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FORMULATION AND EVALUATION OF FLOATING GASTRORETENTIVE MICROSPHERES FOR GASTRIC REFLEX DISEASE

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Abstract:
A potentially effective method for boosting the bioavailability of medications with an absorption window in the upper small intestine is the use of drug delivery systems that float as soon as they come into contact with gastric fluids. However, instantaneous floating is only possible if the device's density is initially low. A significant issue with gastric delivery is achieving the best possible concentration at the site of action while maximizing the drug's bioavailability. Because of its short half-life, the traditional dosage form for peptic ulcer diseases has the drawback of requiring frequent dosing. Only a small portion of an instilled compound will typically reach the target site due to low solubility and low bioavailability between 1.5 and 3.0 hours. In order to improve gastric residence time and boost bioavailability, the current study set out to develop a gastroretentive mucoadhesive pulsatile formulation of nizatidinemucoadhesive microspheres for the treatment of peptic ulcers, primarily at the gastric part of the GIT. Flow properties determination, particle size measurement, shape and surface morphology, mucoadhesive properties, swelling study, percentage yield, drug entrapment efficiency, in-vitro drug release studies, and stability studies were some of the parameters used to evaluate these prepared systems. The goal of the current study was to create mucoadhesiveNizatidine microspheres with varying polysaccharide polymeric combinations in different ratios to improve mucoadhesion at the gastric mucosa, lengthen the gastric residence time, and ultimately increase the bioavailability.Drug entrapment of all formulation was found in range of 41.32 to 76.19% w/w and its efficiency slightly decreases with increasing the HPMC content.

Keywords: Delivery, Floating, Gastric, Mucoadhesive, Nizatidine.

1. Introduction

Even though various drug delivery systems are used for maximizing therapeutic index and reduction in the side effects of the drug, oral route remains the preferred, promising and effective route for the administration of therapeutic agents. Because, low cost of therapy, ease of administration, flexibility in formulation and handling leads to higher level of patient compliance. Approximately 50% of the drug delivery systems available in the market are oral drug delivery system [1].

The novel design of an oral controlled drug delivery system during last two decades, it has limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). This approach has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [2].

Drug delivery system that float immediately upon contact with gastric fluids present promising approach for increasing the bioavailability of drugs with absorption window in the upper small intestine. However, immediate floating can only be achieved if the density of the device is low at the very beginning. Devices with an initially high density (which decreases with time) first settle down in the stomach and thus undergo the risk of premature emptying. Inherent low density can, for example, be provided by the entrapment of air (e.g. hollow chambers) or by the (additional) incorporation of low density materials e.g. fatty substances or oils or foam powder.

The drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of time. The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body, so that the desired drug concentration can be achieved promptly and then maintained. The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery. Spatial placement relates to targeting drugs to specific organs, tissues, cells, or even subcellular compartments; whereas temporal delivery refers to controlling the rate of drug delivery to the target site [27-28].

2. MATERIAL AND METHODS

2.1. Analytical study

2.1.1. Determinatrionabsorption maxima (λ_{max}) by UV spectrophotometric analysis: Accurately weighed 100 mg of drug sample was soluble in 100 ml of simulated gastric fluid containing 0.1 N HCl gastric fluids in 50 ml volumetric flask. The mixture was sonicated with the help of sonication in bath sonicator for 20 min to get 1000 µg/ml solution. The prepared solution was named as **Stock-I**. Withdrawn 1 ml of prepared solution was again diluted up to 100 ml with same solvent separately with sonication for 20 min to obtain 10 µg / ml solution. The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer.

2.1.2. Determination of the calibration curve in simulated gastric fluid 0.1N HCl: Accurately weighed 100 mg of drug sample was soluble in 10 0 ml of simulated gastric fluid containing 0.1 N HCl gastric fluid in 50 ml volumetric flask. The mixture was sonicated with the help of sonication in bath sonicator for 20 min to get 1000 µg/ml solution. The prepared solution was named as **Stock-I**. From the above stock solution 10 ml was again diluted with 100 ml of dissolution medium to obtain 100 µg / ml solution. From above prepared solution was withdrawn as0.2 ml, 0.4 ml, 0.6 ml upto2.0 ml and diluted up to 10 ml with respective solvent in 10 ml volumetric flasks to get concentration of 2µg / ml, 4µg / ml, 6µg / ml, upto20 µg / ml respectively. The absorbance of each solution was measured separately at

237 nm for 0.1 N HCl.

2.2. Preformulation Studies

2.2.1. Organoleptic properties: The organoleptic characteristics of drug sample were determined by using sensory organs of body.

2.2.2. Microscopic examination: The drug sample nizatidine was studied as the nature / texture of the powder. A pinch of drug powder was spread on a glass slide and observed under phase contrast microscope and it was crystalline in nature.

2.2.3. Physical Characteristics: The density of drug powder was exactly weighed (M) and poured gently through a glass funnel into graduated cylinder and the volume was noted and bulk density was determined.

2.2.4. Particle size: The drug particle size was determined by using a microscope fitted with ocular micrometer and stage micrometer.

2.2.5. Flow properties: The flow properties of drug powder were distinguished in terms of carr's index, hausner's ratio and angle of repose. The Carr's index ((IC)) and Hausner's ratio (HR) of drug powders were calculating according to following equation:

Carr's Index (IC) = ρTapped - ρBulk / ρTapped

Hausner's ratio (HR) = ρTapped / ρBulk

The angle of repose (θ) was measured by fixed height method. This was calculated by following equation:

Angle of repose (θ) = tan-1 2 H / D

Where H is the surface area of the free standing height of the powder heap and D is diameter of heap that formed after powder flow from the glass funnel.

2.2.6. Solubility analysis: The solubility of drug was determined in various solvents (Water, 0.1 N HCl, phosphate buffer 6.8 and phosphate buffer 7.4). The excess amount of drug was added to 50 ml of solvent and mixed continuously till to morning at 37±0.5ºC. The solubility value of drug in different medium was determined by above UV-Visible spectrophotometric method.

2.2.7. Partition coefficient: The partition coefficient of drug was determined in n-octanol: 0.1 N HClmedium. The weighed amount 50 mg of drug was mixed into 25 ml each of an n-octanol and buffer phase in a separating funnel and shaken for upto 24h. All phases were separated and drug solubilized was determined by UV-Visible spectrophotometric method. The partition coefficient of drug was calculated using following equation.

Log P ($_{\text{n-oct}}$ / $_{\text{0.1 N HCl}}$) = Log (C $_{\text{n-Oct}}$ / C $_{\text{0.1 N HCl}}$) equilibrium

The partition coefficient of NizatidineHCl was found to be (0.3012).

2.2.8. Drug-excipient compatibility studies: The compatibility i.e. drug-excipient interaction studies are useful for dosage form design. For compatibility studies drug / excipients ratio are chosen and investigated based on the reasonable drug / excipients ratio in the final product.Thedrug sample mixture was determined by FTIR spectrums study for identification of drug excipients compatibility study.

2.3. Preparation of floating microsphere[65-66]: Floating microsphere containing atorvastatin was prepared using emulsion solvent diffusion technique. The drug to polymer ratio was vitiating to prepare the different formulations. The polymer content was a mixture of Eudragit RS 100 (ES 100), Hydroxypropylmethyl cellulose (HPMC) as shown in **Table 2.1**. The drug polymer mixture is dissolved in a mixtureof ethanol (8 ml) and dichloromethane (8 ml) was dropped in to 0.75% polyvinyl alcoholsolution (200 ml). The solution was stirred with a propeller-type agitator at 40°C temperature for 1 hour at 300 rpm. The formed floating microspheres were passed through sieve no # 12 and washed with water and dried at room temperature in a desiccator. The various batches of floating microsphere were prepared as follows.

