Potential Applicabilities of Hydrogels - A Literature Survey

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Abstract: Hydrogels are cross linked polymeric network, which have the ability to hold water within the space available among the polymeric chains. The hydrogels have been used extensively in various biomedical application, viz. drug delivery, cell carriers and/or entrapment, wound management and tissue engineering. Hydrogels are swellable polymeric materials, have been widely as a carrier of drug delivery systems. These biomaterials have gained attention owing to their peculiar characteristics like swelling in aqueous medium, pH and temperature sensitivity or sensitivity towards other stimuli. Hydrogels being biocompatible material have been recognized to function as drug protectors, especially of peptide and proteins, from in vivo environment. Also these swollen polymers are helpful as targetable carriers for bioactive drugs with tissue specificity and environmental sensitive hydrogels have enormous potential for various environmental variables, such as low pH and elevated temperature, are found in the body. For this reason, either pH sensitive and /or temperature- sensitive hydrogels can be used for site specific controlled drug delivery. Light sensitive, pressure- responsive and electro-sensitive hydrogels also have the potential to be used in drug delivery and bioseparation. This article presents an overview to the range of application of hydrogels and advances in hydrogels based drug delivery that have become the interest of researchers.

Keywords: Hydro gels, Drug delivery, Wound healing, Tissue engineering, pH sensitivity, temperature sensitivity.

INTRODUCTION

With ongoing research in advanced drug delivery formulation to provide stable and economical drug delivery systems, the focus is on hydrogels which are known to reduced the problems of not only the conventional dosage forms but also of novel drug delivery systems which require a biocompatible, convenient and stable for drug delivery systems for molecules as small as NSAIDs (Non-steroidal anti- inflammatory drugs) or as large as protein and peptides (Graham and Mc- Neil,1984;Bajpai and Sonkuusley,2002). There are a number of evidences when such delivery devices are imperative such as delivery of insulin at elevated blood sugar level where it is required to constantly provide the drug in system. These controlled drug delivery systems are designed for zero order kinetics which ensures constant drug release over a prolonged period of time. Drug targeting is achieved by using biocompatible polymers along with drug in micronized form and then attaching certain" homing devices "like antibodies. Controlled drug delivery area made for treating many clinical disorder like diabetes and rhythmic heart disorders. In these cases, the drug has to be delivered in response to fluctuating metabolic requirement or the presence of certain biomolecules in the body. In addition controlled drug delivery area needs further development of techniques for delivery of peptide and protein drugs. In the body, the appearance of numerous bioactive peptides is tightly controlled to maintain a normal metabolic balance via a feedback system called "homeostasis".[1] Hydro gels have been used extensively in the development of smart drug delivery systems. A hydro gel is a network of hydrophilic polymer that can swell in water and hold a large amount of water while maintaining the structure. A three dimensional network is formed by cross linking polymeric chains.Crosslinking can be provided by covalent bonds,hydrogen bonding, van der walls interaction or physical enlargement[2,3].Hydro gels can protected the drug from hostile environments, e.g. the presence of enzymes and low pH in the stomach.Hydrogels can also control drug release by changing the gel structure in response to environmental stimuli. Hydro gels containing such sensors properties can undergoes reversible volume phase transition or gel- sol phase transition upon only minute change in environmental conditions. This type of hydro gels called Intelligent or smart hydro gels [4].Smart hydro gels have been used in diverse applications, such as making in artificial muscles[7-11], chemical valves[12] immobilization of enzymes and cells[13-21], and concentrating dilute solution in bioseparation[22-27]. Environmental sensitive hydro gels are ideally developing self regulated drug- delivery systems.

TYPE OF HYDROGELS

    1.1   Temperature –sensitive hydrogels

2.1   p H - sensitive hydrogels

3.1   Glucose –sensitive hydrogels

4.1   Electric- signal sensitive hydrogels

5.1   Light- sensitive hydrogels

6.1   Other stimuli sensitive hydrogels

- Pressure -sensitive hydro gels
- Specific ion- sensitive hydro gels
- Specific antigen sensitive hydro gels
- Thrombin -induced infection -responsive hydro gels

1.1 Temperature sensitive hydro gels

Polymer structure- Temperature sensitive htdrogels are most commonly studied hydro gels in drug delivery research. Many polymers exhibit a temperature responsive phase- transition properties. The structure of some of those polymers shown in Fig. 1 the common characteristics of temperature sensitive hydro gels are the presence of hydrophobic groups, such as propyl, ethyl, methyl groups. Of the many temperature- sensitive polymers, poly (N iso propyl acryl amide) (PNIPAAm) are most commonly extensively used poly (N, N -diethyl acryl amide (PDEAAm) is also widely used because of its lower critical solution temperature (LCST) in the range of 25-32 C, close to the body temperature. Copolymer of NIPAAm can also be made using other monomers, e.g. butyl Mehta acryl ate (BMA) to alter the LCST. Certain type of block copolymers made of poly (ethylene oxide) (PEO) and poly propylene oxide (PPO) also possesses inverse temperature sensitive properties. Because of their LCST   at around the body temperature, they have been used widely in the development of controlled drug delivery systems based on the sol- gel phase conversion at the body temperature. A large number of PEO-PPO block copolymers are commercially available under the names of Pluronic□ (poloxamers)and Tetronic.Their structure are shown in Fig 2.
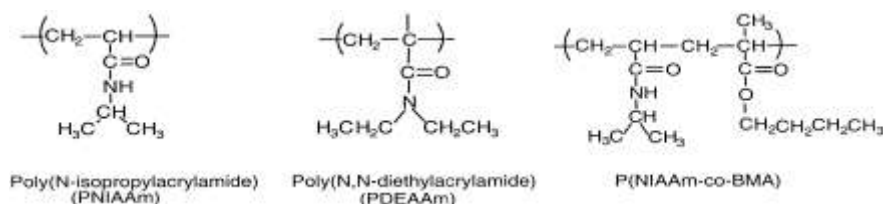

