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DESIGN AND CHARACTERIZATION OF PHENYL EPHRINE HYDROCHLORIDE NASAL IN-SITU GEL

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ABSTRACT

In order to improve the bioavailability of the phenylephrine hydrochloride, in situ mucoadhesive thermo reversible gel was formulated using poloxamer 407 as thermo reversible polymer, chitosan and sodium alginate was used as mucoadhesive polymers Results revealed that as mucoadhesive polymer increased the mucoadhesive strength increased but gelation temperature decreased. Formulation was optimized on the basis of clarity, pH, gelation temperature, mucoadhesive strength, viscosity, drug content. The final formulation released 95.43±1.29% drug in 120min and gelation temperature was 37±0.2°C. Drug excipients compatability studies were conducted by FT-IR spectroscopy and result release studies shown that formulations F11 release the drug 99 percentage at the end of 120 mins.

KEYWORDS: Phenylephrine HCL, Polaxomer 407, Chitosan, HPMC.

INTRODUCTION

Oral drug delivery is the most desirable route for the drug administration. Whenever systemic effects are indented but oral bioavailability of some compounds has promoted the search of more effective route for the systemic delivery. Trans mucosal route of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity) nasal mucosa is the majorroute of administration to achieve faster and higher level of drug absorption.[1] Nasal drug delivery has been recognized as a very promising route for delivery of therapeutic compounds. In recent years many drugs have been shown to achieve better systemic

bioavailability through nasal route, this is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism and readily accessibility.[2]

Nasal mucosa as an alternate route to achieve faster and higher drug absorption Knowledge of the nasal mucosa high permeability and use of the nasal route for drug administration can be traced to ancient times. Realization of the nasal mucosa as a therapeutically viable alternate route came in the last two decades. The nasal mucosa itself and the drug delivery systems affect drug absorption through the nasal route, is invaluable. A stable, safe and effective nasal product can be developed through appropriate and adequate Pre-formulation studies of drug.[3] In the last few years, the nasal route has received a great deal of attention as a convenient and reliable method for the systemic administration of drugs, especially those which are ineffective orally and must be administered by injection.[4] Majority of products available are used for treatment of allergic rhinitis, migraine, cold, pain etc. The various formulations given by nasal route includes nasal gel, spray, powders etc. Thus nasal route is the promising alternative for other drug delivery systems.[5,6]

Advantages of intranasal drug delivery[7,8]

- Rapid drug absorption via highly vascularised mucosa.
- Ease of administration, non-invasive.
- Improved bioavailability.
- Improved convenience and compliance.
- Self-administration.
- Large nasal mucosal surface area for drug absorption.
- Avoidance first-pass metabolism.
- Rapid onset of action.
- Lower side effects.
- Drugs which cannot be absorbed orally may be delivered to the Systemic circulation through nasal drug delivery system.
- Convenient route when compared with parenteral route for long term therapy.
- Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

Disadvantages of intranasal drug delivery

- Some drugs may cause irritation to the nasal mucosa.

- Nasal congestion due to cold or allergies may interfere with absorption of drug.
- Drug delivery is expected to decrease with increasing molecular weight.
- Frequent use of this route leads to mucosal damage.
- The amount of drug reaches to different regions of the brain and spinal cord varies with each agent.

IN SITU GEL

In situ is a Latin word which means in position. In situ gel formation of drug delivery systems can be defined as a liquid Formulation generating a solid or semi-solid depot after administration.[22] In situ activated gel forming Systems are those which are when exposed to physiological conditions will shift to a gel phase. This new concept of producing a gel in situ was suggested for the first time in the early 1980s. Gelation occurs via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking)or Non-covalent bond formation (physical cross-linking).[23]The impact of external stimuli such as temperature, pH and ionic strength, on the cross-linking of polymer chain shave been studied to improve the gel strength or to induce in situ Gelation. Both natural and synthetic polymers can be used for the production of in situ gels. In situ gel forming drug delivery systems are principle, capable of releasing drug in a Sustained manner maintaining relatively constant plasma profiles.[24,22,23]

Advantages of in situ gel

- Prolong drug release
- Reduced systemic side effect
- Reduced number of application
- Ease of administration
- Reduced frequency of administration, better patient compliance

Importance of in situ gelling system

The major importance is the possibility of administering accurate and reproducible quantities compared to already formed gel. It increases the contact time of drug with the mucus at the site of absorption and has better bioavailability, enhancing patient compliance.[25,26]

Principle of in situ gelling system

The principle involving the in situ gelling of nasal formulations is that the nasal formulations imbibe in the nasal fluid after administration and forms gel into the nasal cavity. The

formation of nasal gel avoids the foreign body sensation. Due to bio adhesive property the geladheres the nasal mucosa. It acts as release controlling matrix and thus acts as sustained drug delivery system. In the nose, the mucus lower layer comes and goes around the cilia, forward in the propulsion phase, backward in the preparatory phase. At the propulsion phase, cilia extremity scrapes the upper layer of mucus penetrating it almost 0.5 mm. Ciliary activity zones then occur at various intervals. Cilia situated backwards help to remove any obstacle if there is any interference in the propulsion phase. After the formation of the gel, dissolution occurs and or the mucociliary removal towards the nasopharynx occurs. Therefore there is no need to remove the dosage form after it has been depleted of drug.[27]

MATERIALS AND METHODS

Phenylephrine Hcl, polaxomer, benzalkonium chloride, chitosan, deionized water, simulated nasal electrolyte solution (SNES).