. No.	ormulation Code	Drug (mg)	udragit RS 100 (mg)	PMC (mg)
1	NFM1	100	700	0
2	NFM2	100	600	100
3	NFM3	100	500	200
4	NFM4	100	400	300
5	NFM5	100	300	400
6	NFM6	100	200	500
7	NFM7	100	100	600
8	NFM8	100	0	700

Table 2.1: Formulation of the Floating Microspheres Prepared

2.4. Evaluation of floating microspheres

2.4.1 Particle size analysis: Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of floating microspheres were measured by using an optical microscope, and the mean particle size was calculated by measuring nearly 200 particles with the help of a calculated ocular micrometer.

2.4.2 Floating behaviour of Floating microsphere:100 mg of the floating microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% of tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant microspheres was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in a desiccator over night. The percentage of microspheres was calculated by the following equation:

$$\% \text{ floating microsphere} = \frac{\text{Weight of floating microsphere}}{\text{Initial weight of floating microsphere}} * 100$$

2.4.3 Drug Entrapment: The various formulations of the floating microspheres were subjected for drug content. 50 mg of floating microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatmannfilter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and diluted up to 10 m1 with 0.1 N HCI and the absorbance was measured at 237 nm against 0.1 N HCI as a blank. The percentage drug entrapment was calculated as follows.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} * 100$$

2.4.4. Percentage Yield: The prepared microspheres with a size range of 609-874 μm were collected and weighedfrom different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} * 100$$

2.4.5. Shape and Surface characterization: From the formulated batches of floating microspheres, formulations (F4) whichshowed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope.Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 30KV during scanning. Microphotographs were taken on different magnification and higher magnification (500X) was used for surface morphology.

2.4.6. In-vitro buoyancy percentage: Floating microspheres (250 mg) were spread over the surface of USP XXIV dissolution apparatus (type II) filled with 900 ml 0.1 N HCl containing 0.02 % Tween 80. The medium was agitated with paddle rotating at 100 rpm for 24 h. the floating and the settled portion of floating microspheres were recovered separately. The floating microspheres were dried and weighed. The buoyancy percentage was calculated as the ratio of the mass of the microspheres, that remained floating and the total mass of microspheres.

$$\% \text{ Buoyancy} = \frac{\text{Weight of sample} - \text{Weightof detached particles}}{\text{Weight of sample}} \times 100$$

2.4.7. *In-vitro* Release Studies:The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were suitably diluted with 0.1 NHCl and analyzed spectrophotometrically at 246 nm to determine the concentration of drug present in the dissolution medium. The dissolution studies were repeated using 0.1 NHClas dissolution medium[40].

2.4.8 Drug Release Kinetic Data Analysis: Several kinetic models have been proposed to describe the release characteristics of a drug from environment. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsmeyer-Peppa's equation (Plotted as Log cumulative percentage of drug released vs Log time).To study the release kinetics of drug from the floating microspheres the release data was fitted to these three equations[41-42].

Zero order equation: When a graph of the cumulative percentage of the drugreleased from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$Q_t = k_0.t$ …… (1)

Where $Q_{t\ is}$ the percentage of drug released at time t and k_0 is the release rate constant;

First order equation:

$\ln (100-Q_t) = \ln 100 - k_I.t$ …….. (2)

Where k_I is the release rate constant;

Higuchi's equation:

$Q_t = k_H.t^{1/2}$ …….. (3)

Where K_H is the Higuchi release rate constant

Korseymeyers-Peppas: The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsemeyer's equation.

$Q_t/Q_\infty = k_{KP}.t^n$

Where Q_t/ Q_∞ is the fraction of drug released at time t, k_{KP} a constant compromising thestructural and geometric characteristics of the device and n is the release exponent.

The slope of the linear curve gives the 'n' value. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism. When n = 1, the release rate is independent of time (typical zero order release /case II transport); n = 0.5 for Fickian release (diffusion/ case I transport); and when 0.5 < n < 1, anamalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when n > 1.0 super case II transport is apparent. 'n' is th e slope value of log M_t/M_∞ versus log time curve.

3. RESULT AND DISCUSSION

3.1. UV spectrophotometric study: The maximum absorption (λ-max) of drug sample nizatidine in 0.1 N HCl solutions were found to be at 237 nm.The calibration curves in 0.1 N HClwere prepared with drug solutions of known concentrations. The absorbance was measured and plotted against drug concentration. The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.99.

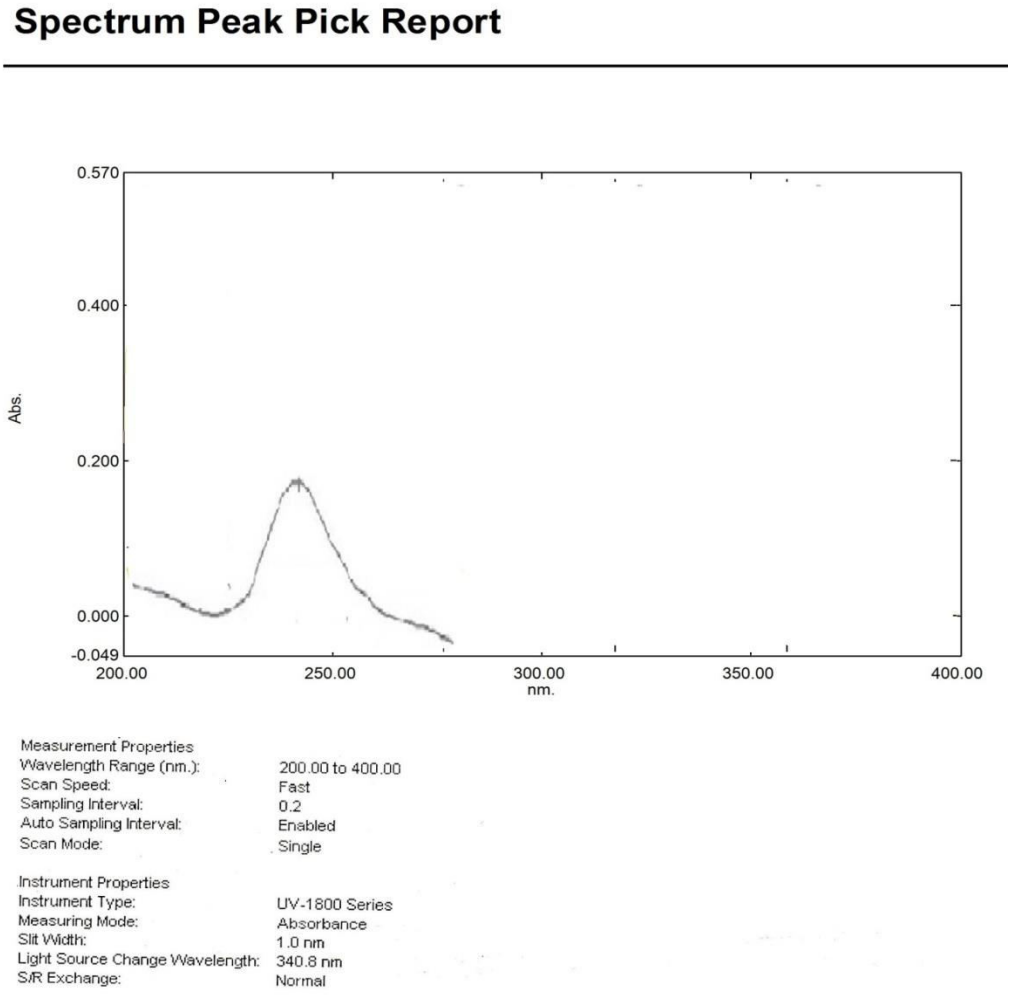


Figure 3.1: Maximum Absorption wavelength (λ-max) of drug in 0.1N HCl solution (10 µg/ml)

