RESEARCH ARTICLE

Development of Nasal *In-situ* Gel Formulation of Fexofenadine HCl Using Gellan Gum (Gelerite®)

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ABSTRACT

This study aimed to develop and assess an *in-situ* nasal gel containing fexofenadine hydrochloride for nasal administration by employing polymers with *in-situ* gelling characteristics. Formulations containing Gelerite, HPMC K4M and β-cyclodextrin were used to formulate in situ nasal gel. Formulations were liquid before administration and quickly converted to gel after nasal administration. The FTIR studies of drugs, polymers and physical mixtures of drug polymers were carried out. These research results indicated that, in comparison to pure drugs, there have been no considerable modifications in the drug bands. Hence, the FTIR study revealed that the formulation doesn't have any drug-polymer interaction. In order to estimate rheological studies, a Fungilab Brookfield viscometer was used to test the formulation's viscosity. The ranges of the rheological properties of the solution and gel were shown to be 91 ± 1.73 to 125 ± 0.77 and 2740 ± 1.55 to 4675 ± 1.43, respectively. The gel strength of formulations F1 to F9 was found to be in the range of 34 ± 1.00 to 51.23 ± 1.77 seconds. It was shown that the viscosity of the formulation decreased at increasing shear stress, exhibiting shear thinning behavior. A viscosity of formulation increase was noticed with an increase in polymer ratio. All formulations were subjected to an *in-vitro* diffusion analysis, which will demonstrate the impact of various factors on the formulation's ability to release the drugs.

Keywords: Fexofenadine hydrochloride, *In-vitro* diffusion, Nasal drug delivery.

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INTRODUCTION

Because of the comparatively highly permeable nasal epithelial membrane, which avoids first-pass metabolism and enhances patient compliance, non-invasive mucoadhesive drug delivery through the nose is the most promising technique.[1-4] However, the formulation's bioavailability is often quite low following nasal administration. One of the barriers to effective drug administration through the nose is nasal mucociliary clearance. As a result, the formulation effectively disallows prolonged medication administration while allowing for drug absorption.[5,6]

Various methods have been employed to improve medication absorption across the nasal mucosa, including the development of acceptable nasal formulations using bioadhesive polymers, solubilizing and penetration enhancers, and proteolytic enzyme inhibitors. The effectiveness of using a solubilizer and penetration enhancer for nasal drug administration needs to be proven among the approaches outlined above.[7,8]

MATERIAL AND METHODS

Material

Fexofenadine HCl, procured gift sample from Sanofi India, Ankleshwar, Gellan Gum (Gelrite®), β-cyclodextrin, HPMC K4M purchased from Yarrow Chemical in Mumbai. Sodium alginate, mannitol, polyethylene glycol, propylparaben and methyl paraben were procured from Loba chemicals.[9-11]

Method of Preparation of Nasal Mucoadhesive Ion Induced *in-situ* Nasal Gel of Fexofenadine HCl

Double-distilled water was used to prepare a polymeric solution of Gelrite® (Gellan gum).[8-10] and HPMC K4M,[11] which was then homogenized with a mechanical stirrer in a water for 30 minutes at 90°C. Polymeric solutions were gently heated in a water bath after preservatives such as ethyl parabens, mannitol, and polyethylene glycol were added appropriately. The solution was subsequently cooled to room temperature. After mixing the drug with a small amount of methanol that included β-cyclodextrin, it was sonicated. To a beaker containing a polymeric mixture, Fexofenadine HCl

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Table 1: Factorial design for *in-situ* Nasal gel of Fexofenadine HCl

Sr. No.	*Ingredients*	*Low*	*High*	*- alpha*	*+ alpha*
1	β-cyclodextrin	0.03	0.05	0.02318	0.05681
2	Gellan Gum	0.2	0.4	0.13182	0.46817
3	HPMC K4M	0.1	0.2	0.06591	0.23409

1% Fexofenadine HCl in all formulation

and β-cyclodextrin were added.[12] After that, the liquid was vigorously stirred until all of the drugs were dissolved. The resulting solution was transferred to a clean glass container and kept in a cool environment after 10 mL diluted with distilled water.

