Nizatidine Based Floating Microspheres by Ionotropic Gelation Technique - Morphology and Release Characteristics

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ABSTRACT

Nizatidine is a histamine H2-receptor antagonist that inhibits stomach acid production and used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. The main aim of the present investigation was to develop gastro retentive floating microspheres for Nizatidine. These are prepared by ionotropic gelation method with an aim of increasing the gastric residence time and for controlled release. The polymeric mixture of Sodium alginate and HPMCK4, HPMC K15M and HPMC K 100M, was used as polymers. Calcium carbonate was used as the gas forming gent. Prepared Microspheres were characterized for the Micromeretic properties, incorporation efficiency, buoyancy test, SEM analysis, FTIR, and in vitro dissolution studies. The dissolution studies were carried out in 0.1N HCl and the results were applied to various kinetic models. Among the total 18 formulations F17 was optimized. The % yield of F17 formulation was found to be 95.47 ± 0.36%. Based on optical microscopy, the particle size was 50.67 ± 0.13µm. The % buoyancy, % entrapment efficiency and swelling index of F17 formulation was 94.23%, 93.62 ± 0.29% and 92.13 ± 0.17%, respectively. The Cumulative % drug release of F17 formulation was 98.23 ± 5.49% in 12 h when compared with marketed product 95.87 ± 0.31 in 12 h. SEM studies showed the particles were in spherical shape. Based on obtained results, Floating alginate Nizatidine microspheres were of good candidate for targeting to GIT.

Keywords: Nizatidine, Floating microspheres, Peptic ulcer, SEM, HPMC.
keeping in view its commercial success. Oral controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications. These microspheres are characteristically free flowing powders consisting of natural or synthetic polymers and ideally having a particle size less than 200μm. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug. Floating microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability and to target drug to specific sites. Floating microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency, and improving patient compliance.

Nizatidine is a histamine H2-receptor antagonist that inhibits stomach acid production and used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. Nizatidine absorption and stability is found from the upper gastric mucosa, short half-life (1-2 h) and rapid clearance of it suggested as rationale drug for gastroretentive drug delivery as microspheres. The present works aims to design gastroretentive drug delivery system for floating Nizatidine using microspheres as the carrier system that could give site specific and controlled drug release. The prepared microspheres were evaluated for particle size, micromeritics, entrapment efficiency, % yield, % drug release, % buoyancy, in vitro drug release studies and characterized by FTIR and SEM analysis.

**MATERIALS AND METHODS**

**Formulation of Nizatidine Floating microspheres**

Nizatidine Microspheres were prepared by using various excipients includes sodium alginate as microsphere core forming agent, HPMC K4M, HPMC K15M and HPMC K100M as rate controlling agent, calcium carbonate as gas generating agent, and calcium chloride as cross-linking agent.

**Floating microspheres Preparation**

Nizatidine Microspheres were formulated by ionotropic gelation technique mentioned in Table 1. Initially, 2% sodium alginate solution was prepared by dissolving in distilled water and stirred thoroughly by magnetically. On complete solution, accurately weighed quantity of drug followed by HPMC K4M, HPMC K15M, HPMC K100M and calcium carbonate of different weights were added to the above dispersion. Then the above dispersion was stirred at 500 rpm, maintained room temperature. The mixture was sonicated for 30 min to eliminate air bubbles that may have been formed during the stirring process. The homogenous dispersion was extruded using a 20G needle fitted with a 10 ml syringe into 100 ml of 1% of calcium chloride solution, being stirred at 100 rpm for 10 min into the gelation medium. Then microspheres were collected, washed with distilled water and oven dried at 60°C.

**Evaluation Parameters**

**Micromeritic properties**

The characterization of prepared microspheres was carried out by particle size, angle of repose, bulk density, tapped density, Carr’s index and %buoyancy.

