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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF PREGABALIN *IN SITU* NASAL GEL

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ABSTRACT

The aim of the present study was to formulate and characterize mucoadhesive pregabalin *in situ* nasal gels for brain delivery. Pregabalin acts as an anti epileptic drug and is used in chronic pain and other psychological disorders. Mucoadhesive nasal gels were prepared using combination of polymers like HPMC K4M, carbopol 934 and sodium alginate. A total of 5 gel bases were prepared and were characterized in terms of clarity, viscosity, gelation temperature, gelation time, muco adhesive strength, gel strength and *in vitro* permeation studies. The results showed that muco-adhesive strength and viscosity increases with increase in polymers concentration. *In vitro* drug permeation profiles showed that pregabaline *in situ* gel F1 provided a better controlled release of 68.89% than the other formulations and it exhibited better *in-situ* gelling properties, pH, gelling temperature, clarity, viscosity and gel strength. Mucoadhesive nasal gel of Pregabalin is a novel dosage form which delivers the drug directly via nasal cavity to brain through trigeminal neural pathways and provides controlled release of the drug.

KEYWORDS: Novel dosage form, Pregabalin, Carbopol 934, HPMC, Sodium alginate, Mucoadhesive nasal gel.

INTRODUCTION

Nasal drug delivery has now been recognized as a promising route for drug delivery due to its capability of transporting a drug to systemic circulation and central nervous system.[1] Though nasal mucosa offers improved bioavailability and quick onset of action of the drug, main disadvantage associated with nasal drug delivery is muco-ciliary clearance due to which drug particles get cleared from the nose before complete absorption through nasal mucosa. Therefore, mucoadhesive polymeric approach can be successfully used to enhance the retention of the drug on nasal mucosal surface.[2] Stimuli responsive polymers possess liquid state at the room temperature and in response to nasal temperature, pH and ions present in mucous, can undergo *in situ* gelation in nasal cavity.[3] Smart polymers are not only able to enhance the retention of the drug in nasal cavity but also provide controlled release, ease of administration, enhanced permeation of the drug and protection of the drug from mucosal enzymes.[4] Thus smart polymeric approach can be effectively used for nasal delivery of peptide drugs, central nervous system drugs and hormones.

In the nasal cavity, nasal mucosa has high blood perfusion rate, providing higher absorption of drug as compared to other route, as well as increased bioavailability of drug.[5] To improve the nasal retention time of *in situ* gel with nasal mucosa bio-compatible mucoadhesive polymers are used. *In- situ* gelation is a process of gel formation at the site of action after the formulation has been applied at the site.[6] *In situ* gel phenomenon is based upon conversion of liquid solution of drug formulation into semi-solid mucoadhesive key depot. It permits the drug to be delivered in a liquid form or solution form.

MATERIALS AND METHODS

Pregabalin was obtained as a gift sample from Symed labs, Hyderabad, India, Carbopol 934, HPMC and sodium alginate were purchased from SD fine chemicals. All the reagents and solvents were of analytical reagent (AR) grade.

Preparation of *in situ* nasal gel bases

Gels were prepared as per the previous research (Kola M etal) using cold method.[7] Benzalkonium chloride and sodium metabisulphite were dissolved in distilled water and sodium alginate was added and stirred for 30 mins

until completely dispersed. HPMC and carbopol 934P were added and allowed to hydrate overnight with stirring using magnetic bead. Dispersion obtained above was stirred at 1000 rpm for 10 mins. Now to get the polymer dispersion enough water was incorporated to make up to 100 mL. (Fig 1) The prepared gel bases were subjected to clarity and gelation tests.[8,9]

Table 1: Preparation and preliminary evaluation of gel bases.

Gel base Codes	Carbopol934p (gms)	HPMC (gms)	Sodium alginate (gms)	Clarity	Gelation
G1	-	1.30	0.75	++	+++
G2	0.45	1.30	-	++	+
G3	0.45	1.0	-	+	+++
G4	0.45	1.30	0.75	++	+++
G5	0.45	1.30	0.50	++	++

Clarity
+++: Very Clear
++: Clear
+: Turbid

Gelation
-: No Gelation
+: Gelation Occurred in Few Mins and Remained for Hours
++: Gelation Immediately Occurred and Remained for Hours
+++: Gelation Occurs Immediately and For Prolonged Periods

Optimization: From the above Table 1 showing gelation and clarity of the gel bases G2, G3 and G5 bases were selected for formulating as they showed better gelation and clarity. Formulations were prepared by adding 25mg of drug to the gel bases. These formulations were further studied for evaluation tests like viscosity determination, pH determination, *EX-vivo* permeation studies etc.

