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FORMULATION AND CHARACTERIZATION OF ION INDUCED *IN SITU* GEL OF MEMANTINE HCl FOR NASAL ADMINISTRATION

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ABSTRACT

Intranasal drug delivery is an optimistic and convenient way for delivery of drugs which are ineffective orally due to extensive hepatic metabolism. The CNS acting drugs which are required to be present in optimum concentration in brain can be best possibly administered by nasal route. The objective of this study was to prepare nasal *in-situ* gel of an anti-Alzheimer drug Memantine HCl for nasal administration. The nasal *in-situ* gel was formulated using ion induced gelling polymer like gellan gum. Mucoadhesive property of gel increases the nasal residence time of drug, which results in enhanced absorption. FTIR and DSC studies were carried out to check the compatibility between drug and excipients used in formulation. The formulations were evaluated for various parameters such as gelation, viscosity, drug content, drug release properties along with good mucoadhesive strength.

Keywords: Nasal *in-situ* gel, ion induce gel, Memantine HCl, gellan gum

INTRODUCTION:

Nasal route are significant for drugs which are used for treatments like for pain and centrally acting drugs [1]. Presence of nasal mucosa in the nasal cavity has been considered as a potential administration route to achieve faster and higher level of drug absorption. Nasal route shows many advantages like, increases in drug bioavailability, rapid onset of therapeutic action and also provides favorable

tolerability profile for drug [2]. Intranasal drug delivery is used for the treatment in Ayurvedic system of Indian medicine [3]. It is an alternate to parental, oral route and also a reassuring systemic delivery for other convectional drug delivery routes [4] [5]. It is an optimistic and convenient way for drug delivery which is ineffective by oral route and it is effective for drugs which are active in low doses or shows minimal bioavailability orally, like peptides and proteins[6][7]. It is the preferable drug delivery system where drugs can be delivered in biophase of central nervous system [8].

To overcome the nasal drug delivery limitations like rapid mucociliary clearance , lower residence time of drug and limited deliverable volumes, *in- situ* gels can be used [9][10].

In situ gel is a dosage form in which medicaments are present in solution form before administration in the body and undergo gelation [11]. They are low viscous solutions, changes their structural conformation to produce a gel upon contact with the nasal mucosa (Fig. no.1) [12]. There are various mechanisms that trigger sol to gel transition such as pH induced, temperature induced and ion induced. [13] The primary advantage of in situ gels is that they can easily administered with accurate and reproducible dose compared with ordinary gels, correct drug dosing, improving drug residence time and increasing the bioavailability. [14][15]

The gellan gum was used as a gelling agent in this preparation. It is an anionic linear polysaccharide derived from bacterium *Sphingomonas elodea* [16]. The gelation involves creating of double helical junction zones then aggregation of double helical structure occurs to form 3-D network followed by combining of cations and hydrogen bonding with water.[17] Hydroxypropyl methylcellulose (HPMC E15), is a semisynthetic, inert viscoelastic polymer used as a vehicle [18].

Memantine HCl is adamantamine base amine and NMDA receptor antagonist, anti-Alzheimer drug, which treats moderate to severe forms of various neurological disorders. [19][20]. It has low affinity, voltage dependent, non-competitive, N-methyl-D-aspartate receptor antagonist. When drug is given it reaches to the central nervous system it binds glutaminergic receptors and inhibits their cation channels which prevents the prolong inflow of calcium ions and associated neuronal excitoxicity and increase cognitive function [21]. Lipophilic drugs are rapidly and efficiently absorbed across the nasal membrane directly into the systemic circulation, and shows grater bioavailability as compared to oral route of administration

[22]. By considering this aspect the ion induced *in situ* nasal gel was formulated and evaluated for various parameters.

Materials and methods:

Materials:

Memantine HCl was obtained from Cipla Ltd. Mumbai, India. Chemicals used are of Analytical reagent (AR) grade (LOBA Chemicals Ltd.).

Methods:

Melting Point Determination: [23]

Add small quantity of Memantine HCl in one end closed capillary tube. Place capillary tube in melting point apparatus. The temperature where the drug starts melting that temperature was noted down. This procedure was implemented thrice and the mean was calculated.

