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# FORMULATION AND EVALUATION OF SUSTAINED RELEASE FLOATING MUCOADHESIVE TABLET OF NIZATIDINE

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**Abstract:** A new drug delivery system for H2 receptor antagonist Nizatidine, was developed utilizing both the concepts of adhesiveness and of flotation, in order to obtain a unique drug delivery system which could remain in the stomach for a much longer period of time. Floating-Mucoadesive tablets of Nizatidine were developed to prolong its release and improve bioavailability. Nizatidine has been the most widely used drug for the treatment of peptic ulcer. A floating drug delivery system (FDDS) was developed using gas sodium bicarbonate, citric acid and hydrocolloids, hydroxypropyl methylcellulose (HPMC) and carbopol 940P. Floating delivery system of Nizatidine was prepared using different grades of HPMC as drug rel retarding polymer and sodium bicarbonate as source for carbon dioxide which helps tablets to float. The prepared tablets were evaluated their physicochemical properties and drug release, excipient compatibility, density, buoyancy test, mucoadhesion force, swelling study, drug content and *vitro* release profile.

**Keywords:** Floating-Mucoadhesive Tablet, Nizatidine , Gastric problems, HPMC

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## INTRODUCTION

Oral route of drug administration is oldest and safest mode of drug administration. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed. In oral controlled drug delivery the amount of drug release is constantly predetermined and these constant releases of drug provide a constant blood plasma level of drug for a therapeutic response. The oral controlled drug deliveries have much advantage to conventional delivery. It decrease the fluctuation of drug plasma conc., it reduce toxicity, provide a sustained effects, reduced the dosing frequency. Apart from other advantage it reduces total amount of drug used, improve patient compliance and reduced patient care time Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with acceptable level of safety to the patient in recent years a wide variety of newer oral drug delivery systems like SR/CR dosage forms are designed and evaluated in order to overcome the limitations of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time as a result the variations of the drug levels in the blood are prevented and minimized drug related side effects. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucus membrane. Transmucosal drug delivery systems show various merits over conventional drug delivery systems. Mucoadhesive polymers facilitate the mucoadhesion by their specific properties. This article reviews desirable properties of mucoadhesive polymers and the latest advancement in the field. Nizatidine is a histamine H2- receptor antagonist that inhibits stomach acid production. It is commonly used in treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD). Nizatidine is also used alongside fexofenadine and other antihistamines for the treatment of skin conditions such as hives.

## MATERIAL AND METHOD

Nizatidine was received gift sample of Watson Pharma from Goa . HPMC K-4, HPMC E-10,

HPMC K-100 used as polymer. Cross povidone, Carmilose sodium, lactose, Magnesium stearate, talc. All ingredient and reagent were of analytical grade.

### Method:

### Preparation of Floating Tablet of Nizatidine

The ingredient were weighed accurately and mixed thoroughly powder passed through 42 mesh sieve. Implies direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. These materials possess

cohesive and flow properties that make direct compression possible. Increasing attention is paid to this method because of incredible economy and efficiency offered by it. Direct compression vehicles or carriers must have good flow and compressible characters these properties are imparted by predisposing these vehicles to slugging, spray drying or crystallization. Tablets were

white and round. Hardness, friability and weight variation were evaluated.

### Evaluation of powder

The flow properties of granules (before compression) were characterized in terms of angle of repose9, tapped density, bulk density, Carr's index and Hausner ratio.

### Physical evaluation of Nizatidine Tablet

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odor, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester) and friability using 10 tablets (Roche type friabilator)

### Determination of Swelling Index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h. The swelling index (SI), expressed as a percentage, and was calculated from the following equation-:

SI = Weight of tablet at time (*t*) -Initial

weight of tablet x 100/ Initial weight of tablet

***In Vitro* buoyancy studies**

*In Vitro* buoyancy studies were performed for all the twelve formulations as per the method. The randomly selected tablets from each formulation were kept in a 100ml beaker contain simulated gastric fluid, pH1.2 as per USP. The time taken for the tablet to rise to the surface and float was

taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

**Drug Content**

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 314nm using 0.1 N HCl as blank.

