ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 12, Issue 11, 2019

Online - 2455-3891
Print - 0974-2441

Research Article

FORMULATION AND EVALUATION OF *IN SITU* MUCOADHESIVE THERMOREVERSIBLE NASAL GEL OF SERTRALINE HYDROCHLORIDE

DIKSHA SHARMA*, SHAWETA AGARAWAL

Department of Pharmacy, L.R Institute of Pharmacy, Ochghat, Solan, Himachal Pradesh, India. Email: sharma25pharmacy@gmail.com

Received: 24 July 2019, Revised and Accepted: 23 September 2019

ABSTRACT

Objective: The objective of the study was to aiming to formulate and evaluate temperature based *in situ* nasal gel of sertraline HCL.

Materials and Methods: Preformulation studies of sertraline hydrochloride including tests for identification, solubility studies, Fourier-transformer infrared (FTIR) spectroscopy, melting point determination, and other studies were carried out and compared with the specification as per literature. The solubility of sertraline hydrochloride was determined in different solvents such as in distilled water, ethanol, acetone, isopropyl alcohol, and 2-propanol. Each value for solubility was determined in triplicate and average values were reported. The drug excipient compatibility study was determined by FTIR. Thermal analysis was performed using a differential scanning calorimetric equipped with a computerized data station. The UV spectrum of sertraline hydrochloride was obtained using UV JascV630. The *in situ* gel formulation was prepared by changing the concentration and using only one polymer (Carbopol 934) has been used at the same concentration. Mucoadhesive strength and *in vitro* permeation study were determined using gout nasal mucosal membrane, whereas *in vitro* drug release study was carried out using diffusion cell through egg membrane as a biological membrane. The stability studies were conducted according to ICH guidelines.

Results: The FTIR studies of formulation show no interaction between drug and excipient. *In situ* gel was prepared using Carbopol 934 and Poloxamer 407 to improve its adhesion property. The optimized formulation (F6) was transparent and clear in appearance with 101.15% drug content. The sol-gel transformation of *in situ* gel was found at temperature 34.92°C with immediate gelation property. The *in vitro* drug release of optimized formulation was found 95.80% drug release in 8 h. Formulations F4 and F6 showed immediate gelation within 60 s and remained stable for an extended period. All the formulations were liquid at room temperature and underwent rapid gelation on contact with simulated nasal fluid.

Conclusion: The results concluded that the formulations of *in situ* nasal gel showing to improve the bioavailability through its longer residence time and ability to sustain drug release.

Keywords: *In situ* gel, Sertraline HCL, Carbopol 934, Poloxamer 407, Bioavailability temperature.

 DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i11.35065

INTRODUCTION

Nasal delivery is the logical choice for topical treatment of local ailments in the nose and paranasal sinuses such as allergic and sinusitis rhinitis. The nose is also considered an attractive route for needle free vaccination and for systemic drug delivery, especially when rapid absorption and effect are desired. Furthermore, nasal delivery may help to solve issues related to slow absorption, poor bioavailability, drug degradation, and adverse events in the gastrointestinal tract and avoids the first-pass metabolism in the liver [1]. Nasal drug delivery system suggests lucrative way of drug delivery of both topical and systemic therapies. The high permeability, high vasculature, and low enzymatic environment of nasal cavity are well suitable for systemic delivery of drug molecules through nose. The noninvasiveness and self-administrative nature of nasal delivery also attract the formulation scientists to deliver protein and peptide compounds. The nasal cavity is covered by a thin mucosa which is well vascularized. This facilitates to quick transfer of drug molecules across the single epithelial cell layer directly to systemic blood circulation without first-pass hepatic and intestinal metabolism. In this way, the effect of a smaller drug molecule can be achieved in 5 min. The nasal administration, therefore, can be used a better route than oral drug administration [2].

The nasal drug delivery is an ancient therapy system of drug for psychological problems. The advent of biotechnology, molecular boil endogenously, and pharmacology has provided lot of endogenous peptide molecules and proteins for therapeutic use the delivery of such molecules is possible through nasal drug delivery (Fig. 1) [3].

The greater permeability of nasal mucosa with large surface area provides a fast onset of therapeutic drug result [4]. Drug candidate series from small metal ions to large macromolecular proteins have also been experienced in various animal models. Complete absorption of certain steroids and hormones for nasal administration has also been reported by nasal drug administration. For several drugs such as the formulation and evaluation of the thermoreversible *in situ* gel of metoprolol succinate [5], flunarizine hydrochloride [6], timolol maleate [7], and many others have been reported by several researchers. The present work is focused on thermoreversible gel administration for sertraline hydrochloride.

PREFORMULATION STUDIES

Preformulation studies of sertraline hydrochloride, including tests for identification, solubility studies, Fourier-transformer infrared (FTIR) spectroscopy, melting point determination, and other studies were carried out and compared with the specification as per literature. Name and source of all chemicals used in whole work are given in Table 1.

Description

The drug was observed for its general appearance.

Melting point determination

Fusion technique was used in which the drug was filled in the fine capillary tube whose end was closed via fusion and situated the tube into the electrical melting point apparatus. The temperature at which the drug starts melting was recorded as melting point.

Solubility analysis
The solubility of sertraline hydrochloride was determined in different solvents such as in distilled water, ethanol, acetone, isopropyl alcohol, and 2-propanol. The samples were added to each test tube containing 5 mL of different solvents with continuous shaking for 30 min to prepare saturated solution. All mixtures were allowed to equilibrate at room temperature (37°C) for 24 h. The samples were filtered through Whatman filter and aliquots were suitably diluted and assayed spectroscopically at 274 nm. Each value for solubility was determined in triplicate and average values were reported [8].

