Research Article

Design and characterization of Sertraline Hydrochloride *in-situ* nasal gel

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Received: 12 January 2025 Revised: 25 February 2025 Accepted: 27 February 2025

Abstract

Objective: The main purpose of the work was to optimize an Ion, pH nasal In-Situ gel formulation to enhance nose-to-brain delivery of Sertraline hydrochloride, an antidepressant agent. An in situ-forming polymeric drug delivery system might be the better option to increase the drug's bioavailability. **Materials and method**s: A preliminary procedure of mixing different combinations of Xanthan gum, Konjac gum, Carbopol, and HPMC K100M, the properties of gels were tested to assess the impact of polymers. All the formulations developed were characterized for the evaluation tests. XF7 and CF6 formulations were selected as optimized formulations. These were subjected to viscosity and *ex vivo* permeation studies in comparison to the plain gels prepared. **Results:** The optimized formulations were defined by a pH value of 6.4±0.2, and a gelation time ranging from 12 to 16 seconds, demonstrating all the characteristics needed by in situ gelling formulations intended for nasal administration. *Ex vivo* studies also confirmed 100 % drug release from XF7 formulation in 24 hr. It retained the potential for improving drug penetration via the nasal mucosa, which is more significant. **Conclusions:** These findings suggest that the optimal gelling system, which uses both direct and indirect pathways at a controlled rate, maybe a practical and easy technique to enhance the delivery of Sertraline hydrochloride to the brain.

***Keywords*:** Sertraline hydrochloride, Nasal in-situ gel, pH-sensitive, Ion-sensitive

Introduction

Nasal drug delivery has been a successful route of administration since ancient times. It offers better brain availability for many drugs and is considered a valuable tool in treating various brain disorders (**Suhagiya et al., 2023**). The olfactory region of the nose is particularly important, because it contains specialized ciliated nerve cells for smell perception, receives ophthalmic and maxillary divisions of the trigeminal nerve, and has direct access to cerebrospinal fluid **(Vigani et al., 2020; Swamy and Abbas, 2012).** Nasal mucosa is considered a prospective route of administration for achieving faster and higher points of drug absorption because of its permeability to a higher number of compounds than the digestive tract, as it lacks pancreatic as well as abdominal enzymatic activity, and possesses neutral pH. Now-a-days, nasal route of drug administration is widespread. The popularity of intranasal administration is increasing with growing pharmaceutical technology and abundant medicinal opportunities **(Alagusundaram et al., 2010).** Depression is a mental health condition that involves a prolonged period of low mood or loss of interest in activities and negatively affects how you feel, think, and act. This is different from regular mood changes and feelings about everyday life. Depressive episodes last most of the day, nearly every day, and for a prolonged period of time. Depression can be linked to low serotonin reuptake levels, meaning that the brain is not effectively reabsorbing serotonin after it has been released, leading to a reduced amount of this neurotransmitter available to signal between neurons, which is often associated with feelings of sadness, low mood, and other depressive symptoms; this is why many antidepressant medications, known as SSRIs (selective serotonin reuptake inhibitors), work by blocking serotonin reuptake, effectively

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DOI: https://doi.org/10.31024/ajpp.2025.11.1.2

increasing its availability in the brain. Sertraline (SRT) is an antidepressant used as a first-line treatment of major depressive disorder which belongs to BCS class 2, selective serotonin reuptake inhibitors (SSRIs), with a molecular weight of 306.229 g/mol and a biological half-life of about 24 hours in adults and oral bioavailability of 44% for which results in low brain availability due to insufficient time for penetration and low permeability. Sertraline works on inhibiting presynaptic serotonin reuptake which results in the accumulation of serotonin. Serotonin in the central nervous system plays a role in regulating mood, personality, and wakefulness, which is why blocking serotonin reuptake is beneficial in disorders such as major depression and emerges as a prominent antidepressant **(Singh et al., 2023).** In brief, SRT has gained widespread acclaim for its efficacy in managing depression and related mental health disorders. The unique chemical structure of SRT is responsible for its therapeutic prowess, which helps alleviate depressive symptoms through a specific pharmacological mechanism. Beyond depression, SRT is utilized in the management of various conditions comprising panic disorder, anxiety, and obsessive–compulsive disorder, serving a diverse demographic ranging from adults to children. To overcome Sertraline low oral bioavailability and permeability issues, nasal drug delivery may be a suitable alternative, but further research is needed.

