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Original Research Paper

FORMULATION AND EVALUATION OF NASAL IN SITU GEL OF PHENYLEPHRINE HYDROCHLORIDE

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ABSTRACT

In situ gel drug delivery systems are in solution form before administration but once administered, undergo gelation *in situ*, to form a gel. In the present study nasal in situ gel of Phenylephrine hydrochloride was prepared for the treatment of nasal infections to provide sustained release of drug and to attain site specific action. Carbopol 934 was used as a pH triggered polymer and Poloxamer 188 was used as thermo sensitive agent. Different formulations were prepared by varying the concentrations of Carbopol 934 and Poloxamer 188 polymers in combination with Hydroxylpropyl Methylcellulose (HPMC), HPMC E5LV, HPMC E15LV, and HPMC E50 LV as viscosity enhancing agents. These formulations were evaluated for parameters like drug excipient compatibility, pH, drug content, gelation temperature, viscosity, *in vitro* drug release, mucoadhesion, *ex vivo* permeation and stability studies. FTIR study revealed that there was no interaction between drug and polymer. pH of all the formulations were found to be in the range of 5.4-6.2 and the drug content for all the prepared formulations was found to be in the range of 94%-99%. The results of *in vitro* drug release and mucoadhesive strength indicated that the optimized formulation F15 and F18 is the most successful formulations of the study, exhibited a sustained drug release of in 77.8% in 6 hours and 70.8% in 8 hours with a mucoadhesive strength of 3124.64 and 3167.76 dyne/cm^2. From the results it is concluded that Phenylephrine hydrochloride nasal *in situ* gel produces prolonged and site specific drug delivery for the treatment of respiratory tract infections especially for sinusitis and bronchitis.

Keywords: Nasal drug delivery, Phenylephrine hydrochlorid, *In Situ* nasal gel, Mucoadhesion.

INTRODUCTION

In the recent years considerable attention has been focused on the development of new drug delivery systems. The therapeutic efficacy and safety of drugs administered by conventional methods can be improved by more precise spatial and temporal placement with in the body through a controlled drug delivery. The use of the nasal pathway for the delivery of drugs is an emerging field in both pharmaceutical sciences and pharmaceutical industry. While the great majority of nasal formulations are designed and used for local delivery to treat nasal allergy, congestion or infections, other applications of nasal delivery have gained importance in recent years.[1] Nasal mucosa has been considered as a potential administration route to achieve faster and higher levels of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents.[2,3] The generation of a new drug molecule is an expensive and time consuming process. Hence the safety and efficacy ratio of "old" drugs can be improved by delivering drugs at controlled or sustained manner to the targeted site. This leads to the development of *in situ* gelling nasal drug delivery systems. In situ gels are the drug delivery systems that are in solution form before administration in the body, but once administered, undergo gelation to form a stiff gel. This new concept was suggested first time in the early

1980's.[4] Compared to liquid formulations, nasal in situ gels are instilled as low viscosity solutions into the nasal cavity, but also release drug slowly and continuously, hence, it is especially useful for those drugs used chronically. There are many mechanisms which triggers the formulation of in situ gels such as solvent exchange, ultra violet irradiation, ionic cross linkage, temperature modification, pH change and ionization from which the drug gets released in a sustained and controlled manner. Prolonged and sustained release of the drug, reproducibility, excellent stability, biocompatibility and accurate quantities of administration makes the in situ gel system more reliable. Phenylephrine hydrochloride is recommended for the treatment of community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) and in the management of acute exacerbations of chronic bronchitis (AECB). It functions by inhibiting the replication and transcription of bacterial DNA by stabilizing the complex formed between DNA and topoisomerases. The objective of present work is to prepare nasal *in situ* gel of Phenylephrine hydrochloride for the treatment of respiratory tract infections especially for sinusitis and bronchitis to attain site specific action and to sustain the drug release for a prolong period which decreases the frequency of dosage administration in order to improve patient compliance.

MATERIALS AND METHODS

Phenylephrine hydrochloride was obtained as a gift sample from Yarrow Chem Products, Mumbai, HPMC, HPMC E5, HPMC E15, HPMC E50 LV, and Carbopol 934 were of pharmaceutical grade purchased from Loba Chemise laboratory reagents and Fine Chemicals Ltd, Mumbai, Poloxamer 188 sample was obtained from Yarrow Chem Products, Mumbai and all the materials and solvents used were of analytical grade.

Methods

Preformulation Studies

Determination of λmax of phenylephrine hydrochloride

Accurately weighed 25mg of Phenylephrine hydrochloride was dissolved in 25ml of pH 6.6 phosphate buffer to give a solution of 1 mg/ml (1000 µg/ml) concentration and this solution was served as the first standard stock solution. From this stock solution 1 ml was taken and diluted to 10 ml using pH 6.6 phosphate buffers to get a solution of 100 µg/ml concentration and served as the second standard solution. From the above solution (10 µg/ml) aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5 ml were pipetted out into a series of 10 ml volumetric flasks. The volume was made up to 10 ml using phosphate buffer of pH 6.6 to get final concentration of 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, and 25 µg/ml respectively. One of the above solutions i.e., 15µg/ml was selected for the determination of λmax. This solution was scanned between the range of 200-400nm.The absorbance of each concentration was measured at λmax of 237 nm using UV Visible spectrophotometer against reagent blank. Standard curve was plotted with concentration on x-axis and absorbance on y-axis.

Fourier transform infrared spectral studies[5]

FT-IR spectroscopy was carried out to check the compatibility between drug and polymer. The FT-IR spectra of drug with polymers were compared with the standard FT-IR spectrum of the pure drug. The FT-IR spectra were taken on FTIR Alpha-T (Bruker1.2.4 IR system) to investigate any possible interactions between the drug, polymer and physical mixture.The scanning range was 400-4000 cm-1. The spectra obtained were compared and interpreted for the functional group peaks.

