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FORMULATION AND EVALUATION OF IN-SITU GELLING SYSTEM FOR NASAL DELIVERY OF DEXTROMETHORPHAN HYDROBROMIDE

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Dextromethorphan hydrobromide, in-situ nasal gel, thermosensitive, mucoadhesion, poloxamer, sustained release, nasal delivery, cilio-toxicity.

Abstract

The nasal delivery of dextromethorphan hydrobromide (DXM) presents a promising approach to overcome the limitations of conventional oral administration, such as first-pass metabolism and delayed onset of action. In-situ gelling systems, which undergo a phase transition from sol to gel upon exposure to nasal physiological conditions, enhance drug retention and absorption. This study aimed to develop and evaluate a thermosensitive and/or mucoadhesive in-situ nasal gel for DXM using polymers such as poloxamer 407, poloxamer 188, chitosan, and gellan gum. The formulations were optimized based on gelation temperature, viscosity, mucoadhesive strength, and drug release kinetics. Rheological studies confirmed the pseudoplastic behaviour and nasal applicability, while in-vitro drug release studies demonstrated sustained release over 8 hours. Ex-vivo permeation studies using sheep nasal mucosa indicated enhanced drug diffusion compared to conventional solutions. Histopathological evaluation confirmed the safety of the formulation with no significant cilio-toxicity. The results suggest that the developed in-situ gelling system can improve the bioavailability and therapeutic efficacy of DXM, offering a potential alternative for effective cough suppression and central nervous system delivery via the nasal route.

Introduction

Antibacterial The most desirable and convenient method of drug administration is the oral route because of their ease of administration. However, in many instances oral administration is not desirable when the drug undergoes degradation via first pass effect in liver. Hence, lack of systemic absorption through the gastrointestinal tract leads to research on different possible routes of drug delivery such as parenteral, intramuscular, subcutaneous, intranasal, transdermal.[1] Nasal drug delivery has been recognized as a very promising route for delivery of therapeutic compound. In recent years there are many drugs which shows better systemic bioavailability through nasal route, due to large surface area and porus endothelial membrane and high blood flow.[2]

In-situ gelling systems are innovative drug delivery platforms that undergo sol-to-gel transition upon exposure to physiological stimuli such as temperature, pH, or ionic strength. These systems are particularly advantageous for nasal drug delivery due to their ability to enhance drug residence time, improve bioavailability, and provide controlled release. Dextromethorphan hydrobromide (DXM), a widely used antitussive agent, suffers from low oral bioavailability due to first-pass metabolism. Nasal delivery via in-situ gelling systems can bypass hepatic metabolism, ensuring rapid absorption and enhanced therapeutic efficacy.

Gels are semisolid form which contains both solid and liquid components. The solid components comprise a three-dimensional network of interlinked molecules which immobilizes the liquid phase.[3]

In-situ is a Latin word which means „In its original place or in position". In this type of drug delivery system, the preparation is in a solution form before administration in body, but it converts into a gel form after administration.[4] It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profile by intravenous injection with 100% bioavailability. Whereas absorption of hydrophilic drugs can be increased by means of absorption enhancer.[5] The preparation of in situ gel using ionic polysaccharides has been disclosed in U.S. Pat. No. 5,958,443, which discloses compositions 3ehavior3ting a drug, a film forming polymer and a gel forming ionic polysaccharide (such as an alginate). [8,9]

Materials And Methods

Materials

Dextromethorphan Hbr was obtained as a gift sample from Wockhardt Ltd., Gujarat, India. Poloxamer 407, Carbopol 934P, HPMC (Hydroxypropyl Methylcellulose), Benzalkonium Chloride and Sodium Chloride was supplied from Vishal chem, Mumbai 400002.

Preformulation Studies

Determination of (λmax) of Dextromethorphan HBr

The stock solution of 100µg/ml was prepared by dissolving Dextromethorphan HBr at concentration of 1 mg/ml in phosphate buffer. Max. Absorbance (λmax) of dextromethorphan HBr was determined by UV visible spectrophotometer by scanning drug samples between 203-280 nm and spectra were found (Shimadzu UV-1800,Japan).

Fourier-Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was performed to evaluate the compatibility of dextromethorphan hydrobromide with selected excipients. Physical mixtures of the drug and excipients (1:1 ratio) were prepared and analysed for any shifts or disappearance of characteristic peaks, indicating potential interactions[10]

Calibration curve

The absorption maximum of dextromethorphan determined as per standard protocol with some modification. In brief, stock solution of dextromethorphan developed at concentration of 1 mg/ml in phosphate buffer. Further, it followed by serial dilution to get concentration of dextromethorphan as 2, 4, 6, 8, 10µg/ml, and then it proceeded to UV spectrophotometric analysis at λmax of 278 nm. Qualification was taken in triplicate and obtained data were analyzed statistically· Stock (100µg/ml) of dextromethorphan was prepared in Phosphate buffer pH 6.8. The solution was kept in Quartz cuvette having thickness 10mm. the UV spectrum was in the range of 200-400nm Shimadzu UV- visible spectrophotometer (UV- 1800) at 1cm, slit width. It showed lambda max at 278 nm using spectrophotometer. The procedure was repeated for accuracy at least three times.

