



Available online at www.ujpronline.com
Universal Journal of Pharmaceutical Research
 An International Peer Reviewed Journal

ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF IBUPROFEN GASTRO-RETENTIVE FLOATING TABLETS

Saddam C Shaikh*¹, Dnyaneshwar Sanap¹, Dipak V Bhusari¹, Shirish Jain¹, Pooja P Kochar¹, Vikram N Sanchati¹

Rajarshi Shahu College of Pharmacy, Buldana, Maharashtra, India.

Article Info:



Article History:

Received: 21 May 2018
 Reviewed: 6 July 2018
 Accepted: 10 August 2018
 Published: 15 September 2018

Cite this article:

Shaikh SC, Sanap D, Bhusari DV, Jain S, Kochar PP, Sanchati VN. Formulation and evaluation of Ibuprofen gastro-retentive floating tablets. Universal Journal of Pharmaceutical Research. 2018; 3(4): 19-23.

<https://doi.org/10.22270/ujpr.v3i4.178>

*Address for Correspondence:

Saddam C Shaikh, Rajarshi Shahu College of Pharmacy, Buldana, Maharashtra, India.
 E-mail: saddamshaikh.bld@gmail.com

Abstract

Objective: The objective of the present study was to formulate the gastro-retentive floating tablets containing Ibuprofen, which would remain in stomach and/or upper part of GIT for prolonged period of time. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. Ibuprofen is an anti-inflammatory drug.

Methods: On trial and error basis formulation design was done. Four different batches of floating tablets of Ibuprofen were prepared using HPMC, Xanthan gum, and gas generating agent sodium bicarbonate and citric acid. The tablets were characterized for the pre and post compression parameters such as friability, hardness, thickness, drug content, weight variation, *in-vitro* buoyancy studies and 13 hrs *in-vitro* drug release studies and the results were within the limits.

Results: There was no interaction found in between drug and other ingredients. Maximum release was shown by formulation of batch F4 (47.38%), and minimum by the formulations of batch F2 (34.46%) in the duration of 13 hrs.

Conclusion: From the results obtained, it was concluded that the optimized formulation F4 desired drug release properties and floating behavior.

Keywords: Citric acid, gastro-retentive floating tablets, HPMC K4M, Ibuprofen, sodium bicarbonate, xanthan gum.

INTRODUCTION

Administration of drugs by oral route offers ease administration and gastrointestinal physiology offers more flexibility in dosage form design than other routes¹. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half lives are eliminated quickly from the systemic circulation. So, there is need of frequent dosing of these drugs is required to achieve desired therapeutic activity. To avoid this, the development of oral sustained/controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. Floating drug delivery systems (FDSS) were first described by Davis in 1968². Floating systems or Hydro-dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time while the system is floating on the gastric content; the drug is released slowly at the desired rate from the floating system. After release of drug, the residual system is emptied from the stomach³.

This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration⁴. Gastro retentive systems confine the dosage forms for several hours inside the stomach and considerably prolong the gastric residence time of drugs⁵. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It is also beneficial for local drug delivery to the stomach and proximal small intestines⁶. Ibuprofen (iso-butyl-propanoic-phenolic acid) is a non-steroidal anti-inflammatory drug (NSAID). It is a propionic acid derivative⁷. It is used for treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, acute musculoskeletal disorders, and low back pain, fever. The bioavailability of the drug is 87-100% and the protein binding capacity is 98%⁸. It is metabolized by liver and it has a plasmatic half-life of 1.8–2.0 h as a result, it has to be administered three to six times a day. It is excreted through urine⁹. Hydrophilic polymer matrix is widely used for formulating sustained release dosage form. HPMC is widely used hydrophilic polymer to prolong drug release due to its rapid hydration, good

compression and gelling characteristics along with its ease of use, availability, and very low toxicity. It regulates the release of drug by controlling the swelling and cross-linking^{10,11}.

