FORMULATION AND EVALUATION OF GASTRIC FLOATING TABLETS CONTAINING CAPTOPRIL AND HYDROCHLOROTHIAZIDE

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Abstract: The present work aimed to formulate and evaluate sustained release floating tablets of captopril and hydrochlorothiazide. The development was started by using direct compression method for process ease. Different rate controlling polymers were selected for initial screening. HPMC K4M, HPMC K100M and Sodium alginate checked for initial primary screening. Drug release of tablets well controlled by the HPMC K100M polymers were another twp polymers are not able to sustained the drug in matrix form and release earlier. Hence the rate controlling polymer HPMC K100M selected and further development done for floating behavior followed by diluent screening. The best combination of Sodium bicarbonate and citric acid optimized. Preformulation study revealed that the drugs were found with the selected excipients. F1-F17 batch developed and physical as well as chemical analysis were done for all batches. Further, formulation F16 found stable during stability study. Hence, F16 formulation optimized. Floating lag time of this batch has only 17 sec and tablet float for more than 12 hours. So, it is suitable for our formulation. So, finally obtained batch F16 which is suitable for our experiment have 30 mg HPMC K100M, 20 mg Sodium bicarbonate, 114 mg DCP and required quantity of glidant and lubricant.

Key Words: Captopril, Hydrochlorothiazide, Floating, Sustained release

1.   Introduction:
1.1 Introduction to Floating Drug Delivery System:
Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. Oral route remains the perfect route for the administration of therapeutic agents because of:

- low cost of therapy,
- ease of administration,
- accurate dosage,
- self-medication,
- pain avoidance,
- versatility, leading to high levels of patient compliance.

Tablets and capsules are the most popular dosage forms.

1.2 Advantages:
- Enhance Bioavailability
- Easily administration
- Reduce counter activity of body.
- Reduce frequency of dosing
- It is good for the drugs which are absorbed in stomach and small intestine.

1.3 Introduction of Drugs:
1.3.1 Introduction of Captopril:
Captopril is an ACE Inhibitor drug and used as an Anti-Hypertensive Agent which has 217.283 g/mole Molecular Weight, 0.34 Log P Value, 3.7 pKa Value, 60-75% Absorption Rate, Excreted in urine with Hepatic metabolism, White to off white colour crystalline powder and freely soluble in Water, Alcohol, Chloroform, Methelyn Chloride.

1.3.2 Introduction of Hydrochlorothiazide:
Hydrochlorothiazide is a Diuretic drug and used as a Antihypertensive Agents, Diuretics, Thiazide which has 297.728 g/mole Molecular Weight, -0.07 Log P Value, 7.9 pKa Value, 50-60 % Absorption Rate, Rapidly Excreted in Kidney, White colour or crystalline powder and freely soluble in Water, dilute ammonia, or sodium hydroxide, soluble in methanol, ethanol, acetone.

2.   Materials and Methods:
2.1 List of Materials:

Material proposed to be used	Role

Captopril	API
Hydrochlorothiazide	API
HPMC K4M/ K15M/ K 100 M	Gel forming agent
Citric Acid	Effervescent agent
Sodium Bicarbonate	Gas forming agent
Dibasic Calcium Phosphate/ Lactose	Diluent
Magnesium Stearate	Lubricant
Sodium Alginate	Binder
IPA	Solvent
Mannitol	Diluent
Talc	Glidant

2.2 Method of Preparation:
2.2.1 Preformulaion Studies:

- **Organoleptic Characteristics:**
  Colour, odour of Drug was characterized and recorded using descriptive terminology.

- **Bulk density and tapped density**
  An accurately weighed quantity of the API (W), was carefully poured into the 100 ml graduated cylinder and the volume (Vo) was measured. Then the graduated cylinder with lid, set into the density determination apparatus (Tapped Density Apparatus) the density apparatus was set for 100 taps and after that the volume (Vf) was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas.
  - $\geq$ Bulk density = W/ V0
  - $\geq$ Tapped density = W/ Vf

- **Compressibility index (CI) / Carr's index**
  It was obtained from bulk and tapped densities. It was calculated by using the following formula.
  - $\geq$ % Carr's index = (Tapped Density – Bulk Density ÷ Tapped Density) × 100

- **Hausner's ratio**
  Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.
  - $\geq$ Hausner's ratio = (Tapped density ÷ Bulk Density)

- **Angle of repose**
  Angle of repose of powder was determined by the funnel method. Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.
  - $\geq$ Tan θ= h/r

- **Calibration Curve**

✓ **Preparation of Standard Calibration Curve of Captopril**

  o *Preparation of standard solution:* 100 mg of Captopril was accurately weighed in to 100ml volumetric flask and dissolved in small quantity of 0.1 N HCl (1.2 pH). The volume was made up with the 0.1 N HCl (1.2 pH) to get a concentration of 1000μg/ml (SS-I). From this 1ml was withdrawn and diluted to 100ml to get a concentration of 100μg/ml (SS-II).

  o *Preparation of working standard solutions*: From (SS-II) aliquots of 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml, 3ml, 3.5ml were pipette into 10ml volumetric flasks. The volume was made up with 0.1 N HCl (1.2 pH) to get the final concentration of 5, 10, 15, 20, 25, 30, 35 μg/ml respectively. The absorbance of each concentration was measured at 205 nm.

  o λmax: 205 nm.

  o *Beer's range:* 5-35 μg/ml.

✓ **Preparation of Standard Calibration Curve of Hydrochlorothiazide:**

- o *Preparation of standard solution:* 100 mg of Hydrochlorothiazide was accurately weighed in to 100 ml volumetric flask and dissolved in small quantity of 0.1 N HCl (1.2 pH). The volume was made up with the 0.1 N HCl (1.2 pH) to get a concentration of 1000 μg/ml (SS-I). From this 1ml was withdrawn and diluted to 100 ml to get a concentration of 100μg/ml (SS-II).
- o *Preparation of working standard solutions*: From (SS-II) aliquots of 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml were pipette into 10ml volumetric flasks. The volume was made up with 0.1 N HCl (1.2 pH) to get the final concentration of 10, 20, 30, 40, 50, 60 and 70 μg/ml respectively. The absorbance of each concentration was measured at 266 nm.
- o λmax: 271 nm.
- o *Beer's range:* 10-70 μg/ml.

2.2.2 Preparation of Floating Tablets of Captopril and Hydrochlorothiazide:
Direct Compression Method
1. Weigh all the drugs and excipients accurately and dry mixing of all drugs and excipients.
2. Mix well all the ingredients and add Lubricant and Glidant into above mixture.
3. Mix them well and compress of mixture: Fill Die, Compress Tablet and Eject Tablet.

