Colloidal and Supramolecular Drug Delivery Systems

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INTRODUCTION

Colloidal dispersions fall somewhere between real solutions and coarse dispersions in terms of dimension. The word "colloidal" is typically used to describe systems where the particle size of the dispersed phase is in nanometer size range. For pharmaceutical applications, the nanoparticles were dispersed in liquid and aqueous polymer dispersions to form colloidal systems [Dickinson 2015, 211-33]. Nanoparticles have the ability to create three-dimensional multi-component structures that lead to the design of drug delivery systems with abundant desired properties, like the ability to deliver hydrophobic drugs [Gelderblom, Verweij, Nooter, Sparreboom*et al.* 2001, 1590-1598], to cross the natal barricades [Dong and Mumper 2010, 597-615] and to selectively target these nanomedicines at desired site in the body [Nkansah, Antipas, Lu, Varma *et al.*2013, 150-161].

The modern era of medical science offers fresh opportunities for probing the essential functions of the human body. The fundamental aim of delivering drugs via innovative systems is to achieve uniform blood or tissue level that is valuable and non-toxic over a comprehensive period of time. The objectives of cutting-edge medicines have been hampered due to the development of nanotechnology. Nanotechnology is a collection of atomic, molecular, or macromolecular scale procedures and techniques that guarantee the controlled creation and application of nanometer-scale objects, devices, or systems [Salata 2004, 3]. The method through which a medicine is administered to the body has an impact on its efficacy. The principle drug delivery system distributed drugs at a desired rate in the body during treatment and shows their actions at the target site only. Recently, no drug delivery system has been able to attain all these goals.

These innovative drug delivery systems (DDS) were developed by combining knowledge from several fields, including polymer science, bioconjugate chemistry, molecular biology, and pharmaceutics.

A supramolecular system is a self-assembled system in which noncovalent bonds help to join the molecular units together to form a complex structure. Examples of these noncovalent interactions include metal coordination, hydrogen bonding, van der Waals forces, hydrophobic attractions, electrostatic, and π-π interactions [Kato and Bara 2008, 128]. Thus, supramolecular chemistry involves the study of amassed molecules or ions that are joined by noncovalent relations, like electrostatic interactions, dispersion interactions, and solvophobic effects [Steed, Turner DR, and Wallace 2007]. The requirement for energy depends on the driving force. The amphiphilic nature of the component molecules acted as the driving force to form the lipid bilayer structure. Thus, various supramolecular structures can be created by different types of amphiphile molecules using the principles of supramolecular chemistry [Yoon and Jang 2010, 211-222; Kumar, Sharma, Singh, Singh *et al.* 2012, 474830].

Different supramolecular structures, like liposomes, microemulsions, surfactant/polymer micelles, etc., have the potential to act as drug carriers to amend the pharmacokinetic and physicochemical characteristics of drugs. Among those liposomes are already commercialized as formulations like Doxil for the management of Kaposi's sarcoma, ambisome as an antifungal agent, visudyne for age-related macular degeneration and choroidal neovascularization. Scantily soluble drugs can be delivered orally in the form of microemulsions due to changes in bioavailability and expected absorption behavior. An immune suppressant like neural is used after transplant operations in the form of a microemulsion. Numerous formulations of polymer micelles have already been evaluated in clinical studies and are being researched as potential drug carriers. Supramolecular systems can be customised by designing the molecular components with effective drug delivery to specify body regions [Kawakami, Ebara, Izawa, Sanchez-Ballester et al. 2012, 2388-2398].

Colloidal and supramolecular drug delivery systems have found wide applications in drug delivery [Zhang and Ma 2013,1215-1233], gene therapy [Mellet, Fernandez, Benito 2011, 1586-1608], and medical imaging [van de Manakker, Vermonden, van Nostrum and Hennink 2009, 3157-3175; Zhang and Ma 2013, 1-39]. These new drug delivery systems (DDS) have various advantages that are listed in table1-1. These innovative drug delivery systems (DDS) were developed by combining knowledge from several fields, including polymer science, bioconjugate chemistry, molecular biology, and pharmaceutics. The following is a list of the desirable characteristics of a novel drug delivery system to be used for therapeutic purposes [Desai 2012, 282-295]:

1. Complete knowledge of essential elements and how they work together.
2. A description of important traits and how performance is affected by them.
3. The capacity to mimic important properties throughout production.
4. Simple to create in sterile form.
5. Ability to penetrate constrictive biological barriers and target or accumulate at the intended place of action.
6. It is reliable to use, stable, and simple to administer and store.

