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## TREND OF INJECTABLE HYDROGEL IN FORMULATION AND RESERACH.

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### ABSTRACT

Hydrogel are three-dimensional, cross-linked networks of water-soluble polymers. Hydrogels can be made from virtually any water-soluble polymer. Injectable hydrogels are hydrogels which can given by parenteral route by use of injection and syringe. Such hydrogels are of particular interest because drugs, proteins, and cells can be easily incorporated into polymer solutions prior to administration. Injectable hydrogel administrated in solution form by use of standard needles and syringes, it solidifies upon contact with aqueous body fluids to form gel. Drug release occurs over time as polymer biodegrades. This review will provide summary of recent progress in Injectable hydrogel, polymer used and method of preparation of Injectable hydrogel, evaluation of hydrogel and recent application of Injectable hydrogel.

**Key words:** Hydrogel, Injectable hydrogel, Thermal and pH sensitive Injectable hydrogel, novel drug delivery system of Injectable hydrogel.

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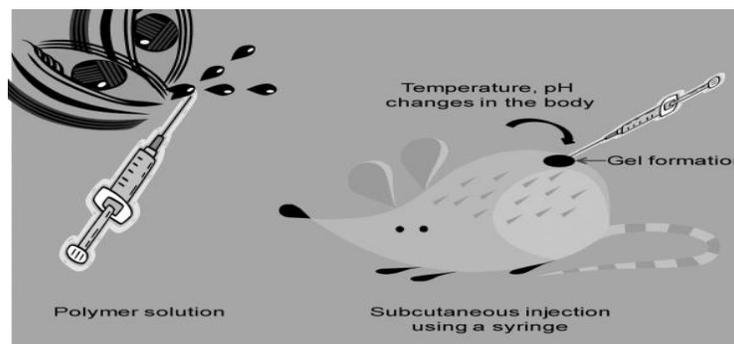
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## INTRODUCTION

Hydrogel are three-dimensional, cross-linked networks of water-soluble polymers. Hydrogels can be made from virtually any water-soluble polymer. Hydrogels are commonly used in clinical practice and experimental medicine for a wide range of applications, including tissue engineering and regenerative medicine, diagnostics, cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions. Newer advantage in the field of hydrogel drug delivery is Injectable hydrogel preparations.

Injectable hydrogels are hydrogels which can given by parenteral route by use of injection and syringe. Such hydrogels are of particular interest because drugs, proteins, and cells can be easily incorporated into polymer solutions prior to administration. Importantly, no surgical procedures are required for the insertion of gels into the body the gels are administered by simple injection.<sup>1,2</sup>

Injectable biodegradable copolymer hydrogels, which exhibit a sol–gel phase transition in response to external stimuli, such as temperature changes or both pH and temperature (pH/temperature) alterations, have found a number of uses in biomedical and pharmaceutical applications, such as drug delivery, cell growth, and tissue engineering. These hydrogels can be used in simple pharmaceutical formulations that can be prepared by mixing the hydrogel with drugs, proteins, or cells. Such formulations are administered in a straightforward manner, through site-specific control of release (Figure 1) behavior.<sup>3-5</sup>



**Figure 1: Temperature and pH sensitive Injectable Hydrogel**

Biodegradable Injectable in situ gel forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. It consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using standard needles and syringes, it solidifies upon contact with aqueous body fluids to form solid implant. If a drug is incorporated into the polymer solution, it becomes entrapped within polymer matrix as it solidifies. Drug release occurs over time as polymer biodegrades.

Biodegradable polymers used in these systems are Polyhydroxyacids, polyanhydrides, polyorthoesters, polyesteramides and others (Figure 2).<sup>6</sup>



**Figure 2: Injectable hydrogel in Solution form.**

### INJECTABLE HYDROGEL POLYMERS:

**Poly (ethylene glycol):** Including hydrophilicity and biocompatibility<sup>8</sup>. In addition, its properties of limited immunogenicity, antigenicity, and minimal protein and cell adhesion make PEG-based hydrogels have utilized photocurable methods to encapsulate various cell types. Due to the inert nature of PEG, there is no interaction between the polymer and encapsulated cells.