Method of preparation[6,7]

Composition of *in situ* gel were shown in table 1 and 2. The formulations F1-F15 were prepared by dispersing carbopol 934 in distilled water with continuous stirring (Thermostatic hot plate with magnetic stirrer) until completely dissolved and allowed to hydrate overnight. HPMC was dissolved in distilled water using magnetic stirrer and allowed to hydrate. Then the carbopol solution was sprinkled over this solution and allowed to hydrate overnight. After the complete hydration of polymers, a separate solution of

Phenylephrine hydrochloride in water along with propylene glycol was added to the polymeric solution. The resultant solution was thoroughly mixed, benzalkonium chloride was then added and mixing was confirmed until a uniform and clear solutions were formed. Final volume was made by adding required amount of distilled water. All the formulations were adjusted to pH 5.4 to 6.2 by using freshly prepared 0.5 M sodium hydroxide solution.

The formulations F16-F18 were prepared by using cold method. The method involves slow addition of polymer, drug and other additive in cold water with continuous agitation. The formed mixtures were stored overnight at 4°C until a clear solution is formed. Final volume was made by adding required amount of distilled water. Formulations showing satisfactory gelation temperature (30°c - 38° C) were selected.

Evaluation of Prepared Formulations

Appearance

The clarity of formulated solution was determined by visual inspection against black & white background.[8]

pH

pH is one of the most important parameter involved in the nasal formulation. The two areas of critical importance are the effect of pH on solubility and stability.[9] The pH of nasal formulation should be such that the formulation will be stable at that pH and at the same time there would be no irritation to the patient upon administration of the formulation. Nasal formulations should have pH range in between 5.4 to 6.2. The developed formulations were evaluated for pH by using Elico India Systronics digital pH meter which was calibrated using buffers of pH 4 and pH 7 before the measurement.

Drug content

Uniform distribution of active ingredient is important to achieve dose uniformity. The drug content was determined by diluting 1 ml of the formulation to 100 ml with phosphate buffer of pH 6.6 and shaken vigorously. From the above solution 10 ml was withdrawn and further diluted to 100 ml with pH 6.6 phosphate buffer. The absorbance of above solution was measured at 237 nm by using UV-Vis spectrophotometer.[10]

Gelation temperature

Two milliliter aliquot of gel was transferred to a test tube, immersed in a water bath. The temperature of water bath was increased slowly at a constant rate of 1°C for 2 min from room temperature to the temperature at which gel formed. The sample was then examined for gelation, which was said to have occurred when the meniscus would no longer move upon tilting the test tube through an angle of 90°.

In vitro gelation studies

All prepared formulations were evaluated for gelling capacity and viscosity in order to identify the compositions suitable for use as *in situ* gelling systems.[11] The gelling capacity was determined by placing a drop of the system in a vial containing 2 ml of freshly prepared phosphate buffer of pH 6.6 and equilibrated at 37°C and visually assessing the gel formation and noting the time for gelation and the time taken for the gel formed to dissolve.

Rheological studies[12]

For the development of optimum *in situ* gelling system, two major prerequisites viz. viscosity and gelling capacity should be taken into consideration. Viscosity of instilled formulation is an important factor in determining residence time of drug in the nasal cavity. The developed formulation was placed into the sample adaptor of the Brookfield DV II + pro viscometer. The viscosity of solution and gel was measured at 10 rpm for purposes of comparative evaluation.

In vitro drug Release Studies

In vitro release study of in situ gel formulations was carried out by using Franz diffusion cell of 10 ml capacity. The formulation is placed in donor compartment & 10 ml of freshly prepared phosphate buffer of pH 6.6 was placed in receptor compartment. Between receptor & donor compartment, dialysis membrane previously soaked overnight in the dissolution medium is placed. The whole assembly is placed on thermostatically controlled magnetic stirrer. The

temperature of the medium is maintained at 37ºc± 0.5ºc. 1ml sample was withdrawn at predetermined time interval of 1hr for 8hrs. The sample volume of fresh medium is replaced. The withdrawn samples were suitably diluted & analyzed by UV spectrophotometer at 237 nm using reagent blank. The drug content was calculated using an equation generated from standard calibration curve.[13]

Determination of mucoadhesive strength

Mucoadhesive force was determined by using goat nasal mucosa[14] and phosphate buffer solution of pH 6.6 as the moistening fluid. In this experimental study, section of the goat nasal mucosa was chosen for the following reasons. It is easy to obtain goat nasal mucosa from slaughter house. The area of the respiratory mucosa in the snout is relatively large, and this makes it possible to obtain more material from each animal. It is also easy to handle the tissue.[15] Most importantly, it is of ethical advantage as sacrifice of animals for only a small piece of the animal is avoided. At the time of testing, a section of goat nasal mucosa was secured from the nasal cavity of goat. After the removal of blood and bony cartilage from the mucosal membrane, the membrane was washed with saline and then with phosphate buffer of pH 6.6. Mucoadhesive strength was measured using modified balance as shown in fig 1. The balance was mainly composed of a two-arms. The right arm of the balance was replaced by a small plastic cap suspended through a thread. To the other side of the arm two cylindrical glass vials with 2cm diameter were taken. The vial with a section of goat nasal mucosal membrane was tied with rubber band and placed in inverted position while the other vial was hooked to the balance. Fixed amount (0.5 g) gel of each formulation was applied onto the mucosal surface of lower vial and the height of it was adjusted to attain intimate contact. Gel and the tissue was allowed to contact for 2 minutes. Then sand was added in small amounts to the plastic cap until the detachment of two surfaces of the vials was observed. Weight of sand was measured. The mucoadhesive force, expressed as the detachment stress in dynes/cm^2, was determined from the minimal weight that detached the two vials using the equation:

Detachment stress (dyne/cm^2) = m*g /A

where, m = weight added to the balance,

g = acceleration due to gravity taken as 980 cm/sec^2, and

A = area of tissue exposed and is equal to πr^2 (r-radius of the exposed membrane).