Animal studies have demonstrated that the concentration of cocaine in the brain is higher after nasal administration compared to intravenous injection at early time points, the existence of a pathway from the nose to the brain (**Selvaraj et al., 2018; Erdo et al., 2018**). For instance, in a mouse model, [3H]-dopamine reached the olfactory lobe after nasal administration, and after 4 hrs, the concentration in this tissue was 27 times higher than after intravenous injection (**Dahlin et al., 2000).** Using mucoadhesive gel formulations could be a possible strategy to extend the residence time at the nasal absorption site. Approaches to improving nasal bioavailability include using viscosity-enhancing or in-situ gelling polymers to prolong the contact time with the nasal surface. An in-situ gel is a drug delivery system that undergoes a sol-to-gel phase transition by changing specific physicochemical parameters such as ionic, temperature, or pH **(Devi et al., 2014; Singh et al., 2021).** This drug delivery system can release the drug sustainably; due to a high lipophilicity value (Log P (water/octanol)) of 5.1, confirming the good absorption and distribution in the body. Therefore, using nasal in-situ gel could enhance its bioavailability by delivering the drug to the brain through the olfactory region while also eliminating the adverse effects of first-pass metabolism and gastrointestinal disturbances. The objective of the present study was to prepare an in-situ nasal gel with improved residence time in the nasal cavity, achieving prolonged drug release, and quick onset of action by accessing the nose-to-brain route. These could benefit the patients suffering from depression in real life without the need for frequent and high dosing and fast action of the drug via nose to brain. Challenges would be the minimization of patient variability in human trials and acceptance of this drug delivery system although there are nasal sprays, solutions, and gels available in the market, in-situ gels are yet to hit the market after approval from the regulatory authorities.

Materials and methods

Sertraline Hydrochloride was a kind gift sample from Asphar Research Labs Pvt. Ltd, Hyderabad, India. Carbopol 934, HPMC K 100 M, and Xanthan gum were procured from SD Fine Chem. Limited, Hyderabad, India. Tween 80 was from Sisco Research Laboratories Pvt. Ltd, Hyderabad.

Drug-excipient compatibility studies

FTIR analysis: FTIR spectra were collected to evaluate interactions between the drug and the excipients over the range of 650-4000 cm^{-1}.

Selection of dissolution medium

Various surfactant-containing simulated nasal fluid solutions were screened for their ability to solubilize the drug and use it as the dissolution medium. For the former study, 10 mL of known % w/v solution of different ratios with simulated nasal fluid (SNF with 0.5%, 1% tween 80, SNF with 0.5%, 1% SLS and PEG: water (1:1, 1.25:3.75 and 3.75: 1.25) were prepared and transferred to clean glass vials. Excess amount of drug was introduced into each vial. These vials were kept on a rotary shaker for 48 h under ambient conditions. The solutions were filtered, suitably diluted, analyzed, and selected as media for dissolution and receptor medium.

Method of preparation of in-situ nasal gel

In-situ nasal gels are prepared by cold technique as mentioned in Table 1 and 2. Sertraline Hydrochloride was dissolved completely in 2-3 ml methanol and 3 ml of PEG was used as a co-solvent. Combinations of Xanthan gum, Carbopol 934P in the concentration range 1–2.5 %w/v) was added to the above solution using a magnetic stirrer at 200 rpm. Copolymer (HPMC K 100M in the concentration range 0.1–2.5 %w/ v added into the above primary solution and placed in cool conditions overnight to obtain the final solution. The final solution was then subjected to various evaluation tests.

Evaluation of In-Situ Nasal gels

Table 1. Solubility of sertraline in different dissolution media

S. No	Solubility media	Solubility (µg/ml)
1	**SNF+ 1% Tween 80**	**79.3±0.2**
2	SNF+ 0.5% Tween 80	49.77±0.2
3	SNF+1% SLS	66.13±0.1
4	SNF+0.5% SLS	75.62±0.2
5	PEG: water 1:1	3.29±0.3
6	PEG: water 1.25:3.75	71.0±0.3
7	PEG: water 3.75:1.25	72.58±0.1