Why Colloidal and Supramolecular Drug Delivery Systems Were Created

The ability of nanoparticles to create three-dimensional multi-component structures may accomplish copious required properties for pioneering systems of drug delivery, such as the ability to cross biological barriers to deliver hydrophobic drugs and the potential to selectively target these nanomedicines at a selected site in the body.

1. **Biological barriers to drug delivery:** A drug has to navigate several biological barriers to reach successfully to its targeted disease sites. To achieve high systemic bioavailability, oral medications need to penetrate deeply into the intestinal epithelium and remain stable in the gastrointestinal tract [Alonso 2004, 168-172].

As the blood-brain barrier (BBB) prevents numerous hydrophilic compounds from diffusing into the cerebrospinal fluid, it acts as a significant obstacle in curing many CNS and brain illnesses. Several nanoparticle-based approaches, including nanospheres, liposomes, and cationic albumin nanoparticles, are designed to carry medications over the BBB to solve this issue [Silva 2008, S4].

The tumour is diversified in nature [Jang, Wientjes, Lu and Au 2003, 1337-1350]. The existence of collagen in the tumour extracellular matrix [Netti, Berk, Swartz, Grodzinsky et al. 2000, 2497-2503] and injured lymphatic drainage [Maeda, Sawa, and Konno 2001, 47-61] are the main barriers to drug delivery. For both nanoparticles and macromolecules, high permeability and retention effects in the microenvironment of tumours are engaged to augment the delivery of tumour medication [Greish 2007, 457-464].

2. **Delivery of hydrophobic drugs**: The pharmaceutical industry has to face many challenges for the effective and secure delivery of hydrophobic medicinal molecules. Toxic solvents and surfactants are required for the manufacture of a suitable dosage form for hydrophobic drugs, which compromises the drug distribution and leads to severe adverse effects [Gelderblom, Verweij, Nooter, and Sparreboom 2001, 1590-1598]. Nab-paclitaxel is an albumin-bound chemotherapeutic nanoparticle formulation that does not contain cremophor. It eliminates the cremophor ethanol vehicle to prevent hypersensitivity reactions caused by solvents. Since micelle entrapment with solvent-based paclitaxel cannot occur, nabpaclitaxel also displays linear pharmacokinetics.

3. **Desire for targeting:** Targeting improves effectiveness, lowers adverse effects, and decreases systemic medication exposures to undesirable regions. Therapeutic drugs can be delivered more precisely and with less toxicity by incorporating prearranged structures of nanoparticles into different moieties for targeted delivery [Lammers, Hennink, Storm 2008, 392-397]. Targeting molecules for receptors, peptides, proteins, and antibodies make up the majority of nanoparticles' active targeting components [Duncan 2006, 688-701]. A few nanomedicines are also made to specifically target tumour endothelial cells [Danhier, Vroman, Lecouturier, Crokart et al. 2009, 166-173]. A common technique to solve the solubility issue with pharmaceuticals is nanonization, which produces drug nanocrystals. Various techniques, like precipitation, milling, self-assembly, and high-pressure homogenization produced drug particles in the nano range [Nkansah, Antipas, Lu, Varma et al. 2013, 150-161].

Table 1-1: Advantages of colloidal and supramolecular drug delivery system.

