Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Research Article

Formulation development and evaluation of gastroretentive floating drug delivery system using natural polymer.

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Received 12 July 2018; received in revised form 19 July 2018; accepted 12 August 2018

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ABSTRACT

With the objective to develop floating drug delivery system using natural polymer to increase its residence time in stomach as high solubility, chemical and enzymatic stability and absorption profile was observed in acidic pH value. The floating tablets were prepared by direct compression method using sodium bicarbonate as floating agent and Xanthan gum as rate retarding polymer. A 3^2 full factorial design was constructed to study the effect of the amount of Xanthan gum and sodium bicarbonate on the drug release profile from the formulations. The formulations were evaluated for floating lag time, floating duration time and in vitro drug release studies. The optimized formulation showed sufficiently sustained drug release and remained buoyant on the surface of medium for more than 10 hours. It was observed that the increase of floating agent concentration displayed a common phenomenon that the drug release rate and extent were increased in all cases. It was also evident that as the concentration of Xanthan gum increases in the formulation the release rate was found to be decreased.

KEYWORDS

Floating, gastroretentive, natural polymer.

1. INTRODUCTION

Oral drug administration has been the predominant route for drug delivery. Oral route has been the most popular and successfully used route for controlled delivery of drugs due to some reasons like convenience, ease of production, ease of administration and low cost of such system [1]. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. This has led to the evolution and development of several drug delivery systems. In recent years, oral dosage forms for gastric retention have drawn more and more attention for their theoretical advantage in permitting control over the time and site of drug release. This is particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine and dissolve better in the acidic environment of the stomach. In another way gastroretentive drug delivery system is dosage form which enhances gastric residence time (GRT) and release drug without affecting the intrinsic rate of gastric emptying for several hours [2]. A number of systems have been pursued to increase the gastric residence time of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention [3].Techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems have been employed. These methods include bioadhesive system, swelling system, expanding system, raft forming system, magnetic system, superporous hydrogels and floating system [4].

2. MATERIALS AND METHODS

To achieve the objectives of the present study various in-vitro method were applied for the development and evaluation of floating gastroretentive drug delivery system.

2.1. Preformulation Studies [5]

Prior to the development of dosage forms, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder along with polymers were determined. The Drug and polymer were characterized for different parameters. It includes Organoleptic, Micromeritic properties, Solubility Profile, Fourier transform infra red spectrophotometer (FTIR), UV-Visible Spectroscopy and Calibration Curve were determined.

2.2. Preliminary studies

The preliminary studies were done in order to determine minimum amount of polymer needed to form a matrix and minimum amount of sodium bicarbonate needed to float the tablet. The tablets were then evaluated for floating lag time, in vitro drug release, and matrix integrity.

2.3. Preparation floating tablets [6]

The composition of preliminary formulations was depicted in Table1.The tablets were prepared by direct compression method. All the ingredients listed in the composition table1 were initially passed through sieve #40 separately before mixing. The required quantity of drug and other ingredients were weighed according to formulation and transferred to a mortar and triturated for thorough mixing using geometric dilution principle. The resultant mixture was blended thoroughly in polyvinylchloride (PVP) bag for 10 minutes. The powder blend was lubricated

with magnesium stearate and mixed further for 2 minutes. The blend was compressed using 8 station tablet punching machine-Karnavati-Minipress-D-II Link, Mumbai. All the tablets were punched by using 11mm flat punch. The compression force was adjusted to obtain tablets with hardness in the range of 5 to 6 kg/cm^2.

2.4. Optimization of Formulations By Factorial Design [7]

Factorial designs were used in experiments where the effects of different factors or conditions on experimental results were to be elucidated. They were the designs of choice for simultaneous determination of the effects of several factors and their interactions .A factor is an assigned variable such as concentration, temperature, lubricating agent, drug treatment or diet. It can be qualitative or quantitative. The levels of a factor are the values or designations assigned to the factor. The runs or trials that compromise factorial experiments consist of all combinations of all levels of all factors. The effect of a factor is the change in response caused by varying level(s) of the factor. A 32 full factorial design was used in this study. In this factorial design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of Xanthan gum (X1) and NaHCO3(X2) were selected as independent variable while all other quantities remained constant. Percent cumulative drug release and floating lag time were selected as dependent variables. Variable levels which used in factorial design were depicted in table 2 and code values were depicted in table 3.

