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BIOMATERIAL BASED INJECTABLE HYDROGEL FOR CONTROLLED DRUG DELIVERY: A REVIEW

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ABSTRACT: The aim of a pharmaceutical product is to obtain excellent therapeutic and favorable treatment. Controlled drug release coatings have been around for more than 50 years and their performance has increased significantly since the beginning. The main drawbacks of the controlled drug delivery system are its poor bioavailability, high-dose requirements, adverse side effects, low therapeutic indices, development of multiple drug resistance and non-specific targeting. To overcome this disadvantage, the researcher focused on controlled drug delivery system Injectable hydrogels. It is an emerging trend in the field of biomaterial drug delivery systems. Injectable Hydrogel overcomes the limitation of a pre-formed hydrogel, as they are injected with minimum invasive procedure into target sites and used for irregularly shaped sites. The recent studies of injectable hydrogels for the drug delivery applications suggested that multi-functional injectable hydrogels are capable of entrapping and systematically delivering the multiple therapeutic agents like drugs and macromolecules. The Injectable hydrogel shows shear thinning property when injected into the body. In this review, various aspects of Injectable hydrogel like introduction, Properties, preparation methods, drug loading and drug release strategies and applications of injectable hydrogels were discussed.

INTRODUCTION: The aim of a pharmaceutical product is to obtain excellent therapeutic and favorable treatment. Controlled drug release coatings have been around for more than 50 years and their performance has increased significantly since the beginning. A conventional drug delivery system often requires high doses or repeated administration, which may lead to severe toxicities some times, which can reduce efficacy and patient compliance.

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They have a poor *in-vitro*, *in-vivo* correlation. They suffer from the limitation of the high cost of formulation. They prefer oral administration route most of the time, is frequently limited due to first-pass metabolism, short circulation time and poor targeting of active drug. To overcome this disadvantage of oral drug delivery system researcher focused on controlled drug delivery systems including nanoparticles, liposomes, membranes and hydrogels [1].

These systems can control how the drugs are available to cells and tissue over time and space. In the current scenario, the hydrogel drug delivery system gained popular demand. It is an emerging trend in the field of biomaterial drug delivery systems. Hydrogels are a unique class of macromolecular networks that can hold a large

fraction of an aqueous solvent (mostly water) within their structures. They have ability to stimulate the biological tissue; hence, they are particularly suitable for the biomedical application, including controlled drug delivery.

Many hydrogel-based network systems have been designed and fabricated to meet the needs of the pharmaceutical and medical fields. Hydrogel drug delivery system has a spatial and temporal control over the release of various therapeutic agents like macromolecules, drugs and cells.

Hydrogel has been noticed among the biomaterial, as they meet requirements such as biocompatibility, biodegradability, bio-functionality and tuneable properties for therapeutic agent delivery and tissue engineering. The biomaterials composed of hydrophilic polymers that are cross-linked either physically or chemically to form a network and they are capable of retaining a significant amount of water. Hydrogels potentially provide the drug delivery system for the various life-threatening diseases. However, due to patient incompliance, the use of a hydrogel system is limited. Hydrogel properties and structure are determined by compositions and synthesis conditions of hydrogel.

The controlled release of a therapeutic agent from the hydrogel is well regulated due to its porous structure, which is formed due to the 3D network of hydrogel which helps to permit therapeutic agent well adhered and entrapped in a hydrogel. Hydrogel system is adequately used as scaffolds; hence they are vigorously researched for various biomedical applications.

Depending upon the nature of material used, biodegradability, mechanism of gel formation, nature of side group, physiochemical properties such as degree of swelling and porosity hydrogels are classified into the synthetic, natural or hybrid hydrogel, chemically or physically cross-linked hydrogel, cationic, anionic or neutral hydrogels, non- degradable or degradable, low, high, swelling or superabsorbent hydrogel, micro, macro or super-porous hydrogel [2].

Classification of Hydrogels: [3]

1. Classification based on Source: Hydrogels can be classified into two groups based on their natural or synthetic origins.

2. Classification According to Polymeric Composition: The method of preparation leads to formations of some important classes of hydrogels. These can be exemplified by the following:

(a) Homopolymeric Hydrogels: This is referred to a polymer network derived from a single species of a monomer, which is a basic structural unit comprising of any polymer network. Homo-polymers may have a cross-linked skeletal structure depending on the nature of the monomer and polymerization technique.

(b) Copolymeric Hydrogels: This is comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network.

(c) Multipolymer Interpenetrating Polymeric Hydrogel (IPN): This is an important class of hydrogels, is made of two independent cross-linked synthetic and/or natural polymer components, contained in a network form. In semi-IPN hydrogel, one component is a crosslinked polymer and another component is a non-cross-linked polymer.

3. Classification based on Configuration: The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows.

- **a.** Amorphous (non-crystalline).
- **b.** Semi-crystalline: A complex mixture of amorphous and crystalline phases.
- **c.** Crystalline.

4. Classification based on Type of Cross-linking: Hydrogels can be divided into two categories based on the chemical or physical nature of the Cross-link junctions.

- **a.** Chemically cross-linked networks have permanent junctions.
- **b.** While physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions.

5. Classification based on Physical Appearance: Hydrogel's appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process.

6. Classification according to Network Electrical Charge: Hydrogels may be categorized into four groups on the basis of presence or absence of electrical charge located on the cross-linked chains:

1. Nonionic (neutral).
2. Ionic (including anionic or cationic).
3. Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.
4. Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.

7. Classification According To Mechanism Controlling The Drug Release They Are Classified Into:

- **a.** Diffusion controlled release systems.
- **b.** Swelling controlled release systems.
- **c.** Chemically controlled release systems.
- **d.** Environment responsive systems.