The nasal mucosa was changed for each measurement.

Ex vivo permeation studies

The use of natural membranes is very important to predict the drug release characteristics. The modified Franz diffusion cell was used for permeation studies. It consists of two compartments, one is donor compartment and another is receptor compartment of 10 ml capacity. Within 1.5 h, a piece of nasal mucosa was mounted as flat sheet in between the donor and receptor compartment of Franz diffusion cell. Receptor compartment was filled with 10 ml of phosphate buffer of pH 6.6. A magnetic bead was placed in the receptor compartment, and the whole assembly was placed on the magnetic stirrer. The optimized formulation containing drug equivalent to 10mg was placed in the donor compartment. At predetermined time, aliquot of 1 ml was withdrawn from the acceptor compartment and equal amount of fresh buffer solution was replaced and were suitably diluted and analyzed spectrophotometrically at 237 nm. The study was continued for 8 hours.

Release kinetics and mechanism of drug release

In order to understand the kinetic and mechanism of drug release, the result of *in vitro* drug release study of nasal in situ gels were fitted with various mathematical models. Based on the R^2-value or n-value, the best-fitted model was selected.[16-18]

Zero - order kinetic model - Cumulative % drug release versus time.

First - order kinetic model - Log cumulative percent drug remaining versus time.

Higuchi's model - Cumulative percent drug released versus square root of time.

Korsmeyer equation / Peppa's model - Log cumulative % drug release versus log time.

Erosion model - Cubic root of unreleased fraction of the drug versus time.

Stability studies[19]

Stability studies were conducted for the best formulation of Phenylephrine hydrochloride in situ gel. The stability of the formulation was assessed by keeping the formulation at three different temperature conditions, i.e., refrigeration temperature (4-8^{0}C), room temperature and oven (45±2^{0}C). Throughout the study, nasal in situ gel formulation was stored in aluminium foil sealed glass bottles. The stored formulations were evaluated periodically for drug content, pH, viscosity and *in vitro* drug release at predetermined time interval.

RESULTS AND DISCUSSION

Eighteen formulations of Phenylephrine hydrochloride in situ gelling systems were prepared by using various concentrations of carbopol 934 along with different grades of HPMC and poloxamer 188.

Compatibility Studies

The prepared in situ gelling systems were evaluated for interaction studies to ensure that there was no interaction occurred in between drug and polymers. For confirmation of stability of drug in the prepared formulations the IR spectra was taken and compared with that of pure drug. The results of these studies revealed that there were no definite changes obtained in the bands of drug with respect to pure drug as shown in fig.2, fig.3 and fig. 4.

Calibration Curve of Phenylephrine Hydrochloride

Standard plot of Phenylephrine hydrochloride was done as per the procedure in experimental methods. The curve was found to be linear in the concentration range of 5- 25 µg/ml at λmax of 237 nm with correlation coefficient of 0.999 which indicates that it obeys Beer's – Lambert's Law (fig. 5). The calculation of the drug content, *in vitro* release, and stability studies are based on this calibration curve.

Clarity, pH and Content Uniformity

All the prepared in situ gelling systems were evaluated for preliminary tests such as visual appearance, clarity, pH, and drug content. All the formulations were light yellow in colour and were clear except the formulations F6, F15 & F18. It is known that the normal physiological pH of the nasal mucosa is 5.4-6.2. However, the nasal mucosa can tolerate solutions within a pH range of 3-10. The pH of all the formulations (F1 to F18) was found to be in the range of 5.4-6.2. i.e., within the physiological range of pH of nasal mucosa. Hence, we can ensure that there would not be any irritation to the nasal mucosa. The percentage drug content was found to be in the range of 94-99% which indicates that all formulations were of uniform (table 3).

Rheological Studies

The viscosity of in situ solutions was determined by Brookfield viscometer at 10 RPM and the results were tabulated in Table 5.The formulation F1 shows least viscosity and F6 shows maximum viscosity. From this we can conclude that increase in polymer concentration would result in increase in viscosity of the formulation.

In Vitro Release Studies

The *in vitro* release of Phenylephrine hydrochloride from the prepared formulations was studied through dialysis membrane using Franz diffusion cell. The release studies of prepared in situ gelling systems were carried out up to 8 hours and the cumulative percentage drug released was shown in fig. 6, fig 7 & fig. 8. At fixed drug concentrations, the release rate depends on carbopol concentration, the higher the carbopol concentration, the lower the rate of drug release. The release of the drug from the formulation depends upon the type of polymer used, its concentration and the viscosity of the formulation. The results showed that, formulation F1 containing 75 mg of carbopol 934 alone showed 99.2 % drug release within 3 hours. As the carbopol concentration increases, it prolongs the drug release but increase in carbopol 934 concentration (> 130mg) alone turns the formulation more acidic which causes nasal irritation. So, to avoid nasal irritation, different grades of HPMC as a viscosity enhancer were added. From the results, it was observed that even at low concentration of carbopol 934 along with

different grades of HPMC, the drug release was sustained for an extended period. Among all the formulations, F15 containing 100 mg of carbopol 934 with 100 mg of HPMC E50LV showed a drug release of 98.8 % at the end of 8 hours and F18 containing 100 mg of carbopol 934 and 1000mg of poloxamer 188 showed a drug release of 98.9% at the end of 8 hours which prolongs the drug release for an extended period and considered as an optimized formulations.

