International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

Role Of In Situ Gel in Drug Delivery System

Swarnim Srivastava
M. Pharma Pharmaceutics Hygia institute of Pharmaceutical Education & Research

Date of Submission: 5-11-2020 Date of Acceptance:15-11-2020

ABSTRACT: The 'in situ gel' structure has significantly increased; compared to other latest drug transport structures, it helps manage and assist drug delivery from its proprietary 'Sol a Gel' brand. The In situ gelling structure is a concept found in the arrangement structure until entering the body, but it can change to the gel structure under various physiological conditions. There are various polymers with in situ gel structure and probably used for various drug organization courses. In today's life, there are several apps and focal points of the in situ gelling structure. This survey focuses primarily on the in situ gel's prologue, its tool, various polymers, and applications.

Keywords: in situ gel, novel drug delivery system, polymers.

I. INTRODUCTION

In situ is a process of Latin that is genuinely understood as in location. In situ gels are drug delivery systems inserted in the body before the organization, but they undergo in situ gelations to form a gel until aimed. Organizational classes: oral , visual, rectal, genital, injectable and intraperitoneal classes for in situ gels. As one of the several modern drug transport systems, the 'in situ gel' framework has been highlighted, the in situ gel framework leads to the assisted and regulated arrival of drugs enhances patient quality and comfort**[1]** with its outstanding 'Sol a Gel' brand of development. In situ gelling structure is a plane that is in a structure of arrangement before entering the body, but that under various physiological conditions, will change to a gel form. Multiple components, such as temperature, pH variance, soluble trade, UV radiation, and proximity of explicit atoms or particles, are the basis of progress from sol to gel. For the continuous planning of vehicles to transport bioactive particles, drug transport facilities having the above-mentioned 'development from sol to gel' properties will usually be used. In the "in situ gelling system," there are some beneficial circumstances that include the ease of dosage usage, the reduction of organizational recurrences, and the protection of drugs against changing ecological conditions. A variety of characteristics and generated polymers are subjected to in situ gel frames and may be used**[2]** for oral, visual, transdermal, oral, intraperitoneal, parenteral, injectable, rectal, and vaginal applications. In different gastrointestinal tract districts, continuous improvement in in-situ gels has made it possible to misuse physiological uniqueness**[3,4]** to enhance medication consumption, accommodation, and patient quality. Gelatin, gellanic acid, chitosan, alginic acid, guar gum, carbopal, xyloglucan, xantham gum, HPMC, Poloxamer, etc. are several of the typical polymers which are used for the in situ gelation structure. **[5]**

Gels: Gels are an advanced material with both liquid and solid components. It consists of solid networks in three dimensions. Gels are classified into two groups depending on the bonds' structure since they have a three-dimensional solid network. They are **[6]**

- The physical gels emerge when weak links such as hydrogen relations, electrostatic bonds, and van der Waal bonds constitute the gel network.
- Chemical gels emerge when the gel network consists of strong covalent bonds. The network shows that cross-links help to prevent the dissolution of the hydrophilic polymer in an aqueous medium.

Classification of Hydrogels: Hydrogels: Hydrogels are the three-dimensional structures that have polymeric systems capable of absorbing and holding significant quantities of water and the biological fluids to swell. **They are of two types-**

- Preformed Hydrogels are classified as simple viscous solutions that are not altered after administration.
- In-situ gels are solutions or suspensions which are gelated following physical-chemical changes at the specific site.

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

In situ gelling system: In-situ gelling is now one of the most effective systems in new drug delivery due to various benefits such as increased patient compliance and decreased drug administration frequency. The Latin word 'in-situ' means 'in position.'**[7]**

Several mechanisms induce in-situ gel formation, some of which are pH shift and alteration of temperature and solvent exchange. As gel formed by an in-situ gelling system, it is lighter than gastric fluids and floats above the stomach since polymers produce organic adhesive properties that result in extended gastric retention time. n In situ gelling system are formulations that are in sol form before administration as in body but are gelation once administered. The dental, nasal, ophthalmic, vaginal, injectable, intraperitoneal, and rectal routes are used for various routes.

1.1 Significance of in situ gelling systems [8,9,10]

- It helps drugs arrive monitored and assisted by their unique 'Sol-Gel' transition.
- It helps in minimizing drug organisation recurrence in the body.
- A small portion of the medication is needed, and medicines or symptoms will not be collected.
- The drug's bioavailability would be higher.
- The drug's start time is prolonged due to gel growth.
- The gel frame on-site eliminates drug waste.
- Liquid measuring structures are ideal that can still calm the discharge and maintain prolonged contact with the cornea of the eye.
- Decreased essential intakes of spent drugs may cause adverse reactions in the nasolacrimal canal. It helps the controlled and supported the arrival of drugs with its unusual change 'Sol-Gel.

1.2 Ideal characteristics of polymers for preparation of in situ gel [11,12]

- The mucous membrane must adhere to the polymer.
- It should be compatible and not risky.
- Must pseudoplasticity.
- The polymer can minimize viscosity by increasing the cutting speed.
- Good tolerance and optical clarity is more ideal for the preparation of in situ gel.
- Must influence tear behavior.

II. ADVANTAGES OF IN SITU GEL SYSTEM [13,14]

- Controlled and Prolonged drug release.
- Quick drug administration.
- May be given to unconscious patients.
- It improved patient compliance and comfort.
- Reduce dose and pharmaceutical toxicity.
- Improved bioavailability.
- Natural polymers are biocompatible and biodegradable.
- The inherent biocompatibility, biodegradability, and biologically identifiable fractions of natural polymers support cellular function.
- Synthetic polymers have well-defined structures that can typically be adjusted to establish tolerable functionality and degradability.
- In situ gels may also be configured to demonstrate adherence for collecting medicinal products for non-invasive drug delivery, mainly through mucous membranes.
- In situ gels provide an important in vivo function because of their hydrophilicity, which increases the in-vivo release device's circulation time by evading the host's immune response and decreasing phagocytic activity.

