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IN SITU GEL: A NOVEL PARENTERAL CONTROLLED DRUG DELIVERY SYSTEM

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Abstract:

Even though oral route is the most conventional route for the medications, it is associated with limitations like first pass metabolism, low elimination half-life, poor bioavailability and patient inconvenience. A recent advancement in pharmaceutical dosage development is the technique of in situ biodegradable implant system. These are liquid formulation which upon administration will undergo a sol to gel transformation in response to a physical change at site of administration. They form a drug depot that continuously releases the drug molecules at a pattern providing a sustained drug action. In order to reduce the frequency of drug administration and to avoid the drug level fluctuations in plasma, an implant of the particular drug could be formulated which can deliver the drug in a controlled manner. In situ gel forming polymeric drug delivery systems are reported to possess advantages such like ease of administration, reduced frequency of administration, improved patient compliance etc. They can also overcome the rapidly increasing cost of treatment due to their simple formulation approach. This review includes advantages, disadvantages, approaches, evaluations and applications of in situ gel based drug delivery systems.

Key words: in situ, gel, drug, polymer, controlled, gelation

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INTRODUCTION:

Now the drug delivery techniques are focused on utilizing the advantages of the active ingredients and minimizing its side effects and other limitations. Oral route is most preferred and favourable among patients for oral administration of drug in the body. It has certain limitations such as absorption of drug, drug that undergo first pass metabolism, low elimination half-life, poor bioavailability and patient inconvenience. Other than these most of the oral drug delivery system do not deliver the drug from weeks to months. [1], [2]

Parenteral route is the most effective route of administration for delivery of active ingredients with low bioavailability, narrow therapeutic index and those undergo first pass metabolism etc. The different route of parenteral administration includes subcutaneous, intramuscular, intravenous, intradermal, and intra-arterial. It possesses good absorption characteristics and provides good bioavailability of drugs due to direct absorption into systemic route hence there are no chances of first pass metabolism. In conventional parenteral drug delivery systems, it requires frequent injections in order to maintain the effective therapeutic drug concentration which ultimately leads to patient discomfort. Novel technologies were developed to reduce the frequency of injection and also to provide sustained as well as controlled drug release for longer periods. [3], [4], [5]

A recent advancement in pharmaceutical dosage development is the technique of *in situ* biodegradable implant system (ISFIs). *In situ* is derived from a Lain term that means “in process”. *In situ* forming system is an alternative drug delivery system to overcome the problems associated with other parenteral drug delivery system. These systems consist of biodegradable polymer dissolved in a biocompatible solvent. The system is initially in a fluid form, which upon administration inside the body transforms in to gel form. Since it is biodegradable, so we can effectively solve the problem associated with conventional implants such as pain, surgical procedures etc. [6] These are polymeric or novel gum based drug delivery system in which sol to gel transformation occur due to receipt of stimuli like change in temperature, pH, presence of ions, ultraviolet (UV) rays etc and have the ability to inject a drug to a localized site and form a drug depot at injection site. [7]

Advantages [8], [9], [10]

- Simple to prepare and scale up.
- Ease of administration and less complicated fabrication.
- Less stressful manufacturing conditions for sensitive drug molecules.
- Provide controlled and sustained release of drug.
- Reduce frequency of drug administration and there by improving patient compliance.
- Reduce side effects by reducing peak valley plasma fluctuations.
- Biocompatible with biological systems.
- Less invasive technique.
- Direct delivery to target area.
- It is a convenient method for the delivery of liable bio macromolecules such as protein and vaccines.
- Water soluble or insoluble, high or low molecular weight drug molecules can be easily administered.
- No need of reconstitution before drug administration.
- Less painful compared with pre-shaped implants.
- Less viscous compared to other oleaginous solutions.
- Increase residence time at a particular site.
- Reduce investments and manufacturing costs.
- Better product uniformity and reproducibility.

Disadvantages

- Inconsistent shape which results in inconsistent drug release.
- Fast drug release during initial hours i.e. burst effect.
- As drug release and tissue response are complex, heterogeneous and interconnected hence *in vitro–in vivo* correlation cannot be explained properly.
- Lack of data related to toxicity of solvents and phase separation.
- Thermoplastic pastes require high temperature for administration hence it is more painful.
- Many drugs show instability in organic solvents.

POLYMERS USED IN *IN SITU* GELLING SYSTEM [2], [8], [11]

Smart polymer is the term used to describe polymers used in the formulation of *in situ* forming systems. Smart polymers are actually macromolecules that show physicochemical change due to change in pH, temperature, solvent, magnetic field, or ions.

Properties of polymers:

- It should possess wide margin of safety on both locally and systemically.
- Nontoxic and non-irritant.
- It should have pseudo-plastic behaviour.