Table 2. Formulation table of Ion sensitive In situ gels

Ingredients	XF1	XF2	XF3	XF4	XF5	XF6	XF7	XF8	KF1	KF2	KF3
Drug(mg)	100	100	100	100	100	100	100	100	100	100	100
Xanthan gum (mg)	100	150	200	250	250	250	250	200	-	-	-
Konjac gum(mg)	-	-	-	-	-	-	-	-	0.05	0.05	0.1
HPMC k 100 M(mg)	100	100	100	100	100	200	250	250	0.05	0.1	0.1
Benzalkonium chloride	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled Water	75	75	75	75	75	75	75	75	75	75	75

Table 3. Formulation table of pH-sensitive In situ gels

Ingredients	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8
Drug(mg)	100	100	100	100	100	100	100	100
Carbopol (mg)	100	150	200	250	250	250	250	200
HPMC k 100 M(mg)	100	100	100	100	100	200	250	250
Benzalkonium chloride	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled Water	75	75	75	75	75	75	75	75

Visual Appearance, Clarity

All the formulations were evaluated for visual appearance and clarity

pH, drug content, and gelation time

This study assessed the formulated gels for pH, drug content, and gelation time. To determine the pH of each formulation, a pH meter was used, which was calibrated initially using buffer solutions, and the results were evaluated in triplicate. For drug content determination, 0.5 g of formulation was taken in a 50 ml volumetric flask and diluted with 25 ml of SNF. The mixture was shaken for 10 min in an incubator to dissolve the drug in SNF. The solution was then filtered and appropriately diluted to determine the drug content spectrophotometrically at 274 nm.

The time of gelation of each test formulation was placed into a vial with two milliliters of SNF to record the gelation of each formulation.

Spreadability

A measured quantity of formulation was placed in the middle of the petri plate, which was then held up by a known weight and another glass plate which was inverted. A minute after that, the diameter area was measured and the weight was taken out.

***In vitro* drug release**

In-vitro drug release was conducted using a Franz diffusion chamber and a dialysis membrane. As mentioned above after the solubility studies in different dissolution mediums the medium with highest drug solubility makes up the receptor Compartment. Two ml of test formulation was added to donor compartment. The donor and receiver compartment were separated by a dialysis membrane that had been immersed in the receptor medium (simulated nasal fluid) for all of the night. After placing the complete assembly on the magnetic stirrer, it was agitated at 100 rpm. A constant temperature of 37±1°C was maintained. For 24 hours, 2ml aliquots were taken out at regular intervals, replaced with an equivalent volume of receptor media, and examined using a UV Spectrophotometer at 274 nm. After

the characterization of all 19 formulations, the optimized formulations selected were subjected to viscosity determinations and *ex vivo* permeation studies.

Viscosity

The viscosity of the optimized formulations was measured using a thermostatically controlled Brookfield viscometer using Spindle number 62. The spindle was then lowered perpendicularly into the gel and rotated at different RPMs (50 and 100) while maintaining the temperature at 28 ± 0.5 °C, and measurements were performed in triplicate.

***Ex-vivo* permeation studies**

Freshly dissected goat nasal mucosa from a local slaughterhouse was used in an ex vivo diffusion experiment for the study. The nasal mucosa was maintained in SNF for one hour to allow tissue equilibration. A Franz diffusion cell was used to mount the removed superior nasal membrane after the superior nasal concha was located and detached from the nasal membrane. SNF was added to both cell compartments and agitated with a magnetic stirrer for 15 minutes to stabilize the tissue. The solutions from both compartments were taken out after 15 minutes, and the receptor compartment was then filled with 20 mL of dissolution medium. In the donor compartment, two ml of in-situ gelling solution were added. Samples were withdrawn from the receptor compartment at predetermined time intervals and analyzed at 274 nm. For *ex vivo* studies plain gel containing xanthan gum and Carbopol were prepared and their drug release was compared with the optimized formulations.

Stability studies

A short-term accelerated stability study was performed for an optimized in-situ gelling solution at 40 ± 2 ºC temperature and 75 ± 5 % relative humidity for one month, examined and evaluated for pH, drug content and, viscosity, and the outcome was reported.

Results and discussion

The melting point of Sertraline hydrochloride was determined to be 248°C. According to the literature review, the melting point was 245°C-249°C, which was quite near to the experimental value (**Sharma et al., 2019**).

