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# Formulation and Evaluation of Furosemide Tablets as Gastroretentive Dosage Forms Using Various Polymers

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**Abstract:** ***The objective of present study is to formulate and in-vitro evaluation of non-effervescent of Furosemide gastroretentive floating tablets, and to interpret the in-vitro dissolution studies. The purpose of this research was introduce low cost of the therapy, ease of administration lead to high levels of patient compliance and prepare floating drug delivery (FDD) as non effervescent tablets (Furosemide) containing furosemide by direct compression method. This present study were used various polymers such as HPMC K4M, K100M and K15M at various proportions. Among all the formulations, F6 formulations were produced desire drug released up to 9th hour, findings were satisfactory and flow property. The finding of tablets parameters for flow properties such as (angle of repose, compressibility index, Hausner ratio, bulk density and tapped density were performed as an indication of good flow properties also prepared tablets were determined floating parameters like swelling index and invitro buvyancy test and estimated the mechanism of the drug release rate kinetics of the dosage form, the data were supported with zero-order, first order, Higuchi, and Korsmeyer-Peppas release model. Among all the formulation, formulations [F6] were followed Higuchi model.***

**Keywords:** gastroretentive floating tablets, HPMC, swelling index, buvyancy test

## 1. Introduction

Furosemide, is 5-(aminosulphonyl) - 4-chloro – 2-[(2-fuanyl-methyl) amino] benzoicacid and it is a potent "high-ceiling" (loop) [1] diuretic drug and its act at the ascending loop of Henle in the Kidney. They are primarily used in medicine to treat hypertension and edema often due to congestive heart failure or renal insufficiency. While thiazide diuretics are more effective in patients with normal kidney function, loop diuretics are more effective in patients with impaired kidney function[2].Loop diuretic drug, is indicated for congestive heart failure, chronic renal failure, and hepatic cirrhosis. Furosemide is absorbed mostly in the stomach and upper small intestine, possibly due to its weak acidic properties (pKa.93), Furosemide is rapidly but incompletely absorbed following oral administration and undergoes first pass metabolism. The physicochemical properties of Furosemide is low bioavailability (43-50%), molecular weight (330.7g/mol) and short biological half life is (1-2.0 hrs) of Furosemide following oral administration favors development of a floating drug release formulation[3].

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances. Floating drug delivery system (FDDS) is a gastroretentive system that can be effervescent FDDS or non-effervescent FDDS[4].

The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability[5]. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[6]. The gastric retentive drugs were include furosemide, famotidine, cyclosporine, allopurinol, ciprofloxacin and metformin also Antibiotics, sedative, analgesics, anticonvusants, muscle relaxants, antihypertensive and vitamins can be administered in hydrodynamically balanced system (HBS).

Floating drug delivery system (FDDS) is classified into three categories: Single unit, multiple unit floating and raft forming systems and this present study formulation were prepared floating sustained release tablets (FDDS) of Furosemide using various formulation using grades of HPMC K4M, HPMC K15M, HPMC K100M and Methyl Crystalline Cellulose QS by direct compression into floating tablets. Post compression study were evaluated by weight variation, hardness, friability, disintegration, uniformity of content, in-vitro buoyancy study, in-vitro dissolution, floating lag time and swelling study. Swelling of hydrophilic polymer such as Hydroxy Propyl Methyl Cellulose (HPMC) greatly depends upon the contents of the stomach and the osmolarity of the medium. These eventually influence the release, slowing action and the residence time[7].

The present study were using different grades of polymers, in order to optimize the therapy research efforts have been focused on the development of oral sustained release

preparations as well as controlled release gastroretentive dosage forms. The above drawbacks provide a rationale for developing Furosemide as a gastro retentive dosage form. This enhances the bioavailability of the drug, reduces frequency of dosing, thus minimizes side effects and enhances patient compliance. The present study aims to formulate and in-vitro evaluation of non-effervescent of Furosemide gastroretentive floating tablets and to interpret the in-vitro dissolution studies.

