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Research Article

DESIGN AND OPTIMIZATION OFRANITIDINE HYDROCHLORIDE FLOATING MICROSPHERES

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ABSTRACT

Objective: The aim of this study was to develop a gastroretentive microspheres system of an anti-ulcer drug Ranitidine hydrochloride (RH), floating on simulated gastric fluid for more than 12 hours was formulated by solvent evaporation technique.EudragitE-100(E E100) and Ethyl Cellulose(EC), biocompatible polymers were used to form microspheres of RH by response surface methodology

Methodology: The formulated microspheres were characterized for their micromeritic properties,optical microscopy, in-vitro buoyancy studies, percentage drug entrapment efficiency (EE %) and in-vitro drug release studies.Optimization studies were carried out by taking RPM (stirring speed), polymer ratio and type of polymer as independent variables and percentage drug entrapment and in vitro release after 2,6 and 12 hr as responses using 3-level factorial design.

Results and discussion: The formulated microspheres were free flowing and optical microscopy studies indicated that the microspheres were almost spherical in shape. The prepared microsphere formulations having EE% of 47.5%- 79.3% %, and buoyancy of 72 -92% with floating time up to 12 hours. In-vitro drug release studies of RH microspheres showed a controlled release of 12 hours.

Conclusion: The data obtained in this study thus suggest that floating microspheres of an anti-ulcer drug can be successfully designed to give controlled drug delivery and improved oral bioavailability.

Keywords: Gastroretentive, Microspheres, Optimization, Ranitidine hydrochloride.

INTRODUCTION

Drug absorption from oral controlled release (CR) dosage forms is often limited by the short gastrointestinal retention time, available for absorption. Floating drug delivery systems are among the several approaches that have been developed in order to increase the gastric residence time of the dosage forms[1].The synthetic polymer has been used to prepare floating microspheres.The Present study was based on floating microspheres of both hydrophilic and acrylic polymers using (RH) as a model drug. It is an anti ulcer drug that has been widely used in treating gastric and duodenal ulceration and also in Zollinger Ellison syndrome. It is poorly absorbed from the lower GIT and has a short elimination half life of 2-3 hours and bioavailability of 50 %. [2]

MATERIALS AND METHODS

Materials

RH, kindly donated by Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt); EC (BIO BASIC INC, Markham, Ontario-3R1G6, Canada); E E100 (Rohm Pharma GMBH 50.277 1-243 Germany); N-Hexane, Acetone, Heavy liquid Paraffin, Hydrochloric acid (pure lab. Chemicals, USA, El-Nasr chemical company, Cairo, Egypt); SorbitanMonooleate (Span 80), CuangdongUanghuaChemical Co., India. All other chemicals were analytical reagent grades.

Methods

Preparation of Microspheres

RH microspheres were prepared by the emulsion–solvent evaporation technique.The external phase was prepared by addition of (1%) Span 80 in heavy liquid paraffin. The polymers used (EC or E E100) were dissolved in acetone until clear solution was obtained. The required amount of the drug was then added to obtain the internal phase. The external phase was mixed with the internal phase to carry out the emulsification process. Acetone was allowed to evaporate by continuous stirring at different speeds and then at room temperature using magnetic stirrer. Stirring was continued at room temperature until complete evaporation of the solvent, (about 5 hours). Liquid paraffin was decanted and the microspheres produced were filtered off, washed three times with n-hexane (3× 50 ml) to remove the remaining oily phase and then dried over night at room temperature (25°C).

Table 1: Suggested formulae of RH microspheres

Formula No.	RH (mg)	EC (mg)	E E100 (mg)	Span 80	D:P R	Speed (rpm)
F1	500	1250	---	1%	1:2.5	300
F2	500	625	625	1%	1:2.5	400
F3	500	625	625	1%	1:2.5	400
F4	500	500	---	1%	1:1	400
F5	500	---	500	1%	1:1	400
F6	500	---	1250	1%	1:2.5	500
F7	500	1000	1000	1%	1:4	500
F8	500	250	250	1%	1:1	300
F9	500	---	2000	1%	1:4	400
F10	500	---	1250	1%	1:2.5	300
F11	500	250	250	1%	1:1	500
F12	500	1000	1000	1%	1:4	300
F13	500	2000	---	1%	1:4	400
F14	500	625	625	1%	1:2.5	400
F15	500	1250	---	1%	1:2.5	500

