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An Overview of Nanogel Drug Delivery System

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ABSTRACT

Nanogels based materials have high drug loading capacity, biocompatibility, and biodegradability which are the key points to design a drug delivery system effectively. The pursuit of this review article is to concisely describe the recent development of nanogel drug delivery system in terms of drug loading and swelling of drug from nanogels. Furthermore, biomedical application and current clinical trial studies of nanogel are summarized briefly. Here, different types of nanogels along with the synthetic procedure and mechanism of drug release from nanogel carrier are mainly focused. An intensive study of clinical trial in future will confirm nanogel as a suitable carrier for drug delivery.

INTRODUCTION

The term 'nanogels' defined as the nanosized particles formed by physically or chemically crosslinked polymer networks that is swell in a good solvent. The term "nanogel" (NanoGel™) was first introduced to define cross-linked bifunctional networks of a polyion and a nonionic polymer for delivery of polynucleotides (cross-linked polyethyleneimine (PEI) and poly (ethylene glycol) (PEG) or PEG-*cl*-PEI) (Kabanov and Vinogradov, 2008). Sudden outbreak in the field of nanotechnology have introduced the need for developing nanogel systems which 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. (Dorwal et al., 2012).

Nanogels are superior drug delivery system than others because

1. The particle size and surface properties can be manipulated to avoid rapid clearance by Phagocytic cells, allowing both passive and active drug targeting.
2. Controlled and sustained drug release at the target site, improving the therapeutic efficacy and reducing side effects. Drug loading is relatively high and may be achieved without chemical reactions; this is an important factor for preserving the drug activity.
3. Ability to reach the smallest capillary vessels, due to their tiny volume, and to penetrate the tissues either through the paracellular or the transcellular pathways (Gonçalves *et al.*, 2010).
4. Highly biocompatible and biodegradable. A model of drug release from nanogel is given in figure 1.

ROUTES OF ADMINISTRATION

- Oral,
- pulmonary
- nasal
- parenteral
- intra-ocular
- topical

PROPERTIES OF NANOGELS

Biocompatibility and degradability

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

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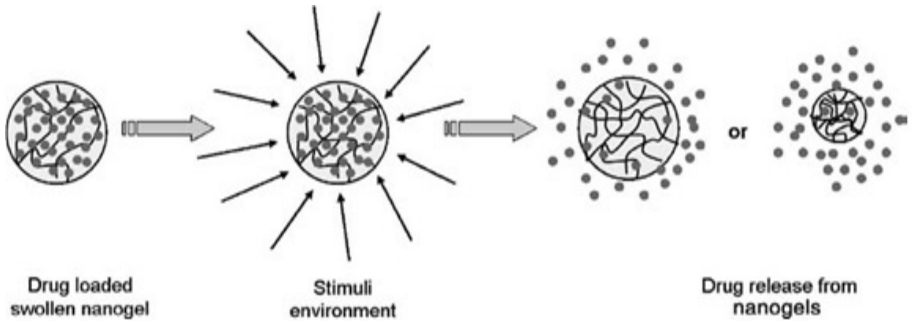

Fig. 1: Drug release model from nanogel.

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.

These pendent functional groups of polymeric chains contribute toward establishing hydrogen bonding or van der Waals forces of interactions within the gel network and thus facilitate the drug-carrying efficiency. Moreover, the presence of functional groups at interface with drug/protein molecules is also responsible for higher loading.

Particle size

Nanogels typically range in size of 20–200 nm in diameter and hence are effective in avoiding the rapid renal exclusion but are small enough to avoid the uptake by the reticuloendothelial system (Labhasetwar *et al.,* 2007).

Good permeation capabilities due to extreme small size. More specifically, it can cross the blood brain barrier (BBB).

Solubility

Nanogels are able to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel.

Electromobility

Nanogels could be prepared without employing energy or harsh conditions such as sonication or homogenization, which is critical for encapsulating biomacromolecules.

Colloidal stability

Nanogels or polymeric micellar nanogel systems have better stability over the surfactant micelles and exhibit lower critical micelle concentrations, slower rates of dissociation, and longer retention of loaded drugs.

Non-immunologic response

This type of drug delivery system usually does not produce any immunological responses.

Others

Both type of drugs (hydrophillic and hydrophobic drugs and charged solutes) can be given through nanogel.

Such properties of nanogel are significantly influenced by temperature, presence of hydrophilic/ hydrophobic groups in the polymeric networks, the cross-linking density of the gels, surfactant concentration, and type of cross-links present in the polymer networks.

DISADVANTAGES OF NANOGELS

a) Expensive technique to completely remove the solvent sand surfactants at the end of preparation process.
b) Surfactant or monomer traces may remain and can impart toxicity (Rossetti *et al.,* 2002, Xu *et al.,* 2007).

CLASSIFICATION OF NANOGELS

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 non-responsive.

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 (Gupta *et 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:

Physical cross-linked gels

Physical gels or pseudo gels are formed by weaker linkages through either (a) van der 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 in only a few minutes. Physical gels can also be formed by the aggregation and/or self-assembly of polymeric chains.