The main intention of this work was to formulate a single unit floating tablets of ibuprofen with use of HPMC for the release of the drug after a definite lag time and provides required concentration of drug at regular intervals of time which results reduction in frequency of dose of administration and will improve patient compliance¹².

MATERIALS AND METHODS

Ibuprofen was obtained as a gift sample from Leben Parma, Akola, Maharashtra, India. HPMC K4M, Xanthan gum, Citric acid, lactose and Sodium bicarbonate, Talc and MCC were obtained from Research Lab, Akola, Maharashtra, India. All the chemicals and reagents required for the present experimental work are of analytical grade.

Standard Calibration Curve

10 mg of Ibuprofen was weighed and dissolved in 10 ml of phosphate buffer 6.8, to give a solution of 1000 µg/ml concentration. From this solution 1 ml was taken and diluted to 10 ml using Phosphate buffer 6.8 to produce a stock solution of 100 µg/ml. From this stock solution different concentrations were prepared. The absorbance of these solutions was measured at 221 nm by UV spectrophotometer (Jasco V530 plus)¹³.

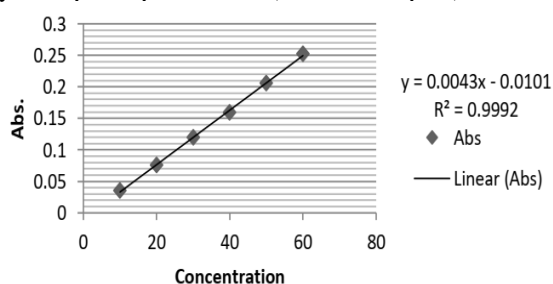


Figure 1: Standard calibration curve of Ibuprofen.

Fourier Transform Infra-Red (FTIR) Spectroscopy

Interaction of drug with excipients was confirmed by carrying out IR interactions studies. Drug and excipients used in study were placed in air tight screw cap amber colored vials, then vials were kept at room temperature as well as in hot air oven at 40°C for one week to get them moisture free and FT-IR analysis was carried out with saturated potassium bromide using pellet making method. Standard and KBr were taken in the ratio of 1:300 to make a solid disc or pellet with the help of Hydraulic Pellet Machine^{14,15}.

Powder characterization

Bulk Density: It refers to packing of particles. The bulk density of the formulated granules was evaluated using a bulk density apparatus¹⁶. It is expressed in gm/ml and is given by below equation-

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Volume of the bulk powder}}$$

Tapped density

Weighed quantity of tablet blend was into a graduated cylinder. Volume occupied by the drug was noted

down. Then cylinder was subjected to 100, 200 and 300 taps in tap density apparatus¹⁷.

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}$$

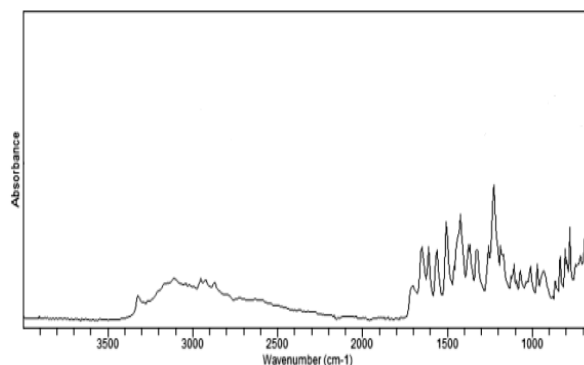


Figure 2: FTIR spectrum of Ibuprofen.

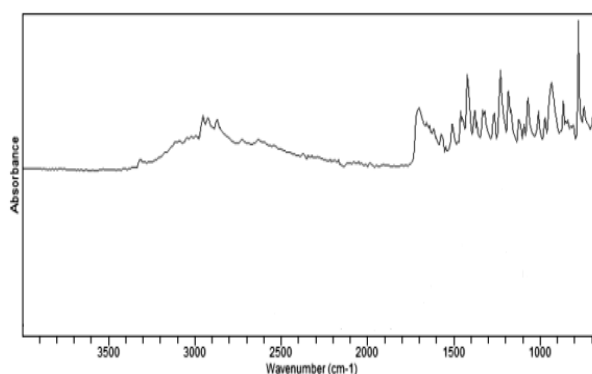


Figure 3: FTIR spectrum of mixture of Ibuprofen, HPMC K4M.

