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Review Article

PARTICULATE CARRIER SYSTEMS: A REVIEW

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ABSTRACT

Extent of therapeutic action of drug depends on its absorption which interns depends on the concentration of drug at the absorption site. Targeted drug delivery system is now regarded as 4th generation drug delivery and API shall be targeted to the required site by variety of drug carriers. Since last three decades researchers have developed different types of drug carriers. This article briefs about different drug carriers and their applications and limitations.

KEYWORDS: Particulate carriers, cellular carriers, nanoparticles, vesicles, bioavailability, sustained drug delivery

INTRODUCTION

Research has been carried out in the past, is being carried now and shall be carried out to in the future also to enhance the comfort ability.

Development of a new drug molecule is an expensive, time consuming and tedious process hence not preferred. To meet the desired objectives, the alternative is to enhance the performance of the existing drug molecules[1]. Different approaches were considered by the researchers to achieve the desired goals with existing molecules which includes changing the route of administration, chemical structure of drug molecules, type of dosage form, developing new drug delivery system[2], etc. Drug carriers are one of the important approaches among new drug delivery systems. Drug carriers introduced into the field to achieve different goals like enhancement of bioavailability, stability, preventing the drug interactions[3], etc. Since three decades researchers developed different types of pharmaceutical drug carriers which include, cellular carriers, particulate carriers, lipoidal carriers, etc. The present article describes about their unique nature and applications, etc. These carrier systems were developed for various purposes depending on the needs. They vary from each other in their structure, characteristics, composition, manufacturing procedure, etc.

PURPOSES FOR DEVELOPMENT OF PARTICULATE CARRIER SYSTEMS

1. Using these carriers one can target the different organs to produce desired action without causing harm to the other healthy organs.
2. Enhances the bioavailability of the drugs administered orally by avoiding first pass metabolism and/or increasing the MRT in systemic circulation.
3. Enhances the drug absorption when administered across the biological membranes because of its small micro/nano sizes.
4. Because of this unique small size, they enhance the solubility of poorly soluble drugs.
5. These shall be used to deliver vaccines.
6. These carriers shall be used to improve the stability of the drugs.
7. Drug molecules having large molecular weights like proteins, peptides can be administered through these carrier systems.
8. By modifying surface characteristics one can target particular organs in the body.
9. These carriers find the applications not only useful in the pharmaceutical field but also in variety of other fields like textiles, painting, electronics etc
10. Sustained and controlled release of the drugs shall be achieved by means of these drug carriers.

LIMITATIONS

The applications of these carriers are minimized because of the following reasons.

1. Sometimes, these carriers will exhibit the dose dumping.
2. These are associated with problems like storage, leaching, aggregation, etc
3. Extra care should be taken while manufacturing these carriers.
4. Expensive.

TYPES OF DRUG CARRIERS

Microspheres - Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200μm[4]. These are developed using different methods like emulsion techniques, polymerization techniques, spray drying, spray congealing, solvent evaporation etc[5]. These are developed for variety of applications like controlled drug delivery, vaccine delivery, as drug carrier, etc. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

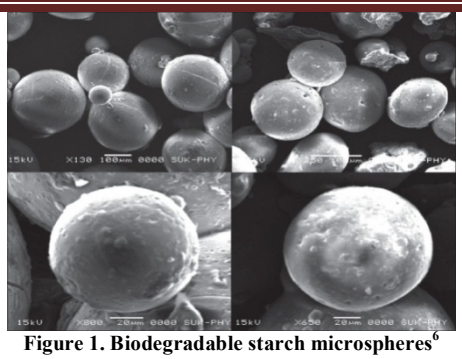

Figure 1. Biodegradable starch microspheres[6]

Nanoparticles – Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm[7]. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly(ethylene glycol) (PEG) known as long-circulating particles.

Nanoparticles have been prepared most frequently by three methods[8]: (1) dispersion of preformed polymers; (2) polymerization of monomers; and (3) ionic gelation or coacervation of hydrophilic polymers.

These are used as potential drug delivery devices because of their ability to circulate for a prolonged period time in systemic circulation and are useful to target a particular organ. Apart from these, they can also acts as carriers for DNA in gene therapy. They are capable in delivering the proteins, peptides, genes etc. these have applications not only in pharma field but also in textile, cosmetics, biotechnology fields etc.[9]

Nanotubes - Tubular carbon structures were first observed by Iijima[10] in the year 1991. There are two main types of carbon nanotubes[11] that can have high structural perfection. Single walled nanotubes (SWNT) consist of a single graphite sheet seamlessly wrapped into a cylindrical tube.Multiwalled nanotubes (MWNT) comprise an array of such nanotubes that are concentrically nested like rings of a tree trunk.