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).

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 various drug or biomacromolecules by physical entrapment. Furthermore, the hydrophilic blocks may form hydrogen bonds with the aqueous media that lead to a perfect shell formation around the core of micelle. Therefore, the drug molecules in the hydrophobic core are protected from hydrolysis and enzymatic degradation. Researchers (Li *et al.,* 2006) successfully developed highly versatile *Y*-shaped micelles of poly(oleic acid-*Y*-*N*-isopropylacrylamide) for drug delivery application. In this study, the delivery of prednisone acetate above its lower critical solution temperature (LCST) was demonstrated. A representation of micelle formation is shown in Figure 2.

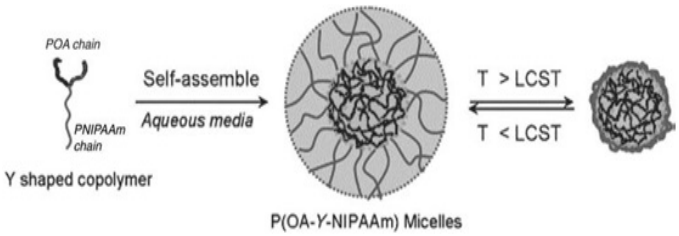

Fig. 2: *Y*-shaped copolymer self-assembly to give micelle structures.

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 self-assembly 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 of liposomes, particles, and solid surfaces including cells (Nishikawa *et al.,* 1996; Kuroda *et al.,* 2002).These hybrid nanogels are also capable of delivering insulin and anticancer drugs more effectively. CHP is composed of pullulan backbone and cholesterol branches. The CHP molecules self aggregate to form mono-dispersed stable nanogels through the association of hydrophobic groups that provide physical cross-linking points as shown in Figure 3

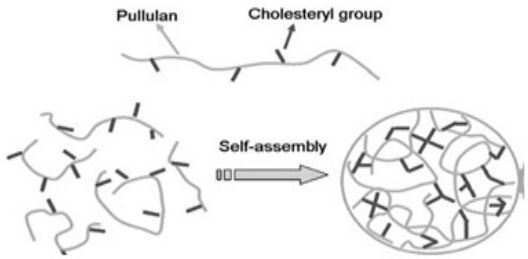

Fig. 3: Schematic representation of CHP nanogel preparation by physical cross-linking (self-assembly).

Chemically cross-linked gels

Chemical gels are comprised of permanent chemical linkages (covalent bonds) throughout the gel networks. The properties of cross-linked gel system depend on the chemical linkages and functional groups present in the gel networks. Different nanogels have been synthesized using different strategies for chemical linking of polymeric chains. Usually, hydrophilic polymers and hydrophilic–hydrophobic copolymers are obtained by the polymerization of vinyl monomers in the presence of multifunctional cross-linkers that are the launch cross-linking points within and between the polymeric chains. These cross-linking points allow modifying entire physicochemical properties of the gel systems. A few versatile cross-linking agents have been reported (Labhasetwar *et al.,*2007).

Example

It has been demonstrated a facile approach for nanogel (20–200 nm) preparation in which pendant thiol groups are incorporated into the polymeric chains and their subsequent intramolecular disulfide cross-linking is achieved through “environmentally friendly chemistry” (green chemistry) (Aliyer *et al.,* 2005) .

SYNTHESIS OF NANOGELS

Photolithographic techniques

Photolithography has been explored to fabricate 3D hydrogel particles and microgel or nanogel rings for drug delivery. The photolithographic method requires the development of techniques for surface treatment of stamps or new materials for replica molds to permit the release of molded gels from stamps or replica molds (Jung *et al.,* 2008). As shown in Figure 4**,**

photolithography consists of five steps. In the first step, the UV cross-linkable polymer, which possesses low surface energy, as a substrate is released on the pre-baked photo resist-coated water. The next step involves molding the polymer into patterns on the silicon wafer by pressing the quartz template onto the polymer and exposed it to the intense UV light.

In the third step, the particles with a thin residual interconnecting film layer are uncovered by removing the quartz template. Subsequently, this residual thin layer is removed by a plasma containing oxygen that oxidizes it. In the last step, the fabricated particles are directly collected by dissolution of the substrate in water of buffer (Glangchai *et al.*, 2008; Sasaki and Akiyoshi, 2010).

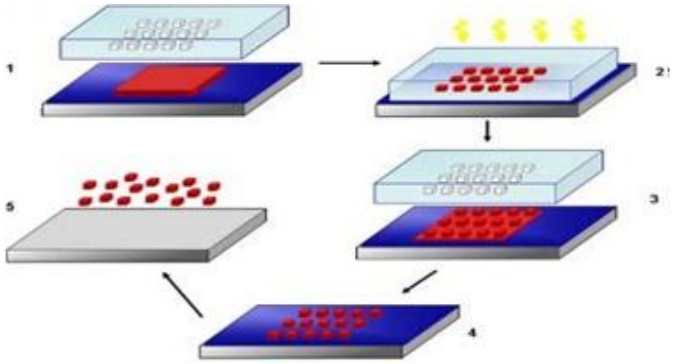

Fig. 4: Schematic diagram of five steps involved in photolithography (Glangchai *et al.*, 2008).