Evaluation Parameters of Nasal Mucoadhesive Ion Induced *in-situ* Nasal Gel of Fexofenadine HCl

Gelation Studies

When ions are present, the gellan gum can change from a liquid state to a gel state. The process of transforming a liquid phase into a gel is known as gelation. Magnetic beads are placed in a 10 mL test tube containing a 2 mL formulation. The simulated nasal fluid (SNF) was made by mixing double-distilled 250 mL of water with 8.77 w/v NaCl, 0.59, and 2.98 w/v KCl concentrations was gradually introduced into the 2 mL test solution. The gelation point was identified after the liquid phase was transformed into a gel. Finally, the gel's consistency and viscosity were examined.[13,14]

Gelling Capacity

The formulation's gelling capacity was determined and graded as follows depending on the time required for a firm gel to form.

- **Lower score (+):** After 60 seconds, the solution undergoes phase transition and forms a gel that collapses in 1 to 2 minutes.
- **Moderate score (++):** solution which formed the gel after 60 seconds. However, the gels formed didn't remain stable for more than 3 hours.
- **Higher score (+++):** The solution underwent a phase change in just 60 seconds and then gelled, remaining steady for over 7-8 hours.[13,14]

Mucoadhesive Strength

Mucoadhesion is an important key factor of the formulation design for the delivery of drugs through nasal cavity.

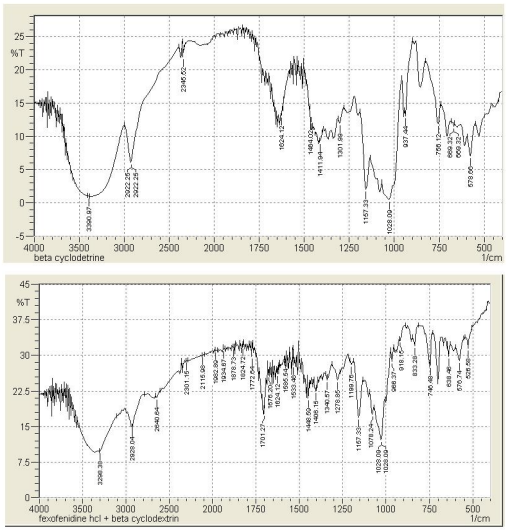
Mucoadhesion force is the composition that gels use to adhere to nasal mucosa. Greater bioadhesive gels will remain in the nasal cavity for longer, preventing the formulation from draining from the nasal cavity.[15]

Rheological Studies

The Fungilab digital viscometer was used to evaluate the formulation's viscosity. For 30 seconds, viscosity was measured for both liquid and gel formulations at various shear rates to determine the flow type.[16]

%Drug Content

By using UV spectroscopy and taking into account the observed absorbance, the percentage of drugs in the formulation is estimated.[17,18]



Graph No 1: FTIR spectra of drug and polymer

Table 2: Principal peaks obtained in fexofenadine HCl pure drug

Sr. No	*Standard peak (cm^{-1})*	*Observed peak (cm^{-1})*	*Interpretation*
1.	1200–1020	1068.60	C-OH stretching (carboxylic acid)
2.	3600–2500	3298.38	O-H stretching (carboxylic acid)
3.	2960–2850	2891.39	C-H stretching (aldehyde)
4.	1600–1400	1402.30	C=C stretching
5.	1250–1050	1163.11	C-O-C stretching