***In Vitro* dissolution studies**

The release rate of Nizatidine from floating tablets was determined using United States Pharmacopeia (USP). Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1Nhydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these

solutions was measured at 314 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

**Comparison with marketed product**

The promising formulation was compared with marketed product of Nizatidine. The evaluation parameters tested and compared were drug content uniformity and in-vitro dissolution profile.

***In Vitro* drug release kinetic studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release

from the tablets, drug release data was analyzed according to zero order16, first order 17,Higuchi square root 18, Korsmeyer- Peppas model 19. Thecriteria for selecting the most appropriate model was chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

**Stability studies**

The promising formulation was tested for a period of 30 days at 30° c with 75% RH, for their drug content and other parameters.

**RESULTS AND DISCUSSION**

Formulation development & evaluation parameters have been performed in satisfactory data. Title of this study will be done for prolonged the bioavailability of the dosage form. It is a new drug delivery system to maximize effectiveness and compliance. Nizatidine is use for gastric problems. The advantage of floating drug delivery system is to extend the release of drug, increases gastric retention time and enhances bioavailability by superior technology of floatation and adhesion to achieve gastric retention.

**Swelling Index studies**

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics off swelling is important because the gel barrier is formed with water penetration. Swelling is also a vital factor to ensure floating and drug dissolution. To obtain floating, the balance between swelling and water acceptance must be restored 23-24. Tablets containing Carbopol 940 P (F9 and F10) showed less swelling index at the beginning but higher swelling index was observed at the end of 12 h. While HPMC K4M and HPMC E 10 (F1to F8) swelled rapidly at the beginning in 0.1 N HCl and could not remain their matrix integrity up to 12 h. Tablets containing combination of Carbopol 940P, HPMC K4M and HPMC E 10 (F12) showed constant increasing in swelling index up to 12 h. Combination of HPMC K4M and HPMC E 10 resulted in a higher swelling index compared with HPMC E 10 alone. The HPMC grade also affects the swelling and hydration with considerably higher swelling index for HPMC K4M than HPMC E 10. HPMC E 10 exhibited low swelling index, but there was no decrease in swelling rate. The reason for this appeared to be its high viscosity and high water retention property. Further, no significant effect of effervescent on swelling indices was observed. Swelling index values start decreasing when polymer erosion starts in the medium.

***In Vitro* dissolution studies.**

The performance of floating formulations has been reported to be greatly affected by physiological conditions such as food transport, gastrointestinal motility, and so on. A study 25 on floating mini tablets of atenolol has indicated lower bioavailability of drug. The reason for this lower bioavailability is attributed to small size of the dosage form, causing too short of a residence time and a premature exit from the stomach. The tablets in this investigation are much larger in size and are expected to be retained for longer duration in upper GIT. *In Vitro* dissolution studies of all the formulations of floating tablets of Nizatidine were carried out in 0.1NHCl. The study was performed for 24 h and cumulative drug release was calculated at every one hour time interval. *In Vitro* dissolution studies of all the formulations are shown in figure 2, 3 and 4. Three different polymers and their combinations (Table 1) were used to prepare floating tablets. It was observed that the type of polymer influences the drug release pattern. All the formulations contained equal amount of gas generating agent(sodium bi carbonate) a citric acid. A significantly higher rate and extent of drug release was observed from the batches based on HPMC K4M.Varying the amount of HPMC K4M affect the drug release. Drug release from HPMC E 10 was lesser owing to its high viscosity and also due to less permeability of water to HPMC E 10 . Moreover the HPMC containing tablets F1- F8 could not bear their matrix shape until 24 h and the released the drug before24 h. After 1 h the drug dissolved from floating tablets composed of carbopol 934P, F9(16.0) and F10 (11.0) was less than tablets containing different grade of HPMC. This showed that HPMC hydrated more rapidly than carbopol 940P in the presence of 0.1 N HCl. Although combination of HPMC E 10 and HPMC K4M sustains the drug release for a longer time. As expected, the drug release rate was dependent on the viscosity grade and the concentration of the polymer used. Tablets containing HPMC and Carbopol combination (F12) showed constant drug release up to 24hr (98). This controlled release of drug from F12 could be attributed to the formation of a thick gel structure that delays drug release from the tablet matrix c.

