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PREPARATION AND *IN VITRO* EVALUATION OF FLOATING TABLETS USING BIODEGRADABLE POLYMERS

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ABSTRACT

Floating tablets of furosemide were prepared using Albizia gum, Dammar gum and Copal gum as polymers for controlling the drug release. Furosemide is poorly water-soluble drug (Class IV) and its bioavailability is very low from its crystalline form. The rate of absorption and the extent of bioavailability for such insoluble drug are controlled by the rate of dissolution in the gastrointestinal fluids. Hence, number of attempts were made to increase the rate of dissolution of such poorly water soluble drugs, to increase their effectiveness and simultaneously reduce their doses and hence the toxic effects. Two types of diluents were used and the drug release was compared. Pure drug and optimized formulation were subjected to the drug excipient compatibility studies using FTIR and DSC. The studies revealed that there was no interaction between the drug and excipients. In order increase the drug release channeling agents were introduced namely Lactose and DCP. Lactose is water soluble diluent and DCP is water insoluble diluent. Precompression parameters were performed to all the formulations and were found to be in the acceptable limit which ensures the good flow properties. Formulation FFRA4 containing albizia gum and lactose as channeling agent showed good results when compared with other formulations. The floating lag time of the optimized formulation was very short and the percentage of drug release at the end of 12 hours was found to be high. The drug release kinetics revealed that formulation FFRA4 follows zero order kinetics and the mechanism was nonfickian.

KEY WORDS: **Furosemide, DCP, Lactose, Albizia gum, Dammar gum and Copal gum**

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INTRODUCTION

Furosemide (4-chloro-N-furfuryl-5-sulphamoylanthranilic acid) is a diuretic and has a highly variable bioavailability (<60%) when administered as commercially available tablets. The bioavailability studies carried out on animals have pointed out that there may be regions in the stomach and/or upper part of the small intestine in which furosemide is specifically absorbed and it has been thought that the short stay of controlled[1,2,3,4] release preparations in this specific region of absorption leads to bioavailability[5] problems. Passive diffusion is the major mechanism of transport of the drug across the gastrointestinal tract. Furosemide has a pKa of 4.6 and since the stomach environment is acidic, there is an increase in the unionized moiety of the drug with subsequent increase in the absorption [6]. A high peak diuresis is observed after the administration of a conventional tablet of furosemide. Due to this, it is only administered experimentally in the therapy for ascites, and edema due to liver cirrhosis. To eliminate such an effect, various efforts have been made to formulate furosemide in prolonged release forms. Studies showed that the bioavailability of furosemide was excessively increased compared to conventional forms and that absorption of furosemide taken place vastly in stomach and upper parts of small intestine when administered as a floating[7] tablet formulation. Buoyant preparations offer a simple and practical approach to not only achieve increased gastric residence time for the dosage form but also modify the drug release profile. The present study aims in designing floating tablets of Frusemide using Albizia gum, Dammar gum and Copal gum and evaluating the prepared tablets for physicochemical properties, buoyancy lag time, total floating time, swelling index and in-vitro drug release.

MATERIALS AND METHODS

Furosemide procured from Microlabs, Banglore and Lactose, DCP, Magnesium Stearate and Talc were from S. D fine chemicals. All materials used were of Pharmacopoeial grade. Albizia gum, Copal gum and Dammar gum were obtained from Girijan cooperative stores, Vishakapatnam.

Development of Calibration curve [8]

Standard solution

Accurately weighed 50 mg of furosemide was dissolved in 50 ml of pH 1.2 hydrochloric acid buffer to get a solution containing 1000 µg/ml of drug.

Scanning

From the standard solution, a solution was prepared to give a concentration of 10 µg/ml in pH 1.2 hydrochloric acid buffer and UV scan was taken between the wavelengths of 200-400 nm. The spectrum is reported in the figure 1. The absorption maxima of 230 nm was selected and utilized for further studies.

Standard Plot

From the stock solution 2, 4, 6, 8 and 10 µg/ml concentrations of furosemide were prepared respectively. The absorbance of prepared solutions of furosemide in pH 1.2 hydrochloric acid buffer were measured at 230 nm spectrophotometrically against pH 1.2 Hydrochloric acid buffer as blank. Standard plot data of furosemide in pH 1.2 Hydrochloric acid buffer is reported in table 1 and graph in figure 2.

Preparation of Floating tablets [9]

The Floating tablets containing furosemide were prepared by a direct compression technique. Albizia gum, Dammar gum and Copal gum were used as polymers for controlling the drug release. The compositions of various floating tablet formulations were given in tables. The Controlled release tablet formulations consisted of a drug and polymer [10] were prepared in different ratios. The amount of sodium bicarbonate [11, 12] added as gas generating agent was same in all the formulations in order to produce floating properties to the tablets. The dose of the drug was maintained constantly while the proportion of polymers was varied for various Floating tablets.

Evaluation of the tablets

The formulations prepared are shown in tables 5, 6, 7 together with their compositions. The drug, polymer/s, gas generating agent and diluent were screened through # 40 and pre blended using a lab scale double cone blender. The lubricant was added and the blend was mixed again prior to compression. The tablet blends were directly compressed by using a Elite 10 station minipress with 8mm round punches. To avoid processing variables all batches of Floating tablets were compressed under identical conditions. All the floating tablets prepared were further evaluated for physical parameters such as weight uniformity, hardness, friability and uniformity of drug content.

