1. Aims and Objectives

"The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them." .......

.....William Lawrence Bragg
1. Aims and Objectives of present work

In situ forming gels are formulations, applied as solutions, which undergo gelation swelling after instillation due to physico-chemical changes inherent to biological fluids. In situ gel forming systems can also be described as low-viscosity solutions that undergo phase transition in the respective physiological condition to form viscoelastic gels due to conformational changes of polymers in response to physiological environment. The main advantage of this formulation is the possibility of administering accurate and reproducible quantities in contrast to already gelled formulations. These in situ gelling systems are used for various types of drug delivery systems like oral, ocular, periodontal, rectal and vaginal drug delivery system.

We have explored development and optimization of in situ gelling systems for ocular and periodontal application.

The development of novel ophthalmic formulations is highly desirable for improving therapeutic index and patient compliance. While a wide variety of novel and advanced drug delivery systems and technologies are introduced in treating ophthalmic conditions, eye drops remain as a primary ophthalmic dosage forms for eye diseases. In ophthalmic drug delivery, the physiological constraints imposed by the protective mechanisms of the eye lead to low absorption of drugs and sometimes a short duration of the therapeutic effect. When a conventional ocular formulation is dropped into the eye, there is 10-fold reduction of the drug concentration in 4–20 min because of effective tear drainage and blinking occurring in eye. The limited permeability of the cornea also contributes to the low absorption of ocular drugs. Because of tear drainage the main part of the administered drug is transported via the naso-lacrimal duct to the GI-tract where it may be absorbed, sometimes causing side effects. The rapid elimination of administered eye drops often results in a short duration of the therapeutic effect making a frequent dosing regimen necessary, which results into patient non-compliance. Hence controlled delivery of drugs to the ocular tissues is also growing in importance with the emergence of more potent drugs and those with short biological half-lives for treatment of diseases in which there was no previous satisfactory therapy, such as age-related macular degeneration. A variety of methods
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have been used to prolong precorneal drug retention of a formulation such as, the use of viscous polymer solutions, ointments, gels, colloidal carriers, and solid polymeric devices. However, some of these delivery systems interfere with vision (e.g., ointments), may cause crusting of eyelids and are often very uncomfortable (e.g., inserts). These drawbacks can be overcome by the concept of in-situ gel systems. A significant increase in precorneal residence time of drugs, improving corneal penetration of drugs and consequently increase in bioavailability can be achieved using delivery systems based on concept of in situ gel formation. Literature survey have reported that sustained in-situ gel forming ophthalmic formulations can be formulated using polymer which is either pH responsive (carbopol 940 0.6% w/v) or temperature sensitive (poloxamer-407 24%w/v) or ion sensitive (gellan gum 0.6 - 0.8% w/v).

Gellan gum is a gel-forming polysaccharide approved by the US Food and Drug Administration in 1992 for food use. Gellan gum is an anionic polysaccharide which forms a clear gel in the presence of mono or divalent cations. Carbopol is a polyacrylic acid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5. Carbopols are mucoadhesive polyacrylic acid polymers and mucoadhesion is an attractive property to exploit for extending residence time in the eye. It has been reported in literature that when formulating sustained in-situ gel forming system using single physiological approach (pH or Temperature or Ion responsive) the polymer content required is very high and which may result into several problems. Therefore, it was necessary to explore the simultaneous use of ion sensitive polymer gellan gum and pH sensitive/mucoadhesive carbopol polymers to overcome the problems associated when using only one polymer for ocular in situ gelling systems. In order to reduce the total polymer content and improve the gelling properties, an ocular drug delivery system based on a combination of Gellan gum and Carbopol could be developed. Few efforts on ophthalmic ion-sensitive in situ gelling and mucoadhesive/ pH sensitive dosage form were available to date. There has been no systemic study on ocular drug delivery system using gellan gum and carbopol utilizing Design of Experiments (DOE) to explore combined use of these polymers for ocular drug delivery.
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Hence it was decided to apply a statistical technique – Design of Experiments to optimize the selected polymers. Olopatadine hydrochloride is indicated for the treatment of the signs and symptoms of allergic conjunctivitis. The recommended dose of Olopatadine HCl is 1-2 drops of 0.1 % w/v solution in affected eye every 6 hrs and 2 hourly in the case of severe allergic infections. This required a frequent dosing which results into patient non-compliance and increase in cost. Olopatadine HCl is a drug having low permeability which results into poor bioavailability.

An ideal ophthalmic formulation should be one that has a suitable strength to endure the lacrimal fluid dilution without rapid precorneal elimination after administration; and has a suitable mucoadhesive force to improve the retention of the drug in the precorneal area with enough corneal permeability. Hence considering the above points it was necessary to employ simultaneously ion sensitive gellan gum and mucoadhesive/pH sensitive carbopol 934P to formulate ocular in situ gelling systems along with cornea permeability enhancer.

