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Effect of superdisintegrant on the release of ofloxacin from gastric floating drug delivery systems

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Abstract
Gastic floating drug delivery systems are the most suitable dosage forms for the drugs with narrow absorption window in the proximal part of duodenum. Drugs in this category can be formulated into sustained release dosage forms along with gastroretention for optimum therapeutic drug. Ofloxacin which has a low solubility in alkaline pH was formulated with hydrophilic polymer such as xathan gum, superdisintegrant like Crosspovidone and sodium bicarbonate as gas generating agent. Formulated tablets floated in the 0.1N Hcl within 145seconds and floated for a period more than 24hrs at 10% sodium bicarbonate. Based on the integrity of the tablets at 10th hour, concentration of crosspovidone was fixed at 50mg per tablets. Upon changing the concentration of xanthan gum from50 to 200mg, HF1 with 200mg of xanthan gum was found to be best in terms of tablettting charecterstics. All the tablets HF1 to HF4 complied with the IP limits. Cumulative percentage drug release of HF1 was close to the theoretical drug release of ofloxacin. release profile of the optimized formulation HF1 were fitted to kinetic models which showed that release of drug from the dosage form followed zero order release.

Keywords: Gastroretention, floating drug delivery, ofloxacin, xanthan gum

1. Introduction
Oral route of administration is most often preferred route in view of its versatility in physiological conditions and it can release the drug for its desired therapeutic benefits optimally [1]. In conventional dosage forms, patient has to take the dosage form several times a day to achieve the desired drug concentration for intended therapeutic effect. Main advantage of Gastic floating drug delivery systems (GFDDS) is to maintain a constant concentration od drug within the absorption window thereby reducing the frequency of administration eventually improving the efficacy of drugs [2].

GFDDS are less prone to the effect of gastric emptying thereby resulting in reduced variability in inra day and inter day subject observations [3]. Absroption of the drug will be enhanced in case of GFDDS as the system will release the drug in controlled manner form the formulation during floating and the most of the drug released have a whole surface area of upper git for absorption [2]. Various researchers worked on dosage forms using the principle of floating technology such as – nonefferevescent tablets [4], effervescent tablets [5], fused deposited modeling 3D printed tablets [6].

In the present investigation the drug ofloxacin was selected for the design of GFDDS. Ofloxacin is having absorption window in upper small intestine. But the sudden gastric emptying often affects their therapeutic efficacy. Xanthan gum is a complex exopolysaccharide produced by Xanthomonas campestris [7]. Selected polymer xanthan gum has good swelling property [8]. when xanthan gum comes in contact with the intestinal fluid, it forms viscous gel matrix and retard the release of the drug from the dosage form [9]. Gas entrapped within the matrix decreases the density of the tablet below the gastric fluid as result, the tablets floats. (16, 18) The drug will be released from the dosage form slowly at a controlled rate without affecting the emptying time of gastric contents [10-12]. (7-19). Based on the literature, it was concluded that floating lag time of a GFDDS will significantly change based on the concentration of the sodium bicarbonate in the tablet [13].

Although, very few gastric retention systems were developed based on swelling and expansion for ofloxacin, there are no reports on the use of floating concept in the formulation of gastric retention systems of ofloxacin using different concentrations of Xanthan gum along with superdisintegrant. Hence in the present investigation, it is aimed to develop GFDDS of ofloxacin (effervescent floating tablets) with swellable polymer, Xanthan gum and superdisintegrant.

The major objectives of the investigation are as follows.

- To formulate and evaluate the Ofloxacin floating tablets using xanthan gum and cross povidone
- Evaluation of the prepared tablets for floating lag time and floating time.
- Optimization of the prepared formulations using the floating lag time and floating time.
- Evaluation of the optimized GFDDS for tabletting characteristics like weight variation, hardness, friability, drug content.
- *In vitro* drug release studies from the Optimized formulation

Materials and Methods

Materials

Ofloxacin Gift sample from M/S. orchid USP Life Sciences, Haryana., Xanthan gum, Polyvinylpyrrolidone (S.D. Fine Chemicals Ltd., Mumbai), Sodium bicarbonate and magnesium stearate (S.D. Fine Chemicals Ltd., Mumbai), Crospovidone (Gift sample from M/s. Ajantha Pharma Ltd., Mumbai), Hydrochloric acid (Qualigens Fine Chemicals Ltd., Mumbai), Methanol (Qualigens Fine Chemicals Ltd., Mumbai)