UV-Visible Spectroscopy [23]

The UV-visible spectrum of Memantine HCl (drug) solution in phosphate buffer pH6.8 was scanned at 600 nm to 200 nm.10 mg of drug was dissolved in 10 ml of 6.8pH of phosphate buffer solution. The solution prepared has concentration of 1000µg/ml. From this solution 1ml was withdrawn and diluted up to 10 ml with buffer to produce a solution of 100µg/ml conc. The resultant solution used as stock solution and dilutions were prepared from same solution. In10ml volumetric flask aliquots of 0.1mg/ml of Memantine HCl working standard solutions were added to compose solution of concentration range of 10, 20, 40, 60, 80 and 100µg/ml. To each flask 6.8pH phosphate buffer was added up to volume followed by 1.4ml of eosin reagent and the solution were stirred well before adding 1.2 ml of 0.2M acetate buffer pH 3.6. The volumes were filled with buffer and color solutions were measured and the absorbance was calculated.

Drug and excipients compatibility studies [24][25]:

a) Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectrum was studied using a Shimadzu FTIR. After drying the samples in hot air oven for 1 hour, the pure drug and physical mixture such as Memantine HCl with gellan gum and HPMC separately were prepared with KBr and was stored in desiccators before scanning the spectra.

b) Differential Scanning Calorimetry (DSC)

The thermal behaviour of drug Memantine HCl and the physical mixture of Memantine HCl with gellan gum and HPMC E15 were carried out for 10 °C/min heating rate in differential scanning calorimeter. The results were carried out by examining the samples at a heating range of 30-400 °C under the nitrogen atmosphere.

Preparation of *in situ* gel [25]:

Weighed quantity of gellan gum was disperse in distilled water and dispersion

was mixed for 20 min by stirring at 85-90˚C with the help of magnetic stirrer. Dispersion was cooled at room temperature HPMC E15, D-mannitol, benzalkonium chloride and Tween 80 was added simultaneously under continuous stirring to dispersion. Finally Memantine HCl was added under stirring. All the formulations were filled in amber coloured glass container and cap with rubber closures and sealed with aluminum caps. Formulations were kept at optimum temperature.

Table 1: Composition of *in situ* gel

Sr. no.	Ingredients	Formulation composition (%w/v)			
		F1	F2	F3	F4
1	Memantine HCl	0.5	0.5	0.5	0.5
2	Gellan gum	0.1	0.2	0.3	0.4
3	HPMCE15	0.2	0.2	0.2	0.2
4	Tween 80	0.1	0.1	0.1	0.1
5	D-mannitol	5	5	5	5
6	Benzalkonium chloride	0.002	0.002	0.002	0.002
7	Distilled water	100	100	100	100

EVALUATION OF *IN SITU* GEL [25]:

Gelation studies:

A transparent vial of 10 ml was set on a magnetic stirrer, along with a magnetic bar inside the vial. Each formulation was placed in a vial. Simulated Nasal Fluid (SNF) was added slowly while stirring. When the magnetic stirrer stops moving gelation occurs and that gelation point was determined.

Viscosity measurement [23]

Viscosity of formulations was measured by Brookfield Viscometer. To calculate or to estimate viscosity, 50 and 100 rpm speed was kept, using spindle no 63 and 64.

Drug Content:

Drug content is a principal parameter to assure the availability and uniformity of drug in a formulation. In a volumetric flask, formulation was added along with 10 ml of phosphate buffer pH 6.8 and 1.4 ml of eosin reagent and the solution was blended well before adding 1.2 ml of 0.2M acetate buffer pH 3.6 and analysed at 550 nm in a UV spectrophotometer. The drug concentration in prepared formulation was determined by extrapolating from standard curve. Drug content of was estimated.

Mucoadhesive Strength: [25]

Mucoadhesive force of prepared formulations was determined using sheep nasal mucosa. Modified balance method with slight modification was used. A rubber closure tied with a thread was fixed on single side of balance and empty polyethylene bag on the other side. One section of mucosa was placed to rubber closure using aluminum cap and another mucosa was fixed to the glass vial opening and then place into a beaker. The phosphate buffer of 6.8pH was added in a beaker. Exposed mucosal membrane was having

diameter of 1.1 cm and the gel was applied. Slowly the beaker was elevated until contact time between sheep nasal mucosa and gel was generated. On rubber closure a constant weight was placed for 2 min and then removed. Until reaching the contact time balance was kept in a reading position. Add water drop by drop in the polyethylene bag with pipette at a constant rate. When the upper mucosal site was detached from lower one addition of water was stopped. Weight was noted. The mucoadhesive force expressed as detachment stress in dyne/cm^2 and determined using following equation:

Detachment stress (dyne/cm^2) = mG/A.

