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EVALUATION OF ANTI ULCER ACTIVITY OF NIZATIDINE MICROSPHERES BASED DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of present study to develop Gastro-retentive drug delivery formulation for enhancing GRT including the physiological and formulation variables affecting gastric retention. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges like poor bioavailability. Floating microspheres were prepared by Solvent evaporation (oil-in–water emulsion) technique. In this 225mg polymethyl methacrylate (PMMA) were dissolved in a mixture of dimethyl formamide and dichloromethane (1:1) at room temperature. And 75mg Nizatidine hydrochloride was added in the above mixture. This was poured into 250ml water containing 0.02% tween 80, maintained at a temperature 30-40^{o}C and subsequent stirred at ranging agitation speed for 20 minute to allow the volatile solvent to evaporate.The microspheres formed were filtered, washed with water and dried in vaccum. The prepared Floating microspheres were characterized in different way like size distribution 131.4±1.6µm and 89.5±1.4% entrapment efficiency was found, *In vitro* floating test of optimized floating microspheres formulation was studied in SGF (pH 1.2). The percent Cumulative amount of drug release was found 87.2±2.6% in SGF (pH 1.2), 90.2±3.5% in SIF (pH 6.8) and 93.2±3.5 % in PBS (pH 7.4) upto 24 hrs. The ulcer protection of the microspheres formulation were 79.84% as compared to the nizatidine pure drug (66.05%) in ulcer induced rats. The C-max value Of Nizatidine as obtained from the graph was 575.14 ± 55.43 ng/ml with T-max value 2h and for formulation was 206.58 ± 7.71 ng/ml. Floating microspheres drug delivery system provides the possibility of enhancing the bioavailability and control the release of formulation exhibiting absorption window by prolonging the gastric emptying time of the dosage form ensuring availability of drug at the absorption site for the desired period of time.

Key words: Floating drug delivery systems, Gastric residence time, in vitro and in vivo.

INTRODUCTION

Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period .While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration.

An ulcer is a round or oval shaped hole (also called parietal defect), 2 to 4 cm in diameter with perpendicular borders and a smooth base. A Peptic Ulcer is an ulcer in the gastrointestinal tract that is characteristically acidic and thus extremely painful. [1-3].

The oral route is predominant and most preferred route for drug delivery but drug absorption is unsatisfactory and highly variable in the individuals despite excellent *in-vitro* release pattern. These aspects lead to developing a drug delivery system which will remain in the stomach for prolonged and predictable time [4-5].

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The genuinely effective ulcer healing agents histamine H_2 receptor antagonists Nizatidine hydrochloride requires frequent dosing due to short biological half-life (1.9 ± 0.1 hr) and absorbed only in the stomach and in the initial part of small intestine,with 35% absolute bioavailability. The traditional oral sustained release formulation releases most of the drug in intestine and colon thus the drug has a narrow absorption window and the colonic metabolism of is partly responsible for poor bioavailability from the colon therefore sustained release dosage form of nizatidine hydrochloride prepared by the conventional technology may not be very successful and clinically acceptable. So that controlled release intragestric floating microspheres of nizatidine hydrochloride eliminates the problems associated with conventional dosage forms.

The major objectives of the present study are: -

1. To develop a intragastric floating and sustained release floating microspheres for gastric retention using polymethyl methacrylate (PMMA) as floating carrier.
2. To study the effect of important formulation and processing variables on the floating and drug release behavior of these systems.

Gastro retentive drug delivery systems have made it possible to deliver the drugs in GIT for prolonged period of time in a controlled manner. Thus it is envisaged to develop a floating drug delivery system, which can be retained in the stomach for prolonged period of time by virtue of their floating properties.

Hence it is advantageous to prepare a small sized floating microspheres which could float and simultaneous adhere to directly to the mucous network where the absorption window of H_2 receptor antagonist can exists. Floating microspheres of nizatidine could localize the drug within the peptic region to enhance the drug absorption process in a site specific manner. Developed floating system of nizatidine increase the local drug concentration by prolonging the residence time of the formulation in the stomach. [5-8].

To develop oral drug delivery system, it is necessary to optimize both the residence time of the system within the gastrointestinal tract and the release rate of drug from the system. Various attempts have been made to prolong the residence time of dosage forms within the stomach. The prolongation of gastric residence time (GRT) of delivery devices could be achieved by adhesion to the mucous membranes by preventing there passage through pylorus, using high density systems, delayed gastric emptying devices or by maintaining them in buoyant fashion in gastric juice [9-10].

MATERIALS AND METHODS

Materials

Nizatidine hydrochloride was generously supplied as a gift samples by Dr. **Reddy Laboratories Hyderabad. Polymethylmethacrylate, Dichloromethane** and Dimethylformamide were purchased from CDH India. All other chemicals and reagents were used of analytical grade.