## 2. Methodology

Furosemide procured from Natco Labs, Hyderabad, India, HPMC K4M, Accrual, and magnesium stearate from Merck pvt ltd, Mumbai, India, HPMC K15M, HPMC K100M and Talc from SD fine chemical, Mumbai, India, Microcrystalline cellulose from Heligent phama, Mumbai, India and other chemicals were consumed of analytical grade.

**Standard graph of Furosemide in 0.1N HCl (244 nm) [8]**
A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N Hydrochloric acid was using by Double beam UV visible spectrophotometer. The scanned solution of UV range is 200nm – 400nm.

**Preparation of stock solution, working solution and Standard curve[9]**
Weighed accurately 100mg of standard Furosemide and transferred into a 100ml volumetric flask contains 0.1N Hyderochloric acid. From this stock solution, 10ml was taken and made up with 100ml of 0.1N HCL (100µg/ml). Again, 10ml was taken and made up with 100 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 1-5µg/ml of Furosemide solution. The absorbance was recorded at 244 nm by using UV-Spectrophotometer making with 0.1N HCl. Standard curve was plotted (Figure No 1.1) by the observations measured in (Table No 1) and Linearity of standard curve was assessed from the square of correlation coefficient ($R^2$) which determined by least-square linear regression analysis.

**Compatibility study by FTIR:** The FTIR of furosemide detects characteristic peaks of wavelength of 3500 cm to 500cm. The FTIR of optimized form also detected the peaks in the same range of wavelengths.

**Formulation of gastroretentive tablets of Furosemide:**
Present study, different formulations were formulated by direct compression technique *(Wu. W et al)*, using HPMC K4M, HPMC K15M and HPMC K100M (floating agent) as polymers is shown in Table 1. Granulation was done with HPMC K4M, HPMC K15M and HPMC K100M. All ingredients were weighed accurately and granulated, passed (40#) and dried in Tray drier at 50·C. After, granules were observed loss on drying (LOD) pharmacopoeial limitation is (1.0% to 2.0%) and measured by moisture balance at 105·C. Then the dried granules, passed through 40/60 mesh, and lubricated with magnesium stearate and talc. Then, lubricated granules were compressed by using single punch tablet machine (Cadmach Machinery Ltd., Ahmedabad, India).

**Evaluation Parameters:**
The formulated floating tablets were evaluated for uniformity of weight using 10 tablets[10], hardness (Monsanto tester)[11] for friability using 10 tablets (Roche type friabilator)[12], drug content, disintegration test[13], buoyancy lag time[14] and *in vitro* dissolution studies. The results are expressed as mean ± SD.

**Determination of floating parameter**
***In-vitro* buoyancy test:**
As per Rosa literature, in-vitro buoyancy estimated and the tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required the tablet to rise to the surface and float was considered as the floating lag time.

**Swelling study[15]**
For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of distilled water. Then, each and every hour the tablet were taken out from beaker and reweighed until 8 hours. The percentage of swelling by the tablet was recorded by using the formula: Swelling index[13] (SI) = {(Wt-Wo)/Wo} x 100; Where, SI = swelling index; Wt = Weight of tablet at time t; Wo = Weight of tablet before immersion.

**Uniformity of content:**
Equivalent weight of 10 tablets were finely powdered and transferred into volumetric fask (100ml) containing 0.1N hydrochloric acid, and stirred for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 265nm using 0.1 N hydrochloric acid as blank solution.

***Invitro* dissolution study:** *Invitro* release studies was carried out by using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test performed using 900 ml of 0.1N HCl (pH 1.2) at 37±0.5·C and 50 rpm was maintained, 5 ml of sample was withdrawn at predetermined time intervals for 12 hours and the same volume of the fresh medium was replaced. The absorbance of the withdrawn sample was measured spectrophotometrically at a wavelength of about 244 nm and cumulative percentage drug release was calculated using an equation obtained from a standard curve[15].

**Mechanism of the drug release rate kinetics to dissolution data[16 - 20]:**
To examine the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted in zero-order, first order, Higuchi, and Korsmeyer - Peppas release model. Referenced from literatures,

**Zero order release rate kinetics:** To study the zero–order release kinetics the release rate data are fitted to the following equation.
F = Ko t, Where, 'F' is the drug release at time 't', and 'Ko' is the zero order release rate constant. The plot of % drug release versus time is linear.