Method

Preparation of GFDDS: In order to enhance the flow and compaction properties, the drug sufficient for a batch of 10 tablets was passed through mesh no. 100 and granulated by using 5% polyvinylpyrrolidone solution. The polymer, effervescent agent and superdisintegrant and drug sufficient for a batch of 10 tablets according to the formulae were passed through mesh no. 12 and were dried in a hot air oven at not more than 50°C until LOD (loss on drying) reaches within 2 to 3%. Dried granules were passed through sieve no. 16. Then the blend was lubricated with magnesium stearate. Tablets containing Ofloxacin equivalent to 400 mg were compressed by using 9.0 mm, round shaped caplet shaped punches, on 16- station tablet punching machine (Cadmach) at the hardness of 4 to 6 kg/cm^2. Initially, concentration of sodium bicarbonate was optimized with formulations F1 to F4 (Table 2) by using floating lag time and total floating time. After fixing the concentration of sodium bicarbonate, concentration of crosspovidone was varied between 25to 75mg (Table 3) and finally the concentration of the xanthan gum was varied (Table 4).

Evaluation of tablets: The floating properties of the tablets prepared by the above method were evaluated by determining floating lag time and floating time. The tablets were also subjected to various quality control tests such as uniformity of weight, hardness, friability tests and drug content uniformity.

Floating Lag Time and Floating Time: The time taken by the tablet to emerge on to the surface of the liquid (floating lag time) after adding to the dissolution medium was measured using stopwatch. The time up to which the tablet float constantly on the surface (floating time) was evaluated in a dissolution vessel filled with 900ml of simulated gastric fluid without pepsin, pH 1.2, temp. 37 ± 0.5^{0}C, paddle rotation 50 rpm.

Uniformity of Weight: According to Indian Pharmacopoeia twenty tablets were selected at random, weighed together and then individually for the determination of uniformity of weight of tablets. The mean and standard deviation were determined.

Hardness: Five tablets were selected at random and the hardness of each tablet was measured on Monsanto hardness tester.

Friability: The friability test was carried out in Roche Friabilator. Ten tablets were weighed (w_o) initially and put in a rotating drum. Then, they were subjected to 100 falls of 6 inches height. After completion of rotations, the tablets were again weighed (w).
The percent loss in weight or friability (f) was calculated by the formula given below and the results are given in tables 5 & 9.

$$f = \left(1 - \frac{w}{w_0}\right) x\,100$$

Estimation of drug content

From each batch of the prepared tablets, five tablets were randomly collected and powdered. A quantity of powder equivalent to 100 mg was transferred into a 100 ml volumetric flask; sufficient amount of methanol was added and shaken for 20 minutes. The solution was filtered and finally made up to 100ml with methanol. The solution was suitably diluted with distilled water and assayed for the drug content of Metoprolol succinate at 274 nm using a single beam UV spectrophotometer (Elico SL-150, Taiwan).

***In vitro* dissolution studies**

Dissolution test was carried out using USP XXIV (model DISSO 2000, M/s. Labindia) rotating basket method (apparatus 1). The stirring rate was 100 rpm. 0.1 N hydrochloric acid was used as dissolution medium (900 ml) and was maintained at 37 ± 1°C. Samples of 5 ml were withdrawn at predetermined time intervals, filtered and replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the ofloxacin at 293 nm by using a double beam UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation and erosion equation.

Analytical method for the estimation of ofloxacin

Analytical methods are available such as HPLC, potentiometry, Polarography, UV- Visible Spectrophotometric methods were reported for the estimation of Ofloxacin in biological fluids and Pharmaceutical formulations.

Methods used in the Present Research Work: UV – Visible Spectrophotometric method based on the measurement of absorbance at 293 nm in water stock solution was used in the present work for the estimation of ofloxacin. The dissolution studies were carried out in 0.1 N Hcl. Hence the calibration curve was constructed in 0.1 N Hcl.

Materials

Ofloxacin – Gift sample from M/S. orchid USP Life Sciences, Haryana.
Hydrochloric acid – (Exela R, Qualigens Fine Chemicals Ltd., Mumbai)

Stock solution: 100 mg of Ofloxacin was dissolved in 10 ml of 0.1 N Hcl in a 100 ml volumetric flask and made up to volume with 0.1 N Hcl.

