Fabrication and Characterization of Floating Microspheres of H₂ Receptor Antagonist

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Abstract In the current exploration a novel oral drug delivery system was developed utilizing the concepts of controlled release and mucoadhesiveness. Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive microspheres exhibited a prolonged residence time at the site of application or absorption and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved and/or better therapeutic performance of drugs. Nizatidine microspheres were equipped by emulsification-ionic gelation technique using mucoadhesive polymers such as Carbopol 934P, Hydroxypropyl methylcellulose (HPMC K15M) and Carboxy methyl cellulose with a rate controlling polymer sodium alginate. The arranged formulations were subjected to particle size and shape analysis, % drug entrapment efficiency, in vitro floatability, swelling rate, in vitro mucoadhesion test and in vitro drug release kinetics. The primed microspheres were discrete, spherical with a mean particle size in the range of 478±0.99μm to 640 ±2.67 μm. Entrapment efficiency was found to be in the range of 59.56±0.99 to 79.90± 1.78%. Formulations containing Carbopol 934P showed amplified in vitro mucoadhesion compared to formulations with Hydroxypropyl methylcellulose and CMC. In vitro drug release for all the formulations in 0.1N HCl was diffusion controlled progressively over a period of 12 h and followed First order kinetics. The *in vitro* drug release mechanism was nonfickian type controlled by swelling and relaxation of polymer. There was no noteworthy alteration in physico-chemical characteristics of the microspheres stored at diverse storage condition after 3 months of stability study. The fabricated system has the twofold advantages of being gastroretentive, to augment oral bioavailability and releasing drug in a controlled manner, to diminish the required frequency of administration thereby promoting patient compliance.

Keywords Gastroretentive drug delivery system, Nizatidine, HPMC, CMC, Non-fickian diffusion.

1. Introduction

The delivery of drug to a human body can be achieved through several routes like oral, transdermal, topical and parenteral administration. Among this the oral ingestion is the predominant and most preferable route for drug delivery [1]. More than 50% of drug deliveries available in the market are oral drug delivery system. Oral route is the most convenient and extensively used for drug administration [2]. The route has high patient acceptability, primarily due to ease of administration. Several approaches are being designed and developed for increasing the residence time of dosage form in the GIT such as: high density systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid [3], mucoadhesive systems, unfoldable, extendible, or swellable systems, super porous hydrogels systems [4], magnetic systems [5] etc. The other various floating preparations such as microballoons, granules, foam powders [6], capsules, tablets, in situ gelling systems [7] and laminated films are also attempted. Floating and bioadhesive drug delivery systems offer the advantages of

increased contact time with stomach mucosa, more effective absorption and bioavailability of drugs with absorption windows near proximal intestine and stomach, and low dosing frequencies [8]. Amongst the various floating and bioadhesive drug delivery approaches, mucoadhesive hollow microspheres is an attractive concept in which the dosage form adhere to the mucus layer, prolonging the drug residence time in the GI tract and release the loaded drug in a sustained manner.

In the present investigation, Nizatidine, a H_2 receptor antagonist, was used as a model drug. Nizatidine is a competitive inhibitor of gastric acid secretion and is used for the treatment of acid reflux disorders (GERD), peptic ulcer disease, active benign gastric ulcer and active duodenal ulcers. It is having an oral bioavailability of 70% with a very short biological half life of 1-2 hours [9]. It mainly acts by inhibiting acid production by reversibly competing with histamine. Oral administration of nizatidine in the form of fast dissolving films [10] and immediate release tablets [11] has already been reported. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger- Ellison syndrome and gastro esophageal reflux disease in a dose of 20 mg b.i.d. With the conventional dosage forms of nizatidine, the treatment becomes ineffective in some patients with reflux oesophagitis who are being treated with proton pump inhibitors and may continue to produce acid secretion throughout night and could be benefited by taking a sustained release formulation of H_2 receptor antagonist. It also finds applications in the field of local delivery of drug to the stomach and proximal small intestine and importantly in treating microorganisms [12, 13] which colonize the stomach because the major factors governing reduced luminal drug delivery are gastric acidity, gastric emptying and the epithelial mucus layer and therefore it helps to provide better availability of new products with new therapeutic possibilities and increased patient compliance. The intention of the study was to design mucoadhesive hollow microspheres containing nizatidine with gastroretentive properties, with an aspire to develop oral bioavailability of the drug, and the ability to endow with a sustained release profile.

