19 | 5.1±0.30 | 0.54±0.37 | 98.45±0.53 | 4.5±0.56 | 86±2.2 | 296±5.9 |
| **F8** | 255.56± 0.84 | 6.5±0.72 | 0.20±0.06 | 98.21±0.76 | 4.9±0.68 | 98±1.7 | 263±4.6 |
| **F9** | 255.89± 0.16 | 5.9±0.25 | 0.78±0.34 | 97.53±0.36 | 4.3±0.77 | 55±1.5 | 425±5.8 |

All values are mean of 3 readings ± standard deviation

***In vitro* floating studies and *in vitro* buoyancy studies**

*In-vitro* buoyancy test shows onset of floating ranges between 27-92 seconds and duration of floating ranges between 16-24 hrs Sodium bicarbonate was essential to achieve optimum buoyancy. In general, gastric emptying time was 4 h. Moreover, during formation of the floating tablets, evolving gas permeated through the matrix leaving gas bubbles or pores, which also increased the release rate of the active ingredient from the matrix. The amount of sodium bicarbonate also played an important role in floating lag time of tablets, the higher the amount the lesser the floating lag time, and *vice versa*.

**Table 7: Effect of Sodium bicarbonate on onset and duration of floating of gastroretentive tablet**

| Amount of sodium bicarbonate (mg) | Onset of floating (s) | Duration of floating (h) |
|---|---|---|
| 10 | 92±3.86 | 16±0.81 |
| 20 | 62±2.96 | 21±0.36 |
| 30 | 32±2.50 | 24±0.69 |
| 40 | 27±0.05 | 18±0.75 |

*Standard deviation, n=3

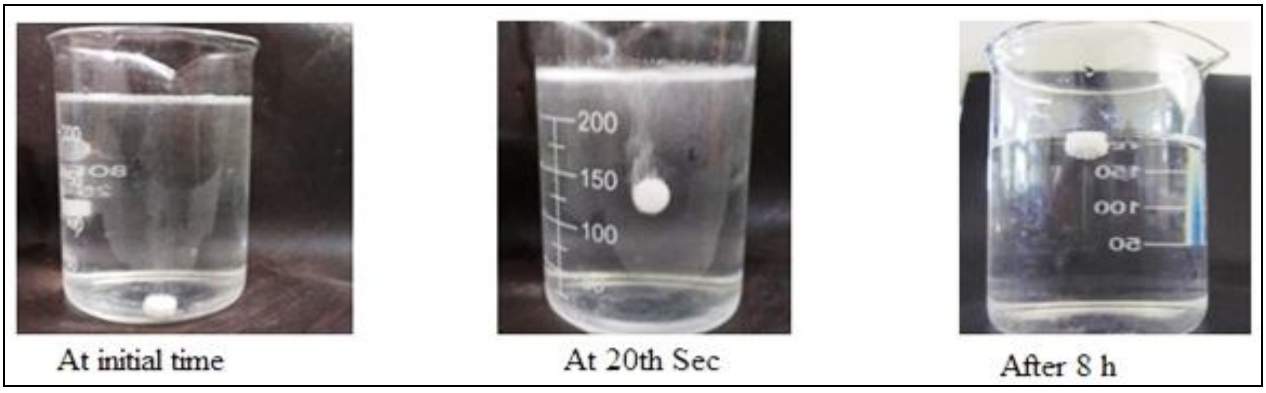


**Figure 6: Photographs of *in vitro* floating behavior gastroretentive tablet at different time intervals**

**Water uptake studies**

Water uptake studies are the ability to absorb water and swell. The water uptake study of the tablet was done using a USP dissolution apparatus type-II (basket) in 900 ml of pH 1.2 Hydrochloric acid buffer at 100 rpm. The medium was maintained at 37 ± 0.5°C throughout the study. At regular time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. Results showed that formulation F4 shows better results and % water uptake found to be 183-477% in 1-8 hrs.