A top-down method called ‘‘Particle Replication In Nonwetting Templates (PRINT)’’was developed to fabricate submicron-sized microgels with control over particle size, shape, and composition. Using PRINT, DNA, proteins, and small-molecule therapeutics were incorporated into 200 nm PEG-based microgels by a simple encapsulation technique to demonstrate the compatibility of PRINT with (bio) molecules. Their sizes were ranged from 200nm to micron-scale in diameter with various shapes such as trapezoidal, bar, conical, and arrow (Jung *et al.*, 2008). In addition, PRINT is a GMP-compliant (GMP=good manufacturing practice) platform amenable for particle fabrication on a large scale (Xu *et al.*, 2008).

Micromolding method

The methods are similar to photolithographic techniques. However, they can minimize the need to use costly lithographic equipment and clean room facilities. In the process, cells were suspended in a hydrogel precursor solution consisting of either methacrylated hyaluronic acid (MeHA) or PEGDA or a photoinitiator in water. The resulting mixture was deposited onto plasma-cleaned hydrophilic PDMS patterns and then photocrosslinked via exposure to UV light. The resulting cell-laden microgels were removed, hydrated, and then harvested. They were also molded into various shapes including square prisms, disks, and strings.

Fabrication of biopolymers

Chitosan (CS), hyaluronan (HA), and Dex are naturally occurring carbohydrate-based biopolymers. Many methods have been developed for the preparation of microgels of these biopolymers.

They can be classified into four categories: waterin-oil (W/O) heterogeneous emulsion, aqueous homogeneous gelation, spray drying method, and chemical cross linking of Dex (Jung *et al.*, 2008).

Water-in-oil (W/O) heterogeneous emulsion methods

W/O emulsion methods involve generally two steps: emulsification of aqueous droplets of water soluble biopolymers in continuous oil phase with an aid of oil-soluble surfactants and cross linking of biopolymers with water-soluble cross linkers.

Inverse (mini) emulsion method

- A W/O emulsion is formed from a mixture consisting of aqueous biopolymer droplets and a continuous oil phase using either a homogenizer or a high-speed mechanical stirrer.
- Resulting aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents.
- then crosslinked microgel particles are prepared as dispersion in organic solvents
- purified by precipitation, centrifugation, washing with organic solvents such as isopropanol, and lyophilization.
- the size of the prepared microgel particles can be controlled by amount of surfactants and crosslinking agents as well as stirring speed during the formation of inverse emulsion.

Example

preparation of HA-based microgels, carboxylic acids of HA were crosslinked with adipic dihydrazide (ADH) as a crosslinker in the presence of ethyl-3-[3-dimethylamino]propyl carbodiimide (EDCI) in aqueous droplets.

Reverse micellar method

Similar to the inverse (mini) emulsion method, the reverse micellar method also involves a W/O dispersion; however, a relatively large amount of oil-soluble surfactants is used to form a thermodynamically stable micellar solution consisting of aqueous droplets dispersed in the continuous oil phase .The resulting micellar droplets have a submicron size ranged from tens to hundreds of nanometers in diameter (Figure 5).

Tumor targeted CS-based nanogels were prepared in inverse microemulsion of hexane containing Aerosol OT as a stabilizer in the presence of doxorubicin (Dox)-modified Dex. Aqueous glutaraldehyde was used to crosslink CS. The resulting Dox-encapsulating CS-based nanogels have a diameter of around 100nm.

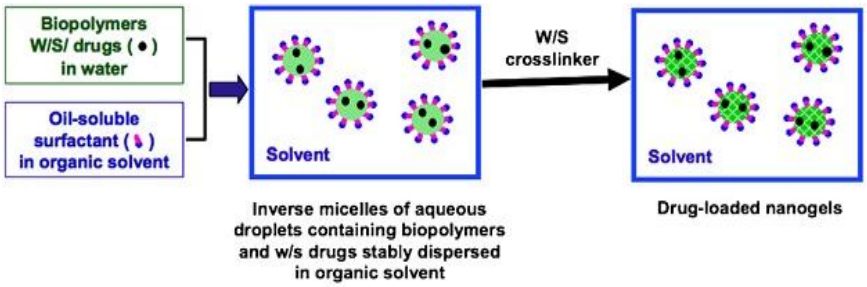

Fig. 5: Illustration of the reverse micellar method for the preparation of nanogels.