Preparation of In-Situ Gel

The first step was Hydration of Polymers in this Gel was prepared by dissolving Poloxamer 407 in cold distilled water by stirring and refrigerated overnight at 4°C to ensure proper dissolution. Then Prepare a separate dispersion of 1 gm of Carbopol 934 or HPMC separately in purified water (50 ml) with constant stirring at optimum speed by mechanical stirrer to avoid lump formation. In the second steps drug DXM HBr was added in a small quantity of phosphate buffer pH 5.5. The pH was adjusted by using NaOH or HCl ensuring it remains between 5.0–6.5 (compatible with nasal mucosa). Then Slowly added the drug solution to the polymer dispersion with gentle stirring to avoid foam formation. sodium chloride added to maintain isotonicity. benzalkonium chloride was added as a preservative to the above mixture with constant stirring. Finally, Make up the final volume with distilled water. Stirring continuously until a uniform solution was formed. Then the prepared formulation was stored in a sterile container at refrigerated conditions (4°C) before use.

Formulation optimization
Among the evaluated batches, F Batch 9 was identified as the optimized formulation based on its superior composition and performance across critical parameters. This batch contains 0.75% dextromethorphan hydrobromide, providing a higher drug loading compared to earlier batches (F1-F5), which is expected to enhance therapeutic efficacy.

Excipient	Formulation Batches								
	DXM HBr F01	DXM HBr F02	DXM HBr F03	DXM HBr F04	DXM HBr F05	DXM HBr F06	DXM HBr F07	DXM HBr F08	DXM HBr F09
Dextromethorphan hydrobromide (%W/V)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Poloxamer 407(%W/V)	0.25	0.25	-	0.25	0.25	0.20	0.25	0.15	0.25
Carbopol 934P (%W/V)	0.15	0.10	0.15	0.30	-	0.25	0.25	0.25	0.25
HPMC(Hydroxypropyl Methylcellulose)(%W/V)	0.18	0.18	-	0.18	0.18	0.19	0.20	0.19	0.19
Sodium chloride(%W/V)	0.7	0.7T	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Benzalkonium chloride(%W/V)	1	1	1	1	1	1	1	1	0.01
Purified Water(qs)(ml)	100	100	100	100	100	100	100	100	100

Table 1.Formulation Design (Composition in % w/w)

Clearity
The clearity of various formulations was determined by visual inspection under black and white background.[11]

pH
pH of the gel was determined using digital pH meter. Digital pH meter was previously calibrated by pH 4 and pH 7. About 1.0gm of each formulation was taken in beaker and volume was made up to 50ml then glass electrode was sufficiently dipped into samples of formulations, and pH of the solution was determined in triplicate. [12]

Drug content
1gm of gel was dissolved in small amount of phosphate buffer pH 6.8 in a 100ml flask and was shaken till it was completely dissolved and then volume was made up to 100ml by using phosphate buffer pH 6.8. The solution was filtered through whatman filter paper. The absorbance of the solution was measured at 278nm using a UV spectrophotometer and Calculated drug concentration from the calibration curve.[13]

Viscosity
The Brook field Viscometer LVD was used to measure the viscosity of formulations. With shear rates ranging from 0.20 s-1 to 1.0 s-1, measurements were made over a variety of speed settings of 5,10, 15,20,25,and 30 rpm. The determination of viscosity was done at room temperature.

In vitro drug release
In vitro drug diffusion study of various formulations was performed using Franz diffusion cell. Dialysis membrane having molecular weight cut-off range of 12 000–14 000 kDa was used as diffusion membrane. Dialysis membrane was allowed to soak in phosphate buffer pH 6.4 for 24 h before experiment. Diffusion cell was filled with 21 ml phosphate buffer pH 6.4 and dialysis membrane was mounted on cell. The gel containing drug equivalent to 10 mg was placed onto donor chamber. The temperature was maintained at 32–34 °C by circulating water bath. Samples of 1 ml were withdrawn at different time intervals replaced with same volume of fresh solution, filtered and amount of drug was determined by UV visible spectrophotometer at 226 nm.[14]

Spreadability

Spreadability is the area travelled per unit time (cm^2/min) by the gel formulation. Whatmanns filter paper (0.45mm) was used for determination of spreadability of solution formulations F1 to F9. A 1ml graduated pipette with rubber bulb was clamped vertically to the stand in such way that the tip of the pipette was at 2cm above the horizontal surface of round shape filter paper. A 0.1ml sol formulations dropped at centre of filter paper. At fixed time interval, 20s the surface area covered by the formulation was measured.[15]

Mucoadhesive strength

It was determined by the mucoadhesion of the gel by measuring the detachment force from nasal mucosa. The modified balance technique using two glass vials and sheep nasal mucosa was used. A nasal mucosa with thickness of 0.6mm and surface area 2.835cm^2 was cut from the olfactory region of sheep nasal cavity and instantly secured with the mucosal side out onto each glass vial using a thread. The vials were stored at 32-34^{0}c for 10min. one vial was attached to one side of balance and 0.5ml of gel sample was placed between two mucosal membranes attached to bottom of the vials. The minimum weight of water required to break the mucosal adhesion was measured.
Mucoadhesion strength (dynes/cm^2) = mg/A Where m is weight required for detachment in g, g is acceleration due to gravity (980cm/s^2) and A is surface area of mucosa exposed (cm^2)[16]

Gel strength determination

A sample of 50g of the nasal gel was put in a 100ml graduated cylinder and gelled in a thermostatically controlled water bath at 37^{0}c. A weight of 35g was placed onto the gelled solution. The gel strength, which is an indication for the viscosity of the nasal gel at physiological temperature, was determined by the time in seconds required by the weight to penetrate 5cm into the gel.[17]

Stability studies

Short term accelerated stability study performed for optimized in situ gelling solution at 40±2^{0}c temperature and 75±5% relative humidity for one month and evaluated for appearance, pH, drug content, gelling strength, gelation time and in vitro drug release.[18]

Result And Discussion

Determination of (λmax) of Dextromethorphan HBr

UV Spectrum of the drug was determined λmax at 278 nm in phosphate buffer (pH 6.8). The lambda max was found to be 278 nm in Phosphate buffer pH 6.8.

