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DEVELOPMENT AND EVALUATION OF FLOATING TABLET USING NOVEL FLOATING AGENT *SACCHAROMYCES BOULARDII* AND HYDROPHILIC POLYMERS

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ABSTRACT

Saccharomyces boulardii, is the unique yeast probiotic that has been effectively used as a good biotherapeutic agent. In aerobic respiration it produces CO_2 and H_2O and in anaerobic alcoholic fermentation it generates ethanol and CO_2. In present investigation this property of yeast is used to generate carbon dioxide in floating tablet. Furosemide is selected as model drug for the development of a floating drug delivery system. Floating tablet prepared by direct compression using Saccharomyces boulardii probiotics formulations as floating agent due to its ability to generate carbon dioxide gas and its safety. Different grades of Hydroxy propyl methyl cellulose (HPMC), Carboxy methyl cellulose sodium (CMC sodium) are used as hydrophilic polymers . Calcium hydroxide is used as PH modifier which enhance solubility of furosemide and also maintain integrity of matrix. we concluded that HPMC has capacity to form a more stable gel than CMC sodium . *In vitro* buoyancy study and dissolution study showed that floating tablet containing HPMC E 15 LV floated for more than 24 hr and 85.36 ± 0.53 % drug release up to 12hr. *Saccharomyces boulardii* formulation was good floating agent and it's very easy to prepare tablet using this novel floating agent in combination with different hydrophilic polymers.

Keywords: *Saccharomyces boularddii*, probiotics, facultative anaerobe, hydrophilic polymers, furosemide

INTRODUCTION

Yeasts are eukaryotic microorganisms prevalent in natural environments including the normal microbial flora of humans, on plants, on airborne particles, in water, in food products, and in many other ecological niches. Yeasts are heterotrophic organisms, in other words, energy metabolism and carbon metabolism are closely linked. In aerobic respiration yeast produces CO_2 and H_2O and in anaerobic alcoholic fermentation it generates ethanol and CO_2. In present investigation this property of yeast used to generate carbon dioxide in floating tablet **[1]**.

Saccharomyces boulardii, is the unique yeast probiotic that has been effectively used as a good biotherapeutic agent to prevent and/or treat variety of gastrointestinal diseases. *Sacchromyces boulardii* is generally administered in lyophilized powder form. Lyophilized products are stable at room temperature, have the benefit of portability and maintain high viability counts for extended periods **[2]**. *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 **[3]**, its high tolerance to gastric acidity, proteolysis enables it to attain high populations in the GI tract. They can forever colonise in the colon and do not easily translocate out of the intestinal tract **[4]**. They can also be perceived alive throughout the GIT, if they are given in lyophilized form **[5]**. *Sacchromyces boulardii* is facultative anaerobe so that it can grow under aerobic or anaerobic conditions **[6]**.

Furosemide is BCS class IV drug having poor aqueous solubility and permeability. It is mainly absorbed in stomach and the upper part of gastrointestinal tract and has a short half life of less than 2hrs. The conventional dosage form shows erratic absorption which results in poor bioavailability (30–60%) **[7]**. It shows high permeability and better absorption through stomach. Thus furosemide have pH dependent solubility and permeability **[8]**. So it is selected as 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 floating dosage forms using *Saccharomyces boularddii* probiotics formulation. It is used as floating agent due to its ability to generate carbon dioxide gas and its safety. Solubility and release rate of furosemide controlled by choosing best hydrophilic polymers among HPMC E LV 15, HPMC 50 cp, CMC sodium 200 and 2000 cps. Calcium hydroxide used as PH modifier which increase rate of dissolution of furosemide and also maintain integrity of matrix.

MATERIALS & METHODS

Materials

Furosemide was gifted by (FU) Suleshvari Pharm, Ankaleshwar, Gujarat. Hydroxy propyl methyl cellulose E LV 15 was gifted by Loba chemie pvt.ltd , Hydroxy propyl methyl cellulose 50 cps purchased from John Baker INC., Carboxy methyl cellulose sodium 200 cps and 2000 cps purchased from SDFCL S D Fine Chem Ltd and Fisher Scientific respectively, *Saccharomyces boulardii* probiotic preparation 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 of furosemide were formulated by direct compression technique using polymers like HPMC E 15 LV, HPMC 50 cp , CMC Sodium 200 and 2000 CPs and other ingredients like calcium hydroxide, magnesium stearate, and *Saccharomyces boulardii* probiotic formulation. All ingredients were passed through sieve no # 40, except yeast preparation. First HPMC E 15 LV, calcium hydroxide and furosemide were first mixed using mortar and pestle to get a uniform tablet blend. Finally

Sacchromyces boulardii preparation and magnesium stearate were mixed delicately to 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 **[9, 10]**. Similarly, different formulations were prepared as given in **Table 1**.