Table 2: Box-Behnken design for RH microspheres

Formula No.	Speed (X1) RPM	Drug-polymer ratio (X2) Ratio	Type of polymer (X3) Polymer
F1	300	1:2.5	EC
F2	400	1:2.5	EC/E E 100
F3	400	1:2.5	EC/E E 100
F4	400	1:1	EC
F5	400	1:1	E E 100
F6	500	1:2.5	E E 100
F7	500	1:4	EC/E E 100
F8	300	1:1	EC/E E 100
F9	400	1:4	E E 100
F10	300	1:2.5	E E 100
F11	500	1:1	EC/E E 100
F12	300	1:4	EC/E E 100
F13	400	1:4	EC
F14	400	1:2.5	EC/E E 100
F15	500	1:2.5	EC

Optimization of microspheres formulation using factorial design (Box-Behnken design)

Optimization was carried out by the 3 level factorial design to produce the desirable effective percent drug entrapment and a sustained drug release pattern over 12 hours. The optimization of the floating microspheres was carried out by taking into consideration the type of polymer used, the amount of polymer and the stirring rate (RPM) as formulation variables and the percentage drug entrapment and the in vitro drug release at different times(2hr-6hr-12hr) as responses. The relationship between the process variables and the responses were evaluated by the 3 level full factorial design and response surface methodology[3,4].

The suggested formulae of RH microspheres were tabulated in tables (1, 2).

Determination of the entrapment efficiency in the prepared microspheres:

The EE% of RH microspheres was determined in 0.1 N HCl by the following Method:[5]

A weighed quantity of microspheres equivalent to 100mg of the pure drug was 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 (0.45 µm membrane filter). The absorbance was measured after suitable dilutions with 0.1 N HCl solutions at 312.6 nm by using 0.1N HCl as blank. All analyseswere carried out in triplicates.

Micromeritic properties of the prepared RH microspheres

The prepared microspheres were evaluated through determination of the following parameters:

a-Densities of microspheres

Both loose bulk density (Db) and tapped bulk density (Dt) were determined. A quantity of 10g microspheres from each batch was introduced into a 10 ml measuring cylinder. The initial volume was observed, and then the cylinder was allowed to stroke. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula:[6]

D b = Wt/ bulk volume = W/V b

D t = Wt/ tapped volume = W/V t

b-Hausner Ratio

It is the ratio between bulk density and tapped density. It gives an idea about the flow characters of powder particles. [7]

Hausner ratio = D t / D b

c- Compressibility percent (Car's Index)

Compressibility is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. The compressibility percent of a material can be estimated as:[8]

Compressibility % = (D t – D b / D t) × 100

d- Angle of Repose

It was measured by passing the microspheres through a funnel which was maintained at a fixed height in all experiments. The height (h) and radius (r) of the cone were determined. The angle of repose is calculated from the equation:[9]

Tan Θ = h/r

In-vitro buoyancy of RH microspheres

The floating microspheres (100 mg) were spread over the surface of the dissolution medium (simulated gastric fluid, SGF, pH (1.2) that was agitated by a paddle rotated at 100 rpm. after agitation for a predetermined time interval, the microspheres that floated over the surface of the medium and those settled at the bottom of the flask were recovered separately. after drying, each fraction of the microspheres was weighed and their buoyancy was calculated by the following equation: [1]

Buoyancy (%) = Qf / (Qf + Qs)

Where Qf and Qs are the weight of the floating and the settled microspheres respectively

In-vitro Release Study

The in-vitro release of RH from the prepared microspheres in hard gelatin capsules filled with known amount of microspheres (equivalent to 100 mg of RH) was carried out at 37 ± 0.5 °C for 12 hours, using apparatus II[1].The baskets were rotated at 100rpm. The dissolution medium was 900 ml 0.1 N HCl pH 1.2. Samples of 5 ml were withdrawn and replaced with fresh medium at appropriate time intervals.The drug content in the filtered samples was measured spectrophotometrically at 312.6 nm after suitable dilutions. The release experiments were repeated in triplicates.