**CONCLUSION**

This study discusses the preparation of floating tablets of Nizatidine. The effervescent-based floating drug delivery was a promising approach to achieve *In Vitro* buoyancy. The addition of gel-forming polymer HPMC K4 M, HPMC E 10, carbopol 940P and gas-generating agent sodium bicarbonate was essential to achieve *In Vitro* buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release. The type of polymer affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer combinations. The *In Vitro* drug release profiles obtained for tablets (F12)

made with combinations of HPMC K4M, HPMC E10 FLT(30 s) and a prolonged floating duration (> 24hrs) which was a controlled release characteristic ( 98%) for 24h. Good stability was observed for 3 months during stability studies. Since the formulation showed sufficient release for prolonged period, the dose can be reduced and possible incomplete absorption of the drug can be avoided.

**Dissolution rate of Floating tablet for batches FT-III to FT-VI**

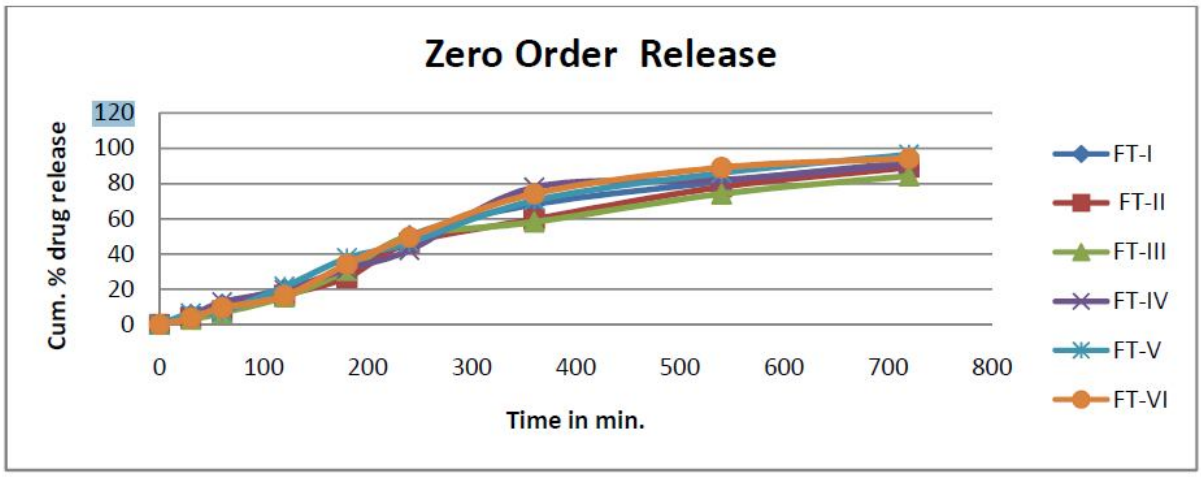