Table 1. Formulation of all Batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
Captopril	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Hydrochlor-othiazide	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
HPC K4M	80	-	-	30	-	-	-	-	-	-	-	-	-	-	-	-	-
HPMC K100M	-	80	-	-	30	-	50	40	30	20	30	30	30	30	30	30	30
Sodium Alginate	-	-	80	-	-	30	-	-	-	-	-	-	-	-	-	-	-
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20	20	20	-	15	20	25	20	20
Calcium Carbonate	-	-	-	-	-	-	-	-	-	-	-	20	-	-	-	-	-
Citric Acid	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
DCP	84	84	84	134	134	134	114	124	134	144	134	134	139	134	129	134	-
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Lactose	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	134
Mg. stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250

- Batch F1 to F6 is for selection of Polymer.
- Batch F7 to F10 is for Optimization of concentration of HPMC K100M as matrixing agent.
- Batch F11 and F 12 is for Selection of Gas generating agent using HPMC K100M as matrixing agent.
- Batch F13 to F15 is for Optimization of the concentration of sodium bicarbonate as a Gas generating agent.
- Batch F 16 and F 17 is for Selection of diluents using release profile of HPMC K100M floating matrix tablets.

3. Evaluation Parameters:
3.1 Pre-Compression Parameters:
- **Bulk density and tapped density**
  An accurately weighed quantity of the blend (W), was carefully poured into the graduated cylinder and the volume (V0) was measured. Then the graduated cylinder with lid, set into the density determination apparatus (Tapped Density Apparatus) the density apparatus was set for 100 taps and after that the volume (Vf) was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas.
  - ➤ Bulk density = W/ V0
  - ➤ Tapped density = W/ Vf

- **Compressibility index (CI) / Carr's index**

It was obtained from bulk and tapped densities. It was calculated by using the following formula.

> % Carr's index = (Tapped density – Bulk density ÷ Tapped density) × 100

- **Hausner′s ratio**

  Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

  > Hausner's ratio = (Tapped density ÷ Bulk Density)

- **Angle of repose**

  Angle of repose of powder was determined by the funnel method. Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

  > Tan θ = h/r

3.2 Post Compression Parameters:

- **Weight variation test**

To study weight variation 20 tablets of the formulation were weighed using a Sartorius electronic balance.

- **Hardness**

The hardness of five tablets was determined using the Monsanto hardness tester and the average values were calculated.

- **Thickness**

The thickness of the tables was determined by using Vernier calipers. Five tablets were used, and average values were calculated.

- **Tablet friability**

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 10 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

> **% Friability** = $\dfrac{W_0\text{-}W}{W}$ ×100

- **Assay**

Ten tablets were weighed individually, and the drug was extracted in 0.1 N HCl, filter through 0.45 μ membrane. The absorbance was measured after suitable dilution using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer.

- **Floating Lag Time and Total Floating Time**

The in vitro buoyancy was determined by using dissolution testing apparatus USP type-1.The tablets were placed in 900 ml 0.1 N HCL at 100 rpm basket rotation at 37±0.5°C. The time require for tablets to ascend to the surface of dissolution medium and time taken by tablet to buoyant on surface of medium was recorded as floating lag time and total floating time.

- **Swelling index**

The swelling index of tablets was in 0.1 N HCL. Tablets were weighed individually named as W_0 and then it is placed in separately in glass beaker containing 200 ml 0.1N HCL at 37±0.5° C. At periodical time interval tablets were removed from beaker and extra amount of surface water discarded by blotting paper and then tablets were weighed, and it is referred as W_t and swelling index was calculated using following formula:

> **Swelling index** = $\dfrac{W_t - W_0}{W_0}$

  Where
  W_t = weight after swelling
  W_0 = weight before swelling

- **Content Uniformity**

Randomly selected 10 tablets were weighed and make powdered individually. Take powder of individual tablet which is equivalent to 25 mg was weighed and dissolve in 100 ml of 0.1 N HCl, then the solution was sonicated for 15 min, then undissolved matter was removed by filtration. The absorbance of the diluted solutions is measured.

- *In Vitro* **Dissolution Studies**

USP apparatus II was used to test the dissolution profile using 900 ml of 0.1N HCl as dissolution medium at 50 rpm and $37°C \pm 0.5°C$. six tablets from each batch were placed into respective basket containing HCl. 10ml of the sample was withdrawn hourly for 12 h. The sample was filtered and from the filtrate 3ml was withdrawn. The volume was adjusted to 100ml with 0.1N HCl in the 100 ml to prepare 10 mcg/ml solutions. Absorbance of the solution was measured using UV spectrophotometer.

- **Drug Release Kinetic Study**

Data obtained form in vitro drug release studies were fitted to disso calculation software. The kinetic models used are zero order, first order, Korshmers and papps, Hexon crowell, and Higuchi equation. The rate and mechanism of release of Drug from the prepared tablets were analyzed by fitting the dissolution data into the zero-order equation:

$$Q = k0t$$

Where, Q is the amount of drug released at time t, k0 is the release rate constant. The dissolution data fitted to the first order equation:

$$\ln (100-Q) = \ln 100 - K_1 t$$

Where, k1 is the release rate constant. The dissolution data was fitted to the Higuchi's equation:

$$Q = k_2 t^{1/2}$$

Where, k2 is the diffusion rate constant.
The dissolution data was also fitted to Korsmeyer equation, which is often used to describe the drug release behavior from polymeric systems:

$$\text{Log} (M_t/M\infty) = \log k + n \log t$$

Where Mt is the amount of drug released at time t, M∞ is the amount of drug release after infinite time, K is a release rate constant incorporating structural and geometric characteristics of the tablet, n is the diffusion exponent indicative of the mechanism of drug release.

- **Stability Study**

Optimized Batch of prepared floating tablet subjected to accelerated stability studies at 40 °C and 75% RH for 1 month in a humidity chamber. The tablets of best batch were packed in aluminum foil pouch and analyzed for floating behavior and in-vitro drug release study.

4. Result and Discussion:
4.1 Preformulation Studies:
4.1.1 Characterization of Captopril:

Table 2. Characteristics of Captopril

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Characteristics	Colour	White to off-white solid
2		Odour	Characteristic odour
4	Flow Properties	Bulk density (g /ml)	0.30
5		Tapped density (g /ml)	0.34
6		Carr's index (%)	11.76
7		Hausner's ratio	2.94
8		Angle of repose (θ°)	26.13
9	Solubility	Solubility	• Soluble in 0.1 N HCl • Soluble in water.