RESULTS AND DISCUSSION

Entrapment efficiency (EE%) of RH microspheres

The range of the EE% of the prepared microspheres was found to be between 47.5% for formula F5and 79.3% for formula F13 as shown in table (3)

Figures (1-2)showed the effect of the different independent variables on EE% of RH microspheres.As the polymer ratio increased (X_2), the EE% (Y_1) decreased[10,11, 12,and 13]. Increasing the speed of rotation (X_1), EE% was decreased. Polymer type (X_3) affected the EE% of RH microspheres as EE%increase in case of RH/EC microspheres as compared with RH/E E100 microspheres.

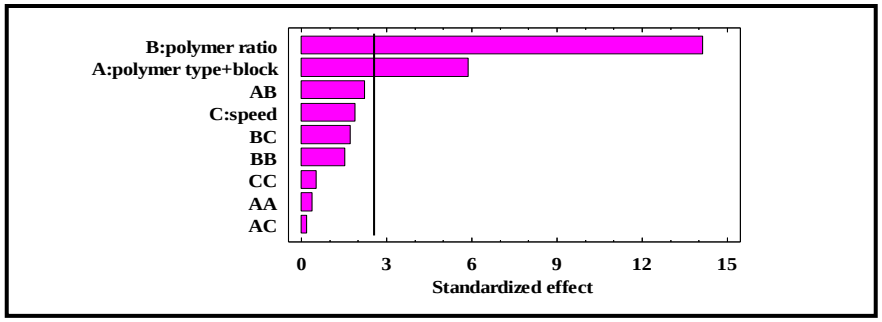

Fig. 1: Standardized pareto chart for Entrapment efficiency

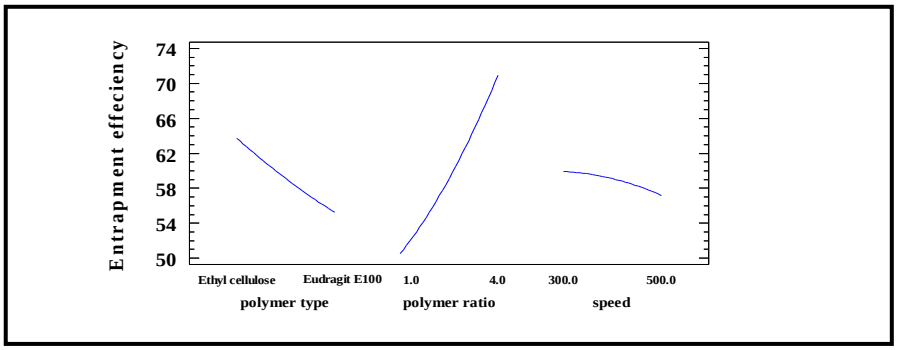

Fig. 2: Main effect plot on Entrapment efficiency

From the figures, there is a direct proportionality between X_2 and (Y_1). While, there is an inverse proportionality between $X_1$and (Y_1).

Micromeritic properties of RH microspheres

The prepared RH microspheres were studied for their micromeritic properties, which include the angle of repose, bulk and tapped densities, Hausner ratio, and compressibility index.

a- Angle of repose (θ)

The values of angle of repose of prepared RH formulae ranged from 19.8° to 29.14° which may give indication that microspheres had good flowability. Concerning the data obtained for the angle of repose for the prepared RH microspheres,See table (3).It was found thatF9showed the best value (19.8°) with excellent flowability while formula F11 showed the worst value (29.14°) with good flowability

b- The bulk and tap densities

The flow properties of the microspheres were investigated by measuring the bulk density, tapped density and Carr's index[14, 15]. Both the bulk and tap densities were determined with equations described above.

c- The Hausner ratio

The value of the Hausner ratio was found to give indication about the flow properties of microspheres. The values<1.25 indicate better flowability than values>1.25 [16].According to the data obtained for Hausner ratio for the prepared RH microspheres, it was found that F13showed the best value (1.11) which indicated good flowability while formula F11 showed the worst value (1.22) which indicated poor flowability.

d- Compressibility % (Carr's index)

The maximum compressibility percent for the tested RH formulae was 18.51% for formula F11 which indicatedfair passable flowability and the minimum one was 10% for formula F13 whichindicated excellent flowability.

