INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Review Article

HYDROGELS: A SMART DRUG DELIVERY SYSTEM

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ABSTRACT

Design and development of novel drug delivery system (NDDS) has two prerequisites. First, it should deliver the drug in accordance with a predetermined rate and second it should release therapeutically effective amount of drug at the site of action. Conventional dosage forms are unable to meet these requisites. At this juncture, novel formulations like hydrogels etc. come into existence. Hydrogels are three dimensional, crosslinked polymeric networks that are not soluble, but can absorb large quantity of water or biological fluids. The networks consist of hydrophilic homo-polymers or co-polymers crosslinked physically or chemically. The physical crosslinks can be entanglements, crystallites or weak association like vander waal forces or hydrogen bonds. The crosslinks provide the network structure and physical integrity.The review highlights the hydrogels classification, use, method of preparation and their characterization.

Keywords: NDDS, Hydrogels, smart/intelligent polymer

INTRODUCTION

With ongoing research in advanced drug delivery formulations to provide stable and economical drug delivery systems, the focus is on hydrogels which are known to reduce the problems of not only conventional dosage forms but also of novel drug delivery systems which require a biocompatible, convenient and stable drug delivery system for molecules as small as NSAIDs (Non-steroidal anti-inflammatory drugs) or as large as proteins and peptides [1- 2]. Basically hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids [3-4]. The networks are composed of homo-polymers or co-polymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystallites [5-10]. The latter provide the network structure and physical integrity. These hydrogels exhibit a thermodynamic compatibility with water which allows them to swell in aqueous media [3, 4, 11-13].

Hydrogels 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 materials have been recognized to function as drug protectors, especially for peptides and proteins, from *in vivo* environment [14].

The existence of hydrogels dates back to 1960, when Wichterle and Lim first proposed the use of hydrophilic networks of poly (2-hydroxyethyl methacrylate) (PHEMA) in contact lenses [15]. Since then, the use of hydrogels has extended to various biomedical [16] and pharmaceutical [17] applications. In comparison to other synthetic biomaterials, hydrogels resemble living tissues closely in their physical properties because of their relatively high water content and soft and rubbery consistency. Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration.

Several terms have been coined for hydrogels, such as ‘intelligent gels’ or ‘smart hydrogels’ [18]. The smartness of any material is the key to

its ability to receive, transmit or process a stimulus, and respond by producing a useful effect [19]. Once acted on, stimuli can result in changes in phases, shapes, optics, mechanics, electric fields, surface energies, recognition, reaction rates and permeation rates. Hydrogels are 'smart' or 'intelligent' in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behaviour, resulting in the release of entrapped drug in a controlled manner [20].

CLASSIFICATION OF HYDROGELS

There are various ways to classify hydrogels are:

Firstly classified on basis of the nature of the side groups; can be either neutral or ionic. The chemical nature and number of these pendent groups can be precisely controlled by the choice of the chemical entities used in the polymer synthesis. A summary of monomers most commonly used in the preparation of polymeric materials in the pharmaceutical field is given in Table 1.

Table 1: Monomers most often used in the synthesis of synthetic hydrogels for pharmaceutical applications

Monomer abbreviation	Monomer
HEMA	Hydroxyethyl methacrylate
HEEMA	Hydroxyethoxyethyl methacrylate
HDEEMA	Hydroxydiethoxyethyl methacrylate
MEMA	Methoxyethyl methacrylate
MEEMA	Methoxyethoxyethyl methacrylate
MDEEMA	Methoxydiethoxyethyl methacrylate
EGDMA	Ethylene glycol dimethacrylate
NVP	N-vinyl-2-pyrrolidone
NIPAAm	N-isopropyl AAm
VAc	Vinyl acetate
AA	Acrylic acid
HPMA	N-(2-hydroxypropyl) methacrylamide
EG	Ethylene glycol
PEG	Poly(ethylene glycol)
PEGA	PEG acrylate
PEGMA	PEG methacrylate
PEGDA	PEG diacrylate
PEGDMA	PEG dimethacrylate
MAA	Methacrylic acid

Secondly to their mechanical and structural characteristics, they can be classified as affine or phantom networks. Additionally, they can be homo-polymer or co-polymer networks, based on the method of preparation. Finally, they can be classified based on the physical structure of the networks as amorphous, semicrystalline, hydrogen-bonded structures, super molecular structures and hydrocolloidal aggregates [3-10, 21-25].

