ISSN (O): 2349-5332
CODEN: IRJPHY

FORMULATION AND EVALUATION OF IBUPROFEN GASTRO RETENTIVE FLOATING TABLETS

M. Maheshwar

Department of Pharmaceutics, MLR Institute of Pharmacy, Dundigal, Medchal, Telangana, India.

Submitted on: 21.12.18; Revised on: 04.01.19; Accepted on: 08.01.19

ABSTRACT

The objective of the present study was to formulate the optimised gastro-retentive floating tablets containing Ibuprofen, which would remain in upper part of GIT for prolonged period of time. Ibuprofen is a medication in the non steroidal anti-inflammatory drug class that is used for treating pain, fever, and inflammation. Floating systems will have low bulk density so that they can float on the gastric juice in the stomach. Ibuprofen is an anti inflammatory drug. Various approaches have been followed to encourage gastric retention of an oral dosage form. The present work attempts have been made to prepare Ibuprofen by Direct compression method. On trial and error basis formulation design was carried. 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 subjected to pre compression parameters such as Angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index and post compression parameters such as friability, hardness, thickness, drug content, weight variation, *in-vitro* buoyancy studies and *in-vitro* drug release studies and the results were within the limits. From the results obtained, it was concluded that the optimized formulation F4 was having desired drug release properties and floating behaviour when compared with that of marketed product.

KEYWORDS: Ibuprofen, gastro-retentive floating tablets, Xanthan gum, sodium bicarbonate, citric acid.

Corresponding Author: M. Maheshwar
E-mail: maheeshh02@gmail.com

Indian Research Journal of Pharmacy and Science; 19(2018)1718-1725;
Journal Home Page: https://www.irjps.in
DOI: 10.21276/irjps.2018.5.4.11

INTRODUCTION

Administration of drugs by oral route offers ease administration and gastrointestinal physiology offers more flexibility in dosage form design than other routes[1]. 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 (FDDS) were first described by Davis in 1968[2]. 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 stomach[3]. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration[4]. Gastro retentive systems confine the dosage forms for several hours inside the stomach and considerably prolong the gastric residence time of drugs[5]. 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 intestines[6]. Ibuprofen (iso-butyl-propanoic-phenolic acid) is a non-steroidal anti-inflammatory drug (NSAID). It is a propionic acid derivative[7]. 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 hr as a result, it has to be administered three to six times a day. It is excreted through urine[9]. 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 compliance[12].

MATERIALS AND METHODS

Ibuprofen was obtained as a gift sample from Vive Med Labs, Hyderabad, Telangana, India. HPMC K4M, Xanthan gum, Citric acid, lactose and Sodium bicarbonate, Talc and MCC were obtained from Research Lab, Hyderabad, Telangana, 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 10ml 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[13].The standard curve of the ibuprofen shown in the Figure-1.

Table 1: Standard Curve of Ibuprofen

S. No	Concentration (µg/ml)	Absorbance
1	10	0.340
2	20	0.548
3	30	0.724
4	40	0.862
5	50	0.974

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 the sieve 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 mixture was passed through the sieve 44 and compressed on rotary tablet punching machine[14,15].

Table-2: Formulation Development of Ibuprofen floating tablets

atch code	Ibuprofen (mg)	HPMC K4M (mg)	Xanthan gum (mg)	NaHCO3 (mg)	M.C.C (mg)	Citric acid (mg)	Lactose (mg)	Magnesium 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

Pre compression parameters of Ibuprofen floating tablets

1. 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.

$$\tan\theta = h/r$$

Where, θ = Angle of repose. h = powder heap. r = Radius of the powder cone.

