

# Formulation Development, Characterization, and Evaluation of Controlled Nasal Drug Delivery Systems for Cefuroxime Axetil

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## Abstract

**Objective:** This current study objective is to develop cefuroxime axetil (CA) nasal mucoadhesive microspheres for an alternative utilization of dosage form for respiratory tract infections. **Materials and Methods:** CA microspheres were prepared by modified emulsion-lyophilization method in which chitosan and beta-cyclodextrin were used as a release retardant polymer. The model is optimization by 2<sup>4</sup> factorial designs and validated using ANOVA. CA microspheres evaluated for entrapment efficiency, ex vivo mucoadhesion and % drug release. The optimized formulations were performed for its Fourier transform infrared (FT-IR) analysis, particle size and polydispersity index (PDI) and zeta potential, thermal analysis DSC and XRD, and surface morphology by scanning electron microscopy followed by *in vitro* and *ex vivo* release kinetic studies. **Key Findings:** Results of these evaluations showed that entrapment efficiency was found to be 69.21–80.45%, particle size in the range of 12.55–17.22  $\mu\text{m}$ , mucoadhesion in the range of 72.51–79.68%, and drug release in the range of 72.21–83.65%. FT-IR studies ensured that no drug-polymer interaction in the formulated microspheres. PDI and zeta potential were measured and the mean particle size and distribution of microspheres were in the range and the surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. DSC and XRD were found to be in fairly acceptable and *in vitro* and *ex vivo* release profile of microspheres formulation was found to be 80.25 and 76.28% at the end of 6 h. Stability studies for 6 months revealed that the optimized formulation was stable, no changes in physical appearance. **Conclusion:** Finally, it was concluded that the nasal microspheres of CA may have potential enough for effective drug delivery.

**Key words:** Cefuroxime Axetil, Nasal Microspheres, 2<sup>4</sup> factorial designs, Chitosan and Beta-cyclodextrin.

## INTRODUCTION

Nasal drug delivery received a great attention as alternative way for systemically acting drugs that are difficult to deliver through other routes other than injections. The nasal mucosa provides rapid, non-invasive route for drug administration due to its highly perfused tissues; permeable epithelial surface and rapid absorption resulting directly reach to the systemic circulation,<sup>[1]</sup> and due to possibility for by passing the blood-brain barrier and targeting the brain directly through drug absorption through olfactory mucosa (Ganger *et al.*, 2018, Pires *et al.*, 2018). Nanoparticles may provide improved targeting and transport through the nasal mucosa. Nanoparticles are particles usually made from

biocompatible, biodegradable polymers<sup>[2-4]</sup> such as poly-D, L-lactic-co-glycolic acid (PLGA) with diameter <100 nm that can be used as drug carriers and they have abilities to bypass the various biobarriers due to their small sizes. PLGA degrades by the hydrolysis and converted to CO<sub>2</sub> and H<sub>2</sub>O in the Krebs cycle and can deliver drug without causing long-term damage or toxicity.<sup>[5]</sup>

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Nanotechnology is one of the effective methods used to improve solubility and dissolution behavior of poorly soluble drugs and the same time mucosal routes of administration offer advantages as improved bioavailability of active pharmaceutical ingredients, possibility of targeting particular organs (Porfirryeva *et al.*, 2019). Cefuroxime axetil (CA) is selected as a model drug, a poor soluble, broad-spectrum, beta-lactamase stable cephalosporin antibiotic which undergoes enzymatic degradation in GI tract. It is used orally for the treatment of respiratory tract infections, pharyngitis, tonsillitis, skin infections, and many more diseases. In humans, GI absorption of CA is negligible and average bioavailability about 37%. When given orally, it goes hepatic first-pass metabolism, thereby reducing the bioavailability drastically. Therefore, CA missing the absorption site causing high concentration of antibiotic entering colon leading to colitis.<sup>[6]</sup>

Administering CA through nasal route will avoid such undesirable functions such as first-pass metabolism and increase the bioavailability. Reaching efficacious site concentrations of antibiotics are essential and suppress the progressive resistance. The majority of lung infections and the site of infection are the epithelial lining fluid (ELF). Thus, reach to the ELF, antibiotics need to pass lung capillary into the interstitial space and move across the alveolar wall epithelium. The quantification of antibiotic concentrations in ELF during development of antibiotic agents for bronchial infection is considerable importance.<sup>[7]</sup> Well-designed drug delivery system can overcome some to the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are several such approaches are there but one such approach is using microspheres as a carrier for drugs. Microspheres based formulations can be formulated to provide a constant drug concentration in the systemic circulation or to efficacy site of cells or organs.

Therefore by developing a model that can be used to provide effective alternative drug delivery of nasal drug targeting for upper and lower respiratory tract infections. This study describes the intranasal mucosal drug delivery systems to achieve desired release profile, complete dissolution and also highlights the bioavailability to improve the effectiveness. The main objective of the present work is to formulation development, optimization, characterization, and evaluation of the nasal drug delivery for CA.

## MATERIALS AND METHODS

### Materials

Cefuroxime axetil (CA) was obtained from Orchid Chemicals and Pharmaceuticals Limited, Chennai, India. Chitosan (87% deacetylated), beta-cyclodextrin, and liquid paraffin (light) purchased from Yarrow Chem Products, Mumbai; Span 80, glacial acetic acid, diethyl ether, and isopropyl alcohol purchased from Merck; all other chemicals used were in analytical grade.

