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Review article

A Role of Supramolecular Systems in Targeting Drug Delivery to Specific Sites-A Review

Krishnamoorthy.B[1]*, Muthukumran.M[1], and Sumithira G[2]

[1]Montessori Siva Sivani Institution of Science & Technology-College of Pharmacy, Andhra Pradesh-521230
[2]The Erode College of Pharmacy and Research Institute, Erode, TamilNadu, India.
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Abstract

This review aims to presenting importance of supramolecular chemistry in the development of new pharmaceutical therapies by understanding the interactions at a drug binding site. The area of drug delivery has also made critical advances as a result of supramolecular system providing encapsulation and targeted release mechanisms. In addition, various supramolecular systems can be used as drug carriers to alter physicochemical and pharmacokinetic characteristics of drugs. Representative supramolecular systems that can be used for this purpose include surfactant/polymer micelles, microemulsions, liposomes, layer-by-layer assemblies and various molecular conjugates. Especially, microemulsions have been used oral drug delivery of poorly soluble drugs to improvements in bioavailability and predictable of absorption behavior. Neoral®, an immunosuppressant used after transplant operations, is one of the most famous microemulsion-based drugs; liposomes are established supramolecular drug carriers, which have already been marketed in formulations including “AmBisome”, “Visudyne”, and “Doxil”. This review signifies supramolecular drug delivery systems which may improve usability of drug candidates or add worth to existing drugs are introduced.

Corresponding author

Tel +918008359619
Department of Pharmaceutics
Montessori Siva Sivani Institution of Sci & Tech
-College of Pharmacy,
Andhra Pradesh-521230,
India

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Target drug delivery

INTRODUCTION

The term *Ubermolekelan* (supermolecule)[1] was introduced in the mid 1930s and which deals with the study of structures and functions of supermolecules is called supramolecular chemistry. In the 1990s supramolecular chemistry became even more sophisticated with researchers developed molecular machinery and highly complex self-assembled structures and later, it developed sensors and methods of electronic and biological interfacing. During last few years, molecular self-assembly processes in particular have been applied to the development of new material in order to improve pharmaceutical therapies by understanding the interactions at a drug binding site. The area of drug delivery has also made critical advances as a result of supramolecular chemistry providing encapsulation and targeted release mechanisms.

TYPES OF SUPRAMOLECULAR SYSTEMS

Host guest supramolecular systems

The host molecule which made through atoms by covalent interactions, whereas the guest molecule interacts with host by noncovalent forces and they ultimately forms supramolecules. Macrocyclic compounds possessing an intermolecular cavity of molecular dimension like cyclodextrins (CDs), cyclophanes, crown ethers shows capacity to interact with a small guest molecules and forms inclusion complexes.

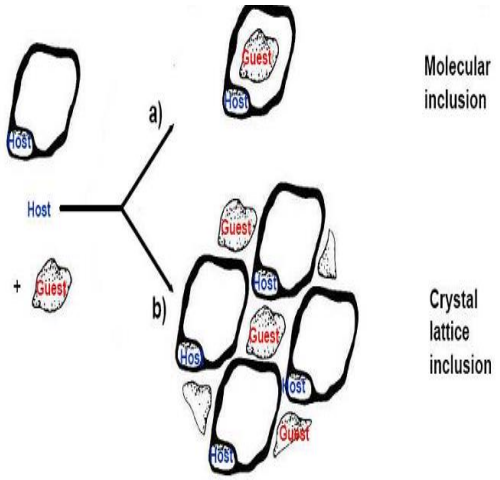

Fig1. Schematic illustrating the difference between a cavitate and a clathrate. A) Conversion of a cavid and into a cavitate by inclusion of a guest into the cavity of the host molecule; b) inclusion of guest molecules in cavities formed between the host molecules in the lattice resulting in conversion of a clathrand into a clatharte

Self-assembling supramolecular systems

Molecular self-assembly is the construction of systems without guidance or management from an outside source (other than to provide a suitable environment). The molecules are directed to assemble through non-covalent interactions. Self-assembly may be subdivided into intermolecular self-assembly (to form a supramolecular assembly), and intramolecular self-assembly (or folding as demonstrated by foldamers and polypeptides). Molecular self-assembly also allows the construction of larger structures such as micelles, membranes, vesicles, liquid crystals, and is important to crystal engineering.

