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Review Article

# HYDROGELS: AN INTELLIGENT CARRIER FOR TARGETED DRUG DELIVERY

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***ABSTRACT***

*Targeted drug delivery is an advanced method of delivering drugs to the patients in such a targeted sequences that increases the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells) which in turn improves efficacy of treatment by reducing side effects of drug administration. Hydrogels are high-water content materials prepared from cross-linked polymers that are able to provide sustained, local delivery of a variety of therapeutic agents. Hydrogels are under investigation as a delivery system for bioactive molecules, because of their similar physical properties as that of living tissue, which is due to their high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids. Many hydrogel-based networks have been designed and fabricated to meet the needs of pharmaceutical and medical fields. This review encompasses the use of hydrogels as intelligent carriers for targeted drug delivery.*

**Keywords:** *Hydrogels, carrier, targeting, drug delivery*

## INTRODUCTION

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. The therapeutic response of a drug depends mainly upon the interaction of drug molecules with cell or cell membrane- related biological events at receptor sites in concentration dependent manner. To achieve this goal, the correct amount of drug has to be delivered to the site of action along with simultaneous control of the drug input rate. The limitations of conventional drug delivery can be circumvented by targeting the drug to the site of action in the required amount by employing various purpose-specific drug delivery systems.

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Targeted drug delivery system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body; therefore avoiding any damage to the healthy tissue via the drug [1].

Hydrogels have been used extensively in the development of the smart drug delivery systems. Hydrogels are three-dimensional, hydrophilic, polymeric networks that can swell in water and hold a large amount of water while maintaining the structure. Due to the contribution of these groups and domains in the network, the polymer is thus hydrated to different degrees (sometimes, more than 90%wt.), depending on the nature of the aqueous environment and polymer composition [2]. Hydrogels exhibit a thermodynamic compatibility with water which allows them to swell in aqueous media. There are numerous applications of

these hydrogels in particular in the medical and pharmaceutical sectors. Hydrogels resembles natural living tissue more than any other class of synthetic biomaterials. This is due to their high water contents and soft consistency which is similar to natural tissue. Furthermore, the high water content of the materials contributes to their biocompatibility. Hydrogels are also used as carriers that can interact with the mucosa lining in the gastrointestinal (GI) tract, colon, vagina, nose and other parts of the body due to their ability to prolong their residence time at the delivery location [3].

## CHARACTERIZATION OF HYDROGELS [3-9]

Generally hydrogels are characterized for their morphology, swelling property and elasticity. Morphology is indicative of their porous structure. Swelling determines the release mechanism of the drug from the swollen polymeric mass while elasticity affects the mechanical strength of the network and determines the stability of these drug carriers. Some of the important features for characterization of hydrogels are as follows:

### *Morphological characterization:*

Hydrogels are characterized for morphology which is analyzed by equipment like stereomicroscope. Also the texture of these biomaterials is analyzed by SEM to ensure that hydrogels, especially of starch, retain their granular structures.

### *X-ray diffraction:*

It is also used to understand whether the polymers retain their crystalline structure or they get deformed during the processing pressurization process.

### *In-vitro release study for drugs:*

Since hydrogels are the swollen polymeric networks, interior of which is occupied by drug molecules, therefore, release studies are carried out to understand the mechanism of release over a period of application.

### *FTIR (Fourier Transform Infrared Spectroscopy):*

FTIR (Fourier Transform Infrared Spectroscopy) is a useful technique for identifying chemical structure of a substance. It is based on the principle that the basic components of a substance, i.e. chemical bonds, usually can be excited and absorb infrared light at frequencies that are typical of the types of the chemical bonds. The resulting IR absorption spectrum represents a fingerprint of measured sample. This technique is widely used to investigate the structural arrangement in hydrogel by comparison with the starting materials. Any change in the morphology of hydrogels changes their IR absorption spectra due to stretching and O-H vibration. Formation of coil or helix which is indicative of cross linking is evident by appearance of bands near 1648 $cm^{-1}$.