### Methods

#### **Preparation of microspheres by modified Emulsion-Lyophilization method.<sup>[8]</sup>**

CA containing microspheres were prepared by adding into previously water dispersed with beta-cyclodextrin ( $\beta$ CD) of appropriate concentrations kept aside for 24 h. Then, the solutions of drug (100 mg) with  $\beta$ CD were added into chitosan solutions of different concentrations which were prepared accordingly. Then, the complete mix of drug,  $\beta$ CD, and chitosan solutions was dropwise poured into appropriate mixing speed using T 25 digital Ultra-Turrax<sup>®</sup> dispersing instrument as per design experimentation of trials containing light liquid paraffin and surfactant. After stirring with design specification, resulting solutions were separated by repeated wash with solvents and filtered to remove insoluble ingredients followed by freeze-drying appropriately.

### Experimental design

A 2<sup>4</sup> factorial design with four factors at two levels with center point value was considered in this model which was selected to optimize the various response variables. Statistical design of experiments implemented by software DESIGN EXPERT<sup>®</sup> version 9.0.2.0 (Trial Version of Stat-Ease Inc., Minneapolis, USA). Experimental trials performed for nine formulations of possible combinations. In this model, four factors at two levels in coded with low and high settings (-1, and +1 one-to-one) were considered for dependent variables; polymer concentration (X1), enhancer concentration (X2), mixing speed (X3), and freeze-drying temperature (X4) were selected as independent variables, and four responses as particle size (Y1), % entrapment efficiency (Y2), mucoadhesion (Y3), and maximum drug release (Y4) were measured for each trial and taken as dependent variables. 3D response surface graph is utilized to study of factor's interaction between the factor and responses. The factorial design parameters with respective formulations are drawn in Table 1. All the formulations variables and processing variables were kept constant during this model.

In this model, analysis was carried out ANOVA calculation with parameters of analysis results of R<sup>2</sup>: Coefficient of regression, SD: Standard deviation, CV: Coefficient of variation, SS: Sum of squares, DG: Degree of freedom, MS: Mean sum of squares, and f: Fisher's ratio. These results of variance of these observations pooled over all to get an estimate of pure error of variance.<sup>[9]</sup>

### Microsphere characterization

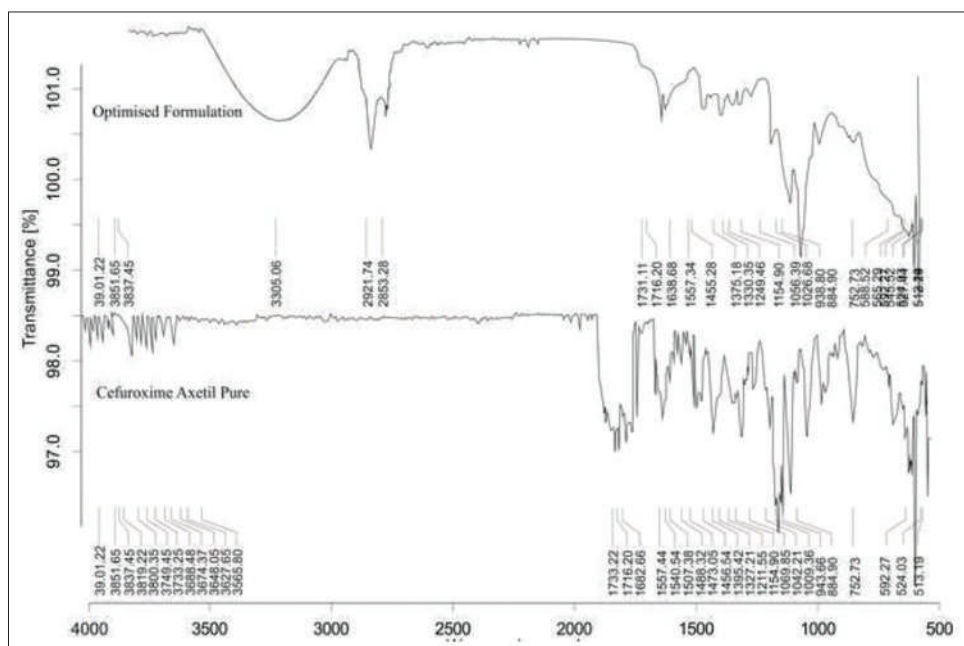
#### **Percentage yield**

The percentage yield of microspheres was determined as the percentage weight of dried final product (practical weight) with respect to theoretical weight of CA microspheres used.<sup>[10]</sup>

**Table 1:** Summary of regression analysis and ANOVA for measured responses

Responses	Model	R <sup>2</sup>	Adjusted R <sup>2</sup>	SD	CV	SS	DG	MS	F-value	P-value	Model significance
R1	Linear	0.9961	0.9922	0.139	0.9398	19.86	4	4.96	256.4	<0.0001	Significant
R2	Linear	0.9387	0.8775	1.29	1.75	102.64	4	25.66	15.32	0.0108	Significant
R3	Linear	0.9657	0.9313	.7888	1.04	70.02	4	17.51	28.13	0.0035	Significant
R4	Linear	0.9681	0.9255	1.21	1.54	132.37	4	33.09	22.75	0.0140	Significant