2. Materials and Methods:

Nizatidine was obtained as a gift sample from Dr. Reddy's Labs Limited, Hyderabad. Sodium alginate, Hydroxypropyl methylcellulose and CMC were procured from S.D.Fine chemicals limited, Mumbai. Carbopol 934P was purchased from Coloron Ltd, Goa. All other reagents used were of analytical grade.

2.1 Preparation of floating microspheres:

Table 1: Composition of different formulation of nizatidine loaded microspheres

Fabrication code	API	Sodium alginate	HPMCK15M	Carbopol 934	CMC
FMH1	1.0	2.0	2.0	---	---
FMH2	1.0	2.0	2.5	---	---
FMH3	1.0	2.0	3.0	---	---
FMC1	1.0	2.0	---	2.0	---
FMC2	1.0	2.0	---	2.5	---
FMC3	1.0	2.0	---	3.0	---
FMCM1	1.0	2.0	---		2.0
FMCM2	1.0	2.0	---	---	2.5
FMCM3	1.0	2.0	---	---	3.0

Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and poly cationic ions like calcium to produce a hydrogel network of calcium alginate.

Sodium alginate and the mucoadhesive polymer were dissolved in same ration in 30 ml of distilled water to form a homogeneous solution. Nizatidine was added to the polymer solutionand mixed homogenously to get a smooth viscous dispersion. The consequential dispersion was then added in a thin stream to about 100 ml light liquid paraffin contained in a 500 ml beaker, stirring with 1000 rpm for 15 min to emulsify the added dispersion as fine droplets. Calcium chloride (10 % w/v) solution (40 ml) was then added slowly while stirring for ionic gelation reaction. Stirring was continued for one hour to complete the curing reaction and to generate spherical microspheres. The concoction was then centrifuged and the microspheres thus estranged were washed repetitively with ethanol.

The microspheres were dried at 450C for 4 h and kept in desiccators for one day. Diverse formulations were prepared using sodium alginate and the mucoadhesive polymers viz. Carbopol 934P, CMC and HPMC K15M, in the different ratios. While keeping the amount of active pharmaceutical ingredient constant. The opus of different formulations is represented in Table 1 [14].

3. Characterization of floating microspheres of nizatidine:
3.1 Determination of percentage yield:
The practical percentage yield was calculated from the weight of dried microspheres recovered from each batch in relation to the sum of the initial weight of starting materials. The percentage yield was calculated using the following equation: [15]

$$\% \text{ Yield} = \text{Weight of product/Total weight of excipients and drug} \times 100$$

3.2 Micromeritic properties of prepared microspheres: [16]
(a) Compressibility index:
It was measured by tapped density apparatus for 100 taps for which the difference should be not more than 2 %. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

$$\% \text{ Compressibility} = [(\text{Tapped density} - \text{Bulk density})/ \text{Tapped density}] \times 100$$

(b) Hausner'sratio:
It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of microspheres is called Hausner ratio.

$$\text{Hausner ratio} = \text{Tapped density} / \text{Bulk density}$$

(c) Angle of Repose
Angle of repose was determined using fixed funnel method. The blend was poured through funnel that can rise vertically until a maximum cone height (h) was obtained. Radius of the pile(r) was measured and angle of repose was calculated as follows.