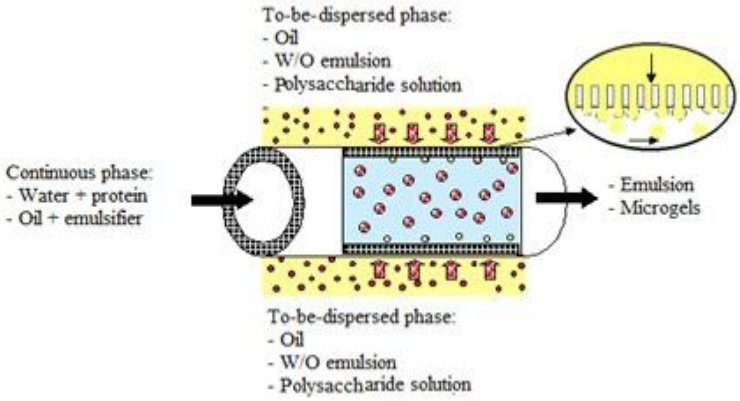

Fig. 6: Schematic diagram of the membrane emulsification technique.

Membrane emulsification

In the membrane emulsification technique, the to-be-dispersed phase is passed through the membrane (glass or ceramic), which possesses uniform pore size. Under certain conditions the emulsion droplets or microgels with specific morphology are formed on the surface of the membrane and afterwards, with a continuous phase that is flowing across the membrane, these fabricated emulsion droplets or microgels are recovered (Nakashima *et al.,* 2000). These fabricated emulsion droplets can be in different emulsion formation such as water-in-oil (W/O), oil-in-water (O/W), oil-in-water-in-oil (O/W/O), and water-in-oil-in-water (W/O/W) (Oh *et al.*, 2008b). The size of the formed droplet is controlled by the membrane pore size, velocity of the continuous phase, and pressure of the trans-membrane. Figure 6 represents the diagram using this synthesizing technique.

Chemical cross linking

Biodegradable Dex-based microgels and hydrogels were prepared by various methods based on chemical cross linking including Carbodiimide coupling, Michael addition reaction, Free radical polymerization.

Carbodiimide coupling

Novel pullulan chemistry modification

Synthesis of cholesterol based pullulan nanogel (CHP) was done by reacting mixture of cholesterol isocynate in dimethyl sulfoxide and pyridine. Pullulan was substituted with 1.4 cholesterol moieties per 100 anhydrous glucoside units. The preparation was freeze dried and in aqueous phase it formed nanogel which was complexed with W-9 peptide for delivery in osteological disorders. The capacity of pullulan has been known to act as good protein carrier hence was used in nanogel formulation for drug delivery.

Further CHP has been modified with acrylate group and their thiol group was modified with polyethylene glycol by adopting Michael addition reaction, this allowed reduction in mesh size to 40 nm encapsulating 96% interleukin-12. These nanosystems have also been investigated by modifying cholesterol units by 1.1 units of cholesteryl group per 100 glucose units of parent pullulan shown significant interaction with Aβ oligomer and monomer for alzhiemer's disease treatment enhancing microglia and cortical cell viability.

More recently pullulan have been used in folate receptor targeted system in which folate was substituted to pullulan by 1.6 glucose units. Further Coupling of pullulan and photosensitizer (pheo-A) was done with carbodimide to produce the conjugate which was converted to nanogel by dialysis in DMSO against deionised water, investigated for photodynamic therapy and were successfully localized at tumor cells to cause cell death by photo destruction (Dorwal *et al.,* 2013).

Heterogeneous free radical polymerization

Various heterogeneous polymerization reactions of hydrophilic or water-soluble monomers in the presence of either difunctional or multifunctional crosslinkers have been mostly utilized to prepare well-defined synthetic microgels. They include-precipitation, inverse (mini) emulsion, inverse micro emulsion, and dispersion polymerization utilizing an uncontrolled free radical polymerization process.

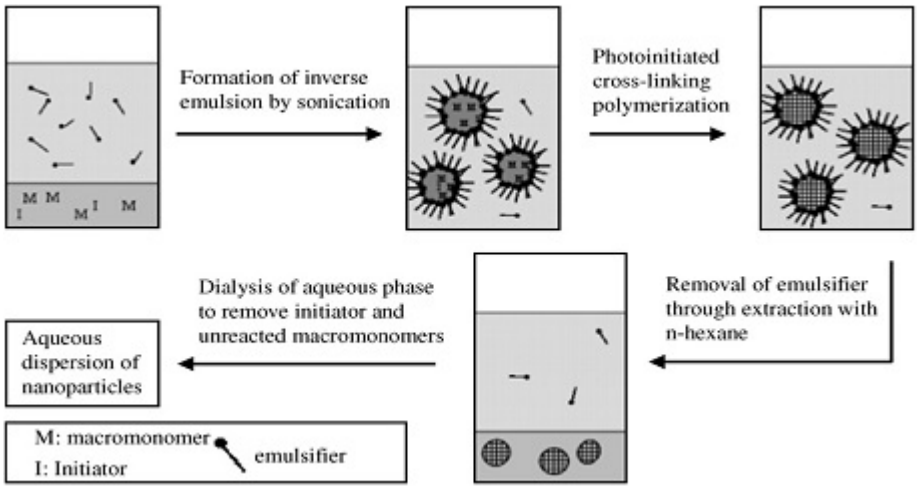

Fig. 7: Illustration of preparation for microgels of PEO-b-PPO-b-PEO via inverse emulsion polymerization.

