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DEVELOPMENT AND CHARACTERIZATION OF FLOATING NIZATIDINE MICROSPHERES

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ABATRACT

The purpose of this investigation is to develop and characterize floating Nizatidine microspheres. The Solvent Evaporation method was used to make Nizatidine floating microspheres. The preparations were optimized by using two level factorial design and three independent variables, which were the HPMC conc. (A), EC conc. (B) and the stirring time (C). Particle Size analysis, enncapsulation efficiency, SEM (scanning electron microscopy), zeta potential, buoyancy studies, and an *in vitro* drug release study were used to characterize the floating microspheres. average particle size of the stable floating microspheres was 476.5 m. The optimized batch's buoyancy and entrapment efficiency were found to be 83.70% and 88.5±15 % (w/w, respectively). Nizatidine floating microsphere preparations were formulated and found sustained drug release up to 24 hrs, resulting in increased bioavailability, patient compliance by decreasing dosing frequency, and enhanced gastric residence time. *In vitro* drug release revealed a controlled drug release with up to 90.13±1.26 % in 24 hours.

Keywords: Microsphere, SEM, TEM, encapsulation efficency, *in-vitro*

1. INTRODUCTION

Drugs are delivered to the circulatory system via oral controlled release systems. Even though these drug release systems can precisely and predictably control the release rate at which the pharmacological active drug is released for a long time-even over a number of days-they don't all the time work well if they pass through the drug absorption site before the loaded drug is released **[1]**. To create the best oral controlled release formulation, it is important to pay close attention to both modulating the rate of drug release in accordance with the system's predictions and extending the drug residence time of the formulation in order to achieve complete drug release in the gastrointestinal tract (stomach or small intestine) **[2,3,4]**. When developing per-oral sustained release dosage forms, one of the numerous physiological limitations that must be controlled is the gastrointestinal transit time. By the release of the drug continuously for a longer time before it comes the absorption site, GRDDs (gastro-retentive drug delivery systems) can enhance controlled drug delivery. With the assistance of floating systems, bioadhesion systems, system with high density, low density systems, floating ion exchange resins, and expandable systems, gastro-retention can be achieved **[5]**. Through controlled drug delivery, GRDDs also reduce the fluctuation occuring in plasma drug concentration. The floating type of drug delivery system is one promising method that has been used to enhance the time that oral dosage stays in to the stomach.

Acid-reflux disorders, active benign gastric ulcer, active duodenal ulcer and peptic ulcer disease are all treated with Nizatidine. Antihistamine Nizatidine blocks H2 receptors. Histamine is inhibited by Nizatidine in a competitive and reversible manner at H2 receptors, specifically those which are present in the gastric parietal cells. The drug Nizatidine decreases the production of acid in the stomach by reducing the histamine's action on the cells of stomach. The drug did not appear to have any anti androgenic effects **[6]**. After active duodenal ulcer healing, it has been observed that maintenance therapy by using lower dose of Nizatidine is very effective. The metabolism of Nizatidine by bacteria in the colon has implications for drug delivery and absorption. Therefore, increasing the

dosage form's gastric residence time at the absorption site is a logical way to increase the drug's therapeutic efficacy **[7]**.

1.1. MATERIAL AND METHODS

Bangalore Fine Chemicals supplied Nizatidine. Loba Chemie Pvt. provided HPMC and polymer ethyl cellulose. Limited, Mumbai Dichloromethane and ethanol came from CD H. New Delhi. SD Fine Chemicals supplied Tween 80.

1.2. METHODOLOGY

1.2.1. DRUG INTERACTION STUDIES

1.2.1.1. FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

A FTIR (Shimadzu) was utilized for structural analysis of the drug. A small amount of the drug Nizatidine was taken and scanned between 400 and 400 cm^{-1} **[8]**.

1.2.1.2. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC tracks the temperature-dependent heat effects of chemical reactions and phase transitions. The temperature-dependent difference in the flow of heat between the sample and a reference taken when temperature remains the same which is recorded in Differential Scanning Calorimetry (DSC). Both the sample and the reference temperature rise at the same rate **[9]**.

