INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.8 | Issue 4 | Oct - Dec-2019
Journal Home page: www.ijpar.com

Research article ***Open Access***

Formulation development and in vitroevaluation of nizatidine microspheres

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ABSTRACT

Emulsion cross linking method can be successfully employed to fabricate Nizatidine microspheres than Ionotropic gelation method. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of polymer, uneasy in dropping through syringe , air pollution, toxicity and difficult to remove traces during filtration .FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymer used. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range 540µm to 644µm.Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The in-vitro mucoadhesive study demonstrated that microspheres of Nizatidine using chitosan as polymer and glutaraldehyde as cross linking agent adhered to the mucus to a greater extent than sodium alginate along with Carbopol934.The invitro drug release decreased with increase in the polymer and copolymer concentration.

Keywords: Tablet Dosage Form, FTIR, Nizatidine

INTRODUCTION

The oral route for drug delivery is the most popular, desirable, and most preferred method for administrating therapeutically agents for systemic effects because it is natural, convenient, and cost effective to manufacturing process. Conventional drug therapy require periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability.

For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges.Some drugs also possess solubility problems.In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in Figure1.1

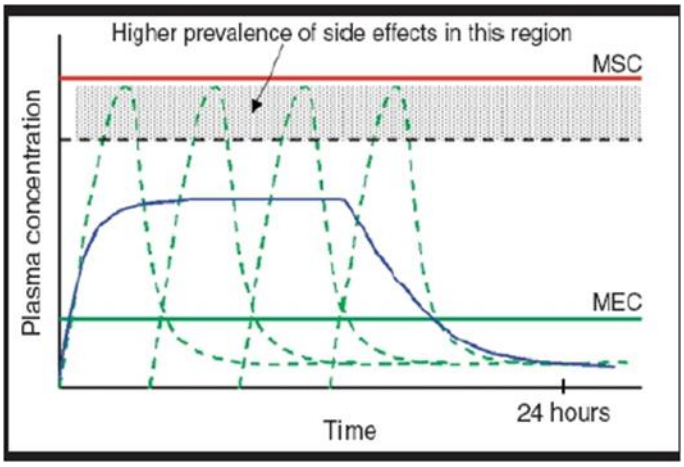


Figure 1.1: Plasma drug concentration profiles for conventional tablet or capsule

Formulation (----) and a zero order controlled release formulation ( )

MEC = Minimum Effective Concentration; MSC = Maximum Safe Concentration.

METHODS OF PREPARATION OF MUCOADHESIVE MICROSPHERES

Mucoadhesive microspheres can be prepared using any of the following techniques.

Air suspension

This process consists of the dispersing of solid particles of core materials in a supporting air stream and the spray coating of the air suspended particles.

Coacervation

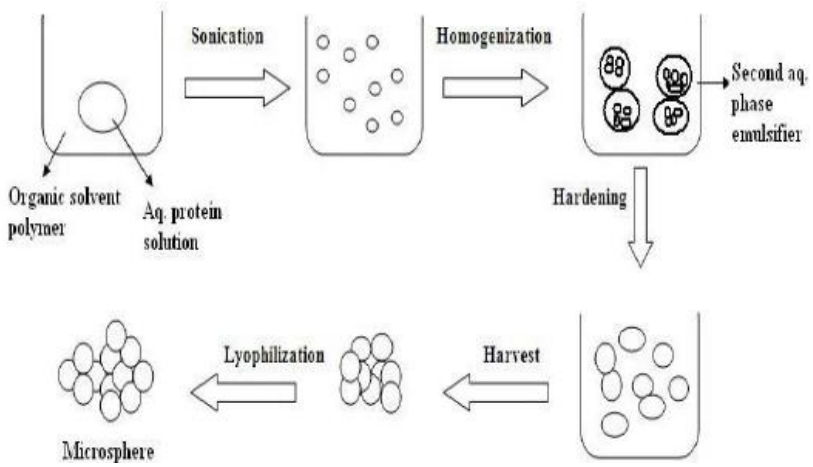
This process consists of mainly three steps carried out under continuous agitation.

Spray drying

In spray drying, the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization.

Solvent evaporation

This process is carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.



Steps involved in solvent evaporation method.