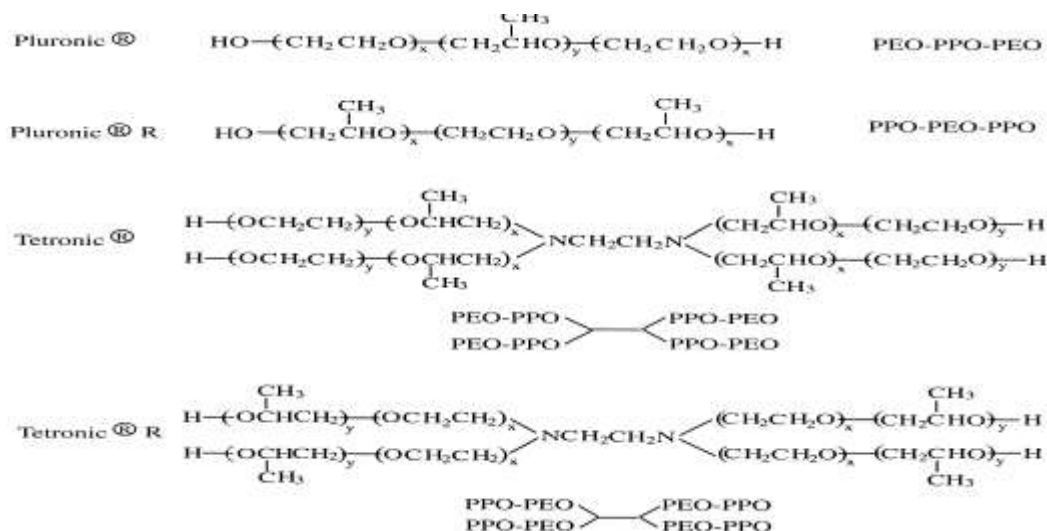
Fig. 1. Structures of some temperature-sensitive polymers.

Fig. 2. Polymer structures of Pluronic□, Pluronic□R, Tetronic□ □and Tectonic□ □R.

1.2 Properties of temperature sensitive hydro gels

Most polymers increase their water solubility as the temperature increases. Polymers with LCST however decrease their water-solubility as the temperature increases. Hydro gels made of LCST Polymer shrink as the temperature increases above the LCST. This type of behavior is known as inverse (or negative) temperature –dependence. The inverse temperature- dependent hydro gels are made of polymer chains that either posses moderately hydrophobic groups. Or contain a mixture of hydrophilic and hydrophobic segments. At lower temperatures, hydrogen bonding between hydrophilic segments of the polymer chain and water molecules are dominates, leading to enhance dissolution in water. As the temperature increases, however, hydrophobic interactions among hydrophobic segments become strengthened. While hydrogen bonding becomes weaker. The net result is shrinkage of hydro gels due to inter polymer chain association through hydrophobic interaction. In general as the polymer chain contains more hydrophobic substituent, LCST becomes lower [29]. The LCST can be changed by adjusting the ratio of hydrophilic and hydrophobic segments in the polymer. One way is to make copolymer of hydrophobic e.g. (NIPAAm) and hydrophilic (e.g. acrylic acid) monomer [29-32].The continuous phase transition of PNIPAAm known to be changed in a discontinuous phase by incorporating a small amount of ionizable groups in to the gel network [33,34] or by changing solvent composition [35]. Copolymerization of NIPAAm with different type of monomers results in hydro gels with more versatile properties, such as faster rate of shrinking when heated through the LCST [36], and sensitivity to additional stimuli. If the polymer chains in hydro gels are not covalently cross linked, temperature sensitive hydro gels may undergoes sol-gel phase transition instead of swelling –shrinking transition. The thermally reversible gels with inverse temperature dependence become sol at higher temperature. Polymers that show this type of behavior are block copolymers of PPO and PEO as shown in Fig. 2. The hydrophobic PPO block can be replaced with other hydrophobic polymers. For example PEO- containing block –copolymer with poly (lactic acid) show the same thermal reversible behavior. In this case poly(lactic acid)provides a biodegradable property. Temperature –sensitive hydro gels can also be made using temperature -sensitive cross-linking agents.

Temperature sensitive hydro gels classified in to negatively thermo sensitive, positively thermosensitive, and thermally reversible gels.
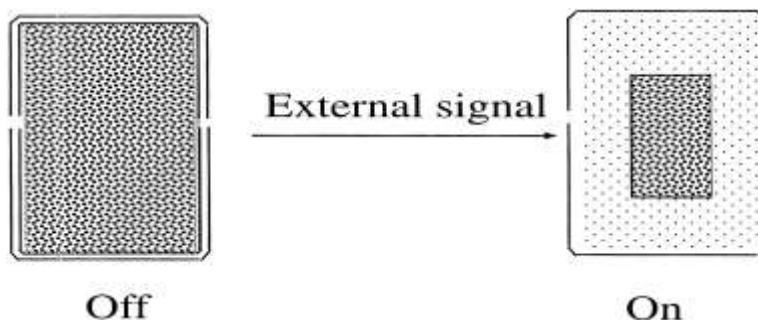

Fig. 3. Schematic illustration of on–off release from a squeezing hydro gel device for drug delivery (from Ref. [46].

1.3. 1. Negatively thermo sensitive drug release systems

Thermo sensitive monolithic hydro gels were used to obtain an on –off drug release profile in response to a stepwise temperature change [38, 40]. The hydro gels used in these studies include cross linked P(NIPAAm-co-BMA) hydro gels[40,42] and inter penetrating polymer network (IPNs) of P(NIPAAm) and poly (tetramethyleneether glycol) (PTMEG) hydrophobic co monomer BMA was introduced in to NIPAAm gels to increase their mechanical strength. The on-off release profile was achieved with on at low temperature and off at high temperature. It was explained by formation of a dense, less permeable surface layer of gel, described as a skin- type barrier. The skin barrier was formed upon a sudden temperature change due to the faster collapse of the gel surface than the interior. This surface shrinking process was found to be regulated by the length of the methyaacrylate alkyl side -chain, i.e. the hydrophobicity of the co monomer [43-44] .This result also suggested that the drug in the polymer matrices diffused from the inside to the surface during the off state even when no drug release was seen.

Temperature-sensitive hydro gels can also be placed inside a rigid capsule containing holes or apertures. As shown in Fig. 3, the on-off release is achieved by the reversible volume change of temperature sensitive hydro gels.[45,46]

Such a devices is called squeezing hydro gel device because the drug release is affected by the dimension of the hydrogel.A similar approach was used to develop a reservoir type microcapsule drug delivery system by encapsulating the drug core with ethyl cellulose containing nano-sized PNIPAAm hydro gel particle [48].For making stable thermally controlled on –off devices, PNIPAAm hydro gel can be grafted on the entire surface of a rigid porous polymer membrane[49].

