

Formulation And In-Vitro Evaluation Of Furosemide Gastroretentive Multiparticulate System

*Zaara Majeed, Asfia Kauser, Ayesha Haseena, Faheem Unnisa Begum, Afreen Jahan

*Assistant Professor, Shadan Women's College of Pharmacy,
Khiartabad, Hyderabad Department of Pharmaceutics
Corresponding Author: *Zaara Majeed

Abstract: The aim of the present study was to develop formulation of Furosemide to maintain constant therapeutic levels of the drug for over 12 hrs. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Then the formulation was developed by using different concentrations of polymers of various grades of HPMC and Guar gum. Gastroretentive floating beads of Furosemide were prepared with an aim to provide the drug for prolonged period of time in the stomach. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits Among all the formulations the formulations prepared by using Guar gum were in the concentration of 120mg (F4) showed maximum drug release 99.76% in 12 hours. Hence F4 formulation is optimized. It followed zero order release kinetics mechanism.

Keywords: Furosemide, HPMC polymers,

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I. Introduction

Oral route have been known for decades as the most prominent and convenient for systemic delivery of drugs designed in various dosage forms. The attractiveness of these dosage forms is mainly due to ease of administration, low cost, patient compliance, awareness of toxicity and ineffectiveness of drug when administered through tablets and capsules.¹⁻³

Oral Controlled release drug delivery systems (OCRDDS) that can be retained in the stomach for a long time have many advantages over sustained release formulations. Controlled drug delivery system release the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption site in the upper gastrointestinal tract.

Controlled release Gastroretentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a prolonged period of time and thereby improved the bioavailability. GRDDS extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.⁵

In general, appropriate candidates for controlled release gastroretentive dosages form (CRGRDF) are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

II. Biological Aspects Of Crgrdfs

STOMACH PHYSIOLOGY: The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae.

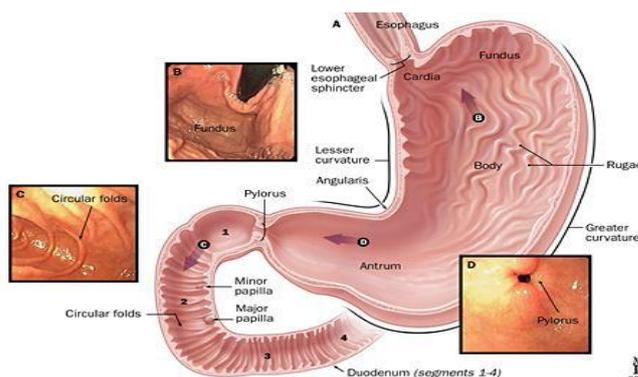


Fig. 1: Physiology of stomach

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.⁹This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC).

APPROACHES TO GASTRIC RETENTION FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery system is also called the hydrodynamically balanced system (HBS). Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. This delivery system is further divided into noneffervescent and effervescent (gas-generating system).

(A) NON-EFFERVESCENT SYSTEMS

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as Polycarbonate, Polyacrylate, Polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol.

(B) EFFERVESCENT SYSTEMS

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.

I. VOLATILE LIQUID CONTAINING SYSTEMS

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

II. GAS GENERATING SYSTEMS

These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime

ADVANTAGES OF FDDS

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.

DISADVANTAGES OF FDDS

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

I. MATERIALS

S.No	Names of materials
1	Furosemide
2	Olive oil
3	Sodium alginate
4	Calcium chloride

III. Methodology

3.1 STANDARD GRAPH OF FUROSEMIDE

The UV scanning of drug sample was carried out using a solution of drug dissolved in 0.1 N NaOH solution at concentration of 100 µg/ ml. The λ_{max} was observed at 271 nm. The calibration curve of Furosemide was obtained by dissolving the drug in 0.1 N NaOH solutions and absorbance was measured at 271 nm in 0.1 NaOH solution used a blank.

3.2 METHOD OF PREPARATION OF 0.1N NAOH

8gms in 1000ml of distilled water gives 0.1N NaOH.