Hardness

Five tablets were selected at random and the hardness of each tablet was measured on Monsanto hardness tester and is shown in table 2.

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 given formula.

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

Uniformity of weight [13, 14]
According to IP 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 and is shown in table 2

Floating lag time and floating time [15]
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 900 ml of pH1.2 buffer, maintained at a temp. 37±0.5^{0}C and is shown in table 3.

Swelling study [16]
Swelling of hydrophilic polymers 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. For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of pH 1.2. After each hour the tablet was removed from beaker and weighed. The percentage weight gain by the tablet was calculated by using the formula and is shown in table 3.
Swelling index (S.I) = $\{(Wt-W_O)/W_O\}$ X100
Where S.I=Swelling index
W_t=Weight of tablet at time t
W_O= Weight of tablet before immersion

Fourier transform infrared spectroscopy (FT-IR)
Furosemide and optimized Floating tablet formulation FFRA4 were subjected to FT-IR spectroscopic analysis using Pekin-Elmer 841IR spectrophotometer, to ascertain whether there is any interaction between the drug and the polymers used. The obtained spectra are given in figures 3, 4. Characteristic peaks of furosemide were compared with the peaks obtained for its Floating tablet formulation FFRA4. The data for the same is given in table 4. The characteristic bands of furosemide were identifiable and there was no major shift in them when combined with polymers used in the preparation of floating tablet. This indicates that the drug is intact and has not reacted with the excipients used in the formulation and hence they are compatible.

Differential scanning calorimetry (DSC)
DSC studies were carried out for furosemide and formulation FFRA4 using Shimadzu DSC-50 Thermal analyser under static nitrogen atmosphere of 30ml/min and the thermograms obtained are presented in figure 5. Thermogram of pure drug showed a sharp endothermic peak at 215.9^{o}C, which corresponds to its melting point. Floating tablet formulation FFRA4 also showed endothermic peak at 215.9^{o}C, which corresponds to the melting point of the drug. The evaluation of thermograms revealed no interaction between the drug and the excipients. From the thermograms shown in figure, it was evident that the melting point of furosemide has not changed after it was formulated as a floating tablet.

RESULTS

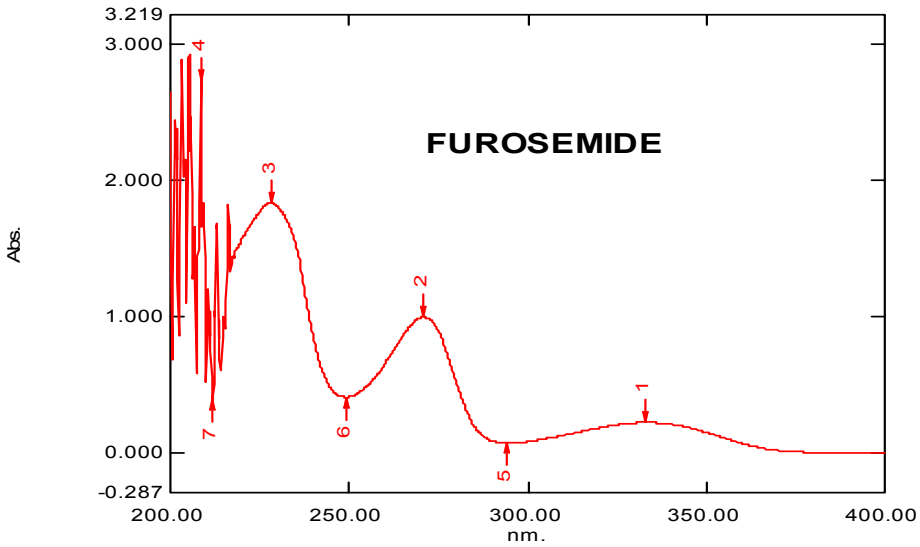

Figure 1
UV-Spectra of Furosemide in pH 1.2 hydrochloric acid buffer

Table 1
Standard plot data for Furosemide in pH 1.2 hydrochloric acid buffer

Concentration (µg/ml)	Absorbance at 271 nm (Mean ± S.D*)
2	0.093 ± 0.0031
4	0.161 ± 0.0025
6	0.245 ± 0.0020
8	0.331± 0.0030
10	0.401 ± 0.0035