1.3.2. Positive thermo sensitive drug release systems

Certain hydro gels formed by IPNs show positive thermo sensitivity i.e. swelling at high temperature and shrinking at low temperature .IPNs of poly (acrylic acid) and poly acryl amide (PAAm) and P (AAm-co-BMA) have positive temperature

dependence of swelling [50]. Increasing the BMA content shifting the transition temperature to higher temperature. The swelling of those hydro gels was reversible, responding to stepwise temperature changes. This resulted in reversible changes in the release rate of a model drug, ketoprofen, from monolithic devices.

1.3.3. Thermo reversible gels

The most commonly used thermo reversible gels are used Pluronics☐and Tetronics☐. A review on the properties and application of Pluronics☐ in drug delivery is available [28].For parenteral application of thermo reversible gels, it is most desirable that they are biodegradable. To add biodegradable capacity, the PPO segment of PEO-PPO-PEO block copolymer is often replaced by a biodegradable poly (lactic acid) segment [51-53]. The molecular architecture was not limited to the A-B-A type block copolymer, but expanded to the three dimensional, hyper branched structures, such as a star shaped structure. Proper combination of molecular weight and polymer architecture resulted in gels with different LCST values. When the hydro gels are formed by injecting the polymer solution loaded with model drugs' in to a 37 C aqueous environment, the release of a hydrophilic model drug (ketoprofen) and a hydrophobic model drug (spironolactone) were first order and S-shaped ,respectively.

2. p-H sensitive Hydrogels

2.1 polymer structures

 All the p-H sensitive polymers contain pendant acidic (e.g. carboxylic and sulphonic acids) and basic (e.g. ammonium salts) group that either accept or release proton in response to change in environmental p-H. The polymer with a large number of ionizable groups is known as polyelectrolytes. Fig. 4 shows structure of example of anionic and cationic polyelectrolyte's and their pH dependent ionization. Poly (acrylic acid)(PAA) becomes ionized at high p-H, while poly(N, N '–dimethylaminoethyl methacrylate) (PDEAEM) because ionized at low p-H. As shown in Fig. 4, cationic polyelectrolyte, such as PDEAEM, dissolve more or swell more, if cross- linked at low p-H due to ionization . On the other hand polyanions, such as PAA dissolve more at high p-H.
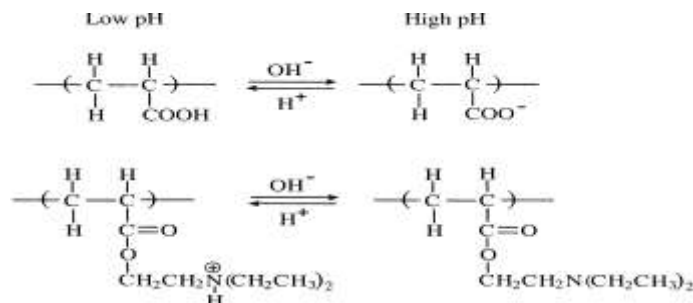

Fig. 4. pH-dependent ionization of polyelectrolyte, Poly (acrylic-acid) and poly (N, N9-diethylaminoethyl methacrylate).

2.2 Properties of p-H Sensitive hydro gels

 Hydro gels made of cross linked polyelectrolyte display big difference in swelling properties depending upon the p-H and environment. The pendant acidic or basic group on polyelectrolyte undergoes ionization just like acidic or basic group of monoacids or monobasic. Ionization on polyelectrolyte however, is more difficult due to electrostatic effects exerted by other adjacent ionized group. This tend to make the apparent dissociation constant (Ka) different from that of the corresponding monoacid or monobasic. The presence of ionizable group on polymer chains results in swelling of the hydro gels. Since the swelling of polyelectrolyte hydro gels is mainly due to the electrostatic repulsion among charges present on the polymer chains, the extent of swelling is influenced by any condition that reduced electrostatic repulsion, such as p-h, ionic strength and type of counterions[54].The swelling and p-H responsiveness of polyelectrolyte hydro gels can be adjusted by using neutral comonomer, such as 2-hydroxyethyl methacrylate , methyl methacrylate and maleic anhydride [55-58].Different co monomers provide different hydrophobicity to the polymer chain, leading to different p-H sensitive behavior.
Hydro gels made of poly(meth acrylic acid) PMA grafted with poly(ethylene glycol) PEG have unique p-H sensitive properties[59]. At low p-H , the acidic protons of carboxylic group of PMA interact with the ether oxygen of PEG through hydrogen bonding, and such complexation results in shrinkage of hydrogels.As the carboxyl group of PMA become ionized at high p-H, the resulting decomplexation leads to the swelling of hydro gels.

2.3 Application of p-H sensitive Hydro gels

2.3.1. Controlled drug delivery

p-H sensitive hydro gels most frequently used to develop controlled release formulation for oral administration. The p-H in stomach (<3) is quite different from neutral p-H in the intestine, and such a difference is large enough to elicit p-H dependent behavior of polyelectrolyte hydro gels. For polycationic hydro gels, the swelling is minimal at neutral p-H, thus minimizing drug release from the hydro gels. This property has been used to prevent release of foul-tasting drugs in to the neutral p-H environment of mouth. When caffeine was loaded in to hydro gels made of copolymers of methyl -methacrylate and N,N' dimethylaminoethylmethacrylate(DMAEM), it was not released at neutral p-H , but released at zero –order at p-H 3-5 where DMAEM became ionized[60]. Polycationic hydro gels in the form of semi-IPN have also been used for drug delivery in the stomach. Semi-IPN of cross linked chitosan and PEO showed more swelling under acidic condition. This type of hydro gels would be ideal for localized delivery of antibiotics, such as amoxicillin and metrinidazole, in the stomach for the treatment of Helicobacter pylori [61].

