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Original Article

Formulation and Characterization of Paroxetine Hydrochloride Nasal Gel: An Innovative Approach

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ABSTRACT

Background: Serotonin Reuptake Inhibitors (SSRIs) like paroxetine are selective. It is used to treat several illnesses, such as premenstrual dysphoric disorder, post-traumatic stress disorder, obsessive-compulsive disorder, social anxiety disorder, severe depressive disorder and panic disorder. Intranasal medications travel straight to the brain through the olfactory and trigeminal nerves bypassing the blood-brain barrier. As a result, the drug's high concentration reaches the intended location with less systemic exposure and related adverse effects. Paroxetine hydrochloride is formulated as a nasal gel for the treatment of depression. **Materials and Methods:** Paroxetine hydrochloride nasal gel was prepared using HPMC K100M, Guar gum and Carbopol 934. Both formulations were developed using the dispersion method. The prepared nasal gels were assessed for physical appearance, pH, viscosity and stability. Drug release from the formulations was determined using an *in vitro* diffusion experiment. **Results and Discussion:** Both formulations showed satisfactory physical characteristics concerning color, clarity, texture and consistency. pH of the Formulations was 5.8 (F1) and 5.4 (F4) which is under the limits of pH of nasal mucosa i.e. 5.5-6.5 making it non-irritant to the nasal cavity. The viscosity of the formulations was found to be 250 cP (F1) and 215 cP (F4). The spreadability of both formulations showed satisfactory results. The percentage of drug diffused was 91.87% (F1) and 94.37% (F4) in 5 hr. Both formulations were found to be stable when subjected to freeze-thaw cycling. **Conclusion:** Nasal gels prepared using HPMC K100M and Carbopol 934 are a suitable dosage form for administration of paroxetine hydrochloride.

Keywords: Blood-brain barrier, First pass metabolism, *In vitro* diffusion studies, Nasal gel, Paroxetine HCl.

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INTRODUCTION

A psychological disorder called depression is typified by a loss of interest and a continuous sense of despair. There are five primary categories of depressive disorders: major depressive disorder, premenstrual dysphoric disorder, persistent depressive disorder (dysthymia), disruptive mood dysregulation disorder and depressive disorder brought on by another illness. Sorrow, emptiness, or angry mood are typical traits of all depressive disorders. These are followed by physical and cognitive changes that substantially impact an individual's ability to operate (Chand and Arif, 2024; Salik and Marwaha, 2022; Singh *et al*., 2023). Mild Medication and psychotherapy are both effective treatments for depression. Moderate to severe depression may require therapy that involves both medicine and psychotherapy (Ormel *et al*., 2019). Psychotropic medications called antidepressants come in a wide variety of dosages. They are used to treat mental health conditions like obsessive-compulsive disorder, clinical depression, anxiety disorders like panic, post-traumatic stress disorder and social and major phobias. Table 1 below includes several antidepressant types, dosages and modes of action. Second-generation, first-line antidepressants called Selective Serotonin Reuptake Inhibitors (SSRIs) are used to treat severe depression.

The oral bioavailability of several antidepressants is limited due to the Blood-Brain Barrier (BBB). BBB which is otherwise a protective layer of the brain acts as a barrier to the entry of therapeutic agents. There is a need to develop alternate routes of administration for brain targeting to treat central nervous system disorders. The nasal route of administration is being developed as an alternate route for delivering therapeutic agents to the brain.

Premenstrual dysphoria, vasomotor symptoms of menopause, social phobia, generalized anxiety disorder, panic disorder, Obsessive-Compulsive Disorder (OCD), depression and other

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significant disorders are treated with paroxetine hydrochloride, a selective serotonin reuptake inhibitor. It usually comes in 10 mg, 20 mg, 30 mg and 40 mg immediate-release tablets. Additionally, it is offered as an extended-release oral tablet in 12.5 mg, 25 mg and 37.5 mg. This medication uniquely inhibits serotonin reuptake with great potency and selectivity while not affecting other neurotransmitters. The serotonin reuptake is more strongly inhibited by this medicine than by others in the same class. When it comes to adrenergic receptors (alpha-1, alpha-2 and β-adrenergic), dopamine receptors (D1 and D2), histamine receptors (H1) and serotonin receptors (5-HT1A, 5-HT2A and 5-HT2C), paroxetine has a low affinity. This medicine has a moderate affinity for 5-HT2B and muscarinic cholinergic receptors. The delayed beginning of paroxetine therapeutic benefits may be explained by the early actions of the drug on the 5-HT neurons. Absorption of paroxetine from the gastrointestinal system is easy. Its first-pass metabolism results in a bioavailability of 30-60% (ACP, 2009).

