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NANOGEL DRUG DELIVERY SYSTEM

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ABSTRACT:

Nanogel has attracted considerable attention as one of the most versatile drug delivery systems especially for site-specific and/or time-controlled delivery of bioactive agents owing to their combining features of hydrogel and nanoparticle. Physically synthesized nanogels can offer a platform to encapsulate various types of bioactive compounds, particularly hydrophobic drugs and biomacromolecules, but they have poor mechanical stability, whereas nanogels prepared by chemical cross-link have a wider application and larger flexibility. As an ideal drug-delivery carrier, nanogel has excellent drug loading capacity, high stability, biologic consistence and response to a wide variety of environmental stimuli. Nowadays, targeting and response especially multiresponse of the nanogel system for drug delivery have become an issue in research.And the application studyof nanogels mainly focuses on antitumor agents and proteins. This review focuses on the formation of nanogels (physical and chemical cross-linking) and their release behavior. Recent application of nanogels is also discussed.

Introduction:

Nanogels may be defined as nano-sized hydrogen systems which are highly cross linked systems in nature involving polymer systems which are either co-polymerised or monomers.

Sudden outbreak in the field of nanotechnology have introduced the need for developing nanogel systemswhich proven their potential to deliver drugs in controlled, sustained and targetable manner.

With the emerging field of polymer sciences it has now become inevitable to prepare smart nano-systems which can prove effective for treatment as well as clinical trials progress. Nevertheless, these systems havebeen investigated from a longer period of time for making advancements in synthetic procedures not only for drug delivery but for miscellaneous agents like quantum dots, dyes and other diagnostic agents .

Traditionally in the name of gels we have heard of semisolid formulations with three dimensional network of organic systems encompassing fluids and drugs. Majorly these systems have been the part of traditionalsystem of topical drug delivery for local effects. Prospects of targeted drug delivery perhaps could not been established with these preparations.

The significance of nano-sized microgel and hydrogel have arisen due to specific delivery system anticipation. Wide variety of polymer systems and the easy alteration of their physico-chemical characteristics has given advantage for versatile form of nanogel formulations.

\Recent studies at clinical level have shown promising value of nanogels. Nanogels have revolutionized the field of gene therapy, since delivery of gene has now become possible within cellular organales for gene silencing therapy systems.

Literature Review

Yoshiro Tahara, Kazunari Akiyoshi

Advanced drug delivery reviews 95, 65-76,2015

Since nanogels (nanometer-sized gels) were developed two decades ago, they were utilized as carriers of innovative drug delivery systems. In particular, immunological drug delivery via self-assembled nanogels(self-nanogels) owing to their nanometer size .

Sakineh Hajebi, Navid Rabiee, Mojtaba

Nanogels are three-dimensional nanoscale networks formed by physically or chemically cross-linking polymers. Nanogels have been explored as drug delivery systems due to their advantageous properties, such as biocompatibility, high stability, tunable particle size, drug loading capacity, and possible modification of the surface for active targeting by attaching ligands that recognize cognate receptors on thetarget cells or tissues.

Brielle Stawicki, Tyler Schacher, Hyunah Cho

Chemotherapy and radiation remain as mainstays in the treatment of a variety of cancers globally, yet sometherapies exhibit limited specificity and result in harsh side effects inpatients. Brain tissue differs from other tissue due to restrictions from the blood–brain barrier, thus systemic treatment options are limited. The focus of this review is on nanogels as local and systemic drug delivery systems in the treatment of brain cancer.

Yanlong Yin, Ben Hu, Xiao Yuan, Li Cai, HuileGao, Qian Yang

Nanogel-based nanoplatforms have become a tremendously promising system of drug delivery. Nanogelsconstructed by chemical crosslinking or physical self-assembly exhibit the ability to encapsulatehydrophilic or hydrophobic therapeutics, including but not limitedto small-molecule compoundsproteins .

Aim

A Review of Nanogel Drug Delivery System

Objectives:-

1 Doxorubicim uptake accelerated
2 Minimal phototoxicity of phenophorbide
3 Elevated activity and reduced cyototoxicity of fludarabin
Efficient siRNA delivery

Routes Of Administration:

1. Oral
2. Pulmonary
3. Nasal
4. Parenteral
5. Intra-ocular
6. Topical

Properties of Nanogels

Biocompatibility and degradability-

Nanogel based drug delivery system is highly biocompatible and biodegradable due to this characteristicsit is highly promising field now a days.

