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DESIGN AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF DIURETIC FUROSEMIDE

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ABSTRACT

The present study concerns the development of gastroretentive floating tablets of diuretic drug Furosemide which release the drug in a sustained manner over a period of 12 h. Direct compression technology was employed for formulating the tablets. Various natural polymers like xanthan gum, carbopol and sodium alginate were used. In the present study furosemide floating tablets were prepared by effervescence method using sodium bicarbonate as a gas generating agent. Formulations were evaluated for weight variation, thickness, hardness, friability, content uniformity, swelling index, floating lag time and in vitro drug release. The dissolution studies was evident that the optimised formulation of sodium alginate showed better and desired drug release of 93% in 12 hrs. In vitro drug release pattern of furosemide floating tablets was fitted to different kinetic models which showed highest regression for zero order kinetics with non fickian diffusion mechanism.

KEYWORDS: Gastroretentive tablet, Furosemide, xanthan gum, sodium alginate, Carbopol.

1. INTRODUCTION

One of the most convenient and feasible route of drug delivery is by oral route. However, the problems associated with this route are short gastro-intestinal transit time, unpredictable gastric emptying rate and existence of an absorption window in the gastric and upper small intestine for several drugs leading to low and variable oral absorption over shorter period of time. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Gastro retentive dosage form can remain in the

gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine.

The approaches used to retain the dosage form in the stomach are bioadhesive system, swelling and expanding systems, floating systems and other delayed gastric emptying devices. Floating systems or dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentrations. Floating tablets are designed based on gas generating phenomenon.[1,2]

In the present investigation the drug furosemide was selected for the design of GFDDS. It is mainly absorbed in the upper gastro intestinal tract and has a short half life of less than 2h. The conventional dosage form shows erratic absorption which results in poor bioavailability (30–60%) and the requirement for dosing 3–4times / day6. In addition, the peak diuretic effect results in significant adverse effects in some geriatric patients. On this basis, a controlled release formulation of furosemide is very desirable. Hence, it is aimed to Design and evaluate furosemide effervescent floating matrix tablets with different swellable polymers.[3,4,5]

2. MATERIALS AND METHODS

Furosemide is given as gift sample by Celon Laboratories, Hyderabad. Xanthan gum, sodium alginate, Carbopol 974 P, Sodium bicarbonate, citric acid, povidone, lactose, and talc and magnesium stearate was procrurred from Asian Scientific, Hyderabad.

2.1. Drug excipients interaction study and identification

2.1.1. Fourier transform infrared spectroscopy (FTIR)

IR spectra were routinely analysed for drug-polymer interaction. FTIR spectra were taken for pure drug (furosemide) and physical mixture of drug and polymers (xanthan gum, sodium alginate and carbopol) to check the compatibility. The samples were prepared in KBr discs prepared at a hydrostatic pressure of 5 tonnes/cm^2 for 2 min. Any change in spectrum pattern of drug due to presence of polymers was investigated to identify any chemical interaction.

2.1.2. Differential scanning calorimetry (DSC)

The possibility of drug excipient interaction was further investigated by differential scanning calorimetry. DSC spectra were routinely analysed for drug polymer interactions. The DSC instrument was designed to supply heating to a sample, so that its temperature rises precisely. Thermograms were run in aluminum pans (reference cells) using indium metal as a standard. The heat rate was 5 °C per minute under nitrogen atmosphere (flow rate 50-60 ml/minute). The energy required to maintain the samples at the required temperature was recorded on a chart, which is geared to the temperature rise. Thermograms were obtained for furosemide, individual polymers and mixture of drug- polymer.

2.2. UV spectroscopy (determination of lambda max)

The furosemide 10 µg/ml was scanned by UV-Visible spectrophotometer in the wavelength range of 200-400 nm on Elico double beam UV visible spectrophotometer. The spectrum and wavelength of maximum absorption were recorded. A wavelength of 276 nm was selected as the analytical wavelength.