2.1 DISADVANTAGES OF IN SITU GEL SYSTEM [15-16]

- Needs high fluid levels.
- The solar shape of the drug is more degradable.
- Possible stability issues due to the degradation of the chemical.
- Eating and drinking can be restricted for a few hours after taking the drug.
- The volume and homogeneity of the drug's load in hydrogels, particularly in hydrophobic drugs, can be reduced.
- Only small-dose medicines can be given. Requires a high level of fluids.

III. IN SITU POLYMERIC DRUG DELIVERY SYSTEM [17, 18]

3.1 Ocular drug delivery system

In the ocular drug release scheme, natural polymers, including corrosive alginic, inulin, and xylglucan, are the most commonly used inulin. Different mixtures, for example, autonomous medications, a relaxing substance, and an antimicrobial agent, are used in the quasi-ophthalmic transport system to alleviate intra-visual pressure in glaucoma. Often due to the high level of tear fluid and the elements that direct the

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

rapid removal of drugs from the eyes along these lines, the gel's bioavailability problem survived in situ. For example, to improve the bioavailability thickness, enhancers, carboxymethylcellulose, hydroxypropylmethylcellulose, carbomers, polyvinylvinor liqueur used to improve the consistency of the definition to delay the precorneal time at home and expand bioavailability, easy to do. For example, the infiltration enhancer, additives, chelation specialists, surfactants is used to create the corneal entrance.The penetration enhancer is used to access the corneal medication, such as additives, chelation specialists, and surfactants.

3.2 Nasal drug delivery system

Thickener and gum in the in situ nasal gel system. Gum is used as polymers forming in situ gel. The creature research is used to perform the susceptibly unfavorable rhinitis model, and the effects of the gel in situ have been observed on nasal indications of the antigen in the most acute rodents. The in situ gel has been found to prevent nasal expansion and to oppose the encouraging Nasonex disposition (0.05% methason furoate suspension).

3.3 Rectal and vaginal drug delivery system

The rectal path can be used to transmit several medications, comprehensive as fluids, semisolids (ointments, creams, and foam), and robust metabolisms (suppositories). Paracetamol is an in situ rectal gel used in polycarbonate and poloxamer F188 and poloxamer 407 for the in situ gel fluids made of a polymeric framework known as an engineering polymer that forms the assumption for in situ gelling fluids that are considered to be a viable technique bioavailability.

3.4 Injectable drug delivery system

In this context, they are also classified as in situ gels acquired over the past decade due to their uses since surgery and continuous consistency are not needed. Most of the generated square polymers and copolymers are used on the injectable gel surface. Bupivacaine, formulated as an in situ injectable gel using poly(D, L-lactide), poly(D, L-lactide), and PLGA, is an inflammatory medicine example because it has training operation. Under gel conditions, calms down.

3.5 Dermal and transdermal drug delivery system

Pluronic F127 was tested as a vehicle for the percutaneous administration of indomethacin in the thermally reversible gel. In vivo, studies claim that a 20 % w / w fluid gel should be used based on the drug's topical administration. The combination of iontophoresis and mixtures increased insulin penetration synergistically.

IV. CLASSIFICATION OF IN- SITU GELLING SYSTEMS [19]

Table 1:

S.No	In situ gelling system	Polymers
1	Temperature-dependent system	chitosan,pluronics,tetronics,xyloglucans,Hydroxypropylmethylcellulose or Hypromellose (HPMC)
2	pH triggered system	Cellulose acetate phthalate (CAP) latex, carbopol, polymethacrylic acid (PMMA), polyethylene glycol (PEG) pseudolatexes
3	Ion activated systems (osmotically induced gelation)	Gelrite,gellan, hyaluronic acid alginates

V. MECHANISM OF SITU IN GEL [20]

The in situ gel system's formation is ready by two mechanisms such as physical mechanism and chemical mechanism

5.1 Physical mechanism

In situ formation based on physical mechanism consist of the following

5.1.1 Diffusion

Diffusion **[21]** is a physical type used in the formulation of in situ gel. This approach involves spreading the solvent from the polymer to the surrounding tissue, resulting in the polymer matrix being precipitated or solidified. N-methyl pyrrolidone (NMP) was a polymer widely used in situ gelation system formation.

5.1.2Swelling

Swelling is an on-site formulation method of physical focus. In this type of treatment, the polymers are encircled by the absorption of polymers and fluids that reside in the exterior and

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

swell from the inside to the outside. Myverol (glycerol monooleate) is a polar lipid which typically swells in water to form a type of liotropic liquid crystalline structure. This material has many types of bioadhesive properties and can often be enzymatically degraded in vivo.

5.2 Chemical Mechanism [22]

In situ gelation formation dependent on chemical reaction mechanisms. The chemical reaction that causes gelling in situ will result in further processes

5.2.1Enzymatic cross-linking

Enzyme cross-linking is the best approach for the creation of the in situ gelation system. The gel is typically produced by cross-linking enzymes in body fluids with this process. Training on the ground convinces natural enzymes and has not been tested thoroughly, but seems to have some chemical and photochemical benefits. For example, an enzymatic method manages physiological conditions' effectiveness and does not involve potentially damaging chemicals such as monomers and initiators. Hydrogels are essentially used in smart release systems that respond to stimuli and release insulin that has been studied. Change in enzyme quantity also ensures an adequate control mechanism for the gel formulation, which admits that the mixtures must be injected before the gel form.

5.2.2 Photo-polymerization

During the in situ gelation device creation, electromagnetic radiation is used in the photopolymerization process **[23].** A tissue site may be injected with an intrusive or monomer or macromere reagent, and electromagnetic radiation is typically employed to form a gel. The most suitable polymers for photopolymerization are polymers subjected to various dissociations by a functional group that may be polymerized in photoinitiators' appearance as acrylates or similar monomers. Short wavelength ultraviolet rays are not commonly used because they partly penetrate the tissue and are very damaging biologically. This process is used as an initiator for ultraviolet lighting by ketone, such as 2,2-dimethoxy-2-phenyl acetophenone. In visible light systems, Camphorquinone and ethyl eosin initiators are used.

