International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

In-Situ Gel: Popular Novel Sustained Release Technique

[1]Hasanji F.M., [2]Patel A.K., [3]Patel V.M.
[1]*student APMC College of pharmaceutical education and research, Himmatnagar, Gujarat, India, 383001*
[2,3]*Faculty, APMC College of pharmaceutical education and research, Himmatnagar, Gujarat, India, 383001*
Corresponding Author: Hasanji fatmakhatum.M

Submitted: 15-01-2022 Accepted: 27-01-2022

ABSTRACT:
Nowadays controlled and sustained drug delivery has become popular in upcoming pharmaceutical products and a wide research has been done to achieve much better drug product efficacy and safety The 'in situ gel' system has emerged as one of the best novel drug delivery systems; it helps for the sustained and controlled release of the drugs by its special characteristic feature of 'Sol to Gel' transition. The main aim of pharmacotherapeutics is the attainment of effective drug concentration at the intended site of action for a sufficient period of time to elicit the response. In situ gelling system is a formulation that is in solution form before entering in to the body, but it will change to gel form under various physiological conditions. There are various polymers which under go in situ gel forming and potentially used for various routes of drug administration. There are several applications and advantages of in situ gelling system in today's life. Pectin, gellan gum, chitosan, alginic acid, guar gum, carbopol, xyloglucan, xanthan gum, HPMC, poloxamer etc. are some of natural polymers used for in situ gelling system. In situ gels has become an outstanding among novel drug delivery system (NDDS) in recent years due to its pros like sustained and prolonged drug action, improved patient compliance and reduced frequency of administration of the drug as compared to conventional drug delivery system (DDS). There are several applications and advantages of in situ gelling system in today's life. This review mainly focus on introduction to in situ gel, its mechanism, various polymers used and its applications.

KEYWORDS: in situ gel, novel drug delivery system, polymers, pharmacotherapeutics.

I. INTRODUCTION

GELS:

Gels are semisolid system which contains both solid and liquid components. It consists of three dimensional solid network [3].

In-situ is a Latin phrase which translated is literally as "in position". In-situ gel drug delivery are in solution form before administration in the body, but once administered undergoes gelation in-situ, to form gel. Gelation occurs due to cross linking of polymer chain through covalent and non-covalent bond formation [6]. In-situ gelling system has become one of the best among the novel drug delivery system due to its sustained and controlled release action, improved patient compliance and comfort, reduced frequency of dosing [1,2]. In situ gel formation occurs due to one or combination of different stimuli or triggering mechanisms like change in pH, temperature or solvent exchange, ionic cross linkage, ionization, UV irradiation[3]. In-situgel forming system via different route such as oral, nasal, ophthalmic etc. can be formulated. The system basically utilizes polymers that undergo transformation from sol to gel like consistency, due to the change in physicochemical properties [8].

- Over the past 30 years greater attention has been focused on the development of controlled and sustained drug delivery systems. The goal in designing these systems is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of the action.

- Amongst the extensive research has been carried in designing of polymeric drug delivery systems, the development of in situ gel systems has received considerable attention over the past few years. These systems are capable of releasing the drug in a sustained manner maintaining relatively constant plasma profiles and they are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. This is a characteristic property of temperature dependent, pH dependent and cation induced gelation. In situ gel forming drug delivery is a type of mucoadhesive drug delivery system.[4]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

- In contrast to very strong gels, they can be easily applied or used in liquid form to the site of drug absorption, where, 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

❖ **Advantages of in-situ gelling system**[6, 3]

It shows various advantages like

- Ease of administration.
- Improved patient compliance.
- Reduced dosing frequency.
- Site specificity and local action.
- Increased bioavailability.
- Sustained and prolonged release.
- It can also be administered to unconscious patient.

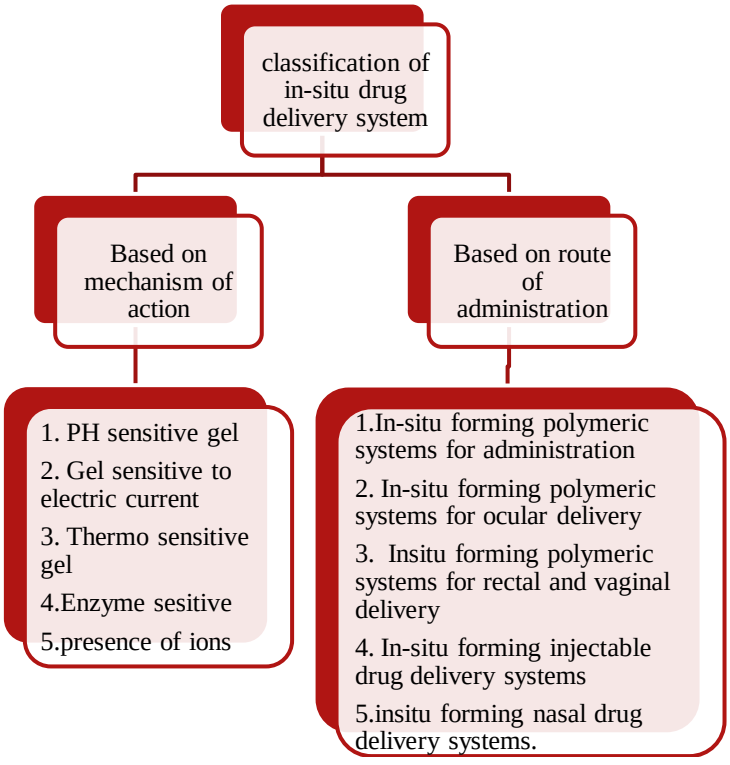
❖ **Disadvantages of in-situ gelling system**[8]

- It requires an elevated level of fluids
- Only small doses can be administered
- The solution dorm of drug is more susceptible to degradation.
- Due to chemical degradation, there is a chance of instability.
- It may results in premature dissolution due to low mechanical strength.

