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Novel Polymeric *In Situ* Gels for Liquid Oral Sustained Release Drug Delivery System

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ABSTRACT

The pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. These type of drug delivery system in principle are capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. Compared to conventional controlled release formulations, *in-situ* gel systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance, and comfort. *In-situ* gel reduces fluctuation in drug effect, counter activity of the body and extended time over effective concentration. Substantial amount of work has been done on the basis of the route of administration through nasal, ocular, oral, vaginal, and rectal drug delivery systems by using different classes of drugs. Controlled drug delivery of an anti-diabetic agent can be greatly achieved by using various solid oral dosage forms but may not be suitable for patients with age related dysphagia or clinical/pathological conditions like tracheostomy, congestive heart failure, postoperative conditions etc. The liquid oral sustained release *in-situ* gel drug delivery systems are very suitable for the pediatric, geriatric, dysphagic or bed ridden patients. Present review emphasized on importance, ideal characteristics of polymers used, methodology and evaluation of *in-situ* gelling system.

INTRODUCTION

Active Pharmaceutical Ingredient (API) is rarely administered solely as pure substance but almost always given in the form of dosage form or delivery system. The drug delivery system is formulated invariably using drug and excipient(s) in appropriate proportions. Drug delivery is the technique or process of administering active pharmaceutical ingredient to achieve a therapeutic response in humans or animals. The objective of any drug delivery system is to make available therapeutic amount of drug to the proper site in the physiological system. Principally a dosage form is formulated to achieve predictable therapeutic response of the drug included in the formulation.

The drug delivery system can be classified as:

- Conventional drug delivery system
- Modified controlled drug delivery system.

It has been recognized that conventional drug delivery system, for instance, simple tablets, solution and injections may not be the best mode of drug administration. To improve the compliance towards drug administration and reduce the dosage fluctuation, more efforts, novelty, and innovations have been entrusted to designing effective delivery systems, specially controlled drug delivery system.

The above problems of conventional dosage form stimulate the formulator both in industry and laboratory level to develop modified release dosage form. “The delivery of a drug at predetermined rate and/or location according to the need of body and disease for definite time period is termed as modified/controlled drug delivery. [2]

In-situ gel forming systems are mainly used as vehicles for sustained drug delivery. *In-situ* forming polymeric delivery systems are having ease of administration and reduced frequency of administration, improved patient compliance and comfort. *In-situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation, and solvent exchange. So, *In-situ* gelling system is administered as different route such as oral, nasal, ophthalmic etc.

Importance of *In-Situ* Gelling System

The major importance of the delivery system is the possibilities of administrating accurate and reproducible quantities compared to already formed gel.

- *In-situ* forming polymeric delivery system is having ease of administration and reduced frequency of administration which improve patient compliance and comfort.

- Poor bioavailability and therapeutic response of the conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that is instilled as drops into eye and undergoes a sol-gel transition from instilled dose.

- Liquid dosage formulation that can sustain drug release and remain in contact with cornea of eye for an extended period of time is ideal.

Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects. Various examples of the natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and polycaprolactone are used for formulation development of *in-situ* forming drug delivery systems.

Ideal Characteristics of Polymers Used In *In-Situ* Gelling System

A polymer used to formulate *in-situ* gels should have following characteristics:

- It should be biocompatible.

- It should be capable of adhering to mucus.

- It should have pseudoplastic behavior.

- It should have good tolerance & optical activity.

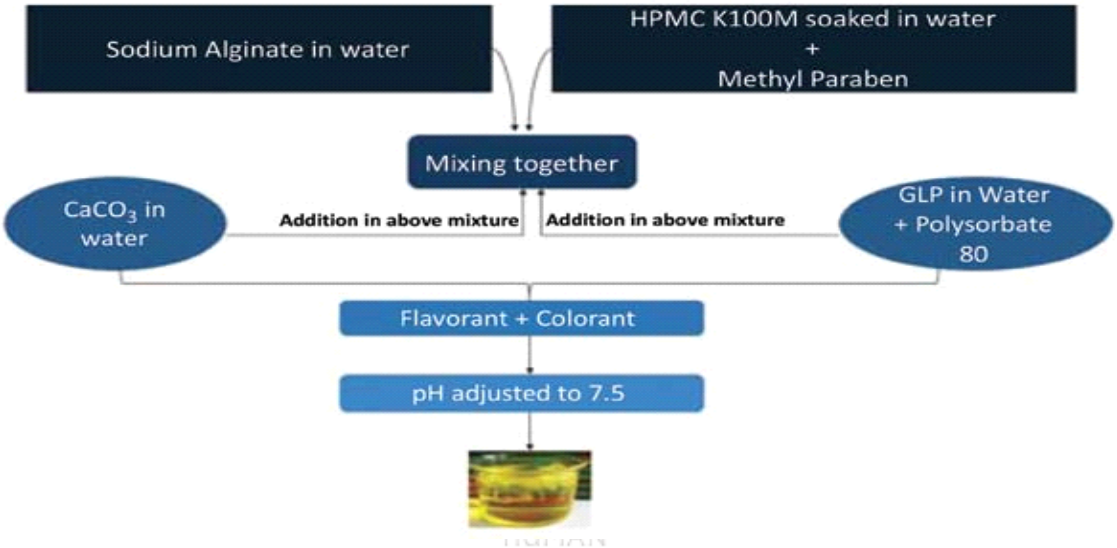
- It should influence the tear behavior.

