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Formulation and Development of Nasal in Situ Gel Containing CNS Acting Drug

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ABSTRACT:

Nasal drug delivery system offers lucrative way of drug delivery of both topical and systemic therapies. Identification of drug was carried out by melting point determination, infrared spectroscopy , and UV spectroscopy. In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. At the site of drug absorption they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Nasal mucoadhesive drug delivery system is designed with an aim to target the drug and to maintain the dosage form at its absorption site for an extended period of time. This will result in the enhancement of the absorption of the drug , which will in turn reduced the presystemic metabolism ; increase the bioavailability of the drug ; initiate rapid onset of action .The present study was aimed towards formulating the nasal mucoadhesive in situ gels of Lurasidone HCLusing thermoreversible polymer Pluronic F127 and mucoadhesive polymer carbopol 934. The in situ gels so prepared were characterized for its gelation properties, viscosity, gel strength, Mucoadhesion, drug content, drug release rate and for its histopathological studies.

Keywords: UV spectroscopy, FTIR, Histopathology, Nasal in Situ gel, In vitro diffusion.

1. Introduction

Delivery from the nose to the CNS occurs within minutes along both the olfactory and trigeminal nerves. Delivery occurs by an extracellular route and does not require that the drugs bind to any receptor or undergo axonal transport. The nasal mucosa is readily accessible and nasal drug delivery is potentially a convenient route of drug administration. The effects produced by nasal administration may be local or systemic, and nasal delivery has received recent attention as a means of administration of polypeptides or proteins which have poor oral bioavailability.[1] In situ Nasal Gel Recently in situ gel/ in vivo gel/ environment sensitive gel is a new dosage form, which has been applied in nasal drug delivery. Nasal in situ gels are instilled as low viscosity solutions into the nasal cavity, and upon contact with the nasal mucosa, polymer changes conformation producing a gel. Phase transition systems (Sol-gel) Phase transition to In situ gel is induced by, 1. A shift of temperature 2. A shift of pH 3. There are two preparation of gels, cold method and hot method. Both method of preparation generally yield gels with comparable properties. Cold method is preferred. In case of hot process, lumps formation of polymer occurs. Cold Process: Gels were prepared on a weight basis using a cold process. Carefully Weighed an amount of Pluronic F127 sufficient to yield 20% was slowly added to cold water (5%); constant stirring was maintained . Each dispersion was then refrigerated until a clear solution is formed (5hr‟s). Hot Process: Pluronic F-127 dissolved in water approximately at 700C.Active substances that are insoluble in water are dissolved in ethanol, Isopropyl alcohol or propylene glycol at 700Cand mixed with warm aqueous phase to form a homogeneous mass before addition. The gel forms when the solution cools to room temperature. [2]

1.1. Lurasidone HCl: [3]

Molecular weight : 492.68 g/mol Solubility : Sparingly soluble in methanol; Insoluble in water Appearance : White, bitter, odorless, flappy powder Melting point : 176 – 1780C Category : Antipsychotic Bioavailability : 9- 19 % (oral) Biological half life : 18 – 40 hrs Dose : 40 – 80 mg Dosage form : Tablet.

1.2. POLYMER PROFILE:

1.2.1. PLURONIC F- 127:

Synonyms : Poloxamer 407, Lutrol, Supronic Chemical name : a- Hydro ω Hydroxypoly (oxyethylene)a poly(oxypropylene)β poly(oxyethylene)a block copolymer. Molecular weight : 9840 to 14600Da Description : white, waxy, free flowing flaskes. Practically tasteless Solubility : Freely soluble in water and in organic solvents. Solution pH : 5.0 – 7.4 (as a 2.5 % w/v solution) Melting point : 52-57℃ Incompatibilities: Concentration dependent incompatibility with phenols and parabens.[4]

1.2.2. Carbopol:

Carbopol 934 polymer is a cross linked polyacrylate polymer. It is an extremely efficient rheology modifier capable of providing high viscosity and forms sparkling clear water or hydro alcoholic gels and creams. [5]

2. Materials and methods:

2.1. Materials:

Lurasidone Hcl was obtained as a gift sample from Emcure Ltd., Pune, Carbopol 934P was Apex Drug House, Mumbai, Pluronic F127 was obtained from Loba chemicals Pvt. Ltd ,Sodium chloride was obtained from Loba Chemicals Ltd., Benzalkonium chloride was obtained from Loba chemicals Pvt Ltd.

2.2. Methodology:

2.2.1 Verification of ƛmax

Accurately weight about 10 mg of Lurasidone HCl was dissolved in 100ml of SNF to obtained 100µg/ml concentration of drug (stock solution). From stock solution were dilute to obtained concentration of 2 µg/ml of Lurasidone HCl. The dilution was scan from 400 to 200 nm against SNF as a blank. The spectrum of the drug was studied to verify ƛ max and calibration curve was plotted with absorbance versus concentration.[6]

2.2.2. Calibration curve for Lurasidone Hcl: [6]

Calibration curve of Lurasidone Hcl in pH 6.5 Simulated Nasal Fluid and Methanol were prepared using UV visible spectrophotometer (UV 1700, Shimadzu) at _max 234nm.