These have good applications in different fields like pharma, biomedical, mechanical, electrical, electronics etc. because of its unusual properties like extraordinary thermal conductivity, mechanical and electrical properties.

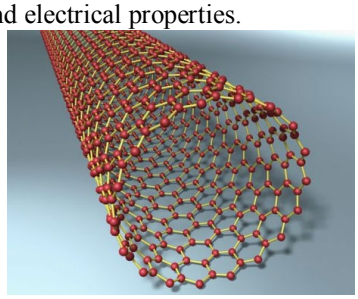

Figure 2. Carbon nanotube

Liposomes - Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments with a diameter ranging from 25-100µm. According to their size, liposomes are known as Small Unilamellar Vesicles (SUV) (10-100 nm) or Large Unilamellar Vesicles (LUV) (100-3000 nm). If more than one bilayers are present, then they are referred to as Multilamellar Vesicles (MLV).

Liposomes are manufactured by means of different methods like film hydration technique, ether injection method, reverse phase evaporation method, membrane extrusion technique etc. All these methods involve two steps to manufacture: drying of lipids from lipid solution followed by dispersion of lipid film in aqueous medium[12].

These have wide applications in drug delivery because they can administer from almost all routes, and can be used as carrier for all drugs (both lipophilic and hydrophilic drugs).

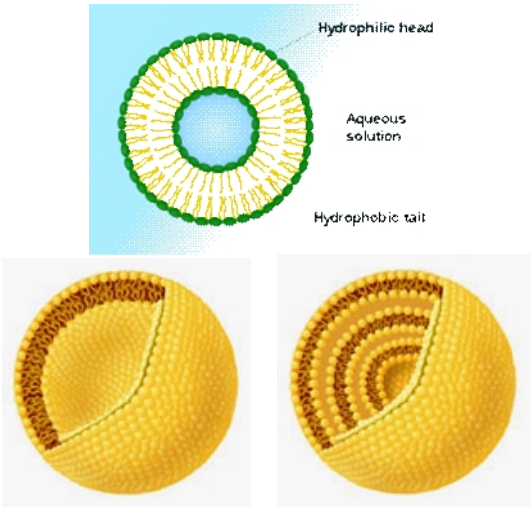

Figure 3. a. Structure of liposomes b. Unilamellar vesicle c. Multilamellar vesicle

Niosomes – These are developed to avoid the problems associated with the liposomes like ranicidity, handling and storage etc. These are developed using non-ionic surfactants instead of lipids. Hence these will have more stability and their handling and storage is easy[13]. Proniosomes are modified forms of niosomes and are developed to further enhance the physical stability of the niosomes. These are available as dry powders which are to be hydrated with aqueous media just before administration with vigorous shaking [14].

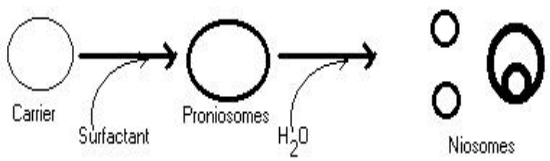

Figure 4. Formation of niosomes from proniosomes

Transferosomes – These are modified form of liposomes and are developed to increase the penetrability of the drugs across the biological membrane. These will have special characteristic i.e. ultra deformability. Transferosomes can penetrate the barrier membrane more easily than the liposome though it has bigger size than the pore size of the membrane because of its ultradeformability. The ultradeformability can be achieved by using "edge activators" in the manufacturing process[15].

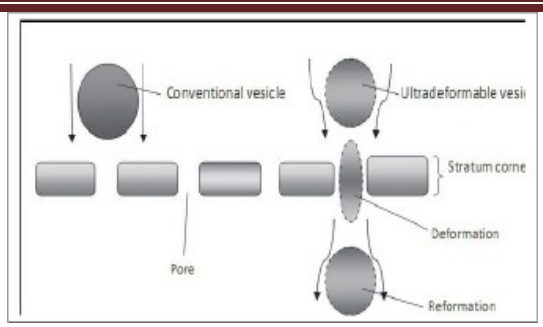

Figure 5. Passage of Transferosomes across the barrier membrane

Microemulsions - "Microemulsions are liquid dispersions of water and oil that are made homogenous, transparent (or translucent) and thermodynamically stable by the addition of relatively large amounts of a surfactant and a co-surfactant and having diameter of the droplets in the range of 100 – 1000 A.

