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Research Article

DESIGN AND OPTIMIZATION OF MULTIPARTICULATE GASTRORETENTIVE DELIVERY SYSTEM OF RANITIDINE HYDROCHLORIDE

V JHANSIPRIYA MARABATHUNI, R.DEVESWARAN*, S.BHARATH, B.V.BASAVARAJ, V.MADHAVAN

M.S. Ramaiah College of Pharmacy, M.S.R. Nagar, M.S.R.I.T Post, Bangalore 560054. Email: devs_mdu@yahoo.com.

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ABSTRACT

In the present study, a gastroretentive Microparticulate system of an anti-ulcer drug Ranitidine hydrochloride, capable of floating on simulated gastric fluid for more than 24 hours was formulated by solvent evaporation technique. Eudragit RL-100, a biocompatible polymer was used to form microspheres of Ranitidine hydrochloride by response surface methodology. The formulated microspheres were characterized for their micromeritic properties, surface morphology by SEM and optical microscopy, drug-polymer compatibility studies by FTIR and DSC, *in-vitro* buoyancy studies, percentage drug entrapment efficiency and *in-vitro* drug release studies. Optimization studies were carried out by taking RPM (stirring speed) and amount of polymer as independent variables and percentage drug entrapment and time taken to release 90% drug ($t_{90\%}$) as responses using 3-level factorial design. The formulated microspheres free flowing and SEM studies indicated that the microspheres were porous and almost spherical in shape. The prepared microsphere formulations having percentage drug entrapment of 83.40- 85.24%, and buoyancy of 86.42 -95.58% with floating time up to 12 hours. *In-vitro* drug release studies of Ranitidine hydrochloride microspheres showed a controlled release of 11 hours with Eudragit RL-100. The data obtained in this study thus suggest that a Microparticulate floating dosage form of an anti-ulcer drug can be successfully designed to give controlled drug delivery and improved oral bioavailability.

Keywords: Microspheres, Optimization, Ranitidine hydrochloride, Sustained release

INTRODUCTION

Oral controlled release drug delivery systems that can be retained in the stomach for a long time have many advantages over the sustained formulations. It release the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption site in the upper gastrointestinal tract and it implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug ingradients from a controlled- release drug delivery system proceeds at a rate profile that is not predictable kinetically, but also reproducible from one unit to another [1]. Drugs that are easily absorbed from GIT and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time [2]. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the GRT, i.e. controlled release gastro retentive dosage form [3]. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Such retention systems are important for drugs that are degraded in the intestine or for drugs like antacids or certain antibiotics, enzymes that should act locally in the stomach [4,5]. Peptic ulcer is one of the most common chronic diseases in the world, which is the disorder of the upper gastro intestinal tract. Worldwide accepted therapy of peptic disease is based on histamine H_2 receptor. Ranitidine hydrochloride is an anti-ulcer drug and works on H_2-receptor mainly in stomach. The primary absorption region of this drug is stomach. Since it is an anti-ulcer drug, it will be beneficial to retain the drug in gastric region. The short biological half-life of ranitidine hydrochloride and the low dose of drug also make it a suitable candidate for sustained release dosage form [6]. Floating drug delivery system is also called the hydrodynamically balanced system (HBS). Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. This delivery system is further divided into in to noneffervescent and effervescent (gas-generating system) [7, 8]. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric content and remain in stomach for prolonged period. The drug released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration [9, 10]. Microspheres are the multi particulate delivery systems in which the drug is encapsulated in a polymer to deliver the drug to target site with specificity without untoward effects. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug [11, 12]. The purpose of this study was involved design and optimization of sustained release microspheres of Ranitidine hydrochloride as a model drug to prolong gastric residence time.

MATERIALS AND METHODS

Ranitidine hydrochloride was obtained as a gift sample from Minopharma Pvt. Ltd., Ongole. Eudragit RL-100 was obtained from Rohm pharma polymers, Germany and other solvents like acetone, liquid paraffin and petroleum ether used were obtained from Ranbaxy fine chemical limited, New Delhi and were of AR grade.