1.3. PREPARATION METHOD OF NIZATIDINE'S FLOATING MICROSPHERES

The Solvent Evaporation method was chosen for preparing floating type of microspheres containing Nizatidine. By altering the formulation's polymer concentration, various batches of Nizatidine Microspheres were made. At room temperature, weighed amounts of the drug and polymers (EC and HPMC) were stirred to dissolved in a mixture of Dichloromethane and ethanol (1:1 v/v). This solution is poured into 250 ml of distilled water which contains 0.1% Tween 80. To allow the volatile solvent to evaporate, the resulting emulsion was stirred at 300 revolutions per minute. After being filtered, the water-washed microspheres were dried overnight at room temperature **[10]**.

Table: 1. Formulation of Microspheres Batch Code Standard Order

Bar Code	Standard Order	A	B	C (min.)
F1	1	-(250)	-(100)	-(20)
F2	2	+(350)	-(100)	-(20)
F3	3	-(250)	+(200)	+(40)
F4	4	+(350)	+(200)	+(40)
F5	5	-(250)	-(100)	-(20)
F6	6	+(350)	-(100)	-(20)
F7	7	-(250)	+(200)	+(40)
F8	8	+(350)	+(200)	+(40)

HPMC conc. (A); Ethyl Cellulose; Stirring Time (C)

2. EVALUATION OF FLOATING MICROSPHERES

2.1. PARTICLE SIZE ANALYSIS

The dynamic light scattering method particle size analyzer (Anton Paar) was used to measure the size of the prepared floating microspheres. Deionized water was used to dilute the prepared formulations, and the average particle size was measured **[11]**.

2.2. ZETA POTENTIAL

The zeta potential is a measurment of charge present on the surface of dispersed particles in the relation to the dispersion medium. Anton Paar Zeta Sizer determined the Nizatidine's charge. Clear disposable zeta cells were used in the experiment, and water with a refractive index (RI) of -1.330 and a viscosity (cPs) of -0.88 was used as a dispersant. The temp. was taken 250^0 Celsius. The sample was observed three times to reduce error.

2.3. MORPHOLOGICAL EVALUATION BY FIELD EMISSION SCANNING ELECTRON MICROSCOPY (FE- SEM)

FESM was used for the examination of the morphology of a fractured or sectioned surface as well as the topography and texture of the surface. Due in large section to the simplicity of sample formulation and easy to operation, FE-SEM is probably the best method that can be used for the characterization of drug delivery systems. The (JEOL) scanning microscope was used for the SEM studies. On a brass stub for an electron microscope, dry floating microspheres were coated with an ion sputter. The stub was randomly scanned in order to take a picture of floating microspheres.

2.4. DRUG ENTRAPMENT EFFICIENCY

The precise amount of Nizatidine in the various gastro-retentive Floating Microspheres formulations was estimated by crushing the precisely weighed Microspheres (50 mg) with a pestle and mortar and transferring them into 50 ml of methanol. The entire system was kept for 24 hours before Whatmann filter paper was used to filter it. Using a UV-VIS spectrophotometer at a wavelength of 325.6 nm and a suitable blank, the clear supernatant liquid was taken for spectrophotometric determination of nizatidine content. Experiments were conducted in triplicate to maintain accuracy **[12]**. **Eq 1.** was used to calculate the drug loading capacity and average drug entrapment efficiency values.

$$\textit{Drug Entrapment Efficiency} = \frac{\textit{Actual drug content}}{\textit{Theoratical drug contet}} \times 100 \qquad \textbf{Eq.1.}$$

2.5. *IN-VITRO* BUOYANCY STUDIES (96)

The lag time of floating and total time of floating were used to calculate the *in-vitro* buoyancy. In a 100-milliliter container having 0.1N HCl at pH of 1.2, microspheres were placed. Prepared microspheres' floating lag time (FLT) was time taken for them to come to the surface and float, and their total floating time (TFT) on the dissolution medium was recorded, according to **Eq 2**.