Properties of Hydrogel:

1. Swelling Properties: All polymer chains in hydrogels are cross-linked to each other either physically or chemically and thus, considered as one molecule regardless of its size. For this reason, there is no concept of molecular weight of hydrogels and therefore, sometimes called infinitely large molecules or super macromolecules. One of the variables that affect the capacity of water absorption is the degree of cross-linking and the type of cross-linking agent used. A small change in environmental conditions may trigger fast and reversible changes in a hydrogel.

The alteration in environmental parameters like pH, temperature, electric signal, presence of enzyme or other ionic species may lead to a change in the physical texture of the hydrogel. These changes may occur at the macroscopic level as precipitate formation, changes in size and water content of hydrogels.

The amount of the aqueous medium incorporated in a hydrogel is determined gravimetrically and can be expressed by its swelling ratio.

Swelling Ratio = Ws - Wd / Wd

Where Ws is the weight of hydrogel in swollen state & Wd is the weight of hydrogel in dry State.

The difference in concentration of mobile ions in the hydrogel interior relative to the external solution (osmotic pressure), changes in solvent pH, drives the volume change. Hydrogels with acidic or basic functional groups respond to the fluctuations in the external environmental pH. The degree of ionization of the functional groups dictates its swelling profile and hence the volume changes [4].

2. Mechanical Properties: Mechanical properties of hydrogels are very important from the pharmaceutical and biomedical point of view. The evaluation of a mechanical property is essential in various biomedical applications *viz*. ligament and tendon repair, wound dressing material, a matrix for drug [5].

3. Inhomogeneity of Hydrogels: Drug delivery, tissue engineering and cartilage replacement material. The mechanical properties of hydrogels should be such that it can maintain its physical texture during the delivery of therapeutic moieties for the predetermined period of time. By changing the degree of crosslinking the desired mechanical property of the hydrogel can be achieved. An increase in the degree of crosslinking, a stronger hydrogel that can be obtained through the higher degree of crosslinking decreases the % elongation of the hydrogels creates a more brittle structure [6].

4. Elasticity of Hydrogel: The elastic modulus of hydrogels depends on the cross-link and charge densities of the polymer network as well as on the cross-linked polymer concentration after the gel preparation. The several interesting molecular features control the elastic behavior of the hydrogel. In 1998 Shibayama discovered the spatial gel in homogeneity of a hydrogel. It is the non-ideal behavior of hydrogel. It is an undesirable property of hydrogel as it dramatically reduces the optical clarity and strength of hydrogel. The spatial gel inhomogeneity of hydrogel is the cross-link density distribution. The gel inhomogeneity is connected to the spatial concentration fluctuation. The different methods have been employed to investigate the spatial in homogeneities such as

light scattering, small-angle X-Ray scattering and small-angle neuron scattering.

In 1997 Lindemann reported the method to measure the gel in homogeneities by comparing the scattering intensities from the gel and from a solution of the same polymer at the same concentration. It was reported that the scattering intensity from gels is always larger than that from the polymer solution. The gel in homogeneity increases with increasing the cross-linking network across the gel polymer, however, it decreases with the ionization degree of gel [7].

5. Biocompatible Properties: It is important for the hydrogels to be biocompatible and nontoxic in order to make it applicable in the biomedical field. Most polymers used for this purpose must pass cytotoxicity and *in-vivo* toxicity tests Bio-compatibility is the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility studies consist of two parameters namely biosafety and bio-functionality:

a. Biosafety *i.e.* appropriate host response not only systemic but also local (*i.e.* surrounding tissue), the absence of cytotoxicity, mutagenesis, and/or carcinogenesis.

b. Bio functionality *i.e.* the ability of material to perform the specific task for which it is intended. This definition is particularly relevant in tissue engineering since the nature of tissue construct is to continuously interact with the body through the healing and cellular regeneration process as well as during scaffold degradation. Furthermore, initiators, organic solvents, stabilizers, emulsifiers, unreacted monomers and cross-linkers used in polymerization and hydrogel synthesis may be toxic to host cells if they seep out to tissues or encapsulated cells. To remove hazardous chemicals from preformed gels, various purification processes should be followed such as solvent washing or dialysis [8].

Desired Features of Hydrogel Material:

- The functional features of an ideal hydrogel material can be listed as follows.
- Must have the highest absorption capacity (maximum equilibrium swelling) in saline.
- Must show the desired rate of absorption (preferred particle size and porosity) depending on the
- Application requirement.
- Must exhibit the highest absorbency under load (AUL).
- Should show the lowest soluble content and residual monomer.
- Must have the highest durability and stability in the swelling environment and during the storage.
- Must have the highest biodegradability without the formation of toxic species following the degradation.
- pH neutrality after swelling in water.
- Colorless, odorless, and absolutely non-toxic.
- Must have good photostability.
- Re-wetting capability (if required) the hydrogel has to be able to give back the imbibed solution or to maintain it; depending on the application requirement (*e.g.*, in agricultural or hygienic applications).

Limitations of Hydrogel:

- Hydrogels are expensive Hydrogels causes sensation felt by movement of the maggots.
- The surgical risk associated with device implantation and retrieval.
- Hydrogels are non-adherent; they may need to be secured by a secondary dressing.
- Hydrogels used as contact lenses cause lens deposition, hypoxia dehydration and red-eye reactions.
- Hydrogels have low mechanical strength.

Hydrogels potentially provide the drug delivery system for the various life-threatening diseases. However, due to patient in compliance, the use of the hydrogel system is limited. Hence, Injectable Hydrogel is an emerging trend in the field of biomaterial drug delivery systems. Injectable Hydrogel overcomes the limitation of the preformed hydrogel, as they are injected with minimum invasive procedure into target sites and used for irregularly shaped sites.