Mucoadhesive Strength

Mucoadhesion strength was determined by measuring the force required to detach the formulation from mucosal surface i.e., detachment stress. All the formulations were subjected to mucoadhesion study by using modified balance in our laboratory (fig.10).The mucoadhesion force is an important parameter for in situ gelling nasal formulations since it prolongs the nasal clearance of gels and increases its residence time in the nasal cavity. The reinforcement of the mucoadhesive forces in the nasal in situ gels by the use of mucoadhesive polymers could be explained by the fact that secondary bond forming groups (hydroxy, ethoxy and amine) are the principle sources of mucoadhesion. The bioadhesive force generally depends on the nature and concentration of bioadhesive polymers. The stronger the bioadhesive force, longer is the nasal residence time. But if the mucoadhesion is too strong, the gel can damage the mucosal membrane. As per Table 6, it reveals that the variable concentration of carbopol 934 and HPMC increases the mucoadhesive strength but in case of different grades of HPMC, HPMC showed the highest mucoadhesion.

Drug Release Kinetics

In order to elucidate the mode and mechanism of drug release and release rate kinetics of the dosage form, the in vitro drug release data obtained from in situ nasal gel formulations in Phosphate buffer of pH 6.6 were fitted in to various kinetic models. The results were shown in table 7.

The kinetic and the release mechanisms were estimated by regression plots for zero order, first order, higuchi model, erosion model and kores meyer peppas model. When the R^2 values of regression plots for first order and zero order were considered, it is evident that the drug release from all Phenylephrine formulations, follow zero order kinetics.

So all the formulations in this study were best expressed by zero order. To further confirm the exact mechanism of drug release, the data was incorporated in to kores meyer peppas model and the mechanism of drug release was indicated according to the value of exponent 'n'. For all the in situ nasal gel formulations the release exponent 'n' value found to be between 0.5 to 0.89, so it indicates all the in situ nasal gel formulations followed non –fickian diffusion.

Ex Vivo Permeation Study

Ex vivo drug release was carried out for optimized formulation using nasal mucosa of goat. The percentage drug release from the nasal in situ gel containing Phenylephrine hydrochloride was 75.8 % at the end of 8 hours for F15 formulation and F18 is 70.8%.

Short Term Stability Studies

The nasal in situ gel forming solution of Phenylephrine hydrochloride was developed successfully to achieve drug release in sustained manner. Optimised in situ formulations of phenylephrine hydrochloride (F15 and F18) showed promising results in all evaluation parameters when subjected to short term stability studies at three different temparatures 4^0- 8^0 c, room temperature and 45 ± 2^0c . From the stability studies it was confirmed that in situ gelling formulations of Phenylephrine hydrochloride remained more stable at room temperature.

CONCLUSION

The method employed for the preparation of in situ gel was simple and reproducible. Infrared spectroscopy studies of Phenylephrine hydrochloride, polymers and their physical mixture revealed that, phenylephrine hydrochloride is compatible with all the polymers used. The clarity of the prepared formulations was found satisfactory. The pH of the formulations varied from 5.4-6.2 which is

considered safe for nasal delivery. All the formulations were found to have desired amount of drug content, indicating that the method adopted for making of the formulation is suitable. Optimized formulation F15 and F18 (composed of 100mg of carbopol 934, and 100mg of HPMC E50LV), F18 composed of 100mg of carbopol,1000mg of poloxamer 188) better with respect to its rheological properties, gelation, pH, mucoadhesive strength, *in vitro* drug release and *Ex vivo* permeation studies when compared to other formulations. The results of *Ex vivo* release studies revealed that, all the in situ gel formulations showed good mucoadhesion which prolongs the drug release. From the stability studies it was confirmed that in situ gelling formulations of Phenylephrine hydrochloride remained more stable at room temperature.

RECOMMEND FUTURE RESEARCH

All the results of the studies showed positive sign towards successful development of desired formulation. As *in-vitro* dissolution studies and *ex-vivo* permeation study showed satisfactory results, it can be further subjected to clinical trials in normal and diseased volunteers to find out the adverse effects, by Pharmacodynamic and Pharmacokinetic parameters to confirm the nasal in situ gel therapeutic efficacy.

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Table 1: Composition of nasal in situ gel formulations of Phenylephrine hydrochloride F1-F15

Ingredients	Formulation Code														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Phenylephrine Hydrochloride	62	62	62	62	62	62	62	62	62	62	62	62	62	62	62
Carbopol 934 (%w/w)	75	100	125	50	75	100	75	100	125	75	100	125	50	75	100
HPMC (%w/w)	-	-	-	75	100	125	-	-	-	-	-	-	-	-	-
HPMC E5 (%w/w)	-	-	-	-	-	-	50	75	100	-	-	-	-	-	----
HPMC E15	-	-	-	-	-	-	-	-	-	50	75	100	-	-	-
HPMC E50	-	-	-	-	-	-	-	-	-	-	-	--	50	75	100
Poloxamer	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Propylene Glycol(ml)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Benzalkanium Chloride (ml)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled Water (ml)	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25

Table 2: Composition of nasal *in situ* gel formulations of Phenylephrine hydrochloride F16-F18

Ingredients	Formulation Code		
	F16	F17	F18
Phenylephrine Hydrochloride (%w/w)	10	10	10
Carbopol 934 (%w/w)	-	-	100
HPMC	-	-	-
HPMC E5(%w/w)	-	-	--
HPMC E15(%w/w)	-	-	-
HPMC E50(%w/w)	-	-	-
Poloxamer 188(%w/w)	900	1000	1000
Propylene Glycol(ml)	2	2	2
Benzalkanium Chloride (ml)	0.01	0.01	0.01
Distilled Water (ml)	10	10	10