Table 3: Micromeritics parameters, EE%and Percentage of buoyant RH microspheres

F. No.	Angle of repose (θ) (AR)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio (HR)	Carrs index (CI)	EE%	%of buoyant microspheres
F1	23.14	0.525±0.005	0.610±0.002	1.161	13.88	62.1±0.2	79+2.2
F2	24.05	0.489±0.002	0.579±0.001	1.184	15.55	59.1±0.5	83+2.5
F3	24.05	0.489±0.002	0.579±0.001	1.184	15.55	59.1±0.4	83+3.3
F4	28	0.450±0.001	0.536±0.001	1.190	16	53.9±1.3	90+4
F5	22	0.325±0.003	0.395±0.002	1.217	17.85	47.5±1.4	92+4.4
F6	20.85	0.462±0.004	0.555±0.002	1.2	16.66	55.4±1.1	86+3.9
F7	23.7	0.557±0.003	0.644±0.001	1.155	13.46	66±1.23	78+2.1
F8	27.47	0.398±0.003	0.472±0.002	1.185	15.62	50.8±1.6	88+2.3`
F9	19.8	0.531±0.004	0.616±0.001	1.16	13.79	63.8±1.5	75+2.2
F10	20.3	0.484±0.003	0.564±0.001	1.16	14.28	56.5±1.4	80+3.1
F11	29.14	0.363±0.001	0.446±0.003	1.22	18.51	49.6±0.46	91+2.7
F12	21.04	0.599±0.006	0.674±0.002	1.125	11.11	74.3±0.7	72+1.9
F13	20.3	0.627±0.005	0.696±0.001	1.11	10	79.3±1.3	73+2.8
F14	24.05	0.489±0.004	0.579±0.002	1.184	15.55	59.1±0.9	83+1.7
F15	24.9	0.505±0.005	0.594±0.002	1.176	15	61.8±0.3	84+3.4

In-vitro buoyancy of RH microspheres

Microspheres still continued to float without any apparent gelation, thus indicating that microspherescan exhibit excellent buoyancies. The relative density of the microspheres is higher at higher polymer concentrations. So, the microspheres having higher polymer concentrations were less buoyant than those with lower polymers concentrations[1, 2]. The formula F5 showed highest buoyancy of 92±4.4% while the formula F12 showed the lowest buoyancy of 72±1.9% as showed in table(3).

In-vitro release of RH microspheres

In vitro drug release showed a biphasic release pattern for all formulae with an initial brust effect as showed in figures (9-11).The cumulative percentage of drug release after 12 hr ranged from 53.1%to 99.9%for the formulaeF13, F5 respectively. Figures(3-8) showed the main effect plot and interaction effects of X_1, X_2 and X_3 on Y_2,$Y_3$and Y_4 (release of RH after2, 6 and12hr). Increasing speed of rotation(X_1); in-vitro release of RH was increased.It was also observed that as polymer ratio (X_2) increased, the drug release was decreased as the increased density of the polymer matrix at higher polymer concentration resulted in an increased diffusional path length.

Furthermore, smaller microspheres were formed at lower polymer ratio and had a larger surface area exposed to dissolution medium,resulted in faster drug release[17, 18, 19]The polymer type (X_3) either EC or E E100 or combination of the both polymers was affected the release of RH as the release of drug from RH/E E100 microspheres was higher than RH/EC microspheres.