R1: Particle Size, R2: Entrapment Efficiency, R3: Mucoadhesion, R4: Maximum drug release, ANOVA: Analysis of variance, R<sup>2</sup>: Coefficient of regression, SD: Standard deviation, CV: Coefficient of variation, SS: Sum of squares, DG: Degree of freedom, MS: Mean sum of squares, f: Fisher's ratio



**Figure 1:** Compatibility studies by FT-IR of (a) cefuroxime axetil pure drug (b) optimized formulation microspheres

Percentage yield = (Practical weight of microspheres / Theoretical weight of microspheres) × 100

### Particle size and size distribution and polydispersity index (PDI)<sup>[11]</sup>

The mean particle size was determined by dynamic light scattering (Zetasizer Nano ZS, Malvern Instruments, UK). Samples after appropriate dilutions in Milli-Q water were taken for analysis. Particle size analysis for the formulations was carried out following proper dilutions in Milli-Q water at 25.1°C with equilibration time is 70 s and eight attenuation. PDI used to measure of broadness with molecular weight distribution.

### Drug entrapment efficiency<sup>[12]</sup>

The microspheres (100 mg) loaded with CA were added in a mixture of 10 mL of phosphate buffer pH 6.2 and methanol (9:1) under stirring. The mixture was filtered and the amount of CA was determined spectrophotometrically at 277 nm on UV spectrophotometer (Shimadzu UV 1800, Japan).

Preliminary UV studies of system suitability adjustment for polymers present in the formulation were controlled to study the drug absorbance interference. The percentage entrapment efficiency was calculated using Equation (1).

Entrapment efficiency = (Practical drug content / Theoretical drug content) × 100

### Ex vivo mucoadhesion studies<sup>[13]</sup>

The falling liquid film technique was followed to carry out mucoadhesive property. A freshly cut piece, 5 cm long, of sheep nasal mucosa obtained from a local abattoir within 2 h of killing the animal was prepared by washing with isotonic saline solution. Accurately weighed amount of microspheres was sprinkled on the nasal mucosa, which was attached over a glass slide. This glass slide was kept aside for 15 min in a desiccator at 90% relative humidity to permit the polymer complex of microspheres to interact with the membrane and then position of stand changed to 45° angle. Previously heated (37 ± 0.5°C) phosphate buffer pH 6.2 was allowed to flow over the microspheres present in membrane

with (1 ml/min) for 5 min using peristaltic pump. The drug content concentration was determined spectrophotometric method. The amount of microspheres equivalent of drug amount in perfusate was calculated. The amount of retained microspheres drug amount was calculated from the difference among the applied microspheres and surged microspheres amount with percentage of mucoadhesion strength.

### Drug diffusion studies

*In vitro* drug permeation test of the microspheres was performed using Franz diffusion cell of 140 ml capacity. The semipermeable membrane molecular weight cut of 12–14 kDa was placed on mouth of the diffusion cell. The microsphere drug equivalent to 100 mg taken in the donor compartment was incorporated in simulated nasal fluid (8.77 g sodium chloride, 2.98 g potassium chloride, and 0.59 g calcium chloride with 1 L). The receptor compartment was made with full volume capacity of phosphate buffer of pH 6.2, similarly to that of pH range of nasal cavity and maintained at  $37 \pm 0.5^\circ\text{C}$ . A magnetic stirrer was placed in the receptor compartment. One milliliter sample was periodically withdrawn and replaced with same amount of buffer solution during 6 h study. Appropriately diluted drug sample solutions were determine using UV–VIS spectrophotometric method and 277 nm as  $\lambda_{\text{max}}$ .

*Ex vivo* drug permeation was performed using afresh slice ( $\sim 2.5 \text{ cm}^2$ ) of goat nasal mucosa which was obtained from local slaughterhouse (Bengaluru, India) as membrane to place on the mouth of the Franz diffusion cell instead of semipermeable membrane as like experimentation of *in vitro* drug diffusion study. The drug retained in goat nasal mucosa during drug release was adjusted for the calculation for optimal drug concentration determination.