❖ **Importance of in-situ gelling system** [1, 2]

- It helps for the controlled and sustained release of the drug by its special 'Sol Gel transition.'
- It helps to reduce frequency of drug administration.
- Low drug dose required and there will be no drug accumulation and no side effects.
- More bioavailability of the drug.
- Increased residence time of the drug due to gel formation.
- The in situ gelling decreases wastage of the drug.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.

Ⅱ. Classification of in-situ drug delivery systems



ⅲ. Approaches for forming in-situ gels

There are 4 triggering mechanisms for in-situ gelling of biomaterials

1. In situ gel formation due to physiological stimuli

a. Temperature triggered in situ gel systems
b. pH triggered in situ gelling systems

2. In situ gel formation due to ion-activated system

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

3. In situ gel formation due to physical mechanism
a. Swelling
b. Diffusion

4. In situ gel formation due to chemical reactions
a. Ionic cross-linking
b. Enzymatically cross linking
c. Photo-polymerization

1. In situ gel formation due to physiological stimuli
There are some polymers which undergo large and unexpected physical and chemical changes in response to small external variation or changes in their environmental conditions. Such polymers are called Stimuli-responsive polymers [3].
Some examples of multi-stimuli responsive in-situ gelling system.

Model drugs	Polymers	Stimuli	Major finding
Sparfloxacin [29]	Sodium alginate and methylcellulose	Ion and pH sensitive	Rapid gelation upon raising pH to 7.4, in vitro sustained drug release over period of 24 h, significantly enhanced corneal permeation.
Nepafenac [48]	Carboxymethyl chitosan (CMC) and poloxamer	pH-induced and thermo-sensitive	The gelation temperature of 32–33 °C and retarding the drug diffusion rate was observed.
Timolol [49]	Chitosan with gellan gum	pH-sensitive and ion-activated polymer	Enhanced transcorneal drug permeation and prolonged the retention at the corneal site.
Levofloxacin [50]	Sodium alginate and chitosan	Ion and pH-triggered	Better retention time was observed.
Ciprofloxacin [51]	Carbopol/HPMC and Poloxamer	pH-induced and thermo-sensitive	Improved therapeutic efficacy and offers sustained release of the drug over an 8 h period.

a. Temperature triggered in situ gel system
Temperature sensitive polymers are most widely studied class of environmentally responsive polymer systems in drug delivery. This is because change in temperature is easily applicable on both in vivo and in vitro, and controlling of temperature is also very easy. In this system, gelling of solution is triggered by body temperature, thus sustaining the drug release and no need of external heat. These hydrogels are in liquid form at room temperature (20- 25°C) and undergo gelation when comes in contact with body fluid (35-37°C) (Fig.1). The use biomaterial whose transition from sol-gel induced by increase in temperature is an amazing way to approach in situ formation. The best critical temperature range for such systems is ambient and physiologic temperature; so there is no need for external heat, as gelation is triggered by body heat. There are three type of temperature induced system:

TYPE	EXAMPLE
Negative thermo sensitive	Poly (N-isopropyl acrylamide)
Positive thermo sensitive	polyacrylic acid
Thermally reversible	Poloxamer, pluronics, tetronics

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

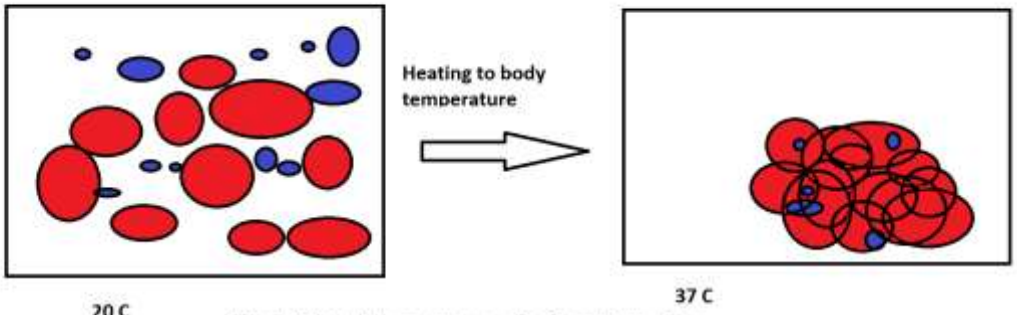


Fig. 1: Effect of temperature on in situ gel formation

b. PH triggered in-situ gelling systems;

In this system gelling is triggered due to pH changes. PH sensitive polymers or pH responsive are used in this method. In pH sensitive polymers includes pendant acidic or basic groups that either accept or release protons in counter to changes in environmental ph. The large number polymers of the ionizable groups are known as poly electrolytes. The poly electrolytes are present in the formulation causes increase in external pH that results into swelling of hydrogel that forms in situ gel.