$$\%\ \textit{Buoyancy} = \frac{Qf}{(Qf + Qs)} \times 100 \qquad Eq.2.$$

where the weights of the settled and floating microspheres are Qf and Qs. **[13].**

2.6. *IN-VITRO* DRUG RELEASE STUDY

The pattern of drug release by Solvent Evaporation Method-prepared microsphere formulations was the subject of an *in-vitro* release of drug study. The formulated microspheres were placed into the dialysis bag, which had previously been soaked in distilled water and washed several times. This was placed in 100 milliliters of 0.1 N HCL buffer solution (pH 1.2) and dissolved constantly on a magnetic stirrer. At regular intervals, the entire sample was taken out and the same values were replaced with buffer. After that, the samples underwent spectrophotometric analysis at wavelengths between 200 and 400 nm. **[13].**

3. DISCUSSION AND RESULTS

3.1. PREFORMULATION STUDIES

3.1.1. DESCRIPTION

The Nizatidine's powder was white, odorless, and amphorphous when received.

3.1.2. MELTING POINT DETERMINATION

The Nizatidine's melting point was determined was found between 130°C and 134°C, which is within the standard range of Nizatidine

3.1.3. SOLUBILITY ANALYSES

The sample which was received of Nizatidine found to be freely soluble in methanol, sparingly soluble in water of pH1.2 HCL buffer.

3.2. INDENTIFICATION OF DRUG

The characteristic functions of a substance can be identified through IR spectral analysis. FTIR spectra of sample drug were taken and compared with standard reference drug spectra from the literature in order to identify the sample. A fourier transform infrared

spectroscopy (FTIR) investigation was carried out on the sample of Nizatidine that was obtained. It is confirmed that the obtained sample is Nizatidine by comparing the peaks of the Nizatidine using fourier transform infrared spectroscopy (FTIR) to those of the standard.

