HYDROGELS: A REVIEW

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ABSTRACT

Polymers play a vital role in pharmaceutical development. Efforts have been continuously made to search a polymer that act in a controlled and desired way. Hydrogel development has solved many such issues. This article deals with the fundamental and some recent advances made in the fabrication and design criteria of hydrogel based drug delivery.

Keywords: Hydrogels, Tissue engineering, Reservoir, Matrix, Polymers.

INTRODUCTION

With the establishment of the first synthetic Hydrogels by Wichterle and Lim in 1954[1], the hydrogel technologies may be applied to food additives[2], pharmaceuticals[3], biomedical implants[4] tissue engineering and regenerative medicines[5], diagnostics[6], cellular immobility[7], separation of biomolecules or cells[8] and barrier materials to regulate biological adhesions[9], Biosensor and BioMEMs devices and drug carriers[10]. Additionally the ever growing spectrum of functional monomers and macromeres widen its applicability.

Hydrogels are hydrophilic polymeric network of three dimensional cross linked structures that absorb substantial amount of water[5]. Cross linking facilitates insolubility in water because of ionic interaction and hydrogen bonding[11]. It also provides required mechanical strength and physical integrity to the Hydrogels[12].

Thus, hydrogels can imbibe water nearly 10-20 times its molecular weight and hence become swollen[13]. Some examples of Hydrogels include contact lenses[14], wound dressing[15,16], superabsorbents[17-19].

BENEFITS

- Biocompatible
- Can be injected
- Easy to modify
- Timed release of growth factors and other nutrients to ensure proper tissue growth
- Entrapment of microbial cells within polyurethane hydrogel beads with the advantage of low toxicity
- Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature or the concentration of metabolite and release their load as result of such a change.
- Natural hydrogel materials are being investigated for tissue engineering, which include agarose, methylcellulose, hylaronan, and other naturally derived polymers[12].

LIMITATIONS

- High cost.
- Low mechanical strength
- Difficult to load
- Difficult to sterilize
- Nonadherent
- In contact lenses - lens deposition, hypoxia, dehydration and red eye reactions[20-24]

CLASSIFICATION

1. On the basis of the nature of the cross linked junctions[20]

a. Chemically crosslinked networks having permanent junctions.

b. Physical networks have transient junctions arising from polymer chain entanglements or physical interactions viz. ionic interactions, hydrogen bonds or hydrophobic interactions.

2. Table – 1 On the basis of origin[21].

Characteristics	Natural origin	Synthetic polymers
Preparation	By using natural polymer	By chemical polymerization
Advantages	-Biocompatible -Biodegradable -Supports cellular activities	-Inherent bioactive properties absent
Disadvantages	-Does not possess sufficient mechanical properties -May contain pathogen -Evoke immune and inflammatory responses	____
Examples	-Proteins like collagen and gelatin -Polysaccharides like alginate and agarose	-Acrylic acid -Hydroxyethyl - methacrylate (HEMA) -Vinyl acetate -Methacrylic acid(MAA)

Hydrogel – Network design and structure

Mathematical understanding of various properties viz. interaction parameters, material properties, kinetic profile and transport mechanisms aids in designing the network of complex hydrogel systems by identifying the determining parameters which decides the rate and extent of drug release. Additionally mathematical modeling leads to device design by decreasing the number of experiments performed by researches for understanding the release mechanisms[22].

Table – 2 Hydrogel structure[12].

Structure	Range	Release Mechanism
Macroporous	0.1-10µm	Depends on drug diffusion coefficient
Microporous	100-1000µm	Molecular diffusion and convection
Non-porous	10-100µm	Diffusion

The deciding parameters that describe the nanostructure of cross linked hydrogel networks are

1. Polymer volume fraction in swollen state, v_f.
2. Number average molecular weight between crosslinks, $\overline{M_n}$
3. Network mesh size, ξ[21].