**Determination of swelling index**

For determining the swelling index, the accurately weighed quantities of Nizatidine microspheres were suspended in 0.1 N HCl with pH 1.2 (simulated gastrointestinal fluids). Liquid droplets adhered to the surface of microspheres was removed by using blotting paper and then weighed it with the help of a microbalance. The swollen microspheres were dried in oven at 60°C for 5 h or until showed the constant weight. The variation in swelling of microspheres before and after drying was used to calculate the % of swelling index. The following equation was used.

\[ \text{Swelling index} = \frac{\text{Mass of swollen microspheres} - \text{Mass of dry microspheres}}{\text{Mass of dry microspheres}} \times 100 \]

**% yield of microspheres**

The prepared Nizatidine microspheres were collected and weighed. The actual weight of obtained microspheres divided by total weight of added drug and polymer was used for the calculation of % yield and mentioned below.

\[ \% \text{ yield} = \frac{\text{Total weight of microspheres}}{\text{Total weight of drug and polymer}} \times 100 \]

**Entrapment efficiency**

Nizatidine incorporation efficiency was analyzed by weighing 10 mg of floating microspheres then dissolved in methanol. The above solution was agitated to solubilize the drug and polymers and to extract the drug. Then solution was filtered using membrane filter (0.45μm) to separate shell fragments. The drug was determined using spectrophotometer (Shimadzu, UV-1800) at the \( \lambda_{\text{max}} \) of 224 nm. The encapsulation efficiency was determined using the following equation.

\[ \% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100 \]

**Test for buoyancy**

Buoyancy test was carried out by weighing 100 mg of the microspheres and transferred to a USP type II dissolution test apparatus containing 900 ml of simulated gastric fluid (0.1N HCl) at 37°C. The content of the beakers was stirred at 100 rpm. Then microspheres were separated at different time intervals and dried until a constant weight obtained. The % of buoyancy is calculated by using following equation.

\[ \text{Buoyancy ( % )} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100 \]

**In vitro drug release**

Nizatidine floating microspheres release studies of were conducted in 900 ml of simulated gastric fluid (0.1N HCl pH 1.2) at 37 ± 0.5°C by using USP.
dissolution apparatus II. Accurately weighed quantity of 100 mg floating microspheres was transferred into 900 ml of 0.1N HCl medium and stirring at 100 rpm. Aliquots of samples were withdrawn at prespecified time intervals, filtered and diluted with similar medium finally assayed at 224 nm using double beam spectrophotometer. The samples withdrawn were replaced with same dissolution medium and all the samples were analyzed in triplicate. [11]

**Release order kinetics**

Drug release data of optimized floating microspheres formulation were fitted to various kinetic models to reveal the drug release mechanism from the microspheres. Those consist of Zero order, first order, Higuchi model and Korsmeyer-Peppas exponential equation and $r^2$ values were determined.

**Mathematical modeling of optimized formulation (F17)**

![Graph of Zero order plots for the optimized formulation of floating microspheres (F17)](image)

**Fig. 4: Zero order plots for the optimized formulation of floating microspheres (F17)**

![Graph of First order plot for the optimized formulation of floating microspheres (F17)](image)

**Fig. 5: First order plot for the optimized formulation of floating microspheres (F17)**

![Graph of Higuchi model for the optimized formulation of floating microspheres (F17)](image)

**Fig. 6: Higuchi model for the optimized formulation of floating microspheres (F17)**

![Graph of Korsmeyer Peppas model for the optimized formulation of floating microspheres (F17)](image)

**Fig. 7: Korsmeyer Peppas model for the optimized formulation of floating microspheres (F17)**
Table 1: Formulation trials of Nizatidine Floating microspheres

| Formulation code | Nizatidine (mg) | Sodium alginate (%) | HPMCK 4M (mg) | Calcium Carbonate (mg) | Calcium Chloride (%) |
|------------------|-----------------|---------------------|----------------|------------------------|----------------------|
| F1               | 150             | 2                   | 300            | 50                     | 1                    |
| F2               | 150             | 2                   | 250            | 100                    | 1                    |
| F3               | 150             | 2                   | 200            | 150                    | 1                    |
| F4               | 150             | 2                   | 150            | 200                    | 1                    |
| F5               | 150             | 2                   | 100            | 250                    | 1                    |
| F6               | 150             | 2                   | 50             | 300                    | 1                    |
| F7               | 150             | 2                   | 300            | 50                     | 1                    |
| F8               | 150             | 2                   | 250            | 100                    | 1                    |
| F9               | 150             | 2                   | 200            | 150                    | 1                    |
| F10              | 150             | 2                   | 150            | 200                    | 1                    |
| F11              | 150             | 2                   | 100            | 250                    | 1                    |
| F12              | 150             | 2                   | 50             | 300                    | 1                    |