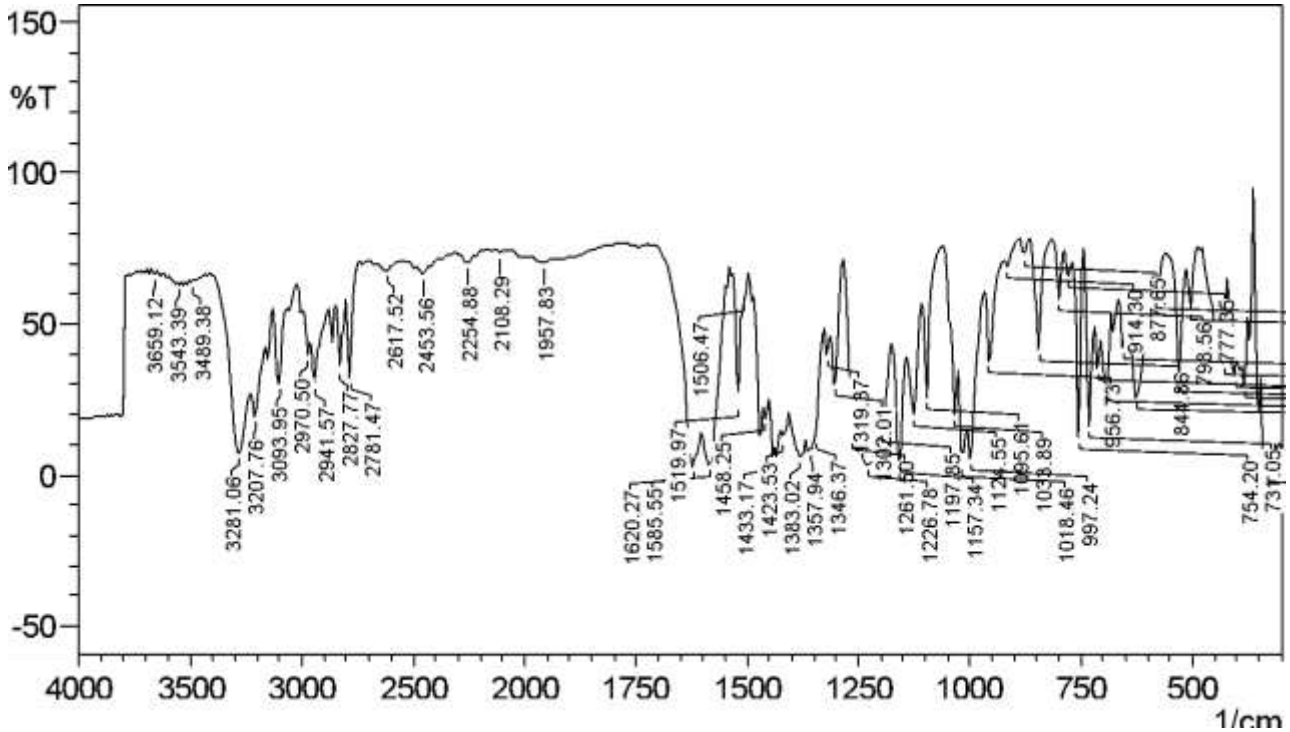

Fig. 1: FTIR spectrum of Nizatidine

3.3. **DIFFERENTIAL SCANNING CALORIMETRY (DSC)**

DSC is a thermal analysis technique that is frequently utilized in the pharmaceutical sector. The DSC thermogram of Nizatidine is shown in **Figure 2**, which shows a melting endothermic peak at 135.46^{0}C, indicating that the obtained Nizatidine is pure.

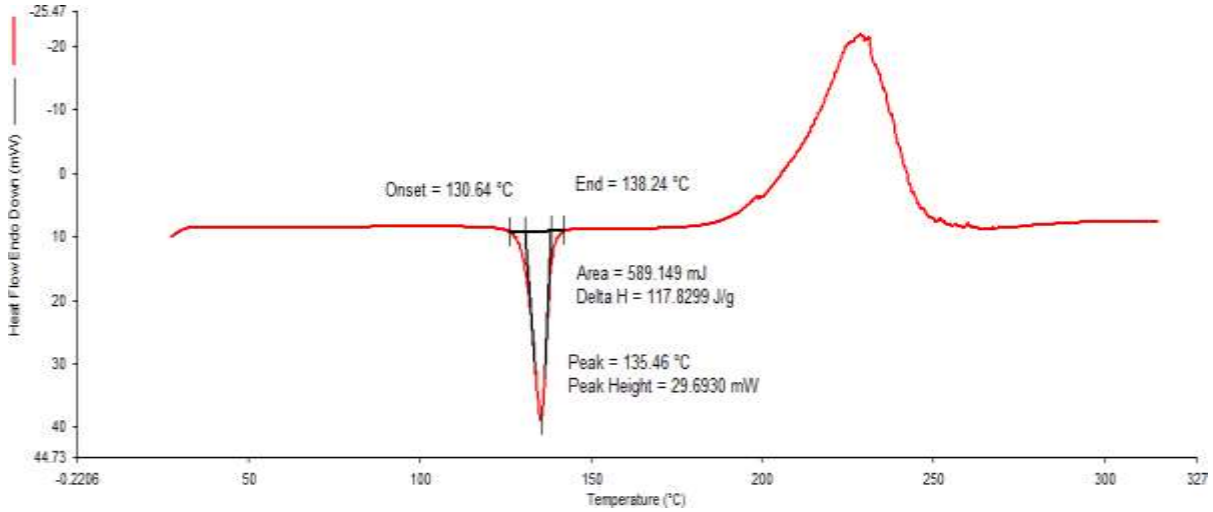

Fig. 2. Nizatidine's differential scanning calorimetry (DSC)

3.4. DRUG EXCIPIENT COMPATIBILITY STUDY

FT-IR analyses were carried out to detect the possible interactions between Nizatidine, and ethyl cellulose hydroxide propyl methylcellulose, Span80. In FT-IR spectra, the characteristic peaks of Nizatidine with the physical mixtures of EC, HPMC, Span 80 are shown below in **Figure 3.** It was discovered that the peaks of the absorption bands did not change, indicating that there were no interactions between Nizatidine and Excipients in the solid state.