Carr's Index (Compressibility)

The compressibility index was measures the property of powder to be compressed. The packing ability of tablet blend was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping¹⁸.

It was indicated as Carr's compressibility index was calculated by following formula-

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

It is measurement of frictional resistance of tablet blend¹⁹. The ideal range should be 1.2-1.5. It was determined by the ratio of tapped density and bulk density

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose

It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane. It was determined by the following equation:

$$\tan \theta = \frac{h}{r}$$

Where, θ = Angle of repose, h = of powder heap.

r = Radius of the powder cone.

Preparation of Ibuprofen floating tablets

The composition of different formulations of Ibuprofen floating tablets is shown in Table 2. All the ingredients

were accurately weighed and passed through mesh 60#. In order to mix the ingredients thoroughly drug and polymer were blended and geometrically in a mortar and pestle for 15 minutes then magnesium stearate, sodium bicarbonate, talc, lactose and magnesium stearate were mixed one by one. After thoroughly mixing the ingredients, the powder was blend was passed through 44# sieve and compressed on rotary tablet punching machine^{21,22}.

Post compression parameters of Ibuprofen floating tablets

Weight uniformity test

Twenty Ibuprofen tablets were weighed individually, average weight was calculated and individual tablet weights were compared to the, average weight. The tablets met the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit²³.

Hardness test

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm². Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated²⁴.

Friability

A friability test was conducted on Ibuprofen floating tablets using a Roche friabilator. Twenty tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The tablets were initially weighed and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the tablets were removed. Any loose dust was removed from the tablets as before and the tablets were weighed again^{25,26}. The percentage friability was then calculated by,

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Lag Time

The *In-vitro* buoyancy was determined by the lag time. The Ibuprofen tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for a tablet to rise to the surface for floating was determined as the lag time²⁷.

Floating Time

The Ibuprofen tablets were placed in a 100 ml glass beaker containing 0.1 N HCl. The time for which the tablet remained floating on the surface of medium was determined as floating time²⁸.

Drug Content

Ten Ibuprofen tablets were weighed and average weight was calculated. All the 10 tablets were crushed in a mortar. The powder equivalent to 10 mg was accurately weighed, dissolved in 5 ml of Methanol and made up to 100 ml of 0.1 N HCl. The volumetric flask was then shaken for approximately 20 minutes. The solution was filtered and 1 ml of filtrate was diluted to 10 ml using 0.1 N HCl. Absorbance was measured at 221 nm using 0.1 N HCl as a blank. The amount of drug present in one tablet was calculated²⁹.

In vitro release studies

In vitro drug release study for the prepared Ibuprofen floating tablets were conducted for period of 13 hours using a six station USP XXVI type II (paddle)

apparatus at 37±0.5°C and 50 rpm speed. The dissolution studies were carried out in triplicate for 10 hours in phosphate buffer of pH 6.8 under sink condition. At first half an hour and then every 1 hour interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 221 nm for Ibuprofen by a UV- spectrophotometer²⁹.

Statistical analysis

Experimental results were expressed as mean±SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at *p*<0.05.

RESULTS AND DISCUSSION

Floating tablets of Ibuprofen were developed in order increase the gastric residence time of drug, so that they can be retained in stomach for longer time to reduce the frequency of administration. Four different batches of tablets were made using HPMC K4M, along with effervescent agent sodium bicarbonate and citric acid to optimize the drug content, *in-vitro* buoyancy and *in-vitro* drug dissolution studies.