Drug excipients compatibility study

FTIR Spectroscopy

The drug excipient compatibility study was determined by FTIR. The infrared absorption spectrum of sertraline hydrochloride was recorded with number 4000 to 650 cm^{-1} using FTIR (Cary 630, Agilent technology) [8].

Differential scanning calorimetry (DSC)
Thermal analysis was performed using a differential scanning calorimetric equipped with a computerized data station. The sample of the pure drug was weighed and heated at a scanning rate of 10°C/min between 40 and 300°C and 40 ml/min of nitrogen flow. The differential scanning calorimetric analysis gives an idea about the interaction of different materials at different temperatures. It also allows us to study the probable degradation of the material (Mettler Toledo) [8].

Determination of ultraviolet absorption maxima (λ_{max})
The UV spectrum of sertraline hydrochloride was obtained using UV JascV630. Sertraline hydrochloride (10 mg) was accurately weighed and transferred to 100 ml volumetric flask. It was then dissolved and diluted up to 100 ml with distilled water, ethanol, IPA, and simulated nasal fluid. The above-made solution was further diluted to obtain a concentration of 12 µg/ml. The resulting solution was scanned from 200 to 400 nm and the spectrum was recorded to obtain the value of maximum wavelength. The λ_{max} was found to be 274 nm in all solvents [8].

Establishment of calibration plot

Preparation of simulated nasal fluid (pH 6.4)

Sodium chloride 0.745 g, potassium chloride 0.129 gm, and calcium chloride dehydrated 0.005 g in distilled water q.s 100 ml [8].

Table 1: List of chemicals used in experimental work

S. No.	Name of chemicals	Supplier
1.	Sertraline hydrochloride	Gift sample from Sun Pharma Pharmaceuticals (I) Pvt. Ltd.
2.	Propylene glycol	SPB Laboratories
3.	Poloxamer-407	SPB Laboratories
4.	Carbopol 934	SPB Laboratories
5.	Ethanol	Avantor Performance Materials (I) Ltd.
6.	Sodium chloride	Avantor Performance Materials (I) Ltd.
7.	Potassium chloride	Central Drug House (P) Ltd.
8.	Calcium chloride dehydrate	Central Drug House (P) Ltd.
9.	Methanol	Avantor Performance Materials (I) Ltd.

Preparation of stock solution
Stock solutions of drug samples were prepared in the simulated nasal fluid (SNF). 40 mg of sertraline hydrochloride was accurately weighed and transferred to a 100 ml volumetric flask volume was make up the volume up to 100 ml with simulated nasal fluid pH 6.4 (i.e., 100 µg/mL solution was obtained).

From this solution, aliquots of 2 mL, 4 mL, 6 mL, 8 mL, 10 mL, and 12 mL were taken and diluted up to 100 mL to get the concentration 2,4, 6, 8,10, and 12 µg/mL. These concentrations were used to determine the absorbance at λ_{max} 274 nm against blank using UV-visible spectrophotometer.

Method of preparation
The *in situ* gel formulation was prepared by changing the concentration and using only one polymer has been used at the same concentration. Different concentrations of polymers were used to prepare nasal solution as per the composition is shown in Table 2. Accurately weighed poloxamer 407 was dispersed in 50 ml of purified water, Carbopol 934 was sprinkled over this solution, and allowed to hydrate overnight. The solution was stirred with an overhead stirrer. Sertraline hydrochloride was dessolved in small quantity. The drug solution was added to the polymer solution. Purified water was then added to make up the volume to 100 ml. This resulting formulation was then kept at room temperature overnight [8].

Formulation study

Clarity

The formulations were visually checked for clarity [8].

pH
pH of each formulation was determined using digital pH meter. This was previously calibrated by pH 4 and pH 7. The pH values were recorded immediately after preparation in triplicate [8].

Drug content
Drug content was determined by taking 1 ml of formulation was taken in 100 ml volumetric flask. It was dissolved in ethanol properly and final volume was made to 100 ml with ethanol. 1 ml quantity from this solution was transferred into the 10 ml volumetric flask and final volume was made to 10 ml using ethanol; finally, the absorbance of prepared solution was measured at 274 nm using UV visible spectrophotometer. Using absorbance value percentage drug content in the formulation was calculated [9].

Viscosity

Viscosity (rheological properties of prepared gel were determined with the help of Brookfield Viscometer) type DV-2+PRO using spindle no 62. Viscosities of formulations were determined at two different pH, formulation pH, and pH 7.4 with varying shear rate [5].

Gelation temperature
Formulation equivalent to 10 mg was transferred to a test tube and immersed in 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 move upon tilting through 90°C [10].

Table 2: Composition of *in situ* nasal gel

S. No.	Compositions	Concentration (% w/v)					
		F1	F2	F3	F4	F5	F6
1.	Sertraline hydrochloride	0.4	0.4	0.4	0.4	0.4	0.4
2.	Poloxamer-407	0.36	0.36	0.36	0.36	0.36	0.36
3.	Carbopol-934	0.0024	0.0028	0.0032	0.004	0.0044	0.0048
4.	IPA	10	10	10	10	10	10
5.	Purified water	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g

Gelling capacity

The gelling capacities of formulations were determined by placing one drop of the prepared formulations into a vial containing 2 ml of SNF freshly prepared. Gelation was assessed visually and noting the time for gelation and the time taken for the gel formed to dissolve [10].

Gel strength

A sample of 25 mL of the gel was put in 50 mL graduated cylinder. A weight of 14.33 g was placed on the gel surface. The gel strength, which is an indication for the nasal gel at physiological temperature, was determined by the time in seconds required by the weight to penetrate 5 cm into the gel. All measurements were performed in triplicate (n=3). The apparatus used for measuring gel strength at room temperature and 37°C [10].