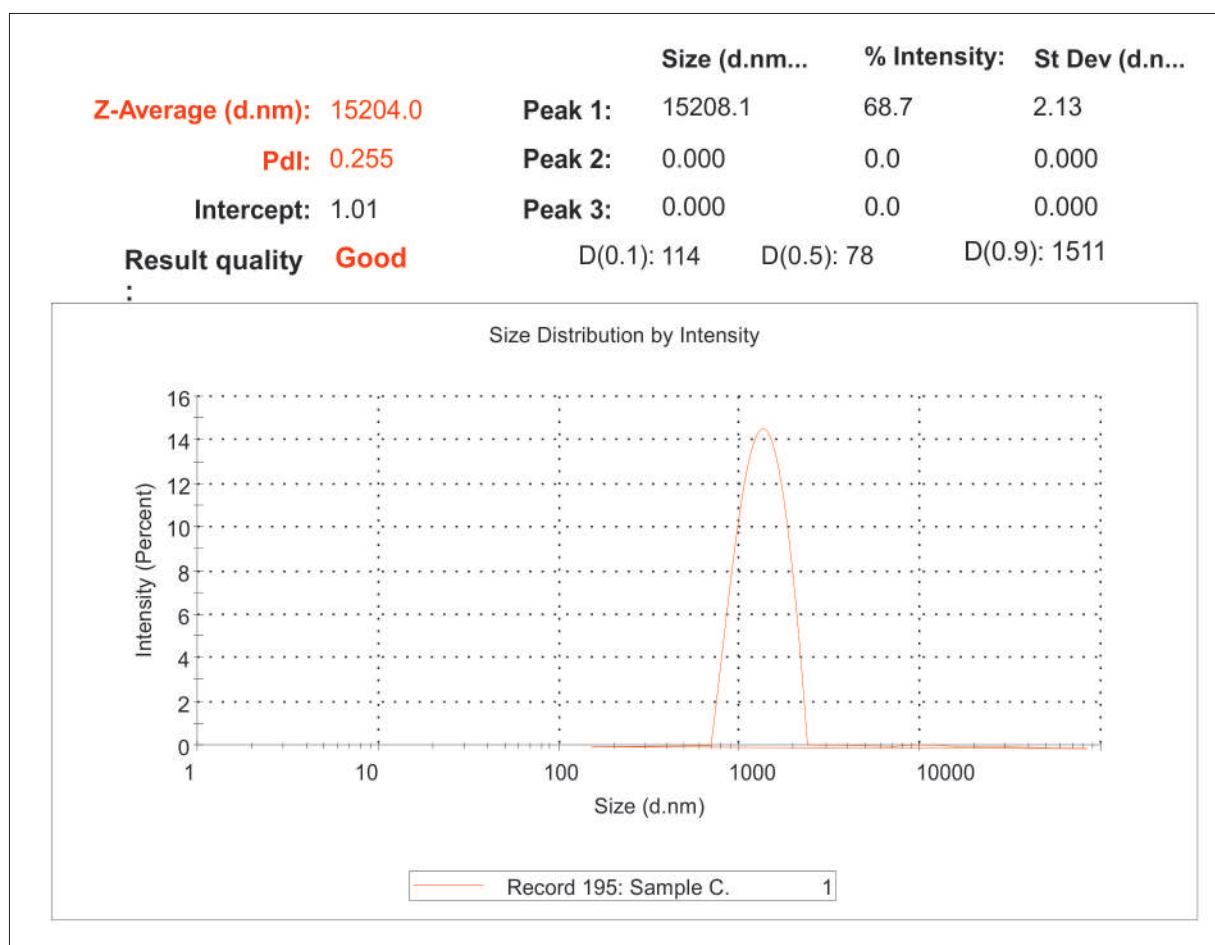
### Zeta potential<sup>[14]</sup>

Electrophoretic light scattering was performed to attain the electrophoretic mobility of microspheres in using a Zetasizer nano ZS (Malvern Instruments, UK). Measurements were carried out in eight runs at  $25.1^\circ\text{C}$  using water as a dispersant (refractive index: 1.59) in a clear disposable zeta cell.

### Thermal analysis<sup>[14]</sup>

#### FT-IR and differential scanning calorimetry (DSC)

Pure drug and optimized microspheres were subjected to FTIR analysis (Model used to analysis, BRUKER).



**Figure 2:** CA microsphere particle size and polydispersity index

The pure drug and optimized formulation were investigated using a DSC Shimadzu DSC 60. Thermograms concealed the range of 0°C–300°C with heating and cooling rates of 10°C/min. The melting point was observed on from endothermic peak of the DSC curve documented in the first heating scan. The glass transition temperatures ( $T_g$ ) were recorded from the second heating scan.

### X-Ray diffraction (XRD) studies

X-ray diffraction studies were verified to analyze the crystallinity of pure drug and optimized formulation by DY 1042-Empyrean diffractometer/furnished with a Ni-filtered Cu  $K\alpha$  radiation ( $k = 1.54060$ ) with Gonio scan axis in the angle range of 100–500 at a speed of 50/min.

### Surface morphology

#### Scanning electron microscope (SEM)<sup>[15]</sup>

Surface morphology scanning electron microscopy was performed for pure drug and optimized formulation. By carry out at low accelerating voltage of about 15 kV with load current about 80 mA and working distance  $WD = 9.1$  mm using a standard error mean (SEM) (Model JSM 840 A, Jeol, Japan).

### Accelerated stability studies<sup>[16]</sup>

The stability testing will assist the robustness of prepared microspheres to evident the quality of a drug encapsulated in microspheres with quality attributes drug product varies with age under the various environmental factors influence such as temperature, humidity, and light as per the approved ICH guidelines. Stability studies were carried out on optimized microspheres according to ICH guidelines to ensure their shelf life. The optimized formulation was packed in amber colored glass vials closed with airtight closures and stored in a programmable environmental test chamber at 40°C and 75% RH for 6 months and evaluated at 1, 2, and 3 months interval.

## RESULTS AND DISCUSSION

This current investigation was performed to design, development, and optimization of nasal mucoadhesive microspheres of CA for an alternative dosage form as novel formulation with improved physicochemical characters that may exhibit in utilization for respiratory tract infections.

