International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1639-1647 www.ijprajournal.com ISSN: 2249-7781

Deveopment and Optimization of Nasal Mucoasdhesive Microshpres for Fexoefanadine Hcl

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Submitted: 10-04-2023 Accepted: 22-04-2023

ABSTRACT

The purpose of research work was to develop and optimize nasal mucoadhesive microspheres of Fexofenadine hydrochloride for nasal delivery with the aim to enhance the residence time and improve therapeutic efficacy. Nasal Mucoadhesive drug delivery systems are those that provide intimate contact of the drug with the mucosa for an extended period of time. In our present work, mucoadhesive chitosan microspheres were prepared by ionic gelation method. Thirteen different formulations were developed. Results show that as the concentration of polymer increases it affects the particle size, production yield, encapsulation efficiency, in-vitro mucoadhesion and in-vitro drug release of nasal mucoadhesive microspheres. The in vitro mucoadhesion of microspheres was investigated using freshly isolated goat nasal mucosa.These formulations were further used for SEM for particles size analysis, mucoadhesion test and in-vitro drug release. The In-vitro % drug release data suggest that the maximum and sustained drug release was obtained for formulation F1. The present study showed that Fexofenadine hydrochloride chitosan microspheres can deliver intranasally which can improve the therapeutic outcome for the Epileptic seizure.

Fexofenadine has a half-life of 14-15 hr and is taken twice daily in large number of patients which leads to patient compliance. Thus, the development of nasal mucoadhesive microspheres for controlled release would be advantageous. The objective of this study was to formulate and evaluate fexofenadine nasal mucoadhesive microspheres using mucoadhesive polymers viz., chitosan with sodium hyaluronate, kappa carrageen, and tripolyphosphate.

Key words:Nasal mucoadhesive microspheres, Fexofenadine hydrochloride, chitosan, sodium hyaluronate, kappa carrageen and tripolyphosphate. Particle size, Drug Entrapment efficiency,Orifice ionic gelation method.

I. INTRODUCTION

Recently, an increased focus has been on developing micro-sized formulations that can serve as oral vehicles for drug encapsulation. Micro-sized formulations can protect the drug from the acidic environment in the stomach and facilitate release at the absorption site. Examples of such micro-sized formulations are microspheres and microcontainers. For example, Zhu et al. developed microspheres with a three-layer structure consisting of Eudragit, chitosan and pH sensitive hydroxypropyl methylcellulose acetate maleate for local delivery of berberine hydrochloride.[1]

The nasal microsphereshave far higher permeability than other mucosal surfaces including the various regions of the GIT, buccal, and vaginal cavities. Recently, mucoadhesive dosage forms have received substantial attention to improve the bioavailability of drug by prolonging the residence time and controlling drug release characteristics. Thus, mucoadhesion may lead to the solution of bioavailability problems resulting from a too-short stay of thepharmaceutical dosage form at the absorption site of the active ingredients. Faster absorption and easy administration through nasal cavity make the nasal drug delivery a promising route for administration of drugs.[2]

Ionic gelation microspheres have been demonstrated as controlled release carriers for water- soluble and water insoluble drugs This technique can be used either for both heat resistant and heat- sensitive drugs or for both water soluble and water- insoluble drugs or for both hydrophilic and hydrophobic polymers. In addition, it is a one-stage continuous process, easy to scale-up, and only slightly dependent upon solubility of drug and polymer. The particle size of the microspheres prepared by the spray-drying method ranged from a micron to several tens of microns and had a relatively narrow distribution.[3]

H1 antihistamines have been the first line treatment of the allergic disease. Recently, H1

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1639-1647 www.ijprajournal.com ISSN: 2249-7781

antihistamines are recognized as inverse agonists that combine and stabilize with the inactive conformation of H1 receptor and, thus, inhibit this constitutive H1 receptor signalling (Church and Maurer, 2014). First generation H1 antihistamines, some of which have been in clinical use since the 1940s, provide symptomatic relief of allergic rhinitis and urticaria. However, they are associated with adverse anticholinergic effects and undesirable central nervous system effects. Second generation H1 antihistamines such as loratadine, astemizole.[4]

By above literature review to develop anti-histamine based mucoadhesive microsphere using preparation method of microspheres.Microsphere model having a specific release on the particular site of nasal cavity can facilized to have improved drug utilization, reduce dose frequency and cast effective.

