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Review Article

REVIEW ON: NOVEL APPROACH IN PHARMACEUTICAL GEL

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ABSTRACT

R*eview on novel approach in pharmaceutical gel explains about gels and its novel development as hydrogel. Gel which is defined as intermediate state of matter consists of liquid and solid components. Hydrogels are also briefly discussed in the review that is defined as three dimensional structures which has capacity to retain bulk amount of water and also biological fluids to swell. In novel approach in pharmaceutical gel is In-Situ gels. In-situ gels are type of hydrogels that are solution in form and undergo gelation in contact with body fluids or change in pH. Some of the polymers that are used in in-situ gelling system are Carbopol-934, HPMC, gellan gum, xanthan gum, carrageenan, xyloglucan, pectin, chitosan etc. This review focuses on the classification, Mechanism of formulation and applications of gel and hydrogels (In-Situ gel) as novel approach systems in pharmaceutical.*

KEYWORDS: *Gels, In-Situ gel, Hydrogels, Polymers.*

INTRODUCTION

1. Gel:

Gels are an intermediate state of matter containing both liquid and solid components. Gel is a two-component, cross linked three-dimensional network consisting of structural materials interspersed by an adequate but proportionally large amount of liquid to form an infinite rigid network structure which immobilizes the liquid continuous phase within. The structural materials that form the gel network can be composed of inorganic particles or organic macromolecules, primarily polymers [1]. Cross links can be formed via chemical or physical interactions. This leads to gel classification into chemical and physical gel systems, respectively. Chemical gels are associated with permanent covalent bonding while physical gels result from relatively weaker and reversible secondary intermolecular forces such as hydrogen bonding, electrostatic interactions, dipole dipole interactions, Vander Waals forces and hydrophobic interactions [2]. The **U.S.P**. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels consist of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains [3].

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2. Structure of Gels:

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles gelling agent. The nature of the particles and the type of force that is responsible for the linkages, which determines the structure of the network and the properties of gel. The individual particles of hydrophilic colloid may consist of either spherical or an isometric aggregates of small molecules, or single macromolecules. In linear macromolecules the network is comprised of entangled molecules, the point of contact between which may either be relatively small or consist of several molecules aligned in a crystalline order. The force of attraction responsible for the linkage between gelling agent particles may range from strong primary valencies, as in silicic acid gels, to weaker hydrogen bonds and vander waals forces. The weaker nature of these latter forces is indicated by the fact that a slight increase in temperature often causes liquefaction of gel [4].

3. Characteristics of Gels:

3.1. Swelling:

When a gelling agent is kept in contact with liquid that solvates it, then an appreciable amount of liquid is taken up by the agent and the volume increases. This process is referred to as swelling. This phenomenon occurs as the solvent penetrates the matrix. Gel-gel interactions are replaced by gel solvent interactions. The degree of swelling depends on the number of linkages between individual molecules of gelling agent and on the strength of these linkages [5].

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Fig. 1: Swelling of gel polymer

3.2. Syneresis:

Many gels often contract spontaneously on standing and exude some fluid medium. This effect is known as syneresis. The degree to which syneresis occurs, increases as the concentration of gelling agent decreases. The occurrence of syneresis indicates that the original gel was thermodynamically unstable. The mechanism of contraction has been related to the relaxation of elastic stress developed during the setting of the gels. As these stresses are relieved, the interstitial space available for the solvent is reduced, forcing the liquid out [6].

3.3. Ageing:

Colloidal systems usually exhibit slow spontaneous aggregation. This process is referred to as ageing. In gels, ageing results in gradual formation of a denser network of the gelling agent.

3.4. Structure:

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles of the gelling agents. The nature of the particle and the stress, straightening them out and lessening the resistance to flow.

3.5. Rheology:

Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic i.e. exhibiting Non-Newtonian flow behaviour, characterized by a decrease in viscosity with increase in shear rate. The tenuous structure of inorganic particles dispersed in water is disrupted by applied shear stress due to breaking down of interparticulate association, exhibiting a greater tendency to flow. Similarly, for macromolecules the applied shear stress aligns the molecules in the direction of Organic (single phase system) [7].

4. Classification of Gels: [8]

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.

4.1. Based on colloidal phases: They are classified into Inorganic (two phase system) type of force that is responsible for the linkages determine the structure of the network and the properties of the gel.

