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Original Article

NOVEL FLOATING AGENT *SACCHAROMYCES BOULARDII* FORMULATION BASED FLOATING DRUG DELIVERY SYSTEM

SUVARNA CHITTAM*, ASHOK BHOSALE

Department of Pharmaceutics, PDEA'S Seth Govind Raghunath Sable, College of Pharmacy, Saswad, Pune (Maharashtra, India)
Email: cssgrs@gmail.com

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ABSTRACT

Objective: The objective is to design and optimize a floating tablet of furosemide using a novel floating agent *Saccharomyces boulardii.*

Methods: In this study floating tablet based on principle of combination of floating and swelling prepared by direct compression technique. *Saccharomyces boulardii* probiotics preparation is used as a floating agent due to its bloating property i.e. production of CO_2 gas and hydrophilic polymer HPMC E LV 15 used as swellable polymer. Furosemide is a BCS class IV drug selected as model drug which shows pH dependent solubility and permeability and it is better absorbed from the gastric region, hence to improve dissolution and residence at absorption site of such drug, floating drug delivery system is needed. Calcium hydroxide used as pH modifier which increase rate of dissolution of furosemide and also maintain integrity of tablet matrix. Formulation designed and developed using central composite design response surface methodology technique, so as to explore the effect of formulation variables such as amount of *Saccharomyces boulardii* preparation and calcium hydroxide on floating lag time and % drug release after 12h.

Results: The numerical and graphical optimization technique were used to choose the optimal formulation. Floating lag time was found to be 12.6 min and 88.18% drug release for the optimized formulation. *In vivo* buoyancy studies depicted that formulation stay more then 6h in stomach**.**

Conclusion: Study indicate that *Saccharomyces boulardii* is a promising floating agent, and the formulation containing this novel floating agent is suitable for gastro retention and it increases bioavailability of furosemide**.**

Keywords: *Saccharomyces boulardii,* Probiotics, Furosemide, Response surface methodology, Bloating

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INTRODUCTION

Yeasts are a significant source for procurement products with probiotic activity and a good alternative to probiotic bacteria [1]. *Saccharomyces boulardii* is the unique yeast probiotic that has been effectively used as both a preventive and therapeutic agent for diarrhea and other GI complaints. *Saccharomyces boulardii* retains many properties that make it an impending probiotic agent, i.e. it survives during GI transit, it grow well at temperature 37 °C, both *in vitro* and *in vivo* [2], its high tolerance to gastric acidity, proteolysis and are able to attain higher populations in the GI tract. They can forever colonize in the colon and do not easily move out from the intestinal tract [3]. They can also be perceived alive throughout the GIT, if they are given in lyophilized form [4]. *Saccharomyces boulardii* is generally administered in lyophilized powder form [5]. *Saccharomyces boulardii* is used in a variety of gastrointestinal disorders but its major drawback is it's certain side effects such as gas and bloating [6]. Bloating is a feeling of increased gas in the stomach that subsides over a few days [7].

Saccharomyces boulardii is an anaerobe, which means it can grow under aerobic or anaerobic conditions. *Saccharomyces boulardii* consume sugars from the simplest form to the complex form by tapping order i.e. they first consume glucose, fructose and secondly lactose and finally, they devour starch, resulted in the manufacture of ethanol and carbon dioxide [8]. *Saccharomyces boulardii* are a heterotrophic organism, meaning they cannot produce its own food but obtain their energy or nutrition from carbon source. Though it prefer to use glucose, it can also use monosaccharides, polysaccharides, oligosaccharides, alcohol, organic acids, pyruvate, and lactate. *Saccharomyces boulardii* prefers fermentation over respiration 98 to 2%. The fermentation pathway is documented as Embden-Myer of Pathway (EMP), which prepares ethanol products. The depletion of glucose ultimately will lead to a condition known as "cell depression", which generate product like carbon dioxide and water from oxidation of ethanol [9]. Thus in aerobic respiration, it produces CO2 and H2O and in anaerobic alcoholic fermentation, it generates ethanol and CO2.

