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Novel Polymeric in Situ Gels for Ophthalmic Drug Delivery System

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ABSTRACT

Ophthalmic drug delivery is most interesting and challenging to upcoming Pharmacists. Ophthalmic conventional formulations like solution, suspension, ointment are available in market but it has some disadvantages like rapid precorneal elimination of drug, high variability in efficiency and blurred vision respectively. Poor bioavailability of the ophthalmic solution caused by dilution and drainage from the eye, to overcome these problems recently in situ gelling system has been developed. In situ forming gels are liquid upon instillation and undergoes phase transition in the ocular cul de-sac to form viscoelestic gel and these gel provides a response to environmental changes (pH, temperature, ion exchange). Various biodegradable polymers are used like carbopol, pluronics, alginate; gelrite etc.The aim of this article is to present a concise review on different classifications of hydrogel, development of hydrogel based drug delivery systems while highlighting the applications of hydrogel in pharmaceutical field. Now day's in situ gel has been used as vehicles for the delivery of the drugs for both local treatment and systemic effect. Different administration routes other than ocular have been explored and these cutaneous and subcutaneous delivery, dental, buccal delivery, delivery to esophagus, stomach, colon, rectum, and vagina. In situ gelling system is a convenient, ease to administer, improve the bioavailability, better patient compliance.

KEY WORDS: - Conventional formulation, Precorneal elimination, Poor bioavailability, Viscoelastic gel, Hydrogel.

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1. INTRODUCTION:-

1.1 HYDROGEL

Aqueous gel (hydrogel) consists of high molecular weight, hydrophilic, cross- linked polymers or co-polymers that form a three- dimensional network in water. These gels have been shown to combine significantly longer residence times in the cul-de-sac with increased drug bioavailability[1]. Kim et al define the hydrogels as polymers which have the ability to swell in water or aqueous solvents, and induce a liquid-gel transition[2]. The efficacy of ophthalmic hydrogel is mostly based on an increase of ocular residence time via enhanced viscosity and mucoadhesion properties.[3]

1.2 IN SITU GEL:-

In-situ gel refers to polymer solution which can be administered as liquid & undergoes a phase transition to semisolid gel upon exposure to physiological environment.[4] The gelation can be triggered by temperature, pH change, ionic change & also UV induced gelation, Solvent exchange induced gelation.[5-7]

1.2.1 CHANGE IN TEMPERATURE:-

Change in temperature sustained drug delivery can be achieved by use of polymer that changes from sol- gel at temperature of the eye. Temperature dependent system includes pluronics F127[8-10] & tetronics . The poloxamers F127 are polyols which thermal gelling properties where solution viscosity increases when temperature is rised to eye from critical temperature.

1.2.2 CHANGE IN pH:-

Change in pH triggered system shows sol – gel transformation when pH is raised by tear fluid to pH 7.4. PH triggered system cellulose acetate Hydrogen phthalate latex (pH 5.0 to 7.2 -7.4 from a gel with lacrimal fluid), carbopol pH 4.0 – 7.4 sol – gel transformation. Cellulose acetate phthalate is polymer with potentially useful properties for a sustained drug delivery to eye since latex is free flowing

solution at pH 4.4 which undergoes coagulations. When pH raised by tear fluid of pH 7.4. pH triggered in situ gelling system are low viscosity polymeric dispersion in water which undergoes spontaneous coagulations & gelation after instillation in conjuctival cul –de-sac.[11]

1.2.3 CHANGE IN ELECTROLYTE COMPOSITION:-

Change in electrolyte composition ion activated system shows sol- gel transformation in presence of the mono or divalent cations ($Na^{+,}$ Ca^{++} etc) typically found in tear fluids. Ion activated system include Gelrite & Alginate. [12-14] Gellan gum is an anionic extracellular polysaccharide secreted by pseudomonas elodea. Gellan gum formulated in aqueous solution forms clear gel in the presence of mono or divalent cataions. These system shows sol-gel transformation in presence of ions.[11]

2. IN SITU GELLING SYSTEM :-

This is a more desirable dosage form which can be deliver drug in solution form & create little to no problem of vision & frequently doses are not needed. This in situ gelling system is when exposed to physiological condition will shift to a gel phase.