- It should have the capability of decreasing the viscosity with increasing shear rate.
- It should be adhering to mucus and compatible.
- It should have good tolerance and optical clarity.

Polymers are classified into

a) **Phase sensitive polymers: -**These are water insoluble polymers which undergo sol to gel transition due to polymer phase separation and precipitation. Polymers mainly used in these systems are chemically polyhydroxy acids, polyanhydrides and polyorthoesters.
b) **pH sensitive polymers: -** Polymers contain acidic or basic groups that either accept or donate protons in response to change in environmental pH. E.g.: chitosan, carbopol, cellulose acetate phthalate (CAP), polyethylene glycol (PEG), pseudo latexes.
c) **Thermo sensitive polymers: -**Polymer that undergo sol to gel transition due to change in temperature due to change in solubility. These polymers show phase transition at particular temperature which may be lower critical solution temperature (LCST) or upper critical solution temperature (UCST). Polymers exhibiting LCST contract and form a gel by heating above LCST, whereas polymers showing UCST form gel by cooling below UCST. E.g.: Pluronics, Poloxamers, xyloglucan, tetronics, hydroxyl propyl methyl cellulose, chitosan.
d) **Photo sensitive polymers :-** Polymers having atleast one water soluble and biodegradable region and two free radicle region. These systems transforms from sol to gel forming a network by photo polymerisation. E.g.: PEG-DL-lactic acid-diacrylate, poly (N-iso-propyl acrylamide).
e) **Ion sensitive polymers:-**Polymers undergo phase transition due to the presence various ions. E.g.: Sodium alginate, carrageenan, gellan gum, hyaluronic acid, gelrite.

Carbopol

Carbopol also known as polyacrylic acid (PAA) is a high molecular weight polymer synthesised by crosslinking acrylic acid with divinyl glycol. It is a pH-dependent anionic polymer, which forms a low viscosity gel at alkaline pH (7.4) and stays in solution form at acidic pH. To impart the viscosity of carbopol, hydroxyl propyl methyl cellulose (HPMC) is used in combination with carbopol and reduces the acidity of the solution. [2] Also it is safe, effective and non-sensitising water soluble polymer. A sustained release of Clotrimazole for oral candidiasis was observed for a period of 6hrs invitro by using pH dependent polymer combination (carbopol and HPMC) was designed and developed by Harish *et al*. [12]

Chitosan

Chitosan is a biodegradable thermo sensitive, polycationic pH dependent polymer obtained from crab shell. It is a linear polysaccharide composed of β-(1→4)-linked D-glucosamine and *N*-acetyl-D-glucosamine. Chitosan consists of ionic pendant groups which ionize and form network with electrostatic forces. The amino group present in chitosan leads to protonation in acidic to neutral solution results in sol to gel transition. Hence it acts as a pH dependent polymer which forms gel at pH above 6.2. [13] Thermo sensitive properties of the chitosan occur at lower critical solution temperature because of extreme hydrophobic interactions. [14]

Pluronic F-127

Poloxamers and pluronics are triblock copolymers of non-ionic nature. Triblock consist of poly (ethylene oxide)–poly (p-phenylene oxide)–poly (ethylene oxide) (PEO–PPO–PEO) copolymers that show gelation at body temperature at a concentration greater than 15%. Triblock copolymers are available in various grades differing in molecular weights and physical forms. The grades are assigned as F for flakes, P for paste, L for liquid depending upon the physical designation .When these molecules are immersed into the aqueous solvents; they form micellar structures above critical micellar concentration due to the PEO/PPO ration of 2:1.They undergo *in situ* gelation by temperature change. The concentrated solution changes the osmolality of the formulation and cause discomfort during administration. A natural polymer such as chitosan is used to counteract this problem, which also shows thermo sensitive behaviour. An *in situ* gel was formulated using suitable combination of poloxamer 407 and modified chitosan to sustain release of Moxifloxacin HCl for infectious diseases designed and developed by Kadam et al. [15]

Pectin

Pectin's are natural polysaccharides in which polymer backbone is made up of α-(1-4) D galacturonic acid residues present in walls of terrestrial plants. They are cationic in nature, the monovalent cations salts of pectinic and pectic acids are soluble in water. Divalent and trivalent cationic salts are weakly soluble or insoluble in water. The clumps are formed when water is added to dry powdered pectin due to its tendency to hydrate. Clumps consist of semi dry packets of pectin contained in an envelope of highly hydrated outer coating. It can be solubilised by mixing the pectin powder with water soluble carrier. [13]