Table 3: Evaluation of Phenylephrine hydrochloride nasal *in situ* gel

Formulation Code	Visual appearance	Clarity	pH	Drug Content (%)	Gelling Capacity
F1	Light white	Transparent	5.7	96.26	+
F2	Light white	Transparent	6.1	97.46	++
F3	Light white	Transparent	5.4	98.61	++
F4	Light white	Transparent	6.2	98.57	++
F5	Light white	Transparent	5.8	97.64	++
F6	Light white	Transparent	5.4	99.08	+++
F7	Light white	Transparent	6.0	95.29	++
F8	Light white	Transparent	5.8	97.19	++
F9	Light white	Transparent& less viscous	6.2	98.97	+++
F10	Light white	Transparent	5.8	97.43	++
F11	Light white	Transparent & less viscous	5.9	98.53	++
F12	Light white	Transparent & less viscous	5.7	99.42	++
F13	Light white	Transparent	5.8	97.56	+
F14	Light white	Transparent	6.2	96.28	++
F15	Light white	Transparent	5.6	97.12	+++
F16	Light white	transparent	5.8	96.23	++
F17	Light white	Transparent	6.1	97.21	++
F18	Light white	Transparent	5.9	94.23	+++

Note: (-) No gelation, (+) Gels slowly and dissolves, (++) Gelation immediate and remains for a few hours, (+++) Gelation immediate and remains for an extended period.

Table 4: Gelation temperature

Formulations	Gelation temperature (˚c)
F16	35
F17	37
F18	38

Table 5: Rheological studies

Formulation code	Viscosity of solution (cP)	Viscosity of gel (cP)
F1	75	118
F2	82	150
F3	93	168
F4	189	253
F5	198	281
F6	202	295
F7	92	138
F8	108	148
F9	118	159
F10	129	169
F11	131	181
F12	149	198
F13	154	215
F14	192	252
F15	198	271
F16	138	221
F17	167	273
F18	198	292

Table 6: Evaluation of Mucoadhesive Strength.

Formulation Code	Mucoadhesive Strength dynes/cm^2
F1	1256.72
F2	1284.54
F3	2279.68
F4	3187.27
F5	3458.80
F6	3556.06
F7	2159.37
F8	2261.81
F9	2312.72
F10	2418.26
F11	2468.84
F12	2648.96
F13	2732.92
F14	2867.76
F15	3124.64
F16	2818.84
F17	2938.26
F18	3167.76

Table 7: Correlation coefficient values of Phenylephrine hydrochloride nasal in situ gel formulations F1-F18

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Erosion R^2	Korsmeyer-Peppas R^2	n
F1	0.893	0.840	0.974	0.413	0.896	0.718
F2	0.972	0.852	0.976	0.417	0.895	0.687
F3	0.977	0.943	0.979	0.422	0.899	0.660
F4	0.959	0.942	0.983	0.481	0.927	0.635
F5	0.975	0.939	0.986	0.479	0.931	0.629
F6	0.981	0.942	0.964	0.482	0.942	0.627
F7	0.974	0.933	0.951	0.489	0.944	0.622
F8	0.972	0.928	0.990	0.481	0.946	0.614
F9	0.970	0.920	0.989	0.465	0.940	0.596
F10	0.944	0.907	0.944	0.444	0.926	0.581
F11	0.935	0.933	0.935	0.463	0.911	0.559
F12	0.952	0.892	0.952	0.460	0.912	0.551
F13	0.976	0.921	0.976	0.446	0.915	0.659
F14	0.962	0.936	0.982	0.472	0.921	0.641
F15	0.951	0.942	0.981	0.460	0.921	0.631
F16	0.976	0.929	0.976	0.446	0.911	0.623
F17	0.947	0.932	0.977	0.472	0.913	0.615
F18	0.952	0.922	0.989	0.466	0.915	0.623

Table 8: Short term stability study of optimized formulation F15

Storage Condition	Drug Content %				pH				Viscosity of Solution (cP)			
	Days				Days				Days			
	Initial	15	30	60	Initial	15	30	60	Initial	15	30	60
4-8 ^{0}C	99.42%	98.38%	95.25%	92.89%	5.7	5.6	5.9	5.9	376	380	384	380
Room Temperature	99.42%	99.43%	99.40%	99.38%	5.8	5.8	5.7	5.6	376	376	375	373
45±2 ^{0}C	99.42%	99.42%	98.76%	98.54%	5.8	5.7	5.6	5.6	376	374	372	370

Table 9: Short term stability studies of optimized formulation F18

Storage Condition	Drug Content %				pH				Viscosity of solution (cP)			
	Days				Days				Days			
	Initial	15	30	60	Initial	15	30	60	Initial	15	30	60
4-8 ^{0}C	97.12%	97.38%	97.25%	92.89%	5.7	5.6	5.9	5.9	379	381	386	386
Room Temperature	97.12%	97.10%	97.08%	97.03%	5.8	5.8	5.7	5.6	379	379	374	373
45±2 ^{0}C	97.12%	96.42%	94.76%	94.54%	5.8	5.7	5.6	5.6	379	374	372	370