This new concept of production a gel in-situ was suggested first time in the early 1980s.Gelation occurs via the cross linking of polymer chain that can be achieved covalent bond formation (chemical cross linking) or non covalent bond formation (physical cross linking) [17]. This system described as low viscosity solution that undergoes phase transition in conjuctival cul-de-sac to form viscoelestic gel due to conformational changes of polymer in response to physiological environment[18]. The rate of in situ gel formation is important because between instillation in eye & before a strong gel is formed; the solution or weak gel is produced by the fluid mechanism of eye. [19]

3. IMPORTANCE OF IN SITU GELLING SYSTEM:-

- The major importance is the possibilities of administrating accurate &reproducible quantities compared to already formed gel .[20]
- In-situ forming polymeric delivery system such as ease of administration &reduced frequency of administration improved patient compliance & comfort.[21]
- Poor bioavailability & therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are instilled as drops into eye &undergoes a sol-gel transition from instilled dose .[22]

➢ Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.[23]

➢ Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects .[24,25]

Table 1: Advantages and Constraints of Conventional Dosage Forms of Ophthalmic Drug Delivery System [15-16]

Sr. No	Dosage forms	Benefits	Constraints
1	Solution	Convenient	Rapid precorneal elimination. Loss of drug by drainage. Non sustained action.
2	Suspension	Patient compliance. Best for drug with slow dissolution.	Drug properties decide performance. Loss of solution &suspension solid.
3	Emulsion	Prolonged release of drug from vehicle.	Blurred vision. Patients non compliance. Possible oil entrapment.
4	Ointment	Flexibility in drug choice. Improve the drug stability. Resistance to non lacrimal drainage.	Sticking of eyelids. Blurred vision. Poor patient compliance. Partition coefficient.
5	Gel	Comfortable. Less blurred vision.	Matted eyelids after use. No rate control on diffusion.
6	Erodible inserts	Sophisticated and effective delivery system Flexibility in drug type and dissolution rate Need only be introduced into eye and not removed	Patient discomfort Requires patient insertion Movement of system around eye can cause abrasion
7)	Non-erodible inserts	Controlled rate of release prolonged delivery. Flexibility for deliver type of drug selected sustained delivery.	Patient discomfort Irritation to eye Patient placement an removal

4. IDEAL CHARACTERISTICS OF OCULAR DRUG DELIVERY SYSTEM [26,27]

- A good corneal penetration.
- A prolonged contact time with corneal tissue.
- Simplicity of installation for the patient.

- A non irritative & comfortable form (the viscous solution should not provoke lacrimation & reflex blinking).
- Appropriate rheological properties & conc. of viscolyzer.

5. IDEAL CHARACTERISTICS OF POLYMERS [28]

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

- It should be biocompatible.
- It should be capable of adherence to mucus.
- It should have pseudo plastic behaviour.
- It should be good tolerance & optical activity.
- It should influence the tear behaviour.
- The polymer should be capable of decrease the viscosity with increasing shear rate there by offering lowered viscosity during blinking & stability of the tear film during fixation.

The first use of gel for medical preparation was represented by Wichterle & Lim in 1960 in manufacturing of soft contact lenses & implant material from Hydroxyethyl Methacrylate polymer.[29]

6. APPLICABILITY OF IN SITU POLYMERIC DRUG DELIVERY SYSTEM:-

6.1 ORAL DRUG DELIVERY SYSTEM :-

The pH-sensitive hydrogels have a potential use in site-specific delivery of drugs to specific regions of the GI tract. Hydrogels made of varying proportions of PAA derivatives and crosslinked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastroprotective property [30]. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amidaded pectins, guar gum and inulin were investigated in order to develop a potential colon-specific drug delivery system. W. Kubo et al. [31] developed the formulations of gellan and sodium alginate both containing complexed calcium ions that undergo gelation by releasing of these ions in the acidic environment of the stomach. Oral delivery of paracetamol was studied.