Procedure: Accurately weight about 10 mg of Lurasidone HCl was dissolved in 100ml of SNF to obtained 100µg/ml concentration of drug (stock solution). From stock solution were dilute to obtained concentration of 2, 4, 6, 8, and 10 µg/ml of Lurasidone HCl. All dilutions were scan from 400 to 200 nm against SNF as a blank. The spectrum of the drug was studied to verify ƛ max and calibration curve was plotted with absorbance versus concentration.

2.3. Formulation:

2.3.1. Preparation of thermoreversible in situ gel system:

The solubalization of polymer in water with continuous stirring using thermostatic magnetic stirrer at 30˚C followed by addition of sodium chloride, benzalkonium chloride and triethanolamine(pH adjuster) then the thermoreversible polymer was solubilized in this dispersion and the solution was maintained at 4˚C for 4 h. Lurasidone was added with continuous agitation at 50 rpm using mechanical stirrer (Remi) for 10 min and further probe sonicated for 10 min. Stored overnight in refrigerator (4˚C) until transparent solution was formed. Then final volume was adjusted by using cold distilled water. [7]

2.3.2. Preparation of pH induced nasal in situ gel system:

The in situ gel was prepared containing 0.5% w/v CP and 0.75% w/v HPMC (concentrations derived from the experimental design study). Accurately weighed required amount of HPMC was added to distilled water allowed to hydrate overnight. CP was sprinkled over the solution and then allowed to hydrate overnight to get polymeric dispersion. The required quantity of Lurasidone added gradually to the polymeric dispersion of CP and HPMC and mixed well. Benzalkonium chloride solution was added as a preservative to get 0.01% v/v concentration in the formulation and then added triethanolamine (pH adjuster) until the gel formed. Then formulations were stored in a refrigerator prior to evaluation. [8]

2.4. Evaluation of in situ gel system

Prepared formulations were evaluated for following physical parameter-

2.4.1. Gelation studies:

In gelation the liquid phase makes a transition to gel. 10 ml transparent vial containing a magnetic bar and each formulation were placed on a magnetic stirrer. The gelation point was determined when the magnetic bar stopped moving due to gelation.

2.4.2. Viscosity measurements:

Viscosities of formulations before and after gelation were measured by using Brookfield DV-E viscometer using Spindle number 64 at 0.5 rpm shear rate.

2.4.3. Gel strength determination :

It is expressed in terms of time (in seconds). These method was done by Texture Analyser Apparatus.

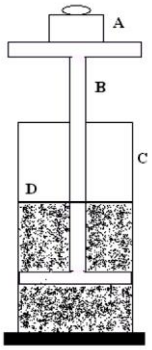


Figure : Gel strength measuring apparatus.

(A)Weight; (B) Shaft; (C) measuring cylinder; (D) Polymer gel

2.4.4. Evaluation of the mucoadhesive strength

The mucoadhesive potential of each formulation was determined by measuring the force required to detach the formulation from nasal mucosal tissue using a modified method. At the time of testing, a section of nasal tissue was secured (keeping the mucosal side out) to the upper probe using a cyanoacrylate adhesive. The upper probe was attached to precalibrated force displacement transducer connected to the Student's Physiographic apparatus. The surface area of each exposed mucosal membrane was 4.2 cm2.

At room temperature, fixed amount of samples of each formulation were placed on the lower probe. The probes were equilibrated and gelation was induced by means of temperature. Probe with nasal tissue was lowered until the tissue contacted the surface of the sample. Immediately, a slight force was applied for 2 minutes to ensure intimate contact between the tissues and the samples. The probe was then moved upwards at a constant speed of 0.15 mm/s. The bioadhesive force, expressed as the detachment stress in dyne/cm2, was determined from the minimal weights that detached the tissues from the surface of each formulation.

2.5. Drug content:

1 ml of formulation was taken in 10 ml volumetric flask, diluted to 10 ml with SNF pH6.5 and shaken to dissolve the drug. The content of the drug was estimated on UV Visible Spectrophotometer.

2.5.1. In vitro diffusion study

It is carried out on Franz diffusion cell having 1.8 cm diameter and 16 mL capacity.

Dialysis membrane (Himedia) having molecular weight cut off range 12000 – 14000 KDa was used as diffusion membrane. Pieces of dialysis membrane were soaked in boiled water before the experimentation . Diffusion cell was filled with simulated nasal fluid ; dialysis membrane was mounted on cell. The temperature was maintained at 34 ± 0.5˚C. pure drug solution and formulation equivalent to 10 mg of Lurasidone Hcl was placed in the donor chamber. 1ml samples were withdrawn from the acceptor compartment, replacing the sampled volume with simulated nasal fluid after each sampling, for a period of 360 minutes. The samples withdrawn were filtered and used for analysis. The amount of permeated drug was determined using a UV-spectrophotometer at 234nm.

2.5.2. Ex vivo permeation study

Fresh nasal mucosa were carefully removed from the nasal cavity of sheep.

Tissue samples were inserted in Franz diffusion cells displaying a permeation area of 3.14 cm2. SNF pH 6.5 was added to the acceptor chamber. The temperature was maintained at 34 ± 0.5˚C. After 20 minutes, formulation 1gm of Lurasidone Hcl was placed in the donor chamber. 1 ml samples were withdrawn from the acceptor compartment, replacing the sampled volume with SNF pH 6.5 after each sampling, for a period of 6 hours. The samples withdrawn were filtered and used for analysis.The amount of permeated drug was determined using a UV-visible spectrophotometer at 234 nm.