The rate at which gel formation takes place is affected by degree of esterification (DE). Based on degree of esterification, pectin is of two type's i.e. low methoxy pectins and high methoxy pectins. Low methoxy pectins readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains based on 'egg box' model. Since it is water soluble, so organic solvents are not necessary in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is administered orally. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation. [16] *In situ* gel containing pectin for the sustained delivery of Paracetamol has been reported by Kubo et al. [17]

Gellan gum

Gellan gum is an anionic deacetylated exocellular and water soluble polysaccharide secreted by *Pseudomonas elodea.* Commercially it is available as Gelrite TM or Kelcogel TM. Tetrassacharide is the repeating units of gellan gum which consist of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residue.[18] It is a type of temperature dependent or cation induced polymer that causes gelation which involves the formation of double helical zones which forms a three dimensional network by complexation with cations and hydrogen bonding with water.[19] Ca2+ or Mg2+ divalent cations that induce gelation by cross-linking to form a gel network. At low polymer concentrations, it causes rapid gelation when the liquid solution comes in contact with mucosal layer that is present in the stomach region. Since it is swelling in nature, it gives good bio adhesive nature in the GIT region. [20] The formulation consisted of gellan gum with calcium chloride and sodium citrate complex. The calcium ions are released in acidic environment of the stomach when administered orally which leads to gelation of gellan thus forming an *in situ* gel. *G*elrite has been prepared for controlled release of ketotifen, which showed an increase in retention time of drug. [21]

Alginic acid

Alginic acid also known as alginates is a natural polysaccharide polymer isolated from brown seaweed. It is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidic linkages. Depending on the algal source, proportion of each block and the arrangement of blocks along the molecule may vary. They are widely used because of their non-toxicity, biocompatibility and biodegradability. Gelation occurs due to ionic interaction between carboxylic acid moieties and bivalent counter ions. The homogenous block of alginates are separated by blocks made up of random or alternating units of mannuronic acid and glucoronic acid which undergo proton catalysed hydrolysis which depends on time, pH and temperature.[22],[23] Because of its mucoadhesive properties alginic acid increases the precorneal residence which shows it is a good candidate for ophthalmic delivery.[24]

Carageenan

Carrageenan is a natural polysaccharide or marine hydrocolloids obtained from some membranes of the class Rhodophyceae. It is a polysaccharide made up of repeatative sequence of disaccharide β–D galactopyranose residue linked at 1, 3 position called A residue and α –D galactopyranose residue linked at 1,4 called B residue. Based on number and position of ester sulphate groups and also in the arrangement of 3, 6- anhydro galactose, carrageenan is classified into three i.e. (i) Iota (ι-) carrageenan has the capability to form gels in the presence of potassium or calcium ions. It forms elastic gel in which there is no draining of water occurs and also possesses good freeze thaw stability. (ii) Kappa (κ-) carrageenan has the capacity to form gels in the presence of potassium salts. It has similar properties to that of locust bean gum and it is soluble in hot water and is a good gelling agent. It has poor freeze thaw stability because it forms clear, brittle gel. (iii) Lambda (λ) carrageenan does not induce gel formation instead, it forms highly viscous solutions. Hot aqueous solution of kappa and iota carrageenans has the ability to form thermo-reversible gels upon cooling. This phenomenon occurs due to the formation of a double helix structure that is present in carrageenan. [25]

Xyloglucan

Xyloglucan is also called as tamarind gum which is a polysaccharide obtained from the endosperm of tamarind the seed. It is composed of a (1-4)-β-D-glucan backbone, which has (1-6)-α-D-xylose branches that are partially substituted by (1-2)-β-D-galactoxylose.[26] Gelling of xyloglucan occurs by degradation in the presence of xyloglucan β-galactosidase enzyme, addition of polyphenols, alcohols and iodine solution. Its gelation does not require the presence of H+ ions and its use is not restricted by the nature of the drug. It also consists of three units of xyloglucan oligomers with heptasaccahride, octasaccharide and nonasaccaride. [25] Based on the degree of galactose elimination the phase transition from sol to gel may vary. Xyloglucan gels are potentially been used for oral, ocular and rectal drug delivery. *Vazir Ashfaq* et al designed and developed Brimonidine tartarate *in situ* gel by polymers, such as gellan gum, xyloglucan and hydroxy propyl methyl cellulose for the management of glaucoma. [27]

Guar gum

Guar gum also known as guaran is a naturally occurring gum or galactomannan polysaccharide extracted from the extracted from guar beans. It is a thermo reversible polymer. As the temperature increases gelling property of guar gum decreases. At lower concentrations, the gum has the capacity of forming high viscous solution. The galactose side chain attached to mannose backbone interacts with water molecules which lead to the formation of intermolecular side chain. This causes entanglement of gum molecules in the solution and results in formation of gel.[28] Stomach Specific *in situ* Gel of Metoclopramide Using Polymers such as guar gum with sodium alginate was formulated by *W. Vinay et al* .[29]