3.3 EVALUATION TECHNIQUES

In vitro evaluation of floating tablets Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

3.4 PRE-COMPRESSION PARAMETERS

A) ANGLE OF REPOSE (θ)

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

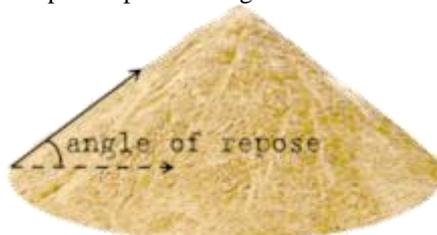


Fig : Angle of repose

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ = angle of repose

h = height of the heap

r = radius of the heap

The relationship between Angle of repose and powder flow is as follows in table

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Table : Relationship between angle of repose and powder flow

B) COMPRESSIBILITY INDEX

The flowability of powder can be evaluated by comparing the bulk density (ρ_0) and tapped density (ρ_t) of powder and the rate at which it packed down. Compressibility index was calculated by –

$$\text{Compressibility index (\%)} = \frac{\rho_t - \rho_0}{\rho_t} \times 100$$

Where ρ_0 = Bulk density g/ml
 ρ_t = Tapped density g/ml.

3.5 POST-COMPRESSION PARAMETERS

A) SHAPE OF TABLETS

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

B) TABLET DIMENSIONS

Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

C) HARDNESS

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm^2 . Three tablets were randomly picked and hardness of the tablets was determined.

D) FRIABILITY TEST

The friability of tablets was determined by using Roche Friabilator. It was expressed in percentage (%). Ten tablets were initially weighed (W_{initial}) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by –

$$\%F = 100 (1 - W_0/W)$$

% Friability of tablets less than 1% was considered acceptable.

E) TABLET DENSITY

Tablet density was an important parameter for floating tablets. The tablet would float only when its density was less than that of gastric fluid (1.004). The density was determined using following relationship.

$$V = \pi r^2 h$$
$$d = m/v$$

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (g/cc)

m = mass of tablet

F) WEIGHT VARIATION TEST

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed show in table .

Average weight of a tablet	Percent deviation
130 mg or less	10
>130mg and <324mg	7.5
324 mg or more	5

Table : Percentage deviation in weight variation

G) BUOYANCY / FLOATING TEST

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

H) SWELLING STUDY

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$WU = \frac{(W_t - W_0) \times 100}{W_0}$$

W₀

W_t = Weight of dosage form at time t.

W₀ = Initial weight of dosage form.

J) IN VITRO DRUG RELEASE STUDIES

The test for buoyancy and in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1N HCl as a testing medium maintained at 37°C. The time required to float the HBS dosage form is noted as floating (or floatation) time.

3.6 FORMULATION OF FUROSEMIDE FLOATING ALGINATE BEADS

Sodium alginate solutions of different concentrations were prepared by dissolving required amount of sodium alginate (Table 1) in 100 ml of deionized water under gentle agitation. Furosemide and olive oil were dispersed in alginate solution under constant stirring to make 100gm mixtures. To ensure emulsion stabilization, the mixtures were homogenised at 10000 rpm using homogenizer for 10 mins. This solution was dropped through 23G needle into 1%, 2%, 3% and 4% w/v CaCl₂ and left at room temperature for 20 mins. The resultant beads were washed with distilled water and dried at room temp. upto 12 hrs.

Master formulation of Floating beads

Ingredients (gm)	F1	F2	F3	F4	F5	F6
Furosemide	1gm	1gm	1gm	1gm	1gm	1gm
Olive oil	5%	7.5%	10%	12.5%	15%	20
Sodium alginate	0.5%	1.0%	1.5%	2.0%	2.5%	3.0%
Calcium chloride	1%	2%	3%	4%	1.0%	2%

IV. Results And Discussion

STANDARD CALIBRATION CURVE OF FUROSEMIDE

Standard Curve of Furosemide was determined by plotting absorbance (nm) versus concentration (µg/ml) at 271 nm. The results obtained are as follows

conc	abs
2	0.11
4	0.224
6	0.367
8	0.488
10	0.572
12	0.687
14	0.786
16	0.896

Table: Standard calibration curve of Furosemide

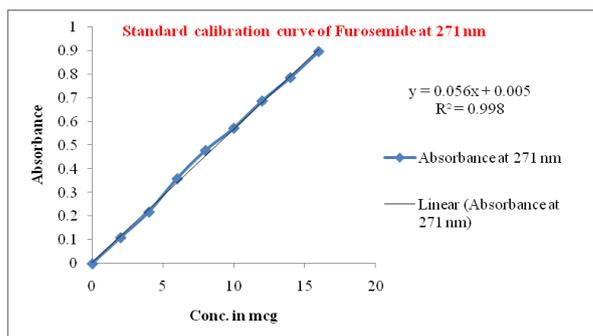


Fig. : Standard calibration curve of Furosemide

The linear regression analysis was done on absorbance data points.