**First order release rate kinetics:** The release rate data is, Log (100-F) = kt, A plot of log cumulative percent of drug

remaining to be released vs. time is plotted then it gives first order release.

**Higuchi release model and kinetics:**
F = k t1/2, Where, 'k' is the Higuchi constant.
In Higuchi model, a plot of % drug release versus the square root of time is linear.

**Korsmeyer and Peppas release model:** The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

Mt/ M∞ = K tn, Where, Mt/ M∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (Mt/M∞) versus log (time) is linear.

**Hixson-Crowell release model:** Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets). $(100\text{-}Qt)^{1/3} = 1001/3 - KHCt$, where, k is the Hixson - Crowell rate constant.

## 3. Results and Discussion

Standard graph were plotted for furosemide 0.1N hydrochloric acid (pH 1.2) at 244nm by using various concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 at 0.371, 0.122, 0.198, 0.288, 0.385 and 0.458 respectively.

**Table 1:** Estimation analytical methods of absorption maxima

| Concentration | Absorbance |
|---|---|
| 0 | 0 |
| 0.1 | 0.0371 |
| 0.2 | 0.122 |
| 0.3 | 0.198 |
| 0.4 | 0.288 |
| 0.5 | 0.385 |
| 0.6 | 0.458 |

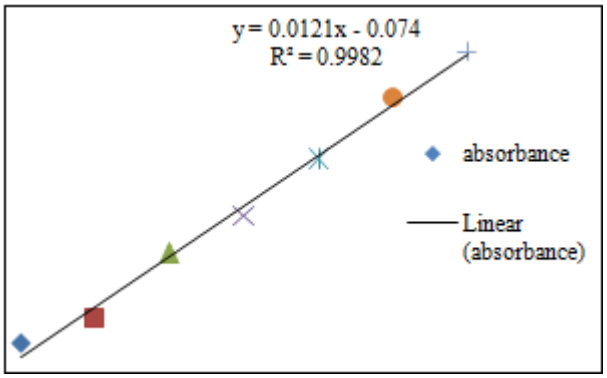


**Figure 1.1:** Standard graph of Furosemide

**Formulation of non – effervescent gastroretentive tablets of Furosemide:** In present study, all formulations of physicochemical evaluation parameters of Furosemide tablets and in vitro drug release studies showed in Table.2. Physicochemical parameters like thickness around the range (4.61 - 4.94). All the floating tablets were comprised the drug within 103 ± 5% of the label claim and all formulations of percentage of weight variation test, were complied the pharmacopoeial specifications of ± 5% of average weight.

The percentage of drug content was found to be 98.1% to 100.8% of Furosemide, comprised pharmacopoeial limits. The ranges of hardness of the tablets were in the range of 4.1 to 4.9 kg/cm$^2$ and F6 formulation (4.98) were obtained adequate mechanical strength. In friability, of the tablets were in the range of (0.43- 0.56 kg/cm$^2$) and all the formulation friability were found less than 1%, it was assuring that all tablets were having mechanically stable. In Floating lag time, ranges of 4.0 to 4.8. Formulation F6 were used HPMC K15M (30mg) of total weight and found to be satisfactory than other formulations which showed good physical properties, drug content and percentage of drug release rate.

**Table 2:** Formulation of non – effervescent gastroretentive tablets of Furosemide

| Sl.No | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Furosemide | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2 | HPMC K4M | 10 | 20 | 30 | - | - | - | - | - | - |
| 3 | HPMC K15M | - | - | - | 10 | 20 | 30 | - | - | - |
| 4 | HPMC K100M | - | - | - | - | - | - | 10 | 20 | 30 |
| 5 | Accrual | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| 6 | Magnesium Stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 8 | MCC | QS | QS | QS | QS | QS | QS | QS | QS | QS |

(All quantities were expressed in mg, Total weight of the Tablet is 100mg)

**Study of flow properties**
The furosemide granules were subjected to various pre-formulation studies such as Angle of repose, Bulk and Tapped density, Hausner's ratio, compressibility and carr's index for Furosemide granules. The finding of all formulations of angle of repose, bulk density, tapped density, compressibility index and hausner ratio in the range 22.62 - 27.12, 0.39 - 0.58, 0.54 – 0.68, 16.11 – 17.99 and 0.9 – 1.29 were found good flow, respectively.