Table 2: Micromeretic properties of Nizatidine floating microspheres

| Formulation Code | Particle Size (μm) | Bulk density (g/ml) | Tapped density (g/ml) | Angle of repose | Carr's Index (%) | Buoyancy % |
|------------------|--------------------|---------------------|-----------------------|-----------------|------------------|------------|
| F1               | 55.45 ± 0.04       | 0.59                | 0.58                  | 27.93           | 14.56            | 50.13      |
| F2               | 60.12 ± 0.08       | 0.66                | 0.59                  | 23.91           | 9.34             | 64.42      |
| F3               | 65.29 ± 0.13       | 0.74                | 0.62                  | 29.67           | 8.34             | 78.86      |
| F4               | 73.43 ± 0.04       | 0.76                | 0.73                  | 30.54           | 13.36            | 69.53      |
| F5               | 62.35 ± 0.04       | 0.59                | 0.57                  | 27.94           | 8.12             | 91.24      |
| F6               | 79.67 ± 0.09       | 0.89                | 0.83                  | 30.15           | 9.23             | 67.12      |
| F7               | 75.45 ± 0.09       | 0.67                | 0.72                  | 25.54           | 13.95            | 90.17      |
| F8               | 55.23 ± 0.14       | 0.51                | 0.63                  | 22.91           | 10.32            | 65.08      |
| F9               | 63.22 ± 0.11       | 0.79                | 0.75                  | 23.70           | 11.04            | 52.05      |
| F10              | 83.34 ± 0.10       | 0.68                | 0.65                  | 30.24           | 12.34            | 66.74      |
| F11              | 78.45 ± 0.21       | 0.67                | 0.55                  | 22.91           | 10.98            | 87.29      |
| F12              | 65.32 ± 0.09       | 0.82                | 0.82                  | 25.54           | 13.95            | 70.18      |
| F13              | 55.23 ± 0.14       | 0.56                | 0.63                  | 22.91           | 10.32            | 75.30      |
| F14              | 73.22 ± 0.11       | 0.72                | 0.77                  | 21.70           | 8.08             | 75.64      |
| F15              | 81.34 ± 0.10       | 0.68                | 0.65                  | 30.24           | 12.34            | 80.47      |
| F16              | 50.67 ± 0.13       | 0.47                | 0.51                  | 20.74           | 7.67             | 94.23      |
| F17              | 74.35 ± 0.32       | 0.80                | 0.72                  | 29.67           | 11.43            | 85.16      |

Table 3: % yield, % swelling index, and entrapment efficiency of Nizatidine Floating microspheres formulations

| Formulation Code | Percentage Yield (%) | Swelling index (%) | Entrapment Efficiency (%) |
|------------------|----------------------|--------------------|---------------------------|
| F1               | 90.35 ± 0.12        | 82.24 ± 0.24       | 70.23 ± 0.31              |
| F2               | 84.35 ± 0.35        | 78.24 ± 0.16       | 89.14 ± 0.22              |
| F3               | 77.95 ± 0.27        | 80.15 ± 0.31       | 87.63 ± 0.17              |
| F4               | 92.45 ± 0.21        | 70.51 ± 0.28       | 83.45 ± 0.34              |
| F5               | 68.75 ± 0.32        | 87.31 ± 0.25       | 78.29 ± 0.12              |
| F6               | 83.92 ± 0.28        | 80.19 ± 0.17       | 67.83 ± 0.35              |
| F7               | 65.45 ± 0.19        | 76.17 ± 0.23       | 73.16 ± 0.30              |
| F8               | 74.35 ± 0.17        | 82.93 ± 0.36       | 65.27 ± 0.21              |
| F9               | 88.65 ± 0.36        | 85.31 ± 0.24       | 78.13 ± 0.15              |
| F10              | 78.35 ± 0.33        | 69.27 ± 0.19       | 75.52 ± 0.28              |
| F11              | 86.98 ± 0.29        | 89.11 ± 0.33       | 82.94 ± 0.11              |
| F12              | 91.23 ± 0.12        | 83.34 ± 0.27       | 71.11 ± 0.32              |
| F13              | 62.75 ± 0.25        | 73.92 ± 0.12       | 78.25 ± 0.33              |
| F14              | 82.34 ± 0.31        | 88.92 ± 0.26       | 73.16 ± 0.14              |
| F15              | 76.95 ± 0.11        | 81.62 ± 0.31       | 70.19 ± 0.26              |
| F16              | 85.45 ± 0.24        | 77.24 ± 0.32       | 68.10 ± 0.15              |
| F17              | 95.47 ± 0.36        | 92.13 ± 0.17       | 93.62 ± 0.29              |
| F18              | 80.42 ± 0.29        | 79.19 ± 0.30       | 84.73 ± 0.13              |