2.5. Evaluation of Tablets [8, 9, 10, 11]

Tablets were evaluated for colour and shape visually. Physical dimensions like Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using digital Vernier Calipers. 6 tablets were selected at random and thickness was measured using digital Vernier calipers. The hardness of tablet of each formulation was measured by Monsanto hardness tester. Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min. the tablets were then dedusted and weighed again and percent friability was calculated. Tablet density is an important parameter for floating tablets. The tablet will float only if its density is less than that of gastric fluid (1.004). Density (d) was determined using the relationship: $d = m/v$, where $v = \pi r^2 h$.

2.6. Swelling characteristics

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by the water uptake study. The tablet was placed in the USP dissolution apparatus II. The medium used was 0.1N HCl, 900 ml rotated at 100 rpm. The medium was maintained at 37±0.5◦C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and the weight gain was measured. The water uptake (WU) or swelling index (S.I.) was determined from the following relation:

$$\text{Water Uptake (\%)} = \frac{Ws - Wi}{Wp}$$

Where, Ws is the weight of the swollen matrix at time t,
Wi is the initial weight of the matrix,
Wp is the weight of the polymer.

2.7. In Vitro Buoyancy Studies [13, 14]

The time taken for tablet to emerge on the surface of medium is called as the floating lag time (FLT) or buoyancy lag time and the duration of time the dosage form constantly remained on surface of medium is called the total floating time (TFT). The in-vitro buoyancy was determined by floating lag time, per the method determined by Rosa et al. The tablets were placed in a 100-mL beaker containing 0.1N HCl (pH1.2) and the time required for tablet to emerge on the surface of medium was determined.

2.8. In-vitro Dissolution Studies [13, 14]

The release rate of drug from floating tablet was determined using USP dissolution testing apparatus II (Basket type).The dissolution test was performed using 900ml 0.1N HCl (pH1.2). The basket rotation speed was kept at 100 rpm and temp of 37± 0.5 °C was maintained. At predetermined time interval of 1, 2, 3…12 hours, samples were withdrawn from the dissolution apparatus and the volume of dissolution medium was adjusted with the fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 262nm. The cumulative percentage release was calculated using 'PCP Disso v3' software (Poona College of Pharmacy, Pune, India).Dissolution profile of all the batches was fitted to zero order, first order, Matrix, Peppas and Hixon Crowell models to ascertain the kinetic modeling of drug release by using a 'PCP Disso v3' software, and the model with the highest correlation coefficient was considered to be the best model.

2.9. Accelerated stability studies [15]

In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. The stability studies were carried out according to the ICH and WHO guidelines to assess the drug and formulation stability. The optimized formulations were sealed in aluminum packaging material. Samples were kept in a stability chamber (Thermolab) maintained at 45 ºC and 75 % RH for 3 months. The samples were withdrawn at 0, 7, 15 days, 1, 2 and 3 months. The samples were observed periodically for any change in the following physico-chemical parameters;

1. Appearance
2. Hardness
3. Drug Content
4. Buoyancy Lag Time
5. In-vitro dissolution studies

3. RESULTS AND DISCUSSION

Prior to the development of dosage form, preformulation studies were carried out in order to determine certain fundamental properties of the drug molecule and polymers. The micromeritic properties Bulk density, Tap density, Compressibility Index, Angle of repose and Hausner ratio of the drug and polymer showed that the drug have % Compressibility within the prescribed limits and can be used for direct compression. The results of solubility profile confirmed that the drug had considerable solubility in acidic condition, the condition for which the drug formulation was being developed. The calibration curve at 262 nm followed Beer-Lambert's law in the concentration ranging from 2-20 □ g/ml. The slope and R value of the curve were found to be 21.8487 and 0.9990 respectively. The slope, constant and R value obtained from the calibration curve were further used to calculate the release of drug from the formulations. Preliminary formulations with varying quantity of polymer yielded a wide variety of release profiles. The Floating properties data and % drug release values after12 hours are given in table No.5.The drug release profile of the preliminary formulations is depicted in the figure No.1.The study showed that minimum amount of polymer required to form a proper matrix was 60 mg for both hydroxypropyl methyl cellulose (HPMC) and xanthan gum. The minimum amount of sodium bicarbonate required to make a tablet float for more than 10 hours was found to be 30 mg.