Hydro gels made of PAA and PMA can be used to develop formulation that release drug in a neutral p-H environment [57-58]. Hydro gels made of polyanions (e.g. PAA) cross linked with azoaromatic cross linkers were developed for colon-specific drug delivery. Swelling of such hydro gels in the stomach is minimal and thus, the drug release is also minimal. The extent of swelling increasing as the hydro gel passes down the intestinal tract due to increase in p-H leading to ionization of carboxylic group. But only in the colon, can the azoaromatic cross-links of the hydro gel be degraded by azoreductase produced by the microbial flora of the colon [62, 63]. As shown in Fig. 5. The degradation kinetics and degradation pattern can be controlled by the cross linking density [62].The kinects of hydro gel swelling can be controlled by changing the polymer composition [63].
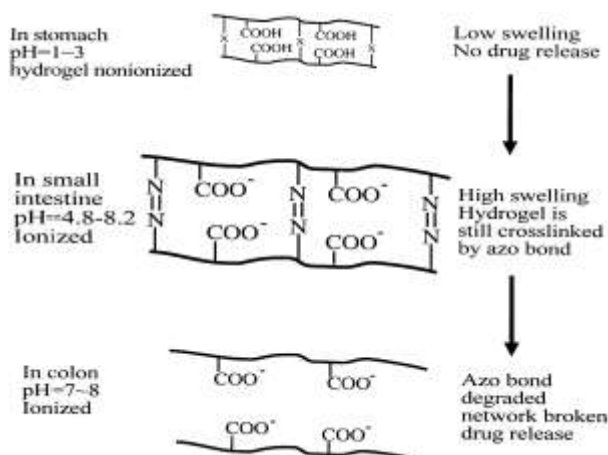

Fig. 5. Schematic illustration of oral colon-specific drug delivery using biodegradable and pH-sensitive hydro gels. The azoaroma moieties in the cross-links are designated by –N☐N–; from Ref.[62].

The polymer composition can be changed s the p-H of the environment changes. Some pendant groups, such as N-alkonyl (e.g. propionyl,hexanoy land lauroyl) and O- acylhydroxylamine moieties' can be hydrolyzed as the p-H changes from acidic to neutral values , and the rate of side chain hydrolysis is dependent on the length of the alkyl moiety.

p-H sensitive hydro gels were placed inside capsules[46] or silicone matrices [64,65] to modulate the drug release. In the squeezing hydro gel system [46], drug release is controlled by a mechanism as shown in Fig. 3. The only difference is that the swelling-shrinking of hydro gels is controlled by changing p-H, instead of temperature. In the silicone matrix system [64, 65], medicated p-H dependent hydro gel particles made of semi-IPN of PAA and PEO were used .The release pattern of several model drugs having different aqueous solubility and portioning properties were correlated with the p-H dependent swelling pattern of semi-IPN .At p-H1.2 the network swelling was low and the release was limited to an initial burst. At p-H 6.8, the network becomes ionized and higher swelling resulted in increased released.

Poly (vinyl acetal diethylaminoacetate) (PVD) has p-H dependent aqueous solubility .Both the turbidity and SEM results showed that PVD formed a hydro gel upon increase in p-H from 4-7.4 [66]. T he release of a model drug chlorpheniremine maleate was fast right after the PVD solution was introduced in to a p-H 7.4 buffer solution, but became very slow after the PVD hydro gel was formed [66].The p-H dependent so-to- gel transformation AEA was used to develop nasal spray dosage forms for treating allergic rhinitis and sinusitis [67]. The in vivo rat study showed that the apparent disappearance rate constant of chlorpheniramine maleate decreased with increased in PVD concentration. The hydro gel formation on the mucous membrane in the rat nasal cavity was visually confirmed. If the time for sol-to-gel transition is shortened and the mucoadhesive property is added, the PVD system could be an ideal system for nasal delivery.

Hydro gels that are responsive to both temperature and p-H can be made by simply incorporating ionizable hydrophobic (inverse thermo sensitive) functional group to the same hydrogels.When a small amount of anionic monomer, such as acrylic acid, is incorporative in a thermo reversible polymer, the LCST of the hydro gel depends on the ionization of the pendant carboxylic group

i.e. the p-H of the medium. As the p-H of the medium is increased above the pKa of the carboxyl group of polyanions, LCST shift to higher temperatures due to the increased hydrophilicity and charge repulsion. Terpolymer hydrogels made of NIPAAm, vinyl terminated poly-dimethylsiloxane macromer and acrylic acids were used for the delivery of indomethacin and amylase [36, 68]. Other terpolymer hydro gels containing NIPAAm, acrylic acid and 2-hydroxyethyl meth-acryl ate were prepared for the pulsatile delivery of streptokinase and heparin as a function of stepwise p-H and temperature changes [69, 70].p-H sensitive hydro gels have also been used in making biosensors and permeation switches [5].

3. Glucose -Sensitive Hydro gels

 Most challenging problems in controlled drug delivery area is the development of self- regulated (modulated) insulin delivery systems .Delivery of insulin is different from delivery of other drugs, since insulin has to be delivered in an exact amount at the exact time of need .Thus , self –regulated insulin delivery system require the glucose sensing ability and an automatic shut –off mechanism .Many hydro gels system have been developed for modulated insulin delivery , and all of them have a glucose sensor.

3.1. p-H- sensitive membrane systems

Glucose oxidase is probably the most widely used enzyme in glucose sensing. It oxidizes glucose to gluconic acid, resulting in a p-H change of environment .This make it possible to use different type of p-H sensitive hydro gels for modulated insulin delivery. For hydro gel membrane made of polycations, such as PDEAEM the lowering of p-H leads to hydro gel membrane swelling due to ionization of PDEAEM. When a membrane swells, it tends to release more drugs, including insulin, than the membrane in the less swollen state [73, 74]. If the hydro gel membranes are made of polyanions, self- regulated insulin release is controlled by different mechanism. Glucose sensitive hydraulic flow controller can be designed using a porous membrane system consisting of a porous filter grafted with polyanions, e.g. poly (meth acrylic acid co-butyl methacrylate), and immobilized glucose oxidase. The grafted polyanion chains are expanded at p-H 7 due to electrostatic repulsion among the charges on the polymer chains. When glucose oxidase converts glucose to gluconic acid, however, the chain collapse due to the protonation of the carboxyl group of the polymer. Thus, the pores are open for the diffusion of insulin [75]. In other formulation , insulin can be loaded inside a hydro gel matrix which can be collapsed as a result of lowering of p-H.In this case ,insulin release is enhanced due to the 'squeezing' action of the collapsing hydrogel[76].In a system where a glucose oxidase containing hydrogel covers a p-H sensitive erodible polymer that contains insulin . The polymer erosion, and thus insulin release, is controlled by the lowering of the local p-H [77].

3.2. Con A-immobilized systems

Concanavalin A (ConA) has also been frequently used in modulated insulin delivery. Con A is a glucose-binding protein obtained from the jack been plant, Canavalia ensiformis. In this type of systems, insulin molecules are attached to a support or carrier through specific interaction which can be interrupted by glucose itself. This generally requires a introduction of functional groups on to insulin molecules. In one approach, insulin was chemically modified to introduced glucose, which themselves binds especially to Con A[78]. The glycosylated insulin Con-A systems exploits the complementary and competitive binding behavior of Con –A with glucose and gylcosylated insulin. The free glucose molecule compete with glucose -insulin conjugates bound with Con A and thus , the glycosylated insulin is desorbed from the Con A host in the presence of free glucose. The desorbed glucose-insulin conjugates are released within the surrounding tissue, where study have shown that they are bioactive .Various glcosylated insulin having different binding affinities to Con A have been synthesized in an effort to manipulate the displacement of immobilized insulin from Con A at different glucose levels[79-84].