Drug-exciptient compatibility studies
Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR technique can be used to recognize the functional groups in the pure drug and drug-excipient compatibility. Pure Nizatidine FTIR spectra and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and excipients were taken in the ratio 100:1 and mixed by mortar. [11] The samples were made into pellet by the application of pressure. Then the FTIR spectra were recorded between 4000 - 400 cm⁻¹.

SEM studies
Surface nature of microspheres includes size and shape was examined with the help of Scanning Electron Microscope (HITACHI, S-3700N). The microspheres were dried completely prior to analysis and SEM was carried out at various magnifications. [12]

Stability studies
Optimized formulation was subjected to stability testing at 40°C ± 2°C/75% RH ± 5% RH for 6 months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0,
RESULTS AND DISCUSSION

The particle size, % buoyancy and micromeritic properties of the microspheres were determined in the form of bulk density, tapped density, angle of repose and carr’s index results mentioned in Table 2. The size of prepared microspheres ranged from 50.67 ± 0.13 to 83.34 ± 0.10μm, comparatively, lower particle size was observed in HPMC K100M as rate retarding polymer. The bulk density and tapped density of were ranged from 0.47 to 0.89 g/ml and 0.51 to 0.83 g/ml, respectively. The angle of repose values was in the range of 20°74 - 30°54, which shows excellent to good flow properties, while the carr’s index for all formulations was in the range of 2.13%. The swelling index results from 69.27% to 92.13%. The better results were observed in F17 formulation prepared with HPMC K100M as rate retarding polymer and the results are shown in Table 3.

The % yields ranged from 62.75% to 95.47% with the % entrapment efficiency being between 65.27% to 93.62%. The swelling index results from 69.27% to 92.13%. The better results were observed in F17 formulation prepared with HPMC K100M as rate retarding polymer and the results are shown in Table 3.

![Image](https://example.com/image1.png)

**Fig 8: Zero order plot for Marketed product**

![Image](https://example.com/image2.png)

**Fig 9: First order plot for Marketed product**

![Image](https://example.com/image3.png)

**Fig 10: Higuchi model for Marketed product**

![Image](https://example.com/image4.png)

**Fig 11: Korsmeyer Peppas model for Marketed product**

Table 4: Release order kinetics of optimized formulation

| Formulation code | Zero order R² | First order R² | Higuchi R² | Korsmeyer-Peppas R² | Peppas n value |
|------------------|---------------|---------------|-----------|----------------------|---------------|
| F1               | 0.905         | 0.668         | 0.911     | 0.922                | 0.555         |
| F2               | 0.911         | 0.711         | 0.914     | 0.933                | 0.636         |
| F3               | 0.965         | 0.815         | 0.922     | 0.944                | 0.387         |
| F4               | 0.925         | 0.718         | 0.922     | 0.924                | 0.688         |
| F5               | 0.954         | 0.804         | 0.931     | 0.941                | 0.647         |
| F6               | 0.907         | 0.709         | 0.918     | 0.933                | 0.599         |
| F7               | 0.913         | 0.804         | 0.949     | 0.916                | 0.596         |
| F8               | 0.939         | 0.721         | 0.922     | 0.951                | 0.666         |
| F9               | 0.957         | 0.807         | 0.949     | 0.55                 | 0.647         |
| F10              | 0.981         | 0.819         | 0.933     | 0.922                | 0.720         |
| F11              | 0.977         | 0.824         | 0.952     | 0.970                | 0.567         |
| F12              | 0.984         | 0.785         | 0.944     | 0.958                | 0.679         |
| F13              | 0.957         | 0.824         | 0.919     | 0.949                | 0.622         |
| F14              | 0.944         | 0.829         | 0.958     | 0.971                | 0.597         |
| F15              | 0.954         | 0.819         | 0.911     | 0.947                | 0.711         |
| F16              | 0.980         | 0.824         | 0.957     | 0.967                | 0.714         |
| F17              | 0.989         | 0.839         | 0.964     | 0.976                | 0.720         |
| F18              | 0.944         | 0.816         | 0.954     | 0.967                | 0.711         |
| Marketed product | 0.77          | 0.936         | 0.921     | 0.948                | 0.393         |