The study reported by Beg Sarwar *et al.*, 2020, the optimized microspheres prepared with 4.4% of BSA and 0.25 mL glutaraldehyde and stirring speed 1500 rpm. This exhibited particle size of 34  $\mu\text{m}$ , entrapment efficiency of 88.6%, Q6h of 94.67%, T60% of 3.2 h, and bioadhesion efficiency of 93.2%. *In vivo* pharmacokinetics in rabbits showed remarkable in the drug absorption parameters.<sup>[9]</sup>

Microspheres for the treatment of respiratory infections described by Dimer *et al.*, 2015, a dry powder inhaler formulation prepared by spray drying method containing clarithromycin improved lung drug target to eradicate bacteria. This formulation was effective against both Gram-positive and -negative bacteria, also showed efficient deposition of clarithromycin particles at bronchial cells (Calu-3) without prompting apparent toxicity.<sup>[17]</sup>

The correlation study states that the significant of result obtained from correlation between the *in vitro* Calu-3 cell permeability and nasal mucosal drug permeation rate ( $r^2 = 0.812$ ,  $P < 0.001$ ) indicated that nasal mucosal drug permeability can be best possible method to estimable from *in vitro* membrane permeability study.<sup>[18]</sup>

With the reported references given that current mechanistic understanding, formulation of CA microspheres, chitosan was used as a controlled delivery component; Span 80 is used as emulsifying agent. In all the trail formulation, maximum yield of drug product obtained when increase of drug-to-polymer ratio with minimum mixing speed rate and minimum efficiency of lyophilization drying process. Drug release of all the formulations F1–F9 was in the range of 72.21%–83.65% [Table 2]. In this experimentation result, the particle size was found to be in the range of 12.55–17.22  $\mu\text{m}$

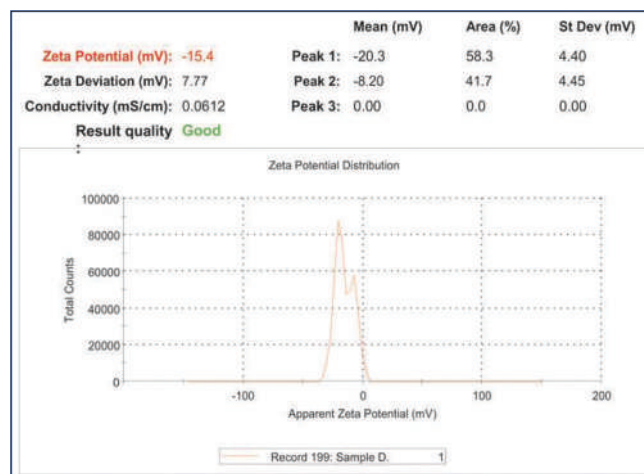


Figure 3: CA microsphere zeta potential

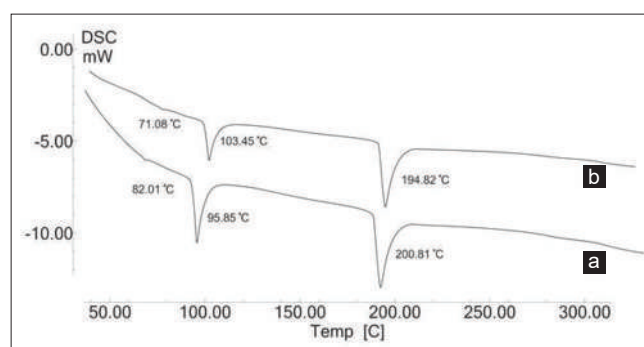


Figure 4: DSC graph of (a) cefuroxime axetil pure drug and (b) optimized formulation of cefuroxime axetil

Table 2: Design formula, characterization of cefuroxime axetil microspheres by factorial model

Formulation code	A: Chitosan (%)	B: Beta-cyclodextrin (%)	C: mixing speed (RPM)	D: Lyocycle temperature (°C)	Particle size (µm)	Entrapment efficiency (%)	Mucoadhesion (%)	Maximum drug release (%)	Percentage yield (%)
F1	1	1	6000	40	17.22±0.12	78.21±0.22	78.61±0.14	82.41±0.26	73.57±0.15
F2	1	0.5	6000	100	16.14±0.09	73.25±0.20	77.87±0.24	80.22±0.29	71.58±0.14
F3	0.5	1	6000	100	14.51±0.14	72.53±0.19	72.33±0.26	73.13±0.31	65.84±0.26
F4	1	1	12000	100	16.35±0.12	80.45±0.23	79.68±0.22	83.65±0.27	74.60±0.31
F5	1	0.5	12000	40	15.08±0.14	75.29±0.25	79.16±0.18	81.04±0.19	72.45±0.34
F6	0.5	0.5	12000	100	12.55±0.07	69.87±0.26	73.45±0.17	74.25±0.18	65.47±0.27
F7	0.75	0.75	9000	70	14.85±0.16	71.68±0.18	74.32±0.26	79.31±0.24	69.22±0.22
F8	0.5	1	12000	40	13.15±0.21	74.58±0.23	73.95±0.20	78.05±0.20	67.54±0.25
F9	0.5	0.5	6000	40	13.41±0.26	69.21±0.29	72.51±0.27	72.21±0.032	63.68±0.028

[Table 2]. With increase in polymer concentration in the microspheres from F1 to F9, the particle size of microspheres increased. This is because the viscosity and mucoadhesive property complement the polymer solution increases with increasing polymer concentration. The effect was elucidated within of 3D [Figure 7]. The entrapment efficiency was in the range of 69.21–80.45% [Table 2], increased efficiency was observed with increased concentration of polymer and enhancer. The relative entrapment efficiency of all the formulations is depicted in 3-D [Figure 3].