In the present work, an attempt has been made to develop a floating tablet using novel floating agent and which based on the principle of combination of floating and swelling. S*accharomyces boulardii* probiotics formulation used as floating agent due to its bloating property as well as its resistance to gastric acidity and high temperature and hydrophilic polymer HPMC used as the swellable polymer. Furosemide is a loop diuretic used in the recovery of hypertension [10]. Furosemide is a weekly acidic drug having pKa 3.9 [11] and having a short half-life of 2h. Oral bioavailability of conventional tablet is 30 to 60% due to its variable and erratic absorption. It is a BCS class IV drug having insignificant aqueous solubility and permeability. It is mainly absorbed from the stomach and the upper part of the gastrointestinal tract [12]. It shows high permeability and better absorption through the stomach. Thus furosemide having a pH-dependent solubility and permeability [13]. So it is selected as a model drug for the development of a floating drug delivery system. In present investigation, an attempt has been made to improve the bioavailability of furosemide by prolonging its duration in the stomach via the floating dosage forms using novel floating agent such as *Saccharomyces boulardii* formulation and also enhance its solubility by using hydrophilic polymers such as HPMC and calcium hydroxide used as pH modifier which increase rate of dissolution of furosemide and also maintain integrity of matrix.

MATERIALS AND METHODS

Materials

Furosemide was gifted by (FU) Suleshvari Pharma, Ankaleshwar (Gujarat). Hydroxypropyl methylcellulose was gifted by Loba Chemie Pvt. Ltd. *Saccharomyces boulardii* probiotic preparation was purchased from local market. Hydrochloric acid was gifted by Themis Research lab, Mumbai. Calcium hydroxide, Magnesium stearate and Sodium hydroxide purchased from Poona chemical laboratory, Pune.

Methods

Preparation of floating tablet of furosemide

Floating tablets containing *Saccharomyces boulardii* formulation and furosemide were formulated by direct compression technique using

polymer like HPMC E 15 LV and other ingredients like calcium hydroxide, magnesium stearate, and probiotic preparation containing *Saccharomyces boulardii.* All ingredients were passed through sieve no # 40, except *Saccharomyces boulardii* preparation. HPMC E 15 LV, calcium hydroxide and furosemide were first mixed using a mortar and pestle to get a uniform tablet blend. Finally, *Saccharomyces boulardii* preparation and magnesium stearate were mixed delicately to the above-prepared mixture blend. The mixture was then weighed accurately according to the formula and compressed into tablets using Minipress tablet punching machine (Karnavati) to obtain tablets of desired specifications [14, 15]. The different formulations were prepared as given in table 1.

Evaluation test

Hardness test

Monsanto hardness tester used for evaluation of hardness [15].

Thickness

Vernier caliper was used for the evaluation of tablet thickness [15].

Friability

Friability was expressed in terms of percentage weight loss. % friability was evaluated using the following formula [16].

$$\% \text{ Friability} = \frac{W1 - W2}{W1} \times 100$$

Where,

W1 = Weight of Tablets (Initial/Before Tumbling) and

W2 = Weight of Tablets (After Tumbling or friability)

Determination of swelling index

Swelling degree defines the change of dimension or weight gain of the dosage form. First, a tablet was weighed (W1) and placed in a glass beaker containing hot 0.1 N HCl (PH 1.2) having temp. 37±0.5 °C. Tablets were removed at intervals of 1, 2, 3, 4, 6 and 8 h; excess water was carefully removed using filter paper and tablets were again weighed. Water uptake is measured in terms of percent weight gain. The % swelling index (SI) was measured by the following formula [17].

$$\% \text{ Swelling index} = \frac{\text{Final Weight of tablet } (W_2) - \text{Initial weight of tablet } (W_1)}{\text{Initial weight of tablet}(W_1)} \times 100$$

Uniformity of weight

Twenty tablets were selected randomly weighed individually using electronic balance and the average weight was calculated. The % weight variation was calculated and checked for weight variation as per IP [18].

$$\%\text{Weight variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Individual weight}} \times 100$$

Drug content

10 tablets were weighed and crushed using motor pestle. The crushed powder equivalent to an average weight of tablets was weighed accurately and put in 100 ml 0.1N NaoH solution for complete extraction of drug and stirred continuously. The solution is filtered using a Whatman filter paper, diluted with 0.1N NaoH solution and the drug content is determined spectrophotometrically [19].