2.5.3. Stability Study

Formulations showing optimum gelation, gel strength, and drug release rate were selected for stability studies. Stability studies were carried out on gel formulation according to ICH (International Conference on Harmonization) guidelines. The stability chamber was placed at 40±5˚C, and samples were withdrawn at 30 days interval. The physical stability of gel was observed periodically for the occurrence of turbidity and gelation

2.5.4. Histopathalogy study

Permeation carried out for the optimized formulation PF4 and CF8 for period of 11 h. After completion of diffusion study , nasal mucosa were preserved in 10% formalin solution and then studied for histopathological changes embedded in paraffin then observed microscopically.

3. Result and Discussion:

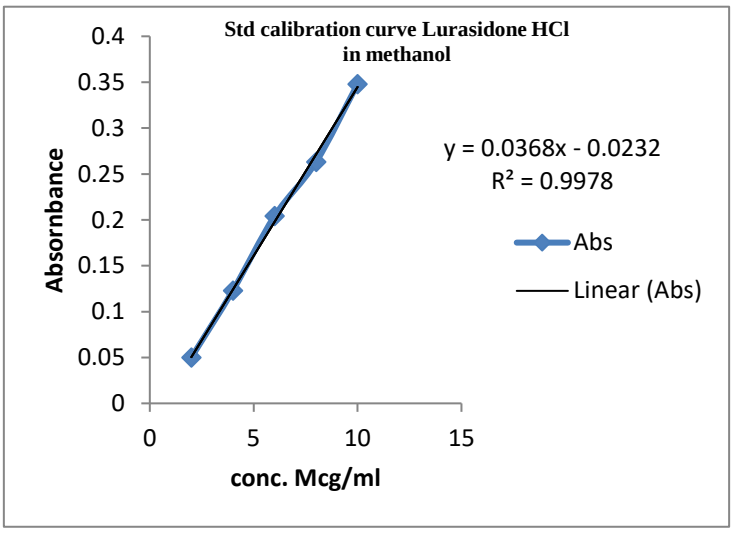
3.1. Melting Point Determination:

The melting point of Lurasidone HCl was found to be 176 - 178˚C.

3.2. Calibration curve for Lurasidone Hcl in methanol:

Scanning of Lurasidone Hcl solution in methanol by UV Spectrophotometer showed the λ max 229 nm. On this wavelength the standard curve followed the Beer- Lambert's law in the concentration range 20 - 100 µg / ml with R2 = 0.997.

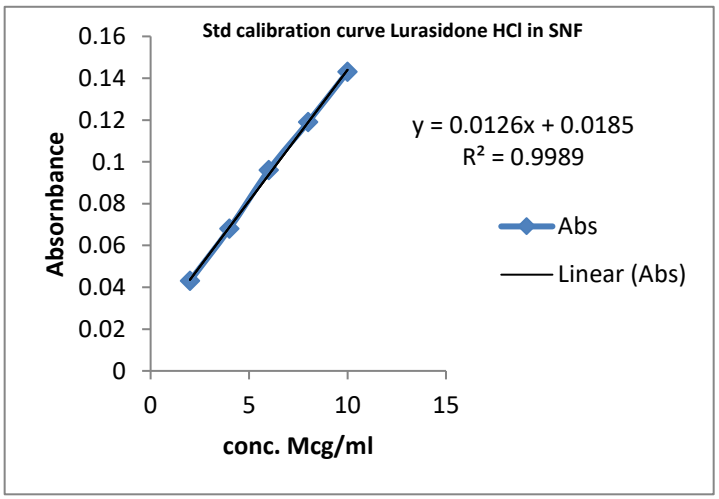
3.3. Calibration curve of Lurasidone Hcl in methanol:



Sr no	Conc (ug/ml)	Absorbance
1	2	0.050
2	4	0.123
3	6	0.204
4	8	0.263
5	10	0.348

3.4. Calibration curve of Lurasidone Hcl in Simulated Nasal Fluid

Scanning of Lurasidone Hcl solution in simulated nasal fluid pH 6.5 by UV Spectrophotometer showed the λmax 234 nm. On this wavelength the standard curve followed the Beer- Lambert"s law in the concentration range 20 to 100 µg / ml with R2 = 0.998.



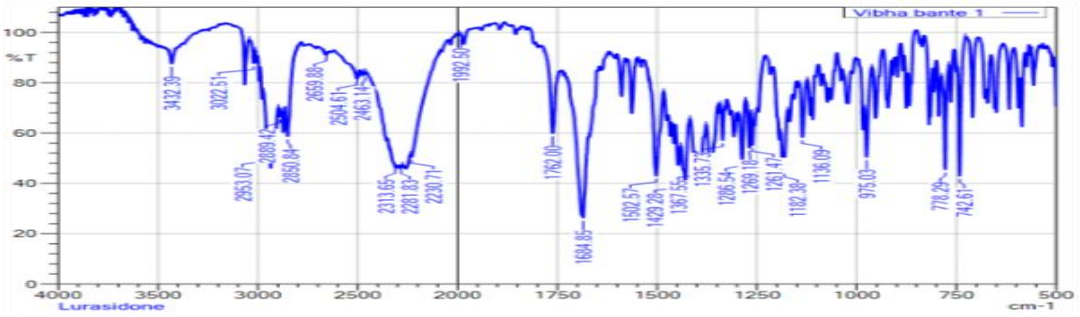
Sr no	Concug/ml	Absorbance
1	2	0.043
2	4	0.068
3	6	0.096
4	8	0.119
5	10	0.143

