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DOI: https://doi.org/10.64388/IREV10I1-1719713

Formulation and Characterization of Nanostructured Lipid Carrier Loaded in Situ Intranasal Gel for Brain Delivery of Venlafaxine

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Abstract- ***Depression is a common neurological disorder that requires effective drug delivery to the brain for improved therapeutic outcomes. Venlafaxine, an antidepressant, exhibits limited brain availability due to extensive first-pass metabolism and the blood–brain barrier. The present study aims to formulate and characterize a venlafaxine-loaded nanostructured lipid carrier (NLC) incorporated into an in situ intranasal gel for direct nose-to-brain delivery. The NLCs are prepared using the hot homogenization–ultrasonication method and evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency, and in vitro drug release. The optimized NLC formulation is incorporated into a thermosensitive in situ gel and assessed for pH, gelation temperature, viscosity, mucoadhesive strength, and ex vivo nasal permeation. The developed formulation is expected to enhance nasal residence time, improve brain targeting, provide sustained drug release, and increase the therapeutic efficacy of venlafaxine. Therefore, the proposed NLC-loaded in situ intranasal gel represents a promising and non-invasive strategy for efficient brain delivery of venlafaxine.***

Keywords- ***Venlafaxine, Nanostructured Lipid Carrier, In Situ Gel, Intranasal Delivery, Brain Targeting, Mucoadhesion.***

I. INTRODUCTION

Depression is one of the most prevalent mental health disorders worldwide and is characterized by persistent sadness, loss of interest, impaired cognitive function, and reduced quality of life. According to the World Health Organization (WHO), depression affects millions of people globally and is a leading cause of disability. Effective management of depression requires maintaining adequate concentrations of antidepressant drugs in the central nervous system (CNS). However, conventional oral administration of antidepressants often results in delayed onset of action, extensive first-pass metabolism, systemic side effects, and limited drug transport across the blood–brain barrier (BBB), which significantly reduces therapeutic efficacy.

Venlafaxine is a serotonin–norepinephrine reuptake inhibitor (SNRI) widely prescribed for the treatment of major depressive disorder, generalized anxiety disorder, panic disorder, and social anxiety disorder. Although venlafaxine is effective, its oral bioavailability is affected by hepatic first-pass metabolism, and only a limited amount of the drug reaches the brain due to the restrictive nature of the BBB. Therefore, the development of an alternative drug delivery system capable of directly transporting venlafaxine to the brain has become an important area of pharmaceutical research.

Intranasal drug delivery has emerged as a promising non-invasive approach for brain targeting because it allows drugs to bypass the BBB through the olfactory and trigeminal nerve pathways. This route provides rapid drug absorption, avoids hepatic first-pass metabolism, reduces systemic exposure, and enhances drug bioavailability in the brain. However, the nasal cavity possesses physiological barriers such as mucociliary clearance and limited residence time, which can reduce drug absorption. To overcome these limitations, in situ gelling systems have been developed. These formulations remain in a liquid state during administration and undergo gelation upon contact with nasal physiological conditions, thereby increasing residence time and improving drug absorption.

Nanostructured lipid carriers (NLCs) are second-generation lipid-based nanocarriers composed of a mixture of solid and liquid lipids stabilized by suitable surfactants. Compared with solid lipid nanoparticles, NLCs provide higher drug-loading capacity, improved

stability, controlled drug release, and enhanced penetration across biological membranes. Their nanoscale particle size facilitates close interaction with the nasal mucosa and promotes efficient transport of the encapsulated drug to the brain. Furthermore, the lipidic nature of NLCs improves the solubility of poorly water-soluble drugs and protects them from enzymatic degradation.

The incorporation of venlafaxine-loaded NLCs into an in situ intranasal gel combines the advantages of nanotechnology and mucoadhesive gel systems, resulting in prolonged nasal residence, sustained drug release, improved permeation, and enhanced brain targeting. Such a delivery system has the potential to reduce dosing frequency, minimize systemic adverse effects, and improve patient compliance. Therefore, the present study focuses on the formulation and characterization of a venlafaxine-loaded nanostructured lipid carrier incorporated into an in situ intranasal gel as a novel and effective strategy for direct nose-to-brain drug delivery in the management of depression.

II. MATERIALS AND METHODS

1.1. Material

The objectives of the present investigation were to prepare NLC containing venlafaxine and formulate the NLC as in situ intranasal gel; assess the formulations for the formulations for various parameters and mucoadhesion. The materials used and procedures utilized for the entire study is presented in detail in the present section

Table I.