METHODS

Preparation of floating microspheres by (Solvent evaporation method)

Floating microspheres were prepared by Solvent evaporation (oil-in–water emulsion) technique. In this 225mg polymethyl methacrylate (PMMA) were dissolved in a mixture of dimethyl formamide and dichloromethane (1:1) at room temperature. And 75mg Nizatidine hydrochloride was added in the above mixture. This was poured into 250ml water containing 0.02% tween 80, maintained at a temperature 30-40^{o}C and subsequent stirred at ranging agitation speed for 20 minute to allow the volatile solvent to evaporate[11-16]. The microspheres formed were filtered, washed with water and dried in vaccum.

Characterization of Prepared Floating Microspheres

The prepared floating microspheres were characterized for shape and surface morphology, size, percent drug loading and in vitro drug release in different GIT $P^{H.}$

Shape and surface morphology

In order to examine the surface morphology, the formulations were viewed under scanning electron microscopy. The samples for SEM were prepared by lightly sprinkling the floating microspheres powder on a double adhesive tape, which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300Å using a sputter water. The samples were then randomly scanned for studying surface morphology but show the images of coating to prove internal surface [17].

Particle size determination

The particle size of formulation was determined by optical microscopy using a calibrated ocular micrometer [19].

% Drug Entrapment

100 mg of floating microspheres was dissolved in 3 ml of dichloromethane and shaken vigorously for 2 min. The solution was then filtered through 0.45µm syringe filter (Millipore Millex HN, USA). After suitable dilution with PBS (pH 7.4) solution was assayed for Combined drug spectrophotometrically [9]. The percent drug entrapped was calculated.

$$\% \text{ DE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

***In Vitro* Buoyancy Test of Optimized Floating Microspheres Formulation**

The floating test of the prepared optimized floating microspheres formulation was carried out using dissolution test apparatus USP XXII method II. 500 mg of floating microspheres were immersed in 900 ml simulated gastric fluid SGF (pH 1.2) maintained at 37 ± 2°C, which was agitated by a paddle rotated at 100 rpm. The paddle blades were positioned at the surface of dissolution medium. The floating microspheres floating on the surface of SGF (pH 1.2) were recovered with a sieve No. 120 (34µm) at every 1 hr time interval for 8 hours. The floating microspheres so collected were dried and weighed. The floating percentage of the floating microspheres was defined as the weight ratio of the floating microspheres against the total weight of floating microspheres in the floating test [19]. The buoyancy of the floating microspheres was calculated by the following equation:

$$\text{Bouyancy}\,(\%) = \frac{Q_f}{Q_f + Q_S} \times 100$$

Where Q_f and Q_s are the weights of the floating and settled floating microspheres respectively.

In Vitro BuoyancyOf Floating Microspheres In SGF (PH 1.2)

IN VITRO DRUG RELEASE IN DIFFERENT GASTROINTESTINAL FLUIDS

Optimized formulation was evaluated for the *in vitro* drug release study in different GIT fluids. The dissolution test of floating microspheres was carried out by the paddle type dissolution apparatus specified in USP XXIII under perfect sink condition.

500 mg of floating microspheres was weighed accurately and gently spread over the surface of 500 mL of dissolution medium. The media was rotated at 100 rpm and thermostatically controlled at 37±2°C. Perfect sink condition was prevailed during the drug dissolution. The release was tested in dissolution medium of pH 1.2, pH 6.8 and pH 7.4 solutions[10]. An aliquot of the release medium was withdrawn at every 1 hr time interval and an equivalent amount of fresh medium was added to the release medium. The collected samples were filtered through 0.45µm-syringe filter (Millipore millex HN) and after suitable dilution sample were analyzed spectrophotometrically. % cumulative drug release are Calculated.

STABILITY STUDIES

The stability of a preparation is usually defined as the capacity of the formulation to remain within defined limits over a predetermined period of time and is known as shelf life of the product. Stability of a formulation may also be defined as the capability of a particular formulation packaged in a specific container to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications. A stable drug delivery system should maintain its integrity and morphology, and at the same time should preserve various characteristics such as nature of the entrapped drug, drug content and release rate etc. In most of the stability studies, the major emphasis has been directed towards the accelerated stability studies but the stability studies of aged products have been of greater pharmaceutical significance [20].

The stability of the drug-loaded floating microspheres during storage is undoubtedly another important prerequisite for its successful clinical application. Degradation is likely to occur under tropical conditions of higher ambient temperature and humidity. Hence the prepared floating microspheres were subjected to accelerated stability testing.

Effect of storage on structural integrity of optimized floating microspheres formulation

The optimized formulation was stored in amber colored glass bottles at 4±1°C, 25±1°C and 40±1°C for a period of 45 days and observed for any change in particle size (optical microscopy) and surface morphology by phase contrast microscope (Leica MPS, Germany)[20].