Hydrogels may also show a swelling behavior dependent on the external environment. These polymers are physiologically-responsive hydrogels [26], where polymer complexes can be broken or the network can be swollen as a result of the changing external environment. These systems tend to show drastic changes in their swelling ratio as a result. Some of the factors affecting the swelling of physiologically-responsive hydrogels include pH, ionic strength, temperature and electromagnetic radiation [26]. A list of few pH sensitive polymers is given in Table 2 along with their corresponding threshold pH.

Table 2: pH sensitive polymer with their threshold pH

Polymer	Threshold pH
Eudragit L 100	6.0
Eudragit L-30D	5.6
Eudragit S 100	7.0
Eudragit FS 30D	6.8
Eudragit L100-55	5.5
Polyvinyl acetate phthalate	5.0
Hydroxy propyl methyl cellulose phthalate	4.5-4.8
Hydroxy propyl methyl cellulose phthalate-50	5.2
HPMC 55	5.4
Cellulose acetate trimelliate	4.8
Cellulose acetate phthalate	5.0

ADVANTAGES OF HYDROGELS

Hydrogels being three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids may offer several advantages [3-10]:

1. Sustained and prolonged action in comparison to conventional drug delivery systems
2. Decreased dose of administration.
3. Decreased side-effects.
4. Improved drug utilization.
5. Improved patient compliance.
6. Drug targeting to specific site like colon.
7. Protection of mucosa from irritating drugs.
8. Drug loss is prevented by extensive first pass metabolism.
9. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
10. Drug adapts to suit circadian rhythms of body functions or diseases.

METHODS TO PRODUCE HYDROGELS

Cross-linked networks of synthetic polymers such as polyethylene oxide (PEO) [27], polyvinyl pyrollidone (PVP) [28], polylactic acid (PLA) [29], polyacrylic acid (PAA) [30], polymethacrylate (PMA) [31], polyethylene glycol (PEG) [32], or natural biopolymers [33] such as alginate, chitosan, carrageenan, hyaluronan, and carboxymethyl cellulose (CMC) have been reported. The various preparation techniques adopted are physical crosslinking [34], chemical cross-linking [35], grafting polymerisation [36], and radiation cross-linking [37-38]. Such modifications can improve the mechanical properties and viscoelasticity for applications in biomedical and pharmaceutical fields [35, 39-41]. The general methods to produce physical and chemical gels are described below:

A. Physical cross-linking

There has been an increased interest in physical or reversible gels due to relative ease of production and the advantage of not using cross-linking agents. These agents affect the integrity of substances to be entrapped (e.g. cell, proteins, etc.) as well as the need for their removal before application. Careful selection of hydrocolloid type, concentration and pH can lead to the formation of a broad range of gel textures and is currently an area receiving considerable attention, particularly in the food industry. The various methods reported in literature to obtain physically cross-linked hydrogels are:

A.1 Heating/cooling a polymer solution

Physically cross-linked gels are formed when cooling hot solutions of gelatine or carrageenan. The gel formation is due to helix-formation, association of the helices, and forming junction zones [42]. Carrageenan in hot solution above the melting transition temperature is present as random coil conformation. Upon cooling it transforms to rigid helical rods. In presence of salt (K+, Na+, etc.), due to screening of repulsion of sulphonic group (SO_{-3}), double helices further aggregate to form stable gels (Figure 1). In some cases, hydrogel can also be obtained by simply warming the polymer solutions that causes the block copolymerisation. Some of the examples are polyethylene oxide-polypropylene oxide [43], polyethylene glycol-polylactic acid hydrogel[34].

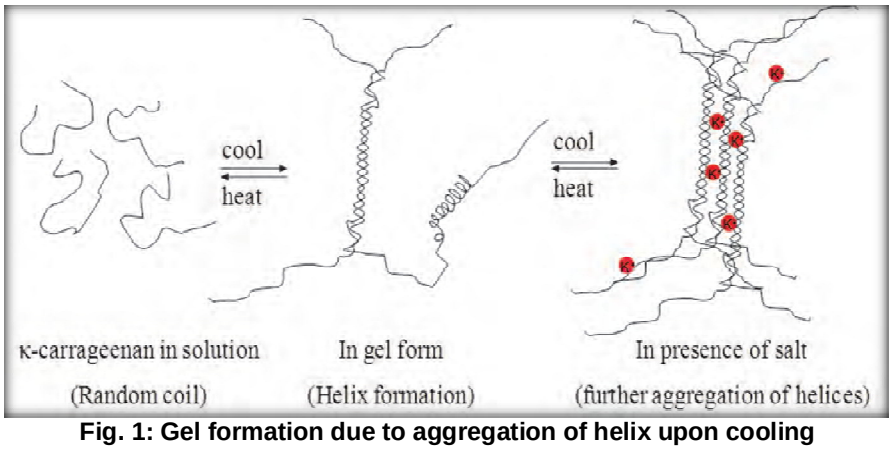

Fig. 1: Gel formation due to aggregation of helix upon cooling a hot solution of carrageenan