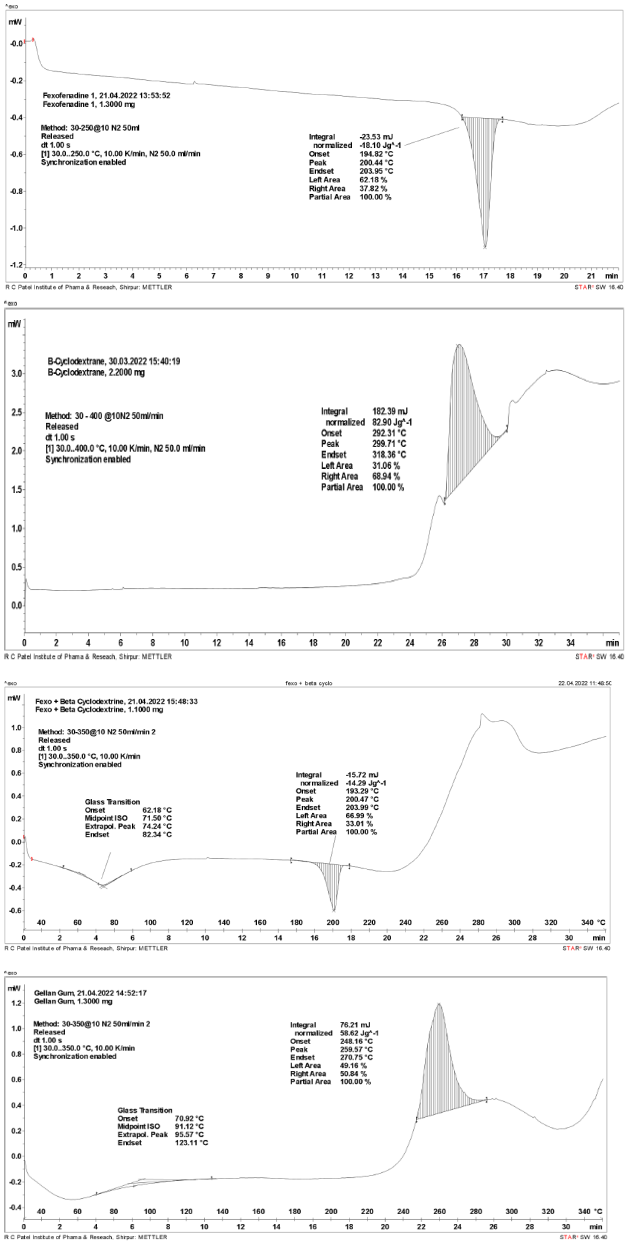
In-vitro Drug Diffusion Study

Franz diffusion cells with a 0.785 cm^2 permeation area are filled with tissue samples. The receptor compartment was filled with 20 mL of pH 6.8 phosphate buffer solution (PBS), and kept at 34°C. A constant 34°C is maintained in the diffusion cells. In the donor compartment, 25 mg of the formulation were filled. A 1-mL samples from the receptor compartment were taken out at regular intervals throughout the course of hours and replaced with freshly prepared phosphate buffer solution pH 6.8. Filtered samples after withdraw were then analysed spectrophotometrically. Blank samples can be performed continuously during the experiment to check for interference. Using a UV-visible spectrophotometer set to a λ_{max} of 227 nm, the amount of permeated drug was quantified.[17, 18]

RESULT AND DISCUSSION

FTIR Spectroscopy

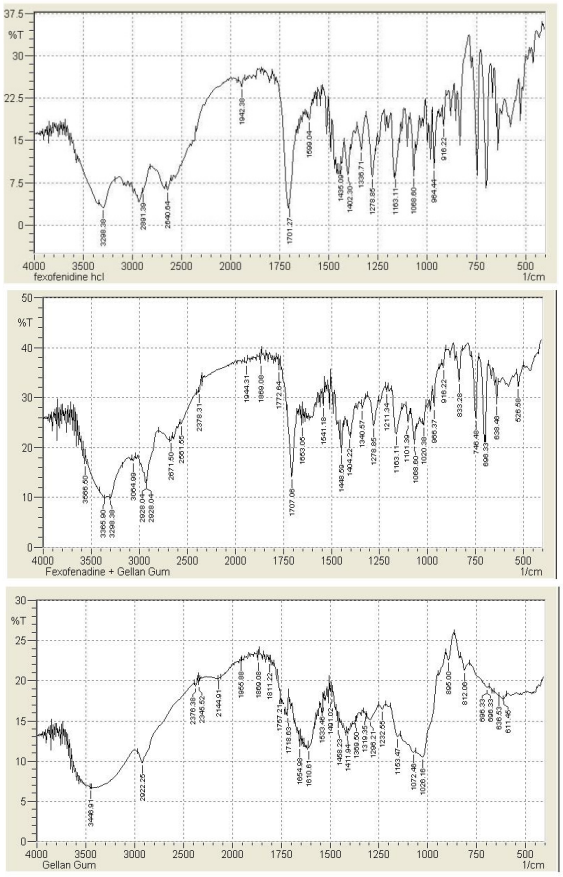
The FTIR spectra of fexofenadine HCl was captured and analyzed. The drug sample showed the expected IR absorption peaks, confirming the fexofenadine HCl purity. A compatibility study of the polymer and drug was conducted to investigate potential interactions between the polymer and drug. The resulting drug and polymer mixture showed no new peak. As a result, fexofenadine HCl was compatible with selected polymers and excipients, according to IR spectrum results.