An injectable hydrogel is clinically more convenient and simple to be used than traditional hydrogels. Injectable hydrogel has control over the release of a therapeutic agent and can be used for tissue regenerative medicine and immunotherapy. The recent studies of injectable hydrogels for drug delivery applications suggested that multi-functional injectable hydrogels are capable of entrapping and delivering multiple therapeutic agents. They potentially provide the drug delivery system for various life-threatening diseases like cancer, hypertension and diabetes. The studies on stimuli-responsive hydrogel area now are the most trending research [9].

As scaffolds, they have provided a flexible residence space of cells and stimuli to be immobilized and delivered for the tissue repair and regeneration of the desired tissues (cartilage, bone, retina, brain, and, neural tissue repair, vascular regeneration, and wound healing). As carrier hydrogel can be incorporated with drug or biomolecule to be delivered to the specific site in the body for the treatments of infectious and inflammatory diseases (Parkinson's disease, bacterial and antimicrobial infection, and diabetes) and cancers (colon, lung, breast, ovarian, and lymphoma cancer) [10].

It used as a life treating formulation in repair and regeneration of tissue, due to its ability of permeability to oxygen and nutrient, bio-compatibility, its porous structure which allows loading of therapeutic agents. Injectable hydrogels, of which network morphology and properties could be tuned, have shown to control the load and release of therapeutic agents, consequently producing significant therapeutic efficacy. An injectable hydrogel is formed by a cross-linking polymer, where there is a phase transition from sol-gel. The changes in the viscoelastic behavior of injectable hydrogel through the phase transition were observed by rheological properties. The injectable hydrogel is formed by gelation mechanism either by chemical or physical gelation. Injectable hydrogel offers the advantage of sustain release of medicament from several days to a month and reduces the need for frequent dosing, thus it increases patient compliance. They become soft when they are hydrated. Because of hydration, the capacity of adherence to tissue is decreased and the permeation of drug increases. It imparts the use of crosslinker, to give sufficient mechanical strength to polymers.

Cross-linking agents which are used in the preparation of injectable hydrogel are either from natural origin or from synthetic origin [11]. If gelation is slow, then hydrogel obtained with the poor hydrogel properties, precursors are likely to perfuse from the site of injection to surrounding. If it becomes rapid, then shear-thinning hydrogel was obtained, which affects gel mechanical properties. The use of cross-linker prevents the burst release of medicament, but it suffers from the limitation of the presence of residue. Injectable hydrogel has a unique property of complete defect filling, leading to neovascularization from healthy tissue.

Like conventional hydrogels, the preparations of injectable hydrogels have been achieved via either chemical or physical cross-linking methods. Therapeutic agents are typically entrapped in the hydrogel by mixing with a precursor solution, and the sterilization process of the mixture is carried out before injection to the body part. The injectable hydrogel has a unique shear- thinning property, which has been engineered such that their viscosity reduces under higher shear rates, thus they deform easily through needles. They have a significant property that they return to their original shape after the removal of mechanical force. Shear-thinning is one promising technique for the application of injectable hydrogels, where preformed hydrogels can be injected by application of shear stress (during injection) and quickly self-heal after removal of shear. Importantly, these gels can be used to deliver biological molecules and cells during the injection process [12].

Biopolymer Classification: There are various polymers which are used for the fabrication of hydrogel. Chitosan, cellulose derivatives, alginate, polycaprolactone, polaxamore are some of them which are widely used. Among them, cellulose and chitosan are the most abundant biopolymers found naturally. They are used alone or along with the cross-linking agent depending upon the nature of the biopolymer to fabricate into the gel [13].

Biomaterials are obtained from natural and synthetic sources as mentioned in **Fig. 1**.

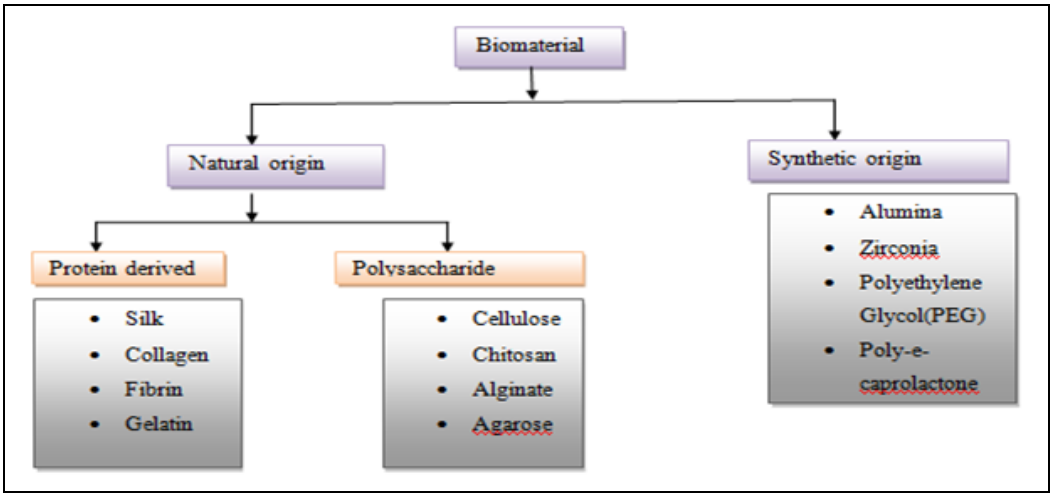

FIG. 1: CLASSIFICATION OF BIOMATERIAL

Chitosan: Chitosan is a natural polymer, Second most abundant polysaccharide which has a similar structure and bioactivity with glycosaminoglycan, and is a potential material for use as injectable hydrogels. Chitosan has the ability to swell 10 - 1000 times more than its weight.

Chitosan is derived from chitin by deacetylation; It consists of (1–4) linkage of randomly arranged D-glucosamine and a small proportion of N-acetyl-D glucosamine. It has excellent biocompatibility and low toxicity. The free amino groups in chitosan enable covalent bonding with small molecules and macromolecules. These chemical reactions facilitate the use of chitosan for the development of injectable hydrogels. The gelation of chitosan-based injectable hydrogels is less invasive and can be initiated by either physical stimulus or chemical reaction. Chitosan is a highly versatile biopolymer. Chitosan was applied in drug, gene delivery & cell encapsulation. Chitosan was used in wound healing, bio-imaging & Food industry. Chitosan was applied in binding to implants, contact lenses & protein drugs. It is used as antioxidant & antibacterial.