Single-phase system: These consist of large organic molecules existing on the twisted strands dissolved in a continuous phase. This larger organic molecule either natural or synthetic polymers are referred as gel formers, they tend to entangle with each other their random motion or bound together by Vander waals forces.

Two phase system: If partial sizes of the dispersed phase are relatively large and form the three dimensional structure throughout gel, such a system consists of floccules of smallparticles rather than larger molecules and gel structure, in this system is not always stable. They must be thixotropic-forming semisolids on standing and become liquid on agitation.

4.2. Based on nature of solvent Hydro gels (water based): They contain water as their continuous liquid phase E.g. bentonite magma, Gelatin, cellulose derivatives, carpooler, and poloxamer gel.

Organic Gels (with a non-aqueous solvent): These contain a non-aqueous solvent on their continuous phase. E.g. plastibase (low molecular wt. polyethylene dissolved in mineral oil & short Cooled) Olag (aerosol) gel and dispersion of metallic stearate in oils.

Xerogels: Solid gels with low solvent concentration are known as xerogels. These are produced by evaporation of solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid, they swells and can bereconstituted. E.g. Tragacanth ribbons, acacia tear β-cyclodextrin, dry cellulose and polystyrene.

4.3. Based on rheological properties: Usually gels exhibit non-Newtonian flow properties. They are classified into, a) Plastic gels b) Pseudo plastic gels c) Thixotropic gels.

(a) Plastic gels: E.g. - Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.

(b) Pseudo-plastic gels: E.g. - Liquid dispersion of tragacanth, sodium alginate, Na CMC etc. exhibits pseudo-plastic flow. The viscosity of these gels decreases with increasing rate of shear, with no yield value. The rheogram results from a shearing action on the long chain molecules of the linear polymers. As the shearing stress is increased the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from gel matrix.

(c) Thixotropic gels: The bonds between particles in these gels are very weak and can be broken down by shaking. The resulting solution will revert back to gel due to the particles colliding and linking together again (the reversible isothermal gel-sol-gel transformation). This occurs in colloidal system with nonspherical particles to build up a scaffold like structure. E.g.: Kaolin, bentonite and agar.

4.4. Based on physical nature:

(a) Elastic gels: Gels of agar, pectin, Guar gum and alginates exhibit an elastic behavior. The fibrous molecules being linked at the point of junction by relatively weak bonds such as hydrogen bonds and dipole attraction. If the molecule possesses free –COOH group then additional bonding takes place by salt bridge of type –COO-X-COO between two adjacent strand networks. E.g.: Alginate and Carbapol.

(b) Rigid gels: This can be formed from macromolecule in which the framework linked by primary valance bond. E.g.: In silica gel, silic acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

5. Preparation of Gels: [9]

Gels are normally in the industrial scale prepared under room temperature. However few of polymers need special treatment before processing.

Gels can be prepared by following methods.

1. Thermal changes
2. Flocculation
3. Chemical reaction

5.1. Thermal changes: Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reducing, the degree of hydration is reduced and gelatin occurs. (Cooling of a concentrated hot solution will produce a gel). E.g.: - Gelatin, agar sodium oleate, guar gummed and cellulose derivatives etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.

5.2. Flocculation: Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitant. E.g.: Solution of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are Thixotropic in behaviour. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to "salt out", the colloidal and gelation doesn't occur.

5.3. Chemical reaction: In this method gel is produced by chemical interaction between the solute and solvent. E.g.: aluminium hydroxide gel can be prepared by interaction in aqueous solution of an aluminium salt and sodium carbonate, an increased concentration of reactants will produce a gel structure. Few other examples that involve chemical reaction between PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates (TDI), methane diphenyl isocyanine (MDI)hat cross-links the polymeric chain.

6. Gel Forming Substances: [10]

Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

1. Natural polymer:

a. Proteins:

i. Gelatin
ii. Collagen

b. Polysaccharides:

i. Alginic acid
ii. Agar
iii. Tragacanth
iv. Sodium or Potassium carrageenan
v. Pectin
vi. Gellum Gum
vii. Xanthin
viii. Cassia tora
ix. Guar Gum

2. Semisynthetic polymers:

a. Cellulose derivatives:

i. Hydroxyethyl cellulose
ii. Methylcellulose
iii. Hydroxypropyl methyl cellulose
iv. Hydroxypropyl cellulose
v. Carboxymethyl cellulose

3. Synthetic polymers:

a. Carbomer:

i. Carbopol -941
ii. Carbopol -940
iii. Carbopol -934

b. Poloxamer:

c. Polyvinyl alcohol:

d. Polyacrylamide:

e. Polyethylene and its co-polymers :

4. Inorganic substances:

a. Bentonite
b. Aluminium hydroxide

5. Surfactants:

a. Brij-96
b. Cetostearyl alcohol

Noval Approach in Gel:

1. Hydrogels: Hydrogels are the three dimensional structures that has polymeric networks which has the capacity to absorb and retain large amounts of water and biological fluids to swell [11].