Method: For the estimation of Ofloxacin in 0.1 N Hcl, the stock solution was diluted subsequently with 0.1N Hcl to get a series of dilutions containing 2, 4, 6, 6, 8 and 10 µg / ml of solution. The absorbances of these solutions were measured at 293 nm against reagent blank. The results are shown in Fig. No. 2. and Table No. 1.

Table 1: Calibration curve for estimation of Metoprolol succinate

S. No	Concentration (µg/ml)	Absorbance (Avg ± s.d)
1.	2	0.252 ± 0.0019
2.	4	0.452 ± 0.0041
3.	6	0.612 ± 0.0038
4.	8	0.813 ± 0.002
5.	10	0.943 ± 0.0008

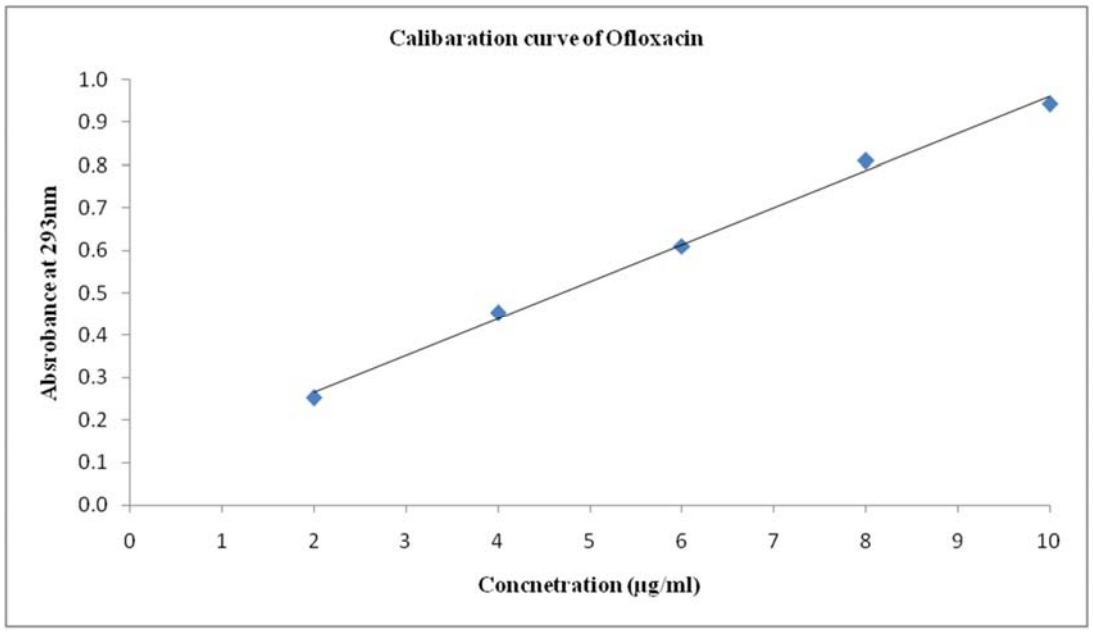

Fig 1: Calibration curve for the estimation of Ofloxacin

Results and Discussion: The present analytical method obeyed Beer's law in the concentration range of 2 – 10 µg / ml and is suitable for the estimation of ofloxacin from different solutions. The correlation coefficient (r) value for the linear regression equation was found to be 0.999, indicating a positive correlation between the concentration of Ofloxacin and its corresponding absorbance values (Fig 1).

Table 2: Formulation of GFDDS of Metoprolol succinate at different levels of Sodium bicarbonate

Ingredient	F1	F2	F3	F4
Ofloxacin	400	400	400	400
Xanthan gum	100	100	100	100
Cross povidone	50	50	50	50
Magnesium stearate	20	20	20	20
Sodium bicarbonate (%)	5	10	15	20
Lag time(Sec)	320	145	151	Tablet disintegrated
Floating time (Hours)	>24hrs	>24hrs	>24hrs	>24hrs

Table 3: Formulation of GFDDS of Ofloxacin with different concentrations of Crosspovidone

Ingredient	S1	S2	S3
Ofloxacin	400	400	400
Xanthan gum	100	100	100
Cross povidone	75	50	25
Magnesium stearate	20	20	20
Sodium bicarbonate	20	20	20
Tablet integrity at 10^{th} hour	poor	Good	Good