The polymer volume fraction in the swollen state (v_f) is that amount of liquid which can be imbibed in hydrogels and is expressed as the ratio of the polymer volume (v_p) to the swollen gel volume (v_g). It is also the reciprocal of the volumetric swollen ratio (Q) which relates to the densities of the solvent (ρ_s) and polymer (ρ_p) and mass swollen ratio (Q_m) as given by equation (1)

Equation 1 $$v_f = \frac{v_p}{v_g} = Q^{-1} = \frac{1/\rho_p}{\frac{Q_m}{\rho_s} + \frac{1}{\rho_p}}$$

Number average molecular weight between two adjacent crosslinks ($\overline{M_n}$) gives the degree of cross linking of the hydrogel networks. M_n is expressed by Flory- Rehner [24] given in Eq. (2)

Equation 2 $$\frac{1}{\overline{M_n}} = \frac{2}{\overline{M_a}} - \frac{\left(\frac{v}{V_1}\right)\left[\ln(1-v_{2,s}) + \chi_{12} v_{2,s}^2\right]}{1/3 \, v_{2,s} - \frac{v_{2,s}}{2}}$$

$\overline{M_a}$= average molecular weight of linear polymer chain

$\overline{v}$= specific volume of the polymer

$V_{1=}$=Molar volume of water

χ_{12}= polymer-water interaction parameter

Peppas and other have given more complex versions of the Flory- Rehner equation to describe the swelling behavior of ionic gels or gels crosslinked during polymerization .At highly swelling conditions for neutral gels (Q > 10), equation (2) can be simplified as given below:[25]

Equation 3 $$Q = \left[\frac{\bar{v}^{(1/2 - 2\chi_{12})} \overline{Mn}}{V_1}\right] = \beta(\overline{M_n})^{3/5}$$

Network mesh size can be described as[26]

Equation 4 $$\xi = v_{2,s}^{-\frac{1}{3}} (\overline{r_o^2})^{1/2} = Q^{1/3} (\overline{r_o^2})^{1/2}$$

Q = Volumetric swollen ratio

$(\overline{r_o^2})^{1/2}$ = root mean squared end to end distance of network chains between two adjacent cross links in the unperturbed state. It can be calculated by the following relationship[27]

Equation 5 $$(\overline{r_o^2})^{1/2} = l(C_n N)^{1/2} = l\left(C_n \frac{2\overline{M_n}}{M_r}\right)^{1/2}$$

C_n= Flory characteristics ratio

l = bond length of the polymer backbone

N = number of bonds between adjacent cross links

M_r= Molecular weight of the repeating units of the composed polymer

Eqs (4) and (5) together can help in determining the mesh size of a hydrogel network and comparing it with the hydrodynamic radii of the molecules to be delivered. Theoretically within a hydrogel matrix no solute diffusion is possible when mesh size approaches the size of the solute[27].

Factors affecting mesh size are

- Degree of cross linking of the gel
- Chemical structure of the constituting monomers
- External stimuli viz. temperature, P

Mesh size dictates the physical properties of the hydrogels (mechanical strength, degradability and diffusivity of the releasing molecules)[25, 28].

Preparation of hydrogels

1. Use of crosslinkers

- Copolymerization of monomers using multifunctional co-monomer, which acts as cross linking agent, chemical initiator initiates the polymerization reaction which can be carried out in bulk, solution or suspension.
- Cross linking of linear polymers by irradiation or by chemical compounds. Monomers used here contain an ionizable group that can be ionized or can undergo a substitution reaction after the polymerization is completed.

  Thus, the hydrogels synthesized may contain weakly acidic groups like carboxylic acids or weakly basic

groups like substituted amines or a strong acidic and basic group like sulfonic acid and quaternary ammonium compounds.

Cross linkers incorporated are glutaraldehyde, calcium chloride and oxidized konjac glucomannan (DAK). They impart sufficient mechanical strength to the polymers and thus prevent burst release of the medicaments[29].

2. Isostatic ultra high pressure(IUHP)

Suspension of natural biopolymers (eg.-starch) are subjected to ultra high pressure of 300-700 MPa for 5 or 20 minutes in a chamber which brings about changes in the morphology of the polymer (i.e. gelatinization of starch molecules occur).Temperature in the chamber varies from 40 to 52^{O}C[30].

3. Use of nucleophilic substitution reaction

A pH and temperature sensitive hydrogel viz. hydrogel of N-2-dimethylamino ethyl-methacrylamide (DMAEMA) has been prepared using nucleophilic substitution reaction between methacyloyl chloride and 2-dimethylamino ethylamine[31].

4. Use of gelling agent

Gelling agents like glycophosphate1-2propanediol, glycerol, trehalose, mannitol etc have been used in the preparation of hydrogels. However, presence of negative charged moieties and turbidity are the problems associated with the method[32].