Some suitable polymers for this approach

Cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes and poly methacrilic acid (PMC) etc. (2, 3)

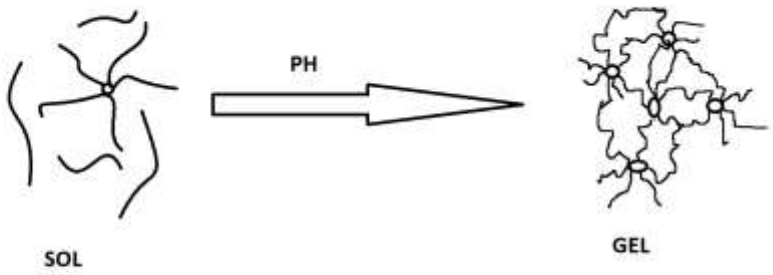


Fig. 2: mechanism of PH triggered in-situ gel system

2. In situ gel formation due to ion activated system

Here, gelling of the biomolecules solution is induced by the change in ionic strength. It is assumed that in ion activated system the osmotic gradient across the surface of the gel determines the rate of gelation. Polymers that shows osmotically induced gelation include gelrite or gellan gum, hyaluronic acid, alginates, etc. (3, 2)

Model Drug	Polymers	Major finding
Gatifloxacin[43]	Alginate with HPMC	A higher ocular bioavailability and extended residence time in aqueous humor than

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

		conventional ophthalmic solutions.
Fluconazole[44]	HPBCD complexed gellan gum and κ-carrageenan	Showed effective control of fluconazole release and good Bioadhesive properties.
Acetazolamide[45]	Gellan gum with xanthan gum, HPMC or carbopol.	Enhanced therapeutic efficacy and more extended intraocular pressure lowering effect compared to that of marketed eye drops and oral tablet.
Terbinafine hydrochloride [46]	Gellan gum	Significantly higher C max, delayed t max, and prolonged mean residence time and increased bioavailability.

3. In situ gel formation due to physical mechanism

a. Swelling: In-situ gelling occurs when the material absorbs water present in the surrounding environment and then expands to occupy desired space. Example of such a substance is myverol 18-99 (glycerol mono-oleate)

b. Diffusion: This method involves diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N methyl pyrrolidone (NMP) has shown to be useful solvent for this system.

4. In situ gel formation due to chemical reaction

a. Ionic cross-linking

There are some ion sensitive polysaccharides which fall into the class of ion-sensitive ones, such as gellan gum, pectin, sodium alginate which undergo phase transition in presence of various ions. An anionic polysaccharide, Gellan gum, undergoes in situ gelling in presence of mono- and divalent cations, i.e. Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxy pectin's can be caused by divalent cations, especially ca2+.

b. Enzymatically cross linking

Enzymatic cross linking is most suitable and convenient method that can be used in formulation of in-situ gelling system. In this method gelling occurs by cross linking with the enzymes which are present in the body fluids. In situ formation catalyzed by natural enzymes has not been studied and investigated widely but it possesses some advantages over chemical and photochemical approaches. For example, under physiologic conditions, an enzymatic process works efficiently without need for potentially harmful and destructive chemicals such as monomers and initiators. Modifying the amount of enzyme provides a convenient and suitable mechanism for controlling the rate of gel formation, which allows the mixture to be injected before gel formation. [3, 2].

c. Photo-polymerization

Electromagnetic radiations are used in photo-polymerization method during formation of in situ gelling system. A solution of reactive macromere or monomers and invader can be injected into a tissues site for gelling process. The most suitable polymers for photo polymerization are the polymers that undergo dissociation by polymerisable functional group in the presence of photo initiator like acrylate or similar monomers and macromeres that are typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet have limited penetration of tissue and biologically harmful so they are not widely used. In this method, ketone, such as 2, 2 dimethoxy-2-phenyl acetophenone, is used as the initiator for ultraviolet photo- polymerization. Camphor Quinone and ethyl eosin initiators are used in visible light systems. [2]

ⅳv. Ideal characteristics of polymers for preparation of in situ gel[14, 15]

- The polymer should be capable of adhering to the mucous membrane.
- It should be well compatible and should not provide any toxic effects.
- It should have pseudo plastic behavior.
- The polymer should be capable of decreasing the viscosity with increase in shear rate.
- Preferred pseudo plastic behavior of polymer.
- Good tolerance and optical clarity is more preferred.
- It should influence the tear behavior

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

POLYMER	PROPERTIES
PECTIN[4]	➢ Pectin's are a family of polysaccharides, in which the polymer backbone contains mainly, α- - (1-4)--D galacturonic acid residues. ➢ Low methoxy pectin's (degree of esterification <50%) in presence of free calcium ions readily forms gels in aqueous solution, which crosslink the galacturonic acid chains in a manner described by egg-box model. ➢ Pectin used mainly for these formulations is due to its water solubility, so organic solvents are eliminated in the formulation. ➢ Divalent cations present in the stomach, carry out the transformation of pectin to gel form when it is orallyadministered(11)
GUAR GUM[14]	➢ Guar gum is also known as guaran of naturally occurring gum which is obtained from the endosperm of the seed. ➢ Guar gum is insoluble in hydrocarbons, fats, esters, alcohols and ketones but soluble in water. ➢ These show its dispersibility in both cold and hot water that it is soluble in both cold and hot water to form colloidal solution at low amount. ➢ Guar gum has derivatives are used in targeted delivery systems in the formation of coating matrix systems, nano-microparticles and hydrogels. ➢ It can also be used as a polymer in matrix tablets which shows controlled release.
CARBAPOL[4,5]	➢ Carbopol is a polyacrylic acid (PAA) polymer, also known as PH dependent polymer which changed to gel as the pH is raised from 4.0 to 7.4. ➢ Carbopol stays in solution form at acidic pH but transform into a low viscosity gel at alkaline Ph. ➢ HPMC is generally used in combination with carbopol to enhance viscosity of carbopol solution, and to reduce the acidity of the solution.
XYLOGLUCAN[8]	➢ Xyloglucan is also called as tamarind gum as it is obtained from endosperm of tamarind seeds (3). ➢ Xyloglucan consists of three different oligomers like heptasaccharide, octasaccharide, nonsaccharide, which differ in number of galactose side chain. ➢ It is potentially used in oral, rectal, ocular drug delivery due to its non- toxic, biodegradable and biocompatible property. ➢ Various water soluble polymers such as: carbopol system- hydroxypropylmethylcellulose system, poly (methacrylic acid)-poly (ethylene glycol) come under the class of pH-induced in-situ precipitating polymeric systems.(6)
GELLAN GUM[2,5]	➢ Gellan gum (Gelrite) is a linear, anionic