The formulations containing chitosan are particularly exploited in protein and vaccine delivery as it acts as a penetration enhancer by opening the tight junctions. The protein loading and drug delivery are influenced by the molecular weight and degree of deacetylation of chitosan. The degree of deacetylation increases entrapment efficiency; however, it decreases the drug release. The cationic nature of chitosan is advantageous for ionic interaction [13].

Cellulose: Cellulose is the most abundant biopolymer. It is a naturally occurring polymer of glucose. The glucose units are held together by 1, 4- β-glucosidic linkages. The glycosidic linkage is responsible for the high crystallinity of cellulose. It is insoluble in water and another common solvent. The main source of cellulose is the cotton and linen natural fiber. The bacterial cellulose and plant cellulose are the main two types of cellulose sources. They are chemically identical to each other.

Cellulose and its derivatives are eco-friendly, as they are biodegradable. The bacteria and fungi present in the air, water, and soil are responsible for the degradation of cellulose and its derivatives. The degradation leads to the synthesis of cellulose specific enzymes (cellulases). The investigation reported the mechanism of biodegradation of cellulose. Degradation progressively leads to a decrease in molecular weight, lower mechanical strength and increased solubility. The solubility issue related to the cellulose and its derivatives is solved after its degradation.

The cellulose-based devices have to gain a matter of importance in biomedical applications because of their biocompatibility and biodurable properties. The animal and human cells are not able to synthesize the enzyme cellulases; hence the resorption of cellulose in animal and human tissue does not occur. Some materials have an ability to be degraded by a microorganism. The term is referred to as bioresorbability. The most widely used cellulose derivatives are used for the preparation of cellulose-based hydrogels.

The hydrogels are formed by properly crosslinking solution of cellulose ethers such as methylcellulose (MC), hydroxypropyl methyl-cellulose (HPMC), ethyl cellulose (EC), hydroxy-ethyl cellulose (HEC) and sodium carboxy-methylcellulose (NaCMC).

It is worth highlighting among the above-mentioned cellulose ethers, only NaCMC is a polyelectrolyte. NaCMC itself have a property of conduction of electrostatic charges. Thus the hydrogel prepared with the NaCMC shows the sensitivity to pH and ionic strength variations [14, 4].

Cross-Linking Agents: Cross-linking is a highly versatile method to improve the physical and mechanical properties of the hydrogel. Biopolymers are fabricated into hydrogel by cross-linking with the various cross-linking agents such as glyoxal, glutaraldehyde, genipin, carboxymethyl cellulose, boric acid *etc*. The addition of a cross-linking agent affects the physical and mechanical properties of hydrogel depending upon the degree of cross-linking between biopolymer and cross-linking agents and the presence and absence of crystallinity.

Cross-linking results in:

1. Elasticity- Ability to stretch and return to their original form after removal of the force.
2. A decrease in viscosity- Permits resistance to flow for the cross-linked polymer.
3. The insolubility of polymer- Cross-linking agents are not able to dissolve in solvent but can absorb solvent. Cross-linking results in holding polymer chains together which results in the insolubility of polymer.
4. Increased glass transition temperature (Tg), increase strength and toughness.
5. Lower melting point- a result due to the decrease in crystallinity.

a. Advantages of Cross-Linked Hydrogel:

1. Covalently cross-linked hydrogels are the only system characterized by the permanent network, due to their irreversible chemical cross-link.
2. Other types of hydrogels are more liable as compare to covalently cross-linked as they exhibit good mechanical properties due to covalent bonds and can overcome dissolution, even in the extreme pH conditions.
3. The covalently cross-linked hydrogel can be used as a drug delivery system from which drugs are released by diffusion.
4. Depending on the structure of hydrogel, the covalently cross-linked structures are porous due to cross-linked networks, which is a matter of importance in a controlled drug delivery system.

b. Disadvantages of Cross-Linked Hydrogel:

1. Most of cross-linkers used are more toxic or their fate in the human body is unknown
2. There is a lack of data concerning the biocompatibility of crosslinker
3. Before the administration of cross-linker into the hydrogel, cross-linker require to perform additional purification steps. 5. The main drawback of this system is the use of safe and biocompatible crosslinkers, which is quite limited.

The different cross-linking agents which are employed for the synthesis of the hydrogel are enlisted in **Table 1**.

TABLE 1: LIST OF CROSS LINKING AGENTS

S. no.	Biopolymer	Hydrophilic polymer/cross linking agent	Drug	Biological properties
1	Chitosan	Mucin glycoprotein	Polysaccharides	Mucoadhesive
2	Chitosan	PEG forming polymer sodiumalginate, polycarbophile	Nifedipine	Buccal membrane adhesion
3	Chitosan	PLGA	Ipriflavone	Promote bone density
4	Chitosan	PEG	Metronidazole, amoxicillin	Bypass acidic environment of stomach
5	Chitosan	PEG	Insulin	Diabeties mellitus
6	Chitosan	PEG	5- fluorouracil	Colon carcinoma

Methods of Cross-Linking:

A. Chemical Cross-Linking:

a. Radical polymerization
b. High energy irradiation
c. Enzyme mediation
d. Chemical reaction complimentary group.

Cross-linking with:

- Aldehyde
- Addition reaction
- Condensation reaction

e. Diels Alder reaction
f. Photopolymerization

B. Physical Cross-Linking:

a. Ionic interaction
b. Physically cross-linked hydrogels from an amphiphilic block and graft copolymer
c. Crystallization by

- Homopolymer system
- Sterocomplex system

d. Host Ghost interaction

C. Stimuli Effect: Temperature, Lights, PH, electric fields, ultrasounds, biomolecular species. When an unswollen hydrogel comes in contact with external stimuli then it will be converted to swollen hydrogel [15].