Figure 1: Modified balance for Mucoadhesion study

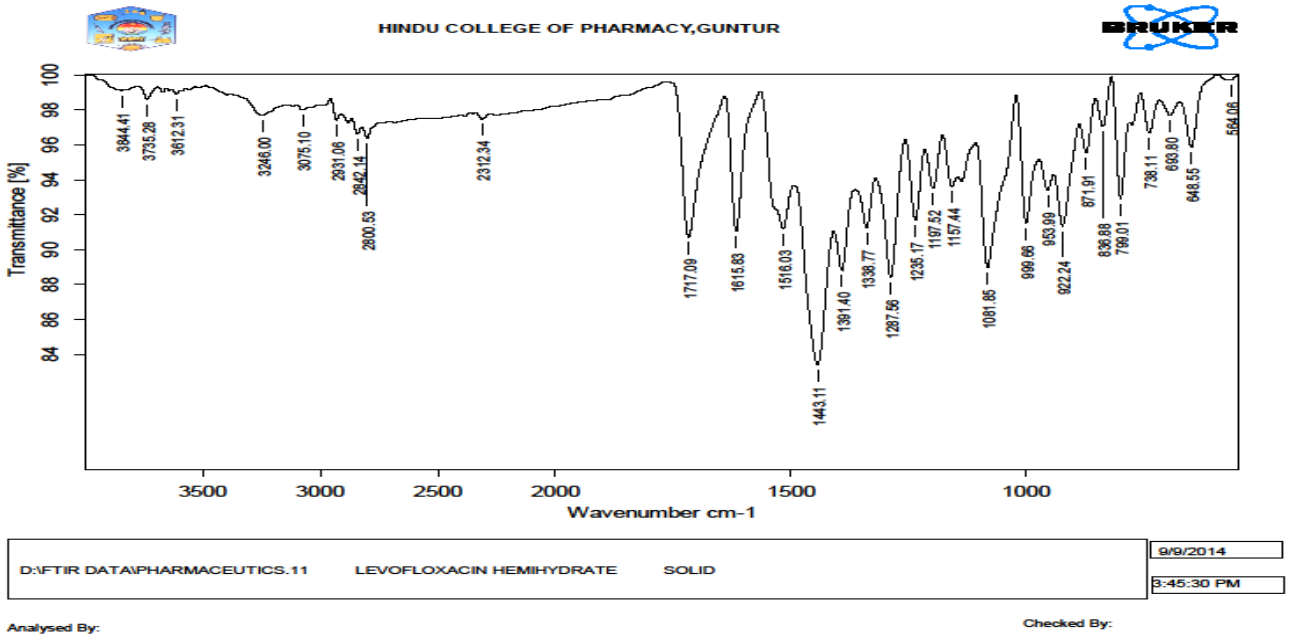

Figure 2: FT-IR spectrum of Phenylephrine hydrochloride

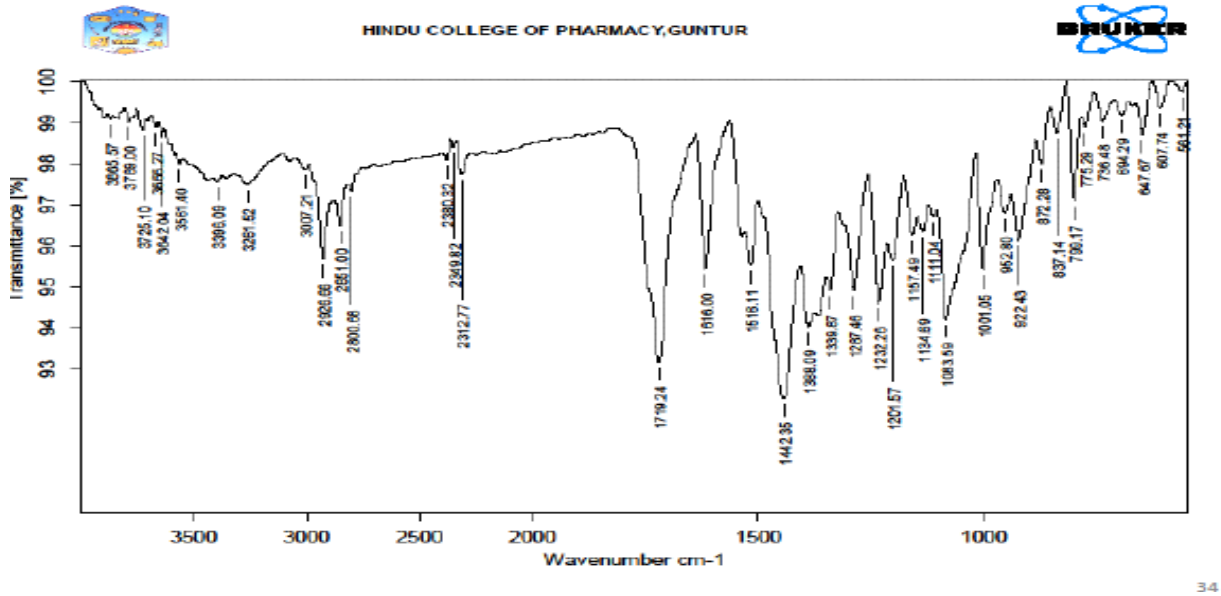

Figure 3: FT-IR Spectrum of *in situ* nasal gel of F15

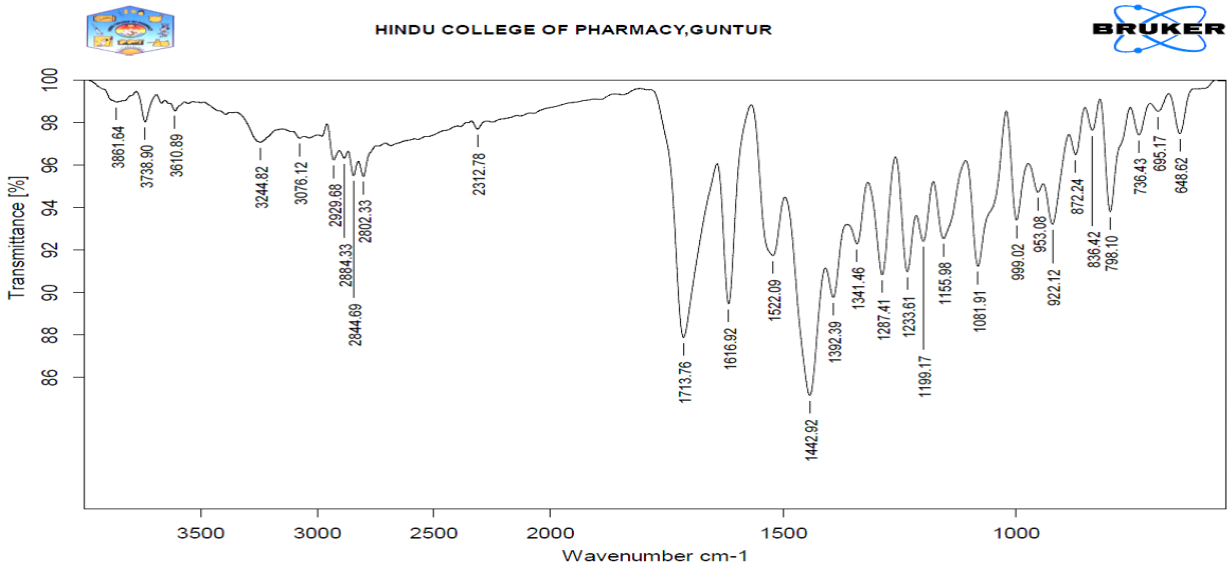

