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COMPREHENSIVE REVIEW ON THERMOSENSITIVE IN-SITU GELLING SYSTEM

Ms. Rajeshwari G. Khairnar[1*], Ms. Rachana v. vadnere[2], Ms. Praditi P. Vishe[3], Dr. Rupali R. Tasgaonkar[4]

[1*] Assistant Professor of Pharmaceutics, Yadavrao Tasgaonkar Institute of Pharmacy, University of Mumbai, Mumbai.
[2]Bachelor of Pharmacy, Yadavrao Tasgaonkar Institute of Pharmacy, University of Mumbai, Mumbai.
[3]Bachelor of Pharmacy, Yadavrao Tasgaonkar Institute of Pharmacy, University of Mumbai, Mumbai.
[4] Principal and Professor of Pharmaceutics, Yadavrao Tasgaonkar Institute of Pharmacy, University of Mumbai, Mumbai.
*Corresponding Author prajeshwari91@gmail.com

ABSTRACT:-

Drug delivery systems known as in situ forming polymeric formulations are those that are in sol form prior to body administration but undergo in situ gelation to form a gel once delivered. The drug is released in a regulated and sustained manner from gels, which are formed in response to various stimuli including pH changes, temperature fluctuations, ion presence, and ultraviolet light. In situ gels are made using a variety of polymers, such as gellan gum, poly(DL-lactic acid), poly(DL-lactide-co-glycolide), alginic acid, xyloglucan, pectin, chitosan, and poly-caprolactone. The solubility of the polymer utilized determines the choice of solvents for these.

Comparing the in situ gel forming polymeric formulations to traditional drug delivery methods reveals a number of benefits, including prolonged and sustained activity. The paper provides a thorough analysis of these kinds of polymeric systems, including their assessment, developments, and commercial formulations. Producing such devices is less complicated from a manufacturing perspective, which reduces investment and manufacturing costs.

Keywords: In situ gelling system, novel drug delivery, thermosensitive gel, polymers, formulations.

INTRODUCTION :

Any drug delivery system's main goal is to effectively alter the drug's tissue distribution and pharmacokinetic characteristics . The development of controlled and sustained release medication delivery devices has received a lot of attention throughout the last 60 years . One of the most effective new medication delivery methods has emerged: the "in situ gel" technique. With its unique feature of switching from "sol to gel," the in-situ gel drug delivery system promotes patient compliance, comfort, and a sustained and regulated release of the medication [1-3]. An in situ gelling system is a formulation that, prior to entering the body, is in solution form but that, given certain physiological conditions, will convert to gel form.[3]

1.2. Rationale for In situ gelling system

Owing to its "Sol-Gel" transition, in-situ gel aids in the regulated and prolonged release of medications. It aids in lowering the body's frequency of drug administration. The medications only need to be taken at low dosages; adverse effects and drug buildup are not possible. It makes medications more bioavailable. The gel formation will lengthen the drug's residence period. The in-situ gel drug administration method reduces medication waste.[4]

1.3. Advantages

1) Provide a medication that is released gradually and under control;
2) Make drug administration simple
3) May be given to patients who are unconscious
4) Better comfort and compliance from patients
5) Reduce the frequency of doses and toxicity of the medicine
6) Enhanced absorption capacity
7) Because natural polymers are used, they offer biocompatibility and biodegradation.
8) The biocompatibility, biodegradability, and physiologically identifiable moieties of natural polymers are distinctive qualities that promote cellular activity.[5]

1.4. Disadvantages

The in situ gel system's drawbacks

1. A lot of fluids are needed.
2. The drug's sol form is more prone to deterioration.
3. The possibility of stability issues brought on by chemical deterioration.
4. Eating and drinking may be prohibited for a few hours after the medication is placed[6]

Characteristics features of polymers in in-situ gelling system:

1. The polymer need to have the ability to stick to the mucous membrane.
2. It should not have any harmful effects and be highly compatible
3. Its behavior ought to be quasi-plastic.
4. The polymer need to have the ability to reduce viscosity as the shear rate increases.
5. The polymer's preferred pseudoplastic behavior.
6. Optic clarity and good tolerance are highly desirable[7]

Various Types of In-situ gelling system:

1. Temperature triggered in situ gel systems
2. pH triggered in situ gelling systems
3. In situ gel formation due to ion-activated system[8]

Thermo sensitive- In Situ Gel

One specific example of an ophthalmic product vehicle that responds to temperature changes is a thermoresponsive in situ gel, which is a liquid at room temperature and turns into a gel when it comes into contact with body temperature. Pluronics, or poloxamers, are a well-known class of polymers with thermo-responsive behavior. Because of their ability to increase the bio adhesiveness of ophthalmic solutions, in situ gel-forming technologies, particularly the thermosensitive ones, have recently demonstrated their potential to extend the residential duration and maybe allow for controlled release of therapeutic molecules for eye disorders. When the ambient temperature approaches or surpasses the low critical solution temperature (LCST), a thermosensitive polymer solution behaves as a liquid. It was determined that thermosensitive in situ gel was a good method since it increased the precorneal
residence duration by increasing bioavailability. The longer the drug was delivered continuously, the higher the solution's viscosity with increasing concentration. [9]

Figure 1: Sol to gel formation of In situ gelling system.

Mechanism of gelling in thermosensitive in-situ gel

There are several possible mechanism leading to in-situ implant formation. The solvent exchange approach consists of dissolving a water-insoluble polymer in a water -miscible biocompatible solvent. Upon contact with body fluids the solvent diffuses out of the polymer while water permeate the liquid polymer matrix. Due to its insolubility in water the polymer precipitates resulting in the formation of a solid polymeric implant. However, the incompletes implant formation can be observed in vivo resulting in a high initial release and local or systemic toxicity.
Also the organic solvent used to solubilized the polymer can physically denaturated labile compounds such as proteins photopolymerization has also been proposed to prepare in situ implants. This approach has been taken to produce depot formulation biological adhesives for soft tissues and

orthopedic biomaterials however photopolymerization requires the presence of a photo initiator at the gelation site which can be toxic. Furthermore, the penetration capacity of the radiation source limits the number of application sites and the reaction can evoke enough heat to damage surrounding tissues.[10]

2.2 Polymers used in thermosensitive in-situ gel

Some polymer undergo abrupt changes in solubility in response to increase in environmental temperature. It mainly reviews the characterization and use of polysaccharides, N-isopropylacrylamide (NIPAM) copolymer, poly(ethylene oxide-b-propylene oxide-b-ethylene oxide) (PEO-PPO-PEO) and its copolymer, poly(ethylene oxide) /(D,L-lactic acid-co-glycolic acid)copolymer.[11]

1.N-isopropylacrylamide copolymer

Poly(N-isopropylacrylamide) is a non-biodegradable polymer with LCST 32C in water and cross linked gels of this material collapse around this temperature. It mainly reviews the characterization and use of polysaccharides, N-isopropylacrylamide (NIPAM) copolymer, poly(ethylene oxide-b-propylene oxide-b-ethylene oxide) (PEO-PPO-PEO) and its copolymer, poly(ethylene oxide) /(D,L-lactic acid-co-glycolic acid)copolymer.[12]

2.Poloxamer

More than thirty distinct non-iconic surface active agents make up the Poloxamer. The Poloxamer series of polymers includes a variety of liquids, solids, and pastes. These polymers are ABA-TYPE triblock copolymers made of PEO(A) and ppo units (B).[13]

3.Poly(ethylene oxide)/poly(D,L-lactic acid co-glycolic acid)

Describe different thermosensitive , biodegradable hydrogels based on poly(lactic acid) .block copolymer solution of PEO and poly(L-lactic acid) were shown to be in the sol state at 45c .[14]

4.Hydroxy Propyl Methyl Cellulose

Hydroxypropyl methylcellulose is composed of glucan chains with repeating glucopyranose units. Methylcellulose is a natural polymer composed of native cellulose with alternating methyl substitute on the chain. At low temperature the polymer hydrates and there is little polymer polymer interaction other than simple entanglement.[15]

5.Cabopol

Carbopol is high molecular weight cross-linked polycrylic acid derivative.it is water soluble vinyl polymer. Carbopol remains in solution at acidic PH but turns into low viscosity gel at alkaline PH.

