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Formulation, Characterization and Evaluation of Gastro-Retentive Floating Tablets of Norfloxacin

Richa Srivastava, Devdutt Chaturvedi*
Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University, Uttar Pradesh, Lucknow Campus, Lucknow-226028, India

Research Article

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*For Correspondence

Devdutt Chaturvedi, Richa Srivastava, Assistant Professor, Department of Applied Chemistry, Amity School of Applied Sciences, Amity University, Uttar Pradesh, Lucknow Campus, Lucknow-226028, India.

E-mail: mdevduttchaturvedi@gmail.com; richasri12@gmail.com

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ABSTRACT

The purpose of the research work was to develop gastro-retentive drug delivery system of Norfloxacin. Floating tablets were prepared by wet granulation method using sodium bicarbonate and citric acid anhydrous, like Hydroxypropyl Methylcellulose (HPMC K100M), Xanthum gum, and Microcrystalline Cellulose (MCC). Norfloxacin floating tablets prepared were found to be good without chipping, capping and sticking. The drug content was found to be uniform in all the tablet formulations. Formulation F3 and F5 showed desired drug release and thus selected as the best formulation. Finally optimized formulation F3 and F5 complying with all properties of floating tablets were found to be satisfactory in all aspects.

INTRODUCTION

The most promising and safest route of drug delivery is the oral route and is considered as the most promising route of drug delivery. Effective oral drug delivery depends upon the factors such as bowel emptying, transit time of dosage form through the Digestive tract, therapeutic delivery from the dosage form etc. These factors affect the humans in variable ways. The factors such as neutralization by acid or delayed absorption may also lead to precipitate formation of may cause neutralization of drug leading to non-uniform absorption and makes the bioavailability unpredictable. Controlled- release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and monitored rate. Hence a beneficial delivery system should possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. Upper part of the small intestine) [1-5].

Such gastro retentive systems remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs [6,7]. Thus the prolonged retention enhances bioavailability, reducing the wastage of drug improving solubility for drug. All the above requirements are met by the floating drug delivery systems and hence effective delivery of drugs occurs to the absorption window for the treatment of gastric disorders such as gastro-esophageal reflux etc [8-12].

Norfloxacin is a fluoroquinolones, broad spectrum antibiotic, and is used in the treatment of urinary tract infections, prostatitis and gonorrhea. Norfloxacin is least absorbed from the lower part of the gastrointestinal tract and is better absorbed from the stomach. This drug has a repetitive dose schedule (400 mg twice daily), short biological half-life (3–4 h) and reduced bioavailability (30–40%). Thus, Norfloxacin is a candidate for the development of a gastro-retentive drug delivery system. In this work, the details of formulation development and evaluation of floating tablets of Norfloxacin is described.

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MATERIALS AND METHODS

Materials Used

Norfloxacin was received as generous gift sample from Solisto Pharmaceuticals Pvt Ltd, India. Hydroxypropyl methylcellulose (HPMC), micro crystalline cellulose (MCC), polyvinylpyrollidine (PVP), magnesium stearate was taken from Pharmaceutics Laboratory, Amity University, Lucknow. All chemicals used were of analytical grade.

Methods

Preformulation Studies

The Preformulation for the drug was performed which included Appearance testing, Solubility and melting point analysis of the drug.

Development of Tablets

Accurately weighed quantities of Norfloxacin, HPMC and MCC were passed through a 0.425 mm sieve to get uniform size particles, then they were mixed geometrically for 5 to 10 minutes and the mixture was placed in a polyethylene bag and further mixed for 5 minutes to ensure a homogeneous mass. Accurately weighed quantity of PVP was added. The powder mixture was compressed into tablets using a 16-station punching machine (Rimek, India) **(Table 1).**

Table 1. Ingredients for the Norfloxacin formulation.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug (Norfloxacin)	100	100	100	100	100	100	100	100
HPMC	100	80	100	100	100	100	100	100
Sodium Bicarbonate	100	50	25	-	50	-	-	-
Citric acid	100	50	25	-	25	-	-	-
Magnesium stearate	6	6	6	3	3	3	3	-
MCC	94	94	94	47	47	47	47	47
Xanthum gum	-	-	200	1000	250	120	-	-
Gum karaya	-	20	-	-	-	-	-	-
PVP	-	-	-	-	-	-	30	50
Isopropyl Alcohol (ml)	-	-	-	-	-	-	10	-

Evaluations

Pre-Compression Parameters

Angle of Repose

The angle of repose of powder blend was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using following formula:

Tan è = h/r, Where, è: angle of repose, h: height, r: radius.

Bulk Density

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and therefore more resistant to powder flow. The ease with which a powder consolidates can be used as an indirect method of quantifying powder. Apparent bulk density (g/ml) was determined by pouring preserved bulk powder into a graduated cylinder via a large funnel and measuring the volume and weight. Bulk density can then be calculated by the following formula:

Bulk density = W/Vo

Where, W = wt. of powder, V = initial volume.

Tapped Density

A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. Tapered density was calculated using the following equations:

Tapped density = W/Vf, Where, W = wt. of powder, V = final volume.