PREFORMULATION STUDIES

The Preformulation studies performed are

1) Physical characterization of drug

2) Drug identification

3) Analytical method development of drug

Physical characterization of Phenylephrine hydrochloride

Table No 5.1: Physical properties of Phenylephrine hydrochloride.

	Physical Properties	Inference
1.	Physical appearance	White (or) colourless crystalline powder
2.	Melting point	142 degree
3.	Solubility in water	Freely soluble in water

2) Drug Identification

Fourier transform infrared spectroscopy (FTIR)

Infra red spectrum of pure drug was recorded by using Bruker Alpha FTIR spectrophotometer. FTIR was a sampling technique used in conjunction with infrared spectroscopy which enables samples to be examined directly in the solid state without further preparation. In this, enough samples were placed on crystal area and the pressure arm was positioned over the sample area. Force applied to the sample pushing it on to the surface. Later the sample was analyzed. The IR spectrum of pure Phenylephrine hydrochloride was given in the figure**.**

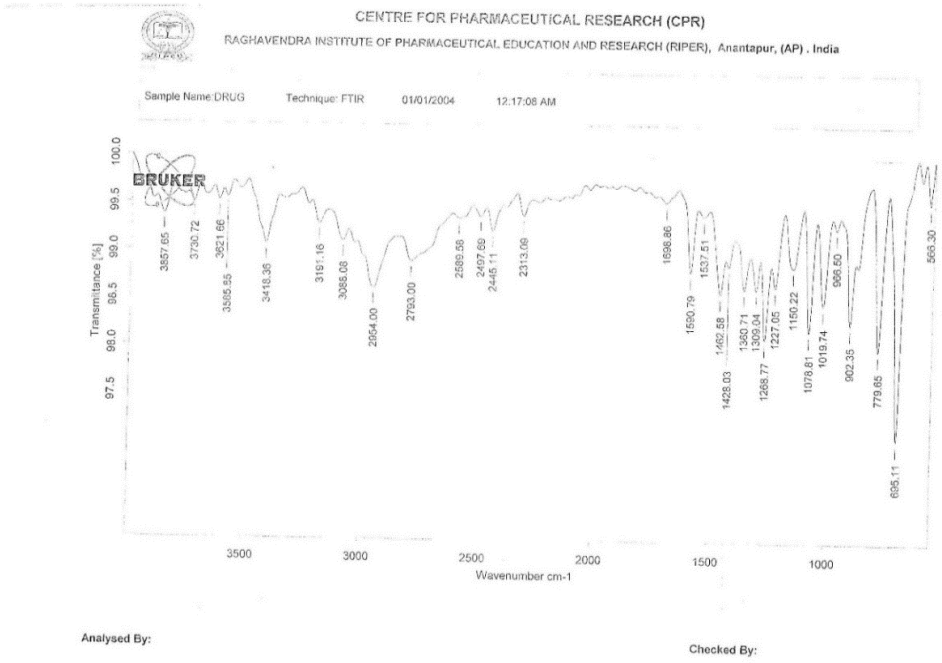


Figure No. 5.1: FTIR spectrum of Phenylephrine hydrochloride.

Fourier transform infrared spectroscopy (FTIR)

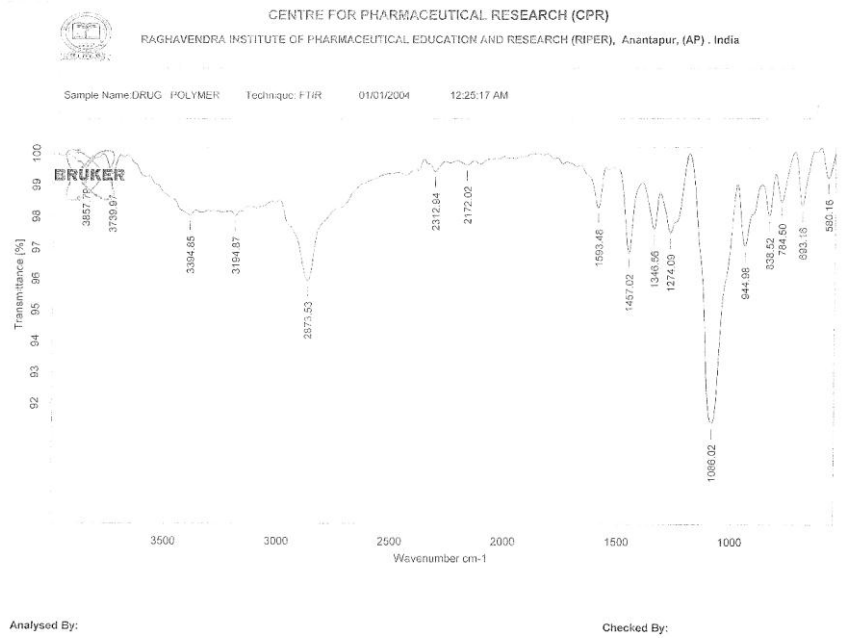


Figure No. 5.2: FTIR spectrum of Phenylephrine hydrochloride and poloxamer-407 physical mixture.