Xanthan gum

Xanthan is a long-chain polysaccharide produced by bacterium Xanthomonas campestris. It consists of d-glucose, d-mannose, and d-glucuronic acid as building blocks in a molecular ratio of 3:3:2. Due to the presence of glucuronic acid and pyruvic acid groups present in the side chain it exhibits anionic nature. [30] When xanthan gum is dissolved in water at room temperature, it forms lumps due to binding of water molecules. When this solution is annealed, they rearrange among themselves. The molecular chain moves freely at room temperature and form firm and stiff gels when it is cooled.[31] *S. P. Hiremath et al* formulated *in situ* gel of Linezolid which exhibits a sustained release over a period of 6hr by using xanthan gum.[32]

SOLVENTS USED IN *IN SITU* GELLING SYSTEM [2]

The solvents used for the preparation of *in situ* gelling system should have following properties:

- Water and body fluid miscibility
- Good solubility for polymers
- Chemical compatibility
- Non-toxic and non-irritant
- Facilitate transition from flowing liquid to solid gel
- Metabolite product of solvent should not have any deleterious effect

Solvents are classified into two categories: high water-soluble solvents and low water-soluble solvents.

High water-soluble solvents:

High water-soluble solvents are known as hydrophilic solvents which is miscible to dispersible in body fluids. These solvents undergo phase transition within minutes and leading to the formation of a highly porous *in situ* gelling system. It forms a less viscous system and easy for injection.

Eg: N-methyl-pyrrolidine (NMP), dimethyl sulphoxide, propylene glycol, acetone etc.

Low water-soluble solvents:

Low water-soluble solvents are also known as weak or poor solvents which are hydrophobic in nature and water immiscible solvents. The burst effect produced is less as compared to highly water soluble solvents because, these solvents takes hours to months about phase transition and leading to the formation of a less porous *in situ* gelling system.

Eg: Benzyl benzoate, ethyl benzoate, benzyl alcohol etc

APPROACHES OF *INSITU* FORMING SYSTEMS [2], [25], [33], [34]

In situ forming systems can be classified depending on type of stimuli or mechanisms that convert the systems.

I. *In situ* gelling system due to physiological stimuli
- Temperature
- pH

II. *In situ* gelling system due to physical stimuli
- Swelling
- Diffusion/ solvent exchange

III. *In situ* gelling system due to chemical changes
- Chemical crosslinking
- Enzymatic crosslinking
- Ionic crosslinking
- Photo-polymerisation

I. *In situ* gelling system due to physiological stimuli

Physiological stimuli such as temperature and pH play an important role in the formation of *in situ* gelling system.

Temperature triggered system

Temperature is the most widely used stimulus in environmentally responsive polymeric system. This system contains thermoplastic pastes and thermally induced gelling systems. The ideal critical temperature is ambient and physiological temperature, such that clinical manipulation is facilitated. Also gelation process does not require any external source of heat other than that of the body temperature**.** The mechanism is shown in Fig No.1

- **Thermoplastic pastes: -** This system form solution when heated above a particular temperature and solidify upon cooling. Polymers used in such a system should have the melting point or glass transition temperature in between 25ºC to 65ºC. Before injection system must be heated above their melting point. Drugs are introduced in to molten polymer without the application of solvents. Polymers such as polyanhydrides, polylactic acid, polycaprolactone etc were used.

- **Thermally induced gelling systems: -** These systems are solution at room temperature and form gel at physiological temperature. It does not require any external agent or organic solvent for gel formation. The change in temperature may causes hydrogen bonding and polymeric interaction between the molecules, which leads to the formation of the gel system.