Compressibility Index (Carr's Consolidation Index)

The Compressibility index is measure of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index. The compressibility index is calculated using measured values for bulk density (D) and tapped density (D) as follows:

Compressibility index = Dt-D /D X 100

Where D = Bulk density, D = Tapped density

Post-compressional Parameters

Thickness and Diameter

Thickness and diameter were tested in 5 different randomly selected individual tablets from each batch. The thickness and diameter of tablets were measured by vernier calipers.

Hardness

The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. Hardness (crushing strength) is a force required to break a tablet cross the diameter. The hardness was tested by using Monsanto hardness tester. The averages of five determinations were taken.

Friability

Previously weighed 5 tablets were taken in a Roche's friabilator and the friability was checked at 25 rpm for 4 minutes. Then the tablets were dusted and reweighed and the percentage of powder eroded during 4 minutes was recorded.

Uniformity of Weight

Average weight of the tablet was calculated by weighing 10 tablets individually and all together. The percent weight deviation of each tablet was computed as per official method **(Table 2).**

Table 2. IP standards of percentage of weight variation.

Percentage variation allowed under weight variation	
Average weight of tablet	Percentage variation
100 mg or less	Nil
More than 60 mg but less than 250 mg	2
250 mg or more	3

Drug Content Uniformity of the Tablets

10 tablets were weighed and triturated. The tablet triturate equivalent to 100 mg of the drug was weighed accurately, dissolved in pH 1.2 buffers and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 mcg/ml with simulated gastric fluid pH 1.2. Absorbance was read at 278 nm against the reagent blank, and the concentrations of Norfloxacin in mcg / ml was determined.

Drug content in mg / tablet = conc. mcg / ml * dilution factor

In-Vitro Buoyancy Test

The *in-vitro* buoyancy was determined by the floating lag time. The tablets were placed in a 100-mL beaker containing 0.1 mol L−1 HCl. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observation

In-Vitro Drug Release Studies

The *in-vitro* drug release studies were conducted using the USP 28 type II(paddle) Dissolution apparatus (TDT-06T, Electro lab, India). Hydrochloric acid (pH 1.2), 900 ml, was used as medium. The study was conducted at 37 ± 0.5°C and at paddle rotation of 50 rpm. Samples of 1 ml were collected at predetermined time intervals and replaced with fresh hydrochloric acid. The samples were filtered and diluted and the drug content in the samples was estimated at 278 nm by using a UV-visible spectrophotometer (ELCO U.V., India).

Floating Lag Time

A tablet was placed in a dissolution flask with 100 ml of simulated gastric fluid maintained at 37 ± 1°C. Then the time in minutes taken by tablet to move from bottom to top of the flask was measured.

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Accelerated Stability Studies

The accelerated stability studies were performed as per the ICH guidelines. Selected formulations of Norfloxacin were packed in aluminum pouch and subjected to short term stability at 25°C/60% RH and accelerated stability at 40°C/75% RH for a period of 3 months. Samples from each formulation which are kept for examination were withdrawn at definite time intervals. The withdrawn samples were tested for hardness, in vitro buoyancy and assayed for drug content and in vitro drug release.

RESULT AND DISCUSSION

The development of floating tablets of Norfloxacin was intended through this work and the main aim was to enhance the retention time of the drugs by increasing the buoyancy time of the delivery system. The results have shown that tablets were found to have good properties as well as enhanced buoyancy time which provided good retention time to the drug in the body. In the present study, a total of 8 formulations of gastro retentive floating tablets of Norfloxacin were prepared by wet granulation technique using different polymers like HPMC K100M, Xanthan gum and MCC as semi synthetic and natural polymers, using sodium bicarbonate and citric acid as gas generating agents, magnesium stearate and talc as lubricants. Formulations were optimized by different ratios of polymers. The appearance of the drug was found to be whitish in colour, odour was found to be odorless and the taste was found to be tasteless.

The melting point test of drug was performed using melting point apparatus and was found to be at 220°C. The other parameters were found to be as discussed in the above section.

Pre-compression Evaluations

Bulk Density, Tapped Density, Carr's Index and Angle of Repose

The drug and ingredients were evaluated for the above said parameters and it was found that all the observations were within the prescribed limits of IP. All the formulations were fallen in good flow character based on angle of repose, and compressibility index **(Table 3).**

Table 3. Precompression factors for Norfloxacin floating tablets.

Precompression parameters	A	B
Bulk Density	0.458	0.469
Tapped density	0.589	0.654
Carr's index	0.777	0.717
Angle of repose	26.8	29.78

Post Compression Evaluations

Weight Variation, Thickness and Diameter, Hardness, Friability and Drug Content

Weight variation of floating tablets ranged from 648.45 to 653.5.Thickness ranged between 5.5 to 6.3. The hardness lies between 3.0 to 4.5. The friability of all gastro retentive floating tablets of Norfloxacin was found between 0.1 to 0.9. Drug content ranged between 96.9 to 98.7.The average weights were found to be within (± 7.5) the prescribed official limits. The thickness of the floating tablet indicated that die fill was uniform. The thickness depends upon the size of the punch (12 mm) and the weight of the tablet (650 mg).Formulations showed favorable drug content which were within the limits of specifications **(Table 4).**

Table 4. Post Compression Parameters of Norfloxacin Tablets.