Polymerization

This method involves the reaction of monomeric sub units located at the interface existing between a core material substance and a continuous phase in which the core material is dispersed.

Wet inversion technique

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyposphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol diglysidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of CS microspheres.

Hot melt microencapsulation

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5 °C above the melting point of the polymer.

Solvent removal

It is a non-aqueous method of microencapsulation, particularly suitable for water labile polymers such as the ploy anhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is then suspended in silicone oil containing span 85 and methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether is added and stirred until solvent is extracted into the oil solution. The resulting microspheres can then be dried in vacuum.

Preparation of microspheres by thermal cross-linking

Citric acid, as a cross-linking agent was added to 30 mL of an aqueous acetic acid solution of chitosan (2.5% w/v) maintaining a constant molar ratio between chitosan and citric acid ($6.90 \times 10{-}3$ mol chitosan : 1 mol citric acid). The chitosan cross-linker solution was cooled to 0°C and then added to 25 mL of corn oil previously maintained at 0°C, with stirring for 2 minutes. This emulsion was then added to 175 mL of corn oil maintained at 120°C, and cross-linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40 minutes. The microspheres obtained were filtered and then washed with diethyl ether, dried, and sieved.

Preparation of microspheres by glutaraldehyde cross linking

A 2.5% (w/v) chitosan solution in aqueous acetic acid was prepared. This dispersed phase was added to continuous phase (125 mL) consisting of light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 containing 0.5% (w/v) Span 85 to form a water in oil (w / o) emulsion. Stirring was continued at 2000 rpm using a 3- blade propeller stirrer. A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25% v/v) was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60 °C- 80 °C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The microspheres were then finally dried in vacuum desiccators.

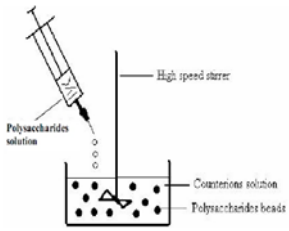
Preparation of microspheres by Tri polyphosphate

Chitosan solution of 2.5% w/v concentration was prepared. Microspheres were formed by dropping the bubble-free dispersion of chitosan through a disposable syringe (10 mL) onto a gently agitated (magnetic stirrer) 5% or 10% w/v Tri polyphosphate solution. Chitosan microspheres were separated after 2 hours by filtration and rinsed with distilled water, and then they were air dried.

Iontropic gelation technique

In the ionotropicgelation method polysaccharides (alginate, gellan and pectin) are dissolved in water or in weak acidic medium (chitosan). These solutions are the nadded drop wise under constant stirring to the solutions containing other counterion. Due to the complexation between oppositely charged species, polysaccharides undergo ionic gelation and precipitate to form spherical particles. The beads are removed by filtration, washed with distilled water and dried. The method involves an all-

aqueous system and avoids residual solvents in microspheres



Schematic representation of preparation of polysaccha rides particles by ionic gelation method.

The counterions used for ionotropic gelation c an be divided in two major categories

Low molecular weight counter ions (e.g.$CaCl_2$,B aCl_2, $MgCl_2$, $CuCl_2$, $ZnCl_2$,$CoCl_2$, pyrophosphate,tri polyphosphate,tetrapolyphosphate,octapolyphosphate, hexametaphosphate and $[Fe(CN)6]^4$ / $[Fe(CN)6]^3$).

- High molecular weight ions (e.g. Octyl sulphate, l auryl sulphate, hexadecylsulphate, cetylstearyl sul phate).

Orificeionic gelation method

- It involves reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (25 mL) to form a homogeneous polymer mixture

MATERIALS

Nizatidine, Sodium alginate, Carbopol-934, carbopol 971, HPMC K4M.

METHODOLOGY

Preformulation studies

Pectroscopic studies

Preparation of 0.1n hcl (ph 1.2)

Take 8ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water

DETERMINATION OF λMAX

Stock solution (1000µg/ml) of Nizatidine was prepared inmethanol. This solution was appropriately diluted with 0.1N HCl(pH 1.2) to obtain a concentration of10µg/ ml. The resultant solution was scanned in the range of 200nm to 400nmon UV-Visible spectrophotometer. The drug exhibited a λmaxat 315nm.