2.3. Preparation of standard curve

Concentrations of 2, 6, 10, 14 and 18 µg/ml were prepared. The absorbance of these solutions were measured at 276 nm against a blank i.e. 0.1 N HCl. A calibration curve was plotted. Slope, regression coefficient and equation for the line was determined.

2.4. Preparation of furosemide solid dispersion

Furosemide solid dispersion was prepared by solvent evaporation method with 1:7 drug and polymer ratio. Drug and PVP was dissolved in methanol. Solvent was evaporated on magnetic stirrer at 40° C. Resulting mixture was rapidly cooled in chilled water and stored in desicator for 24 hrs. Optimized based on the release profile of the drug. This mixture is used for preparation of tablets.[6]

2.5. Preparation of furosemide floating tablet

The composition of different formulations of furosemide floating tablets is shown in Table no 1**.** All the ingredients were weighed and passed through sieve no. 44. The powder blends were lubricated with Magnesium stearate (2% w/w) and Talc (2% w/w) and mixed for two to three minutes. These lubricated blends were compressed into tablets using 9 mm flat faced round tooling on a multiple punch tablet machine.

2.6. Pre-compression evaluation

The granules were evaluated for flow property i.e. angle of repose, bulk density, tapped density, compressibility index (Carr's index) and Hausner's ratio using standard procedures.[7]

Table-1: Formulations containing different concentrations of polymers.

Ingredients	Quantity (mg) present in Formulation								
	F1	F2	F3	F4	F5	F6	F8	F7	F9
Furesomide SD	60	60	60	60	60	60	60	60	60
Xanthan gum	15	30	45	-	-	-	-	-	-
Carbopol 934	-	-	-	15	30	45	-	-	-
Sodium alginate	-	-	-	-	-	-	15	30	45
Sodium Bicarbonate	30	30	30	30	30	30	30	30	30
Citric acid	10	10	10	10	10	10	10	10	10
Povidone K 30	60	60	60	60	60	60	60	60	60
lactose	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
talc	6	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total mg	300	300	300	300	300	300	300	300	300

2.7. Post-compression evaluation

The prepared tablets were evaluated for their physical parameters like thickness, weight variation, friability, hardness and drug content.[8]

The swelling properties of the matrix tablets were determined in 0.1 N hydrochloric acid solution. Samples of tablets of known weight were placed in a dissolution basket containing 500 ml of swelling solution and allowed to swell at 37 °C. The basket was rotated at 50 rotations per minute. The swollen tablets were removed and blotted them with filter paper to remove the adhering moisture on the surface. The wet mass was weighed. Percentage swelling was calculated. Experiments were conducted in triplicate.

$$SI\ \% = (Wt - W0/W0) * 100$$

Where, Wt = weight of tablet at time t, W0 = initial weight of tablet.

The floating abilities of the effervescent tablets were determined using USP Dissolution apparatus type II (50 rpm, 37 ± 0.5º C, 500 ml, and enzyme free).[16] Tablets were placed in the medium and the time required to float was measured by visual observation. Since the dosage form was floating type, a sinker was used for immersing the matrix tablet into the dissolution medium. 900 ml of 0.1 N hydrochloric acid solutions was placed into the cylindrical glass vessel of the dissolution apparatus.5 ml Sample of dissolution medium were withdrawn periodically at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0 11.0 and 12 hours. The

same volume of medium was replaced. The samples were filtered, suitably diluted, and analysed at λ_{max} of 276 nm.

Release Studies – Analysis

The obtained dissolution data was fitted to zero order, first order, Higuchi and Korsmeyers Peppas equations to understand the rate and mechanism of drug release from the prepared formulations. The correlation coefficients values were calculated and used to find the fitness of the data. Release data were analysed as per zero order and first order. The release mechanisms were analysed as per Higuchi and Peppas equation models.[9,10,11,12]

3. RESULTS

3.1. Determination of lambda max

The wavelength of maximum absorbance was obtained at 276 nm "Fig. 1". The calibration curve was found to be linear in the range of 0 to 20 µg /ml and straight line equation was obtained having the regression coefficient value of 0.998.