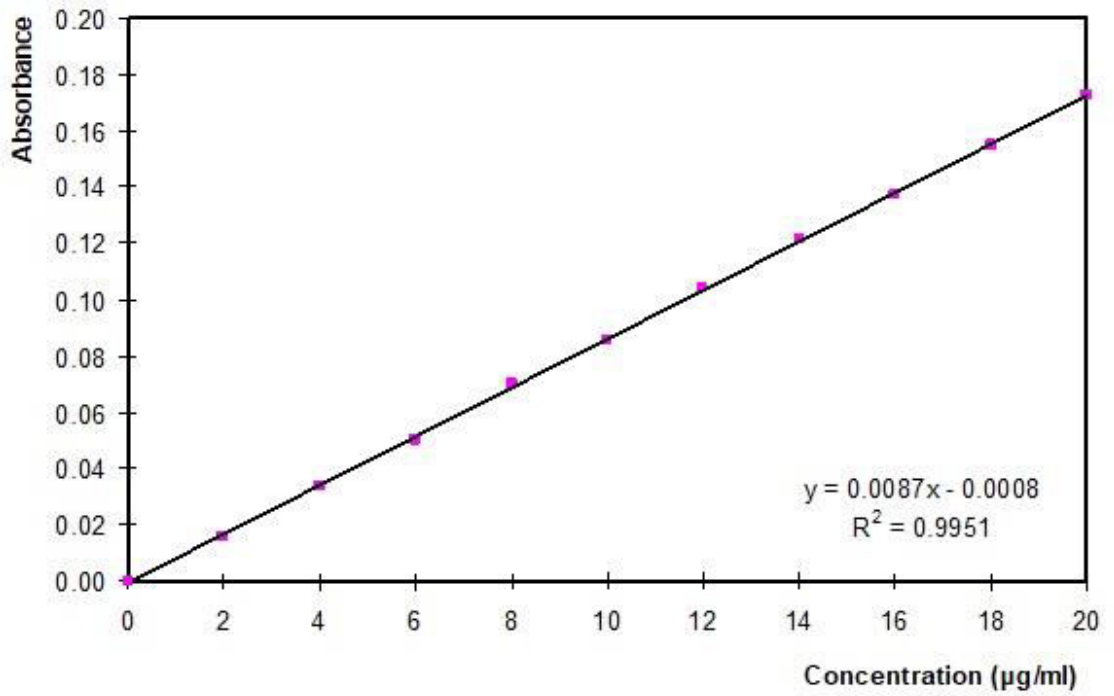


Figure 3.2: Standard curve of NizatidineHCl in 0.1N HCl solution (237 nm)

3.2. Preformulation Studies: Preformulation studies are the first step for the rational development of dosage forms of model drug substances. It is an investigation of physical and chemical properties of drug substances alone and in combination with excipients in research. The overall objective of preformulation studies is to produce information constructive to the formulator in development of stable and bioavailable dosage forms.

NizatidineHCl is Whitish yellow, slightly pungent odor, Slightly sweet taste and crystalline powder in nature. The tapped density was determined using tapped density apparatus. A bulk and tapped density of nizatidineHCl is to be 0.221 gm / cm^3 to 0.229 gm / cm^3.The particle size of drug powder was 93µm. The drug showed carr's index (%)12.28±0.011; hausner's ratio 1.13±0.011 and angle of repose θ 26.6±0.10, thus showed excellent flow properties. The solubility of drug was determined in various solvents (Water, 0.1 N HCl, Phosphate buffer pH 4.5, pH 6.8, pH 7.4) at room temperature (25±2 ºC). The solubility in water is 18.93(mg / ml); 0.1 N HCl 22.33 (mg / ml); Phosphate buffer pH 6.8 is 13.01(mg / ml), Phosphate buffer pH 4.5 is 11.23 mg / ml and in Phosphate buffer pH 7.4 is 17.94 mg / ml). The results indicated that the drug have maximum solubility water, and also soluble in 0.1 N HCl. The partition coefficient of NizatidineHCl was found to be (0.3012). In order to study the interaction between drug and excipients the samples were studied for FTIR detection and physical study. The change in the physical properties of drugs was studied, drug content of the mixtures was determined and FTIR studies were performed showed in **Figure 3.3**. The characteristic peaks of drug was observed at 3280, 3210, 3107, 3094, 2945, 2860, 2829, 2784, 1622, 1587, 1470, 1458, 1435, 1422, 1377 and 1359 cm^{-1}.

Properties	Drug
Color	Whitish
Odor	Slightly pungent odor
Taste	Slightly sweet

Table 3.1: Organoleptic characteristics of drug

Drug	Carr's index (%)a	ausner's ratio a	gle of repose θ a
Nizatidine	12.28±0.012	1.13±0.012	26.6±0.104

a; all values are in mean ± Standard deviation

Table 3.2: Flow properties of drug (n = 3)

Media	Solubility (mg / ml)
Water	18.93
0.1 N HCl	22.33
Phosphate buffer pH 4.5	13.01
Phosphate buffer pH 6.8	11.23
Phosphate buffer pH 7.4	17.94

Table 3.3: The solubility of drugat different pH medium (n=3)

++ Indicated no color change and no lump formation

ch No.	tial observation	40±2 ºC				25±2 ºC or Room temperature			
		week	week	week	week	week	week	week	week
S1	e yellow Crystals	++	++	++	++	++	++	++	++
S2	Yellow Crystals	++	++	++	++	++	++	++	++

Table 3.4: Results of physical observation

tch No.	al observation (%)	40±2 ºC		25±2 ºC or Room temperature	
		week (%)	week (%)	week (%)	week (%)
S1	99.99	98.81	96.87	99.34	97.17
S2	99.94	98.69	97.02	99.02	97.03

Table 3.5: Results of content determination

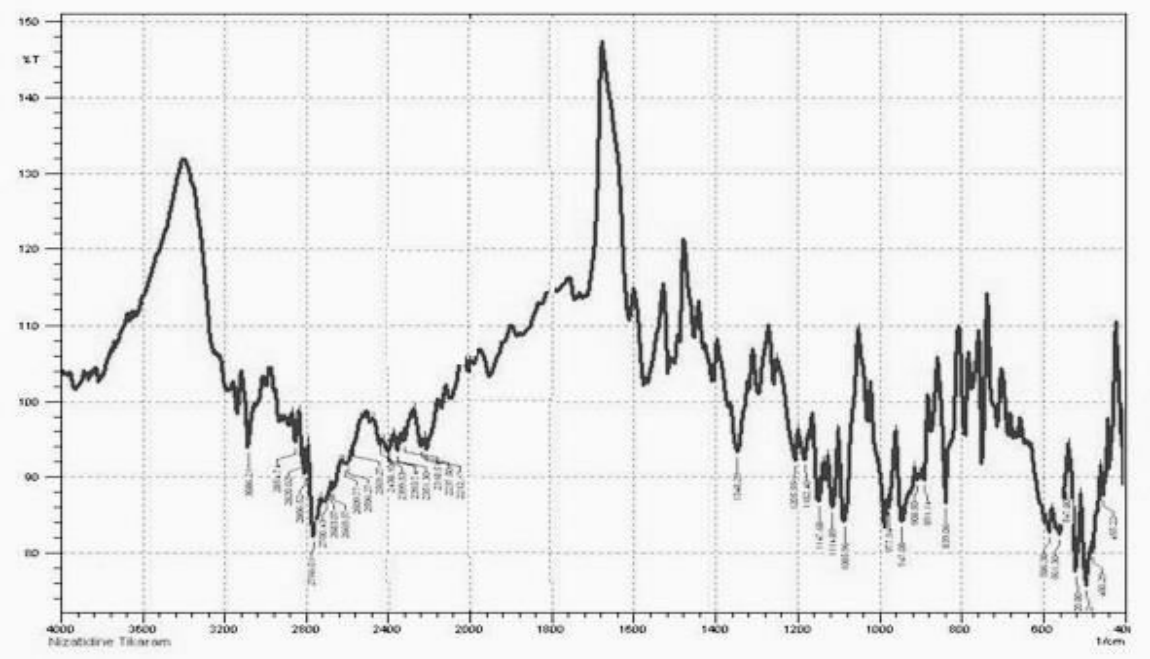


Figure 3.3: The FTIR Spectrum of sample of drug and all excipients

3.3. Evaluation of floating microspheres:

3.3.1. Particle size analysis: Particle size was determined by Optical microscopy method. It plays important role in floating ability and release of drug from floating microspheres. If size of floating microspheres is less than 500 µm release rate of drug will be high and floating ability will reduce, white floating microspheres ranging between 500 µm – 1000 µm, the floating ability will be more and release rate will be in sustained manner. The mean particle size of floating microsphere was in range 609. - 874 µm as shown in **Table 3.6.**