$$\text{Ø}= h/r$$

Where, h= height of the pile, r= radius of the pile

3.3 Drug Entrapment Efficiency:
Microspheres equivalent to 100 mg of NIZ were crushed in a glass mortar and pestle and the powdered microspheres were suspended in 100 ml of 0.1N HCl. After 24 h, the solution was filtered, 1 ml of the filtrate was pipetted out and diluted to 25 ml and analyzed for the drug content using Elico SL- 159 UV Visible spectrophotometer at 314 nm [17]. The drug entrapment efficiency was calculated using the following equation:

$$\% \text{ Drug entrapment efficiency} = \text{Practical drug content/Theoretical drug content} \times 100$$

3.4 Particle size analysis:
Samples of the micro particles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 12.5μm. Nearly about 100 Micro particles sizes were calculated under 45 x magnifications. The average particle size was determined by using the Edmondson's equation: [18]

$$D_{mean} = nd/n$$

Where,
n – Number of microspheres observed and d – Mean size range

3.5 *In-vitro* mucoadhesion studies:
The mucoadhesive property of microspheres was evaluated by an *in vitro* adhesion testing method known as wash-off method. Freshly excised pieces of goat stomach mucous were mounted on to glass slides with cotton thread. About 20 microspheres were spread onto each prepared glass slide and immediately thereafter the slides were hung to USP tablet disintegration test apparatus, when the test apparatus was operated, the sample was subjected to slow up and down movement in simulated gastric fluid pH 1.2 at 37 °C contained in a 1-litre vessel of the apparatus. At

an interval of 1 hour up to 8 hours the machine is stopped and number of microspheres still adhering to mucosal surface was counted [19].

% Mucoadhesion = Number of microspheres adhered/Number of microspheres applied × 100

3.6 *In vitro* floating ability study:

Fifty milligrams of the floating microspheres were placed in 100 ml of the simulated gastric fluid (pH 2.0) containing 0.04% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 12 hours, the layer of buoyant microspheres was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. The percentage of floating microspheres was determined by the following formula [20-22].

% Buoyancy = $W_f/W_s + W_s X 100$

Where W_f and W_s are the weights of the floating and settled micro particles, respectively. The tests were carried out in triplicate.

3.7 *In-vitro* release kinetics:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, diffusion and Peppa's- Korseymeyers equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's- Korsemeyer equation [23-26].

3.8 Stability studies:

To assess long-term stability, the optimized microsphere formulation was put in hard gelatin capsules and sealed in aluminum packaging coated inside with polyethylene. Stability studies for the formulations were carried out as per ICH guidelines. Selected formulations were packed in amber coloured glass containers, closed with air tight closures and stored at, room temperature 25 ± 2 °C / 60% RH ± 5% RH and accelerated temperature 40 ± 2 °C / 75% RH ± 5% RH for three months using Programmable environmental test Chambers (ICH Q1A (R2), 2003). The formulations were then analyzed at the end of 30, 60 and 90 days for % drug entrapment efficiency, particle size, % *in vitro* floating and in vitro drug release studies [27-28].

4. Result and Discussion:

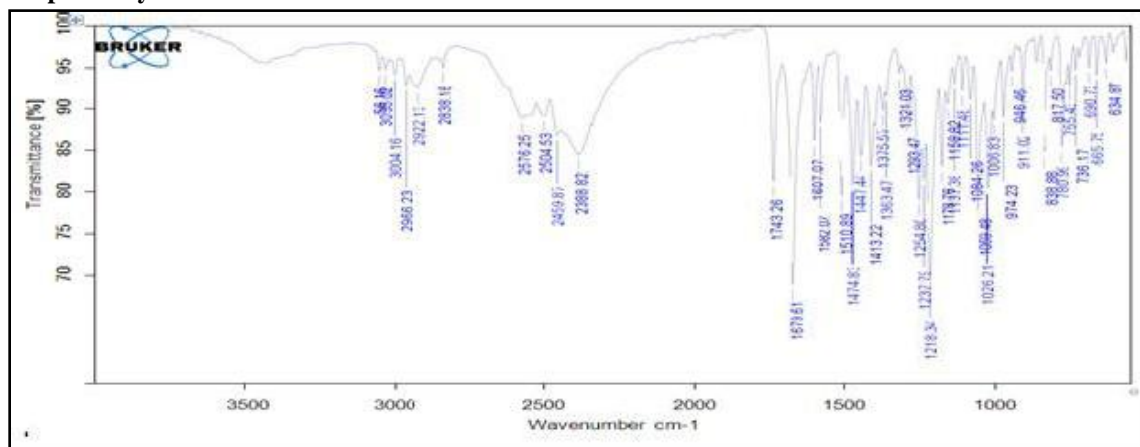### 4.1 Compatibility studies:

Figure 1: FT-IR spectra of active pharmaceutical ingredient

The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug. The results showed that the characteristic absorption peaks due to pure drug have appeared in the formulated microspheres, without any noteworthy change in their arrangement after triumphant encapsulation, indicating that there was no chemical interaction between pure drug and polymers.
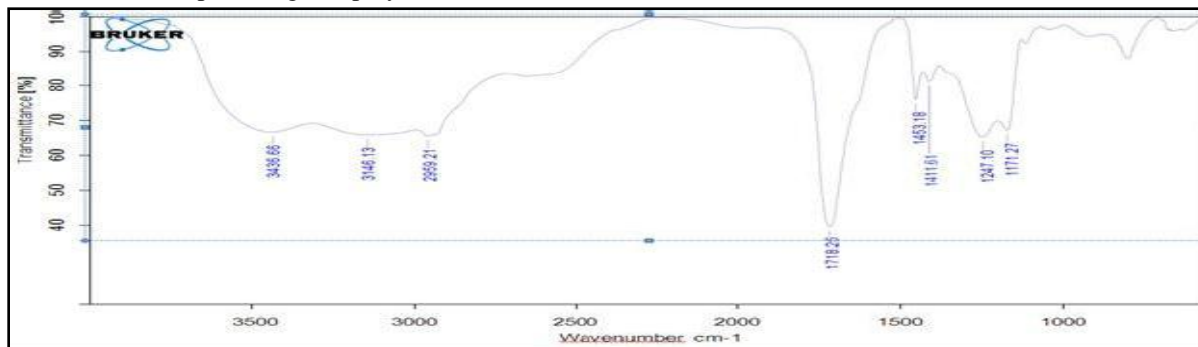
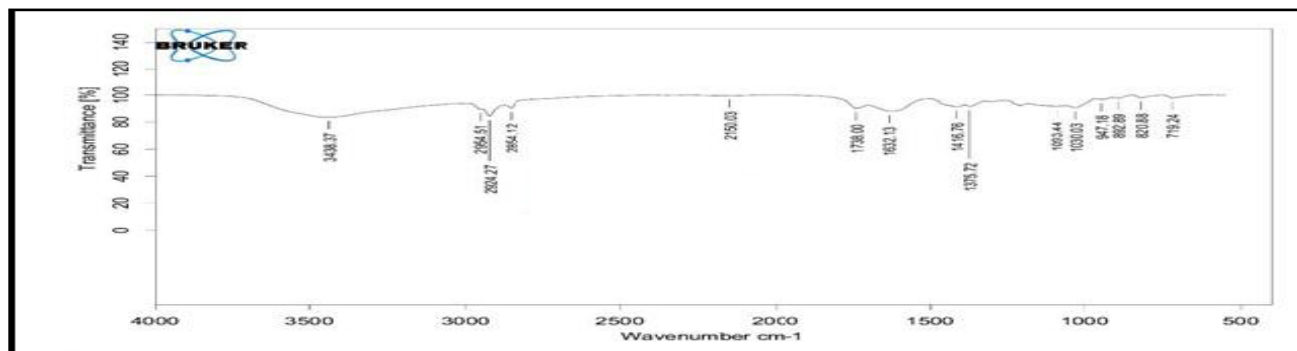

Figure 2: FT-IR spectra of carbopol 934

Figure 3: FT-IR spectra of sodium alginate

4.2 Micrometrics of prepared microspheres:
The micrometric studies Table 2 of prepared microspheres FMH1 to FMCM3 revealed that all the formulations possessed good flow properties with angle of repose values ranging from 14-22,compressibility index values from 3.01-16.57 and hausner's ratio values from 1.03 to 1.19.