**Poly (vinyl alcohol):** Poly (vinyl alcohol) (PVA) gels have been formed through chemical cross linking with aldehydes or photo-polymerization. Since chemical cross linking can create harsh environments that are potentially toxic to cells, PVA also has elastic properties that may be beneficial to seeded cells, such as enhancing the transmission of mechanical stimuli to induce cell orientation or matrix synthesis<sup>9-12</sup>. Like PEG hydrogels, PVA is non-adhesive to cells and proteins, but can be covalently modified with cell attachment peptides for bioactive regulation.

**Poly (propylene fumarate):** Poly (propylene fumarate) (PPF) is an unsaturated linear polyester that has been applied as a biomaterial for orthopedic applications such as bone cements. Cross-linking performed with a vinyl monomer produces a mechanically strong polymer network with applications for bone tissue. Recently, PPF has been employed as cell encapsulation scaffolds<sup>9-12</sup>.

**Alginate:** Alginate is a natural polymer found in brown algae, a form of seaweed, and has been applied as a biomaterial for drug delivery vehicles and cell-encapsulating scaffolds<sup>13-15</sup>. Alginate is a bloc copolymer that forms a gel through the interaction of divalent cations with blocks of gluronic acid on the polysaccharide chains<sup>7</sup>. Alginate is also degradable, but the process is not easily controlled and can be unpredictable. Alginate alone does not interact with cells and has limited bioactivity.

## PRINCIPLE OF INJECTABLE HYDROGEL:-

Injectable hydrogels can be divided into two main classes according to synthesis mechanism: physically cross-linked hydrogel and chemically cross-linked hydrogels. Simultaneously physical and chemical cross-linking is expected to be a good method for the preparation of injectable hydrogels, which can yield superior hydrogels with regard to gelation kinetics and ultimate mechanical properties.

### Physical cross linking:-

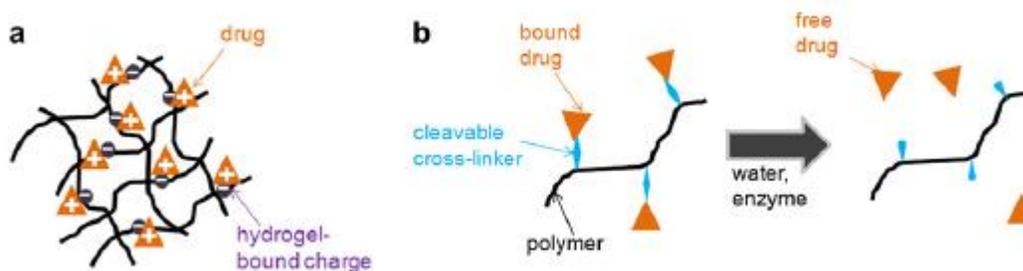
Physical hydrogels have several advantages over chemical hydrogels, because they do not require photo irradiation, use of organic solvents or cross-linking agents, and do not release heat during polymerization at the gelation site, which may denature incorporated proteins and damage embedded cells and surrounding tissues. Thus, the physical systems have recently attracted increased attention. For use in drug/cell delivery and tissue engineering, hydrogels should be low-viscosity solutions (free flowing) prior to subcutaneous injection, and should rapidly gel in the human body, where ultimate degradation of the hydrogels is desired.<sup>(16-18)</sup>

### Chemically cross linked:-

Chemically cross linked hydrogels, prepared through photopolymerization, disulfide bond formation, or reaction between thiols and acrylate or sulfones, undergo significant volume changes during the phase transition. In contrast to chemical hydrogels, physically cross-linked hydrogels, formed by the self-assembly of polymers in response to environmental stimuli (for example, temperature, pH, or both) display sol-gel transitions without marked volume changes. The sol-gel transitions systems are relatively low viscosity aqueous solutions (sol state) prior to injection, but rapidly convert into a gel under physiological conditions post-injection<sup>17-19</sup>.