Therefore the,current study is focused formulate and evaluate mucoadhesive nasal microsphere for anti-histamine drug. (Fexofenadine or suitable anti-histamine drug) with ionic gelation method.investion also include influence of electrical factors,physico-chemical factors under other physicochemical evaluation and characterization of optimize formulation will be conducted.stability studies will performed for optimize formulation as per ICH guideline

II. MATERIALS AND METHODS

FexofenadineHCl was the gift sample from Yarrowcem Industries, Mumbai: Chitosan was procured from LNR chemicals, Mumbai: Sodium hyaluronate and Tripolyphosphate were procured from Sd Fine chemicals, Mumbai: All other reagents used were of analytical grade. Distilled water was used throughout the study.

METHODS

Analytical Method

6.8 phosphate buffer was adjusted with aliquots of fexofenadine HCl 10µg /mL of working standard solution and scanned in UV wavelength range of 200 - 225 nm utilizing as a blank. Averages of triplicate readings were taken.[5]

The primary standard stock solution of Fexofenadine was prepared by dissolving fexofenadine hydrochloride in pH 6.8 phosphate buffer to make a concentration of 1000µg/ml. Different aliquots were taken from the stock `1 solution and diluted with pH 6.8 phosphate buffer separately to prepare series of concentrations of 2, 4, 6, 8, 10, 12µg/ml. The absorbance of all samples was measured at 225 nm against pH 6.8 phosphate buffer as a blank after determining λ max by scanning drug solution in UV region of 200-400 nm. The calibration curve was prepared by plotting Concentration versus Absorbance of Fexofenadine.[6]

Preparation of mucoadhesive microspheres

Orifice ionic gelation method was used for the preparation of nasal mucoadhesive microspheres: Chitosan and mucoadhesive polymer sodium hyaluronates was dissolved in purified water (10 ml) separately. Then both the solutions were mixed to form homogeneous polymer solution. The drug was added to the polymer solution and mixed throughly with the help of pestle and mortar to form viscous dispersion. The resulting dispersion was added drop wise into 10% w/v tripolyphosphate solution (100 ml) through a syringe with needle (size no 21) with continuous stirring at 50 rpm. The added droplets were retained in the tripolyphosphate solution for 15 min to produce spherical rigid microspheres. The microspheres were collected by decantation and the product thus separated was washed repeatedly with water and dried at 45^0C for 12 h and stored in desiccators.

Formulation table

	Factor 1	Factor 2	Factor 3
Run	A:Chitosan	B:S Hyaluronate	C:TPP
	%	%	%
F1	1	1	0.375
F2	0.75	1	0.5
F3	1	0.5	0.375
F4	1	0.75	0.25

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F5	0.75	0.5	0.5
F6	0.75	0.5	0.25
F7	1	0.75	0.5
F8	0.75	1	0.25
F9	0.75	0.75	0.375
F10	0.5	1	0.375
F11	0.5	0.5	0.375
F12	0.5	0.75	0.25
F13	0.5	0.75	0.5

Table No 1 : Formulation table for nasal mucoadhesive microspheres

Optimization

Optimization is an approach to search along process variables of input variables to satisfy a goal such as maximizing/minimizing/targeting a response variable. Chitosan, sodium hyaluronate, tripolyphosphate current density and time of application of current were selected as design factor and the other parameters were kept constant in the formulation. The ultimate goal of the DOE was to optimize the critical process parameters to achieve desired Drug entrapment efficiency, drug release, particle size profiles. Response surface design wasselected to carry out with 13 experimental runs for formulation design each base was optimize the formulation of nasal mucoadhesive microspheres. The DOE runs were performed by Box-Behnken(for formulation design) and 2 FI model. The analysis was performed, ANOVA, interaction profile, prediction profile, 3D surface graph, actual Vs. predicted and optimization were conducted in box behnken and 2 Level Factorial design in 13.0.1.0 version.