4.3 Characterization of microspheres:
4.3.1 Percentage yield:
The percentage yield Table 2 & Figure 4 of optimized formulation FMC2 was found to be 94.35%.It was pragmatic that as the drug to polymer concentration augmented, the product yield also amplified. The small percentage yield in some formulations may be due to microcapsules lost during the washing process.
4.3.2 Particle size analysis:
The particle size Figure 5 of the microspheres enlarged with augmented polymer concentration. This is due to the swell in micro-viscosity, which in turn enhance the droplet size during addition of the polymeric dispersion to the harvesting medium. The SEM photographs of the optimized formulation FMC2 are mentioned in the Figure 4. The photographs discovered that the microspheres were discrete and spherical in shape with a rough outer surface morphology which could be because of the surface association of the drug with the polymer. SEM photographs in show porous surface which is indicated by the existence of minute pores on the surface of the hollow microspheres.
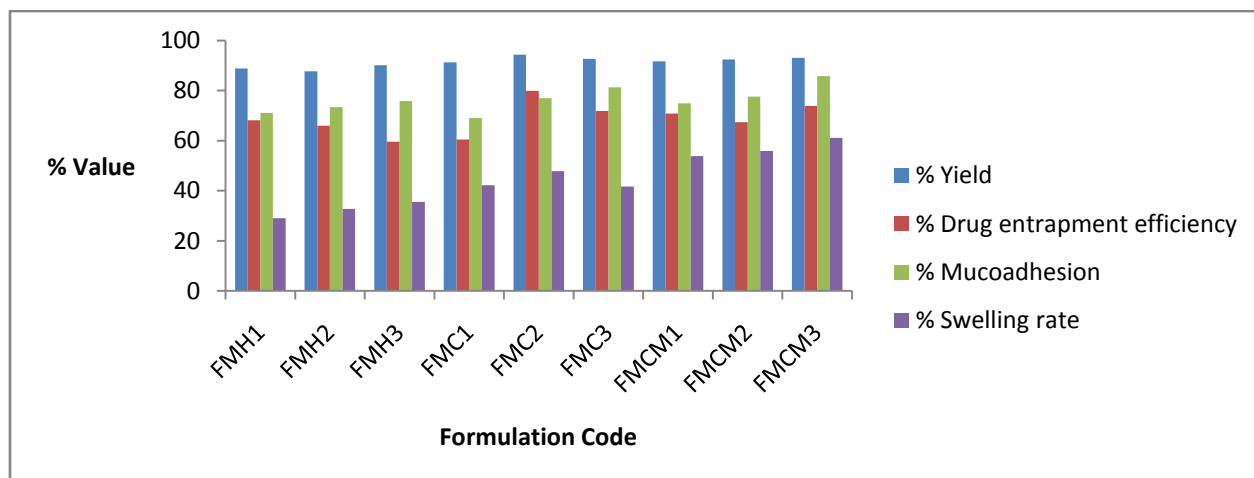
Figure 4: Showing % yield, % drug entrapment efficiency, % mucoadhesion and % swelling rate of formulated microspheres.
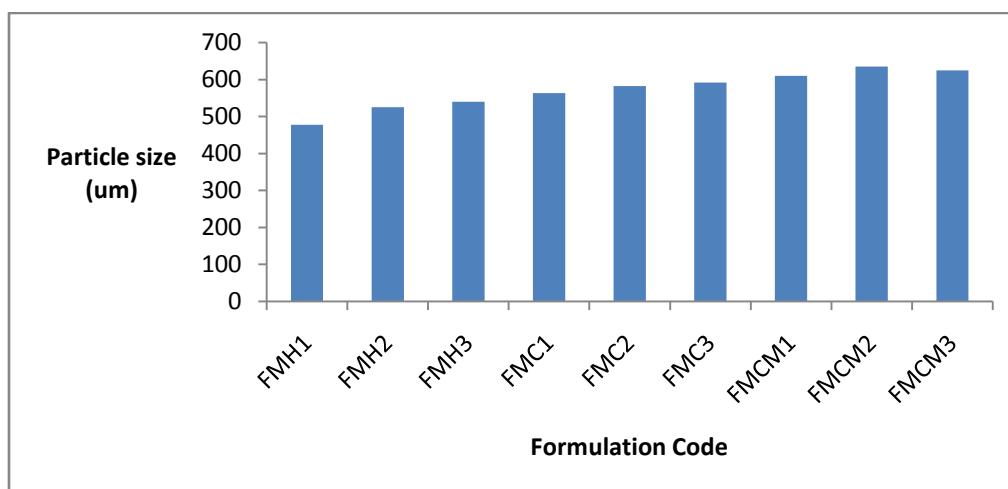