Graph 2: Differential scanning calorimetric thermogram of fexofenadine HCl, gellan gum, β-cyclodextrin and mixture of fexofenadine HCl + gellan gum, fexofenadine HCl + β-cyclodextrin.

Table 3: Gelling capacities of prepared formulation

Formulation	*Gelling capacity*
F1	+
F2	+
F3	++
F4	++
F5	+++
F6	+++
F7	+++
F8	+++
F9	+++



Differential Scanning Calorimetry (DSC)

The fexofenadine HCl DSC curve exhibits an endothermic peak at 200.44°C. Gellan gum DSC curve shows an endothermic peak at 259.57°C. While the DSC curves of fexofenadine HCl and β-cyclodextrin of physical combination exhibits broad endothermic peaks at 193.29 and 203.99°C, the DSC curve of β-cyclodextrin exhibits an endothermic peak at 299.71°C. The DSC curve of the fexofenadine HCl and Gellan gum physical mixture, on the other hand, exhibits fewer endothermic peaks at 187.72°C and 203.42, corresponding to the disappearance of free fexofenadine HCl.

Appearance

Visual examination of all formulations on a white and black background demonstrated clear, grittiness-free solutions.

pH

The tested formulation's pH was found to be between 5.7 ± 0.003–6.0 ± 0.012; the optimum formulation pH is expected to be between 4.5 and 6.5.

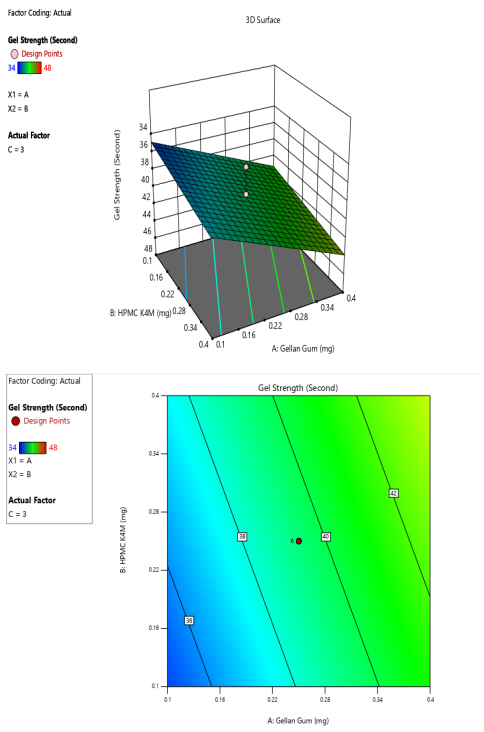
Gelation Study and Gelling Capacity

As the concentration of gellan gum increases, gelation time decreases. In the gelation process, the development of a double-coiling junction zone is the initial step. Secondly, by crosslinking with Ca^{+2} ions and forming hydrogen bonds with water, the double-helical segments conglomerate to create a three-dimensional network.

Table 4: Gel strength of formulation

Formulation code	*Gel strength (Seconds)**
F1	40 ± 2.00
F2	34 ± 1.00
F3	47.33 ± 1.52
F4	35 ± 2.08
F5	49.6 ± 1.15
F6	51.23 ± 1.77
F7	39.45 ± 2.45
F8	39.23 ± 1.57
F9	39.13 ± 1.65

(Where n = 3, Mean = ± SD)



Graph 3: Surface response of Gel Strength

Gel Strength

Compared to the gel state of the same formulation series, the viscosities of the formulations in batches F1 to F9 varied significantly.

In F8 formulation, this is to show that gel strength with of 3% glycerine with 0.3% gellan gum and β-cyclodextrin exhibit gelling properties slightly better than that of F9, 4% glycerine.

The gel strength of formulations F1 to F9 was found to be in the range of 34 ± 1.00 to 51.23 ± 1.77 seconds. Due to changes in chain interaction brought about by increased polymer concentration, formulation gel strength rises.