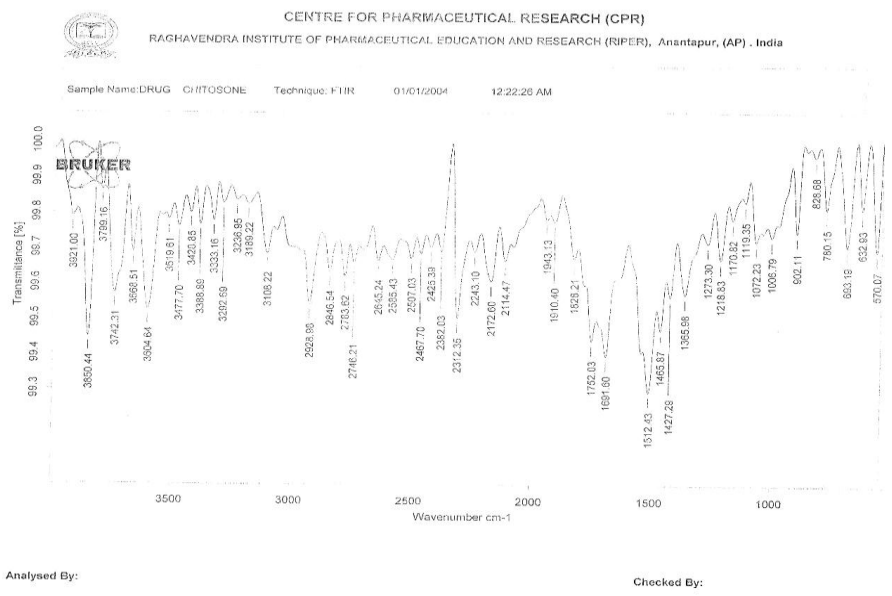


Figure No 5.3: FTIR spectrum of Phenylephrine hydrochloride and chitosan physical mixture.

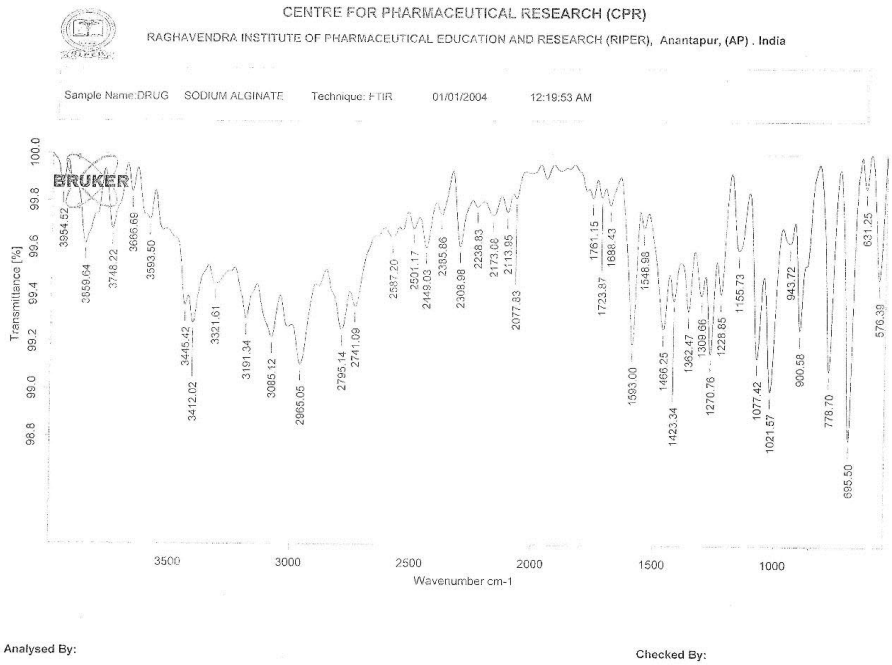
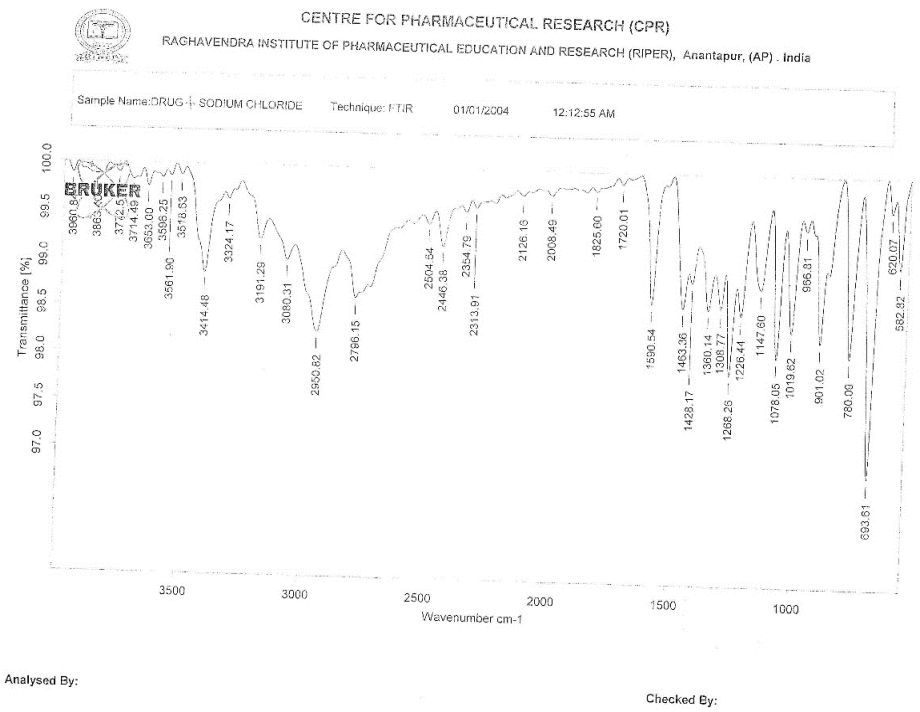
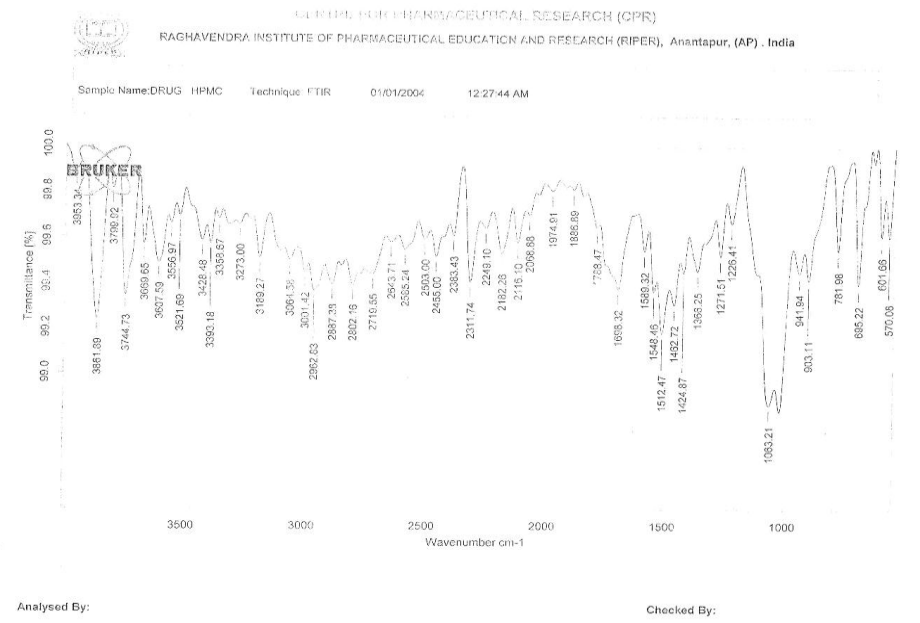