Figure 5: Average particle size of different formulated microspheres

4.3.3 Drug entrapment efficiency:

Formulation FMC2 showed best entrapment efficiency Table 2.The superior viscosity of the polymer solution at the chief polymer concentration would be expected to diminish the diffusion of the drug into the external phase which would outcome in high entrapment efficiency.

4.4.4 *In-vitro* mucoadhesion test:

Polymer swelling is known to correlate with mucoadhesion. The *in-vitro* mucoadhesion data is presented in Table 2 and figure 4. The degree of mucoadhesion amplified with raise in the mucoadhesive polymer concentration. The following stages have been occurred during mucoadhesion. Initially, an close contact between the mucus gel and the swelling of mucoadhesive polymer that is (wetting), which makes the polymer strands to relax which is followed by penetration of the mucoadhesive polymer into the mucus gelnetwork and finally the formation of secondary chemical bonds between the mucus and the mucoadhesive polymer. [29].

4.4.5 Swelling rate:

All formulations showed a degree of buoyancy instantaneously when placed in aqueous media of pH 1.2. The superior buoyancy behavior of the microspheres may be attributed to the hollow nature of the microspheres. The

swelling rate at pH 1.2 tells a plodding augment in swelling over time commencement as soon as the formulations were in contact with aqueous media.

Table 2: Characterization parameter of nizatidine loaded microspheres

| Formulation code*	% Yield	% Drug entrapment efficiency*	Particle size* (μm)	Swelling Rate* (%)	% Mucoadhesion*
FMH1	88.87	68.13±1.12	478±0.99	29.08±0.99	71.11±2.34
FMH2	87.76	65.98±2.11	525±1.78	32.78±2.56	73.45±1.21
FMH3	90.18	59.56±0.99	540±3.12	35.55±1.55	75.89±1.11
FMC1	91.27	60.45±2.45	563±1.56	42.19±1.99	69.09±2.56
FMC2	94.35	79.90±1.78	582±1.29	47.89±1.32	76.98±1.45
FMC3	92.67	71.89±2.33	592±2.78	41.65±1.26	81.34±3.23
FMCM1	91.69	70.85±1.08	610±2.33	53.89±2.18	74.89±1.09
FMCM2	92.44	67.44±0.55	635±1.23	55.91±0.05	77.65±0.87
FMCM3	93.11	73.89±1.45	640±2.67	61.09±1.11	85.78±0.53