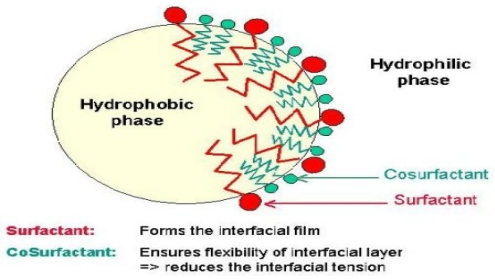

Figure 6. Structure of micro emulsion

Microemulsions were not really recognized until the work of Hoar and Schulman in 1940, who generated a clear single phase solution by titrating a milky emulsion with hexanol.[16] The term "microemulsion" was first used even later by Schulman et al. in 1959 to describe a multiphase system consisting of water, oil, surfactant and alcohol, which forms a transparent solution.[17]

Microemulsions have wide variety of applications in different fields like pharmaceuticals, biotechnology, cosmetics, analytical applications, environmental remediation and detoxification, coatings and textile finishing etc[18].

Nanocrystals and Nanosuspensions - Nanocrystals are aggregates of around hundreds or thousands of molecules that combine in a crystalline form, composed of pure drug with only a thin coating comprised of surfactant or combination of surfactants. The production technique of nanocrystals is known as 'nanonisation'. To produce nanosuspensions, the drug powder is dispersed in an aqueous surfactant solution by high speed stirring[19].

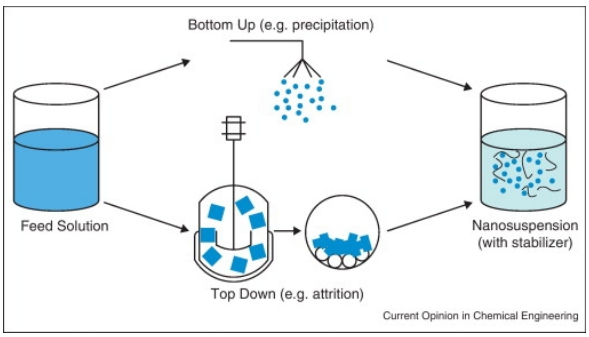

Figure 7. Preparation of nano suspension

Aquasomes – Aquasomes are like "bodies of water" and their water like properties help to protect and preserve the fragile biological molecules. It is comprised of a solid phase nanocrystalline core coated with oligomeric film to which the drug moieties or bio-chemically active molecules are adsorbed with or without modification. These three layered structures are self assembled by non covalent and ionic bonds.

These are prepared using self assembly principle which consists of three steps i.e. preparation of core, coating of core and immobilization of drug molecule. These have versatile application potential as a carrier for delivery of vaccines, haemoglobin, drugs, dyes, enzymes and even gastric material[20].

Pharmacosomes - Pharmacosomes are the colloidal dispersions of drugs covalently bound to lipids and may exist as ultrafine vesicular, micellar, or hexagonal aggregates, depending on the chemical structure of the drug–lipid complex. Because the system is formed by linking a drug (pharmakon) to a carrier (soma), they are called pharmacosomes. These are prepared using two methods. They are the hand-shaking method and the ether-injection method. Comparatively pharmacosomes have more advantages than the conventional vesicular systems [21].

Dendrimers – The term dendrimer derived from the words Dendron (tree/branches) and meros (part). These posses three distinguishing architectural components. i.e. a. an interior core b. interior layers (generations) composed of repeating units of radially attached to the interior core and c. exterior (terminal functionality) attached to the outermost interior generation. Variety of dendrimers is available i.e. simple dendrimers, liquid crystalline dendrimers, chiral dendrimers, micellar dendrimers, hybrid dendrimers, metallodendrimers, etc.

Two fundamentally different methods have been developed for stepwise synthesis of dendritic polymers[22]. They are divergent growth method and convergent growth method. These have wide applications in the pharmaceutical field like solubilization, controllable gene therapy/non viral gene therapy, drug carrier, magnetic resonance imaging contrast agents, as vaccines, artificial proteins, enzymes etc.