Preparation of standard calibration curve of Nizatidine

- 10mg of Nizatidine was accurately weighed and dissolvedin 10ml of methanol(StockSolution - I) to get a concentration of 1000 µg/ml.
- From the stock solution I,1ml of aliquots was tak en and suitably dilutedwith0.1NHCl(StockSolutio n-II) to get
- concentrations of 100µg/ml.

From the stock solution-II, liquots were taken and suitably diluted with0.1N Cl(pH1.2)to get concentrations in the range of2to 10µg/mlThe absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 314nm against reference solution 0.1N HCl (pH 1.2).

The Linear Regression Analysis

The linear regression analysis was done on Absorance points. The standard calibration curve obtained had a Correlation Coefficient of 0.998 with of slope of 0.0290 and intercept of 0.0028.

COMPATIBILITY STUDIES

A proper design and formulation of a dosage form requires considerations of the physical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. If the excipient(s) are new and if noprevious literature regarding the use of that particular excipient with an active ingredient is available, then compatibility studies are of paramount importance. Hence, before producing the actual formulation, compatibility of Nizatidinewith different polymers and other

excipients was tested using the Fourier Transform Infrared Spectroscopy (FT-IR) technique.

Fourier transform infrared spectroscopy (FTIR)

In order to check the integrity (Compatibility of drug in the formulation, FTIR spectra of the formulations along with the drug and other excipients wereobtained and compared using Shimadzu FT-IR 8400 spectrophotometer.In the presentstudy, Potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromidecrystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The FT-IR spectra of the formulations were compared with the FT-IR spectraof the puredrug and the polymers.

METHOD OF PREPARATION

Ionotropic gelation method

Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, Nizatidine (100mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried.

Photograph of prepared microspheres

Prepared formulation of Bioadhesive Microspheres

S.No.	FORMULATION CODE	DRUG:POLYMER RATIO	
1	F1	1:1	Sod.alginate:carbopol 934(3:1)
2	F2	1:2	Sod.alginate:carbopol 934(3:1)
3	F3		Sod.alginate:carbopol 934(3:1)
		1:3	
4	F4	1:1	Sod.alginate:carbopol 971(3:1)
5	F5		Sod.alginate:carbopol 971(3:1)
		1:2	
6	F6		Sod.alginate:carbopol 971(3:1)
		1:3	
7	F7	1:1	Sod.alginate:HPMC K4M(3:1)
8	F8		
		1:2	Sod.alginate:HPMC K4M (3:1)
9	F9		
		1:3	Sod.alginate:HPMC K4M(3:1)

PERCENTAGEYIELD

The percentage of production yield was calculate from the weight of dried microspheres recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nizatidine(mg)	150	150	150	150	150	150	150	150	150
Carbopol 934(mg)	150	300	450	--	--	--	--	--	--
Carbopol 971(mg)	--	--	--	150	300	450	--	--	--
HPMC K4M (mg)	--	--	--	--	--	--	150	300	450
Na-Alginate (mg)	150	300	450	150	300	450	150	300	450
water	10 ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml
Calcium chloride(4%)	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

Drug entrapment efficiency

Microspheres equivalent to 15 mg of the drug Nizatidine were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres. The powder was transferred to a 100 mlvolumetric flask and dissolved in 10ml of methanol and the volume was made up usingsimulated gastric fluid pH 1.2. After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 315 nm. The amount of drug entrapped in the microspheres was calculated by the following form

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Particle size analysis

Samples of the microparticles were analyzed for particle sizeby optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 Microparticles sizes were calculated under 45x magnification. The average particle size was determined by using the Edmondson's equation:

$$D_{mean} = \frac{nd}{n}$$

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

Swelling study

Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2 .The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$\text{Swelling ratio} = \frac{(Wt - W0)}{(W0)} \times 100$$

Where W0 & Wt are initial weight and Final weight of microspheres respectively.

Evaluation of mucoadhesive property

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 on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test, when the test apparatus was operated, the sample is subjected to slow up and down movement in simulated gastric fluid pH 1.2 at 37^0C 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.

$$\% \text{ Mucoadhesion} = \frac{\text{Number of microspheres adhered}}{\text{Number of microspheres applied}} \times 100$$

In-vitro drug release study

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml). A quantity of accurately weighed microspheres equivalent to 20mg Nizatidine each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 314nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment.