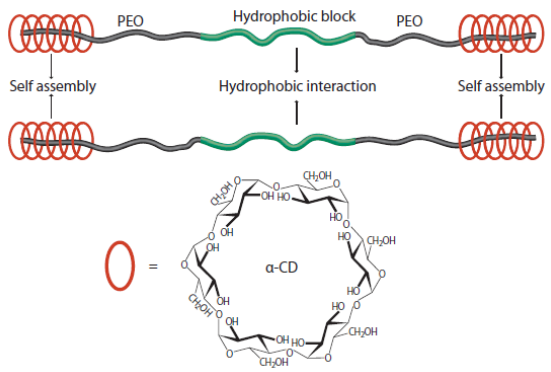

Fig 2. Supramolecular self-assembly of α-CD and a triblock copolymer consisting of two PEO blocks flanking a central hydrophobic block

Self assembly in Amphiphiles[1]

Amphiphiles which can be viewed as providing a link between two phases of markedly dissimilar polarities are a great pharmaceutical significance. Amphiphiles like phospholipids exhibit domain oriented behavior. The larger molecule associates with relatively small number of partners to form stable, definable super structures. Amphiphiles hold large hydrophobic surface capped by highly hydrophilic head group. These Amphiphiles show a strong tendency to self organize in aqueous media into supramolecular assemblies in order to minimize the water lipid interface, while maximum with the lipid-lipid and head group-water interface. Various organized structure formed like monomolecular and bimolecular membranes, micelles, microemulsion, vesicles, tubular aggregation etc.

APPLICATION OF SUPRA-MOLECULES IN DRUG DELIVERY

Design of supramolecular approach to targeting the desire sites

Many approaches have been attempted to achieve targetable properties of supramolecular system. Self-assembled supramolecular hydrogels based on polymer–cyclodextrin inclusion complexes for drug delivery[2].

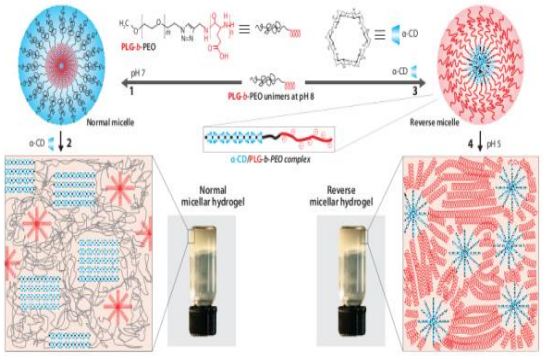

Fig 3. Illustrate of possible structures and gelation mechanism of supramolecular hydrogels[2]

The non-covalent association of cell specific antibodies with liposomes, coating of liposomes with heat aggregated immunoglobulin M (IgM), covalent attachment of poly and monoclonal antibodies to the liposomes, glycoprotein bearing liposomes[3].

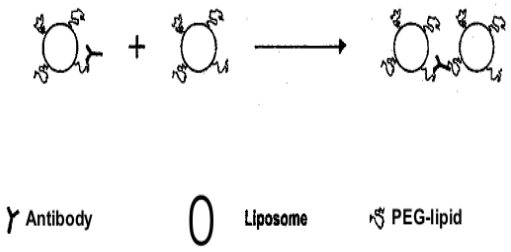

Fig 4. Antibodies tethered on the distal end of PEG may react with the distal ends of PEG molecules on a second liposome, resulting in cross linking

Lipoprotein and their mimics

Lipoproteins are spherical particles composed of an internal core of cholesteryl esters and / or triglycerides surrounded by a monolayer of phospholipid, in which cholesterol and one or more specific apoproteins are embedded. Researchers developed synthetic low-density lipoprotein-like nanoparticles from commercial lipids and a bi-functional synthetic peptide containing the low-density lipoprotein receptor-binding domain and the lipid-binding motif in three steps. The first is via covalent attachment to the amino acid residues of apolipoprotein (apo)B-100 protein of LDL (protein labeling); the second is through intercalation into the phospholipid monolayer of LDL (surface labeling); the third is via substitution of agents into the lipid core of LDL (reconstitution core loading), these novel LDL–drug complexes were shown to behave similarly to native low-density lipoproteins and also to bind to the low-density lipoprotein receptor on cancer cells and more efficacious against carcinoma cells than their conventional counterparts[4].