S.No.	Advantages of colloidal and supramolecular drug delivery system
1.	The solubility issue related to a drug can be solved by entrapping it in nanoparticles. Depending on the design of nanoparticles prepared to increase solubility and control drug administration, different nanoparticles have distinct pharmacokinetic characteristics [Vega-Villa, Takemoto, Yanez, Remsberg et al. 2008, 929-938].
2.	To improve the therapeutic efficacy or lessen unfavourable side effects, nanoparticles can be targeted at specific cells of the human body [Italia, Bhatt, Bhardwaj, Tikoo et al. 2007, 197-206].
3.	Lower dose frequency and dosage are necessary to maintain the appropriate therapeutic response.
4.	The amount of drug administered during drug rehabilitation is reduced.
5.	Multiple dosages of standard dosage forms cause fluctuations in drug levels in the blood, which a novel drug delivery mechanism helps to prevent.
6.	There are fewer negative effects as a result of high plasma concentrations [Moghimi, Hunter, and Murray 2005, 311-330].
7.	The degradation of drugs in the first pass of metabolism and due to the digestive system is reduced.
8.	The maximum therapeutic effect is observed at minimum dose of a drug.
9.	High-potency medications' safety margins can be raised [Vega-Villa, Takemoto, Yanez, Remsberg et al. 2008, 929-938].
10.	When a medication molecule is specifically focused on a particular tissue or organ, normal tissues are unaffected [Italia, Bhatt, Bhardwaj, Tikoo et al. 2007, 197-206].
11.	Enhanced patient compliance by: ➢ Site-specific medication delivery ➢ Increased drug efficacy. ➢ Improved convenience. ➢ Lessen toxicity / side effects. ➢ A shorter stay in the hospital. ➢ Effective therapies for diseases those were once incurable. ➢ Potential for preventative use. ➢ Decreased long-term and short-term health care costs. ➢ Improved patient compliance.

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2

CLASSIFICATION OF COLLOIDAL AND SUPRAMOLECULAR DRUG DELIVERY SYSTEM

Colloidal carrier system includes different carriers which are shown in Fig. 2-1. Details of some colloidal carrier systems are shown in table 2-1.

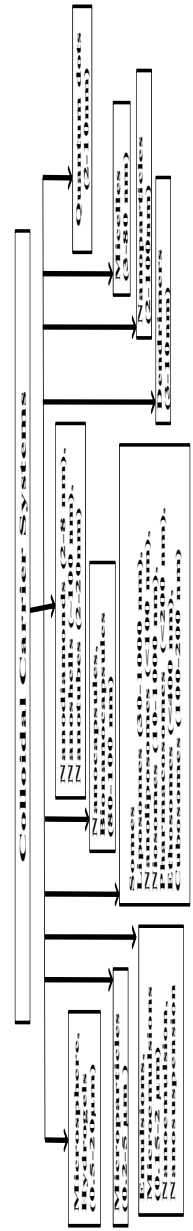

Fig. 2-1: Schematic represen ion of colloidal carrier systems.

Table 2-1: Colloidal carrier systems.

S. No.	Nanocarriers and their size range	Preparation methods	Characteristics	Applications	References
1.	Nanoparticles (10-1000 nm)	• Polymerization • Emulsification evaporation, • By solvent displacement • Emulsification diffusion.	Solid or hollow particles in which drugs particles are encapsulated, entraped or binded.	They stimulate penetration through cell membranes and boost stability in the blood circulation with their nano size ranges. They are therefore employed to direct medications, proteins, and DNA to specific cells and organs.	Domínguez-Delgado, Rodríguez-Cruz, Escobar-Chávez, Calderón-Lojero et al. 2011, 102-107
2.	Liposomes (25 nm-100 μm)	• Sonication • Extrusion • Mozafari method	Concentric lipid bilayers that are spaced apart by aqueous buffer compartments form the structure of these vesicles.	used to deliver proteins, chemotherapeutics, RNA, DNA, xenobiotics, antigens and in the treatment of cancer, infections, meningitis	Barichello, Ishida, Kiwada 2010, 461-472
3.	Dendrimers (3-10 nm)	• Polymerization	These are three-dimensional in nanoscale, regularly branched proportioned core-shell structure with a core, branches, and functional end groups	They serve as biomarkers for *in vitro* cell labelling and the delivery of medicinal and analytical drugs.	Menjoge, Kannan, Tomalia 2010, 171-185