**Table 3:** Preformulation studies of Furosemide granules

| *Code* | *Angle of repose (Θ)* | *Bulk density (gm/cm$^3$)* | *Tapped density (gm/cm$^3$)* | *Hausner ratio (Hg)* | *Carr's Index (%)* |
|---|---|---|---|---|---|
| F1 | 25.09 | 0.48 ± 0.05 | 0.56 ± 0.03 | 1.18 ± 0.05 | 16.11 ± 0.05 |
| F2 | 24.72 | 0.55 ± 0.02 | 0.61 ± 0.04 | 1.29 ± 0.05 | 17.99 ± 0.04 |
| F3 | 22.62 | 0.53 ± 0.04 | 0.68 ± 0.06 | 1.28 ± 0.04 | 16.77 ± 0.04 |
| F4 | 25.31 | 0.54 ± 0.03 | 0.64 ± 0.07 | 1.11 ± 0.07 | 16.67 ± 0.03 |
| F5 | 26.09 | 0.53 ± 0.05 | 0.66 ± 0.07 | 1.02 ± 0.05 | 16.12 ± 0.05 |
| F6 | 26.12 | 0.56 ± 0.04 | 0.66 ± 0.05 | 1.17 ± 0.04 | 17.34 ± 0.04 |
| F7 | 27.12 | 0.58 ± 0.07 | 0.54 ± 0.02 | 0.91 ± 0.03 | 16.45 ± 0.03 |
| F8 | 25.11 | 0.47 ± 0.05 | 0.67 ± 0.01 | 1.13 ± 0.03 | 17.33 ± 0.02 |
| F9 | 25.39 | 0.39 ± 0.07 | 0.66 ± 0.02 | 1.12 ± 0.01 | 17.23 ± 0.05 |

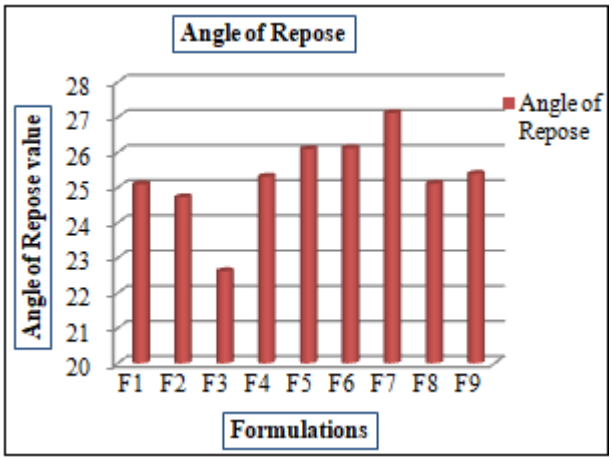


**Figure 3.1:** Prediction of Angle of Repose for Furosemide Granules

In this present study, evaluation parameters were performed such as weight variation, hardness, friability, thickness, drug content and floating lag time. All the formulations [F1 – F9] were complied specifications and shown in Table 4. Among all formulations, F6 were found to be the best formulation because it is stabilized during six months.