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

	deacetylated exocellular polysaccharide secreted by the microbe Pseudomonas elodea with a tetra saccharide repeating unit of one α-L rhamnose, one β-D-glucuronic acid and two β- D-glucuronic acid residues. ➢ Gelation of gellan gum is temperature dependent or cation induced. ➢ This gelation involves formation of double helical junction zones followed by aggregation of the double helical segments which gives rise to a 3-dimensional network by complexation with cations and hydrogen bonding with water.(3)
ALGINIC ACID[4]	➢ Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-guluronic acid residues joined by 1, 4-glycosidic linkage. ➢ Depending on the algal source, the proportion of each block and the arrangement of blocks along with the molecule varies. ➢ Dilute aqueous solutions of alginates form firm gels on addition of di- and tri-valent metal ions by a cooperative process involving consecutive glucoronic residues in the α-L- guluronic acid blocks of the alginate chain. ➢ Alginic acid is mucoadhesive, biodegradable and non-toxic polymer, due to which it is widely used as a vehicle for ophthalmic in situ gelling system.(6)
XANTHUM GUM[5]	➢ Xanthum gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram negative bacteria Xanthomonas campestris. ➢ The primary structure of this naturally obtained cellulose derivative contains a cellulose backbone (β-D-glucose residues) and a trisaccharide side chain of β-D- mannose-β-D-guluronic acid-α-D-mannose attached with alternate glucose residues of the main chain. ➢ The anionic character of this polymer is due to the presence of both glucuroniacid and pyruvic acid groups in the side chain(7,3)
CHITOSAN[9]	➢ Chitosan is a biodegradable, thermo sensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. ➢ Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolvedin aqueous solutions up to a pH of 6.2(7) ➢ Neutralization of chitosan aqueous solution to a pH exceeding 6.2leads to the formation of a hydrated gel like precipitate. ➢ The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.(7)

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

HPMC[4]	➢ Cellulose consists of glucan chain which has repeating β-(1, 4)-D-glucopyranose unit. ➢ Some natural polymers like HPMC, MC and EC exhibit temperature sensitive sol-gel phase transition. ➢ Cellulose material will increases its viscosity when temperature will decreases while its derivatives like HPMC, MC, will increase its viscosity when temperature is increased. ➢ MC is a natural polymer composed of native cellulose with alternate methyl substitution group on its chain. ➢ At low temperature (30C) solution is in liquid form and when temperature is increases (40-50C) and gelation occurred.(4)
POLOXAMER[5]	➢ Poloxamer are water soluble tri-block copolymer. ➢ It consists of two polyethylene oxide (PEO) and polypropylene oxide (PPO) core in an ABA configuration(4) ➢ Pluronics or Poloxamers consists of more than 30 different non-ionic surfactants. ➢ There in situ gel formation is based on temperature change. ➢ These are triblock copolymers consisting of poly (oxyethylene) and poly (oxypropylene) units that undergo alteration in solubility with alteration in surrounding temperature. ➢ Pluronic F217 gives colorless and transparent gel, and is one of the most commonly used polymer in pharmaceutical technology. ➢ A concentration of 20% weight of Pluronic F217 at 25°C is required for gelation. The solution behaves as a mobile viscous liquid at room temperature (25°C), which is altered into a semisolid transparent gel at body temperature (37°C).(3)

v.FORMULATION OF INSITU

TYPE	API	POLYMER
FOR OPTHALMIC[25]	Moxifloxacin hydrochloride Linezolid Gatifloxacin	HPMC 50 LV HPMC K 4M Xanthan gum Hydroxyl ethyl cellulose Carbopol 934P
FOR NASAL[24]	Vitamin B12 Chlorpheniramine maleate Ondansentron Flumarizine hydrochloride zolmitriptan Salbutamol sulphate	Pluronic F68 Pluronic F127 Carbopol 934P Chitosan Gellan gum
FOR PARENTRAL[56]	Gatifloxacin Doxycylin Leuprolide	Sodium alginate Gellan gum Alginic acid

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

		Poloxamer Pluronic F127
FOR ORAL[4]	Clotrimazole Ofloxacin Nifedipine Roxatidine Omeprazole diltiazem	Gellan gum Chitosan Carbopol Xanthan gum

vi.Method of preparation

1. Solution polymerization or cross linking [4]

In this method, multifunctional cross linking agents are mixed with ionic or neutral monomers. The polymerization is initiated thermally or by UV light or by redox initiator system. Solvent present minimizes the temperature control problem as well as serves as heat sink. The finished hydrogels requires washing with distilled water for removal of the unreacted materials, cross linking agent and the initiator. One of the best example of this method is poly (2-hydroxyethyl methacrylate) hydrogels from hydroxyethyl methacrylate, using ehtylene glycol dimethacrylate as cross linking agent.