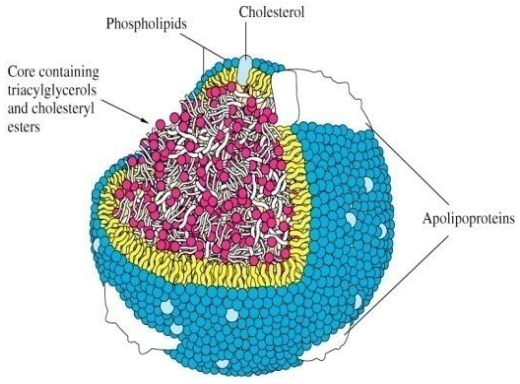

Fig5. Structure of lipoprotein

Supramolecular Bio Vectors (SMBV)[5]

Antisense oligodeoxynucleotides are potential therapeutic agents incorporated into the Supramolecular Bio Vectors (SMBV) and elicits the simultaneous oligonucleotide uptake. The oligonucleotide amount that goes through cells within 5 h can be up to 30 times higher than for free oligonucleotides and the fraction of oligonucleotides that is present in the cytosol is increased upto 10 fold after incorporation into the SMBV[6]

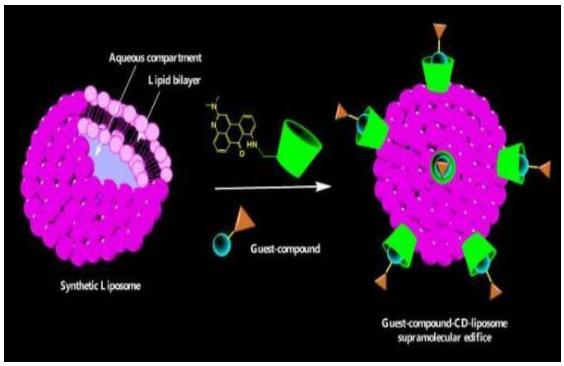

Fig 6. Structure of SMBVs

Lipospheres(LS)

Another research approach for increasing the beneficial action of drugs and decreasing systemic adverse effects is to deliver the necessary amount of drugs to the diseased sites, where they are most needed, for the appropriate period of time is lipid microspheres, often called lipospheres (LS), have been proposed as a new type of fat-based encapsulation system for drug delivery of bioactive compounds (especially lipophillic compounds). LS consist of solid microparticles with a mean diameter usually between 0.2 and 500 m, composed of a solid hydrophobic fat matrix in which the bioactive compounds are dissolved or dispersed. LS can be administered by different routes such as orally, subcutaneously, intramuscularly or topically or they can be used in cell encapsulation, thus allowing them to be proposed for treatment of a number of diseases. For

instance, the *in vivo* distribution of LS demonstrated a high affinity to vascular wells (including capillaries), inflamed tissues, and granulocytes[7]. LS have been used for the controlled delivery of various types of drugs, including vasodilator and anti-platelet drugs, anti-inflammatory compounds, local anesthetics, antibiotics, and anticancer agents; they have also been used successfully as carriers of vaccines and adjuvant[8].

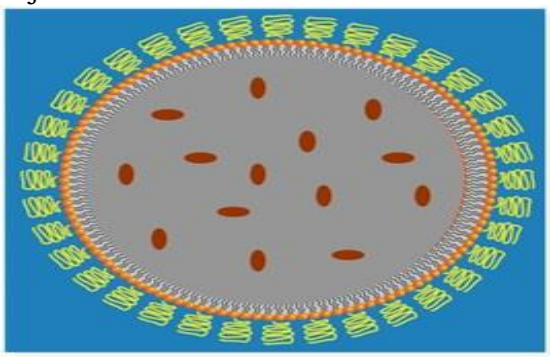

Fig 7. Liposphere is a nano-particle with a lipophilic core (such as triglycerides) coated with a monolayer of lipids. Lipophilic drugs are loaded in the oil core.

Linear–dendritic copolymers (LDBCs)[9]

Linear–dendritic hybrid nanomaterials, which combine the highly branched architectures and multifunctionality of dendrimers with the processability of traditional linear–linear block copolymers, as ideal carriers in anticancer drug delivery applications, this could help to overcome the poor bioavailability, due to the low water solubility of the anticancer drugs by improving the water solubility and achieving the targeted delivery of the anticancer drugs.

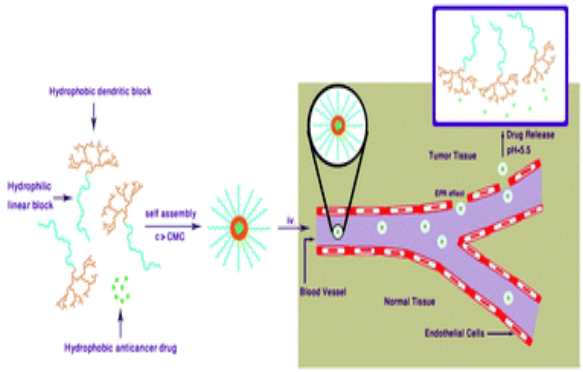

Fig 8. Linear–dendritic hybrid nanomaterials, which combine the highly branched architectures and multifunctionality of dendrimers[9].