Mucoadhesive strength

The mucoadhesive strength of formulation was determined as reported previously. A section of goat nasal mucosa was obtained from local slaughterhouse immediately after its sacrifice. Two cylindrical glass vials with 2 cm diameter and modified balance instrument were taken. The goat nasal mucosa was tied to one side of the both vials nasal mucosa was attached together for 2 min. Water was poured drop by drop into the container of the balance instrument until the two vials got detached from each other. The water was weighed. The mucoadhesive strength of formulation was expressed as the detachment stress in dyne/cm^2 and was determined by minimal.

Mucoadhesive strength (dyne/cm^2) = n×g/A (m = Weight required for detachment of two vials in grams, g = Acceleration due to gravity (980 cm/s^2),

A = The area of nasal mucosa exposed), [11] (Fig. 2).

***In vitro* drug release studies**

In vitro release study of the formulated *in situ* gel was carried out using diffusion cell through egg membrane as a biological membrane. Diffusion cell with inner diameter 1.4 cm was used for the study. The formulation 1 ml was placed in donor compartment and freshly prepared 100 ml stimulated nasal electrolyte solution (sodium chloride 0.745 g, potassium chloride 0.129 g, calcium chloride dehydrated 0.005 g, and distilled water q.s 100 ml) in receptor compartment. Egg membranes were mounted in between donor and receptor compartment. The position of the donor compartment was adjusted, so that egg membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C±0.5°C. 2 ml of sample is withdrawn from receiver compartment after 30 min, 1, 2, 3, 4, 5, 6, 7, and 8 h and same volume of fresh medium is replaced. The withdrawn samples were diluted to 10 ml in volumetric flask with simulated nasal fluid and analyzed by UV spectrophotometer at 274 nm [8].

***In vitro* permeation study**

Natural membranes are utilized to determine *in vitro* permeation study to mimic the *in vivo* permeation patterns. In this experiment goat nasal mucosa was utilized because the respiratory area of goat is large and it is easy to get. Fresh mucosal tissue was removed from the nasal cavity of goat. The tissue was placed on the diffusion cell with permeation area 0.786 cm^2. The acceptor chamber of the diffusion cell (laboratory designed) with a volume capacity 100 ml was filled with simulated nasal fluid (SNF) contained accurately 7.45 mg/ml Nacl, 1.29 mg/ml KCl, and 0.32 mg/ml $CaCl_2.2H_2O$.0.5 (10 mg equivalent) ml of formulation was placed in donor compartment. At predetermined time intervals of 30 min, 1, 2, 3, 4, 5, 6, 7, and 8 h. 1 ml of sample was withdrawn from the acceptor compartment replacing the sample removed with simulated nasal fluid after each sampling for period of 8 h. Then samples were specifically diluted and absorbance was noted at 274 nm. Permeability coefficient (p) was calculated by the following formula:

$$P=(dQ/dt)/(CO\times A)$$

Where dQ/dt is the flux or permeability rate (mg/h), C_o is the initial concentration in the donor compartment, and A is the effective surface area of nasal mucosa [8] (Fig. 3).

Accelerated stability study

Stability studies were conducted according to ICH guidelines 40°C±2°C/75%±5% RH to test the physical and chemical stability of the developed *in situ* nasal gel. A sufficient quantity of pH sensitive *in situ* gel, i screw capped vials was stored at different stability condition.

RESULTS AND DISCUSSION

Preformulation studies

Every drug has intrinsic chemical and physical properties, which has been consider before development of pharmaceutical formulation. This property provides the framework for drug's combination with ingredients in the fabrication of dosage form. Preformulation studies serve as an important establishment tool early in the development of both API and drug products. They generally influence:

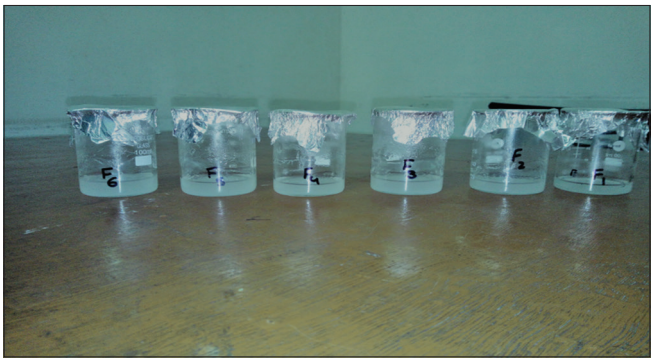

Fig. 1: Formulation of prepared gel

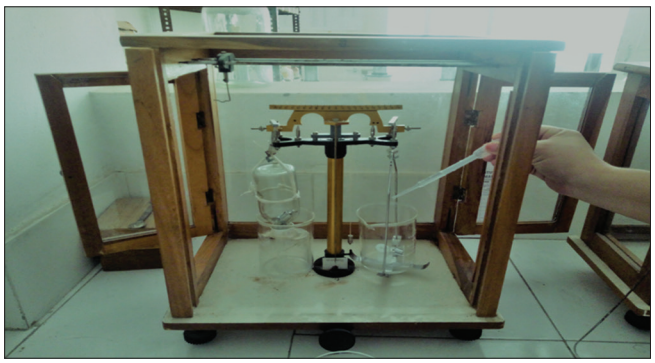

Fig. 2: Modified balance for mucoadhesive study

Fig. 3: Laboratory designed diffusion cell

- Selection of drug
- Selection of formulation components
- Drug development manufacturing process and
- Development of analytical methods.

Description of drug

Description of sertraline hydrochloride found to be as per IP. The organoleptic properties of sertraline hydrochloride were found to be in Table 3.

Melting point determination

Melting point of sertraline hydrochloride (Table 4) was determined by melting apparatus and it was found to be 240°C–246°C which is of the pure drug. Hence drug sample was free from any type of impurities.