Tablet floating behavior

The floating lag time and total floating duration were determined using USP type II (paddle) apparatus at speed 50 rpm in 900 ml 0.1N HCl at 37±0.5 °C to simulate *in vivo* conditions. And on the basis of visual inspection, time were recorded [20].

***In vitro* dissolution studies**

In vitro dissolution studies were conducted by using paddle dissolution apparatus (Electrolab) at 50 rpm using 900 ml of 0.1 N HCl, (pH 1.2) as a dissolution medium at 37±0.5 °C and the absorbance of the sample solution was recorded using UV spectrophotometer at 274 nm. The *in vitro* dissolution study calculation was conducted using disso software (PCP disso V3). The *in vitro* release profile was determined [21].

Drug Release mechanism and model fitting

In the present study, several mathematical models such as zero-order, first-order, matrix, Higuchi's, Peppas and Hixson–Crowell model can be tested to determine the best fit model [22, 23].

Statistical analysis and optimization

Design-Expert software used for statistical analysis of the data and optimization polynomial models. The best-fitting model was elected on the basis of comparisons of several statistical parameters. ANOVA used to ascertain the significant effect of factors on responses. The relationship between the factors and response was further clarified using response surface plots. Subsequently, a numerical optimization techniques used to engender the best-optimized solution [24].

***In vivo* buoyancy study by using X ray**

The tablets are prepared by replacing some quantity of drug with barium sulfate. The *in vivo* buoyancy study conducted using healthy albino rabbits. Prepared optimized tablet containing barium sulphate administered to rabbits. X ray was taken at intervals of 1, 2, 4, 6 and 12 h [25].

RESULTS AND DISCUSSION

The prepared FDDS tablets were evaluated and data is enclosed in table 2. From this data, it was clear that the evaluation parameters of all batches were in the acceptable range. Uniformity of weight, uniformity of drug content not much deviate from the mean value.

Table 1: Composition of furosemide floating tablets (mg/tablet)

Formulation code	Ingredients (mg)				
	Furosemide	HPMC E 15 LV	*Saccharomyces boulardii* preparation	Calcium hydroxide	Magnesium stearate
F1	20	40	25	15	2
F2	20	45	20	15	2
F3	20	50	15	15	2
F4	20	45	25	10	2
F5	20	50	20	10	2
F6	20	55	15	10	2
F7	20	50	25	5	2
F8	20	55	20	5	2
F9	20	60	15	5	2

HPMC E 15 LV-Hydroxy Propyl Methyl Cellulose E 15 LV

The percentage swelling index, which is expressed in terms of weight gain of all batches shown in fig. 1. As the concentration of calcium hydroxide increases, swelling index decreases and as the concentration of hydrophilic polymer HPMC E15 LV increases, swelling index increases. hence formulation F9 shows a higher swelling index and formulation F1 shows a lower swelling index. Buoyancy is achieved due to hydration of swelling material like polymer Hydroxypropyl methylcellulose and carbon dioxide gas [26] generation from *Saccharomyces boulardii* formulation when it come in contact with water from acidic media.