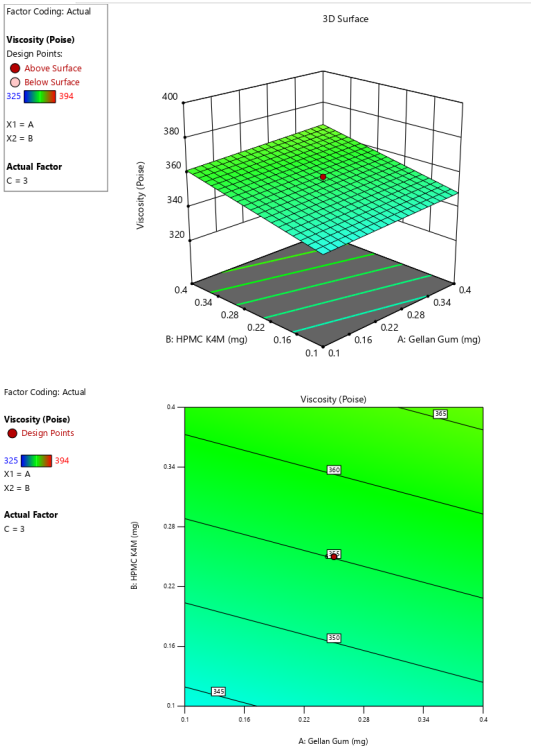
Rheological Study

The viscosity of the formulation was a key essential factor for intranasal *in-situ* gel. As stated previously, a formulation intended for use in the nasal cavity should preferably have a low viscosity when applied and transform into a high-viscosity

Table 5: Viscosity of formulation

Formulation code	*Viscosity (cp)**	
	Solution	*Gel*
F1	91 ± 1.73	2950 ± 1.15
F2	111 ± 1.00	4200 ± 1.73
F3	112 ± 2.30	4500 ± 2.08
F4	95 ± 2.88	3000 ± 2.51
F5	119 ± 0.57	4090 ± 1.16
F6	125 ± 0.77	4590 ± 1.24
F7	93 ± 1.23	2740 ± 1.55
F8	115 ± 0.45	3100 ± 1.75
F9	118 ± 0.65	4675 ± 1.43

(Where n = 3, Mean = ± SD)



Graph 4: Surface response of viscosity

formulation following administration to retain at the site of application. The formulation should have enough low viscosity to be easily administered into the nasal cavity as a liquid, followed by an immediate sol-to-gel change brought on by ionic exchange with nasal epithelium. The solution and gel viscosities are in the range of 91 ± 1.73 to 125 ± 0.77 and 2740 ± 1.55 to 4675 ± 1.43, respectively.

Viscosity of gel was increased because of an increase in the concentration of polymer form 0.2 to 0. 4% of gellan gum due to ionic interaction with the mucosal membrane.

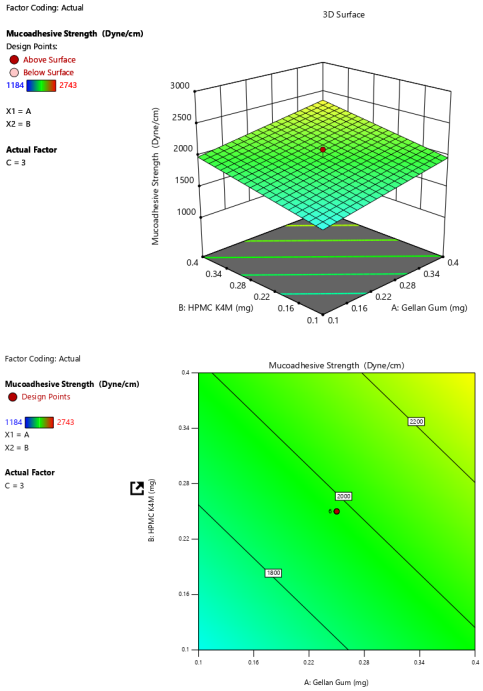
The viscosity of the formulation after and before gelation was directly proportional to the concentration of mucoadhesive polymer and gellan gum. As the HPMC-K4M, gellan gum and glycerine ratio increase, viscosity of the gel before gelation and after gelation increases.