Effect of storage on residual drug content

Stability of floating microspheres formulations on storage is of great concern as it is the major factor in their development as marketed preparation. The prepared formulation was tested for stability at 4±1°C, 25±1°C and 40±1°C temperatures. Formulation was stored in amber colored glass vials, and then it was evaluated after 15, 30 and 45 days for change in residual drug content.[7] For the determination of residual drug content floating microspheres formulation were dissolved in 3ml dichloromethane filter through polycarbonate membrane (Millipore, USA) of 200 nm pore size than after suitable dilution with PBS (pH 7.4) the drug content estimated spectrophotometrically using UV-visible spectro photometer.

***in vivo* Radiographical study**

In order to assess the gastro retentive efficacy of floating formulations, the Percent buoyancy in a biological system was determined by using barium sulphate X-ray contrast medium containing 15% barium sulphate as a contrast agent were prepared for radio graphical study. The study was carried out with one healthy male rabbits free of detectable gastrointestinal diseases or disorders. The study was carried out under the guidelines compiled by CPCSEA (Committee for the purpose of control) Supervision of Experiments on Animal, Ministry of Culture, Government of India and the local institutional Animal Ethics Committee approved all the study protocols. The rabbits were fasted overnight. The rabbits were administered optimized floating microspheres formulation with 25ml of

water and X- ray photograph was taken after every one hour of administration and intragastric behavior of the floating microspheres was observed by taking a series of X- ray photographs at different time intervals [5].

***In-vivo* studies**

Albino rat of either sex weighing 400 – 450 gm were chosen for the present studies. All in vivo studies on animals were approved by animal ethical committee of the Adina Institute of Pharmaceutical Sciences, Sagar (MP), India constituted under the guidelines of CPCSEA, New Delhi, India through their vide letter no. animal eths. Comm. 1546/PO/E/S/11/CPCSEA dated 21/05/2016.

Induction of Gastric Ulcer

The experiment was conducted on Albino rat, whose average body weight of 400 – 450 gm and age nearly 03 month. Animals were kept in standard cages for constant room temperature at 25 ± 1 ^{0}C. Rats were keep in Fasted condition for 18 hour where no food but water was provided ad-libitum. Gastric Ulcers were induced by administered ethanol in the range of (95%, 01ML/200gm body weight) orally through a feeding tube [20].

Experimental design

The anti ulcer activity of the formulation was carried out in Albino rat. The oral dose of 20 mg/kg was chosen for this purpose. The healthy rats were divided into four groups with five animal each. The animals in the test groups were administered 1ml / 100 gm of rat with necrotizing agent (80% ethanol) orally which is known to produce gastric lesions. The dosage schedule for the study is as follows

Group 1: Animals were given the normal saline with dose of 10 ml / Kg and served as negative control. **Group 2**: Animals were administered with Ethanol (80%) orally and served as positive control. **Group 3**: Animals were administered ethanol 1 ml /100gm and treated with pure Nizatidine 20mg/kg. **Group 4:** Animals were administered with ethanol and treated with formulation (equivalent 20 mg Nizatidine)and ulcer index (UI) was estimated [20].

$$UI = \frac{\text{Ulcerated area (mm}^2\text{)}}{\text{Total stomach area (mm}^2\text{)}}$$

***In vivo* Bioavailability study**

The bioavailability study was carried out in albino rats of either sex weighing 200 – 250 gm. The animalwere divided into three groups of five animals each and were fasted overnight before starting the experiment with free access to water. The pure Nizatidine and prepared microspheres formulation was administered orally with dose 20mg/kg body weight with the help of cannula after anaesthetizing for a very short period of time with diethyl ether , after administration 0.3 ml blood samples were collected from retro- orbital plexus into the heparinized tubes at pre set period of 0.5, 1,2,4,8,12,24h. The blood samples were centrifused at 4000rpm for 10 minutes and the separated samples were stored at - 20 ^{0}C until analysis had completed.

Estimation of Nizatidine in plasma sample by RP-HPLC analysis

The amount of Nizatidine in blood samples was measured by RP-HPLC method (Haque et al., 2011.The method was validated prior estimation. The measurement was carried out at 280 nm .The mobile phase used consist of mixture of 0.1(M) orthophosphoric acid (P^H 3.0) and methanol in the ratio of 30:70 and the pump flow rate was 1ml/min and C18 (250mm × 4.6 mm) column was used..The mobile phase was filtered with nylon membrane filter and degassed befor use.

To 0.1 ml plasma 50 µL of standard nizatidine (50 ng/ml) was added in a micro centrifuge tube and volume was made up to 2 ml with acetonitrile to precipitate the protein. Then tha sample was centrifuged at 4000 rpm for 25 min. The supernatant was collected and transferred into an eppendorf tube and was dried. The residue was dissolved in 200 µL of mobile phase and 10 µL was injected to the HPLC system. The analysis was carried out by RP-HPLC method using flow rate 1.0 ml/min and measurement was made at 280 nm. The amount of the nizatidine in the sample was determined from the peak area ratio correlated with standard curve prepared under the same identical condition.