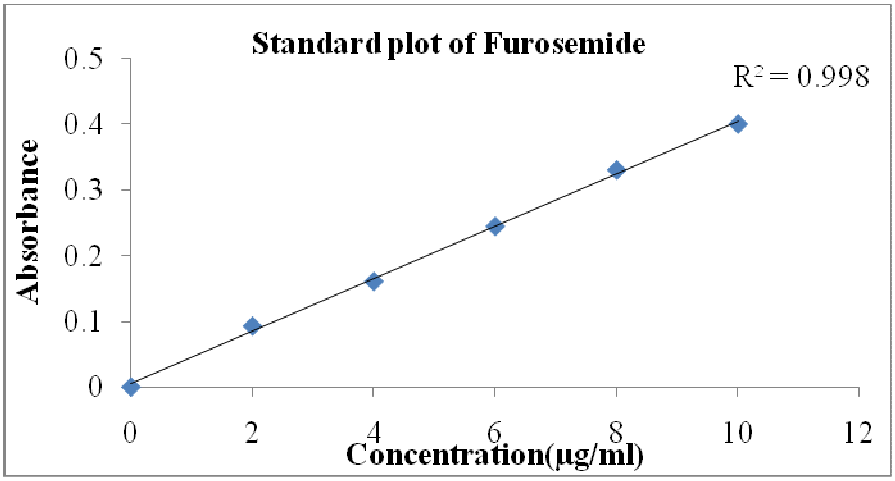

Figure 2
Standard plot of Furosemide

Table 2
Weight Variation, Hardness, Friability, Thickness and Drug Content of furosemide floating tablets

Formulation Code	Weight Variation	Friability (%)	Hardness (Kg/Cm^2)	Thickness (mm)	Furosemide (%)
FFRA1	145±0.19	0.16 ± 0.01	4.50 ± 0.74	3.3-3.5	91.90 ± 0.42
FFRA2	144±0.42	0.24± 0.18	3.67 ± 0.21	3.4-3.6	93.61 ± 0.70
FFRA3	144±0.27	0.29 ± 0.22	3.09 ± 0.95	3.2-3.5	93.22 ± 0.57
FFRA4	143±0.63	0.21 ± 0.16	4.33 ± 0.61	3.1-3.3	96.02 ± 0.33
FFRA5	145±0.39	0.23 ± 0.27	3.50 ± 0.12	3.3-3.6	97.27 ± 0.21
FFRA6	144±0.27	0.25 ± 0.22	4.41 ± 0.57	3.1-3.4	99.14 ± 0.17
FFRD1	145±0.91	0.16 ± 0.54	4.21 ± 0.84	3.2-3.5	99.47 ± 0.58
FFRD2	143±0.22	0.25 ± 0.92	3.45 ± 0.17	3.1-3.3	98.13 ± 0.14
FFRD3	144±0.67	0.24 ± 0.73	4.65 ± 0.29	3.3-3.4	99.28 ± 0.78
FFRD4	145±0.42	0.23 ± 0.18	4.29 ± 0.27	3.2-3.5	96.24 ± 0.77
FFRD5	145±0.38	0.22 ± 0.12	3.40 ± 0.29	3.1-3.4	99.19 ± 0.61
FFRD6	144±0.23	0.24 ± 0.64	4.29 ± 0.51	3.1-3.5	98.22 ± 0.36
FFRC1	144±0.21	0.21 ± 0.26	4.74 ± 0.57	3.2-3.6	97.24 ± 0.80
FFRC2	145±0.19	0.21 ± 0.24	3.25 ± 0.28	3.1-3.5	99.21 ± 0.33
FFRC3	144±0.45	0.13 ± 0.64	4.88 ± 0.15	3.2-3.6	98.19 ± 0.37
FFRC4	144±0.39	0.22 ± 0.02	5.21 ± 0.19	3.1-3.3	98.26 ± 0.14
FFRC5	145±0.22	0.26 ± 0.93	4.02 ± 0.14	3.2-3.3	96.46 ± 0.85
FFRC6	144±0.08	0.03 ± 0.25	4.12 ± 0.18	3.3-3.4	96.55 ± 0.91

Table 3
Floating characteristics of Furosemide tablets using Albizia gum, Dammar gum and Copal gum

Formulation Code	Floating lag time (Sec)	Duration of floating (hrs)	Swelling Index at end of 12hr
FFRA1	142	12	69.4±0.34
FFRA2	133	12	72.18±0.9
FFRA3	129	12	74.26±0.21
FFRA4	124	12	70.3±0.49
FFRA5	120	12	73.0±0.63
FFRA6	118	12	76.3±0.81
FFRD1	139	12	47.11±0.41
FFRD2	131	12	51.2±0.42
FFRD3	128	12	54.3±0.33
FFRD4	120	12	48.13±0.12
FFRD5	119	12	53.0±0.22
FFRD6	117	12	55.73±0.09
FFRC1	138	12	47.11±0.41
FFRC2	126	12	51.2±0.42
FFRC3	124	12	54.3±0.33
FFRC4	120	12	48.13±0.12
FFRC5	116	12	53.0±0.22
FFRC6	114	12	55.73±0.09

Table 4
FT-IR spectral data of Furosemide and floating tablet formulation FFRA4

Functional groups	Frequency of pure drug (cm^{-1})	Frequency of formulation (cm^{-1})
C=O Stretching	1712.00	1712.85
C-Cl	709.21	709.83
N-H Stretching (2^0 Amine)	3468.28	3470
Ar-H	3043.04	3043.77
N-H Stretching (1^0Sulphonamide)	3232.16(Asymmetric) 3246.04(Symmetric)	3381(Asymmetric) 3246.31(Symmetric)
S=O Stretching	1352.14(Asymmetric) 1057.40(Symmetric)	1352.14(Asymmetric) 1055.10(Symmetric)
S-N Stretching	931.36	939.87

