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# REVIEW ON HYDROGEL NANOPARTICLES IN DRUG DELIVERY

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## ABSTRACT

Hydrogel nanoparticles have gained considerable attention in recent years as one of the most promising nanoparticulate drug delivery systems owing to their unique potentials via combining the characteristics of a hydrogel system with a nanoparticle. Therefore, it seems that the pharmacy world will benefit from the hydrophilicity, flexibility, versatility, high water absorptivity, and biocompatibility of these particles and all the advantages of the NPs, mainly long life span in circulation and the possibility of being actively or passively targeted to the desired bio-phase. Several polymeric hydrogel nanoparticulate systems have been prepared and characterized in recent years, based on both natural and synthetic polymers, each with its own advantages and drawbacks. Several cross linking methods have been used in the way to form the hydrogel matrix structures. The remainder of this text presents various types of nanogels prepared and characterized, using a classification based on the type of polymeric materials used in preparation of the NPs.

**Key words**: Hydrogel, Nanoparticles, Hydrogel nanoparticles, Nanogels, Hydrogel.

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# INTRODUCTION

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as Poly Ethylene Glycol (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes[1-4].

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties[5,6].

**Advantages of Using Nanoparticles as a Drug Delivery System:**

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
5. The system can be used for various routes of administration including oral, nasal, parenteral, and intra-ocular.

In spite of these advantages, nanoparticles do have limitations. For example, their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms. In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available. The present review details the latest development of nanoparticulate drug delivery systems, surface modification issues, drug loading strategies, release control and potential applications of nanoparticles.

## HYDROGELS A BRIEF OVERVIEW:

Hydrogels are polymeric networks with three-dimensional configuration capable of imbibing high amounts of water or biological fluids. Their affinity to absorb water is attributed to the presence of hydrophilic groups such as –OH, –CONH–, –CONH2–, and –SO3H in polymers forming hydrogel structures. Due to the contribution of these groups and domains in the network, the polymer is thus hydrated to different degrees, depending on the nature of the aqueous environment and polymer composition. Polymeric networks of hydrophobic characteristics PLA or PLG have limited water absorbing capacities (5–10%).

While the water content of a hydrogel determines its unique physicochemical characteristics, these structures have some common physical properties resembling that of the living tissues, than any other class of synthetic biomaterials, which is attributed to their high water content, their soft and robbery consistency, and low interfacial tension with water or biological fluids. Their major disadvantage is their low mechanical strength. To reinforce their structure, the hydrogels are cross linked. Despite their high water absorbing affinity, hydrogels show a swelling behavior instead of being dissolved in the aqueous surrounding environment as a consequence of the critical cross links present in the hydrogel structure.

These crosslink are from two main categories including: i) physical (entanglements or crystallites), and ii) chemical (tie-points and junctions)[7-12]. The cross links in the polymer network are provided by covalent bonds, hydrogen binding, Van-Der Waals interactions, or physical entanglements[13-14]. As mentioned, water content plays an important role in determining

the overall characteristic of a polymeric network. Accordingly, hydrophilic hydrogels with high amounts of water in their structures show distinctive properties compared to hydrophobic polymeric networks. Furthermore, hydrogels have significantly milder conditions for preparation with gel formation occurring at ambient temperatures and organic solvents are rarely required[15]. Hydrogels, particularly those intended for applications in drug delivery and biomedical purposes, are required to have acceptable biodegradability and biocompatibility which necessitates the development of novel synthesis and cross linking methods to design the desired products. In this way, a great variety of cross linking approaches have been developed to prepare desired hydrogels for each particular application[16] (figure 1-3). The characteristics and potential applications of hydrogels of different structures rely not only on the preparation methods but also on the monomers used in the synthesis of hydrogel polymeric networks[17,18].