Experimental method

Formulation of microspheres

Microspheres containing Ranitidine hydrochloride as core material were prepared by *non-aqueous solvent evaporation* technique. Drug and Eudragit RL100 in varying ratios (1:1 to 1:8) were weighed and dissolved in 20ml of acetone with agitation to form uniform drug-polymer dispersion. This dispersion was slowly introduced into the medium consisting of 50 ml heavy liquid paraffin while being stirred at varying rpm (400-1200) by a mechanical stirrer equipped with a three bladed propeller at room temperature. The solution was stirred for 2hrs to allow the solvent to evaporate completely. Liquid paraffin was decanted and the microspheres were collected by filtration through Buckner funnel. The microspheres were washed thrice with petroleum ether until free from oil and dried at room temperature overnight and stored in desiccator [13].

Optimization of microspheres formulation using factorial design

Based on the preliminary trials, optimization was carried out to by 3 level factorial design to produce an effective desirable percent drug entrapment and sustained drug release over 10 hours.

The optimization of the floating microspheres was carried out by taking into consideration the amount of polymer and stirring rate (RPM) as formulation variables and the percentage drug entrapment and time taken to release 90% drug as responses. The relationship between the process variables and the responses were evaluated by 3 level full factorial design and response surface methodology using the software Design Expert 8.04 version [14, 15].

Evaluation of prepared microspheres

a) Micromeritic studies

The microspheres were characterized for their micromeritic properties such as bulk density, tapped density, carr's index and angle of repose. All the analysis was carried out in triplicate [16].

b) Particle size and shape

The surface morphology and internal structure of the products were observed by Scanning electron microscopy (JEOL JSM-T scanning electron microscope, Japan) and particle size was determined using optical microscope (Olympus LITE image) [17].

c) Compatibility studies

The drug-polymer interactions were studied by FTIR and DSC techniques[18].

d) Drug entrapment efficiency

A weighed quantity of microspheres equivalent to 100mg of the pure drug were taken in 100ml volumetric flask and dissolved in 0.1 N HCl using sonication for 5min and the volume was made up to 100ml with 0.1 N HCl. The solution was then filtered through Whatmann filter paper. The absorbance was measured after suitable dilutions with 0.1 N HCl solutions at 225nm by using 0.1N HCl as blank. All the analysis was carried out in triplicate [19].

The percentage drug entrapment was determined using the following equation,

$$\% \text{ Drug entrapment efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoritical drug loaded expected}} \times 100$$

e) *In-vitro* buoyancy studies

This study was carried out using 0.1N HCl as a dispersion medium. 100mg microspheres were weighed and placed over the surface of 300ml of 0.1N HCl at 37±0.5^{0}C with continuous agitation at 100rpm using magnetic stirrer for 8hrs. The microspheres which were floating after 8hrs were collected separately and dried properly and weighed. All the analysis was carried out in triplicate.

The percentage of buoyancy was calculated using the following formula,

$$\% \text{ Buoyancy} = \frac{\text{weight of floating microspheres after 8hrs}}{\text{weight of actually added microspheres}} \times 100$$

f) *In-vitro* drug release studies

This study was carried out in dissolution test apparatus USP type II (Volume 27). The drug loaded microspheres equivalent to 100mg of Ranitidine hydrochloride were introduced in to the 900ml of 0.1N HCl, which was maintained at 37±0.5^{0}C and stirred at 50rpm. 5ml of aliquot was withdrawn at regular predetermined intervals and sink conditions were maintained throughout the study by replacing equal volume of fresh dissolution medium. The samples were diluted to 50ml with 0.1N HCl and analyzed spectrophotometrically at 225nm using 0.1N HCl as blank. All the analysis was carried out in triplicate [20].

g) Drug release kinetics

Data obtained from *in-vitro* drug release studies were fitted to various kinetic models like zero-order, 1st order, higuchi, Korsemeyer and peppas using PCP DISSO V3 to predict the drug release mechanism.

h) Stability studies

Stability studies of the optimized formulation were carried out for accelerated stability testing at 40^{0}C ±2^{0}C with 75% RH ± 5% for a period of 6 months. The selected optimized formulations were packed in high density polyethylene containers, which were tightly plugged with cotton and capped. They were then stored for 6 months and evaluated for their physical appearance, % drug entrapment and $t_{90\%}$ at specified intervals of time and the shelf life of the optimized microsphere formulation was predicted.

