NANOGEL AS A CONTROLLED DRUG DELIVERY SYSTEM

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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 (e.g., hydrophilicity and extremely high water content) with a nanoparticles (e.g., very small size). Several polymeric hydrogel nanoparticles systems have been prepared and characterized in recent years, based on both natural and synthetic polymers, each with its own advantages and drawbacks. Among the natural polymers, chitosan and alginate have been studied extremely for preparation of hydrogel nanoparticles and form synthetic group. Hydrogel nanoparticles based on poly (vinyl alcohol), poly (ethylene oxide), poly (ethyleneimine), poly (vinyl pyrrolidone), and poly-N-isopropylacrylamide have been reported with different characteristics and features with respect to drug delivery. Regardless of the type of polymer used, the release mechanism of loaded agent from hydrogel nanoparticles is complex, while resulting from three main vectors, i.e., drug diffusion, hydrogel matrix swelling, and chemical reactivity of the drug/matrix. Several crosslinking methods have been used in the way to form the hydrogel matrix structures, which can be classified in two major groups of chemically and physically-induced crosslinking.

Keywords: Hydrogel, Nanoparticles, Hydrogel-nanoparticles, Nanogels, sodium alginate, PVP, PEO.

INTRODUCTION

Nanogels are cosslinked particles of sub-micrometer size made of hydrophilic polymers. They are soluble in water, but have properties different from linear macromolecules of similar molecular weight. Such structures, along with their bigger analogues.

As a family of nanoscale particulate materials, 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. tumour 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. 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.

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 19th 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[1]. 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[2]. From a technical point of view, it is extremely important that chitosan is hydro-soluble and positively charged. These properties enable this polymer to interact with negatively charged polymers, and even with certain polyanions upon contact in aqueous environment. These interactive forces and the resulting so-gel transition stages have been exploited for nano-encapsulation purposes[3]. 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. 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. The interesting biocompatibility and low toxicity[4]. Many articles on the potential of chitosan for pharmaceutical applications have been published[5]. Therefore our purpose is to focus on the specific feature and application of the chitosan-based nanoparticulate systems prepared and characterized to date for delivery of macromolecular compounds such as peptides, proteins, antigens, oligonucleotides, and genes.

Alginate-based hydrogel nanoparticles:

In 1993, Rajaonarivony et al. Proposed a new drug carrier made up of sodium alginate[15]. They represented alginate NPs with a wide range of particle sizes (250-850nm), formed within a sodium alginate solution following the addition of calcium chloride followed by poly-Lydine. In this study, the concentrations of both polymer and counterion solutions were lower than those regularly

used for gel formation. Additionally, with doxorubicin as the model drug, they reported that loading capacity could be reached at more than 50mg of drug per 100mg of alginate. Since the end of 1990s until now, the number of studies involving alginate-based NPs is increasing, using the therapeutic agents such as insulin, antitubercular and antifungal drugs, and even it has shown promising remarks in the field of gene delivery.

Table 1: Chitosan based hydrogel nanoparticles prepared by different method.