2. Classification of hydrogels:

- ***Preformed hydrogels:*** are defined as simple viscous solutions which do not undergo any modification after administration.
- ***In-situ gels:*** are the solutions or suspensions that undergo gelation after reaching the particular site due to physico-chemical changes.

In-situ gelling system has become one of the most prominent among novel drug delivery systems due to many advantages such as improved patient compliance, reduced frequency of drug administration. 'In-situ' is a Latin word which means 'in position.

There are many triggering mechanisms in in-situ gel formation some of them are pH change, temperature modification and solvent exchange. As the gel formed from in-situ gelling system, being lighter than gastric fluids float over stomach contents due to the presence of bio adhesive nature of polymers resulting in prolonged gastric retention time. In-situ gels are the formulations that are in sol form before administration in the body, but once administration undergo gelation to form gel. Various routes administration of in-situ gelling systems is oral, nasal, ophthalmic, vaginal, injectable, intraperitoneal and rectal route [12].

3. Advantages of *in-situ* gelling system: [13]

- In-situ gels shows ease of administration and good patient compliance.
- It shows increased gastric retention with slow drug release4.
- It reduces dosing frequency.

- It shows local action and site specificity by acting directly onto the targeted site.
- It shows less adverse effects compared to other pharmacological dosage forms.

4. Disadvantages of *in-situ* gelling system: [14]

- It is more susceptible to stability problems due to chemical degradation.
- It requires high level of fluids.
- It leads to degradation due to storage problems.

5. Classification of *in situ* gels: [15]

In situ gel formulating systems have been classified in two categories as below:

- Based on mechanism of gelation
- Based on route of administration

5.1. Based on mechanism of gelation:

a) pH Sensitive Gel
b) Gel sensitive to electrical current
c) Thermosensitive gel
d) Enzyme sensitive
e) Presence of ions or Ion trigger

5.2. Based on route of administration:

a) *In situ* forming polymeric systems for oral administration
b) *In situ* forming polymeric systems for ocular delivery
c) *In situ* forming polymeric systems for rectal and vaginal delivery
d) *In situ* forming nasal drug delivery
e) *In situ* forming injectable drug delivery systems

In the present work, preparation of *in situ* gels was carried out by ion trigger mechanism by using various polymers like gellan gum and sodium alginate.

6. Mechanism involved in formation of *in-situ* gels:

In-situ gels are the hydrogels that are liquids at room temperature but undergo gelation when in contact with body fluids or change in pH. The in-situ gelling systems utilises various polymers that converts from solution and gel due to change in physicochemical properties. In this system when low viscosity solution comes in contact with body fluids undergo changes in confirmation of polymers and a viscous gel of density lower than gastric fluid is formed.

Approaches of in-situ gelling system: Approaches of in-situ gelling system are of three types

Based on physiological stimuli:

Thermally Trigged System (Temperature induced in-situ gelling system): Temperature induced systems are most widely used systems in in-situ gelling formulations. In this type of systems, no external heat other than body temperature is required to cause gelation. There are three types of temperature induced systems. Some of them are

- Negatively thermo sensitive type
- Positively thermo sensitive type
- Thermally reversible type [16]

In temperature induced gelling system, temperature responsive polymers or thermo responsive polymers are used that exhibit a drastic and discontinuous change in their physical properties with temperature. This type of polymers belongs to the category of stimuli responsive materials that change their properties continuously with environmental conditions. These polymers exhibit a miscibility gap at high or low temperatures an upper or lower critical solution temperature exists.

The range at which the solution exists at upper critical solution temperature is 0◦ -100◦ C. In this approach, the solution is liquid at room temperature and when reaches the body fluid due to exposure to body temperature it converts into gel. As the body cannot maintain upper critical solution temperature, lower critical solution temperature suitable polymers are used that undergo polymer-polymer interaction that causes sudden change in polymer solubility. As the solution is in liquid form, at lower critical solution temperature the hydrogen bonding between polymer and water cause an abrupt changes and leads to the formation of gel [17].

pH triggered systems: In this system change in pH causes formation of gel. In this approach, pH responsive or pH sensitive polymers are used. pH sensitive polymers have acidic or alkaline ionisable functional groups which are called as polyelectrolytes. The polyelectrolytes those are present in the formulation causes increase in external pH that leads to the swelling of hydrogel that leads to the formation of in-situ gel.