3.3. Sol-gel phase reversible hydrogel systems

Htdrogels can be made to undergo sol-gel phase transformation depending on the glucose concentration in the environment. Reversible sol-gel phase transformation require glucose- responsive crosslinking.A highly specific interaction between glucose and Con A was used to form cross links between glucose-containing polymer chains .Because of the non covalent interaction between glucose and Con A, the formed cross links are reversible as shown in Fig. 6[85-89].As the external glucose molecules diffuse in to the hydrogels,individual free glucose molecules can compete with the polymer attached glucose molecules and exchange with them . The concentrations of Con A and glucose- containing polymers can be adjusted to make hydro gels that that respond (i.e. undergo gel-to sol transformation)at specific free glucose concentration .It has been shown that diffusion of insulin through the solution (Sol) phase is an order of magnitude faster than that through the hydrogel(gel) phase, and that insulin release can be controlled as a function of the glucose concentration in the environment. Other similar systems utilized poly (glucosyloxymethacrylate)-Con –A complexes [90-91] and polysaccharide (e.g. polysucrose, dextran, glycogen)-Con A gel membranes [92-94].
Glucose- sensitive phase reversible hydro gels can also be prepared by using Con A .Polymers having phenylboronic groups (e.g. poly [3-(acrylamido) phenylboronic acid] and its copolymers) and polyol polymers (e.g. PVA) form a gel through complex formation between the pendant phenyl borate and hydroxyl groups, as shown in Fig.7[95-97]
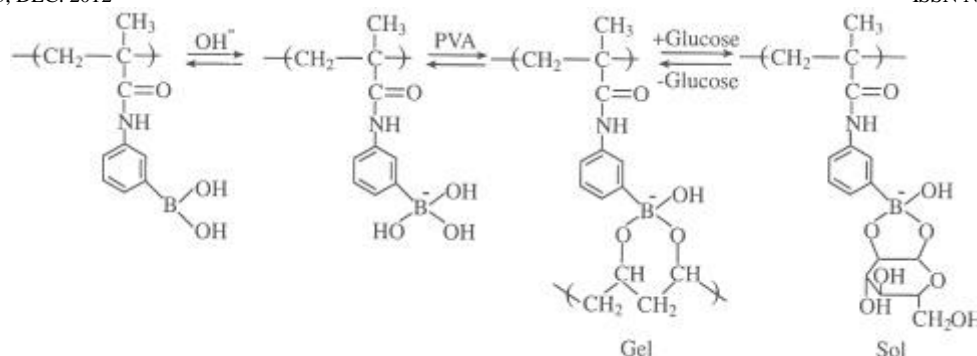
Fig. 7. Sol–gel phase-transition of a phenyl borate polymer. At alkaline pH, phenyl borate polymer interacts with poly (vinyl alcohol) (PVA) to form a gel. Glucose replaces PVA to induce a transition from the gel to the sol phase.

Glucose, having pendant hydroxyl group, compete with polyol polymers for the borate crosslinkages.Since glucose is nonfunctional, it cannot function as a cross linking agent as polyol polymer does. Thus as the glucose concentration increase s the cross linking density of the gel decreases and the gel swells /erodes to released more insulin .With higher glucose concentration, the gel becomes a sol. The glucose exchange reaction is reversible and borate –polyol crosslinlinking is reformed at a lower glucose concentrations .Instead of long chain polyol polymers ,shorter molecules,diglucosylhexanediamine,can be used as a crosslinling agent, Since the phenylboronic acid   gel is sensitive to glucose only at alkaline condition (p-H 9), various copolymers containing phenylboronic acid were synthesized to provide glucose sensitivity at physiological p-H.The main problem of this system is the low specificity of PBA-containing polymers to glucose.

Pharmaceutical applications of hydrogels

To provide sustained or controlled drug delivery into systems, the hydro gels are designed, modulated and characterized for the expected in –vivo results. These hydrogelshave gained existence in drug delivery through parenteral, ocular, rectal,, vaginal,dermal and nasal routes.

➢ Wound healing
➢ Colon specific drug delivery
➢ Cosmetology
➢ Topical drug delivery
➢ Ocular drug delivery
➢ Industrial applicability
➢ Modified dosage forms
➢ Tissue engineering
➢ Protein drug delivery

A. Applications of hydrogels in drug delivery
Hydro gels have been used for the development of controlled delivery systems for a long time. When the drug bearing hydro gel comes in contact with aqueous medium, water penetrates into the system and dissolves the drug. Diffusion is the main phenomena by which the dissolved drug diffuses out of the delivery systems to the surrounding aqueous medium. Diffusion is defined as the movement of the individual molecules from the region of high solute concentration to a region of low concentration when the systems are separated by a polymeric membrane. This phenomenon of diffusion is mainly attributed to the Brownian motion. The delivery systems employing hydrogels for controlled release can be categorized into reservoir and matrix devices. As mentioned earlier, hydrogels are 3-dimensionally cross-linked polymer networks and hence act as a permeable matrix/membrane for the drug thereby governing the release rate of the drug. The diffusion of the drug through the hydrogels may be affected by the property (viz. pH sensitivity, light sensitivity, pressure sensitivity) of the hydro gel depending on the chemistry of the hydrogels and has been used successfully to design delivery systems which may release drug at a suitable environment. The drug transport mechanisms can be determined by fitting the early time release data to the following empirical relationship [98-99]:

$$M_t/M_\infty = kt^n$$

Where M_t is amount of drug released at a given time t, M_∞ is amount of drug released at infinite time and k and n are the constants (characteristics of drug-polymer system). The diffusional exponent, n, is dependent on the geometry of the device as well as the physical mechanism of release Lowman reported that the diffusional exponent (n) can give relative information about

the release behavior of the bioactive agent from the hydro gel systems. He classified delivery systems based on the release profile of the bioactive agent from the system which include Fickian system (n=0.5), anomalous transport system (n=0.5-1), case II transport system (n=1) and super case II transport system (n>1) (Table 1) [100].