Invitro drug release kinetic

The release data obtained was fitted into various mathematical models. The parameters ‘n’ and time component ‘k’, the release To examine the release mechanism of Nizatidine from the microspheres, the release data was fitted into Peppa’s equation, $Mt / M\infty = Ktn$ Where, $Mt / M\infty$ is the fractional release of drug, ‘t’ denotes the release time, ‘Represents a constant incorporating structural and geometrical characteristics.

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport or non-Fickian	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

If n < 0.5, the polymer relaxation does not affect the molecular transport, hencediffus-ion is Fickian.

If n > 0.5, the solid transport will be non-fickian and will be relaxationcontrolled.

Other equations to study the drug release kinetics from dosage forms

Zero Order

% R = kt

This model represents an ideal release in order to achieve prolonged pharmacologic action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as Matrix tablets containing low soluble drugs.

First Order

log (fraction unreleased) = kt/2.303

The model is applicable to hydrolysis kinetics and to study the release profiles

ofpharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

Matrix (Higuchi Matrix)

$$\% R = kt^{0.5}$$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

Peppas Korsmeyer Equation

$$\% R = kt^{n}$$

$$log \% R = logk + nlogt$$

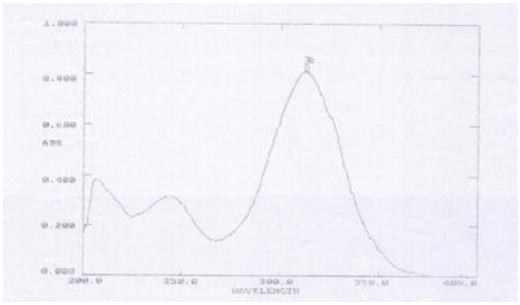
This model is widely used when release mechanism is well known or when more thanone type of release phenomenon could be involved. The 'n' values could be used to characterize different release mechanisms as

Value of 'n'	Mechanism
0.5	Fickian Diffusion (Higuchi Matrix)
0.5<n<1	Anomalous Transport
1	Case – II transport (Zero Order Release)
n>1	Super Case Transport

RESULTS AND DISCUSSIONS

Preformulation studies

Determination of λmaxA solution of 10µg/ml of Nizatidine was scanned in the range of 200 to 400nm. The drug exhibited a λ max at 315nm in simulated gastric fluid pH 1.2 and had good reproducibility. Correlation between the concentration and absorbance was found to be near to 0.9999, with a slope of 0.0290and intercept of 0.00280.Figure 7.1: UV Spectrum of Nizatidine in simulated gastric fluid (pH 1.2)x

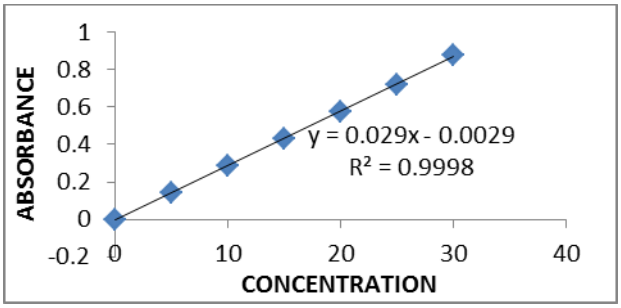


Calibration curve of Nizatidine in simulated gastric fluidpH1.2

Figure shows the calibration curve data of Nizatidine in simulated gastric fluid pH1.2 at 315nm. The curve was found to be linear in the concentration range of 2-10µg/ml.

Calibration curve data for Nizatidine in simulated gastric fluidpH 1.2

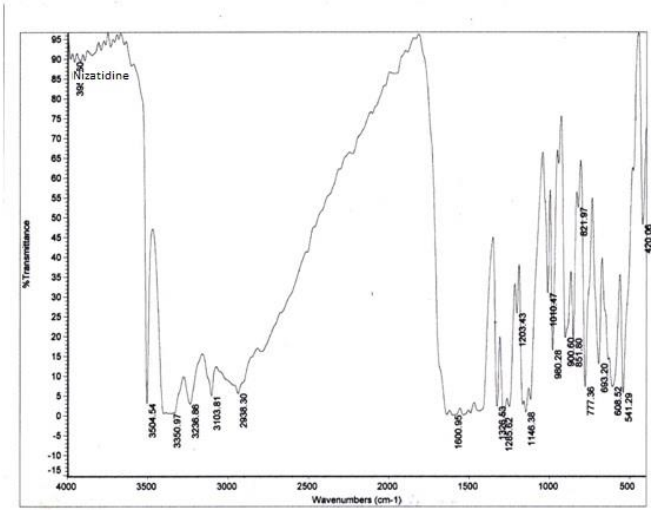
CONCENTRATION (µg /ml)	ABSORBANCE
0	0
5	0.143
10	0.288
15	0.429
20	0.574
25	0.718
30	0.876