4.1.2 Characterization of Hydrochlorothiazide:

Table 3. Characteristics of Hydrochlorothiazide

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Characteristics	Colour	white to practically white fine powder
2		Odour	Characteristic odour
4	Flow Properties	Bulk density (g /ml)	0.44
5		Tapped density (g /ml)	0.52
6		Carr's index (%)	15.38
7		Hausner's ratio	1.18
8		Angle of repose (θ°)	58.32
9	Solubility	Solubility	• Soluble in 0.1 N HCl • Soluble in water.

4.1.3 FTIR Study:
The IR spectra of the pure drug and the optimized formulation showed in below figure no. 1 and 2. From the figure it concluded that there was no any interaction between drug and excipients found.
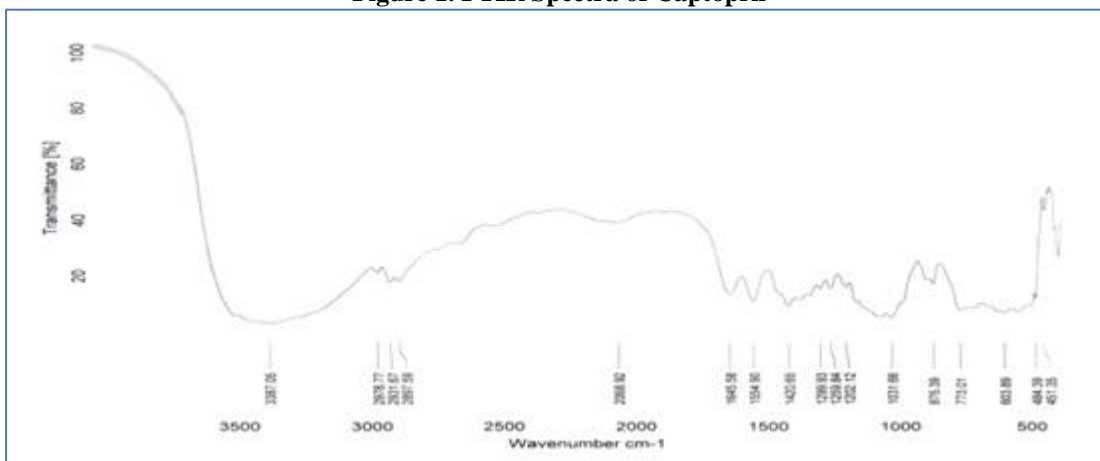
Figure 1. FTIR Spectra of Captopril

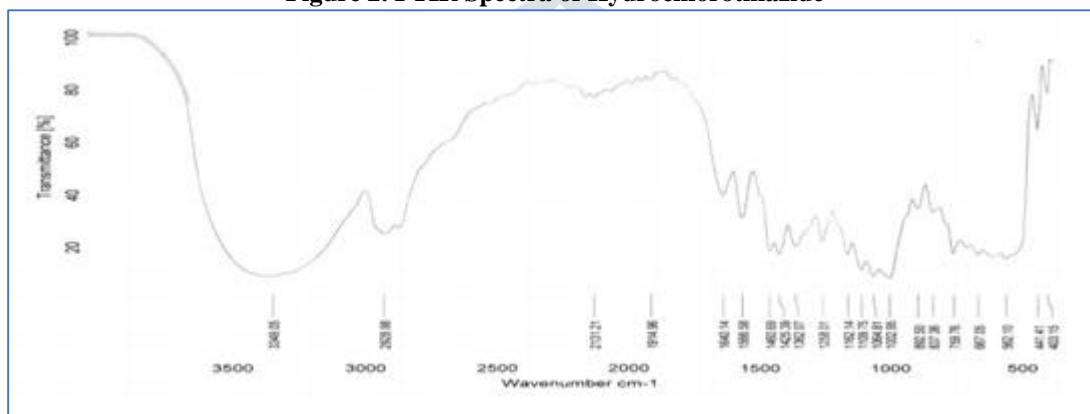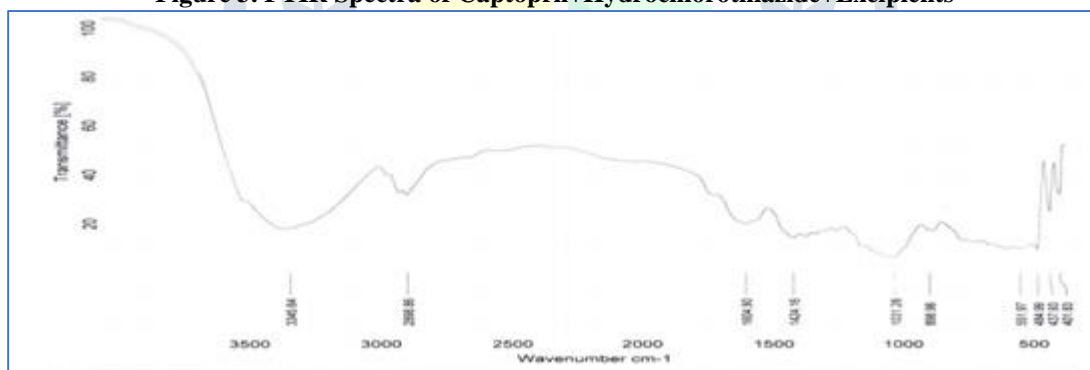**Figure 2. FTIR Spectra of Hydrochlorothiazide**

Figure 3. FTIR Spectra of Captopril+Hydrochlorothiazide+Excipients

4.2 Calibration Curve:
4.2.1 Calibration Curve of Captopril:

Table 4. Calibration curve of Captopril

Sr. No	Concentration (μg/ml)	Absorbance (n=3)
1	0	0
2	5	0.0006 ± 0.0001
3	10	0.0010 ± 0.0002
4	15	0.0017 ± 0.0001
5	20	0.0025 ± 0.0001
6	25	0.0039 ± 0.0003
7	30	0.0045 ± 0.0001
8	35	0.0051 ± 0.0002