S. No.	Formulation code	Mean particle size (µm)
1	NFM1	874
2	NFM2	836
3	NFM3	794
4	NFM4	776
5	NFM5	752
6	NFM6	748
7	NFM7	632
8	NFM8	609

Table 3.6: Mean particle size of different batches of floating microsphere

3.3.2. Floating behaviour of floating microspheres: Floating microspheres were dispersed in 0.1 HCl containing Tween 20 (0.02 % w/v) to simulate gastric fluid. Floating ability of different formulation was found to be differed according to Eudragit and HPMC ratio. NFM1 - NFM4 formulations showed best floating ability (91.47 - 72.97 %) in 6 hours. NFM5 - NFM8 formulation showed less floating ability (66.12 - 36.18 %) as showed in **Table 3.7**. The floating ability of microsphere is decreased by increasing the HPMC ratio.

Formulation code	1 hour	2 hours	4 hours	6 hours
NFM1	98.41	97.08	93.23	91.47
NFM2	98.11	95.58	92.17	87.34
NFM3	98.54	95.64	85.34	78.45
NFM4	99.54	92.49	80.57	72.97
NFM5	98.72	91.95	73.49	66.12
NFM6	98.45	86.62	65.14	57.76
NFM7	88.34	75.41	56.04	45.09
NFM8	81.51	67.23	52.2	36.18

Table 3.7: Percentage Buoyancy for Different Formulation

3.3.3 Drug Entrapment: The drug entrapment efficacies of different formulations were in range of 41.14 - 74.19 % w/w as shown in **Table 3.8**. Drug entrapment efficacy slightly decrease with increase HPMC content and decreased Eudragit ratio in microballoons. This is due to the permeation characteristics of HPMC that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of floating microspheres.

Formulation code	Drug entrapment (% w/w)
NFM1	76.19
NFM2	70.59
NFM3	66.23
NFM4	64.76
NFM5	61.01
NFM6	57.38
NFM7	48.47
NFM8	41.32

Table 3.8: Drug entrapment for floating microspheres

3.3.4 Percentage Yield: Percentage yield of different formulation was determined by weighing the floating microspheres after drying. The percentage yield of different formulation was in range of 54.35 - 82.87% as shown in **Table 3.9**.

Formulation code	Percent Yield (%)
NFM1	82.87
NFM2	78.53
NFM3	76.47
NFM4	71.56
NFM5	69.31
NFM6	66.03
NFM7	56.84
NFM8	54.35

Table 3.9: Percentage Yield for floating microspheres

3.3.5. Flow properties: The truedensity value of hollow microsphere range from 0.475-0.975 gm/cm^3. The true densities of hollow microsphere were less than of gastric fluid (1.004 gm/cm^3) will suggest that it will exhibit good floating property.The tapped density ofdifferent floating microspheres was range from 0.232 - 0.415 gm/cm^3. The density values of floating microspheres were less than the density of gastric fluid (1.004 g/cm^3) thereby; it will have good buoyancy property in stomach. The percentage compressibility index range is 8.39-17.68 % and concluded the percentage compressibility value l less than 20 for all formulation suggested excellent flow property. The angle of repose of microballoons was determined by fixed funnel method. Anglerepose of floating microspheres was in range of 25°.39' - 37°.72'. Allformulation shown excellent flow ability as represented in term of angle of repose (<40°).

Formulation code	True density (gm/cm^3)	Tapped density (gm/cm^3)	% Compressibility index	Angle of Repose
NFM1	0.475	0.232	8.39	25°.39'
NFM2	0.518	0.256	9.77	27°.82'
NFM3	0.537	0.267	10.46	29°.68'
NFM4	0.689	0.279	11.63	29°.18'
NFM5	0.697	0.331	13.49	31°.39'
NFM6	0.716	0.364	12.67	33°.81'
NFM7	0.853	0.375	16.45	35°.54'
NFM8	0.975	0.415	17.68	37°.72'

Table 3.10: Flow properties for floating microspheres

3.3.6. Scanning Electronic Microscopy: Shape and surface characteristic of hollow microspheres examine by Scanning Electronic Microscopy analysis. Surface morphology of F4 formulation examine at to different magnification 40X and 200X, which illustrate the smooth surface of floating microballoons and small hollow cavity present in microsphere which is responsible for floating property.

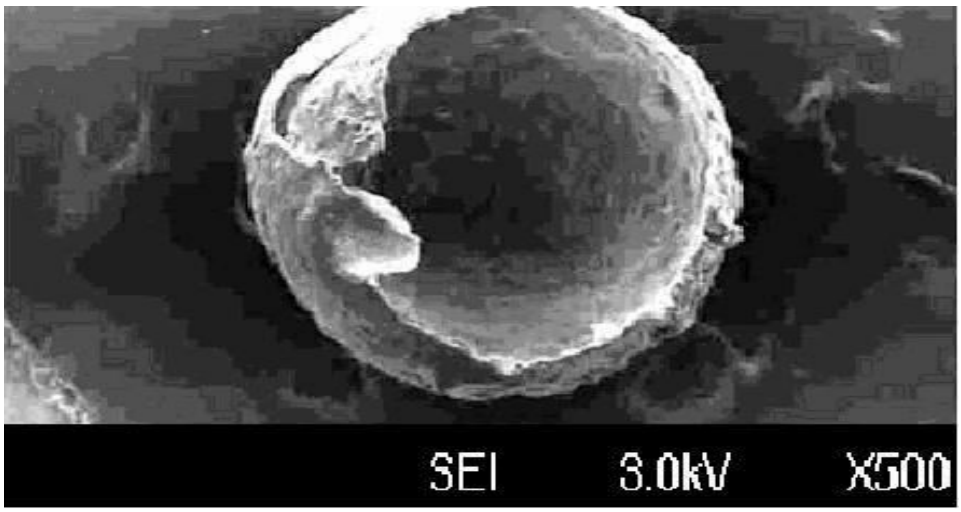
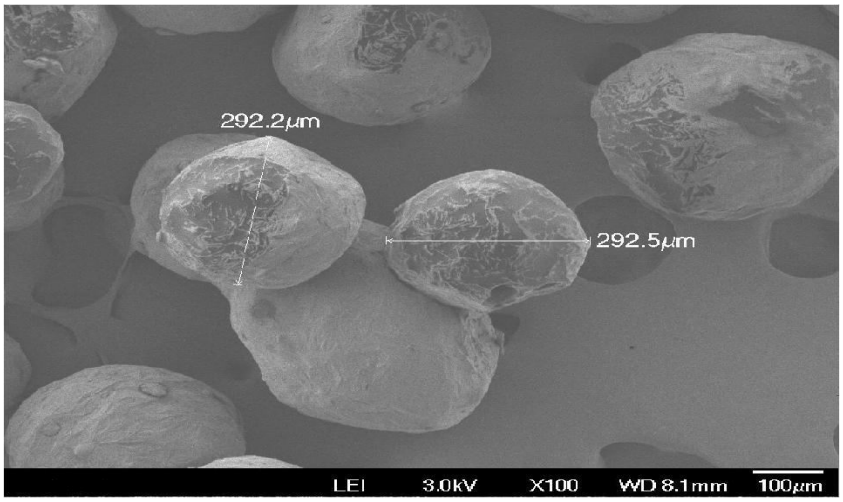