3.5. Drug Excipient compatibility study-

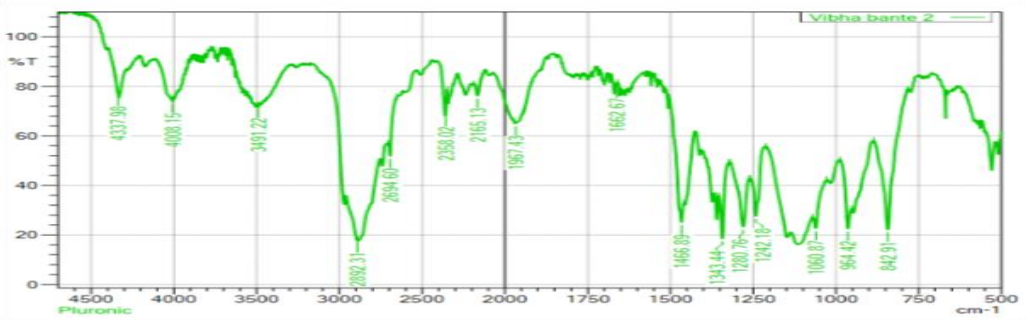
Drug-polymer interaction studies were performed by FTIR Spectroscopy. Spectrum were given as below:

3.5.1. Temp induced nasal in situ gel:

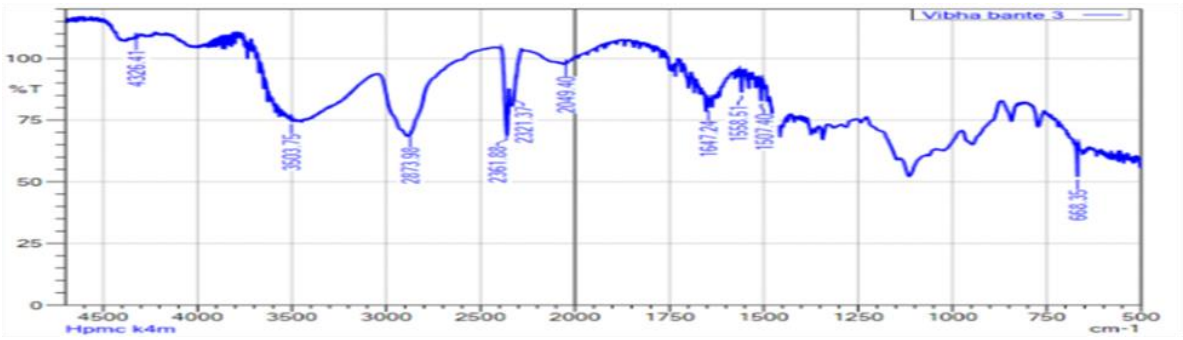
3.5.1.1. FTIR Spectra of Lurasidone HCl:



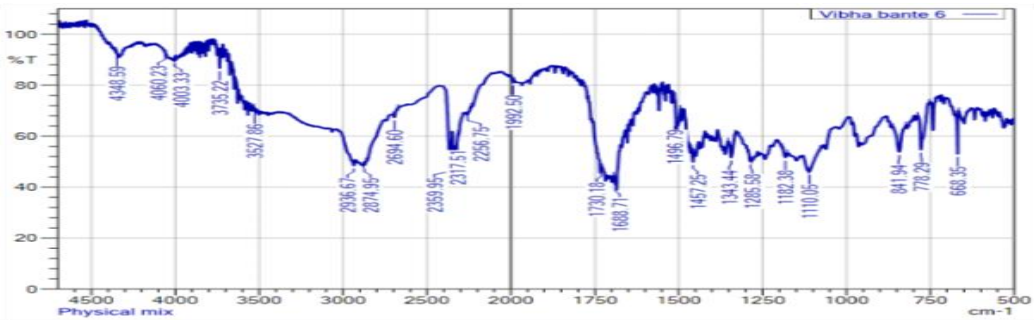
3.5.1.2. FTIR Spectra of Pluronic F-127: .



3.5.1.3. FTIR Spectra of HPMC K4M:



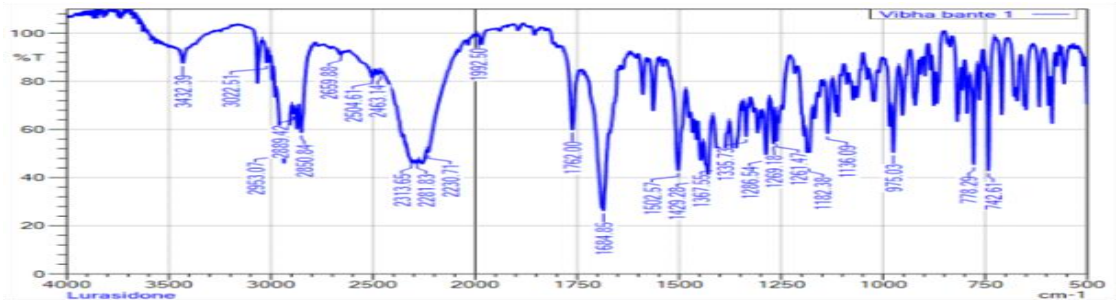
3.5.1.4. FTIR Spectra of Physical mixture of temp induced gel:



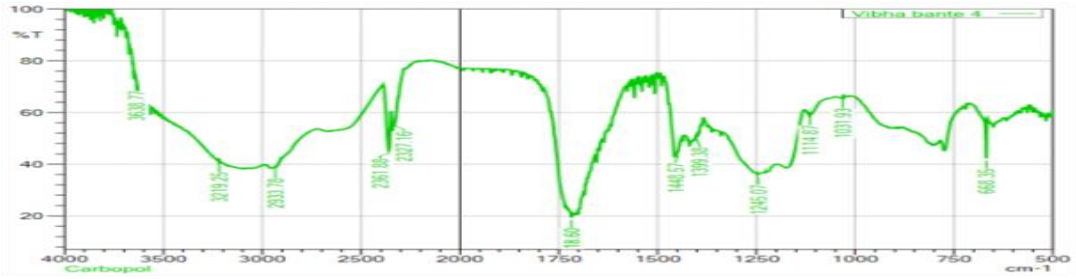
The IR spectrum of Lurasidone HCl obtained in figure. Results shows the presence of characteristic peaks such as N-H bending at 1647, Carbonyl C=O stretching 1684,C-H stretching 2892, Aldehyde C-H stretching on 2936.This observation clearly suggest that the LurasidoneHCl has no prominent change in its characteristics even in its physical mixture. The results of FTIR spectra indicated the absence of any well defined interaction between drug and polymer. It showed that Lurasidone HCl was compatible with Pluronic F 127.

3.5.2. pH induced nasal in situ gel:

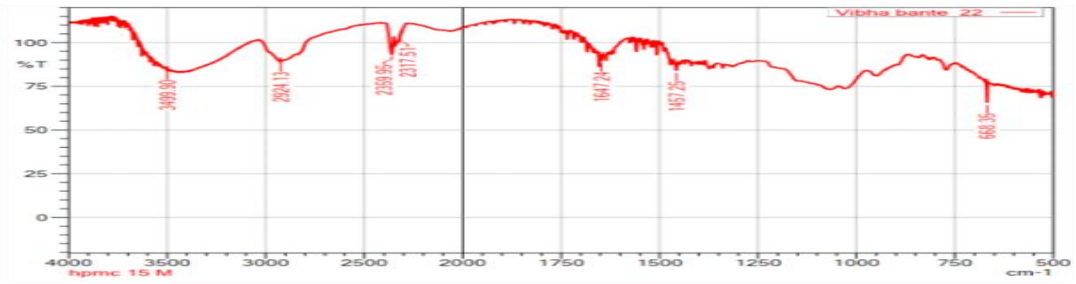
3.5.2.1. FTIR Spectra of Lurasidone Hcl



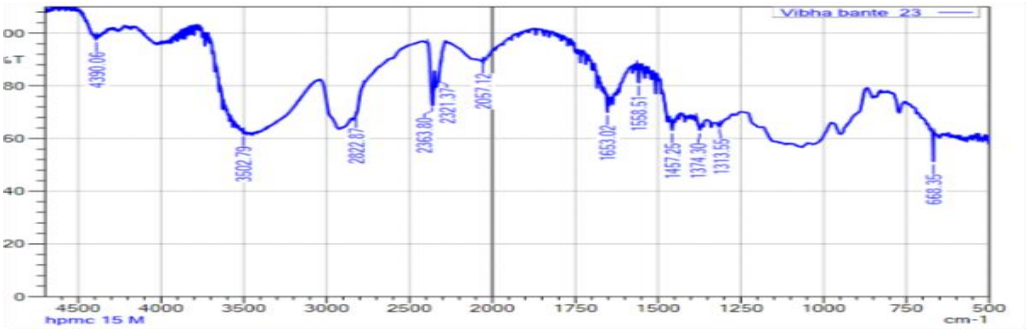
3.5.2.2. FTIR Spectra of Carbopol 934



3.5.2.3. FTIR Spectra of HPMCK100M



3.5.2.4. FTIR Spectra of Physical mixture



The IR spectrum of Lurasidone HCl obtained in figure. Results shows the presence of characteristic peaks such as C-H stretching at 2953, Carbonyl C=O stretching 1718, N-H bending 1653,and Halogen compound at 668. This observation clearly suggest that the Lurasidone HCl has no prominent change in its characteristics even in its physical mixture. The results of FTIR spectra indicated the absence of any well defined interaction between drug and polymer. It showed that Lurasidone HCl was compatible with Carbopol 934.

3.5.3.Formulation effect of Temp and pH of gel formulation

pH of in situ gel formulation

pH of the formulation was found to be satisfactory and was in the range of 5.5-6.5

Viscosity study

The apparent viscosity values were measured for liquid formulations and gel using Brookfield viscometer DV-E with spindle no.64 at 0.5 rpm. The marked increase in viscosity of formulations in solution form of Pluronic F127 was observed. The viscosity of formulations in gel state; was found to be proportionate with the increasing polymer concentration. In PF4 and CF8 series of formulations there was slight difference in viscosities of solutions.