FTIR analysis

Drug, excipient interaction was studied before developing the formulation by using FTIR spectroscopy, which is one of the most important analysis to describe the stability of the formulation, the presence of the drug, and its compatibility with used excipients. From the FTIR spectra of pure sertraline and physical mixture reported in Figs 1& 2, it was clear that there are no possible physicochemical interactions between them.

Selection of dissolution medium

The solubility studies were conducted in different dissolution mediums as was reported in Table 1 and Fig 3. Based on the highest solubility of drug SNF+ 1% Tween 80 was selected as the dissolution medium.

Characterization of *in-situ* nasal gel of Sertraline hydrochloride

Clarity, Texture and Visual appearance

It explains the texture of the gel and solution, the clarity of the sol phase both before and after the pH is altered, and the clarity of the gel at pH 6.5 was determined and reported in Table 4. It indicated that all the formulations were clear, and smooth in appearance (semi-quantitative).

pH, drug content, gelation time

pH of the gel-forming formulations were recorded and the results were reported in Table 4. The pH of all formulations

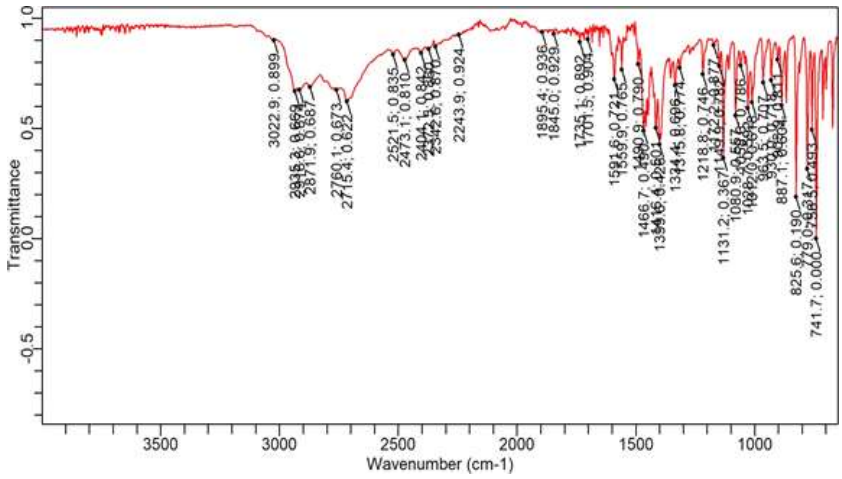

Figure 1. Representing the FT-IR Spectrum of Sertraline hydrochloride

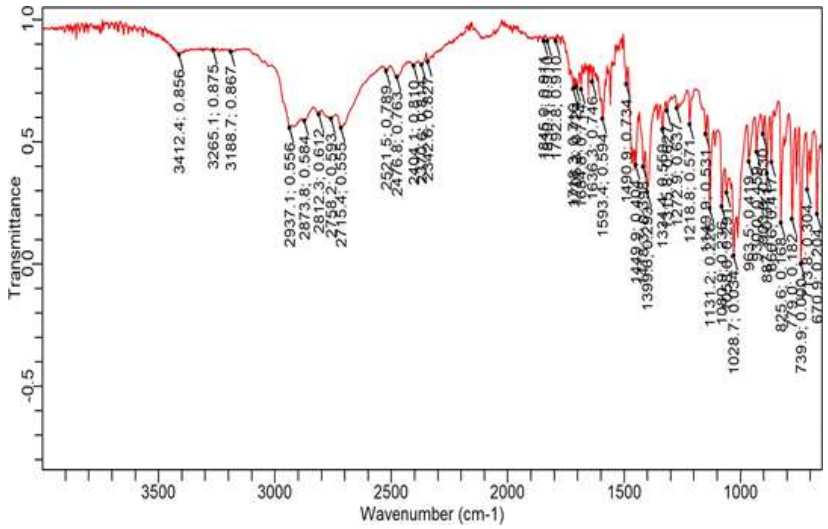

Figure 2. FTIR analysis of pure drug and drug with polymers

Table 4. Evaluation tests of In situ gels

Formulation	pH	Drug content (%)	Gelation time (sec)	Spreadability (cm)
XF1	5.4±0.2	93.9±0.2	-	6
XF2	5.5±0.1	92.2±0.1	-	7
XF3	5.8±0.2	93.4±0.2	210±2	6
XF4	5.7±0.2	93.2±0.2	72± 1	4
XF5	5.8±0.2	93.4 ±0.1	36 ±2	5
XF6	5.8±0.2	94.2 ±0.1	45± 1	4