Table 2: Evaluation of physical parameters of furosemide floating tablets

Batch code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Weight variation	Drug content uniformity (%)	Total floating time (h)
F1	5.1±0.22	3.4±0.08	0.62±0.09	103.1±3.6	97.66±2.45	>12
F2	5.2±0.08	3.5±0.08	0.49±0.08	101±3	98.70±2.98	>12
F3	5.0±0.21	3.36±0.05	0.56±0.05	101±4.17	100.20±1.85	>12
F4	5.2±0.21	3.33±0.05	0.53±0.05	100.5±3.26	102.91±2.87	>12
F5	5.0±0.25	3.36±0.05	0.49±0.08	101.7±2.86	100.29±1.30	>12
F6	5.4±0.12	3.33±0.12	0.45±0.12	102.8±3.06	97.57±1.73	>12
F7	5.2±0.12	3.43±0.12	0.55±0.10	102.9±3.38	101.41±2.66	>12
F8	5.3±0.24	3.5±0.08	0.48±0.08	102.4±5.31	99.35±2.32	>12
F9	5.3±0.24	3.46±0.09	0.55±0.05	102.5±3.80	103.66±1.87	>12

*Represents mean±SD (n =3)

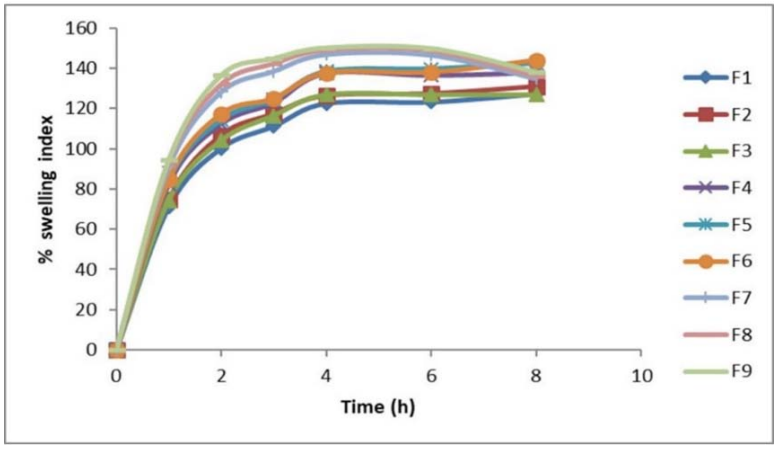

Fig. 1: Maximum % swelling index of all the formulations

From data of factorial design, it is clear that floating lag time changes as the amount of floating agent (*Saccharomyces boulardii* preparation) and calcium hydroxide changes. As the amount of floating agent is changed from 15 to 25 mg the floating lag time decreased because more amount of floating agent contain more Colony Forming Unit of *Saccharomyces boulardii,* which produce more amount of carbon dioxide gas, but as the concentration of calcium hydroxide changed from 5 to 15 mg floating lag time increased because swellability and viscosity of polymer layer also affect on floating lag time, hence as the quantity of calcium hydroxide increased it affect on the viscosity of HPMC layer. The reduction in viscosity at lower pH is mainly because of the more coiling nature of HPMC when ionic strength increased. At the lowest pH i. e in acidic pH of dissolution medium, the coiling of polymer molecules takes place, which preferred HPMC-water interaction and the possibility for polymer-polymer interaction is less prominent [26]. In the case of basic pH due to the addition of calcium hydroxide, which act as pH modifier for the microenvironment of tablet, the HPMC molecules are relatively extended and due to the extended conformation of polymer molecules, the polymer-polymer interaction is preferred, which leads the molecules to overlap and coiling and then entangles to become a thermo co reversible gel, which leads to polymer-polymer interactions. Thus their was an upsurge in velocity and viscosity of HPMC at a higher pH range [27] and a good gel layer is formed due to the addition of calcium hydroxide. This gel layer prevents matrix disintegration and any further rapid water penetration [28]. As water penetrate slowly in matrix of the tablet, activation of *Saccharomyces boulardii* and carbon dioxide formation rate also slows down and this is one reason of increased floating lag time with an increase in calcium hydroxide, but an increased concentration of calcium hydroxide also increased integrity of matrix due to formation of good gel layer.

And thus, it was found that as we change the quantity of calcium hydroxide, it affects on floating lag time, in a formulation containing F1 to F3 where the concentration of calcium hydroxide is high it changes its viscosity and ability of polymer to swell and hence tablet from these batches require more floating lag time then further batches which consists of less calcium hydroxide thus floating lag time is influenced by both quantity of floating agent and amount of calcium hydroxide in the formulation. Total floating duration and matrix integrity also increases with an increase in the quantity of calcium hydroxide.