Table 4: Formulation of GFDDS of Ofloxacin at different levels of Xanthan gum

Ingredient	HF1	HF2	HF3	HF4
Ofloxacin	400	400	400	400
Xanthan gum	200	150	100	50
Cross povidone	50	50	50	50
Magnesium stearate	20	20	20	20
Sodium bicarbonate	70	70	70	70
Total weight of tablet (mg)	730	680	630	580

Results and discussion

The effect of various formulation factors such as concentrations of effervescent agent, superdisintegrant on floating properties and drug release were studied to optimize the formulation. The floating lag time mainly depends up on the concentration of effervescent agent present in the matrix. In the present study sodium bicarbonate was used as effervescent agent, as it is cheap and safe.

GFDDS formulated with Xanthan gum represented as F1, F2, F3 and F4 (Table 4.) contained the sodium bicarbonate in the concentrations of 5%, 10%, 15% and 20% w/w of total formula were selected to study the effect of effervescent concentration on lag time. It was found that increasing the amount of sodium bicarbonate decreased the floating lag time. Among the various formulae prepared, formulation F2 showed less lag time compared to. The data of floating lag time and total floating time at various concentrations of sodium bicarbonate are given in Table 2.

The floating lag time decreased in the rank order:

F1 > F3 > F2 > F4

From the literature it was believed that high levels of the sodium bicarbonate degrade the drug because of the alkaline pH developed in the microenviroment of the tablet and also disintegrates the tablet. So, we have selected 10% - 15% as the optimum concentration of sodium bicarbonate as effervescent agent. From the preliminary trails we have decided to use the 70mg of the sodium bicarbonate per a tablet weight of 600mg to 800mg.

Superdisintegrants such as crosspovidone, cross caramellose sodium and sodium starch glycolate were selected for formulating GFDDS of ofloxacin. Based on the tablet integrity in 0.1N HCl, it was inferred that cross povidone is the best superdisintegrant that can be used for formulating the GFDDS of ofloxacin. Cross povidone was taken as superdisintegrant in the present study.

It was observed that by increasing the concentration of superdisintegrant, tablet integrity was decreased. At lower concentration, super disintegrant acted as a rapid swelling agent and improved the floating characteristics, but at higher concentrations it decreased the compactness of the tablet due to its disintegrant action. The results are given in Table 3.

Formulations based on different levels of xanthan gum are prepared and the formulations are given in Table 4. The tabletting charecterstics such as weight variation, drug content uniformity, hardness and friability are calculated and results are given in Table 5. The release profile of the formulations at different levels of xanthan gum HF1, HF2, HF3, HF4 are given in Table 6. The data shows that the release of Ofloxacin at 12th hour was 96.58, 76.02, 54.95, 69.45 for the formulations HF1, HF2, HF3 and HF4 respectively. Upon comparison with Theoretical drug profile calculated for the ofloxacin it was found that HF1 has the release profile closer to therotical drug release profile. Moreover the tabletting charectersitcs such as weight variation, drug content uniformity, hardness and friability were also in acceptable range. Xanthan gum at a concentration of 200 mg was found to give good release profile. dissolution data of optimized formulation HF1 was fitted to four different models such as zero-order, first-order, diffusion and erosion equations. Kinetic profile study (Figures 5 & 6) mechanism of the drug release from the optimized formulation followed zero order and mechanism of the drug release cannot be confirmed as the two values of R^2 were close (Fig 3 & Fig 4)

Summary and conclusions

Retention of drug delivery systems in the stomach prolongs overall G.I. transit time, thereby, resulting in improved oral bioavailability of the drugs. Various approaches have been developed to retain the dosage form in the stomach. Gastric floating drug delivery systems offer numerous advantages over other gastric retention systems. There are very few reports on the formulation of gastric retention systems of ofloxacin using xanthan gum and cross povidone. Hence, in the present investigation, GFDDS of Ofloxacin were developed with hydrophilic polymer like xanthan gum, superdisintegrant like cross povidone to deliver ofloxacin to the upper parts of the small intestine in a controlled manner to improve its bioavailability.

The GFDDS of Ofloxacin prepared from all the polymers were found to be of good quality fulfilling all the official and other requirements of compressed tablets. The effect of different formulation parameters such as concentrations of effervescent agent and superdisintegrant on floating properties and drug release were studied and the formulations were optimized. The concentration of the effervescent agent greatly influenced the floating lag time. By increasing the concentration of effervescent agent, decreased lag times were obtained.