Table 5: Stability studies of optimized floating microspheres

| Retest Time for Optimized formulation | % yield ± SD | Entrapment efficiency (%) | In vitro drug release profile (%) |
|--------------------------------------|-------------|---------------------------|----------------------------------|
| 0 day                                | 95.47 ± 0.36| 92.13 ± 0.17              | 96.54 ± 0.72                     |
| 30 days                              | 94.75 ± 0.242| 91.91 ± 0.186            | 96.25 ± 0.293                  |
| 60 days                              | 94.28 ± 0.173| 91.26 ± 0.153            | 95.33 ± 0.184                  |
| 120 days                             | 93.61 ± 0.265| 90.87 ± 0.291            | 94.19 ± 0.253                  |
| 180 days                             | 93.12 ± 0.321| 90.33 ± 0.172            | 93.65 ± 0.341                  |
In vitro drug release studies
The drug release from the floating microspheres of Nizatidine was controlled over a period of 12h and graphical representation of all the formulations were shown in Figures 1, 2 & 3. The Cumulative % drug release of optimized formulation F17 was found to be 96.54 ± 0.72% at the end of 12h where as marketed product noted 94.53 ± 0.26% within 12h.

Release order kinetics
The in vitro drug release profiles of all the formulations were fitted to several kinetic models and release data followed by their R² and n values shown in Table 4. The optimized formulation was best fitted in Zero Order and Korsmeyer-Peppas (Figure 4-7). The optimized formulation n value was 0.720 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion. The marketed conventional formulation followed the first order kinetics indicating drug release is directly proportional to the concentration of drug (Figure 8-11).

Drug excipient compatibility studies
FTIR spectroscopy of Nizatidine microspheres
The FTIR spectrum of pure drug (Figure 13) showed characteristic sharp peaks at 3421 cm⁻¹ (C-N stretch), 2951 cm⁻¹ (C-H stretch), 1436 cm⁻¹ (C=H deformation in NCH, CH), 1500 cm⁻¹ (CH & OCH groups), 1587 cm⁻¹ (Conjugated with NO), 1419 cm⁻¹ for CH₂ bond. There were no new significant bonds observed in the pure
drug (Figure 12) and optimized formulation (Figure 13), which indicates that no interaction observed between the drug and excipients.

**SEM studies of Nizatidine microspheres**
The microspheres surface was rough and spherical in shape as seen in Figure 14. The surface of the Nizatidine microspheres was rough due to higher concentration of drug consistently discreted at the molecular level in the matrices.

**Stability studies**
Stability studies of optimized Nizatidine microspheres as per ICH guidelines was carried out for 6months at 40°C ± 2°C/75% RH ± 5% RH showed in the Table 5. At predetermined time intervals samples were withdrawn and subjected to % yield, entrapment efficiency and in vitro drug release analysis. Significant change was not observed in results before and after stability studies. Indicating the optimized formulation (F17) was stable. Nizatidine loaded floating microspheres were prepared by ionotropic gelation method. From the results it concluded that formulation F17 was found to be satisfactory results in terms of excellent Micromericet properties, particle size (50.67 ± 0.13μm), yield of microsphere (95.47 ± 0.36%), entrapment efficiency (95.67 ± 0.29%), % buoyancy (94.23%), swelling index (92.13 ± 0.17%) and highest in vitro drug release of 98.23 ± 5.49% in a sustained manner with constant fashion over extended period for 12 h compared with marketed product 95.87 ± 0.31 in 12 h. The drug and excipients were compatible studied by using FTIR. Drug release from Nizatidine microspheres followed first order and Higuchi model. It was suggested that mechanism of drug release from microspheres was diffusion controlled. The prepared microspheres were spherical in shape studied by SEM studies. The optimized formulation F17 was stable. Hence the formulated and prepared floating Nizatidine microspheres may establish to be potential candidate for safe and effective sustained drug delivery and improve the bioavailability.

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