S. N.	Item	Source
1	Distilled Water	Freshly prepared in lab
2	Venlafaxine	Yarrow Pharmaceuticals, Mumbai
3	Oleic Acid	CDH
4	PEG 600	CDH
5	Tween 20	CDH
6	Tween 80	CDH
7	Ethanol	MSG Chemicals
8	Methanol	Qualikem
9	Chloroform	SRL
10	Pluronic F127	Yarrow Pharmaceuticals
11	Stearic acid	CDH
12	Acetone	Loba Chemie
13	Sodium dihydrogen phosphate	CDH
14	Disodium hydrogen phosphate	CDH
15	Sodium hydrogen carbonate	Loba Chemie
16	Sodium chloride	Finar
17	Potassium chloride	Finar

2.2 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of the pure drug and a physical mixture of the drug and the polymers under study were obtained and observed for deletion of the characteristic peaks of the drug. The drug was dispersed in dry potassium bromide and placed in the sample holder of the instrument. The samples was scanned in the range of 400 to 4000 cm^{-1} using the FT-IR spectrophotometer.

2.3 Formulation of NLC

Stearic acid was used as the solid lipid for preparation of NLCs. Oleic acid was used as the liquid lipid and Tween 80 as the surfactant. For preparation of NLC, weighed quantity of stearic acid was melted at 80°C in a clean beaker. Separately, Oleic acid was dissolved in ethanol and Tween 80 was dissolved in deionized water (Table II). To the molten stearic acid was added oleic acid and venlafaxine (5 mg). Finally, solution of Tween 80 maintained at 80°C was added drop-wise to the lipid phase and stirred for 10 min. The mixture was then sonicated at 25°C using probe sonicator at pulse of 2 sec on and 3 sec off for 5 min.

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DOI: https://doi.org/10.64388/IREV10I1-1719713

Table II. Formulation of NLCs

Formulation	earic acid (mg)	oleic acid (mg)	Tween (%)	Drug (mg)
NLC1	50	5	10	5
NLC2	50	10	10	5
NLC3	50	15	10	5
NLC4	50	5	7.5	5
NLC5	50	10	7.5	5
NLC6	50	15	7.5	5
NLC7	50	5	5	5
NLC8	50	10	5	5
NLC9	50	15	5	5

2.4 Formulation of NLC based intranasal 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 containing drug with continuous stirring at 4°C (Table III). Formulated gels where then finally stored at 4°C for further evaluation.[71]

Table III. Composition of intranasal gel formulations

Formulation Code	NLC (% w/v)	Poloxamer 407 (%w/v)	Carbopol 934 (%w/v)
NLCG1	0.5	18	--
NLCG2	0.5	18	0.1
NLCG3	0.5	18	0.2
NLCG4	0.5	18	0.3
NLCG5	0.5	18	0.4
NLCG6	0.5	18	0.5

2.5 Particle size and zeta potential

The particle size and zeta potential of the NLCs was determined by dynamic light scattering using Malvern zeta sizer. The samples were directly added in a quartz cuvette, and all measurements were carried out at 25°C.

2.6 In vitro Drug Release

The release of venlafaxine from NLCs was determined by Franz-diffusion cell. Dialysis membrane was placed between the donor and receptor compartments and the receptor compartment was filled with phosphate buffer pH 7.4. Optimized NLC formulation equivalent to 1 mg of venlafaxine was placed in the donor compartment. The cell was incubated at 37°C with continual stirring at 100 rpm. Samples were withdrawn at predetermined time intervals and analyzed by UV spectrophotometery to calculate the amount of drug released.[70]

2.7 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.

2.8 Viscosity Determination

Viscosity of *in situ* gel system was determined using Brook field viscometer DV-1. Temperature of 37±0.5ºC 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.

2.8.1 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.

2.8.2 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

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DOI: https://doi.org/10.64388/IREV10I1-1719713

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.

2.8.3 *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 groves 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.[73]

II. RESULTS AND DISCUSSION

1.2. FTIR Analysis (Drug-polymer compatibility study)

The FTIR spectra of the pure drug and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm^{-1}). Deletion of the peaks of the pure drug in the mixture spectra is usually taken as an indication of incompatibility of the drug and excipients. On comparison of the FTIR spectra of the drug and the mixture it was observed that no peak was deleted and only the intensities of the existing peaks changed which might be due to the coupling of absorption frequencies. This provides evidence of compatibility between the drug and the matrix forming polymers.