Pharmacokinetic Analysis

Determination of C_{max} and T_{max}

The peak plasma concentration (C_{max}) and the time of peak plasma concentration (T_{max}) were determined from the plasma drug concentration vs time plot for the pure drug and prepared microspheres.

Determination of area under curve (AUC):

The area under the time versus plasma concentration curve (AUC) was measured by applying trapezoidal rule . $(AUC)_{0-\alpha}$ was calculated as given below

$$(AUC)_{0-t} = \int_0^t C(t)\,dt$$

$$(AUC)_{0-\alpha} = (AUC)_{0-t} + C_t / K_{el}$$

Determination of relative Bioavailability

The relative bioavailability (F_r) of Nizatidine was calculated using the following equation:

$$F_r (\%) = \frac{\text{AUC (Nizatidine microspheres)}}{\text{Pure nizatidine suspension}}$$

RESULT AND DISCUSSION

Floating microspheres were prepared by solvent evaporation method. Polymethylmethacrylate (225mg) was dissolved in a mixture of dimethylformamide and dichloromethane (1:1) at room temperature and drug (Nizatidine Hydrochloride - 75mg) was dispersed in above mixture. This drug-Polymer mixture was poured into 250ml water containing 0.02% tween 80, maintained at a temperature 30–40^{o}C, and subsequent stirred at ranging

agitation speed 300-400rpm to allow the volatile solvent to evaporate. The microsphere formed were filtered, washed and dried in vacuum.

For this floating microspheres formulation were prepared with varying drug concentration *viz*. 25, 50, 75mg. It was observed that on increasing the concentration of drug, the entrapment efficiency increased. While on further increasing drug concentration the entrapment efficiency gradually decreased.

Average particle size of floating microspheres reduces with increased in temperature. Narrow size distribution 131.4±1.6µm and 89.5±1.4% entrapment efficiency was found to formulation at 37^0C temperature. *In vitro* floating test of optimized floating microspheres formulation was studied in SGF (pH 1.2).

The results showed that the percentage buoyancy of floating microspheres formulation was significantly decreased after 5 hr.The buoyancy (%) of optimized Nizatidine hydrochloride floating microspheres formulation in SGF (pH 1.2) are reported.

In vitro drug release from optimized floating microspheres were carried out in SGF (pH 1.2), SIF (pH 6.8) and PBS (pH 7.4) by dissolution test of floating microspheres was carried out by the paddle method specified in the U.S.P. XXI. No initial burst release was observed in any medium suggested that the nizatidine hydrochloride molecules are entrapped over the floating microspheres. The percent Cumulative amount of drug release was found 87.2±2.6% in SGF (pH 1.2), 90.2±3.5% in SIF (pH 6.8) and 93.2±3.5 % in PBS (pH 7.4) upto 24 hrs. The results clearly suggest that floating microspheres formulation could also be utilized for sustained and drug delivery purpose.

Stability studies were carried out with optimized floating microspheres formulation which was stored for a period of 45 days at 4±1°C, 25±1°C and 40±1°C. The particle size of formulation was determined by optical microscopy using a calibrated ocular micrometer. The particle size of the floating microspheres was found to increase at 25±1°C, which may be attributed to the aggregation of floating microspheres at higher temperature. At 40±1°C the floating microspheres aggregated and a no change in spherical shape. to ellipsoidal shape with irregular observed i.e. these floating microspheres were unstable at higher temperature like 40±1°C.

The selected optimized floating microspheres formulation was stored at 4±1°C, 25±1°C and at 40±1°C and the residual drug content of the formulation was determined after 15, 30 and 45 days. It was observed that the formulation stored at 4±1°C and 25±1°C was quite stable as less drug was degraded on storage for 45 days while it was quite unstable at 40±1°C for 45 days.

The *in vivo* study with X-ray contrast medium containing floating microspheres was conducted to determine the *in vivo* floating performance of optimized floating microspheres formulation. X-ray photograph taken after each 1hr interval shows intragastric behavior of the floating microspheres. It is clear from the X-ray photographs that floating microspheres remained buoyant even after 4 hrs which is a satisfactory time for a gastro retentive property obtained by floating microspheres formulation.

In case of Invivo Study the ethanol induced ulcer model, the oral administration of 95% ethanol in control group, produce characteristic lesions in the stomach which shows as the bands of broad red lesions. The In vivo evaluation showed the Ulcer Index (UI) were, 1.090 ±0.04 for Group 1 (Normal saline –treated group), 23.92 ± 0.58 for Group 2 Ethanol Induction, 8.12 ± 0.28** for Group 3(Nizatidine solution) and 4.83± 0.86* for Group 4 Nizatidine loaded microspheres. Microspheres -treated group showed significant ($p < 0.01$) ulcer protection index as compared to free drug-treated group.