Table 6: Mucoadhesive strength

Formulation code	*Mucoadhesive strength (dyne/cm^2)*
F1	3100 ± 0.56
F2	4332 ± 0.61
F3	4789 ± 0.43
F4	3378 ± 0.58
F5	4012 ± 0.41
F6	4243 ± 0.67
F7	4354 ± 0.72
F8	4983 ± 0.63
F9	4887 ± 0.58

Table 7: Drug content

S. No.	*Formulation Code*	*Drug Content (%)*
1	F1	99.20 ± 0.12
2	F2	98.23 ± 0.13
3	F3	99.52 ± 0.04
4	F4	98.45 ± 0.12
5	F5	98.55 ± 0.12
6	F6	98.33 ± 0.15
7	F7	99.19 ± 0.11
8	F8	99.52 ± 0.04
9	F9	99.45 ± 0.13



Graph 5: Surface response of Mucoadhesive strength

Different shear rates have been used to measure viscosity. Viscosity decreases with increasing shear rate, indicating pseudo-plastic flow in the gel. The viscosity of the gelrite ion induced in situ nasal gel increased as its concentration increased. The formulation with the highest polymer concentration exhibits the maximum viscosity at a given sharing rate.

Determination of Mucoadhesive Strength

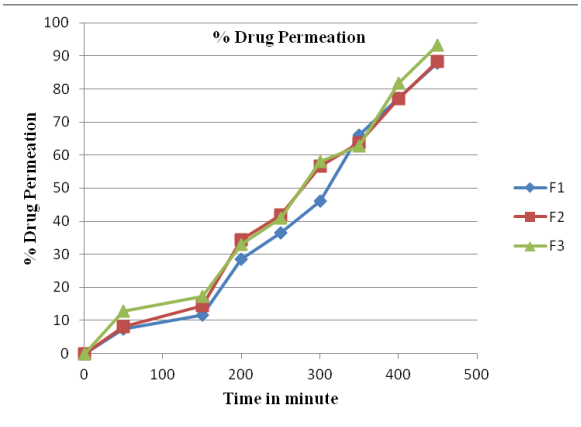
The formulation's mucoadhesive strength was determined, and its range is between 3100 ± 0.56 to 4989 ± 0.43 dynes/cm^2. The F8 formulation has the highest mucoadhesion strength as compared with the F9 because of the increase in the concentration of glycerine, but its mucoadhesion strength is decreasing. The components β-cyclodextrin, gellan gum, and glycerine all significantly impact the gelling to adhere to mucous membranes. Mucosal adherence is the key important factor in the mucoadhesive formulation and increases drug absorption across the mucosal surface. The suitable formulation for nasal drug administration must be transited into gel, and after gelling, the mucoadhesive gel must remain at the site of application for a long period of time to produce the therapeutic response. An increase in the polymer concentration may lead to a progressively decreased interaction of glycerol, gellan gum, and mucin, which ultimately weakens the hydrogen bond. That leads to loss of mucosal adherence.

Percentage Drug Content

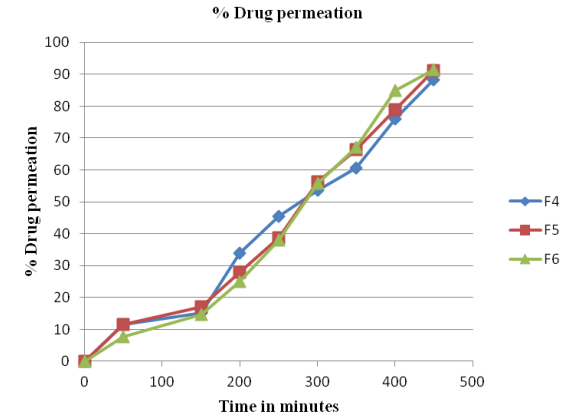
The percentage drug content of all formulations F1–F9 was determined, and the values found from 98.23 to 99.52%, as shown in Table 7.