Table 2: Formulation of Pregabalin *in situ* nasal gel.

Formulations	F1	2	F3
Drug	25mg	25mg	25mg
Sodium alginate	-	-	0.07g
Hpmc	0.13g	0.1g	0.13g
Carbopol 934p	0.045g	0.045g	0.045g

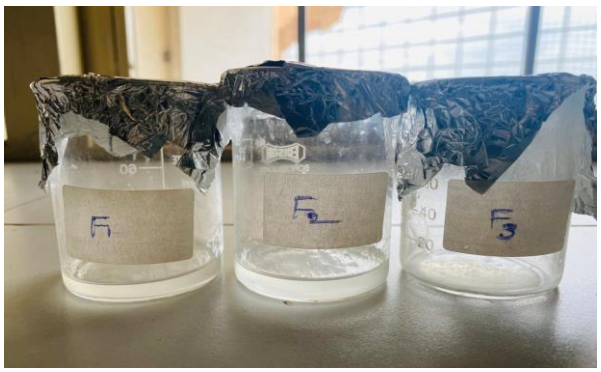

Fig. 1: Formulations of Pregabaline *in situ* nasal gel.

Evaluation parameters of *in situ* gels

Gelation:[8,9] The gelling ability was assessed by placing a drop of dispersion in a vial containing 2ml of simulated nasal electrolyte solution (SNES), freshly prepared and maintained at 37°C using a thermostat regulated water bath the gelling ability was scored in terms of consistency, ability to flow freely and ability to retain gel intactness.(Table 3)

Table 3: Composition of SNES.

Composition of SNES	Quantity
NaCl	0.877g
KCl	0.298g
$CaCl_2$	0.059g
Distilled water	100ml

Viscosity:[10] Viscosity of the *in-situ* gel systems was determined using Brookfield viscometer DV-II+Pro coupled with S-94 spindle (Brookfield Engineering Laboratories Inc., MA, USA). The prepared gel formulations were transferred to the beaker. The spindle was lowered perpendicularly into the gel at l00 rpm and temperature was maintained at 37 ± 0.5 °C. All the measurements were performed in triplicates.

Determination of pH:[12] One ml of the prepared gels was transferred to a 10 ml volumetric flask, and the solution was diluted with distilled water. The pH of resulting solution was determined using a digital pH meter, which was previously calibrated using phosphate buffers at pH 4 and pH 7.

Gel strength:[13] Sample (50 g) was placed in a 100 ml graduated cylinder. Gelation was carried out by placing the formulations in a thermostat at 37 °C. The strength of the gel was determined by measuring the time taken by a weight of 35 g to sink 5 cm in the gel.

Mucoadhesive strength:[14] *Ex vivo* mucoadhesive strength was determined using fresh sheep nasal mucosa. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed thrice with distilled water and phosphate buffer (pH 6.4). Modified balance method was used to design the experiment.

***In vitro* diffusion studies**[15]**:** Franz diffusion cell having a capacity of 15ml was used for in vitro diffusion study of in-situ gel. Dialysis (0.22micro meter) or cellophane

membrane (12000-18000 mol.wt) with diffusion area 0.8 cm^2 is used.60 ml of phosphate buffer (6.4-6.6pH) was prepared and membrane was soaked with phosphate buffer (6.4- 6.6 pH). The receptor compartment was filled with phosphate buffer (pH 6.4) at 37 °C. The solution was stirred at 100 rpm. The gel (25 mg) was placed on the nasal mucosa and the compartments were clamped together. One ml of the sample was withdrawn at predetermined time intervals from receptor compartments and immediately replaced using phosphate buffer (pH 6.4). After filtering through 0.45 µm filter and appropriate dilution, the samples were analyzed for drug content at 210nm.

Gelation Temperature[16]: A magnetic bead and 10 ml of sample solution were put into a 30 ml transparent vial placed in a low temperature digital water bath. A thermometer was placed in the sample solution. The solution was heated at the rate of I'C/m with the continuous stirring. The temperature at which the magnetic bead stopped moving due to gelation was considered as gelation temperature.

