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NANOGEL: A DRUG DISCOVERY & DRUG CONTROLLED DELIVERY SYSTEM

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ABSTRACT: Nanogels are an innovative drug delivery system that can play an integral partin pointing out many issues related to old and modern treatment courses such as nonspecific effects and poor stability. Nanogels may be defined as highly cross-linked nano-sized hydrogels ranges from 20-200 nm. They can be administered through various routes, including oral, pulmonary, nasal, parenteral, intra-ocular etc. They have a high degree of drug loading capacityand it shows better permeation capabilities due to a smaller size. They release the drug by pH-responsive, thermosensitive, volume transition, photochemical internalization and Photoisomerization. Nanogel can be synthesized by Photolithographic, modified pullulan, emulsion polymerization, reverse microemulsion polymerization, inverse miniemulsion polymerization and free radical cross- linking polymerization technique. Nanogels can be used for the treatment of cancer, diabetes, inflammation and bone regeneration. This review aims at providing a general introduction on nanogels, recentsynthesis methodology and their novel application in different fields.

Keywords: Nanogels, Drug delivery systems; Drug release mechanism; Stability controlled release, drug delivery, nanogels, polymerization.

INTRODUCTION

Nanotechnology, a relatively novel the technique offers a broad scope for a smart drug delivery and drug manufacturing (nanomedicine) approach involving the design, synthesis and characterization of materials or molecules and devices that have the effective function at the nanometer scale. Nanogels may be defined as highly cross- linked nano-sized hydrogel systems that are either co-polymerized or monomers, which can be ionic or non-ionic [1, 2]. The size of nanogels ranges from 20-200 nm [3]. They can escape renal clearance and prolonged serum half-life period dueto their size. Nanogels are three- dimensional hydrophilic networks that have the tendency to imbibe water or physiological fluid in a large amount, without changing in the internal network structure. Chemical modifications can be made to help to incorporate plenty of ligands that can be used for targeted drug delivery, stimulus-responsive drug release or preparation of composite materials [4]. Nanogels are known to exhibit great qualities that contribute to the drive towards it as a delivery system. They include remarkable thermodynamic stability, the elevated capacity of solubilization, relatively low viscosity, and the capability of undergoing vigorous sterilization techniques [5]. Nanogels are nanoparticles composed of a hydrogel with a cross-linked hydrophilicpolymer with 100–200 nm particle size (Garg et al. 2012b). Physically and chemically cross-linked synthetic polymers (Bencherif et al. 2009) or biopolymers (Kabanov and Vinogradov 2009) constitute nanogels. The pores ofnanogels are filled with micromolecules ormacromolecules (Lee et al. 2007). Nanogels have swelling and degradationproperties with flexible size, large surface area and high water content (Hayashi et al. 2004). Nanogels are used to deliver all biologically active agents and are drugs in a controlled and sustained release manner. Nanogels occur in the form of three- dimensional structures in which drugs, polymers and dispersed phases of liquidcan be entrapped (Alvarez-Lorenzo et al. 2011) (Vintiloiu and Leroux 2008). Theavailability of various polymer systems and ease of alteration of their relatively high affinity to aqueous solutions,

outstanding stability, inertness in the systemic circulation as well as the internal fluids, and appropriateness for molecular incorporation in bulk, they are considered promising carriers for delivery and cellular uptake of proteins, peptides, and other biological compounds [6].

PROPERTIES OF NANOGELS

Biocompatibility and degradability:

Nanogel is made up of either natural or synthetic polymers.The are highly biocompatible and biodegradable, thereby avoiding its accumulation in the organs. Chitosan, ethylcellulose, methylcellulose and various polysaccharide-based polymers like dextran, pullulan and dextrin can be used to prepare the nanogel. Polysaccharides are mostly carbohydrate- based polymers, formed of repeating monosaccharide units linked by glycosidic bonds. These polymers are stable, non- toxic, hydrophilic and biodegradable in nature [7].