Table 1: Results of physical evaluation of pre-compression blend.

| Batch code | Angle of repose (θ) | Bulk Density | Tapped Density | Carr's Index | Hausner's ratio |
|------------|---------------------|--------------|----------------|--------------|-----------------|
| F1 | 21 | 0.224 | 0.264 | 15.15 | 1.17 |
| F2 | 22 | 0.222 | 0.260 | 14.61 | 1.17 |
| F3 | 26 | 0.251 | 0.289 | 13.14 | 1.15 |
| F4 | 25 | 0.229 | 0.260 | 11.92 | 1.13 |

The selection of viscosity grade of a polymer is an important consideration in the formulation of tablet. All the formulations were prepared by direct compression method. Preformulation is the first step in development of new formulation. Characteristic absorption bands in FTIR spectrum of the drug sample showed and proved identity of drug. There was no interaction found in between drug and other ingredients. Absorption maxima of the Ibuprofen were determined by UV spectrophotometric method using UV/Visible spectrophotometer. The λ_{max} of Ibuprofen in phosphate buffer 6.8 is 221 nm. The standard curves of Ibuprofen were prepared in Phosphate buffer 6.8 in the concentration range of 10 to 50 µg/ml. A straight line with r²=0.9992 was found indicating that the drug follows Beer's law within the specified concentration range. The value of Hausner's ratio varies from 1.13-1.17. Bulk density varies from 0.222-0.251 and tapped density varies from 0.260-0.289. Whereas angle of repose varied from 22-31° which ensured good flow properties of powder. Carr's Index varies from 11.92 - 15.15. The general appearance of tablets, its visual identity and overall 'elegance' is essential for acceptability, the shape of all the formulation remained off white, smooth, flat faced circular and no visible

cracks. In a weight variation test, the Pharmacopoeial limit for percentage deviation for the tablets of more than 250 mg is $\pm 5\%$ ¹⁸. The average percentage deviation of all the tablet formulations was found to be within the above limit, and hence all the formulations passed the test for uniformity of weight as per the official requirements. The hardness of the tablet was measured by Monsanto tester and was ranged between 3.7 ± 0.93 to 6.3 ± 0.98 kg/cm². Increasing tablet hardness provided a much great control over dissolution rate. The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness²².

Friability is the measure of tablet strength. The friability was measured by Roche friabilator and was found 0.2 to 0.7%, and this parameter given the satisfactory mechanical resistance of the tablet. In the present study the percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits²⁶. The drug content estimations showed values in the range of 97.58 ± 0.47 to $99.57 \pm 0.06\%$. These results showed the good drug content uniformity of the tablet. The release profiles of formulations F1, F2, F3 and F4, are shown in Figure 4.

Table 2: Composition of different Ibuprofen floating tablets.

| Batch code | Ibuprofen (mg) | HPMC K4M (mg) | Xanthan gum (mg) | NaHCO ₃ (mg) | M.C.C (mg) | Citric acid (mg) | Lactose (mg) | Mg stearate (mg) | Talc (mg) |
|------------|----------------|---------------|------------------|-------------------------|------------|------------------|--------------|------------------|-----------|
| F1 | 100 | 25 | 12 | 20 | 38 | 15 | 13 | 5 | 5 |
| F2 | 100 | 12 | 25 | 18 | 38 | 12 | 11 | 5 | 5 |
| F3 | 100 | 37 | 37 | 25 | 38 | 18 | 18 | 5 | 5 |
| F4 | 100 | 50 | 50 | 30 | 38 | 25 | 20 | 5 | 5 |

Table 3: Evaluation parameters of Ibuprofen floating tablets.