Properties of Injectable Hydrogel: Injectable hydrogels have recently proved as promising vehicles for the delivery of drugs and biomolecules. Injectable hydrogels are three-dimensional network structures that can be formed in vivo, as opposed to pre-formed hydrogels.

1. The aqueous precursor of the hydrogel must have low viscosity before gelation (*i.e.*, before the application of shear), and be cross-linkable *in-vivo* after injection.

2. If targeted for biomedical applications, the gelation must take place in a physiologically benign environment without the use of toxic chemicals or heat, physical cross-linking takes place in this case by using the external stimuli.

3. Furthermore, any release of gaseous by-products can cause tissue damage. But the use of cross-linker prevents the degradation of hydrogel upon exposure to the organic solvents. The material should be biocompatible and biodegradable.

4. For the controlled release of the medicament the added therapeutic agent *i.e.* the drug or biomolecule (active component) must be as a homogeneous dispensation

5. The mobility of the injectable precursor allows the hydrogel to adapt to defects but must have the necessary mechanical properties (stiffness and strength) after injection.

6. Injectable hydrogels are also expected to show pronounced porosity to allow the transportation, growth, and rearrangement of cells.

7. Injectable hydrogel must have a shear-thinning property.

8. By the application of force i.e. shear, the system changes its viscosity. The macroporous gel is compressed to the compressed gel after the application of shear.

9. Shear-thinning gels have been engineered such that their viscosity reduces under higher shear rates.

10. These gels deform easily through the needle and rapidly returned to their original shape after the removal of mechanical force and restore into the solid gel [17].

a. Shear Thinning Property of Injectable Hydrogel: Shear-thinning in the Non-Newtonian behavior of fluid whose viscosity decreases under shear strain. It is sometimes considered as a pseudoplastic behavior excluding time-dependent defects such as thixotropy, shear-thinning behavior. It is generally not seen in pure liquids with non-molecular mass and the ideal solution of small molecule sucrose, or sodium chloride but is often seen in polymeric solutions and polymers such as fluids, suspensions or catch up, cream blood and

nail polish. Some of these are considered to be the case of thixotropic behavior because of the recovery of the microstructure of the liquid to its initial state. It will always require a non-zero time and the recovery of viscosity is very rapid [18].

Thixotropy means to change by touch and may be described as a reversible isothermal transformation from sol to gel.

Gel Application of shear stress **Sol** Removal of shear stress **Gel**

Thixotropic system contains asymmetric particles that set up a loose three-dimensional structure. This structure conforms certain rigidity on the system and it resembles a gel. As shear is applied to the system, the structure breaks down and material changes from a gel to sol structure. Upon the removal of stress, the structure begins to reform slowly and initial structure reform after a lag time.

The most common example of thixotropy is the bentonite gel which is made up of a random network of hydrated elongated particles. On the application of shearing stress, the elongated particle links are broken. The network therefore disintegrates and apparent viscosity decreases. On removal of the shearing forces, the arrangement of dispersed particle gradually become less orderly under the influence of Brownian motion and gel network is reformed after a lag time.

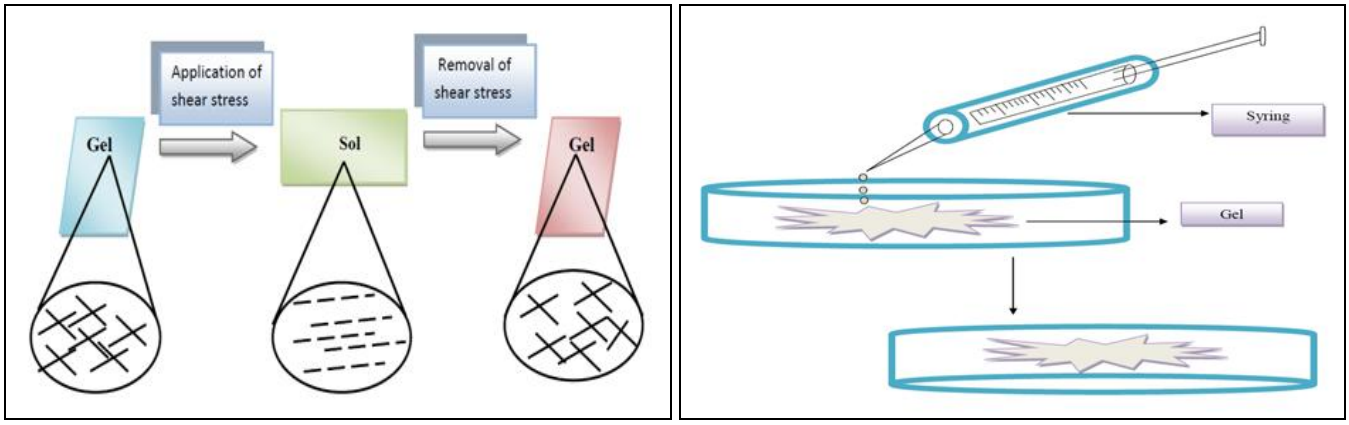

FIG. 2(A, B): SHEAR THINNING PROPERTY OF INJECTABLE HYDROGEL

Characteristics of the Shear Thinning Injectable Hydrogel:

1. Rheological characterization of hydrogels
2. Measurement of hydrogel injection forces, and
3. Injection of hydrogels into a specific site of action

1. Rheological Characterization of Hydrogels: The rheological quantitative measurement parameters of hydrogel injectability are viscosity, storage and loss moduli. Viscosity is the resistance to the flow of fluid in response to stress. It is the direct measurements of the relative ability of hydrogel formulation in response to external stimuli *i.e.* shear stress during the injection. However, in response to oscillatory shear, the storage and loss moduli provide information about the elastic and viscous behavior of hydrogel. The storage and loss moduli measure the extent to which a hydrogel response to stress or either absorbs energy (loss moduli). These parameters explain the information about the behavior of hydrogel during the injection process [19].