***In-vitro* release profile**

*In-vitro* drug release after dispersion were studied for all formulations F1-F9 and % cumulative drug release on compared with all other batches formulation F4 shows better drug release in 12 hrs between 12-51% indicates that tablet releases the loaded drug in uniform pattern and will release up to next 12 hours. Based on above study, tablet can be classified as sustained release dosage form.

**Table 8: Percentage water uptake studies**

| Time (h) | % Water uptake | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 226±2.3 | 189±2.8 | 213±1.4 | 183±1.1 | 139±3.1 | 263±2.5 | 203±1.4 | 216±2.3 | 129±3.1 |
| 2 | 234±4.1 | 206±3.2 | 217±2.5 | 265±0.9 | 196±6.0 | 235±1.5 | 219±2.5 | 239±4.1 | 176±6.0 |
| 3 | 245±5.6 | 247±3.6 | 243±1.9 | 299±1.5 | 261±4.2 | 267±2.1 | 253±1.9 | 248±5.6 | 281±4.2 |
| 4 | 271±3.7 | 277±7.1 | 268±4.3 | 340±2.1 | 263±3.8 | 276±2.6 | 278±4.3 | 279±3.7 | 263±3.8 |
| 5 | 291±5.2 | 284±2.4 | 289±5.1 | 345±2.6 | 271±4.3 | 309±1.6 | 279±5.1 | 293±5.2 | 221±4.3 |
| 6 | 312±2.3 | 296±1.6 | 295±6.2 | 411±2.3 | 277±1.9 | 325±2.5 | 290±6.2 | 315±2.3 | 297±1.9 |
| 7 | 327±5.2 | 305±2.9 | 266±2.3 | 441±2.5 | 270±5.2 | 332±4.1 | 259±2.3 | 389±5.2 | 220±5.2 |
| 8 | 396±4.5 | 226±3.1 | 223±4.4 | 477±2.1 | 265±5.5 | 311±3.9 | 227±4.4 | 391±4.5 | 264±5.5 |