Table 1. Percent buoyancy of optimized Nizatidine hydrochloride Floating microspheres formulations in SGF (pH 1.2)

S. No	Time (hr.)	% Buoyancy
1	0	100
2	1	95
3	2	89
4	3	81
5	4	71
6	5	68
7	6	44
8	7	31
9	8	26

(n=3) mean±SD

Table 2. Percent cumulative drug release from optimized floating microspheres formulation in SFG (pH 1.2)

S No.	Time interval (hr)	% cumulative drug released
1	1	13.4 ±1.4
2	2	22.8±1.5

3	3	31.6±1.3
4	4	40.3±1.9
5	5	49.8±3.2
6	6	54.2±2.8
7	7	61.6±3.1
8	8	69.7±2.7
9	24	87.2±2.6

(n=3) mean±SD

Table 3. Percent cumulative drug release from optimized floating microspheres formulation in SIF (pH 6.8)

S No.	Time interval (hr)	% cumulative drug released
1	1	16.4 ±0.8
2	2	26.8±1.7
3	3	34.6±1.2
4	4	43.3±2.1
5	5	51.8±3.4
6	6	56.2±3.3
7	7	63.6±3.7
8	8	73.7±3.4
9	24	90.2±3.5

(n=3) mean±SD, *SIF – Simulated Intestinal Fluid

Table 4. Percent cumulative drug release from optimized floating microspheres formulation in PBS (pH 7.4)

S No.	Time interval (hr)	% Cumulative drug released
1	1	13.5±0.7
2	2	19.6±0.9
3	3	30.3±1.2
4	4	38.6±1.4
5	5	49.3±2.3
6	6	61.6±3.1
7	7	72.2±3.4
8	8	77.6±3.7
9	24	93.2±3.5

(n=3) mean±SD * PBS- Phosphate Buffer Solution

Table 5. Effect of storage temperature on particle size and surface morphology of optimized floating microspheres formulation

S. No.	Formulations	Storage Temperature	Particle size (µm)				Vesicles shape after 45 days
			Initial	15 days	30 days	45 days	
1	MFD	4±1°C	131.4± 3.4	134.7± 2.9	138.8± 3.1	141.4± 3.3	Spherical
		28±1°C	131.4± 3.4	139.6± 3.4	146.± 3.7	154.5± 2.9	Spherical
		40±1°C	131.4± 3.4	146.4± 2.7	153.± 2.1	162.2± 2.6	No Change in shape

(n=3) mean±SD

Table 6. Percent residual drug content in optimized floating microspheres formulation stored at different temperatures

S No.	Time in days	% Residual drug content		
		4±1°C	25±1°C	40±1°C
1	Initial	100	100	100
2	15	98.3 ± 1.2	96.8 ± 2.7	92.2 ± 2.2
3	30	96.2 ± 2.5	93.2 ± 2.3	86.4 ± 2.6
4	45	92.2 ± 2.3	84.7 ± 2.1	78.4 ± 2.9

(n=3) mean±SD

Table 7. Anti ulcer activity of the Nizatidine formulation in ethanol induced ulcer in rat

Groups	Induction	Dose	Ulcer Index
Group – I	Normal Saline	10ml/kg	1.090 ±0.04
Group –II	Ethanol	1ml/gm	23.92 ± 0.58
Group –III	Nizatidine	20 mg/kg	8.12 ± 0.28**
Group – IV	Nizatidine Formulation	20 mg/kg	4.83± 0.86*

Note : Values express mean ± SEM ; n=4; *p<.0.05 bversus control, **p<0.01versus control

Table 8. Drug Plasma concentration vs. Time data following oral administration of pure Nizatidine (Standard) to rat.

	Plasma Concentration in ng / ml vs. Time	
Time (Hrs.)	**Pure Nizatidine**	**Nizatidine formulation**
0	0	0
1.5	269.65± 42.31	45.250±8.42
1	391.72±56.25	69.250± 9.81
2	575.14±55.43	138.26±13.94
4	283.5±33.960	189.250 ±7.03
8	61.790±7.720	206.58± 7.71*
12	16.430±4.570	97.750±10.38

Table 9. Phamacokinetic Profile of pure Nizatidine and Nizatidine loaded Microspheres after oral administration in rats

Pharmacokinetics Parameters	Units	Nizatidine Standard	Nizatidine Formulation
C_{max}	ng / ml	575.14±55.43	206.58±7.71
T_{max}	H	2 ± 0	8 ± 0
AUC $_{(0-24)}$	h x (ng / ml)	2064.07	2272.22
Fr	(%)		110.07

Fig 1. Drug absorption from (a) conventional dosage forms and (b) gastroretentive drug delivery system