Swelling property in aqueous media:

Due to the fact that Nanogels are very small, soft materials, they have the ability to swelling the presence of an aqueous medium. It is considered to be the fundamental property influencing the mechanism of action followed by this drug delivery system. It depends on:

The structure of Nanogels:

This includes the Polymer chain's chemical nature as well as cross-linkingdegree and, in the case of polyelectroly gels, the charge density. Environmental parameters which are related to the variables of the aqueous medium. For instance, in polyelectrolyte gels, pH, as well as ionic strength and ions' chemical nature, are influential factors.

Physical entrapment:

It can refer to the linkage between hydrophilic chains and hydrophobic regions of the polymer or dissolving hydrophobic molecules in hydrophilic vehicles. Covalent attachment of bioactive molecules leads to the formation of dense drug-loaded core.

Controlled self-assembly:

Which is generally for polyelectrolyte- based nanogel. The high loading efficiencyis attributed to the interaction between oppositely charged electrolytes [2]. Other factors also contribute to the high loading capacity, such as the composition, molecular weight, the possible interactions between the drug and the employed polymer and the different functional groups in each polymeric unit [7, 9]

ADVANTAGES OF NANOGELS

- High biocompatibility, which makes nanogels a very promising approach todrug delivery systems [9].
- High biodegradability, which is crucial to avoid accumulation of nanogel material in the bodily organs, thereby leading to toxicity and adverseeffects [7].
- Nanogels are inert in the blood stream and the internal aqueous environment, meaning that they do not induce any immunological responses in the body [6].
- Extremely small size, which induces anumber of effects such as Enhanced permeation capability Avoidance of rapid renal exclusion. Escaping renal clearance leads to prolonged serumhalf-life [9].

LIMITATIONS OF NANOGELS

- The only limitations to using nanogels include:
- It is expensive to remove the surfactant and the solvent at the end of the preparation process although the manufacturing process itself is not very pricey.
- Adverse effects may occur if any traces of polymers or surfactant remain in the body.

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CLASSIFICATION OF NANAOGEL ACCORDING TO THEIR STRUCTURE

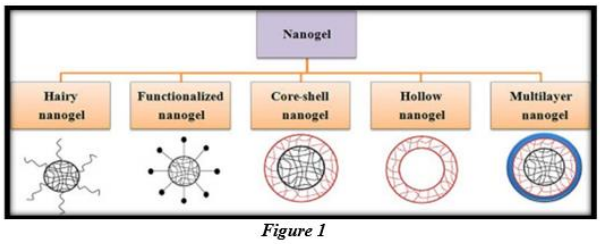

Figure 1

MECHANISM OF NANOGEL

Physical self-assembly of interactivepolymers

Nanogels are formulated using the physical self-assembled polymers method with amphiphilic polymers, where interaction between the drug and solvent occurs by the Van der Waals' interaction, hydrogen bonding, etc. Micro- and macromolecules are entrapped within the nanogels' structure during self-assembly (Booth and Attwood 2000, Riess 2003). Different protein-loaded nanogels are prepared by self-associating hydrophilic polymers. For example, Akiyoshi et al. prepared insulin hydrogels by the cholesterol-modified pullulan method, where they obtained a 20– 30 nm particle size. In this method, the size of the nanogels is controlled by the proper concentration of polymers and different environmental conditions, such as pH, ionic strength, and temperature (Figure 6.1). [11] For example, prepared oppositely charged protein (ovalbumin and lysozyme or ovotransferrin) nanogels by temperature-induced gelation method. Chitosan or ovalbumin can be used to prepare nanogel in the pH- and temperature-induced gelation method. Self-assembled nanogels (120–150 nm) are also prepared using different concentrations of two more stable polymers and suitable for long-term storage.

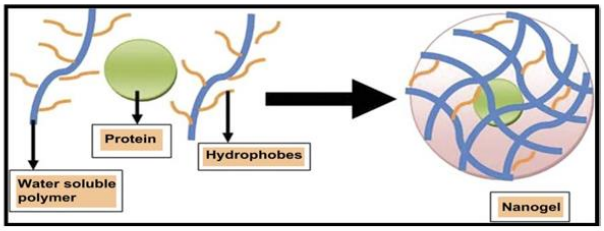

Figure 2: Aggregation of hydrophobically modified polymer, cholesterol-pollutant, in the presence of insulin molecules results in nanogels containing entrapped protein.