**Table 3:** Evaluation of non- effervescent tablets of Furosemide

| Physical Parameters | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Weight variation (mg) | 100.3 | 101.5 | 98.2 | 100.4 | 99.1 | 103.2 | 100.3 | 101.3 | 98.3 |
| Thickness (mm) | 4.61 | 4.68 | 4.72 | 4.74 | 4.94 | 4.81 | 4.72 | 4.91 | 4.88 |
| Hardness ($Kg/cm^2$) | 4.22 | 4.14 | 4.45 | 4.22 | 4.26 | 4.98 | 4.12 | 4.51 | 4.23 |
| Friability (%) | 0.49 | 0.43 | 0.55 | 0.53 | 0.52 | 0.22 | 0.55 | 0.54 | 0.56 |
| Drug content (%) | 98.0 | 99.3 | 99.9 | 98.9 | 99.8 | 100.8 | 98.1 | 98.3 | 99.3 |
| Floating lag time(mins) | 4.0 | 4.6 | 4.4 | 4.2 | 4.1 | 4.5 | 4.7 | 4.8 | 4.2 |

***In-Vitro* Drug Release Studies**

**Table 4:** *In-Vitro* Drug Release Studies for Furosemide Tablets

| *Time (hrs)* | *F1* | *F2* | *F3* | *F4* | *F5* | *F6* | *F7* | *F8* | *F9* |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 29.22 | 34.26 | 24.02 | 58.21 | 21.66 | 14.12 | 50.10 | 18.80 | 15.54 |
| 2 | 68.88 | 71.65 | 74.55 | 99.52 | 37.44 | 21.05 | 98.73 | 32.58 | 31.23 |
| 3 | 97.25 | 95.82 | 99.69 | - | 71.85 | 30.29 | - | 60.28 | 49.85 |
| 4 | - | - | - | - | 95.66 | 43.83 | - | 72.01 | 50.31 |
| 5 | - | - | - | - | - | 58.21 | - | 97.06 | 61.86 |
| 6 | - | - | - | - | - | 62.70 | - | - | 79.98 |
| 7 | - | - | - | - | - | 72.33 | - | - | 95.26 |
| 8 | - | - | - | - | - | 85.26 | - | - | - |
| 9 | - | - | - | - | - | 99.17 | - | - | - |

***In-vitro* drug release studies:** This Present study shown in table 4. All the formulations (F1 – F9) were performed six tablets. Formulations F1 (97.3%), F2 (95.8%) and F3 (99.7%) (HPMC K4M) drug release rate is retarded maximum concentration at end of 3rd hour. HPMC K15M were used as a polymer in formulations of F4 (99.5% at 2nd hour) & F5 (95.7% at 4th hour), the results were found not satisfactory (HPMC K15M 10 & 15mg, respectively), among all the formulations, F6 formulation, (HPMC K15M & HPMC K100M) were used and the percentage of drug release rate is increased at maximum dose concentration, at the end of 9th hour (99.2%) and results were found satisfactory. Formulations F7, F8 and F9, maximum dose of drug released and retarded at 2nd (98.8%), 5th (97.0%) and 7th hour (95.3%). Thus, the concentration of polymer and ratio of lactose had major influence on swelling process, matrix integrity, as well as on floating capability[13].