Precipitation polymerization

Precipitation polymerization involves the formation of homogeneous mixture at its initial stage and the occurrence of initiation and polymerization in the homogeneous solution. As the formed polymers are not swellable but soluble in the medium, the use of crosslinker is necessary to crosslink polymer chains for the isolation of particles. As a consequence, the resulting crosslinked particles often have an irregular shape with high polydispersity.

Peppas *et al.*,synthesized narrow size distribution poly (methacrylic acid-*g*-ethylene glycol) (P (MAA-*g*-EG)) nanospheres through precipitation polymerization for the oral delivery of proteins. They obtained better control over particle size and particle size distribution by controlling monomer concentration in water. They also revealed that increasing the cross-linker concentration during polymerization decreased the equilibrium swelling of the nanospheres (Robinson and Peppas, 2002; Thomas *et al.*, 2006).

Inverse (mini) emulsion polymerization:

Inverse (mini) emulsion polymerization is a W/O polymerization process that contains aqueous droplets (including water-soluble monomers) stably dispersed with the aid of oil-soluble surfactants in a continuous organic medium. Stable dispersions are formed by mechanical stirring for inverse emulsion process and by sonification for inverse miniemulsion polymerization. Upon addition of radical initiators, polymerization occurs within the aqueous droplets producing colloidal particles.

Inverse microemulsion polymerization

While inverse (mini) emulsion polymerization forms kinetically stable macroemulsions at, below, or around the critical micellar concentration (CMC), inverse microemulsion polymerization produces thermodynamically stable microemulsions upon further addition of emulsifier above the critical threshold. This process also involves aqueous droplets, stably dispersed with the aid of a large amount of oil-soluble surfactants in a continuous organic medium; polymerization occurs within the aqueous droplets, producing stable hydrophilic and water-soluble colloidal nanoparticles having a diameter of less than 50–100nm.

Inverse microemulsion polymerization was explored for the synthesis of well-defined nanogels. Poly(vinylpyrrolidone)-based nanogels incorporated with Dex as a water-soluble macromolecular carbohydrate drug were prepared (Gaur *et al.*, 2000; Bharali *et al.*, 2003).

Dispersion polymerization

In the process, most ingredients including monomers, polymeric stabilizers, and initiators are soluble in an organic solvent as a continuous phase.

At the onset, polymerization occurs in a homogeneous reaction mixture; however, the formed polymers become insoluble in the continuous medium, ultimately leading to the formation of stable dispersion of polymeric particles with an aid of colloidal stabilizers Hydrophilic monodisperse micron-sized particles of PHEMA were also prepared by dispersion polymerization in the presence of PEO-b-poly (1,1,2,2-tetrahydroperfluorodecyl acrylate) diblock copolymer as a stabilizer in supercritical carbon dioxide, and methacryloyl-terminated PMMA in a 55/45 (wt/wt) mixture of 2-butanol/tolune. Drugs and magnetic nanoparticles were either physically incorporated or chemically attached to microgels. The resulting microgels were effective as drug delivery carriers and for DNA applications (Jung *et al.*, 2008).

Heterogeneous controlled/living radical polymerization

Recently, CRP has been explored as a tool to preparation of well controlled polymer–protein/peptide bioconjugates. Various methods for CRP have been developed; however, the most successful techniques include atom transfer radical polymerization (ATRP), stable free radical polymerization (SFRP), and reversible addition fragmentation chain transfer (RAFT) polymerization (Jung *et al.*, 2008).

Addition fragmentation transfer (RAFT) process

Reversible addition fragmentation transfer (RAFT) process adopted a single step of synthesis for PEGylated poly (N,N'-dimethylaminomethyl methacrylate) nanogel utilizing an ampiphilic macro RAFT agent trithiocarbonate with hydrophobic dodecyl chain supporting polymerization rather than two step process which produced 500-800 nm size. However single step process presented advantage of reduced radii of nanogel (10 nm) apt for gene delivery (Dorwal *et al.,* 2012, Yan and Tao, 2010).

- dodecanethanoil and tetrabutyl ammonium bromide mixed and N_2 passed at 10˚c temperature
- then carbon di -sulfide and acetone added drop wise
- After then,chloroform and sodium hydroxide added
- 30 minutes later yellow ppt obtained
- Ppt dissolve in isopropanolol and crystallized in hexane, RAFT agent obtained
- PEG reacted with RAFT in dichloroethane
- polymerization in polymer with aqueous dispersion with RAFT agent to obtain nanogel

Conversion of Macroscopic Gels to Nanogels

Several synthetic methodologies are identified to prepare macroscopic gel networks (bulk gel networks or wall-to-wall cross-links) and are easy to prepare, because it is not necessary to control the synthetic parameters as are required in nanogel or microgel synthesis to control the size.The macroscopic gel networks are generally prepared by bulk polymerization, which produce a solid and the network structure with macroporous blocks.

These blocks are then crushed, grounded, and sieved to obtain gels of desired particle size. However, this is a time- and energy-consuming process and results in significant loss of material. Nevertheless, micro- and nanogels obtained from this method have particles of different shape and sizes (Labhasetwar *et al* ., 2007).

