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FORMULATION AND EVALUATION OF FLOATING MICROSPHERE OF NIZATIDINE

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ABSTRACT

In the last three decades, oral controlled release dosage forms have been developed due to their major therapeutic benefits, such as ease of administration of patient compliance and flexibility in formulation. These factors contributed to the production in the gastrointestinal tract of a novel orally regulated release dosage form with Gastro retentive properties. Gastro retentive dosage forms (GRDFs) will stay in the gastric region for many hours, greatly increasing the period of drugs in the gastric field. Prolonged gastric retention increases bioavailability, reduces drug loss, and improves less soluble drug solubility in a high pH environment. Floating microspheres of Nizatidine were prepared by the solvent diffusion method of evaporation. The drug was encapsulated in various Eudragit and ethanol polymer ratio combinations. The prepared microspheres are evaluated for particle size, percent buoyancy, study of in-vitro release, and stability studies. The buoyancy level was found to be between 80.22% and 88.54%. The good buoyancy behaviour of the microspheres showed that the microspheres are hollow in nature and maintained for more than 12 hours in the upper part of the GIT to improve gastric residence time. In order to ensure in vivo efficacy, the formulations prepared should be clinically tested. The current study compared the combination of polymers and revealed their effect on the release of drugs and various other parameters in floating microsphere preparation.

KEYWORDS: Floating, Microspheres, Gastroretentive, Nizatidine

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INTRODUCTION

Floating systems are low-density systems first described by Davis that have sufficient buoyancy to float over the gastric contents and remain in the stomach for an extended period of time. As the system floats over the gastric material, the drug is released slowly at the optimal rate, resulting in increased GRT and reducing variations in the concentration of plasma drugs [1].

Formulation Requirements for Floating Drug Delivery

Device must comply with these criteria:

- It must have sufficient structure to form a cohesive gel barrier.
- It must maintain an overall specific gravity lower than that of gastric content (1.004 – 1.010).
- It should dissolve slowly enough to serve as a drug reservoir.

Floating Microspheres

Gastro-retentive drug delivery systems, based on a non-effervescent approach, are floating microspheres. In a strict sense, hollow microspheres are empty spherical particles without a nucleus. These microspheres are characteristically free-flowing protein or synthetic polymer powders, preferably smaller than 200 micrometres in size.

The potential for controlled release of drugs[2] is present in solid biodegradable microspheres containing a drug dispersed or dissolved in the particle matrix. Low-density structures that have adequate buoyancy to float over gastric contents and stay in the stomach for an extended time are gastro-retentive floating microspheres. As the device floats over the gastric substance, the drug is released slowly at the optimal rate, resulting in improved gastric retention with decreased plasma drug variability.

Gel formers, polysaccharides and polymers hydrate as microspheres come into contact with gastric fluid to form a colloidal gel barrier that regulates the rate of fluid penetration into the device and the consequent release of drugs. The gel layer is preserved by the hydration of the surrounding hydrocolloid layer as the outer surface of the dosage form dissolves. The air trapped by the swollen polymer decreases density and provides the microspheres with buoyancy. However, a minimal gastric content was required to allow buoyancy to be properly achieved. The new innovations are hollow microspheres of acrylic resins, Eudragit, PMAA, Polyethylene oxide and Cellulose acetate; Polystyrene floatable shells; Polycarbonate floating balloons and Gelucire floating microspheres [2].

MATERIALS AND METHODS

Materials

Nizatidine purchased from Wings Biotech, Baddi (H.P.) Eudragit-S100, cellulose acetate, ethyl acetate, dichloromethane purchased from S.D. Fine-Chem Ltd., Mumbai.

Methods

Preparation and Optimization of Floating Microspheres

Design of Experiment

A formulation design was selected to study the main effects and interaction of two factors on entrapment efficiency and particle size. The independent factors investigated were polymer concentration & emulsifying concentration. The optimization was done on the basis of particle size and drug loading efficiency [3].