Gelation Time[17]: Gelation time of prepared *in situ* gel formulation was measured by placing 2 ml of the gel in 15 ml borosilicate glass test tube. This test tube was placed in water bath (37‡2"C) and gelation time was noted when there was no flow of the gel when test tube was inverted.

Determination of gel strength[18]: Gel strength was measured by placing 50 g of formulation in a 100 cm3 graduated cylinder and gelled at 37°C using thermostat. A piston of weight 35 g was placedonto the gelled solution and allowed to penetrate 5cm in the gel. Time taken by weight to sink 5cm was measured.

Spreadability[19,.20]: To determine the Spreadability of the gel, approximately 1 g gel was placed at the center of the glass plate (20 cm × 20 cm). This glass plate was covered with another glass plate of the same size. Next, the weight of 1 g was carefully applied on the upper side of the plate; as a result, the gel spreads out in between the plates. After one minute the weight was removed and the diameter of the spread area (cm) was measured.

RESULTS AND DISCUSSION

Selected gel bases were utilized to prepare pregabalin formulations. The pH of the formulations were measured using a digital pH meter and the pH range of the formulations were in the range (5.5 to 6.5). F1 formulation exhibited highest viscosity, less gelation time, good spreadibility and gel strength.(Table 4) It exhibited controlled release of 68.89% in 6 hours.(Fig 2)

Table 4: Evaluation parameters of pregabalin *in situ* nasal gel.

Formulation codes	pH	Clarity	Viscosity (cps)	Gelation	Gelation time(sec)	Mucoadhesive force(dynes/cm2)	Spreadability (gm.cm/sec)	Gel strength (seconds)
F1	5.9±0.01	+++	70.8	+++	20±0.15	3740.79±0.33	26.33±1.22	130±0.77
F2	5.6±0.01	++	16.8	+	100±0.14	3621.10±0.12	27.41±0.98	120±0.31
F3	5.2±0.01	+	29.3	++	60 ±0.12	3536.76±0.41	20.56±1.10	80±0.55

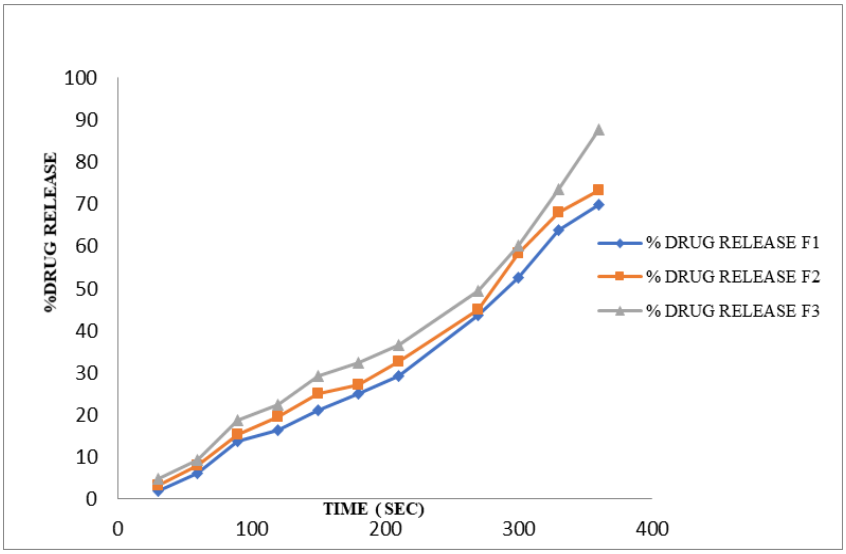

Fig. 2: Cumulative Drug Release of Pregabalin Formulations.

CONCLUSION

Gel bases were prepared using combinations of polymers. Depending on the clarity and gelation, gelation time, gelation temperature, gel strength of gel bases **G_2**, **G_3**and **G_5** gel bases were selected. To these gel bases drug was added and **F_1**, **F_2**, **F_3** formulations were prepared.

Prepared formulations were evaluated for clarity, pH, gelation, gel strength, gelation temperature, viscosity, mucoadhesive strength, drug content and *in vitro* drug permeation. Among all formulations, $\mathbf{F_1}$ formulation exhibited better *in situ* gelling properties, mucoadhesive properties and prolonged drug release. Thus nasal *in situ* gels can be used for prolonging drug delivery to brain.

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