Figure 4. ZCP of Captopril (205)
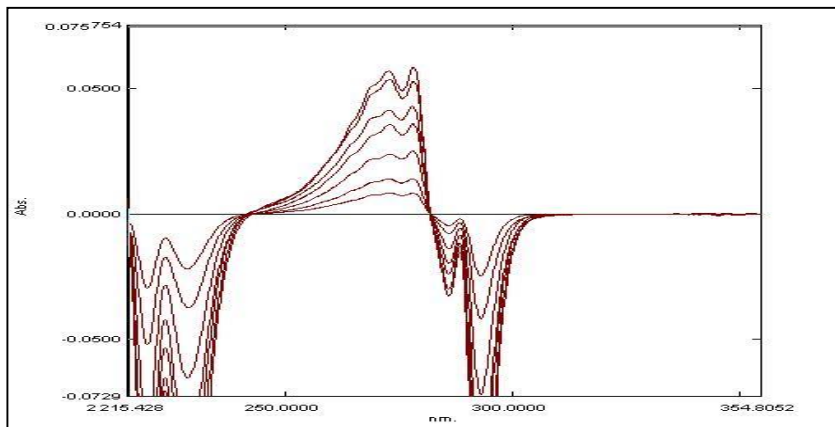
Figure 5. Calibration curve of Captopril in 0.1 N HCl at 205 nm

y = 0.0001x - 0.0005
R² = 0.9811
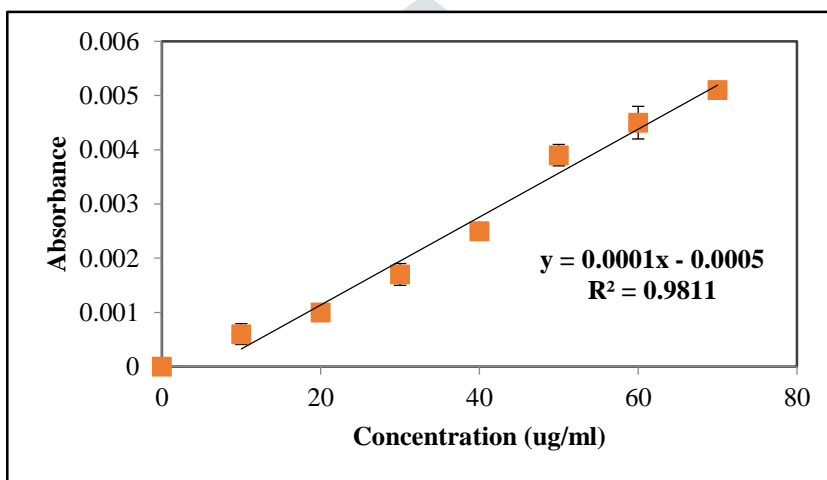
4.2.2 Calibration Curve of Hydrochlorothiazide:

Table 5. Calibration curve of Hydrochlorothiazide

Sr. No	Concentration (μg/ml)	Absorbance (n=3)
1	0	0
2	10	0.0026 ± 0.0002
3	20	0.0041 ± 0.0004
4	30	0.0053 ± 0.0005
5	40	0.0068 ± 0.0001
6	50	0.0092 ± 0.0002
7	60	0.0114 ± 0.0003
8	70	0.0152 ± 0.0002

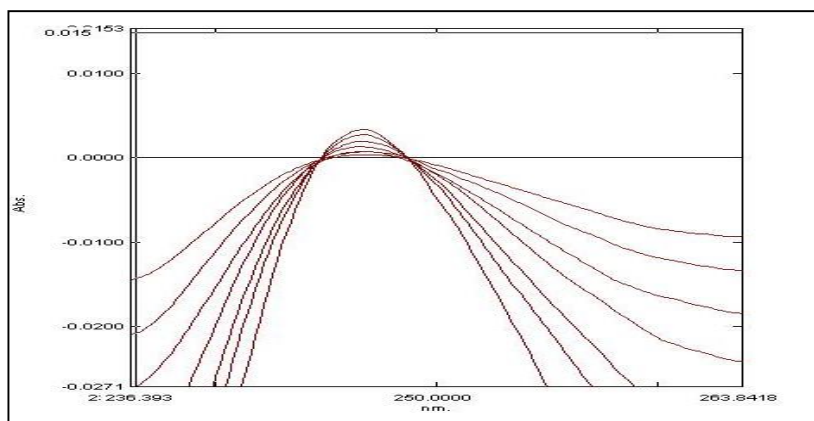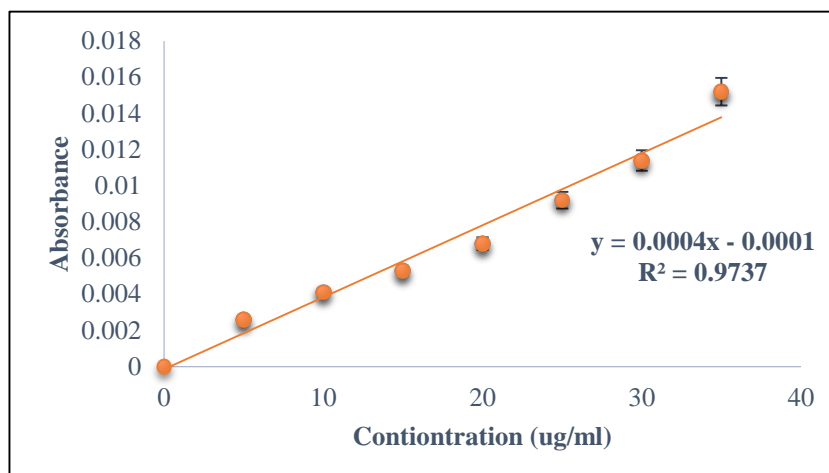**Figure 6. ZCP of Hydrochlorothiazide (271)**

Figure 7. Calibration curve of Hydrochlorothiazide in 0.1 N HCl at 271 nm

4.3 Pre-Compression Parameters Evaluation:

Powder blend of formulation F1-F17 checked for pre-compression parameters like,

- Bulk density
- Tapped density
- Compressibility index (CI) / Carr's index
- Hausner's ratio
- Angle of repose

Observed results are mentioned in following table 6.