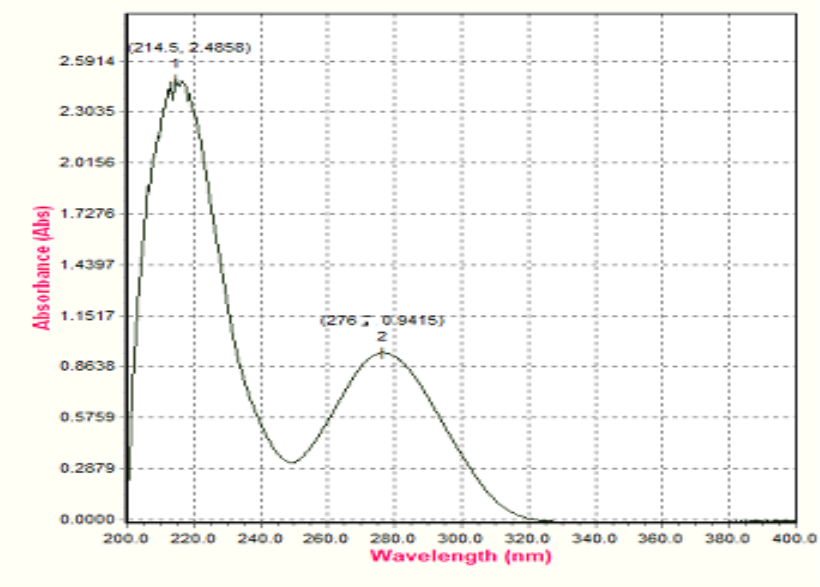

Figure 1: UV-spectrum of furosemide in 0.1 N hydrochloric acid solution.

3.2. Drug excipients interaction and identification

FTIR spectrum of furosemide and optimized formulation showed slightly varied streching bands after pre-formulation study, revealing no chemical interaction "Fig. 2,3". DSC thermogram showed a sharp endothermic peak at 213 Cal for drug and 215 for optimized formulation indicating that there was no incompatibilities "fig 4,5"

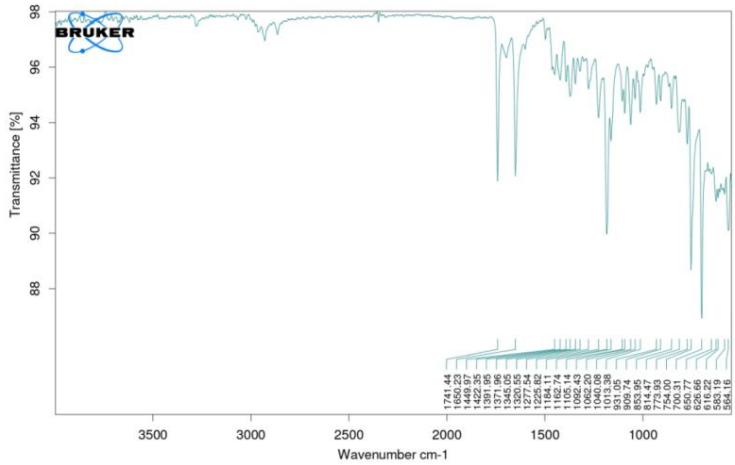

Figure-2: FTIR spectra of furosemide.

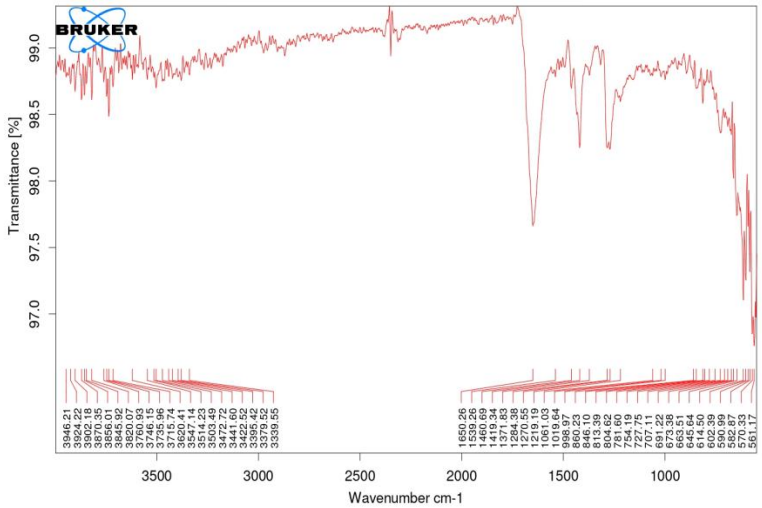

Figure-3: FTIR spectra of furosemide, xanthan gum, sodium alginate and carbopol 974P.

