The aim of the study was to formulate and evaluate novel \textit{in situ} gelling drug delivery systems as controlled drug delivery systems. The drugs employed in the study are Azithromycin Dihydrate, Pilocarpine Hydrochloride, Methotrexate Sodium and Losartan Potassium. Different environment sensitive polymer/s was used to formulate \textit{in situ} gels which were evaluated by \textit{in vitro} and \textit{in vivo} studies. The research work consisted of four studies, whose significant findings are summarized below.

\textbf{I. Azithromycin dihydrate \textit{in situ} gels}

- Azithromycin dihydrate \textit{in situ} gels were aimed to provide a novel injectable and biodegradable system for the treatment of chronic periodontitis
- Azithromycin \textit{in situ} gels were prepared by “cold technique” using Pluronic F-127 (22 & 24%) and Hydroxy Ethyl Cellulose (0.5-1.5%). The prepared \textit{in situ} gels were clear & transparent with good appearance
- Azithromycin \textit{in situ} gels were free flowing solutions at refrigerated temperature; transformed to stiff transparent gels at body temperature
- Azithromycin \textit{in situ} gels were sterile, exhibited thermosensitivity; they transformed into stiff gel within short duration of time at gelation temperature
- All prepared \textit{in situ} gels were syringeable through blunt canula (needle no. 18) used for clinical procedures
- The viscosity of \textit{in situ} gel system increased with increase in both temperature of system and concentration of polymer/s employed
- The drug release from \textit{in situ} gels was retarded for 66 h, formulation A4 and A8 recorded a release of 98.67\% (54 h) and 98.89\% (66 h) respectively
- Azithromycin release from \textit{in situ} gels was by non-fickian diffusion and followed first order kinetics
• Optimized formulation A8 was selected for *in vivo* studies based on its *in vitro* characterization studies

• *In vivo* efficacy evaluation was done in human patients; 20 patients suffering from chronic periodontitis participated in the *in vivo* studies

• Clinical parameters like gingival index, plaque index, bleeding index, probing pocket depth and clinical attachment level were evaluated in human patients

• *In vivo* results indicated that azithromycin *in situ* gel was effective in reducing the severity of periodontitis; it improved all the clinical parameters evaluated

• Azithromycin *in situ* gels was stable during the stability testing period

• The results of study indicated that azithromycin *in situ* gels is a suitable alternative for the non-surgical treatment of chronic periodontitis

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**II. Pilocarpine Hydrochloride *in situ* gels**

✓ Pilocarpine hydrochloride *in situ* gels were prepared for increasing the pre-corneal contact time of delivery system (drug) and the eye surface

✓ Pilocarpine *in situ* gels were prepared using water soluble chitosan (1.75-2.25%) and sodium glycerophosphate (25-27.5%) as *in situ* gelling agents

✓ The prepared gels were clear and transparent with good appearance.

✓ Pilocarpine was uniformly distributed in the gels, the concentration varied from 97.82±0.17% to 99.20±0.09%.

✓ The *in situ* gels exhibited thermosensitivity with gelation temperature close to body temperature and gelled quickly

✓ A significant increase in viscosity was observed between the formulations at 8°C and 37°C. Formulation P3 and P2 exhibited the highest viscosity values of 877.67±21.2 cps (at 8°C) and 10132.00±48.1 cps (at 37°C) respectively.
✓ Pilocarpine in situ gels were isotonic to lachrymal secretions
✓ Release of pilocarpine from in situ gels were sustained for 6 to 12 h
✓ The mechanism of drug release was by non-fickian diffusion, followed first order kinetics; best fit model was “peppas” model
✓ Optimized formulation P5 was selected for in vivo irritancy testing in rabbits
✓ Ocular irritation studies were conducted by using 6 rabbits. Various corneal and conjunctival parameters were studied during in vivo studies
✓ Results of in vivo studies in rabbits indicated that formulation P5 is non irritant; an excellent ocular tolerance was noted. No ocular damage or abnormal signs to the cornea, iris and conjunctivae was observed
✓ Pilocarpine in situ gels were stable during the stability study period
✓ The results indicated that delivering pilocarpine as in situ gel is a novel approach for prolonging the pre-corneal contact time and increasing drug residence time in eye