**Hydrogel Classifications:**

To achieve a hydrogel system with predetermined and well defined physicochemical parameters and release profiles, knowledge of polymer network synthesis and chemistry, quantitative and modelistic features of materials, interaction parameters and release kinetic, and transport phenomena seems to be playing fundamentally important roles. In a general view, hydrogels can be classified based on a variety of characteristics, including the nature of side groups (neutral or ionic), mechanical and structural features, method of preparation, physical structure and responsiveness to physiologic environment stimuli (pH, ionic strength, temperature, electromagnetic radiation, etc.)[19-21]. The polymers commonly used in preparation of hydrogels with pharmaceutical and biological applications are from natural or synthetic origins[20,21]. Typical examples of natural, synthetic and combinational, i.e., semi synthetic polymers used in hydrogel preparations are summarized in (Table 1**)**. Although hydrogels of natural origin may show mechanically sub-optimal characteristics and may exert immunogenicity or evoke inflammatory responses due to the presence of immunogen/pathogen moieties, they do offer various advantageous properties such as being usually non-toxic, biocompatibility, and showing a number of remarkable physicochemical properties that make them suitable for different applications in drug delivery systems[19,21]. In comparison, the well-defined structure of synthetic polymers may lead to hydrogels with well-defined and fine-tunable degradation kinetic as well as mechanical properties.