Formulation Code	**Temp**	**Viscosity(cP)**	**Temp**	**Viscosity**	**pH**	**pH**
State	Solution	Solution	Gel	Gel	Solution	Gel
PF4	25 C	1278±1.5	35˚C	923000±2.1	3.2	6.2

Table : Optimized batch of formulation of temp induced gel

Formulation code	**pH**	**pH**	**Viscosity**	**Viscosity**
State	Solution	Gel	Solution	Gel
CF8	2.4	6.4	3200±0.56	936000±0.5

Table : Optimized batch of formulation of pH induced gel

3.5.4. Drug content study:

Drug content study of optimized formulations

Sr no	**Formulations**	**%Drug content**
2	TPF4	94.18±0.01
8	TCF8	93.87±0.33

The drug content of the formulations TPF4,TCF8was found to be 94.18±0.01, 93.87±0.33 respectively. On the basis of gelation properties, gel strength, viscosity, mucoadhesion, percent drug content, the optimum in situ gelling formulation of (TPF4 ,TCF8) were selected and subjected for further studies.

3.5.5. Evaluation of In Situ Gelling System

Gelation studies were carried out using temperature change and pH change. In these studies the gelling capacity (speed and extent of gelation) for all formulations were determined. After easy instillation in to nasal cavity the liquid polymeric solutions should undergo rapid sol to gel transition by means of thermo sensitivity and pH change. Thus the in situ formed gel should preserve its integrity without dissolving so as to localize the drug at absorption site for extended duration. As per the visual inspection the preformed gels were graded in following grades

3.5.5.1. Evaluation of gelation for optimized batches

Sr No	**Formulation code**	**Gelation study**
1	PF4	++++
2	CF8	++++

(-) No gelation

(+) weak gelation; dissolves rapidly,

(+ +) Immediate gelation remains for few hrs (Less stiff gel),

(+ + +) Immediate gelation remains for extended period (Stiff gel),

(+ + + +) Very stiff gel

3.5.5.2. Evaluation of the gel strength

Gel strength of formulation was done by using Texture Analyzer Apparatus.

Table : Gel Strength of*In Situ* Gel Formulations.

Sr. No.	**Formulation code**	**Gel strength (sec)**
1	PF4	20.17±0.89
2	CF8	30.50±0.39

***n = 3 ± S.D**

In the development of nasal in situ gelling system, the gel strength is important in finding the condition, which can delay the post nasal drip or anterior leakage. The gel strength was found to be affected by concentrations of gelling and bioadhesive polymers. Optimal in situ gel must have suitable gel strength so as to be administered easily and can be retained at nasal mucosa without leakage after administration. In the formulations Pluronic F127 and Carbopol 934 were found to increase the gel strength.

3.5.5.3. Evaluation of mucoadhesive strength

All the formulations were subjected to Mucoadhesion studies. The Mucoadhesion force is an important parameter for in situ gelling nasal formulations since it prolongs the nasal clearance of gels and increase its residence time in nasal cavity.

Table :Evaluation of the mucoadhesive strength

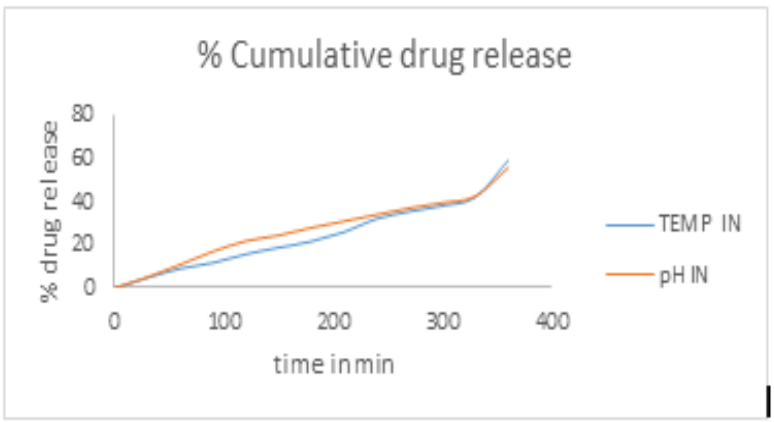
Sr. No	Formulation Code	Mucoadhesion Force(dyne/cm$^{2)}$
1	PF4	4768.67
2	CF8	5220.10

In case of Pluronic gels the mucoadhesion force proportionally increased with increase in HPMC K4M concentration. At 0.25 % w/v concentration of HPMC K4M with 9 % w/v concentration of Pluronic F127 showed the significant mucoadhesion. Mucoadhesion in Pluronic F127 gels was very high. 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 source of mucoadhesion.

3.6. In vitro diffusion study

In vitro release studies of formulations were performed using the Franz diffusion cell with dialysis membrane. SNF 6.5 was used as diffusion media.