Figure No 5.4: FTIR spectrum of Phenylephrine hydrochloride and sodium alginate physical mixture



FigureNo 5.5: FTIR spectrum of Phenylephrine hydrochloride and HPMC physical mixture.



FigureNo 5.6: FTIR spectrum of Phenylephrine hydrochloride and sodium chloride physical mixture.

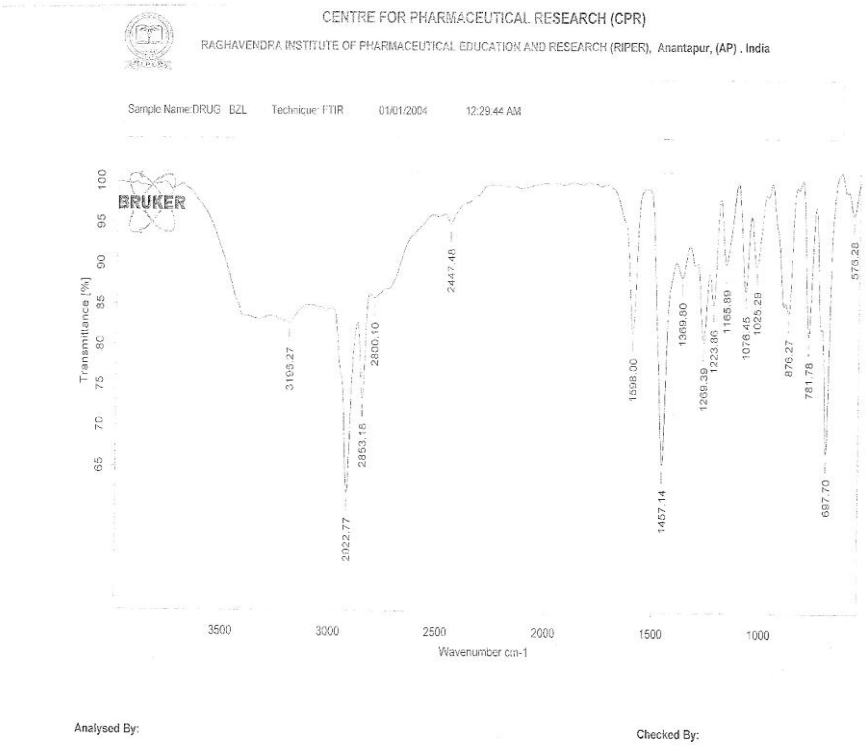


Figure No 5.7: FTIR spectrum of Phenylephrine hydrochloride and Benzalklonium chloride physical mixture.

IR Interpretation

The different functional groups stretching's of pure drug were identified and in the spectra of drug with excipients these stretching's were reproduced and no new peaks were observed indicating there is no interaction of the drug with excipients (John, 2000). IR interpretation of pure drug and excipients was explained in the table.

Table No 5.2: Interpretation of IR.