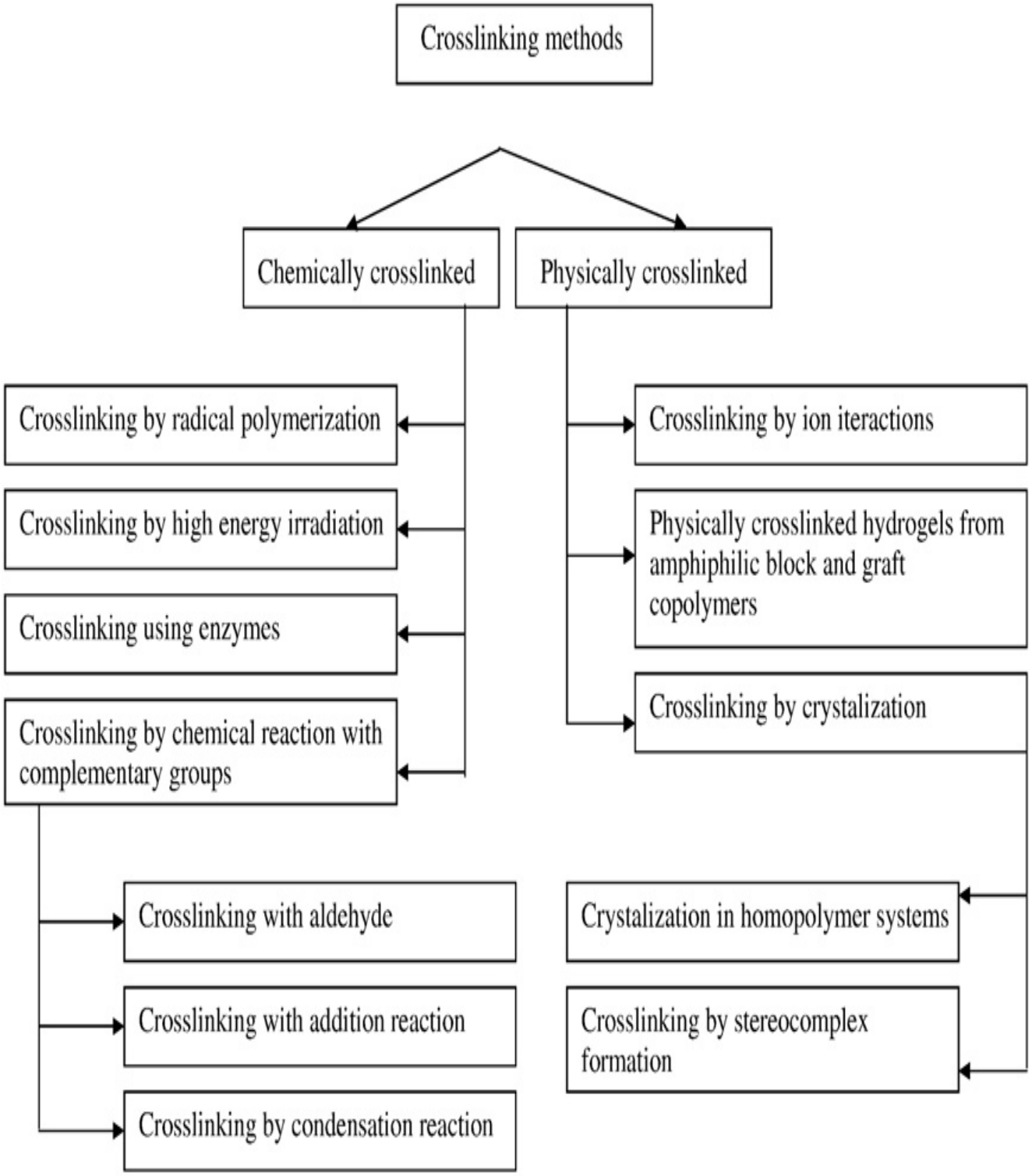


**Figure 1: Novel cross linking methods used in hydrogels.**

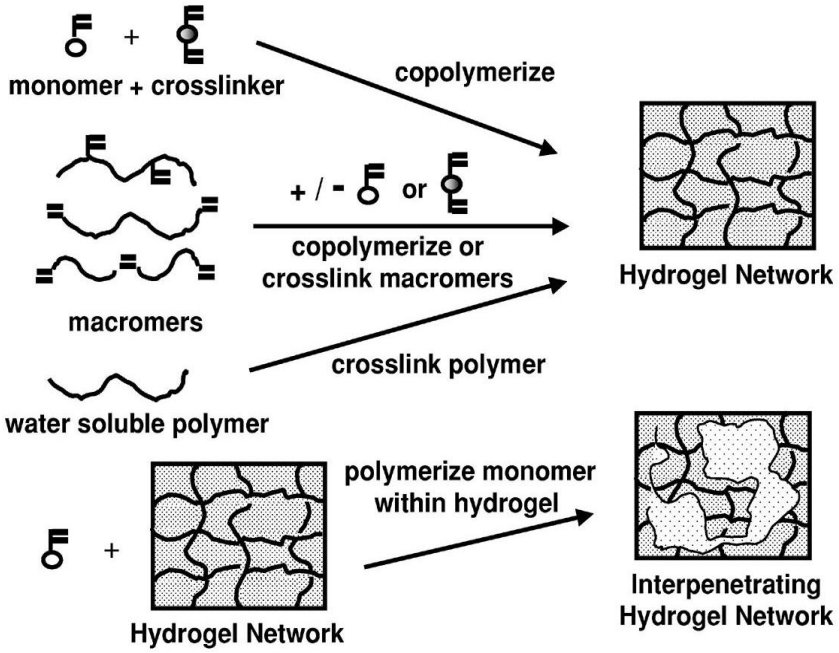


**Figure 2: Schematic of methods for formation of cross linked hydrogels by free radical reactions, including a variety of polymerizations and cross linking of water-soluble polymers. Examples include cross linked PHEMA and PEG hydrogels.**