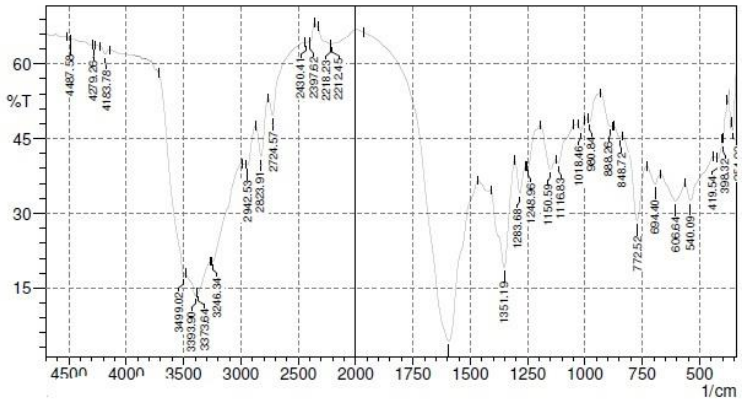
Standard graph of Nizatidine in simulated gastric fluid pH 1.2

Compatibility studies

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Nizatidine with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug. The results indicated that the characteristic absorption peaks due to pure Nizatidine have appeared in the formulated microspheres, without any significant change in their position after successful encapsulation, indicating no chemical interaction between Nizatidine and Polymers.



FTIR of Nizatidine pure drug



FTIR of Nizatidine optimized formulation

EVALUATIONANDCHARACTERISATIONOF MICROSPHERES

Percentage yield

The percentage yield was found to be in the range of80.3 to 83.4% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 77.6 to 86.4% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 80.2 to 83.7% for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The percentage yield of the prepared microspheres is recorded.

Drug entrapment efficiency

Percentage Drug entrapment efficiency of Nizatidine ranged from 82.66 to 84.66% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 76.42 to 89.05% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 80.06 to 82.32% for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency.

Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	% Drug entrapment efficiency
1	F1	80.3	82.66
2	F2	82.3	84.47
3	F3	83.4	84.66
4	F4	86.4	89.05
5	F5	77.6	76.42
6	F6	79.7	78.73
7	F7	83.7	80.06
8	F8	80.2	82.32
9	F9	81.2	81.36

PARTICLE SIZE ANALYSIS

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing sodium alginate along with carbopol 934 as copolymer had a size range of 540µm to 644µm, microspheres containing sodium alginate along with carbopol 971 as copolymer exhibited a size range between 512µm to 624µm and microspheres containing sodium alginate along with HPMC K 4 M as copolymer had a size range of 588µm to 626µm.The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

Table: Average particle size of Nizatidine microspheres

S.No	Batches	Mean Particle Size(µm)
1	F_1	540 µm
2	F_2	602 µm
3	F_3	644 µm
4	F4	512 µm
5	F5	528 µm
6	F6	624 µm

7	F7	588 µm
8	F8	598 µm
9	F9	626 µm

SWELLING STUDY

The percentage of swelling also increases. Thus we can say that amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 31 to 67% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 46 to 85% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 65 to 78 for microspheres containing sodium alginate along with HPMC K 4 M as copolymer.

