



Formulation And Characterization Of Venlafaxine As Mucoadhesive Gel Based Intranasal Drug Delivery System

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ABSTRACT :

The objective of the investigation was to improve the bioavailability of venlafaxine by formulating it as in situ intranasal gel delivery system thereby bettering the management of depression. The in situ intranasal gel delivery system loaded with venlafaxine was prepared using cold stirring method and evaluated for various parameter. The identity of the drug sample was confirmed by observing its organoleptic characters, melting point, solubility profile and FT-IR spectroscopy. The drug-excipient interaction was studied using FT-IR spectroscopy and no incompatibility was found between venlafaxine and the polymers (poloxamer 407 and carbopol 934). The pH of all the formulations was found to be from 6.1 to 6.2; viscosity of the sol formulation ranged between 31 to 81 cps whereas that of the in situ gel ranged from 112 to 205 cps. The drug content ranged from 91.5 to 95.8 %. The in vitro release studies of different formulations of drug loaded in situ gels were carried out for 20 min in PBS pH 6.8. The maximum drug release from the formulations ranged from 76.9 to 100.1 % over the duration of in vitro release study.

Keywords: Poloxamer, carpool, intranasal gel, venlafaxine, depression

Introduction:

Gel formulations with suitable rheological properties increase the contact time with the mucosa at the site of absorption. The increased contact time is caused by the mucoadhesive properties of the polymer in the gel and by the rheological properties of the formulation reducing the clearance by the nasal and ocular protective mechanisms [1-3]. Liquid nasal sprays are useful dosage forms for local and systemic delivery but often suffer from poor retention, dripping out of the nose or down the back of the throat, which leads to reduced bioavailability [4]. A way to address this problem is by formulating nasal sprays that contain polymers that are mucoadhesive.

Venlafaxine is an antidepressant and a serotonin and norepinephrine reuptake inhibitor (SNRI). Its active metabolite, desvenlafaxine, works by blocking the reuptake of serotonin and norepinephrine, which are key neurotransmitters in mood regulation. Venlafaxine is officially approved to treat major depressive disorder (MDD), generalized anxiety disorder (GAD), social anxiety disorder, and panic disorder in adults [5]. Venlafaxine hydrochloride is widely used for the treatment of CNS disorders but it undergoes rapid metabolism and has an oral bioavailability of 14%. Particulate drug carrier systems administered through nasal mucosa may protect the drug from enzymatic degradation, increase the drug dissolution rate, intensify the contact of the formulation with the mucosa, enhance the uptake by the epithelium, and act as a controlled release system resulting in prolonged blood concentrations [6-10]. It was therefore hypothesized that utilizing the intranasal mucoadhesive route for delivery of Venlafaxine may be able to overcome the rapid metabolism and increase the bioavailability of the drug.

Material and Methods

Preformulation Studies [11]

The preformulation studies were carried out for confirming the identity of the drug and to ascertain the compatibility amongst the drug and the excipient (polymers) used in formulation.

Calibration Curve in phosphate buffer pH 6.8

Accurately weighed 10 mg of venlafaxine was taken in 10 mL volumetric flask and dissolved in water to the mark resulting in a stock solution of 1000 µg/mL. 1 mL of the above stock solution was taken in another 10 mL volumetric and volume was made up with phosphate buffer pH 6.8 to mark resulting in a solution of 100 µg/mL. Aliquots of 1-6 mL of stock solution were taken into a series of 10 mL volumetric flask and volume was made up to the mark using phosphate buffer pH 6.8 and were analyzed at 225 nm using UV spectrophotometer. A standard curve was constructed against absorbance and concentration [12].

Determination of gelation temperature

Temperature at which the liquid (sol) phase converts to gel form is termed as gelation temperature. The sol–gel transition temperature of the prepared *in-situ* gel formulations was determined by visual inspection method [13]. Briefly, the solutions of poloxamer 407 in the concentrations (15–20 % w/v) were prepared by stirring on a magnetic stirrer in a transparent 10 ml glass bottle sealed with paraffin. The vial was heated at constant rate with an increment of 1°C and the temperature at which the magnetic bead stopped moving due to gelation was considered as gelation temperature. Gels which showed gelation temperature very close to nasal temperature (32–34°C) were selected for further evaluation. Effect of Carbopol 934 on phase transition temperature was evaluated by dispersing different concentration (0.1–0.5 % w/v) in optimized poloxamer 407 solutions.