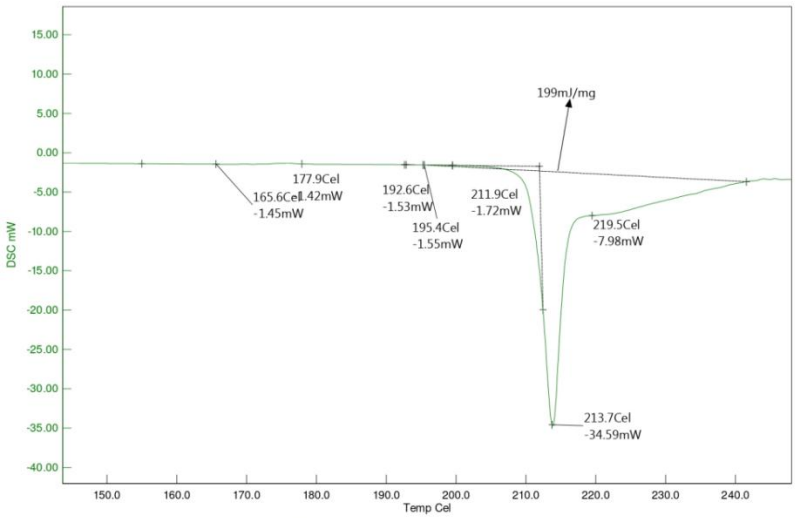

Figure 4: DSC thermogram of furosemide.

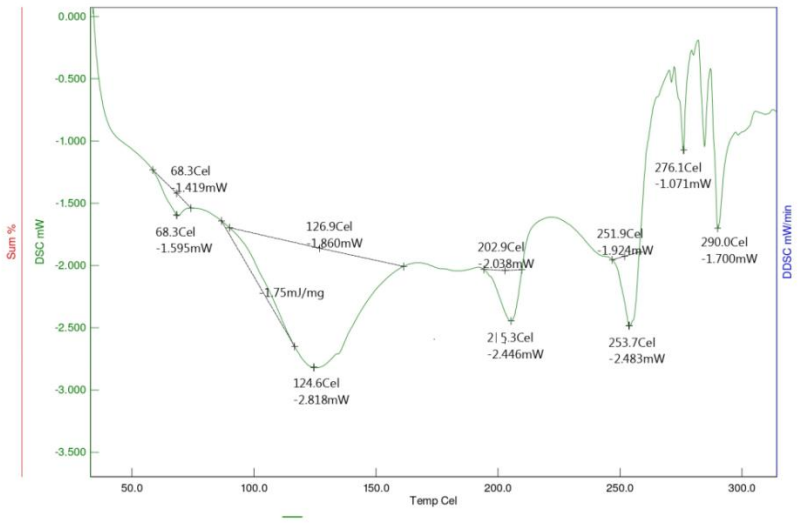

Figure 5: DSC thermogram of optimized formulation.

3.3. Physical characteristics

The powder blend of all nine formulations (F1 to F9) was evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. It showed that the pre-compressed blend has good flow property (Table 2). Formulated matrix tablets were evaluated for physical parameters such as hardness, thickness, weight variation, friability, drug content and swelling index, the results are shown in Table 3. It was found that all the powder blends have good flow property as they showed angle of repose value was between 22° and 27°. Carr's index value was between 11 and 17. Hausner's ratio was found to be less than 1.4 showing good flow property. The total weight of each formulation was maintained constant; the weight variations of the tablets were within the permissible limits. Tablet thickness was also used to assess the quality of tablets. The thickness of floating tablets ranged from 4.58 to 5.06 mm. Tablet hardness of all formulations was found to be satisfactory. Friability test of all the formulations was found satisfactory less than 1% showing enough resistance to the mechanical shock and abrasion. Drug content in all formulations was calculated and the presence of active ingredient ranged from 98.5 to 102.63%. The formulation with higher concentration has increased swelling characteristic. Percentage swelling index of F1-F9 are shown in table 4.

