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Original Article

Preparation and evaluation of raft forming systems of furosemide

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ABSTRACT

The aim of the present investigation is to prepare and evaluate raft forming systems of furosemide. Furosemide is a potent loop diuretic agent that comes under anthranilic acid derivative. Sodium alginate was used as the gelling agent, sodium bicarbonate and calcium carbonate were used as effervescent agents. For sustained release of drug, the polymers used were HPMC K15M, K100 and K200. The objectives are to sustain the drug release for 12 hours with floating characteristics of raft forming system. The results indicated that the raft strength, floating behaviour, drug release and other tableting characteristics of the optimized formulation are meeting the objectives.

Keywords: Furosemide, Raft forming systems, Tablets

INTRODUCTION

Raft forming systems comprise of carbonate component which generate carbon dioxide gas bubbles that transform the material into gel, upon interaction with gastric fluid. Thus, obtained gel or raft floats over the surface of the gastric fluid. The gas generated fluid allows the swelling of each portion of the liquid resulting in formation of continuous layer called as raft[1–4]as shown in **Figure 1**.

The formulation is comprised of a polymeric gel former (e.g., sodium alginate) and bicarbonates to generate carbon dioxide gas which keep the system less dense and allow the system float over the gastric fluid as a raft. The formed raft acts as barrier and avoids the reflux of gastric contents into the oesophagus.

Sodium alginate, gellan gum, carrageenan, and pectin are the examples of ion sensitive polysaccharides which undergo phase transition in the presence of sodium, magnesium, calcium, and/or potassium ions. These results in *in situ* gelling with the already formed carbon dioxide from existing carbonates that enables the gel to raft.

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The advantages of raft systems are rapid and long duration of action, noninterference with pyloric sphincter, promotility and antisecretory agents and used in symptomatic treatment of heartburn and oesophagitis.

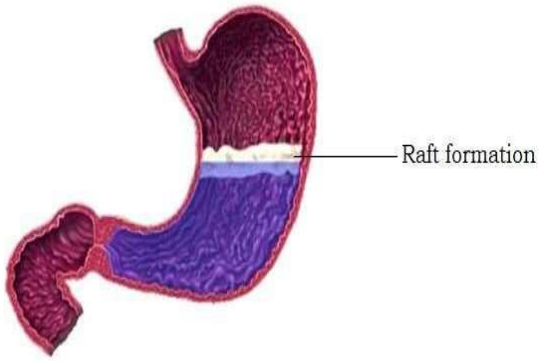

Figure 1: Raft formation in stomach[5]

MATERIALS AND METHODS

Furosemide, sodium alginate, HPMC grades are purchased from Yarro chemicals, Mumbai. All other chemicals used are of analytical grade.

Analytical method for *in vitro* estimation of furosemide[6]: For preparation the calibration solutions, 100mg of furosemide was transferred to a volumetric flask of 100mL, 5mL of ethanol was added to solubilize the drug and the solution was made upto the mark with 0.1N HCl to obtain a stock solution (Stock1) containing 1000 µg/mL of furosemide. From this Stock 1, 10mL was diluted to 100mL with 0.1N HCl to obtain the concentration of 100µg/mL (Stock2). Stock 2 solution was suitably diluted with 0.1N HCl solution to obtain the concentrations 2,4,6,8 and 10 µg/mL.

Absorbance was measured at 275 nm against 0.1N HCl by using ThermoFisher Scientific Genesys 180 UV-Visible spectrophotometer. The experiment was performed in triplicate and average values are reported. Calibration curve was plotted against absorbance verses concentration and the calibration curve is shown in **Figure 2**. Correlation coefficient was found to be 0.9970 indicating a good linear relation between independent and dependent variables and the regression line equation was found to be y=0.0043x+0.002.