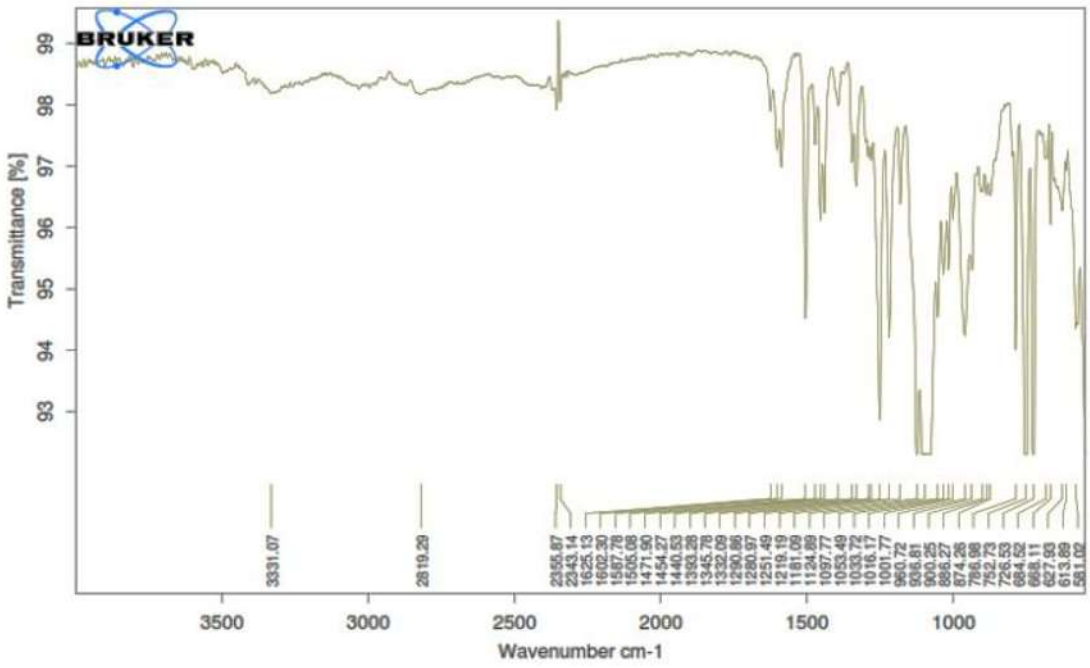

Fig. 1. FTIR spectra of venlafaxine

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DOI: https://doi.org/10.64388/IREV10I1-1719713

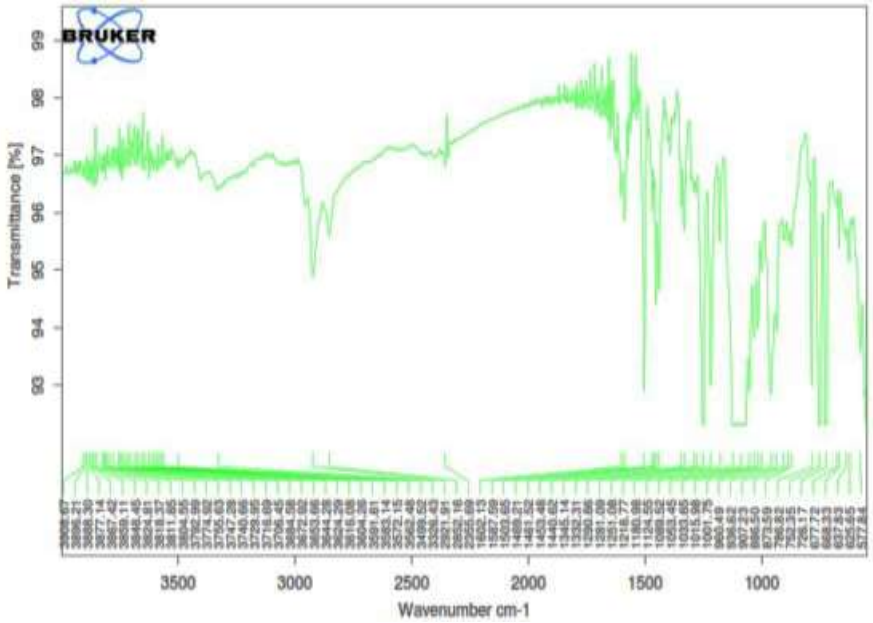

Fig. 2. FTIR spectra of physical mixture (venlafaxine+stearic acid)

3.2 Evaluation of particle size

The particle size of NLC plays vital role in its topical applicability as well as prolonging the release of the active ingredient. Smaller particles can more easily penetrate into the superficial layers of the stratum corneum and hair follicles. The particle size of the NLC varied from 645.5 nm to 9.780 µm and the PDI of the formulations varied from 0.408 – 0.865 (Table 6.6).