Table 6. Pre-Compression Parameters of Formulation F1-F17

Formulation	Bulk density (g /ml) (n=3)	Tapped density (g /ml) (n=3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ°) (n=3)
F1	0.54 ± 0.02	0.61 ± 0.03	11.48 ± 0.01	1.13 ± 0.02	17.25 ± 0.05
F2	0.48 ± 0.03	0.52 ± 0.05	7.69 ± 0.02	1.08 ± 0.01	19.22 ± 0.08
F3	0.47 ± 0.05	0.55 ± 0.03	14.55 ± 0.04	1.17 ± 0.02	21.12 ± 0.07
F4	0.57 ± 0.07	0.60 ± 0.04	5.00 ± 0.07	1.05 ± 0.01	19.26 ± 0.08
F5	0.47 ± 0.04	0.54 ± 0.04	12.96 ± 0.05	1.15 ± 0.02	25.15 ± 0.07
F6	0.42 ± 0.05	0.54 ± 0.02	16.00 ± 0.06	1.19 ± 0.02	21.15 ± 0.05
F7	0.51 ± 0.08	0.56 ± 0.05	8.93 ± 0.04	1.10 ± 0.01	19.56 ± 0.04
F8	0.52 ± 0.02	0.58 ± 0.04	10.34 ± 0.05	1.12 ± 0.01	18.75 ± 0.03
F9	0.47 ± 0.04	0.54 ± 0.02	12.96 ± 0.05	1.15 ± 0.01	17.84 ± 0.03
F10	0.58 ± 0.03	0.65 ± 0.03	10.77 ± 0.02	1.12 ± 0.01	19.29 ± 0.05
F11	0.49 ± 0.04	0.58 ± 0.08	15.52 ± 0.03	1.18 ± 0.02	22.14 ± 0.08
F12	0.47 ± 0.05	0.54 ± 0.08	12.96 ± 0.04	1.15 ± 0.02	21.04 ± 0.07
F13	0.48 ± 0.06	0.59 ± 0.07	18.64 ± 0.02	1.23 ± 0.01	18.56 ± 0.05
F14	0.58 ± 0.05	0.64 ± 0.05	9.38 ± 0.03	1.10 ± 0.01	17.45 ± 0.06
F15	0.48 ± 0.04	0.53 ± 0.06	9.43 ± 0.05	1.10 ± 0.02	16.84 ± 0.04
F16	0.43 ± 0.03	0.49 ± 0.04	12.24 ± 0.06	1.14 ± 0.01	19.84 ± 0.06
F17	0.46 ± 0.07	0.52 ± 0.07	11.54 ± 0.02	1.13 ± 0.01	21.54 ± 0.04

4.4 Post Compression Parameters Evaluation:

In process test for tablets should be performed for acceptance of batches. All batches were performed IPQC test like weight variation, Drug content, Hardness and Thickness. Optimized batch F16 passed all the specified range of parameter. F16 batch was shown weight variation in the range of 250 ± 3.5 mg. It had also sufficient hardness to stand mechanical shock. Friability of batch F16 was 0.65 ± 0.17 % which was desirable for our formulation.

Table 7. Post-Compression Parameters of Formulation F1-F17

Batch	Weight variation test (mg)	Thickness (mm) (n=3)	Hardness (kg/cm²)	Friability (%)	Drug Content of Captopril (%) (n=3)	Drug Content of Hydro-chlorothiazide (%) (n=3)	Swelling Index (%) (n=3)
F1	255 ± 2.82	4.51±0.09	4.8 ± 0.12	0.84 ± 0.14	99.2 ± 0.3	99.4 ± 0.4	58.2 ± 4.4
F2	250 ± 2.57	4.49±0.11	4.5 ± 0.05	0.70 ± 0.29	99.8 ± 0.4	98.5 ± 0.5	62.5 ± 2.2
F3	250 ± 3.51	4.50±0.12	4.5 ± 0.06	0.73 ± 0.18	98.5 ± 0.5	99.5 ± 0.7	54.6 ± 5.3
F4	250 ± 2.54	4.52±0.11	5.0 ± 0.15	0.61 ± 0.24	97.8 ± 0.7	97.8 ± 0.5	51.6 ± 6.2
F5	255 ± 2.74	4.51±0.11	5.0 ± 0.13	0.62 ± 0.24	99.5 ± 0.5	99.8 ± 0.6	62.4 ± 4.3
F6	250 ± 2.62	4.48±0.13	5.5 ± 0.05	0.77 ± 0.16	99.4 ± 0.4	99.4 ± 0.5	68.5 ± 5.2
F7	250 ± 3.59	4.52±0.14	5.0 ± 0.15	0.82 ± 0.11	99.5 ± 0.5	98.4 ± 0.4	72.1 ± 1.6
F8	255 ± 2.88	4.51±0.12	6.0 ± 0.11	0.84 ± 0.15	99.7 ± 0.6	99.4 ± 0.2	68.6 ± 3.2
F9	250 ± 2.56	4.51±0.10	5.0 ± 0.14	0.70 ± 0.29	98.4 ± 0.4	98.8 ± 0.4	69.4 ± 2.5
F10	255 ± 2.86	4.50±0.13	4.5 ± 0.03	0.73 ± 0.18	100.5 ± 0.5	99.7 ± 0.2	68.5 ± 3.2
F11	253 ± 2.34	4.49±0.14	5.0 ± 0.16	0.61 ± 0.24	100.8 ± 0.4	99.9 ± 0.6	67.4 ± 3.6
F12	251 ± 3.51	4.47±0.08	6.0 ± 0.19	0.68 ± 0.14	98.7 ± 0.2	99.8 ± 0.4	66.5 ± 5.6
F13	259 ± 3.88	4.51±0.09	4.5 ± 0.06	0.65 ± 0.13	99.5 ± 0.3	99.4 ± 0.5	69.7 ± 3.9
F14	250 ± 2.54	4.48±0.11	6.0 ± 0.11	0.54 ± 0.21	98.6 ± 0.4	99.7 ± 0.7	78.5 ± 2.9
F15	256 ± 2.88	4.47±0.06	5.0 ± 0.12	0.81 ± 0.15	99.7 ± 0.5	98.7 ± 0.5	71.5 ± 3.4
F16	**250 ± 3.54**	**4.49±0.11**	**5.6 ± 0.02**	**0.65 ± 0.17**	**99.8 ± 0.5**	**99.6 ± 0.8**	**85.6 ± 5.6**
F17	251 ± 2.46	4.52±0.14	4.5 ± 0.06	0.73 ± 0.16	98.7 ± 0.4	98.9 ± 0.4	74.1 ± 4.5

In Vitro Drug release study of Captopril and Hydrochlorothiazide is determined for 1 hr, 8 hr and 12 hr. On the basis In Vitro Study, Floating Time and Total Floating Time it is concluded that formulation F16 was desirable.

Table 8. In Vitro Study, Floating Time and Total Floating Time Parameters of Formulation F1-F17

Time in hour	% Drug Release in Captopril			% Drug Release in Hydrochlorothiazide			Floating Lag Time (sec)	Total Floating Time (hr)
	1	8	12	1	8	12		
F1	2.45	33.42	46.27	3.12	34.69	46.98	840	> 12 hrs.
F2	6.32	59.24	72.32	7.21	60.21	73.64	35	> 12 hrs.
F3	5.41	41.35	63.45	8.64	39.54	66.32	30	> 12 hrs.
F4	13.65	99.98	-	15.21	99.14	-	45	> 8 hrs.
F5	18.65	69.74	95.14	19.32	70.32	93.66	19	> 12 hrs.
F6	23.14	86.95	-	20.31	89.32	-	105	> 9 hrs.
F7	8.32	55.3	74.12	9.32	56.39	75.12	35	> 12 hrs.
F8	9.14	61.35	86.54	9.47	62.54	87.65	43	> 12 hrs.
F9	7.32	54.62	96.42	8.14	55.85	88.74	40	> 12 hrs.
F10	16.35	79.67	-	17.21	80.96	-	50	> 10 hrs.
F11	10.32	73.68	92.13	11.65	74.95	93.15	20	> 12 hrs.
F12	8.65	61.54	84.27	9.64	62.35	85.64	66	> 12 hrs.
F13	31.32	76.32	95.17	32.36	77.98	95.42	41	> 12 hrs.
F14	32.15	77.32	92.14	33.65	78.96	92.68	20	> 12 hrs.
F15	33.14	79.21	93.45	33.47	80.32	94.65	35	> 12 hrs.
F16	24.12	72.68	99.12	24.65	73.65	99.6	17	> 12 hrs.
F17	21.36	78.98	97.45	22.14	77.98	98.42	28	> 12 hrs.