S. No.	Functional Group	Wave number(cm^{-1})						
		Pure Drug	Drug+ Chitosan	Drug+ sodium chloride	Drug+ sodium alginate	Drug+ Benzalk-onium chloride	Drug+ HPMC	Drug+ Poloxamer
1.	O-H Str	1360	1365	1368	1362	1369	1366	1364
2.	C-NStr	1227	1218	1226	1228	1223	1226	1274
3.	C-H	2954	2948	2950	2965	2922	2962	2950
4.	$>CH_2$	2792	2783	2796	2795	2800	2802	2782
5.	phenol	1428	1427	1428	1423	1457	1424	1437

3) Analytical method development of drug

Calibration of Phenylephrine hydrochloride in simulated nasal electrolyte solution

Preparation of simulated nasal electrolyte solution

Weighed quantity of 7.45 gm of Nacl, 1.29 gm of Kcl, 0.32 gm of $Cacl_2$, all ingredients were dissolved in sufficient distilled water and these made up to 1000 ml by using of distilled water.

Determination of Absorption Maxima (λ_{max}) For Phenylephrine hydrochloride

Standard stock solution of concentration of 1mg/ml solution was prepared. From that stock, different aliquots were taken and diluted to 10ml mark with simulated nasal electrolyte solution to obtain series of concentrations. The solutions were scanned on spectrophotometer in the UV range 200-400 nm. The λ_{max} of Phenylephrine Hcl is determined by UV first order spectrum. The graph indicates that the maximum absorbance is observed at 272 nm and it is the $\lambda_{max}$of Phenylephrine hydrochloride. The zero order and first order spectra was shown in figure 4.8 and 4.9 respectively.

LINEARITY OF PHENYLEPHRINE HYDROCHLORIDE IN SNES:

1. Prepare a primary stock solution by taking 10mg of drug and by dissolving it in SNES and prepare 1mg/ml solution.
2. From that primary stock solution secondary stock solution was prepared of 100µg/ml.
3. From the secondary stock solution further concentrations of 10, 20, 30, 40, 50, 60, 70, 80, 90 µg/ml were prepared.
4. The absorbance of those dilutions was measured at 272 nm.

Table No. 5.3: Linearity graph of Phenylephrine hydrochloride in SNES.

Concentration (µg/ml)	Absorbance
0	0
10	0.106
20	0.189
30	0.289
40	0.375
50	0.453
60	0.529
70	0.594
80	0.738
90	0.823

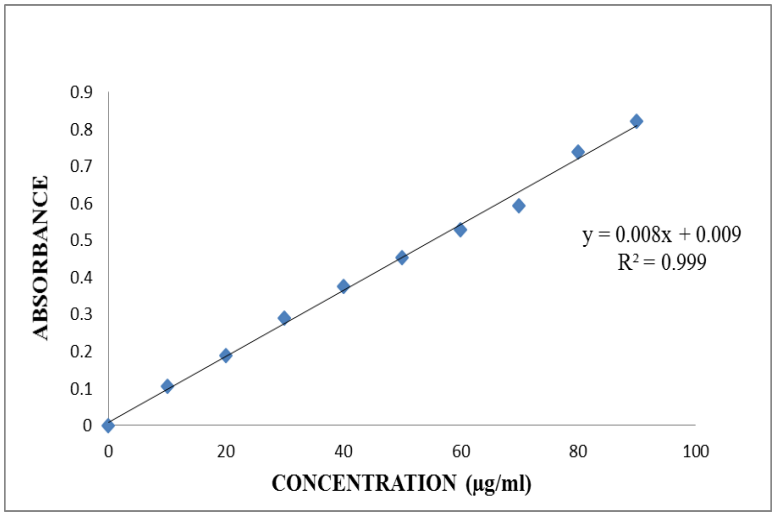


Figure No. 5.8: Linearity plot of Phenylephrine hydrochloride in SNES.

Preparation of pH-6.8 phosphate buffer

Place 50.0 ml of 0.2M potassium dihydrogen phosphate in a 200ml volumetric flask, added 22.4 ml of 0.2M sodium hydroxide and then added water to produce 200ml.

Linearity of Phenylephrine hydrochloride in phosphate buffer pH-6.8

1. Prepare a primary stock solution by taking 10mg of drug and by dissolving it in 10ml of phosphate buffer pH-6.8 and prepare 1mg/ml solution.
2. From that primary stock solution secondary stock solution was prepared of 100µg/ml.
3. From the secondary stock solution further concentrations of 10, 20,30,40,50,60,70,80, 90,100µg/ml were prepared.
4. The absorbance of those dilutions was measured at 272 nm.

Table No. 5.4: Linearity of Phenylephrine hydrochloride in phosphate buffer p^H-6.8.

