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DEVELOPMENT AND OPTIMIZATION OF RANITIDINE HYDROCHLORIDE NANOSPHERS BY 3^2 FACTORIAL DESIGN

Sundar lal tripathi*, kapil rana, vaibhav rathore, abhinav kumar
Teerthanker mahaveer college of pharmacy,Teerthanker mahaveer university Moradabad (U.P.)

Abstract
The preparation and physico-chemical evaluation of ranitidine hydrochloride loaded namosphers as per 3^2 Factorial Design are describe the eudragit s (X1) and polaxamer338 solution (X2) as a stabilizing agent were used as independent variables where Particle size (PS) (Y1), Entrapment Efficiency (EE) (Y2) and % Drug Release at 12th h (REL)(Y3) were taken as dependant variables. Rantidine nanosphers were prepared by nanoprecipetation method. The results showed the method as reproducible, easy and efficient is the entrapment of drug as well as formation of spherical nanosphers. Effect of polymer concentration was also evaluated with respect to their % drug entrapment efficiency. The *in vitro* release studies indicated the rantidine-loaded eudragite s nanosphers provide sustained drug release over a period of 12h. The f_5 optimized batch was shown particle size 195 nm, EE59 and57% drug release at 12th h. Infrared spectroscopy analysis revealed that there was no known chemical interaction between drug and polymer. Hence, this investigation demonstrated the potential of the experimental design in understanding the effect of the formulation variables on the quality of ranitidine nanosphers.

Keywords: - Ranitidine hydrochloride, nanoprecipitation, nanosphers,factorial design.

Introduction
Nanosphers are solid colloidal particles or dispersion with diameters ranging from 1 - 1000 nm.(1)Nanosphers can be prepared from various type of compounds such as proteins, polysaccharides and synthetic polymers. The selection of nanosphers prepareing materials is dependent on many factors including (a) size of nanosphers required; (b) inherent properties of the drug, e.g., aqueous solubility and stability; (c) surface characteristics such as charge(zeta potencial) and permeability; (d) degree of biodegradability, biocompatibility and toxicity; (e) Drug release profile desired; and (f) antigenicity of the final product(2)nanosphers can avoid rapid clearance by phagocytes due to their small tiy volume size and duration of the nanosphers in blood strem is greately prolonged(3) naosphers are protects the drugs against premature degradation and controle the time and rate of drug release(4)nanosphers targets the drug at desire site ,improve the therepeutice efficiency and minimizing the unwanted toxice effects(5) Nanocarriers resistance occurred by the physiological barriers in the body because delivery of drug to various parts of the body is directly affected by particle size. (6) Nanosphers have a very high surface to volume ratio. This provides a high driving force for diffusion, especially at elevated temperatures(7) Nano carriers are some where 100 to 10000 times smaller human cells. They are similar in size to biological molecules such as enzymes and receptors.(8)

Correspondence Address:
Sundar lal tripathi
Teerthanker mahaveer college of pharmacy
Teerthanker mahaveer university, Moradabad (U.P.)
E-mail: sundertripathi@yahoo.com
Ph. no.: +91 – 9897956515

Material and Methods
Rantidine hydrochloride Eudragit S-100 obtained from sigma Aldrich Mumbai, polaxamer 338 methenol , ethanol and dichloromethane was purches from s.d fine chemical Mumbai

Preparation of nanosphers
Rantidine loaded nanosphers were prepared using nanoprecipitaion method , Drug and polymer in different proportions were weighed and co-dissolved at

room temperature into a mixture of ethanol and dichloromethane (1:1% v/v) by magnetic stirring.This was slowly poured drop wise into the dispersion medium consisting 20mlof 1% poloxamer 338,and containing 1.5% span 80 During sonication by prob sonicators for 2hrs in presence of ice bath after that system was put on magnetice stirrer for over night for complete evaporation of organice solvents. The prepared suspension was centrifuged at 19,000 rpm for 2 hours The supernatant was removed and the sediment was freeze dried for 48 hrs for further analysis.

Factorial Design

A 3^2 full factorial design was used in the present study. In this design 2 factors namely amount of eudragit s100 (X1) and the polaxamer 338 solution (X2) are evaluated, each at 3 levels (table no.1a & 1b), and experimental trials were performed at all 9 possible combinations. The amount of eudragit s100 (X1) and the Polaxamer solution (X2) were chosen as independent variables. As shown in equation (1), a statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X_1^2 + b22X2^2 \text{-(1)}$$

Where Y are the dependent variables, namely, particle size (nm) (Y1), % entrapment efficiency (Y2) and release at 12th h (Y3); b0 is the arithmetic mean response of the 9 runs. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X1X2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X12 andX22) are included to investigate nonlinearity. The simplified models were then utilized to produce threedimensional response surface plots and contour plots to analyze the influence of independent variables .(9,10)

Evaluation of the nanosphers

Particle size and zeta-potential analysis (11)

The mean particle size of drug-loaded Nanosphers and zeta potential of all formulations was determined by a Malvern Zetasizer Nano ZS (Malvern Instrument Ltd., Worcestershire, United Kingdom). The mean particle size (Z average) of each sample was determined.