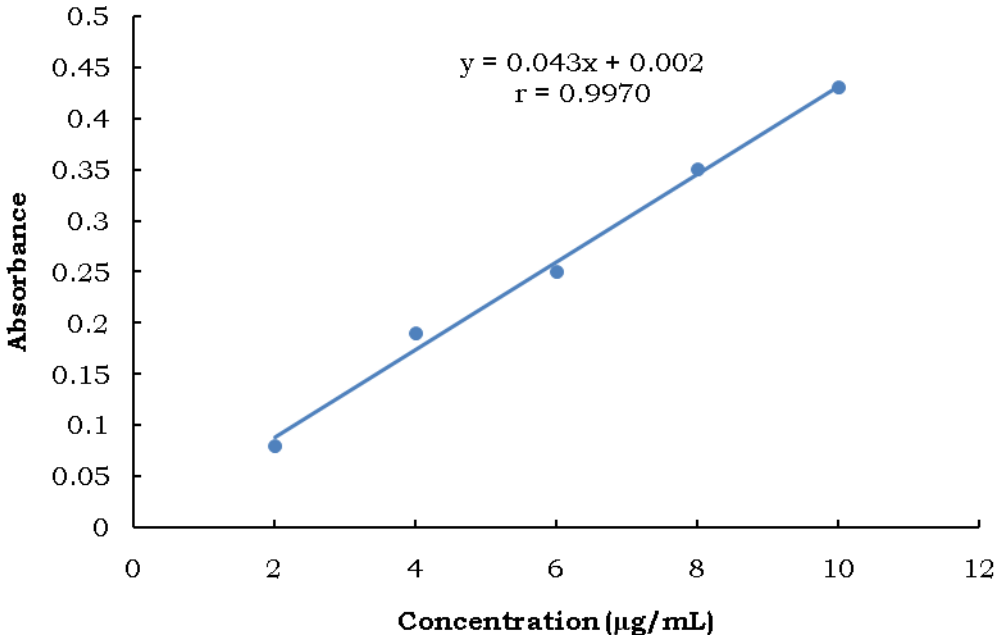

Fig. 2: Calibration curve of furosemide in 0.1 N HCl

Formulation of raft forming gastroretentive tablets of furosemide

Pre-compression studies: All the ingredients as per the formulae given in **Table 1**are weighed accurately and the pre-compression blend was prepared. Pre-compression evaluation tests were carried for the prepared drug and excipient powder blends.

Preparation of furosemide raft forming tablets[7]: The tablets were compressed by direct compression technique using Natoli NP-RD10A tablet compression machine with 12 mm flat and round punches.

Table 1: Formulae of furosemide raft forming tablets

Ingredients (mg)	FR1	FR2	FR3	FR4	FR5	FR6	FR7	FR8	FR9
Furosemide	250	250	250	250	250	250	250	250	250
Sodium alginate	30	40	50	30	40	50	30	40	50
Sodium bicarbonate	35	45	55	35	45	55	35	45	55
Calcium carbonate	10	20	30	10	20	30	10	20	30
HPMC K15M	30	60	90	-	-	-	-	-	-
HPMC K100	-	-	-	30	60	90	-	-	-
HPMC K200	-	-	-	-	-	-	30	60	90
MCC	135	65	20	135	65	20	135	65	20
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Total weight (mg)	510	500	515	510	500	515	510	500	515

Evaluation of furosemide raft forming tablets: The prepared furosemide raft forming tablets were evaluated for tablet characteristics like thickness and diameter, hardness, friability, weight variation, drug content, floating lag time, floating time, raft formation and raft strength and % drug release. The procedures followed for thickness, hardness, friability, weight variation, and drug content tests.

***In vitro* buoyancy and floating lag time and floating time**[8,9]: The tablet was dropped in a 500 mL beakercontaining0.1NHCl.Floating lag time was determined as the time difference between introduction of tablet and floating on the simulated gastric fluid. The floating time was determined as the time during which the dosage form remain buoyant. Each experiment was replicated three times and average values were noted.

