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Formulation and Evaluation of in Situ Gel Model Naproxen

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Abstract: ***The development of in situ gel system has received considerable attention over the past few years. This interest has been sparked by advantages shown by in situ forming delivery system such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation from which the drug gets released in a sustained and controlled manner. Various biodegradable polymers that are used for the formation of in situ gels. Mainly in situ gel administered by oral ocular, recta1, vaginal, injectable and intaperitoneal routes. This review presents a brief introduction to in situ gels, various approaches for in situ gelling system, different types of polymers used and evaluation of in situ gelling system.[1] In situ gel , Hydroxy propyl methyl cellulose K4, and Sodium alginate were used with different ratios in an attempt to develop topical gel formulations of naproxen.[2] The overall results of this study suggest that the F3 formula could be used in the preparation of naproxen gel containing in situ gel as a topical dosage form to be used in the treatment of inflammation.[3]***

Keywords: Naproxen, Hydroxy propyl methyl cellulose K4, Sodium alginate, Water, Topical Drug Delivery, Gel

1. Introduction

Topical drug delivery is a very attractive route for local and systemic treatment. It can easily penetrate deeper into the skin and hence give better absorption. In the topical gel, effectiveness of the drug is achieved easily and successfully whereas the systemic side effects can be minimized or avoided. They are more effective and lesser toxic as compared to conventional oral dosage forms. They avoid gastrointestinal (GI) - irritation and prevent the metabolism of the drug in the liver. Topical preparations of many drugs are available in the market that includes GI-irritating, non-steroidal antiinflammatory drugs, local anesthetic and antihistaminic agents, antibacterial, antifungal [4]. In situ gelling systems consist of polymer that exhibit sol-to-gel phase transitions in the cul-de-sac which improves patient compliance due to change in specific physico-chemical parameters like pH, temperature and ionic strength in the environment.

The development of in situ gel systems has received considerable attention over the past few years. This interest has been sparked by the advantages shown by in situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. In situ gelling systems are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. In contrast to very strong gels, they can be easily applied in liquid form to the site of drug absorption. At the site of drug absorption they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymerscan be used for the production of in situ gels. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and ionic crosslinking. So, in situ gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. Recent advances in in situ gels have made it possible to exploit the changes in physiological uniqueness in different regions of the GI tract for the improved drug absorption as well as patient's convenience and compliance. In the current niche of drug delivery technologies, in situ gels have made an irreplaceable space because of their unique characteristics. This review presents a brief introduction to in situ gels, various approaches for in situ gelling system, different types of polymers used and evaluation of in situ gelling system.

The sol-to-gel phase transition on the eye surface depending on the different methods employed which consist of thermo-sensitive, ion-activated and electric-sensitive, magnetic field-sensitive, ultrasonic-sensitive and chemical material-sensitive varieties[5]. Sodium alginate, an ophthalmic gel forming mucoadhesive polymer was chosen, as the polymer and Hydroxy Propyl Methyl Cellulose (HPMC) as copolymer. Sodium alginate, family of linear un-branched polysaccharides, the sodium salt of alginic acid, is a natural hydrophilic polysaccharide containing two types of monomers, β-D-mannuronic acid (M units) and α-L glucuronic acid (G units) residues. The polymer, Sodium alginate, which undergoes instantaneous gel formation due to formation of calcium alginate by virtue of its interaction with divalent cation (Caþ2) present in lachrymal fluid (pH 7.4). Alginate can be ionically crosslinked in the presence of divalent cations. Hydroxy Propyl Methyl Cellulose (HPMC) is incorporated as a viscosity enhancer to further aid in accomplishment of sustained drug delivery. HPMC is semisynthetic, inert, viscoelastic polymer which is non-ionic nontoxic, a good carrier for pharmaceutical application which exhibits high swelling capacity[6].

2. Materials and Methods

Naproxen was taken as gift sample by Arti chemicals Ltd., Mumbai. Hydroxy Propyl Methyl Cellulose was received from Svas International, Mumbai. Sodium alginate was obtained from Arti chemicals mumbai. All other ingredients used in this study were of analytical grade.

2.1 Methods

1) Using magnetic stirrer different ratio of polymer & Copolymer dissolved in Distilled Water.
2) To this aqueous solution of drug added with contineous stirring.
3) PH of resultant solution was adjudted to 6.5 using 0.1N HCL.

Preparation of in Situ Gel

When the preparation of gel Using the magnetic stirrer at different ratio of polymer (f1,f2 f3) and copolymer dissolution in distil water .when this aqueous solution of drug added with continuously stirring and PH of resultant solution was adjust to 6.5 using 0.1NACL.

Table 1: Composition of in Situ Gel

Ingredient	F1	F2	F3
Naproxen	1mg	1mg	1mg
Sodium alginate	1.5mg	1mg	0.5mg
HPMC	1mg	1.5mg	0.5mg
Distilled Water	100ml	100ml	100ml

2.2 Evaluation of In situ gel

- **Clarity**

Clarity test was observed by visual inspection under a good light, viewed against a black and white background, with the contents set in motion with a swirling action. Also it was observed for formation of turbidity or any unwanted particles dispersed in the solution.