2. Measurement of Hydrogel Injection Forces: Injection force determines whether or not a material is clinically relevant for injection. Controlled methods to measure injection force, such as a force sensor or a material testing machine, allow us to compare quantitatively the injectability of various hydrogels of differing material formulations. The factors that influence the injection force are flow rate, a needle gauge and needle length. Injection force is not only relevant as physical property, but also has an effect on hydrogel contents that are sensitive to force, such as cells [21].

3. Injection of Hydrogel into Specific Site of Action: Hydrogels have been investigated *in-vivo* in various types of tissue; however in various areas where the minimum invasive procedures are required for the delivery of the drug, injectable

hydrogel have been widely investigated at various tissue in the human body. And there are several hydrogel formulations that have undergone testing in clinical trials. Herein, hydrogels are used for mechanical bulking, modulating, and remodeling or therapeutic drug delivery of cells, small molecules or macromolecules after an infraction. An additional advantage of injectable hydrogel over conventional hydrogel systems is the potential to deliver material through a minimum invasive procedure such as subcutaneous injection or percutaneous route through a catheter (in cardiac tissue). After the injection of a drug to the specific site of action, the drug release through hydrogel takes place by employing the various drug release strategies such as through reservoir system or matrix system [21].

Injectable Hydrogel Preparation: Hydrophilic polymer is the major basic structural component of hydrogel preparation, the extent of hydrogel preparation is based on the different parameters,

a. The amount of water the hydrophilic polymer is expected to absorb

b. The method of cross-linking the polymer chains within the gel network.

Depending on the density of hydrophilic groups present on the polymer, the hydrophilic polymer has the capability to absorb different amounts of water. Water absorption for the hydrophilic polymers can range from a fraction to several thousand times of their own weight. Gel dissolution is prevented by the functional moieties which form the stable linkages by binding between chains. Polymer binding is accomplished either by non-covalent physical associations, such as secondary forces (hydrogen, ionic, or hydrophobic bonding), covalent cross-linkages and physical entanglements.

Both methods can sufficiently restrain hydrogel swelling, but the physical associations are reversible bonds, whereas the covalent cross-linkages between polymer chains are irreversible bonds. The distinction is important for the biodegradation and drug release kinetics of hydrogels. During gel hydration, the polymer chains interact with the solvent molecules and expand to the fully solvated state. While the material expands, the cross-linked structure offers the retractive force to restrain the polymer chains as described by Flory's rubber elasticity theory.

The counterbalance of the expanding and retracting a force reaches equilibrium in the solvent at particular temperatures. The swelling characteristics of a hydrogel are the main parameter in its use in diverse applications because the equilibrium swelling ratio (i.e. weight ratio of swollen hydrogel over the dry hydrogel) influences the solute diffusion coefficient, surface wettability and mobility, and the optical and mechanical properties of the hydrogel. The physical properties of swollen hydrogels are regulated by the molecular weight (MW) of the polymer, charges on the polymers, density of the cross-linking (covalently bonded networks), and physical associations. Each of these conditions regulates the relative amount of bonding between polymer chains. For example, the more robust hydrogel is formed by the multiple cross-linking between high molecular weight polymers, while smaller polymers are required at higher concentrations to produce potential gel rigidity. The mechanical properties of the hydrogel are regulated by the extent of cross-linking *i.e.* increases in the hydrogel cross-linking results in an increase in both the moduli and stiffness.

These properties are useful in the protection of encapsulated biomolecules from mechanical deformation at the transplantation site and during hydrogel migration (*e.g.,* during oral delivery). The material's pore or mesh size and the hydrodynamic size of the drug properties are used to regulate the diffusion of encapsulated therapeutics out of hydrogel [22].

The Drug Release Strategies form the Injectable Hydrogel:

a. Addition of Drug to Polymer: Hydrogel systems have been used for the controlled delivery of different biomolecules, ranging from small molecular weight drugs, and high molecular weight biomolecules such as nucleic acid, proteins, and peptides. Depending upon diversity in chemistry and the size of delivered molecules, the drug loading for controlled release in any particular hydrogel can differ widely from one application to another. The drug loading methods directly impacts the availability of the drug during release. Hence,

different approaches to drug incorporation have been developed.

b. Drug loading and Release: Polymeric materials are easy to process and their chemical and physical properties can be controlled *via* molecular synthesis. There are two broad categories of polymer system called microspheres reservoir devices and matrix devices.

Reservoir Devices: Encapsulated pharmaceutical products within a polymeric shell.

Matrix Devices: The drug is physically entrapped into the shell.

Biodegradable polymer systems degrade into biologically acceptable compounds by hydrolysis and the medication is left behind. The degradation process involves the breakdown of the polymer.

In an aqueous environment, the polymeric hydrophobic domains can crosslink *via* thermal gelation. The gelation process is supposed to be driven *via* the hydrophobicity of a biopolymer. The polymer amphiphile is prepared via two methods such as post-polymerization grafting or by direct synthesizing block copolymer. The hydrophobic segment is coupled to the hydrophilic polymer to prepare water-soluble amphiphilic polymer. However, polymer amphiphile is soluble at low temperature, as the temperature increases hydrophobic domains aggregate to minimize the hydrophobic surface area, which reduces the amount of structured water surrounding the hydrophobic domains and minimizing solvent entropy. The factors which affect the gelation process are the concentration of polymer, length of the hydrophobic block and chemical structure of polymer. These factors also triggers the temperature at which gelation occurs. Chemical structures of some common hydrophobic blocks which undergo gelation at or near physiological temperature *via* reverse thermal gelation. Some natural polymers also undergo reverse thermal gelation. Chitosan-glycerol phosphate-water system is an interesting example, which has being investigated for protein delivery, gene delivery and tissue engineering applications [23].