Formulation of *in situ* nasal gel

Poloxamer 407 gel was prepared by dissolving the optimized poloxamer 407 concentration in cold (4°C) water. The hazy solution formed was kept in refrigerator (2–4°C) overnight for complete dissolution resulting in a clear solution. Carbopol 934 (0.1 to 0.4 % w/v) concentration was added slowly to the optimized poloxamer 407 solution [14] containing drug with continuous stirring at 4°C (Table 4.1). Formulated gels were then finally stored at 4°C for further evaluation.

Table 1 Composition of intranasal gel formulations

Formulation Code	Drug (% w/v)	Poloxamer 407 (%w/v)	Carbopol 934 (%w/v)
VNS	Pure drug solution (0.5%)	--	--
VNG	0.5	18	--
VNG1	0.5	18	0.1
VNG2	0.5	18	0.2
VNG3	0.5	18	0.3
VNG4	0.5	18	0.4
VNG5	0.5	18	0.5

Evaluation of the gel formulations [15]

Determination of pH

The pH of each formulation was determined by pH meter. Initially, the pH meter was calibrated using standard buffer solutions of pH 4 and pH. 1 mL of the formulation was diluted with distilled water and the pH of the solution was recorded by dipping the electrode in the solution.

Clarity testing

The clarity was checked visually by viewing the formulation alternately against white and black background and was graded as turbid (+), clear (++) and very clear (+++).

Drug content

Drug content was determined spectrophotometrically using UV at 225 nm. 1 mL of the formulation was dissolved in 10 mL PBS 6.8 and suitably diluted. The absorbance of the resulting dilution was recorded on UV spectrophotometer.

Viscosity Determination

Viscosity of *in situ* gel system was determined using Brook field viscometer DV-1. Temperature of 37±0.5°C was maintained and the spindle was lowered perpendicularly into both *in situ* sol and gel formulations which were placed in a beaker. The viscosity of each formulation was determined by applying 100 rpm speed.

Rheological Studies

The measurement of viscosity of prepared *in situ* gel was done with Brookfield viscometer. The *in situ* formulations were rotated for 2 minutes at different speeds (10-100 rpm) for selected spindle. At each speed the corresponding dial reading was noted. The viscosity of different *in situ* gel formulations was measured at different speeds at room temperature.

Gel Strength

Gel strength was determined by placing a standard weight of 35 g onto 50 g of thermoreversible gel (placed in 100 ml beaker) maintained at gelation temperature using controlled water bath. The time in seconds by the weight to penetrate 5 cm deep into the container was recorded as gel strength.

In-vitro drug release study

Drug release from gel was determined by using Franz diffusion cell. Artificial dialysis membranes were soaked in receptor medium for 2h prior to use. Phosphate buffer saline (12 ml) pH 6.4 was added into the receptor chamber maintained at $34 \pm 1^\circ\text{C}$. Gel equivalent to 2.5 mg of drug was placed into donor compartment and the setup was kept on stirring. Aliquots of 1ml were withdrawn at predetermined time intervals from receptor compartment and replaced with fresh buffer till 12 h. The samples were diluted suitably and analyzed spectrophotometrically at 225 nm and the amount of drug released was determined using calibration curve.

Stability Study

Stability studies of the formulations were carried out at $40 \pm 2^\circ\text{C}$, $75 \pm 5\%$ RH at an interval of one month for 3 consecutive months. The results were compared with respect to gelation temperature, pH, viscosity, drug content and drug release to indicate stability for optimized formulation [16].

In-vitro mucoadhesion wash-off test

Mucoadhesive property of gel was determined by *in-vitro* adhesion test. Eggshell membrane was used for this purpose. A 2x1 cm piece of eggshell membrane were taken and fixed on a glass slide (kept at an angle of 45°C). About 100 mg intranasal gel were spread on rinsed, tissue specimen and hung onto one of the grooves of a USP tablet disintegrating test apparatus containing 6.8 pH phosphate buffer. The disintegrating test apparatus was started, the tissue specimen showed regular up and down movements in a beaker. The time required for detaching of microspheres from mucosal surface membrane was recorded by visual inspection [17].

Results and Discussion

The procured venlafaxine was white, odourless crystalline powder with melting point of $217\text{-}218^\circ\text{C}$, soluble in water and ethanol. The linear regression analysis for the calibration curve was $\text{Abs} = 0.057(\text{concentration}) - 0.004$ with a regression coefficient of 0.999.