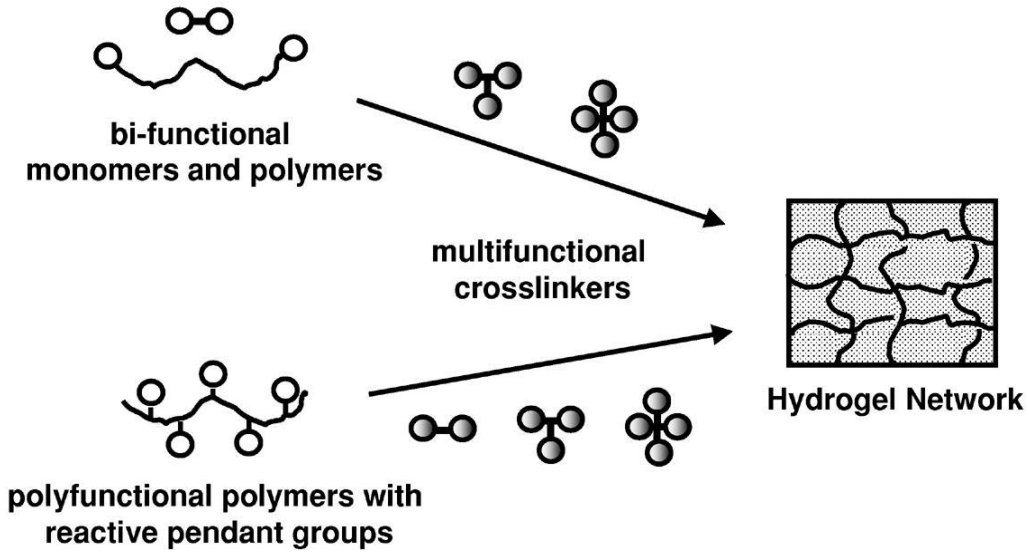


**Figure 3: Schematic of methods for formation of cross linked hydrogels by condensation reactions of multifunctional reactants.**

**Table 1: Hydrophilic polymers used in preparation of hydrogels.**

| | | |
|---|---|---|
| Natural polymers and their derivatives | Anionic polymers | HA, alginic acid, pectin, carrageenan, chondroitin sulfate, dextran sulfate |
| | Cationic polymers | chitosan, polylysine |
| | Amphipathic polymers | collagen (and gelatin), carboxymethyl chitin, fibrin |
| | Neutral polymers | dextran, agarose, pullulan |
| Synthetic polymers | Polyesters | PEG–PLA–PEG, PEG–PLGA–PEG, PEG–PCL–PEG, PLA–PEG–PLA, PHB, P(PF-co-EG)6acrylate end groups, P(PEG/PBO terephthalate) |
| | Other polymers | PEG-bis-(PLA-acrylate), PEG6CDs, PEG-g-P(AAm-co-Vamine), PAAm, P(NIPAAm-co-AAc), P(NIPAAm-co-EMA), PVAc/PVA, PNVP, P(MMA-co-HEMA), P(AN-coallyl sulfonate), P(biscarboxy-phenoxy-phosphazene), P(GEMA-sulfate). |
| Combinations of natural and synthetic polymers | | P(PEG-co-peptides), alginate-g-(PEO–PPO–PEO), P(PLGA-co-serine), collagen-acrylate, alginate-acrylate, P(HPMA-g-peptide), P(HEMA/Matrigel®), HA-g-NIPAAm. |

Abbreviations: HA (Hyaluronic Acid); PEG (Poly Ethylene Glycol); PLA ( Poly Lactic Acid); PLGA (Poly Lactic-co-Glycolic Acid); PCL (Poly Capro Lactone; PHB (Poly Hydroxyl Butyrate); PF (Propylene Fumarate) ; EG (Ethylene Glycol) ; PBO (Poly Butylene Oxide); CD (Cyclo Dextrin); PAAm (Polyacrylamide); PNIPAAm (Poly N-isopropyl Acrylamide); PVA (Poly Vinyl Alcohol); PVamine (Poly Vinyl amine); PVAc (Poly Vinyl Acetate); PNVP (Poly N-vinyl Pyrrolidone); PAAc (Poly Acrylic Acid); HEMA (Hydroxy Ethyl Meth Acrylate); PAN (Polyacrylonitrile); PGEMA (Poly Glucosylethyl Methacrylate); PEO (Poly Ethylene Oxide); PPO (Poly Propyleneoxide); PHPMA (Poly hydroxypropyl methacrylamide); PEMA (Poly ethyl methacrylate); PAN (Polyacrylonitrile); PMMA (Poly methyl methacrylate).