Solubility study

Solubility was determined in different solvents systems such as distilled water, acetone, and 2-propanol and ethanol (Table 5).

FTIR

FTIR spectra of the drug with each excipient were recorded us FTIR spectrometer. The infrared absorption spectrum of sertraline hydrochloride was recorded with number 4000 to 650 cm^{-1} using FTIR spectrophotometer (Cary 630, Agilent Technology) (Fig. 4).

The obtained spectra revealed that there was no interaction between the drug and the excipients. FTIR spectral studies: Sertraline hydrochloride showed characteristics sharp peak FTIR spectra of Sertraline hydrochloride with Carbopol 934 showed various characteristic peaks of Carbopol 934 without any significant shifting or deviation in characteristic peaks of drug.

FTIR spectra of sertraline hydrochloride in combination with Carbopol 934 and Poloxamer 407 showed various characteristic peaks of Poloxamer 407 without any significant shifting or deviation in characteristic peaks of drug (Figs. 5-7).

FTIR interpretation of sertraline HCL drug (Table 6)

- The absorption spectrum consists of few bands and the substance is, therefore, relatively not simple.
- The presence of –NH- is indicated by absorption at 1339 and 1357 as narrow intensity peaks and can be confirmed by peak at 762 cm^{-1}.
- The compound is aromatic should by the band at 1596 as medium intensity peak.
- The aromatic ring can be confirmed as α-naphthalene as it showed the peak 1596.
- The strong high intensity peaks at 665,680 and 762 cm^{-1} indicate presence of more than one aromatic rings.
- The C-Cl stretching can be indicated by the peak at 747 cm^{-1} which shows intensity at high level.
- The presence of halogen- chlorine can be confirmed by the peak at 1473 cm^{-1} with UV medium broad band absorption.

Table 3: Organoleptic properties of sertraline hydrochloride

Drug	Test	Observation
Sertraline hydrochloride	Color	White crystalline powder
	Odor	Odorless
	Taste	Slightly bitter

Table 4: Melting point of sertraline hydrochloride by visual melting apparatus

Experimental value	Literature value
240°C–246°C	246°C–249°C

Table 5: Solubility data of sertraline hydrochloride in different solvents

S. No.	Solvent	Solubility
1.	Distilled water	Slightly soluble
2.	Acetone and 2-propanol	Slightly soluble
3.	Ethanol	Sparingly soluble

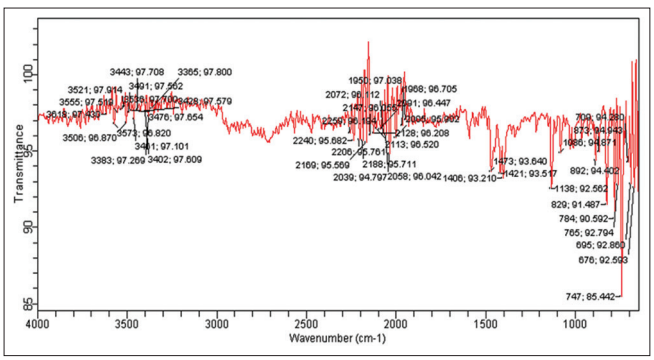

Fig. 4: Fourier-transformer infrared plot of sertraline hydrochloride

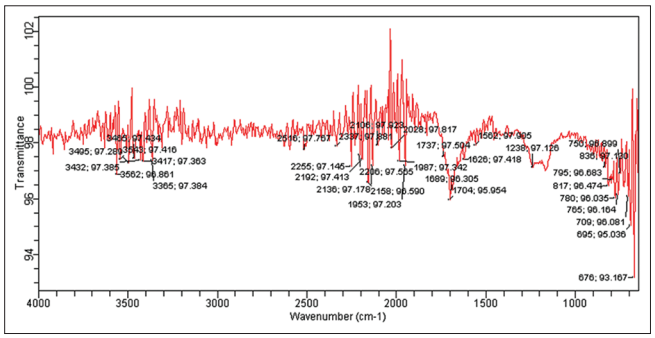

Fig. 5: Fourier-transformer infrared plot of Carbopol 934

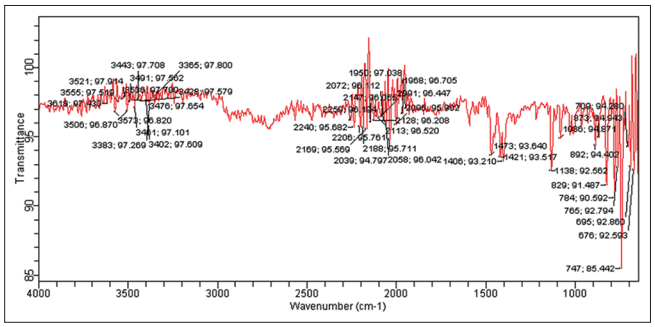

Fig. 6: Fourier-transformer infrared plot of poloxamer 407

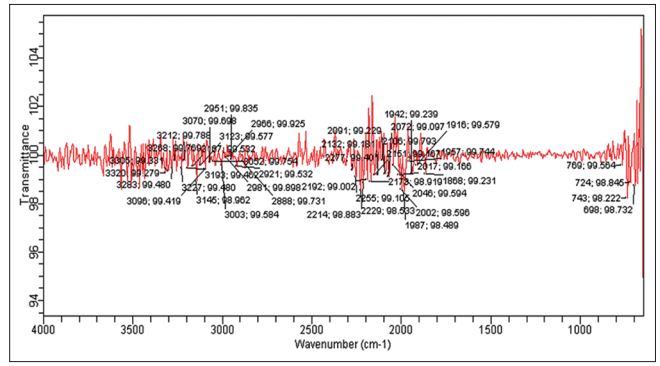

Fig. 7: Fourier-transformer infrared plot of sertraline hydrochloride+Carbopol 934+Poloxamer 407

- The chlorine may also be present in the form of HCL is indicated by the peaks at 1942, 1968, and 1987 cm^{-1}.
- The small intensity peaks at 1339 and 1406 cm^{-1} indicate C-H stretching of $–CH_2$- group.