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

Formulation code	PF1	PF2	PF3	PF3
Ingredients (mg)				
Furosemide	20	20	20	20
Calcium hydroxide	10	10	10	10
Saccharomyces boulardii preparation	20	20	20	20
Magnesium stearate	2	2	2	2
HPMC E 15 LV	50	-	-	-
HPMC 50 cp	-	50	-	-
CMC sodium 200 cps	-	-	50	-
CMC sodium 2000 cps	-	-	-	50

EVALUATION TEST

Hardness Test

Monsanto hardness tester was used for evaluation of hardness **[10]**.

Thickness

Vernier caliper was used for evaluation of thickness of tablets **[10]**.

Friability

Friability was expressed in terms of percentage weight loss. For determination of friability Roche Friabilator was used. % friability was evaluated using following formula **[11]**.

Friability (%) = W1 – W2/ W1 X 100

Where,

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

W2 = Weight of Tablets (After Tumbling or friability)

Drug content

10 tablets were weighed and crushed using motor pestle. The crushed powder equivalent to 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 was filtered using the whatsman filter paper, diluted with 0.1N NaoH solution and the drug content was determined spectrophotometrically **[12]**.

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 **[13]**.

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

Tablet Floating Behavior

The floating lag time and total floating duration was determined by visual inspection. The test was performed using USP type II (paddle) apparatus at speed of 50 rpm in 900 mL 0.1N HCl at 37 ± 0.5°C to simulate *in vivo* conditions **[14]**.

In vitro dissolution studies

In vitro dissolution studies were conducted by using paddle dissolution apparatus (Electerolab) at 50 rpm using 900 mL of 0.1 N HCl, (pH 1.2) as a dissolution medium at 37 ± 0.5°C. The absorbance of the sample solution was recorded using UV spectrophotometer at 274 nm. Calculation was carried using disso software (PCP disso

V3) and *in vitro* release profile was determined **[15]**.

RESULTS AND DISCUSSION

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

The best release was found to be with lower viscosity grade of HPMC E 15 LV containing formulation PF1, while comparing with higher viscosity grade of HPMC and CMC sodium .

Drug release rate of formulation PF2 was slow as compare to PF1 formulation. The reduction in gel formation. Highly viscous gels cause retardation of drug release **[16, 17]**. Thus the higher viscosity gel layers of HPMC 50 cps matrices provided a more tortuous and resistant barrier to diffusion, resulting in slower release of drugs from these matrices **[18]**.

In formulation PF3 and PF4 CMC sodium 200 and 2000 cps used as matrix former respectively. CMC sodium a polyelectrolyte gel, is very sensitive to pH changes. The neutralization of charges in acid medium affects the polymer chain conformation and results in a tight network structure. The chain arrangement generates a system of drug release rate as polymer (HPMC) content or viscosity increase may be attributed to stronger connected channels with in the gel matrix that controls the drug release process in a biological environment **[19]**. And thus it shows lower drug release as compare to PF1 and PF2 but unexpectedly PF3 batch which contain CMC sodium having 200 cp viscosity shows higher drug release than PF2 formulation because HPMC has capacity to form a more stable gel than CMC sodium. In other words the gel layer formed by the CMC sodium polymer seems to be lower in strength and therefore could not entrap the evolved gas efficiently **[20]**. hence it breaks down slowly into pieces or erode and shows rapid drug release than PF1.

PF4 formulation which containing higher viscosity grade of CMC sodium shows slow drug release due to formation of tight network structure..

HPMC has capacity to form a more stable gel than CMC sodium **[21]** and hence formulation PF1 and PF2 shows higher floating duration. This might be due to the faster swelling rate and rapid formation of thick gel around the tablets at higher polymer concentration causing rapid entrapment of generated CO_2. The gas generated is imprisoned and protected within the gel formed by hydration of the polymer, thus lowering the density of the tablet below that of gastric contents, causing buoyancy or floatation **[20]**.

