Controlled drug delivery is the phasing of drug administration to the needs of a condition at hand so that an optimal amount of drug is used to cure or control the condition in a minimal time. Research in controlled drug delivery during the past decade has led to increasingly sophisticated means to sustain drug delivery. It has also created greater awareness among the pharmaceutical industry, regulators, health care professionals and the public at large about the therapeutic advantages of controlled drug delivery systems. Presently, the majority of these systems are based on synthetic polymers that differ in the degree of erodibility, swellability, and sensitivity to the biological environment in which they are placed.¹

The area of controlled drug delivery is also growing wider in scope and in terms of route of administration. There has been explosion in the research on drug delivery via different routes which sustain the drug release to the systemic circulation. Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional delivery systems.

The primary aim of controlled drug delivery systems is to achieve as well as to maintain the drug concentration within the therapeutically effective range required for the treatment for a predetermined period. These delivery systems are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of drug to a tissue. Although, significant progress has been made in this area, more needs to be explored and utilized in treating many clinical disorders which needs special attention.²

The advancements in the field of controlled drug delivery led to the development of novel drug delivery systems, which revolutionized the manner in which medication are given and offer many advantages like³

- Controlled delivery of active agent at predetermined rate
Introduction

Chapter 1

- Maintenance of optimal and effective drug level for prolonged duration
- Reduction of untoward effects
- Increase in patient compliance
- Reduction in frequency of dosing
- Delivery of drug in the vicinity of site of action
- More efficient utilization of active agent

The drug can be used effectively in treating an ailment/disease/condition by employing/incorporating drug into novel drug delivery systems, where the drug release is controlled by various mechanisms.²

1. Rate pre-programmed drug delivery systems
   - Polymer membrane permeation-controlled drug delivery systems
   - Polymer matrix diffusion-controlled drug delivery systems
   - Microreservoir partition-controlled drug delivery systems

2. Activation-modulated drug delivery systems
   - Physical means (Osmotic pressure, hydrodynamic pressure, mechanically activated, magnetically activated, sonophoresis activated, iontophoresis activated, and hydration activated DDS)
   - Chemical means (pH-activated, ion-activated, and hydrolysis-activated DDS)
   - Biochemical means (Enzyme activated and biochemical-activated DDS)

3. Feedback regulated drug delivery systems
   - Bioerosion regulated DDS
   - Bioresponsive DDS
   - Self-regulating DDS

4. Site-targetting drug delivery systems
In general, controlled release systems can be broadly classified as:

- Diffusion controlled systems
- Dissolution controlled release systems
- Diffusion and dissolution controlled systems
- Water penetration controlled systems
- Chemically controlled systems
- Hydrogels
- Ion-exchange resins

In situ gels are the hydrogels formed by chemical or physical cross-linking that imbibe a considerable amount of water, while maintaining their shape. In situ gels have wide applications in applying hydrogels for macromolecular drugs, protein/gene, tissue barrier and tissue engineering. The polymeric system forms hydrogels by a simple phase transition (sol-gel transition) in water without any chemical reaction. This system provides simplicity and safety in in vivo situations.
1.1 NEED FOR THE STUDY

Controlled drug delivery represents one of the most rapidly advancing areas with significant contribution to human healthcare. This field of pharmaceutical technology has grown and diversified rapidly in recent years. The development of in situ gels has received considerable attention over 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, site-specific delivery, improved patient compliance and comfort. The formulation is liquid prior to injection and gels upon contact with stimuli much like a semi-solid implant. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. These systems can be injected in to the body, unlike implants which may require surgical implantation. In situ gels improve availability of drug at the site of action, bypasses first pass metabolism and a desirable level of drug is released in a controlled manner.

By developing such novel in situ gelling systems, it may be possible to reduce the toxic effects caused by repeated systemic/oral administration of drugs, prevent drug resistance and reduces cost of therapy.

In this direction, the research involved design, formulation and evaluation of in situ gels with drug that is targeted for specific ailments/ organs;

1. In situ gels of Azithromycin dihydrate for treatment of chronic periodontitis
2. In situ gels of Pilocarpine hydrochloride for prolonged pre-corneal residence
3. In situ gels of Methotrexate sodium for treatment of rheumatoid arthritis
4. Floating in situ gels of Losartan potassium for prolonged retention in stomach
1.1.1 In situ gels of Azithromycin dihydrate for treatment of chronic periodontitis