**Release Mechanism from Hydrogel Matrices:**

Since the most common mechanism of drug release from hydrogels is **passive diffusion**, molecules of different sizes and characteristics would freely diffuse into/out of hydrogel matrix during the loading and storage periods. The hydrophilic nature of a hydrogel makes it highly different from non-hydrophilic polymer matrices with respect to the release behavior of the incorporated agents. From various modelistic studies on the possible release mechanisms of an active compound from a hydrogel device, focused on the rate-limiting step of the release phenomena, drug release mechanisms from hydrogels can be categorized as: **i) diffusion-controlled, ii) swelling-controlled, and iii) chemically controlled.** According to Fick's first law

of diffusion (with constant or variable diffusion coefficients), the diffusion-controlled behavior is the most dominantly applicable mechanism to describe the drug release from hydrogels[22]. The drug diffusion out of a hydrogel matrix is primarily dependent on the mesh sizes within the matrix of the gel[23], which, in turn, is affected by several parameters, including, mainly, the degree of cross linking, chemical structure of the composing monomers, and, when applicable, type as well as intensity of the external stimuli. Meanwhile, mechanical strength, degradability, diffusivity, and other physical properties of a hydrogel network are greatly dependent on its mesh size. Typical mesh sizes reported for biomedical hydrogels range from **5 to 100nm** (in their swollen state) **,** which are much larger than most small-molecule drugs. As a result, diffusion of these drugs is not considerably retarded in swollen state, whereas macromolecules like oligonucleotides, peptides, and proteins, due to their hydrodynamic radii, will have a sustained release unless the structure and mesh size of the swollen hydrogels are designed appropriately to obtain desired rates of macromolecular diffusion[24]. In the case of the swelling-controlled mechanism, when diffusion of a drug is significantly faster than hydrogel distention, swelling is considered to be controlling for the release behavior[24,25]. Finally, chemically-controlled release is determined by chemical reactions occurring within the gel matrix. These reactions include polymeric chain cleavage via hydrolytic or enzymatic degradation, or reversible/irreversible reactions occurring between the polymer network and the releasing drug. In addition to the abovementioned release mechanisms, under certain circumstances, surface or bulk erosion of hydrogels or the binding equilibrium among the drug binding moieties incorporated within the hydrogels, are two different mechanisms reported as controlling the rate of drug release[22,23].

## CONTROLLED-RELEASE HYDROGEL SYSTEMS:

Controlled-release or controlled-delivery systems are intended to provide the drug or compound of interest at a specific predetermined temporal and/or spatial manner within the body to fulfill the specific therapeutic needs. Hydrogels, among the different controlled-release systems exploited so far, have particular properties which make them to be potentially considered as one of the ideal future controlled release systems. The hydrogel-based delivery systems are of two major categories: i) **time-controlled systems** and ii) **stimuli-induced** release systems[22]. The latter, stimuli-induced release systems, are also referred to as ‘stimuli-sensitive’, ‘stimuli-responsive’, ‘environment sensitive’, ‘environment-responsive’, or ‘responsive’ hydrogel systems. Responsive hydrogel systems are developed to deliver their content(s) in response to a fluctuating condition in a way that desirably coincides with the physiological requirements at the

right time and proper place. Despite the huge attraction centered towards the novel drug delivery systems based on the environment sensitive hydrogels in the past and current times, these systems have disadvantages of their own. The most considerable drawback of stimuli-sensitive hydrogels is their significantly slow response time, with the easiest way to achieve fast-acting responsiveness being to develop thinner and smaller hydrogels which, in turn, bring about fragility and loss of mechanical strength in the polymer network and the hydrogel device itself[26]. Dependent on changes in the nature of the external environment, responsive hydrogels undergo drastic alterations in their structure behavior[23,24]. The environment (stimuli)-sensitive hydrogel systems which are also famous as 'intelligent' or 'smart' systems, can be further sub-classified to:

i) **Physically-induced release systems;**

ii) **Chemically-induced release systems;**

iii) **Other stimuli-induced release systems.**

Temperature, electricity, light, pressure, sound, and magnetic field are among the physical stimuli of , while pH, solvent composition, ions, and specific molecular recognition events are chemical stimuli. Temperature-sensitive (thermo-responsive) hydrogels have gained considerable attention due to their ability for repeated swelling–deswelling conversion in response to the environmental temperature changes[27,28]. Chemical-responsive hydrogel systems propose several classes of hydrogels which can trigger drug release from a depot with respect to changes in the concentration of a specific molecule or bioactive compound in the surrounding media. Furthermore, the challenge of potential need for chronotherapy has currently resulted in the development of electrically assisted release technologies using hydrogels, as well[29–34]. These technologies include iontophoresis, infusion pumps, and sonophoresis. pH-responsive hydrogel systems are of great importance due to their unique pH dependant swelling–deswelling behavior[35–40]. Several environmental stimuli are being exploited extensively in drug delivery researches. e.g. physical stimuli such as light, magnetic field, electric current and ultrasound, while chemical stimuli such as pH, solvent composition, ions, and specific molecular recognition events. Finally, a series of studies on development of novel infection-responsive drug release systems has been performed by Suzuki et al.[41–49].

## HYDROGEL NANOPARTICLES[50-53]

Hydrogel nanoparticles (NPs) (recently referred to as nanogels) have been the point of convergence of considerable amount of efforts devoted to the study of these systems dealing with

drug delivery approaches. Interestingly, hydrogel nanoparticulate materials would demonstrate the features and characteristics hydrogels and NPs separately posses, at the same time. Therefore, it seems that the pharmacy world will benefit from both the hydrophilicity, flexibility, versatility, high water absorptivity, and biocompatibility of these particles and all the advantages of the NPs, mainly long life span in circulation and the possibility of being actively or passively targeted to the desired biophase, e.g. tumor sites. Different methods have been adopted to prepare NPs of hydrogel consistency. Besides the commonly used synthetic polymers, active research is focused on the preparation of NPs using naturally occurring hydrophilic polymers. This text presents various types of nanogels prepared and characterized, using a classification based on the type of polymeric materials used in preparation of the NPs.

**Chitosan-Based Hydrogel Nanoparticles**

Chitosan, α(1-4)-2-amino-2-deoxy β-D-glucan, is a deacetylated form of chitin, an abundant polysaccharide present in crustacean shells. Even though the discovery of chitosan dates back from 19$^{th}$ century, it has only been over the last two decades that this polymer has received attention as a material for biomedical and drug delivery applications. The accumulated information about the physicochemical and biological properties of chitosan led to the recognition of this polymer as a promising material for drug delivery and, more specifically for the delivery of macromolecules. it is extremely important that chitosan is hydro-soluble and positively charged. These properties enable this polymer to interact with negatively charged polymers, macromolecules, and even with certain polyanions upon contact in aqueous environment. These interactive forces and the resulting sol–gel transition stages have been exploited for nano-encapsulation purposes. On the other hand, chitosan has the special possibility of adhering to the mucosal surfaces within the body, a property leading to the attention to this polymer in mucosal drug delivery[54-59]. The potential of chitosan for this specific application, has been further enforced by the demonstrated capacity of chitosan to open tight junctions between epithelial cells though well organized epithelia[60–65]. The interesting biopharmaceutical characteristics of this polymer are accompanied by its well documented biocompatibility and low toxicity.