Table IV. Particle Size and PDI of NLCs

Formulation	PS (nm)	PDI	EE (%)
NLC1	918.1	0.534	76.29
NLC2	2906	0.492	56.73
NLC3	2549	0.748	48.29
NLC4	1604	0.834	89.64
NLC5	1897	0.698	55.77
NLC6	7933	0.657	20.36
NLC7	645.5	0.408	74.34
NLC8	7814	0.865	91.84
NLC9	9780	0.719	78.56

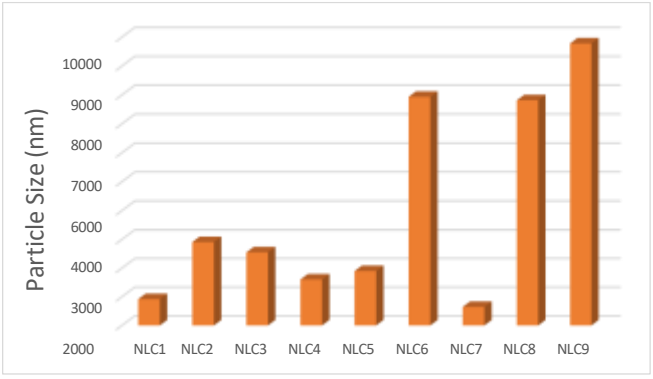

Figure 3. Effect of process variables on particle size of NLCs

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3.3 Zeta Potential of NLC7

Zeta potential is crucial in formulation of nanocarriers as it directly influences particle stability, aggregation behaviour, and ultimately the efficiency of drug delivery. Zeta potential reflects the surface charge of NLC particles.

The zeta potential of the prepared NLC 7 was found to be -14.6 mV suggesting adhesion to the skin surface and penetration into deeper layers. The results revealed that at lower concentration of the non-ionic surfactant (Tween 80) decreased the negative potential of the particles (Figure 6.8).

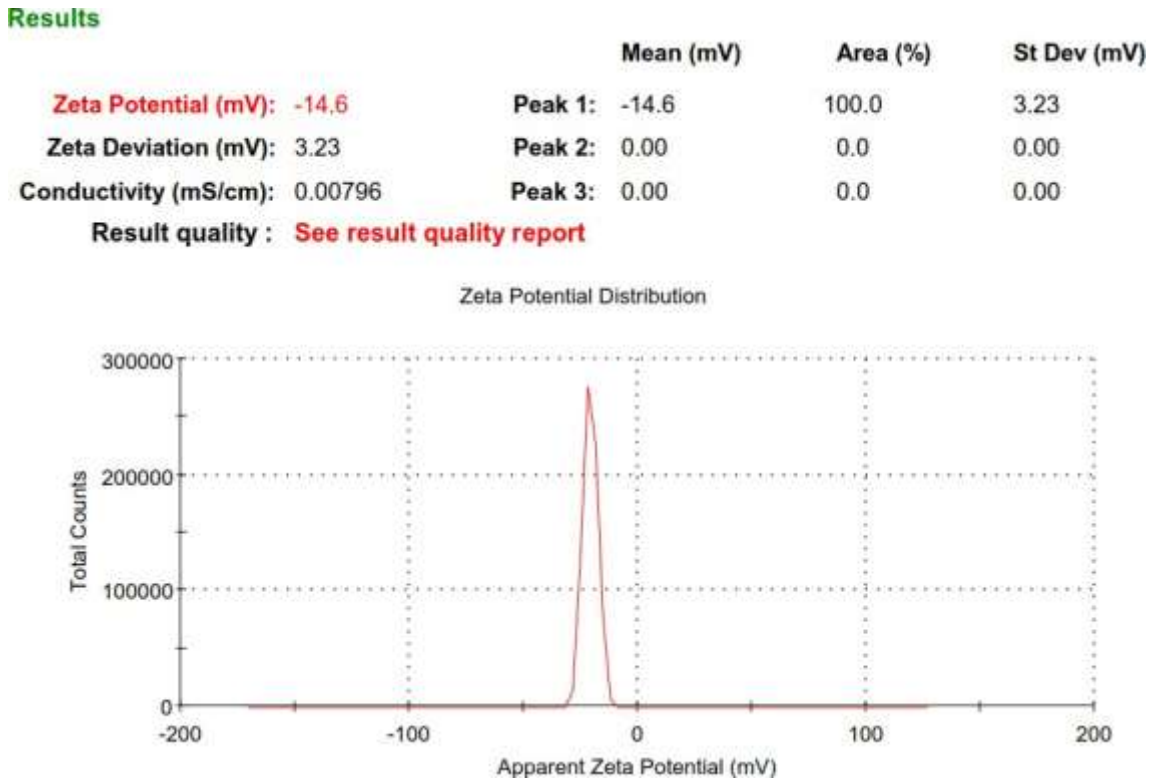

Fig. 4. Zeta potential of NLC7

3.4. *In vitro* release of venlafaxine from NLC

The *in vitro* release of the NLC7 was studied using Franz diffusion cell with the aid of egg membrane as the dialysis membrane to simulate the skin. The study was carried out for a period of 12 h to observe the sustained release effect of the delivery system (Table 6.7).

