

Microsponge Based *In Situ* Ocular Gel: A Review

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Abstract:

The microsponge delivery system is a patented polymeric system consisting of porous microspheres typically 5-300 microns in diameter. They are tiny sponge-like spherical particles that consist of numerous interconnecting voids within a non-collapsible structure. They have large porous surface through which active ingredient is released in a controlled manner. This drug delivery system was employed for the improvement of performance of topically applied drugs. Microsponges are non-toxic, non-irritating, non-allergic, can entrap or suspend a wide variety of substances, and can then be incorporated into a formulated product such as gel, cream, liquid or powder. *In situ* gelling systems are viscous liquids, which undergo a sol to gel transition when applied to the human body due to the change in a physicochemical parameters such as pH, temperature or ionic strength. In-situ gelling systems are more acceptable for the patients, since they are instilled into the eye as a solution and immediately converted into a gel when it contact with the eye.

Keywords: microsponges, *in situ* gel, sustained release, hydrogel, stimuli responsive

INTRODUCTION

Microsponges are polymeric delivery system consisting of porous microspheres of an inert polymer that can entrap the active ingredients and control their release. They are tiny sponge like spherical particles that consist of numerous interconnecting voids within a non-collapsible structure. The size of the microsponges varies usually from 5-300 μ m diameter. Microsponge delivery is one of the techniques used to sustain the release of active ingredient from topical formulations. Moreover, They can enhance the stability, reduce the toxicity by sustaining the release of the drug. Microsponges are designed to deliver an active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release. Microsponges are non-toxic, non-irritating, non-allergic, can entrap or suspend a wide variety of substances. Microsponges can be prepared by various methods such as emulsion system and liquid – liquid suspension polymerization method. Emulsion system include w/o/w emulsion solvent diffusion, o/o emulsion solvent diffusion and quassi emulsion solvent diffusion method. Quassi emulsion solvent diffusion method is the most commonly used method for the preparation of microsponges^[1]. Representation of structure of microsponge is shown in fig:1

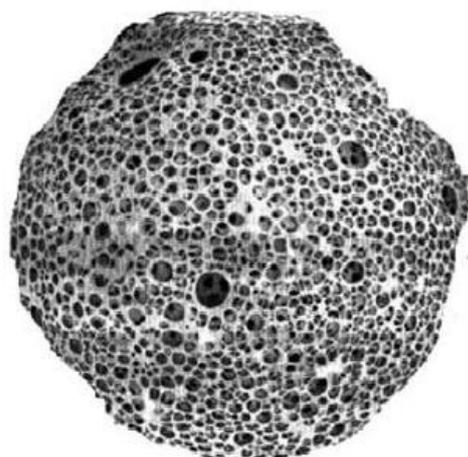


Fig:1

Systemic administration of ocular drugs has the advantage of convenient administration, yet it suffers from the disadvantage of systemic side effects and poor bioavailability. Microsponges can be incorporated into a formulated product such as gel, cream, liquid or powder. Topical administration of ocular drugs via conventional dosage form like solutions and suspensions has several problems such as nasolacrimal drainage, tear turnover, poor bioavailability. The rapid clearance of the topically applied drug into the eye often results in a short duration of pharmacological activity and therefore, they need a frequent dosing regimen. Moreover, 50%–100% of an instilled dose could undergo systemic absorption through drainage via the nasolachrymal duct. This could lead to a possible increased risk of unwanted systemic toxic effects. To overcome these problems an increase in the contact time between drug and corneal surface is required. High viscous topical dosage forms cause blurred vision and patient discomfort [2].

In situ gelling systems are viscous liquids, which undergo a sol to gel transition when applied to the human body due to the change in a physicochemical parameters such as pH, temperature or ionic strength. In-situ gelling systems are more acceptable for the patients, since they are instilled into the eye as a solution and immediately converted into a gel when it contact with the eye. Several studies showed that the pre-corneal residence time of such in-situ gelling systems are for several hours^[3].

ADVANTAGES OF MICROSPONGE BASED INSITU OCULAR GEL:

- In situ gelling system promotes mainly the ease and convenience of administration of drugs.
- Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
- To circumvent the protective barriers like drainage,

lacrimation and conjunctival absorption.

- To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
- To provide better housing of delivery system.
- Non-toxic, non-allergic

METHODS OF PREPARATION OF MICROSPONGES

Drug loaded microsponges can be prepared by one-step process or by two-step process i.e., Liquid suspension polymerization (Free Radical Suspension Polymerization) and Quasi-emulsion solvent diffusion techniques which are based on physicochemical properties of drug to be loaded. If the drug is an inert non-polar material, will create the porous structure which is called as porogen, stable to free radicals and can be entrapped with onestep process^[2,6]. Schematic representation of preparation methods of MSPs were shown in fig. 2