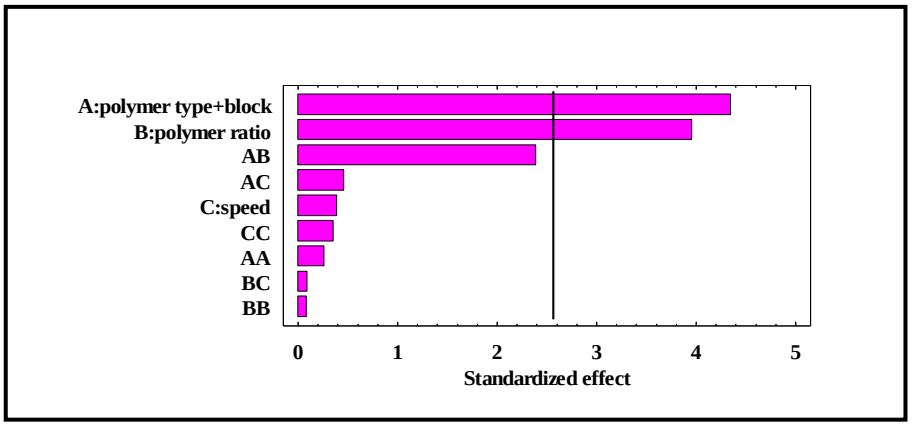

Fig. 3: Standardized pareto chart for in vitro 2 hr

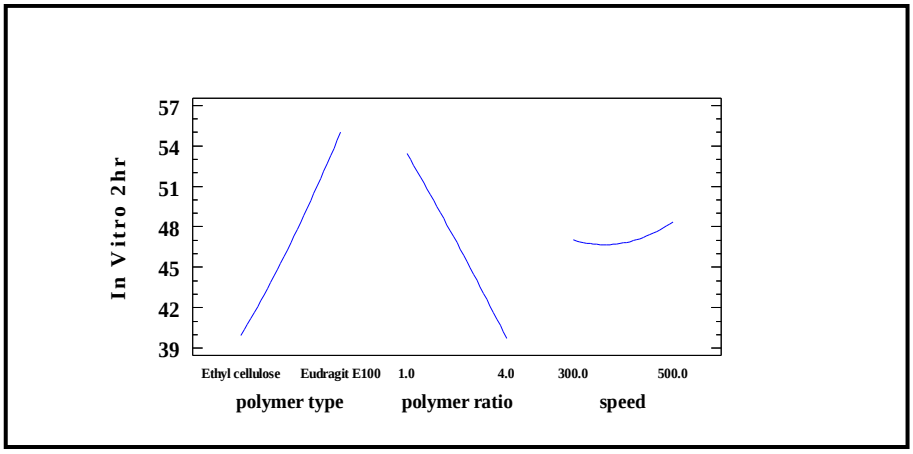

Fig. 4: Main effect plot for in vitro 2 hr

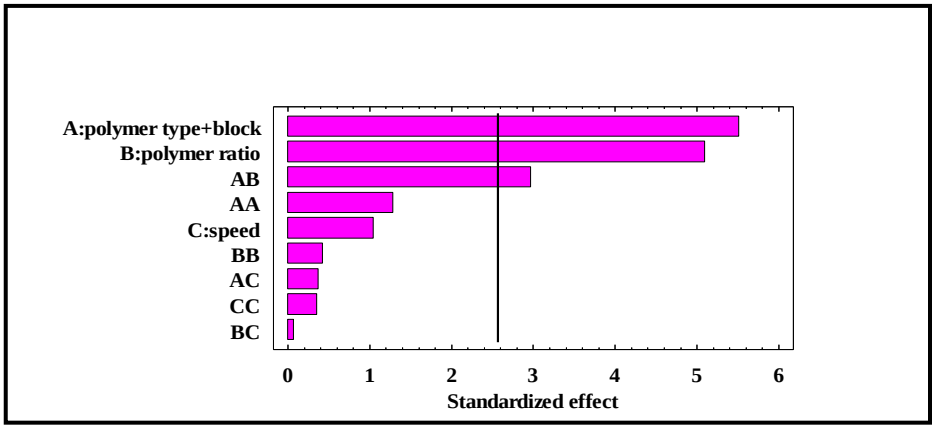

Fig. 5: Standardized pareto chart for in vitro 6hr

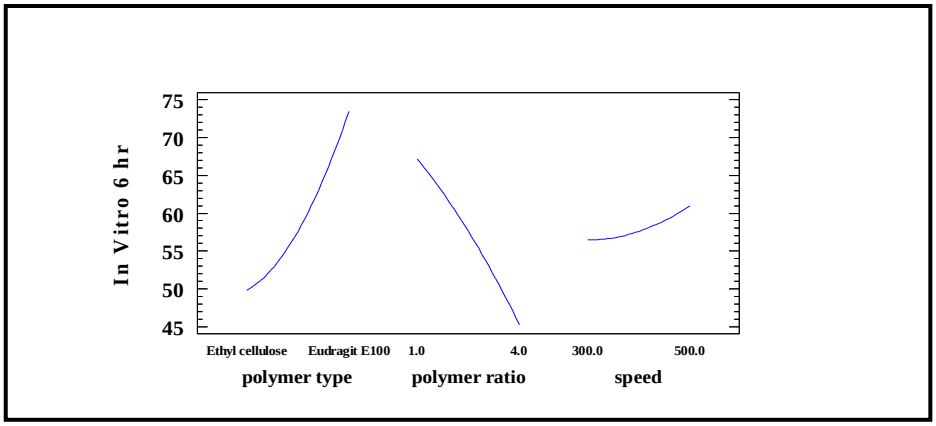

Fig. 6: Main effect plot for in vitro 6hr

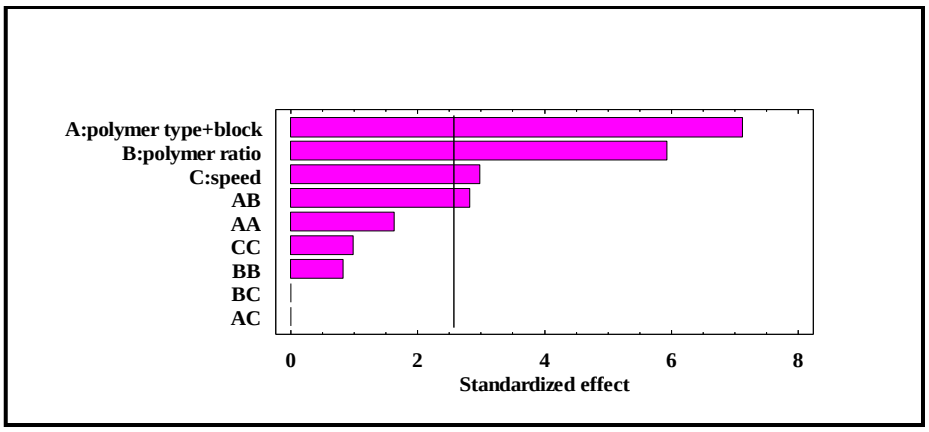

Fig. 7: Standardized pareto chart for in vitro 12hr

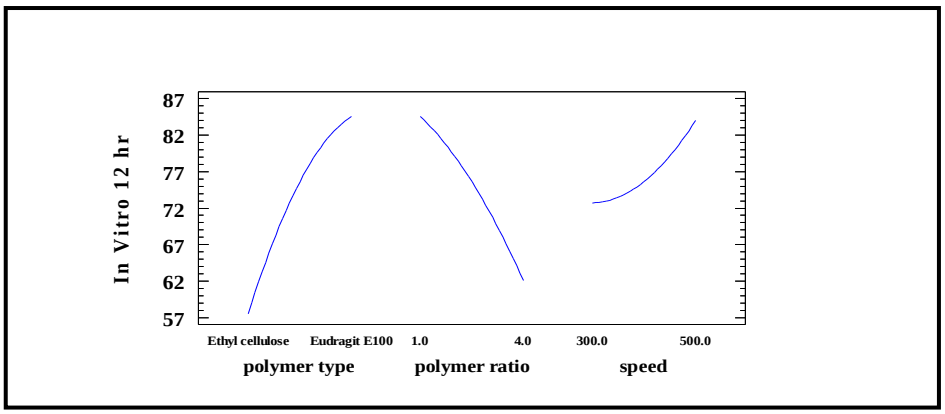