Identification of presence of sertraline HCL drug in formulation

Differential scanning calorimetry

DSC thermogram of sertraline hydrochloride shows broad endothermic peak at 249°C which is its melting point as sertraline melt with decomposition over the range 246–249°C (Fig. 8).

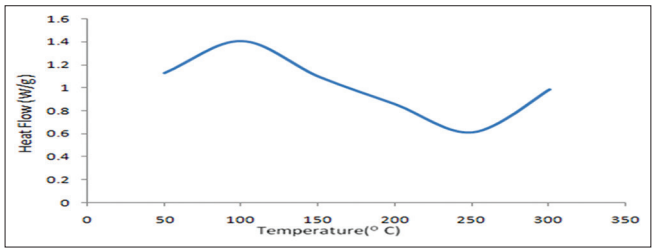

Fig. 8: DSC thermogram of sertraline hydrochloride

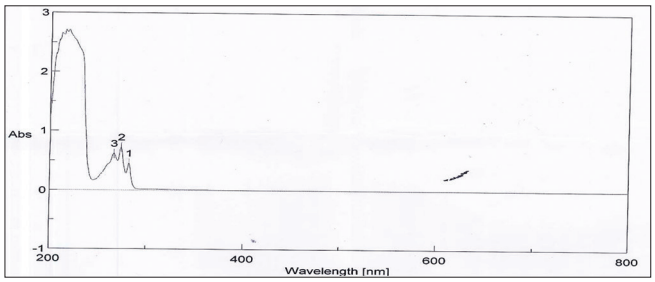

Fig. 9: λmax scan for sertraline hydrochloride

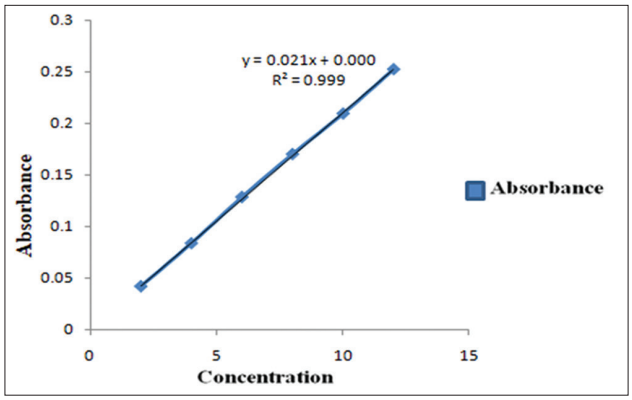

Fig. 10: Calibration curve of sertraline HCL in PH 6.4 simulated nasal fluid

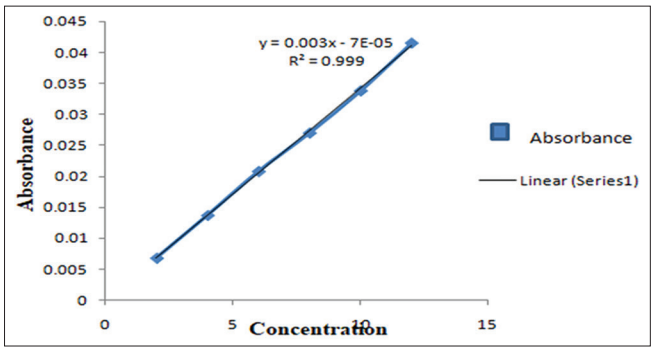

Fig. 11: Calibration curve of sertraline hydrochloride in ethanol

λ_{max} scanning

λ_{max} scanning helps in identifying the drug's purity. The λ_{max} in scanned graph was found at 274 nm which is according to reported literature which confirmed that the obtained drug sample was sertraline hydrochloride (Fig. 9).

Calibration curve of sertraline hydrochloride

The calibration data, as shown in Tables 7-9, was collected according to the method mentioned in literature and then the regression analysis was applied. The Beer's law was found to obey in the range of 2–12 µg/mL as revealed in figure. The obtained R^2 value is high (0.999), close to 1. From this study, it was concluded that there was a good correlation between the experimental and theoretical values.

The obtained R^2 value is high (0.999), close to 1. From this study, it was concluded that there was a good correlation between the experimental and theoretical values. Various calibration curves were prepared in different solvents for the determination of solubility of drug in a particular solvent. Calibration curve is also utilized for the determination of unknown concentration of drug sample (Figs. 10-13).

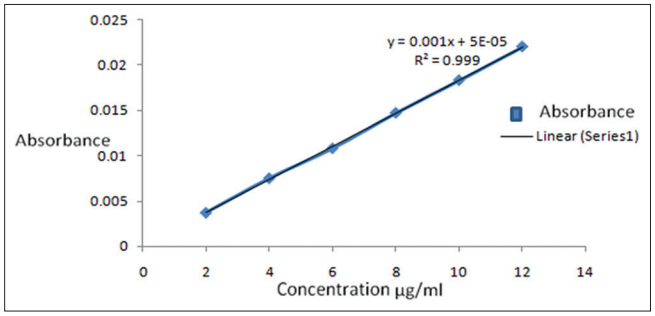

Fig. 12: Calibration curve of sertraline hydrochloride in IPA

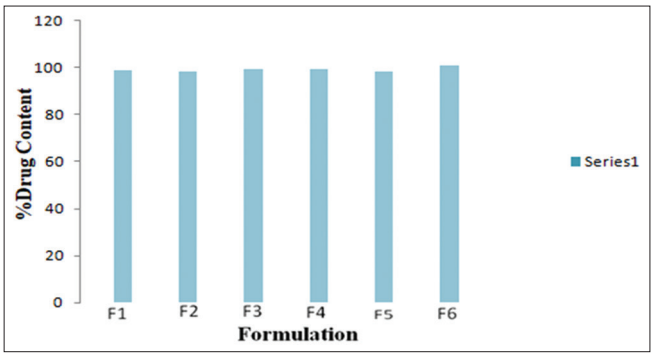

Fig. 13: Percentage drug content of formulations (F1-F6)