Tablet(F3)	Weight Variation	Friability	Hardness	Thickness	Drug content Uniformity
1	650.34	0.934	3.0	6.002	243.56
2	648.45	0.101	3.5	5.550	234.56
3	649.78	0.506	4.5	6.390	245.78
4	650.23	0.432	3.4	6.103	245.67
5	653.56	0.654	4.0	6.102	248.78
Tablet (F5)	**Weight Variation**	**Friability**	**Hardness**	**Thickness**	**Drug content Uniformity**
1	647.34	0.897	3.5	5.998	267.78
2	648.75	0.201	4.0	6.109	248.98
3	650.78	0.405	4.0	6.098	245.67
4	649.31	0.678	3.5	6.276	248.98
5	652.56	0.879	4.0	5.997	245.67

In-vitro Buoyancy Test

Floating lag time and total floating time of prepared gastro retentive floating tablets of Norfloxacin was found to be as shown in the table. Floating lag time varied by different polymers and polymer ratios. This showed that as the polymer concentration increased floating lag time decreased and total floating time increased **(Table 5).**

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Table 5. In-vitro Buoyancy studies.

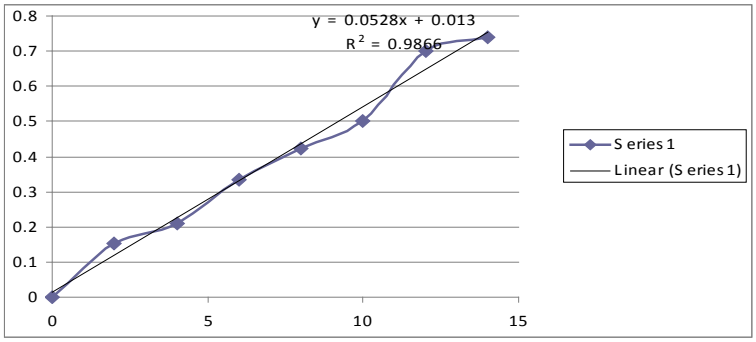
Formulation code (F3)	Buoyancy lag time	Total floating time
1.	15 mins	3 hrs
2.	20 mins	4hrs 24 mins
3.	15 mins	3hrs 40 mins
Formulation code (F5)	**Buoyancy lag time**	**Total floating time**
1.	10mins	2 hrs 40 mins
2.	15 mins	3hrs 15 mins
3.	20 mins	4 hrs 23 mins

Accelerated Stability Studies Test

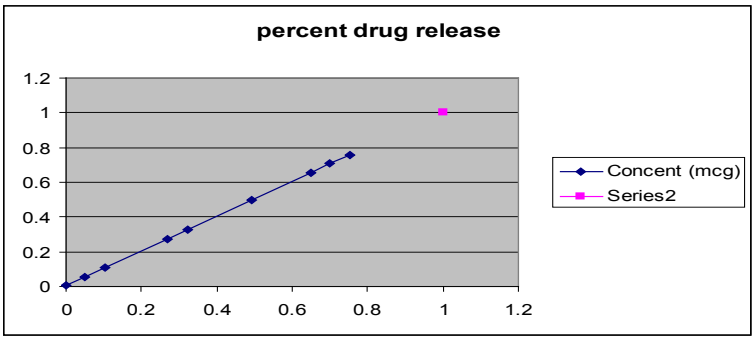
The formulations F3 and F5 were found to be stable at the given set of conditions.

GRAPHS

Standard curve for Norfloxacin and Percentage Drug Release from Tablets are shown in **Graphs 1 and 2.**



Graph 1. Standard curve for Norfloxacin.



Graph 2. Percentage Drug Release from Tablets.

CONCLUSION

Controlled release gastro-retentive dosage forms (CR-GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. CR-GRDF provides a means to utilize all the pharmacokinetic (PK) and pharmacodynamics (PD) advantages of controlled release dosage forms for such drugs. Among all the eight tablet formulations, F3 and F5 were found to be having the most appropriate parameters. Thus the study shows that the tablets having proper amount of Xanthum gum had proper binding properties and was found to be have good buoyancy time due to citric acid. The tablet F3 was found to show delayed release with time which shows that it provides more retention as compared to F1 and F2. Thus the formulation F3 and F5 will provide best retention time of Norfloxacin among all the eight formulations.

Based on the literature surveyed, it may be concluded that drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. Thus gastro retentive dosage forms provide an additional advantage for drugs that are absorbed primarily in the upper segments of gastrointestinal tract, i.e. stomach, duodenum and jejunum. Due to the complexity of pharmacokinetic and pharmacodynamics parameters, *in vivo* studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its pharmacokinetic and pharmacodynamics parameters will determine the effectiveness and benefits of the controlled release gastro retentive forms as compared to other dosage forms.

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