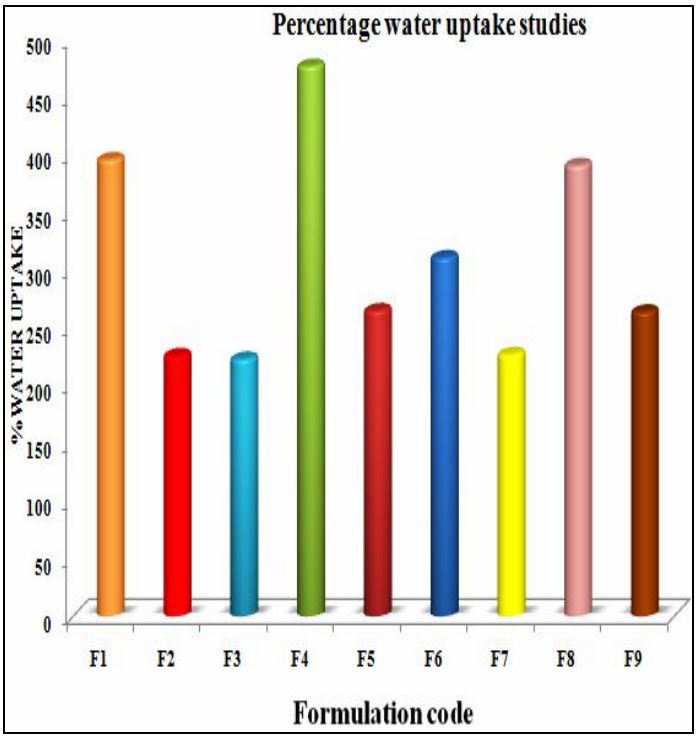


**Figure 7: Effect of various concentrations of ingredients on water uptake at the end of 8 h**

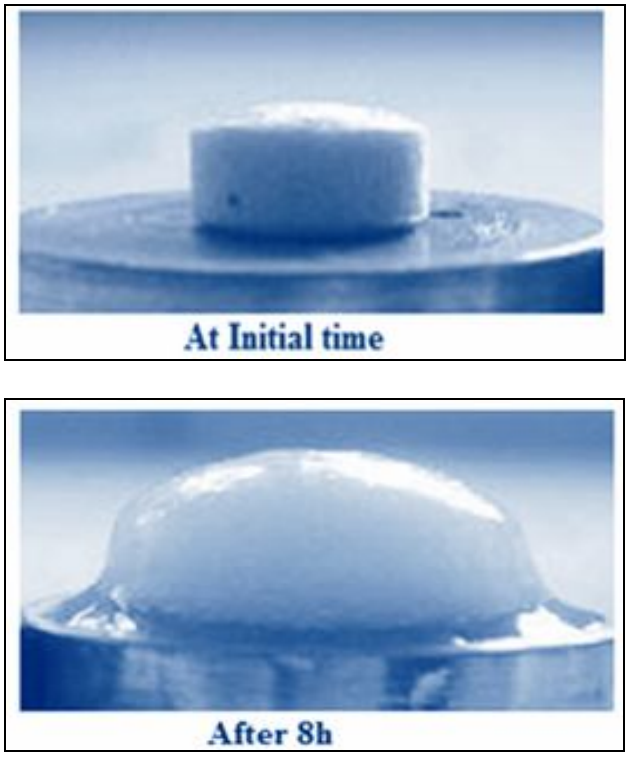


**Figure 8: Swelling behavior of gastroretentive tablet**

**Table 9: Percentage Cumulative drug release of formulated tablets**

| Time (h) | % Cumulative drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 30.86±0.21 | 15.20±0.45 | 17.41±0.13 | 12.73±0.32 | 21.32±0.18 | 15.57±0.91 | 19.41±0.13 | 17.57±0.91 | 13.20±0.45 |
| 2 | 40.74±0.43 | 21.62±0.33 | 26.25±0.10 | 18.68±0.43 | 29.96±0.21 | 24.91±0.85 | 23.25±0.10 | 26.91±0.85 | 22.62±0.33 |
| 3 | 46.05±0.14 | 29.44±0.12 | 33.87±0.22 | 22.74±0.56 | 34.27±0.29 | 34.15±0.48 | 34.87±0.22 | 33.15±0.48 | 32.44±0.12 |
| 4 | 52.74±0.19 | 33.55±0.32 | 40.49±0.31 | 28.49±0.76 | 45.63±0.43 | 45.64±0.39 | 41.49±0.31 | 44.64±0.39 | 36.55±0.32 |
| 5 | 58.12±0.26 | 38.21±0.33 | 45.29±0.41 | 31.77±0.89 | 51.56±0.47 | 53.78±0.31 | 46.29±0.41 | 54.78±0.31 | 42.21±0.33 |
| 6 | 62.66±0.43 | 42.91±0.42 | 52.16±0.26 | 36.40±0.71 | 56.03±0.59 | 62.20±0.11 | 50.16±0.26 | 64.20±0.11 | 44.62±0.42 |
| 7 | 65.54±0.56 | 46.72±0.21 | 55.37±0.39 | 38.82±0.44 | 60.30±0.62 | 68.49±0.39 | 56.37±0.39 | 69.49±0.39 | 49.72±0.21 |
| 8 | 66.48±0.20 | 47.47±0.19 | 56.21±0.43 | 39.42±0.64 | 64.22±0.47 | 69.41±0.29 | 59.21±0.43 | 71.41±0.29 | 56.47±0.19 |
| 12 | 78.36±0.25 | 63.45±0.12 | 71.02±0.56 | 51.83±0.13 | 76.97±0.67 | 77.09±0.35 | 73.02±0.56 | 83.09±0.35 | 72.45±0.12 |

**Mathematical model fitting of obtained drug release data**

The *in vitro* drug dissolution profiles were fitted to various models and release data was analyzed based on Korsmeyer-Peppas equation and Higuchi kinetics. The diffusion exponent ranges from 0.3771–0.6997. The release rates k and n values of each model were calculated by PCP disso v2.08 software. Co-efficient of correlation ($R^2$) were used to evaluate the accuracy of the model fitting.