Table-2: Physical parameters of the powder blend before direction compression.

Formulation code	Angle of repose (Ɵ) ± SD	Bulk density (gm/cc)m3) gm/cm3) (gm/cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner ratio (HR)
F1	26.01±0.002	0.361	0.652	13.95	1.16
F2	24.7±0.0031	0.322	0.655	17.25	1.20
F3	22.64±0.002	0.298	0.598	14.71	1.17
F4	26.42±0.001	0.30	0.650	11.10	1.11
F5	25.32±0.004	0.342	0.651	11.52	1.13
F6	27.08±0.004	0.529	0.597	11.39	1.12
F7	25.45±0.002	0.512	0.598	14.38	1.16
F8	25.21±0.003	0.520	0.591	12.01	1.13
F9	26.89±0.007	0.512	0.611	16.2	1.19

Table-3: Important parameters of evaluation for tablets.

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm2)	Friability (%)	Drug content (%)	Weight variation (mg)
F1	4.58±0.05	8.9±0.09	4.93±0.25	0.503	99.89±1.75	349.6±1.17
F2	4.65±0.03	8.9±0.1	5.23±0.25	0.543	99.93±2.71	350±1.13
F3	4.59±0.04	8.8±0.15	6.16±0.28	0.488	102.63±2.1	349.8±0.78
F4	4.54±0.036	8.9±0.11	5.03±0.05	0.644	99.56±0.75	349.8±0.73
F5	5.06±0.025	8.9±0.05	5.06±0.11	0.488	99.96±0.56	349.7±1.08
F6	4.85±0.025	8.9±0.11	5±0.2	0.689	98.5±1.00	399.8±0.8
F7	4.97±0.092	8.9±0.05	5.16±0.35	0.472	101.7±1.60	350.05±1.14
F8	4.59±0.025	8.8±0.11	5.83±0.28	0.644	101.51±0.7	349.85±1.11
F9	4.68±0.053	8.9±0.02	5.82±0.25	0.722	99.87±0.04	358.28±1.01

Table-4: Swelling studies of GFDDS formulations.

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	35.02	38.65	43.87	27	45.06	54.05	47.94	62.5 77.81	56.94
2	65.02	55.85	63.14	38.93	61.81	75.59	56.17	77.81	89.54
3	77.65	75.68	72.81	68.73	94.54	101.25	77.52	88.28	101.38
4	84.98	98.75	86.42	91.01	101.81	114.84	91.011	95.39	117.01
5	101.24	109.48	99.02	95.66 6698	111.27	121.95	94.75	103.94	146.07
6	75.45	114.85	123.41	98	134.18	145.05	102.24	118.45	158.66
7	66.78	125.04	132.25	106.66	145.57	154.78	111.58	121.42	164.25
8	-	132.73	145.87	113.87	158.25	165.02	118.25	126.56	176.68

3.4. Evaluation of buoyancy of the tablets

As the dissolution medium was imbibed into the matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the formation and entrapment of carbon dioxide gas within the

swollen gel thus causing floatation, as the matrix volume expanded and its density decreased below one. The buoyancy time was up to the expectation, i.e., 12 hours. It is the criterion for drug release from sustained/controlled release formulations, 20 hours – not less than 80%. The optimized formulations were found to be satisfactory. Formulations F3 which had higher concentration of polymer showed FLT of than 5min, this may be due to thick matrix tablet formation which may cause the prevention of the entry of the medium into the tablet, due to which gas generation occurs slowly, while other formulation had the floating lag time of less than 2 min and the floating duration of 12 h. formulation F4 and F7 have total floating time of less than 12 h due to low concentration of polymer. As the concentration of polymer was increased, floating lag time was increased. Therefore the proposed mechanism of buoyancy was achieved.

