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Formulation and Evaluation of Floating Beads of Norfloxacin

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Abstract:- The purpose of this research was to prepare and evaluate floating gastroretentive beads of Norfloxacin an antibiotic drug for prolonged gastric residence time and increased drug bioavailability. Floating beads were prepared by iontotropic gelation method using different polymers in varying ratios. The formulations were optimized on the basis of floating ability and in-vitro drug release. The floating beads were evaluated for micromeritic properties, entrapment efficiency, as well as in-vitro buoyancy study and drug release. The shape and surface morphology of the beads were characterized by scanning electron microscopy. The floating microspheres showed particle size, drug entrapment efficiency, buoyancy and yield in the ranges of 285.78 – 432.20 µm, 65.25 – 88.36 %, 79.25 – 91.36 %, and 89.85 – 96.85 % respectively. In vitro drug release study confirms formulation F8 was the best formulation as it releases 97.96 % of Norfloxacin at the end of 12 hrs in controlled manner. This confirms the developed Norfloxacin floating gastroretentive system is a promising floating drug delivery system for oral sustained administration of Norfloxacin.

Keywords*:* *Norfloxacin, Buoyancy time, Floating beads, Gastroretentive*.

I. INTRODUCTION

Oral administration is the most convenient and commonly employed route of drug delivery for the drug candidates who show absorption window in the GIT and proximal gut. [1] But it has limitation of less absorption, poor residence time and subsequently poor bioavailability which is the major obstacle to the development of oral delivery of such agents. Due to this considerable attention has been focused on the development of Novel Drug Delivery Systems (NDDS) like microspheres, nanoparticles, liposomes, etc. The gastroretentive drug delivery systems (GTDDS) can assist in improving the oral bioavailability of various pharmaceutical drugs that have an absorption window in a particular region of gastrointestinal (GI) tract. Gastroretentive dosage forms have the potential to improve local therapy with an increase of short gastric residence time and unpredictable gastric emptying time and decrease the variation in bioavailability which is unobserved, in other commercially available preparations. The objective of present work was to develop gastroretentive formulation, which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. Example of drug whose bioavailability is strongly dependent on the physiology in the GI tract and which preferably is absorbed in the higher sections of the intestine is Norfloxacin. Norfloxacin is a broad-spectrum antibiotic used to treat infections of Gram-positive and Gram-negative bacteria and is readily soluble in the acidic environment of the stomach. However, precipitation of the active compound occurs in the lower sections of the intestine which adversely affects absorption and subsequently bioavailability. There is a need for systems that reside in the stomach over a relatively long time and release the active compound there in a sustained manner. This necessitated the development of floating gastroretentive drug delivery system for Norfloxacin. Floating gastroretentive beads of Norfloxacin were prepared with an objective to increases the bioavailability and site specific and local therapy. [1, 4]

II. MATERIALS AND METHODS

2.1. Materials:

Norfloxacin was received as a kind gift from Neon Pharmaceuticals, Mumbai. Sodium Alginate, Sodium bicarbonate and Ethyl Cellulose were procured from Loba Chemie, Mumbai. Fenugreek Powder procured from Arkashala, Satara. Tamarind Gum procured from V P Enterprises, Pune.

2.2. Method of preparation of floating beads:

Ionotropic gelation method:

Floating alginate beads of Norfloxacin were prepared by ionotropic gelation technique using different proportion of polymers as shown in Table No.1. A 4% w/v solution of sodium alginate solution was added to weighed amount of ethyl cellulose dissolved in required quantity of distilled water. Weighed quantity of drug and polymers was triturated to form fine powder then added to above solution. Sodium bicarbonate, a gas forming agent was added to this mixture and the resulting solution was stirred uniformly. Using a 26 G syringe needle the above solution was dropped into 100 ml of gently agitated calcium chloride (5% w/v) solution to

obtain beads. The solution containing beads was stirred slowly using magnetic bead for about 10 min. The beads were further allowed to remain in the same solution for 20 min to improve mechanical strength. The formed beads were filtered, washed with distilled water, air-dried at room temperature and stored in desiccators. [5]

Table 1: Composition of Floating beads of Norfloxacin

Ingredients (mg, %)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Norfloxacin	100	100	100	100	100	100	100	100	100
Sodium Alginate	4%	4%	4%	4%	4%	4%	4%	4%	4%
Tamarind Gum	50	100	150	-	-	-	50	100	150
Fenugreek Powder	-	-	-	50	100	150	50	100	150
Sodium Bicarbonate	100	100	100	100	100	100	100	100	100
Ethyl Cellulose	100	100	100	100	100	100	100	100	100

III. EVALUATION OF BEADS

3.1. Micromeritic Properties:

3.1.1. Angle of Repose:

Angle of repose helps to evaluate powder flowability by assessing interparticulate friction. In general, the higher is the angle of repose poor is the flowability of powder. The angle of repose of each powder blend was determined by glass funnel method, using following equation, [6, 7]

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

$$\theta = \tan^{-1}(h/r)$$

Where, θ = Angle of repose,
h = Height of the pile,
r = Radius of the cone made by powder blend.