Percentage swelling of the prepared microspheres

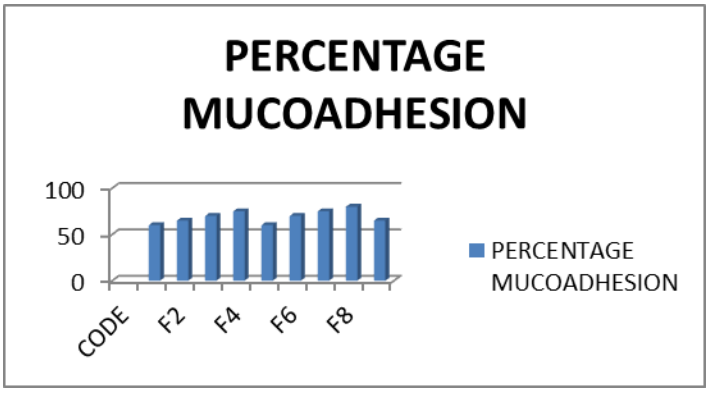
S.NO.	FORMULATION CODE	INITIAL (Wt)	FINAL (Wt)	PERCENTAGE SWELLING
1	F1	10	13.1	31
2	F2	10	15.3	53
3	F3	10	16.7	67
4	F4	10	18.5	85
5	F5	10	12.4	24
6	F6	10	14.6	46
7	F7	10	16.5	65
8	F8	10	17.4	74
9	F9	10	58.5	78

IN-VITRO MUCOADHESION TEST

As the polymer to drug ratio increased, microspheres containing sodium alginate along with carbopol 934 as copolymer exhibited % mucoadhesion ranging from 60 to 70%, microspheres containing sodium alginate along with carbopol 971 as copolymer exhibited % mucoadhesion ranging from 60 to 75% and microspheres containing sodium alginate along with HPMC K 4 M as copolymer exhibited % mucoadhesion ranging from 65 to 80%

Percentage mucoadhesion of the prepared microspheres

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESION
		INITIAL	FINAL	
1	F1	20	12	60
2	F2	20	13	65
3	F3	20	14	70
4	F4	20	15	75
5	F5	20	12	60
6	F6	20	14	70
7	F7	20	15	75
8	F8	20	16	80
9	F9	20	13	65



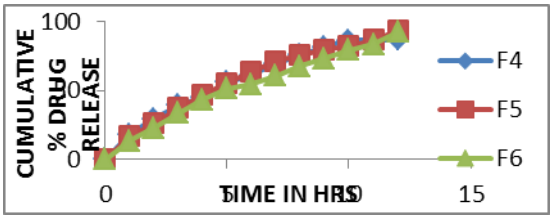
Comparison of percentage mucoadhesion of prepared microspheres

In-vitro drug release studies

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2.The results of the in-vitro dissolution studiesofformulationsF1toF3, F4 to F6 and F7 to F9 are shown intable. The plots of Cumulative percentage drug release Vs Time. Figure shows the comparison of % CDR for formulations.

***In-Vitro* drug release data of Nizatidinemicrospheres containing sodium alginate along with carbopol 934 as copolymer**

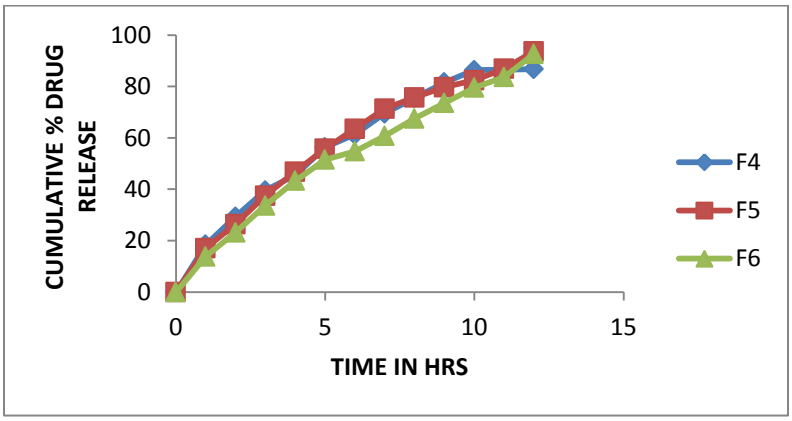
TIME (h)	CUMULATIVE PERCENT OF DRUG RELEASED		
	F1	F2	F3
0	0	0	0
1	24.88	21.11	18.66
2	31.55	31.55	28.11
3	42.44	39.77	37.44
4	53.55	47.77	44.66
5	60.21	56.66	54.67
6	68.54	65.44	63.33
7	77.55	75.55	73.11
8	86.33	83.33	78.11
9	92.66	84.66	82.33
10		91.06	86.66
11			92.66
12			93.55