For the oral in situ gel delivery system pectin, xyloglucan & gellan gum natural polymers are used. Pectin formulation for sustained delivery of paracetamol has been reported.[32] Advantages of pectin is water soluble so, no need to add organic solvent.

6.2 OCULAR DRUG DELIVERY SYSTEM:-

In ocular delivery system natural polymers like gallen gum, alginic acid & xyloglucan are most commanaly used. For local ophthalmic delivery system various compounds like antimicrobial agent, anti-inflammatory agent & autonomic drugs are used to relieve intra ocular tension in glaucoma. Conventional delivery system often result in poor availability & therapeutic response because high tear fluid turn over & dynamics which cause rapid elimination of the drug from the eye so, the overcome the bioavailability problem ophthalmic in-situ gel were developed. [33]

To improve the bioavailability viscosity enhancers such as Hydroxy Propyl Methyl Cellulose , Carboxy Methyl Cellulose , Carbomers , Poly Vinyl alcohol used to increase the viscosity of formulation in order to prolong the precorneal residence time & improve the bioavailability , ease to manufacture .[33] Penetration enhancer such as preservatives , chelating agent , surfactants are used to enhance corneal drug penetration .[34]

6.3 NASAL DRUG DELIVERY SYSTEM :-

In nasal in-situ gel system gallan gum & xanthan gum are used as in-situ gel forming polymers Momethasone furoate was evaluated for it's efficacy for the treatment of allergic rhinitis .[35] Animal study were conducted using allergic rhinitis model & effect of in-situ gel on antigen induced nasal symptoms in sensitizes rats was observed . In-situ gel was found to inhibit the increase in nasal symptoms are compared to marketed preparation nosonex (Momethasone furoate suspension 0.05%).

6.4 RECTAL DRUG DELIVERY SYSTEM:-

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum, sometimes they can migrate up-wards to the colon that makes them possible for drug to undergo the first-pass effect. Choi et al. [36] developed novel in situ gelling liquid suppositories with gelation temperature at 30–36°C. Poloxamer 407 and/ or poloxamer 188 were used to confer the temperature-sensitive gelation property.

In-situ gel possesses a potential application for rectal & vaginal route .Miyazaki et al. investigated the use of xyloglucan based thermo reversible gel for rectal drug delivery of Indomethacin. Administration of Indomethacin loaded xyloglucan based system to rabbit indicated broad drug absorption & a longer drug residence time as compared to that resulting after administration of commercial suppository.

For better therapeutic efficacy & patient compliance, mucoadhesive, thermo sensitive, prolonged release vaginal gel incorporating Clotrimazole-β-cyclodextrin complex formulated for treatment of vaginitis.[37]

6.5 VAGINAL DRUG DELIVERY SYSTEM:-

The vagina, in addition to being an important organ of reproductive tract, serves as a potential route for drug administration. Formulations based on a thermo-plastic graft copolymer that undergo in situ gelation have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins [38]. Chang et al. [39] have recently reported a mucoadhesive thermo-sensitive gel (combination of poloxamers and polycar-bophil), which exhibited, increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