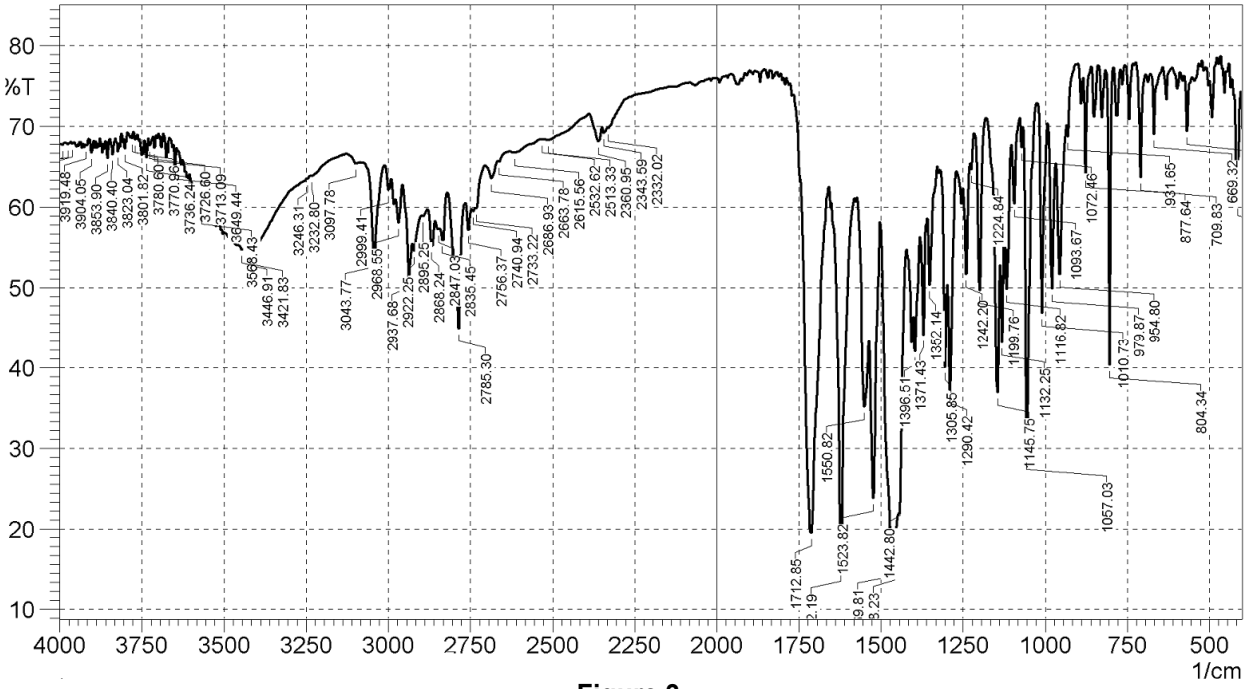

Figure 3
FT-IR spectral data of Furosemide pure drug

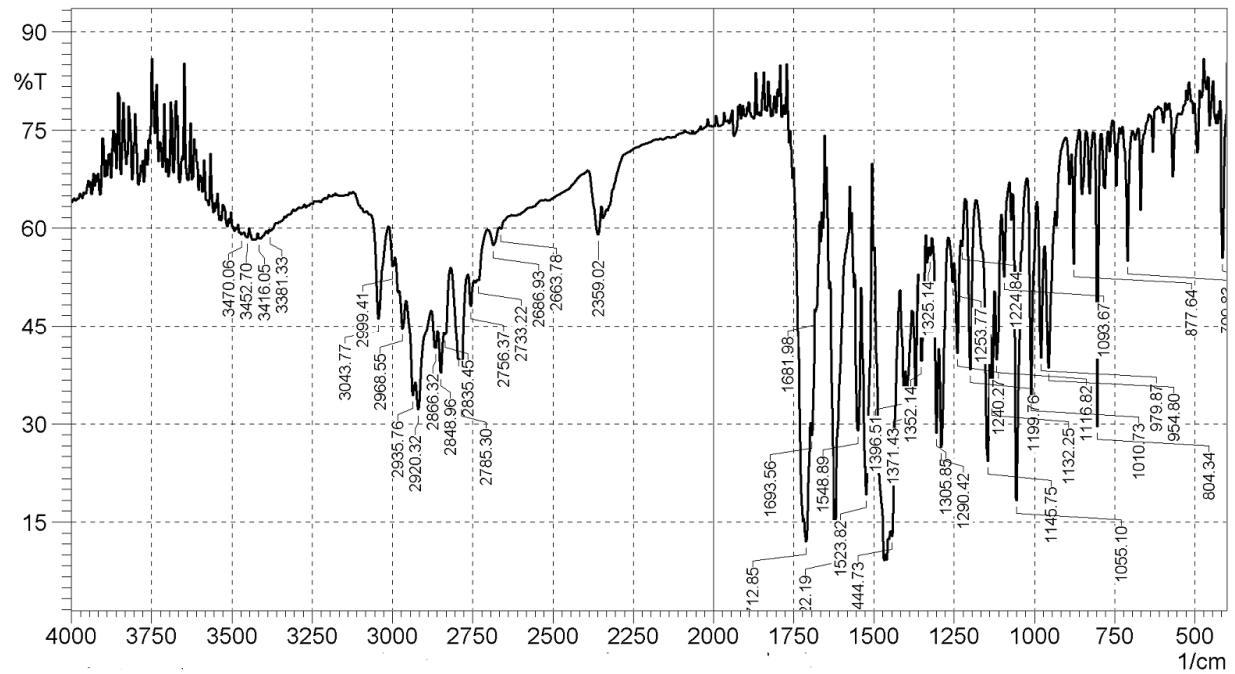

Figure 4
FT-IR spectra of Floating tablet formulation FFRA4

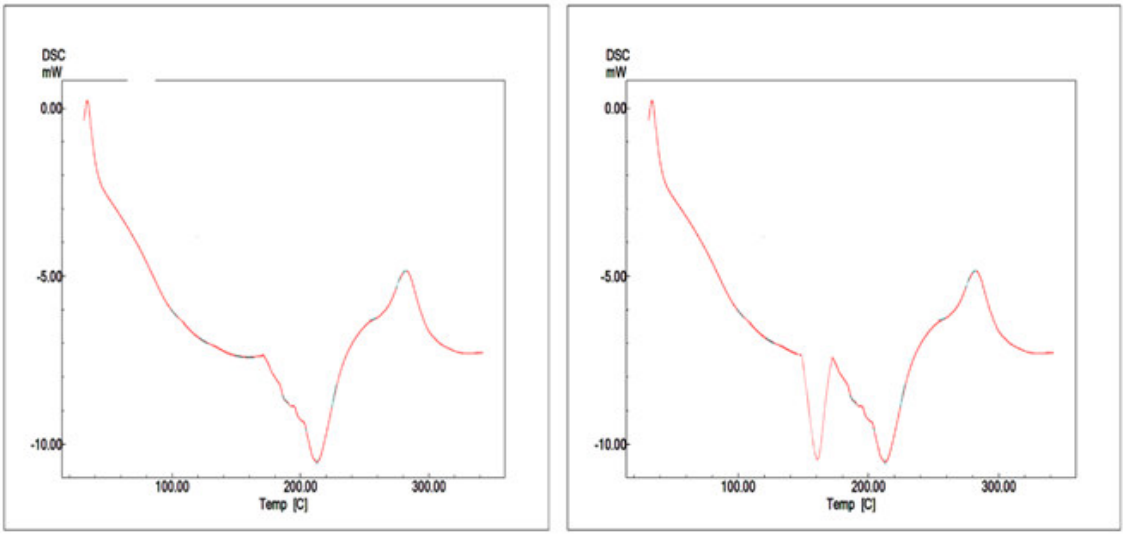

Figure 5
DSC thermogram of pure Furosemide and Optimized formulation (FFRA4)

Table 5
Composition of Furosemide (40 mg) Floating Tablets Formulated Using Albizia gum

Ingredients [mg/tablet]	FORMULATIONS					
	FFRA1	FFRA2	FFRA3	FFRA4	FFRA5	FFRA6
Furosemide	40	40	40	40	40	40
Albizia gum	20	30	40	20	30	40
DCP	50	40	30	---	---	---
Lactose	---	---	---	50	40	30
Sodium bicarbonate	25	25	25	25	25	25
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total wt of tablet (mg)	145	145	145	145	145	145

Table 6
Composition of Furosemide (40 mg) Floating Tablets Formulated Using Dammar gum

Ingredients [mg/tablet]	FORMULATIONS					
	FFRD1	FFRD2	FFRD3	FFRD4	FFRD5	FFRD6
Furosemide	40	40	40	40	40	40
Damar gum	20	30	40	20	30	40
DCP	50	40	30	---	---	---
Lactose	---	---	---	50	40	30
Sodium bicarbonate	25	25	25	25	25	25
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total wt of tablet (mg)	145	145	145	145	145	145

Table 7
Composition of Furosemide (40 mg) Floating Tablets Formulated Using Copal gum

Ingredients [mg/tablet]	FORMULATIONS					
	FFRC1	FFRC2	FFRC3	FFRC4	FFRC5	FFRC6
Furosemide	40	40	40	40	40	40
Copal gum	20	30	40	20	30	40
DCP	50	40	30	---	---	---
Lactose	---	---	---	50	40	30
Sodium bicarbonate	25	25	25	25	25	25
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total wt of tablet (mg)	145	145	145	145	145	145