A.2 Ionic interaction

Ionic polymers can be cross-linked by the addition of di- or tri-valent counter ions. This method underlies the principle of gelling a polyelectrolyte solution (e.g. Na^+ alginate$^-$) with a multivalent ion of opposite charges (e.g. $Ca2^+ + 2Cl^-$). Some other examples are chitosan-polylysine [44], chitosan-glycerol phosphate salt [45], chitosan-dextran hydrogels [34].

A.3 Complex coacervation

Complex coacervate gels can be formed by mixing of a polyanion with a polycation. The underlying principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on the concentration and pH of the respective solutions. One such example is coacervating polyanionic xanthan with polycationic chitosan [46]. Proteins below its isoelectric point are positively charged and likely to associate with anionic hydrocolloids and form polyion complex hydrogel (complex coacervate) [47].

A.4 H-bonding

H-bonded hydrogel can be obtained by lowering the pH of aqueous solution of polymers carrying carboxyl groups. An example of such hydrogel is a hydrogen-bound CMC (carboxymethyl cellulose) network formed by dispersing CMC into 0.1M HCl [48]. The mechanism involves replacing the sodium in CMC with hydrogen in the acid solution to promote hydrogen bonding (Figure 2). The hydrogen bonds induce a decrease of CMC.

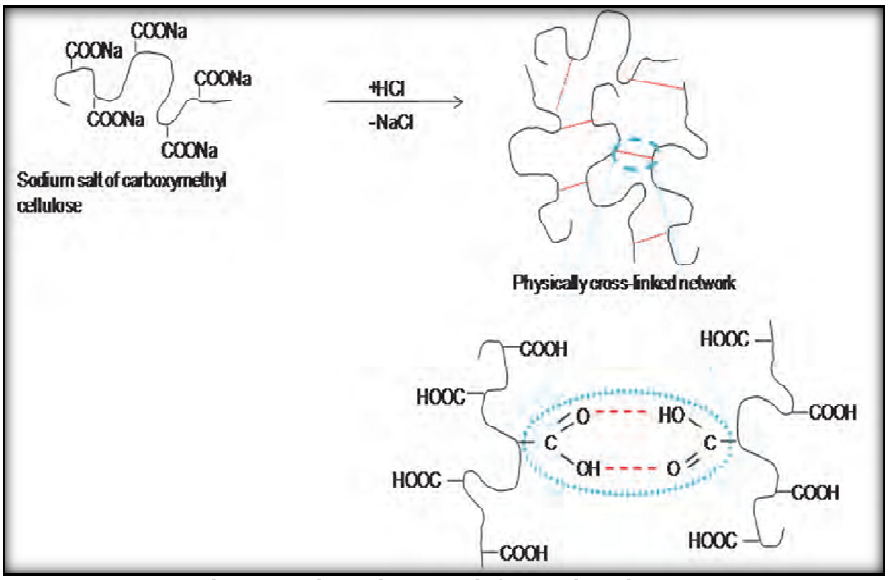

Fig. 2: Hydrogel network formation due to intermolecular H-bonding in CMC at low pH

solubility in water and result in the formation of an elastic hydrogel. Carboxymethylated chitosan (CM-chitosan) hydrogels can also prepared by cross-linking in the presence of acids or polyfunctional monomers (2008). Another example is polyacrylic acid and polyethylene oxide (PEO-PAAc) based hydrogel prepared by lowering the pH to form H-bonded gel in their aqueous solution [43]. In case of xanthan-alginate mixed system molecular interaction of xanthan and alginate causes the change in matrix structure due to intermolecular hydrogen bonding between them resulting in formation of insoluble hydrogel network (2007).

A.5 Maturation (heat induced aggregation)

Gum arabic (Acacia gums) is predominately carbohydrate but contain 2-3% protein as an integral part of its structure [49]. Three major fractions with different molecular weights and protein content have been identified following fractionation by hydrophobic interaction chromatography with different molecular weights and protein content [50]. These are arabinogalactan protein (AGP), arabinogalactan (AG) and glycoprotein (GP).