***In vitro* raft formation and raft strength**[4,7,10]
Raft strength was measured by an in-house method. Furosemide raft tablets (FR1- FR9) were powdered and a tablet equivalent weight of the individual formulation powder was transferred to a 150 ml beaker with 0.1N HCL maintained at 37°C. 'L' shaped steel wire probe was introduced which is about 1.2 mm in diameter and help upright in the glass beaker for a period of 30 min until the raft was formed. Using a modified balance, the strength of each raft formed around an L-shaped stainless-steel wire probe for the formulations AR1 to AR4 was measured. The force (g) required to pull the wire probe up through the raft, was recorded.

***In vitro* drug release studies**[8,10]
In vitro drug release studies were carried out for the prepared formulations using USP type-II (paddle method) dissolution rate test apparatus Hansen Research SR8PLUS using 900 mL of 0.1N HCl as dissolution medium maintained at a temperature of 37°C±0.5°C. The shaft rotation speed was maintained at 50 rpm. The study was performed for 12 hours and 5 mL samples were withdrawn at fixed time intervals using a syringe fitted with prefilter. 5 mL of fresh medium maintained at 37°C±0.5°C was used for replacement at every time interval by washing the particles back to dissolution medium adhered to prefilter. The samples collected were analysed for furosemide content by measuring the absorbance at 275 nm using Thermo Fisher Scientific Genesys 180 UV-Visible spectrophotometer against blank of 0.1N HCl. The samples were diluted wherever necessary. All the *in vitro* drug release studies were performed in triplicate and average values are reported.

Release kinetics and mechanisms: The release kinetics and mechanism of the prepared raft forming gastroretentive systems were assessed by fitting the dissolution data to the respective models.

RESULTS AND DISCUSSION

Pre-compression studies: The drug and excipient powder blends were prepared and evaluated for their flow characteristics like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The results are shown in **Table 2.** The angle of repose of the powder blend was found to be in the range of 27.51°- 31.47° which indicated excellent flow property. The Carr's index values are in the range of 12.70 to 17.19whereas the Hausner's ratio values of all the formulations were in the range of 1.15 to 1.21. The results indicated fair to excellent flow for the prepared powder blends and hence direct compression method was used for compression of tablets.

Table 2: Flow properties of furosemide raft forming formulation powder blends(mean±s.d., n=3)

Formu-lation	Angle of repose (Θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
FR1	27.51±1.11	0.52±0.02	0.61±0.03	14.75	1.17
FR2	31.47±1.12	0.53±0.03	0.62±0.02	14.52	1.17
FR3	30.96±0.96	0.55±0.03	0.65±0.02	15.38	1.18
FR4	29.36±0.99	0.53±0.03	0.63±0.02	15.87	1.19
FR5	29.25±1.04	0.53±0.02	0.64±0.01	17.19	1.21
FR6	30.11±0.98	0.54±0.01	0.62±0.02	12.90	1.15
FR7	30.05±1.10	0.53±0.02	0.62±0.10	14.52	1.17
FR8	29.03±1.06	0.52±0.02	0.62±0.02	16.13	1.19
FR9	29.29±1.07	0.55±0.01	0.63±0.11	12.70	1.15

Evaluation of furosemide raft forming tablets
Results of the post compression studies conducted for the prepared raft forming tablets of furosemide are discussed below.

Thickness and diameter: The measured thickness values of the tablets are shown in **Table 3**. The results showed a uniform thickness of prepared tablets.

Hardness: The measured hardness of tablets ranged between 3.9 to4.1 kg/cm^2. This test ensures that prepared tablets have good handling characteristics. The results are shown in **Table 3**.

Friability: The friability values ranged between 0.24 to 0.50%. The % friability was found to be<1% ensuring that the tablets were mechanically stable. Results are shown in **Table 3**.

Uniformity of weight: Based on the weight of the tablet (500 mg), the allowed deviation is ±25 to 25.75 mg for a tablet weight of 500 to 515 mg. The results indicated that all the tablets passed weight variation test as the deviation in weight was within the Pharmacopoeia limits of ±5% of the average weight. Results are shown in **Table 3**.