The tablet consisting solely of low viscosity Na CMC eroded in simulated gastric solution so temporary floating or break down in pieces was observed for these formulations.

Formulation PF 4 contain Na CMC having high viscosity, as a polyelectrolyte gel, is very sensitive to pH changes. The neutralization of charges in acid medium affects the polymer chain conformation and leads to a tight network structure and due to this tight network structure it forms rigid tablet **[19]** and so it shows temporary floating or sinks at a bottom. However, further investigation should be carried out to establish stability and reproducibility of this dosage form.

Table 2: Evaluation of physical parameters of Furosemide floating tablet

Formulation code	Hardness (kg/cm^2) mean ±SD	Thickness (mm) mean ±SD	Friability (%) ±SD	Drug Content Uniformity (%) mean ± SD	Weight variation Average wt in (mg) ± SD	Total Floating time(h)
PF1	5.0±0.25	3.36±0.05	0.49±0.08	100.29±1.30	101.7±2.86	>12
PF2	5.16±0.04	3.33±0.08	0.55±0.06	102.59±1.97	101.1±3.00	>12
PF3	5.13±0.12	3.26±0.12	0.48±0.17	100.57±1.55	100.9±3.23	Float (< 12)
PF4	5.26±0.12	3.2±0.08	0.61±0.048	102.63± 1.92	101.65±2.81	Temporary Float or sink at bottom

*Represents mean ± S.D (n =3)

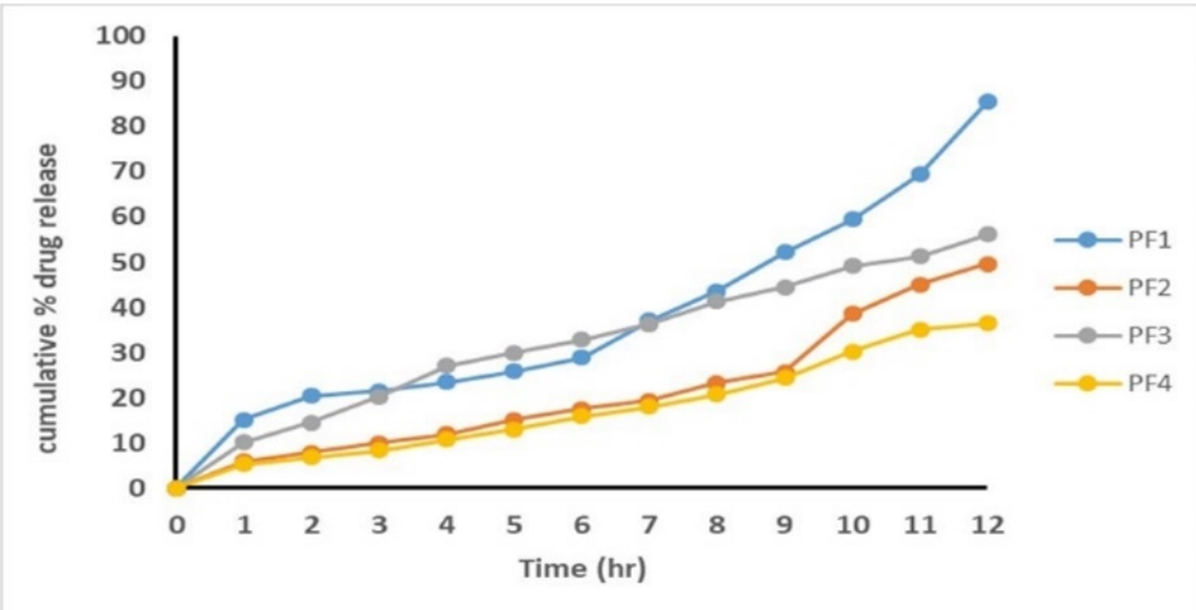

Figure 1 : *In vitro* Drug Release profiles of all the formulations

CONCLUSION

From present study we concluded that floating tablets of furosemide were successfully developed using novel floating agent *Sacchromyces boulardii* formulation. HPMC E LV 15 is more suitable polymer for designing of GRDDS. However, further studies should be carried out, including *in vivo* investigations, to confirm the findings of this work and to establish stability and reproducibility of this dosage form.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

HPMC: Hydroxy propyl methyl cellulose; carboxy methyl cellulose sodium : CMC sodium ; NaoH: Sodium hydroxide; Hcl :hydrochloric acid; FDDS: Floating Drug Delivery System

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