The result of ANOVA [Table 1] demonstrates that the model was significant. Regression analysis was carried out to determine the regression coefficients. All the independent variables and model were found to be significant for all response variables. Hence, the above result indicates that the factors play an important role in the formulation of microspheres containing CA. By this optimization, factorial design model consists of material and process parameters as variable with responses, it was observed that desirability conclusive report accordingly

Table 3: Correlation of *in vitro* and *ex vivo* drug release profile

Time in h	<i>In vitro</i> release	<i>Ex vivo</i> release
0	0	0
0.5	17.53±0.22	12.85±0.29
1	22.33±0.25	17.26±0.26
1.5	27.5±0.24	22.64±0.28
2	33.68±0.14	28.65±0.22
2.5	40.12±0.30	32.65±0.31
3	46.8±0.11	41.21±0.19
3.5	53.62±0.13	45.87±0.25
4	59.93±0.23	51.64±0.34
4.5	66.99±0.17	60.55±0.28
5	71.16±0.21	63.88±0.27
5.5	76.33±0.14	70.54±0.31
6	80.25±0.21	76.28±0.33

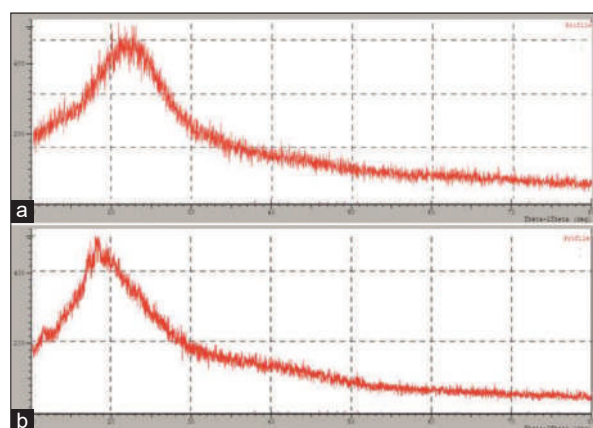


Figure 5: XRD graph of (a) cefuroxime axetil pure drug and (b) optimized formulation of cefuroxime axetil

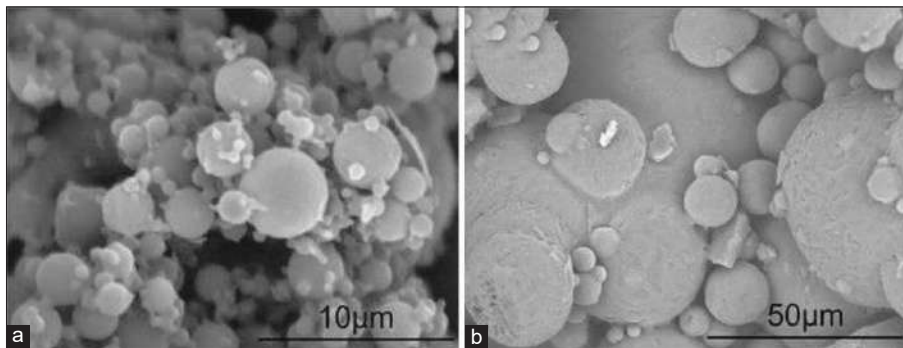


Figure 6: (a) Surface morphology SEM of pure drug cefuroxime axetil and (b) optimized formulation