4.	Quantum dots (2-10nm)	• Viral assemblage • Colloidal assemblage • Electrochemical assemblage.	These tiny colloidal semiconductor nanocrystals, which range in size from 2 to 8 nm, are made up of natural surfactants, predecessors, and solvents.	They are used in living tissue imaging, high throughput screening, optical encoding in gene expression investigations, and cancer identification and management.	Rzigalinski and Strobl, 2009, 280-288
5.	Ethosomes (<400 nm)	• Cold method • Hot method	These are used as carriers for delivery of drugs into deep skin layers and/or the systemic circulation.	Used in cosmetics and for delivery of drug into systemic circulations.	Elsayed, Abdallah, Naggar, and Khalafallah 2006, 60-66
6.	Aquasomes (60-300 nm)	Preparation of the core ↓ Carbohydrate coatings ↓ Immobilization of drugs	Aquasomes is a self-assembled three-layered structure having a nano crystalline core, carbohydrate and drug coating. The inorganic cores are coated with polyhydroxyl compounds which are responsible for their hydrophilic character.	They are utilised to transport insulin, enzymes like DNAase, pigments and colours, xenobiotics and antigens, as well as red blood cells, viral antigens, and vaccines.	Rojas-Oviedo, Salazar-López, Reyes-Gasga, Quirino-Barreda2007, 223-230

7.	Niosomes (10-1000 nm)	• Hand shaking method • Ether injection method • Microfluidization • Sonication method • Multiple membrane extrusion method • Bubble method • Formation of niosomes from proniosomes	Bilayered structures prepared with non-ionic surfactants	Used as carrier for targeting of bioactive agents and in neoplasia and leishmaniasis	Hong, Zhu, Jiang, Tang et al. 2009, 96-102
8.	Nanoemulsions (20-200nm)	• High-pressure homogenization • Microfluidization • Phase Inversion temperature	Nanoemulsions are heterogeneous systems made up of two immiscible liquids, in which one phase is distributed as nanometric droplets with the aid of an emulsifier into another that act as continuous phase	Used to distribute medications intranasally and sublingually as well as to increase the penetration of formulation through the epithelium layer	Elnaggar, El-Massik, and Abdallah 2009, 133-141

9.	Nanoliposomes (<100nm)	• Sonication technique • Emulsification-evaporation method • Lipid layer hydration method • Extrusion method • Microfluidization method • Ethanol method • Heating Method	Nanoliposomes are nano form of liposomes	Nanoliposomes have important applications in various fields, like cancer therapy, in nanotherapy for identification, in cosmetics, in gene delivery, in agriculture and in food technology	Rohilla and Dureja 2009, 213-224
10.	Carbon nanotubes (2–20 nm)	A pioneer solution is injected ↓ the product is deposited onto a process tube ↓ On cooling the process tube, the multi-walled CNT material is formed which is collected by scraping from the wall of tube.	They are hollow graphitic nanomaterials, in which the simple layers of graphite, rolled in a tubular shape to produce a single- or multi-walled structure	They are used as a carrier for anticancer drugs, immunoactive compounds, proteins and genetic materials, used in photothermal therapy of cancer, in biosensors, used as tips for AFM	Ivanova, Lamprecht, Loureiro, Huzil et al. 2012, 403-415

11.	Cubosomes (100-200 nm)	• Sonication	These are self-assembling aqueous surfactant systems that form thermodynamically secure bicontinuous cubic liquid phases with crystalline structure.	They are utilised for the delivery of enzymes, peptides, antibiotics, antimuscarinic medications, and analgesics.	Bei, Marszalek, and Youan 2009a, 1032-1039; Bei, Marszalek, and Youan 2009b, 1040-1047
12.	Nanoshells (~100 nm)	• Coprecipitation reaction • Gold-seeded method	Possessing a non-conductive glass interior that is encased in a gold- and silver-colored metallic shell	Nanoshells are used to detect DNA, microorganisms, cancer cells, tumors, antibodies	Gheorgh, Cui, Karmonik, Brazdeikis et al. 2011, 554
13.	Nanospheres (25-115 nm)	• Self-assembly of block copolymers • Emulsion polymerization • Templates polymerization	Nanospheres are submicron size particles which entrapped drugs for enteral and parenteral administration to prevent drug dispossession, metabolism and cellular efflux.	Hollow nanospheres are used as electronic, optical, magnetic and controlled drug-delivery carriers, their antioxidant properties can counterbalance the side effects of chemotherapeutics and other cytotoxic drugs on normal cells and tissues, also used to prepare both nanocapsules and nanospheres	Wang, Luo, Shao, and Zhou 2010, 376-383