5. Use of irradiation and freeze thawing

Irradiation method is suitable as well as convenient but the processing is costly along with the poor mechanical strength of the product .Freeze thawing method imparts sufficient mechanical strength and stability to the hydrogels except that they are opaque in appearance with little swelling capacity. However, hydrogels prepared from microwave irradiation are more porous than conventional methods[33].

6. Synthesis of hydrogel in industry

Formulation of monomer along with initiators and additives lead to polymerization which forms the gel. The gel is dried, sieved and mixed with other additives and post treatment is done if needed. The final formulation is packed and dispatched.

DESIGN CRITERIA FOR HYDROGELS IN DRUG DELIVERY FORMULATIONS

Nature of material and network fabrication governs the rate and mode of drug release from hydrogel matrices. There are various design criteria for drug that must be evaluated before hydrogel fabrication and drug loading. These criteria play a vital role in Mathematical modeling of drug release. Design criteria for hydrogels in drug delivery formulations are shown in the table - 3.

Table 3: Design criteria for hydrogels

Design Criteria	Design Variables
Polymer Transport properties Molecule diffusion	Molecular weight of polymer Molecular weight and size of protein Cross linking density Hydrogel degradation rate
Physical properties Gelling mechanisms/conditions Structural properties Biodegradability	Polymer/ cross-linker /initiator concentrations Temperature, P^{H}, ionic strength Molecular properties of polymer Mechanical strength
Biological properties Biocompatibility	Cytotoxicity of the hydrogel Capsule formation

Hydrogel formulation even designed with proper physical and transport properties, may still fail to show therapeutic effect when implanted in vivo due to a localized inflammatory response. Fibrous capsule formed around the delivery device gives rise to additional diffusion barriers that may limit drug release rates while increased proteolytic activity may increase rates of matrix and drug degradation. Thus, proper material selection, fabrication process and surface texture are important parameters in designing biocompatible hydrogel formulations for controlled release.

Drug incorporation into hydrogel device can be achieved by one of the following methods.

1. Post Loading

Table 4: Drug absorption occurs after hydrogel networks are formed.

Hydrogels	Drug Uptake	Release Mechanism
Inert hydrogels	Diffusion	Diffusion and/or gel swelling
Hydrogel containing drug –binding ligands	—	Drug-polymer interaction and diffusion

2. In-situ Loading

Drug or drug polymer conjugates are mixed with polymer precursor solution and hydrogel network formation and drug encapsulation are achieved simultaneously. Here release of drugs occurs through diffusion, hydrogel swelling, reversible drug-polymer interaction, degradation of labile covalent bonds.

DRUG RELEASE MECHANISMS FROM HYDROGEL DEVICES

Hydrogels imbibe more water than 90% of their weight due to hydrophilicity, thus differing in their release mechanisms from hydrophobic polymers. Various models have been developed to predict the release of an active agent from a hydrogel device as a function of time. These models are based on the rate limiting step for controlled release and are divided into three categories viz.

- Diffusion controlled
- Swelling controlled
- Chemically controlled

DIFFUSION CONTROLLED

It is most widely applicable mechanism relating to drug release. Fick's law of diffusion is commonly used in modeling this release[28].

Table 5: Drug Diffusion Coefficients

HYDROGELS	DRUG DIFFUSION COEFFICIENTS
Porous Hydrogels- pore size >>> molecular dimensions of drug.	Related to porosity
Non- porous Hydrogels Porous gels with pore sizes comparable to the drug molecular size[34,35]	Decreases due to stearic hindrance from polymer chains with in cross linked networks.

Types of diffusion - controlled hydrogel delivery systems are as follows

- Reservoir system
- Matrix system

For reservoir system, drug depot is surrounded by a polymeric hydrogel membrane. Fick's first law describes drug release through the membrane.

$$J_A = -D\frac{dC_A}{dx}$$

Where

J_A = Flux of the drug/ drug corresponding to the mass average velocity of the system

D = Drug diffusion coefficient (assumed constant)

C_A = Drug concentration

For matrix system (drug uniformly dispersed throughout the matrix), unsteady state drug diffusion in a one dimensional slap- shaped matrix may be described using Fick's second law of diffusion

$$\frac{dC_A}{dt} = D\frac{d^2C_A}{dx^2}$$

Drug diffusion coefficient is assumed to be constant. Other assumptions are sink condition and a thin planar geometry where the release through the edges is neglected. Drug diffusion coefficient is a function of drug concentration except in very dilute solutions. Diffusivities of encapsulated molecules depend on the degree of swelling and cross linking density of the gels for hydrogel devices. Diffusion coefficient used to describe drug release is sensitive to environmental changes or degradation of the polymer network and varies over the time scale of release[22, 28].