% drug releases of all floating tablets were represented in fig. 2a and 2b. Average % drug release from batch F1 to F9 varies from 90.01% to 77. 79% also affected by the quantity of both calcium hydroxide and floating agent. Cumulative % drug release increases with an increase in the quantity of calcium hydroxide (pH modifier) and *Saccharomyces boulardii* preparation. Addition of calcium hydroxide in the tablet as a pH modifier maintained a microenvironment gel matrix pH greater than pH with buffer ions in the surrounding media (pH 1.2), but without the pH modifier, the internal matrix was essentially retained same pH as that of surrounding media. If an acidic drug-like furosemide is buffered to a pH above its pKa and is ionized, the drug may have a greater solubility, resulting in faster drug-release rates; this is the reason why formulation F1, F2 and F3 shows higher drug release though the swelling index is lower due to thermoreversible gel formation. This emphasizes pH modifiers play an important role to alter drug solubility and to change microenvironment pH, which might increase drug release [29]. Second reason for an increase in drug

release with an increase in quantity of calcium hydroxide is pH gradient. pH of the gel matrix microenvironment plays an important role in drug release. The gel matrix cannot maintained a neutral environment inside the tablet matrix in the presence of pH modifier and the pH of an internal matrix was higher than the acidic buffer of the surrounding media. There might be pH gradient developed across the gel structure, with the outer gel layer having a lower pH than the inner layer, which exist near to tablet core [29].

Table 3: Experimental design and observed response of the formulation in central composite design

Std	Run	Factor 1	Factor 2	Response 1	Response 2
		A: *Saccharomyces boulardii* preparation (mg)	B: calcium hydroxide (mg)	Floating lag time (min)	Cumulative % drug release after 12 h
4	1	25	15	16.5	90.81
8	2	20	15	18	87.84
3	8	15	15	19.5	84.36
6	3	25	10	12.3	88.82
11	4	20	10	14	85.92
12	5	20	10	14.5	84.83
10	7	20	10	15.5	85.31
13	9	20	10	15	85.06
9	11	20	10	15.2	85.32
5	12	15	10	17	82.53
2	10	25	5	9.5	84.22
7	13	20	5	11.1	81.11
1	6	15	5	13	77.79