HPMC is used in combination with carbopol which increases the viscosity of the carbopol solution while reducing the acidity of the solution.[16]

2.3.Evalution Of Thermo sensitive In-situ Gel

- Drug Content

The drug content was determined by using phosphate buffer PH 7.4 as medium. The concentration was determined at 288nm by using UV-visible spectrophotometer[17]

- Rheological Studies

After allowing the produced solution to gel in the tear fluid simulation, the viscosity was measured using a Brookfield viscometer, which could run at angular velocities between 10 and 100 rpm.[18]

In-vitro release study The in vitro release from the formulation was studied through cellophane membrane using a modified Franz diffusion cell. The dissolution medium used was artificial tear fluid freshly prepared [19]

- HPMC analysis:

Using the HPLC approach, quantitative measurement in tear fluid was completed. HiQsil C18 column was utilized as the stationary phase. The mobile phase consisted of a filtered and degassed combination of acetonitrile and phosphate buffer (0.02M) with a pH of 3.0. A 1.0 ml flow rate was used to provide the mobile phase. [20]

- Antimicrobial Efficacy Testing :

Antimicrobial efficiency studies were carried out to ascertain in the biological activity of sol-to-gel systems against microorganisms. This was determined in the agar diffusion medium employing cup plate technique.[21]

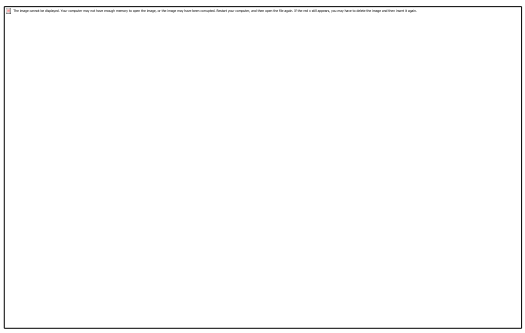
- Sterility Testing

To determine the growth of anaerobic bacteria and aerobic bacteria and fungi in the formulation, the formulation was incubated for a minimum of 14 days at 30 to 35 °C in the fluid thioglycolate medium. The experiment was then repeated at 20 to 25 °C in the same medium.[22]

2.4.MARKETED FORMULATIONS OF INSITU GEL

Ophthalmic thermosensitive gels have been created and put on the market to treat bacterial infections in the eyes and glaucoma.[23]

- Azasite



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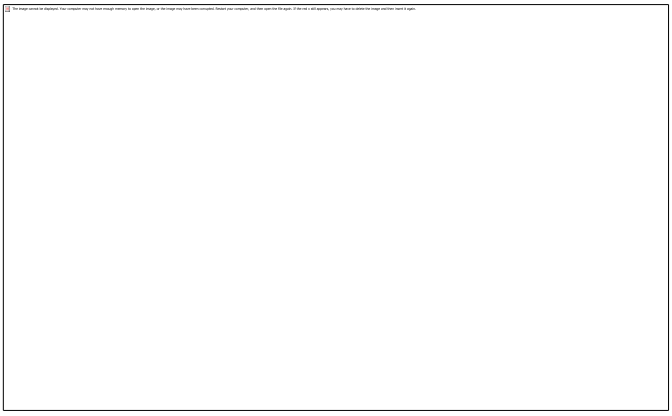

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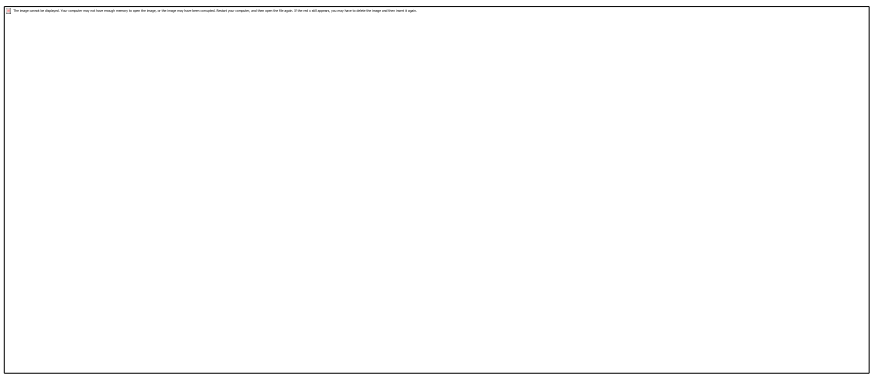

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