Where, m = weight of water added to polythene bag in grams, G = acceleration due to gravity

taken as 980 dyne/cm^2 , A = area of the tissue exposed and is equal to πr^2.

2.2.5 *In vitro* drug release study: [21]

The study was performed using a glass fabricated Franz diffusion cell. Dialysis membrane (MW cut-off 12000–14000) was used as diffusion barrier. The membrane was balanced before addition of formulation into the donor compartment. Phosphate buffer (pH6.8) in the receptor compartment was filled. Prepared buffer solution was in the pH range as of the pH of nasal cavity. Placing the donor compartment such, as it just touches the diffusion medium of receptor compartment. Maintain temperature at 37±1 °C. At set time intervals, 0.5 ml of samples was withdrawn from the receptor compartment. Replace the sample volume with phosphate buffer solution of pH 6.8 after each sampling. Then 1.4 ml of eosin reagent was added to solution and the solution was stirred well before adding 1.2 ml of 0.2 M acetate buffer pH 3.6 and analysing it spectrophotometrically at 550 nm.

Drug Release Kinetics.

Drug release kinetics was accomplished by using obtained data from in vitro drug release studies and graphs was plotted in various kinetic models: zero order (Equation (1)) as cumulative amount of drug released verses time, first order (Equation (2)) as log cumulative percentage of drug remaining verses time and Higuchi's model (Equation (3)) as cumulative percentage of drug released verses square root of time.

- Zero order model:
  Q = K0t
  Where, K0 = zero-order rate constant expressed in units of conc/ time , t = time
- First order model:
  Log C = LogC0−Kt/2:303
  Where, C0 = initial concentration of drug, K = first order constant, t = time.

- Higuchi model:

  Qt = Kt 1/2

Where, Qt = amount of drug release in time t, K = kinetic constant and t = time

A more stringent test was used to differentiate between the mechanisms for release of drug. The release data was fitted to the Peppas exponential model as log cumulative percentage of drug released verses log time. The release exponent n and K value were calculated through the slope of the straight line. If the exponent n=0.43 then the drug release mechanisms Fickian diffusion, if 0.43<n<0.85 then it is non-fickian diffusion, if n<0.85 mechanism is non-Fickian case II diffusion.

- Korsemeyer-Peppas

  $$Q = Ktn$$

  Where, Q = percent of drug release at time t, K = diffusion rate constant, n = diffusional exponent.

RESULTS AND DISCUSSION:

Melting point determination:

The melting point of drug Memantine HCl was determined and it was found 291-293˚C by calculating the mean of three observations. (Table 2).

Determination of λ-max and calibration curve of Memantine HCl.

The λ-max of Memantine HCl was observed by using UV-visible spectrophotometer and its calibration curve was plotted using phosphate buffer of pH 6.8. The absorption maximum was observed at 550 nm obtained from the spectrum. Hence 550 nm was selected as λ-maximum for further studies. Absorbance of various concentration of Memantine HCl was determined. (Table no.3) Calibration curve of Memantine HCl was plotted. (Fig 4).

Fourier transformed infrared spectroscopy (FTIR)

FTIR studies were carried out on pure drug Memantine HCl as well as in combination with selected polymers. Drug spectrum shows prominent peaks at 3400 cm^{-1}, 2839.27 cm^{-1}, 1617.34 cm^{-1} and 1473 cm^{-1} at N-H stretching, C-H stretching, C=N stretching and CH3 stretching respectively, (Fig.5). There were no considerable changes observed in positions of characteristic absorption bands and bands of various functional groups present in the drug. Memantine HCl shows no prominent changes in its characteristics even in its physical mixture with polymers that is with gellan gum and HPMC respectively. (Fig. 6 and 7) It showed that Memantine HCl was compatible with gellan gum and HPMC E15. (Table.4)

Differential scanning calorimetery (DSC)

The thermal analysis of pure drug and physical mixture of Memantine HCl along

with gellan gum and HPMC E15 were studied by using Differential Scanning Calorimetry (DSC). Memantine HCl showed sharp melting endotherm at 50˚C and 232˚C (Fig.8). Where, thermogram of mixture of drug with gellan gum and HPMC E15 showed two endothermic peaks at 72.83˚C and 229.32˚C. (Fig. 9).