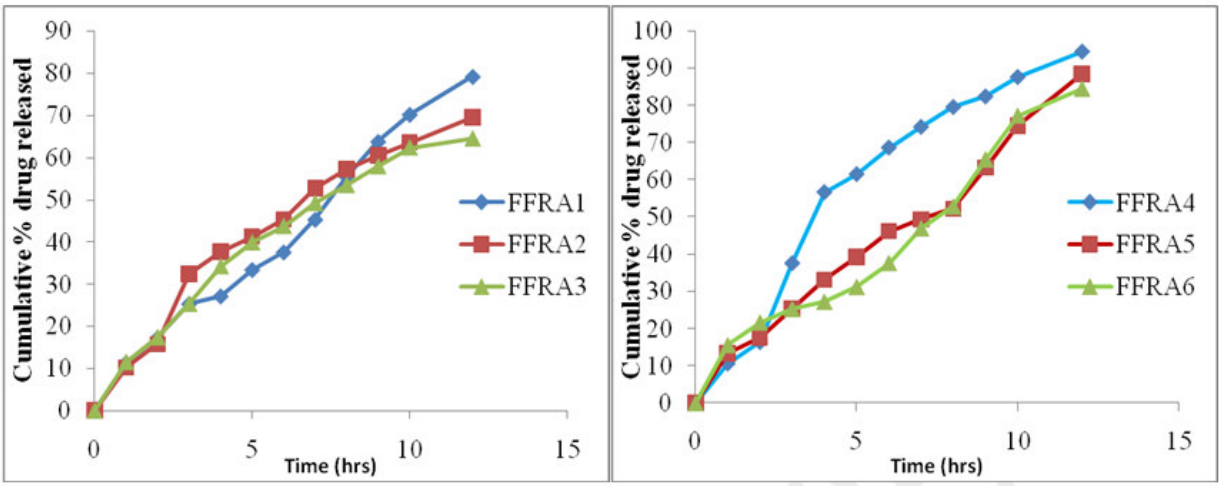

Figure 6
Drug Release Profiles of Furosemide Floating Tablets Prepared Employing Albizia Gum Using DCP and Lactose as Diluent

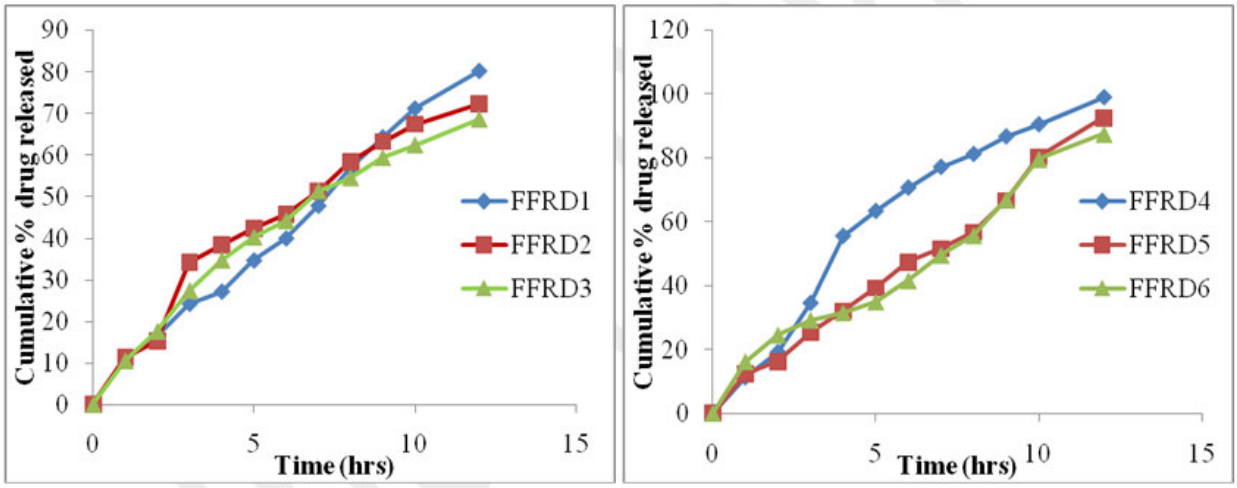

Figure 7
Drug Release Profiles of Furosemide Floating Tablets Prepared Employing Dammar Gum Using DCP and Lactose as Diluent

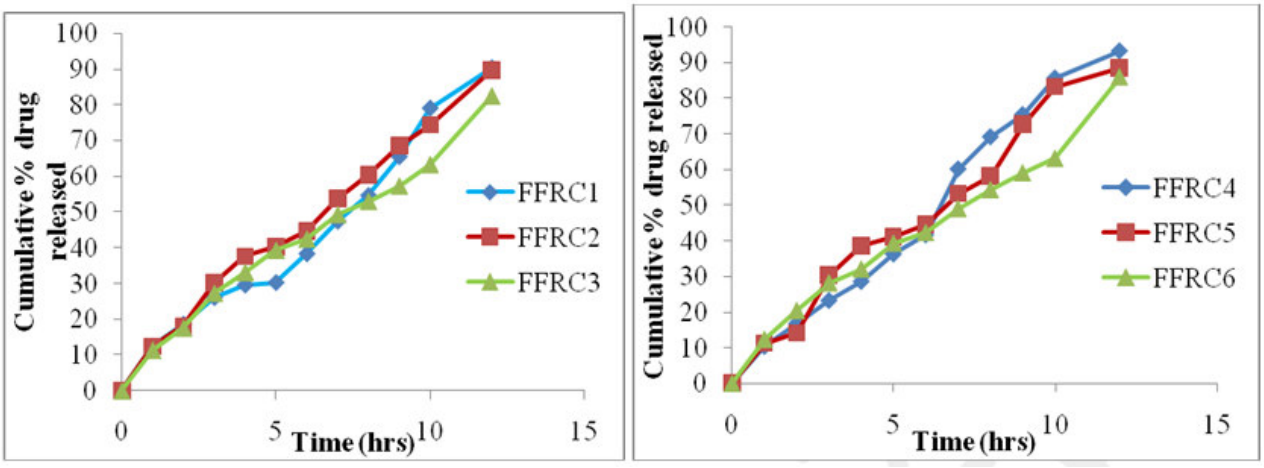

Figure 8
Drug Release Profiles of Furosemide Floating Tablets Prepared Employing Copal Gum Using DCP and Lactose as Diluent