Table 8: *In-vitro* percentage drug permeation

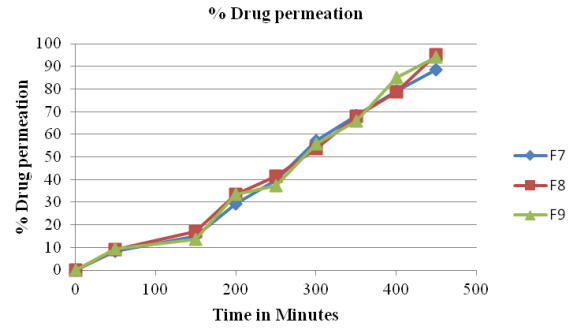
Time (Min)	*Percentage Drug Permeation*								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
50	7.34	8.11	12.78	11.61	11.61	7.72	8.51	8.91	9.30
150	11.69	14.42	17.32	15.09	17.02	14.70	15.09	16.96	13.52
200	28.49	34.47	32.88	33.91	28. 01	25.10	29.27	33.34	33.30
250	36.59	41.89	41.04	45.42	38.68	37.95	39.69	41.43	37.43
300	46.08	56.55	58.14	53.52	56.28	55.81	57.01	53.81	55.69
350	65.98	63.62	62.69	60.61	66.37	67.09	68.25	67.92	65.81
400	77.33	76.95	81.70	75.93	78.80	84.90	78.93	78.92	85.02
450	87.87	88.22	93.15	88.32	91.23	91.33	88.62	95.10	94.22



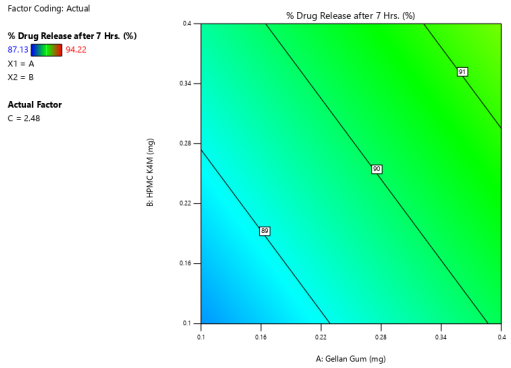
Graph 6: *In-vitro* drug permeation of F1-F3



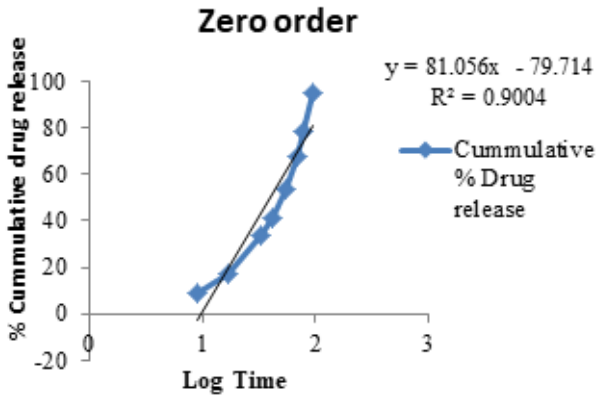
Graph 7: *In-vitro* drug permeation of F4-F6



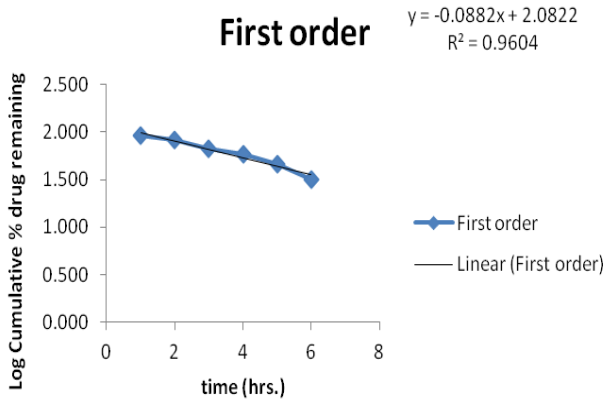
Graph 8: *In-vitro* drug permeation of F7-F9



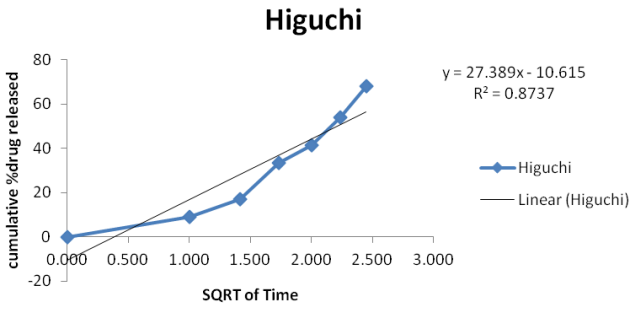
Graph 9: Surface response of effect polymer on drug permeation