Figure 4: FT-IR Spectrum of *in situ* nasal gel of F18

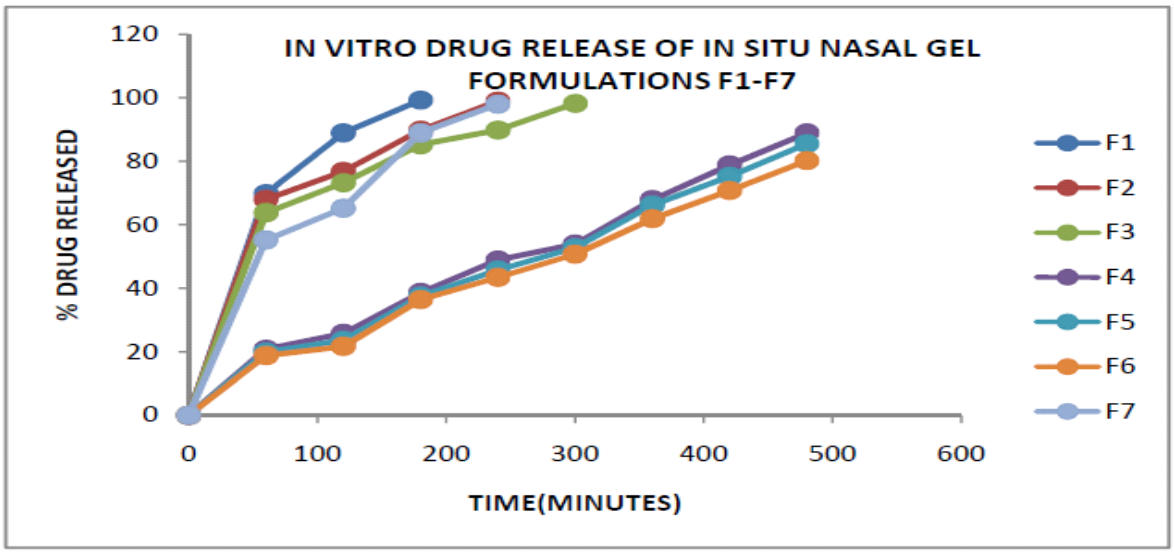

Figure 5: *In vitro* cumulative % drug release (F1- F7)

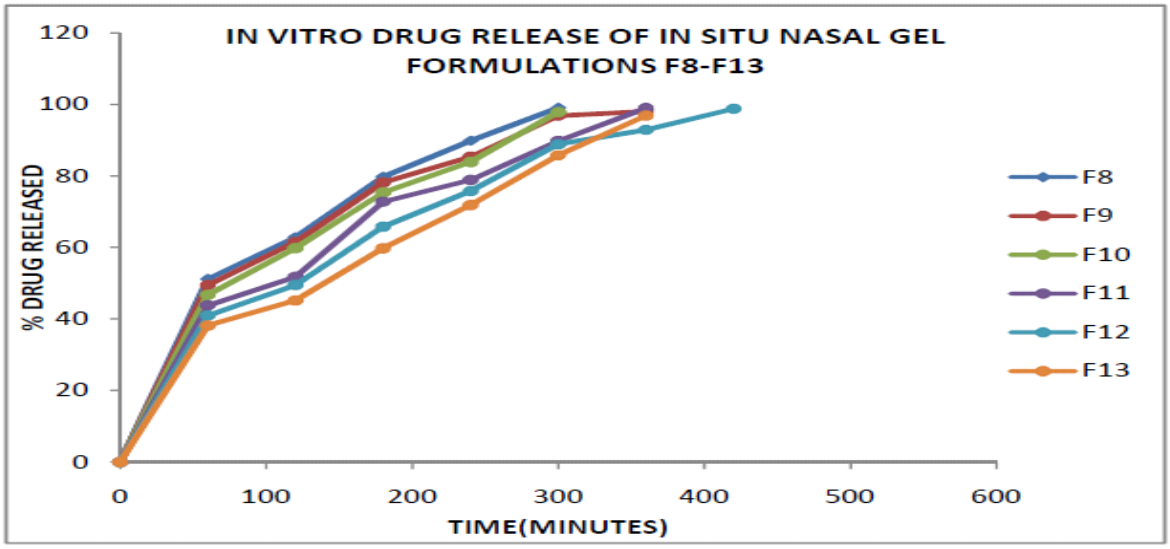

Figure 6: *In vitro* cumulative % drug release (F8- F13)