Sr. No.	Time (sec)	Cumulative % drug release	Cumulative % drug release
		PF4	**CF8**
1	30	11.72 ± 0.2	8.00 ± 0.01
2	60	14.96 ± 0.1	15.81 ± 0.02
3	90	16.66 ± 1.3	16.91 ± 0.1
4	120	18.62 ± 0.4	20.72 ± 0.3
5	150	27.63 ± 2.5	34.35 ± 0.12
6	180	35.55 ± 0.01	40.89 ± 0.01
7	210	43.90 ± 0.5	44.91 ± 0.1
8	240	47.07 ± 1.2	49.98 ± 0.04
9	270	54.55 ± 0.1	55.99 ± 0.2
10	300	62.08 ± 0.01	65.43 ± 0.01
11	330	71.07 ± 0.2	75.77 ± 0.1



The initial rapid release of Lurasidone HCl . The results showed that the formed gels had the ability to extend the release of LurasidoneHcl for the duration of about 330 minutes. In vitro release study indicated that the release of drug varied according to the type and concentration of polymers. The results further showed that the amount of the drug released in first hour decreased with the increasing polymer concentration and this pattern continued till the entire duration of study.

3.7. Drug Release Kinetics of In Situ Gel Formulation (PF4& CF8)

Table : Drug release kinetics data from selected *in situ* gel formulation

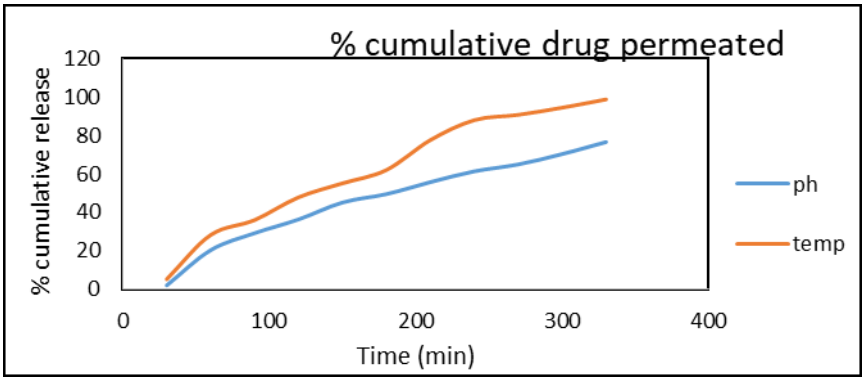
FORMULATION	ZERO ORDER EQUATION	HIGUCHI EQUATION REGRESSION COEFICIENT(R^2)
PF4	0.994	0.915
CF8	0.974	0.968

3.8. Ex vivo permeation study

The *Ex vivo* study was done on optimized batch i.e. PF4 & CF8 selected on basis of results of all evaluation parameters. Among them gelation temperature and diffusion data was important.

The *Ex vivo* permeation study was conducted using sheep nasal mucosal membrane and Simulated Nasal Fluid 6.5 as an *ex vivo* study fluid in the receptor compartment of a Franz diffusion cell. . The percent drug permeated after 6 hours was found to be 97.82% and 76.61

Sr. No.	**Time (sec)**	**Cumulative % drug release**	**Cumulative % drug release**
		PF4	CF8
1	30	5.17 ± 0.05	1.95 ± 0.01
2	60	28.17 ± 0.02	20.28 ± 0.2
3	90	36.00 ± 0.03	29.17 ± 0.01
4	120	47.84 ± 0.17	36.31 ± 0.05
5	150	55.11 ± 0.12	45.11 ± 0.3
6	180	62.03 ± 0.22	49.51 ± 0.2
7	210	77.61 ± 0.11	55.72 ± 0.5
8	240	88.01 ± 0.01	61.35 ± 0.06
9	270	90.78 ± 0.02	64.94 ± 0.15
10	300	94.52 ± 0.1	70.35 ± 0.21
11	330	97.82 ± 0.01	76.61 ± 0.1



3.9. Release Kinetics of in situ Gel Formulation (PF4 & CF8)

Table : Drug release kinetics data from selected *in situ* gel formulation

FORMULATION	ZERO ORDER EQUATION	HIGUCHI EQUATION REGRESSION COEFFICIENT(R^2)
PF4	0.976	0.940
CF8	0.964	0.948

3.10. Histopathological study

Safety is important concern for administration of formulation. Hence, it was important to investigate the safety of the optimized in situ gel formulation (PF4), (CF8). Permeation carried out for Group A treated with phosphate buffer pH 6.5 and Group B treated with optimized formulation for period of 11 h. Then sections were stained with hematoxylin and eosin and also embedded in paraffin then observed microscopically. The microscopic observations were indicated that no significant effect of optimized formulation on the microscopic structure of mucosa. As shown in Figure, neither cell necrosis nor removal of epithelium from nasal mucosa was observed after permeation of optimized batch. The epithelium layer was intact and there was no sign of remarkable destructive effect of formulation on the treated nasal mucosa. Thus histological study was revealed the safety of formulation on sheep nasal mucosa.