Suitable polymers for pH triggered systems are the polymers that are having anionic groups. Some of them are cellulose acetate phthalate (CAP), Carbomer and its derivatives, Polyethylene glycol (PEG), Pseudo latexes and poly methacrilic acid (PMC) etc.

Physical changes in Biomaterials:

- ***Swelling:*** Swelling is a type of physical approach that is used in the formation of in-situ gel. In this approach, the polymers that are surrounding the polymer imbibe the fluids that are present in the external environment and swell from inside to outside and slowly release the drug.

- ***Diffusion:*** Diffusion is a type of physical approach that is used in in-situ gel formation. In this approach, solvent gets diffused out from the polymer solution into surrounding tissues which results in the formation of precipitate or solidification of polymer matrix. The most commonly used polymer in diffusion approach of formation of in-situ gelling system is N-methyl pyrrolidone (NMP) [18].

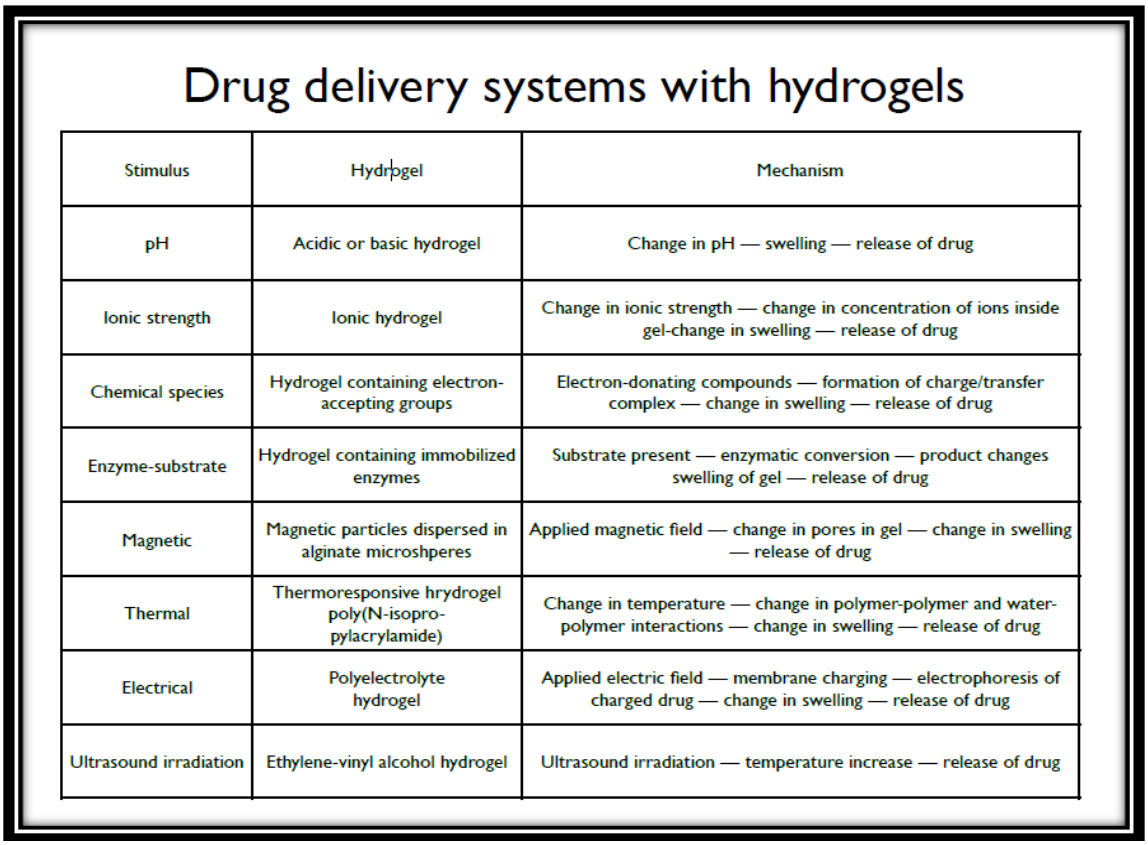
Chemical induced systems: In this approach, chemical reactions are involved to form in-situ gel. The formation of in-situ gel includes ionic cross linking, enzymatic cross linking and photo polymerization.