Comparison of In-Vitro drug release profile of Nizatidine micro spheres containing sodium alginate along with carbopol 934 as copolymer

In-Vitro drug release data of Nizatidine microspheres containing sodium alginate along with carbopol 971 as copolymer

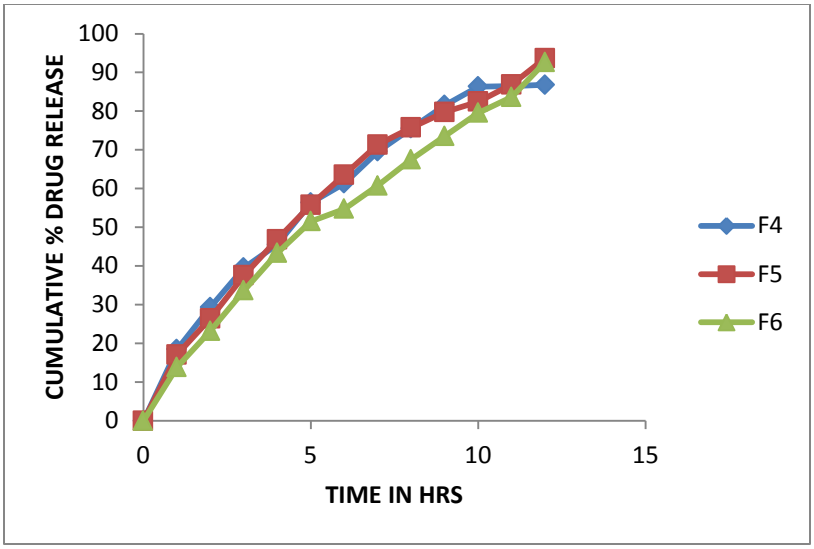
TIME (h)	CUMULATIVE PERCENT OF DRUG RELEASED		
	F4	**F5**	**F6**
0	**0**	0	0
1	16.88	27.77	22.44
2	25.22	36.44	32.22
3	35.66	43.77	40.88
4	39.33	54.66	48.66
5	52.55	64.01	57.55
6	55.77	75.77	63.55
7	61.77	84.65	70.44
8	69.55	90	76.55
9	77.55	92.22	85.55
10	85.55		91.33
11	90.66		
12	95.66		



Comparison of In-Vitro drug release profile of Nizatidine micro spheres containing sodium alginate along with carbopol 934 as copolymer

In-Vitro drug release data of Nizatidine microspheres containing sodium alginate along with carbopol 971 as copolymer

TIME (h)	CUMULATIVE PERCENT OF DRUG RELEASED		
	F7	**F8**	**F9**
0	0	0	0
1	18.44	17.11	13.88
2	29.33	26.44	23.22
3	39.55	37.55	33.66
4	45.55	46.88	33.33
5	56.33	55.77	51.55
6	61.33	63.55	52.77
7	69.55	71.33	60.77
8	75.56	75.77	67.55
9	81.55	79.77	73.55
10	86.33	82.44	79.55
11	86.5	86.88	83.66
12	86.8	93.66	92.66



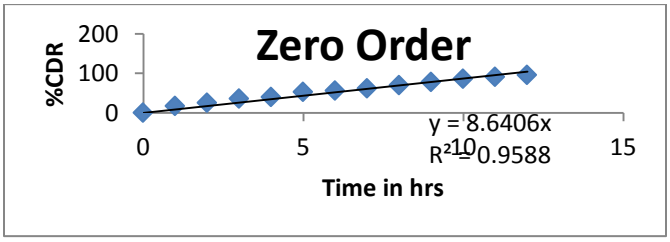
Comparison of In-Vitro drug release profile of Nizatidine micro spheres containing sodium alginate along with HPMC K 4 M as copolymer