Fig. 8: Main effect plot for in vitro 12hr

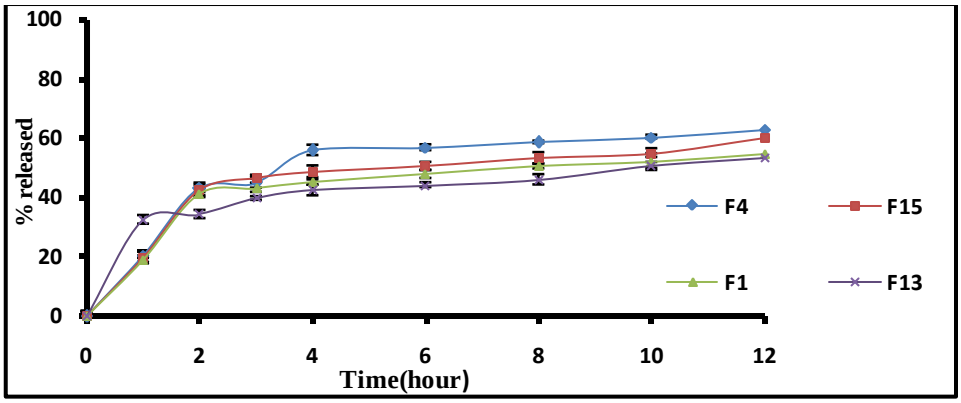

Fig. 9: In-vitro release of drug from RH-EC microspheres

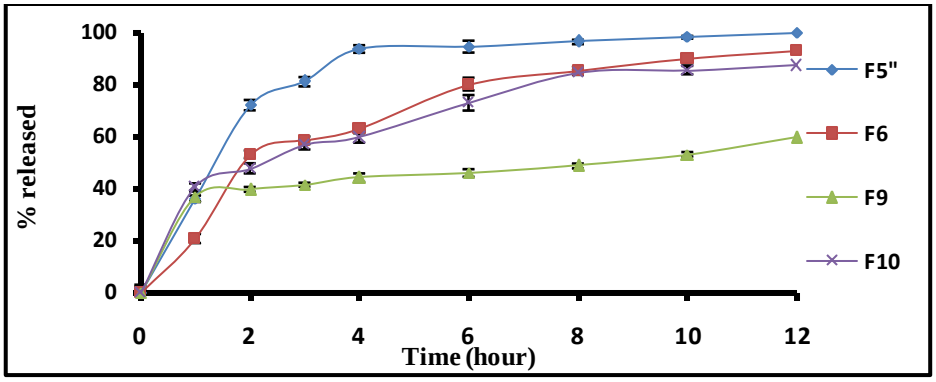

Fig. 10: In-vitro release of drug from RH-E E100 microspheres

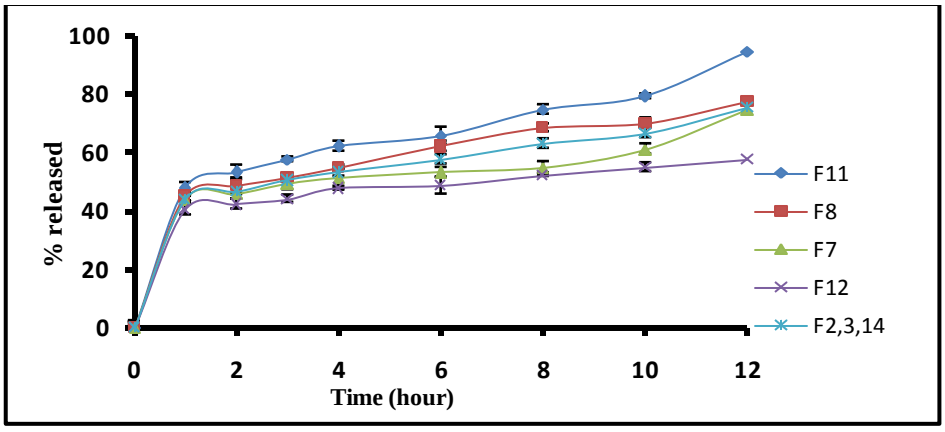

Fig. 11: In-vitro release of drug from RH-EC/E E100 microspheres

These variables were optimized with a fifteenth run Box-Behnkendesign as shown in table (1), when using E E100 as a polymer of ratio 1.8 and rotation of speed 450 rpm, optimum response for the entrapment efficiency (51.5%), for the in-vitro release after two hour (60.3), for the in-vitro release after six hours (83.6%), and for the in-vitro release after twelve hours (95.5%) and the resulted microspheres had spherical shape as showed in figure (20).

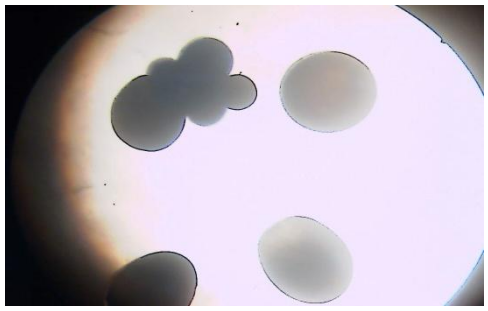

Fig.12: Microscopic evaluation of optimized formula

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.