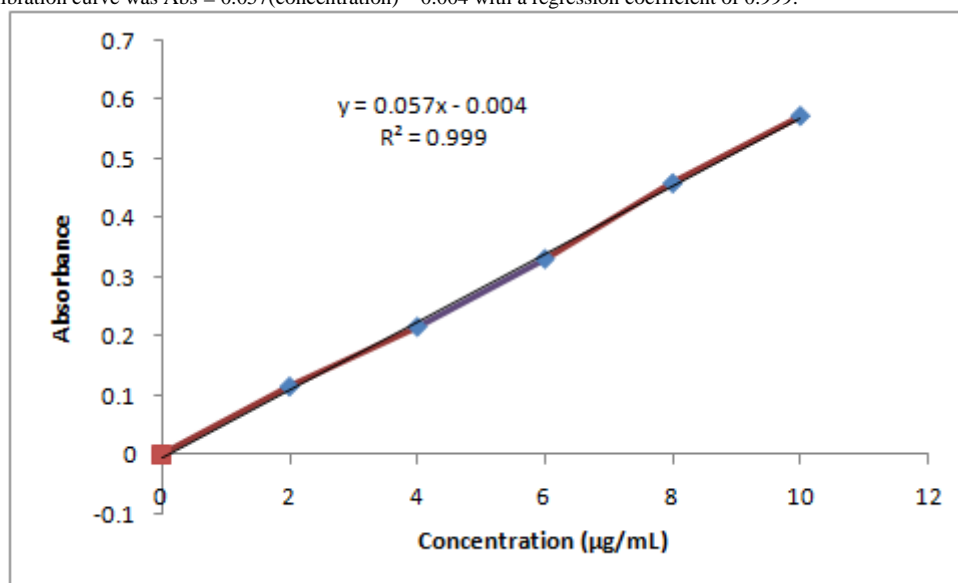


Figure 1 Calibration curve of venlafaxine

Determination of gelation temperature

Phase transition temperature determination is a preliminary step in the formulation of the *in situ* gel. Gelation temperature of gel formulations is shown in Table 2 which suggests that Poloxamer in the concentration of 18% w/v showed best results for phase transition at 32-34°C. As the concentration of poloxamer increased from 18 to 20 %, transition temperature decreased from 34 to 25 °C.

Table 2 Gelation temperature of Poloxamer 407

S.No.	Poloxamer 407 (%w/v)	Gelation Temperature (°C)
1	15	No gelling till 42
2	16	No gelling till 42
3	17	Viscous solution at 37
4	18	32-34
5	19	29-30
6	20	25-26

In situ intranasal gels must transform to gel form at nasal temperature and exist in solution form when stored at room temperature. If the gelation temperature of is lower than 25°C, a gel may be formed at room temperature whereas when the gelation temperature is higher than 34°C, solution form will not show phase transition at the nasal temperature resulting in the nasal clearance of the administered drugs at an early stage.

The addition of carbopol 934 also affected the gelation behaviour of the formulations. The effect of varying concentration of carbopol 934 on gelation temperature revealed that all the formulations were able to transform to gel form at temperature from 25-32°C. Increasing the concentration of carbopol 934 led to a decrease in gelation temperature of the formulations (Figure 2). A concentration of 0.4% and higher of carbopol 934 decreased the gelation temperature to 25°C making the concentrations unsuitable for *in situ* intranasal gel delivery.