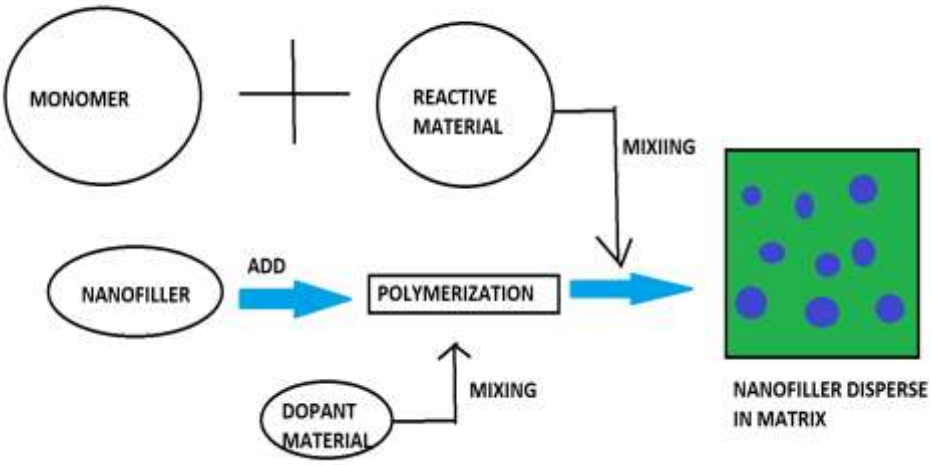


Fig.3: solution polymerization

2. Suspension polymerization[5]

This method is widely used for preparation of spherical hydrogel microparticles with size ranging from 1µm to 1mm. In this method, the monomer solution is dispersed in the non- solvent forming fine droplets, which are stabilised by addition of stabilizer. The initiation of the polymerization is by thermal decomposition of free radicals. The prepared microparticles require further washing to remove unreacted monomers, cross linking agent and initiator. Hydrogel microparticles of poly (vinyl alcohol) and (hydroxyl ethyl methacrylate) have been prepared by suspension polymerization method.

3. Polymerization by irradiation [6]

High energy radiations such as gamma and electron beam are used to prepare the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains, which results in formation of microradicals. Recombination of the microradicals on different chains results in the formation of covalent bonds, and finally a cross linked structure is obtained. Polymerization microradicals may interact with oxygen during radiation, that's why radiation is performed in an inert atmosphere using nitrogen or argon gas. Example of this method include poly (vinyl alcohol), poly (ethylene glycol) and poly (acrylic acid).

4. Chemically crossed linked hydrogels [3]

Polymers which contain functional groups like - OH, -COOH, -NH2 are soluble in water. Due to presence of such functional groups on the

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

polymer chain, it can be used to prepare hydrogels by forming covalent linkages between polymer chains and complimentary reactivity, such as amine-carboxylic acid, isocyanate -OH or -NH2 or by Schiff's base formation. Gluteraldehyde can be used as a cross linking agent for preparation of hydrogels of polymers containing -OH groups such as poly (vinyl alcohol) and also polymers containing amine groups (albumin, gelatin, polysaccharides). This cross linking agent reacts with the functional groups present on the polymer via addition reaction. Since cross linking agents are highly toxic, unreacted agents have to be extracted. Also the reaction has to carried out in organic solvents since water can react with the cross linking agent. The drugs are loaded after the formation of hydrogel, hence the release is typically first order

5. Physically cross linked hydrogel[4]

Almost all of the covalent cross linking agents are known to be toxic, even in small traces. Hence to overcome this problem and to avoid a purification step, hydrogels are prepared by reversible ionic cross linking. Chitosan, a polycationic polymer reacts with positively charged components, either ions or molecules forming a network through ionic bridges between the polymeric chains. In case of anionic molecules, phosphate containing groups, particularly sodium triphosphate is widely studied. Ionic cross linking is an effortless and easy-going procedure. Compared to covalent cross linking, no auxillary molecules such as catalysts are required. Chitosan is also known for forming polyelectrolyte complex with poly (acrylic acid).

vii. Evaluation and characterization [5]

Following parameters are used for evaluation and characterization of in situ gel:

1) Clarity

The clarity of the formulated solution is determined by visual inspection under black and white background.

2) Texture analysis

The firmness, consistency and cohesiveness of hydrogels are examined using texture analyzerwhich significantly indicates the syringeability of solution so that the formulation can be easily administered in vivo. Higher values of adhesiveness of gels are required to maintain an intimate contact with surface.

3) PH of gel

Formulation is taken in a beaker and 1ml NaOH added dropwise with continuous stirring, pH is checked by using pH meter.

4) Sol-Gel transition temperature and gelling time

For in situ gelling systems with thermoreversible polymers, the sol-gel transition temperature may be defined as the 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 specific rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube.

5) Gel strength

This parameter is evaluated using a Rheometer. Depending on the mechanism of gelling of the gelling agent used, a defined amount of gel is prepared in a beaker form the sol form. This gel containing beaker is raised at a definite rate, so pushing a probe slowly through the gel. The changes in the load on the probe are measured as a function of depth of immersion of the probe below the gel surface.

6) Rheological studies

This is one of the important parameter to be evaluated for in situ gels. Viscosity and rheological properties of in situ gelling drug delivery systems are assessed using Brookfield rheometer, or some other viscometers like Ostwald's viscometer. The viscosity of in situ gelling systems should be such that no difficulties are encountered during their administration by the patient, especially in parenteral and ocular administration. The formulation should have viscosity of 5-1000 mPas.