SWELLING OF NANOGEL PARTICLES

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).

- charge concentration (for polyelectrolyte gels),
- and environmental parameters (such as pH, ionic strength, temperature).

For example, core–shell nanogels of cross-linked PEG-*b*-PMA swelled as pH increased from 5 to 9 due to ionization of carboxylic groups of PMA (Bontha *et al.,* 2006). Conversely, the size of PEG-*cl*-PEI nanogel decreased as pH increased from ca. 8.5 to 10 due to deprotonation of PEI amino groups (Bronich *et al.,* 2001).

DRUG LOADING

Nanogels are widely used as carriers of therapeutic agents. A successful nanodelivery system Should have a high drug-loading capacity,thereby reducing the required amount of carrier. Drugs can be incorporated in nanogels by

Covalent Conjugation

Covalent conjugation of biological agents can be achieved using preformed nanogels or during nanogel synthesis. For example, enzymes modified with acrylic groups were copolymerized with acrylamide either in inverse microemulsion (Khmelnitsky *et al.,* 1992) or dilute aqueous solutions (Yan *et al.,* 2006, 2007) to obtain nanosized hydrogels.

Physical Entrapment

Physical entrapment was employed for incorporation of proteins in cholesterol-modified pullulan nanogels (Akiyoshi *et al.,* 1998) and siRNA in HA nanogels (Lee *et al.,* 2007). In addition, hydrophobic molecules can incorporate into nonpolar domains formed by hydrophobic chains present in selected nanogels. For example, prostaglandin E2 was solubilized in nanogels of cholesterol-modified pullulan (Kato *et al.,* 2007). In another study, *N*-hexylcarbamoyl-5-fluorouracil (HCFU) was noncovalently incorporated in cross-linked nanogels of *N*-isopropylacrylamide (NIPAAm) and *N*-vinylpyrrolidone (VP) copolymers (PNIPAAm/VP) (Soni *et al.,* 2006). Doxorubicin was also loaded in amphiphilic cross-linked nanogels based on pluronic F127 (Missirlis *et al.,* 2005) and POEOMA (Oh *et al.,* 2007a). In most cases, loading achieved due to hydrophobic interaction of the drug molecules with the nanogel result in relatively low degrees of loading (not more than ca. 10%).

Self-Assembly

The self-assembly process, defined as the autonomous organization of components into structurally well-defined aggregates (Gonçalves *et al.,* 2010).It has many beneficial features such as –

- it is cost-effective,
- versatile and facile;
- The process occurs towards the system's thermodynamic minima, resulting in stable and robust structures.

Molecular self-assembly is characterized by diffusion followed by specific association of molecules through non-covalent interactions, including electrostatic and/or hydrophobic associations (Figure 8). Individually, such interactions are weak, but dominate the structural and conformational behavior of the assembly due to the large number of interactions involved.(Zhang,2002) While oppositely charged polysaccharides associate readily as a result of electrostatic attractions (Rinaudo ,2006), interactions among neutral polysaccharides tend to be weaker, or nonexistent, a modification with chemical entities able to trigger assembly being necessary. A convenient strategy consists on

linking hydrophobic grafts to e.g., a highly water-soluble polysaccharide, inducing the formation of nanoparticles via hydrophobic interactions. This kind of amphiphilic polymers can be constructed by three routes:

- hydrophobic chains grafted to a hydrophilic backbone,
- hydrophilic chains grafted to a hydrophobic backbone (grafted polymers)
- or with alternating hydrophilic and hydrophobic segments (block polymers).

Upon contact with an aqueous environment, amphiphilic polymers spontaneously form self-aggregated nanoparticles, via intra- or intermolecular associations between the hydrophobic moieties, primarily to minimize the interfacial free energy. The important feature, from the physicochemical point of view is that the molecule is able to orient itself to expose the hydrophilic regions to the polar environment (normally the aqueous medium) and the hydrophobic segments aggregates in the internal core of the material. The concentration above which the polymeric chains aggregate is called the critical micelle concentration or the critical aggregate concentration.

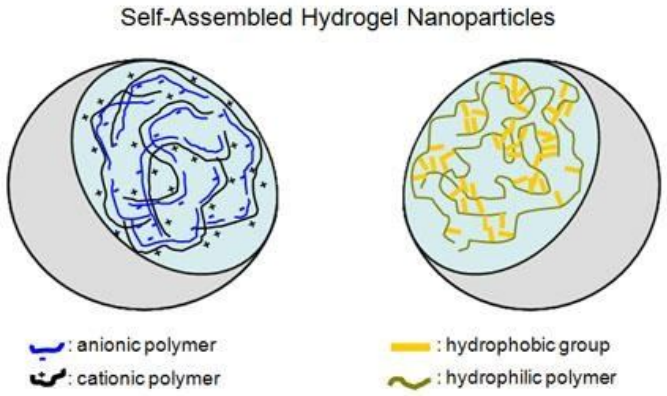

Fig. 8: Schematic representation of intermolecular interactions driving self-assembly processes that includes (a) electrostatic interactions and (b) hydrophobic association.