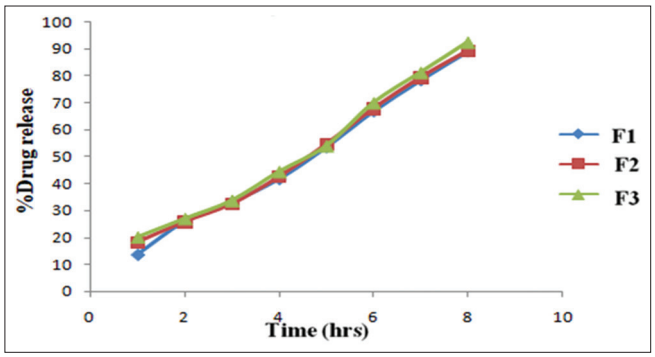

Fig. 14: *In vitro* drug release rate of sertraline HCL (F1-F3)

Table 6: The amine group is identified at 769 cm^{-1} as the peak at 747 cm^{-1} in standard IR graph

Functional group	Prescribed range	Standard peak	Formulation peak
Amino Group-2°amine	700–850 cm^{-1}	762 cm^{-1}	769 cm^{-1}
Aromatic ring	650–800 cm^{-1}	680, 747, 762 cm^{-1}	698, 743, 769 cm^{-1}
C-NH_2-	1800–2050 cm^{-1}	2020, 2143, 2087 cm^{-1}	2017, 2132, 2091 cm^{-1}
H-Cl Group	1800–2000 cm^{-1}	1942 cm^{-1}	1942 cm^{-1}

Table 7: Calibration data of sertraline HCL in 6.4 pH simulated nasal fluid

S. No.	Concentration (µg/mL)	Absorbance Mean±SD
1.	2	0.0418
2.	4	0.0835
3.	6	0.1282
4.	8	0.1698
5.	10	0.2090
6.	12	0.2519

Table 8: Calibration data of sertraline hydrochloride in ethanol

S. No.	Concentration (µg/mL)	Absorbance (Mean±SD)
1.	2	0.0068
2.	4	0.0137
3.	6	0.0208
4.	8	0.0270
5.	10	0.0338
6	12	0.0415

Table 9: Calibration data of sertraline hydrochloride in IPA

S. No.	Concentration (µg/mL)	Absorbance (Mean±SD)
1.	2	0.0037
2.	4	0.0075
3.	6	0.0108
4.	8	0.0147
5.	10	0.0183
6.	12	0.0220

Table 10: pH values of formulations

Formulation code	pH (±S.D)
F1	5.01
F2	5.06
F3	5.11
F4	4.99
F5	5.00
F6	5.06

Table 11: The percent drug content of *in situ* nasal solution (F1-F6)

Formulation code	Drug content (%) (±SD)
F1	99.09
F2	98.22
F3	99.46
F4	99.65
F5	98.59
F6	101.15

Table 12: Gelling Capacity of prepared *in situ* gel

S. No.	Formulation code	Gelling capacity
1.	F1	+
2.	F2	++
3.	F3	++
4.	F4	+++
5.	F5	+
6.	F6	+++

+: Gelation within 50–60 s, dissolves rapidly, ++: Gelation within 60 s and remains stable for 3 h, **+++**: Gelation within 60 s and remains stable for 6 h

Evaluation of drug-loaded gel

Clarity

On careful visual inspection against dark and white background, all prepared nasal gel formulations were found to be free from any suspended particulate matter. All the formulations were found to be clear.

pH

The pH of all the formulations from F1 to F6 was found to be in the range of 4.99–5.11 pH values of formulations shown in Table 10.

Ideally, the nasal solutions should possess pH in the range of 4.5–6.5, so as to minimize discomfort or irritation due to acidic pH and microbial growth due to basic pH.

Drug content

Drug content found in the *in situ* nasal gel formulation resembled that of literature value. Range of drug content was 99–101%. Therefore, uniformity of content was maintained in all formulation. Drug contents all the formulations in Table 11.

The drug content of the nasal formulations of sertraline HCL *in situ* gel was found satisfactory (ranging between 98.22% and 101.15%), indicating uniform distribution of the drug.

GELLING CAPACITY

The formulation should have an optimum viscosity, which would allow easy instillation into the nasal as a liquid (drops), but would also allow the formulation to undergo temperature-based sol-to-gel transition. In addition, to facilitate sustained release of the drug to the nasal membrane, the gel formed *in situ* should preserve its integrity without dissolving for a prolonged period of time. Table 12 shows the gelling capacity of all formulations, which is depicted as + (gel forms in 60 s and dissolves rapidly), ++ (gel forms within 60 s and remains stable for 3 h), and +++ (gel forms within 60 s and remains for 6 h). The gelling capacity increases with increasing concentration of gelling agent. Table 12 shows the gelling capacity of formulations F1 to F6. All the formulations, except F1 and F5, showed instantaneous gelation when contacted with artificial simulated nasal fluid (SNF). However, the nature of the gel formed depended on the concentration of the polymers used. Formulations F1 and F5 showed gel formation within 60 s, which dissolved rapidly. Formulations F2 and F3 showed immediate gelation within 60 s and remained stable for a few hours, whereas formulations F4 and F6 showed immediate gelation within 60 s and remained stable for an extended period.