### Interactions between the Gel and A Target Drug:-

There are two types of interactions occur between the gel and a target drug. First one is physical interaction and second one is chemical interaction. Figure 3.

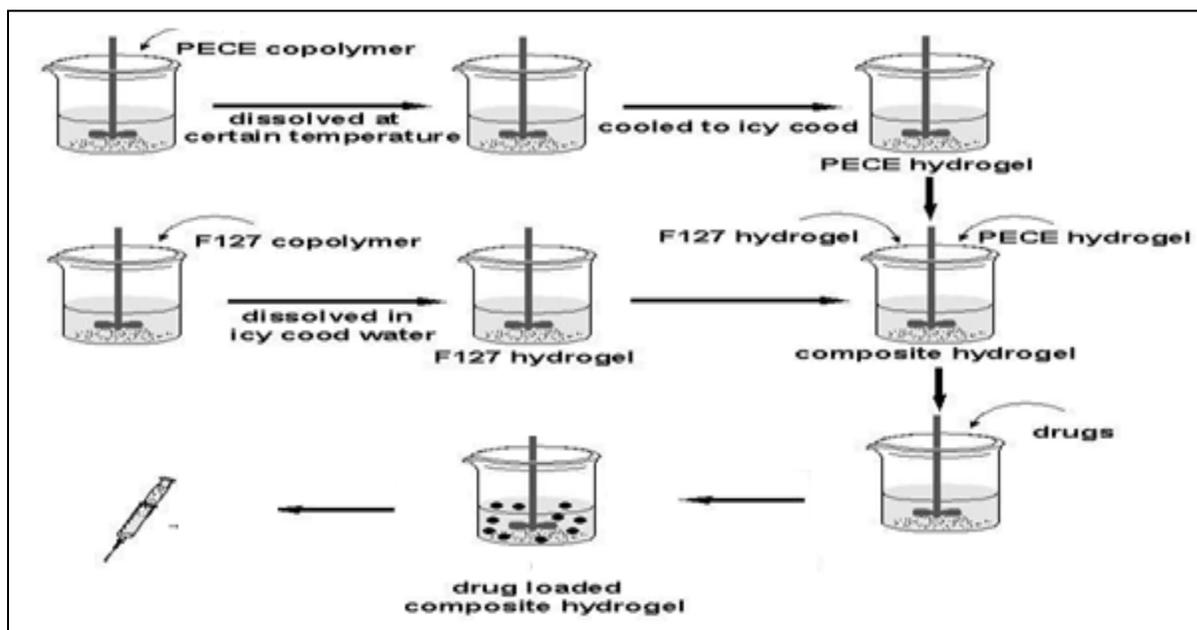


**Figure 3: Physical (a) and chemical (b) strategies for enhancing the interaction between a loaded drug and a polymeric gel to slow drug release.**<sup>20, 21</sup>

**Method of preparation:**

PECE copolymer is triblock copolymer of Poly ethylene glycol (PEG) and POLY Caprolactone (PCL). First PEG-PCL diblock copolymers were prepared by ring opening polymerization of PCL (POLY Caprolactone) initiated by PEG (Poly ethylene glycol) using stannous octoate as catalyst. Then PEG-PCL-PEG triblock copolymers were synthesized by coupling PEG-PCL diblock copolymers using coupling agent.<sup>22</sup>

PECE hydrogel solutions were prepared by dissolving PECE copolymers in deionized water at a designated temperature then cooled to 4°C. Then, pluronic F127 were dissolved in icy cold deionized water to a transparent solution. Subsequently, the obtained two solutions were mixed together under mild agitation to obtain homogeneous liquid solution, and then drug were added into the composite hydrogel. The prepared hydrogel containing drug was inhaled into injector and injected into body. Thus, composite sol turned into gel state and acted as depots for sustained release of drug *in situ* when the cold sol is warmed to body temperature (37°C) *in vivo*. At last, for the degradation of the composite hydrogel, the introduced drug delivery system was gradually emanated from body. Figure 4.