Determination of pH: During pH study it was found that the pH of all the formulations was in the range of 4.7 to 6.1, which was in the expected range of nasal pH i.e. 4.5-6.4 which is essential to avoid the nasal irritation and will help in improvement of the patient compliance.

Gelation study: The gelation study was performed using simulated nasal fluid. All formulations showed immediate gelation within 10-15s. Degree of gelation of various concentration of gellan gum was observed. (Table 5)

Viscosity measurement:

The viscosity values were evaluated for liquid formulations and gel. It was observed that the viscosity of the formulation was increases as the concentration of gellan gum increases. (Table 6). So the optimum concentration of gellan gum is required to produce the stable formulation.

Drug content:

The drug content for all formulation was calculated and found to be in the range of 89.9±3.2, 90.7±1.4 , 85.3±2.6 and 80.4±3.2 resp. (Table 7)

Mucoadhesive strength:

Mucoadhesive strength was found to be directly proportional to the concentration of polymer. As the concentration of polymer increases the mucoadhesive strength also increases. The mucoadhesive strength ranged between 1550.73±0.25 to 6556.45±0.56. (Table 8)

***In vitro* drug release:**

A Franz-diffusion cell was used to perform the *in vitro* drug release study using phosphate buffer pH 6.8. (Table 9, Fig.10.) The initial rapid release of Memantine HCl was determined. *In vitro* release study indicated that the release of drug varied according to concentration of polymer. The results of drug release study showed that decrease in the drug released was occurred with the increase in concentration of gellan gum.

The drug release kinetics was studied. The mechanism of drug release and kinetics of release rate was fitted to various mathematical models via zero order, first order, Higuchi and Korsemeyer-Peppas equations. (Fig.11, 12, 13, 14) The drug release of optimised formulation was treated. The n-values were obtained. (Table no.10) It was found that drug release follows Zero order kinetics and higuchi plot.

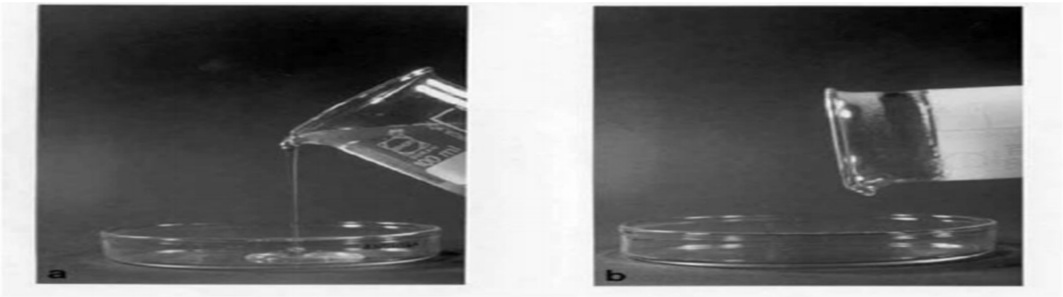

Fig. 1. Sol to gel transition (a- sol, b- gel)