RESULTS AND DISCUSSION

Floating microspheres of Ranitidine hydrochloride were prepared by the solvent evaporation method using various proportions of drug and polymer, Eudragit RL-100, by variation of the stirring speed and amount of polymer for quantitative determination of the microspheric characteristics. The study of IR spectra of Ranitidine Hydrochloride has shown in figure 1(a) demonstrated that the characteristic absorption bands for C-H stretch present in alkanes, nitro group, C-0 stretch and N-H stretch at 2974cm^{-1}, 1353cm^{-1}, 1230cm^{-1} and 3267cm^{-1} respectively. All the characteristic peaks of Ranitidine hydrochloride were present in the combination spectra which showed in figure 1(c) indicating the compatibility of the drug with the polymer used.

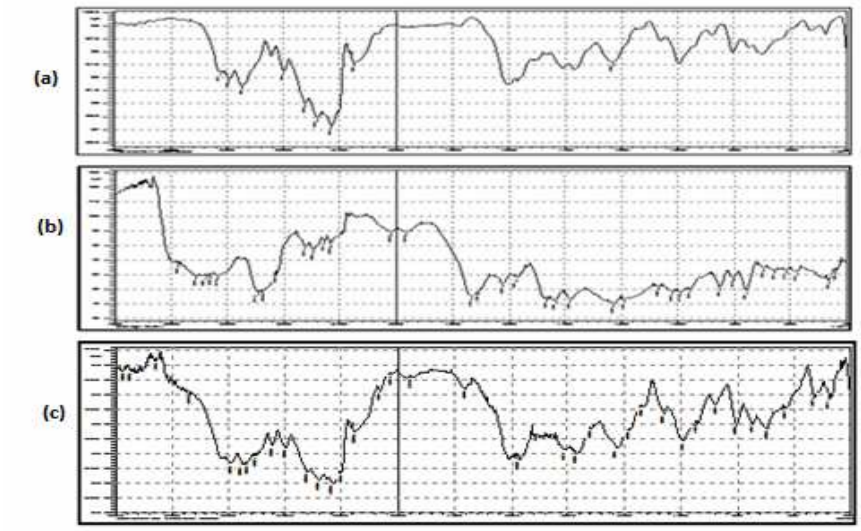

Fig. 1: Infrared spectra of (a) pure drug Ranitidine hydrochloride, (b) polymer Eudragit RL-100 and (c) physical mixture of pure drug and polymer.

The DSC thermogram of pure drug Ranitidine hydrochloride showed a characteristic endothermic peak at 144^{0}C showed in figure 2(a), which is in the range of melting point of Ranitidine hydrochloride. Similar endothermic peak at 146^{0}C as indicated in figure 2(c) was observed in the physical mixture of pure drug and Eudragit RL-100. This study confirmed that there was no interaction between the drug and polymer.

The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules. The compressibility index of the formulations was good, which could be also compressed into tablets. The values of angle of repose were between 22-28^0 that confirmed moderate flow property of the prepared microspheres and the results were shown in table 1.

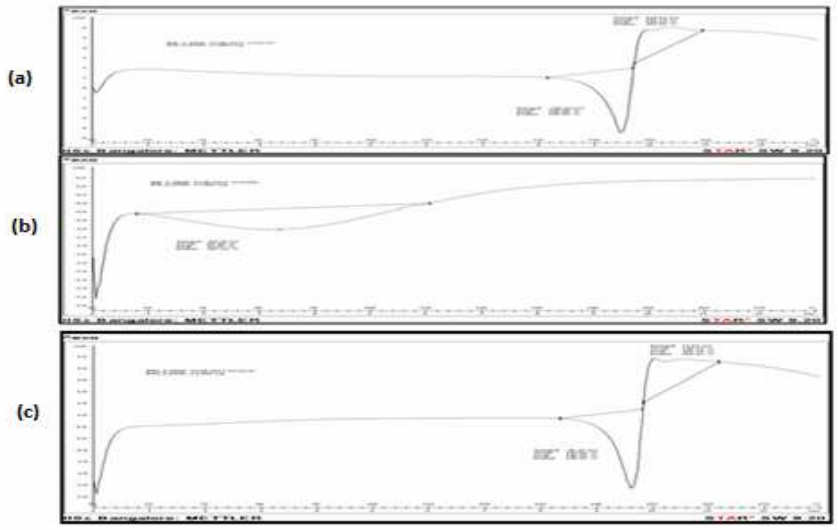

Fig. 2: DSC thermogram of (a) pure drug Ranitidine hydrochloride, (b) polymer Eudragit RL-100 and (c) physical mixture of pure drug and polymer