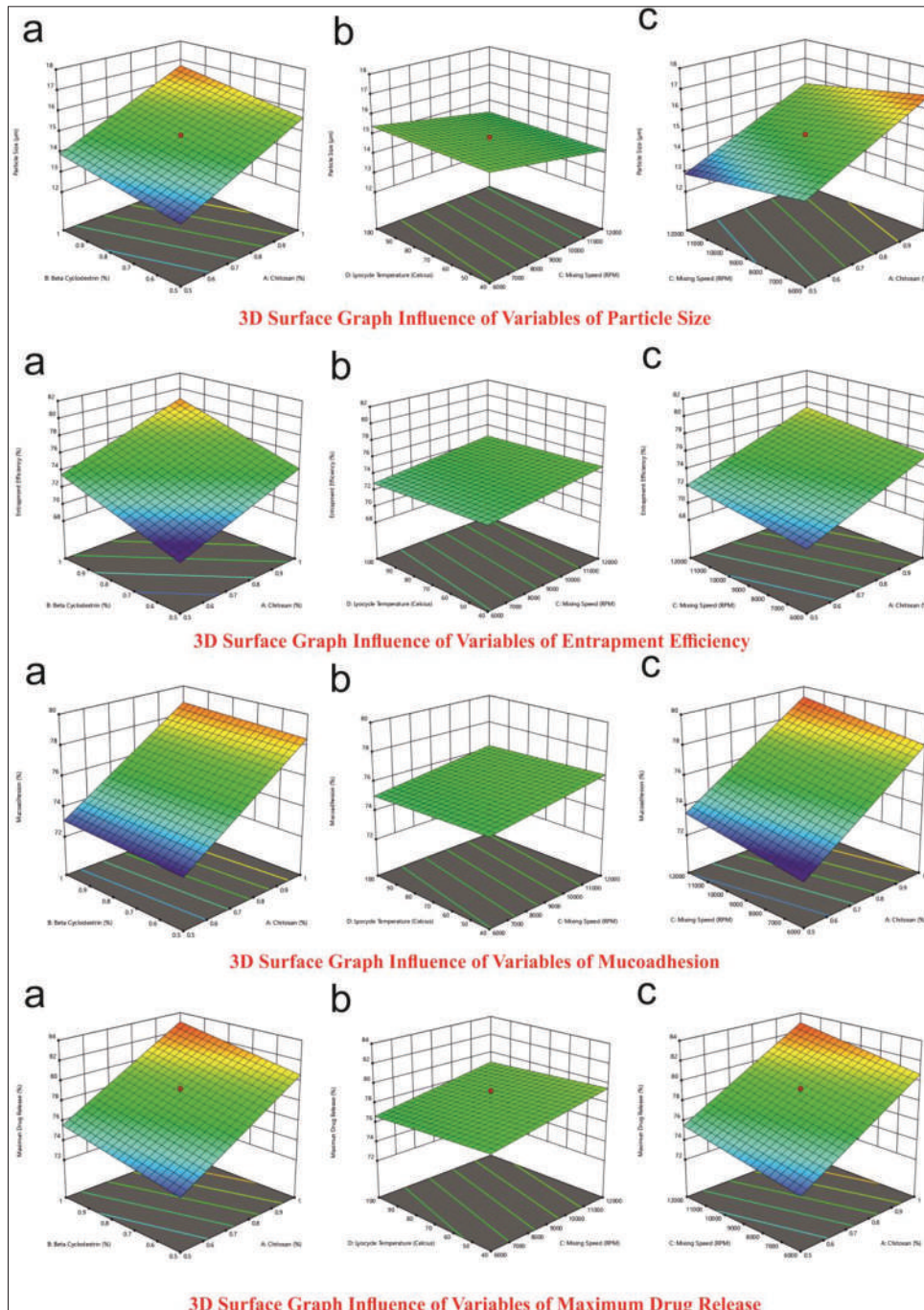


Figure 7: Cefuroxime axetil optimization 3D graphs

**Table 4: Stability study parameters**

Time in months	Particle size ( $\mu\text{m}$ )	Entrapment efficiency (%)	Mucoadhesion (%)	Maximum drug release (%)
Initial	15.21 $\pm$ 0.08	75.31 $\pm$ 0.21	77.15 $\pm$ 0.18	80.62 $\pm$ 0.28
One	15.22 $\pm$ 0.11	75.29 $\pm$ 0.24	77.14 $\pm$ 0.09	80.58 $\pm$ 0.24
Three	15.19 $\pm$ 0.26	75.30 $\pm$ 0.23	77.14 $\pm$ 0.12	80.55 $\pm$ 0.30
Six	15.17 $\pm$ 0.17	75.38 $\pm$ 0.29	77.12 $\pm$ 0.21	80.53 $\pm$ 0.26

with control strategic parameters was suggested with chitosan 0.928, beta-cyclodextrin 0.750, propeller mixing speed 10701, and lyocycle temperature of  $-69.59^\circ$ , particle size 15.50  $\mu\text{m}$ , entrapment efficiency 76.26%, mucoadhesion 78.17 % and maximum drug release 81.40%.

Fourier transform infrared (FT-IR) studies by the observation peaks from the IR spectrum of CA and optimized formulation microspheres show two carbonyl absorption bands at 1681.11  $\text{cm}^{-1}$  and 1633.74 assigned to amide carbonyl stretching. There were two absorption peaks at 3239.83, 3305.06, and 1730.83, 1731.11  $\text{cm}^{-1}$  ensured that no drug-polymer interaction in the formulated optimized microspheres and they are compatible [Figure 1]. Mean particle size and distribution [Figure 2] 15.20  $\mu\text{m}$  and 0.255 and zeta potential [Figure 3]  $-15.20$  of optimized formulation microspheres measured are indicating that with targeted particle size, minimum polydispersity index and slightly anionic nature of surface property were noted. Surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. DSC [Figure 4] and XRD were found to be in fairly acceptable. The observed particle size indicated micron sized nature of the obtained particles with good monodispersity characteristics. XRD of the optimized formulation when compared to the XRD of pure drug showed less peaks indicating the reduction in the crystallinity of pure drug CA [Figure 5]. As the release study indicates a little effect of enhancer on drug release, the decrease in crystallinity may be attributed to the formation of small amount of complexes. The SEM photomicrograph of the optimized formulation is shown in Figure 6. The surface of the microspheres is shown spherical in shape which represents distinct pores in polymeric wall surface of microspheres, this may enhance drug release from the microspheres in better way and even this also indicate effect of lyophilisation process in preparation of microspheres.

*In-vitro* and *ex vivo* release profile of microspheres formulation was found to be 80.25 and 76.28% [Table 3] at the end of 6 h. The drug release slowed down. This may be due to strong binding the polymer when polymer concentration is high.