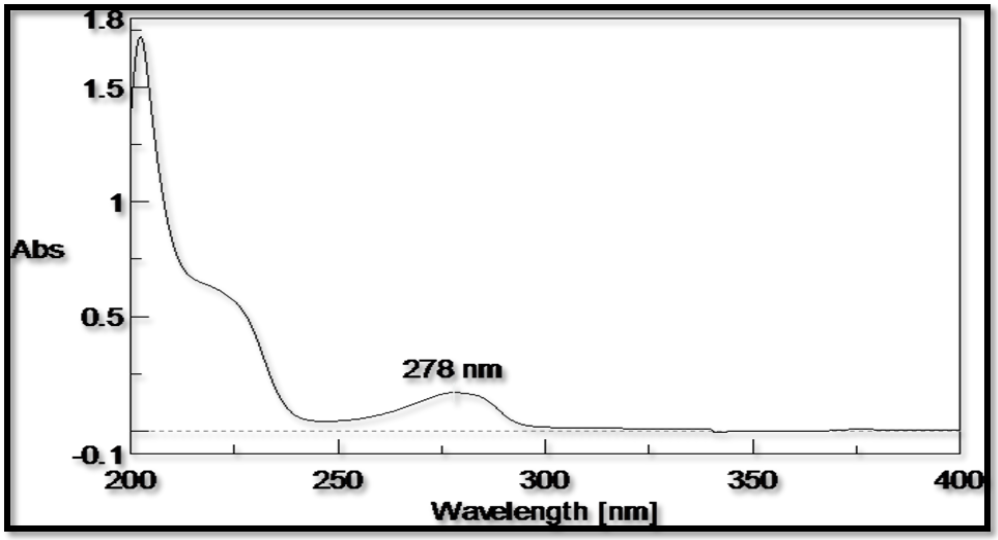

Figure 1: UV Spectrum of DXM At 278 Nm

FTIR

Drug characterization study by FTIR was carried out as per standard procedure. The spectra analysis performed by Win-IR, Bio-Rad FTS spectrophotometer. Individual sample assorted with potassium bromide and later proceeds for spectroscopical observation under range of 4000 to 400 cm^{-1}. These detected principal peaks confirmed purity and authenticity of Dextromethorphan similar to referenced report.