Drug content: The drug content of each individual preparation was found to be within the limits of 90 to 110%.Results are shown in **Table 3**.

Floating lag time and floating time: Floating lag time and floating time of prepared furosemide raft forming tablets are shown in **Table 3**. From the results, it was found that all the formulations shown floating lag time in the range of 98 to 126 seconds whereas the formulations FR3, FR6 and FR9 have shown floating time up to 12 hours. The floating times were observed up to 12 hours as the aim is to complete the drug release over a period of 12 hours. Hence, further *in vitro* dissolution studies were conducted for only these selected formulations FR3, FR6 and FR9.

In vitro raft formation and raft strength: *In vitro* raft strength values of prepared furosemide raft forming tablets are shown in **Table 3**. The results indicated that the formulations FR3, FR6, and FR9 have shown better raft strength in support to the results of floating lag time and floating time, hence further *in vitro* dissolution studies were carried on these three selected formulations.

Table 3: Tablet characteristics of furosemide raft forming tablets

Formulation	Thickness[a](mm)	Diameter (mm)	Hardness[a] (kg/cm^2)	Friability[b](%)	Uniformity of weight[c](mg)	Drug content[d](%)	Floating lag time (sec)	Floating time (hours)	Raft strength[e](g)
FR1	3.21	12	3.9±0.2	0.45	509±5.6	100.37±1.03	120	9	2.68±0.02
FR2	3.19	12	4.1±0.1	0.46	502±6.1	99.70±0.79	110	10	2.82±0.01
FR3	3.23	12	4.1±0.1	0.35	515±5.8	99.34±0.42	98	12	3.75±0.01
FR4	3.22	12	4.0±0.2	0.50	511±7.9	99.68±0.83	126	11	3.10±0.09
FR5	3.20	12	4.1±0.3	0.42	502±8.2	99.58±0.71	105	12	3.59±0.07
FR6	3.23	12	4.1±0.3	0.45	514±8.0	99.97±0.69	109	12	4.15±0.03
FR7	3.22	12	4.0±0.2	0.36	512±7.4	100.05±1.17	121	10	3.50±0.05
FR8	3.19	12	4.0±0.2	0.48	503±8.1	100.26±0.54	98	12	3.90±0.03
FR9	3.22	12	3.9±0.1	0.24	514±8.2	99.79±0.56	95	12	4.59±0.05

a: mean±s.d., n=5; b: tablets equivalent to 6.5 g; c: mean±deviation in mg, n=20;
d: mean±s.d., n=3; e: mean±s.d., n=3

In vitro drug release studies: *In vitro* drug release data and the dissolution profiles are shown in **Table 4**and **Figure 3** respectively. Formulation FR9 (containing HPMCK200) showed greater raft strength and controlled the drug release with 99.81±2.89% drug release in 12 hours.

Table 4: Cumulative % drug release of furosemide raft forming tablets FR3, FR6 and FR9 (mean±s.d., n=3)

Time (hours)	FR3	FR6	FR9
0.25	18.54±3.45	11.27±1.94	13.38±1.15
0.5	21.84±5.24	15.84±2.49	12.41±6.51
0.75	28.18±2.33	18.91±2.60	17.62±1.28
1	39.64±1.89	26.54±4.32	24.14±1.89
2	46.82±5.66	33.8±4.87	30.84±3.45
3	51.95±6.1	45.71±2.78	42.15±4.21
4	60.51±4.62	52.47±1.21	45.21±2.32
5	67.27±3.29	59.83±3.48	53.47±3.44
6	72.54±5.51	64.83±1.41	61.54±1.21
7	84.28±1.84	75.35±6.17	67.28±3.96
8	92.45±2.56	82.49±3.49	74.38±2.43
9	99.54±3.94	86.57±1.84	79.92±2.19
10		90.74±1.46	83.72±1.29
11		99.74±2.12	90.32±3.58
12			99.81±2.89