Parenteral, transdermal, or nasal medication can be administered to prevent hepatic metabolism. However, patients find the parenteral method of medicine delivery uncomfortable. A penetration enhancement approach is usually necessary for transdermal medication delivery to achieve the appropriate levels in the plasma. Most drugs cannot pass across the Blood-Brain Barrier (BBB), a highly selective semipermeable membrane made of endothelial cells, to the central nervous system. Drugs with high molecular weight and hydrophilicity cannot pass the blood-brain barrier (https://en.wikipedia.org/wiki/Paroxetine; https://go.drugbank.com/drugs/DB00715). Direct nasal delivery of a drug can improve its effectiveness in treating psychological conditions compared to tablet-based oral formulations. The nasal epithelium consists of a layer of cells with high permeability. The nose's vast surface area and microvilli increase medication absorption, potentially leading to a faster beginning of effect. Furthermore, the sub-epithelial layer is highly vascularized, allowing venous blood from the nose to bypass first-pass metabolism in the liver. Nasal administration reduces acid and intestinal enzyme disintegration (Yeonoh *et al.*, 2018). The olfactory and trigeminal nerves allow medications to enter the brain intranasally, avoiding the blood-brain barrier (Hetal *et al.*, 2021). In addition to lowering systemic exposure, this allows the drug's high concentration to reach the intended site, perhaps improving the start of action and lowering the dosage and related side effects. Although there are potential advantages for nasal drug administration, there are limitations, such as nasal mucociliary clearance. It works as a protective mechanism protecting the nasal cavity against external elements such as germs and viruses. Using polymeric gels may increase the residence time by minimizing the clearance rate. Increasing the time, a medicine spends in the nasal cavity can improve absorption and uptake, resulting in longer-lasting therapeutic benefits. As a centrally-acting medication, paroxetine is a good agent for intranasal delivery (Serlin *et al.*, 2015).

MATERIALS AND METHODS

Materials

Paroxetine hydrochloride, the active pharmaceutical ingredient was acquired as a gift sample from Simson Pharma; Methanol which was used as a solvent acquired from Fine Chemicals Co. Ltd. Mannitol, which acts as a humectant; propyl paraben, a preservative; Polyethylene Glycol (PEG); guar gum, HPMC K100M, Carbopol 934, used as polymers, were acquired from Yarrow Chem. Triethanolamine, used as pH adjusting agent was acquired from Finar.

Preparation of Paroxetine Hydrochloride Nasal Gel using HPMC K100M and Guar Gum

Paroxetine hydrochloride nasal gel was formulated using the dispersion method (Tajes *et al.*, 2014). Before adding 10 mL of distilled water, the 150 mg of the medication was dissolved in 2.5 mL of methanol because paroxetine is insoluble in water. The mixture was continuously stirred. To the above drug solution, 140 mg of mannitol, 1.25 mL of PEG and 10 mg of propyl paraben were added. To the above solution, 150 mg of guar gum which acts as a binding agent and thickening agent and 200 mg of HPMC K100M which acts as a film-forming agent, thickener, blocker and sustained-release agent, were added along with 10 mL of distilled water. The above resultant mixture was stirred for 15 min with constant stirring on a magnetic stirrer. The above formulation was evaluated by performing various evaluation tests (Omidi and Barar, 2012).

The nasal gel's dosage was determined using Natesto™ Testosterone Nasal Gel as a guide. It can be taken twice or thrice daily (5.5 mg per nostril, 11.0 mg single dose) with a multiple-dosage dispenser (Rogol *et al.*, 2015). Figure 1 demonstrates the usage of metered dose pump.