5.2.3 Ionic cross-linking

The ion-sensitive polymer is used in this process. In the presence of different ions, such as Na +, K +, Ca + and Mg +, ion-sensitive polymers can undergo a phase transition. The ion-sensitive class also includes certain polysaccharides. While k-carrageenan rigidly forms, small amounts of K+ react to fragile gels, elastics are I forms, particularly in the presence of Ca2 +. Gellan pneumatics are available primarily as Gelrite. It is an anionic polysaccharide, subjected to an in situ gelation device in the presence of mono- and bivalent cations. **[24, 25]**

VI. VARIOUS APPROACHES OF IN SITU GELATION

Various approaches are made in order to get in situ gelation system

6.1 Temperature activated in situ gel

Temperature is the most frequently used push in ecologically sensitive polymer structures that work on local gelation information. The temperature difference is simple to control and is both in vitro and in vivo successful.

In this respect, gelation is caused by internal heat and external heat requirements. These are room-temperature fluids (20–25 ° C) and, due to a temperature expansion, are gelated in contact with body fluids (35–37 ° C).

Three types of frames require temperature. Thermally sensitive polyes (N-isopropyl acrylamide) are, for example, undoubtedly thermosensitive, polyacrylic, corrosive, and thermally reversible. They are, for instance, Poloxamer, pluronic, and tetronic. Thermosensitive or temperature-sensitive polymers display a severe and transient shift in their physical characteristics at a temperature in this case. These polymers have a miscibility hole at high or low temperatures, and the disposal temperature is higher or lower.

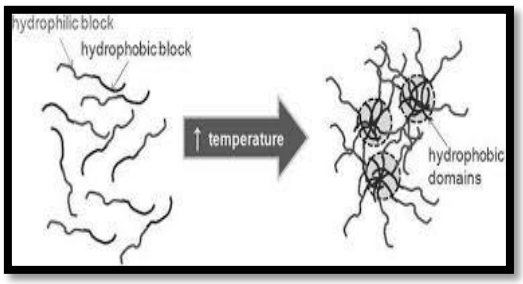

Fig 1: Mechanism of temperature-sensitive system

6.2 PH activated in situ gelation

In this sense, the gel is modeled because of changes in pH. Polymers sensitive to pH or pH

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

are used in this technique. Responsive polymers have exceptional acid or essential concentrations at pH that can identify or unload protons toward changes in the pH of the environment**[26]**. In the ionizable junctions, a significant number of polymers are called polyelectrolytes. Polyelectrolytes are available in specifics that increase the external pH allowing the hydrogel structuring the gel to expand locally. The polymers with anionic concentrations are some appropriate polymers for this approach. Some are cellulose-acetic (CAP) phthalates, carbomers, and their subordinates, polyethylene glycol (PEG), pseudo lactic and corrosive polymethacrylic (PMC), etc. **[27,28,29]**

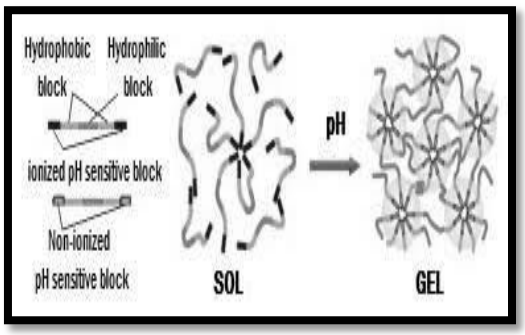

Fig 2: Mechanism of pH triggered in situ gel system

6.3 Particle actuated in situ gelation

The given arrangement's gelation is enabled by the shift in this technique's ionic intensity **[30,31**]. The gel rate should depend on the osmotic tilt outside the gel. Gelrite or gellan gum, corrosive hyaluron, alginate, etc. are the polymer displays osmotic activation gelation.

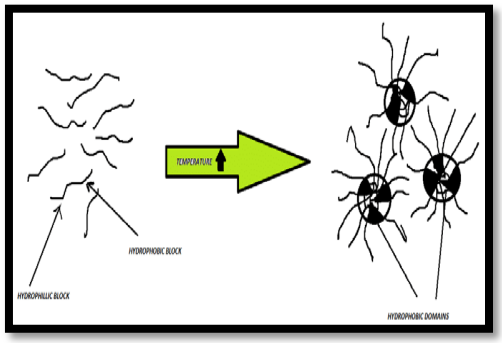

Fig 3: Mechanism of temperature-sensitive system

VII. POLYMERS USED AS IN SITU GELLING AGENTS

7.1 Pectins

Pectins are a polysaccharide group in which the polymer primarily contains a galacturonic α--(1-4)--- D- corrosive accumulation. Given free carbon particles, the gels are easily framed in aqueous arrangements with low methoxy gelatins (esterification level < 50 percent), which connect the galaxy-corrosive chains in a form described by the egg carton model. With the H + particles in mind, gelatinization of gelatine, a source of divalent particles, can occur, mainly calcium particles are required to generate the appropriate gels for transport purposes. The pectin primarily used for these floors is that it can be soluble in water, so it does not use natural solvents. In the stomach, the divalent cations advance the pectin to the gel state when delivered orally **[32]**.

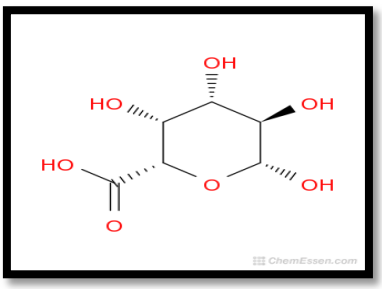

Fig 4

7.2 Guar gum

Guar gum is also known as natural rubber guaran derived from endosperm seed. Guar is insoluble when dissolved in water, in hydrocarbons, fats, esters, alcohols, and ketones. They are spread both in cold and high temperatures, water-soluble in cold and boiling water to frame the colloidal arrangement in a low amount. Guar gum has branches used to create network structures, nano-microparticles, and hydrogels in transport structures. Moreover, guar gum, for example, has branches that bind polymers like Guar gums, which are bonded with polyacrylamide and have excellent colon selection properties **[33].** It can also be employed in meshed tablets with managed discharge as a polymer.