Gel strength

The gel strength of nasal formulation at room temperature and 37°C is shown in Tables 13 and 14 respectively.

The gel strength was found to be affected by concentrations of gelling agent, mucoadhesive polymers, and also by the temperature. Optimal mucoadhesive gel must have gel strength so as to be administered easily and can be retained at nasal region without leakage after

administration. Gel strength of all formulations showed comparable results as that of viscosity results.

Mucoadhesive strength

The detachment stress of formulation is shown in Table 15.

Mucoadhesive force means the force with which gels bind to nasal mucosa. Greater mucoadhesion is indicative of prolonged residence time of a gel and thus prevents its drainage from nasal cavity. The Mucoadhesion force increased significantly as the concentration of Mucoadhesion polymer increased. The detachment stress was determined for nasal gels. Results of this test indicate that the variable. Carbopol 934 having effect on mucoadhesive strength. It shows that mucoadhesive force was increased with the increasing concentration of the Carbopol 934.

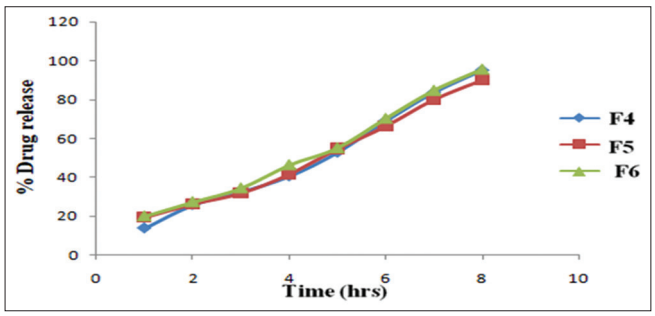

Fig. 15: *In vitro* drug release rate of sertraline HCL (F4-F6)

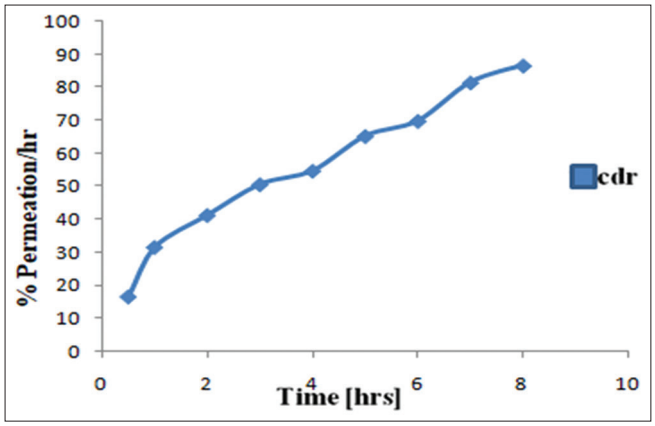

Fig. 16: *In vitro* permeation study for optimized batch F6

Table 13: Gel strength of formulations at room temperature

S. No.	Formulation code	Gel strength (s) (±SD)
1.	F1	0.30
2.	F2	0.33
3.	F3	0.40
4.	F4	0.48
5.	F5	0.56
6.	F6	0.66

Table 14: Gel strength of formulations at 37°C

S. No.	Formulation code	Gel strength (sec) (±SD)
1	F1	0.40
2	F2	0.48
3	F3	0.52
4	F4	0.80
5	F5	0.85
6	F6	0.91

Gelation temperature

Gelation temperature range suitable for nasal gel is 32–35°C. Gelation temperature for all formulations was found in the range of 28–34°C (Table 16).

Viscosity

Viscoelastic fluid with a viscosity that is high under conditions of low shear rate and low under conditions of high shear rates are preferred. To evaluate the rheological behavior, the viscosity of the formulations at room temperature and 37°C was evaluated by a Brookfield viscometer, using increased shear stress and varying the angular velocities or shear rate (Table 17). All the selected formulations were shear thinning and exhibiting pseudo plastic behavior. All the formulations were liquid at room temperature and temperature was increased, the increase in viscosity was observed due to temperature sensitive polymer (poloxamer 407) was used in the formulation. Concentration of poloxamer 407 was major factor affecting viscosity of formulations. In combination with poloxamer 407 and Carbopol 934 has shown considerable increases in viscosity when concentration of poloxamer 407 was 18% w/v.

The rheological profile of the prepared *in situ* gelling systems of sertraline hydrochloride at room temperature and 37°C is shown

Table 15: Mucoadhesive strength of formulations

Formulation code	Detachment force (N) (±SD)	Bond strength (N/m^2) (±SD)
F1	0.0512	0.0080
F2	0.0543	0.0086
F3	0.0610	0.0110
F4	0.0690	0.0114
F5	0.0780	0.0124
F6	0.0811	0.0130

Table 16: Gelation temperature of prepared *in situ* gel

Formulation code	Gelation temperature (°C)
F1	28.56
F2	29.32
F3	30.23
F4	32.08
F5	34.35
F6	34.92

Table 17: Viscosity of formulations at room temperature

RPM	Viscosity (cp) at room temperature					
	F1	F2	F3	F4	F5	F6
5	261.9	333.9	350.9	381.9	402.9	415.6
10	239	220.4	338.6	253.9	366.9	403.6
15	186	204.4	286	237.9	331.6	376.9
20	175.9	197.3	261.4	209.5	279.9	340.2
25	155	179	248.9	191.3	267.9	323.5
30	136.1	161.9	220.4	131.9	254.9	291.9