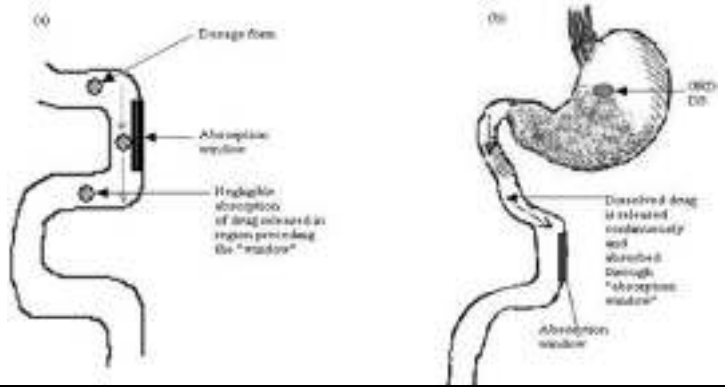


Fig 2. Schematic representation of method of preparation of Floating microspheres

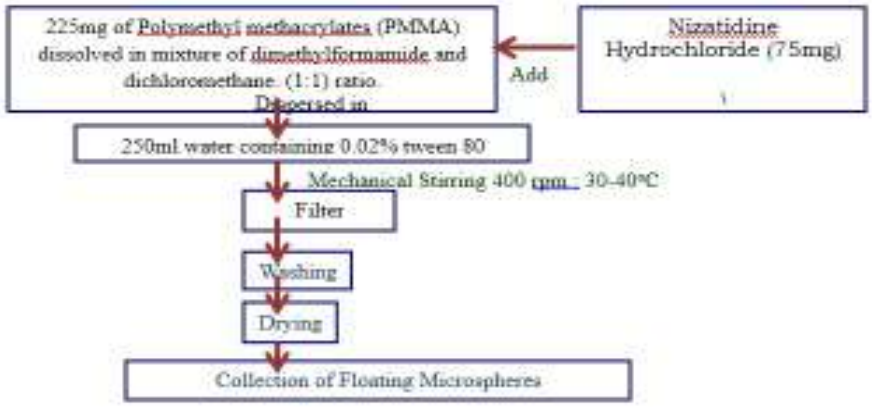
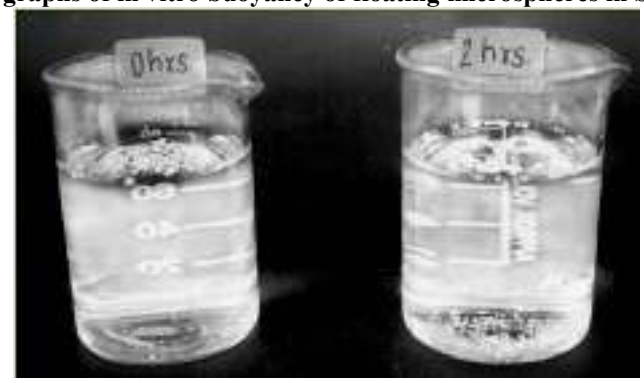


Fig 3. Photographs of in vitro buoyancy of floating microspheres in SGF (pH 1.2)

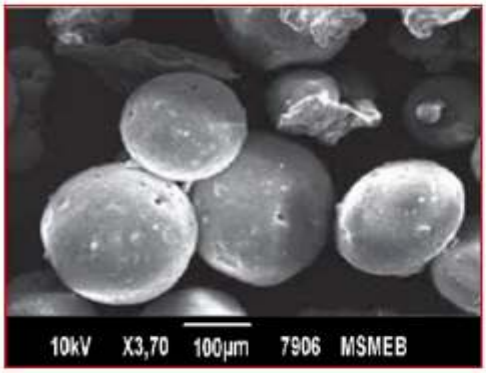


After (0 hr) **After (2 hrs.)**

After (4 hrs) **After (6 hrs.)**

After (8 hrs) **After (12 hrs.)**

Fig 4. SEM photograph of Nizatidine hydrochloride floating microsphere



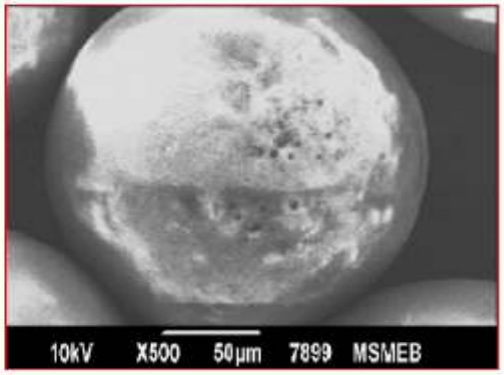


Fig 5. Percent buoyancy of optimized nizatidine hydrochloride Floating microspheres formulations in SGF (pH 1.2)