Method	Preparation technique
Covalent crosslinking	Reacting tetramethoxysilan with hydroxyl groups on the chitosan monomers[6].
Water-in-oil (w/o) emulsion method	Glutaraldehyde crosslinking of the chitosan amino groups, the group produced nanospheres loaded by 5-flurouracil (5-FU), an anticancer drug[7].
Ionic crosslinking	**Ionotropic gelation**- addition of an alkaline phase (pH=7-9) containing tripolyphosphate (TPP) into an acidic phase (pH=4-6) containing chitosan. NPs are formed immediately upon mixing of the two phases through inter and intra molecular linkages created between TPP phosphates and chitosan amino groups[8]. **Insulin-loaded chitosan NPs**-have been prepared by mixing insulin with TPP solution and then adding the mixture to chitosan solution under constant stirring. Chitosan NPs thus obtained were within size range of 300-400nm and loading efficiency of up to 55%[9].
Desolvation method	Dropwise addition of sodium sulphate into a solution of chitosan and polysorbate 80 (used as a stabilizer for the suspension) under both stirring and ultrasonication, desolvated chitosan in a particulate form, the precipitated particles were at micro/nano interface (900±200nm)[10]. **Chitosan-DNA NPs**-have been prepared using the complex coacervation technique. At the amino-to-phosphate groups ratio between 3 and 8 and the chitosan concentration of 100mcg/ml, the particle size was optimized to 100-250nm range with a narrow distribution. The chitosan-DNA NPs could partially protect the encapsulated plasmid DNA from nuclease degradation[11].
Emulsion-droplet coalescence method	A stable emulsion containing aqueous solution of chitosan along with the drug to be loaded is produced in liquid paraffin. At the same time, another stable emulsion containing chitosan aqueous solution containing NaOH is produced in the same manner. When, finally, both emulsions are mixed under high speed stirring, droplets of each emulsion would collide at random and coalesce, thereby precipitaating chitosan droplets to give small solid particles[12].
Reverse micellar method	The surfactant is dissolve in an organic solvent to prepare reverse micelles. To this, aqueous solutions of chitosan and drug are added gradually with constant vortexing to avoid any turbidity. The aqueous phase is regulated in such a way as to keep the entire mixture in an optically transparent micro emulsion phase. Additional amount of water may be added to obtain Nps of large sizes. To this transparent solution, a crosslinking agent is added with constant stirring overnight. The maximum amount of drug that can be dissolved in reverse micelles varies from drug to drug and has to be determined by gradually increasing the amount of dug until the clear dispersion is transformed into a translucent solution. The organic solvent is, then, evaporated to obtain the micellar transparent drug mass. The remaining material is dispersed in water and then, by adding a suitable salt, the surfactant precipitates out. The mixture is, then, subjected to centrifugation. The supernatant solution is decanted, which contains the drug-loaded NPs[13].
Self-assembly via chemical modification	Fractional conjugation of polyethylene glycol, PEG, via an amide linkage to soluble chitosan was shown to yield self-aggregation at basic pH. These aggregates could trap insulin following incubation in phosphate buffer saline (PBS), likely due to the electrostatic interaction between the unconjugated chitosan monomers and the anionic residues of the protein. Depending on the degree of PEGylation, aggregate sizes between 5 and 150nm can be obtained. The degree of PEGylation also influences the release rate, as more extensively PEGylated aggregates release insulin more rapidly[14].

The failure of antitubercular chemotherapy is mainly attributed to the patient non-compliance to frequent long –term multidrug regimens. In a study designed to evaluate the pharmacokinetic and tissue distribution of free and NP-encapsulated antitubercular drugs in different doses, alginate NPs containing isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) were orally administered to mice. The average size of NPs was 235.5 with the drug encapsulation efficiencies of 70-90%, 80-90%, and 88-95% for INH, RIF, and EMB,

respectively. The bioavailability of all drug encapsulated in alginate NPs were significantly higher than those with free drugs[16]. Recently, another study has been published by the same research group, dealing with the chemotherapeutic evaluation of alginate NP-encapsulated azol antifungal and antitubercular drugs again murine tuberculosis. A series of other studies involving NPs of alginate origin is currently available in the literature.

Poly (vinyl alcohol) - based hydrogel nanoparticles:

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[17]. 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± 42.7nm 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 nanoprecipitation, have been used by Galindo-Rodriguez et al, as a comparative scale-up production evaluation to reach PVA-based NPs loaded with ibuprofen[18]. The pilot-scale stirring rates of 790-200rpm led to mean sizes range from 174 to 557 nm for salting-out and 230 to 565 nm for emulsification diffusion.