6.6 INJECTABLE DRUG DELIVERY SYSTEM :-

One of the most obvious ways to provide sustained- release medication is to place the drug in delivery system and inject or implant the system into the body tissue. Thermoreversible gels mainly prepared from poloxamers are predominantly used [40]. The suitability of poloxamer gel alone or with the addition of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (CMC) or dextran was studied for epidural administration of drugs in vitro [41.] The compact gel depot acted as the ratelimiting step and significantly prolonged the dural permeation of drugs in comparison with control solutions. J. M. Barichello et al. [42] evaluated Pluronic F127 gels, which contained either insulin or insulin-PLGA nanoparticles with conclusion, that these formulations could be useful for the preparation of a controlled delivery system. Likewise, poloxamer gels were tested for intramuscular and subcutaneous administration of human growth hormone [43]or with the aim to develop a long acting single dose injection of lidocaine[40]. J. R. DesNoyer and A. J. McHugh[(44)] invented a new class of injectable controlled release depots of protein which consisted of blends of Pluronics with poly (D, L-lactide)/1-methyl-2- pyrrolidone solutions. Some other thermosensitive hydrogels may also be used for parenteral administration. ReGel ® (triblock copolymer PLGAPEG- PLGA) was used as a drug delivery carrier for the continuous release of human insulin [45]. Steady amounts of insulin secretion from the Re- Gel ® formulations up to day 15 of the subcutaneous injections were achieved. B. Jeong et al. [46] reported the

synthesis of a biodegradable poly (ethylene oxide) and poly (L-lactic acid) hydrogel, which exists in a form of sol at an elevated temperature (around 45°C) and forms a gel after subcutaneous injection and subsequent rapid cooling to body temperature. In-situ forming Injectable drug delivery system , cross linking of hydrazide modified by aluronic acid with aldehyde modified version of cellulose derivatives such as carboxy methyl cellulose , methyl cellulose, hydroxy propyl methyl cellulose are used. These in-situ forming gel were used for preventing postoperative peritoneal adhesion thus avoiding pelvic pain, bowel obstruction & infertility. For a better therapeutic efficacy & patient compliance , mucoadhesive , thermo sensitive , prolonged release vaginal gel incorporating Clotrimazole-β-cyclodextrin complex was formulated for treatment of virginities .[47]

6.7 DERMAL AND TRANSEDERMAL DRUG DELIVERY:-

Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of Indomethacin[48]. In-vivo studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin. [49] The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation

7. EVALUATION AND CHARACTERIZATION OF IN SITU GELLING SYSTEM:-

In-situ gel evaluated & characterized by the following parameters-

7.1 CLARITY :-

The clarity of formulated solution is determined by visual inspection under black & white background.[50]

7.2 TEXTURE ANALYSIS:-

The consistency , firmness &cohesiveness of in situ gel are assessed by using texture profile analyzer which mainly indicated gel strength & easiness in administration in vivo higher value of adhesiveness of gel are needed to maintain an intimate contact with mucus surface .[51]

7.3 pH OF GEL:-

pH can be determined formulation is taken in beaker & 1ml NaOH added drop wise with continuous stirring . pH is checked by using pH meter.[52]

7.4 GELLING CAPACITY:-

In-situ gel is mix with simulated tear fluid (in the proportion of 25:7 i.e application volume 25µl & normal volume of tear fluid in eye is 7µl) to find out gelling capacity of ophthalmic product. The gelation assessed visually by noting the time for & time taken for dissolution of the formed gel. [53]

7.5 RHEOLOGICAL STUDIES:-

The viscosity measured by using Brookfield viscometer, cone & plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity 5-1000 mPas , before gelling & after ion gel activation by eye will have viscosity of from about 50-50,000 mPas.[53,54]

7.6 ISOTONICITY EVALUATION :-

Isotonicity is important characteristics of ophthalmic preparation. Isotonicity is maintained to prevent tissue damage or irritation of eye. All ophthalmic preparation are subjected to isotonicity testing, science they exhibited good release characteristics & gelling capacity & the requite velocity. Formulation mixed with few drops of blood & observed under microscope at 45x magnification & compared with standard marketed ophthalmic formulation.[55]

7.7 SWELLING STUDIES :-

Swelling studies are conducted with a cell , equipped with thermo jacket to maintain a constant temperature .The cell contains artificial tear fluid .(composition – 0.67_g Nacl , 0.20_g $NaHCo_3$, 0.008_g $Cacl_2.2H_2o$ & distilled water q.s to 100_g).[(56)] swelling medium equilibrating at 37^0c one milliliter of formulated solution is placed in dialysis bag & put into the swelling medium . At specific time interval the bag is removed from the medium & weight is recorded. The swelling of the polymer gel as a function of time is determined by using the following relationship.[57,58]

$$\% S_t = (W_t - W_0)\ 100/W_0$$

Where,

S_t = Swelling at time‘t’.