On calculating and comparing $R^2$ values for, Korsmeyer-Peppas, Matrix, and other models, F3, F4, and F6 gave a good fit to the Matrix model, and the remaining formulations best fitted the Korsmeyer-Peppas model. F3, F4, and F6 exhibited Fickian release and other formulations showed non-Fickian or anomalous release. If the value of "n" in Korsmeyer-Peppas is 0.5 or less, the release mechanism follows a Fickian diffusion, and for anomalous or non-

Fickian, release the release is mainly by diffusion with n values between 0.5-1.

This model was used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well- known or, when more than one type of release phenomenon could be involved. The fundamental of diffusion is based on Fick's laws, which describes the macroscopic transport of molecules by a concentration gradient.

Overall, based on above results, formulation F4 was found to the best and can be commercialize on large scale to provide sustained release of captopril for effective management of congestive heart failure, kidney problems caused by diabetes.

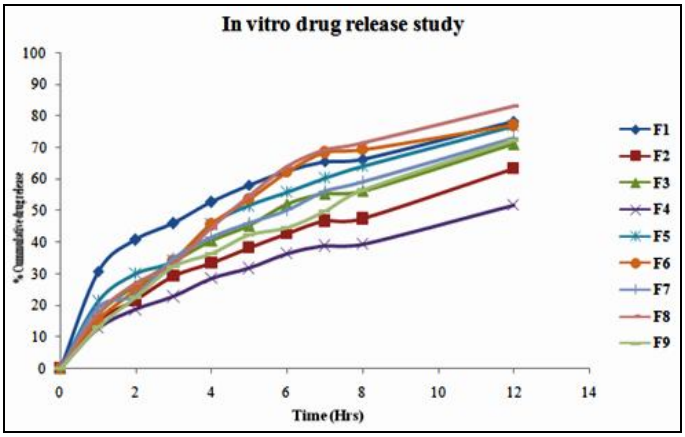


**Figure 9: Percentage Cumulative drug release of formulated tablets**

**Summary and Conclusion**

Based on results revealed from experimented data, pre-compression study for all formulation batches following crucial factors like: angle of repose **(θ)** was in the range of 23-26$^0$ shows excellent flow behavior; Bulk and tapped density were found in the range of 0.41 to 0.54 gm/ml and 0.44 to 0.56 gm/ml respectively. Carr's index were studied and found in range of 14.15 to 16.29 %showing good flowability but needs some flow promoters. Values of Hausner's ratio shows good flowability.

Formulation of gastroretentive drug delivery dosage forms are done based on optimization under factorial design of formula and classed formulation batches as F1-F9 in which concentration of polymer HPMC of various grades (HPMC K15 M, HPMC K100M and HPMC K4M) varied with the ration of sodium bi carbonate and microcrystalline cellulose.

After pre-compression test the powder blend was compressed into tablets and it was evaluated based on post-compression analysis for various factors which includes hardness, friability, weight variation, dispersion time, *in-vitro* drug release after dispersion, wetting time, disintegration time, drug content and drug release.

**Table 10: Drug release kinetics**

| Batch | Korsmeyer – Peppas | | | Matrix | | Mechanism of drug release | Release kinetics |
|---|---|---|---|---|---|---|---|
| | N | $R^2$ | K | $R^2$ | k | | |
| F1 | 0.3771 | 0.9981 | 31.1077 | 0.9811 | 24.7943 | Fickian | Peppas |
| F2 | 0.5737 | 0.9981 | 15.1110 | 0.9950 | 17.3367 | Non-Fickian | Peppas |
| F3 | 0.5714 | 0.9975 | 17.8613 | 0.9966 | 20.3088 | Non-Fickian | Peppas |
| F4 | 0.5675 | 0.9981 | 12.6702 | 0.9956 | 14.3660 | Non-Fickian | Peppas |
| F5 | 0.5380 | 0.9948 | 20.8757 | 0.9967 | 22.3909 | Non-Fickian | Matrix |
| F6 | 0.6997 | 0.9868 | 16.2306 | 0.9775 | 23.3020 | Non-Fickian | Peppas |
| F7 | 0.4675 | 0.9781 | 11.6702 | 0.9656 | 12.3660 | Non-Fickian | Peppas |
| F8 | 0.5880 | 0.9648 | 18.8757 | 0.9567 | 23.3909 | Non-Fickian | Matrix |
| F9 | 0.6797 | 0.9568 | 17.2306 | 0.9475 | 21.3020 | Non-Fickian | Peppas |