It is reported that the hydrogel performance as a drug delivery system depends upon both the physical and chemical properties of gel as well as therapeutics itself. In fact, the choice of biomaterials, extent of cross linking and drug loading mechanisms must be made to complement the hydrophobic properties of the drug and its mechanism of action.

For loading small molecule, the simplest drug loading method is to place the fully formed hydrogel into saturated medium of therapeutics. From the hydrogel, the drug will slowly diffuse into the gel based on the porosity of gel, physical and chemical properties of each, the size of drug. When placed in vivo, the drug will then freely diffuse back out of the hydrogel into the surrounding tissue.

In the case of larger drugs, proteins, macromolecules and bioligands, the payload must be entrapped or encapsulated during the gelation process either by entrapment or covalent bonding. Here, the drug is mixed with a hydrophilic polymer solution, and the cross-linking or complexation agent is added. The use of cross-linker improves the extent of the gelation.

TABLE 2: DRUG RELEASE STRATEGIES

Drug Release	Drug Loading	Loadable drugs	Network formation	*In-situ* gelation	Degree of burst release	Release duration
Permeation	Drugs permeate hydrogel, it is the direct addition of the drug to a hydrogel, drug-loaded by encapsulation. The addition of drugs before or after cross-linking the polymer also alters their release profiles	Small molecule	Physically, covalently, IPN cross-linked	Not possible	High It losses up to 70% of payload	Hours to days
Entrapment	Hydrogel formed around gel	Small molecules proteins, micro, nanospheres	Physically, covalently cross-linked	Possible	Moderate	Days to weeks
Covalent Binding	Drugs covalently linked. Drug release from hydrogel-a. Hydrolysis, Degradation	Small molecule, peptides, proteins	Physically, covalently cross linked	Possible	No	Weeks to month

It prevents the burst release of the drug. It is important to consider the chemistry (3D structure) of the drug molecule to prevent excessive cross-linking or degradation of the therapeutic during gelation.

Both diffusion and entrapment allow for free movement of the therapeutic out of the hydrogel network. This can lead to an initial burst release after implantation of the hydrogel *in-vivo* due to the concentration gradient formed between the gel and the surrounding environment. It has a limitation of the presence of residue of crosslinker. The drug loading strategies are enlisted in **Table 2**.

Biomedical Application of Injectable Hydrogel: Hydrogels have been potentially used in biomedical fields due to their swelling ability and the consequent biocompatibility. Potential applications of hydrogels in tissue engineering, drug delivery are well highlighted in recent work. Due to the incorporation of hydrophilic polymer to the hydrogel they became soft, this nature of hydrogel makes them particularly suitable as novel drug delivery systems.

The drug release will be well triggered by controlling the swelling properties of the hydrogel. Through proper design, hydrogels can be used in numerous applications including controlled, sustained, targeted, or stealth biomolecule or drug delivery. The bioadhesive nature of most of the biopolymer is used to facilitate drug targeting, especially through the mucous membrane, for non-invasive drug administration. Hydrogels have control over the phagocytic activities by evading the host immune responses. Hydrogels give an important "stealth" characteristic *in-vivo* owing to their hydrophilicity which increases the *in-vivo* circulation time of the delivery device.[24]

Recent Advances in Injectable Hydrogel Applications: Recent advancement in the drug delivery for the diabetes treatment is collaborated by the use of the injectable shear-thinning hydrogel system as a depot preparation for modulating the release of insulin. The goal of this delivery is to reduce the frequent dosing of injections as well as glucose-responsive release. The injectable hydrogel is created from cyclodextrin and adamantine mediated cross-linking of hyaluronic acid which demonstrated that these hydrogels can form an injectable depot *in-vivo*.

The collaboration of the localized therapy along with chemotherapy can diminish the toxicity of systemic chemotherapy as well as providing the sustained release of the chemotherapeutic agents at the tumor site. Thus, injectable biodegradable hydrogel as a localized cancer drug delivery system proved to be a more efficacious system than conventional systemic chemotherapy in terms of cancer therapy**.**

Now- a- days, bone deformities lead to serious complications such as a Non-union. Non-union is a permanent failure of healing, which leads to broken bone unless surgery is performed. In this situation, fracture moves too much and has a poor blood supply or gets infected. This type of fracture is observed when blood supply is hindered. The effective treatment for this type of problem is provided by introducing an injectable oestrogenic hydrogel that can deliver cells and vasculogenic growth factors. These are silicate-based shear-thinning hydrogels STHs prepared from poly-caprolactone nanoparticles' that entrap and release vasculogenic growth factor in a controlled manner, this technology engineered an injectable scaffold. The injectable STHs is capable of delivering cells, growth factors and also capable of filling any irregularly shaped defects in bone [25].

Tetronic–adamantane (Tet–Ada) and β-cyclodextrin polymers (poly[β-CD]), were successfully synthesized and used as a shear-thinning injectable hydrogel. Shear-thinning is thixotropic property of gel, whereby the viscosity decreases under shear stress and recovers after the removal of shear stress. This is a unique example of thermal gelation at 37 °C. Doxorubicin (DOX) an anticancer drug is incorporated into a gel. The prepared gel demonstrated the shear-thinning behavior, rapid recovery properties, pH-responsive properties, and long-term release of the hydrophobic drug, doxorubicin (DOX). The thermo-sensitive injectable hydrogel is prepared by comprising chitosan and glycerophosphate. The designed solution is supposed to be liquid at room temperature and gelled at 37 °C. The application of this system is for the sustained release of meglumine antimoniate.