Table-5: Lag times and buoyancy times of the different dosage floating forms.

Parameter	Formulation codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lag time, sec	115	130	380	60	95	110	65	75	82
Buoyancy time, hours	>12	>12	>12	>6	>12	>12	>8	>12	>12

3.5. In vitro drug release

In vitro dissolution studies were performed in 0.1 N HCl (1.2 pH) for 12 hrs and results depicted are in “Fig. 6 and 8.

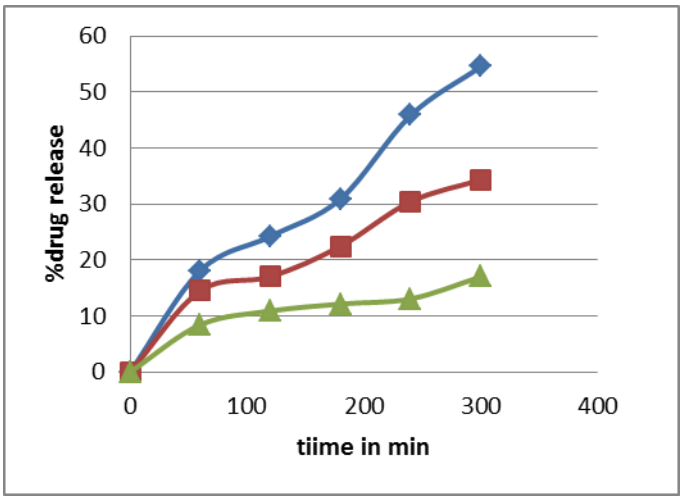

Figure-6: % Cumulative drug release of F1,F2 and F3.

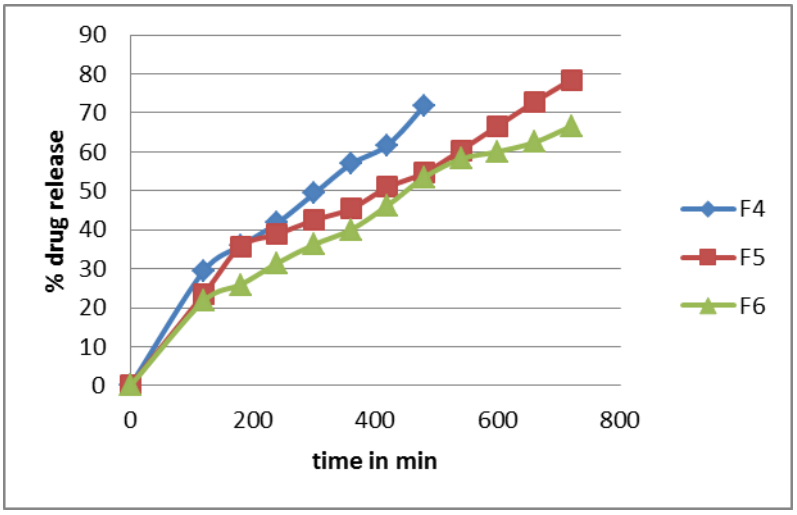

Figure-7: % Cumulative Drug Release of F4, F5 and F6.