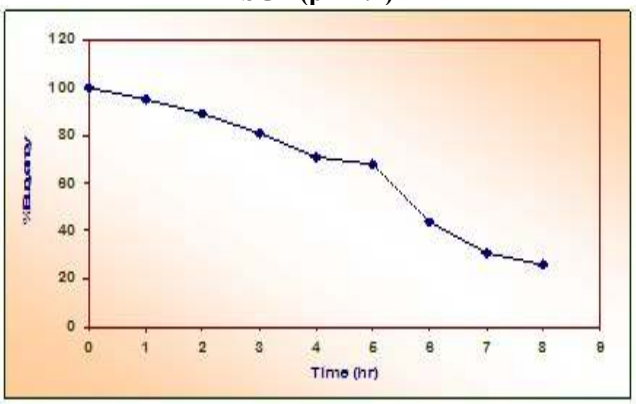


Fig 6. Percent cumulative drug release from optimized floating microspheres formulation in SFG (pH 1.2)

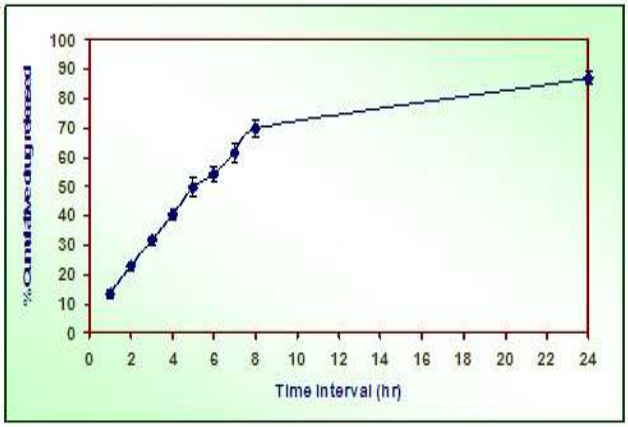
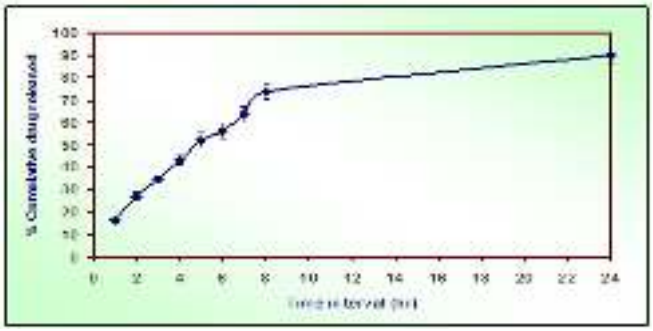
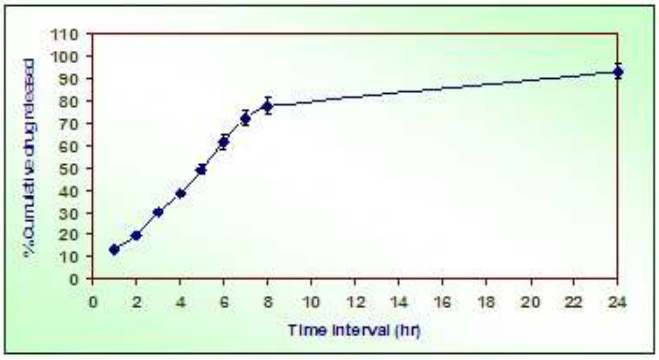


Fig 7. Percent cumulative drug release from optimized floating microspheres formulation in SFG, SIF (pH 6.8).



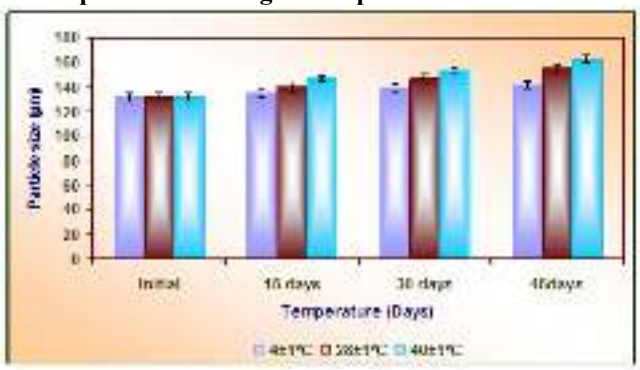
*SGF - Simulated Gastri Fluid *SIF – Simulated Intestinal Fluid

Fig 8. Percent cumulative drug release from optimized floating microspheres formulation in PBS (pH 7.4)



* PBS- Phosphate Buffer

Fig 9. Effect of storage temperature on particle size of optimized floating microspheres formulation



Mean SD ± (n=3)

Fig 10. Percent residual drug content in optimized floating microspheres formulation stored at different temperatures