14.	Bionanocapsules (80-100 nm)		Bionanocapsules are spherical nanoparticles. Due to presence of the pre-S1 peptide at their exterior, they have a special affinity for human hepatocytes. They effectively transferred genes, peptides, and siRNA to the liver without inducing any impact on the brain.	used to deliver recombinant hepatitis B vaccine, and in the treatment of brain tumors	Shishido, Mieda, Hwang, Nishimura et al. 2010, 5726-5731
15.	Nanocapsules (80-100 nm)	• Nanoprecipitation • Double emulsification • Emulsion-diffusion • Emulsion-coacervation, • Layer-by-layer • Polymer-coating	In nano-vesicular systems, the medicine is injected inside a hollow that is encircled by a polymer covering which have a conventional core-shell configuration. The cavity may house the active ingredient in various forms.	used to deliver anti-cancer drugs, anti-inflammatories, immunosuppressants, immunoglobulins, hormones, diuretics, anti-pneumocystics, and vitamins, among other medicines	Mora-Huertas, Fessi, and Elaissari 2010, 113-142

16.	Nanodiamonds (2 to 8 nm)	• Nanodiamonds can be prepared by non-covalent and covalent amendment of functional groups and complex moieties	Nanodiamonds (NDs) are carbon nanomaterials with condensed octahedral diamond like structure.	Nanodiamonds are used in materials science and nanotechnology-based industries for therapeutic molecule delivery, protein immobilization, bioimaging, and biosensorsand also used in delivery of chemotherapeutic agents to breast and liver tumor cells	Zhu, Li, Li, Zhang et al. 2012, 302-312
17.	Micelles (<50 nm)	• Injection method • Solvent-evaporation method • Thin-film hydration method	Micelles are spherical structures with amphiphilic nature poised of a non-aqueous core and aqueous shell. Micelles of amphiphilic copolymers are used to encapsulate hydrophobic organic molecules and polymers to improve their effects in biological environments	They are used to deliver anticancer drugs and as a diagnostic imaging technique in the form of nanomedicine, used as ocular carriers for anti-inflammatory drugs, plasmids and genes.	Wang, Ravi, Martinez, Chinnasamy 2012, 82-92

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DIFFERENT TYPES OF COLLOIDAL AND SUPRAMOLECULAR DRUG DELIVERY SYSTEM

3-i. Nanogels

Nanogels are water-based dispersions of hydrogels formed from nanosized physically or chemically cross-linked frameworks of polymers. Nanogels are a promising technology that is being researched to help in the healing process of wounds. They have the capacity to encapsulate a variety of merchandise, including growth hormones required to promote the creation of new blood vessels and tissues, as well as anti-inflammatory and antibacterial medications. Due to their amazing stability in the environment and high loading capacity, nanogels are used as carriers to deliver drugs to the target site. Unloaded nanogels swell due to the entrapment of a large amount of water. Nanogels collapsed to form stable nanoparticles that entrapped biological agents instinctively through electrostatic, vanderwaals, and hydrophobic interactions between the agent and the polymer matrix.

The agglomeration of nanogels can be avoided by using poly(ethylnene glycol) (PEG) during their formulation to form a defensive hydrophilic layer around them. Due to their remarkable stability, these nanogels guard against biological agent deficiency via cellular metabolic processes. Overall, nanogels have excellent potential for circulatory drug delivery and improving oral and cerebral accessibility of biomacromolecules, as well as lowering the molecular weight of medications.

Preparation of Nanogels

The following methods are used to make nanogels:

(i) Physical self-assembly of interactive polymers
(ii) Chemical cross-linking of preformed polymers

(iii) Polymerization of monomers in a homogeneous phase or in a micro- or nano-heterogeneous environment
(iv) Template-assisted nanofabrication of nanogel particles

1. Physical Self-Assembly

In this technique, the nanogels are prepared in aqueous media under mild conditions. Self-associating hydrophilic polymers can encapsulate biomacromolecules like proteins through hydrogen bonding and electrostatic interactions with each other [Akiyoshi, Kobayashi, Shichibe, Mix *et al.* 1998, 313-320]. Through proper selection of polymer concentration and environmental parameters, the size of self-assembled nanogels can be controlled upto 120-150 nm [Yu, Yao, Jiang, Zhang et al. 2006, 148-158; Yu, Hu, Pan, Yao et al. 2006, 2754-2759]. The resulting nanogels are stable.