For treating life-threatening diseases like ischemic heart diseases, the cell-based therapies are limited because of low cell retention within ischemic myocardium. To deal with this issue a depot shear-thinning injectable hydrogel preparation is developed. It is composed of Hyaluronic acid having an interaction with adamantine- and β-cyclodextrin. The shear-thinning property of hydrogel is the matter of importance, as it is self-healed upon injectable within the ischemic myocardium. This system will surely enhance vasculogenesis to improve myocardial stabilization. This system also helps to preserve the contractility of myocardium.

As injectable hydrogel designed to overcome the limitation of the conventional hydrogel system by addressing the growing demand for a minimally invasive procedure for local and sustained delivery of therapeutic agents. The researchers developed a hyaluronic acid-based shear-thinning hydrogel that forms through non-covalent ghost –host interactions. This system is meant to work as a shear-thinning injectable hydrogel. This unique property of hydrogel is used as a bio-ink in 3D printing applications and drug delivery.

The injectable hydrogel holds a promising therapy for improved cancer treatment and other therapies which require targeted drug delivery at the right place and right time. Thus, Wyss researcher develops a new approach by using alginate, naturally occurring polysaccharide from brown algae. They developed an injectable biocompatible and biodegradable hydrogel. They claimed that the prepared formulation could greatly improve clinical ability to provide controlled drug delivery at the specific site of action [26].

In a conventional drug delivery system for delivering a protein-based therapies or drugs, doctors preferred to give pills or inject the drug into the patient's bloodstream. However, sometimes the drug is not delivered to a targeted site; the doctor wants to target. This could happen due to the delivery of drug throughout the body. To minimize this problem, if large doses are injected to deliver enough drug to targeted sites, then also it could cause harmful side effects. To deal with this issue researcher developed an injectable hydrogel that can be used to deliver a drug or proteins in a minimally invasive manner due to their extreme flexibility and resilience. They have a unique property to compress to a fraction of their size and injected underneath the skin *via* a surgical needle. Once they injected they gain their original shape to do their job.

The various strategies are utilized for dealing with cancer therapy. Recently an approved therapy is a hydrogel system. These prepared formulations of the hydrogel can only play a supporting role that releases bioactive agents against cancer cells rather than the main role. The drug is delivered via a transdermal route, which results in the death of cancerous cells. This system is successfully used in melanoma skin cancer. The anti-proliferative agents are delivered at a specific site in the treatment of skin cancer which has several advantages over other drug delivery systems and conventional therapies. The modified tuneable properties of hydrogel make it more reliable for cancer therapy [27].

The physicochemical properties of the polymer such as mucoadhesive, gastro-adhesive and stimuli-responsive depend upon their interaction with the biological system. Based upon these properties their application is varied. The mucoadhesive property of the polymer is used in the vaginal, nasal, ocular and small intestine administration. While the gastro adhesion plays an important role in the delivery of the drug to the stomach. The swelling, expanding and shrinking are physicochemical properties of hydrogel which are advantageous to reaction with mucosal layers. Because of this interaction, the mucosal layer allows the hydrogel to be internalized in tissue. For the optimization of the drug delivery system, mucoadhesive hydrogel represents the innovative and vital frontier. Recently the polyethylene glycol is its derivative-based hydrogels that have gained significant interest. They have a capacity to be well tolerated *in-vivo* for the application in the field of drug delivery and tissue. The low viscosity precursor polymer solution is advantageous for the non-invasive administration of gel *via* injection.

CONCLUSION: Targeted delivery of the drug is critical in improving therapeutic efficacy and minimizing side effects. The target-specific drug delivery system improves the therapeutic efficacy

and minimizes the unwanted side effects which are occurring due to the deposition of the excessive dose of medicament in the human body. Thus the delivery of drugs through the Injectable hydrogel system at the specific site herein gained the high potential regarding the targeted drug delivery system. Thus for the development of targeted delivery systems, chitosan and its derivatives possess potential advantages such as bio-compatibility, bio-degradability, mucoadhesiveness and other unique biological properties.

This review suggested that the injectable hydrogel has been potentially in the field of research as a scaffold or as carriers of therapeutic agents such as drugs, cells, proteins and bioactive molecules in the treatment of disease, cancer and the repair and regeneration of tissue. The researcher has been focused on the trends in the development of injectable hydrogel for the drug delivery, it is because they have injectability with minimum invasiveness and usability for irregularly shaped sites. They overcome the disadvantage of conventional as well as the hydrogel drug delivery system, because of their biocompatibility, permeability to oxygen and nutrients, properties similar to the characteristics of the native extracellular matrix and porous structure allowing the therapeutic agents to be loaded. They allow the therapeutic agent to be degraded at the specific site in the localized area for better therapeutic efficiency. The drug delivery system can leverage the therapeutically beneficial outcome of drug delivery and found clinical use in the various fields of research such as oncology, cardiology, immunology *etc*. They provide the platform in which the various physicochemical interactions with the encapsulated drugs control their release. Apart from the drug release, they also can protect the liable drug from degradation due to their tuneable physicochemical and mechanical properties. The various drug loading strategies have a potential impact on the drug release through the hydrogel.

In this review, we have seen the development trend of an injectable hydrogel in the field of drug delivery, the unique cross-linking mechanism and new molecular agents that can induce physical gelation. It is reported that there has been significant growth in the variety of hydrogel that can be produced. These gels have an impact on the porosities, mechanical strengths, and the dimensions for deciding the area of application. The article also explains about the mechanism by which the gel from fragment and degrade in the body. The unique properties of the hydrogel are extensively mentioned that they form safely within the body with minimum invasive procedures, trigger drug release at the specific site in the localized area, preventing systemic toxicity and degrade in a controllable manner for the long term and effective drug release. Injectable hydrogel has gained popularity as a vehicle for the delivery of the medicaments to the specific site in the human body. The above-described methods herein discussed the design and assessment of hydrogel for widespread biomedical applications.

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