**Figure 4: Method of preparation of Injectable hydrogel by using PECE copolymer.**

**EVALUATION OF GEL:****pH:-**

The pH of the various gel formulations can be determined by use of digital pH meter.

**Spredability:-**

It can be determined by wooden block and glass slide apparatus. Add 20g to the pan and note the time for upper slide (movable) to separate completely from the fixed slides<sup>23-26</sup>.

Spredability was then calculated by using the formula:

$$S = M.L / T$$

Where,

S= Spredability

M=Weight tide to upper slide

L=Length of glass slide

T=Time taken to separate the slide completely from each other

**Consistency:-**

Measure the consistency of the prepared gels by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the centre of the glass cup filled with the gel and measure the penetration by the cone from the surface of the gel to the tip of the cone inside the gel. Note down the distance traveled by cone after 10sec<sup>26, 27</sup>.

**Homogeneity:-**

Homogeneity, appearance of the gel and presence of any aggregates should be tested by visual inspection after the gels have been set in the container.

**Drug content:-**

Take a specific quantity (100mg) of gel and dissolved in 100ml of phosphate buffer of specific pH. Shake the volumetric flask containing gel solution for 2hr on mechanical shaker in order to get complete solubility of drug. Then filter and estimate spectrophotometrically using phosphate buffer (Specific pH) as blank<sup>23-27</sup>.

**Accelerated stability studies:-**

All the selected formulations were subjected to a stability testing for three months as per ICH norms at a temperature of  $40^{\circ} \pm 2^{\circ}$ . All selected formulations were analyzed for the change in appearance, pH or drug content by procedure stated earlier.

**Swelling studies:-**

Initially the weight of a completely dried hydrogel can be taken and then immersed in excess of swelling medium. The weight of hydrogel at various time intervals after blotting excess of water on surface on the surface was determined<sup>28</sup>.

$$Q = (M_s - M_d) / M_d$$

Where  $Q$ =swelling ratio,  $M_s$ =mass in the swollen state of hydrogel,  $M_d$ =mass in dried state of hydrogel.

### **Water retention:-**

Water retention capacity is a function of time can be determined by following equation:-

$$WR_t = (W_p - W_d) / (W_s - W_d)$$

Where  $W_d$ =weight of dried gel,  $W_s$ =weight of fully swollen gel,  $W_p$ =weight of hydrogel at various exposure times<sup>28</sup>.

### **APPLICATION OF INJECTABLE HYDROGEL:-**

#### **Hydrogel buttock injections**

Injectable hydrogel can be use for change shape and size of buttocks. The most popular forms of injectable body fillers used for buttocks augmentation are PMMA or Hydrogel.

Limitation of hydrogel buttock injections: Illegal in the United States, Extremely expensive and result is not permanent.

#### **Injectable hydrogels for cartilage tissue engineering.**

Current clinical treatments for cartilage injury often involve surgical interventions to remove affected tissues and insert transplanted cartilage or prosthetic devices as replacements. While these procedures may provide relief from pain and restore joint mobility, they can present long-term complications<sup>29-32</sup>. Tissue engineering, a discipline combining engineering and the life sciences, presents a potentially effective method of treating cartilage damage. The aims of tissue engineering are to restore tissue structure and function. Hydrogels are an example of a scaffold with the ability to encapsulate cells and have demonstrated potential for cartilage repair<sup>33-36</sup>. The benefits of hydrogels for tissue development and clinical usage are especially evident in injectable systems.