SWELLING CONTROLLED

It occurs when diffusion of drug is faster than hydrogel swelling. In this condition the modeling of drug involves moving boundary, where molecules are released at the interface of the rubbery and glassy phases of swollen hydrogels. Transition occurs from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules rapidly diffuse. Release of small molecule drugs from HPMC hydrogel tablets are based on this mechanism. For example, Methocel matrices (a combination of methylcellulose and HPMC) from Dow chemical company prepare swelling controlled drug delivery formulations[36, 37].

Drug diffusion time and polymer chain relaxation time are two key parameters determining drug delivery from polymeric devices. In diffusion controlled delivery systems, the time scale of drug diffusion, t (where $t = {\delta(t)^2}/{D}$ and $\delta(t)$ is the time dependent thickness of the swollen phase) is the rate limiting step while in swelling- controlled delivery systems the time scale for polymer relaxation (λ) is the rate limiting step. The Deborah number (De) is used to compare these two time scales.

$$D_e = \frac{\lambda}{t} = \frac{\lambda D}{\delta(t)^2}$$

In diffusion- controlled delivery system (De $\ll$ 1), Fickian diffusion dominates the molecule release process while in swelling- controlled delivery systems (De $\gg$ 1), the rate of molecule release depend on the swelling rate of polymer networks.

Equation showing relationship between drug diffusion and polymer relaxation are –

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}$$

The two terms on the right side represent the diffusion and polymer relaxation contribution to the release profile respectively. Korsmeyer and Peppas introduced a dimensionless swelling interface number Sw, to correlate the moving boundary phenomena to hydrogel swelling[38 – 40].

$$S_W = \frac{V\delta(t)}{D}$$

V = Velocity of the hydrogel swelling front

D = Drug diffusion coefficient in the swollen phase

CHEMICALLY CONTROLLED

It characterizes molecule release based on reactions occurring within a delivery matrix. Most commonly occuring reactions are-

- Cleavage of polymer chains via hydrolytic or enzymatic degradation.
- Reversible or irreversible reactions occurring between the polymer network and releasable drug.

It can be categorized on the basis of reactions occurring during drug release[22, 28, 41].

1. Purely–kinetic – controlled release

Polymer degradation (bond cleavage) is the rate determining step while diffusion contributes almost negligible to the drug release[42-44]. It is of two types viz.

- Pendant chain(prodrugs)
- Surface eroding systems

In pendent chain systems, drugs are covalently linked to the hydrogel network device through cleavable spacers and drug release is controlled by the rate with which spacer bond cleavage occurs[45, 46]. In specific applications where a more targeted delivery approach is desired, it is advantageous to design enzymatically cleavable spacer bonds. In surface eroding systems, drug release is mediated by the rate of surface erosion of the polymer matrix. In hydrophobic polymer networks, surface erosion occurs when the rate of water transport into the polymer is much slower than the rate of bond hydrolysis. Nevertheless due to the inherently high water content of hydrogels, surface erosion occurs slowly in enzymatic degradation systems where the transport of enzyme into the gel is slower than the rate of enzymatic degradation[47] .Models focusing on the release mechanisms are based on hydrolytic degrading polymers [48].

2. Reaction – diffusion-controlled release

Reaction (polymer degradation, protein – drug interaction) and diffusion both contribute to the drug release.

CHALLENGES OF HYDROGEL DEVICES

There are still many challenges associated with the modeling of drug delivery phenomena and release profiles related to complex hydrogel systems. Fundamental understanding of drug transport processes helps in developing a suitable mathematical model. Mass transport governs the translocation of drug from the interior to the surrounding environment of hydrogel devices. Factors affecting mass transport of encapsulated molecules are as follows.

- ✓ Network cross linking density
- ✓ Extent of swelling
- ✓ Gel degradation
- ✓ Size and charge of the encapsulated molecules
- ✓ Physical interactions between the encapsulated molecules and the polymer matrix
- ✓ Drug – ligand binding present within hydrogel devices

a. Dynamic Hydrogel Delivery Devices

Degradable hydrogels – Rate of matrix swelling and degradation mechanism govern the diffusion of encapsulated molecules. With the help of appropriate design of polymer chemistries and network structure, degradable hydrogel matrices are enabled with proper degradation profiles. Mathematical modeling has enriched us with sufficient information to facilitate the design of degradable hydrogels and identify critical parameters dictating molecule release profiles.