| Batch code | Average weight (gm.), n=20 | Hardness (kg/cm ³), n=6 | Friability (%), n=20 | Buoyancy lag time (sec) | Total floatation time (hrs) | % Drug Content, n=10 |
|------------|----------------------------|-------------------------------------|----------------------|-------------------------|-----------------------------|----------------------|
| F1 | 0.485 \pm 0.03 | 3.7 \pm 0.93 | 0.7 | 120 \pm 1.01 | >10 | 98.86 \pm 0.15 |
| F2 | 0.492 \pm 0.14 | 6.3 \pm 0.98 | 0.3 | 100 \pm 1.78 | >8 | 98.32 \pm 0.09 |
| F3 | 0.500 \pm 0.25 | 4.2 \pm 1.26 | 0.5 | 200 \pm 1.46 | >10 | 97.58 \pm 0.47 |
| F4 | 0.468 \pm 0.09 | 5.9 \pm 1.35 | 0.2 | 240 \pm 1.59 | >11 | 99.57 \pm 0.63 |

The release of drug mainly depends upon the polymer concentration. Maximum release was shown by formulation of batch F4 (47.38%), and minimum by the formulations of batch F2 (34.46%) in the duration of 13 hrs. The release profiles showed tri-phasic with initial burst effect (less than 30 min) followed by a polymer-controlled slower release in the second phase.

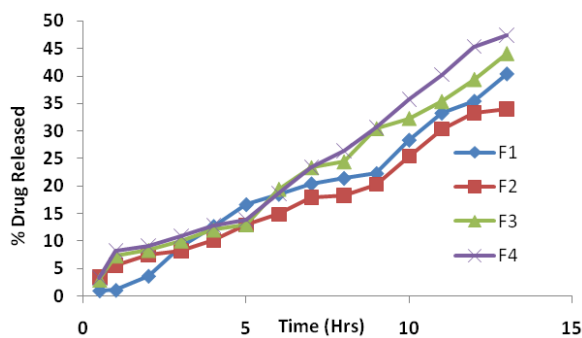


Figure 4: In-vitro % drug release profiles of Ibuprofen floating tablets.

The difference in burst effect was the result of difference in the viscosity of the polymers. It is reported that citric acid level greatly influenced the drug release, irrespective of hydroxypropyl methyl cellulose grade. Lactose was used as diluents as well as channeling agent in the floating delivery of the drug. *In vitro* release profile showed that on increasing the concentration of lactose release rate increased. Floating lag time for formulations of batches was found to be in the range of 100 ± 1.78 to 240 ± 1.59 sec. The concentration

of gas generating agent affected the floating lag time, as the amount of gas-generating agent was increased, the floating lag time decreased. The incorporation of gas generating agent exhibited reduction in the floating lag time. After the analysis of the above formulation and optimization study we can conclude that optimized formulation of batch F4 is the best and promising formulation for the delivery of the Ibuprofen in order to provide the controlled release and increased gastro retentive drug delivery system to reduce frequency of its administration.

CONCLUSIONS

The ultimate aim of the present study was to prepare gastroretentive floating tablet of Ibuprofen using polymers like HPMC K4M by direct compression method. FTIR study concludes no drug polymer interaction. Different pre compression properties like Carr's Index, Hausner's ratio indicate good flow properties of powder. The formulations were evaluated for various parameters like hardness, friability, weight variation, floating lag time, floating time, *in-vitro* drug release etc. Based on different evaluation parameters formulation of batch F4 was concluded as an optimum formulation. The present research work was successful in improving the efficacy of Ibuprofen oral therapy as the drug release was extended reducing dosing frequency thereby improving patient compliance.

ACKNOWLEDGEMENTS

The authors extend their thanks and appreciation to the Rajarshi Shahu College of Pharmacy, Buldana, Maharashtra, India to provide necessary facilities for this work.

AUTHOR'S CONTRIBUTION

Shaikh SC: writing original draft, methodology. **Sanap D:** investigation, formal analysis. **Bhusari DV:** writing, review and editing. **Jain S:** methodology, formal analysis, conceptualization. **Kochar PP:** writing, review. **Sanchati VN:** writing, editing. The final manuscript was read and approved by all authors.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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