Delivery Systems	Mechanism of release
Fickian System	Fickian diffusion
Anomalous transport	Fickian diffusion and polymer relaxation
Case II transport	Polymer relaxation
Super case II transport	Plasticization at gel layer

Table 1. Release mechanism from hydro gel based delivery systems [41]

    a.   Reservoir system:

In reservoir drug delivery system, a drug-enriched core (often termed as reservoir) is encapsulated within a uniform polymeric membrane of hydro gel which allows the diffusion of drug through it (Figure 11) [101-104]. As the system comes in contact with water, water diffuses into the system and dissolves the drug and provides a concentration equivalent to the saturation solubility of the drug (Cs). The drug diffuses through the membrane to the external environment and the concentration falls below Cs.The solid drug present in the core dissolves and restores the concentration back to Cs.Thus the release of the drug from a reservoir system remains constant and follows zero order kinetics so long solid drug is present in the core. Once the solid drug is exhausted, the release becomes concentration dependent following first order kinetics. These kinds of drug delivery systems are mainly used to deliver the active agent by oral, ocular, uterine, or transdermal routes.
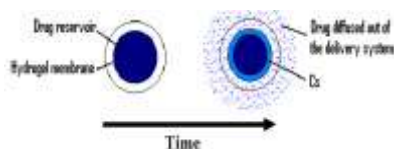

Fig8: drug delivery from typical reservoir device

    b.   Matrix system:

In matrix type delivery system, the active agent is homogenously dispersed as a solid into a hydro gel matrix (Figure 12). The release of drug from the matrix depends on the properties of matrix. When the matrix is placed into the aqueous medium, water starts diffusing into the matrix thereby hydrating the same. The hydration of the matrix starts at the surface and continues towards the center of the core. The release of drug is dependent on the diffusion of water into the matrix followed by the dissolution of the drug and finally the diffusion of the dissolved drug from the matrix. Generally, inert polymer matrices are considered to prepare this kind of delivery systems. Of late bio-degradable polymers have also been used to design such delivery systems [105]. Polymer-drug interaction plays an important role in the release behavior of the drug. Hence, polymers interacting with drugs could be tried to modulate the release profile of the drug. The thickness of the hydrated matrix is considered as the diffusional path length of the drug. If we consider the polymer matrix to be inert and the drug release is diffusion-controlled, then the release rate of the drug could be described by the Higuchi equation [106], which relates
 Drug release with the square root of time:

$$Q = 2ADCsT$$

Where Q is the amount of drug released at time t, A is the total concentration of drug in the matrix, D is the diffusion coefficient and Cs is the saturation solubility of the drug in the mini-matrix.
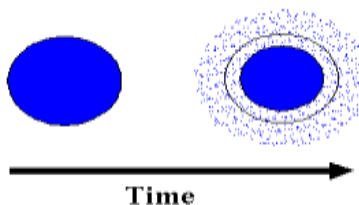

Fig9: Drug delivery from a typical matrix drug delivery system

If the drug delivery system is a true swelling-controlled system, then the diffusional exponent, n, assumes a value of 1 and results in zero-order release kinetics (Case II transport). However, if the drug release occurs due to a combination of macromolecular polymer chain relaxation of the matrix and Fickian diffusion, then the diffusional exponent has a value between 0.5 and 1 and results in anomalous or non-Fickian transport [107].

The chemically controlled release systems can be classified into (a) erodible systems and (b) pendant chain systems. In the erodible systems drug release mainly occur due to the degradation and/or dissolution of the matrix, which exposes the drug to the release media. While in the pendant chain systems, the drug is covalently bonded to the polymer chains of the matrix. The drug is released due to the degradation of these linkages in the physiological environment.

Hydro gels may change their equilibrium water uptake due to the change in the environment, viz. temperature, pH, ionic strength and temperature, of the release media [102, 108]. These kinds of hydrogels can be used for the development of controlled delivery systems. Depending upon the design of the delivery system, the drug may be released either by diffusion while the matrix is in the swollen state or by squeezing during the syneresis process.

Researchers are working on new strategies to develop delivery systems which can deliver the drug in a controlled fashion. For the purpose, hydrogels offer them a wide variety of properties, viz. bio-adhesive and environment sensitive nature, to achieve the goal. Hydro gels have already been successfully used to develop oral, rectal, ocular, transdermal and implantable drug delivery Systems.
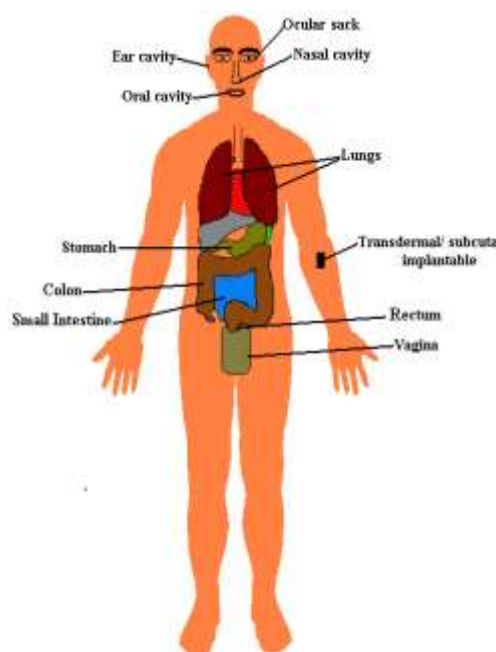

Figure 10 illustrates various sites that are available for the application of hydrogels for drug delivery.

Oral delivery of drug is cheap and allows maximum patient compliance. Through oral delivery system one can target mouth, stomach, small intestine and colon [109]. The bioadhesive property of the hydrogels could help to deliver drugs to the oral cavity or at the specific sites of gastro-intestinal tract (GIT). These hydrogels have been used to locally treat periodontal diseases, fungal and viral infections and oral cavity cancers. The main challenge in the local treatment of diseases of the oral cavity is to keep the delivery system at the site of infection for a long period of time. These delivery systems can also be used for the delivery of liposomes in addition to the topical treatment into the oral cavity. Orabase® (a sodium carboxymethyl cellulose, pectin and gelatin combination in a polyethylene-paraffin base), Carbopol 934P and neutralized poly

(MAA-co-methyl methacrylate (MMA)) have been successfully employed for the delivery of liposome into the oral cavity by Petelin and co-workers [109-110]. The drugs susceptible to high first pass metabolism can also be delivered systemically by sub-lingual/buccal route using this type of delivery system. Pitaressi and co-workers investigated the release behavior of amoxicillin in simulated buccal and gastric conditions [111]. The bioadhesive hydro gels increase the gastric residence time of the delivery system thereby ensuring the release of most of the drug at the delivery site and increase in the bioequivalence. Lectin has been used for long in such delivery systems.

