Original Article

Nasal mucoadhesive thermoreversible *in situ* gel of phenytoin sodium for epilepsy

Gyan Mohan[1], Sandeep K. Singh[1,2], Mary Koshy[3], Pooja Chawla[1,4], Koshy M. Kymonil[1,5]*

[1]Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology and Management, Lucknow, Uttar Pradesh, India, [2]Central Drug Research Lucknow, Uttar Pradesh, India, [3]Babu Yugraj Singh Pharmacy College, Lucknow, Uttar Pradesh, India, [4]ISF College of Pharmacy, Moga, Punjab, India, [5]Yash Raj Institute of Pharmacy, Lucknow, Uttar Pradesh, India

Correspondence:
Koshy M. Kymonil, Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology and Management, Lucknow, Uttar Pradesh, India.
Phone: +918874758393.
E-mail: koshykoshy0571@gmail.com
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ABSTRACT

Introduction: The aim of the present study was to formulate and characterize nasal mucoadhesive thermoreversible *in situ* gel of phenytoin sodium for the treatment of Epilepsy. **Procedure:** The *in situ* gel was prepared by cold method using thermoreversible polymer Pluronic F127, polyethylene glycol 4000, and propylene glycol which would enhance nasal residence time, absorption of drug across nasal-mucosal membrane, improve bioavailability, and dose reduction. The *in situ* gel was characterized in terms of gelation temperature, gelation time, pH, viscosity, drug content, mucoadhesive strength, and percentage cumulative release. **Results:** The gelation temperature and gelation time of the various formulations were found to be in the range of 28–38°C and 90–164 s, respectively. The pH was found to be in the range of 5.9–6.8. Mucoadhesive strength of various formulations was found to be between 47.032 and 126.775 g. The cumulative percentage release of phenytoin sodium from various formulations was found to be in the range of 39.2–53.2%. **Conclusion:** The formulated phenytoin sodium *in situ* gel is an ideal vehicle for specific treatment of epilepsy. Sustained and prolonged release of the drug, good stability, and biocompatibility characteristics make the *in situ* gel dosage forms reliable.

Keywords: Cold method, *in situ* gel, phenytoin sodium, pluronic F127

INTRODUCTION

Intranasal administration represents a viable option for local and systemic delivery of various therapeutic compounds. The large surface area of the nasal mucosa affords a rapid onset of therapeutic effect, potential for direct-to-central nervous system delivery, no first-pass metabolism, and non-invasiveness; all of which may maximize patient convenience, comfort, and compliance.[1]

A gel is a solid, jelly-like material that can have properties ranging from soft and weak to hard and tough. Gels are defined as a substantially dilute cross linked system, which exhibits no flow when in the steady-state. By weight, gels are mostly liquid, yet they behave like solids due to a three-dimensional cross linked network within the liquid.[2]

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The nasal cavity is covered by a thin mucosa which is well vascularized. The absorbed drug from the nasal cavity will pass through the mucus layer which is the first step in absorption. A drug molecule can be transferred quickly across the single epithelial cell layer directly to the systemic blood circulation without first-pass hepatic and intestinal metabolism. The effect is often reached within 5 min for a smaller drug molecule. Nasal administration thus is used as an alternative route to oral administration especially for those drugs which extensively get degraded in the gut/liver and for drugs having poor absorptivity.[3] However, mucociliary clearance is a rate-limiting factor for nasal route administration.[4]

Thermoresponsive gelling materials constructed from natural and synthetic polymers can be used to provide triggered action and therefore customized products such as drug delivery and regenerative medicine types as well as for other industries.[5] Thermosensitive sol-gel reversible hydrogels are the aqueous polymeric solutions which undergo reversible sol to gel transformation under the influence

of environmental conditions such as temperature and pH which results in *in situ* hydrogel formation.[6] The gelation of hydroxypropyl methylcellulose and methylcellulose is due to the hydrophobic interaction between the methoxy substituted molecules. The molecules of these polymers are hydrated at low temperature and there is little polymer-polymer interaction other than simple entanglement. As the temperature is raised, polymers lose their water of hydration and become some gel like structure with low viscosity. Eventually, when sufficient dehydration of the polymer occurs, polymer-polymer association takes place, and the system approaches an infinite network structure. Micelle formation at the critical micellization temperature as a result of poly-propylene oxide (PPO) block dehydration is another mechanism of gel formation in some polymers as poloxamer.[7]

Phenytoin sodium is a potent anti-epileptic drug effective for preventing different kinds of epilepsy. The usual adult dose for seizures is oral (except suspension), loading dose is 1 g orally divided in three doses (400 mg, 300 mg, and 300 mg) given at 2 h intervals. Then normal maintenance dosage started 24 h after loading dose.[8]

Its conventional dosage form such as tablet and suspension give poor bioavailability due to low absorption. Thus, the purpose of envisaging the present study was to develop intranasal delivery system of phenytoin sodium using thermoreversible polymer Pluronic F127 (PF127), polyethylene glycol 4000, and propylene glycol, which would enhance nasal residence time, absorption of drug across nasal-mucosal membrane, improve bioavailability, and dose reduction.