Swelling property in aqueous media -

The most beneficial feature of Nanogels is their rapid swelling/de-swelling characteristics.

Higher drug loading capacity –

The properties of higher drug loading capacity of nanogels depend on the functional group present in the polymeric unit. These functional groups have a tremendous effect on drug carrying and drug-releasing properties, and some functional groups have the potential to conjugate with drugs/antibodies for targeting applications.

Advantages of Nanogels

1. Highly bycompatible
2. Biodegradable
3. Non immunological responses
4. Invasion by reticuloendothlial system is prevented.
5. Release of therapeutics can be regulated by cross-linking densities.
6. Good permeation capabilities due to extreme small size .
7. Applied to both hydrophilic and hydrophobic drugs and charged solutes.

Disadvantages Of Nanogels

1. Expensive technique to completely remove the solvent sand surfactants at the end ofpreparationprocess.

Surfactant or monomer traces may remain and can impart toxicity (Rossetti et al.,2002, Xu et al.,2007

Classification of Nanogel

Nanogels are more commonly classified into two major ways. The first classification is based on their responsive behavior, which can be either stimuli- responsive or nonresponsive.

1. In the case of non-responsive microgels, they simply swell as a result of absorbing water.
2. Stimuli-responsive microgels swell or deswell upon exposure to environmental changes such as temperature, pH, magnetic field, and ionic strength. Multi- responsive microgels are

responsive to more than one environmental stimulus (Guptaet al., 2002; Sasaki and Akiyoshi, 2010).

The **second classification** is based on the type of linkages present in the network chains of gel structure, polymeric gels (including nanogel) are subdivided into two main categories

1) Physical cro\ss-linked gels-

Physical gels or pseudo gels are formed by weaker linkages through either (a) vander Waals forces, (b) hydrophobic, electrostatic interactions, or (c) hydrogen bonding. A few simple methods are available to obtain physical gels.

These systems are sensitive and this sensitivity depends on polymer composition, temperature, ionic strength of the medium, concentrations of the polymer and of the cross-linking agent. The association of amphiphilic block copolymers and complexation of oppositely charged polymeric chains results in the formation of micro- and nanogels inonly a few minutes. Physical gels can also be formed by the aggregation and/or self- assembly of polymeric chains.

2.Liposome Modified Nanogels-

Kono et al.,have disclosed liposomes bearing succinylated poly(glycidol)s; these liposomes undergo chain fusion below pH 5.5 that has been shown to efficiently deliver calcein to the cytoplasm. Liposomes anchored by or modified with poly(N isopropylacrylamide)-based copolymeric groups are suitable for thermo- and pH-

responsive nanogels, which are being investigated for transdermal drug delivery(Labhasetwar et al., 2007).

3.Micellar Nanogels-

Polymer micellar nanogels can be obtained by the supramolecular self-assembly of amphiphilic block or graft copolymers in aqueous solutions. They possess unique core-shell morphological structures, where a hydrophobic block segment in the form of a core is surrounded by hydrophilic polymer blocks as a shell (corona) that stabilizes the entire micelle. The core of micelles provides enough space for accommodating

4.hybrid Nanogels-

Hybrid nanogels are defined as a composite of nanogel particles dispersed in organic or inorganic matrices.Group of studies (Akiyoshi et al., 1999; Akiyoshi et al., 2000) have demonstrated nanogel formation in an aqueous medium by selfassembly or aggregation of polymer amphiphiles, such as pullulan-PNIPAM, hydrophobized polysaccharides, and hydrophobized pullulan. This group has investigated cholesterol- bearing pullulan (CHP) nanogels. These nanogels have the ability to form complexes with various proteins, drugs, and DNA; and it is even possible to coat surfaces ofliposomes, particles, and solid surfaces including cells (Nishikawa et al., 1996; Kuroda et al., 2002).

Synthesis Of Nanogels

1)Photolithographic techniques-

2) Micromolding method-

3.Fabrication of biopolymers

4.Inverse (mini) emulsion method

5.Membrane emulsification

6.Carbodiimide coupling -Novel pullulan

chemistry modification

Swelling of Nanogel particle:-

In water, swelling of nanogels is controlled by several factors:

The cross-linker concentration.