Surface morphology(12)

scanning electron micrographs of ranitidine loaded Nanosphers showed that the sphers have a ununiform shape with a and they are un uniformly distributed. It also confirmed the particle size, which was obtained by particle size analysis.

Determination of drug entrapment efficiency (13)

Appropriate amount of freeze-dried PLGA nanosphers were digested with minimum amount of 0.01N HCl for 24h at room temperature with intermittent shaking. The digested homogenates were filtered and filtrate was analyzed for drug entrapment. The content of ranitidine hydrochloride was determined UV spectrophotometrically at 315 nm using Shimadzu-1700 UV/VIS.

$$\% \text{ drug encapsulation efficiency} = \frac{\text{Actual drugcontent}}{\text{Theoretical drug content}} \text{ X } 100$$

IN vitro release (14)

In vitro release of ranitidine from freeze-dried formulations and pure drug was studied in 0.01N HCl(900ml) using a USP dissolution apparatus type II with rotating paddle at 50 rpm and temperature was maintained at 37±0.20C in triplicate. The sample weight of formulations equivalent to 300 mg of ranitidine was used for dissolution study. At different time interval aliquots were withdrawn, filtered through Whatman (No.40) filterpaper and analyzed using Shimadzu-1700 UV/VIS. Spectrophotometer at 315nm after suitable dilution.

Infrared analysis of samples.

The ir spectra of pure ranitidine hydrochloride ,and ranitidine hcl with eudragit s 100 was taken and interpretet and compared with each other.

Results and Discussion

After preliminary screening eudragit s 100 polymer and polaxamer 338 were decided as suitable carrier and stabilizer respectively. The effect of formulation variables namely amount of eudragit s 100 (X1) and polaxamer 338 (X2) was studied using statistical optimization technique using 3^2 factorial design. Preliminary studies decided the levels at which factors will be studied. The particle size, EE and release at 12th h for the 9 batches (fi to f9) showed a wide variation 120-370nm, 58.50- 62.50 and 27-57 respectively (Table no. 1a). The data clearly indicated the dependence of response variables on the selected independent variables. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries

$$P_S = 218.33 + 114.17x_1 + 8.33x_2 - 1.25x_1x_2 + 37.50x_1^2 - 15.00x_2^2 \text{-(2)}$$
$$E_E = 54.33 + 8.33x_1 + 3.83x_2 + 1.50x_1x_2 - 12x_1^2 - 1.50x_2^2 \text{-(3)}$$
$$R_E = 51.42 + .37X_1 + 3.33X_2 + 1.50X_1X_2 - 13.93X_1^2 - 1.13X \text{----(4)}$$

Three-dimensional response surface plots for all response variables are presented in Fig.1, Fig.2 and Fig.3,

which are very useful to study the interaction effects of the factors on the responses. The response surface depicts effect of factor contributions at different levels on studied response.

Fig.1 reveals a decline in the value of particle size with increase in concentration of surfactant(polaxamer 338). At higher drug: polymer the particle size is more. The highest particle size recorded at low surfactant and high drug polymer ratio.

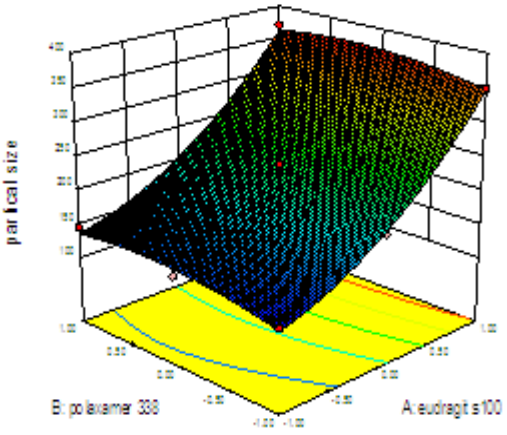


Fig. 1 Response surface plot for Particle size (Y1).

Fig. 2 reveals decrease in the value of % entrapment efficiency with increase in polymer (eudragit s100) content of the formulation, followed by an increase with decreasing value of polymer content and again decreased % EE with lower polymer concentration.