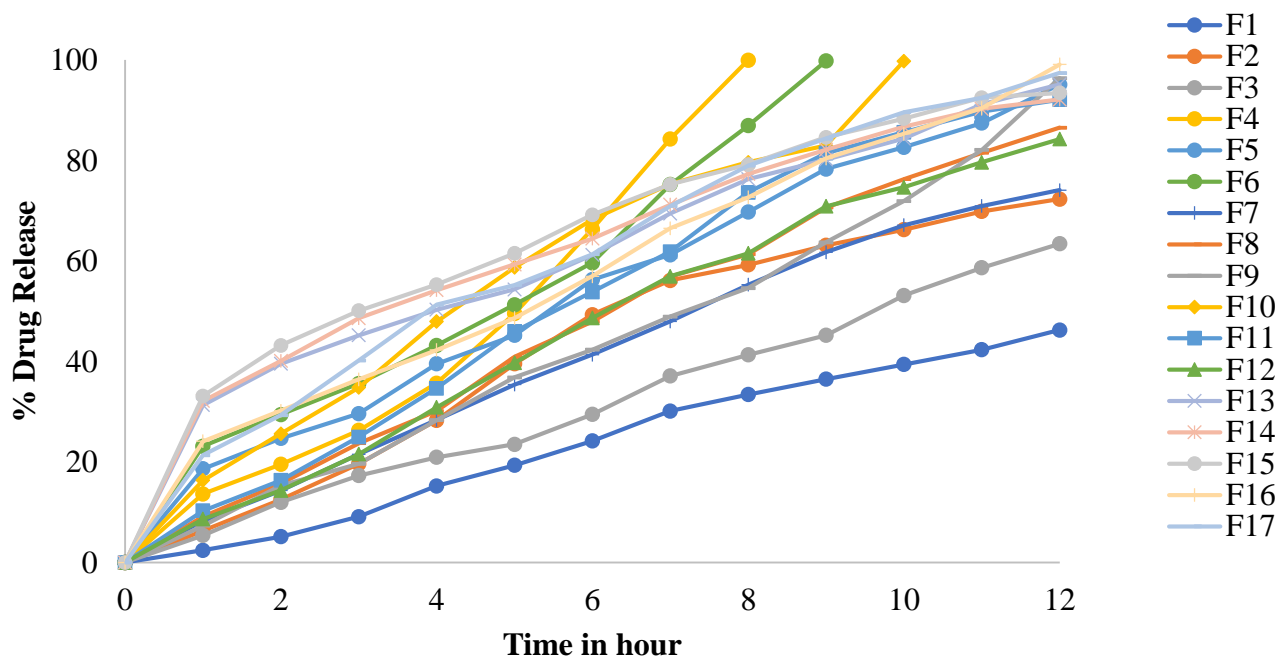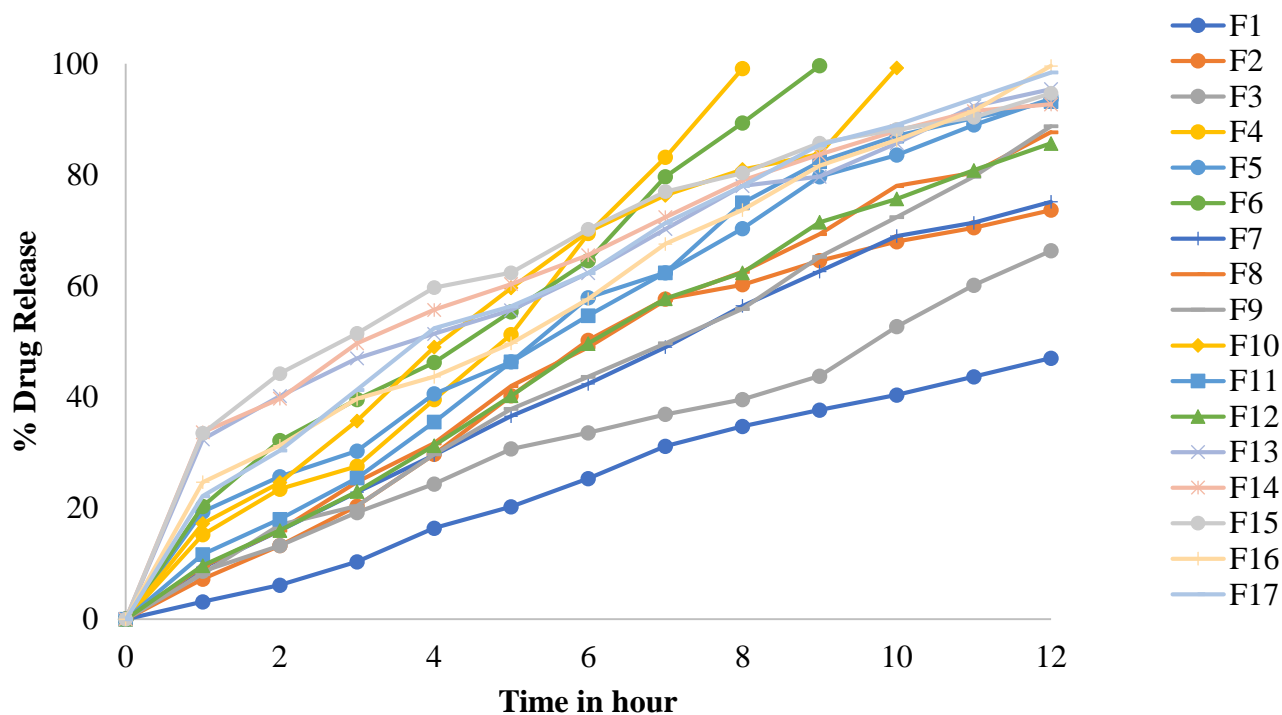Figure 9.In-Vitro Drug release of Captopril
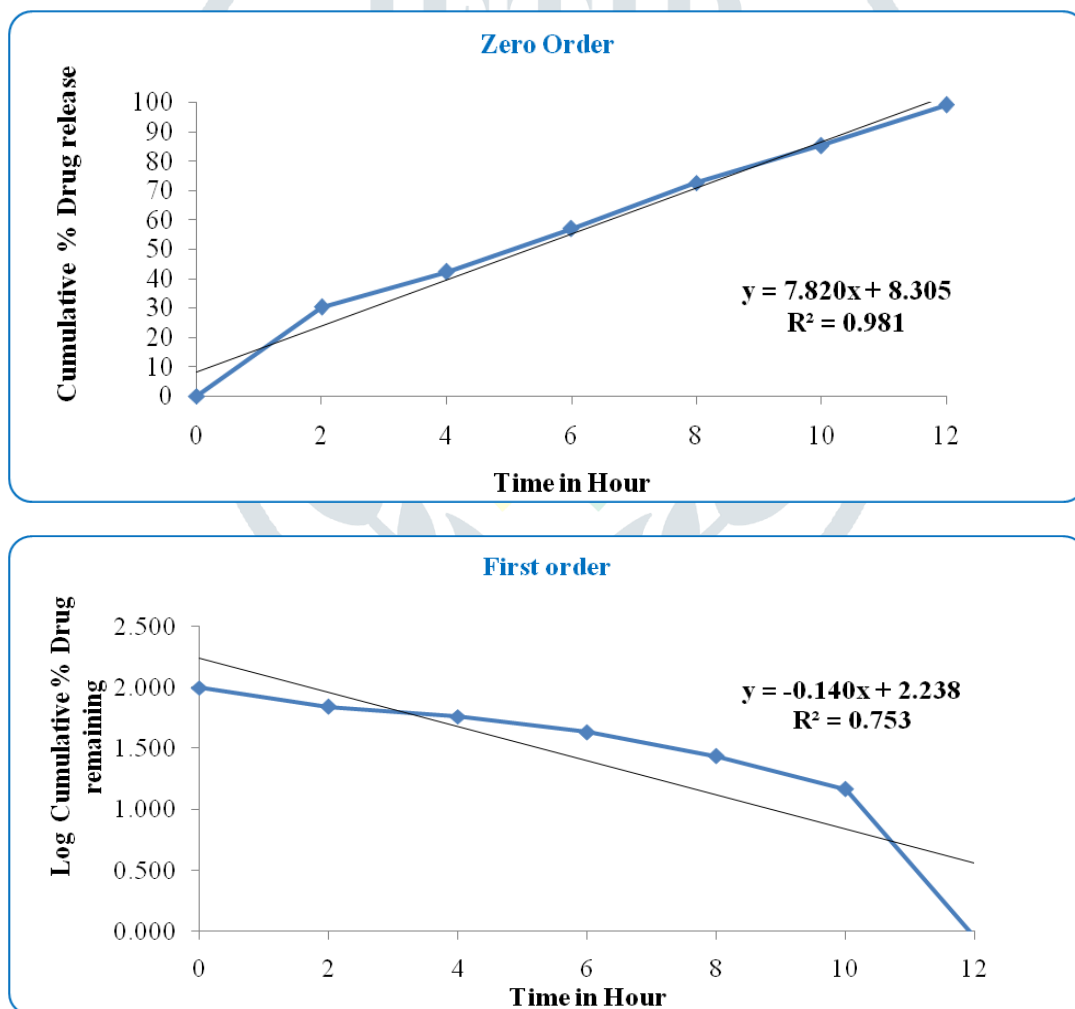