As the amount of HPMC K4 M was increased from 20% to 45%, the floating lag time increased, indicating that a high amount of HPMC-K4-M is undesirable to achieve low floating lag time (less than 3 min). For concentration below 25% of HPMC-K4-M, the tablet lost integrity and busted, as this quantity of polymer might not have sufficient strength to the matrix to prolong drug release upto 12 hours. Hence, it was decided to optimize HPMC-K4-M between 25% and 35%.

Floating lag time values were found to be significantly controlled by citric acid and sodium bicarbonate content. It was reduced due to increased amount of floating agent which caused rapid formation and entrapment of carbon dioxide gas into the hydrophilic polymeric mass. So it was decided to optimize sodium bicarbonate concentration between 10% to 20%.The swelling index values of tablet formulations are shown in table No.6.It was observed that as the amount of polymer in the formulation increased swelling increased too. Floating lag time was found to be less than 55 seconds and total floating time was more than 12 hours. Floating lag time of formulations is depicted in table No.7. Floating lag times were found to be significantly controlled by sodium bicarbonate and citric acid content. It was reduced due to increase of quantity of floating agent which caused rapid formation and entrapment of carbon dioxide gas into the hydrophilic polymeric mass.

3.1. In vitro dissolution studies

The release data were evaluated by model-dependent method using “PCP Disso v3” software. The release rate kinetic for all the formulations with varying quantity of polymer are shown in Table No.8. It was observed that the increase of floating agent concentration displayed a common phenomenon that the drug release rate and extent were increased in all cases. As the concentration of HPMC and Xanthan gum increases in the formulation the release rate was found to be decreased. The Formulations FH3 and FX3 exhibited optimum dissolution profile with

drug release of 95.02 and 87.85 % respectively after 12 hours, hence selected as optimized formulations. The drug release profile of formulations was shown in Figure No.2, 3.4.

3.2. Accelerated Stability studies

The stability studies were carried out on the optimized formulations as per ICH guidelines. The accelerated stability studies were performed on Optimized formulations i.e. FX3. The results indicated that these formulations remained stable for a period of 3 months. The tablets were evaluated for appearance and no significance changes were observed during the entire stability testing period. The results for hardness, drug content, buoyancy lag time and in-vitro dissolution studies are depicted in the table No.9.

4. CONCLUSION

In the present study an attempt was made to develop a gastroretentive drug delivery system using Xanthan gum as matrix forming agent and sodium bicarbonate as gas generating agent. According to B.C.S classification, the drug belongs to Class IV having poor solubility and poor absorbability. It is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability. Further, its solubility is reported to be highly pH dependent, with favored solubility in acidic media. And metabolism is arrested in acidic pH of stomach. The short biological half life of drug (2.5 to 3 hrs) also suggested the requirement for the development of a gastroretentive formulation. Hence, floating tablets were formulated as an approach to increase gastric residence time and thereby improve its bioavailability. Among the polymers used to improve the gastric residence time, Xanthan gum showed better control over drug release. It was also observed that as the concentration of Xanthan gum increases in the formulation the release rates were found to be decreased. The increase of floating agent concentration displayed a common phenomenon that the drug release rate and extent were increased in all cases. The physicochemical evaluation for tablets gave satisfactory results for hardness, tablet density, floating lag time, content uniformity, and in vitro drug release. Thus the objective of formulating a gastroretentive drug delivery system using natural polymer has been achieved successfully.

5. CONFLICT OF INTEREST

None declared.

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Table 1. Composition of Preliminary formulations.