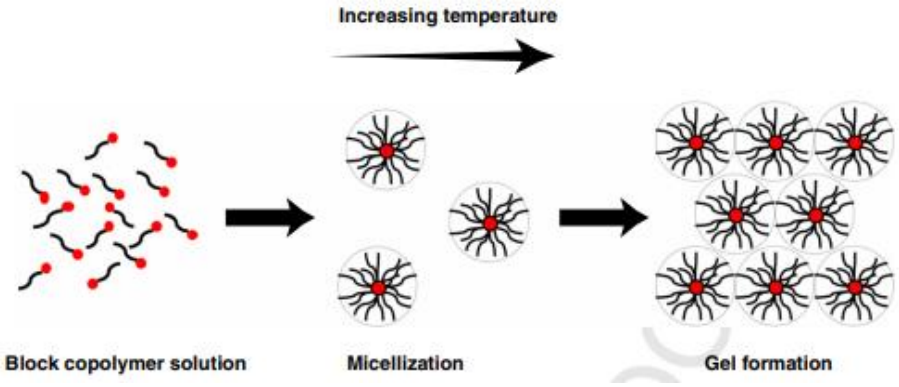

Figure No.1: Mechanism of temperature triggered *in situ* gelling system

pH triggered system

pH triggered systems undergo phase transition from sol to gel due to change in environmental pH. Polymers containing pendent acidic or basic group's i.e., pH sensitive polymers that respond to changes in pH (Fig No.2). The swelling of the polymer occur due to ionisation. Some polymers containing large number of ionisable functional groups, hence it is known as polyelectrolytes. In case of weakly acidic groups, swelling of the polymer increases with increase in external pH while swelling decreases in case of weakly basic groups.

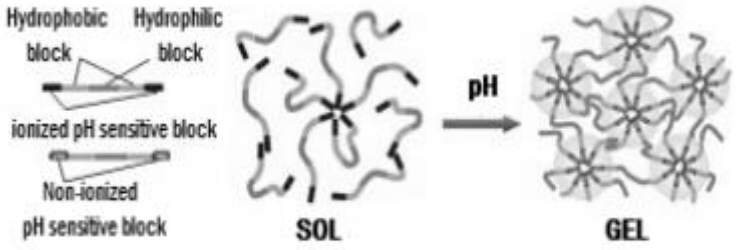

Figure No.2: Mechanism of pH triggered in situ gelling system

II. *In situ* gelling system due to physical stimuli

Physical mechanism for phase transition involves swelling, diffusion/solvent exchange. Physical crosslinking of polymer is due to inter or intra molecular bonding through hydrogen bonding and ionic interactions. This system can be categorised as organogels and *in situ* gelling systems formed by solvent exchange.

- **Swelling: -** Swelling occurs due to absorption of water from the surrounding environment therefore phase transition takes place. Organogels consist of water insoluble amphiphilic lipids that swells in the presence of water and cross linked to form lyotropic liquid crystals. These are three-dimensional network formed by vanderwaals and hydrogen bonding.
- **Diffusion/solvent exchange: -** This involves diffusion of solvent from polymer solution into surrounding tissue. Organic solvent is exchanged with body fluids which result in the formation of depot at injection site due to phase separation. Drug molecules are entrapped in matrix form of depot and release the drug by diffusion.

III. *In situ* gelling system due to chemical changes

The phase transition due to chemical changes is by reversible or irreversible cross-linking of polymeric chains. *In situ* gels are formed by different types of crosslinking such as chemical, ionic, enzymatic and photo-initiated cross-linking.

- **Chemical crosslinking: -**Chemical crosslinking leads to the formation of irreversible covalent bonds. The agents used in this system are classified as natural or synthetic crosslinking agents. For Eg: Benzoyl peroxide, gluteraldehyde, glyoxal and oxalic acid
- **Ionic crosslinking: -**Polymers undergo phase transition in presence of certain ions.

For Eg: Alginic acid undergoes gelation in presence of divalent cations such as Ca2+.

- **Enzymatic crosslinking:** - This method has many advantages over chemical and ionic crosslinking because there is no need of any harmful initiator. Gelation rate can be controlled by adjusting the amount of enzymes. For Eg: Xyloglucan in presence of xyloglucan β-galactosidase degrades partially to form thermally reversible gel.
- **Photo-polymerisation:** - It contains minimum two free radicles polymerisable sites, photo active initiator and UV-visible light. This system when introduced in to injection site via fibre optics, release the drug for longer period of time. The sol form crosslinks by photo-initiation and transforms on to gel form *in situ*. For Eg: Photo-initiated cross linkable chitosan forms hydrogel with in 1 minute on exposed to UV light.

EVALUATION AND CHARACTERIZATION OF *IN SITU* IMPLANT SYSTEM [35], [36], [37]

- **Visual inspection**

General appearances such as clarity, color and odour of the gel is observed. The clarity of gel was visually assessed for detecting the presence of any foreign substances by observing against light in a suitable background.

- **pH**

A digital pH meter was used to determine the pH of the prepared gel formulations. 1ml of the formulation was taken and diluted with distilled water.

- **Viscosity**

Gel should have an optimum viscosity so that it will allow ease of administration, and undergo a rapid sol to gel transition. The instruments such as Brook field viscometer, Cone and Plate viscometer and Ostwald viscometers are used.

- **Texture analysis**

The properties of the *in-situ* gel such as firmness, consistency, adhesiveness and cohesiveness of the formulation are assessed using texture analyser. It is mainly used to determine the syringeability and ease of administration of the formulation.