MATERIALS AND METHODS

Chemicals

Phenytoin sodium was gifted by Zydus Cadila, Ahmedabad while Pluronic F127, polyethylene glycol and propylene glycol were procured from Sigma-Aldrich (St Louis, MO, USA)., Merck India Mumbai and Sd Fine Chem. Ltd. Mumbai, respectively. All solvents and reagents used were of analytical grade.

Methods

Optimization of thermoreversible polymer

Pluronic F127 and Phenytoin sodium were dissolved in distilled water. The concentration of PF127 was selected so as to obtain thermoreversible gel at minimum possible concentration. The physiological range of the nasal mucosal temperature lies between 32 and 34°C. PF127 vehicles with concentration varying from 18% w/v to 21% w/v were screened preliminarily to decide lowest possible concentration [Table 1]. The liquid was left at 4°C until a clear solution was obtained. Thermoreversible gels were prepared using cold method.[9] Optimized concentration of PF127 was used for further study of effect of mucoadhesive polymer on gelation temperature and mucoadhesive strength.

Preparation of *in situ* nasal gel

Phenytoin sodium along with propylene glycol and polyethylene glycol 4000 was dissolved in distilled water by agitation at room temperature. After cooling the solution to 4°C, PF127 was added slowly with agitation. The resulting dispersion was then kept overnight at 4°C until clear and viscous transparent solution was formed. Finally, the volume was adjusted by adding cold distilled water [Table 2]. Furthermore, optimized concentration of PF127 was used to study the effect of PEG 4000 on gelation temperature in the concentration range of 1.5–2.0%.[10]

Characterization of *In situ* nasal gel

Gelation temperature studies

A 5 ml aliquot of gel was transferred to test tubes immersed in a water bath at 25°C and sealed with aluminum foil. The temperature of the water bath was increased in increments of 0.5°C and left to equilibrate for 1 min at each new setting. The samples were then examined for gelation, which was said to have occurred when the meniscus would no longer move on tilting through 90°. The gel melting temperature, the temperature at which a gel starts flowing on tilting through 90° was recorded.[11]

Gelation time studies

For assessing gelation time, a glass slide was used. Provision was made so as to keep the slide in hot water. One drop of formulation was placed on the slide at an angle of 120° and time taken for converting it into gel was recorded.[11]

pH studies

The apparent pH of a product may alter on storage as chemical change. 1 ml quantity was transferred to 10 ml volumetric flask and diluted using distilled water to make 10 ml. pH of the resulting solution was determined using pH meter.

Viscosity studies

The viscosity of various formulations was measured using Brookfield Viscometer.

Table 1: Optimization of Pluronic F127

Conc. of Pluronic F 127(%)	Phenytoin sodium (% w/v)	Gelation Temperature (°C)	Gelation time (s)
18.0	2	38	164
18.5	2	35	152
19.0	2	34	146
19.5	2	32	129
20.0	2	30	120
20.5	2	29	98
21.0	2	28	90

Table 2: Composition of various formulation of *in situ* nasal gel

Formulation code	Propylene Glycol (%w/v)	PEG 4000 (%w/v)	Distilled water
A1	1.0	1.5	q.s.
A2	1.0	2.0	q.s.
A3	2.0	1.5	q.s.
A4	2.0	2.0	q.s.
A5	1.0	1.5	q.s.
A6	2.0	1.5	q.s.

Ex vivo mucoadhesive strength

Mucoadhesive strength is the force required to break the binding between the model membrane and the mucoadhesive material. In general, the equipment used is a texture analyzer. In this test, the force required to remove the formulation from a model membrane is measured. The semipermeable membrane was placed on equipment's platform. A mobile arm containing an analytical probe was then moved down into a sample held in a flask placed on the equipment's platform. Speed rate 0.1 mm s^{-1}, contact time 30 s, and applied force 50 gm were preset. From the resulting force-time curve, adhesiveness was calculated.[8,11]

Drug content

From the formulation, 1 ml was taken in 100 ml volumetric flask, 50 ml of distilled water was added with gentle shaking and final volume was adjusted to 100 ml. From this solution, 1 ml quantity was transferred into the 100 ml volumetric flask and final volume was made to 100 ml using distilled water to get 10 mg/ml. Finally, the absorbance of prepared solution was measured at 222.5 nm using UV-Visible spectrophotometer.[11]The characterization is indicated in Table 3.