Cross-linking of preformed polymers

This method is especially used for preparing large-particle-size nanogels. Cross-linked cationic nanogel was used for polynucleotide delivery. In the cross- linking polymerization method, nanogel was prepared by oil-in-water emulsion, followed by a solvent evaporation method where PEG was conjugated to a branched polyethyleneimine in aqueous media (figure 3). DNA containing cross-linked nanogels was synthesized by mixing thiol-functionalized six-arm branched PEG and DMSO containing DNA by the oxidation process. Both the self-assembled method and the cross-linking method provided opportunities to control the distribution of polymer in nanogels. Various chemically cross-linked nanoparticles found morphologies with spheres, rods, and triodes. Covalent cross-linking of preformed polymer chains provides excellent opportunities for producingfunctional nanogels with large pore sizes for drug delivery

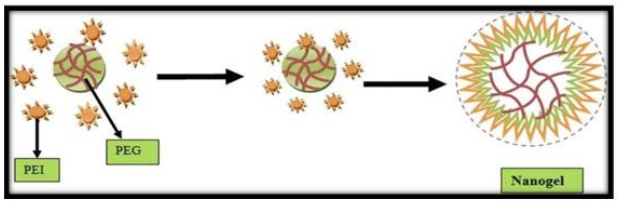

Figure 3: Synthesis of nanogels by cross-linking of the preformed polymer chains

The cross-linking method is especially applied to control the particle size, shape, composition, and surface characteristics of the nanogels. It also provides complete entrapment of the drug in the formulation. Copolymerization method can be carriedout in the presence of vinyl monomers,such as PEG triacrylate, PEG monomethyl ether monomethacrylate, and p-hydroxy styrene.

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Diffusion of the drug from nanogel:-

Diffusion occurs when a drug or otheractive agent passes through a polymer thatforms a controlled released device. The diffusion can occur on a macroscopic scaleas through pores in the polymer matrix oron a molecular level by passing betweenpolymer chains. A normal process ofdiffusion is given in Figure 4. A polymerand an active agent have been mixed to form a homogeneous system, referred to as

The polymer chain binding to each other in micelles structure and characterized by cmc. The aforementioned factors show "thermodynamic" and "kinetic stability" of the formulation, which helps to link both drug and micelles and control the drug release. Diffusionof the drug from the smaller size micelle core is usually not rate limiting (for low-molecular-mass drugs). Simple diffusive process involves polymeric release of doxorubicin for a long period and the initial release is controlled by addition of cationic and anionic polyelectrolyte, which increases the size of the nanogel, and doxorubicin starts to release layer by layer without sudden initial outburst.

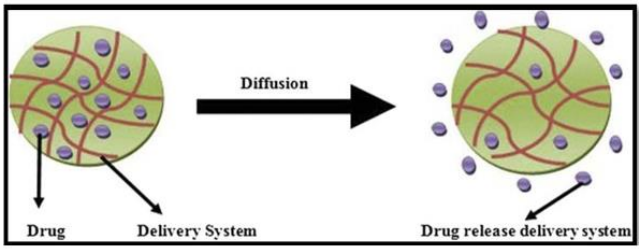

Figure 4: Diffusion of the drug from nanogel

APPLICATIONS

- Applications in cancer therapy
- Applications of nanogels in gene delivery, enzymology, and protein folding.

CONCLUSION

Nanogel systems have been studied for both theoretical and practical aspects. They are widely used for controlled delivery system, targeted delivery system, coatings purpose, and for the cosmetics products. Nanogels show promising future developments, widening the prospects for drug delivery. Every new analysis entails discovery of recent polymer and mechanistic approaches with a promising role in therapies and innovation on fabrication of nanogels design. The use of nanogels permits the advance of biopharmaceutical parameters of anentrapped drug. We increase the use ofthese materials in many fields or other delivery systems. Nanogels are probablyone of the better drug delivery systems to provided controlled or sustained release of the drug. However, we need to design a perfect delivery system that gives proper knowledge of the interaction between the drug and the carrier and the effect of size and drug loading on drug release.

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