An ABA dendritic-linear-dendritic block copolymer consisting of poly(amidoamine) (PAMAM) and poly(propylene oxide) (PPO) was synthesized for a model hydrophobid drug, triclosan. The linear-dendritic block copolymer synthesized was found to be a promising candidate for drug delivery due to its relative stability in aqueous solution and its drug encapsulation and release properties. Overall, the linear-dendritic block copolymer displayed physical characteristics and self-assembly behavior that satisfied the design criteria for a viable drug delivery vehicle, further PPO-PAMAM was functionalized with galactose and targeted to hepatocellular carcinoma cells[10].

Vesicular systems

(Liposomes/Niosomes/Ufasomes/ Sphinosomes)

Surfactant associates: Liposomes are rightly named “the true giants of supramolecular construction”. The liposome is composed of high transition temperature phospholipids and

cholesterol (interface between hydrophobic and polar layer of phospholipid).USFDA approved liposomes based product AmBisome® and licensed to market in about 18 countries. The amphotericin B, after being released from the liposomes, is thought to transfer through the cell wall and bind to ergosterol in the fungal cell membrane. This mechanism of action of AmBisome results in its potent in vitro fungicidal activity while the integrity of the liposome is maintained in the presence of mammalian cells, for which it has minimal toxicity. AmBisome has a circulating half-life of 5-24 h in animals, and in animal models appears to localize at sites of infection in the brain (cryptococcosis, aspergillosis, coccidioidomycosis), lungs (blastomycosis, paracoccidioidomycosis, aspergillosis) and kidneys (candidosis), delivering amphotericin B that remains bioavailable in tissues for several weeks following treatment[11].

Niosomes

In niosomes, the vesicles forming amphiphile is a non -ionic surfactant such as Span –60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate[12].

Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy[13].

Surfactant forming niosomes are biodegradable, non-immunogenic and biocompatible. Incorporating them into niosomes enhances the efficacy of drug, such as nimesulide, flurbiprofen, piroxicam, ketoconazole and bleomycin exhibit more bioavailability than the free drug[14-17]. The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver[18].

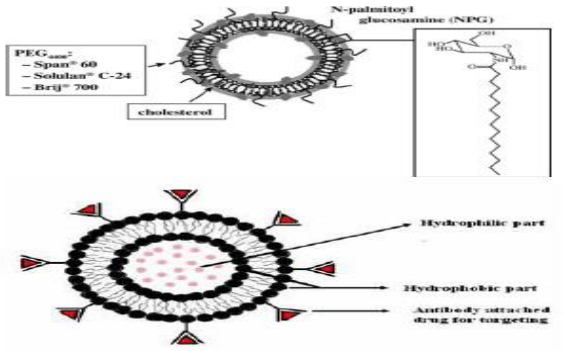

Fig 9 Structure of niosome

Ufasomes

The formation of fatty acid vesicles was first reported by Gebicki and Hicks in 1973 and the vesicles formed were initially named "ufasomes," unsaturated fatty acid liposomes[19-20]. Fatty acid vesicles are colloidal suspensions of closed lipid bilayers that are composed of fatty acids and their ionized species (soap). They are observed in a small region within the fatty acid-soap-water ternary phase diagram above the chain melting temperature (Tm) of the corresponding fatty acid -soap mixture. However, even natural phospholipids are chemically heterogeneous, and pure synthetic phospholipids are not yet available in reasonable quantities. The advantage of

ufasomes over liposomes is the ready availability of fatty acids[21].

Sphingosomes

Liposomal phospholipid can undergo chemical degradation such as oxidation and hydrolysis either as a result of these changes or otherwise liposome maintained in aqueous suspension may aggregate, fuse or leak their content. Hydrolysis of ester linkage will slow at pH value close to neutral. The hydrolysis may be avoided altogether by use of lipid which contains ether or amide linkage instead of ester linkage (such are found in sphingolipid) or phospholipid derivatives with the 2-ester linkage replaced by carbomoyloxy function. Thus sphingolipid are been now-a-days used for the preparation of stable liposome's known as sphingosomes. Sphingosome may be defined as "concentric, bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic sphingolipid. Sphingosomes are administered in many ways these include parentral route of administration such as intravenous, intramuscular, subcutaneous, and intra-arterial. Generally it will be administered intravenous or some cases by inhalation. Often it will be administered into a large central vein, such as the superior vena cava and inferior vena cava to allow highly concentrated solution to be administered into large volume and flow vessels. Sphingosomes may also be administered orally or transdermally[22].