REFERENCES

1. Singh, V. and Chaudhary, K.A., Preparation of Eudragit E100 microspheres by modified solvent evaporation method, ActaPoloniaePharmaceutica Drug Res., 68(6)975-980(2011).
2. Mastiholimath, V.S., Dandagi, P.M., Gadad, A.P., Mathews, R., and Kulkarni, A.R., In vitro and in vivo evaluation of Ranitidine hydrochloride ethyl cellulose floating microparticles, J. of Microencap.,25(5):305-314(2008)
3. Brijesh, S.D., Avani F.A and Madhabhai M.P, Gastro retentive drug delivery system of ranitidine hydrochloride: formulation and in-vitro evaluation, AAPS Pharm. Sci. Tech.; 5(2), pp: 1-6.(2004)
4. Jayavadhan, P., Darshana.P and Jignyasha R., Formulation andevaluation of Propronolol hydrochloride-loaded carbopol934P/Ethyl cellulose muco adhesive microspheres. Iranian J.Pharm. Res.; 9(3), pp: 221-232,(2010)
5. Marabathuni, V.J., Deveswaran, r., Bharath, S., Basavaraj, B.V. and Madhavan, V., Design and optimization of multiparticulategastroretentive delivery system of Ranitidine Hydrochloride,Int.J.of pharmaceutical science,4(2)(2012)
6. Tayade, P.T., and Kale, R.D., Encapsulation of water- insoluble drugs by a cross-linking technique: Effect of process and formulation variables on encapsulation efficiency, particle size, and in vitro dissolution rate, Pharm. Sci., 6, 12 (2004)
7. Kumar, V., Medina, M.L.R., Yang, D., Preparation, Characterization, and Tableting Properties of a New Cellulose-based Pharmaceutical Aid., Int. J. Pharm., 235 (1–2), 129–140 (2002).
8. Staniforth, J., (2002) in "Powder flow In Pharmaceutics", Aulton M.E., (ed.). 2nd Ed., Churchill Livingstone, London, P. 207
9. Sajeev, C., Vinay, G., Archna, R., and Saha, R.N., Oral controlled release formulation of diclofenac sodium by microencapsulation with ethylcellulose, J. Microencapsul., 19, 753- 760 (2002)
10. Shariff, A., Manna, P.K., Paranjothy, K.L.K., and Manjula, M., Entrapment of andrographolide in cross linked alginate pellets, Pak. J. Pharm. Sci., 20, 1- 9 (2007)
11. Punitha k., Khadhir, S., Ravichandiran, V., Umadevi, S.K., Vaijayanthi,V., Padmapriya, S., and Sureshkumar, S., Intragastric floating drug delivery system of Ranitidine hydrochloride: formulation and evaluation, Int.J. of pharm. And pharmaceu.Sci.2(4)(2010)

12. Kumar, H., Kymonil, k.m., Saraf, S.A., Gastro retentive Ethyl Cellulose Floating Microspheres containing Ranitidine hydrochloride, Int.J. of drug devolp.&res. 4(2)(2012)
13. Rafati, H., Coombes, A., Adler, J., Holland, J.,and Davis, S., Protein-loaded poly(dl-lactide-co-glycolide) microparticles for oral administration: formulation, structural and release characteristics, J. Controlled Release, 1997; 43: 89-102.
14. Sahoo, S.K., Mallick, A.A., Barik, B.B., and Senapati, P.C., Formulation and in vitro Evaluation ofEudragit® Microspheres of Stavudine. Trop. J. Pharm. Res., 4, 369-375 (2005).
15. Sahoo, S.K., Mallick, A.A., Barik, B.B., and Senapati, P.C., Preparation and in vitro evaluation of ethylcellulose microspheres containing stavudine by the double emulsion method.Pharmazie, 62, 117-121 (2007).
16. Bhowmik, D., Chiranjib. B., Krishnakanth, Pankaj, R., Chandira, M., fast dissolving tablet., J. Chem. and Pharm. Res., 1(1), 163-177 (2009).
17. Gardouh, A.R.M., A pharmaceutical study on the microencapsulation of fluoxetine hydrochloride, (2007)
18. Ahmed, A.M.S., El-Say, K.M. and Fetouh, M.I., Effect of polymer on the formulation, micromeritic properties, in-vitro evaluation and stability testing on Ibuprofen microcapsules prepared by the emulsion solvent- evaporation technique, Az. J. Pharm. Sci., 28, 267-284 (2001).
19. Murtaza, G., Ahmad, M., and Shahnaz, G., Microencapsulation of Diclofenac Sodium by Nonsolvent Addition Technique, Trop. J. Pharma. Res., 9, 187-195 (2010)