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

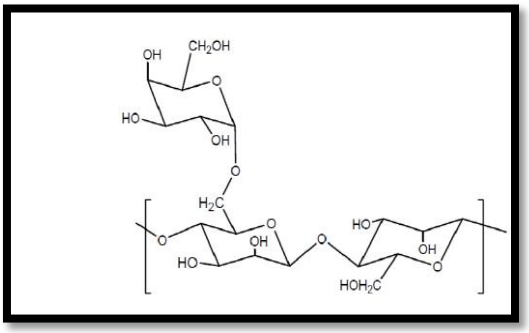

Fig 5

7.3 Carbopol

Carbopol is a corrosive polyacrylic polymer (PAA), which has evolved from 4,0 to 7,4 in pH. Carbopol stays in the structure usable for acid pH but becomes a low consistency gel with soluble pH. HPMC is used in conjunction with carbopol that enhances carbopol consistency and decreases the acidity of the layout. He concluded that Carbopol 940 demonstrated superior appearance and clarity by comparing various poly (corrosive acrylic) (Carbopol 940-934-941 and 910) 47 forms **[34]**.

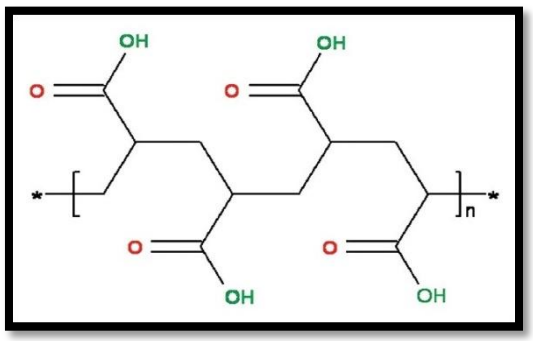

Fig 6

7.4 Xyloglucan

Xyloglucan is also known as tamarind gum; a polysaccharide derived from the endosperm seed. Xyloglucan consists of three oligomers, namely heptasaccharide, octasaccharide, and non-saccharide, which differ in the number of galactose side chains. Due to its harmless, biodegradable, and biocompatible properties, it is primarily used to transport oral, rectal, and visual medicines. Like Poloxamer, gelling **[35]** happens when the refrigerator temperature is heated or cooled at a higher temperature.

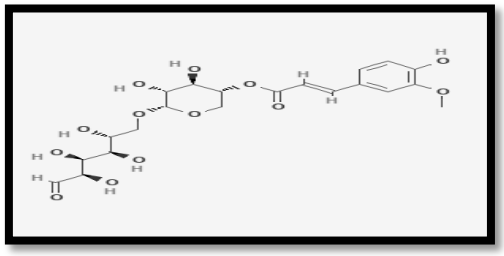

Fig 7

7.6 Gellan gum

Gellan gum is a straight polysaccharide anionic secreted by the microbe of the Sphingomonas elodea. It consists of glucose, rhamnose, glucuronic acid, and combines them to produce a tetrasaccharide unit. Gelrite **[36]** is a gellan gum, deacetylated, obtained using alkaline to eliminate the acetyl group in the molecule. Because of instillation, gel rite is a gel because calcium ions are present. Gelation involves developing double-helical crossings followed by a double helical segment aggregation into three-dimensional networks 30 by complexation with cations and hydrogen connexions with water. Gellan gum is used as a suspension and stabilizing agent in the food industry**.[37]**

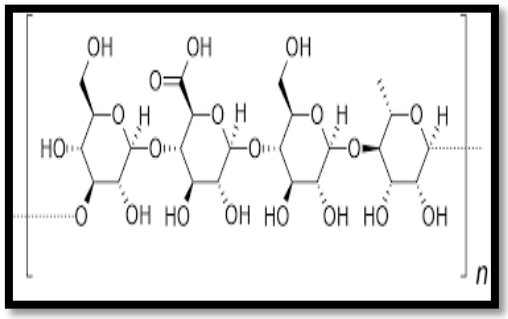

Fig 8

7.7 Alginic acid

It is a straight square copolymer polysaccharide made from the β-D-manuronic corrosive and α-L-glucuronic deposits connected by 1,4-glucoside bonds. The course of action of the squares on each square fluctuates depending on the algae source. **[38]** The weakening of the aqueous alginate arrangements produces strong gels when diandtrivalent metal particles are exposed by an appropriate technique covering sequential glucuronic deposits on the alginate chain glucuronic α-L squares **[39]**. Alginic corrosive, used as an ophthalmic plane vehicle, as it demonstrates strong natural characteristics, such as biodegradability and non-toxicity **[40]**.

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

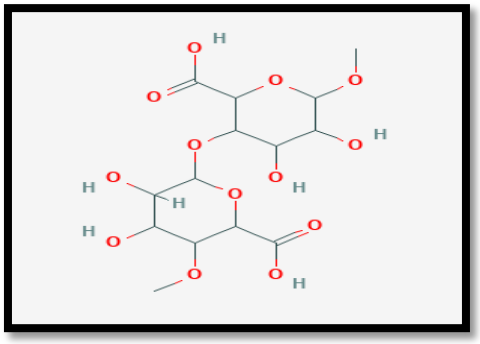

Fig 9

7.8 Xanthum gum

Xanthum gum has a high extracellular polysaccharide atomic weight formed by maturing Xanthomonas campestris, a gram-negative bacterium. This subsidiary's important cellulose structure involves a cellulosic backbone (such as β-D-glucose accumulations) and a β-D-mannose – a β-D-glucuronic α-D-corrosive lateral chain of corrosive glucose chain [50]. In cold, boiling water, the thickener is soluble as underlying and acidic conditions. In primary conditions, it shows excellent stability. **[41]**