Preparation of Paroxetine Hydrochloride Nasal Gel using Carbopol 934

Carbopol 934 was used in different concentrations of 0.5, 1.0 and 1.5% w/w for the preparation of gels. Carbopol was soaked in a known amount of distilled water for 2 h. Propyl paraben was added to the medication solution after the drug had been dissolved in methanol and 5 mL of distilled water. Carbopol when reacts with alcohol reduces its pH and becomes liquid, so to obtain the required consistency the solution is neutralized using Triethanolamine. The drug solution was added to the Carbopol gel with continuous agitation and 2-3 drops of triethanolamine addition which acts as a neutralizing agent will increase the pH which results in the formation of emulsion and activates the gelling effect of the Carbopol (Tai *et al.*, 2022; https://thepharmapedia.com/methods-of-preparation-of-pharmaceutical-gels/

pharmacy-notes; Sherafudeen and Vasantha, 2015; Kisan *et al.*, 2007). Table 2 illustrates the composition of nasal gels using paroxetine hydrochloride.

Evaluation of Nasal Gels

Physical appearance

These tests typically involve evaluating the gel's visual characteristics and physical properties. The prepared formulations were inspected for their color, clarity, homogeneity, texture, consistency and odor. The color of the prepared gels was observed under natural light by placing them against the black and white background. The ambiguity of the gels was done by visual examination under a black-and-white background. Homogeneity of the gels was ensured without any phase separation or lumps. It should have a smooth and consistent texture. After applying the gel preparations to a piece of glass or another appropriate transparent material, a homogeneity test is conducted to determine the preparation's homogeneity. The gel's texture was assessed by spreading a small amount on a clean surface. It should feel smooth and free from grit or particulate matter. Gel's consistency was evaluated by observing how it behaves when a

Table 1: Different classes of antidepressants.

Class	Drug	Brand name	Dose	Mechanism of action
Selective Serotonin Reuptake Inhibitors (SSRIs).	Fluoxetine	Prozac	Immediate-release (20 mg)Delayed-release capsule (90 mg)Capsule (10 mg, 20 mg, 40 mg)tablet (10 mg, 20 mg, 60 mg).	Inhibition of the reuptake of serotonin, thereby increasing the serotonin activity.
	Paroxetine	Paxil	Immediate release tablets (10 mg-40 mg); Extended release tablets (12.5 mg, 25 mg, 37.5 mg).	
	Sertraline	Zoloft	Tablet (25 mg, 50 mg, 100 mg); Capsule (150 mg, 200 mg); Oral concentrate (20 mg/mL).	
	Citalopram	Celexa	Tablet (10 mg, 20 mg, 40 mg); Capsule (30 mg); Oral solution (10 mg/5 mL).	
	Escitalopram	Lexapro	10 mg -20 mg	
Serotonin-norepinephrine reuptake inhibitors	Venlafaxine	Cymbalta	Capsule, extended-release (150 mg, 37.5 mg; 75 mg); Tablet (100 mg, 25 mg, 37.5 mg, 50 mg, 75 mg); Tablet, extended-release (112.5 mg, 150 mg, 225 m; 37.5 mg, 75 mg).	They ease depression by affecting neurotransmitters used to communicate between brain cells.
	Duloxetine	Pristiq	Delayed release capsule (20 mg; 30 mg; 40 mg; 60 mg).	
	Desvenlafaxine	Elavil	Tablet, extended-release (as a base 100 mg, 50 mg); (as succinate 25 mg, 50 mg, 100 mg).	
Tricyclic Antidepressant	Amitriptyline	Norpramine	Tablets (10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg).	They function by inhibiting serotonin and norepinephrine reuptake within the presynaptic terminals, resulting in increased levels of norepinephrine and serotonin in the synapse.
	Desipramine	Nardil	Tablet (10 mg, 25 mg, 50 mg, 75 mg 100 mg; 150 mg).	
Monoamine oxidase inhibitors	Phenelzine	Spravato	Tablet (15 mg).	MAOIs are a class of drugs that inhibit the activity of one or both monoamine oxidase enzymes: MAO-A and MAO-B
N-Methyl D-Aspartate antagonists	Eskatamine		Nasal dosage form 84 mg 2 times per week for 4 weeks.	Competitive NMDA antagonists bind directly to the glutamate site of the NMDA receptor to inhibit the action of glutamate.

small amount is taken between fingers or applied to a surface. It should be neither too runny nor too stiff. Smell the gel to check for any unusual or unpleasant odor. Depending on the formulation, the gel should have a neutral or mildly pleasant fragrance (Romeo *et al.*, 1998).