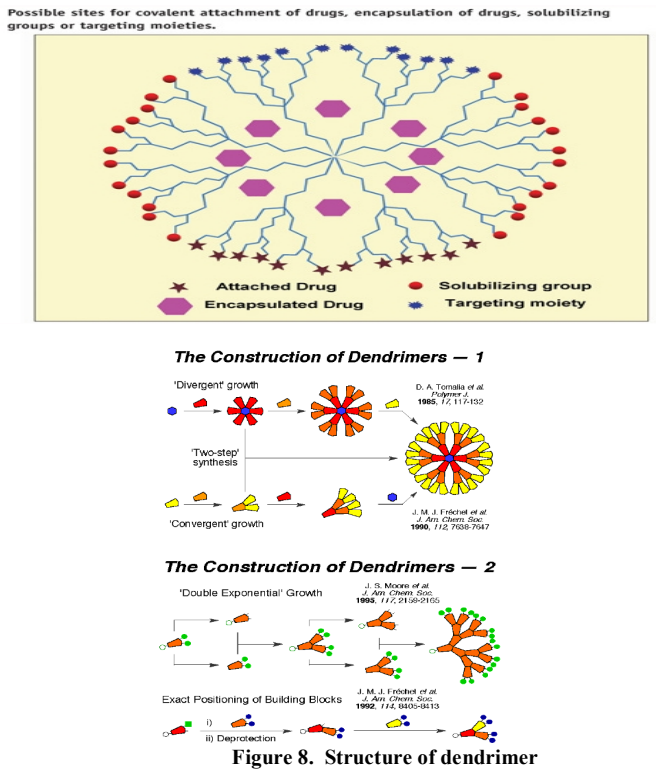

Figure 8. Structure of dendrimer

Lipospheres - Lipospheres were first reported by Domb, as water dispersible solidmicro particles with a particle size between 0.2-100 µm in diameter composed of solid hydrophobic fat core stabilized by a monolayer of phospholipids molecules embedded in a microparticle surface. Lipospheres can contain a biologically active agent in the core, in the phospholipids, or a combination of two[23].

Lipid Emulsions (LES)- Lipid emulsions are heterogenous dispersions of two immiscible liquids (oil-in-water or water-in oil) and they are subjected to various instability processes like aggregation, flocculation, coalescence and hence eventual phase separation according to the second law of thermodynamics. LE may be in the form of oil-in-water (o/w), water-in-oil (w/o), micron, submicron and double or multiple emulsions (o/w/o and w/o/w).The o/w type Les (LE) are colloidal drug carriers, which have various therapeutic applications.[24]

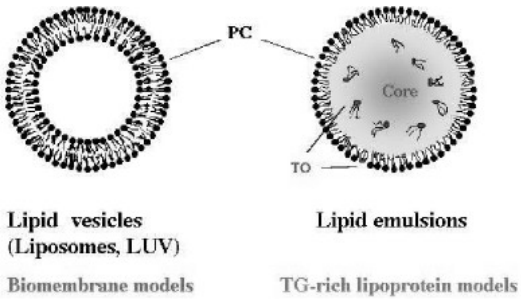

Figure 9. Structure of lipid vesicle and lipid suspension

Resealed erythrocyte[25,26] – Carrier erythrocytes have been evaluated in thousands of drug administration in humans proving safety and efficacy of the treatments. Carrier erythrocytes, resealed erythrocytes loaded by a drug or other therapeutic agents, have been exploited extensively in recent years for both temporally and spatially controlled delivery of a wide variety of drugs and other bioactive agents owing to their remarkable degree of biocompatibility, biodegradability and a series of other potential advantages. Biopharmaceuticals, therapeutically significant peptides and proteins, nucleic acid-based biologicals, antigens and vaccines, are among the recently focused pharmaceuticals for being delivered using carrier erythrocytes. Variety of methods is available to prepare Resealed erythrocytes which include dilution, preswelling, dialysis, osmotic lysis, electro-insertion, lipid fusion etc.

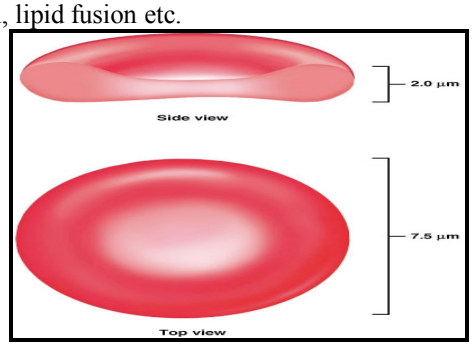

Figure 10. Structure of erythrocytes

Lipopolyplexes[27]**-** These are assemblies, which form spontaneously between nucleic acids and polycations or cationic liposomes, and are used in transfection protocols. The shape, size distribution, and transfection capability of these complexes depends on their composition and charge ratio of nucleic acid to that of cationic lipid/polymer.