MECHANISM OF DRUG RELEASE FROM NANOGELS

The drug can be released from the nanogels as a result of

Diffusion

Example: The diffusional release of doxorubicin from stable hydrogel nanoparticles based on pluronic block copolymer (Missirlis *et al.*, 2006). This release mechanism is simple and has been successfully employed in various nanomedicines, such as polymeric micelles that have already reached a clinical stage (Kabanov and Alakhov, 2002).

Nanogel degradation

The degradation of these nanogels was shown to trigger the release of encapsulated molecules including rhodamine 6G, a fluorescent dye, and Doxorubicin, an anticancer drug, as well as facilitate the removal of empty vehicles.

Example: The release of Doxorubicin was significantly increased due to glycol chitosan nanoparticles sensitivity to pH stimuli due to grafting of diethylaminopropyl group. Significant mesh size alteration has been seen in dietylaminoethyl methyacrylate cationic nanogel for release of medium size molecules by virtue of pH sensitivity (Dorwal *et al.*, 2012).

Displacement by ions present in the environment

There is an increased interest in developing nanogels that can release biological agents in response to environmental cues at the targeted site of action.

For example: disulfide cross-linked POEOMA nanogels biodegraded into water-soluble polymers in the presence of a glutathione tripeptide, which is commonly found in cells (Oh *et al.*, 2007).Cell membrane-triggered release of negatively charged drugs from complexes with cationic nanogels was also proposed to explain cellular accumulation of an NTPs drug delivered with nanogels (Vinogradov, 2006).

Others

Photochemical internalization and photoisomerisation

Excitation of photosensitizers loaded nanogels leads to production of singlet oxygen and reactive oxygen species which cause oxidation of cellular compartment walls such as endosomal barrier walls which effects release of therapeutics into cytoplasm. Polyelectrolyte hydrogels that incorporate biological agents via electrostatic bonds allow for release of biological agents in response to environmental changes. For instance, hydrogels of cross-linked PEG and PAA were shown to release an oppositely charged protein upon 1) addition of calcium ions that reacted with carboxylate groups of PAA and displaced the protein or 2) acidification of the media by decreasing pH from 7.4 to 5.5 (Oh *et al.*, 2007b). A similar mechanism was proposed for release of oligonucleotides from PEG-*cl*-PEI nanogels (Vinogradov *et al.*, 1999). In this case, electrostatically bound oligonucleotides are believed to be displaced by negatively charged cellular components.

APPLICATION 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* study in animal models. There is still some work to do before these products are ready for human trials.

Cancer

Cancer treatment involves targeted delivery of drugs with expected low toxicities to surrounding tissues and high therapeutic efficacy. Nanogels technology assures all these advantages as listed below:

Polymer	Type of nanogel	Remarks
Carboxymethyl chitosan- linoleic acid	-	Adryamycin (Gonçalves et al., 2009)
poly(N-isopropylmethacrylamide) (pNIPMAm)	-	siRNA anti EGFR
PEO-b-PMA	-	Cisplatin or Doxorubicin (Tomasina et al., 2013)
Acetylated chondroitin sulfate	Self organizing nanogel	Doxorubicin loaded
Cross linked polyethyleneimine and PEG/pluronic	Biodegradable nanogel	5'-triphosphorylated ribavirin reduced toxicity
Glycol chitosan grafted with 3-diethylaminopropyl groups	pH-responsive	Doxorubicin uptake accelerated
Pullulan/folate-pheophorbide	Self quenching polysaccharide based	Minimal phototoxicity of pheophorbide
Crosslinked branched network of polyethyleneimine and PEG	Polyplex nanogel	Elevated activity and reduced cytotoxicity of fludarabine
Heparin pluronic nanogel	Self assembled nanogel	RNaseA enzyme delivery internalized in cells
Cross linked poly[2-(N,N-diethylamino)methacrylate] core and PEG	PEGylated and partially quarternized amine nanogel	Efficient siRNA delivery
Polyethyleneimine nanogels	Size dependent property nanogel	Suicide gene hTERT –CD-TK delivered for lung cancer
Cholesterol bearing pullulan nanogels	Sustained release nanogel	Recombinant murine interleukine-12 sustained tumour immunotherapy
Reducible heparin with disulfide linkage	Reducible nanogel	Internalization of heparin for apoptotic death of melanoma cells
Pluronic polyethyleneimine/DNA complex	Temperature responsive and volume transition nanogels	Thermo responsive endosomal rupture by nanogel and drug release
Acetylated hylauronic acid	Specific targeting nanogel	Doxorubicin loaded nanogel
Poly(N-isopropylacrylamide) and chitosan	Thermosensitive magnetically modalized	Hyperthermia cancer treatment and targeted drug delivery
Polyacrylamide	Novel core shell magnetic nanogel	Radiopharmaceutical carrier for cancer radiotherapy
Acylate group modified cholesterol bearing pullulan	Cross linked raspberry like assembly nanogel	Efficient interleukin-12 encapsulation and plasma levels
Cross linked poly(ethylene oxide)and polythyleneimine	Nanosized cationic hydrogel	Enhancing oral and brain bioavailability of oligonucleotides
Cholesterol bearing pullulan with modified amino group	Nanogel quantum dot hybrid	Probe for bioimaging.
Poly(N-isopropylacrylamide-co-acrylamide)	In-situ gelatinized thermosensitive nanogel	Drug loading capacity of low mol.weight 5-flourouracil was higher than that of biomacromolecules, bovine serum albumin.
Hydroxypropylcellulose-poly(acrylic acid)	pH and temperature responsive cadmium(II) ions quantum dots	Optical pH sensing, cell imaging and drug loading (Dorwal et al., 2012)