Table 1: Design Layout for Preparation of Nizatidine Loaded Floating Microspheres with Batch Codes

S. No.	Batch no.	Drug: Polymer	Emulsifying con. w/v %
1	NIZ1	1:1	0.5%
2	NIZ2	1:2	0.5%
3	NIZ3	1:3	0.5%
4	NIZ4	1:1	0.75%
5	NIZ5	1:2	0.75%
6	NIZ6	1:3	0.75%
7	NIZ7	1:1	1.0%
8	NIZ8	1:2	1.0%
9	NIZ9	1:3	1.0%

Preparation of Microspheres by Solvent Diffusion Evaporation Method

1. Microspheres with an internal hollow structure were prepared by solvent diffusion evaporation method.
2. Accurate quantity of polymer i.e. Eudragit S100 (100 mg) was dissolved in 8 ml ethanol followed by the addition of 8 ml dichloromethane.
3. The 200 mg of drug (Nizatidine) was homogeneously dispersed in this polymer solution. This solution was slowly introduced into 200 ml of polyvinyl alcohol aqueous solution with stirring at 350-400 rpm using a mechanical stirrer (Remi India) equipped with a blade propeller.
4. The solution was stirred for 3-4 hrs and microspheres were collected by filtration, washed three times with distilled water and dried at room temperature for 24 hrs of drug loading and particle size [4].
5. The observations are recorded in **Table 2** and graphically shown in **Figure 1**.

Optimization of Process Variables:

- ✓ Optimization of stirring speed
- ✓ Optimization of Temperature

Optimization of Stirring Speed

For the preparation of NIZ7 microspheres, the stirring speed varied from 200 to 500 rpm using optimised formulation parameters, i.e. drug concentration (100 percent polymer weight), polymer quantity 100 mg,

emulsifier concentration (01 percent w/v PVA) [5]. The particle size and percent drug loading were determined which are recorded in **Table 3** and shown in **Figure 2**.

Table 2: Effect of Drug: Polymer & Emulsify Concentration on Particle Size and Drug Loading of Microspheres

Batch no.	Particle Size (µm)	Percentage Drug Loading
NIZ1	148.2	63.12%
NIZ2	143.36	70.57%
NIZ3	150.4	71.50%
NIZ4	120	72.27%
NIZ5	141	73.20%
NIZ6	128.35	75.86%
NIZ7	140.47	77.27%
NIZ8	138.25	73.86%
NIZ9	135.45	67.76%

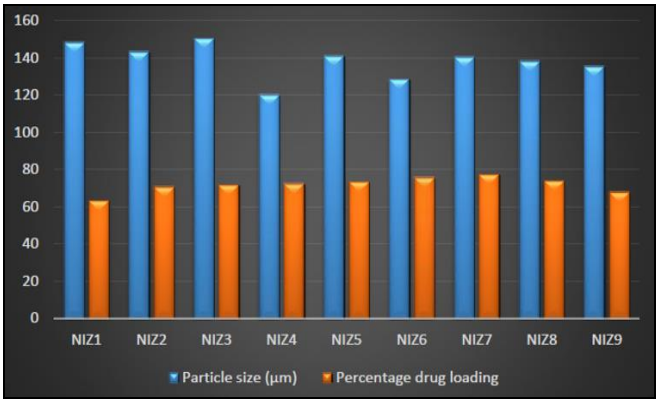

Figure 1: Effect of Drug: Polymer & Emulsify Concentration on Particle Size and Drug Loading of Microspheres

Table 3: Effect of Stirring Speed on Particle Size and Drug Loading of Microspheres

Formulation code	Speed (rpm)	Particle size (µm)	Percentage drug loading
NIZ7S1	200	143.66	77.16
NIZ7S2	300	143.24	77.34
NIZ7S3	400	142.02	77.48
NIZ7S4	500	141.16	77.52

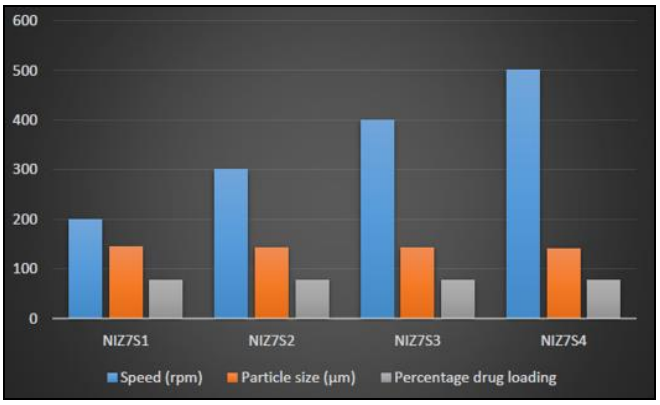

Figure 2: Effect of Stirring Speed on Particle Size and Nizatidine Loading of Microspheres