Although effervescent agent played a major role in bringing up buoyancy, a significant change in the lag time was observed by incorporating super disintegrant. Crospovidone was selected as a superdisintegrant in formulating GFDDS. At lower concentration, super disintegrant acted as a rapid swelling agent and improved floating characteristics, but at higher concentrations it decreased the compactness of the tablet due to its disintegrant action. Hence, the concentration of the superdisintegrant was optimized to protect integrity of the tablet.

The GFDDS of Ofloxacin prepared from crosspovidone at a concentration of 50mg remained intact and the compactness of the tablet was not affected during the *in vitro* dissolution test.

It was found that the drug release from the GFDDS of ofloxacin mainly depended upon the concentration of xanthan gum present in the GFDDS. As the concentration of xanthan gum is increased, decreased dissolution rates were obtained. In case of xanthan gum concentration, 200mg is optimum concentration for a better release of drug HF1.

Table 5: Tabletting Characteristics of ofloxacin GFDDS prepared from Xanthan Gum

Formulation	Weight[a] (mg)	Drug content[a] (%)	Hardness [a] (kg/cm^2)	Friability [b] (%)
HF1	729.06 ± 1.36	98.62 ± 0.18	4.74 ± 0.32	0.48
HF2	678.70 ± 1.46	99.24 ± 1.54	4.82 ± 0.49	0.32
HF3	628.65 ± 1.28	99.74 ± 0.97	5.14 ± 0.24	0.26
HF4	575.19 ± 1.37	98.94 ± 0.48	5.06 ± 0.56	0.45

a: Mean ± S.D., n = 10 tablets, b: Mean, n = 10 tablets

Table 6: Cumulative percent Ofloxacin released from GFDDS containing varying concentrations of Xanthan gum

Time (HRS)	Cumulative percent drug released				
	HF1	HF2	HF3	HF4	Theoretical drug release
0.5	24.35	9.66	5.41	7.48	26.88
1.0	36.45	14.22	6.66	8.52	32.86
2.0	38.31	19.66	11.95	13.49	38.84
3.0	42.57	23.7	15.36	16.47	44.82
4.0	49.56	30.08	24.24	25.33	50.80
5.0	52.84	36.75	26.07	35.82	56.69
6.0	63.56	42.28	31.53	38.71	62.77
7.0	67.95	44.56	33.45	41.12	68.74
8.0	75.45	45.38	35.72	45.39	74.73
9.0	81.25	50.13	34.56	48.56	80.71
10.0	85.45	52.03	38.27	50.28	86.69
11.0	91.45	61.45	47.32	58.36	92.67
12.0	96.58	76.02	54.95	69.45	98.65