III. Methotrexate Sodium in situ gels
   ✷ Methotrexate sodium in situ gels were prepared to provide a novel injectable, biodegradable system for treating/ managing rheumatoid arthritis
   ✷ Methotrexate sodium in situ gels were prepared by “cold technique” using Pluronic F-127 (20%) as polymer and Pluronic F-68 (2-6%)/ Polycarbophil (0.5-1.5%)/ HPMC E15 LV (0.5-1.5%)/ carbopol 934 (0.5-1.5%) as co-polymer
   ✷ Methotrexate in situ gels were clear and transparent with good appearance
   ✷ In situ gels were sterile and methotrexate was uniformly distributed in all the formulations
Methotrexate in situ gels exhibited thermosensitivity; they gelled well below body temperature with short duration of time.

The viscosity of formulations increased with increase in temperature and concentration of polymer and co-polymer used.

All formulations were syringeable through needle no. 18 used during studies.

In vitro drug release studies were conducted by both static and dynamic diffusion methods to study the effect of diffusion condition on drug release.

Methotrexate release from in situ gels were controlled up to 120 h by both methods; Formulation M6 retarded the drug release for 120 h (99.22% - static method, 99.75% - dynamic method).

In vitro release data was subjected to student’s t-Test, a statistically significant difference was observed between two diffusion study conditions, implying that both conditions are different statistically.

Methotrexate release was controlled by non-fickian diffusion process; followed first order kinetics.

Stability studies indicated that the methotrexate in situ gels were stable during the study period.

A novel drug delivery system for prolonged release of methotrexate which reduces dose, dosing frequency, associated side effects, cost of therapy and there by improves patient compliance was developed.

This study demonstrated that methotrexate sodium in situ gels may be suitable for use as an injectable drug delivery system for treating rheumatoid arthritis.
IV. Losartan Potassium *in situ* gels

- Losartan potassium floating *in situ* gels are prepared for increasing the drug retention time in stomach, for increasing drug absorption and bioavailability.

- Losartan *in situ* gels were formulated using gellan gum (0.75-1.0%) and HPMC (0.05-0.2%) as polymers; CaCO$_3$ as gas generating agent.

- Losartan *in situ* gels were capable of floating with short floating lag time, most formulations gelled within 2 min.

- Losartan *in situ* gels gelled quickly when placed in pH 1.2 solution, formulation L4 showed a least gelation time of 1.33 sec and formulation L9 showed a maximum of 5.33 sec. They continued to float for a duration >12 h.

- The water uptake by the gels were low, L1 showed highest water uptake of 13% (2 h) and L4 showed least water uptake of 4.6% (2 h).

- The viscosity of gels increased with an increase in concentration of gellan gum. Increasing the calcium carbonate content in the formulation simultaneously increased the viscosity at all polymer concentrations studied.

- All formulations showed a significant decrease in viscosity with increase in speed of rotation during viscosity evaluation, implying shear thinning behavior.

- The concentration of polymers (gellan and HPMC) affected the drug release from the floating *in situ* gels. As the concentration of polymer increased, the amount of drug release decreased from the formulations.

- All the formulations showed first order release, the release mechanism was found to obey peppas model, drug transport indicated fickian diffusion mechanism.

- An ideal floating *in situ* gel can be prepared by using optimum concentration of gellan gum, HPMC and calcium carbonate to prolong the drug residence time in stomach.
Formulation of floating \textit{in situ} gel was easy and simple, it benefits the patients who have difficulty in swallowing and for those drugs where absorption is predominant in stomach.

Stability studies indicated that the losartan potassium \textit{in situ} gels were stable under normal conditions of storage at room temperature.

This study demonstrated that losartan \textit{in situ} gels may be suitable for use as a gastroretentive drug delivery system.

Thus the present research work has been carried out adopting standard procedures to meet the set objectives. The research findings obtained from the studies were found to be satisfactory. It can be concluded that novel \textit{in situ} gels can be proposed as a suitable drug delivery system to deliver drugs to specific part of the body in a controlled manner.