XF7	6.4±0.1	95.5 ±0.1	**12± 1**	4
XF8	6.6±0.1	92.2 ±0.2	20± 2	5
CF1	5.2±0.1	91.7±0.3	-	6
CF2	5.5±0.2	91.3±0.1	-	7
CF3	5.8±0.1	92.5±0.1	55±2	6
CF4	5.9±0.1	93.2±0.2	42 ±1	4
CF5	5.9±0.1	94.3±0.1	32±1	5
CF6	6.45±0.2	96.8±0.2	**16± 2**	4
CF7	6.6±0.2	93.9±0.1	22± 1	5
CF8	6.6±0.3	92.8±0.1	46± 1	5
KF1	5.4±0.2	88.2±0.3	-	3
KF2	5.5±0.3	91.1±0.1	-	2
KF3	5.5±0.2	92.1±0.1	-	3

ranged from 5.4 to 6.6 which matches with the physiological pH of the nasal cavity which indicates that the gel is unlikely to cause irritation or discomfort in the nose. The drug content of each formulation was ascertained and recorded; all the formulations ranged from 91.1 to 95.5 ±0.2%. The gelation time was recorded for all the formulations and reported in Table 4. The Formulations with low concentration did not form a gel, formulations XF7, XF8, XF5, CF6, CF7, and CF5 showed a quick gel formation. Out of all these XF7 has gelled in 12 seconds and CF6 gelled in 16 seconds. These two formulations were selected as optimized formulations for further evaluation.

Spreadability

It evaluates the gel's ease of application and spreadability on the nasal mucosa without leaking. Results were recorded in Table 4, and was observed that the spreadability values were ranging from 4 to 7 cm which is considered ideal for many in situ gel applications, as it allows for good coverage without being runny or too sticky.

***In-vitro* drug release**: All the formulations were used for evaluated for percentage drug release using dialysis membrane and the results are reported in Fig 4 and 5.

Table 5. Viscosity of the optimized Formulation

RPM	Viscosity of the optimized formulations at temperature 28°C (cps)	
	XF7	CF6
50	935 ± 2	977 ± 2
100	996 ± 2	998 ± 3