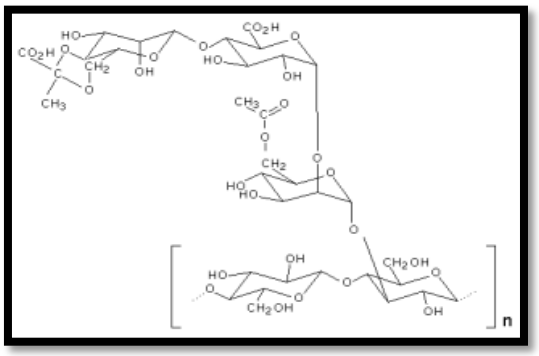

Fig 10

7.9 Chitosan

Chitosan gel formation occurs with two changes, for example, pH-sensitive changes and temperature changes. Chitosan is a characteristic component of the shrimp and crab shells that comprises a thermosensitive and biodegradable polycationic extracted from chitine's simple deacetylation. Chitosan is a cationic polymer subordinated to the pH of biocompatibility that can be processed up to pH 6.2 in aquatic arrangements. By extracting the hydrated gel, the balancing of the aqueous reaction of chitosan to a pH higher than 6.2 induces precipitation **[42, 43]**

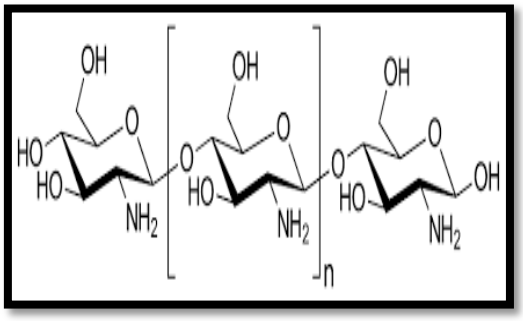

Fig 11

7.10 HPMC (Hydroxy Propyl Methyl Cellulose)

Cellulose is a glucan chain which has a unit of β-(1, 4) -D-glucopyranose. The sol-gel temperature's delicate progress is shown by some usual polymers, such as HPMC, MC, and EC. If the temperature decreases, the cellulosic material increases its thickness, and its branches, such as HPMC and MC, increase their consistency as the temperature grows. MC is a standard local cellulose-based polymer with methyl substitution group exchange in its chain. The structure is fluidized at a low temperature (30 ° C), and the temperature increases (40-50 ° C), and gelation occurs **[44]**.

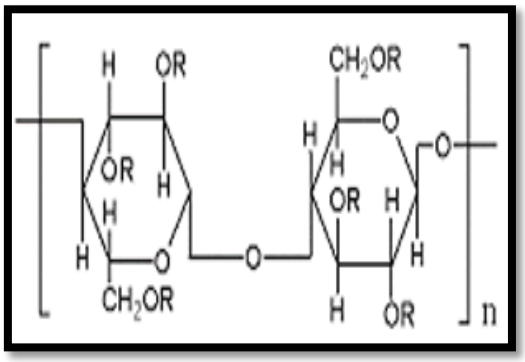

Fig 12

7.11Poloxamer

Poloxamer is a three-block water-soluble copolymer. It consists of two polyethylene oxide (PEO) cores and polypropylene oxide (PPO) in the ABA configuration **[45]** Poloxamer is as cheap as Pluronic Poloxamer and has a robust warming environment and a more extended drug lifecycle correction. It is primarily used as a specialist in gelation, emulsion, and solubilization. Poloxamer gives a dry and direct gel. The hydrophilic and hydrophobic chain's proportion and distribution

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

focus on which a range of atomic charges can be accessed with different gelling characteristics **[46, 47].**

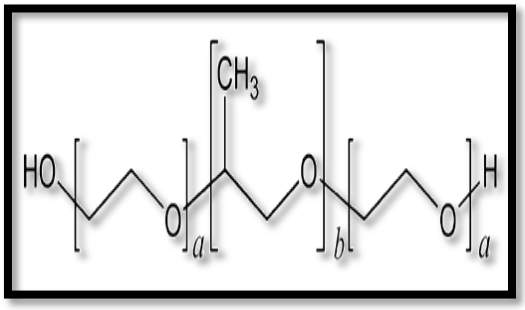

Fig 13

VIII. EVALUATION PARAMETERS OF IN SITU GEL SYSTEM [48,49]

There is various type of evaluation parameters in situ gel system such as:

1. pH

The gelgel's pH was determined by using a calibrated pH meter and readings have been taken for 3 samples on average.

2. Clarity

Clarity test is performed by examining each container with a good light, searching for reflection into the eyes, and presenting against a black and light background.

3. Texture analysis

The purity and durability of the formulation were tested using a texture analyzer, which primarily demonstrates the syringeability of the sol so that the formulation can be conveniently administered in-vivo. Higher adhesive values for gels are necessary to keep close contact with a tissue-like surface.

4. Gelling capacity

The formula prepared's gelling capacity is determined by inserting drops in a vial containing 2 mL of simulated tear fluid freshly prepared and by examining it visually. The time it takes to gelling is noted.

5. Gel Strength

This parameter is measured with a rheometer. A given amount of gel is prepared by the beaker from the sol type depending on the gelling agent's mechanism. This beaker gel is adjusted at a level so that a sample is moved slowly through the gel. · The collateralized on the sample can be calculated as a function of the sample's immersion depth below the gel surface.

6. Rheological Studies

Viscosity experiments are done using a viscometer using Brookfield programmable DVII+Model pro II type (USA). The formulations of the in situ gel are positioned in the sampler tube. Circulated Baths attached to the viscometer adapter before each measurement are analyzed at 37 ° C ± 0.5 ° C. The spindle angular velocity is increased from 1 to 4 and the formulation viscosity is calculated.

7. Sol-gel transition temperature

The temperature of the sol-gel transition can be defined by the temperature at which the fluid transition phase becomes gel. The gelation point is the temperature where formulations will not flow where test tubes are tilted at an angle of 90 ° with a steady temperature rise. When a pH or nasal fluid transition is present in the pH and ion-dependent polymers, they transition from sol to gel.