Table no.2: Melting point determination

Standard range (˚C)	Observed (˚C)	Mean (˚C)
290-295	293	292
	292	
	292	

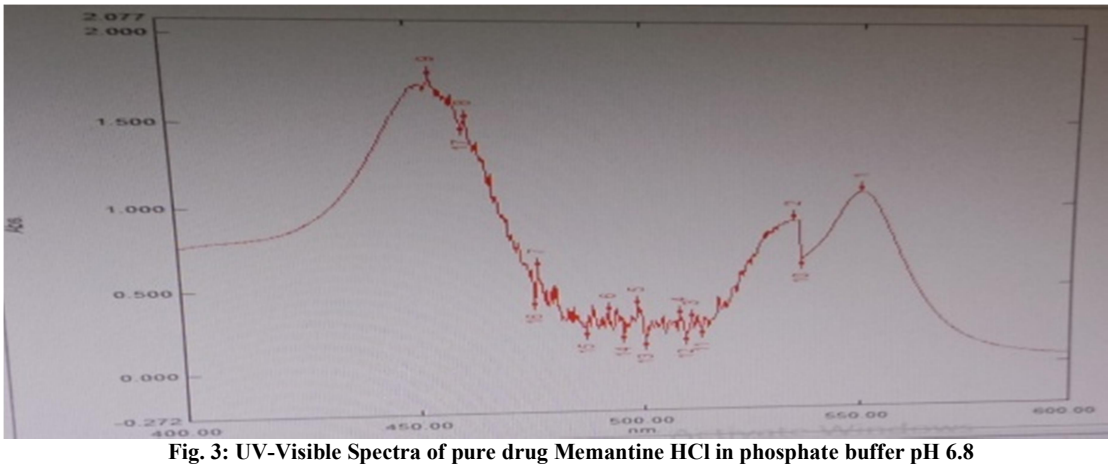

Fig. 3: UV-Visible Spectra of pure drug Memantine HCl in phosphate buffer pH 6.8

Table 3: Absorbance of various conc. of Memantine HCl in phosphate buffer pH 6.8

Sr no.	Conc.(µg/ml)	Absorbance
0	0	0
1	10	0.129
2	20	0.232
3	30	0.329
4	40	0.451
5	50	0.561