### *Swelling behavior:*

A small change in environmental condition may trigger fast and reversible changes in hydrogel. The alteration in environmental parameters like pH, temperature, electric signal, presence of enzyme or other ionic species may lead to a change in physical texture of the hydrogel. The crosslinking ratio is one of the most important factors that affect the swelling of hydrogels. Crosslinking hinders the mobility of the polymer chain, hence lowering the swelling ratio. The chemical structure of the polymer may also affect the swelling ratio of the hydrogels. Hydrogels containing hydrophilic groups swell to a higher degree compared to those containing hydrophobic groups. When the hydrogels are allowed to immerse in aqueous medium or medium of specific pH to know the swellability of these polymeric networks, these polymers show increase in dimensions related to swelling. The amount of the aqueous medium incorporated in a hydrogel is determined gravimetrically and can be expressed by its swelling ratio.

Swelling = Ws-Wd/Wd

Where, Ws is the weight of hydrogel in swollen state and

Wd is the weight of hydrogel in dry state.

***Rheology:***

The rheological properties are very much dependant on the types of structure (i.e. association, entanglement, cross-links) present in the system. Hydrogels are evaluated for viscosity under constant temperature of usually 4°C by using Cone Plate type viscometer.

***Mechanical properties:***

The evaluation of mechanical property is essential in various biomedical applications viz. ligament and tendon repair, wound dressing material, matrix for drug delivery, tissue engineering and as cartilage replacement material. The mechanical properties of hydrogels should be such that it can maintain its physical texture during the delivery of therapeutic moieties for the predetermined period of time. By changing the degree of crosslinking the desired mechanical property of the hydrogel could be achieved. Copolymerization with co-monomer, may result into hydrogen bonding within the hydrogel which has also been utilized by many researchers to achieve desired mechanical properties. On the basis of Young modulus and Flory's theory, it is possible to determine the hydrogels crosslinking density.

***Biocompatible properties:***

It is important for the hydrogels to be biocompatible and nontoxic in order to make it applicable in biomedical field. Most polymers used for this purpose must pass cytotoxicity and in-vivo toxicity tests. Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. Cell culture methods, also known as cytotoxicity tests can be used to evaluate the toxicity of hydrogels. Three common assays to evaluate the toxicity of hydrogels include extract dilution, direct contact and agar diffusion. Most of the problems with toxicity associated with hydrogel carriers are the unreacted monomers, oligomers and initiators that leach out during application. Therefore, an understanding the toxicity of the various monomers used as the building blocks of the hydrogels is very important.

***Differential Scanning Calorimetry & Nuclear Magnetic Resonance:***

The main methods used to characterize and quantify the amount of free and bound water in hydrogels are differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR). The proton NMR gives information about the interchange of water molecules between the so-called free and bound states. The use of DSC is based on the assumption that only the free water may be frozen, so it is assumed that the endotherm measured when warming the frozen gel represents the melting of the free water, and that value will yield the amount of free water in the hydrogel sample being tested. The bound water is then obtained by difference of the measured total water content of the hydrogel test specimen, and the calculated free water content.

***Scanning Electron Microscopy:***

SEM can be used to provide information about the sample's surface topography, composition, and other properties such as electrical conductivity. Magnification in SEM can be controlled over a range of up to 6 orders of magnitude from about 10 to 500,000 times. This is a powerful technique widely used to capture the characteristic 'network' structure in hydrogels. It is used to measure the shape and morphological characteristics of hydrogel. It consist the determination of particle size and distributions. SEM uses electrons transmitted from the surface of the sample.

***Light scattering:***

Gel permeation chromatography coupled on line to a multi angle laser light scattering (GPC-MALLS) is a widely used technique to determine the molecular distribution and parameters of a polymeric system. Hydrogel in a polymeric system can be quantified using this technique. This technique is widely used in quantifying the hydrogels of several hydrocolloids such as gum arabic, gelatine and pullulan. It can be demonstrated how mass recovery data obtained from GPC-MALLS correlate with actual amount of

hydrogel obtained for dextran radiation in solid state.

***Sol – gel analysis:***

For radiation cross-linking, the sol-gel analysis is an important characterization tool as it allows to estimate the parameters such as yield of cross-linking and degradation, gelation dose, etc. and to correlate these with some physico-chemical properties.

**APPLICATIONS**

- Hydrogels can be used for the synthesis of sustained or targeted or stealth biomolecule delivery type dosage forms.
- Hydrogels can exihibit bioadhesive property as well to facilitate the drug targeting mainly for non-invasive drug administration through mucus membranes.
- Contact lenses and surgical dressings synthesized as hydrogels are being used successfully.
- They can also be used: as a super absorbent material in diaper, as insulator construction materials, as water retention material in agricultural applications, in cosmetic and pharmaceutics industry, in artificial organs and tissue engineering, in wound dressings and in fire protection.