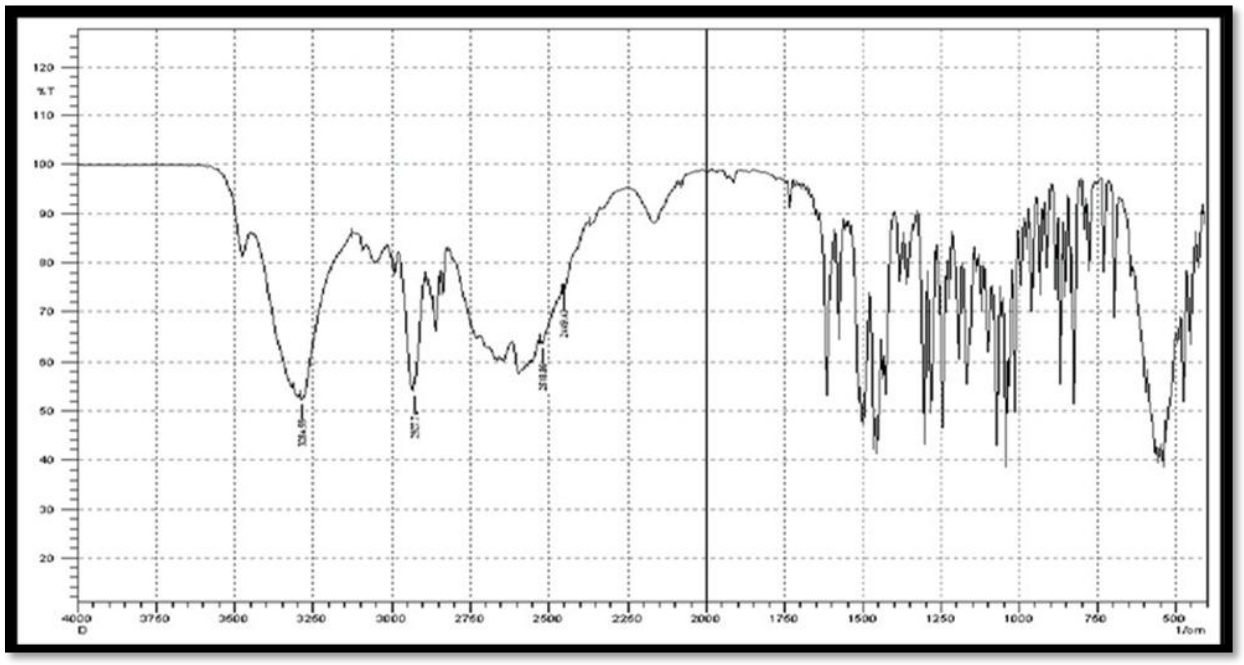

Figure 2: FT-IR Spectrum of Dextromethorphan Hydrobromide

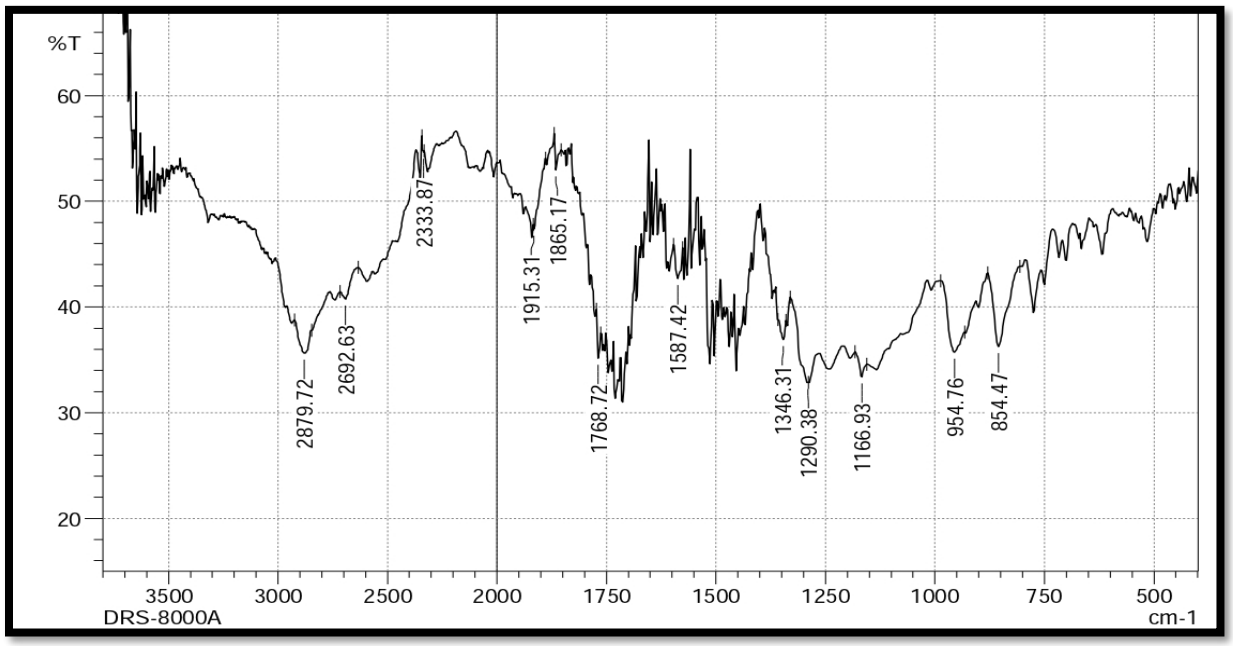

Figure 3: FTIR Spectra of Dextromethorphan Hydrobromide + Poloxmer

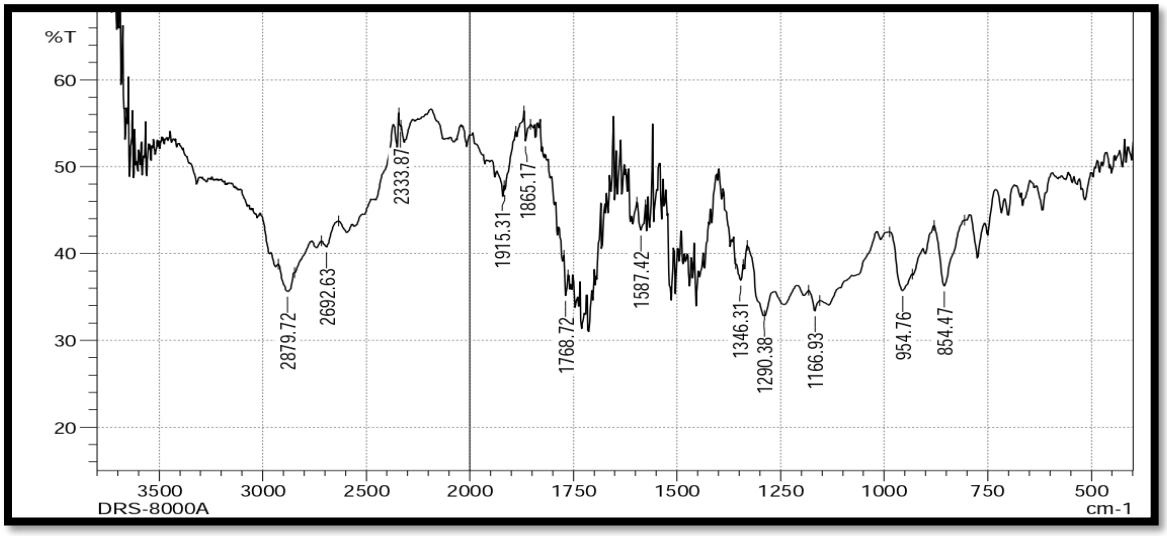

Figure 4: FTIR Spectra of Dextromethorphan Hydrobromide + Excipient

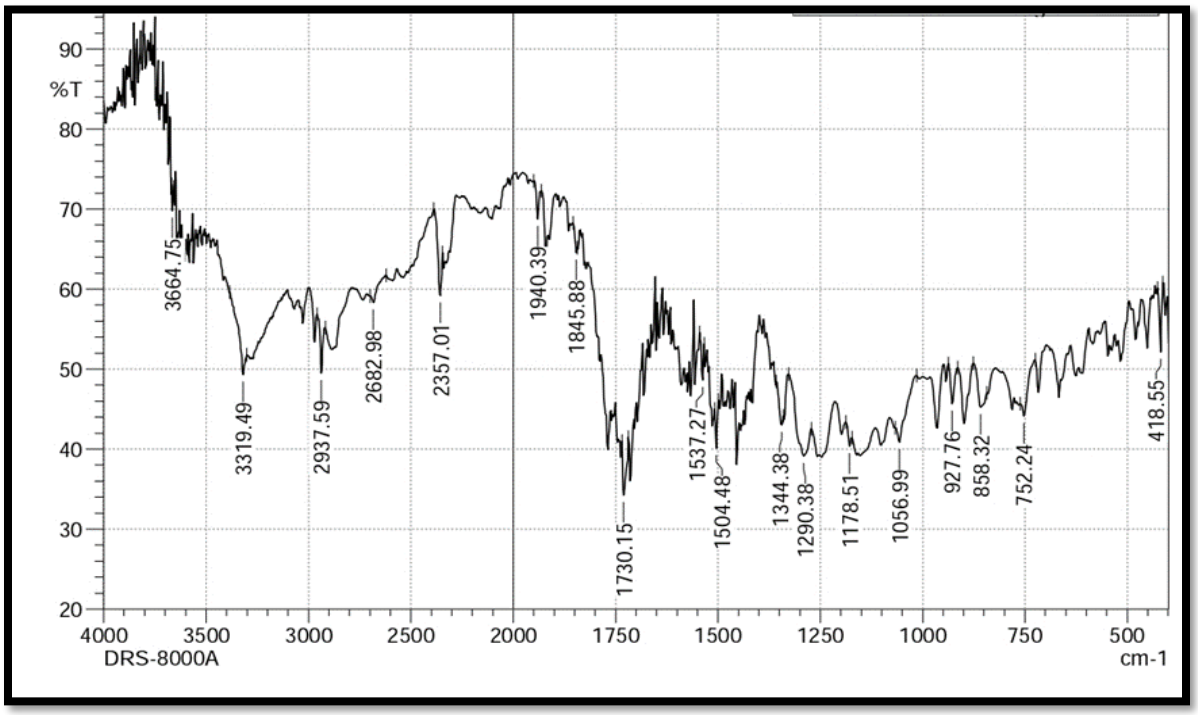

Figure 5: FTIR Spectra of Dextromethorphan Hydrobromide Gel

Calibration Curve

The graph of Value Absorbance Vs Concentration for pure dextromethorphan was achieved at 278 nm with a concentration range of 5 to 25 g/ml. The calibration curve was plotted using both the concentration and absorbance data.

From the standard curve, it was observed that the drug obeys beers law in concentration range of 5 to 25 µg/ml in phosphate buffer pH 6.8. drug shown good linearity with regression of coefficient (r^2=0.9985) and equation for this

line obtained was found to be y=0.004x+0.0033 which is used for the calculation of amount of drug and dissolution study.

Sr.no.	Concentration (µg/ml)	Absorbance
1	05	0.023
2	10	0.042
3	15	0.065
4	20	0.083
5	25	0.102

Table 2: Absorbance value at various concentration of dextromethorphan hydrobromide in Phosphate Buffer Solution pH 6.8