**Alginate-Based Hydrogel Nanoparticles:**

Alginic acid is an anionic biopolymer consisting of linear chains of α-L-glucuronic acid and β-D-mannuronic acid with properties such as a high degree of aqueous solubility, a tendency for gelation in proper condition with high porosity of the resulting gels, biocompatibility, and non-

toxicity . Sequential crosslinking and formation of polymeric networks, results in hydrogel structured drug delivery carriers such as micro- and nanoparticles upon the addition of counter-ions to alginate. Any possible cationic species can initiate the reaction sequence, but calcium chloride is favorably utilized by most researchers. The methods of preparation are usually determined with the aim to control the gelification phenomenon, which leads to desired size ranges depending on various factors including alginate concentration/ viscosity, counter-ion concentration, the speed of adding counter-ion solution onto the alginate solution, etc[66-78].

Sarmento *et al*., prepared insulin-loaded NPs by alginate ionotropic pre-gelation followed by chitosan polyelecterolyte complexation. In their effort, particles in nanometer size range were obtained under optimized condition with a loading capacity of 14.3%. In another study using dextran polysaccharide as the complexing agent, again, insulin was loaded in alginate-dextran nanospheres via nanoemulsion dispersion followed by triggered in situ gelation. The resulting particles ranged in size from 267nm to 2.76μm. Particles prepared demonstrated a unimodal size distribution and insulin encapsulation efficiency was reached to 82.5%. Sarmento *et al.*, prepared insulin-loaded NPs by alginate ionotropic pre-gelation followed by chitosan polyelecterolyte complexation. In their effort, particles in nanometer size range were obtained under optimized condition with a loading capacity of 14.3%. In another study using dextran polysaccharide as the complexing agent, again, insulin was loaded in alginate-dextran nanospheres via nanoemulsion dispersion followed by triggered in situ gelation. The resulting particles ranged in size from 267nm to 2.76μm. Particles prepared demonstrated a unimodal size distribution and insulin encapsulation efficiency was reached to 82.5%.The bioavailability of all drugs encapsulated in alginate NPs were significantly higher than those with free drugs. Moreover, local administration of inhalable alginate-based NPs bearing the same drugs except for EMB has been attempted by Ahmad et al. with both loading capacity and sizes comparable to the previous study[79-80].

**Poly Vinyl Alcohol Based Hydrogel Nanoparticles:**

Poly (vinyl alcohol), PVA, is the product of free radical polymerization of vinyl acetate with subsequent hydrolysis of acetate groups to hydroxyl moieties resulting in a wide molecular weight distribution. The molecular weight distribution is an important characteristic due to its roles in determining polymer properties including crystallizability, adhesion, mechanical strength, and diffusivity. PVA is among the most promising polymer candidates for hydrogel studies. Crosslinking of PVA polymeric chains is carried out using chemical (e.g., crosslinking agents, electron beam, γ-irradiation) as well as physical (e.g., freezing/thawing) methods, with

the crosslinks being critical for PVA in order to be useful for various applications in medical and pharmaceutical fields.

In late 1990s, PVA NPs were prepared with the aim of protein/peptide drug delivery using a water-in-oil emulsion/cyclic freezing–thawing procedure. In this study, the emulsion was kept frozen at − 20°C followed by a thawing phase at ambient temperature and no emulsifier involved. The average diameter of PVA NPs obtained was 675.5±42.7 nm with a skewed or log-normalized size distribution. Bovine serum albumin, BSA, was loaded in this study in nanogels with a notable loading efficiency of 96.2±3.8% and a diffusion-controlled release trend. In another study, three separate production methods, including salting-out, emulsification diffusion, and nano precipitation, have been used by Galindo-Rodriguez et al. as a comparative scale-up production evaluation to reach PVA-based NPs loaded with ibuprofen. Heterogeneously structured composites involving PVA have been interested in the field of hydrogel nanoparticles. Biodegradable polyesters consisting of short poly(lactone) chains grafted to PVAor charge-modified sulfobutyl-PVA (SB-PVA)were prepared and used as a novel class of water soluble comb-like polyesters. These polymers undergo spontaneous self assembling to produce NPs, which form stable complexes with a number of proteins such ashuman serumalbumin, tetanous toxoid and cytochrom C. However, the development of NPs from such polymers does not require the use of solvents or surfactants [81–84].