**Figure no. 1 - Zero Order release rate of Floating tablet for batches FT-III to FT-VI**

**First order release rate of Floating tablet for batches FT-III to FT-VI**


**Figure no. 2 - First Order release rate of Floating tablet for batches FT-III to FT-VI**

**Higuchi Plot of Floating tablet for batches FT-III to FT-VI**

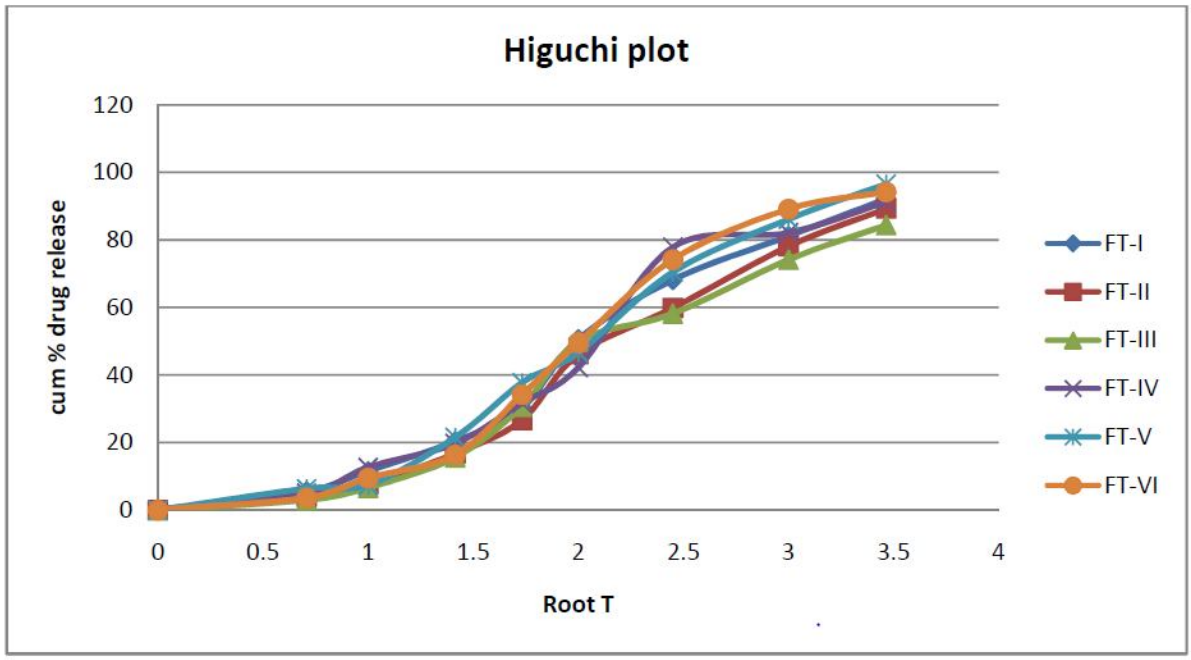


**Figure no. 3 - Higuchi Plot of Floating tablet for batches FT-III to FT-VI**

**Hixon Crowell plot of Floating tablet for batches FT-III to FT-VI**

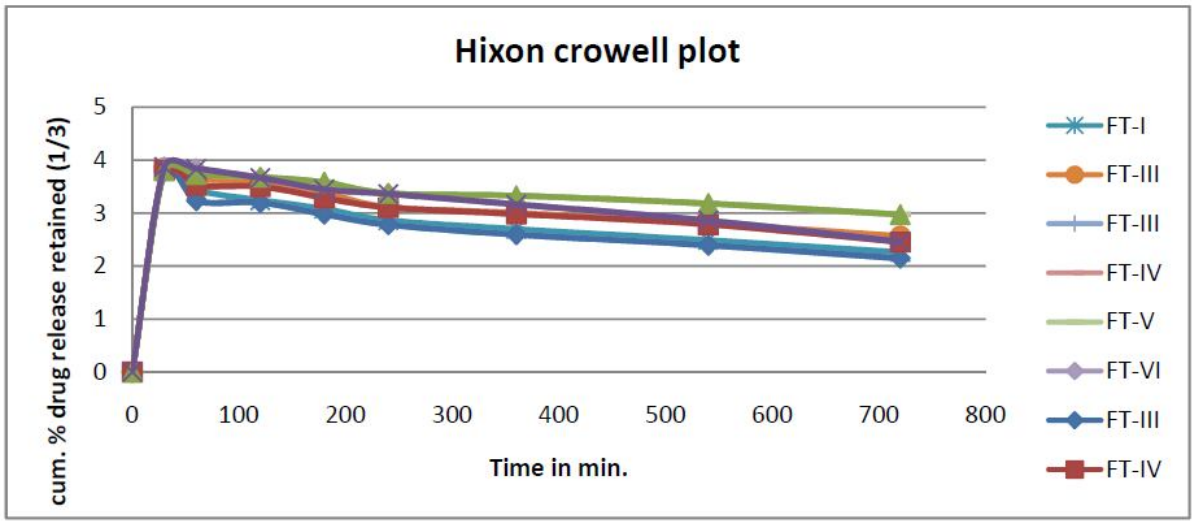


**Figure no. 4 - Hixon Crowell plot of Floating tablet for batches FT-III to FT-VI**

**Table 1: Composition of floating-mucoadhesive tablet of Nizatidine**

| Ingredients | SR 1 mg | SR 2 mg | SR 3 mg | SR 4 Mg | SR 5 mg | SR 6 mg |
|---|---|---|---|---|---|---|
| Nizatidine | 50 | 50 | 50 | 50 | 50 | 50 |
| HPMC K 4M | | | | | 65 | 30 |
| HPMC K 5M | 80 | 70 | | | | |
| HPMC E 10 | | | 60 | | | 30 |
| HPMC K 100M | | | 50 | | | |
| Carbopol 940 P | 20 | 40 | 30 | 30 | 25 | 30 |
| Sodium bicarbonate | 40 | 40 | 30 | 30 | 30 | 30 |
| Citric acid | 20 | 24 | 20 | 20 | 24 | 24 |
| Aerosil | | | 3 | 3 | 3 | 3 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 |
| Lactose | 85 | 75 | 108 | 98 | 98 | 98 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 |