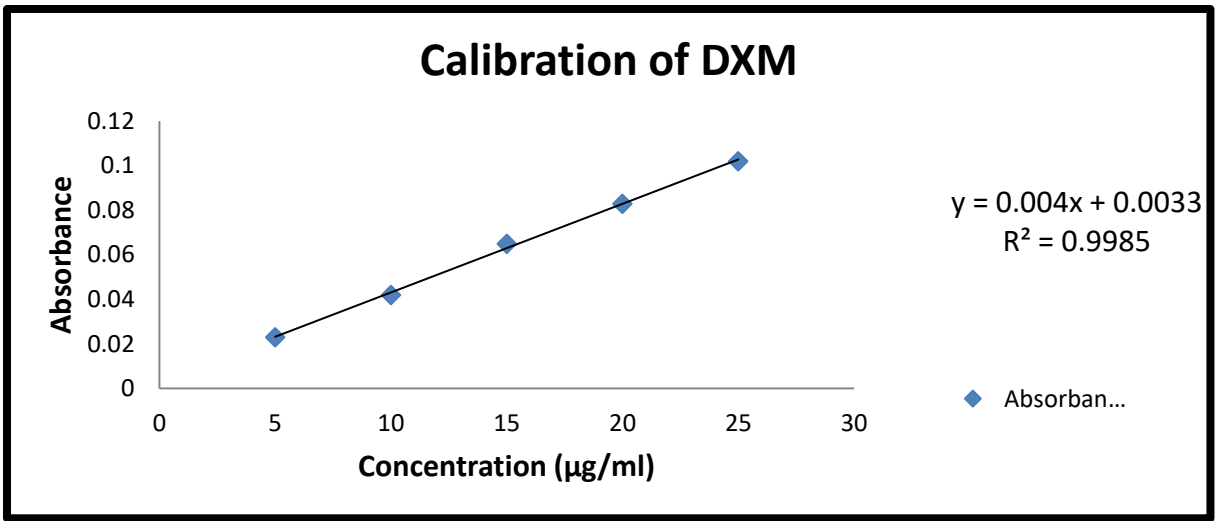

Figure 6: Calibration curve of dextromethorphan hydrobromide in Phosphate Buffer Solution pH 6.8

Clearity, pH and drug content

The visibility of all formulation was found to be clear. Table 3 shows that the pH of dextromethorphan hydrobromide (F1 to F9) was found to be range 4.6 to 6.3 which is in the nasal (4.5-6.4) pH range. Table 3 shows that the percent drug content for all formulations of the drug contents were found in the range of 89-102% which indicates that all formulations were of uniform.

Spreadability

Table 3 shows the data of spreadability measurement. Formulation F9 shows maximum spreadability due to more surface area covered by in situ gel after placing on filter paper.

Gelation Temperature, Time & Gelling capacity

It was measure by placing 5ml of prepared formulation in a test tube. Then sol-to-gel transition temperature achieved by heating the solution gradually (25–40°C) and recorded the temperature at which gelation occurs (+: Gel formed after a few minutes, dissolves rapidly,++: Immediate gelation, remains for few hours,+++: Immediate gelation, remains for extended period) Table 4.