Concentration(µg/ml)	Absorbance (nm)
0	0
10	0.12
20	0.2
30	0.29
40	0.42
50	0.54
60	0.63
70	0.71
80	0.8
90	0.91

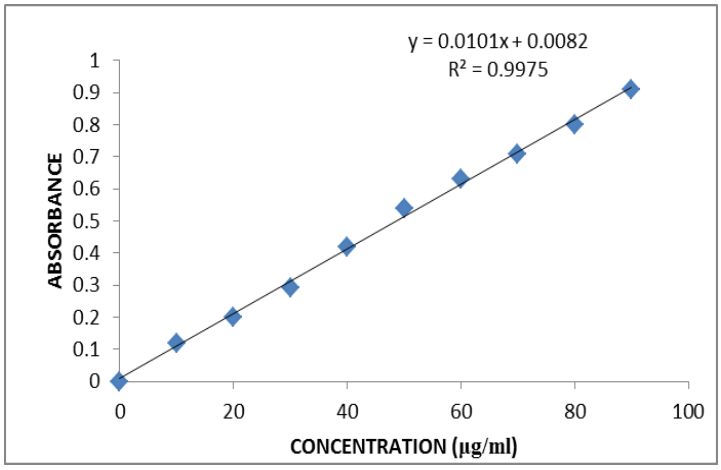


Figure No. 5.9: Linearity plot of Phenylephrine hydrochloride in phosphate buffer in pH-6.

FORMULATION STUDIES

PREPARATION OF NASAL *INSITU* GELS CONTAINING PHENYLEPHRINE HYDROCHLORIDE

Preparation of nasal *insitu* gels containing Phenylephrine hydrochloride and poloxamer 407

Aqueous nasal gel was prepared by using the Cold method described by Schomolka (1972) et al and the procedure followed as

1. only weighed quantity of thermo sensitive polymer, poloxamer 407 (5%,10%,15%,16%,18%,20%w/v), was added to 2mL of distilled water with constant stirring and kept at 4°C in refrigerator overnight until to form a clear solution.
2. To the above clear solution 25mg of Phenylephrine hydrochloride, 0.09gm (0.9%) of sodium chloride, 0.001gm of benzalkonium chloride (0.01%) was dissolved in sufficient quantity of water and make up to 10mL.
3. If necessary again kept at 4°C in refrigerator overnight until to form a clear solution.
4. Optimization of drug-loaded poloxamer 407 gel was done by varying the concentration of poloxamer 407 and evaluating them for Gelation temperature and drug content and the formulation table was shown as follows.

Table 6.1: **Table shows Thermo responsive Nasal gel Formulations containing various ranges of Poloxamers.**

Ingredients (gm)	F1	F2	F3	F4	F5	F6
Phenylephrine hydrochloride	0.025	0.025	0.025	0.025	0.025	0.025
Poloxamer-407	0.5	1	1.5	1.6	1.8	2
Nacl	0.09	0.09	0.09	0.09	0.09	0.09
Benzalkonium chloride	0.001	0.001	0.001	0.001	0.001	0.001
Water (ml) up to	10	10	10	10	10	10

Preparation of nasal *insitu* gels containing Phenylephrine hydrochloride, poloxamer 407 and chitosan

Aqueous nasal gel was prepared by using the Cold method described by Schomolka (1972) et al and the procedure followed as

1. Batch containing optimized concentration of poloxamer 407 (F5) was used for further investigation to study the effect of mucoadhesive polymers on Gelation temperature and mucoadhesive strength. Different concentrations of mucoadhesive polymers were screened. Chitosan (0.2%, 0.4%, 0.6%, 0.8% and 1%), HPMC K15M (0.1%) were tried as a mucoadhesive polymer.
2. Only weighed quantity of thermo sensitive polymer, poloxamer 407 (18%w/v), was added to 2mL of distilled water with constant stirring and kept at 4°C in refrigerator overnight until to form a clear solution.
3. Weighed quantity of chitosan was added to 2mL of 1% acetic acid solution.
4. Weighed quantity of phenylephrine hydrochloride, HPMC, Nacl, Benzalkonium chloride was added to 6mL of distilled water
5. Finally step 2, 3, 4 was added and if requires kept at 4°C in refrigerator until to form a clear solution and the formulation table was shown as follows.

Table 6.2: **Table shows Thermo responsive Nasal gel Formulations containing Poloxamers and various ranges of chitosan.**

Ingredients(gm)	F7	F8	F9	F10	F11
Phenylephrine hydrochloride	0.025	0.025	0.025	0.025	0.025
Poloxamer-407	1.8	1.8	1.8	1.8	1.8
Chitosan	0.02	0.04	0.06	0.08	0.1
HPMC	0.01	0.01	0.01	0.01	0.01
Nacl	0.09	0.09	0.09	0.09	0.09
Benzailklonium chloride	0.001	0.001	0.001	0.001	0.001
Water (mL) up to	10	10	10	10	10

Preparation of nasal *insitu* gels containing Phenylephrine hydrochloride, poloxamer 407 and various ranges of chitoson

1. Batch containing optimized concentration of poloxamer 407 (F5) was used for further investigation to study the effect of mucoadhesive polymers on Gelation temperature and mucoadhesive strength. Different concentrations of mucoadhesive polymers were screened. Sodium alginate (0.2%, 0.4%, 0.6%, 0.8% and 1%), HPMC K15M (0.1%) were tried as a mucoadhesive polymer.
2. only weighed quantity of thermo sensitive polymer, poloxamer 407 (18%w/v), was added to 2mL of distilled water with constant stirring and kept at 4°C in refrigerator overnight until to form a clear solution.
3. Weighed quantity of chitosan was added to 2mL of water.
4. Weighed quantity of phenylephrine hydrochloride, HPMC, Nacl, Benzalkonium chloride was added to 6mL of distilled water
5. Finally step 2, 3, 4 was added and if requires kept at 4°C in refrigerator until to form a clear solution and the formulation table was shown as follows.