2. Chemical Synthesis

Chemical syntheses are carried out in heterogeneous colloidal environments to produce variations in nanogel structure and properties. Speiser*et al*. performed the copolymerization of monomers, which are solubilized in reverse micelles [Speiser 1984, 339-346]. Some scientists consider this strategy to be complete for covalently immobilising the enzymes in nanogranules made of various granules [Khmelnitsky, Neverova, Gedrovich, Polyakov et al. 1992, 751-757]. Consequently, DeSimone *et al*. prepared cationic nanogels using PEGbisacrylate as a bifunctional cross-linker with inverse microemulsion polymerization technique [Sahiner, Godbey, McPherson, and John 2006, 1121-1129]. Copolymerization in an inverse microemulsion can also be used to prepare anionic nanogel with particles of nanorange [Kaneda, Sogabe, and Nakajima 2004, 450-457]. During polymerization labile bonds are incorporated into nanogels to assist release of drug and make them easily degradable.

3. Polymerization Reactions

In this method, the polymerization reactions are performed in aqueous suspensions or o/w emulsions for the preparation of nanogels. The polymerization is initiated in an aqueous solution of hydrophilic monomers to form a colloidal suspension of polymers. During this process, the covalent cross-linking of already prepared polymeric chains produces nanogels of enormous pores [Hennink and van Nostrum 2002, 13-36]. The

cross-linking method synthesizes nanogels with different functional groups for the delivery of different drugs [Vinogradov, Batrakova, and Kabanov 1999, 291-304]. Bronich and coworkers discovered a procedure to prepare the nanogels. This process involves the self-assembly of ionic sections of double-block copolymers combined with a condensing agent of complementary charge to create polyion-complex micelles. The ionic subunits are chemically cross-linked in the core, and the extra condensing agent is eliminated [Bronich, Keifer, Shlyakhtenko, and Kabanov 2005, 8236-8237]. The resulting nanogels incorporated hydrophilic medicines expanded in water due to their cross-linked hydrophilic ionic interior and hydrophilic PEG enclosure [Bontha, Kabanov and Bronich 2006, 163-174].

4. Template-Assisted Nanofabrication of Nanogels Particles

Rolland*et al*., devised a brand-new technique for creating polymeric particles that can be dispensed by incorporating in nanogels [Rolland, Maynor, Euliss, Exner et al. 2005, 10096-10100]. "PRINT" (Particle replication in non-wetting templates) is an imprint photolithographic process that was employed. In this method, perfluoropolyether oligomers that had been functionalized with dimethacrylate were photochemically cross-linked to create non-wetting elastomeric moulds of low surface energy and their networks were formed on patterned silicon master templates. In order to create monodisperse, shape-specific nanoparticles from a wide range of organic precursors, non-wetting moulds are used (Fig. 4). This prevents the formation of a residual linking film between moulded objects. Using this technique, medicinal substances and biomacromolecules are enclosed in nanocarriers with the necessary dimensions, configurations, chemical make-up, and surface properties. For instance, UV-induced copolymerization of numerous vinyl-monomers such as PEG monomethyl ether monomethacrylate, PEG triacrylate, and p-hydroxystyrene, was used to create monodisperse 200 nm PEG-based swellable particles utilising the PRINT approach [Gratton, Pohlhaus, Lee, Guo et al. 2007, 10-18].

In general, many investigations have generated increasingly complex forms of nanogels using the fundamental techniques outlined above. For instance, Richtering and colleagues created thermosensitive core-shel materials by using the layer-by-layer depositing polyelectrolyte multilayers technique on the surface of an anionic poly-(N-isopropylacrylamide-co-methacrylic acid) nanogel [Wong, Muller, Laschewsky, and Richtering 2007, 8527-8531]. Numerous materials like magnetic nanoparticles can be