4.4.6 *In-vitro* drug release studies:
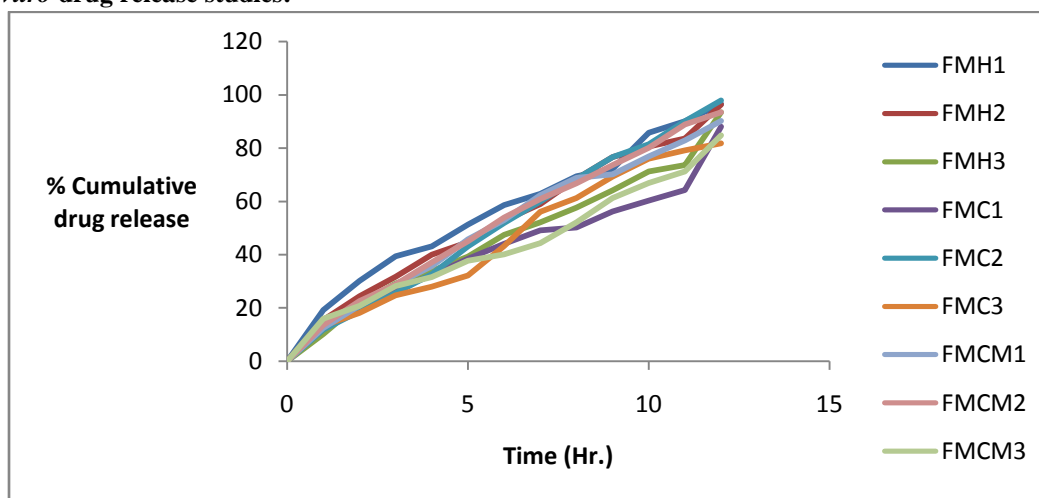
Figure 6: In-vitro drug release profile of nizatidine microspheres

These release studies Figure 6 shows the effect of environment of the body on the drug release pattern from the prepared microspheres. The *In-vitro* release was observed in HCl (pH 1.2) for 12 hrs. It was establish that the release rate from the all formulation was found to be different for the different polymer proportion used in the formulation. The FMC2 showed maximum release. It was found that there was decrease in drug release with increase in mucoadhesive polymer content. This could be attributed to the greater degree of swelling upon hydration with greater mucoadhesive polymer content in the microspheres which leads to increase in the diffusional path length that slows down drug release.
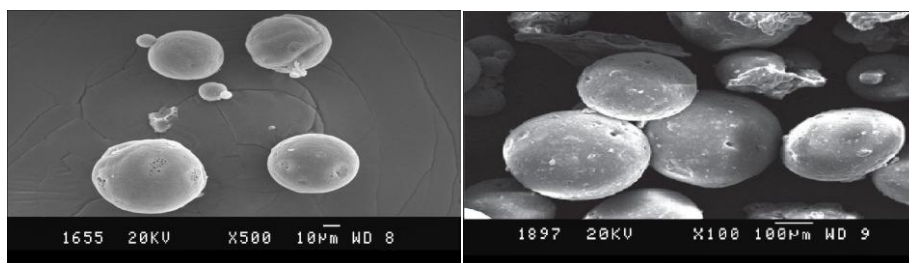
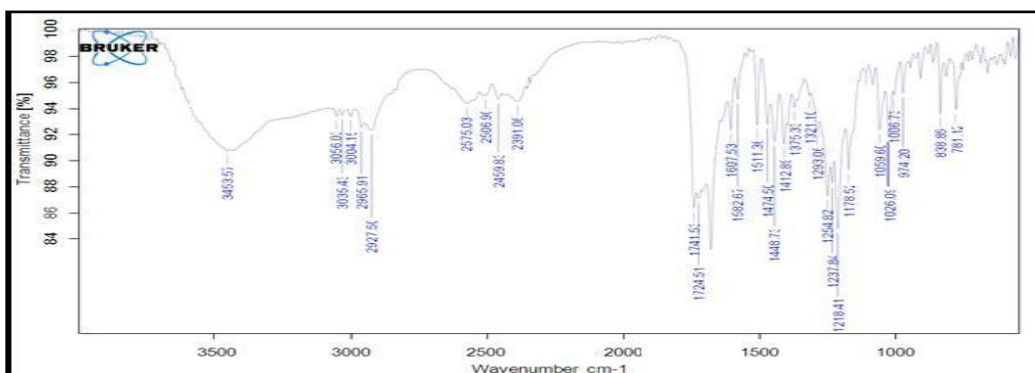*Figure 7: Scanning Electron microphotograph of optimized microsphere formulation*