EVALUATION OF NASAL INSITU GEL

Appearance (or) clarity

The developed Phenylephrine gel were inspected visually for clarity, colour in sol and gel from against white back ground (or) black back ground and the appearance of various formulations was shown in the table7.1.

pH of formulation

1 ml quantity of each Phenylephrine formulation was transferred to a beaker and diluted by using distilled water pH of resulting solution was determined using digital ph meter. pH meter was previously calibrated using standard buffers of pH 4&pH7 and the pH of formulation of various formulations was shown in the table 7.1.

Measurement of Gelation temperature:

Gelation temperature was determined by using method described by miller and Donovan technique. Gelation temperature defined as the temperature at which the liquid phase makes the transition to a gel. A 2ml aliquot of sol was transferred to a test tube which is surrounded by parafilimimmersed in a water bath. The temperature of water bath was increased slowly and left to equilibrate for 5 min at each new setting. The sample was then examined for Gelation, which was said to have occurred when the meniscus would no longer moves upon

tilting through 90 degree centigrade's. After attaining the temperature and the Gelation temperature of various formulations was shown in the table 7.1.

Drug content

One ml formulation was taken in 10ml volumetric flask, diluted with distilled water and volume adjusted to 10ml. One ml quantity from this solution was again diluted with 10ml of distilled water. Finally the absorbance of prepared solution was measured at 274nm by using UV visible spectrophotometer and the drug content of various formulations was shown in the table 7.2.

Determination of mucoadhesive strength

The mucoadhesive of each formulation was determined by measuring a force required to detach the formulation from nasal mucosal tissue. A section of dialysis membrane was fixed on each of two glass slides using thread. 50mg of gel was placed on first slides using slide placed below the height adjustable pan. While another slide with dialysis membrane was fixed in inverted position to the underside of the same pan. Both the slides with gel formulation between them held in contact with each other for 4 min to ensure intimate contact between them. Then weight was kept detached from each other. The mucoadhesive force expressed as the detachment stress in dynes/cm2 was determined from the minimal weight that detached the mucosal tissue from surface of each formulation and the mucoadhesive strength of various formulations was shown in the table 7.2.

Mucoadhesive strength (dynes/cm2) =mg/A

M = WEIGHT REQUIRED FOR DETACHMENT IN GRAMS

G = ACCELARATION DUE TO GRAVITY (980CM/S2)

A = AREA OF MUCOSA EXPOSED

Viscosity measurement

The viscosity of the nasal gel was evaluated by a Brookfield LVDV 11 + CP viscometer (Stoughton, MA). Experiments were performed for each sample and the viscosity of various formulations was shown in the table 7.2.

Spread ability

For the determination of spread ability excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1000g weight for 5min weight

(50) was added to the pan. The time in which the upper glass slide moves over to the lower plates was taken as measure of spread ability and the spread ability of various formulations was shown in the table 7.1.

Table No. 7.1: Clarity, Gelation temperature, Bioadhesive polymer, pH.

Formulation Code	Clarity	Gelation Temperature (^oC)	Bio adhesive Polymer	pH
F1	Clear	>50	**	**
F^4	Clear	>50	**	**
F3	Clear	>50	**	**
F4	Clear	31	**	**
F5(optimized)	Clear	35	**	**
F6	Clear	27	**	**
F7	Clear	31	Chitosan & HPMC	5.6
F8	Clear	33		5.7
F9	Clear	37		5.9
F10	Clear	40		5.4
F11	Clear	42		5.5

In vitro Diffusion Studies

In vitro drug diffusion studies were carried out by using modified dissolution apparatus. It is carried out by dialysis bag method to increase in the surface area available for transport from the donar to the receiver compartment and hence sink conditions are maintained. It is conducted by taking the 400ml of SNES as a diffusion medium and the speed was maintained at 50 RPM. The prepared nasal gel was taken in the dialysis bag(dialysis membrane-70 with molecular weight cut off 1200-1400 KDa) by tying the both ends and the tied bag containing nasal gel was dropped in to the dissolution jar and the samples were taken at regular intervals of time30min and analyzed spectrophotometrically at 272nm. Experiments were performed triplicate of each sample and the in *vitro* diffusion studies of various formulations were shown in the table7.3 and 7.4. The drug release plots were shown in Figure 7.1, 7.2 7.3.

Table No7.2:mucoadhesive strength, drug content, viscosity results.

Formulation code	Bio adhesive Polymer	Mucoadhesive Strength (Dynes/cm^2)	Drug content(%)	Viscosity (cps)
F1		**	98	**
F2		**	98	**
F3		**	96	**
F4		**	97	**
F5(optimized)		**	98	**

F6		**	97	**
F7	Chitosan & HPMC	194.8	96	28
F8		221.6	97	34
F9		244.5	98	38
F10		251.7	96	44
F11		263.8	99	50

Table No. 7.3: *In vitro* drug release formulations containing Poloxamers and various ranges of chitosan.

Time(min)	Cumulative % drug diffused *±SD				
	F7	F8	F9	F10	F11
0	0	0	0	0	0
30	62.56±2.34	33.45±2.39	25.67±3.45	15.67±1.53	13.53±1.52
60	95.94±1.65	69.82±2.12	49.83±2.34	22.38±2.37	20.49±2.46
90		96.78±1.37	72.37±1.25	39.82±1.97	28.73±1.27
120			95.43±1.29	64.54±1.52	36.23±1.41

Table No 7.4: *In vitro* drug releaseFormulations containing Poloxamers and various ranges of chitosan.