Table 1: Results of Micromeritic properties of formulation trials of Ranitidine hydrochloride microspheres

Sl. No	Code	%yield	Bulk density (g/ml)	Tap density (g/ml)	Bulkiness (ml/g)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})	Mean particle size* (µm)
1	JP-1	26.9	0.462	0.493	2.16	6.24	1.06	25^034^l	235.85±1.6
2	JP-2	50.90	0.461	0.500	2.16	7.8	1.08	26^056^l	165.86±5.7
3	JP-3	15.27	0.750	0.791	1.33	5.18	1.05	24^035^l	281.21±0.2
4	JP-4	24	0.571	0.666	1.75	14.36	1.16	27^075^l	245.85±2.5
5	JP-5	14.54	0.625	0.714	1.60	12.46	1.14	23^096^l	301.26±1.9
6	JP-6	48.22	0.500	0.580	2.00	13.79	1.16	24^077^l	203.09±2.8
7	JP-7	63.33	0.337	0.385	2.96	12.49	1.14	24^035^l	144.93±2.3
8	JP-8	54	0.376	0.392	2.65	4.08	1.04	22^083^l	213.47±0.5
9	JP-9	33.33	0.468	0.500	2.13	6.26	1.06	25^034^l	207.21±2.8
10	JP-10	56	0.357	0.380	2.83	7.83	1.08	$24^{05}8^l$	150.17±1.4
11	JP-11	30	0.500	0.571	2.00	12.43	1.14	24^044^l	189.23±0.9
12	JP-12	35.63	0.461	0.500	2.16	7.8	1.06	27^021^l	224.34±3.5
13	JP-13	18.18	0.700	0.800	1.42	12.50	1.14	24^044^l	248.12±0.8

*- Average of three determinations

The values of percentage drug content results of microsphere formulations as per optimization design were shown in the table 2.

Table 2: Characterization of the formulation trials of Ranitidine hydrochloride microspheres

Product code	Process variables		Responses		Floating time (hrs.)	Percent buoyancy after 8hrs
	RPM	Amount of polymer	%drug entrapment	$t_{90\%}$ in hrs		
JP-1	400.00	0.50	66.21	3	24	87
JP-2	800.00	0.50	76.60	4	24	89
JP-3	1200.00	0.50	13.62	10	24	73
JP-4	400.00	2.25	62.06	9	24	82
JP-5	800.00	2.25	12.37	10	24	75
JP-6	1200.00	2.25	71.47	8	24	85
JP-7	400.00	4.00	99.47	1	24	96
JP-8	800.00	4.00	97.00	16	24	92
JP-9	1200.00	4.00	68.92	8	24	84
JP-10	800.00	2.25	98.80	8	24	92
JP-11	800.00	2.25	71.43	8	24	86
JP-12	800.00	2.25	68.48	6	24	84
JP-13	800.00	2.25	15.39	8	24	71

As the concentration of polymer increased the viscosity of the polymer solution increased resulting in the formation of larger polymer/solvent droplets. The larger particles takes much time for hardening, allowing time for drug diffusion out of the particles, which tends to decrease encapsulation efficiency. The 3D response surface methodology graph of optimized microsphere formulations was shown in the figure 4 for the percentage drug entrapment.

Factor: Percentage Drug Entrapment

In-vitro buoyancy studies done for almost 24hours, indicating that the microspheres having excellent floating capacity. The relative buoyancies and floating time for all formulations were shown in the table 2**.** Formulations JP-13, JP-3 and JP-5 were found to be less buoyant may be due to the relative density of the microspheres was higher at higher polymer concentrations. The cumulative percent drug release of all the 13 formulations were depicted in graph as in figure 3.

The formulation JP-7 has shown 90% drug release in 1 hour due to smaller microspheres were formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium giving rise to faster release. The formulation JP-8 has shown 90% drug release in 16 hours may be due to impact of stirring. This may be owing to a more rigid complex formed by increased polymer concentration which help in retaining the drug from the matrix and did not allow rapid diffusion of soluble drug from the matrix. The 3D response surface methodology graph of optimized microsphere formulations was shown in the figure 5 for the time taken to release 90% drug ($t_{90\%}$).