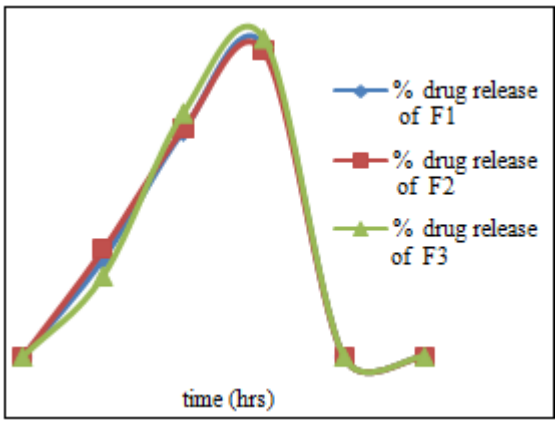


**Figure 4.1:** *In-vitro* drug release profile of formulations (F1, F2, F3)

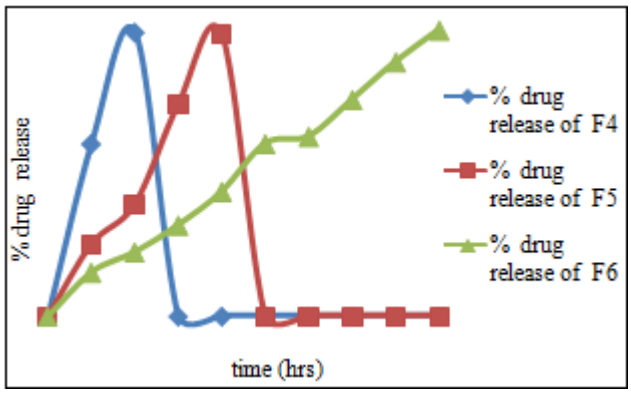


**Figure 4.2:** *In-vitro* drug release profile of formulations (F4, F5, F6)

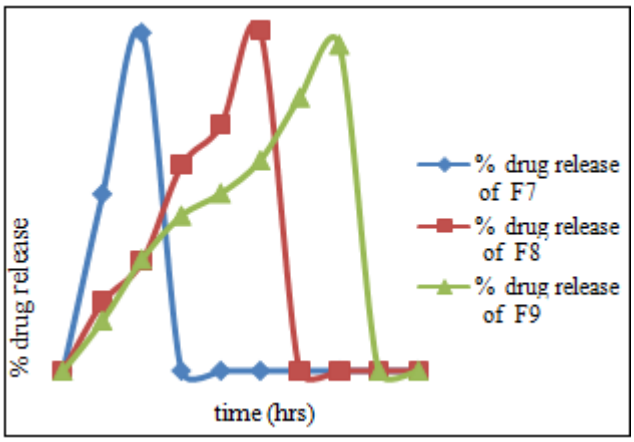


**Figure 4.3:** *In-vitro* drug release profile of formulations (F7, F8, F9)

**Application of Release Rate Kinetics to Dissolution profile:**

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data were co-ordinated with zero-order,

first order, Higuchi, and Korsmeyer-Peppas release model. Formulations [F6] were followed Higuchi model.

**Table 5:** Release kinetics data for optimised formulation of F6

| Cumulative (%) release q | Time ( t ) | Log (%) release | log ( t ) | Log (%) remain | Release rate (cumulative % release/t) | 1/cum % release | Peppas log q/100 | % drug remaining |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | | | 2.000 | | | | 100 |
| 15.12 | 1 | 1.445 | 0.000 | 1.858 | 27.860 | 0.0359 | -0.555 | 72.14 |
| 22.05 | 2 | 1.561 | 0.301 | 1.804 | 18.175 | 0.0275 | -0.439 | 63.65 |
| 31.29 | 3 | 1.618 | 0.477 | 1.768 | 13.817 | 0.0241 | -0.382 | 58.55 |
| 42.83 | 4 | 1.679 | 0.602 | 1.718 | 11.950 | 0.0209 | -0.321 | 52.2 |
| 59.21 | 5 | 1.742 | 0.699 | 1.651 | 11.050 | 0.0181 | -0.258 | 44.75 |
| 61.70 | 6 | 1.780 | 0.778 | 1.599 | 10.040 | 0.0166 | -0.220 | 39.76 |
| 74.33 | 7 | 1.824 | 0.845 | 1.522 | 9.533 | 0.0150 | -0.176 | 33.27 |
| 87.26 | 8 | 1.853 | 0.903 | 1.457 | 8.918 | 0.0140 | -0.147 | 28.66 |
| 98.17 | 9 | 1.895 | 0.954 | 1.332 | 8.724 | 0.0127 | -0.105 | 21.48 |