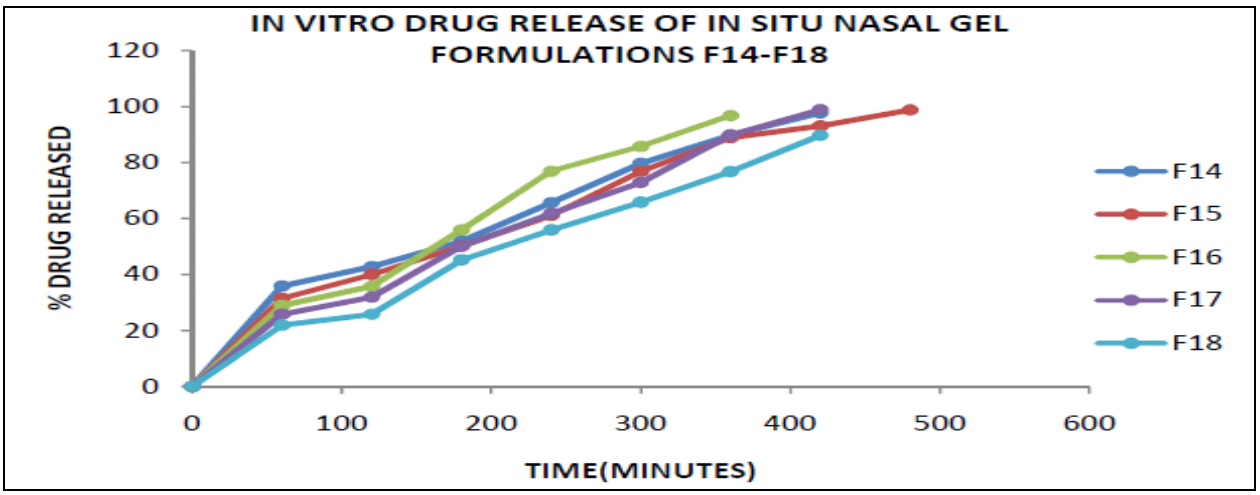

Figure 7: *In vitro* cumulative % drug release (F14- F18)

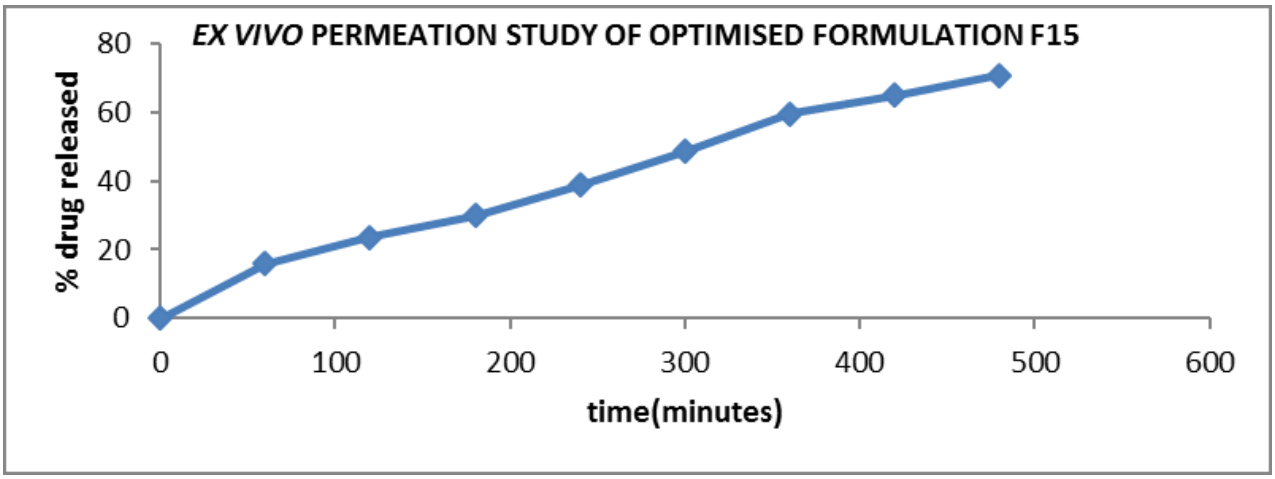

Figure 8: *Ex vivo* permeation of nasal in situ gel formulation (F15)

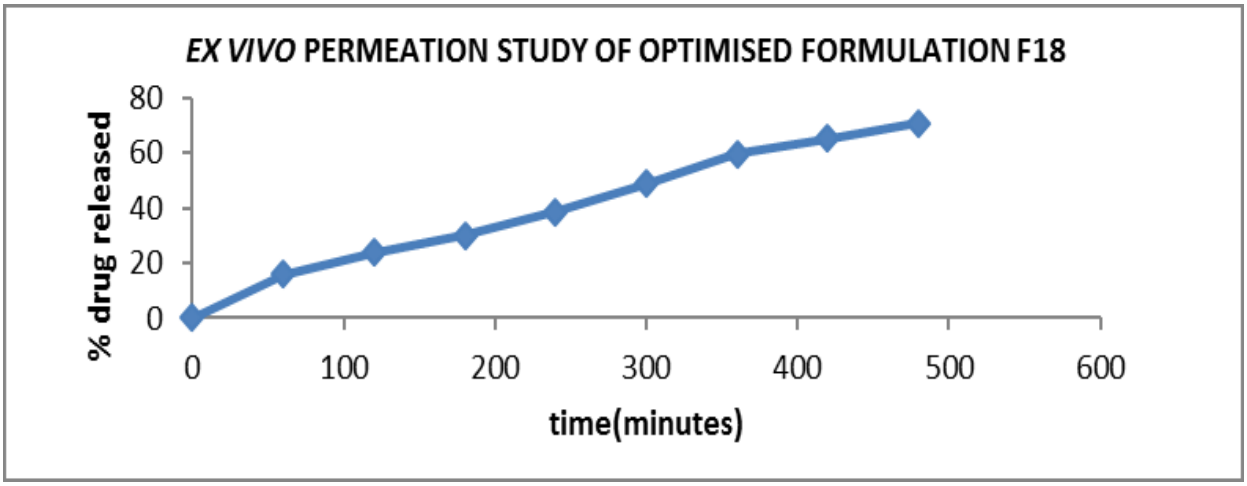

Figure 9: *Ex vivo* permeation of nasal in situ gel formulation (F18)

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