Gelling strength

The gel strength was found to be affected by concentrations of gelling and mucoadhesive polymers. Table 4 shows the data of gel strength measurement. The gel strength of all formulation was found in suitable range of 30-50sec except formulation F4 which showed at 53sec.

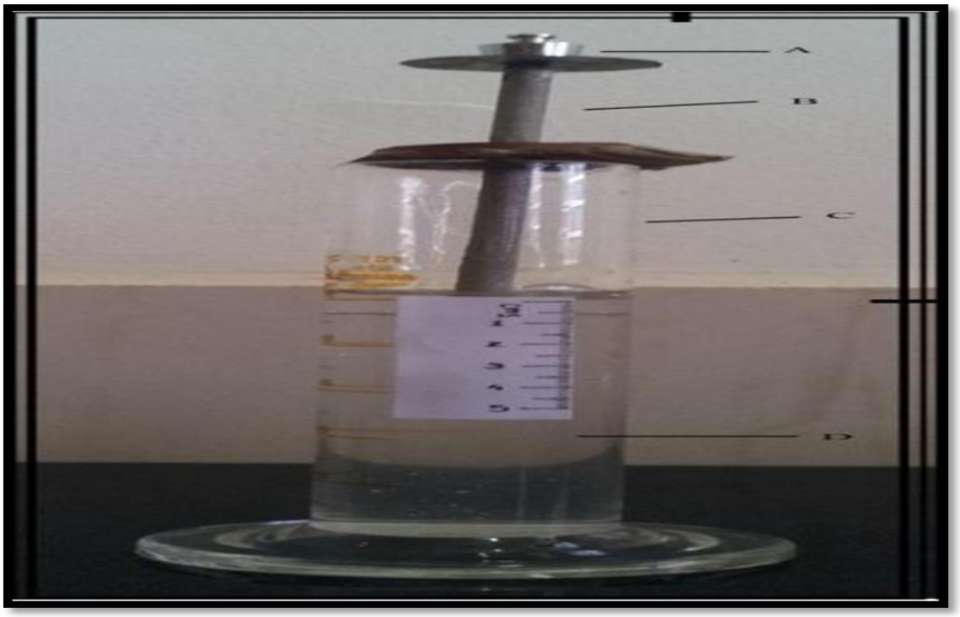

Figure 7: Gel strength measuring device, (a) Weights (B) Device (C) Graduated Cylinder (D) Gel

Mucoadhesive strength

Table 4 shows mucoadhesive strength for formulations. The Mucoadhesive strength is depend on concentration of Carbopol and HPMC used in formulation. The stronger the mucoadhesive force is, the more it can prevent the gelled solution coming out of the nasal cavity as well as drain into the nasopharynx.

Figure 8: Modified balance for mucoadhesive study, A: Modified balance, B: Weighing pan, C: Weight D: Gel, E: Nasal mucosa F: polypropylene cylinder

Table 3: Results of optimized batches (for sol)

Batch code	Visual appearance	Observed pH (±SD)	Drug content (%) (±SD)	Spreadability (cm^2/min)
F1	Clear	4.8±0.01	92.10±0.007	21.195±0.166
F2	Clear	5.7±0.07	89±0.007	18.462±0.144
F3	Clear	4.6±0.02	93±0.007	13.564±0.321
F4	Clear	6.2±0.05	92.10±0.007	15.918±0.185
F5	Clear	5.9±0.03	97.68±0.007	11.397±0.226
F6	Clear	5.3±0.007	102±0.007	7.629±0.183
F7	Clear	6.1±0.01	93±0.007	4.614±0.135
F8	Clear	6.0±0.05	96.05±0.007	9.426±0.153
F9	Clear	6.1±0.1	98.68±0.007	18.462±0.102

Table 4: Results of optimized batches (for gel)

Batch code	Observed pH (±SD)	Gelling temperature(°C)	Gelation time	Gelling capacity	Gel strength (sec)(±SD)	Mucoadhesive strength (dyne/cm2)
F1	6.3±0.01	33.1 ± 0.43	11.3 ± 0.22	+	30±2	0.0031±0.005
F2	5.7±0.07	33.6 ± 0.28	10.1 ± 0.43	+	45±5	0.0037±0.001
F3	6.3±0.02	33.3 ± 0.34	9.2 ± 0.42	++	32±4	0.0042±0.001
F4	6.2±0.05	34.2 ± 0.82	8.0 ± 0.53	+++	53±8	0.0045±0.002
F5	5.9±0.03	34.7 ± 0.28	4.8 ± 0.24	++	41±5	0.0046±0.005
F6	6.3±0.007	33.9 ± 0.42	5.3 ± 0.56	+++	48±6	0.0048±0.001
F7	6.1±0.01	34.6 ± 0.22	6.6 ± 0.54	++	35±3	0.0050±0.005
F8	6.0±0.05	34.5 ± 0.82	7.8 ± 0.76	++	44±6	0.0089±0.002
F9	6.1±0.1	33.1 ± 0.43	11.3 ± 0.22	+++	38±3	0.0051±0.002

Viscosity

By using spindle S4 at various speeds and shear rates, the Brook field Viscometer LVD was used to measure the viscosity of formulations. With shear rates ranging from 0.20 s-1 to 1.0 s-1, measurements were made over a variety of speed settings of 5,10, 15,20,25 and 30 rpm. The determination of viscosity was done at room temperature. The test was performed by using Brook-field viscometer. Results were given in the table 5.