Table V. *In vitro* release of venlafaxine from NLC7

Time (h)	NLC7
0	0
1	10.65
2	16.93
4	21.12
6	27.16
8	29.95
10	38.09
12	44.84

The release of the best formulation (NLC 7) was studied for a period of 12h was found to be 44.84%. The release of venlafaxine from the NLC was found to be steadily controlled throughout the duration of 12h of the study (Figure 5).

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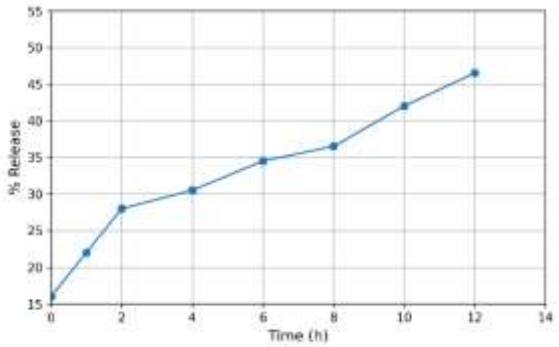

Fig. 5. Cumulative release of venlafaxine from NLC7

3.5 Evaluation of the gel formulations

3.5.1 Physicochemical properties

The pH of all the formulations was found to be 5.9 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 NLCG1, NLCG2, NLCG3 and NLCG4 were found to be clear while NLCG5 and NLCG6 were turbid in appearance revealing that clarity of the gel is inversely proportional to the concentration of Carbopol. The results of pH, viscosity, gelling time and gel strength are presented in Table 6.9.

Table VI. Physicochemical properties of the *in situ* gel formulations

Formulation code	pH	Viscosity (cps)		Gel Strength (g)	Gelling time (sec)
		Sol	Gel		
NLCG1	6.1	32	114	5	13
NLCG2	6.0	39	126	5.7	11
NLCG3	6.1	51	165	6.3	9
NLCG4	6.2	61	183	7	7
NLCG5	5.9	78	201	7.8	5
NLCG6	6.1	80	207	7.8	5

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. NLCG6 formulation was having maximum viscosity. The viscosity of NLCG3 (51 in sol to 165 in gel) was taken as optimum. Viscosity of the sol formulation ranged between 32 to 80 cps while that of the *in situ* gel ranged between 114 to 207 cps.

3.5.2. 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. The effect of agitation speed on viscosity is presented in Table 6.10.

Table VII. Rheological behaviour of the gel formulations

Formulation code	Viscosity (cps)					
	10 rpm	20 rpm	40 rpm	60 rpm	80 rpm	100 rpm
SNG1	137	125	103	81	59	41
SNG2	148	136	112	88	65	47
SNG3	153	142	120	92	81	63
SNG4	161	152	131	108	93	77
SNG5	172	164	140	125	101	89
SNG6	180	172	149	136	118	98

3.5.3 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 1h 15min to 4h 03min (Table 6.11). The mucoadhesion increased with the higher concentrations of carbopol in the formulations.

Table VIII. Mucoadhesion wash off time of the nasal gel

Formulation	Mucoadhesion time (h.min)
NLCG1	1.15
NLCG2	1.57
NLCG3	2.28
NLCG4	3.01
NLCG5	3.54
NLCG6	4.03

III. CONCLUSION

The present investigation successfully demonstrated the formulation and characterization of nanostructured lipid carriers (NLCs) loaded into an in situ intranasal gel for the brain delivery of venlafaxine. Oleic acid and Tween 80 were identified as the most suitable excipients, leading to the optimized NLC7 formulation with desirable particle size, entrapment efficiency, and controlled drug release over 12 hours. The incorporation of NLC7 into a poloxamer–carbopol based in situ gel provided favorable gelation properties, viscosity, syringeability, and mucoadhesion, all within the physiological nasal pH range.

The findings confirm that the developed NLC-based intranasal gel system offers a promising alternative route for venlafaxine delivery, potentially enhancing brain targeting while overcoming limitations of conventional oral administration. This approach may contribute to improved therapeutic outcomes in the management of depression and related neurological disorders, while also opening avenues for further clinical evaluation and scale-up of intranasal nanocarrier systems.

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