Figure 3.4: Cross Section



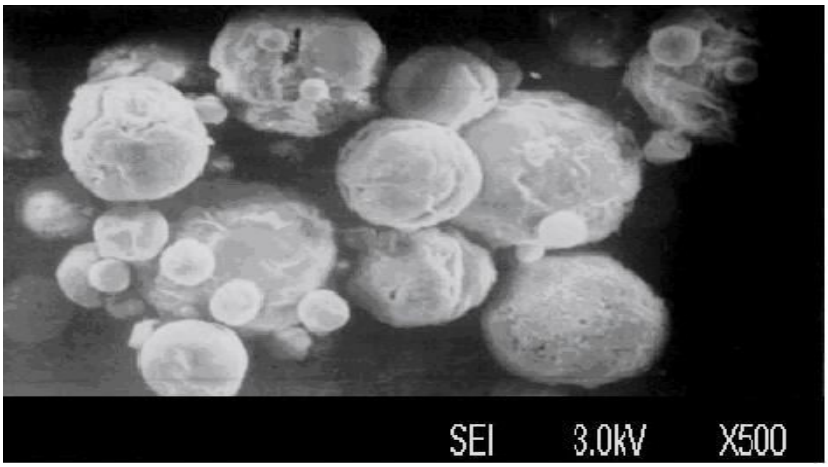


Figure 3.5: SEM Photographs of Formulation NFM4

3.3.7. *in-vitro* Drug release study:*In-vitro* drug release study of microballoons was evaluated in 0.1 N HCl andphosphate buffer pH 6.8. Eudragit RS100 which is present in all formulation has low permeability in acid medium. Since Eudragit is less soluble in acidic pH, release of drug in 0.1 N HCl was generally low compared to other medium. Release rate of NFM1, NFM2, NFM3formulations (43.791%, 56.311%, and 78.809% respectively).It was found to be slow and incomplete in dissolution medium. In order to increase the release rate of drug the ratio of Eudragit and HPMC is decreased and increased respectively. NFM5, NFM6, NFM7, NFM8 (94.681 %, 97.348 %, 96.295 %, 95.329 % respectively) formulations showed high release rate with less floating property. NFM4 formulation showed best appropriate balance between buoyancy and drug release rate.

Table 3.11: *In-Vitro* Drug Release Profile for Formulation NFM1in 0.1 N Hcl

S.No	Time (h)	Sq. root time	Log time	Abs 276 nm	Conc. (g/ml)	Conc.	% release	Cummulative % drug Release	log % drug release
1	0	0	0	0	0	0	0	0	0
2	0.5	0.71	0	0.006	0.269	0.242	2.421	2.421	0.384
3	1	1	0	0.009	0.436	0.393	3.926	3.939	0.594
4	2	1.41	0.301	0.015	0.705	0.635	6.347	6.369	0.803
5	3	1.73	0.477	0.021	0.96	0.864	8.641	8.676	0.937
6	4	2	0.602	0.023	1.07	0.963	9.632	9.68	0.984
7	5	2.24	0.699	0.03	1.405	1.264	12.643	12.697	1.102
8	6	2.45	0.778	0.031	1.457	1.311	13.11	13.18	1.118
9	7	2.65	0.845	0.037	1.725	1.553	15.527	15.6	1.191
10	8	2.83	0.903	0.041	1.918	1.726	17.261	17.347	1.237
11	9	3	0.954	0.047	2.172	1.955	19.552	19.648	1.291
12	10	3.16	1	0.052	2.418	2.176	21.764	21.873	1.338
13	11	3.32	1.041	0.054	2.52	2.268	22.682	22.803	1.356
14	12	3.46	1.079	0.058	2.703	2.433	24.328	24.454	1.386

S.No	Time (h)	Sq. root time	Log time	Abs 276 nm	Conc. (g/ml)	Conc.	% release	Cummulative % drug Release	log % drug release
1	0	0	0	0	0	0	0	0	0
2	0.5	0.71	0	0.006	0.269	0.242	2.421	2.421	0.384
3	1	1	0	0.009	0.436	0.393	3.926	3.939	0.594
4	2	1.41	0.301	0.015	0.705	0.635	6.347	6.369	0.803
5	3	1.73	0.477	0.021	0.96	0.864	8.641	8.676	0.937
6	4	2	0.602	0.023	1.07	0.963	9.632	9.68	0.984
7	5	2.24	0.699	0.03	1.405	1.264	12.643	12.697	1.102
8	6	2.45	0.778	0.031	1.457	1.311	13.11	13.18	1.118
9	7	2.65	0.845	0.037	1.725	1.553	15.527	15.6	1.191
10	8	2.83	0.903	0.041	1.918	1.726	17.261	17.347	1.237
11	9	3	0.954	0.047	2.172	1.955	19.552	19.648	1.291
12	10	3.16	1	0.052	2.418	2.176	21.764	21.873	1.338
13	11	3.32	1.041	0.054	2.52	2.268	22.682	22.803	1.356
14	12	3.46	1.079	0.058	2.703	2.433	24.328	24.454	1.386

Table 3.12: *In-Vitro* Drug Release Profile for Formulation NFM2in 0.1 N Hcl

S. No	Time (h)	Sq. root time	Log time	Abs 276 nm	Conc. (g/ml)	Conc.	% release	Cummulative % drug Release	log % drug release
1	0	0	0	0	0	0	0	0	0
2	0.5	0.71	0	0.007	0.348	0.313	3.131	3.131	0.496
3	1	1	0	0.015	0.696	0.626	6.261	6.278	0.797
4	2	1.41	0.301	0.019	0.901	0.811	8.107	8.142	0.909
5	3	1.73	0.477	0.028	1.305	1.175	11.749	11.794	1.07
6	4	2	0.602	0.034	1.596	1.437	14.366	14.431	1.157
7	5	2.24	0.699	0.039	1.797	1.617	16.169	16.249	1.209
8	6	2.45	0.778	0.046	2.154	1.939	19.385	19.475	1.287
9	7	2.65	0.845	0.054	2.491	2.242	22.419	22.527	1.351
10	8	2.83	0.903	0.058	2.687	2.418	24.184	24.309	1.384
11	9	3	0.954	0.061	2.837	2.553	25.531	25.665	1.407
12	10	3.16	1	0.066	3.052	2.747	26.867	27.609	1.439
13	11	3.32	1.041	0.07	3.244	2.92	29.197	29.35	1.465
14	12	3.46	1.079	0.072	3.354	3.019	30.185	30.347	1.48

Table 3.13: *In-Vitro* Drug Release Profile for Formulation NFM3in 0.1 N Hcl

S. No	Time (h)	Sq. root time	Log time	Abs 276 nm	Conc. (g/ml)	Conc.	% release	Cummulative % drug Release	log % drug release
1	0	0	0	0	0	0	0	0	0
2	0.5	0.71	0	0.012	0.537	0.484	4.836	4.836	0.684
3	1	1	0	0.023	1.071	0.964	9.641	9.668	0.984
4	2	1.41	0.301	0.029	1.345	1.21	12.103	12.157	1.083
5	3	1.73	0.477	0.036	1.686	1.517	15.173	15.24	1.181
6	4	2	0.602	0.046	2.151	1.936	19.359	19.443	1.287
7	5	2.24	0.699	0.053	2.465	2.218	22.183	22.291	1.346
8	6	2.45	0.778	0.066	3.072	2.765	27.648	27.771	1.442
9	7	2.65	0.845	0.072	3.355	3.019	30.194	30.348	1.48
10	8	2.83	0.903	0.079	3.681	3.313	33.131	33.299	1.52
11	9	3	0.954	0.087	4.064	3.658	36.58	36.764	1.563
12	10	3.16	1	0.097	4.496	4.047	40.468	40.671	1.607
13	11	3.32	1.041	0.106	4.95	4.455	44.552	44.777	1.649
14	12	3.46	1.079	0.112	5.195	4.675	46.753	47.001	1.67