Emulsomes

Another vesicular system, emulsomes which is composed of a hydrophobic core of solid fat instead of oils as in case of oil in water emulsions. The core is stabilized by one or more envelopes of phospholipid as in liposomes. The emulsomes contains a phospholipid layer, lipid core, lipid crown, polar core and liposomal crown (which is present on the surface)[23] .

Emulsomes are prepared by mixing triglycerides and phospholipids in the ratio 0.5-1 and it is suspended in aqueous solution, the transition temperature for the preparation is 25°C. By this method a nanoemulsion of particle size 10-250nm is obtained. Then dissolve it in volatile solvents such as dichloromethane and diethyl ether and it is mixed in vacuum to form a lipid film. The formed lipid film is hydrated and an emulsome of size range 140±150nm is obtained. Azidothymidine incorporated into emulsomes shows increased brain levels of AZT and emulsomal entrapment of Methotrexate shows beneficial effects over the unentrapped drugs such as decreased rate of proliferation of the tumor and Ig plasma level accompanied by low elimination[24-25].

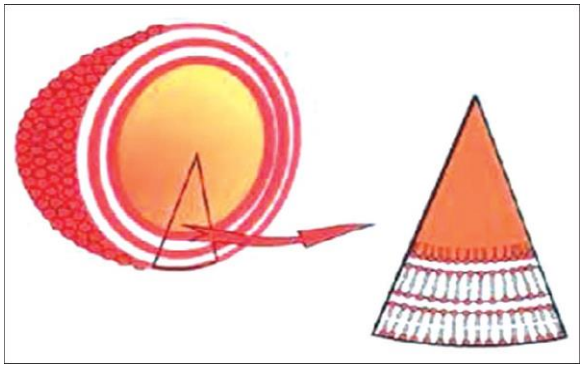

Fig 10.Structure of emulsomes

Vesosome

Multi-compartment structure encapsulates unilamellar liposomes within a second bilayer. For this purpose, it's necessary to form bilayers that can be opened and closed at will, without disrupting the inner content. This is achieved by adding ethanol to a variety of saturated phospholipids in its gel phase, which drives interdigitation of phospholipids bilayers and subsequent fusion of small vesicles to form flat bilayer sheets. These are steady to removal of the residual ethanol until heated above the lipid chain melting temperature (Tm). The bilayers become flexible, and the sheets spontaneously close on themselves to form unilamellar vesicles. During the closure, the sheets can entrap whatever is around in suspension. By adding the vesicles aggregates including drug-loaded vesicles to the pelleted sheets before heating the mixture, encapsulation is carried out to form vesosomes. Vesosome structure has taken advantage of the progress in liposome development as steric stabilization, pH loading of drugs (it is loaded by pH gradient), and intrinsic biocompatibility (it can be modified with a variety of agents, for example to specifically target a disease site, or promote adhesion or fusion)[25].

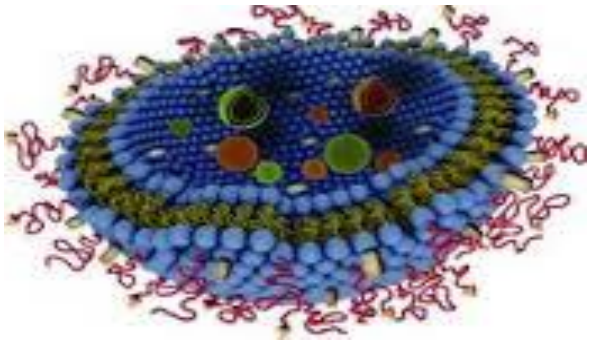

Fig 11.Vesosome multi-compartment structure

Virosomes

Virosomes are lipid-based, synthetic vesicles comprising of viral surface glycoproteins. The presence of these viral peplomers assists there cognition and attachment of these entities specifically to their target cells. A number of properties of virosomes make them a promising candidate for targeted drug and antigen delivery. A chief concern of the virosome based approach is the induction of immune response against the viral glycoproteins [26]. This property is detrimental as it can result in their rapid detection by the immune system resulting in the early clearance of the virosomes from systemic circulation [27]. However, these proteins can help in inducing a prophylactic response against the virus. This property establishes their candidature as vaccine and immunological adjuvants.