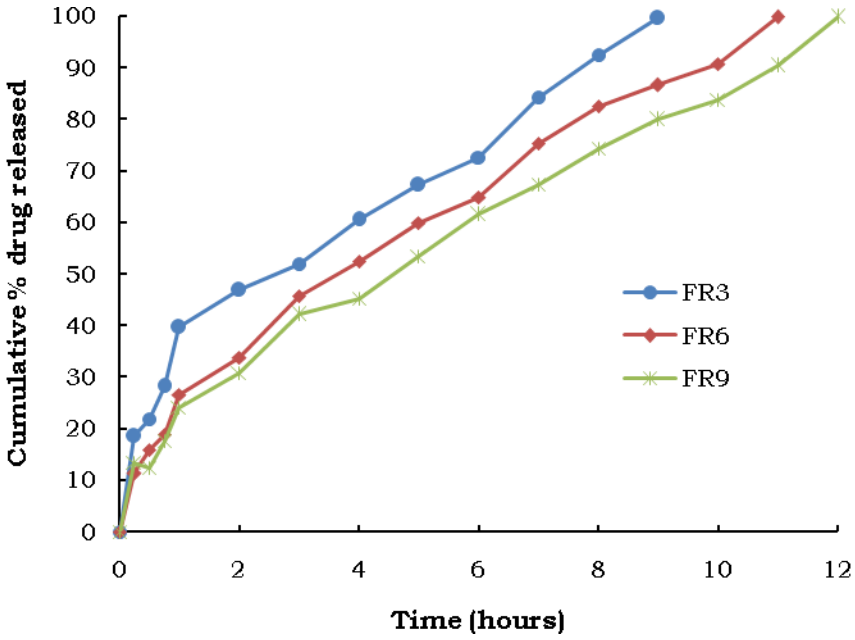

Figure 3: Dissolution profiles of furosemide from raft forming tablets, FR3, FR6 and FR9

Release kinetics and mechanisms: The obtained dissolution data was fitted to different kinetic and mathematical models. The correlation coefficient values and the respective rate constants for zero order and first order and the correlation coefficient values for Higuchi, Hixson-Crowell, and Korsmeyer-Peppas are shown in **Table 5.** All the formulations FR3, FR6 and FR9 were found to follow zero order drug release kinetics and diffusion mechanism based on the 'r' value. The optimized formulation, FR9 was further found to follow non-Fickian diffusion mechanism of drug release based on the 'n' value of Korsmeyer-Peppas plot.

Table 5: Release kinetics of furosemide raft forming tablets

Formula-tion	Zero order (%hr^{-1})		First order hr^{-1}		Higuchi	Hixson-Crowell	Korsmeyer-Peppas	
	r	k_0	r	k_1	r	r	r	n
FR3	0.971	9.367	0.962	0.111	0.993	0.956	0.990	0.463
FR6	0.985	8.304	0.984	0.093	0.996	0.961	0.998	0.578
FR9	0.988	7.466	0.984	0.079	0.993	0.946	0.989	0.563

CONCLUSION

Furosemide raft forming tablets were prepared for optimizing the amounts of gelling agent sodium alginate, effervescent agents sodium bicarbonate and calcium carbonate and polymers HPMC K15M, K100 and K200. Though the floating lag time for all the prepared tablets are within 130 seconds, formulations FR3, FR5, FR6, FR8 and FR9 could float up to 12 hours as tested and remaining could not float up to 12 hours. The raft formation and raft strength also increased with increase in the concentration of gel forming agent and effervescent agents. Based on the properties of floating time and raft strength FR3, FR6 and FR9 were subjected for dissolution which are prepared with three different grades of HPMC. Among these three formulations, FR9 could extend the drug release over a period of 12 hours and hence it was considered as optimized. FR9 also release about 30% of drug which could act as loading dose. Hence, it was concluded that FR9 meet the objectives of present investigation and hence it was confirmed as the optimized formulation.

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