Figure 10. In-Vitro Drug release of Hydrochlorothiazide

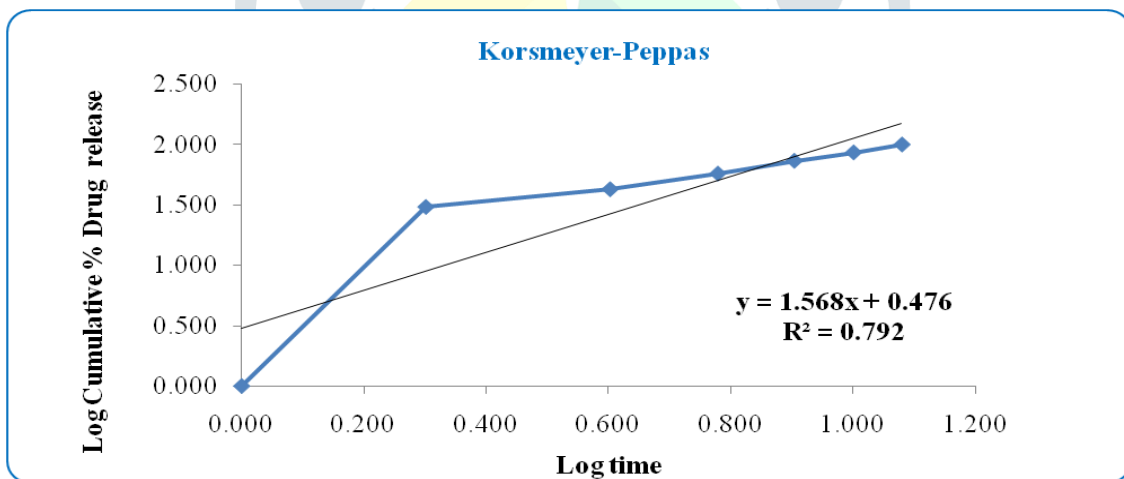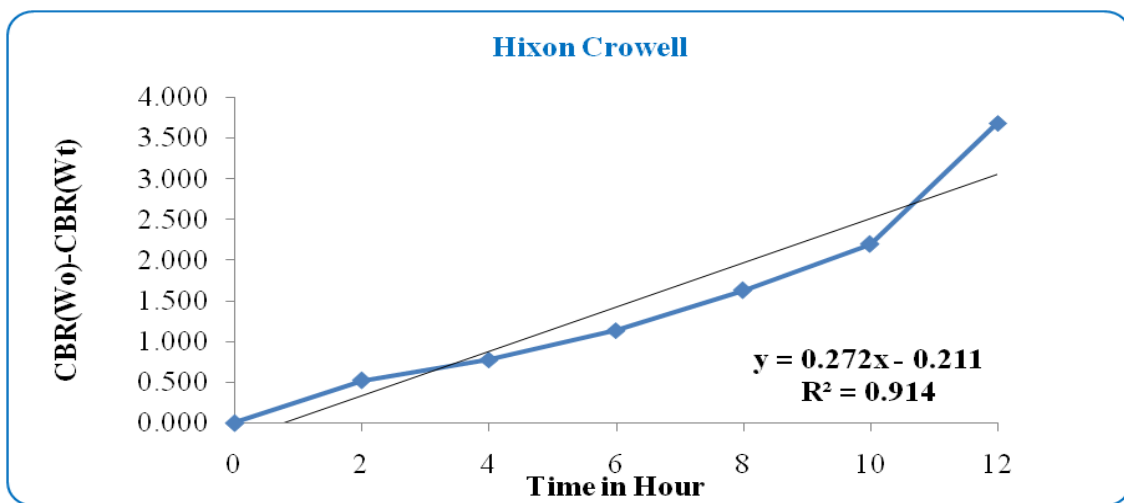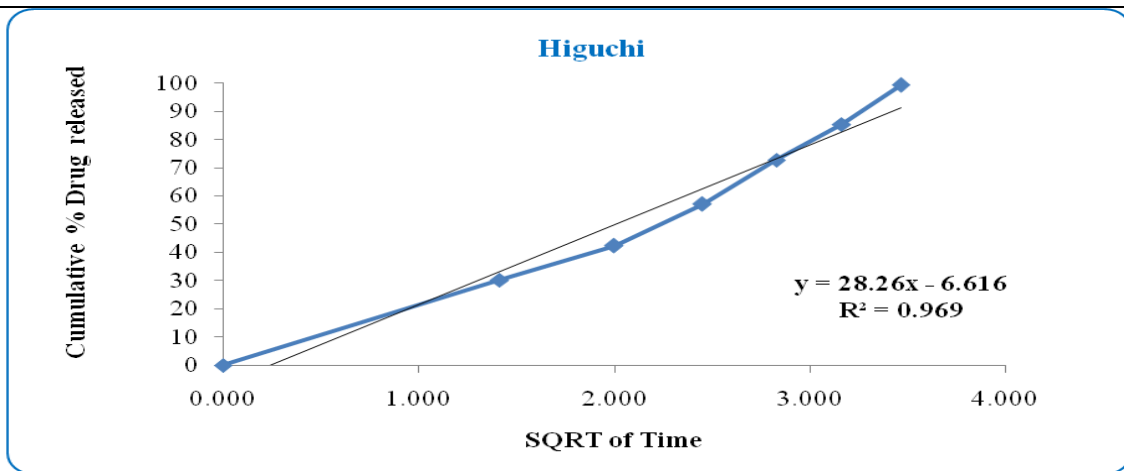**5. Kinetic modeling and mechanism of drug release:**