- **Syringeability**

Syringeability is used to check the ability of formulation to pass through a hypodermic needle. The test was conducted using 5ml syringe. The syringe was modified and kept on support. A weight of 500g was kept over the piston of the syringe. Syringe is fitted with a sufficient needle. The syringe was filled with formulation and weight was added over the piston. The time taken for gel to get expelled from the syringe was noted as the syringeability time.

- **Injectability**

Injectability includes the performance of the formulation before administration.it determines the pressure or force required for injection, consistency and freedom of blockage. Dynamometer, texture analyser are used for this purpose.

- **Gel strength**

Gel strength is determined by using a rheometer. Specific concentration of gel is taken in a beaker and a temperature is maintained by a water jacket. Gel containing beaker is raised at a certain rate, pushing a probe slowly through the gel. The changes in load on the probe are measured as a function of depth of immersion of probe below the gel surface.

- **Thermo sensitive evaluations**

a) Gelation temperature: -The temperature at which the drug solution converted to gel is called gelation temperature. Gelation temperature was determined using test tube inversion method. The test tube containing 2ml of the formulation was immersed in a water bath assisted with thermostat. The temperature is slowly increased by 1°C. Test tube is titled at an angle of 90°. Temperature at which the meniscus of the test tube remains stagnant is noted as gelation temperature.

b) Gel melting temperature: - The formed gel reverses back again to form solution while increasing the temperature. This temperature is noted as gel melting temperature. Also determined by using tube inversion method. Here the meniscus of the liquid starts moving which is titled at 90°.

c) Gelation time:- The time taken for the test formulation to convert in to a gel is noted as gelation time. It is determined by using tube inversion method same as that of gelation and gel melting temperature. 2ml of the formulation was taken in a water bath which is kept over a water bath at 37±0.5°C.

d) Gel duration: - The time for which the gel consistency was maintained by formulation is considered as gel duration. The duration up to which gel remains intact was noted.

- **Fourier transform infrared (FTIR) spectroscopy and thermal analysis**

Nature of interacting forces between the functional group can be evaluated by using FTIR spectroscopy using KBr pellet technique.

Thermal analysis is performed to quantitate the percentage of water in *in situ* gel formulations. Differential scanning calorimetry (DSC) can be used to determine any interaction. It compares any changes in thermograms of gel to pure active ingredients that are used for gelation.

- **Electron paramagnetic resonance (EPR) spectroscopy**

The mechanism of sol to gel transition inside the body can be monitored by using EPR spectroscopy. This method not only detects the presence of free radicle but also about the physical and chemical properties of the compound. Water retention, drug release and polymer erosion of implants were analysed by this method.

- **Drug content**

The drug content estimation was carried out by diluting the prepared formulation with suitable solvents and analysed using UV-visible spectrophotometer.

- **In-vitro drug release studies**

The in-vitro study is carried out using a semi permeable membrane to determine the drug release from the formulation. The test is conducted with a semipermeable visking dialysis membrane. The dialysis bag method is used to perform the In-vitro release studies. 1 ml of the sample was withdrawn at pre fixed time intervals and analysed for percentage drug content using UV spectrometry.

- **Antimicrobial activity**

The activity of formulation against microorganisms is determined by antimicrobial studies. Cup plate method is used for this purpose with agar diffusion medium. The growth of bacteria is measured by comparing the concentration of an antibiotic with known concentration of the standard preparation of antibiotics. The assay is carried by employing serial dilution method.

- **Sterility testing**

Sterility testing is performed for anaerobic and aerobic bacteria and fungi by fluid thioglycholate and soybean casein digest medium as specified in Indian Pharmacopoeia.

- **Accelerated stability studies**

Accelerated stability studies are performed to select the storage conditions of the formulation. It is done as per the ICH guidelines for clarity, pH, gelling capacity, drug content, rheological evaluation and in vitro drug release at 40±2ºC and 75±5%RH for a period of 45 days.

APPLICATIONS OF *IN SITU* IMPLANT SYSTEM

Oral drug delivery system

Oral *in situ* gel is a new dosage form which has been applied in drug delivery recently. Natural polymers such as gellan, sodium alginate, chitosan, carbopol, gellan gum, xanthan gum, xyloglucan and pectin are responsible for providing gelling properties of *in situ* forming oral drug delivery systems. Most of them are biodegradable and water-soluble polymers, hence oral *in situ* gel is more acceptable to patients. *Angel et al designed* and developed an oral *in situ* gel of Diltiazem hydrochloride using suitable polymers such as hydroxy propyl methyl cellulose and sodium alginate for the management of hypertension or angina pectoris. The optimized formulation shows a significant decrease in the rate and extent of the drug release with the increase in polymer concentration and shows extended drug release until the end of 7 hrs. [38]A sustained release of itraconazole mucoadhesive oral *in situ* gel was designed by *Nief et al* using polymers such as carbopol 934 with different viscosity-enhancing agents such as hydroxy propyl methylcellulose, xyloglucan and hyaluronic acid by pH-triggered mechanism. The formulation shows a 80% release over 6hrs. [39]