Hardness was measured using Monsanto tablet hardness tester and it was found to be in range for batches F1-F9, 4.6±18 to 6.5 ± 0.72 Kg/cm$^2$ which showed that tablet could maintain its physical integrity up to ultimate user. Friability was determined using Roche friabilator and it was found to be 0.20 to 0.78 ± 0.34% which indicates that tablet possess sufficient mechanical strength which can resist the shock and abrasion and maintain its physical integrity.

Weight variation was determined using twenty tablets and it was found to be 2.5% indicate content uniformity and showed that there was minimum variation in weight of the prepared tablets.

Floating lag time was found to be between 35-98 seconds indicates that the tablets can be delay release the drug which can be then available for dissolution.

Maximum swelling percentage ranges between 223-425% which can be utilize for extended release property from formulated tablets.

*In-vitro* buoyancy test shows onset of floating ranges between 27-92 seconds and duration of floating ranges between 16-24 hrs Sodium bicarbonate was essential to achieve optimum buoyancy. In general, gastric emptying time was 4 h. Moreover, during formation of the floating tablets, evolving gas permeated through the matrix leaving gas bubbles or pores, which also increased the release rate of the active ingredient from the matrix. The amount of sodium bicarbonate also played an important role in floating lag time of tablets, the higher the amount the lesser the floating lag time, and *vice versa*.

Water uptake studies are the ability to absorb water and swell. The water uptake study of the tablet was done using a USP dissolution apparatus type-II (basket) in 900 ml of pH 1.2 Hydrochloric acid buffer at 100 rpm. The medium was maintained at 37 ± 0.5°C throughout the study. At regular time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. Results showed that formulation F4 shows better results and % water uptake found to be 183-477% in 1-8 hrs.

*In-vitro* drug release after dispersion were studied for all formulations F1-F9 and % cumulative drug release on compared with all other batches formulation F4 shows better drug release in 12 hrs between 12-51% indicates that tablet releases the loaded drug in uniform pattern and will release upto next 12 hours. Based on above study, tablet can be classified as sustained release dosage form.

Drug content of formulation was determined and tablet showed drug content 98.33 ± 0.67% indicating the content uniformity and homogeneity in preparation.

On treatment of the obtained drug release profile, the release rates k and n values of each model were calculated by PCP disso v2.08 software. Co-efficient of correlation ($R^2$) were used to evaluate the accuracy of the model fitting. On calculating and comparing $R^2$ values for, Korsmeyer-Peppas, Matrix, and other models, F3, F4, and F6 gave a good fit to the Matrix model, and the remaining formulations best fitted the Korsmeyer-Peppas model. F3, F4, and F6 exhibited Fickian release and other formulations showed non-Fickian or anomalous release. If the value of "n" in Korsmeyer-Peppas is 0.5 or less, the release mechanism follows a Fickian diffusion, and for anomalous or non-Fickian, release the release is mainly by diffusion with n values between 0.5-1. This model was used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well- known or, when more than one type of release phenomenon could be involved.

The fundamental of diffusion is based on Fick's laws, which describes the macroscopic transport of molecules by a concentration gradient.

Overall, based on above results formulation F4 was found to the best and can be commercialize on large scale so as to provide sustained release of captopril for effective management of congestive heart failure, kidney problems caused by diabetes.

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