- ***Ionic cross linking:*** In this approach, the ion sensitive polymers are used. The ion sensitive polymers induce gelation in the presence of ions like Na+, K+, Ca2+ and Mg2+. The ion sensitive polymers undergo phase transition to form gel.

- ***Enzymatic cross linking:*** Enzymatic cross linking is the most convenient approach used in formation of in-situ gelling system. In this approach, gel is formed by cross linking with the enzymes that are present in the body fluids.

Photo polymerisation: In this approach, electromagnetic radiations are used during formation of in-situ gel [19]. The most suitable polymers for photo polymerisation are the polymers

that have polymerisable functional groups which undergo dissociation in the presence of photo initiators like acrylates or other polymers that usually have long wavelength ultraviolet and visible wavelengths are used. Short wavelengths are not used because they are biologically harmful. In this approach, ketones such as 2,2-dimethoxy-2-phenyl acetophenone is used as the initiator for ultraviolet photo polymerization. Camphorquinone and ethyl eosin initiators are used as visible light systems [20].



Drug delivery systems with hydrogels

Stimulus	Hydrogel	Mechanism
pH	Acidic or basic hydrogel	Change in pH — swelling — release of drug
Ionic strength	Ionic hydrogel	Change in ionic strength — change in concentration of ions inside gel-change in swelling — release of drug
Chemical species	Hydrogel containing electron-accepting groups	Electron-donating compounds — formation of charge/transfer complex — change in swelling — release of drug
Enzyme-substrate	Hydrogel containing immobilized enzymes	Substrate present — enzymatic conversion — product changes swelling of gel — release of drug
Magnetic	Magnetic particles dispersed in alginate microshperes	Applied magnetic field — change in pores in gel — change in swelling — release of drug
Thermal	Thermoresponsive hrydrogel poly(N-isopro-pylacrylamide)	Change in temperature — change in polymer-polymer and water-polymer interactions — change in swelling — release of drug
Electrical	Polyelectrolyte hydrogel	Applied electric field — membrane charging — electrophoresis of charged drug — change in swelling — release of drug
Ultrasound irradiation	Ethylene-vinyl alcohol hydrogel	Ultrasound irradiation — temperature increase — release of drug

Fig. 2: Drug delivery system with hydrogels

Applications:

1. Oral drug delivery systems: As oral route is the most compatible and easy route of administration of drugs, in-situ gelling type of systems are also formulated to deliver through oral route. Formulations of different categories of drugs are reported. Some of the examples are clotrimazole an antimicrobial drug is formulated as an in-situ gelling system by using carbopol 934P, gellan gum and HPMC as polymers showing zero order kinetic release with 8 hours of sustain action of drug. Paracetamol an anti-inflammatory drug is formulated as an in-situ gelling system using xyloglucan a natural polymer showing diffusion controlled release of drug [21].

2. Ophthalmic drug delivery systems: Ophthalmic drug delivery systems are used in the treatment of intraocular tension during glaucoma. Conventional dosage forms show poor bioavailability due to heavy draining of tear fluids from eye leads to rapid elimination of drug. To enhance the bioavailability problems ophthalmic drug delivery systems are used.

Various natural polymers are used in formulation of ophthalmic in-situ gelling systems. Ofloxacin an anti microbial drug is formulated as an in-situ gelling system by using carbopol and HPMC as polymers due to triggering of pH forms in-situ gel by showing sustain release for a period of 8 hours50. Levofloxacin is formulated as an ophthalmic in-situ gel by using gellan gum which is most commonly used polymer in ophthalmic delivery systems showing good drug release with 90.2% 51. Ciprofloxacin is formulated as an ophthalmic in-situ gel using carbopol 940 P, pluronic F-127, gellan gum and 1.5% HPMC as polymers showing drug release of 6 hours [21].

3. Injectable drug delivery systems: Injectable drug delivery systems are also formulated as in-situ gels which received much more interest over the last decade due to its advantages as there is no surgical procedure is required and also patient compliance. Mostly synthetic polymers and block copolymers are used in the formulation of injectable in-situ gels. Bupivacaine an anti inflammatory drug is formulated as an injectable in-situ gel using poly (D,L-lactide), poly (D, L-lactide co-glycolide) and PLGA as polymers showing prolong action of drug in gel conditions. It is investigated that injectable in-situ gels are also used in the treatment of tumours. Paclitaxel is formulated as injectable in-situ gel using implanted EMT-6 tumours subcutaneously in albino mice [22].