2. Bulk Density: It refers to packing of particles. The bulk density of the formulated granules was evaluated using a bulk density apparatus[16]. It is expressed in gm/ml and is given as

Bulk density=Mass of the powder/ bulk volume of the powder

3. Tapped density: Weighed quantity of tablet blend was introduced into a graduated cylinder. Volume occupied by the drug was noted down. Then cylinder was subjected to 100, 200 and300 taps in tap density apparatus[17]. According to USP, tapped density was given by

Tapped density=Mass of the powder/Tapped volume of the powder

4. Carr's Index (Compressibility)

The compressibility index and Hausner ratio 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 tapping[18]. It was indicated as Carr's compressibility index was calculated by following formula.

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

5. Hausner's Ratio: It is measurement of frictional resistance of tablet blend[19]. The ideal range should be 1.2-1.5. It was determined by the ratio of tapped density and bulk density.

Hausner′s ratio=Tapped density/Bulk density

Table-3: Specifications for flow properties

Flow Character	Carr's index (%)	Hausner's ratio	Angle of repose
Excellent	<10	1.00-1.11	25-30
Good	11-15	1.12-1.18	31-35
Fair (aid not needed)	16-20	1.19-1.25	36-40
Passable (may hang up)	21-25	1.26-1.34	41-45
Poor (must agitate/vibrate)	26-31	1.35-1.45	46-55
Very poor	32-37	1.46-1.59	56-65
Very, very poor	>38	>1.60	.>66

Table-4: Results of Pre compression parameters of Ibuprofen powder blend

Batch code	Angle of repose (θ)	Bulk Density(gm/ml)	Tapped Density(gm/ml)	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

Post compression parameters of Ibuprofen floating tablets

1. Weight variation 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 two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit[20].

2. Hardness test

The hardness of the tablets was determined using Monsanto Hardness tester[21,22]. It is expressed in kg/cm^2. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

3. 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[23]. 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[24,25]. The percentage friability was then calculated by

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

4. 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 time[26].

5. Floating Time

The Ibuprofen tablets were placed in a 100 ml glass beaker containing 0.1N HCl. The time for which the tablet remained floating on the surface of medium was determined as floating time[27].

6. 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 with 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 solution[28]. The amount of drug present in one tablet was calculated.

7. *In vitro* drug release studies

In vitro drug release study for the prepared Ibuprofen floating tablets were conducted for period of 15 hours using a six station USP XXVI type II (paddle) apparatus at 37 ± 0.5^0C and 50 rpm speed. The dissolution studies were carried out for 15 hours in phosphate buffer of pH 6.8 under sink condition. At first one hour and then every two hours of time interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume of dissolution medium constant. After filtration and appropriate dilution, the sample solution was analyzed at 221 nm for Ibuprofen by a UV-spectrophotometer.

RESULTS AND DISCUSSION

Floating tablets of Ibuprofen were developed in order to 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 effervescing agent sodium bicarbonate and citric acid to optimize the drug content, *in vitro* buoyancy and *in vitro* drug dissolution studies. 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. 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. These results of post compression parameters are shown in the Table-5.

Table-5: Results of Post compression parameters of Ibuprofen floating tablets

Batch code	Average weight (gm)	Hardness (kg/cm^2)	Friability (%)	Buoyancy lag time (sec)	Total floatation time (hrs)	Drug Content (%)
F1	0.485	3.7	0.7	120	>10	98.86
F2	0.492	6.3	0.3	100	>8	98.32
F3	0.500	4.2	0.5	200	>10	97.58
F4	0.468	5.9	0.2	240	>11	99.57

The release profiles of formulations F1, F2, F3, F4 and marketed product are shown in Figure 2. Maximum release was shown by formulation of batch F4 in the duration of 15 hrs when compared with the marketed product. 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 hydroxy propyl methyl cellulose grade. Lactose was used as diluents as well as channelling 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 in the range of 100 to 240 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.