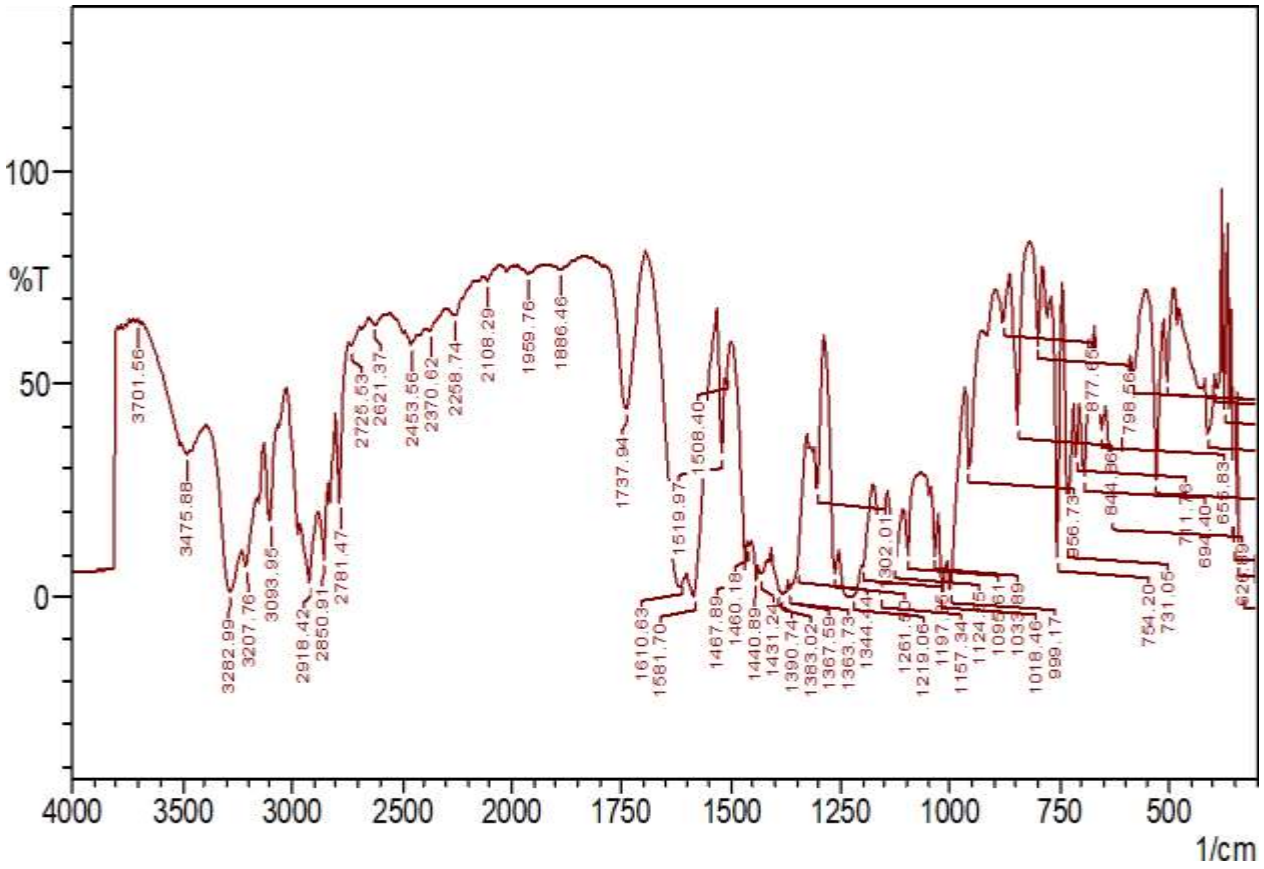

Fig.3. Peaks of Nizatidin + Ethyl Cellulose+ Hydroxy Propyl Methyl Cellulose+ Span 80 in FT-IR spectra

5. EVALUATION OF FLOATING MICROSPHERES

5.1. CHARACTERIZATION OF NIZATIDINE-LOADED FLOATING MICROSPHERES

5.5.1. PARTICLE SIZE

Anton Paar used a particle size analysis to determine that the average size of the particles was 476.5 µm, as depicted in **Figure. 4**.