Table 4: Effect of Temperature on Particle Size and Drug Loading of Microspheres

Formulation code	Speed (rpm)	Particle size (µm)	Percentage drug loading
NIZ7S2T1	25°C	148.66	75.16
NIZ7S2T2	37°C	150.24	77.34
NIZ7S2T3	40°C	157.02	76.48
NIZ7S2T4	47°C	162.16	75.52

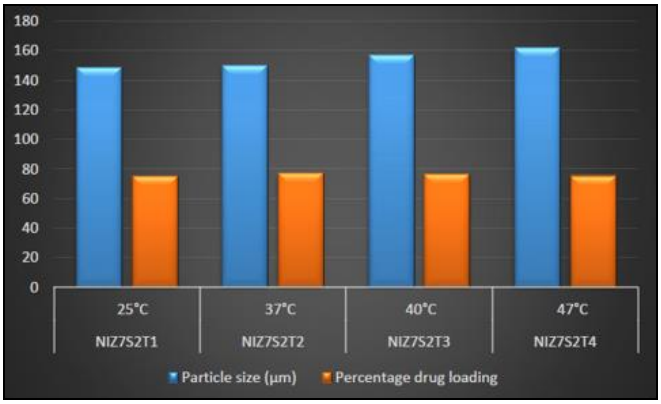

Figure 3: Effect of Temperature on Particle Size and Nizatidine Loading of Microspheres

Characterization of Prepared Microspheres

For form and surface morphology, size and size distribution, percent drug loading and *in-vitro* drug release, the prepared microspheres were characterised.

Shape and Surface Morphology

Optical and scanning electron microscopy studied the microspheres. Microspheres were suspended in water; a drop was placed on a glass slide, covered with a slip cover, and presented to examine their form under the optical microscope (Leitz-Biomed, Germany) [6, 7]. (**Figure 4 and 5**).

In order to examine the surface morphology, the formulations were viewed under scanning electron microscope.

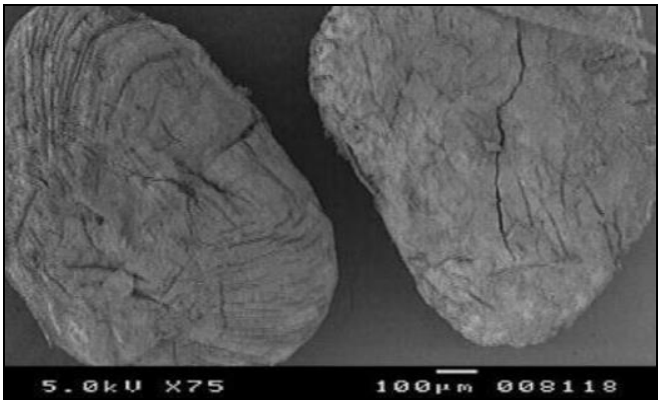

Figure 4: Photomicrograph of Nizatidine Microspheres

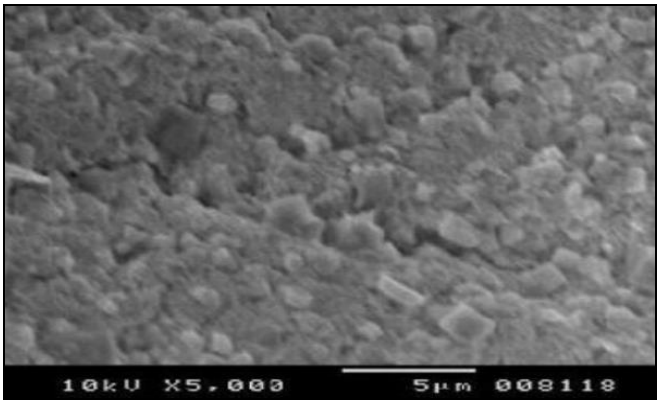

Figure 5: SEM Photograph of Nizatidine Microspheres

Particle Size and Size Distribution

Using a calibrated ocular micrometer [7], microspheres were analysed microscopically for their scale and size distribution. The lowest ocular micrometre count was measured as 16.2 µm. Around 100 particles were seen from each formulation and the data observed for each formulation is shown in **Table 2**.