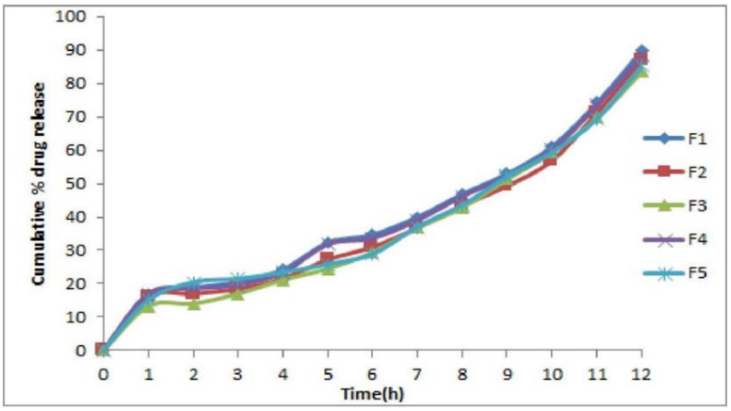

Fig. 2a: Drug release profiles of batch F1 to F5

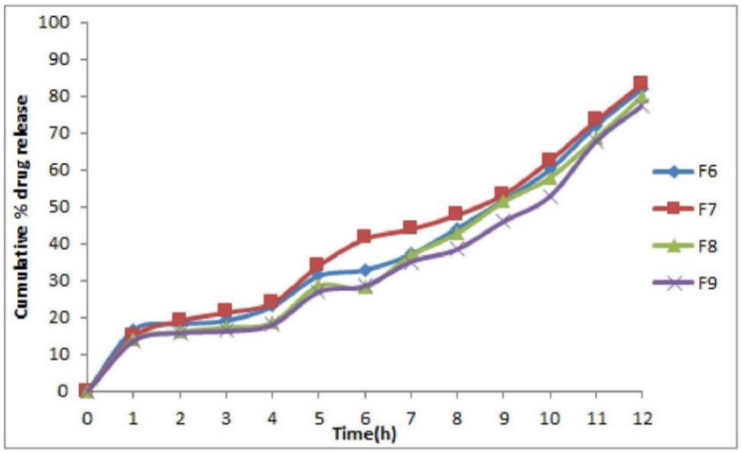

Fig. 2b: Drug release profiles of batch F6 to F9

From regression coefficient (R^2) of release data of formulation from F1 to F9 found by curve fitting method displays zero-order model is best fit model for formulation. In Korsmeyer–Peppas model, the release exponent i.e. n value, is in range from 0.45 to 0.85 for all batches.

Data analysis

Thirteen formulations were prepared as per the central composite design using Design-Expert version 13 software. All dependent variable responses of formulation shown in table 3. From fit summary using Design-Expert software, It was clear that and linear model for floating lag time and quadratic model was suggested for cumulative % drug release after 12h (table 4).

Statistical summary of response shown in table 5 which indicate R^2 value97.46% and 99.33% for response floating lag time and % drug release after 12h respectively. The values of Prob>F were found to be 0.05 for all responses again, indicating that the models are significant. Moreover, the Lack of Fit F-values of 0.44 and 0.47

implies the Lack of Fit is not significant relative to the pure error of the above two parameters. This model can be used to direct the design space.

By using response surface methodology following regression equations obtained (A: *Saccharomyces boulardii* preparation, B: calcium hydroxide)

Floating lag time (Y1) = 15.36–0.37* A+0.68* B ---------- (1)

% Drug Release after 12 h (Y2) = 63.46+0.4557* A+1.52* B+0.0002* A * B+0.0045* A^2-0.043 * B^2 ----- (2)

In Eq. (1), the coefficient of A is negative and the coefficient of B is positive. It indicates that floating lag time (Y1) decreases with an increasing amount of *Saccharomyces boulardii* preparation (A) and Floating Lag Time increases with increasing value of independent variable calcium hydroxide.

It is observed from Eq. (2) that all the coefficients are positive. It signifies % drug release after 12 h (Y2) increases on increasing the amount of *Saccharomyces boulardii* preparation and calcium hydroxide [30].

Table 4a: ANOVA for linear model for response 1: floating lag time

Source	Sum of squares	Df	Mean square	F-value	p-value	
Model	90.27	2	45.13	191.78	<0.0001	Significant
A-*Saccharomyces boulardii* preparation	20.91	1	20.91	88.84	<0.0001	
B-calcium hydroxide	69.36	1	69.36	294.73	<0.0001	
Residual	2.35	10	0.2353			
Lack of Fit	0.9413	6	0.1569	0.4444	0.8208	not significant
Pure Error	1.41	4	0.3530			
Cor total	92.62	12				

Table 4b: ANOVA for the quadratic model for response 2: cumulative % drug release after 12 h

Source	Sum of squares	Df	Mean square	F-value	p-value	
Model	130.74	5	26.15	203.51	<0.0001	Significant
A-Saccharomyces boulardii preparation	61.25	1	61.25	476.69	<0.0001	
B-calcium hydroxide	65.94	1	65.94	513.17	<0.0001	
AB	0.0001	1	0.0001	0.0008	0.9785	
A^2	0.0354	1	0.0354	0.2758	0.6157	
B^2	3.26	1	3.26	25.39	0.0015	
Residual	0.8994	7	0.1285			
Lack of Fit	0.2367	3	0.0789	0.4763	0.7157	not significant
Pure Error	0.6627	4	0.1657			
Cor Total	131.64	12				