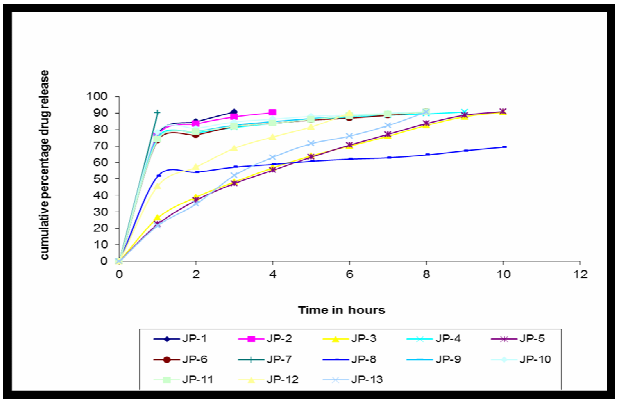

Fig. 3: Cumulative percent drug release of the 13 formulation trials of Ranitidine hydrochloride microspheres, based on optimization.

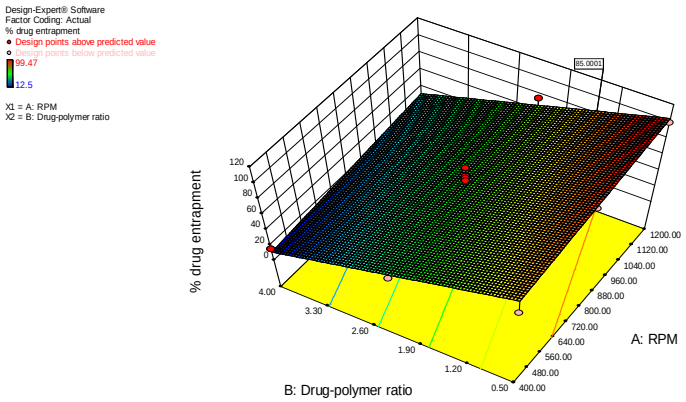

Fig. 4: 3D RSM Graph of Ranitidine Hydrochloride Eudragit Microspheres.

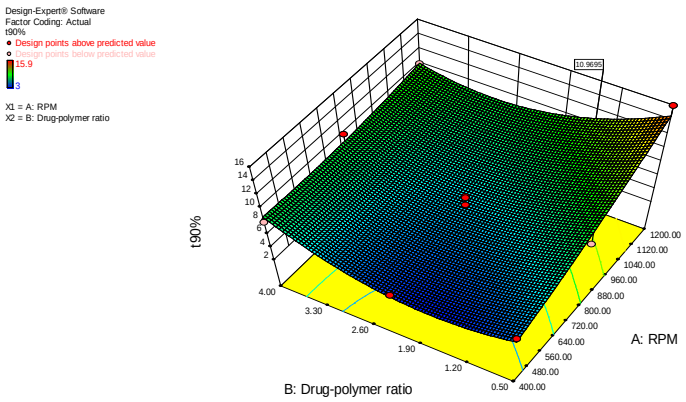

Fig. 5: 3D RSM Graph of Ranitidine Hydrochloride Eudragit microspheres $t_{90\%}$.

Factor: time taken to release 90% drug ($t_{90\%}$)

From the numerical optimization results, JPRH was selected randomly as the optimized formula for the preparation of Ranitidine Hydrochloride microspheres as it showed in table 3 and the results for JPRH were shown in the table 4 which confirmed the closeness of the predicted results with that of the observed results. The optimized formulation JPRH pcp results has shown in table 5 indicating correlation coefficient value 0.983 that showed peppas model would be the most appropriate drug release mechanism where the drug could be release by diffusion process and the curve fit model was shown in the figure 6.

The SEM photograph of the formulation was shown in the figure 7 and the optical microscopic images were shown in figure 8. These showed that the microspheres were smooth, spherical and discrete particles.

Table 3: Optimized formulae and formulation code of Ranitidine hydrochloride microspheres

Method	Drug (g) Ranitidine hydrochloride	Amount of Polymer(g)	Rate of stirring (rpm)	Formulation Code
Solvent evaporation	1.00	1.44	1200.00	**JPRH**

Table 4: Results of the optimized microsphere formulation (JPRH)

Sl.No	Parameters	Observed value*
1	% yield	77.83±3.13
2	Bulk density (g/ml)	0.411±0.08
3	True density (g/ml)	0.453±0.10
4	Bulkiness (ml/g)	2.49±0.48
5	Carr's index (%)	8.86±1.64
6	Hausner's ratio	1.09±0.02
7	Angle of repose (θ)	$24^0 75^{ll} \pm 0.51$
8	% drug entrapment	84.32±0.92
9	% Buoyancy after 8 hrs	91±4.58
10	$t_{90\%}$	9.6±1.52

*- Average of three determinations

Table 5: *In-vitro* curve fits for various release systems for optimized Ranitidine hydrochloride-Eudragit RL-100 microspheres formulation JPRH.