We have also explored the application of In situ Gel forming Systems for periodontal Drug Delivery.

Recent therapies for treating periodontitis have incorporated various antibiotic and antimicrobial agents. Chemotherapeutic agents may be administered systemically or delivered locally for treatment of periodontal diseases. The local delivery of antimicrobial therapy to periodontal pockets has the benefit of putting more drugs at the target site while minimizing exposure of the total body to the drug. Pocket irrigation has been found to reduce microbial levels and provide some improvement in clinical parameters, but the response to therapy has been mixed and the therapy requires daily professional for best results. The lack of drug retention in the periodontal pocket is probably the chief reason for these mixed results. Due to the inadequacies of both peroral administration of antimicrobial agents and the use of antibacterial mouthwashes, recent treatments have focused on the use of controlled release intra-pocket antimicrobial drug delivery systems. By delivering chemotherapeutic agents directly to the periodontal tissue, greater concentrations are achieved and systemic side-effects are reduced. Therefore, it is desirable to develop a novel drug delivery system that would enhance patient compliance and maintain a

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localized, effective drug concentration at the site of infection for a predetermined duration. Such a system should simultaneously erode and release its drug so that the device disappears at the end of the releasing period, thereby eliminating the need for reapplication or device removal. Considering these points in relation to conventional periodontal drug delivery systems it was necessary to formulate a liquid dosage form that should have the following characteristics.

- Easy to deliver into the periodontal cavity.
- Remains in periodontal cavity for extended period of time.
- Provides controlled drug release for longer duration of time.

Drug delivery systems based on the concept of in situ gel formation in the periodontal pocket are able to provide the above-mentioned characteristics to the formulation. Poloxamer-407 is known for exhibiting the phenomenon of reverse thermal gelation under a certain concentration and temperature. However, in this case, the gelation temperature (GT) is most important parameter for its performance. Therefore, PEG 600, could be used as a regulatory substance for gelation temperature. Although the poloxamer-based in situ gel can gel at physiological condition without rapid elimination after administration, but it exhibits a relatively short residence time when compared to gellan gum or carbopol due to gradual dilution by salivary or gingival fluid, which cannot promise a high concentration of drug in periodontal pocket. So, a retentive dosage form based on a so-called muco/bioadhesive polymer, which is capable of attaching to mucosal surfaces, offers the prospects of prolonging the residence time of an periodontal drug delivery system at the sites of drug absorption and ensures optimal contact between the formulation and the absorbing surface. Though thermosensitive poloxamer copolymers are widely employed, they suffer from a major drawback of having weak mechanical strength, which leads to rapid erosion. One interesting approach to solve this problem is to focus on blends of poloxamers with chitosan. Poloxamer and chitosan can be used in combination for the preparation of in situ forming gels with improved mechanical and mucoadhesive characteristics for prolonged residence time in periodontal pocket. Doxycycline has a broad spectrum of activity and is effective against gram-positive and gram-negative aerobic and anaerobic bacteria, spirochetes and mycoplasma. Periodontal pathogens
implicated in the progression of periodontal disease are particularly susceptible to Doxycycline hyclate. Hence it was selected as a model drug for our study.

Objectives of present work

The objective of the present research study was to formulate, develop and optimize in situ gelling systems for ocular and periodontal therapeutic applications. To achieve these objectives the following specific aims of this research work were set.

1. To formulate, develop and optimize ion sensitive and mucoadhesive/pH sensitive in situ gelling ocular drug delivery systems containing Olopatadine HCl using Gellan gum (Gelrite) and Carbopol 934P in combination.

2. To formulate, develop and optimize a novel mucoadhesive, syringeable drug delivery system for controlled delivery of Doxycycline hyclate to periodontal pocket based temperature sensitive in situ gelling systems.

3. To optimize the ratio of gellan gum and carbopol 934P when used simultaneously to formulate an ideal sustained release ocular in situ gel forming drug delivery system using Box-Behnken Experimental Design.

4. To characterize the in situ gelling systems and gels with respect to viscometric properties as a function of polymeric composition. (Gellan gum and Carbopol 934P, Chitosan and Poloxamer-407).

5. To investigate the effect of Benzododecinium bromide as corneal permeability enhancer using its different concentration as per Box-Behnken Experimental Design.

6. To optimize the ratio of chitosan and Poloxamer-407 when used simultaneously to formulate an ideal periodontal in situ gel forming drug delivery system using Box-Behnken Experimental Design.

7. To investigate the effect of chitosan and PEG 600 on gelation temperature of poloxamer-407 using its different concentration as per Box-Behnken Experimental Design.

8. To develop and optimize syringeable periodontal in situ gelling system with sufficient mechanical properties using chitosan, poloxamer-407 and PEG 600.

9. To compare the developed in situ gelling system with respective marketed preparation.