Melting point determination

Melting points of Fexofenadine Hydrochloride and Chitosan were determined with the help of melting point apparatus and compared with standards.

Estimation of drug content

Microspheres equivalent to 25 mg of fexofenadine were powdered and taken in to a 100 ml volumetric flask. They were lysed with 50 ml of methanol for the effective extraction of drug and it was shaken for 15 min. The clear solution was diluted to 100 ml with 0.1 N HCl and then it is filtered. Then 1 ml of this filtrate was diluted to 10 ml with 0.1 N HCl. The drug content was analyzed by measuring absorbance in a UV spectrophotometer at 225nm using 0.1 N HCl as blank. The studies were carried out in triplicate.[8]

Entrapment efficiency

100 mg of nasal mucoadhesive microspheres were accurately weighed. They were powdered and extracted with 100 ml of 0.1 N HCl. Further it was serially diluted with 0.1 N HCl solution. The resulting solution was analysed f or fexofenadine drug content by measuring absorbance in a UV spectrophotometer at 225 nm using 0.1 N HCl as blank. The studies were carried out in triplicate. Encapsulation efficiency (%) was calculated using the formula.[9]

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Production yield

The yields of production were calculated as the weight percentage of the final product after lyophilization (B) with respect to the initial total amount of FEX and chitosan used for the preparations (A) according to the equation:[10]

Yields of production = (B/A) x 100

Particle size

The particle size and particle size distribution of microspheres were measured by Nano Measurer 1.2 on 200 randomly selected spheres in the optical microscope images. The measured data were analyzed by Origin to obtain the mean particle sizes and the corresponding standard deviations, and the data was further statistically analyzed to draw the particle size distribution curves by Gaussian Fitting.[11]

In vitro fexofenadine release study

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Franz's diffusion cells (25 mm internal diameter, multi-station VB6 apparatus, PermeGear Inc., Hellertown, PA, USA) were used to study fexofenadine release profile fromsodium hyaluronate – fexofenadine, according to a previously published protocol (Ong et al., 2011). Briefly, polyamide membrane filters (0.45 µm pore size) were hydrated by sonication in PBS (pH = 6.8, 0.01 M) for 30 min, cut and placed between the receiver and donor compartments of the diffusion cells that were maintained at 37 ± 0.5 °C. Samples were placed in the donor compartments in order to have ~5 mg of fexofenadine on the surface of the membranes, which were sealed using a wax foil to prevent evaporation. The receiver compartments were filled with 23 mL of PBS continuously stirred at 150 rpm. At defined time points (0, 15, 30, 60, 120, 180, 240, 300, 360, min), 1.25 mL of samples were withdrawn from the receptor compartments and replaced with equal volumes of pre-warmed PBS. After 360 min, each filter was washed with 5 mL of PBS and then sonicated with another 5 mL of PBS for 10 min. Samples were assayed for fexofenadine concentration using HPLC. Experiments were performed in triplicate and data were expressed and plotted as mean ± standard deviation of the cumulative percentage of fexofenadine released over time.[12]

Ex vivo mucosal toxicity studies

Were done on excised sheep nasal mucosa, obtained freshly from local slaughter house, to assess any damage on the integrity of nasal mucosal tissues under examination. After treatment with fexofenadine-loaded microspheres, nasal mucosa was fixed in 10% buffered formalin solution. Hematoxylin-Eosin(HE) stained paraffin sections (7mm) were examined under light microscope. Untreated nasal mucosa was used as a control.13

Differential Scanning Calorimetric

Differential scanning calorimeter (DSC) was performed using Perkin Elmer instruments, (Perkin Elmer DSC-7, Norway, USA.) to study the thermal behaviour of Fexofenadine HCl and mixture of drug and polymers.[14 15]