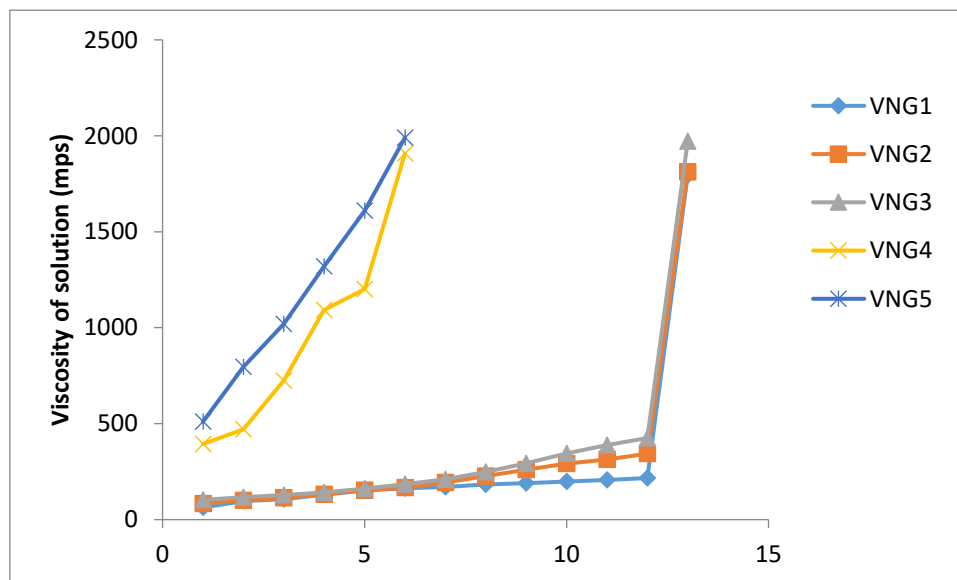


Figure 2 Effect of carbopol 934 on gelation temperature

Evaluation of the gel formulations

Physicochemical properties

The pH of all the formulations was found to be 6.1 to 6.2 lying in the range of nasal pH (5.5 to 6.5). This ascertains that all the formulations are compatible with nasal mucosa. The formulations VNG1, VNG2 and VNG3 were found to be clear while VNG4 and VNG5 were turbidity appearance revealing that

clarity of the gel is inversely proportional to the concentration of Carbopol. The results of pH, clarity, drug content, viscosity, gelling time and gel strength are presented in Table 3.

Table 3 Physicochemical properties of the *in situ* gel formulations

Formulation code	pH	Clarity	Drug content (%)	Viscosity (cps)		Gel Strength (g)	Gelling time (sec)
				Sol	Gel		
VNG1	6.1	+++	91.5	31	112	4.9	14
VNG2	6.2	++	94.4	38	124	5.6	12
VNG3	6.2	++	94.1	49	165	6.4	10
VNG4	6.1	+	95.1	60	182	7.1	8
VNG5	6.2	+	95.8	81	205	7.9	6

The most important feature for intranasal *in situ* gel is viscosity of the formulation. A formulation suitable for application to the nasal cavity should ideally have a low viscosity when applied and after administration should have a high viscosity in order to stay at the application site. All the formulations exhibited a carbopol 934 concentration dependent increase in viscosity. Viscosity of the both *in situ* sol and *in situ* gel was examined at 100 rpm. VNG5 formulation was having maximum viscosity. The viscosity of VNG3 (45 in sol to 161 in gel) was taken as optimum. Viscosity of the sol formulation ranged between 31 to 81 cps while that of the *in situ* gel ranged between 112 to 205 cps.

Rheological Studies

Rheological behaviour study is an important parameter for the *in situ* gels. The viscosity of formulations should be in an optimum range which improves its ease of administration. The flow curve (viscosity against speed/rpm) of the formulations indicated that for the all the polymer concentrations, the formulations exhibited the properties of pseudoplastic systems with shear thinning. The prepared formulations tend to thin when being exposed to shearing force and therefore tend to be easily syringeable and spreadable (Figure 3).