Table 5: Statistical summary of the response

Fit statics	Floating lag time (min)	% Drug release after 12 h
Std. Dev.	0.4851	0.3584
Mean	14.70	84.92
C. V. %	3.30	0.4221
R^2	0.9746	0.9932
Adjusted R^2	0.9695	0.9883
Predicted R^2	0.9610	0.9800
Adeq Precision	45.1997	53.466

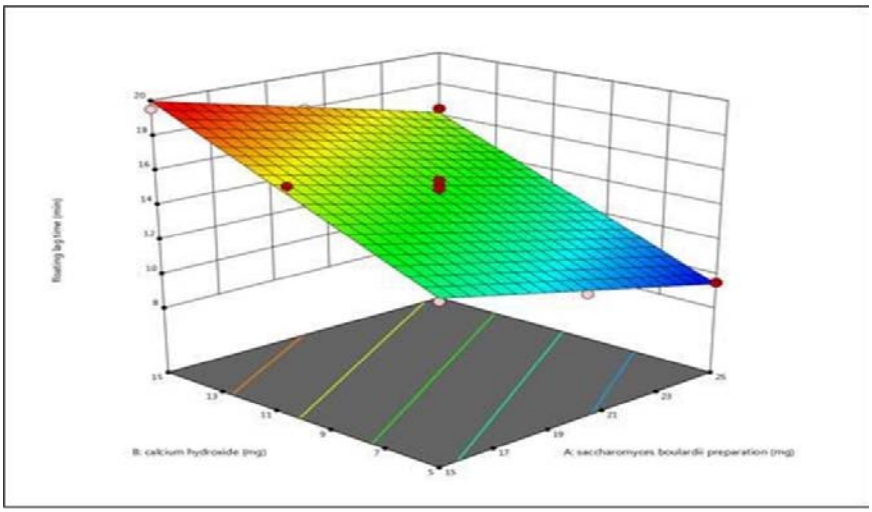

Fig. 3: Response surface plot showing the effect of the amount of *Saccharomyces boulardii* preparation and calcium hydroxide on floating lag time

Response surface analysis

3D surface plot for Floating lag time shown in fig. 3 indicate that floating lag time increases with decreasing amount of *Saccharomyces boulardii* preparation and it increases with an increasing amount of calcium hydroxide.

3D surface plot shown in fig. 4 demonstrates the relation of % drug release after 12 h with *Saccharomyces boulardii* preparation and calcium hydroxide. The effect of *Saccharomyces boulardii* preparation and calcium hydroxide was found to be in an ascending manner i.e. increasing the amount of both increases the response.

By using numerical and graphical optimization techniques best solution found. The statistically optimized formulation selected contained 25 mg of A (*Saccharomyces boulardii* preparation) and 9.98 mg of B (calcium hydroxide) as shown in overlay plot fig. 5. The observed value for floating lag time and cumulative % drug release after 12h were 12.6 min. and 88.18%. Model predicted value of floating lag time was 12.8 min, % drug release after 12 h was 88.66%. The observed values and predicted values of an optimized batch are in close agreement with each other, which confirm the predictability and validity of the model.