- The polymer should be capable of decreasing the viscosity with increasing shear rate thereby offering lowered viscosity during blinking & stability of the tear film during fixation.[3]

METHODOLOGY

The main principle involved in the formation of *in-situ* gel is the pH-induced ionic gelation. Trisodium citrate complexes with free Ca^{++} and maintains the fluidity of *in-situ* gel until it reaches the stomach. When the formulation reaches the stomach, in the presence of acidic environment Ca^{++} get releases and triggers the gelation of sodium alginate.

Preparation of *In-situ* gel



Different formulations of drug were prepared using different concentration of gelling agents, like sodium alginate and calcium carbonate. Polysorbate 80 was used as wetting agent and sodium citrate was included to prevent gelation outside the gastric environment

Preliminary Studies

Preliminary studies were carried out in order to optimize the concentration of gelling agent, and fluidity maintaining agent at a concentration of sodium alginate (0.25% to 3% w/v), calcium carbonate (0.5% to 1.5% w/v) and trisodium citrate (0.15% and 0.2% w/v) respectively[4].

Evaluation

- ***In-vitro* gelling capacity**

In-vitro gelling capacity can be evaluated visually. It is measured by placing 5 ml of the gelation solution (0.1N HCL, pH 1.2) in a 15 ml borosilicate glass test tube. After a constant

interval of time, one ml of formulation is transferred slowly into test tube with the help of a pipette. When the formulation comes in contact with 0.1N HCL, it is immediately converted into stiff gel like structure. *In-vitro* gelling capacity is graded into three categories based on gelation time and time period for which formed gel remains intact.

(+) - Gelation after few minutes but disperse rapidly

(++) - Immediate gelation remains intact for 12 hours

(+++) - Immediate gelation remains intact for more than 24 hours

- ***In-vitro* buoyancy study**

It is carried out using Type II USP dissolution apparatus. The medium used is 0.1 N HCl. The temperature of the bath and medium is maintained at 37 ± 0.5^{o}C. 10ml of the formulation is transferred to 900 ml of 0.1N HCl with the help of syringe then floating lag time and floating time is noted.

- **Swelling index**

Weigh 100 mg (W1) of prepared gel and place in a petri dish containing 50ml of 0.1 N HCl. Keep it aside for 24 hrs. After 24 hrs gel is weighed (W2) and swelling index is calculated using following formulae:

W2-W1/W1 *100

Where, W1 = Initial weight of gel (100mg)

W2 = Weight of gel after 24hrs

- ***In-vitro* dissolution study**

It is carried out using dissolution test apparatus USP type II (Paddle). 900 ml of dissolution medium is used (0.1N HCL, pH 1.2 medium). The temperature and speed of the apparatus are maintained at 37±0.5^{0}C and 50 rpm respectively. Five ml of the formulation equivalent to 10mg of drug is placed into dissolution vessel. Aliquot of 5ml is withdrawn at regular intervals of time and replaced with fresh medium. Dissolution test is carried out for 24hours. Withdrawn samples are analyzed for drug concentration at maximum wavelength (λmax) of drug against the medium as the blank by using UV-Visible spectrophotometer.

- **Sol-Gel transition temperature and gelling time**

In-situ gel forming systems having thermoreversible polymers, the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube.

- **Fourier transform infra-red spectroscopy and thermal analysis**

During gelation process, the nature of interacting forces can be evaluated using this technique by employing potassium bromide pellet method. Thermo-gravimetric analysis can be conducted for *in-situ* forming polymeric systems to quantitate the percentage of water in hydrogel. Differential scanning calorimetry is used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions.

Stability Study

In this study following parameters are evaluated before and after stability study:

- Physical appearance
- Gelling capacity
- Ph
- Floating lag time
- Floating time
- Viscosity

Determination of viscosity

Viscosity of prepared formulations is determined by Brookfield programmable viscometer LV DV-II+PRO using spindle number 62 which was rotated at 100 rpm.

Determination of drug content

5 ml of *in-situ* gel (equivalent to 10 mg of drug) is measured and transferred to 100 ml of volumetric flask containing 0.1N HCL and stirred for 1hour on magnetic stirrer. The solution is filtered and suitably diluted with 0.1N HCl (pH 1.2 medium) and the drug concentration is determined by using a UV-visible spectrophotometer at maximum wavelength of drug against a pH 1.2 medium as blank solution. [1]

CONCLUSION

In-situ gel offers the primary requirement of a successful controlled release product focuses on increasing patient compliance. Exploitation of polymeric *in-situ* gel for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the *in-situ* gel dosage forms very reliable. The use of biodegradable and water soluble polymers for the *in-situ* gel formulations can make them more acceptable and excellent drug delivery systems.

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