Table 3.14: *In-Vitro* Drug Release Profile for Formulation NFM4in 0.1 N Hcl

S. No	Time (h)	Sq. root time	Log time	Abs 276 nm	Conc. (g/ml)	Conc.	% release	Cummulative % drug Release	log % drug release
1	0	0	0	0	0	0	0	0	0
2	0.5	0.71	0	0.007	0.345	0.31	3.103	3.103	0.492
3	1	1	0	0.013	0.582	0.524	5.24	5.257	0.719
4	2	1.41	0.301	0.017	0.794	0.714	7.142	7.171	0.854
5	3	1.73	0.477	0.026	1.205	1.085	10.849	10.889	1.035
6	4	2	0.602	0.032	1.492	1.343	13.429	13.489	1.128
7	5	2.24	0.699	0.039	1.814	1.633	16.326	16.401	1.213
8	6	2.45	0.778	0.044	2.035	1.832	18.318	18.409	1.263
9	7	2.65	0.845	0.054	2.499	2.249	22.493	22.595	1.352
10	8	2.83	0.903	0.064	2.983	2.685	26.851	26.976	1.429
11	9	3	0.954	0.073	3.397	3.057	30.569	30.718	1.485
12	10	3.16	1	0.08	3.702	3.332	33.316	33.486	1.523
13	11	3.32	1.041	0.084	3.908	3.517	35.173	35.358	1.546
14	12	3.46	1.079	0.09	4.188	3.769	37.693	37.888	1.576

Table 3.15: *In-Vitro* Drug Release Profile for Formulation NFM5in 0.1 N Hcl

S. No	Time (h)	Sq. root time	Log time	Abs 276 nm	Conc. (g/ml)	Conc.	% release	Cummulative % drug Release	log % drug release
1	0	0	0	0	0	0	0	0	0
2	0.5	0.71	0	0.015	0.685	0.616	6.163	6.163	0.79
3	1	1	0	0.032	1.485	1.337	13.367	13.401	1.126
4	2	1.41	0.301	0.045	2.081	1.873	18.725	18.799	1.272
5	3	1.73	0.477	0.054	2.495	2.245	22.452	22.556	1.351
6	4	2	0.602	0.062	2.869	2.582	25.819	25.944	1.412
7	5	2.24	0.699	0.07	3.245	2.921	29.208	29.351	1.466
8	6	2.45	0.778	0.079	3.682	3.314	33.139	33.301	1.52
9	7	2.65	0.845	0.09	4.183	3.765	37.648	37.832	1.576
10	8	2.83	0.903	0.098	4.552	4.097	40.97	41.179	1.612
11	9	3	0.954	0.109	5.068	4.561	45.613	45.841	1.659
12	10	3.16	1	0.115	5.369	4.832	48.319	48.572	1.684
13	11	3.32	1.041	0.125	5.808	5.227	52.268	52.536	1.718
14	12	3.46	1.079	0.132	6.133	5.52	55.195	55.485	1.742

Table 3.16: *In-Vitro* Drug Release Profile for Formulation NFM6in 0.1 N Hcl

Table 3.17: *In-Vitro* Drug Release Profile for Formulation NFM7in 0.1 N Hcl

S. No	Time (h)	Sq. root time	Log time	Abs 276 nm	Conc. (g/ml)	Conc.	% release	Cummulative % drug Release	log % drug release
1	0	0	0	0	0	0	0	0	0
2	0.5	0.71	0	0.017	0.805	0.725	7.249	7.249	0.86
3	1	1	0	0.029	1.36	1.224	12.244	12.284	1.088
4	2	1.41	0.301	0.043	2.019	1.817	18.167	18.235	1.259
5	3	1.73	0.477	0.055	2.569	2.312	23.123	23.224	1.364
6	4	2	0.602	0.065	3.019	2.717	27.173	27.301	1.434
7	5	2.24	0.699	0.077	3.595	3.235	32.354	32.505	1.51
8	6	2.45	0.778	0.088	4.102	3.692	36.916	37.096	1.567
9	7	2.65	0.845	0.099	4.587	4.129	41.285	41.49	1.616
10	8	2.83	0.903	0.11	5.133	4.619	46.193	46.422	1.665
11	9	3	0.954	0.12	5.583	5.025	50.248	50.505	1.701
12	10	3.16	1	0.132	6.143	5.528	55.283	55.562	1.743

13	11	3.32	1.041	0.139	6.476	5.828	58.283	58.59	1.766
14	12	3.46	1.079	0.147	6.858	6.172	61.723	62.047	1.79

S. No	**Time (h)**	**Sq. root time**	**Log time**	**Abs 276 nm**	**Conc. (g/ml)**	**Conc.**	**% release**	**Cummulative % drug Release**	**log % drug release**
1	0	0	0	0	0	0	0	0	0
2	0.5	0.71	0	0.018	0.85	0.765	7.648	7.648	0.884
3	1	1	0	0.032	1.498	1.348	13.479	13.521	1.13
4	2	1.41	0.301	0.046	2.152	1.937	19.371	19.446	1.287
5	3	1.73	0.477	0.059	2.731	2.458	24.579	24.687	1.391
6	4	2	0.602	0.07	3.263	2.937	29.37	29.507	1.468
7	5	2.24	0.699	0.085	3.953	3.558	35.581	35.744	1.551
8	6	2.45	0.778	0.099	4.626	4.163	41.631	41.829	1.619
9	7	2.65	0.845	0.113	5.242	4.717	47.174	46.805	1.674
10	8	2.83	0.903	0.125	5.835	5.251	52.513	52.775	1.72
11	9	3	0.954	0.136	6.345	5.71	57.103	57.395	1.757
12	10	3.16	1	0.146	6.796	6.116	61.162	61.479	1.786
13	11	3.32	1.041	0.157	7.306	6.576	65.758	66.098	1.818
14	12	3.46	1.079	0.163	7.591	6.832	68.319	68.684	1.835