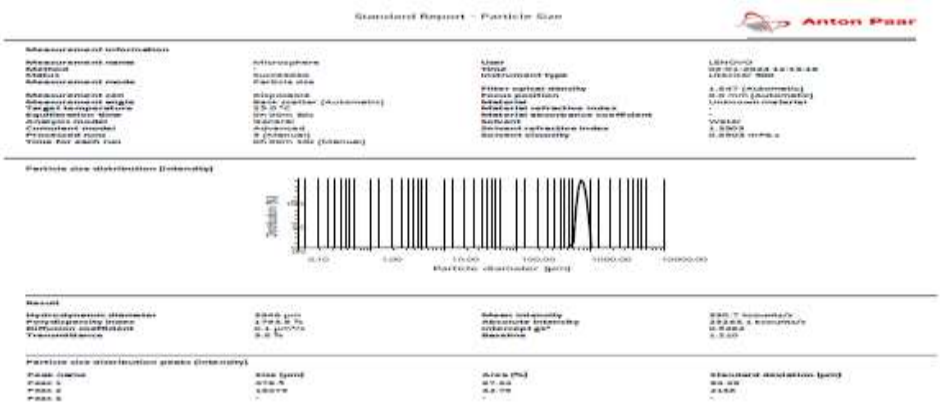

Fig.4. Floating Microspheres' Mean Particle Size

5.5.2. ZETA POTENTIAL

Anton Paar performed the zeta potential, and as depicted in **Figure 5**, the average zeta potential was -2.0 (mV).

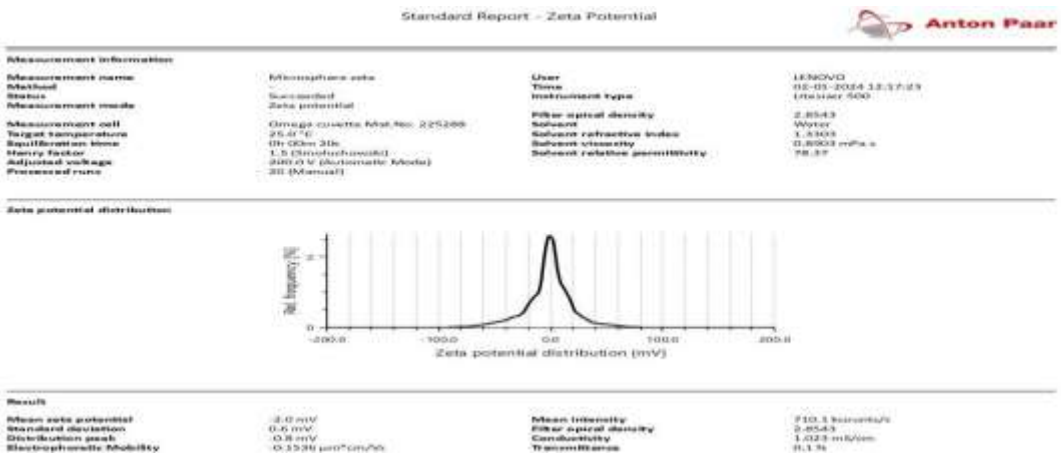

Fig.5. Zeta Potential Analysis

5.5.2. SURFACE AND SHAPE ANALYSIS BY FIELD EMISSION SCANNING ELECTRON MICROSCOPY (FE-SEM)

FE-SEM was used to examine microspheres' surface morphology, as depicted in **Figure 6**. Spherical, smooth, vesicular, and morphologically similar, microspheres were observed.