Aggregation of the proteinaceous components, induced by heat treatment, increases the molecular weight and subsequently produces a hydrogel form with enhanced mechanical properties and water binding capability [51, 52]. The molecular changes which accompany the maturation process demonstrate that a hydrogel can be produced with precisely structured molecular dimensions. The controlling feature is the agglomeration of the proteinaceous components within the molecularly disperse system that is present in of the naturally occurring gum. Maturing of the

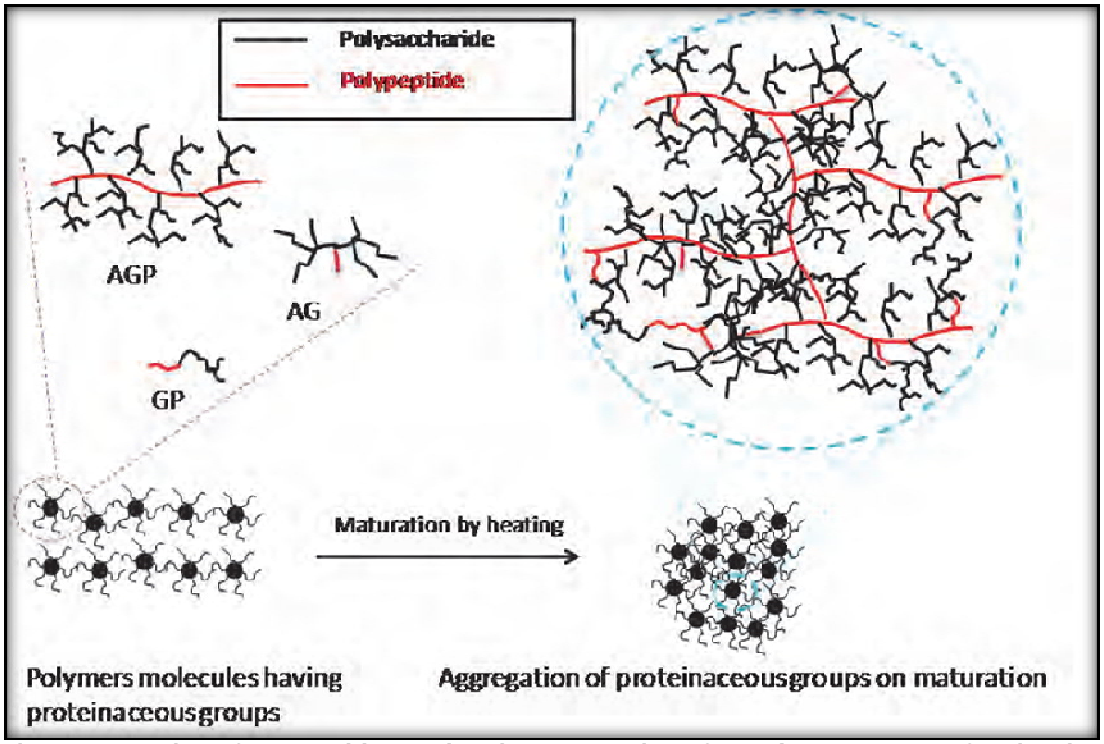

Fig. 3: Maturation of gum arabic causing the aggregation of proteinaceous part of molecules leading to cross-linked hydrogel network

gum leads to transfer of the protein associated with the lower molecular weight components to give larger concentrations of high molecular weight fraction (AGP) (Figure 3). The method has also been applied on to other gums such as gum ghatti and Acacia kerensis for application in denture care [53].

A.6 Freeze-thawing

Physical cross-linking of a polymer to form its hydrogel can also be achieved by using freeze-thaw cycles. The mechanism involves the formation of microcrystals in the structure due to freeze-thawing. Examples of this type of gelation are freeze-thawed gels of polyvinyl alcohol and xanthan [43, 54-55].

B. Chemical cross-linking

Chemical cross-linking covered here involves grafting of monomers on the backbone of the polymers or the use of a cross-linking agent to link two polymer chains. The cross-linking of natural and synthetic polymers can be achieved through the reaction of their functional groups (such as OH, COOH, and NH_2) with cross-linkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). There are a number of methods reported in literature to obtain chemically cross-linked permanent hydrogels. Among other chemical cross-linking methods, IPN (polymerise a monomer within another solid polymer to form interpenetrating network structure) (2003) and hydrophobic interactions [34] (incorporating a polar hydrophilic group by hydrolysis or oxidation followed by covalent cross-linking) are also used to obtain chemically cross-linked permanent hydrogels. The following section reviews the major chemical methods (i.e. crosslinker, grafting, and radiation in solid

and/or aqueous state) used to produce hydrogels from a range of natural polymers.

