Colloidal Drug Carriers
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Abstract

INTRODUCTION
Colloidal drug delivery systems (CDDS) are particulate or vesicular dosage form in nanometer size range. They include liposomes\textsuperscript{1,2}, niosomes\textsuperscript{3}, nanospheres\textsuperscript{4}, multiple emulsion\textsuperscript{5} and ceramics\textsuperscript{6}. CDDS are essentially required for effective transportation of loaded drug to the target site.

Colloidal drug carriers such as liposomes and nanoparticles are able to modify the distribution of an associated substance. They can therefore be used to improve the therapeutic index of drugs by increasing their efficacy and/or reducing their toxicity.\textsuperscript{7}

Colloidal drug carrier is one of the most important entities essentially required for successful transport of loaded drugs. They are drug vectors, which sequester, transport and retain the active drug en route, while they elute or deliver it within or in the vicinity of target. Targeting the drug to the desired site of action would not only improve the therapeutic efficacy but also enable a reduction of the amount of drug, which must be administered to achieve a therapeutic response, thus minimizing unwanted toxic effect. The overall drug consumption and side-effects can be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. This highly selective approach reduces systemic side effects to a great degree.

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties.\textsuperscript{8}

ADVANTAGES OF CDDS
CDDS ARE NEEDED IN DEVELOPMENT OF -

- Nano-drug delivery systems that deliver large but highly localized quantities of drugs to specific areas to be released in controlled ways;
- Controllable release profiles, especially for sensitive drugs;
- Materials for nanoparticles that are biocompatible and biodegradable;
- Architectures / structures, such as biomimetic polymers, nanotubes;
- Technologies for self-assembly;
- Functions (active drug targeting, on-command delivery, intelligent drug release devices/bioresponsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery);
- Virus-like systems for intracellular delivery;
- To improve devices such as implantable devices/nanochips for nanoparticle release, or multi reservoir drug delivery-chips;
- Nanoparticles for tissue engineering; e.g. for the delivery of cytokines to control cellular growth and differentiation, and stimulate regeneration; or for coating implants with nanoparticles in biodegradable polymer layers for sustained release;
- For the delivery of therapeutic peptide/proteins (biopharmaceutics),
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- Combined therapy and medical imaging, for example, nanoparticles for diagnosis and manipulation during surgery (e.g. thermotherapy with magnetic particles);
- Universal formulation schemes that can be used as intravenous, intramuscular or peroral drugs
- Cell and gene targeting systems.
- User-friendly lab-on-a-chip devices for point-of-care and disease prevention and control at home.
- Devices for detecting changes in magnetic or physical properties after specific binding of ligands on paramagnetic nanoparticles that can correlate with the amount of ligand.
- Better disease markers in terms of sensitivity and specificity

PROPERTIES OF AN IDEAL CDDS
An ideal colloidal drug carrier should be engineered to have the following features:

- It must be able to cross anatomical barriers.
- It must be recognized specifically and selectively by the target cells and must maintain the avidity and specificity of the surface ligands.
- The linkage of the drug and the directing unit (ligand) should be stable in plasma, interstitial and other biofluids.
- Carrier should be non-toxic, non-immunogenic and biodegradable particulate or macromolecule and after recognition, and internalization.
- The biomodules used for carrier navigation and site recognition should not be ubiquitous, otherwise the CDDS may cross over to other sites, defeating the concept of targeting.

FATE OF COLLOIDAL DRUG CARRIERS
The administration of colloidal particle to the blood stream has been considered for many years for a variety of reasons. The development of artificial blood has been a long-term research interest and has not been diminished by the risks associated with HIV infection in donor blood. In the field of drug targeting, many different types of delivery system have been considered ranging from numerous synthetic carriers like emulsions, lipoprotein, erythrocytes and viruses. These approaches have had varying degrees of success in laboratory experiments.

Opsonisation is a process whereby materials adsorb to a foreign surface in such a way is to apparently prepare the surface for recognition as foreign and thus for phagocytosis by the MPS (Macrophages System). Probably the conformational changes of opsonins result in the plasma clearance.

Opsonisation can facilitate phagocytic uptake and removal to liver, but also to spleen. This gives an opportunity to target the cells of the MPS, but prevent targeting of the rest of the body. If sites other than MPS are to be reached, then the delivery system must circulate freely without attracting opsonins.

It was observed that small particles are taken up by the MPS, whilst large particles (7 μm and above) are lodged in the first capillary bed that is reached i.e. the lungs following intravenous administration. It shows that the size is the first parameter that could be used to avoid uptake by MPS.

Biological particles are usually negatively charged, while the administered particles can be positively or negatively charged, and the charge can be changed as a consequence of change in the fluid. Charged particles are surrounded by associated charged species of the opposite charge, creating an electrical double layer. When a charged carrier and a bio-molecule are in close proximity, their associated charged layers will overlap. If the two materials have the same charge this will cause repulsion but if they are opposite charges, this will result in attraction. The DLVO theory is named after Derjaguin and Landau, Verwey and Overbeek. The DLVO theory describes the net interaction between two particles of the same charge as they approach each other. In plasma, the ionic strength is such that a secondary minimum is probable, and thus the materials of the same charge will exhibit net attraction in this region. At short distances of separation different forces dominate, and in this region it is the surface nature which becomes important. It might reasonably be asserted that, as bio-molecules are generally negatively charged (in order to prevent charge interaction in the biological environment), administered carriers might best be designed to be also negatively (or at least not positively) charged. In most cases, however, this is not adequate to prevent opsonisation.
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It has been found that biocompatibility is improved if the surface favours albumin adsorption. However, it is known that albumin binds to hydrophobic and hydrophilic surfaces, irrespective of surface charge. Unlike albumin, ribonuclease adsorbs to hydrophobic surfaces of either charge but only to hydrophilic surfaces of opposite charge. The differences between these two molecules are due to the extent of entropic gain that can be achieved by the conformational and dehydration changes during adsorption and to whether the entropic driving force is sufficient to overcome adverse factors such as electrical charge repulsion. It is probable that those surfaces to which either there is very limited protein adsorption, or those to which either albumin adsorbs, but is not displaced are those which will be biocompatible. Workers have reported that the surface charge induced by the adsorption of negatively charged albumin is important in preventing phagocytosis.