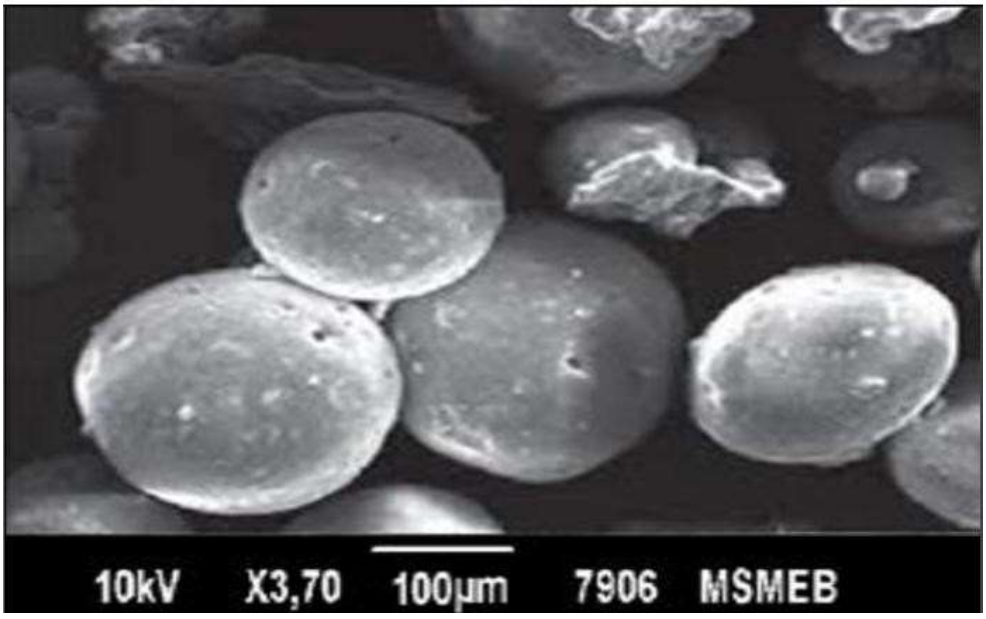

Fig. 6: FESEM of floating Nizatidine-loaded microspheres

5.5.4. OPTIMIZATION OF DIFFERENT PARAMETERS BY FULL FACTORIAL DESIGN

Table 2 presents a summary of the outcomes that were achieved following the implementation of Full Factorial Design (FFD) 2^3.

Table 2: Effects of a Various Factors on the Properties of Floating Microspheres

Batch Code	A: HPMC (mg)	B: EC (mg)	C: Stirring Time (mins)	Y1: Buoyancy (%)	Y2: Entrapment Efficiency (%w/w)
F1	250(-)	100(-)	20(-)	69.27	69.8 ± 0.51
F2	350(+)	100 (-)	20(-)	63.74	65.7 ± 0.5
F3	250(-)	200 (+)	20(-)	68.69	78.3 ± 0.28
F4	350(+)	200 (+)	20(-)	74.78	69.1 ± 0.4
F5	250(-)	100 (-)	40(+)	82.05	73.9 ± 0.7
F6	350(+)	100 (-)	40 (+)	79.44	75.4 ± 0.45
F7	**250(-)**	**200 (+)**	**40(+)**	**83.70**	**88.5 ± 0.15**
F8	350(+)	200 (+)	40(+)	80.98	85.2 ± 0.51

5.5.5. DRUG RELEASE KINETICS

In order to investigate the release mechanism of present drug delivery system, the data obtained from *in vitro* release of final optimized batch were fitted into equations for the zero- order, first-order, Higuchi release model and Korsmeyer-Peppas equation. On the basis of best fit with the highest correlation (R^2) value it is concluded that the optimized formulation of Microspheres follows the Higuchi model.

5.5.5.1. *IN-VITRO* DRUG RELEASE STUDIES

Dissolution study of drug with eight batches (F1-F8) is summarized in **Table number 3** and **Figure 7**.