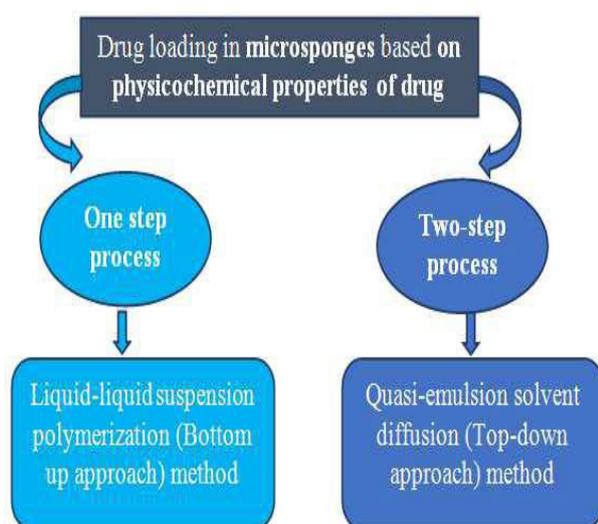


Fig :2

1) Liquid-liquid suspension polymerization

A solution containing monomers and the functional or active ingredients, which are immiscible with water are to be prepared. This is then suspended with agitation in an aqueous phase, which containing additives, such as surfactants and dispersants, to promote suspension. When the suspension is achieved with discrete droplets of the desired size, polymerization is initiated by activating the monomers either by catalysis, increasing temperature or irradiation. As the polymerization continues, a spherical structure is produced containing thousands of microsponges bunched together like grapes, forming interconnecting reservoirs. when the polymerization is complete the solid particles that result from the process are recovered from the suspension. The microsponges are then washed and processed until they are substantially ready for use. The microsp sponge products can be made using ethyl ellulose, polyvinyl alcohol, styrene and divinylbenzene or methyl methacrylate, ethylene glycol, dimethacrylate etc^[2,5,6].

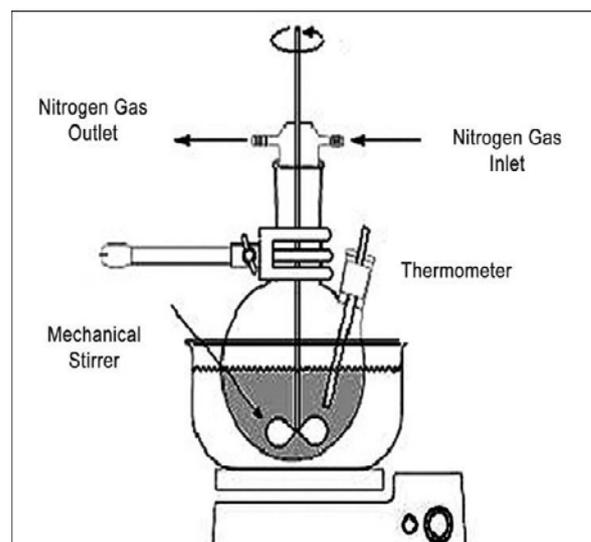


Fig :3

2) Quasi-emulsion solvent diffusion

This method consists of two steps; the internal phase of drug polymer solution should be made in a volatile solvent like ethanol or acetone or dichloromethane and added to external phase consisting aqueous polyvinyl alcohol (PVA) solution with vigorous stirring. Tri ethyl citrate (TEC) was added at an adequate amount to facilitate plasticity. After emulsification, the mixture was continuously stirred for 2 hr to form discrete emulsion globules called quasi-emulsion globules. Then the mixture was filtered to separate the rigid microparticles (MSPs). The product was washed and dried in hot air oven at 40 °C for 24 h^[1,2,6].

The schematic representation of the preparation of porous microsphere by quasi emulsion solvent diffusion is shown in fig:4

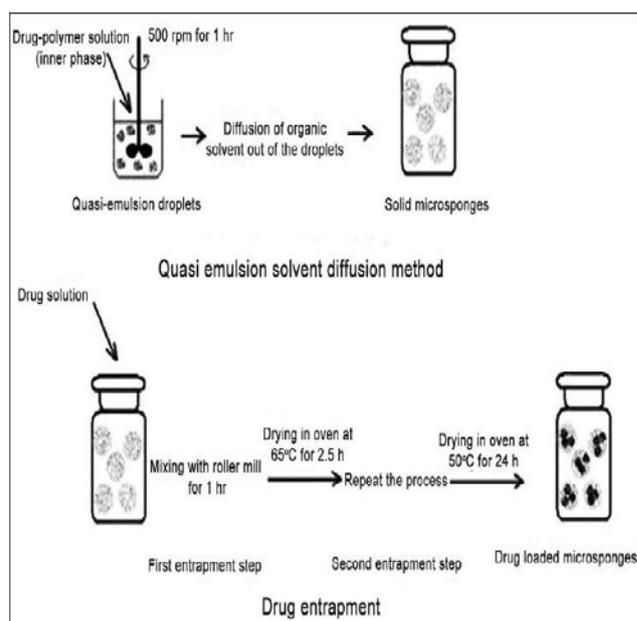


Fig :4

APPROACHES OF *IN SITU* GELLING SYSTEM

In situ gelling systems are viscous liquids, which undergo a sol to gel transition when applied to the human body. 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. But above them the most commonly methods are as follows:

1. pH-triggered system (e.g. cellulose acetate hydrogen phthalate latex),
2. Temperature dependent system (eg. pluronics and tetronics), and
3. Ion activated system (eg. gelrite)

1) INSITU FORMATION BASED ON PHYSIOLOGICAL STIMULI

A) Thermally triggered system:

Temperature sensitive hydrogels are the most commonly studied class of physiologically triggered *in situ* gelling system. These gelling system consist of polymer which undergo sol to gel transition with change in temperature. Temperature triggered *in situ* gel system which utilizes the temperature sensitive polymers that exist as a liquid form below its low critical solution temperature (LCST) and undergoes gelation when the environmental temperature reaches or is above the LCST. The Ideal critical temperature range for such system is ambient and physiological temperatures such as temperature of mucosa or skin.. The gel is formed at the precorneal temperature (35 °C) to endure the lachrymal fluid dilution without rapid precorneal elimination of instilled drug after administration [8,12,13].

B) pH triggered *in situ* gelling systems

pH sensitive *in situ* gel system consists of pH-sensitive polymers which are mainly polyelectrolyte contain an acidic (carboxylic or sulfonic) or a basic group (ammonium salts) that either accept or release protons in response to alteration in pH in the surrounding environment. At lower pH (pH 4.4), the formulation exists as a regular solution, however, it undergoes gel formation at pH 7.4, that is the pH of tear fluid.

- Polymers used in ph triggered *in situ* gel systems

The most commonly used pH-responsive polymers in ophthalmic preparation are Polyacrylic acid (PAA, Carbopol 940), polycarbophil, and cellulose acetate phthalate (CAP) [8,12,13].

C) Ion-activated *in situ* gel system

Ion-activated *in situ* gel systems are also known as osmotically triggered *in situ* gel systems where, the polymer undergoes a sol-gel transition due to changes of ionic concentration, which is typically triggered by mono or divalent cations in tear fluid mainly Na⁺, Mg²⁺ and Ca²⁺. Ion-activated *in situ* gelling systems form a crosslink with cations contained in the tear fluid, thus forming a gel on the ocular surface, which results to an extended corneal contact time. The most commonly used ion-activated polymers in ocular formulations are gellan gum (Gelrite®),

hyaluronic acid and sodium alginates [8,12,13].

Multi-stimuli responsive *in situ* gel: One of the recent excellent strategies in ocular *in situ* gelling system is the use of a combination of polymers with the different gelling mechanism, which have shown an improved therapeutic efficacy and better patient compliance. Over last current years, a number of investigations that involved the combination of thermo-responsive polymers, pH-sensitive polymers or ion-activated polymers in the same ophthalmic formulation have been reported.

EVALUATION AND CHARACTERIZATION OF *IN SITU* GELS SYSTEMS:

In situ gels may be evaluated and characterized for the following parameters:

VISCOSITY AND RHEOLOGY:

This is an important parameter for the evaluation of *in situ* gels. Viscosity and rheological properties of *in situ* forming drug delivery systems can be evaluated using Brookfield viscometer or some other type of viscometers such as Ostwald's viscometer. The viscosity of these formulations should produce any difficulties during their administration by the patient, especially during ocular administration.

SOL-GEL TRANSITION TEMPERATURE AND GELLING TIME:

For the *in situ* gel systems containing 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. Gelling time is the time for first detection of gelation as defined above [13].

GEL STRENGTH:

This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling agent used, a specified amount of gel is prepared in a beaker. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface [1,2].

IN VITRO DRUG RELEASE STUDIES:

For the *in situ* gel formulations to be administered by oral, ocular or rectal routes, the drug release studies are carried out by using the plastic dialysis cell. The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using analytical technique. For injectables *in situ* gels, the formulation is placed in the vials containing receptor media and placed on a shaker

water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed [13].

TEXTURE ANALYSIS:

The consistency, cohesiveness and the texture of *in situ* gels are assessed using texture analyzer which mainly indicates the syringeability of solution, so that the formulation can be easily administered *in vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surfaces like tissues [13].

CONCLUSIONS AND FUTURE PROSPECTS

Despite the challenges in ocular drug delivery, over the past few years, many innovative approaches are being developed to overcome the problems associated with conventional of ophthalmic preparations. The *in situ* gelling system is one the promising and extensively studied strategies that could prolong precorneal resident time and offer the sustained release drug, thus improve ocular bioavailability and therapeutic efficacy and reduce systemic absorption and toxicity. Furthermore, due to its drug release sustaining ability and reduced frequency of administration, *in situ* gel could improve patient compliance. Moreover, exploring the combination of different drug delivery approaches (i.e. microsponges loaded in-situ gelling) to develop in-situ gel has been the attractive strategies to improve ocular drug delivery system. Microsponges are non-irritating, non-allergic, non-toxic, can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as gel, cream, liquid or powder. In *in situ* gel formulation with different stimuli-responsive polymers that have high sensitivity to change in pH, temperature, and ion concentration are used for the incorporation of drug loaded microsponges [5,6,13].

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