B.1 Chemical cross-linkers

Cross-linkers such as glutaraldehyde (2008), epichlorohydrin (2002), etc have been widely used to obtain the cross-linked hydrogel network of various synthetic and natural polymers. The technique mainly involves the introduction of new molecules between the polymeric chains to produce cross-linked chains. One such example is hydrogel prepared by cross-linking of corn starch and polyvinyl alcohol using glutaraldehyde as a cross-linker (2008). The prepared hydrogel membrane could be used as artificial skin and at the same time various nutrients/healing factors and medicaments can be delivered to the site of action.CMC chains can also be cross-linked by incorporating 1, 3-diaminopropane to produce CMC-hydrogel suitable for drug delivery through the pores (2004). Hydrogel composites based on xanthan and polyvinyl alcohol cross-linked with epichlorohydrin in another example (2002). κ-carrageenan and acrylic acid can be cross-linked using 2-acrylamido-2-methylpropanesulfonic acid leading to the development of biodegradable hydrogels with proposed use for novel drug delivery systems [56]. Carrageenan hydrogels are also promising for industrial immobilisation of enzymes [57]. Hydrogels can also be synthesized from cellulose in NaOH/urea aqueous solutions by using epichlorohydrin as cross-linker and by heating and freezing methods [58-59].

B.2 Grafting

Grafting involves the polymerisation of a monomer on the backbone of a preformed polymer. The polymer chains are activated by the action of chemical reagents, or high energy radiation treatment. The growth of functional monomers on activated macroradicals leads to branching and further to cross-linking.

B.2.1 Chemical grafting

In this type of grafting, macromolecular backbones are activated by the action of a chemical reagent. Starch grafted with acrylic acid by using N-vinyl-2-pyrrolidone is an example of this kind of process [60]. Such hydrogels show an excellent pH-dependent swelling behaviour and possess ideal characteristic to be used as drug and vitamin delivery device in the small intestine.

B.2.2 Radiation grafting

Grafting can also be initiated by the use of high energy radiation such as gamma and electron beam. Said, Alla et al. (2004) [36] reported the preparation of hydrogel of CMC by grafting CMC with acrylic acid in presence of electron beam irradiation, in aqueous solution. Electron beam was used to initiate the free radical polymerisation of acrylic acid on the backbone of CMC. Water radiolysis product will also be helpful to abstract proton form macromolecular backbones. Irradiation of both (CMC and monomer) will produce free radicals that can combine to produce hydrogel. They proposed the application of such acrylic acid based hydrogel for the recovery of metal ions like copper, nickel, cobalt, and lead. Also, they reported the application of hydrogels in dressings for temporary skin covers.

Zhai, Yoshii et al. (2002) [61] also reported the preparation of starch based hydrogel by grafting polyvinyl alcohol (PVA). Starch was first dissolved into water to form gel-like solution and then added to PVA solution, continuously stirred to form homogeneous mixture after heating at 90^{o}C for 30 mins. The result showed there was a grafting reaction between PVA and starch molecule besides the cross-linking of PVA molecule under irradiation. Amylose of starch was found to be a key reactive component. The properties of starch/PVA blend hydrogel too were governed by amylose component of starch.

Cai, Zhang et al. (2005) [62] have reported the preparation of thermo- and pH-sensitive hydrogels by graft copolymerisation of chitosan (CS) and N-isopropylacrylamide (NIPA). The results showed that the grafting percentage and grafting efficiency increased with the increase of monomer concentration and total irradiation dose. The CS-g-NIPA hydrogels showed good thermo- and pH-sensitivity and swelling property.

CHARACTERIZATION OF HYDROGELS

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 [63]. Some of the important features for characterization of hydrogels are as follows:

A. Morphological characterization

Hydrogels are characterized for morphology which is analyzed by equipment like SEM (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 [64-67].

