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
Received: 30 May 2021, Revised and Accepted: 28 Jul 2021

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 floating property i.e. production of CO2 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

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 also 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 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. Saccharomyces boulardii probiotics formulation used as floating agent due to its floating 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 weakly 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 in increase rate of dissolution of furosemide and also maintain integrity of matrix.

MATERIALS AND METHODS

Materials
Furosemide was gifted by (FUI) Saleshvari 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].

\[
\text{% Friability} = \frac{W_1 - W_2}{W_1} \times 100
\]

Where,

- \( W_1 \) = Weight of Tablets (Initial/Before Tumbling) and
- \( W_2 \) = 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].

\[
\text{% Swelling index} = \frac{\text{Final Weight of tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100
\]

**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 of 0.1 N 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 sulphate. 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               | 20                                  | 15                   | 2                      |
| F2                   | 20                   | 45             | 20               | 20                                  | 15                   | 2                      |
| F3                   | 20                   | 50             | 15               | 20                                  | 15                   | 2                      |
| F4                   | 20                   | 45             | 25               | 20                                  | 15                   | 2                      |
| F5                   | 20                   | 50             | 20               | 10                                  | 10                   | 2                      |
| F6                   | 20                   | 55             | 15               | 10                                  | 10                   | 2                      |
| F7                   | 20                   | 50             | 25               | 5                                   | 5                    | 2                      |
| F8                   | 20                   | 55             | 20               | 5                                   | 5                    | 2                      |
| F9                   | 20                   | 60             | 15               | 5                                   | 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 generation from *Saccharomyces boulardii* formulation when it come in contact with water from acidic media.

| 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       | 0.6±0.09      | 103.1±3.6       | 97.6±2.45                  | >12                    |
| F2         | 5.2±0.08          | 3.5±0.08       | 0.49±0.08     | 101±3           | 98.7±0.29                  | >12                    |
| F3         | 5.0±0.21          | 3.36±0.05      | 0.56±0.05     | 101±4.17        | 100.2±1.85                 | >12                    |
| F4         | 5.2±0.21          | 3.33±0.05      | 0.53±0.05     | 100.5±3.26      | 102.9±1.28                 | <12                   |
| F5         | 5.0±0.25          | 3.36±0.05      | 0.49±0.08     | 101.7±2.86      | 100.2±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      | 101.4±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.

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 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. 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.
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 maintain 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      |

From regression coefficient (R²) 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 R² value 97.46% 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 \( Y_1 \) = 15.36–0.37 A+0.68 B

% Drug Release after 12 h \( Y_2 \) = 63.46+0.4557 A+1.52 B+0.0002 A * B+0.0045 A²-0.043 * B²

In Eq. (1), the coefficient of A is negative and the coefficient of B is positive. It indicates that floating lag time \( Y_1 \) 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 \( Y_2 \) 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 prep. | 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 prep. | 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  |  
| A²                            | 0.0354         | 1  | 0.0354      | 0.2758  | 0.6157  |  
| B²                            | 3.26           | 1  | 3.26        | 25.39   | 0.0015  |  
| Lack of Fit                   | 0.8994         | 7  | 0.1285      | 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 statistics                 | 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                   |
| R²                            | 0.9746                  | 0.9932                   |
| Adjusted R²                   | 0.9695                  | 0.9883                   |
| Predicted R²                  | 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.
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 then 12h.

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(0) 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.

ACKNOWLEDGEMENT

Author would like to thanks the College of Pharmacy, Akluj and College of Pharmacy, Saswad for providing necessary facilities and support.

ABBREVIATIONS

HPMC: Hydroxpropyl methylcellulose; S. boulardii: Saccharomyces boulardii; NaoH: Sodium hydroxide; Hct: hydrochloric acid; FDDS: Floating Drug Delivery System