Periodontitis is a general term for an inflammatory condition caused by specific microorganism or group of specific microorganisms affecting the physiological and structural organs supporting the teeth, which results in progressive destruction of periodontal ligaments and tooth to become loose and eventually fall off. The first step in periodontal treatment is to improve the oral hygiene by reduction of oral bacteria, associated calcified and non calcified deposits. The most common procedure to manage the disease involves scaling and root planing to remove bacterial deposits in the subgingival area. This may be followed by surgery to reduce the depth of the periodontal pocket. Primary objective is to achieve and maintain therapeutic levels of drug for the required period of time, to inhibit or kill putative pathogens, without any harm to the tissue. The use of antibiotic agents in conjunction with nonsurgical therapy is beneficial and can eliminate the need for surgical intervention. Delivering chemotherapeutic agents directly to the periodontal tissues/pocket is beneficial in eradicating the bacterial population in periodontal pocket. Azithromycin dihydrate, a macrolide antibiotic has wide spectrum of activity against microbes inhabited in periodontal pocket. Azithromycin dihydrate is indicated for use in the treatment of chronic periodontitis.

In the present study, the feasibility of delivering Azithromycin dihydrate locally into periodontal pocket as in situ gel for the non-surgical treatment of chronic periodontitis is evaluated.
1.1.2 *In situ* gels of Pilocarpine hydrochloride for prolonged pre-corneal residence

Conventional dosage forms used for treating eye infections/disorders locally face many constraints in achieving ocular bioavailability. The pre-corneal constraints responsible for the poor ocular bioavailability of conventional ophthalmic dosage forms are nasolachrymal drainage, lacrimation, tear dilution, tear turnover and poor conjunctiva absorption. Drug solution drainage away from the pre-corneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently, ocular bioavailability of topical dosage forms. The instilled dose leaves the pre-corneal area within two minutes of instillation in humans. Further, the amount of solution that can be hold in cul-de-sac is very small (0.8 ml), within this small volume only about 1% of drug may be absorbed and available for systemic circulation. In order to overcome the drawbacks of the conventional dosage forms, there is a need of novel ocular drug delivery system to increase the contact time, corneal permeability and bioavailability. *In situ* gels can be conveniently dropped as a solution into the conjunctival sac of the eye; which transforms into gel upon contact with eye. This delivery system has the ease of administration similar to an ophthalmic solution and has a long retention time because of the gel formation.

The focus of the present investigation was to prepare and optimize Pilocarpine *in situ* gels for improved ocular contact time, enhancing corneal permeability thereby improving bioavailability.
1.1.3 In situ gels of Methotrexate sodium for treatment of rheumatoid arthritis

Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by persistent inflammation of the synovium, local destruction of bone and cartilage and a variety of systemic manifestations which may ultimately result in functional disability. Rheumatoid arthritis is characterized by the inflammation and destruction of multiple joints. It not only disturbs quality of life, but also shortens the lifespan of affected patients by causing co-morbidities such as cardiovascular diseases.

The ultimate goal in the treatment of RA is to prevent joint damage and restore normal life. Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) have been widely used in combination to control disease activity without complete success. Methotrexate (MTX), a folic acid antagonist that inhibits DNA and RNA synthesis, is the most potent, and commonly prescribed synthetic DMARD, and can retard joint destruction. MTX is used in low doses for the treatment of RA and is termed as the “Gold Standard Treatment for Rheumatoid Arthritis”.

Treating RA early with MTX has been recommended, however, the adverse effects and toxicities of prolonged (oral/SC injection) usage have limited the benefits. To reduce the drug related toxic effects on the body, there is a need of dosage form which can ensure the availability of MTX at right amounts with less exposure to body tissues and still be effective in the treatment of RA.

In the present investigation, an attempt has been made to formulate Methotrexate in situ gels as a biodegradable injectable drug delivery system for effective management/treatment of RA.
1.1.4 Floating \textit{in situ} gels of Losartan potassium for prolonged retention in stomach

Oral drug delivery still remains the most convenient and highly preferred route of drug administration. Because of its simplicity and possibility of self dosing, it is regarded as user friendly dosage form with high degree of patient compliance.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time. To achieve gastric retention, the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must also resist premature gastric emptying. Gastro retentive drug delivery systems would be retained in the stomach and can release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. A low density \textit{in situ} gel capable of floating in gastric fluids is a novel concept for prolonging gastric retention. Drug with an absorption window in stomach are suitable candidates for formulating as floating \textit{in situ} gels.

Losartan Potassium is an orally active non-peptide angiotensin II receptor (type AT1) antagonist used in the treatment of hypertension due to mainly blockade of AT1 receptors. It is readily absorbed from the stomach and upper part of small intestine. The main limitation of low therapeutic effectiveness is due to narrow absorption window, poor bioavailability (25-35\%) and short biological half life (1.5-2 h).

In this study, floating \textit{in situ} gels of Losartan potassium was designed and evaluated as a gastro retentive drug delivery system for prolonging gastric residence and improving absorption.