Table 3.18: *In-Vitro* Drug Release Profile for Formulation NFM8in 0.1 N Hcl

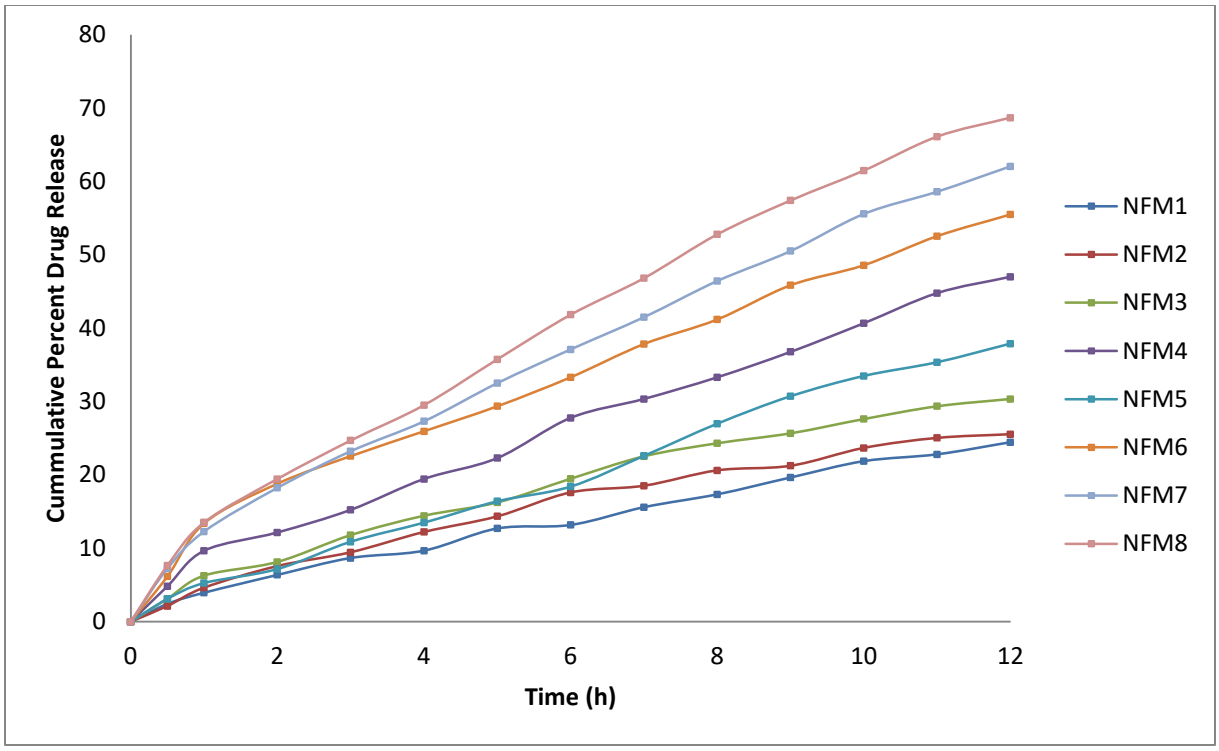


Figure 3.6: Zero-order kinetic plot data (in-vitro drug release)NFM1-NFM8

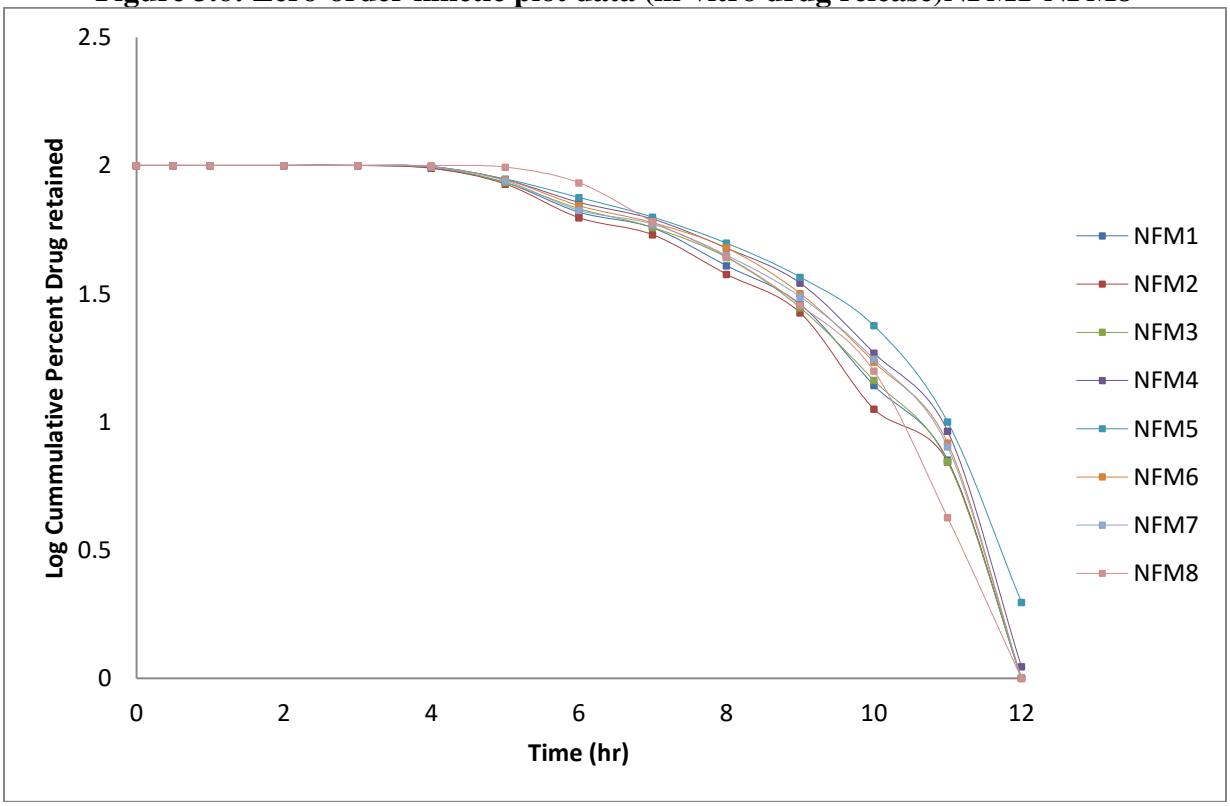


Figure 3.7: First-order kinetic plot data (in-vitro drug release)NFM1-NFM8

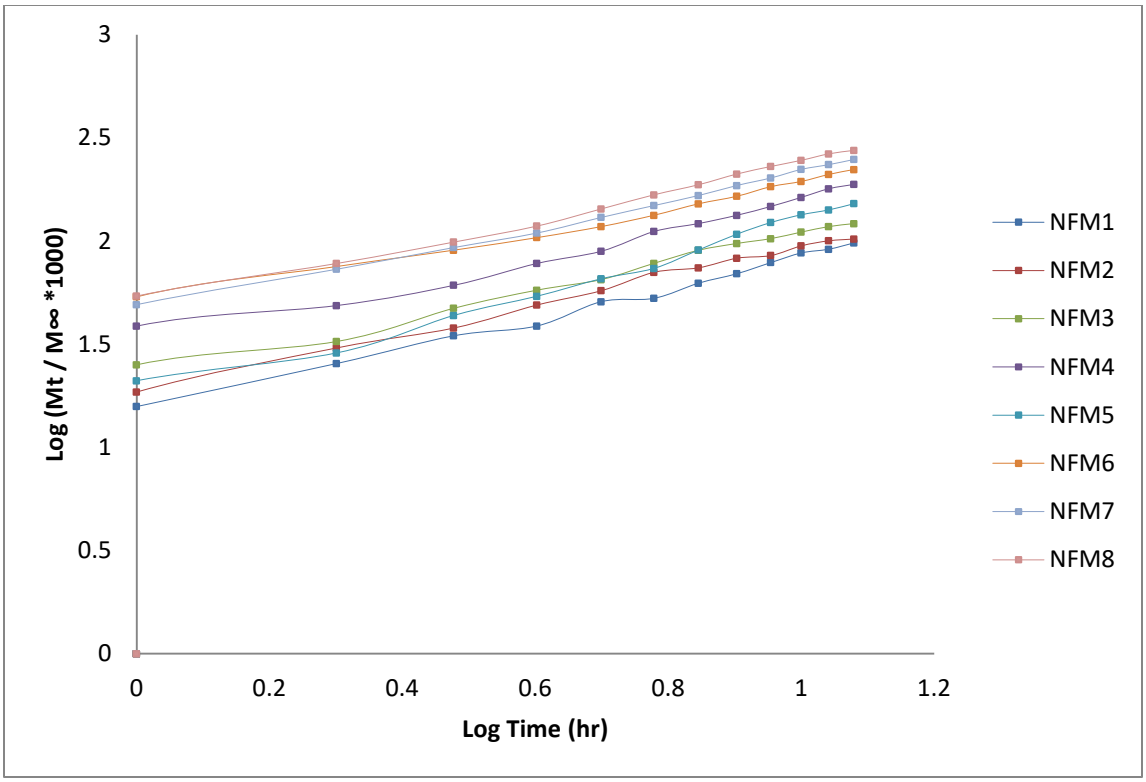


Figure 3.8: Korsmeyer-peppas kinetic plot data (in-vitro drug release)NFM1-NFM8

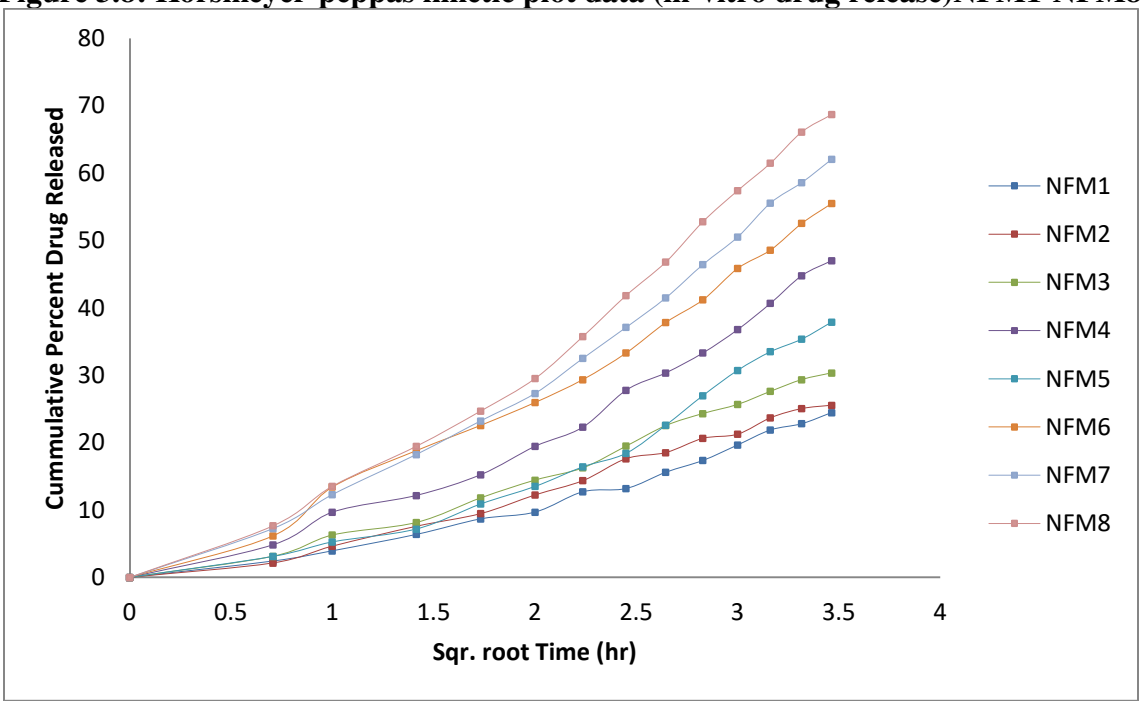


Figure 3.9: Higuchi kinetic plot data (in-vitro drug release)NFM1-NFM8

Release Kinetic: Drug release pattern was evaluated in 0.1 N HCl, release rate of NFM1-NFM8 formulations were found to be slow and incomplete in both dissolution medium. It was found that drug release rate increased by decreasing and increasing the ratio of Eudragit and the HPMC respectively. Kinetics and mechanism of drug release from all formulation was evaluated on the

basis of zero order, Higuchi equation and Peppas model. Correlation coefficient (r2) and slope value for each equation in the range of (r2=0.752-0.937 and n=0.568-0.785 was calculated. Zero order plots for all formulations were found to be linear in acidic and buffer solution of pH 6.8.Which indicates that it may follow zero order kinetics. Higuchi plot was found to be linear, which indicates diffusion may be the mechanism of drug release for each formulation. Peppas plot was found good linear, n > 0.5 for all formulations, indicated that drug release may follow anomalous diffusion (range=0.993-0.998). Zero order plots for NFM4 formulation was found to be linear in both dissolution medium, it considered as a best fit for drug release. That indicates it may follow zero order mechanism.

Formulation Code	Zero Order		Higuchi Equation		Peppas Equation	
	r^2	K_0	r^2	K_H	r^2	n
NFM1	0.951	1.81	0.989	6.946	0.937	0.756
NFM2	0.954	2.08	0.998	8.141	0.817	0.785
NFM3	0.963	2.86	0.994	11.04	0.872	0.769
NFM4	0.948	3.49	0.996	13.66	0.835	0.634
NFM5	0.932	4.03	0.993	16.09	0.752	0.664
NFM6	0.964	4.68	0.996	18.08	0.822	0.612
NFM7	0.956	5.81	0.998	22.42	0.833	0.581
NFM8	0.954	5.85	0.997	22.86	0.759	0.568

Table 3.19: Release Kinetics of Floating Microsphere in 0.1 N HCl

4. SUMMARY AND CONCLUSION

In the present study an attempt was made to develop a mucoadhesive microspheres of Nizatidine with variation in polysaccharide polymeric combination with different ratios to increase mucoadhesion at gastric mucosa, which increase the gastric residence time, thus increase the bioavailability.

The present study floating microspheres of nizatidine was prepared by emulsion–solvent diffusion method by using Eudragit RS100 and HPMC as a polymer. If size of microspheres is less than 500 µm release rate of drug will be high and floating ability will reduce, while floating microspheres ranging between 500µm - 1000µm, the floating ability will be more and release rate will be in sustained manner. Mean particle size range for all formulation wasvaried from 609 to 874 µm, due to change in drug and polymer ratio.