Ophthalmic drug delivery system

Human eye is an isolated organ where the delivery of drug is quite difficult, hence ocular drug delivery system is considered as crucial and challenging. Topical application of drugs to the eye is the well-established route of administration for the treatment of various ocular diseases like dryness, conjunctivitis, keratitis etc. Even though conventional ophthalmic formulations exhibit many drawbacks such as a short pre-corneal residence time and poor bioavailability.[40] Thermo sensitive, specific ion sensitive or pH-sensitive hydrogels have been examined for their potential as vehicles for ocular drugs. Natural polymers like gellan gum, xyloglucan, alginic acid and synthetic polymers like hydroxy propyl methylcellulose, hydroxy ethyl cellulose, Carbopol 934 were used. *Kotreka et al* designed and developed a topical ophthalmic *in situ* gel of Estradiol for the prevention of age-related cataracts using gellan gum as natural polymer. The 80% of drug was released and provide a sustained action up to 8hrs. [41] A sustained release profile for Voriconazole was reported from a novel approach, ion sensitive *in situ* gelling system. *Puranik et al* designed a Voriconazole *in situ* gel using alginate and HPMC K15M which result in increased bioavailability and reduction in dose and dosing frequency. As voriconazole is hydrophobic drug so it becomes necessary to increase its water solubility. Thus hydroxy propyl-β-cyclodextrin was used to prepare

inclusion complex of voriconazole. The developed formulation shows a sustained release of drug up to 8 hrs. [42]

Nasal drug delivery system

Intranasal route is considered as a major route for the drugs that are ineffective orally, that require small doses and chronically where rapid entry into the Circulation is desired. The absorption of drugs from the nasal mucosa takes place via the aqueous channels of the membrane. Nasal mucociliary clearance is one of the most important limiting factors for nasal drug delivery.[43] *Omar et al* developed nasal *in situ* gel of sumatriptan using suitable polymer combinations of poloxamer 407, poloxamer 188, and carrageenan. Based on increasing bioavailability and sustained drug release up to 6hrs, it can be concluded that the *in-situ* gel of SUT-loaded nano-transferosomes were developed as a promising non-invasive drug delivery system for treating migraine.[44]

Rectal drug delivery system

The rectal route is used to deliver the drugs that are formulated as liquid, semisolid and solid dosage forms. Conventional solid dosage forms are unable to retain at a specific position in the rectum, they migrate upwards to the colon which makes the drug to undergo first pass metabolism. *Y. Yuan et al* formulated a thermo sensitive *in situ* gel of Nimesulide. Modulation of the adhesive properties of poloxamer 407 solutions by sodium alginate in the presence of PEG 4000 allowed a faster in vitro release, as well as a quicker absorption by in vivo than the conventional suppository. [45] Mucoadhesive liquid suppositories of carbamazepine (CBZ) were designed by *kamel and khatib* by adding carbopol to formulation of thermally gelling suppositories that contain poloxamer 407 and either poloxamer 188 or methylcellulose. The formulation had a relative bioavailability of 97.7% compared with orally administered CBZ suspension. [46]

Vaginal drug delivery system

The vaginal delivery was considered as a long-time route for the drugs with the purpose to obtain a local and systemic pharmacological effect. The conventional vaginal dosage formulations are associated with limitations of poor retention, leakage and messiness causing inconvenience to users, leading to poor patient compliance and loss of therapeutic efficacy. Muco-adhesive formulations may localize in a particular region and prolong the residence time hence it is very important for treatment of vaginal diseases. Muco-adhesive *in situ* gel of Clotrimazole was designed and developed by *Rencber et al* by using the mixture of poloxamer (PLX) 407 and 188. Hydroxy propyl methylcellulose (HPMC) or E50 was added to improve the mucoadhesive and mechanical properties of formulations and to prolong the residence time in vaginal cavity. In vivo studies show that the formulations remained on the vaginal mucosa after 24 h from application. Since it has suitable gel properties with good vaginal retention this must be a good candidate for treatment of vaginal candidiasis.[47]

Parenteral drug delivery system

In order to provide controlled and sustained release, the medication is applied as a injection or formulated as an implant system in to the body tissue. An injectable *in situ* gel of Metoprolol succinate was reported by thermo sensitive polymer Pluronic F 127 together with carbopol 934P, hydroxy propyl methyl cellulose and Sodium carboxy methyl cellulose. A controlled release of the drug was noted and shows a drug release of 99.53% up to 12 hrs.[48] In parenteral drug delivery system, drug reaches to systemic circulation with rapid absorption. At the site of drug absorption they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of *in situ* gels. [49]