Drug Entrapment Efficiency

Every batch of 10 mg of drug-loaded microspheres was crushed in a mortar and then moved into a 100 ml conical flask containing 50 ml of methanol. To promote swelling and defragmentation of the cross-linked structure, the microspheres were stirred to. The solution was filtered through a membrane. Drug entrapment efficiency was analyzed after suitable dilution by spectrophotometrically with a UV-detector (Jasco, UV-600) at 224nm [8]. The drug entrapment efficiency was calculated as follows:

Drug Entrapment Efficiency = Calculated drug concentration / Theoretical drug content × 100

***In-vitro* Buoyancy Studies**

Floating microspheres of approximately 100 mg were distributed over the surface of the 900 ml simulated gastric fluid (SGF, pH 1.2) dissolution medium mounted in the USP dissolution apparatus II. The medium temperature was held at 37 ° C and agitated at 100 rpm with a paddle. The microspheres that drifted over the surface of the medium and those that settled down at the bottom of the flask were separately retrieved and dried after agitation [9]. The percentage of floating microsphere was determined by the following equation:

Buoyancy % = Weight of microspheres floated on medium/Weight of microspheres floated on medium + Weight of microspheres settled at bottom of flask × 100.

Table 5: Showing % Buoyancy of Various Formulations

S. No.	Batch No.	Percent Buoyancy
1	NIZ1	82.55
2	NIZ2	80.60
3	NIZ3	86.50
4	NIZ4	86.66
5	NIZ5	83.08
6	NIZ6	82.44
7	NIZ7	84.06
8	NIZ8	88.54
9	NIZ9	80.22

***In-vitro* Drug Release Study**

Drug release experiments were performed at 37±0.5 in the USP dissolution research apparatus and sustained approximately 900 ml at 100rpm on 0.1N HCl. All drug release studies have applied 100 mg of microspheres for each formulation.

Table 6: Data for Cumulative % Nizatidine Release from PVA-Eudragit S100 Microspheres in SGF pH 0.1N HCl

S. No.	Time interval (hrs)	Drug release from Eudragit S100- PVA microspheres (%)
1	0	16.20
2	1	28.10
3	2	46.11
4	3	66.18
5	4	72.86
6	5	79.21

At defined time intervals, samples (5ml) were extracted, such as 0, 1, 2, 4, 6 hr and the same medium of fresh 0.1N HCl added immediately during the experiment to maintain sink condition. After sufficient dilution, the aliquot sample was analysed spectrophotometrically at 224 nm to estimate the concentration of nizatidine in the test sample [10, 11].

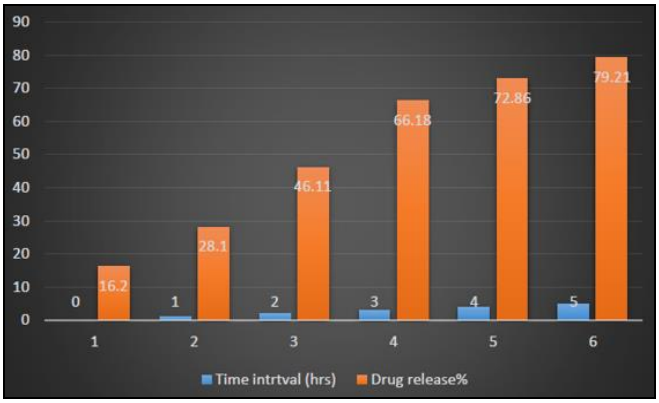

Figure 6: Cumulative % Nizatidine Release from PVA- Eudragit S100 Microspheres in pH 0.1N HCl

RESULTS AND DISCUSSION

Solvent diffusion methods reported by Kawashima et al. (2001) were used to prepare Eudragit S100-PVA complex microspheres. In the external step, the Eudragit S100 solution was sequentially dropped into the PVA solution and dispersed. As the external phase, the PVA solution was selected because the ethanol / dichloromethane (DCM) mixture is not miscible with PVA solution as an internal phase and the Eudragit S100-PVA complex is not soluble in it. They formed an interpolymer complex as the dispersed droplets of the Eudragit S100 solution clashed with those of the PVA solution. Eudragit S100 / PVA complex droplets gradually solidified and hardened as ethanol and DCM spread from the internal process.