Drug entrapment of all formulation was found in range of 41.32 to 76.19% w/w and its efficiency slightly decreases with increasing the HPMC content. When distribution coefficient was high efficiency of drug entrapment into floating microspheres was elevated. This phenomenon was due to the lack of retention of drugs with low distribution coefficient in the emulsion droplet aqueous solution during the process, which led to reduced entrapment of drug into floating microspheres.True density, tapped density values for all formulation were less than that of gastricfluid (1.004gm/cm^3), suggested that it exhibit good buoyancy. Buoyancy of the microspheres decreased with increasing drug release. The floating ability pattern differed according to the formulation tested and medium used. NFM4 gave the best floating ability in all media, as evidenced by the percentage of particles floated at different time intervals. This can be mainly due to its low bulk density value obtained before and after tapping, respectively. All

formulations showed excellent flowability as represented in the terms of angle of repose(<40°), due to the polymer ratio. Angle of repose in range of (25^0.39'-37 ^{0}.72') all formulationshowed excellent flow ability (<40°).Shape of the hollow microsphere was found to be spherical by SEM study; small cavity were present on surface, which may be due to solvent evaporation during drying process, the microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation, which is responsible for floating property. Surface morphology of formulation NFM4 exhibited a smooth surface of the floating microspheres. Hence, it appears that there is no chemical interaction between the drug and polymers used in the preparation of floating microspheres. Ideal property of floating microspheresincludes high buoyancy and sufficient release of drug in pH 6.8. Percent drug release rate of NFM1, NFM2, NFM3 formulations (43.791%, 56.311%, 78.809 %) in 12 h, which is slow and incomplete drug release. In order to increases the percent drug release rate, the ratio of Eudragit and HPMC is decreased and increased respectively. NFM5, NFM6 formulations showed high release rate (94.681 %, 97.348 %) in 10 h and NFM7, NFM8 formulations showed high release rate (96.295 %, 95.329 %) in 12 h, with less buoyancy. NFM4 formulation showed appropriate balance between buoyancy and drug release rate of 99.12 % in 12 h, which is considered as a best formulation.

The in-vitro release data was applied to various kinetic models to predict the drug release kinetic mechanism. The zero order plots for all formulation were found linear in acidic and buffer medium 6.8. Result shows that, drug release rate may follow zero order mechanism. Higuchi and Peppas plot was found good linear, which indicates diffusion may be the mechanism of drug release and n>0.5, that indicated drug release may follow anomalous diffusion.

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