- **Gelling capacity**

The gelling capacity of the prepared formulation was determined by placing a drop of the formulation in a beaker containing 50 ml of freshly prepared concentrated calcium chloride solution and was visually observed for gelling time.

or

Gelling capacity for ion-activated in situ gels was determined by adding 1 ml of the system to a vial containing 3 ml of freshly prepared STF (pH 7.4), shaking for 30 s and visually assessing the strength of the gel formed. Formulae showing appropriate results were selected to be subjected to further testing.

- **Rheological studies**

The primitive ophthalmic solution, suspension, and ointment dosage forms are clearly no longer sufficient to combat these diseases, and current research and development efforts to design better therapeutic systems are the primary focus of this research work. The aim of the present investigation is to formulate an in situ gel and from our prior knowledge we know that gels show thixotropic behaviour, so rheological studies are to be performed.

The viscosity measurements were carried out using Brookfield viscometer. The developed formulations were placed in the sampler tube using spindle no. 4. Viscosity of the prepared formulations was measured by using Research Rotator and Oscillatory Rheometer. The gel under study was placed in the small sample holder and the spindle was lowered perpendicularly into it. The spindle was rotated at varying speeds and the suitable speed was selected .

- **Measurement of pH**

Each formulated batch, pH was measured using pH meter which was previously calibrated using standard buffers of pH 4 and pH 7 as per the established procedure.

- **Stability studies**

The stability of the optimized in-situ gel was conducted on the selected formula. Ten ml of formula was stored in closed amber color glass vials at different conditions, that is, refrigerated condition (5±2 °C), room temperature (23±2 °C) and stress condition, i.e. high temperature (40±2 °C, 75% RH). The sample was withdrawn at a predetermined time interval, that is, 6 and 12 w and the clarity, pH.

- **Effect of storage**

The formulations were selected to study the effect of storage on their stability. For each formula, two amber colored vials each containing 25 ml of the preparation were stored at room and refrigerator temperatures (25 C and 4 C, respectively) for 3 months. Samples were taken at 1, 2, and 3 months and evaluated by performing the following tests.

- **Visual examination**

The samples taken from stored formulae were visually inspected to observe any changes in color or physical properties. The drug content of those samples was determined as described before and values were compared with the samples of freshly prepared formulae.

3. Result and Discussion

Characterization of Naproxen

Description

The sample of naproxen was a white amorphous, odorless powder.

Identification

Melting Point-Melting point of drug sample was observed in the range of 154- 1560C (complied with the literature). The two main prerequisites of an in situ gelling system are viscosity and gelling capacity. Aqueous solutions of varying concentrations of HPMC and alginate were prepared and evaluated for viscosity and gelling capacity. Different concentrations of HPMC and sodium alginate were tailored and their effects were observed. Of them the one with suitable consistency required for in situ gelling was considered for further study. Alginate forms stable hydrogel in the presence of certain divalent cations (e.g. Ca2þ and Sr2þ) through the ionic interaction between the cation and the carboxyl functional group of G moieties located on the polymer chain.

Table 2: Evaluation of gel formulations

Formulatiom	Clarity	Ph	Drug content	Geling capacity	viscocity
F1	Opaque / No turbidity/Clear solution	6.4	95±0.33	6 to 8 (sec)/	13.5cps
F2	Opaque / No turbidity/Clear solution	6.6	98±0.45	Within sec	11.5cps
F3	No turbidity/ Clear solution	6.4	98±1.02	6 to 8 (sec)/	14.5cps

Clarity and pH

The formulation was prepared by using various concentrations of sodium alginate along with HPMC in different ratios. The formulation prepared were clear without any turbidity and suspended particles or impurities. The pH of in situ gel solution was found to be around 6.4

Gelling capacity:

Gelling capacity is coded as describe in Table According that shows immediate gelation and for extended period

Rheological Studies

The viscosity was directly dependent on the polymeric content of the formulations. Addition of HPMC led to increase in the viscosity of formulations and exhibited more pseudo-plasticity. The formulation which is in the solution form should have an optimum viscosity that will allow for easy instillation into the eye, which would undergo a rapid sol to gel transition.

4. Conclusion

Ciprofloxacin hydrochloride was successfully formulated as in situ gel-forming eye drops using sodium alginate and HPMC. Thus the above results demonstrate that the alginate and HPMC mixture can be used as an in situ gelling vehicle to enhance ocular bioavailability and patient compliance. Physicochemical characterization and in vitro drug release studies indicated that the developed formulation may prove to be a viable alternative to conventional eye drops and ointment in terms of ease of administration with added benefits of sustained drug release which may ultimately result into improved patient compliance.

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