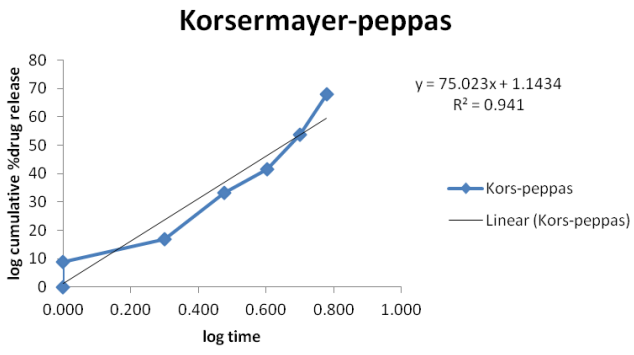
Graph 10: Zero order drug release kinetics of F8



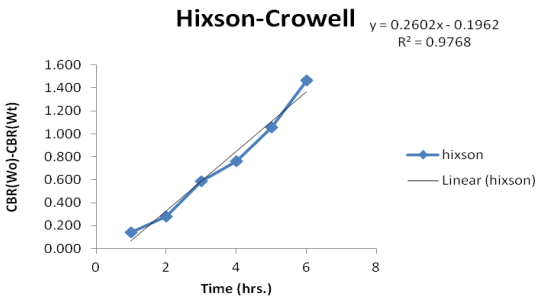
Graph 11: First order drug release kinetics of F8



Graph 12: Higuchi drug release kinetics of F8



Graph 13: Korsermayer-peppas drug release kinetics of F8



Graph 14: Hixson-Crowell drug release kinetics of F8

Table 9: Drug release kinetics of F8 formulation

Zero order		*First order*		*Higuchi*	
R^2	*K*	R^2	*K*	R^2	*K*
0.9004	81.056	0.9604	1.042	0.8737	27.38
Korsermayer-Peppas		Hixson-Crowell			
R^2	*K*	R^2	*N*		
0.941	75.023	0.9768	0.2602		

In-vitro Drug Permeation study

Formulation F8 shows a higher percentage of drug release after 450 minutes, which was found to be 95.10. Formulation prepared with 0.3% gellan gum, 0.15% HPMC K4M and 3% glycerine shows higher percentage of drug release due to good permeation and mucoadhesive characteristic property. However, because the sol transited to the gel and remained in the nasal cavity, drug release from the mucoadhesive nasal formulation was decreased.

Kinetics of Drug Release

Because the F8 formulation demonstrated a higher percentage of drug permeation, it was subjected to a kinetic study.

We investigated the drug release mechanism by applying multiple kinetic models to the release data of the optimized formulations. It has been established that the Hixson-Crowell model is suitable for explaining the mechanism by which 0.3% gellan gum, 0.15% HPMC K4M and 3% glycerine release Fexofenadine HCl.

It has been shown that the Hixson-Crowell model is appropriate for describing the release mechanism of Fexofenadine HCl from 0.3% gellan gum and 3% glycerine. F8 formulation followed Hixson-Crowell diffusion model of drug release (r^2=0.9709) and it was best fitted to Hixson-Crowell diffusion model. Formulation indicated the Fickian mechanism of drug release when the *n* value was less than 0.5.

CONCLUSION

The drug, gellan gum, HPMC-K4M, β-cyclodextrin solubilizer, and glycerine were used to prepare the ion-induced gel successfully. Gellan gum, a naturally occurring, biodegradable polymer, is what gives a formulation its gelling property. When a polymeric solution containing gellan gum interacts with the epithelium of the nasal mucosa, it forms a firm mucoadhesive gel because of the presence of ions in the epithelium mucosa, which slows mucosal clearance and extends the residence time. FTIR and DSC study show no interaction between the polymer and drug; hence polymer used in the formulation was suitable for formulation. F8 was found to be the optimized formulation, with maximum mucoadhesive strength, gelling strength, drug content and drug release of 95.10% within 8 hours. F8 formulation followed Hixson-Crowell diffusion model of drug release (r^2 = 0.9709) and it was best fitted to Hixson-Crowell diffusion model. Formulation indicated the Fickian mechanism of drug release when the *n* value was less than 0.5. Future clinical usage has demonstrated the efficacy of administering a fexofenadine HCl *in-situ* gel formulation into the nasal cavity as an effective substitute for other conventional treatments.

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