Fourier Transform Infrared Spectroscopy

The Infra-Red spectra of fexofenadine HCl, physical mixtures of drug and polymer were conducted using Fourier Transform Infrared Spectrophotometer (Perkin Elmer-spectrum Bx, USA). The procedure consisted of dispersing a sample (drug alone, mixture of drug and polymers) in sodium hyaluronate to prepare 10% of mixture and ground generally in mortar pestle with before sodium hyaluronate being compressed into pellets. This pellet was placed in light path and spectrum was recorded at a resolution of 2 cm-1 over a frequency range of 4000 to 400 cm^{-1} . The background spectrum of sodium hyaluronate was used as blank for determination[16]

Scanning Electron Microscopy

The shape and surface morphology of the prepared microspheres were observed by scanning electron microscope (SEM) (model JXA-840A). The samples were placed on double-sided tape that had previously been secured on aluminium stubs. The stubs were then coated with gold using a cold sputter coater (S150A and then analysed at 20 kV acceleration voltage, under argon atmosphere.[17]

X-Ray diffraction

X-ray diffraction patterns were obtained with a Siemens D5000 diffractometer operating in reflectance mode at a Co-Ka wavelength of 1.789 Å, over an angular range 2u from 5 to 35 and a scan rate of 2/min. The recorded diffractograms were smoothed by a local second order polynomial regression using the software GRAMS/ AI v7.0 (Thermo Galactic, Waltham, MA, USA). The X-ray diffractograms of FU, raw materials, PL- and FU-CMS-MS were compared in terms of peak assignments and relative intensities. To avoid the influence of water content on relative peak intensities (Lemieux et al., 2010), samples were kept at room temperature in a vacuum desiccator containing anhydrous calcium sulphate for two weeks prior to analysis up to a final water contents under 0.5% w/w for all samples. [18]

III. RESULTS AND DISCUSSION

The Fexofenadine Hydrochloride was identified by UV spectroscopy method. The Fexofenadine Hydrochloride exhibited maximum absorption at 225 nm. After scanning the λmax of the Fexofenadine Hydrochloride with methanol it matches with that of the standard λmax given in the articles (225nm). This wavelength was considered as λmax for samples and all the observations by UV spectrophotometer to calculate the amount of drug was taken at this wavelength. The Calibration curve of Fexofenadine Hydrochloride.

It was recorded that as concentration of polymer increases production yield decreases, since increase in polymeric concentration make solution

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more viscous this was difficult to pour and get sticked on the wall of the beaker. The % production yield of microspheres was found to be maximum for F3 (74.6%) having lowest amount of polymer. Lowest % yield was of formulation F4 (63.68%). Stirring rate also affects production yield.

The entrapment efficiencies of drug were recorded in the range of 69.21% to 80.45% for F1 to F9. The F9 revealed lowest entrapment efficiency of drug i.e.69.21%, while F4 displayed 80.45% highest drug entrapment efficiency when compared to other formulations. From results it has been observed that on increasing the polymer ratio the drug entrapment efficiency increases. This might be due to higher concentration of polymer make solution highly viscous which increases the drug entrapment. Meanwhile increasing the stirring rate also enhances the drug entrapment in microspheres because increasing the stirring rate decreases the particle size of microsphere and surface area of microsphere enhanced, this intensifies the drugpermeability inside the microspheres. It is another reason that can which increases the drug entrapment efficiency in microspheres.

Particle size of Fexofenadine microsphere were carried out for mucoadhesive microspheres separately. The particle size of nasal mucoadhesive microsphere by ionic gelation method. Results were found in the range of F1-F13. The F11is lowest of drug particle sizei.e12.7um of nasal mucoadhesive microsphere by ionic gelation method method. while F1 displayed 20.9um highest drug particle size when compared to other formulations.Results were found in the rangeF120.9 µm.

Drug content of nasal mucoadhesive microsphere were carried out, The Results were found in +the range of 74.25% to 80.25%. and the F10 is lowest of the drug contents i.e 74.51 by ionic gelation method and while F5 displayed 80.25% highest drug contents.