Time(min)	Cumulative % drug diffused *±SD				
	F12	F13	F14	F15	F16
0	0	0	0	0	0
30	54.38±1.54	49.83±1.23	29.83±1.27	20.37±2.23	17.28±2.23
60	65.34±2.36	67.42±2.35	53.61±2.42	40.28±1.35	25.67±1.98
90	95.24±1.62	93.57±2.78	72.31±1.96	65.79±2.37	43.53±2.23
120			91.27±2.92	83.45±1.67	72.58±1.29

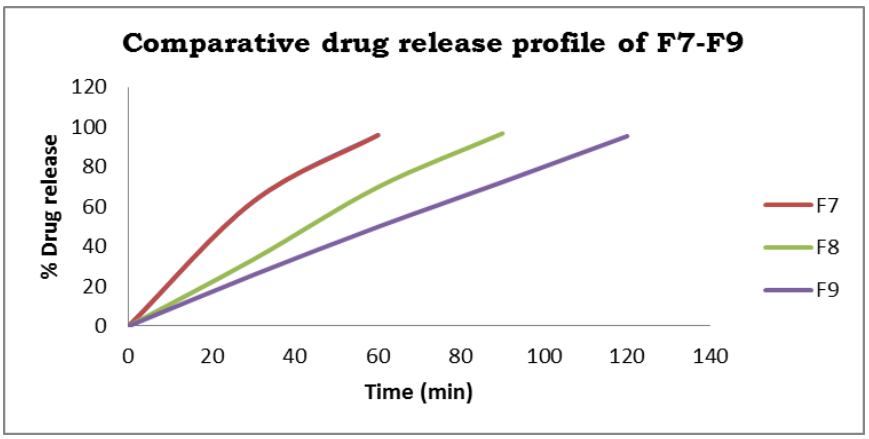


Figure No. 7.1: Comparative drug release profile of F7-F9.

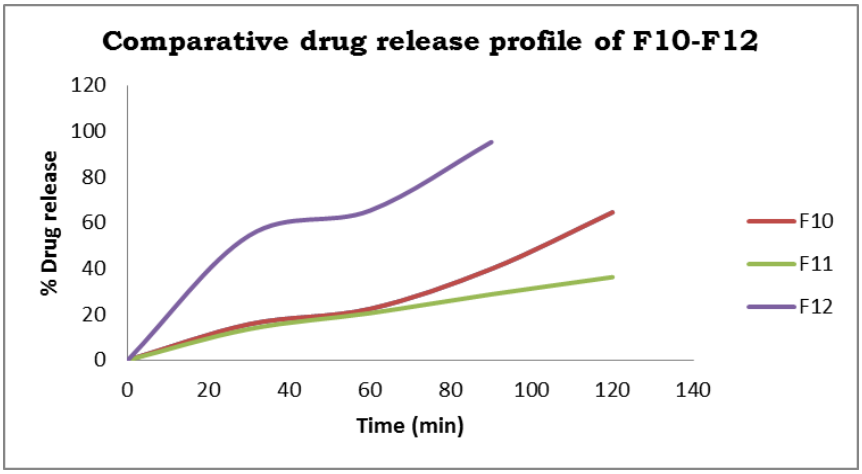


Figure No. 7.2: Comparative drug release profile of F10-F12.

CONCLUSION

- Phenylephrine hydrochloride nasal *insitu* gel were prepared by cold method to avoid the first pass metabolism and to improve the bioavailability of the drug.
- The Phenylephrine hydrochloride was subjected to Preformulation study and drug-excipients compatibility study results obtained with selected excipients showed good compatibility with drug.
- The Compatibility studies were performed to select the poloxamer as thermo reversible polymer, chitosan as mucoadhesive polymer and HPMC as gelling agent.
- The trails were done and the formulations were prepared by optimizing the percentage of chitosan and HPMC, sodium alginate and HPMC mixture in the nasal *insitu* gel.
- The formulation of Phenylephrine hydrochloride nasal *insitu* gel were prepared by using thermo reversible polymer (poloxamer-407), mucoadhesive polymers (chitosan), Gelling agent (HPMC) by cold method.
- The evaluations were performed to the prepared nasal *insitu* gels like Gelation temperature, mucoadhesive strength, Rheological studies, pH analysis, histopathology studies, Drug content and drug diffusion studies were within the limits.
- Fig 7.4 shows the nasal insitu gels had no significant harmful effect on the microscopic structure of the nasal mucosa.
- Among all formulations F9 shows Gelation temperature 37^0C which is nearer to body temperature and *In vitro* drug release was found to be 97with in 2hrs. Hence selected as optimized formulation.
- It is concluded that the Phenylephrine hydrochloride nasal *insitu* gel prepared by cold method. The developed nasal *insitu* gel containing 18% of poloxamer, 0.6% of chitosan,

0.1% of HPMC, 0.9% of Nacl, 0.01% of benzalkonium chloride with a Gelation temperature of 37^0C, pH 5.9, mucoadhesive strength 244.5 Dynes/cm^2, drug content 98%.

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