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Agarbati A, Canonico L, Marini E, Zammini E, Ciani M, Comitini F. Potential probiotic yeasts sourced from natural environmental and spontaneous processed foods. Foods 2020;9:1-25.
2. Czerucka D, Piche T, Rampal P. Review article: yeast as probiotics–saccharomyces boulardii. Aliment Pharmacol Ther 2007;26:767-78.
3. Boyle RJ, Roy MRB, Tang ML. Probiotic use in clinical practice: what are the risks?. Am J Clin Nutr 2006;83:1256-64.
4. Dürst K, Gandhi DN. Biotherapeutic properties of probiotic yeast saccharomyces in fermented dairy products; 2006. Available from: https://www.dairyscience.info/index.php/probiotics/232-yeast-probiotics.html. [Last accessed on 10 Apr 2021]
5. Sindhur SC, Khetarpaul N. Effect of probiotic fermentation on antinutrients and in vitro protein and starch digestibilities of indigenously developed RWGT food mixture. Nutr Health 2002;16:173-81.
6. The health benefits of saccharomyces boulardii a yeast that may help with diarrhea and more. Available from: https://www.everywellhealth.com/the-benefits-of-saccharomyces-boulardii-99509. [Last accessed on 10 Apr 2021]
7. Can probiotics cause side effects? Probiotics are healthful strains of live bacteria and yeast. Taking probiotics can provide a range of benefits, but it can also cause side effects. Available from: https://www.medicalnewstoday.com/articles/323821. [Last accessed on 10 Apr 2021]
8. Mousa AH, Bakry AM. Efficacy of saccharomyces boulardii metabolism during fermentation of milk fortified with wheat grain juice. Food Sci Technol Res 2019;15:657-65.
9. Dickinson JR. Carbon metabolism. In: Dickinson JR, Schweitzer M. eds. The metabolism and molecular physiology of Saccharomyces cerevisiae. London and Philadelphia PA: Taylor and Francis; 1999. p. 23-24.
10. Kumar S, Nand A. Formulation, optimization and in vitro evaluation of gastroretentive mucoadhesive microspheres of furosemide. Int J Pharm Pharm Sci 2016;8:392-8.
11. Meka L, Kesavan B, Kalamara VR, Eaga CM, Bandari S, Vohlabalova V, et al. A design and evaluation of polymeric coated mini-tablets as multiple unit gastroretentive floating drug delivery systems for furosemide. J Pharm Sci 2009;98:2122-32.
12. Dardande SS, Vavia PR. Design of a gastroretentive mucoadhesive dosage form of furosemide for controlled release. Acta Pharm Sin B 2012;2:509-17.
13. Patel RC, Keraliya RA, Patel MM, Patel MM, Patel NM. Formulation of furosemide solid dispersion with microcrystalline cellulose for achieve rapid dissolution. J Adv Pharm Technol Res 2010;1:180-9.
14. Pawar HA, Ghartat PR, Dhavale RV, Joshi PR, Raschit PP. Development and evaluation of gastro retentive floating tablets of an antihypertensive drug using hydrogenated cottonseed oil. ISRN Pharm 2013;2:1-9.
15. Aswatha Ram NN, Lachaque P, Kaushik U, Shreedhara CS. Formulation and evaluation of floating tablets of liquorice extract. Pharmacogn Res 2010;2:304-8.
16. Patil MS, Vidyasagar G, Patil VB. Formulation, optimization and evaluation of floating tablets clarithromycin. Int J Pharm Sci 2015;7:320-6.
17. Shaikh SA, Shaikh SN, Patel SM, Khaliya MI, Makrani SI, Siddiqui HA, et al. Design expert supported formulation development, mathematical optimization and predictability study of floating tablets of bisoprolol fumarate. Int J Appl Pharm 2021;13:242-8.
18. Tekade BW, Jadhao UT, Patil SG, Patil VR. Formulation and in vitro evaluation of floating tablets of cefpodoxime proxetil. Int J Curr Pharm Res 2017;9:18-22.
19. Oussama M, Ghenwa I, Mostafa I, Mais A. Assessment of physicochemical properties of furosemide (40 mg) tablets marketed in Syria. J Chem Pharm Sci 2016;9:2879-81.
20. Tavakoli N, Varhosha J, Dorkoosh F, Motaghi S, Tamaddon L. Development and evaluation of a monolithic floating drug delivery system for acetylovir. Chem Pharm Bull 2012;60:172-7.
21. Tiwari SB, Murthy TK, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech 2003;4:E31.
22. Rashmitha V, Madhusudan Rao Y, Pavan S. Formulation and evaluation of fenofibrate floating tablets. Asian J Pharm Clin Res 2011;14:175-80.
23. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. Int J Pharm 2008;364:328-43.
24. Mohapatra S, Barik B, Kar RK, Sahoo SK, Barik BB. Design, development and optimization of gastro retentive floating tablets of cefixime trihydrate. Asian J Chem 2013;25:5799-606.
25. Arza RAK, Gongunta CSR, Veerareddy PR. Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. AAPS PharmSciTech 2009;10:220-6.
26. Dios P, Nagy S, Pal S, Pernecker T, Kocis B, Budan F, et al. Preformulation studies and optimization of sodium alginate–based floating drug delivery system for eradication of Helicobacter pylori. Eur J Pharm Biopharm 2015;94:196-206.
27. Punitha S, Uvarani R, Pandeeselvam A. Effect of pH in aqueous (Hydroxy Propyl Methyl Cellulose) polymer solution. Results Materials 2020;100120:1-6.
28. Chi LL, Luigi GM, James L, Ford MR. The use of hypromellose in oral drug delivery. J Pharm Pharmocol 2005;57:33-46.
29. Bashar M, Al-Taani, Bassam M Tashouh. Effect of microenvironment pH of swellable and erodable buffered matrices on the release characteristics of diclofenac sodium. AAPS PharmSciTech 2003;4:1-6.
30. Acharya S, Patra S, Panib NP. Optimization of HPMC and carbopol concentrations in non-effervescent floating tablet through factorial design. Carbohydrate Polymers 2014;102:360-8.