Sl.No	Equation	Regression coefficient (r)	K value
1	Zero order	0.6871	9.9322
2	1st order	0.3213	0.1861
3	Matrix	0.5771	29.3331
4	Peppas	0.9831	56.5185
5	Hixon Crowell	0.7932	0.0493

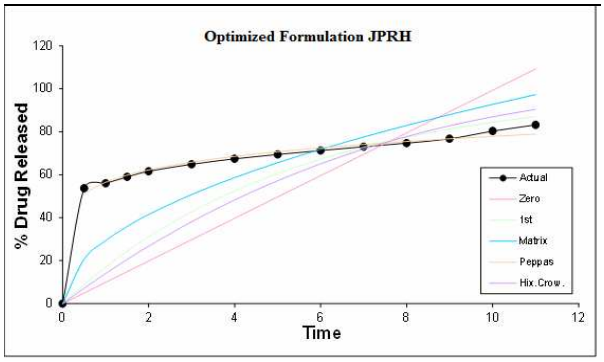

Fig. 6*: In-vitro* release mechanism of optimised Ranitidine hydrochloride-Eudragit RL-100 microspheres formulation (JPRH).

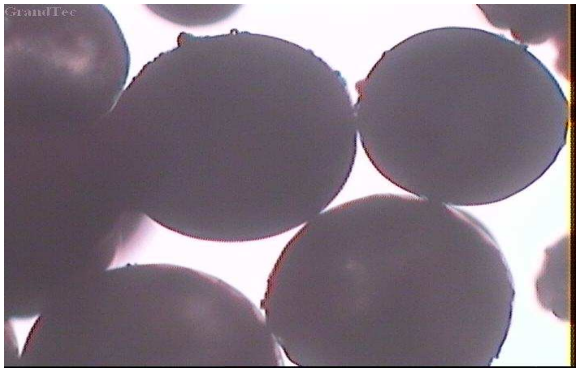

Fig. 7: optical microphotographs of Ranitidine hydrochloride microsphere optimized formulation (JPRH).

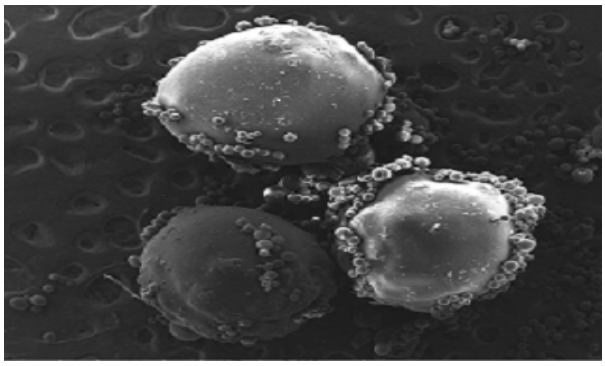

Fig. 8: scanning electron microphotograph of optimized Ranitidine hydrochloride microsphere formulation.

The floating behavior of the optimized formulation was shown in the figure 9.

Fig. 9: Floating behaviour of optimized microspheres formulation (JPRH).

Stability studies revealed that the microspheres kept at elevated temperature of 40^0C and 75% RH showed maximum stability. The values of percentage drug entrapment and $t_{90\%}$ has shown in table 6.

Table 6: Stability studies data of optimized microspheres formulation (JPRH) for accelerated stability condition (40^0C±2^0C with 75%RH±5%).

S.No	Months	Percentage drug entrapment	$t_{90\%}$ in hrs
1	0	100	11
2	2	99.79	11.60
3	4	99.47	11.70
4	6	99.32	12.19

The similarity factor value was found to be 51.561, which were found to be close/ similar to that of initial data confirming that it has an acceptable shelf life up to 2 years.

CONCLUSION

The present study has been a satisfactory attempt to formulate floating microspheres of an anti-ulcer drug, Ranitidine hydrochloride with a view of improving its oral bioavailability and providing a sustained release of the drug.

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