Transdermal drug delivery system

It was reported that a sustained transdermal drug delivery from thermo responsive poloxamer depots formed within the skin micropores following micro needle (MN) application. The sol to gel transition characteristics of poloxamers can be utilized to create in situ forming depots in micropores of skin treated with the MNs to provide the controlled delivery of the active pharmaceutical agent. [50]

COMMERCIAL APPLICATIONS [2], [51]

Atrigel technology

Atrigel® technology is a proven sustained-release drug delivery platform that delivers therapeutic agents over a few days to several months with a single injection. It can be used for parenteral and site-specific drug delivery and was initially developed by Dunn and co-workers. A suitable biodegradable polymers and hydrophilic solvents are employed in the Atrigel system to dissolve the polymers. This includes the dissolution of water insoluble biodegradable polymer in to a nontoxic solvent such as N-methy-2-pyrrolidone. The drug is added to this solution. When the liquid polymer system is placed in the body by intramuscularly and subcutaneously using standard needles and syringes, it solidifies upon contact with aqueous body fluids to form a solid implant.

SABER depot technology

SABER stands for sucrose acetate isobutyrate extended release. It is an injectable, controlled

release, a biodegradable delivery system technology that uses high viscosity carrier such as sucrose acetate isobutyrate (SAIB), solvent and one or more pharmaceutically acceptable additives.. The drug is dissolved or dispersed in the SAIB/solvent solution for subsequent injection subcutaneously or intramuscularly. Co-solvents such as N-methy-2-pyrrolidone or ethanol or triacetin are added to reduce the viscosity of the system. When a more hydrophobic solvent such as benzyl benzoate gives a less viscous depot with slower solvent diffusion. Sustained drug release occurs over a period from several hours to several weeks by diffusion.

Regel Depot Technology

Regel is one of MacroMed's proprietary drug delivery systems. It is based on triblock copolymer of poly (lactide-coglycolide) - poly (ethylene glycol) – poly (lactide-coglycolide) (PLGAPEG-PLGA) in phosphate buffer saline. Thermally reversible gelling materials, such as Regel, a compound being developed for parenteral delivery.it has the ability to deliver both hydrophobic and hydrophilic drug molecules.

Examples,

- **Oncogel**: It is a controlled release frozen formulation of Paclitaxel in regel
- **hGHD-1**: Regel drug delivery system of human growth hormone for hGH deficiency.
- **Cytoryn**: Regel drug delivery system of interleukin-2 (IL-2) for cancer immunotherapy.

TIMOPTIC –XE

It is a sterile, isotonic, buffered aqueous gel of Timolol maleate indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma . TIMOPTIC-XE, when applied topically on the eye, has the action of reducing elevated, as well as normal intraocular pressure, whether or not accompanied by glaucoma.

Relday

Relday is an investigational long-acting, sustained release injectable form of the antipsychotic medication of risperidone, based on Durect's proprietary SABER technology. After subcutaneous injection, it can deliver the drug for one month. The advantage of Relday is no need of reconstitution before injection.

Eligard

Eligard (leuprolide acetate for injectable suspension) is a medicine for the treatment of advanced prostate cancer. It consists of PLGA, leuprolide acetate and requires NMP for dissolving the ingredients based on Atrigel technology. It releases leuprolide acetate at a controlled rate over 1, 3, 4 or 6 months.

Atridox

It is a subgingival controlled-release product of doxycycline hycylate composed of a two syringe mixing system. Syringe A contains 450 mg of the drug, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly (D Lactide) (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone (NMP). Syringe B contains 50 mg of doxycycline hyclate which is equivalent to 42.5 mg doxycycline. Upon contact with the crevicular fluid, the liquid product solidifies and then allows for controlled release of drug for a period of 7 days.

Atrisorb

It is a free flow guided tissue generation (GTR) barrier product used for tissue generation of periodontal tissue. It is quite easy to use, effective and economical and helps in fast and easy tissue regeneration. It is composed of DL-lactide polymer and is available in a three-polymer unit package with three blunt-tip cannula needles.

CONCLUSION:

In situ gelling system is considered as a novel drug delivery system for controlled release of the drugs. *In situ* gel offers the primary need of a controlled release product i.e, increasing patient compliance, minimising the adverse effect and maintains the desired therapeutic concentration over an extended period of time. The uses of biodegradable and water-soluble polymers make them more acceptable, reliable and excellent drug delivery system.

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