A straight-line equation was generated to facilitate the calculation of amount of drug. The equation is as follows.

$$(Y = mx+c)$$

Where Y = Absorbance,

m = slope,

x = Concentration,

c = Intercept.

DRUG AND EXCIPIENTS COMPATABILITY STUDIES BY FTIR

The FTIR of pure drug furosemide shows characteristic peaks of wavelength of 3400.27 , 3122.54 , 1665 , 1560 cm-1.

The FTIR of optimized form also showed the peaks in the same range of wavelengths. After performing the studies we can say that there was no interaction between drug and excipients.

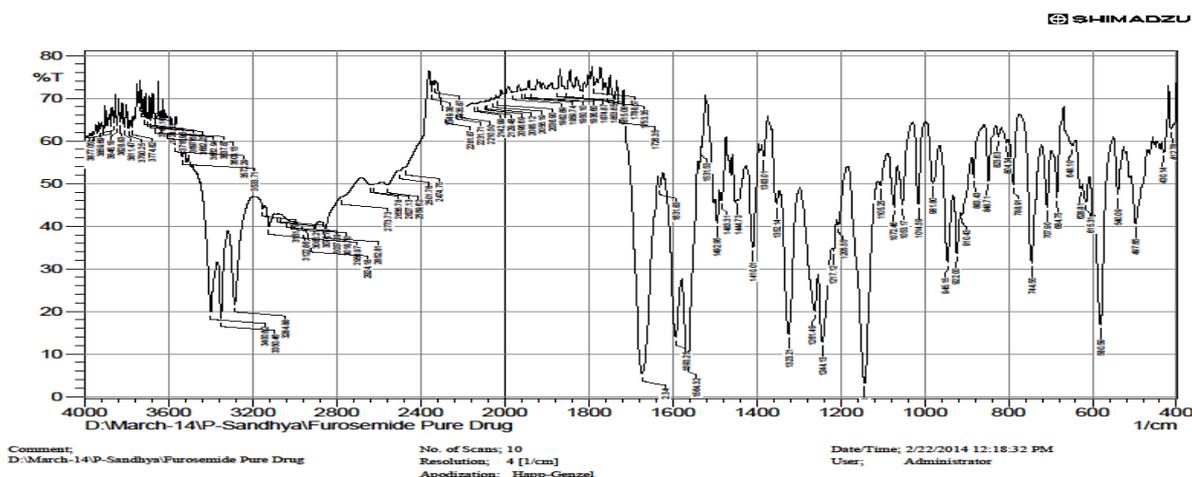


Fig : FTIR analysis of pure drug

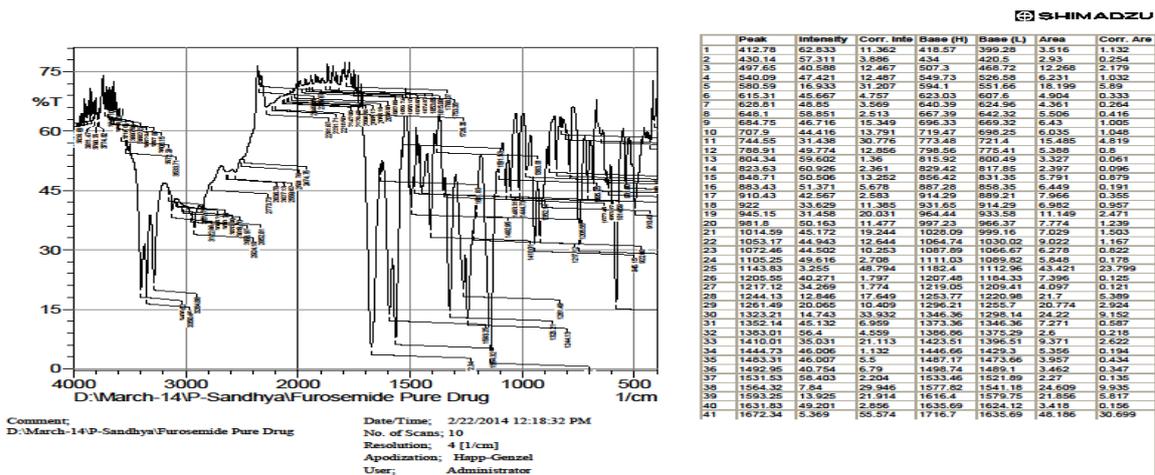


Fig : FTIR analysis of pure drug with peak values

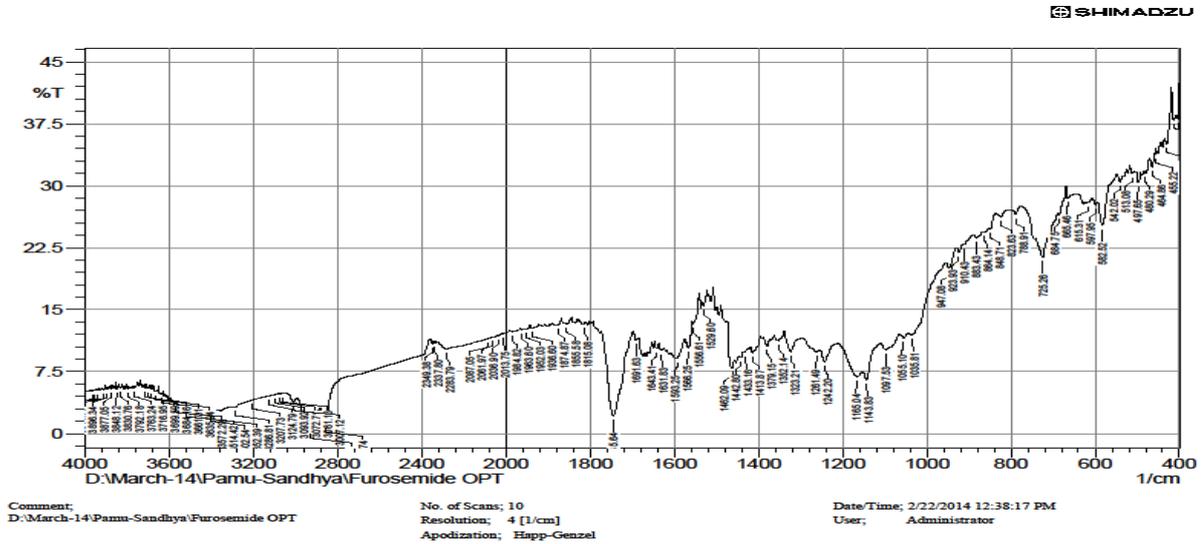


Fig : FTIR analysis of optimized formulation with peak values

DETERMINATION OF DRUG ENCAPSULATION EFFICIENCY

The drug encapsulation efficiency was increased with the increment of drug to polymer ratio. In case of Formulation-1, the % of encapsulation was 75%, wherethe drug to alginate ratio was 1:0.5. But, this was increased in F-2 to F-8 where entrapment efficiency was 78.12 – 92.34%.

Parameters	F1	F2	F3	F4	F5	F6
Encapsulation efficiency	75.45	78.12	85.43	92.34	87.21	76.34
Floating lag time (Seconds)	132	129	120	118	134	143
Total floating time (Hours)	10.34	10.21	11.10	12.2	10.88	10.10

Table : Evaluation of beads

IN VITRO RELEASE KINETICS:

After 12 hours the percent of drug release (Figure 10) for six formulations were 84.7% (F1), 83.5 % (F2), 82.2 % (F3), 99.98% (F4), 79.1 % (F5), 86.10 % (F6). The decrease in drug release was due to simultaneous increase in alginate amount. Because the more the amount of alginate, more would be the cross-linking between sodium alginate and calcium chloride; thus more drug would remain entrapped and decrease the release. In the absence of gas-forming agent the release rate was very slow.