4. Nasal drug delivery systems: Nasal route of drug delivery is the most accepted route of administration of drugs as it has many advantages like patient compliance, avoids first pass metabolism and also provides high degree of absorption as well as transport of substances. Nasal drug delivery is the most suitable route for administration of CNS drugs because the drug shows its effect through olfactory neurons which is considered as the most potential route [23].

5. Rectal and vaginal drug delivery systems: In-situ gels are also administered through rectal and vaginal routes. Acetaminophen an anti inflammatory drug formulated as rectal in-situ gel by using polycarbophil and poloxamer F188 and poloxamer 407 as synthetic polymers forming in-situ gelling liquid suppository which is considered as an effective method showing enhance bioavailability. Itraconazole is an anti inflammatory drug is formulated as vaginal in-situ gel by using poloxamer 407, 188 and HPMC as polymers in the treatment of vaginal candidiasis. Clotrimazole is given through vaginal route is also reported [24].

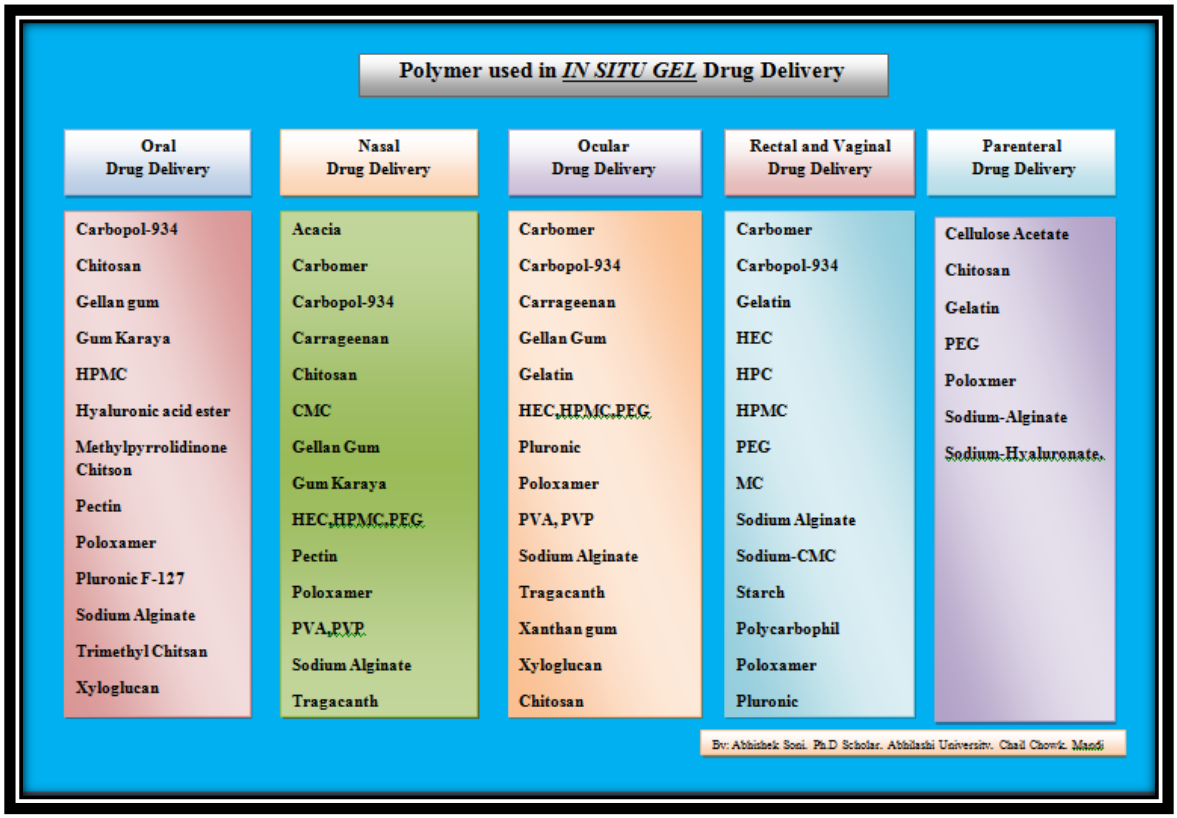


Fig. 3: Polymer used in In-Situ gel

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