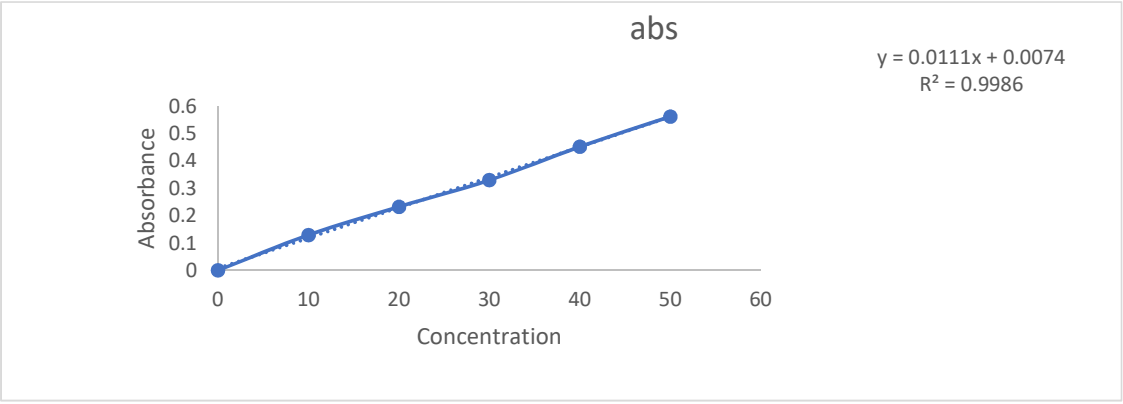

Fig. 4: Calibration curve of Memantine HCl in phosphate buffer pH 6.8

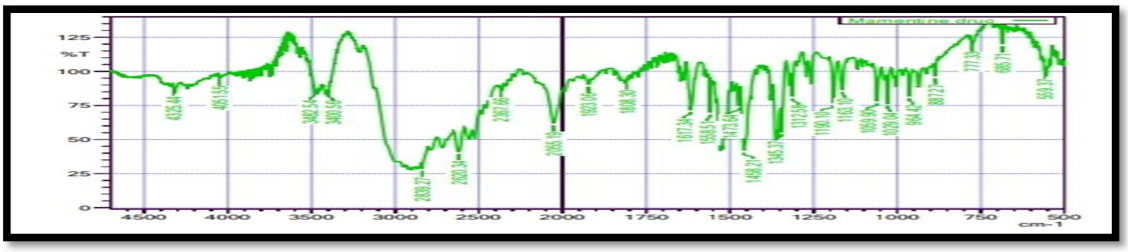

Fig. 5: Spectra of pure drug memantine HCl

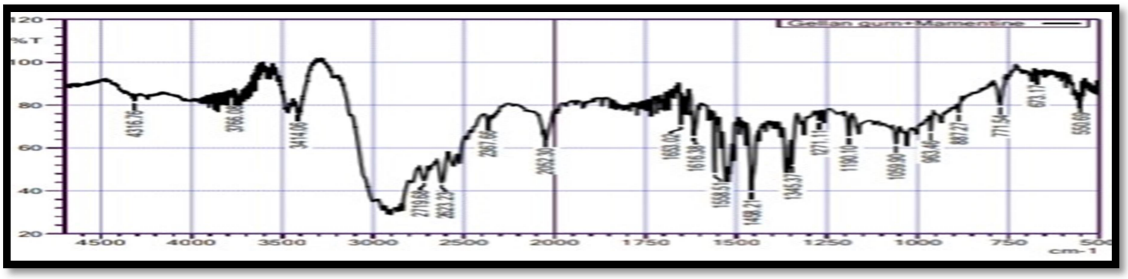

Fig. 6: Physical mixture of memantine HCl + gellan gum

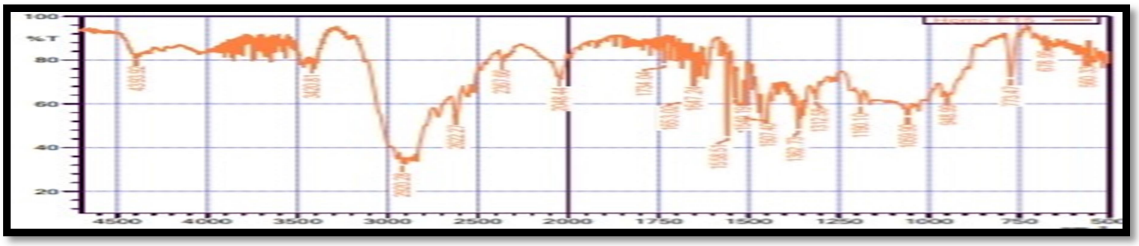

Fig. 7: Physical mixture of memantine HCl + HPMC E15

Table 4: Interpretation data of FTIR

Materials	Characteristics functional group	Standard value peaks (cm^{-1})	Observed value peaks (cm^{-1})
Memantine HCl	N-H Streching	3300-3370	3400
	C-H Streching	2700-3000	2839.27
	C=N Streching	1590-1660	1617.34
	CH_3 Streching	1350-1480	1473.64
	C-C Streching	750-1100	777.33
Physical mixture of memantine HCl and gellan gum	N-H Streching	3300-3370	3414.06
	C-H Streching	2700-3000	2719.68
	C=N Streching	1590-1660	1616.38
	CH_3 Streching	1350-1480	1458.21
	C-C Streching	750-1100	771.54
Physical mixture of memantine HCl and HPMC	N-H Streching	3300-3370	3420.81
	C-H Streching	2700-3000	2920.28
	C=N Streching	1590-1660	1647.24
	C-C Streching	750-1100	773.47

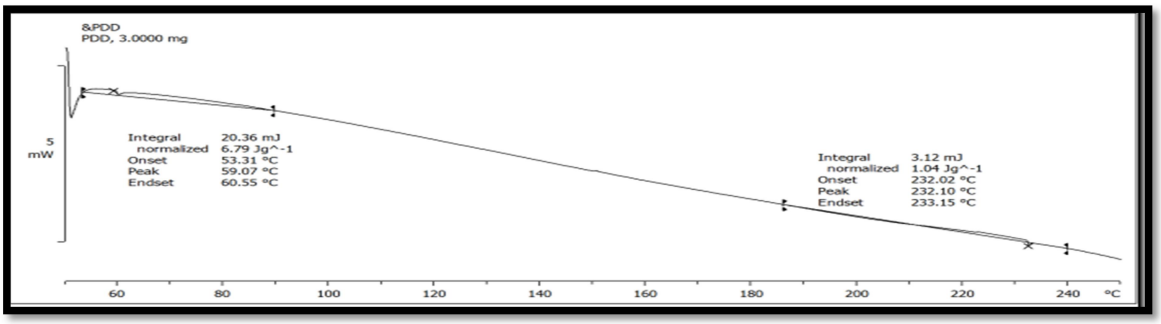

Fig. 8: DSC graph of Memantine HCl

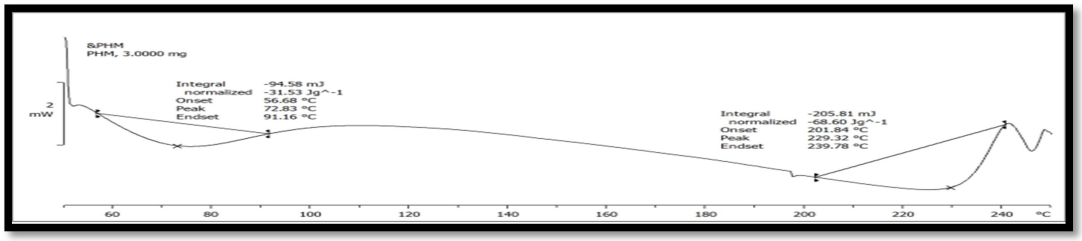

Fig. 9: DSC graph of physical mixture of Memantine HCl + gellan gum + HPMC E15

Table 5: Degree of gelation of gellan gum

No. of formulation	Degree of gelation
F1	(+) weak gelation
F2	(++) immediate gelation for few hours (less stiff gel)
F3	(+++) immediate release for extended release (stiff gel)
F4	(+++) immediate release for extended release (stiff gel)