3.1.2. Bulk Density:

It is ratio of mass to bulk volume. Bulk density may influence dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. Bulk density of formulated beads was determined by taking a known mass of beads in a 5 ml graduated measuring cylinder. The cylinder was dropped three times from a height of one inch at an interval of two seconds. The bulk density was calculated by following equation, [6, 7]

$$\rho_b = M / V_b$$

Where, ρ_b = Bulk density,
M = Weight of the powder,
V_b = Bulk volume.

3.1.3. Tapped density:

Tapped density helps to determine packing geometry and flowability. Tapped density is the volume of powder determined by tapping using measuring cylinder containing weighed amount of sample. Tapped density of beads was calculated by following equation, [6, 7]

$$\rho_t = M / V_t$$

Where, ρ_t = Tapped density,
M = Weight of the powder,
V_t = Tapped volume.

3.1.4. Carr's compressibility index:

This is an important property in maintaining uniform weight. It is calculated using following Equation, [6, 7]

$$\text{Carr's Index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100 \ldots\ldots\ldots \text{"equation 1"}$$

3.1.5. Hausner's ratio:

Hausner's ratio less than 1.25 indicates good flow and greater than 1.5 indicates poor flow whereas between 1.25 and 1.5 indicates glidant normally improves flow. Hausner's ratio can be calculated by formula, [6, 7]

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \ldots\ldots\ldots \text{"equation 2"}$$

3.2. Morphology study:

Scanning Electron Microscopy (SEM) was performed to characterize the surface of formed beads. Beads were mounted directly onto the sample stub and coated with gold ion and analyze for surface morphology. (JEOL -JSM T330A). [8]

3.3. Particle size analysis:

The particle size of drug loaded formulations were measured by an optical microscope fitted with calibrated ocular and stage micrometer and particle size distribution was calculated. 50 particles in five different fields were examined. [9]

3.4. Determination of Percentage yield:

The prepared beads were collected and weighed. The measured weight was divided by the total amount of all non-volatile components, which were used for the preparation of the beads. [10]

$$\text{Percentage Yield} = \frac{\text{Actual weight of products}}{\text{Weight of drug and excipients}} \times 100 \ldots\ldots\ldots \text{"equation 3"}$$

3.5. Drug Entrapment Efficiency:

Beads equivalent to 100 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the beads and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured at 279 nm against appropriate blank. The amount of drug entrapped in the beads was calculated by the following formula, [11]

$$\text{Drug Entrapment Efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug loaded expected}} \times 100 \ldots\ldots\ldots \text{"equation 4"}$$

3.6. In vitro buoyancy study:

Beads (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N HCl containing 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hr. The floating and the settled portions of beads were recovered separately. The beads were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the beads that remained floating and the total mass of the beads. (Dynamica HaLoDB-20). [12]

$$\% \text{ Buoyancy} = \frac{Qf}{(Qf + Qs)} \times 100 \ldots\ldots\ldots \text{"equation 5"}$$

Where,

Qf = Weight of the floating Beads

Qs = Weight of settled Beads

3.7. In-vitro drug release study:

The drug release study from microsphere was performed using USP dissolution apparatus Type I in 900 ml of 0.1 N HCl dissolution media (pH- 1.2) at 100 rpm and 37°C. 2 ml sample was withdrawn at 1 hr. time interval for 12 hr. and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at 279 nm. The drug release was analyzed by UV spectrophotometer. (Dynamica HaLoDB-20). [13]

IV. RESULTS AND DISCUSSION

4.1. Micromeritic properties:

Micromeritic properties for batch F1 to F9 are shown in Table 2. The results showed Bulk Carr's index in the range 5 % to 15%, Hausner's ratio less than 1.25 which confirms good flow properties.