Rpm	**Viscosity (cp) at 37 °C**								
	Formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	476.2	450.1	575	479.2	502.4	575.9	454.1	430.9	600.9
10	430.9	395.5	530	415.1	440	550.4	305.9	403.7	569.9
15	396.1	350.9	490	365	370.9	475.7	290	350	535.4
20	354.9	280	470.2	361.2	339.5	474.2	215	307	490
25	301.2	280.3	420	289.9	335.9	425.2	192.2	292.5	455.9
30	270.3	253	375.8	279	295.7	399	153.3	290.1	415.7

Table 5: At 37 °C

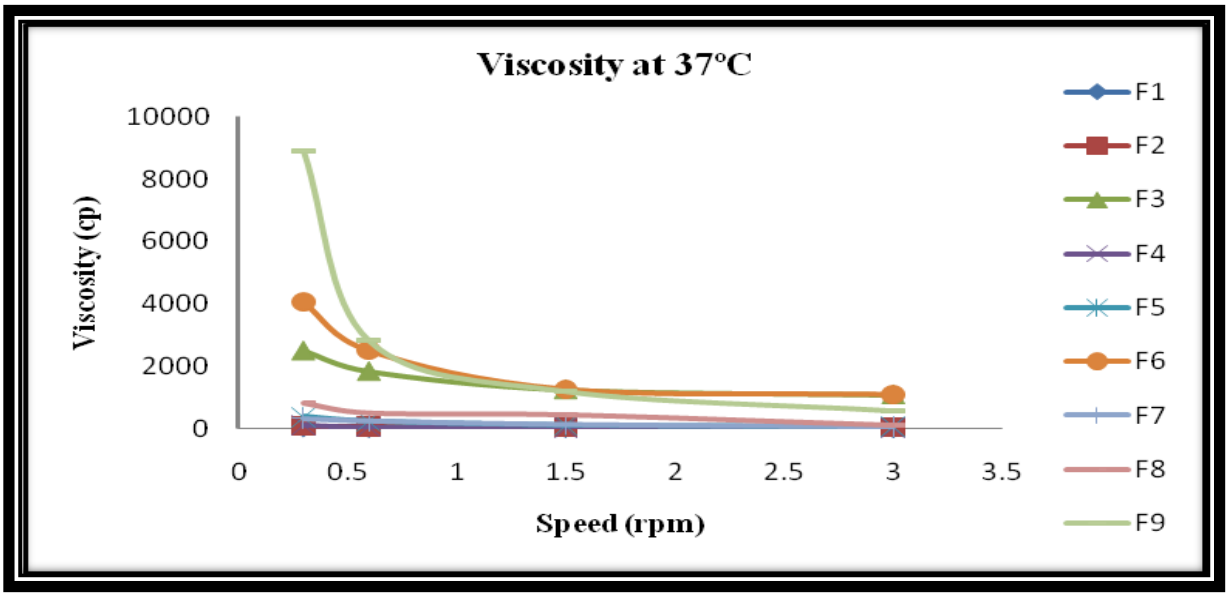

Figure 9: Viscosity profile of formulations at 37 °C

In vitro drug release

The Cumulative % Drug Release of Dextromethorphan Hydrochloride In-Situ Gel of Factorial Batches (F1to F9) Was found to be range 72.64 (8 hours) to 98.45 (8 hours). It was observed that Cumulative % Drug Release of gel depends on concentration of Carbopol and HPMC-K4M. Here, as concentration of Carbopol and HPMC- K4M increases Drug release time of formulation also decreases. Maximum Drug Release i.e., 98.45 (8 hours) was found to be for F9, and prolong Cumulative % Drug Release 72.64 (8 hours) Found to be F1. Here, Carbopol, and HPMC-K4M shows concentration dependence release behaviour for these formulations Formulation showed maximum drug release. Table 6.