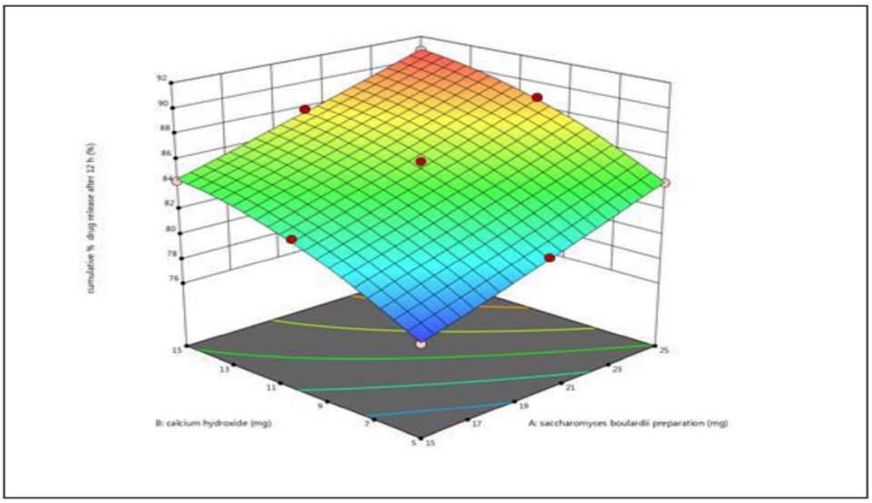

Fig. 4: Response surface plot showing the effect of the amount of *Saccharomyces boulardii* preparation and calcium hydroxide on % drug release after 12 h from furosemide floating tablet

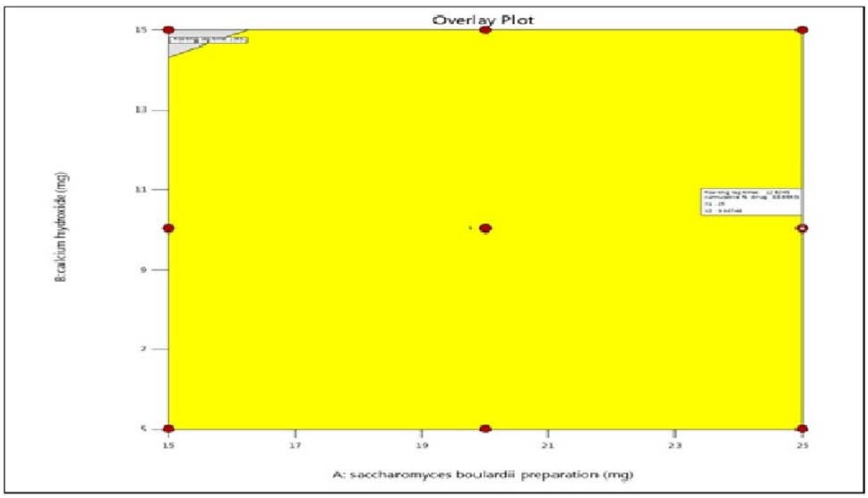

Fig. 5: Optimization of floating tablet's overlay plot

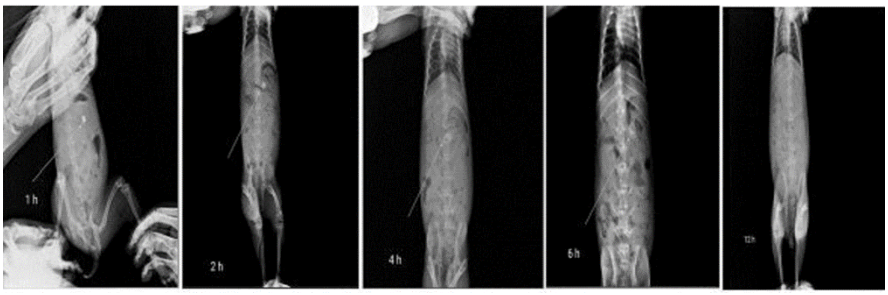

Fig. 6: X ray pictures of tablet at 1, 2, 4, 6 and 12 h

In vivo tablet behavior is shown in X-ray picture of fig. 6 from this it was clear that tablet float intact more then 6h and less then12h.

CONCLUSION

We conclude that *Saccharomyces boulardii* formulation was the good floating agent and it's very easy to prepare tablet using this novel floating agent. The response variables of the formulation was optimized by the response surface methodology technique. The optimized formulation F(O) shows 88.18 % cumulative drug release after 12h and 12.6 min floating lag time. *In vitro and in vivo* buoyancy studies and *in vitro* % drug release study indicate that the formulation is suitable for gastro retention and it increases the bioavailability of furosemide.

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ABBREVIATIONS

HPMC: Hydroxypropyl methylcellulose; *S. boulardii: Saccharomyces boulardii*; NaoH: Sodium hydroxide; Hcl: hydrochloric acid; FDDS: Floating Drug Delivery System

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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