Determination of pH

A 10 mL volumetric flask was filled with 1 mL of the produced gel formulations and distilled water was added to dilute the mixture. A digital pH meter previously calibrated using a phosphate buffer at pH 4 and pH 7 was used to measure the pH of the resultant solution (Shinde *et al.*, 2008).

Viscosity determination

A Brookfield viscometer DV-E with an S64 spindle (Brookfield Engineering Laboratories Inc., MA, USA) was used to measure the viscosities of the produced gels. After transferring the gel to a 100 mL beaker and letting it sit at room temperature, the rheometer was run at 50 rpm with a 64 No. spindle. At 50 rpm, the spindle was dropped into the gel perpendicularly. The viscosities of the formulations were determined (Soliman and Abdou, 2010).

Spreadability

Spread ability is an important characteristic of nasal gels, as it affects the application and distribution of the gel on the nasal mucosa. Between two glass plates was a tiny amount of the sample. The gel was evenly pressed between the two plates using a 100 g weight on the upper plate, creating a thin layer. When the weight was removed, the force of the weight attached to the upper plate allowed it to slide freely. A stopwatch was used to measure how long it took for the gel to completely cover the whole length of the plate. For evaluating and measuring the capacity to disseminate semisolid preparations, the parallel plate method is most frequently used (Shubham *et al.*, 2023). The spreadability can be calculated using the formula:

$$S = m \times L / T$$

Where, S=spread ability, m=weight applied (in g), L=diameter of the gel spread (in cm), T=time taken (in sec).

In vitro diffusion studies

Disintegration tube was used to conduct *in vitro* release test for the manufactured formulation to examine drug penetration and the quantity of drug diffused from the formulation at specific time intervals. In the donor compartment, a weighed amount of gel formulation (2.5 g) was taken. After 2 h. of soaking in the receptor medium, the artificial dialysis membrane (molecular weight 12,000-14,000) was positioned between the donor and receptor compartments. The phosphate buffer (pH 7.4) was put into the receptor compartment. Additionally, any air bubbles were eliminated by tilting the tube. The temperature was kept at 37±2°C and the receptor compartment was stirred at 500 rpm using a magnetic bead. The study lasted for 5 h. At predefined intervals (15, 30, 45, 60, 90, 120, 180, 240 and 300 min), samples were removed from the receptor compartment and to maintain sink condition, an equivalent volume of buffer was added. UV spectroscopy at 293 nm was used to measure the drug absorption in comparison to a blank (Julie *et al.*, 2018).

Studies using Fourier Transform Infrared Spectroscopy (FTIR)

To create an efficient, stable and optimized dosage form that makes administration simple, enhances drug release and bioavailability and guards against degradation, it is crucial to choose the excipients carefully. The investigation of medication and excipient compatibility is crucial. The formulations, F1 and F4 containing drug and every potential excipient that could be utilized in formulation was prepared to conduct the drug-excipient compatibility investigation. Using an FTIR spectrophotometer, the FTIR spectra of the drug and excipients were acquired in order to determine the compatibility of the drug with specific polymers (Paul *et al.*, 2017).

Table 2: Formulation of Paroxetine hydrochloride nasal gels.