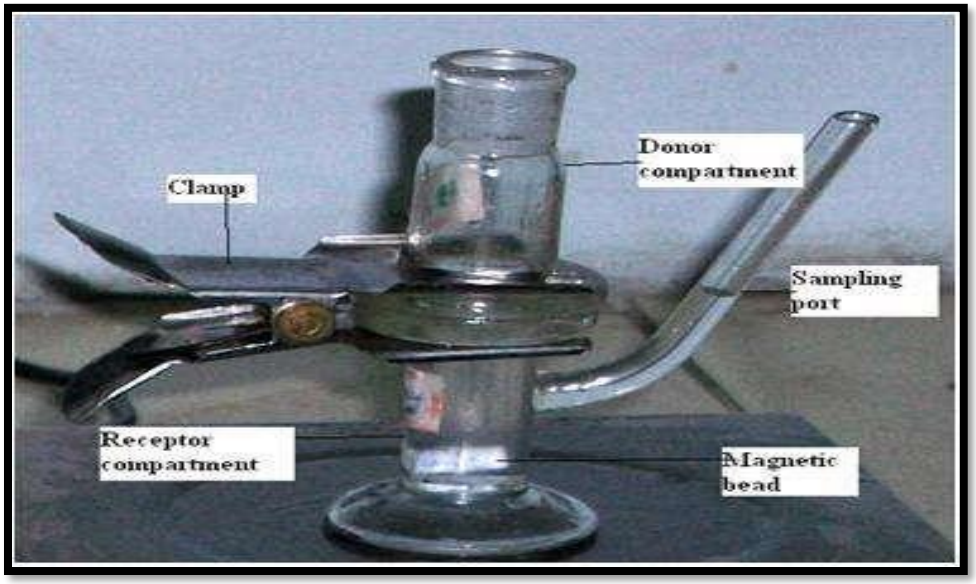

Figure No 10: Franz diffusion cell

Cumulative drug release (%) (±SD)	Formulation code								
Time in (H)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
30 min	4.25± 0.001	6.21± 0.05	10.11± 0.007	3.47± 0.001	8.16± 0.02	23.39± 0.05	8.16± 0.007	23.78± 0.09	23.78± 0.1
1	8.16± 0.04	11.68± 0.019	17.93± 0.05	6.21± 0.005	17.43± 0.001	23.79± 0.005	21.83± 0.007	24.57± 0.1	33.55± 0.09
2	15.97± 0.01	33.55± 0.009	33.55± 0.007	12.07± 0.005	29.65± 0.02	29.65± 0.001	29.26± 0.007	29.65± 0.05	40.98± 0.001
3	27.69± 0.001	45.27± 0.001	45.28± 0.001	27.30± 0.05	32.38± 0.007	35.51± 0.001	39.42± 0.02	35.90± 0.05	49.58± 0.009
4	47.23± 0.009	46.45± 0.007	46.06± 0.034	48.79± 0.04	39.03± 0.5	57± 0.004	55.05± 0.009	56.61± 0.001	70.28± 0.07
5	60.90± 0.001	53.10± 0.001	58.96± 0.007	58.95± 0.001	46.45± 0.09	61.30± 0.05	64.04± 0.01	61.69± 0.001	78.50± 0.2
6	62.80± 0.02	58.18± 0.05	62.09± 0.009	60.13± 0.007	58.57± 0.001	68.30± 0.001	71.07± 0.005	69.90± 0.009	85.54± 0.007
7	66.78± 0.2	68.73± 0.4	66.39± 0.001	65.61± 0.001	67.95± 0.007	80.46± 0.007	72.64± 0.001	82.02± 0.009	96.09± 0.001
8	72.64± 0.05	82.62± 0.04	79.68± 0.009	72.64± 0.001	80.85± 0.001	92.97± 0.004	86.71± 0.007	94.14± 0.004	98.45± 0.001

Table 6: Cumulative drug release (%) (±SD) Factorial Batches F1-F9

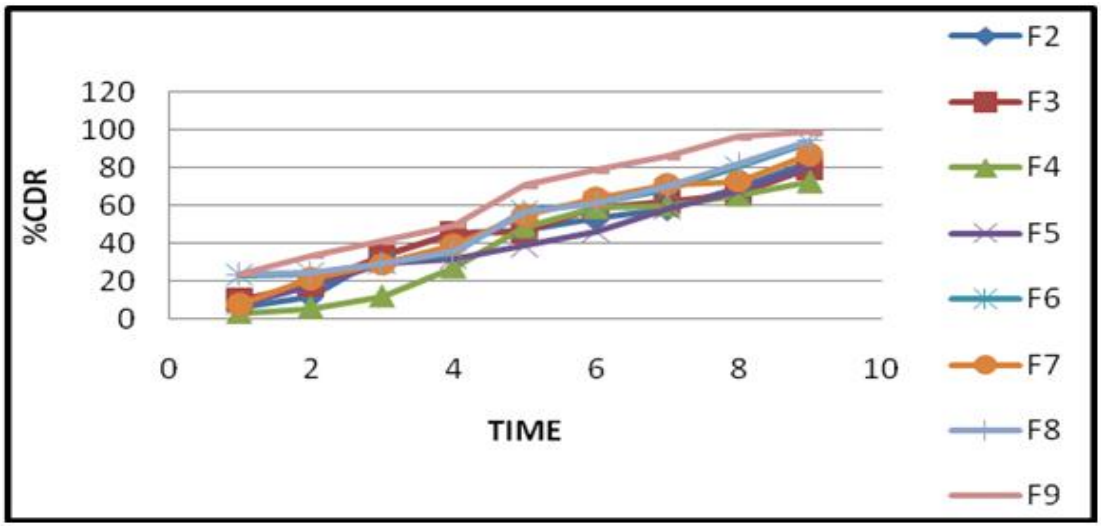

Figure 11: *In vitro* drug release profile

Stability study

Table 7 presents the results of a one-month stability study of the formulation. These findings confirm that the prepared formulation stable after one month period of stability.

Sr no.	Evaluation parameter	Before stability	After stability
1	pH	6.0±0.01	6.1±0.01
2	Drug content (%)	98.32 ± 0.12	99.12 ± 0.14
3	Gelling strength (sec)	38 ±3	37 ±3
4	Gelation time (sec)	11.3 ± 0.22	10.3 ± 0.22
5	*In vitro* drug release (%)	99.52 ± 2.1	99.18 ± 1.8
6	Appearance	No change	No change

Table 7: stability study

Conclusion

The present study successfully developed and evaluated an in-situ gelling nasal delivery system for Dextromethorphan Hydrobromide (DXM HBr) with the aim of enhancing drug bioavailability, prolonging nasal residence time, and ensuring controlled drug release. The formulation was optimized using Poloxamer 407 as a thermoreversible gelling agent, along with Carbopol 934P and HPMC to improve mucoadhesion and viscosity. The prepared formulations exhibited appropriate pH, gelation temperature, viscosity, and drug content, making them suitable for nasal administration.

In-vitro drug release studies demonstrated a sustained release profile, reducing the need for frequent dosing and ensuring prolonged therapeutic efficacy. Ex-vivo permeation studies confirmed efficient drug absorption across the nasal mucosa, supporting the potential for enhanced bioavailability. Additionally, stability studies indicated that the formulation remained physically and chemically stable over time.

The findings suggest that the in-situ gelling nasal system for DXM HBr is a promising alternative to conventional oral and liquid nasal formulations, offering better patient compliance, improved therapeutic effectiveness, and reduced systemic side effects. Further in-vivo studies and clinical evaluations may be conducted to establish its efficacy and safety for commercial use.

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