Ingredient	P1	P2	P3	P4	P5	P6	P7	P8
Drug	145	145	145	145	145	145	145	145
Xanthan gum	50	50	80	80	130	130	155	155
Sodium Bicarbonate	30	50	30	50	30	50	30	50
Citric acid	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4
Aerosil	1	1	1	1	1	1	1	
Total weight	240	260	270	290	320	340	345	365

(Note: All Ingredients are in mg.)

Table 2. Variable levels used in factorial design.

Batch Code	X_1	X_2
F1	-1	**-1**
F2	-1	**0**
F3	-1	**1**
F4	0	**-1**
F5	0	**0**
F6	0	**1**
F7	1	**-1**
F8	1	**0**
F9	**1**	**1**

(Where; X_1 = Xanthan gum X_2 = $NaHCO_3$)

Table 3. Coded values and actual values used in factorial design.

Coded Values	Actual values X_1	Actual values X_2
-1	60	**30**
0	80	**40**
1	**100**	**50**

Table 4. Composition of formulation with Xanthan gum.

Ingredients	FX1	FX2	FX3	FX4	FX5	FX6	FX7	FX8	FX9
Drug	145	145	145	145	145	145	145	145	145
Xanthan gum	60	60	60	80	80	80	100	100	100
NaHCO3	30	40	50	30	40	50	30	40	50
Citric acid	10	10	10	10	10	10	10	10	10
Mag.stearate	4	4	4	4	4	4	4	4	4
Aerosil	1	1	1	1	1	1	1	1	1
Total weight	250	260	270	270	280	290	290	300	310

(Note: All Ingredients are in mg.)

Table 5. Floating properties and % drug release of preliminary formulations.

Formulation	Floating Lag Time (sec.)	Total Floating Time (hrs.)	% Drug Release (After 12 hrs.)
P1	38	7	Bursting
P2	36	8.5	Bursting

P3	45	10.5	85.76
P4	43	12	88.99
P5	40	11.8	76.60
P6	42	12	80.03
P7	50	12	67.97
P8	48	12	72.53

Table 6. Swelling index of formulation.

Formulation Code	**Swelling Index (%)**			
	2hrs.	4 hrs	6 hrs	8 hrs
FX1	73.45	117.82	139.14	159.34
FX4	87.85	157.53	203.55	235.75
FX7	121.76	185.25	244.38	256.26

Table 7. Floating lag time of Formulations.

Formulation	**Floating lag time (sec)**	**Formulation**	**Floating lag time (sec)**
FX1	49	FX6	48
FX2	47	FX7	55
FX3	45	FX8	51
FX4	53	FX9	49
FX5	50		

Table 8. Drug Release profile of formulation FX1 – FX9.

Formulation	**Drug Release (%)**		
Code	1hr	6hrs.	12hrs.
FX1	29.07	58.59	84.27
FX2	29.76	59.06	85.64
FX3	30.31	60.36	87.85
FX4	29.01	52.16	79.91
FX5	28.34	55.24	81.94
FX6	30.09	57.15	83.79
FX7	28.93	50.23	75.85
FX8	23.39	51.32	76.94
FX9	27.70	52.41	78.29

Table 9. Accelerated Stability studies.

Tests	Accelerated Stability studies					
	0 Day	7 Days	15 Days	1 Month	2 Months	3Months
Hardness	5.8	5.8	5.8	5.6	5.4	5.1
Drug Content	99.41	99.45	99.23	99.05	98.67	98.43
Buoyancy Lag Time (sec)	45	44	49	48	48	53
Drug release profile	87.85	87.73	87.77	87.47	87.43	87.38

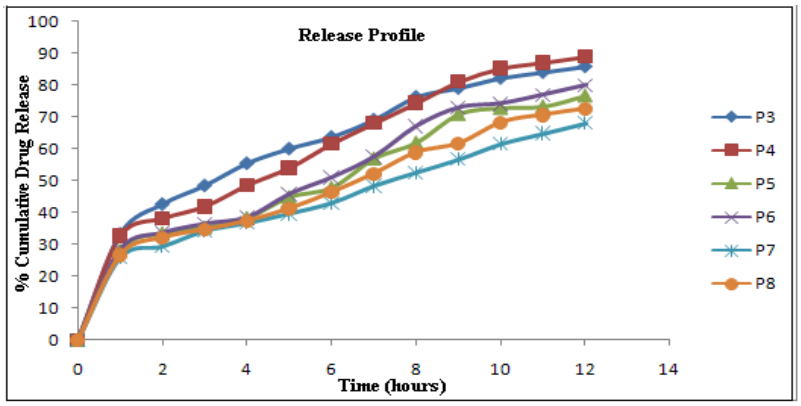

Figure 1. Drug release profiles of preliminary formulations.