8. Fourier Infrared Spectroscopic Transforms

The Fourier infrared transform (FT-IR) spectrometer is generated with an FT-IR spectrometer. The active drug was shaken vigorously with potassium bromide at a defined ratio and a transparent infrared matrix. (typically ratio 1:5). • The KBr discs are formed by pressing the powders in a hydraulic press, at a pressure of 5 tonnes for 5 minutes. The images are obtained at a 4cm-1 resolution between 4000 and 400 cm-1.

9. Drug content estimation

Approximate drug content is made by diluting 1 ml of preparation formula in 100 ml of distillate water and analyzed with a sufficient wavelength using a UV-visible spectrophotometer.

10. In vitro drug release studies [50,51]

In vitro, the in situ gel solution analysis is performed with the Franz diffusion cell. · The formulation is put in the donor section, and the simulated tear fluid in the receptor compartment is freshly prepared. The dialysis membrane is positioned between the donor and the recipient (0.22 µm pore size). The entire structure is mounted on the magnetic stirrer, which is operated thermostatically. The formulation in the donor chamber is correctly pipetted.

1ml of samples shall be taken at a pre-determined time of 1 hour for 6 hours, and the same fresh medium volume shall be substituted.

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

Retract samples are diluted to 10ml in a volumetric flask with the respective solvent and analyzed using the reagent as blank with a UV spectrophotometer at respective nm. The drug content is determined using the normal calibration curve equation. · A cumulative drug release percentage (% CDR) is measured. **[52,53]**

11. Accelerated stabilities studies

The Optimized sterile formulation is tested for stability. The optimized sterile formula is filled in glass vials, sealed with grey butyl rubber closures, and shielded with aluminum caps. The optimized forming vials are held in the stability chamber at 40 ° C ±2 ° C and 75% ± 5% RH for a month. Tests for drug material, pH, visual appearance, gelling and in-vitro release are withdrawn regularly.

12. For ophthalmic formulation following tests are done: Antimicrobial Activity, Ocular irritation studies, Isotonicity evaluation [54, 55]

Antimicrobial Activity

The Agar diffusion test using the cup plate technique decides the antimicrobial activity. A solid agar medium can diffuse the drug. A minimum inhibitory quality concentration of managed and established drug-containing formulations is ready. A sample of 60 ml of nutrient agar media is prepared and sterilized in an autoclave with a pressure of 15 lb / sq inch for 18 minutes, whereas the medium as mentioned above, which is held at a temperature of 52 ° C to 58 ° C, has a suspension of 0.5 ml. This can be achieved in an aseptic state. Each Petri platform immediately receives 20 ml of the microbial agar suspension. The sterile standard solutions and the formulations produced are diluted appropriately with sterile distilled water (test solutions) after solidifying the media and are poured into the container of sterile nutrient agar Petri plates. − After allowing solutions to be diffusion for 2 hours, the agar plates are incubated for 24 hours at 37 ° C. The inhibition zone (ZOI) is measured around each cup and compared to the control zone. The whole procedure in a laminar airflow unit is conducted. Each solution is evaluated in triplets. A positive and negative influence over the entire study is kept.

Occular irritation test

The Draize irritancy test is calibrated for the ophthalmic product's eye irritation potential before marketing. · as per the Draize examination, the volume of eye material is usually put into the lower part of the eye at a designed time interval of 1 hour, 24 hours, 48 hours, 72 hours, and 1 week after administering the body and the rabbits are regularly administered for redness, swelling and watering**.[56]**

Isotonicity Evaluation

The isotonicity of ophthalmic preparations is essential. Isotonicity must be preserved to prevent inflammation and tissue damage or eye irritation. Formulations are combined with a few blood drops and observed under a 45x magnification microscope relative to typical marketable ophthalmic formulations **[57]**

13. The following test is performed for the nasal formulation

Determination of Mucoadhesive strength

The strength of the mucoadhesive is calculated using the updated process. The mucoadhesive formulation potential is determined by calculating the intensity required to remove the formulation from nasal mucosal tissue. A portion of nasal sheep mucosa is fixed with thread on each of the two glass slides. Toward gel is put on the first slide, and this slide just under the adjustable height pan. During another slide with the mucosal section, the underside of the same pan is inverted. Both slides with gel formulation were in contact for 2 minutes to allow near the contact between them. · At the second pan, weight continues to increase until slides are separated from each other. The mucoadhesive force expressed in dyne / cm2 is the minimum weight that separates the mucosal tissue from each formula's surface. **Mucoadhesive strength (dyne / cm2) = mg / A, where, m = required weight in grams detachment, g = gravitational acceleration (980cm / s2), A =Area of mucosa exposed [58]**

14. For oral (floating) formulation, the following research is performed [59]

In vitro floating trials

Floating research in a beaker at 500 ml of 0.1 N HCl (pH 1.2). 10 ml of the solution measured correctly is applied to HCl. After applying a solution, the time taken to immerse gel on the surface (floating lag time) and the overall floating time are measured.

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 449-461 www.ijprajournal.com ISSN: 2249-7781

IX. DRUGS DEVELOPED IN SITU GEL DRUG DELIVERY SYSTEM [59]

Table 2: List of a drug developed as an in-situ gel drug delivery system

S.no	Drugs	Polymer	Route
1	Ciproflaxin	Carbopol 940P,pluronicF-127,gellan gum,1.5% HPMC	Ophthalmic
2	Amoxillin	Sodium alginate, calcium chloride, sodium bicarbonate,sodium citrate, HPMC –K100	Incorporated directly to the stomach
3	Ofloxacin	Carbopol, HPMC	Ophthalmic
4	Levofloxacin	Gelrite	Ophthalmic
5	Doxycycline Hyclate	Poloxamer 188,gellan gum, HPMC, sodium alginate	Ocular
6	Radix bupleri	Gellan gum	Nasal
7	Diclofenac sodium	Carbopol, sodium alginate, HPMC	Ophthalmic
8	Acetaminophen	Polycarbophil, polaxamer F188, 407	Rectal
9	Indomethacine	Gelrite	Ocular
10	Rivastigmine	N-stearoyl L-alanine methyl ester (SAM)	Nasal
11	Curcumin	Capryol 90,solutol HS15, transcutol HP	Nasal
12	Nimesulide	Sodium alginate,poloxamer F188,407	Rectal
13	Paracetamol	Xyloglucan	Oral
14	Itraconazole	Poloxamer 407,188,HPMC	Vaginal
15	Gatifloxacin	Sodium alginate,HPMC	Ocular