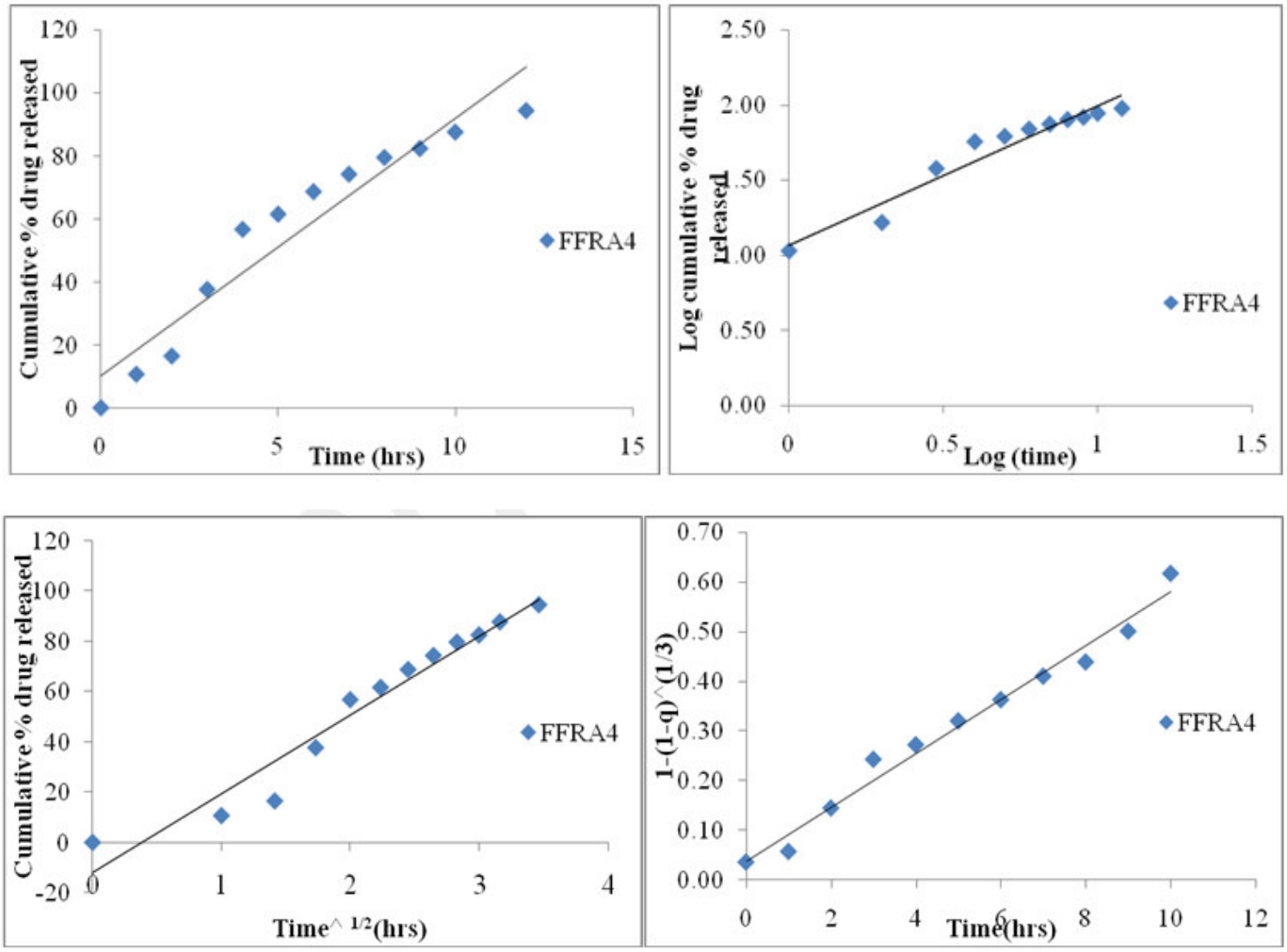

Figure 9
Linear regression plots for Optimized Frusemide floating Tablet Prepared Employing Albizia gum Using Lactose as Diluent (a) Zero order plot, (b) Peppas plot (c) Higuchi plot and (d) Erosion plot

Table 8
Correlation Coefficient (R^2) Values in the Analysis of Release Data of Furosemide floating Tablets Prepared Employing Albizia gum Using Lactose as Diluent as per Various Kinetic Models

Formulation	Correlation Coefficient (R^2) Values			
	Zero order	First order	Higuchi's	Peppas's
FFRA4	0.9782	0.9174	0.9485	0.9387

Table 9
Release Characteristics of Furosemide floating Tablets Prepared Employing Albizia gum Using Lactose as Diluent

Formulation	Polymer Concentration (%)	K_o (mg/h)	K_1 (h^{-1})	'n' in Peppa's Equation
FFRA4	0.5	8.192	0.227	0.89

DISCUSSION

The quality control tests such as uniformity of weight, hardness, friability and drug content for all the formulations prepared according to the formulae was carried out and the results were given. All the formulations complied with compendia standard of IP. The weight variation of the tablets was within the IP limits. (Not more than two of the individual weights deviate from the average weight by more than 5% and none deviates by more than 10%). The hardness for all the formulations was found to be in the range of 5-6 Kg/cm^2 and was satisfactory. For all the batches prepared the friability values was found to be less than 1%. All the formulations satisfied the content of the drug as they contained 100±2% of the drug when assayed spectrophotometrically. All the formulations showed good floating behavior and floating lag time and duration of floating was reported in the table.