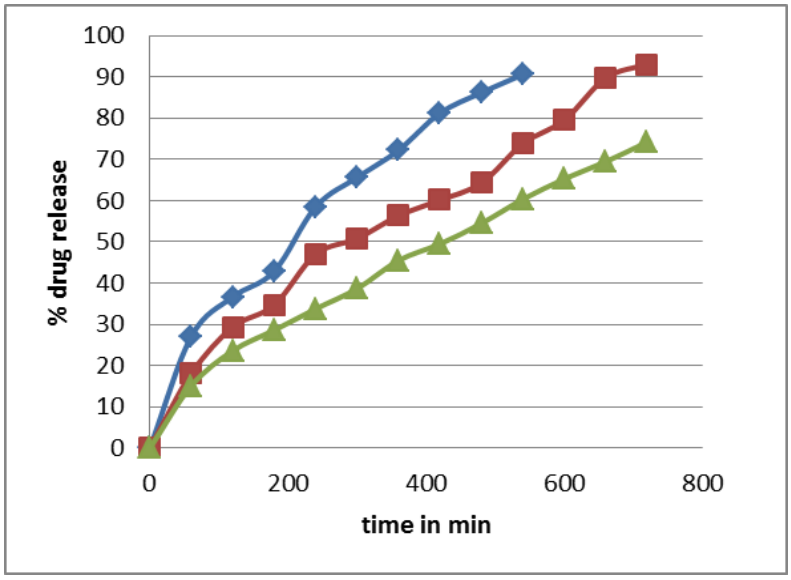

Figure-8: % Cumulative Drug Release of F7, F8 and F9.

3.6 Release Kinetics

The In-vitro release of all the formulations was subjected to pharmacokinetic data analysis and found that the optimized formulation F8, showed first order release kinetics with the R^2 value of 0.899 and the R^2 value of Korsemeyer-peppas 0.998 (nearer to 1) is dominant than the other models which indicates drug release depended on diffusion and erosion.

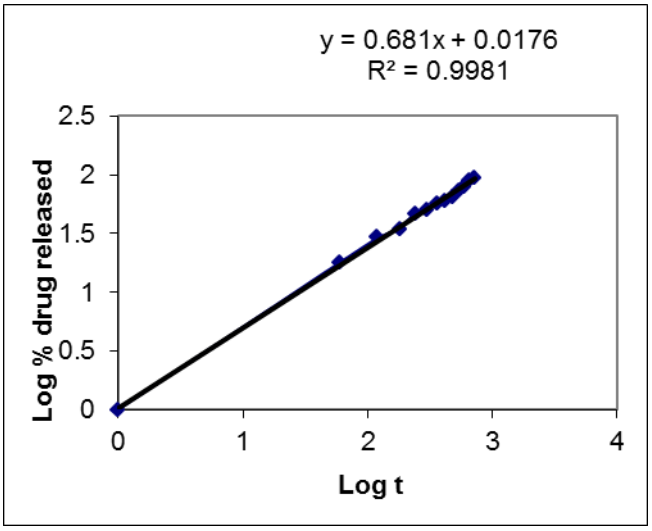

Figure-8: Koresomeyer peppas plot for F8.

4. DISCUSSION

The studies were conducted on the different concentrations of natural polymers (5%, 10%, 15%). The results indicated that among all the natural polymers F-1 formulation which has xanthan gum has shown retardation of drug release with only 85% of the drug release rate even at the end of 8 hrs, F-2 with xanthan gum has 64 % release even till 12 hrs which has much drug release retardation and F-3 with xanthan gum has 26% release till 12 hrs which also has shown more retardation of drug release. Among the formulations of carbopol F-4 has showed the 71% drug release within 8 hrs, F-5 has showed 78% drug release at the end of 12 hours. And F-6 has shown the 66% drug release at the end of 12 hrs. Among the formulations of sodium alginate F-7 has showed the 90% drug release within 9 hrs, F-8 has showed 93% drug release at the end of 12 hours and F-9 has shown the 74% drug release at the end of 12 hrs F-8 has shown best results since the retardation is observed till 12 hrs and drug release is also maximum.

5. SUMMARY AND CONCLUSION

The research was undertaken with an aim to formulate and characterize the sustained release floating tablets of furosemide using xanthan gum, sodium alginate and Carbopol 974P as polymers. The effervescent based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel forming polymer and gas generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. These floating tablets gave slow and sustained release of drug over 12 h which reduces the dosing frequency and improves patient compliance. From the results obtained, it was concluded that the drug release from the

optimised formulation F8 showed required release. The drug release was found to be diffusion and erosion controlled which followed first order kinetics. The optimised formulation increased the residence time of the drug in the stomach and released the drug for extended period of time thereby increasing the bioavailability of the drug.

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