The DSC thermograms depict the reduction of fexofenadine particle size and crystallinity in chitosan ; fexofenadine showed a single sharp endothermic peak at 135 °C. The fexofenadine showed a peak at 55 °C related to F68 and a reduced intensity and shifted peak toward a lower melting point of fexofenadine

The SEM revealed the differences in the surface morphology between fexofenadine and chitosan. Fexofenadine showed an irregular rod-like crystal shape with aggregation. Conversely, Chitosan showed a uniform distribution of microspheres within the matrix of F68.

XRD analyses of the ionic gelation method chitosan– nasal microspheres were performed in order to characterize the physical state of FEXO-loaded in the ionic gelation chitosan microspheres. The characteristic XRD spectra of pure drug (FEXO), ionic gelation chitosan microspheres (control), fexofenadine-loaded chitosan–microspheres, and physical mixture of fexofenadine and drug-free chitosan microspheres are presented. Characteristic crystalline peaks of FEXO were observed in the pure drug sample indicating the presence of crystalline FEXO. Under the present experimental conditions, ionic gelation control chitosan microspheres did not show any peaks. Typical diffraction spectra show that peaks of fexofenadine crystals are present in the physical mixture of fexofenadine and drug-free chitosan microspheres but totally absent in drug-loaded chitosan microspheres indicating that fexofenadine is present in the amorphous form after its entrapment in the chitosan nasal microspheres.

Response 1	Response 2	Response 3
Particle Size	Entrapment Efficiency	Drug Release
µm	%	%
20.9	82.26	91.05
18.5	78.38	89.74
19.1	80.22	88.34
20.5	80.88	89.21
17.8	78.44	92.05
17.2	78.21	92.11
20.6	81.44	89.88

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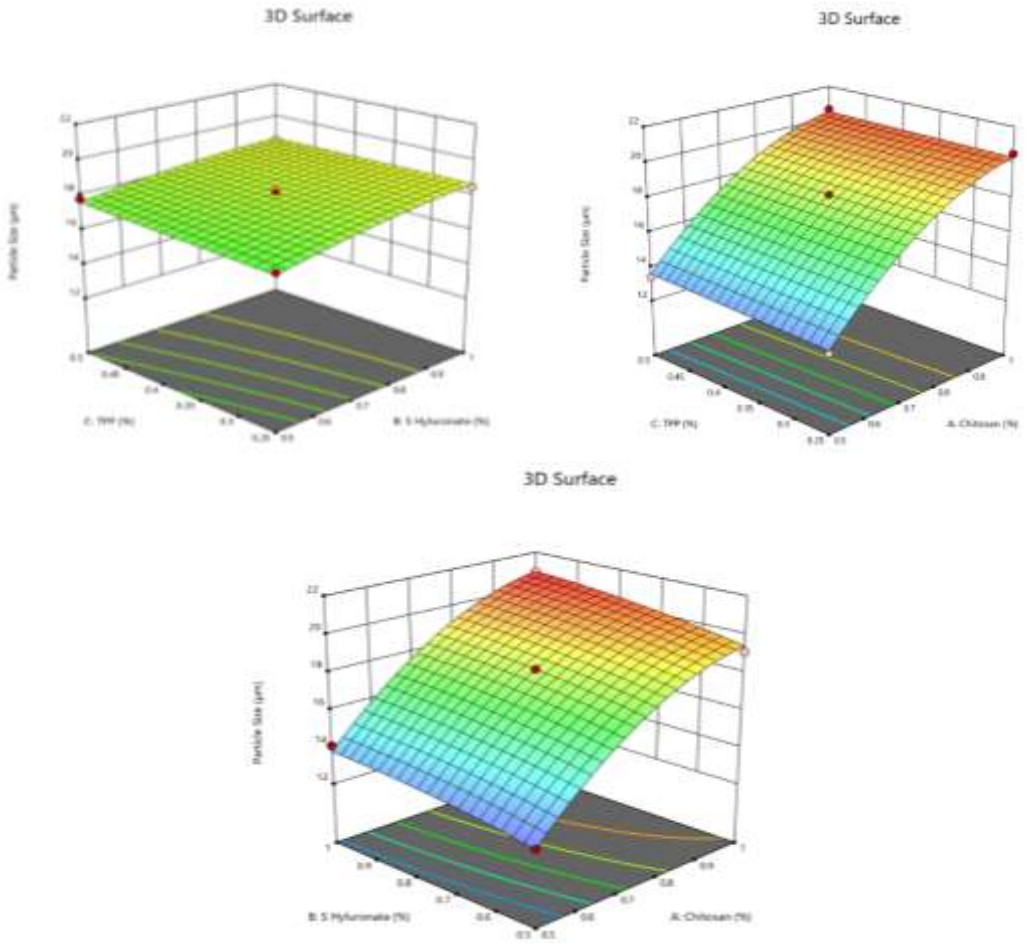
18.5	78.65	89.72
18.2	79.01	90.55
14.1	72.05	76.11
12.7	69.81	74.25
13.1	70.14	75.21
13.4	70.22	75.45