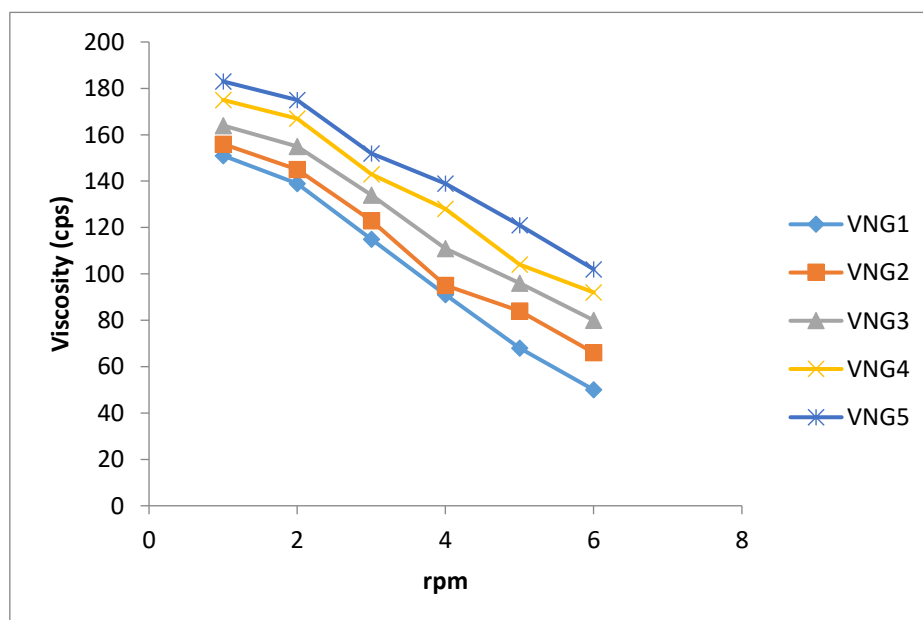


Figure 3 Rheological behaviour of *in situ* gel

In vitro drug release from in situ gel

The *in vitro* release studies of different formulations of drug loaded *in situ* gels were carried out for 20 min in PBS pH 6.8. PBS of pH6.8 was selected as medium for drug absorbance since it resembles nasal pH. Throughout the study the pH and temperature were kept constant. The maximum release was found to be for VNG2 and VNG3 with respective release of 96.6 and 94.2%. The carbopol concentration plays a key role in release pattern of drug.

The release of drug mainly depends on the polymer concentration. Polymer concentration was proportional to release to some extent. It was seen that very low concentration of carbopol 934 resulted in very quick release of the drug from the formulation making it unpleasant for administration. Also, it was observed that too high concentration of the polymer can adversely affect the *in vitro* release as in formulation VNG4 and VNG5.

The VNG3 formulation was showing highest percentage release and was regarded as the optimised formulation. The result of drug release over time has been presented in Figure 4.

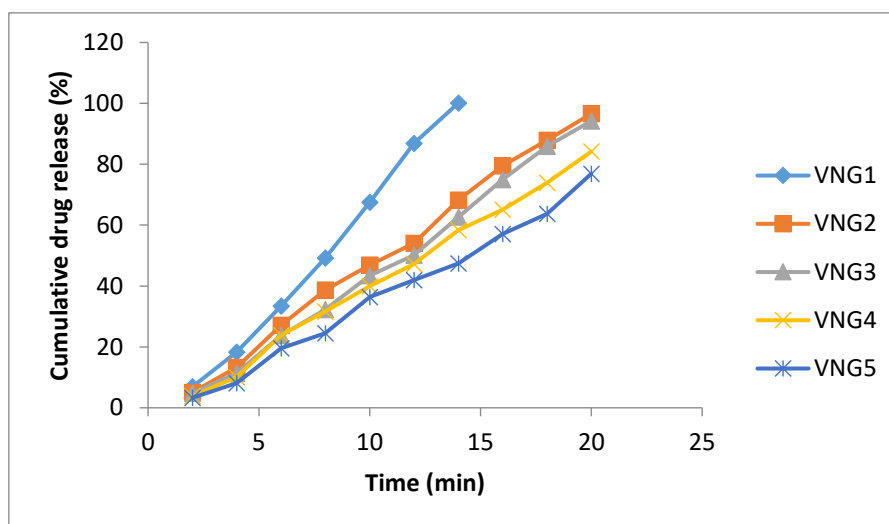


Figure 4 Comparative drug release profile from the formulations

Stability study

Stability studies (ICH guideline Q1A (R2)) of gel formulations were performed with respect to determining factors like gelation temperature, pH, viscosity, drug content and drug release. Sample analysis after 1, 2 and 3 months exhibited no significant change in all determining factors suggesting stability of gel formulations.

Mucoadhesive property of nasal gel

For the evaluation of mucoadhesion eggshell membranes were utilized as the substitute of animal mucosa. The time of mucoadhesion was from 2h 27min to 5h 51min (Table 4). The mucoadhesion increased with the higher concentrations of carbopol in the formulations.

Table 4 Mucoadhesion of the nasal gel

Formulation	Mucoadhesion time (h)
VNG1	2.27
VNG2	3.11
VNG3	5.22
VNG4	5.43
VNG5	5.51

The formulation **VNG3** had the highest mucoadhesion time and released the lowest amount of drug at the end of 12th hour suggesting that it could be able to achieve the highest sustained release. This makes formulation **VNG3** the most desirable formulation of venlafaxine for intranasal delivery.

Conclusion

The present study represents formulation of *in situ* intranasal gel for venlafaxine using poloxamer 407 and carbopol 934. Formulation (VNG3) was found to be optimized due to its desirable gelation temperature, gelling time and gel strength. *In-vitro* release studies suggests that carbopol not only acts as mucoadhesive agent but also as a penetration enhancer whereas poloxamer acts as thermo-reversible polymer leading to sustained release of drug for longer time. In conclusion, intranasal gel of venlafaxine could be better alternative to existing conventional dosage form to improve drug bioavailability and patient compliance.

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