Time in hours	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	21.43	24.30	26.50	24.32	28.40	27.32
4	24.6	29.40	34.62	40.22	34.69	37.89
6	35.26	34.68	46.50	55.32	39.16	47.09
8	48.66	49.62	57.80	71	46.30	56.89
10	76.50	75.61	78.92	84.92	72.65	78.90
12	84.70	83.50	82.20	99.98	79.10	86.10

Table : In vitro drug release profiles of F1-F6

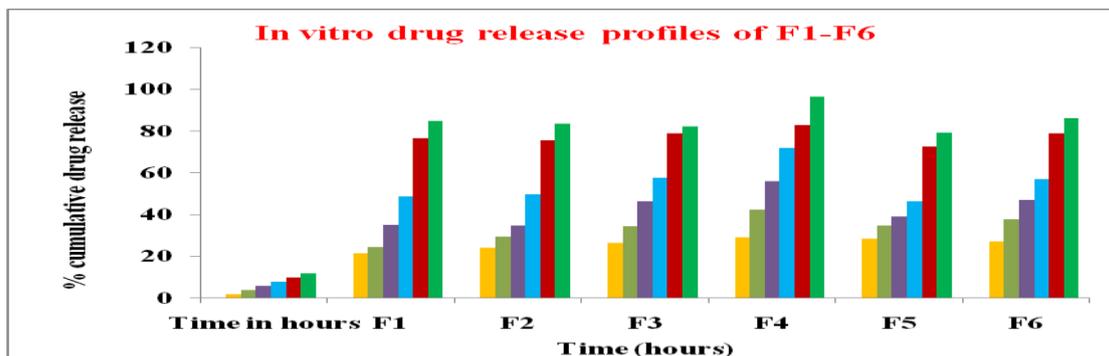


Fig : In vitro drug release profiles of F1-F6

**DRUG RELEASE KINETICS OF OPTIMIZED FORMULATION F4
ZERO ORDER DRUG RELEASE KINETICS**

Time in hours	% drug release
0	0
2	24.32
4	40.22
6	55.32
8	71
10	84.92
12	99.98

Table : Drug release kinetics of optimized formulation F4

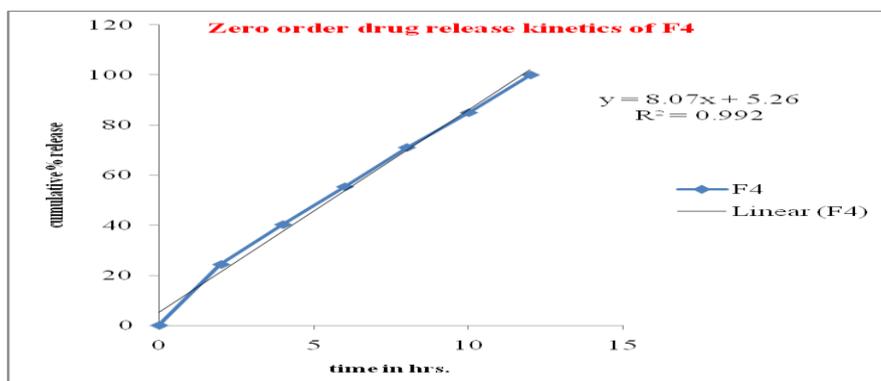


Fig: Zero order drug release kinetics of F4

V. Conclusion

Gastric emptying of the dosage forms is an extremely variable process and is the ability to prolong and control the emptying time which is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Gastroretentive floating beads of Furosemide were prepared with an aim to provide the drug for prolonged period of time in the stomach. Amoxicillin was targeted to stomach because it has the absorption window in upper part of GIT. The floatation was accomplished by incorporating gas generating agent, calcium carbonate into a swellable polymer. FTIR studies of the pure drug and formulations showed that there was no drug polymer interaction. The physico chemical properties of all the formulations were found to be within the prescribed official limits. The increase in polymer concentration and viscosity causes retarding of the drug release. Formulations containing higher polymer concentration had slower drug release when compared to formulations with lower concentration of polymers. From all the formulation F4 formulation showed better release profile and extended the drug release for longer duration of time. Hence F4 formulation is optimized. The drug release pattern from the optimized formulation followed zero order kinetics.

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