**DRUG DELIVERY**

***Hydrogels for Ophthalmic use:***

In ocular drug delivery, many physiological constraints prevent a successful drug delivery to the eye due to its protective mechanisms, such as effective tear drainage, blinking and low permeability of the cornea. The most common way to improve drug retention on the corneal surface is by using polymers to increase the solution viscosity. Hydrogels are polymers with an ability to swell in water or aqueous solvents and induce a liquid gel transition [3,10].

Due to their elastic properties, hydrogels can also represent an ocular drainage-resistant device. In addition, they may offer better feeling, with less of a gritty sensation to patients. In particular, in-situ-forming hydrogels are attractive as an ocular drug delivery system because of their facilityin dosing as a liquid and their long term retention property as a gel after dosing [11].

Hui and Robinson introduced hydrogels consisting of cross-linked PAA for ocular delivery of progesterone in rabbits. These preparations increased progesterone concentration in the aqueous humor four times over aqueous suspensions [12].

Cohen and collaborators developed an in situ gel system of alginate with high guluronic acid content for ophthalmic delivery of pilocarpine. This system significantly extended the duration of the pressure-reducing effect of pilocarpine [13].

Ophthalmic delivery system of an anti-inflammatory drug, indomethacin for the treatment of uveitis based on the concept of pH induced in-situ gelation was formulated and evaluated. The Carbopol solutions which are acidic and less viscous, transform into stiff gels upon increase in pH of eye as the gelling agents and its combination with hydroxypropylmethylcellulose-K15M, a well-known ocular viscosity enhancing agent. The in- vitro release results showed that gels have ability to retain the drug for prolonged periods (8 h) [14].

***Hydrogels for Topical use:***

Cubosome dispersions loaded with silver sulfadiazine (SSD) were formulated and the optimized formulae were incorporated into hydrogels (cubogels). In vivo histopathological study results showed that prepared cubogels were successful in the treatment of deep second degree burn which may result in better patient compliance and excellent healing results with least side effects in comparison with the commercially available product [15].

Hydrogels and microemulsion (ME)-based gel formulations containing 1% terbinafine hydrochloride (TER-HCL) were prepared. In vitro release study & examination of antifungal activity revealed that all the prepared products showed effective

antifungal activity and hydrogels released highest amount of drug than microemulsion based gel & commercial product.
These results indicate that the hydrogel is a good candidate for the topical delivery [16].

***Hydrogels for Colon drug delivery:***

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment [17].

Ornidazole loaded chitosan beads were prepared by ionic gelation technique. Research work concluded that Acrycoat coated chitosan beads are promising controlled release carriers for colon-targeted delivery of ornidazole [18].

Researchers tested the hydrogel's ability to target inflamed areas in mice and found the gel adhered more to the inflamed epithelial surfaces of the colon than it did to the tissue in healthy controls. Then, to test its effectiveness as a drug delivery method, the researchers loaded it with dexamethasone, an anti-inflammatory corticosteroid, and inserted it as an enema into two types of mice, one having ulcerative colitis and the other chemically induced to have ulcerative colitis [19].

Oral drug administration is convenient with pH dependent drug delivery system since the drug has to pass through different pH environments in gastro intestinal (GI) tract. The pH dependent swelling/shrinking behavior of hydrogel drug carrier controls the drug release without affecting the function of drug. pH dependent hydrogels of poly (vinyl alcohol) (PVA) by cross linking with maleic acid (MA) were prepared and characterized. The hydrogel, loaded with model drugs vitamin B12 and salicylic acid also demonstrated colon specific drug release with a relatively higher drug release in SIF (pH: 7.5) than that in SGF (pH: 1.2) [20].

***Hydrogels for Peroral drug delivery:***

Drug delivery through the oral route has been the most common method in the pharmaceutical applications of hydrogels. In peroral administration, hydrogels can deliver drugs to four major specific sites; mouth, stomach, small intestine and colon. Drug delivery to the oral cavity can have versatile applications in local treatment of diseases of the mouth, such as periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers [8].