Stimuli sensitive hydrogels

This advanced hydrogel system detects changes in complex in vivo environments and utilize such triggers to modify drug release rates. As the swelling or deswelling of such hydrogels is mediated by external stimuli, it is critical to model the dynamic swelling response in order to predict solute release [49-51].

b. Composite Hydrogel Delivery Devices

It has been exhausted for delivering multiple protein therapeutics for tissue engineering applications where temporal and spatial control over drug delivery is desirable. It is of two types which are listed below

- Multilayer
- Multiphase

Examples of in-vivo simultaneous delivery of multiple proteins is – angiogenesis, bone remodeling and nerve regeneration.

Multilayer hydrogel devices

The system comprises of a basal polymer layer, followed by lamination of subsequent layer. Different proteins are encapsulated into each layer while fabrication and tunable multiple protein release or unique single-protein release approach are made possible by independently adjusting the cross-linking density of each layer. Various models have been developed for predicting drug release from multilayer hydrogel devices[52]. It employs Fick's second law of diffusion to predict drug release profiles[53].

Sohier et al. have developed a porous scaffold bearing three hydrogel layers with differing porosities to simultaneously deliver lysozyme and myoglobin. These devices can also be used to reduce the problem of burst release. A desirable zero-order release profile was achieved through non-uniform initial drug loading in multi-laminated hydrogels and the results were verified by a diffusion model[54-56].

Multi-phase hydrogel delivery devices

Prefabricated microspheres possessing one or more proteins are uniformly embedded within a hydrogel having a second protein[57-59]. The release of the protein encapsulated in microsphere is delayed due to the combined diffusional resistances of the microsphere polymer and surrounding gel. Richardson and colleagues have prepared a composite polymeric scaffold containing PLGA microspheres embedded in porous PLGA matrices with different intrinsic viscosities to simultaneously deliver VEGF and PDGF. It was the first heterogeneous polymeric system for delivering two proteins with distinct release profiles which can be adjusted by varying the protein loaded in each polymer phase[60].

c) Micro/ nanoscaled hydrogel devices

Mathematical approaches proposed to predict molecule release from hydrogel microspheres are of two types viz.

- Macroscopic diffusion models
- Microscopic Monte carlo simulations

For macroscopic modeling, models used are based on Fick's second law of diffusion. Particle size, geometry and surface area are important parameters in this type of modeling. Further molecule diffusivities must be considered and accurately determined[60].

Monte carlo simulation is useful for describing the transport behaviour of molecules with in degradable microsphere system and has been widely applied to hydrophobic polymer networks viz. PLGA[61,62]. Vlugt wensink et al. utilized this model to predict protein release from degradable dextran microspheres. However, the accuracy of the model is protein specific[63]. One of the disadvantages of this technique is burst release due to the high surface to volume ratio of this particulate systems which causes "dose dumping" effect and is potentially harmful to patients in clinical applications.

IN- SITU HYDROGELS

Recent advancement in hydrogel engineering has led to the development of *in-situ* hydrogel formation for drug delivery applications. The *in-situ* sol-gel transition enables the surgery or implantation procedure to be performed in a minimally invasive manner. Various physical and/or chemical cross linking mechanisms have been used for in-situ network formation. Physical phenomenon involved in the formation of in-situ hydrogels are as follows

- Hydrogen bonding
- Hydrophobic – hydrophobic interactions.
- Electrostatic interactions.

For example, sodium alginate hydrogels are formed physically by cross-linking due to addition of calcium ions but are unstable and disintegrate rapidly and unpredictably[64].

Chemical cross linking mechanism – Covalent cross linking methods performed under physiological conditions produce relatively stable hydrogel networks with predictable degradation behavior. For example, photo polymerization of multi- vinyl macromers. It is a fast process and can be conducted at room temperature without organic solvents[65]. Photo polymerization of degradable hydrogels may be applied to protein and gene delivery[66, 67].

Van de Wetering et al. identified the modification of hGH by reactive thiol macromers in PEG-based hydrogel system prepared by Michael type addition reaction. Quick and Anseth identified that free radicals are responsible for incomplete DNA release when photo polymerization was used to fabricate DNA fabricated hydrogels[67-69].