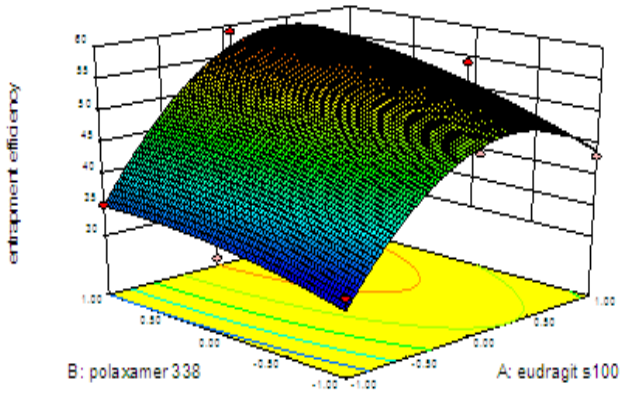


Fig. 2 Response surface plot for Entrapment Efficiency (Y2).

Fig. 3 reveals decrease in the value of % release with increase in polymer (eudragit s 100) content of the formulation.

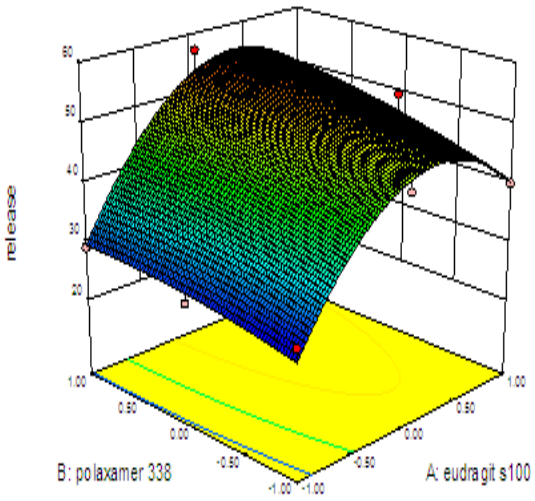
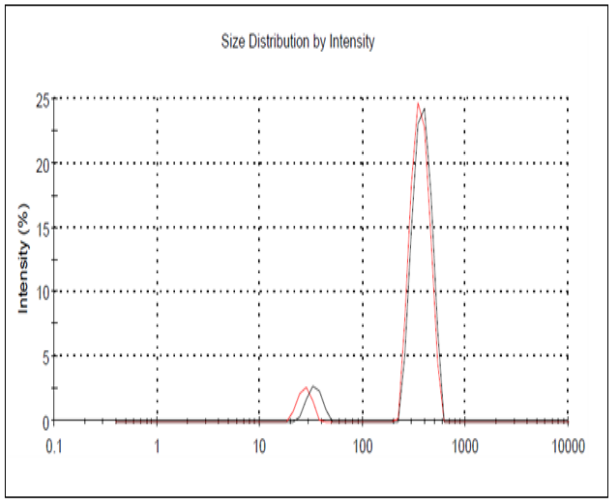
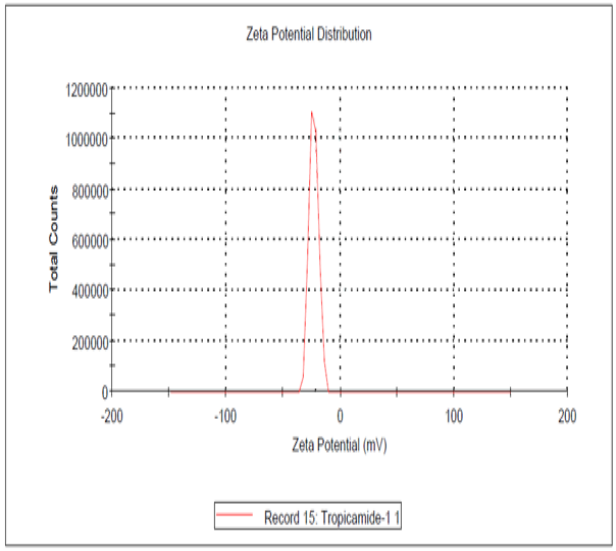


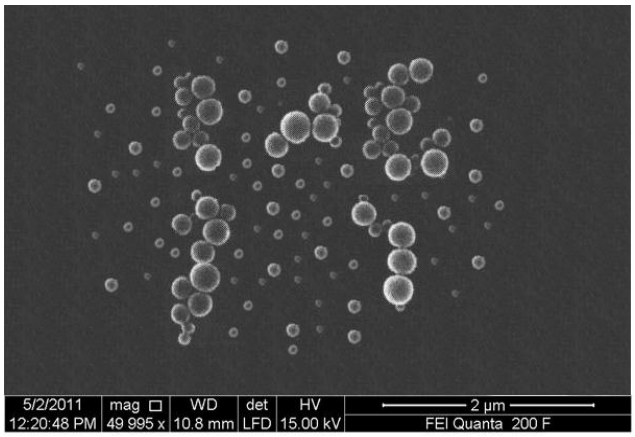
Fig. 3 Response surface plot for release (Y3).