Table-6: Cumulative Percentage Drug Release of Ibuprofen floating tablets

Time (hrs)	F1	F2	F3	F4	Marketed product
1	1.62	6.32	6.45	7.26	7.52
3	9.21	9.61	10.25	11.74	10.68
5	14.23	13.21	13.25	15.95	14.96
7	21.32	20.51	17.24	23.51	22.35
9	22.34	21.54	19.32	29.61	28.55
11	23.36	22.36	25.36	32.54	33.62
13	36.52	32.51	29.92	38.51	37.42
15	38.61	35.61	36.32	46.62	45.51

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.

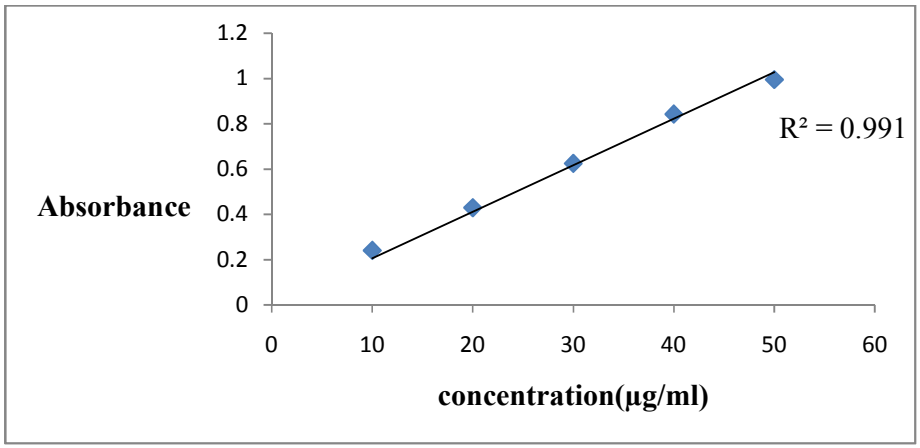

Figure-1: Standard graph of Ibuprofen

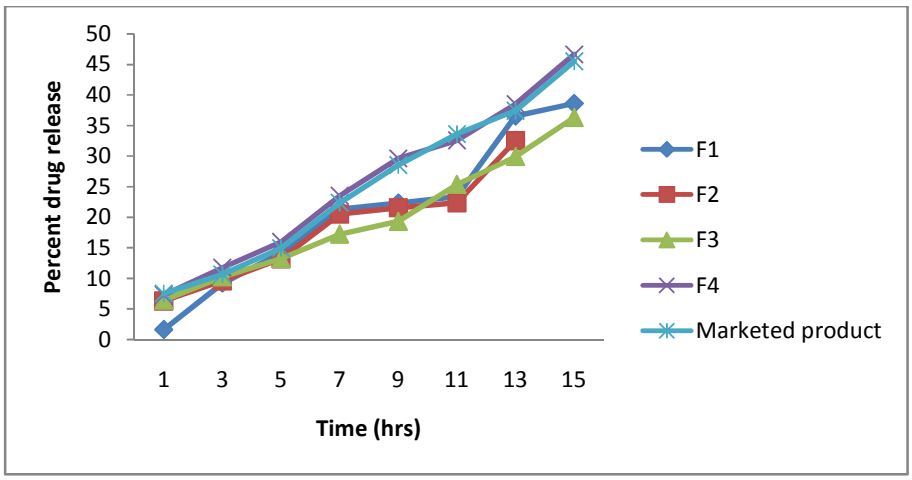

Figure-2: In vitro drug release of Ibuprofen floating tablets

CONCULSION

The ultimate aim of the present study was to prepare gastro retentive floating tablet of Ibuprofen using polymers like HPMC K4M by direct compression method. Different pre compression properties like Carr's Index, Hausner ratio, bulk density and tapped density 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 optimized formulation compared with that of marketed product. 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.

ACKNOWLEDGEMENT

The author was Thankful to Dr. K. S. Murali Krishna, Principal, MLR Institute of Pharmacy for his kind support and encouragement.

CONFLICT OF INTEREST

No conflict of interest was associated with this work.

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CONFLICT OF INTEREST REPORTED: NIL ; SOURCE OF FUNDING: NONE REPORTED