A study describes the in vitro/ex vivo buccal release of chlorhexidine (CHX) from nine mucoadhesive aqueous gels, as well as their physicochemical and mucoadhesive properties: CHX was present at a constant 1% w/v concentration in the chemical form of digluconate salt. The study proved CHX buccal delivery, being able to guarantee both prolonged release and reduced transmucosal permeation [21].

The mucoadhesive hydrogel film was prepared and optimized for the purpose of local drug delivery to oral cavity for the treatment of oral Candidiasis. The mucoadhesive hydrogel film was prepared with the poly(vinyl alcohol) by freeze/thaw crosslinking technique. The films were evaluated for mucoadhesive strength, in vitro residence time, swelling study, in vitro drug release, and effectiveness against Candida albicans. The optimized batch exhibited the sustained release of drug and the antifungal studies revealed that the drug released from the film could inhibit the growth of Candida albicans for 12 hours [22].

This study evaluated the efficacy of bioadhesive hydrogel patches, made of a pharmaceutical grade cellulose derivative, in the control of pain and as an aid to healing of aphthous ulceration. A significant reduction in stimulated pain was recorded following application of the patches to the ulcers {P<0,01). The patches were found to adhere longer to large ulcers in the early stages of ulceration, when they achieved their maximum protective and pain-attenuating

effects. The ulcer size was recorded daily by the patient and patients claimed a reduction in healing time following patch therapy [23].

***Hydrogels for Transdermal drug delivery:***

The pharmaceutical industry has been developing hydrogel based drug delivery system in an advanced manner by tuning the structure, shape and surface modifications of the biopolymers. The use of biodegradable synthetic polymers has shown prominent results in drug delivery [24].

Gel formulations of organogels, hydrogels, and oleo-hydrogel (bigels) were evaluated as transdermal drug delivery systems for diltiazem HCL (DH). The prepared gels were analyzed microscopically, thermally by DTA and for pH, and viscosity. The effect of gelator used, surfactant types and the in vivo performance of various gel formulations were also assessed. The in vivo antihypertensive activity of DH using different transdermal gels is arranged as following: hydrogels > PLO organogel > bigel> Sp 60 organogel [25].

Hydrogel patches based on water swellable polyacrylates have been developed for long-term transdermal drug delivery. Two properties, relevant to the performance of hydrogel patches in-vivo have been investigated in humans over five days. These were: (i) the kinetics of water exchange between the skin and the patches; (ii) the skin compatibility of the patches. The skin compatibility of the patches was satisfactory with no redness or pustulation which may be due to the capability of the patches to exchange water with the skin [26].

Nanoemulgel as transdermal delivery system for poorly water soluble drug, ketoprofen, was investigated in order to overcome the troubles associated with its oral delivery. The study substantiated that nanoemulgel formulation can be used as a feasible alternative to conventional formulations of ketoprofen with advanced permeation characteristics for transdermal application [27].

***Hydrogels for Chemotherapy:***

In a study, the use of a hydrogel to deliver combined therapeutic modalities, radiation and chemotherapy, administered local-regionally in tumor-bearing animal models, was evaluated. The study have demonstrated that in situ hydrogel can be used for local-regional delivery of chemotherapy and radiotherapy while reducing associated toxicities found with traditional delivery methods. In an attempt to incorporate well-known slow-release methodologies for drug delivery with radiotherapy, the developed hydrogel that plays two roles in cancer treatment: (1) slow release of chemotherapeutic agents and (2) trapping of therapeutic radionuclides was highlited. The findings demonstrate the potential uses of image-guided therapy in cancer treatment.

A Pluronic® F127-based thermosensitive hydrogel (Au-DOX-Gel) loading gold nanoparticles (AuNPs) and doxorubicin (DOX) was developed by "cold method" for intratumoral injection. The results of skin safety tests, histological observation of organs, and the body weight changes indicated in vivo safety of Au-DOX-Gel. In conclusion, the Au-DOX-Gel developed in this study could represent a promising strategy for improved cancer chemoradiotherapy [28].

A macroscale injectable and thermosensitive micellar-hydrogel (MHg) depot was constructed by thermo-induced self-aggregation of poly(*ε*-caprolactone-*co*-1,4,8-trioxa[4.6]spiro-9-undecanone)-poly(ethyleneglycol)-poly(*ε*-caprolactone-*co*-1,4,8-trioxa[4.6]spiro-9-undecanone) (PECT) triblock copolymer micelles (Ms). Doxorubicin (DOX) and iodine-131 labeled hyaluronic acid ($^{131}$I-HA) were used as the model therapeutic agents. This hydrogel formulation demonstrated considerable *in vitro* antitumor effect as well as remarkable radiosensitization. Such a thermosensitive MHg formulation, which enabled the precise control over the dosage and ratio of combination therapeutic agents to obtain the desired therapeutic effect with a single drug

administration and reduced side effects, holds great potential for spatiotemporally delivery of multiple bioactive agents for sustained combination therapy [29].