The dissolution profile of the best batch was fitted to zero-order, first-order, Higuchi and korsmeyer models to ascertain the kinetic modeling of drug release. It may be concluded that the drug release from gastro retentive floating tablet is best explained by Higuchi model because R^2 value of Higuchi model has 0.9838. The values of slope and intercept for Higuchi model are 18.517 and 5.5844 respectively.

Table 9. Kinetic modeling data of batch F16

Model	Zero-order	First-order	Higuchi plot	Hixon Crowell	Korsmeyer
R^2	0.981	0.753	0.969	0.914	0.796
K (Constant)	8.305	2.238	6.616	0.211	0.476

Figure 10. Kinetic modeling data of batch F16

Higuchi

$$y = 28.26x - 6.616$$
$$R^2 = 0.969$$

Hixon Crowell

$$y = 0.272x - 0.211$$
$$R^2 = 0.914$$

Korsmeyer-Peppas

$$y = 1.568x + 0.476$$
$$R^2 = 0.792$$

6. Stability Study:

Stability study of optimized batch F16 performed for 1 month at 40 °C/75 % RH and evaluated for various parameters. Resulted parameters are tabulated below;

Table 10. Results of Stability Study of F16

Time	Floating lag time (sec)	Floating Time (hr)	% Drug release of Captopril in 12 hr	% Drug release of HCTZ in 12 hr	% Drug Content Captopril	% Drug Content HCTZ

Initial	17 ± 2	12 ± 1	99.1±0.5	99.6±0.5	99.8±0.5	99.6±0.8
After 1 month	19 ± 5	12 ± 1	98.6±0.3	98.9±0.6	98.5±0.9	99.2±0.4

From the stability study data, it revealed that the formulation F16 stable at 40 °C/75 % RH condition. Results are well within acceptable limits.

7. Conclusion:
- The present investigation aimed that preparation of sustained release floating tablets of captopril and hydrochlorothiazide.
- The development was started by using direct compression method for process ease. Different rate controlling polymers were selected for initial screening.
- HPMC K4M, HPMC K100M and Sodium alginate checked for initial primary screening. Drug release of tablets well controlled by the HPMC K100M polymers were another two polymers are not able to sustained the drug in matrix form and release earlier. Hence the rate controlling polymer HPMC K100M selected and further development done for floating behavior followed by diluent screening.
- The best combination of Sodium bicarbonate and citric acid optimized. Preformulation study revealed that the drugs were found with the selected excipients.
- F1-F17 batch developed and physical as well as chemical analysis were done for all batches. Further, formulation F16 found stable during stability study.
- Hence, F16 formulation optimized. Floating lag time of this batch has only 17 sec and tablet float for more than 12 hours. So, it is suitable for our formulation. So, finally obtained batch F16 which is suitable for our experiment have 30 mg HPMC K100M, 20 mg Sodium bicarbonate, 114 mg DCP and required quantity of glidant and lubricant. Also the Formulation F16 found stable for 1 month stability study.
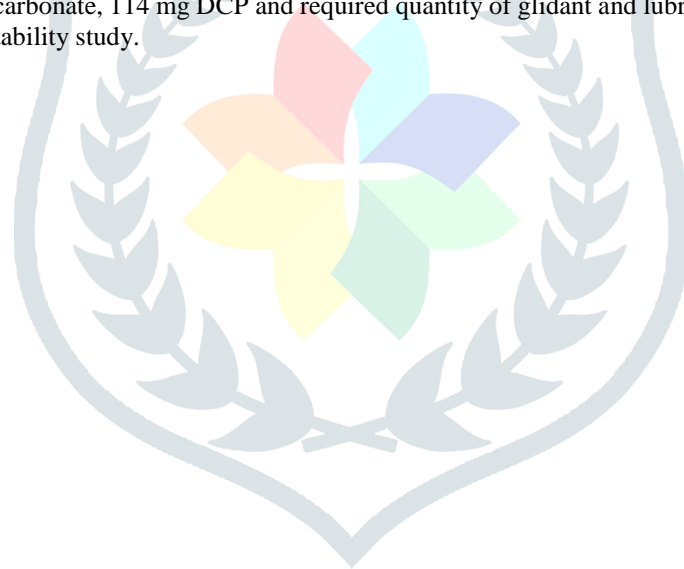
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