Modeling drug release from *in-situ* hydrogels is often challenging. Reduced protein release can only be considered after identifying the sources of protein destabilization and quantifying the extent of fabrication. Such devices assume irregular geometries at the implant site which are difficult to predict prior to injection. This further enhances the difficulty to accurately represent the real system in a mathematical construct.

APPLICATION OF HYDROGELS

- **Wound Healing –** Modified polysaccharide found in cartilage is used in formation of hydrogels to treat cartilage defects. For example, the hydrogel of gelatin and polyvinyl alcohol (PVA) together with blood coagulants are formulated.
- **Soft Contact Lenses (**silicon hydrogels and polyacrylamides) – The first commercially available silicon hydrogels adopted two different approaches. First approach by Bausch and Lomb was a logical extension of its development of silicon monomers with enhanced compatibility in hydrogel forming monomers. The second by Ciba vision was the development of siloxy monomers containing hydrophilic polyethylene oxide segments and oxygen permeable polysiloxane units.
- **Industrial Applicability -** Hydrogels are used as absorbents for industrial effluents like methylene blue dye. Another example is adsorption of dioxins by hydrogel beads.
- **Tissue Engineering –** Micronized hydrogels are used to deliver macromolecules (phagosomes) into cytoplasm of antigen-presenting cells. This property is also utilized in cartilage repairing. Natural hydrogel materials used for tissue engineering include agarose, methylcellulose and other naturally derived products.
- **Drug Delivery in GI Tract –** Hydrogel deliver drugs to specific sites in the GIT. Drugs loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic actions cause liberation of drugs. They are designed to be highly swollen or degraded in the presence of micro flora.
- **Rectal Delivery –** Hydrogels showing bioadhesive properties are used for rectal drug delivery. Miyazaki et al. explored the xyloglucan gel with a thermal gelling property as matrices for drug delivery.
- **Ocular Delivery –** Chitoni et al. reported silicon rubber hydrogel composite ophthalmic inserts. Cohen et al. developed ***in-situ*** forming gelling system of alginate with high gluconic acid contents for the ophthalmic delivery of pilocarpine.
- **Transdermal Delivery –** Swollen hydrogels can be used as controlled release devices in the field of wound dressing. Hydrogel based formulations are being explored for transdermal iontophoresis to obtain

enhanced permeation of products viz. hormones and nicotine.

- **Subcutaneous Delivery –** Hydrogel formulations for subcutaneous delivery of anticancer drugs are being prepared viz. crosslinked PHEMA was applied to cytarabine (Ara-c). Implantable hydrogels are now leading towards the development of biodegradable systems which don't require surgical removal once the drug has been administered[5,6].
- **Novel Hydrogel For Controlled Drug Delivery –** HYPAN is the novel hydrogel having properties useful controlled drug delivery. Physical network of crystalline clusters distinguishes HYPAN hydrogels from others[15,16]**.**
- **Hydrogel For Gene Delivery –** Modification of hydrogel composition leads to effective targeting and delivery of nucleic acids to specific cells for gene therapy. Hydrogel versatility has potential application in the treatment of many genetic and/or acquired diseases and conditions[6].
- **Cosmetology –** Hydrogels when implanted into breast accentuate them for aesthetic reasons. These implants have silicon elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gel.
- **Tropical Drug Delivery –** Instead of conventional creams, hydrogel formulation are employed to deliver active components like Desonide, a synthetic corticosteroid used as an anti – inflammatory for better patient compliance.
- **Protein Drug Delivery –** Interleukins conventionally administered as injection are now given as hydrogels which show better compliance and form *in-situ* polymeric network and release proteins slowly.

CONCLUSION

Hydrogels have played a significant role in biomedical applications. Significant progress has been made in improving the properties of hydrogels used for drug delivery and expanding the range of drugs and kinetics which can be achieved using a hydrogel based delivery vehicle. Reduced release efficiency, burst effects, complex geometries and unknown correlation between *in vitro* and *in vivo* release complicates our understanding of these devices.

There is need for continued improvement in the delivery of not only hydrophobic molecules, but also the delivery of more sensitive molecules viz. proteins, antibodies or nucleic acids which gets deactivated by interactions with the hydrogel delivery vehicle. Solution of such problems would greatly expand the potential of hydrogel based drug delivery to successfully deliver the next generation drugs at the desired rate and location in the body.

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