Table 2: Micromeritic properties

Batch	Angle of repose (□)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	20.15±0.9	0.421±0.02	0.406±0.018	5.23±0.12	1.02±0.005
F2	21.59±1.2	0.523±0.01	0.494±0.029	6.85±0.21	1.09±0.003
F3	19.25±1.6	0.358±0.01	0.521±0.030	7.25±0.23	1.08±0.004
F4	23.15±1.4	0.401±0.03	0.602±0.04	5.89±0.19	1.05±0.005
F5	22.78±1.8	0.509±0.02	0.609±0.041	6.99±0.21	1.10±0.004
F6	19.96±1.5	0.428±0.02	0.548±0.032	7.89±0.15	1.07±0.006
F7	21.78±1.1	0.399±0.03	0.487±.027	8.54±0.26	1.01±0.005
F8	22.12±0.8	0.487±0.01	0.421±0.019	8.21±0.18	1.11±0.004
F9	23.02±1.3	0.525±0.02	0.518±0.029	6.55±0.20	1.03±0.005

Mean S.D. n=3

4.1.1. Angle of repose:

The values were found to be in the range of 19.25±1.6 to 23.15±1.4. Beads showed the angle of repose less than 25º which reveals excellent flow property. The observed results suggest excellent flowability of the beads.

4.1.2. Bulk Density:

Bulk density may influence buoyancy of floating beads. The bulk density of formulations F1 to F9 formulation was found to be between 0.399±0.03 to 0.525±0.02 g/cm^3. This indicates good packing capacity of beads.

4.1.3. Tapped Density:

The tapped density was found to be in the rage of 0.406±0.018 to 0.609±0.041 g/cm^3 shows good packability of beads.

4.1.4. Carr's compressibility index:

Carr's index shows the effects of packing geometry of solids with bulk and tapped density. Carr's index was found in between 5.23±0.12 to 8.54±0.26 %. All batches indicate excellent compressibility.

4.1.5. Hausner's ratio:

Hausner's ratio is a simple method to estimate flow properties. It was ranging from 1.02±0.005 to 1.11±0.004 which indicates all the formulations show good flow properties.

4.2. Morphology study:

The morphology of the beads was examined by scanning electron microscopy (SEM). SEM image figure 1. showed that the beads were almost spherical in shape and were having rough surface.

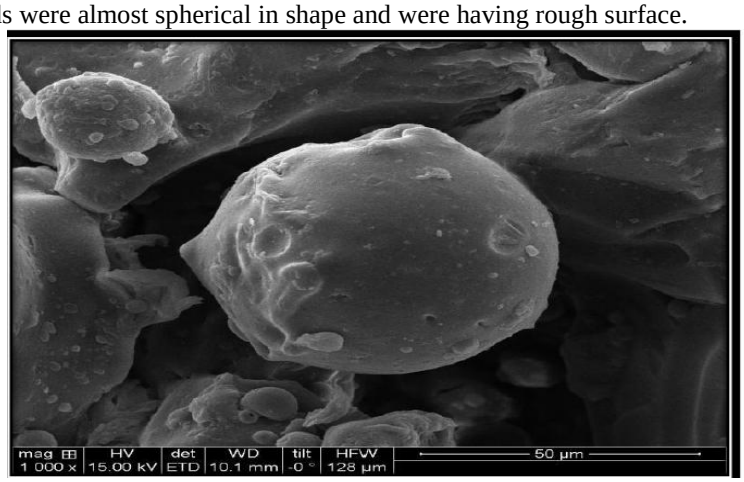

Fig.1: Scanning Electron Micrograph of F8 Formulation

4.3. Particle size analysis:

The particle size of the formulation F1 to F9 was displayed in Table 3. From the results it was observed that with an increase in the concentration of polymers, the particle size of beads was increased which might be attributed to an increase in the concentration of polymer. The viscosity of polymer solution increases due to the higher concentration of polymer, which resulted that formation of large droplets, thus increasing the size of Norfloxacin beads. The particle size of beads was found to be in the range of 285.78 µm to 432.20 µm. It was also observed that by decreasing the stirrer speed, size of beads increases.

Table 3: Particle Size of Floating Beads

Batch	Particle size (m)
F1	333.52
F2	385.42
F3	421.85
F4	348.20
F5	397.11
F6	432.20
F7	320.85
F8	285.78
F9	299.25

4.4. Determination of percentage yield:

It was found that the average percentage yield was greater than 80 % for all formulations. The drug loading was found to be in range of 89.85±0.4 to 96.85±0.5 %. Formulation F8 showed highest loading of 96.85±0.5% whereas formulation F1 showed lowest drug loading of 89.85±0.4%. Overall the drug loading was decreased with increase in the polymer concentration due to its higher viscosity which affects the diffusion coefficient of drug. The reduction in yield was attributed to loss of material during preparation of beads and due to process parameters as well as during filtration of beads.