Accelerated stability studies were performed for a period of 6 months. The microspheres showed no change in physical appearance. There was no drastic change in drug release, % entrapment efficiency, and particle size and mucoadhesion % [Table 4]. Therefore, we can conclude that the formulation is stable.

## CONCLUSION

The present study has been a satisfactory attempt to formulate a CA microsphere for nasal drug delivery. From the experiments, it can be concluded that nasal microspheres of CA were prepared using chitosan and  $\beta$ CD. The FTIR was no interaction between polymers; they are compatible with each other. PDI and zeta potential were measured and the mean particle size and distribution of microspheres were in the range, mucoadhesion, drug release, and entrapment efficiency were found to be fairly acceptable range. SEM studies indicate surface topography having spherical slightly rough surface of the formulation, DSC and XRD were recorded to see the drug status. *In vitro* and *ex vivo* show a significant effect on drug release. Stability studies revealed that optimized formulation was stable. Finally, it was concluded that the prepared nasal microspheres of CA may prove to be potential enough for effective drug delivery.

## CONFLICTS OF INTEREST STATEMENT

We declare that we have no conflicts of interest.

## ACKNOWLEDGMENTS

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## REFERENCES

1. Al-Ghabeish MI. Drug Transporters in the Nasal Epithelia and their Contribution in Drug Delivery. Iowa: The University of Iowa; 2014.
2. Xue M, Zhong X, Shaposhnik Z, Qu Y, Tamanoi F, Duan X, *et al.* pH-operated mechanized porous silicon nanoparticles. *J Am Chem Soc* 2011;133:8798-801.
3. Louis C, Pluchery O. Gold Nanoparticles for Physics, Chemistry and Biology. London: Imperial College Press; 2012.
4. Sonnenberg JF, Coombs N, Dube PA, Morris RH. Iron nanoparticles catalyzing the asymmetric transfer hydrogenation of ketones. *J Am Chem Soc* 2012;134:5893-9.



5. Kaur MA. Poly (D, L-lactide-co-glycolide) 50:50-hydrophilic polymer blends: Hydrolysis, bioadhesion and drug release characterization. Iowa: The University of Iowa; 2008.
6. Bermejo M, Sanchez-Dengra B, Gonzalez-Alvarez M, Gonzalez-Alvarez I. Oral controlled release dosage forms: Dissolution versus diffusion. *Exp Opin Drug Deliv* 2020;17:791-803.
7. Valitalo PA, Griffioen K, Rizk ML, Danhof M, Gaori R, *et al.* Structure based prediction of anti-effective drug concentrations in the human lung epithelial lining fluid. *Pharm Res* 2016;33:856-67.
8. Karmoker JR, Hasan I, Ahmed N, Saifuddin M, Reza M. Development and optimization of acyclovir loaded mucoadhesive microspheres by box -behnken design. *Dhaka Univ J Pharm Sci* 2019;18:1-12.
9. Beg S, Rahman M, Panda SK, Alharbi KS, Alruwaili NK, Singh PK, *et al.* Nasal mucoadhesive microspheres of lercanidipine with improved systemic bioavailability and antihypertensive activity. *J Pharm Innov* 2020;1:133.
10. Shah SS, Gohil DY, Pandya DN, Meshram DB. Preparation and evaluation of spray dried mucoadhesive microspheres for intranasal delivery of prochlorperazine using factorial design. *Asian J Pharm* 2015;9:178-89.
11. Kulkarni AD, Bari DB, Surana SJ, Pardeshi CV. *In vitro*, *ex vivo* and *in vivo* performance of chitosan-based spray-dried nasal mucoadhesive microspheres of diltiazem hydrochloride. *J Drug Deliv Sci Technol* 2016;31:108-17.
12. Fu DC, Ming SY, Ben GY, Yu LF, Liang W, Peng Y, *et al.* Preparation of sustained release nitrendipine microspheres with Eudragit RS and aerosol using quasi emulsion solvent diffusion method. *Int J Pharm* 2003;259:103-13.
13. Rao KV, Buri P. A novel *in situ* method to test polymers and coated microparticles for bioadhesion. *Int J Pharm* 1989;52:265-70.
14. Soisuwan S, Teeranachaideekul V, Wongrakpanich A, Langguth P, Junyaprasert VB. *In vitro* performances and cellular uptake of clarithromycin nanocrystals produced by media milling technique. *Powder Technol* 2018;338:471-80.
15. Selvaraj S, Karthikeyan J, Saravanakumar N. Chitosan loaded microspheres as an ocular delivery system for acyclovir. *Int J Pharm Pharm Sci* 2011;4:125-32.
16. Kyada C, Ranch K, Shah D. Optimization of mucoadhesive microspheres of acyclovir by applying 32 full factorial designs. *J Drug Deliv Sci Tech* 2014;24:61-8.
17. Dimer F, Haupenthal J, Hartmann R, Lehr CM. Inhalable clarithromycin microparticles for treatment of respiratory infections. *Pharm Res* 2015;32:3850-61.
18. Inoue D, Furubayashi T, Tanaka A, Sakane T, Sugano K. Quantitative estimation of drug permeation through nasal mucosa using *in vitro* membrane permeability across Calu-3 cell layers for predicting *in vivo* bioavailability after intranasal administration to incinn in incrats. *Eur J Pharm Biopharm* 2020;149:145-53.

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