Ex vivo permeation study

In vitro studies can help in investigating mechanisms of skin permeation of the drug. The K-C diffusion cell is one of the most widely used static designs for studying *in vitro* permeation. This cell has a static receptor solution reservoir with a side arm sampling port. A thermal jacket is positioned around the receptor compartment and is heated with an external circulating bath. Modified K-C diffusion cell was used to study *in vitro* drug diffusion profile using 100 ml of distilled water which was added to the acceptor chamber. The temperature within the chamber was maintained at 34°C by circulating hot water. After a pre-incubation time of 20 min, formulation equivalent to containing 40 mg of phenytoin sodium was placed in donor chamber. At predetermined time intervals, 1ml of sample was withdrawn from the acceptor compartment and replaced the sample volume with distilled water after each sampling, for a period of 8 h. The samples were diluted to 10 ml using distilled water, filtered, and used for analysis. The amount of permeated drug was determined using UV-visible spectrophotometer (λ_{max} = 222.5 nm).

RESULTS AND DISCUSSION

Nasal *in situ* gel of phenytoin sodium was prepared by cold method using various concentration of Pluronic F127. The formulations were optimized based on gelation temperature, gelation time, drug release, and mucoadhesive strength.

The gelation temperature and gelation time of the various formulations were found to be in the range of 28–38°C and 90–164 s, respectively. Gelation temperature of the optimized formulation A2 was found to be 32°C. Gelation time of the optimized formulation A2 was found to be 71 s. The concentration of PEG 4000 was adjusted in such a manner that could be attributed to its interference with the process of micellar association of PF127 formulations may form gel at nasal physiological temperature.

The pH was found to be in the range of 5.9–6.8. The pH for all formulations was well within range of nasal pH and will not cause irritation in the nose.

Mucoadhesive strength of various formulations was found to be between 47.032 and 126.775 gms. Mucoadhesive strength of optimized formulation A2 was found to be 119.74 g. The addition of PEG 4000 to the formulations decreased the mucoadhesive strength in concentration dependent manner; this might be related to the decrease in viscosity caused by PEG 4000. Viscosity of optimized formulation A2 was found to be 31,650 cps.

In *ex vivo* drug release study, the release enhancing effect of PEG 4000 might be due to its higher water solubility and its viscosity lowering effect. Permeability coefficient increases with increasing concentration of the PEG 4000, which proves its release enhancing effect. The percentage cumulative release of Phenytoin sodium from A2 was found to be 48.17% [Figure 1].

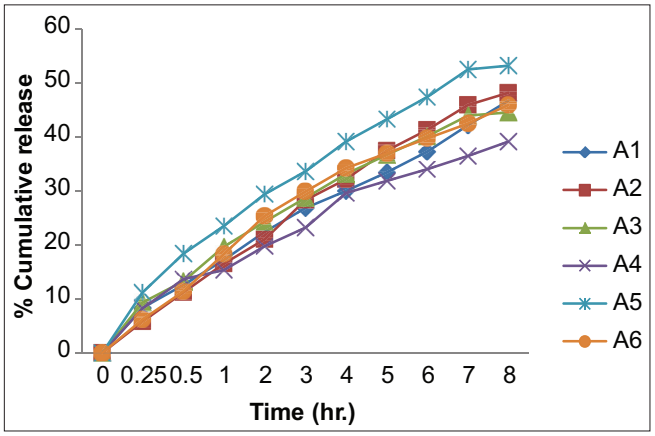

Figure 1: *Ex vivo* nasal permeation study of various formulations

Table 3: Characteristics of all formulations

Code	Appearance	pH	Gelation Temp.(°C)	Gelation Time (Sec)	Viscosity (Cps)	Drug Content (%)	Mucoadhesive Strength (g)
A1	+++	6.1	31	79	30,650	94.46	78.949
A2	+++	6.5	32	71	31,650	96.12	119.742
A3	+++	5.9	33	62	25,650	95.36	126.775
A4	+++	6.8	31	74	29,850	93.86	53.935
A5	+++	6.1	28	68	43,200	96.32	47.032
A6	+++	6.4	30	86	36,200	89.02	61.752

+++Represent glassy clear

CONCLUSION

The primary requirement of a successful controlled release product focuses on increasing patient compliance which the *in situ* gels offer. Nasal *in situ* gel of Phenytoin sodium was prepared by cold method using different ratio of Pluronic F127 and PEG 4000. The formulations were optimized based on gelation temperature, gelation time, drug release, and mucoadhesive strength. Sustained and prolonged release of the drug, good stability, and biocompatibility characteristics make the *in situ* gel dosage forms very reliable.

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