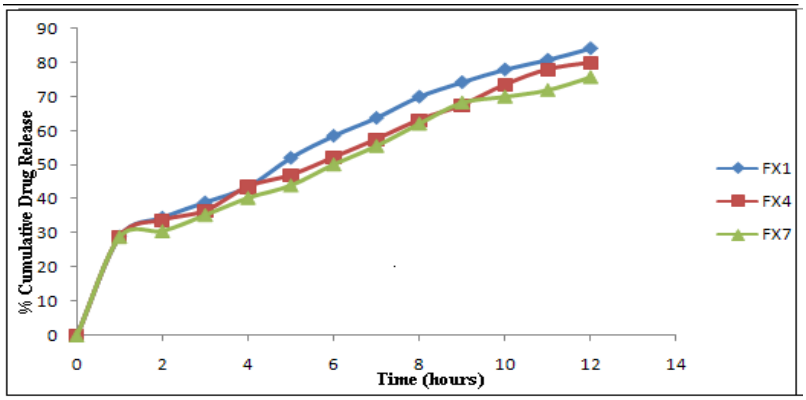

Figure 2. Release profile of formulations FX1, FX4, FX7.

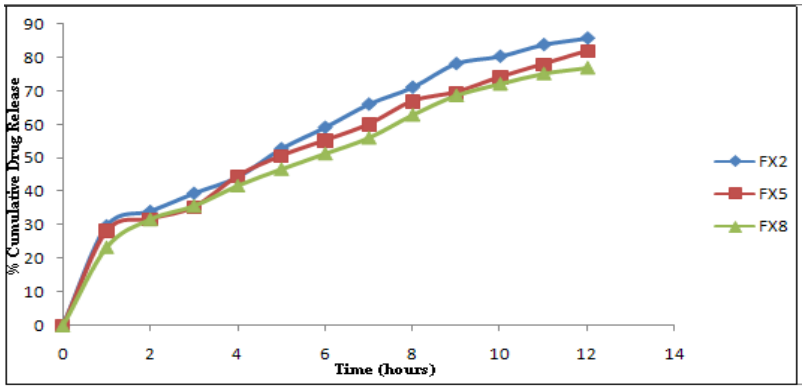

Figure 3. Release profile of formulations FX2, FX5, FX8.

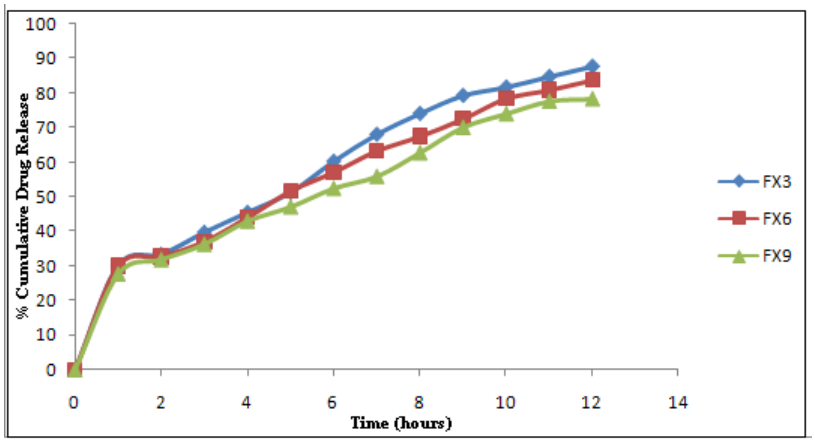

Figure 4. Release profile of formulations FX3, FX6, FX9.