***Hydrogels for Rectal drug delivery:***

The rectal route has been used to deliver many types of drugs, although patient acceptability is variable due to the discomfort arising from administered dosage forms. Its primary applications have been for local treatment of diseases associated with the rectum, such as hemorrhoids. Hydrogels may offer a valuable way to overcome the problem in conventional suppositories, provided that they are designed to exhibit a sufficient bioadhesive property following their rectal administration [3].

Ryu et al. reported that increased bioavailability of propranolol subject to extensive first-pass metabolism was observed by adding certain mucoadhesive polymeric compounds to poloxamer-based thermally gelling suppositories [30].

A significantly reduced irritation by rectal hydrogels prepared with water-soluble dietary fibers, xanthan gum and locust bean gum, was also reported by Watanabe et al [31].

The HPMC and carbopol 934 hydrogels containing DFSCS (Diclofenac sodium-Chitosan) microspheres have been prepared and evaluated. Histopathological evaluation of the selected formula revealed the effectiveness of encapsulation of anti-inflammatory drugs within chitosan microspheres prior to their incorporation into the hydrogel delivery system in reducing the irritation to the mucosal tissues [32].

***Hydrogels for Nasal delivery:***

A study evaluated different mucoadhesive polymeric hydrogels for nasal delivery of acyclovir. Gels containing poly-N-vinyl-2-pyrrolidone (PVP) chitosan and carbopol were prepared and evaluated. Considering the mucoadhesive force, chitosan gel and gel prepared with 3% PVP in presence of polyethylene glycol (PEG) 600 were the most efficient. The in vitro drug release depended on the gel composition. Higher release rates were obtained from PVP gels compared to chitosan or carbopol gels. Histopathological investigations proved that the PVP was a safe hydrogel to be used for mucosal delivery [33].

***Hydrogels for Intestinal delivery:***

Drugs that cause side effects such as stomach irritation, peptic ulcers, nausea or vomiting could benefit from delaying their release till passage into the intestine. Hence, intestinal drug delivery using SPHs could be a useful therapeutic option.

Multiresponsive poly(methacrylic acid-co-N-vinylpyrrolidone) hydrogels were synthesized with biodegradable oligopeptide crosslinks. The microgels exhibited pH-responsive swelling as well as enzyme-catalyzed degradation targeted by trypsin present in the small intestine, as demonstrated upon incubation with gastrointestinal fluids from rats. The microgels demonstrated pH-dependent loading of the protein insulin for oral delivery to the small intestine [34].

Chitosan is a natural polymer which has limited solubility. Chitosan gets solubilized at acidic pH but is insoluble at basic pH. In the present study, carboxymethyl chitosan (CMC) was prepared which shows high swelling in basic pH and thus can delay the drug release and can act as matrix for extended release formulation. CMC was characterized by FTIR and NMR. pH-sensitive hydrogels of theophylline were formulated using CMC and carbopol 934. Hydrogels were evaluated for swelling, drug content, in vitro drug release studies, and in vivo studies on rabbit. In vivo studies showed that the release of theophylline from the prepared hydrogel formulation (Test) exhibit better prolonged action when compared to (standard) marketed sustained release formulation. The studies showed that the pH-sensitive hydrogel of CMC can be used for

extended release of theophylline in intestine and can be highly useful in treating symptoms of nocturnal asthma [35].

A Stimuli-sensitive pectin- based hydrogel (SPH) loaded with the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen [52] were prepared. When taken orally, NSAIDs commonly cause nausea, heartburn, stomach pains and ulceration. Release of ibuprofen from the pectin-based SPHs was dependent on many factors including pH, temperature and hydrogel porosity. This biodegradable hydrogel reacted to changes in its environment, releasing minimal ibuprofen at pH 1.2 (14%) and greater ibuprofen at a higher pH 7.4 (79%), making it an ideal SPH platform for targeted drug delivery to the intestines [36].

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