**Table no. 2: Various Evaluating Parameter of Batch-I to Batch-VI batches of Nizatidine Floating mucoadhesive**

| Code | Angle of repose θ | Bulk density g/cm$^3$ | Tapped density | Compressibility index | Hausner ratio |
|---|---|---|---|---|---|
| SR 1 | 27 | 0.383 | 0.569 | 30.34 | 1.22 |
| SR 2 | 30 | 0.386 | 0.502 | 23.22 | 1.26 |
| SR 3 | 28 | 0.367 | 0.506 | 25.32 | 1.13 |
| SR 4 | 30 | 0.357 | 0.515 | 28.19 | 1.16 |
| SR 5 | 31 | 0.369 | 0.509 | 30.17 | 1.18 |
| SR 6 | 27 | 0.384 | 0.506 | 29.16 | 1.14 |

**Table no. 3: Evaluation Parameter of floating- mucoadhesive tablets**

| Code | Hardness ($Kg/cm^2$) | Thickness (mm) | Friability (%) | Drug content (%) | Weight variation (%) |
|---|---|---|---|---|---|
| SR 1 | 4 ± 0.42 | 4.5 ± 0.12 | 0.25 ± 0.16 | 96.37 ± 0.68 | 5.38 ± 0.57 |
| SR 2 | 4.5 ± 0.24 | 4.5 ± 0.08 | 0.21 ± 0.12 | 97.05 ± 0.41 | 5.28 ± 0.36 |
| SR 3 | 3.4 ± 0.46 | 4.5 ± 0.06 | 0.28 ± 0.13 | 98.83 ± 0.26 | 5.46 ± 0.57 |
| SR 4 | 4 ± 0.51 | 4.5 ± 0.17 | 0.21 ± 0.08 | 97.74 ± 0.24 | 6.55 ± 0.39 |
| SR 5 | 3.5 ± 0.26 | 4.5 ± 0.23 | 0.27 ± 0.09 | 97.57 ± 0.41 | 4.43 ± 0.17 |
| SR 6 | 3.3 ± 0.39 | 4.4 ± 0.06 | 0.23 ± 0.06 | 98.58 0.26 | 5.89 ± 0.16 |

**Table no. 4: Percent swelling index of batches FT-I to FT-VI**

| Time (hrs) | Swelling Index (%) | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 34.46 | 37.87 | 41.18 | 51.42 | 51.59 | 53.88 |
| 2 | 65.59 | 67.72 | 72.29 | 88.63 | 76.74 | 81.73 |
| 3 | 73.38 | 77.43 | 88.76 | 93.61 | 91.25 | 101.81 |
| 4 | 90.89 | 96.89 | 103.88 | 113.28 | 105.69 | 119.88 |
| 6 | 102.94 | 111.78 | 123.57 | 135.96 | 129.91 | 144.64 |

**Table no. 5: *In vitro* dissolution study of floating tablet nizatidine**

| Time (min) | % CDR | | | | | |
|---|---|---|---|---|---|---|
| | SR 1 | SR 2 | SR 3 | SR 4 | SR 5 | SR 6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 6.12 | 19.72 | 10.71 | 9.34 | 4.68 | 2.16 |
| 60 | 8.77 | 25 | 15.40 | 19.43 | 2.88 | 1.08 |
| 120 | 6.87 | 18.33 | 21.42 | 23.22 | 3.24 | 5.4 |
| 180 | 8.16 | 19.17 | 23.43 | 18.43 | 9.72 | 8.28 |
| 240 | 8.87 | 18.89 | 20.75 | 19.05 | 24.43 | 11.88 |
| 360 | 8.39 | 20.58 | 28.99 | 27.33 | 20.88 | 16.2 |

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