7) High performance liquid chromate- graphy

The HPLC system if used in reversed phase mode.

8) Drug-polymer interaction study and thermal analysis

Interaction studies are performed with Fourier Transform Infra-Red (FTIR) spectroscopy. During gelation process, the nature of interacting forces can be determined using thistechnique by employing KBr pellet method. Thermo gravimetric analysis (TGA) can be used for in situ gelling system to determine the percentage of water in hydrogel. Differential scanning calorimetry (DSC)

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 601-614 www.ijprajournal.com ISSN: 2249-7781

used to observe if there are any changes in thermograms as compared to pure active ingredients used for gelation.

9) In vitro drug release studies

For the in situ gel formulations administered by oral, ocular or rectal routes, the drug release studies are done by using plastic dialysis cell. The cell is made up of 2 half cells, donor compartment and receptor compartment and both these compartments are separated with the help of cellulose membrane. The sol form of the formulation is sited in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution is analyzed for the drug release using analytical methods. For injectable in situ gels, the formulation is sited into vials containing receptor media and placed in a shaker water bath at required temperature and oscillation rate, samples are withdrawn periodically and analyzed.

10) Antimicrobial activity

Antimicrobial studies are carried out to determine the biological activity of sol-gel- system against microorganisms. This is done using agar diffusion medium employing 'Cup Plate Techniques'. The microbial growth of bacteria is measured by concentration of antibiotic and compared with that produced with known concentrations of standard preparation of antibiotic and carried out the microbial assay serial dilution method is employed.

11) Sterility Testing

Sterility testing is carried out as per IP 1996. The formulation is incubated for not less than 14 days at 30-35°C in the fluid thioglycolate medium to find the growth of bacteria and at 20-25°C in Soya casein digest medium to find the growth of fungi in formulations.

12) Accelerated stability studies

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

REFERENCE

[1]. Sarada K, Firoz S and Padmini K: In-Situ gelling system: A review. International Journal of Current Pharmaceutical Review and Research, 2014-15; 5[4]: 76-90.
[2]. Nirmal HB, Bakliwal SR and Pawar SP: In situ gel: New trends in controlled and sustained drug delivery system. International Journal of Pharmaceutical Technology and Research, 2010; 2(2): 1398- 408.
[3]. Khan Sarfraz: In situ gelling drug delivery system: An overview. Journal of Innovations in Pharmaceuticals and Biological Sciences, 2016; 3(1): 60-69.
[4]. Kant A, Reddy S, Shankraiah MM, Venkatesh JS and Nagesh C: In situ gelling system - an overview. Pharmacology online, 2011; 2: 28-44.
[5]. Nerkar Tushar S, Gujarathi Nayan A, Rane Bhushan R, Bakliwal Sunil R and Pawar SP: Insitu gel: Novel approaches in sustained and controlled drug delivery system. Journal of Pharmaceutical Research, 2013; 4(4).
[6]. Ramya Devi D, Abhirami M, Brindha R, Gomathi S and Vedha B.N: In-situ gelling system- Potential tool for improving therapeutic effects of drugs. International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5(3).
[7]. Mcdonald Tom and Town Adam: Responsive gelation of nanoparticles/gel composites for sustained drug delivery. Frontiers, 2016; 01-01533.
[8]. Amruta B. Kumbhar, Ashwini K. Rakde and P.D. Chaudhari: In situ gel forming injectable drug delivery system", International Journal of Pharmaceutical Sciences and Research, 2011; 7: 371-93.
[9]. Eaga CM, Jagan MK, Venkatesham A. Preparation and evaluation of in-situ gels for ocular drug delivery. J Pharm Res 2009; 2: 1089-1094.
[10]. Heiko K, Erol Y, Gayle AB, Roland B. In-vitro and in-vivo drug release from a novel in-situ forming drug delivery system. Pharm Res 2008; 25: 6.
[11]. Saraswat R.1, Bhan C. S., Gaur A. A Review on Polymers Used In In-Situ Gel Drug Delivery Systems, 1(2), May-Jun 2011
[12]. Calfrs J, Edsman K, Peterson R. Rheological evaluation of Poloxamer as an in situ gel for ophthalmic use. Eur J Pharm Sci., 6, 2000, 105
[13]. Gurny R, Ibrahim H, Buri P. The development & use of in situ formed gel triggered by pH. In Biopharmaceutics of

ocular drug delivery. ed. Edman, 1993, 81-90.

[14]. Geraghaty P, Attwood D, et al. An investigation of parameters influencing the Bioadhesive properties of Myverol 18-99/ water gels. Biomaterials, 18, 1997, 63-7.

[15]. Guo J-H, Skinner GW, Harcum WW, Barnum PE. Pharmaceutical applications of naturally occurring water-soluble polymers. Pharm Sci & Technol Today, 1, 1998, 254-61.

[16]. Burkoth AK, Anseth KS. A review of photocrosslinked polyanhydrides: In situ forming degradable networks. Biomaterials, 21, 2000, 2395-404.

[17]. Grasdalen H, Smidsroed O. Gelation of gellan gum. Carbohydrate Polymers, 7, 1987, 371-93.

[18]. Miyazaki S, Suisha F, Kawasaki N, Shirakawa M, Yamatoya K, Attwood K, Thermally reversible xyloglucan gels as vehicles for rectal drug delivery, J Control Rel, 56, 1998, 75-83.