The environment sensitive hydrogels have been effectively used to deliver drug at specific sites of the GIT. Enteric polymers like Eudragits have been used for long to deliver drugs at various sites of intestine. It has been stated earlier that the enteric polymers are generally used either to protect the acid-labile drugs (e.g. peptides and penicillin-G) from the harsh environment of the stomach or to avoid the contact of the gastric mucosa with the gastric-irritant drugs (e.g. ibuprofen, indomethacin), which might lead to gastric mucosa perforations. Akiyama and co-workers developed such an enteric system using poly (acrylic acid) product, which inhibited the hydrolytic activity of trypsin [112]. The oral delivery of insulin employing the use of enteric polymers is gaining importance [113]. A complex system of alginate-chitosan micro particles was developed by Hari et al. for the controlled release of bioactive peptides including insulin. In the study, the bioactive peptide dispersed in the cross linked alginate formed the core with a subsequent layer of chitosan over the core [114]. Thermal cross linking of the anionic hydrogel comprising of poly (vinyl alcohol) and poly (γ-glutamic acid) was found to be pH-sensitive in nature and was found to be compatible with the 3T3 fibroblast cell line. The drug diffusion in the hydrogel indicated its probable use for the oral delivery of the bioactive agent [115]. A controlled release system consisting of N-succinyl chitosan/alginate prepared by ionic gelation indicated a pH-dependent release profile of nifedipine [116]. Microspheres of interpenetrating networks of poly (meth acrylic acid) and poly (vinyl alcohol), which were cross linked with glutaraldehyde were able to deliver ibuprofen into the intestine [117]. Cationic hydrogels has the potential to deliver the drug in the stomach and not releasing the drug in the colon and intestinal environment. Such kind of delivery system was developed by Patel and co-workers for the 23 treatment of H. Pylori infection with an antibiotic [118]. Due to the presence of lower proteolytic activity in colon, it is becoming a hot spot to deliver peptide drugs. Of late, the rectal route of administration of drug is also gaining attention even though the patient acceptability is low. The main reason for this can be attributed to the rich blood supply to the region, which helps in increased bio-availability of the drug as the first-pass metabolism is partially bypassed. Rectal route of administration has been used for a long time for the local treatment of hemorrhoids but the main limitation of the delivery route was the migration of delivery device either towards the colon or out of the body. With the discovery of bioadhesive hydro gels and subsequent use of the same in the rectal administration have reduced the chances of delivery system migration and thereby increased the bioavailability of the administered drug [119]. Administration of aqueous drops in ocular cavity is the preferred way to administer drug in the ocular cavity. But most of the drug is removed from the ocular cavity due to tear drainage and blinking. In addition to this, the low permeability of the cornea worsens the situation. Though the use of suspension and ointments increase the ocular retention time, they produce a gritty feeling thereby reducing the patient compliance. The use of in-situ-gelling systems can increase the ocular retention time and ocular availability of the drug to a greater extent. The advantage of this kind of delivery system lies in the fact that it is liquid while dispensing and administering, but forms a drug depot after it is administered in the ocular cavity [109, 120].

Human skin can be easily accessed by a person and has got a large surface area which makes it a potential site for administering drugs, both locally and systemically. Systemic delivery of drug by this route of administration helps in bypassing the first–pass metabolism and delivery of the drug for prolonged period of time at a constant rate [109, 121]. In addition to the above advantages, the hydrogels provide a soothing effect on the skin as compared to occlusive/oily feeling caused by the application of ointments. The various drugs used in this type of delivery system include nitroglycerin and hydrocortisone [122]. Hydro gels have also been proposed as a delivery system to wound surface and in-situ gel forming hydrogels are preferred due to the relative ease of application and increased contact between the hydrogel and wound surface [123]. In spite of the above advantages, the main concern is the permeation of the drug through the keratinized 24

epidermis. Currently research is being carried out to increase the drug permeation through the keratinized layer using either electrical force (iontophoresis) or physical force of ultra-sound (sonophoresis). The drugs whose permeability can be increased by iontophoresis include luteinizing hormone, sodium nonivamide acetate, nicotine and enoxacin while the permeability of insulin and vasopressin can be increased using sonophoresis. The delivery of drug to the ear cavity is mainly carried out by the use of aqueous or oil drops. The main limitation in the use ear drops is the retention time of the drops in the cavity while the person is standing. The use of hydrogel for the delivery of drugs to the ear cavity can be done easily. Lee and co-workers were successful in delivering recombinant human insulin-like growth factor I (rhiGF-1) locally using gelatin hydrogel. The group found that by delivering the rhiGF-1 by this method can be useful in the treatment of noise-induced hearing loss [64]. Of late scientists are working on the local delivery of the drugs in the ear cavity using hydrogels

The local delivery of drugs to the lungs is generally achieved either by powder insufflators or by inhalational aerosols. The limitation of these types of delivery systems includes the immediate absorption of the drug from the site of application. The use of biodegradable hydrogels for the delivery of active agents may help in this regard. Tomoda and Makino studied the effect of lung surfactants on the release properties of rifampicin loaded in inhalable PLGA microspheres on the tubercle bacilli. They found that with the change in the surface properties of the PLGA microspheres there is a change in the uptake efficiency of the drug by the alveolar macrophages, the site where the tubercle bacilli resides in lungs [125]. Due to the presence of wide variation in properties, the hydrogels have been used in a wide variety of pharmaceutical applications. In addition to this, the hydrogels are generally biocompatible and can be tried as an implantable delivery system. Of late the implantable delivery system is being directed to biodegradable matrices, which will be eliminated from the physiological system after the drug supply is depleted. A semi-interpenetrating structure developed by Cho and co-workers comprising poly (ε-caprolactone) and PEG macromer terminated with acryl ate groups is one of the examples of the degradable matrices, which released clonazepam in a controlled manner for a period of 45 days [126].