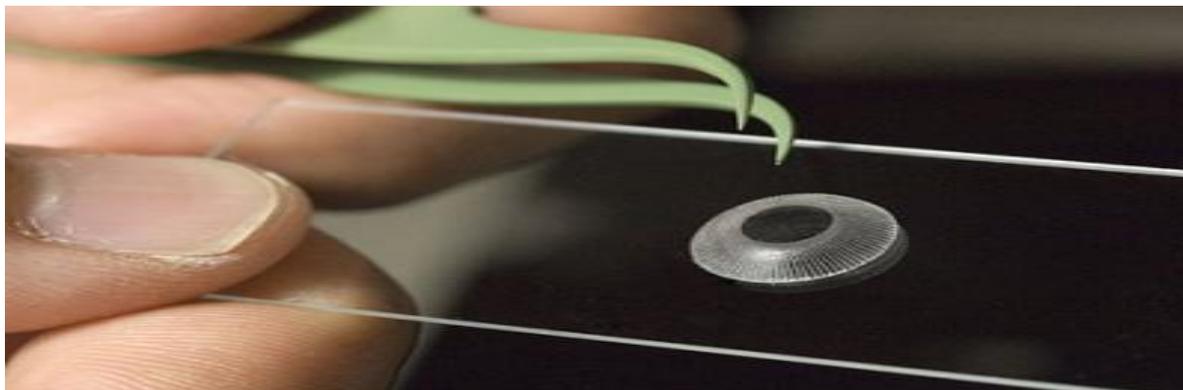
#### **Hydrogels in tissue engineering:**

Tissue engineering has been defined as an “interdisciplinary field that applies the principles of engineering and the life sciences to the development of biological substitutes that restore, maintain, or improve tissue function”.<sup>37</sup> The physical properties and biocompatibility of the polymer must also be able to ensure cellular function *in vivo*. Both synthetic and natural materials have been used to form scaffolds. Synthetic polymers have generated appropriate three dimensional environments to promote tissue development and are beneficial as cell carriers for musculoskeletal tissue engineering.<sup>39</sup> Although not as bioactive as natural scaffolds, synthetic polymers provide the necessary properties to produce scaffolds with desired controllable

physical and chemical characteristics.<sup>38-40</sup> Hydrogels are another option for tissue engineering. Hydrogels have numerous desirable traits including high, tissue-like water content and moldable characteristics that are beneficial for clinical use.

### **Ophthalmic use:**

The artificial cornea is made of a dual network hydrogel with a clear center and peripheral pores. Cells infiltrate the pores and secrete collagen, which integrates artificial cornea into the surrounding natural tissue. Biocompatible, biodegradable, inexpensive hydrogels that can be easily formed into any desired shape for biomedical applications. Figure 5.



**Figure 5: Artificial cornea made of hydrogel.**

### **Limitation of ophthalmic preparation:**

#### 1. Difficult to handle

Hydrogel contacts have low mechanical strength, meaning that they cannot easily withstand the application of outside forces. So when you try to pick up a hydrogel lens with your fingers, it will often temporarily lose its shape, and in a worst-case scenario, it can tear. Handling problems cause the insertion and removal process of hydrogel contact lenses to take longer and can also cause you to accidentally drop a lens.

#### 2. Air permeability limitations

While silicone hydrogel lenses tend to allow for sufficient air permeability, a common problem with traditional hydrogel lenses is that they do not let in enough air. This can cause your contacts and eyes to feel dry after long periods (throughout a day), and in worst-case scenarios, can cause corneal edema.

#### 3. Contamination issues

Possible problems that can result from contamination of silicone hydrogel lenses include the formation of superior epithelial arcuate lesions (SEALs), which are splits in your eye's epithelial,

and contact lens-related papillary conjunctivitis (CLPC), a condition wherein the thin tissue known as conjunctiva swells in the white parts, or sclera, of your eye.