Polymeric Micelles[28,29] – These systems include amphiphilic block copolymers suchas Pluronics (polyoxyethylene polyoxypropylene block copolymers that self-associate in aqueous solution to form micelles). Polymeric micelles offer a number of advantages in terms of thermodynamic stability in physiological solution leading to their slow dissolution *invivo*. Because of their core–shell structure, these serve as suitable carrier for water insoluble drugs, such drugs partition in the hydrophobic core of micelles and outer hydrophilic layer aids in dispersion in aqueous media making it an appropriate candidate for intravenous administration. Nanometric size range helps micelles to evade the RES, and aids passage through endothelial cells.

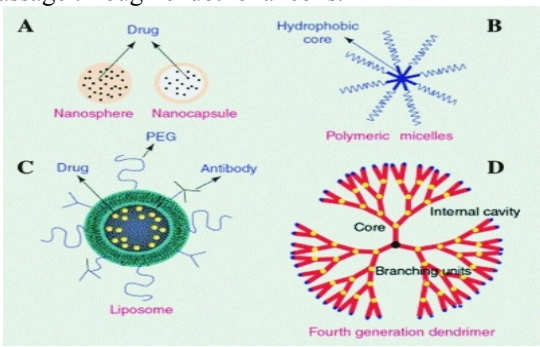

Figure 11. Pictorial comparison of nanospheres, polymeric micelles, liposomes and dendrimers

Lipoprotein[30] - A lipoprotein is a biochemical assembly that contains both proteins and lipids. They allows fats to move through the water inside and outside cells. The proteins serve to emulsify the lipid (otherwise called fat) molecules.

Plasma lipoproteins are transporters of lipids and other hydrophobic molecules in the mammalian circulation. Lipoproteins also have a strong potential to serve as drug-delivery vehicles due to their small size, long residence time in the circulation and high-drug payload. Consequently, lipoproteins and synthetic/reconstituted lipoprotein preparations have been evaluated with increasing interest towards clinical applications, particularly for cancer diagnostics/imaging and chemotherapy. A lipoprotein-based delivery strategy may also provide a novel platform for improving the therapeutic efficacy of drugs that have previously been judged unsuitable or had only limited application due to poor solubility. An additional, and perhaps the most important aspect of the drug-delivery process via lipoprotein-type carriers, is the receptor-mediated uptake of the payload from the lipoprotein complex. Monitoring the expression of specific receptors prior to treatment could, thus, give rise to efficient selection of optimally responsive patients, resulting in a successful personalized therapy regimen.

Many enzymes, transporters, structural proteins, antigens, adhesins, and toxins are lipoproteins. Examples include the high-density (HDL) and low-density (LDL) lipoproteins.

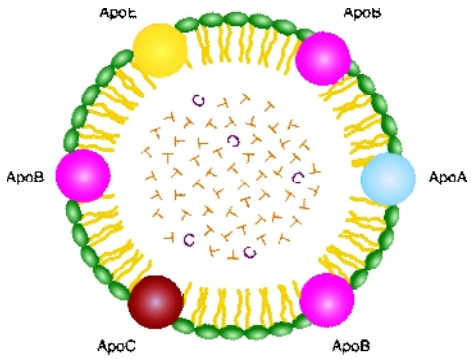

Figure 12. Structure of lipoprotein

Platelets[31] – These are non-nucleated discoid or elliptical cells that originate from the fragmentation of giant polyploidy megakaryocytes located in the bone marrow. Platelets have been used as drug carrier for several biological substances and drugs useful in the management of various hematological diseases. Certain drugs such as angiotensin, hydrocortisone, imipramines, vinka alkaloids and many others are known to bind platelets.

Antibodies[32] – leukocytes are white blood cells involved in the cellular and humoral defense of the organism against foreign materials. Neutrophils and lymphocytes have been reported as potential cellular carriers.

Neutrophils are known to carry a wide range of digestive enzymes and carrier proteins. Unlike erythrocytes, which are constrained to move within blood vessels, neutrophils can leave the capillaries and accumulate in large numbers at localized areas of disease. This property, their ready availability, and their high pure form make them very attractive as a natural drug carrier. These could also be used as carriers for drugs that are effective in the treatment of pyrogenic infections, including diseases such as ulcerative colitis, acute arthritis and other infections.

Lymphocytes present not only in the blood but also present in the lymph and every tissue of the body. These are suggested as potential carriers for transporting macromolecules, particularly DNA, to other cells. Low molecular weight exogenous substances can be introduced into lymphocytes by electrical breakdown method.

CONCLUSION

Present research suggesting that the future will be the particulate carrier systems because as the time going on the world is becoming compact.

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