[19]. Rathore K S; Nema R K; Ishibashi Tejraj; Yokoi N; Born JA; Tiffany MJ; Komuro A. International Journal of Pharm Tech Research ,2009,1(2),164-169.

[20]. Keister JC; Cooper ER; Missel PJ; Lang JC; Hager DF. Journal of Pharmaceutical Sciences, 1991, 80, 50-53.

[21]. Sarada K, Firoz S, Padmini K. In-Situ Gelling System: A Review. International Journal of Current Pharmaceutical Review and Research, 2014-15, 5(4), 76-90

[22]. Kant A, Reddy S, Shankariah MM, Venkatesh J S, Nagesh C. In situ gelling system – An overview. Pharmacol online, 2011;2(1):28-44

[23]. M. Madan, A. Bajaj, S. Lewis, N. Udupa, J. A. Baig, In Situ Forming Polymeric Drug Delivery Systems. Indian j pharma sci. 2009;71(3):242-51·

[24]. Shreeraj Shah, Pratik Upadhyay, Darsh Parikh, Jinal Shah. In Situ Gel: A Novel Approach of Gastroretentive Drug Delivery, Asian Journal of Biomedical and Pharmaceutical Sciences,2012;2 (8):01-08

[25]. Mohammed Gulzar Ahmed, Acharya A, Chaudhari R, Panicker k, Reddy R. Formulation and Evaluation of in situ gel containing Rosuvastatin in the treatment of periodontal diseases: J pharm res 2015;6:14(2):45-50.

[26]. Sarasija S, Shyamala B. Nasal Drug Delivery: An Overview, Indian J Pharm.Sci. 2005, 67(1): 19-25

[27]. Kavitha K., Santhosh KP, RupeshKumar M, Jyothi M, Sunil n. Recent developments and strategies of ocular in situ drug delivery system; a review. Int J and Cli Res, 2013;5(2):64-71

[28]. Nirmal H.B, Bakliwal S.R., Pawar S.P, In-Situ gel: New trends in Controlled and Sustained Drug Delivery System. Int J Pharm Tech Research, 2010;2(2), 1398-408.

[29]. Available from http:www.slideshare.net/shreeraj9183/in situ-gel-delivery system.

[30]. Kawasaki N, Ohkura R, Miyazaki S, Uno Y, Sugimoto S, Attwood D. Thermally reversible xyloglucan gels as vehicles for oral drug delivery. Int J Pharm 1999;181:227-34.

[31]. Marsha Ritter Jones, MS, Philip B. Massersmith, In-situ forming biomaterials, Oral Maxillofacial Surge Clin N Am 14 (2002):29-38.

[32]. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm 2000.

[33]. Soppimath KS, Aminabhavi TM, Dave AM, Kumbar SG, Rudzinski WE. Stimulus-responsive “smart” hydrogels as novel drug delivery systems.

[34]. Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D. In situ gelling Xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int J Pharm 2001;229:29-36.

[35]. Miyazaki S, Hirotatsu A, Kawasaki N, Wataru K, Attwood D. In situ gelling gellan formulations as vehicles for oral drug delivery. J Control Rel 1999;60:287-95.

[36]. Kashyap N, Viswanad B, Sharma G, Bhardwaj V, Ramarao P, Kumar MNV. Design and evaluation of biodegradable, biosensitive in situ gelling systems for pulsatile delivery of insulin. Biomaterials 2007;28:2051-60.

[37]. Divyesh HS., Hitesh DD., Pragna S., Alkesh KB., 2016. Formulation development and evaluation of a gastroretentive In situ oral gel of cefuroxime axetil. J Yun Pharm .8(4):324-329.

[38]. Hareesh BK., Gulzar MA., Narayana CR., 2012. Development and evaluation of in situ gels of Moxifloxacin for the treatment of

Periodontitis. Indonesian J Pharm. 23(3):141-146.

[39]. Harish NM., Prabhu P., Charyulu RN., Gulzar MA., Subrahmanyam EVS., 2009. Formulation and evaluation of in situ gels containing clotrimazole for oral candidiasis. Int J Pharm Sci.10(8):421-27.

[40]. http://home.intekom.com/pharm/hmr/roxit.html

[41]. Pallavi C., Pratibha., Gnanrajan G., Preethi K., 2016. In situ gel: A review. Ind J Pharm Biol Res. 4(2): 11-19

[42]. Patel NA., Mahesh KS., Ravi K., Senthil A., Viral GP., 2012. Development and evaluation of oral gastro-retentive in situ gel of famotidine. Indo-Global Res J Pharm Sci. 2(1):238-43.

[43]. Ramana BV., Jalalu SS., Swapna C., et al., 2016. Design and development of floating in situ gel of pantoprazole. Scholar Res Lib. 8(8): 239-249.

[44]. Roshan RM., Vaishali G., Gupta S., 2015. Novel study in sustained release drug delivery system: A Review. Int J Pharm Med Res. 3(2): 204-215.

[45]. Tripathi KD., 2013. Drugs for peptic ulcer in essentials of medical pharmacology.7th edn. New Delhi: Jaypee Brothers Medical Publishers. 585-91.

[46]. Dey S. Mahanti B., Mazumder B., Malgope A., Dasgupta S. "Nasal drug delivery: An approach of drug delivery through nasal route", Der pharmacia sinica, 2(3), 2011, 94-106.

[47]. Anoop K.R., Nair S.C., John M.S., "In situ Gel: An Innovative Approach for Safe and Sustained Nasal Drug Delivery", International Journal of Pharmaceutical Sciences Review and Research, 24(1), 2014, 1-7.