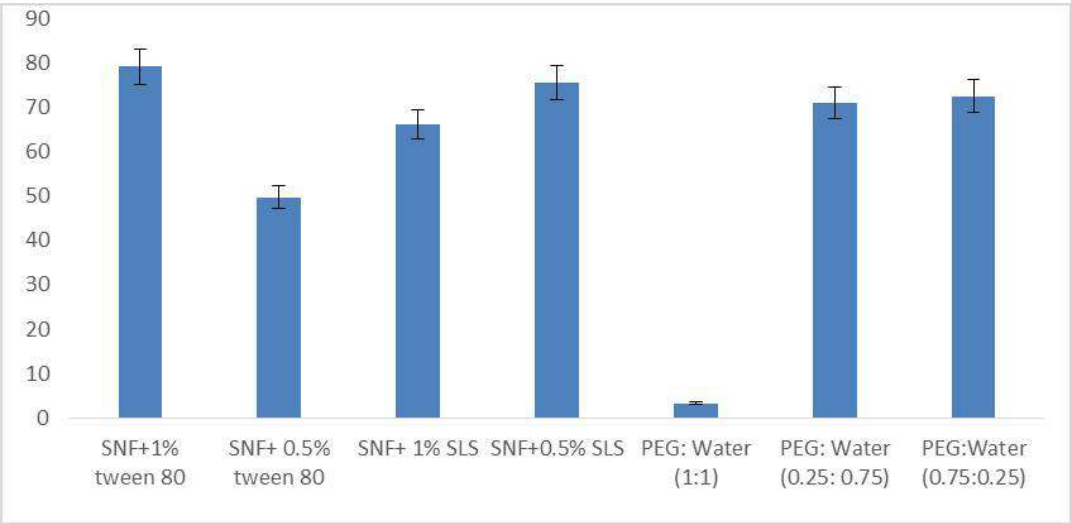

Figure 3. Solubility studies Of Sertraline Hydrochloride

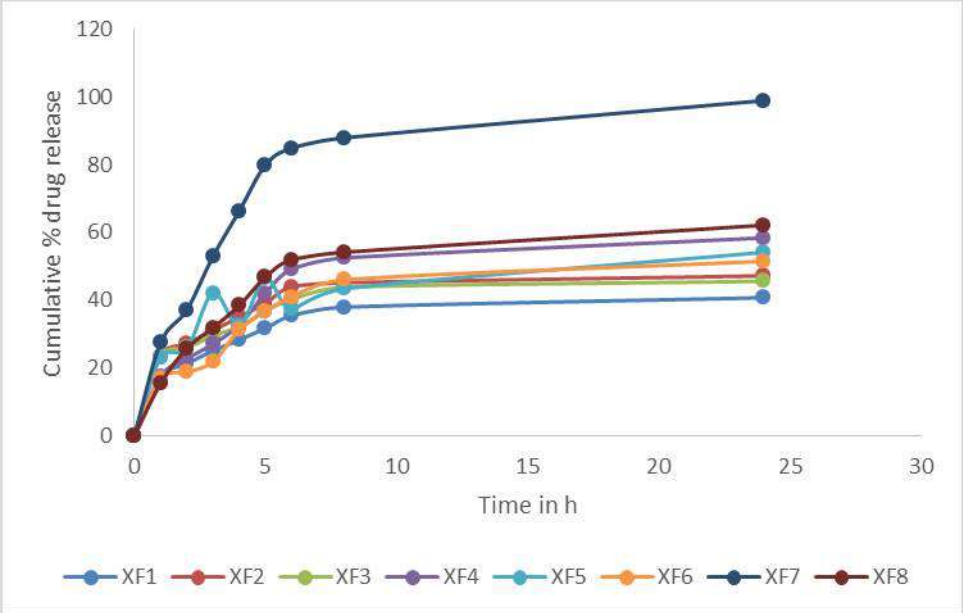

Figure 4. Drug release profile of XF1 to XF8

Formulation Cf6 (combination of Carbopol and HPMC K4M) has the drug release of 98.28% of drug release and among all the formulations XF7 (combination of Xanthan gum and HPMC K4M) showed 99.13 % drug release which is the highest percentage among all the formulations so both were selected as optimized formulations and further subjected to viscosity, *ex vivo* permeation studies.

Viscosity and *Ex-vivo* permeation studies for the optimized formulations

Viscosity: Using a Brookfield viscometer, the formulations (liquid at room temperature) were measured with spindle number 62 at different RPM (50, 100) and results were recorded in Table 5.

Ex-Vivo Permeation Studies

The optimized in situ formulations (XF7 and CF6) are compared using plain Carbopol and xanthan gum gel formulations for *ex vivo* permeation studies, reported in Fig 6. 95.4% drug release from plain xanthan gum gel and 88.5 % from plain Carbopol gel for 4 h indicated an immediate release, whereas the drug release from the optimized in situ gels is at a controlled rate 100. 01% from XF7 and 92.39 % from CF6 throughout 24 h being in prolonged contact with the mucosal membrane. The optimized in situ gel formulations (XF7 and CF6) are superior to plain Carbopol and xanthan gum gels for achieving controlled and prolonged drug release. This is crucial for therapies requiring sustained drug levels over an extended period, as it enhances efficacy and potentially reduces dosing frequency. The in-situ gels provide a much more controlled drug release, over a much longer period.

Stability studies

Short-term stability studies of in situ gels conducted indicated that there was no change in the drug content, pH, and viscosity of the preparations. The formulations are stable under the tested short-term conditions, in essence, the studies confirm that the key properties of the in situ gels are maintained ensuring a reliable and consistent product. which indicated the stability of the formulations.