#### 4. Sterilization requirements

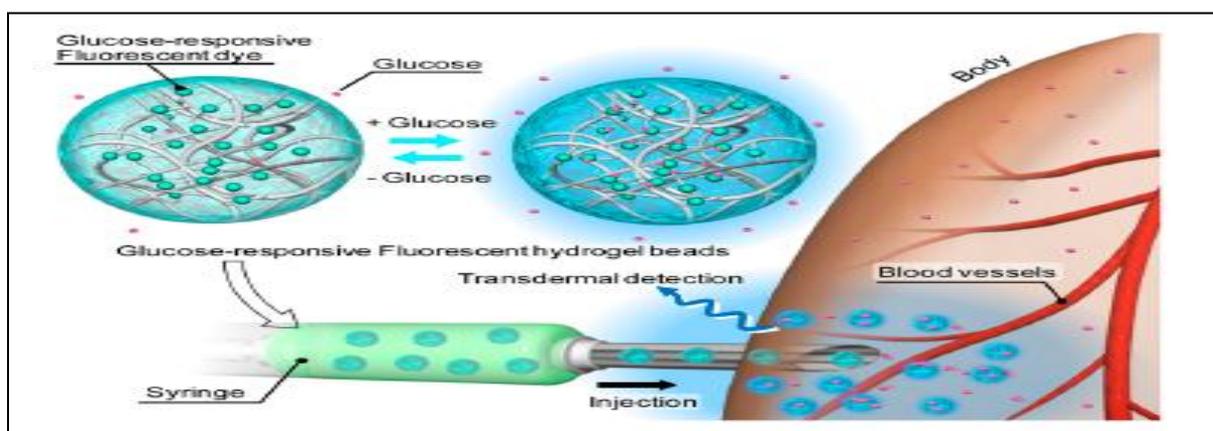
Hydrogel contact lenses require sterilization chemicals that are more complex and thus more expensive than those required for hard contact lenses.

#### **Hydrogel injection impacts mechanics of cardiac tissue.**

To confirm further that the differences in hydrogel mechanics were maintained upon injection into cardiac tissue, the mechanics of bulk hydrogels alone, explanted cardiac tissue alone, and hydrogel/tissue composites were assessed. The modulus of the tissue/hydrogel composite was greater than explanted cardiac tissue alone for the MeHA High group but not for the MeHA Low group. Specifically, with the MeHA Low gel there was no statistical difference in the modulus between the cardiac tissue and the composite; however, there was a statistically significant increase in modulus with the MeHA High composite when compared with normal cardiac tissue. Similar trends were observed when the tissue/hydrogel composites underwent uniaxial tensile testing in the longitudinal direction.

#### **Injectable hydrogel microbeads used for in-vivo continuous glucose monitoring.**

The fluorescence intensity of the microbeads increases as glucose concentration increases. This reversible, powerless, and highly sensitive reaction allows the fluorescent microbeads to continuously monitor glucose concentrations in vivo with long lasting activity and transdermal transmission. The fluorescent microbeads are simply injected under the dermis using a needle, minimizing pain and damage to tissues<sup>41-42</sup>. Figure 6.



**Figure 6: Injectable hydrogel microbeads for fluorescence-based in-vivo continuous glucose monitoring.**

**Table 1: Market Product of Injectable Hydrogel**

<b>Drug</b>	<b>Commercial name</b>	<b>Company</b>
Minocycline	Arestin <sup>®</sup>	Orapharma
Bromocriptine	Parlodel LAR <sup>™</sup>	Novartis
Lanreotide	Somatuline <sup>®</sup> LA	Ipsen-Beaforce
Buserelin	Suprecur <sup>®</sup> MP	Sanofi-Aventis
Triptorelin	Trelstar <sup>™</sup> Depot	Pfizer
	Decapepty <sup>®</sup> SR	Ferring
Somatropin	Nutropin <sup>®</sup> Depot	Genentech/Alkermes
Octreotide	Sandostatin <sup>®</sup> LAR	Novartis
Leuprolide	Lupron Depot <sup>®</sup>	TAP
	Enantone Depot <sup>®</sup>	Takeda
	Trenatone <sup>®</sup>	Takeda
	Enantone Gya	Takeda
Naltrexone	Vivitrol <sup>®</sup>	Alkermes
Risperidone	RISPERDAL <sup>®</sup> CONSTA <sup>®</sup>	Janseen <sup>®</sup> /Alkermes, Inc

**CONCLUSION:-**

Injectable hydrogel is the novel drug delivery system for administration of hydrogel. It has better bioavailability than other delivery system. Injectable hydrogel concerns with several clinical applications like cartilage tissue engineering, mainly buttock injections and in vivo continuous glucose monitoring.

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