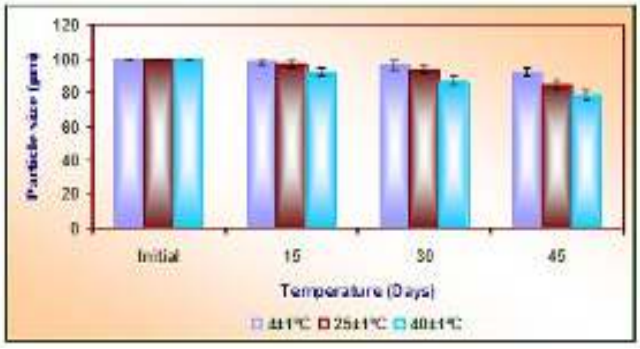


Fig 11. X-ray photographs showing floating microspheres remained buoyant

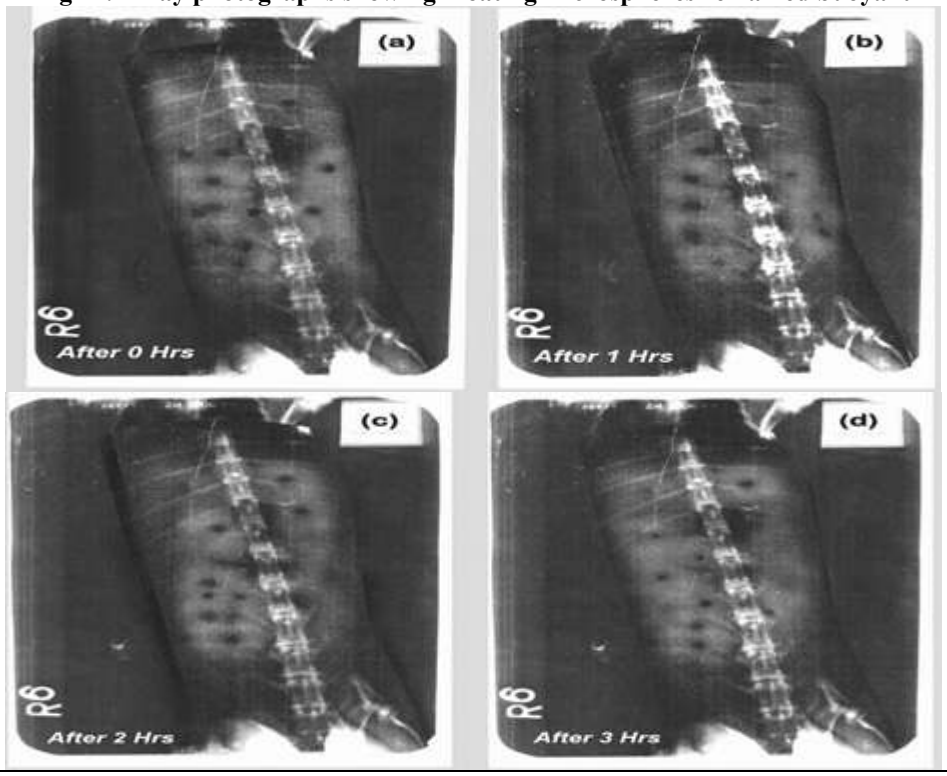
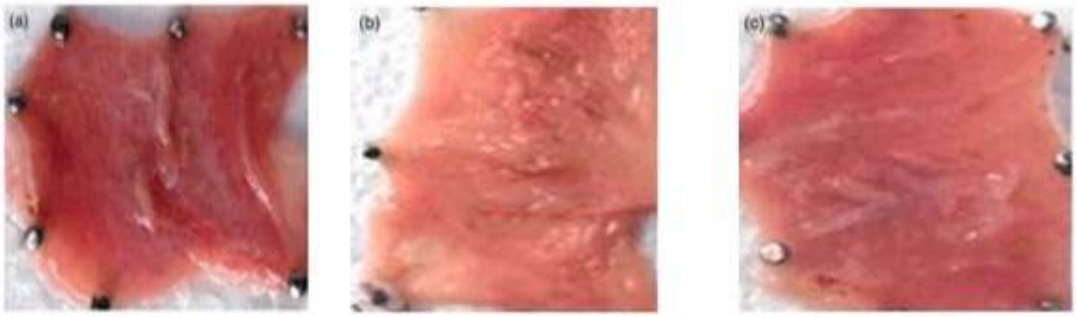


Fig 12. Evidence for the protective effect of Nizatidine loaded Microspheres in rats treated with ethanol



(a) Control group showing normal gastric integrity **(b) Nizatidine solution–treated group (20 mg/kg)** **(c) Nizatidine loaded Microspheres –treated group**

CONCLUSION

The result obtained from all the experiments perform as a part of project work suggested that it is possible to prepare an intragastric floating and sustained release floating microspheres preparation using Polymethyl methacrylate, solvent evaporation method. Floating microspheres drug delivery system provides the possibility of enhancing the bioavailability and control the release of formulation exhibiting absorption window by prolonging the gastric emptying time of the dosage form ensuring availability of drug at the absorption site for the desired period of time. As the floating microspheres showed a good buoyancy and drug release properties so that it has a great potential for its use both in powder form for dry suspension and granular form for table ting.

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Nil.

CONFLICT OF INTEREST

None.

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