W_0=Initial weight of gelling solution.

W_t=Final weight of gel.

7.8 TASTICAL ANALYSIS:-

Analysis of variance (ANOVA) is used the testing the difference between calculated parameters using SPSS statistical package. Statistical difference yielding $P \leq 0.05$ is considered [59]. Duncan multiple

comparison is applied when necessary to identify which of the individual formulations are significantly different. [60]

7.9 HIGH PERFORMACE LIQUID CHROMATOGRAPHY:-

The HPLC system is used in reversed phase mode. Analysis is performed on a Nova pack C_{18} packed column (150 mm length X 3.9 mm i.d) .[61]

7.10 FOURIER TRANSFORMER INFRA RED:-

The possibility of drug excipient interaction is investigated by FTIR studies. The FTIR graph of pure drug & combination of drug with excipient are recorded by using KBR pellets. [61,62]

7.11 THERMAL ANALYSIS:-

Thermo gravimetric analysis can be conducted for in situ forming polymeric system to quantitative the percentage of water in hydrogel. Different scanning calorimetry is used to observed, if there are many changes in thermograms as compared with pure ingredients used thus indicating the interaction. [63]

7.12 IN VITRO DRUG RELEASE STUDIES:-

In vitro release study of in situ gel solution is carried out by using Franz diffusion cell. The formulation is placed in donor compartment & freshly prepared simulated tear fluid in receptor compartment. Between receptor & donor compartment dialysis membrane is placed (0.22 µm pore size). The whole assembly is placed on thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at 37 ^{0}c± 0.5 ^{0}c.

1ml sample is withdrawn at predetermined time interval of 1hr for 6hrs the sample volume of fresh medium is replaced. The withdrawn sample is diluted to 10ml in volumetric flask with respective solvent & analyzed by UV spectrophotometer at respective nm using reagent blank. The drug content calculated using an equation generated from standard calibration curve. The percentage cumulative drug release (% CDR) calculated. The obtained data is further subjected to curve fitting for drug release data. The best fit model is checked for Krosmeyers peppas & Fickinian diffusion mechanism for their kinetics. [64]

7.13 OCULAR IRRITANCY STUDIES:-

Ocular irritancy studies are performed on male albino rabbits, weighing 1-2 kg. The modified Draize technique is used for ocular irritation potential of ophthalmic products.[65]The formulation is placed in lower cul-de-sac & irritancy is tested at time interval of 1hr, 2hrs, 48hrs, 72hrs, & 1 week after administration.[66] The rabbits are observed periodically for redness, swelling,& watering of eyes. [67]

7.14 ANTIMICROBIAL ACTIVITY:-

Antimicrobial efficacy studies are carried out to ascertain the biological activity of sol-gel-system against microorganisms. This is determined in agar diffusion medium employing 'Cup Plate Techniques' [68]. The microbial growth of bacteria is measured by conc. Of antibiotic & compared with that produced by known conc. Of standard preparation of antibiotic & carried out the microbial assay serial dilution method is employed. [69,70]

7.15 STERILITY TESTING:-

Sterility testing is carried out as per the IP 1996. The formulation is incubating for not less than 14 days at 30^0-35^0c in the fluid thioglycolate medium to find the growth of bacteria & at 20^0-25^0 c in Soya bean casein digest medium to find the growth of fungi in formulation.[71]

7.16 ACCELARATED STABILITY STUDIES:-

Formulation is replaced in amber colored vials & sealed with aluminum foil for the short term accelerated stability study at 40± 2^0 c & 75 ±5% RH as per International Conference of Harmonization (ICH) State Guidelines. Sample is analyzed at every month for clarity, pH, gelling capacity, drug content, rheological evaluation & in vitro dissolution. [72]

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