Ingredients	F1	F2	F3	F4	F5
Paroxetine hydrochloride (mg)	150	150	150	150	150
Gelling agent	HPMC K100M 200 mg Guar gum 150 mg	HPMC K100M 150 Guar gum 200 mg	Carbopol 934 0.5% w/w	Carbopol 934 1% w/w	Carbopol 934 1.5% w/w
Methanol (mL)	2.5	2.5	2.5	2.5	2.5
Propyl paraben (mg)	10	10	10	10	10
Mannitol (mg)	140	140	-	-	-
PEG (mL)	1.25	1.25	-	-	-
Triethanolamine	-	-	2-3 drops	2-3 drops	2-3 drops

Freeze-thaw cycling

The prepared sample underwent a freeze-thaw cycle, with the test being conducted over 12 days in 6 cycles, with the substance remaining at a specific temperature for 24 h. in each cycle. The temperature was between 5±2°C and 40±2°C (Dantas *et al.*, 2016). The formulations were evaluated for physical appearance and pH after the completion of freeze-thaw cycles.

RESULTS

Physical Appearance

Both the formulations were evaluated for their physical appearance against a white and black background, gel F1 was clear colorless to pale white color with a smooth consistency exhibited a pleasant odor and a natural consistency neither too runny nor too stiff and texture as any standard gel formulation and is devoid of any particulate matter and showed no phase separation properties when it is evaluated under transparent glass material. Formulations F2 and F3 have pouring consistency and are not transparent. Carbopol gel [F4] was white with a little characteristic odor had the same consistency as any gel and exhibited the same properties as F1. Formulation F5 showed the separation of the drug from the gel after the addition of triethanolamine. Thereby, further evaluation tests were carried out for formulations F1 and F4. Various nasal gel compositions are depicted in Figure 2.

Determination of pH

The pH of the formulations F1 and F4 was 5.8 and 5.4 respectively when determined using a digital pH meter. It is within the limits of the prepared standard formulation of any nasal delivery system. It is also under the limits of pH of nasal mucosa i.e. 5.5-6.5 so it is non-irritant to the mucous of the nose which makes it favorable for the formulation of nasal gels.

Viscosity Determination

The viscosity of the gel was determined using a Brookfield viscometer and the viscosity was found to be 250 cP (F1) and 215 cP (F4) and it is within the limits of standard values of viscosity of any gel formulation.

Spreadability

The spreadability is an important criterion for uniformity and ease of application of topical preparations. The spreadability of creams and gels is measured in terms of the average diameter of the spread circle. The spreadability of the given F1 and F4 formulation were 9.61 g.cm/s and 9.09 g.cm/s respectively.

In vitro Diffusion Studies

The *in vitro* release properties of formulations are assessed in this work using an artificial dialysis membrane. According to the results, F4 exhibits greater diffusion than F1 shown in Figure 3. Drug permeability was calculated to study the permeability of the gel prepared through the membrane. Permeability can be calculated by, P = slope/AC, where, A=area of the membrane, C=concentration. Flux (J) is given by, $J = PC$. The permeability of gel containing Carbopol is 0.0046 cm/hr and the flux is 0.0124 µg/cm^2. hr. The permeability of gel containing HPMC is 0.0039 cm/hr and the flux is 0.0124 µg/cm^2. hr.

FTIR

The FTIR results have shown that the spectrum of Paroxetine hydrochloride characteristic bands at 3333.50 shows N-H stretching and at bands 1609.51 shows C=C stretching. The peaks obtained in the spectra of Paroxetine Hydrochloride formulation with Carbopol, at 3344.18 can be attributed to N-H stretching, which is slightly shifted but still present. The other peak, located at 1636.10 indicates C=C stretching vibration with no significant interaction. The peaks obtained in the spectra of Paroxetine Hydrochloride formulation with HPMC K100M+Guar gum, at

Figure 1: Metered-dose pump.

3337.01 can be attributed to N-H stretching, which is slightly shifted but still present. The other peak, located at 1638.22 indicates C=C stretching vibration with no significant interaction. When the FTIR spectra of pure paroxetine hydrochloride and its formulation with Carbopol 934 and HPMC K100M+guar gum is compared, the drug's distinctive peaks have not changed much. The small changes seen are typical of any formulation process and do not point to a meaningful interaction. Consequently, the conclusion that there is no meaningful interaction between paroxetine hydrochloride and Carbopol, HPMC K100M+Guar gum is supported by the FTIR results. FTIR of the pure medication paroxetine hydrochloride, F1 and F4, is displayed in Figure 4.