Particle size and zeta-potential analysis





Surface morphology



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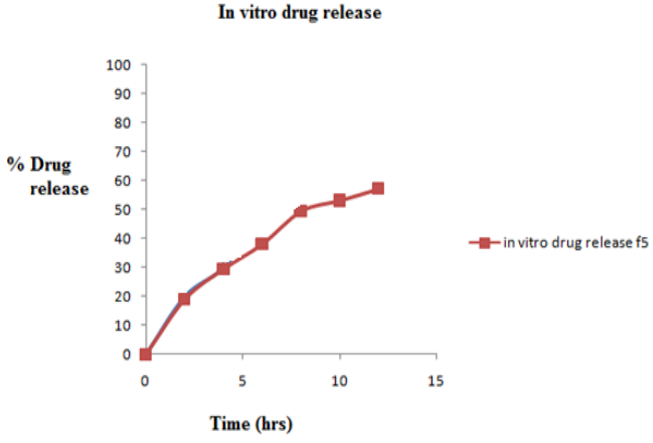

Infrared analysis of samples

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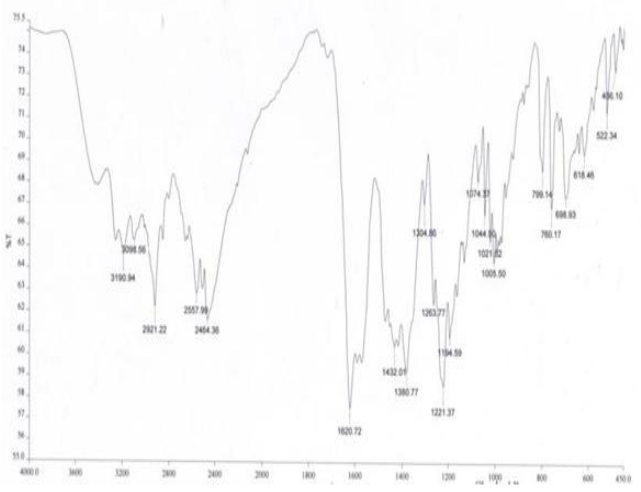
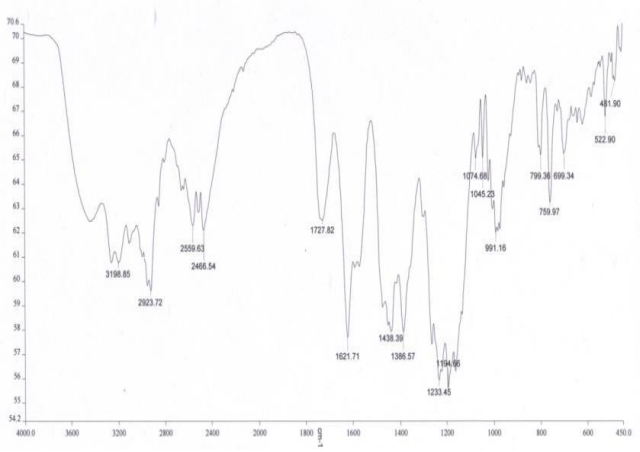


FTIR spectrum of Ranitidine HCl



FTIR spectrum of mixture of Ranitidine HCl and Eudragit S100

Table 1a Design matrix of independent and dependant variables as per 3^2 factorial design.

Run	X_1	X_2	Y_1P_S	Y_2E_E	Y_3R_{EL}
F_1	0.00	0.00	240	53	50
F_2	-1.00	0.00	130	32	27
F_3	0.00	-1.00	190	48	45
F_4	-1.00	-1.00	120	32	28
F_5	0.00	1.00	195	59	57
F_6	1.00	-1.00	350	43	40
F_7	-1.00	1.00	145	35	29
F_8	1.00	1.00	370	52	47
F_9	1.00	0.00	360	54	49.4

Table 1b Coded levels in actual values.

Independent Variable	Coded Levels and Actual Values		
	-1	0	1
X_1 (EUDRAGIT S 100)	300	400	500
X_2 (POLAXAMER%)	1	2	3

Conclusion

In the present study, the potential of eudragit s 100 nanosphers as drug carriers for gastric delivery was investigated. The method of preparation of nanosphers of ranitidine was found to be simple and reproducible. The *in vitro* release studies showed that the drug is released from the formulation over a period of 12 hr in a sustained release manner. This study shows that eudragit s 100 nanosphers could be a useful carrier for ranitidine.

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