Table 4: Percentage yield

Batch	Percentage yield
F1	89.85±0.4
F2	91.25±0.6
F3	93.25±0.7
F4	90.25±0.3
F5	93.21±0.4
F6	94.85±0.5
F7	95.02±0.2
F8	96.85±0.5
F9	94.72±0.4

Mean ±S.D. n=3

4.5. Drug Entrapment Efficiency:

Ionic gelation technique is convenient method for the preparation of floating beads with good drug loading and encapsulation efficiency. In this method drug is dispersed equally in the polymer matrix so drug can be loaded easily in the polymer. The drug entrapment efficiency of the prepared beads was found to be increased progressively with an increase in concentration of polymers. This might be due to increased matrix density. The drug entrapment efficiency was found to be in range of 65.25 to 88.36%. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 5.

Table 5: % Entrapment Efficiency

Batch	Entrapment Efficiency (%)
F1	65.25
F2	69.21
F3	75.42
F4	70.54
F5	76.25
F6	81.87
F7	78.21
F8	88.36
F9	84.21

4.6. In vitro buoyancy study:

Formulation F8 containing Fenugreek and Tamarind combination gave best floating ability of 95.45 % in 0.1N hydrochloric acid for 12 hours. This may be due to its low bulk density. The formulations containing Sodium Alginate and Tamarind combination (F1 to F3) gave the floating ability in the range of 89.25 to 79.25 % and formulations containing Sodium Alginate and Fenugreek combination (F4 to F6) gave the floating ability in the range of 91.36 to 81.15% and formulations containing Sodium alginate, Tamarind and Fenugreek combination (F7 and F9) gave the floating ability 92.24.48 and 89.223 % as shown in Table 6. In this as polymer

concentration increased, increase in viscosity of the polymer solution occurred and porosity decreased which will increase the floating ability.

Table 6: In-Vitro buoyancy study

Batch	In Vitro buoyancy (%)
F1	89.25
F2	85.36
F3	79.25
F4	91.36
F5	88.25
F6	81.15
F7	92.24
F8	95.45
F9	89.23

4.7. In vitro drug release study:

It was observed that the beads ascended to the upper part of the dissolution vessels and remained floated until the completion of release studies. The drug release study was carried for 12 hrs. This showed as the concentration of polymers increases the drug release increases which were attributed to increased density of the polymer matrix at higher concentration causing decreased diffusional path length and increases the drug release from the polymer matrix. Moreover dissolution study data revealed that release from the beads is largely dependent on the polymer swelling, drug diffusion. The percentage drug release for batches F1 to F9 vary from to 82.25 to 97.96%. The in-vitro drug release of the formulation F1 to F9 displayed in Table 7 and 8 and comparative release was shown in figure 2.

Table 7: Drug dissolution study of F1-F9 formulations

Time (mins)	% Cumulative drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
60	2.376	3.89	4.14	1.36	1.87	2.12	4.902	5.66	5.15
120	6.422	8.19	9.20	5.66	6.42	6.92	11.47	12.23	11.48
180	11.48	14.27	15.03	11.73	13.25	14.26	15.79	16.55	14.28
240	12.77	26.17	26.03	14.28	18.33	19.85	28.46	29.72	30.98
300	26.18	36.83	37.35	25.17	28.47	29.49	36.85	37.62	37.87
360	33.57	43.73	44.50	32.81	36.87	37.89	43.75	45.28	44.77
420	37.68	54.94	55.20	37.93	39.98	42.27	51.17	52.95	52.95
480	47.36	60.12	60.88	46.60	48.91	52.46	61.89	63.17	62.41
540	59.08	68.08	69.35	57.82	62.40	63.44	69.61	79.42	70.88
600	68.30	80.60	82.89	68.04	70.37	72.16	80.11	85.70	83.66
660	77.29	88.36	88.88	75.77	77.85	80.66	88.88	92.45	88.90
720	83.53	90.32	94.13	82.25	84.08	88.16	94.12	97.96	94.65

V. CONCLUSION

In the present study, a satisfactory attempt has been made to formulate gastroretentive floating beads of Norfloxacin. From the experimental study result, it was concluded that optimized batch F8 showed good micromeritic properties, entrapment efficiency and releases drug slowly and completely for 12 hours as beads remain in floating condition throughout dissolution study that assures prepared formulation remain floated in stomach without its early passing to lower GIT side. This will help to increase the residence time of Norfloxacin in stomach i.e. in absorption window and achieve sustained release thereby increase the bioavailability of it. Finally the prepared Floating beads of Norfloxacin may prove to be potential gastroretentive delivery system for safe and effective controlled release for an extended period of time.

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