Freeze-thaw Cycling

No significant change in physical appearance and pH was observed in both the formulations after exposure to freeze-thaw cycling.

DISCUSSION

The nasal route of administration of centrally-acting drugs increases their therapeutic efficacy as the nasal cavity is connected directly to the brain through trigeminal nerves, olfactory nerves, the lymphatic system and cerebrospinal fluid. This route decreases adverse effects as only a small amount of drug enters into systemic circulation. Another added advantage is the non-invasiveness of this route of administration. However, the nasal route of administration suffers from limitations of enzymatic degradation, poor permeability and Nasal Mucociliary Clearance (NMCC). NMCC being the most predominant limitation, due to its protective function, is responsible for decreasing the residence time of the drug. Gels, with sufficient viscosity, good drug loading and biocompatibility, are widely used (Miao *et al.*, 2024).

pH of both the formulations was in the range of nasal fluids. The gels prepared with HPMC (F1) and Carbopol (F4) showed good spreadability in less time. The value of spreadability indicates

Figure 2: Different formulations of nasal gel.

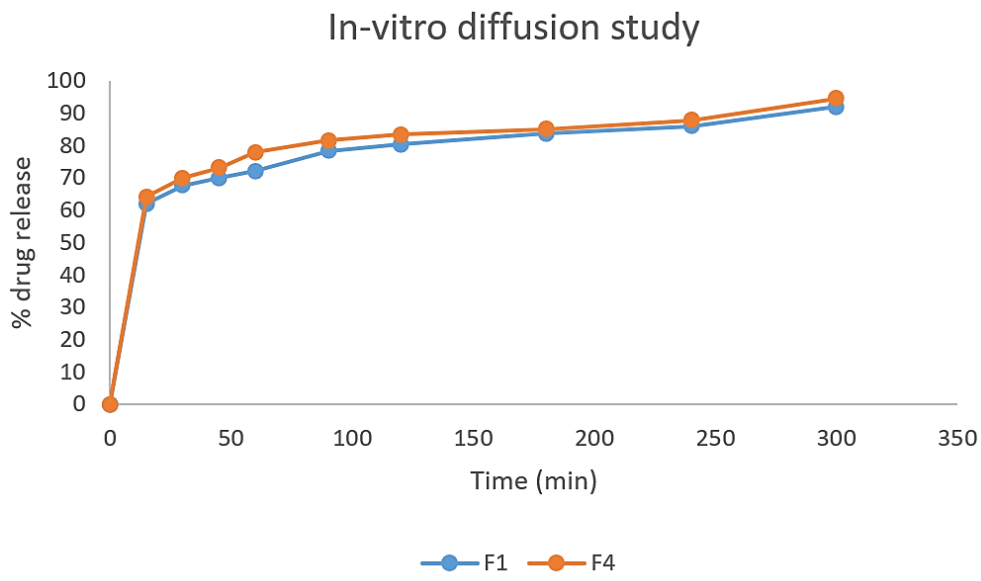

Figure 3: *In vitro* diffusion study.