B. Applications of hydrogels in wound healing

The use of hydrogels in the healing of wounds dates back to late seventies or early eighties. As mentioned earlier, hydrogel is a cross linked polymer matrix which has the ability to absorb and hold water in its network structure. Hydro gels act as a moist wound dressing material and have the ability to absorb and retain the wound exudates along with the foreign bodies, such as bacteria, within its network structure. In addition to this, hydrogels have been found to promote fibroblast proliferation by reducing the fluid loss from the wound surface and protect the wound from external noxae necessary for rapid wound healing. Hydro gels help in maintaining a micro-climate for biosynthetic reactions on the wound surface necessary for cellular activities [127]. Fibroblast proliferation is necessary for complete epithelialisation of the wound, which starts from the edge of the wound. Since hydrogels help to keep the wound moist, keratinocytes can migrate on the surface. Hydro gels may be transparent, depending on the nature of the polymers, and provide cushioning and cooling/ soothing effects to the wound surface. The main advantage of the transparent hydrogels includes monitoring of the wound healing without removing the wound dressing. The process of angiogenesis can be initiated by using semi-occlusive hydrogel dressings, which is initiated due to temporary hypoxia. Angiogenesis of the wound ensures the growth of granulation tissue by maintaining adequate supply of oxygen and nutrients to the wound surface. Hydrogel sheets are generally applied over the wound surface with backing of fabric or polymer film and are secured at the wound surface with adhesives or with bandages [128]

C. Applications of hydrogels in tissue engineering

Tissue engineering (TE) is a multidisciplinary approach and involves the expertise of materials science, medical science and biological science for the development of biological substitutes (tissue/ organ). It is emerging as an important field in regenerative medicine. It has got three basic components namely, cells/tissues, scaffolds and implantation and/or grafting. The principles of TE have been used extensively to restore the function of a traumatized/malfunctioning tissues or organs [10, 129]. In practice, the patient's cells are generally combined with a scaffold for generating new tissue. A scaffold can be made up of either ceramic or polymer, which can be either permanent or resorbable. The pore size of the scaffolds should be >80 μm [130]. This is necessary for the cell migration into the core of the 26 scaffolds, angiogenesis, and supply of nutrients to the cells and to take away the metabolic products away from the cells. The scaffolds made up of polymers are generally hydrogels. Every year thousands of people are victims of tissue loss and organ failure caused either due to disease or trauma. Also, there is a shortage of organ donors because of the religious beliefs and/or medical complications. Keeping the above facts in mind, TE can be a useful tool to replace the damaged/malfunctioning organs or tissues. Recently the use of resorbable hydro gels in TE has gained much importance because (a) it is easy to process the polymers; (b) the properties of the hydrogels can be tailored very easily; and (c) resorbable polymers like polylactic acid (PLA), polyglycolic acid (PGA), and their co-polymers (PLA-co-PGA; PLGA) are being used for biomedical application since long time. Sterilization of the hydrogels is very tricky, which may alter the characteristics of the scaffold. Hence, due consideration on the sterilization method should be given before selecting a particular sterilization method [10].

Examples of various tissue engineering employing various hydrogels have been provided below:

Figure 14.

Collagen-coated tissue culture inserts are used for growing three- dimensional corneal implant, tracheal gland cells etc [131].

Poly (lactic-co-glycolic acid) (PLGA) polymer foams are seeded with preadipocytes for the epithelial cell culture of the breast [131].
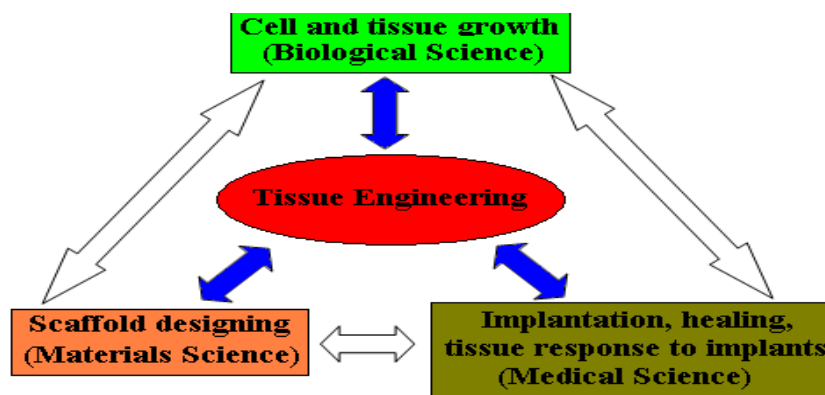

Fig11: Schematic diagram showing multidisciplinary approach of tissue engineering

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 Porous scaffolding (e.g. filter, swatch of nylon, transwell, biodegradable micro carrier) coated with fibrillar collagen, ideally type III collagen mixed with fibronectin or with Matrigel are used for the culture of the normal mature liver cells (polyploidy liver cells) [131].

D. Application of hydrogels for gene delivery

Gene delivery is defined as the incorporation of foreign DNA particles into the host cells and can be mediated by viral and non-viral methods. The delivery of gene into the host cells by utilizing a virus uses the capability of a virus to incorporate its DNA into the host cells. For the purpose retroviruses and adenoviruses have been used. These viral vectors are used as they can provide efficient transduction and high gene expression. At the same time, the use of viral vectors is quite limited as they can produce immunogenic reactions or mutagenesis of transfected cells. Hence, scientists are tuning their interest towards the available non-viral techniques, which produces less complexity. The non-viral techniques include the use of a gene gun, electroporation and sonication. Of late researchers have started the use of polymers, viz. poly-L-lysine (PLL), polyamidoamine dendrimer (PAMAM), polyethylenimmine (PEI), PGA, PLA and PLGA, for gene delivery [132]. Though PAMAM and PEI can provide high transfection efficiency, their use is limited due to their poor degradability. This is why the use of biodegradable polymers, viz. PLA, PLGA and PGA, has gained importance. The use of PEG-PLGA-PEG hydrogel for the delivery of plasmid-beta 1 gene increased the wound healing process in diabetic mouse model [133]. Meilander- Lin and co-workers reported similar results with agarose hydrogels. They concluded that agarose gels can be useful in the wound-healing and TE applications [134]. Mageed and co-workers reported the use of recombinant silk-elastin like polymer hydrogels (SELP) for the delivery of pRL-CMV for the treatment of human breast cancers. Their results suggested an increase in the transfect ion efficiency when SELP hydrogels were used [135]. A recent study describes encapsulation of C2C12 myoblasts in a biocompatible permselective hydrogel such as alginate –poly-L–lysine- alginate (APA) to protect the cell from host immune response; while allowing diffusion of gene products. Inclusion of basic fibroblasts growth factor (BFGF), insulin growth factor II (IGF- II) and collagen within the Induced by B16-Fo/neu tumor cells in mice, the APA microcapsules had an 80% reduction in tumor volume at day 21 [136].

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