X. CONCLUSION

This review article summarizes that the 'in situ gel' method has become one of the best current drug delivery systems for long-term and controlled drug release, increased compliance, and comfort for patients. Synthetic polymers are gel-formed in situ and can also be used for oral, ocular, transdermal, buccal, intraperitoneal, parenteral, injectable, rectal, and vaginal routes at all times. A broad range of research is available on the in situ gel system that enables advanced technology in various drug delivery systems. **[60]**

REFERENCES

[1]. Nisha Patel, Gajanan Shinde, and Rajesh KS. Ophthalmic In situ gel, A genesis journal Pharmagene, 2(4), 2014, 29-33.

[2]. F. Suisha, N. Kawasaki, S. Miyazaki, M. Shirakawa, K. Yamatoya, M. Sasaki, D. Attwood, Xyloglucan gels as sustained-release vehicles for the intraperitoneal administration of mitomycin C. Int. J. Pharm., 172, 1998, 27– 32

[3]. Miyazaki S, Endo K, Kawasaki N, Kubo W, Watanabe H, Attwood D. Oral sustained delivery of paracetamol from in situ gelling xyloglucan formulations. Drug Dev Ind. Pharm., 29(2), 2003, 113-9.

[4]. Nerkar Tushar, Gujarathi Nayan A, Rane Bhushan R, Bakliwal Sunil R, Pawar S.P. In situ gel: Novel Approach in a sustained and controlled drug delivery system. International Journal of Pharmaceutical Sciences, 4(4), 2013, 1-18.

[5]. 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.

[6]. Zhidong L, Jaiwei L, Shufang N,. Study of a Pharma alginate- HPMC based in situ gelling ophthalmic delivery system for gatifloxacin. Int J., 315, 2006, 12- 7.