CLASSIFICATION OF COLLOIDAL DRUG CARRIERS
CDDS CAN BE CLASSIFIED AS FOLLOWS:

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ADVANTAGES AND SUCCESS
Colloidal drug carriers offer a number of potential advantages as delivery systems for, for example, poorly soluble compounds. The first generation of colloidal carriers, in particular liposomes and submicron-sized lipid emulsions, are, however, associated with several drawbacks which so far have prevented the extensive use of these carriers in drug delivery. As an alternative colloidal delivery system melt-emulsified nanoparticles based on solid lipids have been proposed. Careful physicochemical characterization has demonstrated that these lipid-based nanosuspensions (solid lipid nanoparticles) are not just emulsions with solidified droplets.

Colloidal drug carriers such as liposomes and nanoparticles can be used to improve the therapeutic index of both established and new drugs by modifying their distribution, and thus increasing their efficacy and/or reducing their toxicity. This is because the drug distribution then follows that of the carrier, rather than depending on the physicochemical properties of the drug itself. If these delivery systems are carefully designed with respect to the target and the route of administration, they may provide one solution to some of the delivery problems posed by new classes of active molecules, such as peptides and proteins, genes and oligonucleotides. They may also offer alternative modes for more conventional drugs, such as highly hydrophobic small molecules.

Nanoparticle-based drug delivery systems have considerable potential for treatment of tuberculosis (TB). Colloids from an aqueous suspension can cross the skin barrier only through hydrophilic pathways. Various colloids have a different ability to do this by penetrating narrow pores of...
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fixed size in the skin, or the relevant nano-pores in barriers modelling the skin.

Engineering drug itself in nanoparticulate form has emerged as a new strategy for the delivery of hydrophobic drugs due to their unique advantages over colloidal drug carriers. Nanoparticles and nanof ormulations have already been applied as drug delivery systems with great success; and nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumour therapy, gene therapy, and AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, vaccines and as vesicles to pass the blood - brain barrier.

Polymeric micelles have recently emerged as a novel promising colloidal carrier for the targeting of poorly water soluble and amphiphilic drugs. Polymeric micelles are considerably more stable than surfactant micelles and can solubilize substantial amounts of hydrophobic compounds in their inner core. Due to their hydrophilic shell and small size they sometimes exhibit prolonged circulation times in vivo and can accumulate in tumoral tissues.\(^{10}\)

Nanoparticles provide advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine. The main goals are to improve their stability in the biological environment, to mediate the biodistribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. The cytotoxicity of nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research.

Possible areas of exploitation\(^{9}\)

Microparticulates have been investigated intensively during the last decade to explore and exploit intrinsic targeting potential of the plain or surface manipulated carriers. Advent of nanotechnology has infused new dimensions into the target oriented drug delivery through self-assembling supramolecules based nanostructures.

Targeted drug delivery may be achieved by using carrier system, where reliance is placed on exploiting both, intrinsic pathway that these carriers follow, and the bioprotection that they can offer to drug during transit through the body.

Active targeting exploits modification or manipulation of the drug carriers to redefine its biofate. The natural distribution pattern of the drug carrier composites is enhanced using chemical, biological and physical means, so that it approaches and identified by particular biosites.

Surface modifications of the carrier system with particular ligands like sugar or monoclonal antibodies could impart a specific targeting potential to the carrier. Hence in essence to deliver drug selectively to a target we should have versatile putative carriers and site specific ligands.

Most of the carrier systems or bioconjugates explored so far, in general, can be utilized as a cargo-unit for the site specific presentation and delivery of various bioactives using biorelevant ligands including antibodies, polypeptides, oligosaccharides (carbohydrates), viral proteins, fusogenic residue and molecules of endogenous origin.

The role of receptors as molecular target has opened new opportunities for the cellular or intracellular targeting of drug using carrier systems appended with targeting handles.

Several specific and non-specific cellular mechanisms have also been explored to facilitate the internalization and uptake of endogenous and exogenous ligands or ligand-carrier composites. Most of them exploit cell surface receptors or cell surface epitopes that help mediate trafficking of ligands with the help of receptor-mediated endocytosis (RME).

Ligand-mediated events are either currently exploited for targeted therapy of drugs or genes, or may appear as potential targets for future cellular targeting strategies.

Cell surface biochemistry and molecular portals have realized as delivery modules and are exploited for site specific and controlled drug delivery. Cell surface markers such as antigenic determinants or specific sequence of receptors sub units that serve as ligands are exploited and form basis of biochemical and molecular biology assisted delivery units. Receptors mediated cellular events have got major attention in the field of drug/gene delivery during last few years. The events mediated through the endogenous ligands/epitopes could be exploited for the designing of site specific and target oriented delivery systems.

CONCLUSION

Colloidal drug carriers can be used to improve the therapeutic index of drug by increasing their efficacy and / or reducing toxicity. By using colloidal drug carriers the overall drug consumption and side effects can be lowered significantly by depositing the active agent in the morbid region only, so there is no need of higher doses, ultimately
reduces side effects. If these delivery systems are carefully designed with respect to the target and the route of administration, they may provide one solution to some of the delivery problems posed by new classes of active molecules, such as peptides and proteins, genes and oligonucleotides.

References
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