Figure 8: FT-IR spectra of optimized formulation (FMC2)

4.4.7 *In-vitro* drug release kinetics:

From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer -Peppas model along with non- Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion. The drug release data was subjected to kinetic analysis for zero order, first order, Higuchi matrix, Hixon-Crowell and Korsmeyer-Peppas kinetics. The regression values obtained indicated that the drug release pattern from the formulated microspheres was closer to first order kinetics than zero order. This could probably be due to the fact that mucoadhesive microspheres are adhesive micro matrix systems, which consists of drug and mucoadhesive polymers. In this system, the drug is homogenously dispersed throughout the polymer matrix which acts as rate controlling element and release of drug is thus controlled by its diffusion throughout the rate controlling polymer matrix. Since the R values of First order kinetics is closer to 1, the drug release follows first order kinetics. The regression values (R) for all formulations are given in Table 3.

Table 3: Release kinetics of diverse batches of nizatidne loaded microspheres (R^2 Coefficient of regression)

Formulation code	Release models			
	Zero order	**First order**	**Higuchi matrix**	**Koresmeyer-peppas**
FMH1	0.971	0.968	0.955	0.929
FMH2	0.964	0.926	0.971	0.977
FMH3	0.959	0.939	0.988	0.972
FMC1	0.946	0.978	0.963	0.969
FMC2	0.987	0.989	0.978	0.986
FMC3	0.981	0.982	0.975	0.970
FMCM1	0.966	0.945	0.952	0.954
FMCM2	0.987	0.976	0.949	0.956
FMCM3	0.956	0.966	0.937	0.049

4.4.8 Stability studies:

The stability data displayed in Table 4 showed that there was no alteration in the appearance of the microspheres indicating that the formulations were unwavering at diverse conditions of storage. The stability study was performed for the prepared formulation as per the ICH guidelines and it showed that the formulations FMC2 were stable, with no physical transformation and also there was no noteworthy diminution in drug content when compared to the initial. Thus, we may recapitulate that, the drug does not undergo deprivation on storage.

Table 4: Stability studies of FMC2 after 3 months

Evaluation parameter	40 ± 2 °C / 75 ± 5% RH	25 ± 2 °C / 60 ± 5% RH
% Drug entrapment efficiency*	85.2±1.28	83.4±2.51
Particle size*	562±1.11	571.89±2.34
In-vitro floating (%)	67.98	69.91
In-vitro drug release (%)*	92.31±0.91	89.16±1.99

*Data are expressed as mean ±SD, n = 3

5. Conclusion:

We can recapitulate that the microspheres prepared polymer sodium alginate, carbopol and HPMC K100 have a noteworthy effect on the mucoadhesion, drug entrapment efficiency and drug release. carbopol is hydrophilic polymer has superior entrapment efficiency and good mucoadhesion but it releases the drug instantly therefore HPMC K100 was used to control the release rate as well as the other factors to match the recognition criteria. Sodium alginate offers stiffness to microspheres. The microspheres demonstrated good buoyancy and bioadhesion properties. In conclusion, our study demonstrates clearly that the synergic drug delivery system combining hollow structure with bioadhesive properties could increase drug retention time in the gastric chamber to get better the treatment of gastric disease. This new system could play a significant task in pharmaceutical drug delivery for gastric therapeutics.

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