Table 3: *In vitro* drug release data of Microspheres

Time	F1	F2	F3	F4	F5	F6	F7	F8
0.5	10.1± 0.5	15.78± 0.6	7.84± 0.5	6.18± 0.40	7.21± 0.72	8.09± 0.51	**11.84± 0.2**	8.24± 0.8
1	15.68±0. 7	25.31±0. 36	18.6± 0.7	12.98± 0.9	16.85± 0.8	14.32± 1.2	**19.23± 1.0**	17.68± 0.5
2	20.23±0 .40	31.23±0. 46	25.32±0 .41	23.18± 0.72	27.51± 0.16	22.54± 0.41	**29.68± 0.03**	29.74±0. 88
4	26.73±0. 48	34.93±0. 5	29.16±0 .5	34.08± 0.62	36.17± 0.55	33.65± 0.64	**39.42± 1.23**	37.70±0. 90

6	32.15±0.67	39.82±0.6	39.57±0.59	43.20±0.50	44.89±0.70	42.48±0.75	**48.96±0.16**	45.92±0.39
8	40.97±0.5	45.33±0.93	44.23±0.46	55.22±1.27	52.80±0.20	51.78±0.17	**58.62±0.69**	53.83±0.72
10	47.16±0.61	48.15±0.5	49.35±0.42	64.57±0.63	64.71±1.04	62.50±0.56	**68.19±0.12**	61.29±0.44
12	54.83±0.96	52.7±0.7	58.63±0.54	72.64±1.20	73.14±0.95	70.67±1.08	**78.85±0.23**	73.55±0.74
24	57.39±0.70	56.25±0.46	61.13±0.5	80.77±0.63	82.52±0.92	78.71±0.36	**90.13±1.26**	86.36±1.28

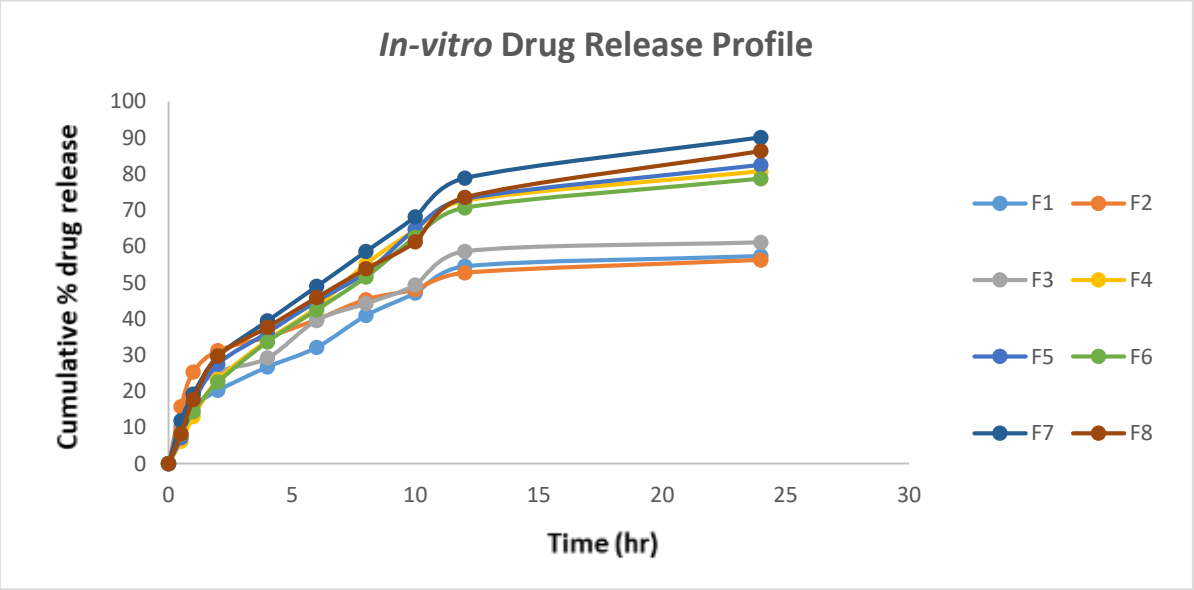

Fig.7: *In-Vitro* drug release profile of microsphere

6. CONCLUSION

In the end, it was concluded that the solvent evaporation method was successful in the formulations of Nizatidine's floating microspheres, which may improve the drug's bioavailability and control the formulation's release, though this has not yet been demonstrated. As a result, the floating microspheres of Nizatidine containing Polymer Ethyl Cellulose and HPMC had good buoyancy and showed promising results when effectively increasing the residence time.

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