Table 6: Viscosity of formulations

State	Spindle no.	Speed (rpm)	Viscosity (Cps)			
			F1	F2	F3	F4
Solution	3	50	162±0.25	416±0.29	716±0.44	756±0.54
		100	263±0.38	545±0.31	818±0.27	840±0.48
	4	50	368±0.21	686±0.26	820±0.056	852±0.32
		100	428±0.44	806±0.52	900±0.39	931±1.112
Gel	3	50	784±1.140	878±1.136	1085±1.42	1325±0.216
		100	861±1.123	983±0.930	1096±1.50	1417±0.393
	4	100	957±0.950	1090±1.101	1112±0.274	1536±1.124

Table 7: Drug Content of formulations

Formulation	Drug Content (%)
F1	89.9±3.2
F2	90.7±1.4
F3	85.3±2.6
F4	80.4±3.2

Table 8: Mucoadhesive strength of formulations

Sr. no	Formulation	Mucoadhesive strength (Mean ± SD) (dyne/cm^2)
1	F1	4271.56±0.32
2	F2	6556.45±0.56
3	F3	1550.73±0.25
4	F4	2812.83±104.50

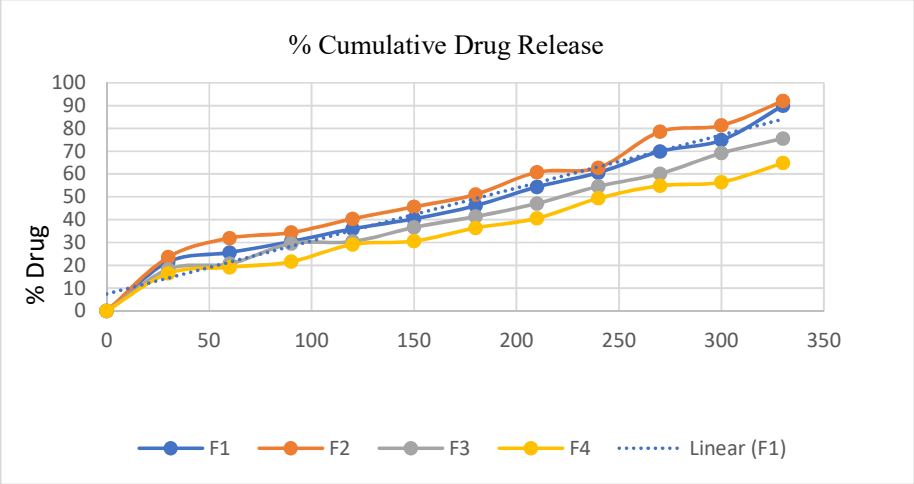

Fig.10: In vitro drug release profile of in situ gel formulation

Table 9: Percentage drug release from in situ gel formulation

Time (min)	% Cumulative Drug Release			
	F1	F2	F3	F4
0	0	0	0	0
30	21.43	23.58	18.25	16.45
60	25.61	31.9	20.67	19.19
90	30.4	34.37	29.55	21.61
120	36.04	40.41	30.4	29.19
150	40.37	45.65	36.65	30.62
180	46.15	51.07	41.37	36.4
210	54.37	60.78	47.07	40.61
240	60.61	62.76	54.62	49.4
270	69.9	78.55	60.15	54.84
300	74.85	81.29	69.19	56.48
330	89.89	91.97	75.58	67.8

Table 10: Drug release kinetic data from selected in situ gel formulation

Equation	Regression coefficient value
Zero order kinetics	0.968
Higuchi plot	0.9457
First order kinetics	0.5621
K.P plot	0.4265

CONCLUSION:

Ion activated *in-situ* gelling system for Memantine HCl was formulated by using gellan gum as a polymer for nasal administration to improve the therapeutic effectiveness. The gel also demonstrated effectively for gelation, viscosity, drug content, drug release properties along with good mucoadhesive strength. Hence the Ion activated *in-situ* nasal gel could be used as a viable alternative to enhance the therapeutic efficacy of Memantine HCl.

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