Heterogeneously structured composites involving PVA have been interested in the field of hydrogel nanoparticles. Biodegradable polymers consisting of short poly (lactone) chains grafted to PVA or charge-modified sulfobutyl-PVA (SB-PVA) were prepared and used as a novel class of water soluble comb-like polymers. These polymers undergo spontaneous self assembling to produce NPs, which form stable complexes with a number of proteins such as human serum albumin, tetanus toxoid and cytochrom C[19].

Preparation of PVA-based NPs encapsulated by poly (lactide-coglycolic acid) (PLGA) microspheres, preparation and release kinetic evaluation of poly (N-vinly caprolactone) NPs loaded by nandolol, propranolol, and tacrine, attempt to aerosol therapy using the biodegradable NPs prepared by branched polyesters diethylaminopropyl amine-poly (vinyl alcohol)-grafted-poly (lactideco-glycolide) (DEAPA-PVA-g-PLGA), DNA nanocarriers formed by a modified solvent displacement method, and the study on local delivery of paclitaxel via drug-loaded PVA-g-PLGA NPs for the treatment of restenosis have all been reported in recent years using PVA or its derivatives as a basis for hydrogel formation[20].

Poly (ethylene oxide) and Poly (ethyleneimine)-based hydrogel nanoparticles:

A new family of nanoscale materials on the basis of disperse 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[21], and oligonucleotides (bound to polycation chains) or hydrophobic molecules (incorporated into nonpolar 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[22]. 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. When conducted in a homogenous aqueous solution, the reaction between amino groups of PEI and imidazolyl carbonyl ends of activated PEO proceeded very rapidly, resulting in formation of transparent hydrogels in only 3-5 min. 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 hydrogels systems, the croslinking reaction was performed by a modified solvent emulsification/evaporation method[23]. 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 formation of a clear suspension. Most of the nanogel particles have a very low density and could not be fractioned by ultracentrifugation. Therefore, crude suspension of nanogel particles was partitioned using gel-permeation chromatography. Several fractions could be separated by particle size from 300 to 400 nm, with a major fraction having average particle diameters between 150 to 240 nm.

Poly (vinyl pyrrolidone)-based hydrogel nanoparticles:

Baharali et al. Have described a procedure for preparation of PVP-based hydrogel NPs with final diameter less than 100 nm, using the aqueous cores of reverse micellar droplets as nanoreactors[24]. Since the reverse micellar

droplets are highly monodispersed 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 el al[25]. Have synthesized and characterized a magnetic micromolecular delivery system based on PVP hydrogel with PVA as crosslinker.

Poly-N-isopropylacrylamide-based hydrogel nanoparticles:

Hydrogel NP networks containing dextran have been developed by G. Huang et al.[26] In their sudy, PNIPAM-co-allylamine NP networks and PNIPAM-co-acrylic acid NP networks are formed by covalently crosslinking. Also, Gan and Lyon[27] have synthesized thermoresponsive core-shell PNIPAM NPs via seeding and feeding precipitation polymerization method. The influence of chemical differentiation between the core and the shell polymers on the phase transition kinetic and thermodynamic behaviour has been examined in their study.

Summary

Nanogels (Hydrogel nanoparticles) are crosslinked particles of sub-micrometer size made of hydrophilic polymers. They are soluble in water, but have properties different from linear macromolecules of similar molecular weight. Such structure, along with their bigger analogues. 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 the hydrophilicity, flexibility, versatility, high water absorptivity, and biocompatibility of these particles. We have reviewed that different methods for the development of Nanogel based on Chitosan, alginate, poly (vinyl alcohol), poly (ethylene oxide), poly (ethyleneimine), poly (vinyl pyrrolidone), and poly-N-isopropylacrylamide polymers. There are different methods based on chitosan polymer for the delivery of macromolecular compounds such as peptides, proteins, antigens, oligonucleotides and genes are covalent crosslinking method, ionic crosslinking method, desolvation method, emulsion-droplet coalescence method, reverse micellar method and self-assembly via chemical modification.

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