Effect of Albizia gum, Dammar gum and Copal gum on dissolution profile of Frusemide Floating Tablets

The *in vitro* dissolution studies of the prepared tablets revealed that these gums behaved depending on the

concentration used in the tablet preparation as shown in Tables. Generally, in hydrophilic Floating controlled release tablets, the initial burst release observed was due to two factors. If the surface area of the polymer was not large enough to cover the drug particle at the surface, there was a great chance of burst effect in drug release. Secondly, if the polymer does not hydrate quickly, the surface barrier cannot be formed immediately, which may cause a large portion of drug to be released during the initial phase of release profile. Thus, the surface area as well as the hydration rate of the polymer can play an important role in drug release from floating tablets, especially at the beginning of the release profile.The quick hydration and subsequent gel formation are the most important properties for an excipient to be used in the controlled release formulation. In tablets Prepared by using these gums, no initial burst effect was observed due to its quick hydration and immediate formation of gel structure around the tablet. The influence of hardness of tablets on release kinetics was not very important for hydrophilic matrices. To prevent the partial or total disintegration, in the present work the compression force of the tablet machine was so adjusted to obtain tablets whose hardness level was between 5-6 Kg/cm^2. The increase in the polymer content with the constant amount of drug (higher polymer-drug ratio) resulted in decreased release rate of drug due to the formation of low porosity and high tortuosity, which would presumably allow gel strength, diffusion and erosion. In order increase the drug release channeling agents were introduced namely Lactose and DCP. Lactose is water soluble diluent and DCP is water insoluble diluent.

Release kinetics

Linear regression plots for the dissolution profile of FFRA1-FFRA6 (Formulation in which Albizia gum is used),FFRD1-FFRD6 (Formulation in which Dammar gum is used),FFRC1-FFRC6(Formulation in which Copal gum is used) for (a) Zero order plot, (b) Peppas plot, (c) Higuchi plot (d) erosion. The release rate constants revealed that the release rate increased as the proportion of gums decreased and correlation coefficient confirmed first order kinetics for the formulations FFRA1 to FFRA3, FFRD1 to FFRD3 and FFRC1 to FFRC3 confirmed zero order kinetics for the formulations FFRA4 to FFRA6, FFRD4 to FFRD6 and FFRC4 to FFRC6 respectively. In order to establish the mechanism of drug release, the dissolution data were fitted to the exponential equation ($M_t/M_\alpha=Kt^n$). The linear correlation coefficients of the slopes and slope values indicated that the release kinetics conformed to non-fickian diffusion (i.e. square root of time profile) with erosion. This classical Higuchi type of release mechanism can be explained as a result of the rapid hydration of the polymer molecules on the surface of the tablets, which results in a gel or a highly viscous solution surrounding the tablet that restricts water penetration into the center. The net result was a reduction in the rate of drug release as a function of time. This was confirmed by the linearity of the plot obtained when cumulative amount of drug released was plotted as a function of square root of time. The drug was released into dissolution medium by diffusion mechanism where the formation of gel layer on the hydrated surfaces occurs during dissolution, then the solvent penetrates into the gel layer, enters into the core of dosage form to solubilise the drug and the drug solution comes out into the medium. The thickness of the gel layer acts as a barrier and if the thickness increases which normally occurs with increase in polymer concentration does not allow the solvent molecule to enter into the gel structure and release of the drug ceases at this point. Though formulations FFRA1 to FFRA3, FFRD1 to FFRD3 and FFRC1 to FFRC3 were able to release the drug with zero order, which was a desirable feature for any controlled release dosage forms but they failed to release the drug. This may be due to the formation of a very thick gel layer of gums due to its high swelling nature which acts as a barrier preventing the entry of dissolution medium into core of the tablet. Another factor that may be responsible for the failure of the dosage form to release the drug was the use of water insoluble chanelling agent. This problem was rectified using lactose as channeling agent. When the concentration of polymer was increased gradually, the release of drug decreased proportionally as evidenced by the results shown above. The above results showed that gums with lactose as diluent showed zero order release where as with DCP as diluent showed first order release. From the various formulations prepared, FFRA4 gave consistent release extended over a period of 12 hours. Hence, floating tablets formulated employing Albizia gum using lactose as diluent (FFRA4) is considered suitable for controlled release of furosemide and this may be considered for further.

CONCLUSION

Floating tablets were successfully prepared using different gums in various ratios by direct compression method. Among all the formulations, FFRA4 was considered to be most promising for controlled release of Furosemide upto 12 hours when compared with other formulations.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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