IN-VITRO DRUG RELEASE KINETICS

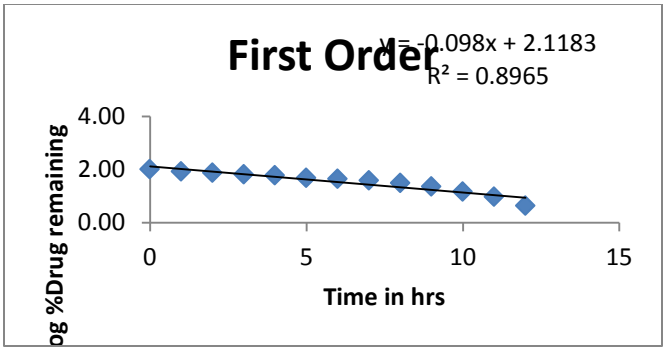
For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the in vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table. The coefficient of determination (R2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Zero order (R2 = 0.958) whereas release exponent. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows higuchis model along with erosion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

RELEASE KINETICS STUDIES OF THE OPTIMIZED FORMULATION

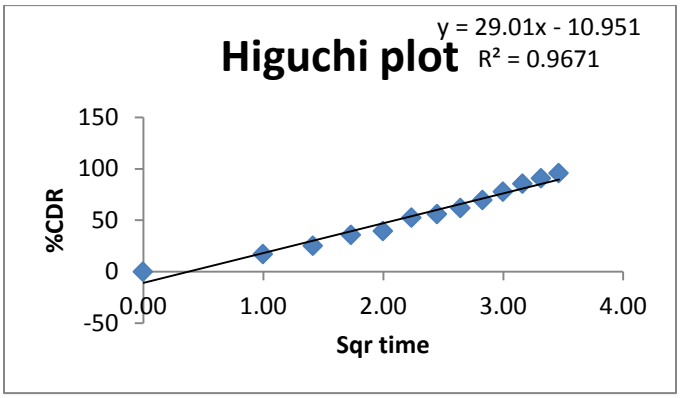
	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.579725275	-0.1445403	29.0101023	1.195069374
Intercept	8.840879121	2.259122878	-10.9512781	0.789416458
R 2	0.985574735	0.697526127	0.967128051	0.714124414



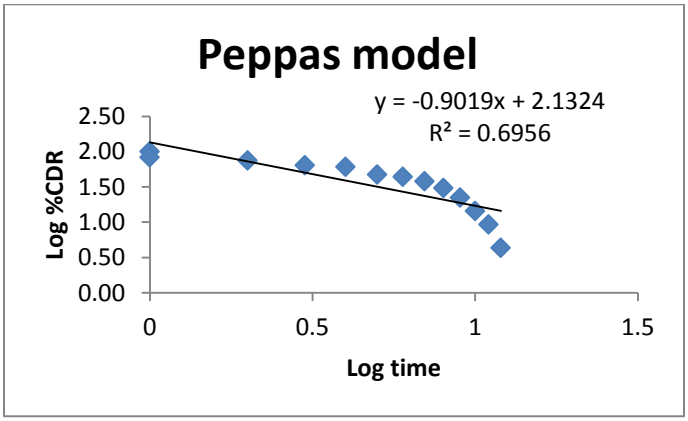
Zero order kinetics graph for F4 formmulation



First order kinetics graph for F4 formulation



Higuchis model graph for F4 formulation



peppas model graph for F4 formulation

SUMMARY AND CONCLUSION

In the present work, bioadhesive microspheres of Nizatidine using Sodium alginate along with Carbopol 934, Carbopol 971, HPMC K4M as copolymers were formulated to deliver Nizatidine via oral route. Details regarding the preparation and evaluation of the formulations have been discussed in the previous chapter. From the study following conclusions could be drawn:-

- The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Nizatidine microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, airpollution, toxicity and difficult to remove traces of organic solvent completely.

- FT-IR spectra of the physical mixture revealed that the drug is compatible with thepolymers and copolymers used.
- Micromeritic studies revealed that the mean particle size of the prepared microspheres was in thesize range of 512-644µm and are suitable for bioadhesive microspheres for oral administration.
- Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion.
- The in-vitro mucoadhesive study demonstrated that microspheres of Nizatidine using sodium alginate along with Carbopol 971 as copolymer adhered to the mucus to a greater extent than the microspheres of Nizatidine using sodium alginate along with Carbopol 934and HPMC K4M ascopolymers.
- The invitro drug release decreased with increase in the polymer and copolymer concentration.
- Analysis of drug release mechanism showed that the drug release from the formulations followed higuchis model of drug release.
- Based on the results of evaluation tests formulatio n coded F 4 was concluded as best formulation.

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