[7]. 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.
[8]. Rathore KS, Nema RK. Formulation & evaluation of ophthalmic films for timolol maleate. Planta indica, 4, 2008, 49-50.
[9]. 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.
[10]. S. Cohen, E. Lobel, A. Trevgoda, Y. Peled. A novel in situ- forming an ophthalmic drug delivery system from alginates undergoing gelation in the eye. J. Control. Release. 44, 1997, 201–208.
[11]. B. Srividya, R.M. Cardoza, P.D. Amin. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling systems. J. Control Release., 73, 2001, 205–211.
[12]. Wen-Di Ma, Hui Xu, Chao Wang, Shu-Fang Nie, Wei-San Pan, Pluronic F127-g-poly(acrylic acid) copolymers as in situ gelling vehicles for ophthalmic drug delivery system, int. j. of pharmaceutics, (350), 2008, 247-256.
[13]. Sirish vodithala, Sadhna Khatry, Nalini Shastri, M. Sadanandam, Formulation and evaluation of ion activated ocular gels of ketorolac tromethamine International Journal of Current Pharmaceutical Research, 2(3), 2010.
[14]. Jothi M, Harikumar SL and Geeta Aggarwal, In-situ ophthalmic gels for the treatment of eye diseases, International Journal of Pharmaceutical Sciences and Research, 3, 2012, 1891-1904.
[15]. Rajas NJ, Kavitha K, Gounder T, Mani T, In-Situ ophthalmic gels a developing trend, Int J Pharm Sci Rev and Res, 7, 2011, 8-14.
[16]. 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.
[17]. Motto F, Gailloud P, et al., In-vitro assessment of new embolic liquids prepared from preformed polymers and water-miscible solvents aneurysm treatment. Biomaterials, 21, 2000, 803-11.
[18]. 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.
[19]. Podual K, Doyle III FJ, Peppas NA. Dynamic behavior of glucose oxidase-containing microparticles of poly (ethylene)-grafted cationic hydrogels in an environment of changing pH. Biomaterials, 21, 2000, 1439-50.
[20]. Burkoth AK, Anseth KS. A review of photocrosslinked polyanhydrides: In situ forming degradable networks. Biomaterials, 21, 2000, 2395-404.
[21]. Sawhney AS, Pathak CP, Hubbell JA, Hill JL, Desai NP. Photopolymerizable biodegradable hydrogels as tissue contacting materials and controlled-release carriers.US Patent 5410016. 1995.
[22]. Qiu Y, Park K, Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev., 53, 2001, 321-39.
[23]. Hoffman A.S., Afrassiabi A, Dong L.C. Thermally reversible hydrogels: II. Delivery and selective removal of substances from aqueous solutions. J. Control. Release, 4, 1986, 213– 222.
[24]. Hong – Ru Lin, K. C. Sung. Carbopol/ Pluronic phase change solutions for ophthalmic drug delivery. Journal of Controlled Release. 69, 2000, 379-388.
[25]. Miyazaki S, Kawasaki N. Comparison of in situ gelling formulations for the oral delivery of cimetidine. Int J Pharm, 220, 2001, 161-8.
[26]. Kokate C.K., Purohit A. P., Gokhale S.B. Pharmacognosy. 14th Ed. Published by Nirali Prakashan, 137, 2008, 141,146,152.
[27]. Davies N.M., Farr S.J., Hadgraft J., Kellaway L.W. Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions, Pharm. Res., 8(8), 1991, 1039–1043.
[28]. Shastri DH, Patel LD, Novel alternative to ocular drug delivery system: Hydrogel, Ind J Pharma Res, 2010; 2: 1-13.
[29]. 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, 229, 2001, 29-36
[30]. Grasdalen H, Smidsroed O. Gelation of gellan gum. Carbohydrate Polymers, 7, 1987, 371-93.
[31]. 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.
[32]. Sechoy O, Tissie G, Sebastian C, Maurin F, Driot JY, Trinquand C. A new long-acting ophthalmic formulation of carteolol containing Alginic acid. Int J Pharm, 207, 2000, 109-16.
[33]. Cohen S., Lobel E., Trevgoda A., Peled Y. A novel in-situ forming Ophthalmic drug delivery system from alginates undergoing gelation in the eye. Journal of Controlled Release., 44, 1997, 201-208.
[34]. Grant G.T., Morris E.R., Rees D.A., Smith P.J.C., Thom D. Biological interactions between polysaccharides and divalent cations: The egg-box model. FEBS Lett., 32, 1973, 195-198.
[35]. Chenite A, Chaput C, Wang D, Combes C, Buschmann MD, Hoemann CD et al. Novel injectable solution of chitosan form biodegradable gels in situ. Biomaterials, 21, 2000, 2155-61.
[36]. Calonge M, The treatment of dry eye, Surv Ophthalmol, 45, 2011, 227-239.
[37]. Nanjawade BK, Manvi FV, Manjappa AS, Review of in-situ forming hydrogels for sustained ophthalmic drug delivery, J Control Rel, 122, 2007, 119-134
[38]. Sterile ophthalmic gel forming solution, Timoptic- XE;, 0.25% and 0.5%, (Timolol maleate ophthalmic gel forming solution), Merck and Company Inc. NJ08889: Whitehouse Station, USA.
[39]. Yumei WU et al., Research Progress of in-situ gelling Ophthalmic Drug Delivery System, Asian Journal of Pharmaceutical Science, 2018; 22-40.
[40]. Hajare A, Mali S, Salunke S, Nadaf S, Bhatia N, Bagal P, Gaikwad S, Pawar K, A Rational Approach to Ocular Drug Delivery System: An Overview, World Journal of Pharmaceutical Science, 2014; 3(2):3324-3348.
[41]. Yerikala R, Kothapalli CB, Peddappi Reddigari JR, A Novel Approach on Ophthalmic Drug Delivery System, Journal of Drug Delivery and Therapeutics, 2017; 7(6):117-124.
[42]. Pandya TP, Modasiya MK, Patel VM, Ophthalmic In-Situ Gelling System, International Journal of Pharmacy and Life Sciences, 2011; 2(5): 730-738.
[43]. Jain S, Jain P, Mishra M, Pathak A, A Review on Triggered Gel for Ocular Drug Delivery System, International Journal of Pharmaceutical and Biological Archieves, 2014; 5(4):19-24.
[44]. Palani S, Joseph NM, Goda CC, Zachariah A, Ayenew Z, Ocular Drug Delivery: A Review, International Journal Pharmaceutical Science and Research, 2010; 1(3):1-11.
[45]. Hoare TR, Kohane DS, Hydrogels in drug delivery: Progress and Challenges, Polymers, 2008; 49: 1993-2007.
[46]. Palani S, Joseph NM, Goda CC, Zachariah A, Ayenew Z, Ocular Drug Delivery: A Review, International Journal Pharmaceutical Science and Research, 2010; 1(3):1-11.
[47]. Hoare TR, Kohane DS, Hydrogels in drug delivery: Progress and Challenges, Polymers, 2008; 49: 1993-2007.
[48]. Sandeep DS, Charyulu NR, Narayanan AV, Smart In Situ Gels for Glaucoma-An Overview, International Journal of Pharmaceutical Science Research and Review, 2018; 50(1):94-100.
[49]. Majeed A., Khan N. A. Ocular in situ gel: An overview. Journal of Drug Delivery and Therapeutics, 2019; 9(1):337-347.
[50]. Singh A, Negi D, Mishra N, Baldi A, Recent trends in Ocular Drug Delivery, Pharmaspire, 2018; 10(2):55-63.
[51]. Prausnitz MR, Noonan JS, Permeability of Cornea, Sclera, and Conjunctivia: A Literature Analysis of Drug Delivery to Eye, Journal of Pharmaceutical Science, 1998; 87(12):1479-1488.
[52]. Ahmed EM, Hydrogel: Preparation, Characterization, and application: A Review, Journal of Advanced Research, 2015; 6: 105-121.
[53]. Saini R, Saini S, Singh G, Dr. Banerjee A, In Situ Gels- A New Trends In Ophthalmic Drug Delivery System, International Journal of Pharmaceutical Science and Research, 2015; 6(5):886-890.
[54]. Nittur JR, Kunchu K, Teetha G, Tamizh M, In Situ Ophthalmic Gels: A Developing Trend, International Journal of Pharmaceutical Science Research and Review, 2011; 7(1):8-14.
[55]. Wadhwa K, Sharma C, Gosawmi M, Thakur N, In-Situ Ocular Gel-A Novel Approach Towards Ocular Drug Delivery, European
[56]. Ramesh CR, Zentner GM, Jeong B. Macro med, Inc. Biodegradable, low molecular weight triblock poly (lactide- co- glycolide)

polyethylene glycolcopolymers are having reverse thermal gelation properties. US patent 6201072. 2001.

[57]. Kast CE, Valenta C, Leopold M, Andreas BS. Design and in vitro evaluation of a novel bioadhesive vaginal drug delivery system for clotrimazole. J.Control. Rel. 2002; 81: 347–354.

[58]. Sreenivas & Pai Thiolated Chitosans: Novel Polymers for Mucoadhesive Drug Delivery –A Review Trop J Pharm Res, 2008; 7 (3): 1077-1088.

[59]. Li B, Gao S, Qiao X. The preparation and analysis of low molecular weight chitosan. Zhongguo Shenghua Yaowu Zazhi ,1999; 20: 292–294.

[60]. Chen RH, Chen JS. Changes of polydispersity and limiting the molecular weight of ultrasound-treated chitosan. Adv. Chitin Sci., 2000; 4: 361–366.