Table no 1 : Formulation of F1-F13 Particle size(um), Entrapment efficiency(%), and Drug release (%).

Model Comparison: Summary statistics for Fexofenadine nasal mucoadhesive microspheres responses of R1-Particle Size, R2- Drug efficiency, R3 - Drug Release in 6 Hrs.

R1-Particle Size					
Source	**Std. Dev**	**R^2**	**Adjusted R^2**	**Predicted R^2**	**PRESS**
Linear	0.7755	0.9487	0.9316	0.8951	11.07
R2-Drug efficiency					
Linear	1.66	0.9027	0.8703	0.8034	49.96
R3 - Drug release 6 Hrs					
Linear	5.03	0.6440	0.5254	0.2527	478.97



3Dsurface graph on particle size for fexofenadine mucoadhesivemicrosphere effects.

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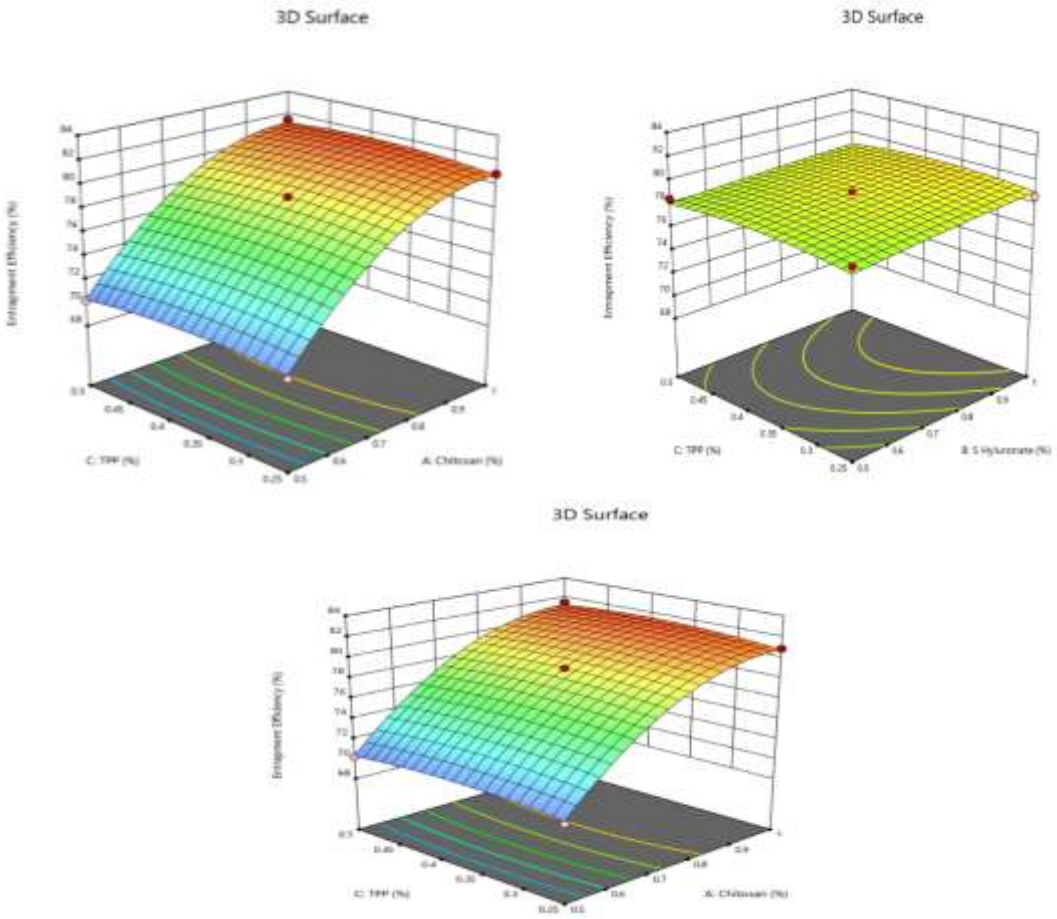
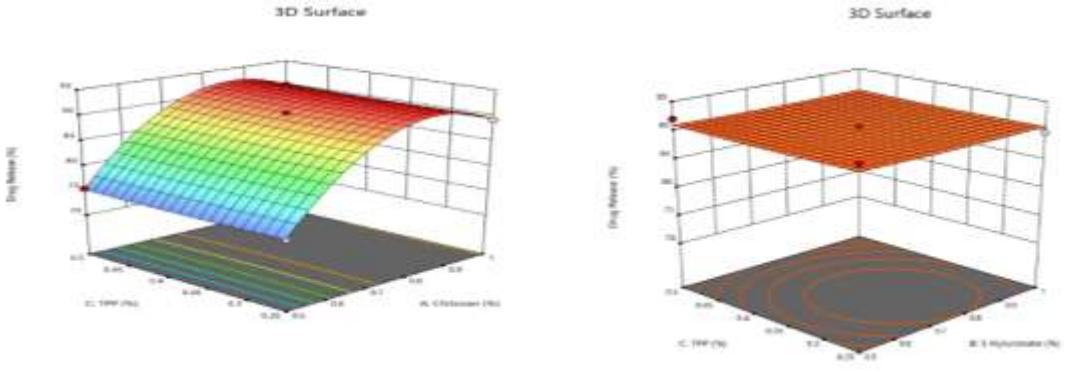


3Dsurface graph on particle size for fexofenadine mucoadhesive microsphere effects.



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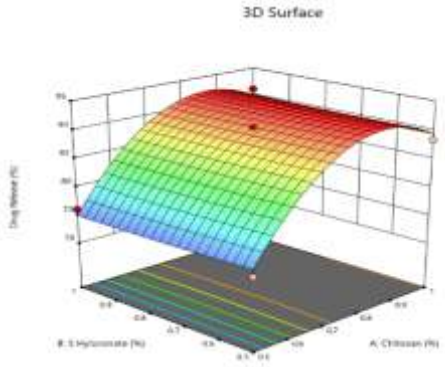

3Dsurface graph on particle size for fexofenadine mucoadhesive microsphere effects.

IV. CONCLUSION

In present experiment, we have developed Fexofenadine-loaded chitosan-based ionic gelation mucoadhesive microspheres intended for nasal administration. The process and formulation variables were optimized using central composite experimental design. Herein, both numerical and graphical optimization techniques were used for optimization purpose, supported by MLR statistical model and second-order polynomial equations. Physicochemical investigations revealed that the optimized formulation sample of microspheres had maximum production yield, drug contents, and an acceptable particle size. Further, results of in vitro characterization suggested that the fabricated microspheres formulation is safe, as assessed on excised sheep nasal mucosa and also, stable at an accelerated stability conditions. Permeation studies, across excied sheep nasal mucosa exhibited good permeability of FEXO. Present formulation could beviewed as a remarkable substitute to conventional dosage forms through enhanced retention of formulation on nasal mucosa and prevention of hepatic first-pass metabolism, provided that the fabricated formulation should be subjected, further, to the in vivo pharmacokinetic studies so as to validate its therapeutic efficacy.

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