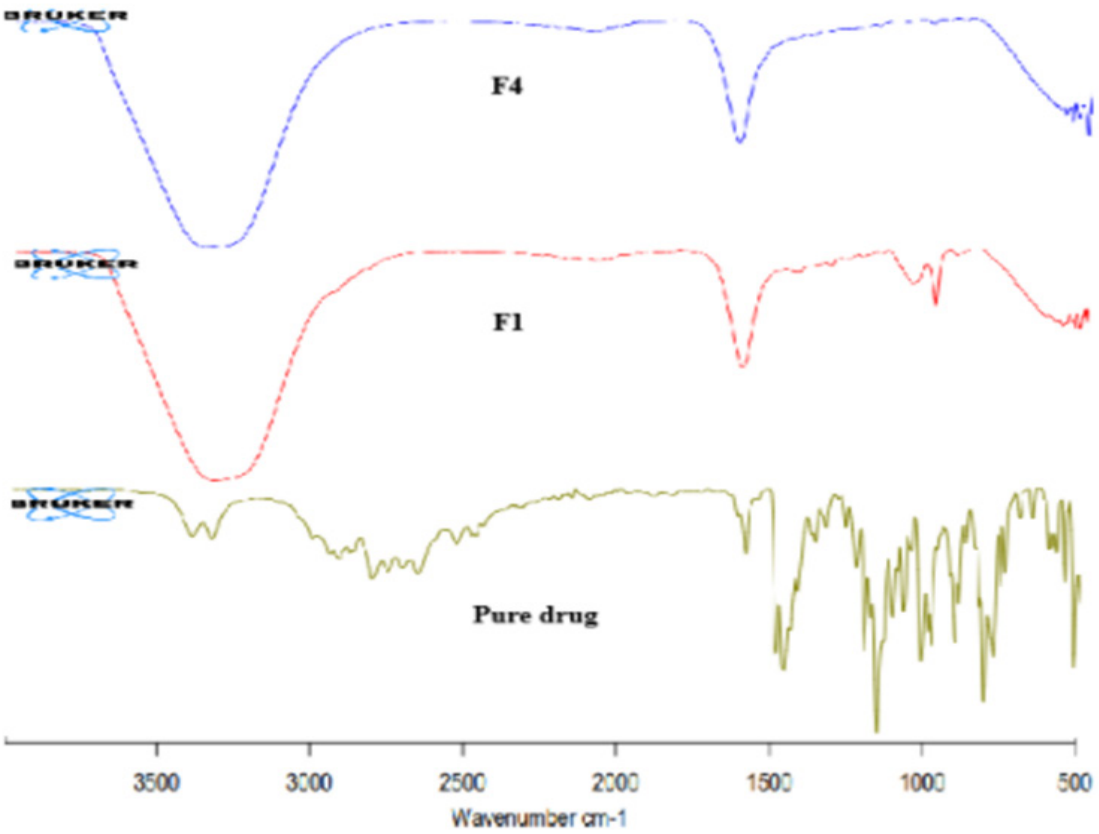

Figure 4: FTIR of Paroxetine hydrochloride pure drug, F1 and F4.

that the gel is easily spreadable by a small amount of shear. The FTIR studies indicated the absence of interaction between the drug and the polymers. The formulations were found to be stable after freeze-thaw cycling studies. The drug release from the gel is influenced by polymer content. The drug is entrapped in polymer cells and is surrounded by other polymer molecules which influence the diffusional resistance. The density of the chain structure influences the movement area of the drug. The drug release is inversely related to the viscosity of the formulation which affects the diffusion of particles. Formulation F1 has a viscosity of 250 cP and percentage drug release in 5 h is 91.87 and the permeability is 0.0039 cm/h. Formulation F4 has a viscosity of 215 cP and percentage drug release in 5 h. is 94.37 and the permeability is 0.0046 cm/h. Viscosity-imparting polymers are necessary for nasal formulations to overcome the limitation of drainage. However, a high increase in viscosity is not advisable as it causes drug delivery issues. Thereby, formulations with optimum viscosity were desirable for nasal delivery (Tas *et al.*, 2006).

CONCLUSION

Paroxetine hydrochloride was selected as the model drug for the preparation of nasal gel formulation. In this present study, paroxetine hydrochloride nasal gel containing different polymers was evaluated. F4 formulation, which is the Carbopol-based nasal gel, exhibited superior *in vitro* diffusion results, demonstrating effective drug release performance. Despite its less favorable physical appearance and characteristic odor compared to the HPMC K100 M-based gel, the Carbopol 934-based gel excels in delivering the drug efficiently. On the other hand, the HPMC-based nasal gel was noted for its better organoleptic properties, including a more pleasant appearance, odor and consistency. Therefore, the choice of formulation depends on the desired outcome: F4 for optimal drug release. The required amount of drug must be administered 2 times a day each consisting of 2 actuations.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

SSRIs: Serotonin Reuptake Inhibitors; **BBB:** Blood-Brain Barrier; **OCD:** Obsessive-Compulsive Disorder; **FTIR:** Fourier Transform Infrared Spectroscopy.

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