[48]. Pagar S. A., Shinkar D.M., Saudagar R.B., "A Review on Intranasal Drug Delivery System", Journal of Advanced Pharmacy Education & Research, 3(4), 2013, 333-346.

[49]. Pires A., Fortuna A., Gilberto A., Amilcar F., "Intranasal Drug Delivery: How, Why and What for?" Journal Pharmaceutical Science, 2009, 12(3), 288-311

[50]. Bajpai V. "In situ Gel Nasal Drug Delivery System – A Review", International Journal of Pharma Sciences, 4, 2014, 577-580. Int. J. Pharm. Sci. Rev. Res., 33(1), July – August 2015; Article No. 37, Pages: 199-207 ISSN 0976 – 044X International Journal of Pharmaceutical Sciences Review and Research Available online at www.globalresearchonline.net © Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited. © Copyright protected. Unauthorised republication, reproduction, distribution, 207

[51]. Chavan P. Dhole S., Yadav M., "nasal drug delivery system: a review" world journal of pharmacy and pharmaceutical sciences, 3(12), 2014, 598-617.

[52]. Ramya D. D., Abhirami M., Brindha R., Gomathi S., Vedhahari B.N., "In-Situ Gelling System – Potential Tool For Improving Therapeutic Effects Of Drugs", International Journal Of Pharmacy And Pharmaceutical Sciences, 5(3), 2013, 27-30.

[53]. Swamy N G N, Zaheer A, "Mucoadhesive In situ Gels as Nasal Drug Delivery Systems: An Overview", Asian Journal of Pharmaceutical Sciences, 7(3), 2012, 168-180.

[54]. Patil P.R., Salve V.K., Puranik P.K., Khadbadi S.S., "Modern Encroachment and Provocation in Nasal Drug Delivery System", International Journal of Pharmaceutical Sciences and Research, 4(7), 2013, 2569-2575.

[55]. Kute J.U, Darekar A.B., Saudagar R.B., "In situ Gel-Novel Approach for Nasal Delivery", World Journal of Pharmacy And Pharmaceutical Sciences, 3(1), 2013, 187-203.

[56]. Tyagi s., Sharma N., Sharma P.K., "A Review on Application of Natural Bioadhesive Polysaccharides for Intranasal Drug Delivery", International journal of applied pharmaceutical sciences and biomedical sciences, 1(2), 2012, 80-94

[57]. Kamble M.S., Bhalerao K.K., Bhosale A.V., Chaudhari P.D., "A Review on Nose-To-Brain Drug Delivery," International Journal of Pharmaceutical and Chemical Sciences, 2(1), 2013, 516-525.

[58]. Nirmal H.B., Bakliwal S.R., Pawar S.P., "In-Situ Gel: New trends in controlled and Sustained Drug Delivery System", International Journal of Pharmatech Research, 2(2), 2010, 1398-1408.

[59]. Panchal D.R., Patel U.L., Bhimani B.V., Daslaniya D.J., Patel G.V., "Nasal In-Situ

Gel: A Novel Drug Delivery System", International Journal for Pharmaceutical Research Scholars, 1(2), 2012, 457-473.

[60]. Devmore P.S., Chothe B.T., Kambale R.P., Waghchoure P.S., Raut S.V., Waghmode R.R., "A Review on In Vitro Methods and Factors Affecting Nasal Drug Absorption", American journal of Pharmatech research, 4(1), 2014, 283-307.

[61]. Chaturvedi M., Kumar M., Pathak K., "A review on mucoadhesive polymer used in nasal drug delivery system", journal of advance pharmaceutical technology and research, 2(4), 2011, 215-222.

[62]. Nerkar T.S., Gujarathi N.A., Rane B.R., Bakliwal S.R., Pawar S.P., "in situ gel: novel approach in sustained and controlled drug delivery system", an international journal of pharmaceutical sciences, 4(4), 2013, 1-18.

[63]. Sarada K., Firoz S., Padmini K. "In-Situ Gelling System: A Review", International Journal of Current Pharmaceutical Review and Research, 5(4), 2014-2015, 76-90.

[64]. Devi R., Chuadhary A., Pandit V., "Mucoadhesive in-situ nasal gel- A novel approach", Journal of Advanced Drug Delivery, 1(6), 2014,1-8.

[65]. Rahisuddin, Sharma P.K., Garg G., Salim M., "Review on nasal drug delivery system with recent advancement", International Journal of Pharmacy and Pharmaceutical Sciences, 3(2), 2011, 1-5.

[66]. Mahakalkar N. G., Upadhay K.P., "Natural Mucoadhesive Polymers in Nasal In-Situ Gel Systems: A Review", International Journal of Pharmacy Technology, 5(2), 2013, 2712-2738.

[67]. Parekh H.B., Jivani R., Jivani N.P., Patel L.D., Makwana A., Sameja K. "novel in-situ polymeric drug delivery system: a review", Journal of Drug Delivery & Therapeutics, 2(5), 2012, 136-145.

[68]. Nasare L., Niranjane K., Nagdevte A., Sumedh M., "nasal drug delivery system: an emerging approach for brain targeting", world journal of pharmacy and pharmaceutical sciences, 3(4), 2014, 539-553.

[69]. Senthil K. K., Varma M G, Vudaykiran A., Kumar R.A., Sudhakar B., "Nasal Drug Delivery System - An Overview", International journal of pharmaceutical and chemical sciences, 1(3), 2012, 1358-1368.