For example, at high ionic strengths, the swelling of cationic PAETMAC nanogels was governed by the cross-linker concentration, while at low ionic strengths the swelling was influenced by both the cross-linker and charge concentration (McAllister et al., 2002).

Applications of Nanogels:-

Nanogel-based drug delivery formulations improve the effectiveness and safety of certain anti-cancer drugs, and many other drugs, due to their chemical composition, which have been confirmed from in vivo studyin animal models. There is still some work to do before these products are ready for human trials.

1 Autoimmune disease -

Nanogels were fabricated by remotely loading liposomes with mycophenolic acid (MPA) solubilized withincyclodextrin, oligomers of lactic acid-poly(ethylene glycol) that were terminated with an acrylate end group, and Irgacure 2959 photoinitiator. Particles were then exposed to ultraviolet light to induce photopolymerization of the PEGoligomers. The Nanogels are attractive because of their intrinsic abilities to enable greater systemic accumulations of their cargo and to bind more immune cells in vivo than free fluorescent tracer, which, we reason, permits high, localized concentrations of MPA. This new drug deliverysystem increases the longevity of the patient and delays, the onset of kidney damage, a common complication of lupus (Michael et al., 2013).

2 Opthalmic -

pH-sensitive polyvinyl pyrrolidone-poly (acrylic acid) (PVP/PAAc) nanogels prepared by γ radiationinduced polymerization of acrylic acid (AAc) in an aqueous solution of polyvinyl pyrrolidone (PVP) as a template polymer were used to encapsulate pilocarpine in order to maintain an adequate concentration of the pilocarpine at the site of action for prolonged period of time (Abd et al., 2013).

Current Status In Clinical Trials And Future Perspectives Of Nanogels

Nanogels have already been employed as DDS in vivo and in clinical trials, primarily for cancer therapy. In mice with subcutaneous fibrosarcoma, subcutaneous injections ofrecombinant murine interleukin - 12 (IL - 12) encapsulated in CHP nanogels, via incubation at room temperature, led to a prolonged elevation of IL - 12 in the sera and resulted in significant growth retardation of the tumor (Shimizu et al .,2008). Clinical trialof Cholesteryl pullulan (CHP) nanogels has shown tremendous potential in delivering peptides. The CHP- HER-2 vaccine was administered to nine patients biweekly dosing of 300μg with booster doses. The vaccinewas well tolerated with some skin sensitivity at site of subcutaneous injection. All the patients showed CD4+and CD8+ T- cell response suggestingbetter therapeutic activity (Dorwal et al., 2012). CHP nanogels have further proved their prospects for clinical trails by reducing cytotoxicity of nervous system cells by showing increase in binding capacity to Aβ oligomer in treating Alzheimer's disorder (Lee et al., 2009). Researchers(Nukolova et al., 2011) have used PEO-b-PMA diblock copolymers to form nanogels with free OH groupsat the PEO termini. Nanogels were then conjugated to activated folic acid with terminal amino groups, and further loaded with cisplatin or doxorubicin. On human ovarian carcinomas A2780 overexpressing folate-

receptor-a, targeted nanogels would be able to specifically recognize their target. Recent prospects in diabetes management by optical sensitive insulin loaded silver nanoparticle nanogel of poly(4vinylphenylboronic acid-co-2-(dimethylamino) ethyl acrylate) have been designed opening new era in the field of clinical trial (Wu et al., 2010

Conclusion :-

Nanogels are promising and innovative drug delivery system that can play a vital role by addressing the problems associated with old and modern therapeutics such as nonspecific effects and poor stability. Futuredesign anddevelopment of effective nanogel based DDSs for in vivo applications requires a high degree ofcontrol over properties. Nanogels appearto be excellent candidates for brain delivery. One future goal of research in this area shouldbe the improved design of microgels/nanogels with specific targeting residues to enable highly selective uptake into particular cells. Thiswill be especially important for the targeting of cancer cells, thereby reducing non-specific uptake into healthy cells. More and more in vivo and in vitro study should be needed to confirm the use of this delivery system on human being.[12]

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