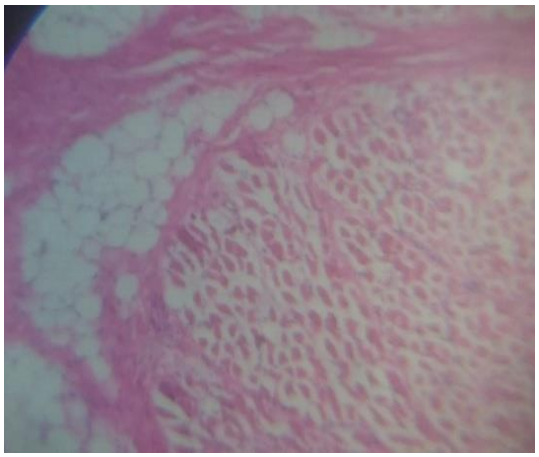


Fig : Blank sample treated with PBS 6.5

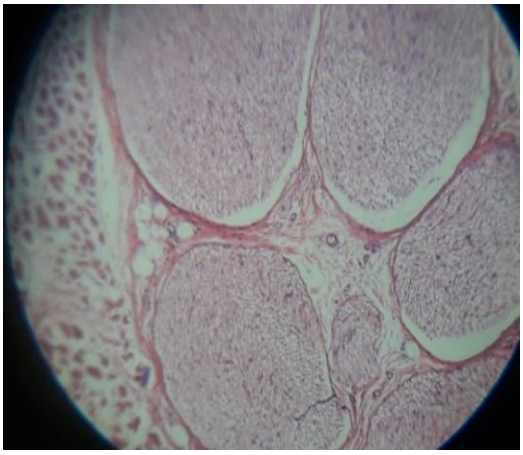


Fig : Sample treated with PF4

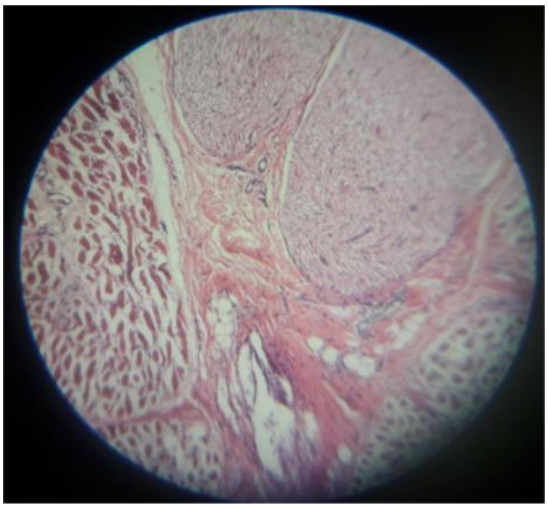


Fig : Fig : Sample treated with CF8

3.11. Stability study

The stability studies carried out on optimized formulation PF4 and CF8 at 40±2 ˚C temperature and 70±2 % RH for 30 days. The formulation was showed good stability with no remarkable change in drug content, gelation property, gel strength and in vitro drug release profile.

Table :Stability study data of PF4 & CF8 formulation.

Sr. No.	Parameters	Storage period (PF4) (Days)	At 40±2˚C temperature and 70±2%RH	Storage period (CF8) (Days)	At 40±2˚C temperature and 70±2%RH
		0	**30**	**0**	**30**
1	**Appearance**	Clear white	Clear white	Clear white	Clear white
2	**Drug content (%)**	94.18%±0.01	93.87±0.33	94.12%±0.12	93.19±0.2
3	**Gelation study**	+++	+++	+++	+++
4	**Gel strength(s)**	22.23±0.05	22.12±0.2	33.45±1	33.34±0.31
5	**Ph**	-	-	6.5±0.2	6.4±0.12
6	**Viscosity(cps)**	923000±0.12	922000±0.1	888000±1.2	887000±0.54

4. CONCLUSION:

Nasal mucoadhesive drug delivery system is designed with an aim to target the drug and to maintain the dosage form at its absorption site for an extended period of time. This will result in the enhancement of the absorption of the drug, which will in turn reduce the presystemic metabolism; increase the bioavailability of the drug, initiate rapid onset of action and thus will decrease the dosing frequency and dose related side effects of the drugs. For this purpose in situ gelling system is preferred over conventional solution systems as it has several advantages like ease of administration, less irritation, enhanced retention period.

The aim of the present study was to formulate thermoreversible mucoadhesive nasal in situ gel and pH induced gel of Lurasidone Hcl by using Pluronic F-127 as a thermoreversible polymer and HPMC K4M as a mucoadhesive polymer by cold technique and evaluate them and carbopol 934 as a mucoadhesive polymer and HPMC K100M as a viscosity enhancing polymer used in pH induced gel. The preformulation study like melting point, solubility were evaluated and FT- IR study were carried out to rule out any possible interaction between the drug and excipients, and there has no such interaction and it showed good compatibility between drug-PF-127 and HPMC K4M & carbopol 934 and HPMC K100M. These in situ gels so prepared were characterized for its gelation properties, viscosity, gel strength, mucoadhesion, drug content, drug release rate and for its histopathological studies.

Pluronic F-127 and HPMC K4M based in situ gel (PF4) &Carbopol934 and HPMC K100M based in situ gel (CF8) is air bubble free, homogeneous, smooth and transparent and effective gelation, viscosity, gel strength and drug release properties along with good mucoadhesive strength. The drug release mechanism from the gel matrix was found to be anomalous and following the Higuchi equation.

Histological examination of formulations did not show any remarkable damage to nasal mucosa so it seems to be safe for preclinical use. The formulation also retained the good stability conditions over the period of 30 days. Owing to these properties it can be used as an effective delivery system for the nasal route.

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