**Poly Ethylene Oxide and Poly Ethyleneimine Based Hydrogel Nanoparticles:**

A new family of nanoscale materials on the basis of dispersed networks of crosslinked poly (ethylene oxide) (PEO) and poly (ethyleneimine) (PEI), PEO-cl-PEI, has been developed . Interaction of anionic/amphiphilic molecules or oligonucleotides with PEO-cl-PEI results in formation of nanocomposite materials in which the hydrophobic regions from polyion complex are joined by the hydrophilic PEO chain . Formation of polyion complex leads to the collapse of the dispersed gel particles. However, the complexes form stable aqueous dispersions due to the stabilizing effect of the PEO chain. These systems allow for immobilization of negatively charged biologically active compounds such as retinoic acid, indomethacin [85] and oligonucleotides (bound to polycation chains) or hydrophobic molecules (incorporated into non polar regions of polyion–surfactant complexes) . The nanogel particles carrying biologically active compounds have been modified with polypeptide ligands to enhance receptor-mediated delivery. Efficient cellular uptake and intracellular release of oligonucleotide immobilized in PEO-cl-PEI nanogel have been demonstrated. Antisense activity of an oligonucleotide in a cell

model was enhanced as a result of formation of oligonucleotide-nanogel association. This delivery system has a potential of enhancing oral and brain bioavailability of oligonucleotides as demonstrated using polarized epithelial and brain micro vessel endothelial cell mono layers. PEO-cl-PEI nanogels were synthesized by crosslinking of branched PEI with bis-activated PEO molecules .When conducted in a homogenous aqueous solution, the reaction between amino groups of PEI and imidazolylcarbonyl ends of activated PEO proceeded very rapidly, resulting in formation of transparent hydrogels in only 3–5min. These bulk hydrogels retained large quantities of water reaching approximately 50-fold by weight, compared to the dried substance. Rigid hydrogels could be produced at the minimal PEO/PEI molar ratio of 6 or higher. To obtain fine disperse systems, the crosslinking reaction was performed by a modified solvent emulsification /evaporation method. According to this method, activated PEO solution in dichloromethane was emulsified in the aqueous solution of PEI by sonication. The organic solvent was removed from the mixture in vacuo resulting in formation of a clear suspension. Most of the nanogel particles have had a very low density and could not be fractioned by ultracentrifugation[86-90]. Therefore, crude suspension of nanogel particles was partitioned using gel-permeation chromatography. Several fractions could be separated by particle size from 300 to 400nm, with a major fraction having average particle diameters between 150 and 240 nm.

**Poly Vinyl Pyrrolidone Based Hydrogel Nanoparticles:**

Poly (vinyl pyrrolidone), PVP, is a hydrophilic polymer generally known and approved by FDA as a biocompatible and non-antigenic compound and is therefore safe for biological experiments. Baharali et al. have described a procedure for preparation PVP-based hydrogel NPs with final diameter less than 100nm, using the aqueous cores of reverse micellar droplets as nano reactors . Since the reverse micellar droplets are highly mono dispersed and the droplet sizes can be well-controlled, the NPs prepared using a reverse micellar medium are ideally monodispersed with narrow size distribution. Moreover, their size can be modulated by controlling the size of the reverse micellar droplets . Guowie et al. have synthesized and characterized a magnetic micromolecular delivery system based on PVP hydrogel with PVA as crosslinker. The PVP hydrogel magnetic nanospheres exhibited passive drug release that could be exploited to enhance therapeutic efficacy. The results indicated that hydrogel PVP-based magnetic nanospheres have the potential as drug carriers in magnetically guided chemotherapeutic drug delivery[91].

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