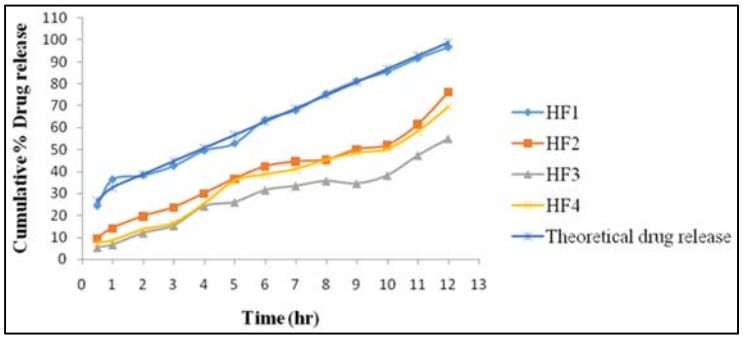

Fig 2: Effect of xanthan gum on cumulative % release of Ofloxacin GFDDS

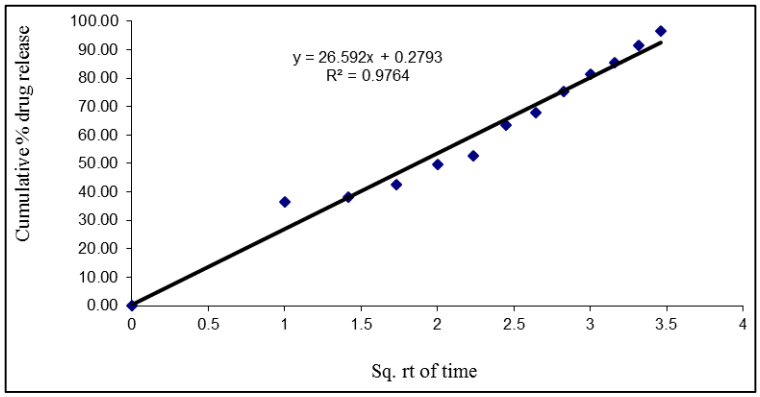

Fig 3: Higuchi plot for formulation F1

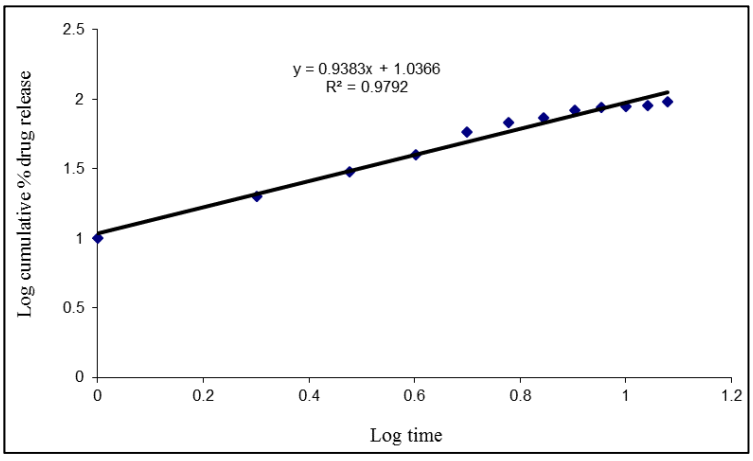

Fig 4: Korsmeyer-peppas plot for formulation HF1

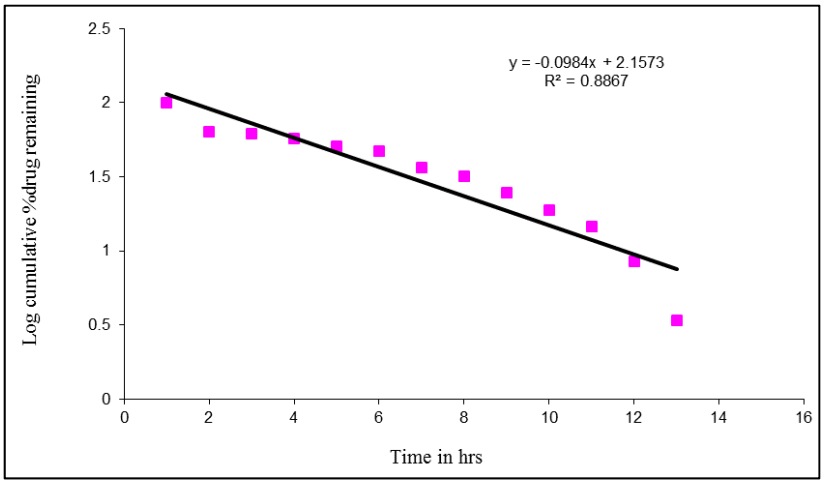

Fig 5: First order plot for formulation HF1

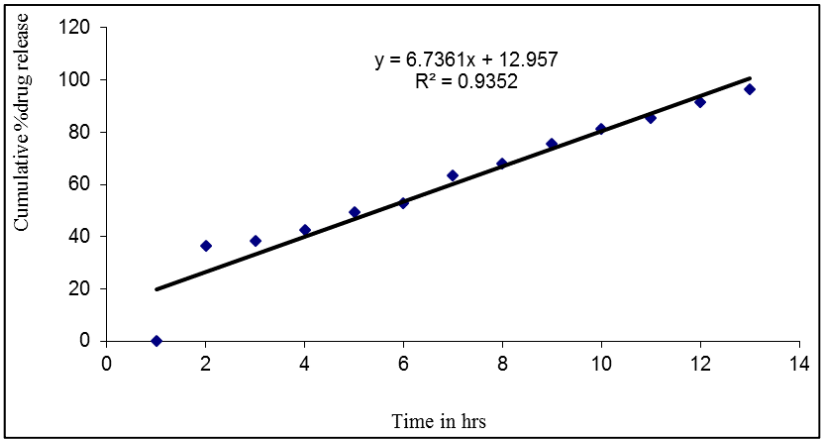

Fig 6: Zero order drug release plot for formulation HF 1

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