B. 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 [68-70].

C. 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 [68- 69].

D. 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 [71-72].

E. Swelling behavior

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 [69, 73-74].Various methods for swelling measurement are as follows:

E.1 Method A

The Japanese Industrial Standard K8150 method has been used to measure the swelling of hydrogels. According to this method the dry hydrogel is immersed in deionised water for 48 hours at room temperature on a roller mixer. After swelling, the hydrogel is filtered by a stainless steel net of 30 meshes (681 μm). The swelling is calculated as follows [75]:

$$\textbf{Swelling} = W_s - W_d / W_d$$

Where, W_s is the weight of hydrogel in swollen state and W_d is the weight of hydrogel in dry state. The terms 'swelling ratio' [76], 'equilibrium degree of swelling' (EDS) [77] or 'degree of swelling' [78] has been used for more or less similar measurements.

E.2 Method B

Alternatively, to measure the swelling of hydrogel, in a volumetric vial (Universal) the dry hydrogel (0.05-0.1g) was dispersed into sufficiently high quantity of water (25-30 ml) for 48 hrs at room temperature. The mixture is then centrifuged to obtain the layers of waterbound material and free unabsorbed water. The free water is removed and the swelling can be measured according to Method A above.

E.3 Method C

The swelling can also be measured according to the Japanese Industrial Standard (JIS) K7223. The dry gel is immersed in deionized water for 16 h at room temperature. After swelling, the hydrogel was filtered using a stainless-steel net of 100-mesh (149 μm). Swelling is calculated as follows [79]:

$$Swelling = (C/ B) * 100$$

Where C is the weight of hydrogel obtained after drying and B is the weight of the insoluble portion after extraction with water.

F. Solubility

Various methods for solubility measurement of hydrogels are as follows:

F.1 Method A

Normally the hydrogel content of a given material is estimated by measuring its insoluble part in dried sample after immersion in deionised water for 16 h [80] or 48 h at room temperature [75]. The sample should be prepared at a dilute concentration (typically ~ 1%) to ensure that hydrogel material is fully dispersed in water. The gel fraction is then measured as follows:

$$\textbf{Gel Fraction (hydrogel \%)} = (W_d / W_i) * 100$$

Where, W_i is the initial weight of dried sample and W_d is the weight of the dried insoluble part of sample after extraction with water.

F.2 Method B

A more accurate measure of the insoluble fraction (also termed as hydrogel can be determined by measuring the weight retained after vacuum filtration. This is essentially the

method prescribed by JECFA (Joint Expert Committee on Food Additives) for hydrocolloids which we have modified by changing the solvent from mild alkaline to water [53]. The weight (W_1) of a 70 mm glass fibre paper (pore size 1.2 micron) is determined following drying in an oven at 105°C for 1 hour and subsequently cooled in a desiccators containing silica gel. Depending on the test material, 1-2 wt% (S) dispersion can be prepared in distilled water followed by overnight hydration at room temperature. The hydrated dispersion is then centrifuged for 2-5 minutes at 2500 rpm prior to filtration. Drying of the filter paper is carried out in an oven at 105°C followed by cooling to a constant weight (W_2). % Insoluble can then be calculated:

$$\% \textit{ Hydrogel} = (W_2 - W_1 / S) * 100$$

Depending on the test material different mesh size can be also used, e.g. the use of a 20-mesh steel screen (1041 µm) to determine the gel fraction [80].

G. Rheology

Hydrogels are evaluated for viscosity under constant temperature of usually 4°C by using Cone Plate type viscometer [81].

The rheological properties are very much dependant on the types of structure (i.e. association, entanglement, cross-links) present in the system. Polymer solutions are essentially viscous at low frequencies, tending to fit the scaling laws: $G' \sim \omega^2$ and $G'' \sim \omega$. At high frequencies, elasticity dominates ($G' > G''$). This corresponds to Maxwell-type behaviour with a single relaxation time that may be determined from the crossover point and, this relaxation time increases with concentration. For cross-linked microgel dispersions, it exhibits G' and G" being almost independent of oscillation frequency [82-83]. This technique has been used to characterize the network structure in seroglucan/borax hydrogel [84], chitosan based cationic hydrogels [85-86] and a range of other hydrocolloids [87].

CONCLUSION

There are enough scientific evidences for the potentiality of hydrogels in delivery of drug molecules to a desired site by triggering the release through an external stimulus such as temperature, pH, glucose or light. These hydrogels being biocompatible and biodegradable in nature have been used in the development of nano biotechnology products and have marvelous applications in the field of controlled drug delivery as well. That is why these turn-able biomedical drug delivery devices are gaining attention as intelligent drug carriers.

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