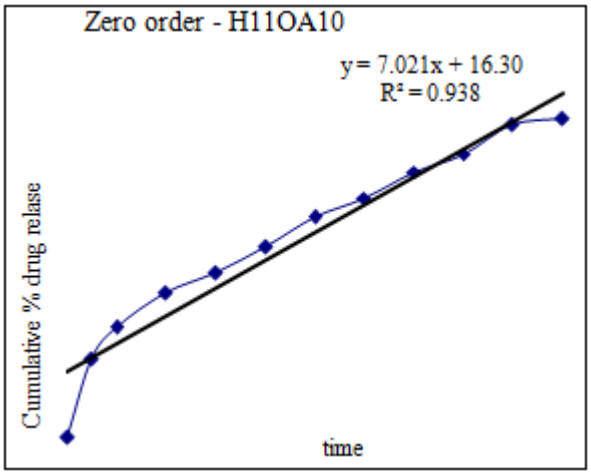


**Table 5.1:** Release kinetics data for optimised formulation of F6

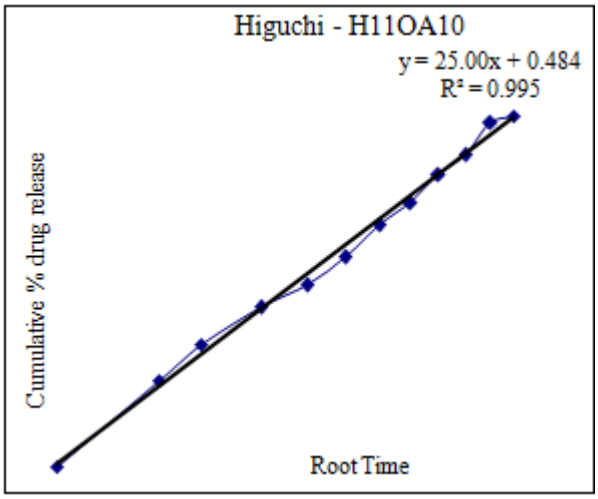


**Figure 5.2 :** Zero order release kinetics of F6

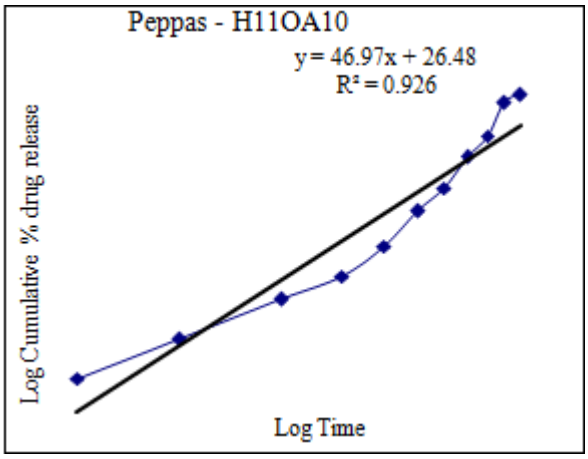


**Figure 5.3:** Higuchi release kinetics graph

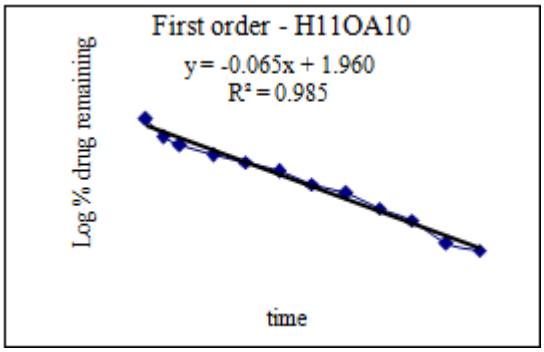


**Figure 5.4:** Kars mayer peppas graph

## 4. Conclusion

This present study, gastroretentive non-effervescent floating matrix formulation of Furosemide by using various hydrophilic polymers in order to achieve in vitro floating tablets. The addition of non-effervescent ingredient is used, as accrual was very essential to achieve gastro retentive floating drug. Present study, nine formulations were formulated by using various concentrations of gel forming polymer like HPMC K100M, K15M and HPMC K4M. The physico chemical properties of all the formulations were found to be within prescribed official specifications.

In preformulation studies, flow properties were found better result for all the formulations, its indicating that, blend was having very good flow property. Gel forming (HPMC K4M) polymer were retarded the drug release at end of 3rd hour. Hence, formulation F6 was optimized. Among all the

formulations, Formulation [F6] were produced desire drug release up to 9th hour, drug releases were gradually obtained and satisfactory. Also analyzed the mechanisms of the drug release rate kinetics of the dosage form, the data were supported with zero-order, first order, Higuchi, and Korsmeyer-Peppas release model. Among all the formulation, formulations [F6] were followed Higuchi model.

## 5. Acknowledgement

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## 6. Conflict of Interest

None

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