Table 18: Viscosity of formulations at 37°C

RPM	Viscosity (cp) at 37.4°C					
	F1	F2	F3	F4	F5	F6
5	386	402.7	430.9	535.2	840.9	853.9
10	361	383.6	400	390.6	726.9	705.9
15	343.6	331.6	390.9	375.2	595.9	588.2
20	297.6	303.7	374.9	338	457.7	432
25	262.4	277.5	354.9	320.9	314.9	317.2
30	252.8	293.8	327	213.2	287.2	297.2

Table 19: *In vitro* release studies of formulation (F1 to F6)

Time (hr)	F1	F2	F3	F4	F5	F6
1	13.47	18.15	20.11	13.90	19.50	20.15
2	25.80	25.74	26.95	25.90	26.40	27.50
3	33.04	32.35	33.70	32.50	32.01	34.60
4	41.60	42.44	44.40	40.60	41.77	46.50
5	53.40	54.53	53.93	52.80	54.85	55.30
6	66.78	67.75	69.91	68.90	66.43	70.40
7	78.35	79.32	81.19	83.50	80.14	84.93
8	89.07	89.23	92.41	94.90	90.14	95.80

Table 20: *In vitro* permeation study for optimized batch F6

S. No.	Time (hr)	Drug permeation rate (mg/cm/hr.) (±S.D)	Percentage cumulative drug permeation (±S.D)
1.	0.5	0.4572	16.53
2.	1	0.3996	31.52
3.	2	0.2457	41.22
4.	3	0.1927	50.53
5.	4	0.1337	54.64
6.	5	0.1361	65.14
7.	6	0.1167	69.74
8.	7	0.1120	81.4
9.	8	0.090	86.52

in Table 18. To assess the rheological behavior, the viscosity of the formulation (F1-F6), at room temperature and 37°C was evaluated using a Brookfield viscometer (Spindle no. 62), varying the angular velocities.

***In vitro* drug release study**

Of six formulations maximum release, after 8 h was found for F6 formulation. This indicates release of 95.80% drug available for antidepressant activity of the drug. F6 formulation showed steady state release up to 8 h which also indicates that this formulation would show better contact with biological membrane. Drug release of all the formulation is listed in Table 19. *In–vitro* drug release profile of all formulations shown in Figs. 14 and 15.

***In vitro* permeation study**

In vitro drug release was observed for the optimized formulation using goat nasal mucosa. Permeation of the drug from goat nasal mucosa was studied for 8 h. It was found to be 86.52% at 8th h. Permeation of the drug shows synergistic mechanism with that of *in vitro* drug release. Permeation study of the optimized formulation is listed in Table 20. *In vitro* drug permeation profile of optimized formulation shown in Fig. 16.

Accelerated stability study

Results of the stability studies showed that there is no change in the physical parameters of the formulation. Drug content of the formulation was also found to be same as that before stability testing.

CONCLUSION

The novel nasal temperature-monitored *in situ* thermoreversible gel drug delivery was successfully formulated using Carbopol 934 and Poloxamer 407. The formulated *in situ* thermoreversible systems were characterized for appearance, clarity, pH, gelling capacity, gel strength, mucoadhesive strength, gelation temperature, *in vitro* release in simulated nasal fluid, *in vitro* permeation study, and accelerated stability study. The formulation was liquid at room temperature and underwent rapid gelation at temperature on raising the 34.92°C. The temperature-triggered *in situ* thermoreversible system showed sustained drug release over 8-h period of time. Hence, this formulation is an alternate to conventional nasal drops to improve the bioavailability through its longer nasal residence time and ability to sustain drug release. The patient compliance may be improved due to the decrease in frequency of drug administration.

ACKNOWLEDGMENT

I would express my gratitude to the L. R. Institute of Pharmacy, Solan, Himachal Pradesh, India, to provide me all facilities to conduct my research work.

AUTHORS' CONTRIBUTIONS

The author declares that this work was done by the author named in this article.

CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

REFERENCES

1. Djupeslan PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective-a review. Drug Deliv Transl Res 2013;3:42-62.
2. Bhise SB, Yadav AV, Avachat AM, Malayandi R. Bioavailability of intranasal drug delivery system. Asian J Pharm 2008;2:201-15.
3. Available from: https://www.en.wikipedia.org/wiki/Anatomy_of_the_human_nose.
4. Bhise SB, Yadav AV, Avachat AM, Malyandi R. Bioavailabilty of intranasal drug delivery system. Asian J Pharm 2018;2:201-15.
5. Jaiswal J, Anantvar SP, Narkhede MR, Gore SV, Mehta K. Formulation and evaluation of thermoreversible *in-situ* nasal gel of meoprolol succinate. Int J Pharm Pharm Sci 2012;4:96-102.
6. Patel M, Thakkar H, Kasture PV. Preparation and evaluation of thermo reversible formulations of flunarizine hydrochloride for nasal delivery. Int J Pharm Pharm Sci 2010;2:116-20.
7. Jagdale S, Shewale N, Khuchekar BS. Optimization of thermoreversible *in situ* nasal gel of timolol maleate. Scientifica (Cairo) 2016;2016:6401267.
8. Gondkar SB, Kakad JK, Saudagar RB. Formulation and evaluation of nasal *in-situ* gel of losartan potassium. Int J Univers Pharm Bio Sci 2015;4:34-59.
9. Bhalerao AV, Lonkar SL, Deshkar SS, Shirolkar SV, Deshpande AD. Nasal mucoadhesive *in situ* gel of ondansetron hydrochloride. Indian J Pharm Sci 2009;71:711-3.
10. Parmar VJ, Lumbhani AN. Formulation and development of thermoreversible mucoadhesive intranasal *in situ* hydrogel by using a combination of polymers. Bull Pharm Res 2012;2:167-74.
11. George M, Joseph L, Kavitha AK. Formulation and evaluation of intra nasal *in situ* mucoadhesive gel of domperidone maleate. Eur J Pharm Med Res 2017;4:249-53.