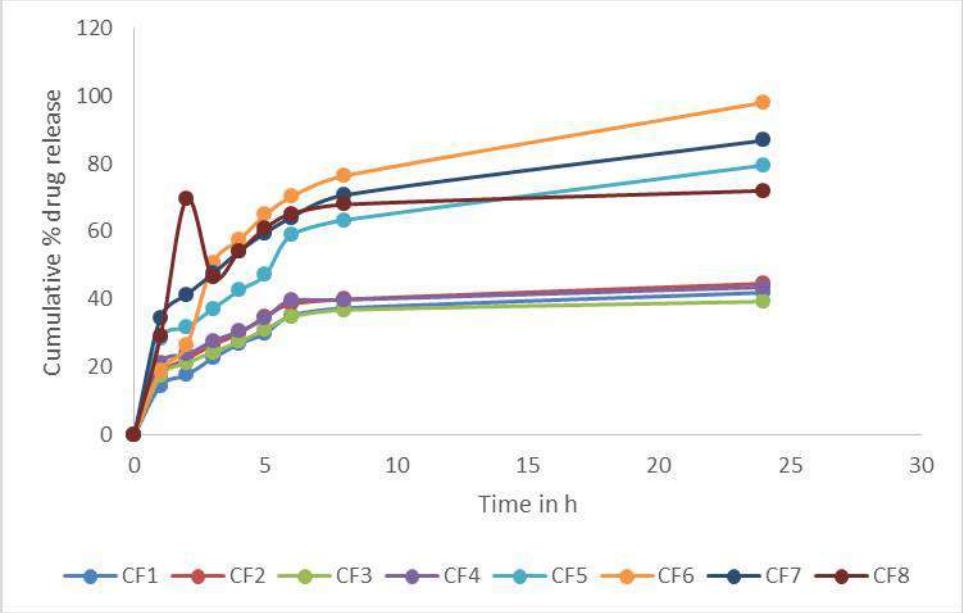

Figure 5. Drug release profile of CF1 to CF8

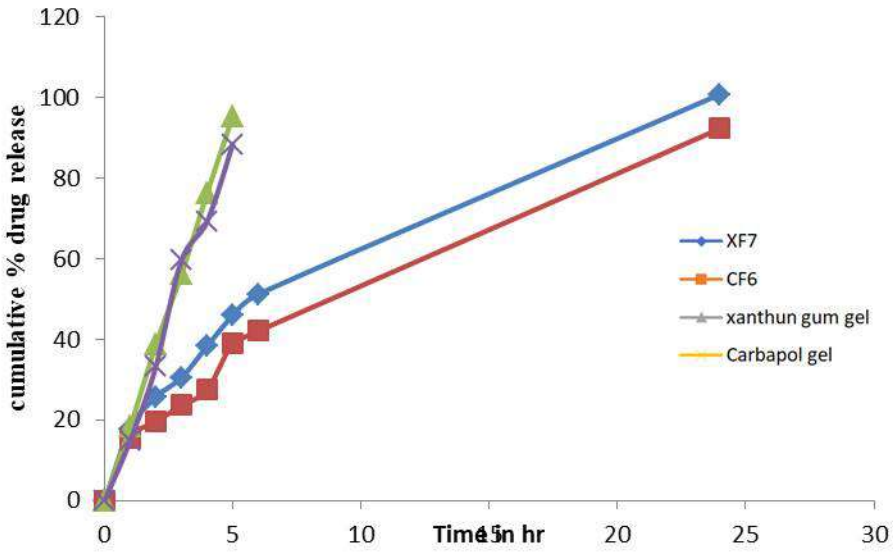

Figure 6. Drug release profiles of optimized formulations XF7 and CF6 comparison with plain gel

Conclusion

In this study, a total of 19 different batches of in situ gel formulations, with varying concentrations of Carbopol 934, xanthan gum, konjac gum, and HPMC K4M were formulated and characterized for visual appearance, clarity, pH, gelation time, mucoadhesive strength and gel strength. Formulations were optimized based on gelation time and drug release. Optimized formulations were tested for viscosity and ex vivo permeation studies and compared with plain gels. Short-term stability studies were also conducted for the optimized formulations which also proved the reliability of the prepared in situ gels. To conclude, the development of optimized in situ gelling systems for intranasal brain drug delivery presents a promising strategy for overcoming the limitations of conventional therapies. The demonstrated controlled drug release, prolonged residence time on the nasal mucosa, and favorable stability profiles of these formulations suggest their potential to enhance drug transport to the brain. By bypassing the blood-brain barrier and minimizing systemic exposure, this approach offers a non-invasive and efficient method for treating various neurological disorders like depression. Further, in vivo studies and clinical trials are warranted to validate the efficacy and safety of these in situ gels, paving the way for their translation into effective therapeutic interventions for patients suffering from brain abnormalities.

Acknowledgement

I would like to thank Asphar Research labs Pvt. Limited for providing the gift sample of the drug. The authors are grateful to the principal and management of Sri Venkateshwara College of Pharmacy, Madhapur, for providing necessary facilities to carry out research work.

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