Autoimmune disease

Nanogels were fabricated by remotely loading liposomes with mycophenolic acid (MPA) solubilized within cyclodextrin, 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 PEG oligomers.

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 delivery system increases the longevity of the patient and delays, the onset of kidney damage, a common complication of lupus (Michael *et al.*, 2013).

Opthalmic

pH-sensitive polyvinyl pyrrolidone-poly (acrylic acid) (PVP/PAAc) nanogels prepared by γ radiation-induced 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).

Diabetics

"An Injectable Nano-Network that Responds to Glucose and Releases Insulin"has been developed. It contains a mixture of oppositely charged nanoparticles that attract each other. This keeps the gel together and stops the nanoparticles drifting away once in the body. To make the nanogel respond to increased acidity dextran, a modified polysaccharide, was used. Each nanoparticle in the gel holds spheres of dextran loaded with insulin and an enzyme that converts glucose into gluconic acid. Glucose molecules can easily enter and diffuse through the gel. Thus when levels are high, lots of glucose passes through the gel and triggers release of the enzyme that converts it to gluconic acid. This increases acidity, which triggers the release of the insulin. There is still some work to do before the gel is ready for human trials (www. medical newstoday. com/articles/ 260664. php, accessed 19th june2013).

Neurodegenerative

Nanogel is a promising system for delivery of ODN to the brain. A novel system for oligonucleotides delivery to the brain based on nanoscale network of cross-linked poly (ethylene glycol) and polyethylenimine ("nanogel") is used for the treatment of neuro- degenerative diseases. Nanogels bound or encapsulated with spontaneously negatively charged ODN results in formation

of stable aqueous dispersion of polyelectrolyte complex with particle sizes less than 100 nm which can effectively transported across the BBB. The transport efficacy is further increased when the surface of the nanogel is modified with transferrin or insulin (Vinogradov *et al.,* 2004) .

In stopping bleeding

A nanogel composed of protein molecules in solution has been used to stop bleeding, even in severe gashes. The proteins self-assemble on the nanoscale into a biodegradable gel (http://en.wikipedia.org/wiki/Nanogel).

Anti-inflammatory action

Poly-(lactide-*co*-glycolic acid) and chitosan were used to prepare bilayered nanoparticles and the surface was modified with oleic acid. Hydroxypropyl methyl cellulose (HPMC) and Carbopol with the desired viscosity were utilized to prepare the nanogels. Two anti-inflammatory drugs, spantide II and ketoprofen drugs which are effective against allergic contact dermatitis and psoriatic plaque were applied topically along with nanogel. The result shows that nanogel inncreases potential for the percutaneous delivery of spantide II and ketoprofen to the deeper skin layers for treatment of various skin inflammatory disorders (Punit *et al.*, 2012).

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 of recombinant 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 trial of 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 vaccine was well tolerated with some skin sensitivity at site of subcutaneous injection. All the patients showed $CD4^+$ and $CD8^+$ T- cell response suggesting better 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 groups at 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. In a A2780 model subcutaneously inoculated to mice maintainedon a folate deficient diet, iv administration of the targeted nanogels would permit to enhance anti-tumor efficacy of cisplatin and to decrease the kidney toxicity compared to the free drug.This is a ongoing approach for clinical trial. Recent prospects in diabetes management by optical sensitive insulin loaded silver nanoparticle nanogel of poly(4-vinylphenylboronic acid-co-2-(dimethylamino) ethyl acrylate) have been designed opening new era in the field of clinical trial (Wu *et al.,* 2010). Development of antibiotic conjugated nanogels and their in-vivo application have given promising approach towards phase 1 clinical trail (Vinogradov, 2004). Nanogel seems to be excellent candidates for drug delivery system; more study need to be conducted at the single cell level. An investigation into the mechanisms of uptake not only at the blood – brain barrier, but also at the level of neurons and/or glial cells within the central nervous, will demonstrate which nanogels favor a cytosolic destination over an endosomal or nuclear, for example. Such studies are necessary if nanogels are ever to be proposed as specific drug delivery systems for targeting at the subcellular level.

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. Future design and development of effective nanogel based DDSs for in vivo applications requires a high degree of control over properties. Nanogels appear to be excellent candidates for brain delivery. One future goal of research in this area should be the improved design of microgels/nanogels with specific targeting residues to enable highly selective uptake into particular cells. This will 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.

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