It was also observed that, over a relatively short period of time, Eudragit S100 and PVA aggregated and precipitated out in the ethanol-DCM mixture, resulting in the formation of a PVA / Eudragit S100 interpolymer complex, indicating that the hydrogen bonding strength between Eudragit S100 and PVA is very high. It was thought that this effective complexity could be used to prepare floating microspheres. In order to optimise the formulation, the effects of formulating variables such as drug concentration, solvent ratio of internal phase (ethanol / DCM), emulsifying concentration, and process variables such as stirring speed and temperature were studied. The results indicated that these variables affect the distribution of form , size and size, total drug loading efficiency and release of drugs in vitro. Therefore, these parameters were configured to prepare small microspheres with narrow size distribution, good drug loading performance, and good gastrointestinal pH drug release.

The drug concentration as a percentage of polymer weight as the formulation code NIZ1, NIZ2, NIZ3, NIZ4, NIZ5, NIZ6, NIZ7, NIZ8, NIZ9 was initial and optimal according to the matrix that encapsulated the drug. The optimum drug concentration was found to be 100 percent in relation to the weight of the polymer. The effect of polymer concentration on particle size and trapping efficiency has been found to affect. The polymer concentration was found to be optimal in the 200 mg of drug weight.

In formulation code NIZ7, the highest entrapment was found. The lower polymer concentration resulted in low entrapment efficiency and further decreased the entrapment efficiency from 77.27 percent to 72.27 percent by reaching the polymer concentration above 100 mg. The explanation for this may be that the increase in polymer concentration increases the density of the matrix and thus all drug moieties were encapsulated and thus the effectiveness of the trap was poor due to the increase in matrix density. On the basis of particle size and trapping ability of microspheres, the emulsifying agent concentration was optimised. In the case of an emulsifying concentration of 0.50 percent w / v, the particle size was significantly greater than NIZ7. The explanation behind this is that the emulsifying concentration of 0.50 percent w / v was not adequate to emulsify so that the particles were aggregated and resulted in an increase in particle size, although the efficiency of the trap was high in the NIZ7 formulation. The reason might be due to increase in particle size resulting increase in entrapment efficiency of drug into the increased matrix.

To achieve optimum particle size and percent drug trapping, stirring speed was optimised. In NIZ7S1, the stirring speed was 200 rpm and it resulted in larger particle size and low efficiency of trapping. The explanation may be that the rpm was low, the shear stress was low and therefore resulted in greater particle size relative to NIZ7S2, NIZ7S3 and NIZ7S4, while the drug trap was low in NIZ7S1, which may be due to a reduction in shear stress. This resulted in increase in leaching of drug from matrix cavity to external phase and thus entrapment efficiency was low. Therefore, NIZ7S3 was chosen as optimum for further study. NIZ7S2T2 37°C was found to be optimum as compared to NIZ7S2T1, NIZ7S2T3 and NIZ7S2T4 formulation code NIZ7S2T1 prepared at 25°C showed larger particle size and low entrapment efficiency than NIZ7S2T2. The particle size was higher in the NIZ7S2T1 case.

This may be due to lower preparation temperatures that have resulted in particle size aggregation. However, at all temperatures, the entrapment efficiency was roughly the same. The type and size of microspheres have been confirmed by surface and particle morphology (SEM). The particle size was found to be less than 200µm as shown in **Figure 3** and **4**. Similarly surface morphology was found be plain and spherical.

The floating tendency of microspheres was found by % buoyancy in which all formulations showed buoyancy more than 80%. The in-vitro drug release analysis, conducted at all pH levels, reported that floating microspheres resulted in continuous and sustained drug release in GIT fluids. More than 80% of the trapped medication was found to have been released within 24 hours. The microscopic analysis of the microspheres showed that the mean diameter of the complexed microspheres of Eudragit S100-PVA ranged from 121.24 μm to 143. On altering the concentration of all influences. Total drug loading efficiency varied from 65.12 to 78.34%. Thus, it may be concluded that the prepared microspheres were of spherical shape with good entrapment efficiency. The optimized formulation NIZ7S2T2 was used for further studies.

CONCLUSION

In the field of targeted drug delivery systems such as binding molecules (ligands) to the surface of the microspheres, which have the ability to recognise cell surface structures such as lectin, adhesion invasins, antibodies or sugars, which can give site-specific drug delivery, it is proposed that the work should be further developed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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