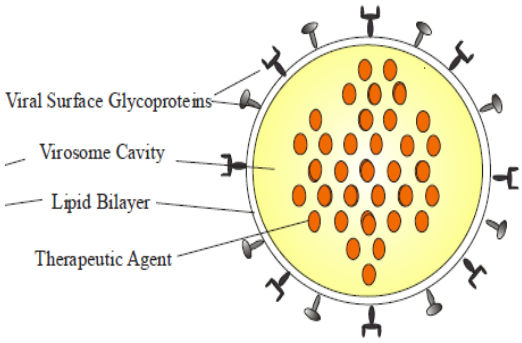

Fig 12. Structural composition of virosome comparsing virus surface glycoproteins[28]

Cryptosomes

The Lipid vesicles composed of phosphatidylcholine and suitable polyoxyethylene-derivatives of phosphatidyl-ethanolamine (cryptosomes) remain in circulation 8–10 times longer than standard liposomes after an i.v. administration in mice. The longevity is not destroyed by

the net charges on the lipid vesicle surface and is not a direct consequence of the high surface hydrophilicity; also bilayer fluidity is not an obstacle for the attainment of long circulation times[29].

Tab 1. Some of Vesicular Drug Delivery Systems

Vesicular system	Description	Application
Aquasomes	Three layered self-assembly compositions with ceramics carbon nanocrystalline particulate core coated with glassy cellobiose	Specific Targeting, molecular shielding
Cryptosomes	Lipid vesicles with a surface coat composed of phosphotidyl choline and of suitable polyoxoyethylene derivative of phosphotidyl ethanolamine	Ligand mediated drug Targeting
Discomes	Niosomes solublized with non-ionic surfactant solutions (polyoxyethylenecetyl ether class)	Ligand mediated drug Targeting. Naltrexone HCl containing Niosomes for ocular delivery shows enhance its corneal permeability[30]
Emulsomes	Nanosize Lipid particles (bioadhesives nano emulsion) consisted of microscopic lipid assembly with a polar core. Emulsomal formulations composed of solid lipid core material and stabilized by cholesterol and soya lecithin.	Parenteral delivery of poorly water soluble drugs Use of antimony in emulsome form for the treatment of Leishmaniasis showed that it was possible to administer higher levels of the drug without triggering the side effects, and thus allowed greater efficacy in treatment[31-32]
Enzymosomes	Liposomal constructs engineered to provide a mini bioenvironmental in which enzymes are covalently immobilized or coupled to the surface of liposomes.	Targeted delivery to tumor Cell
Ethosomes	Ethosomes are lipid “Soft malleablevesicles” embodying a permeation enhancer and composed of phospholipid, ethanol and water	Targeted delivery to deep skin layer
Genosomes	Artificial macromolecular complexes for functional gene transfer .Cationic lipids are most suitable because they posess high biodegradability and stability in blood serum. It is a lipid and DNA complex that is used to deliver genes. It can be a form of non-viral gene therapy as the complex does not require any components of a virus in order to transport genetic material. In presence of CT-DNA, genosomes can form through surface electrostatic interaction[33]	Cell specific gene transfer

Photosomes	Photosome® is constituted of photolyases included in liposomes. Photolyase is a bacterial enzyme that can repair ultraviolet B (UVB)-induced cyclobutane pyrimidine dimers (CPD) in eukaryotic cells[34]	Photodynamic Therapy
Virosomes	Liposomes spiked with virus glycoprotein, incorporated into the liposomal bilayers based on retro viruses derived lipids.	Immunological adjuvants
Vesosomes	Nested bilayer compartment in vitro via the interdigested bilayer phase formed by adding ethanol to a variety of saturated phospholipids	Multiple compartment of the vesosomes give better protection to the interior
Proteosomes	High molecular weight multi-submit enzyme Complexes with catalytic activity, which is specifically due to the assembly pattern of enzymes	Better catalytic activity turnover than non associated enzymes

CONCLUSION

Supramolecular systems have gained somewhat in recent years due to the focus of pharmaceutical industries in the drug design where understanding of structural and chemical interactions between host-guest systems, self assembling systems is essential for designing molecule which can mimic natural substrates. This review is to explore the benefits of supramolecular delivery system based on a new concept of the bio-mimetism of endogenous transport systems such as lipoproteins could be hold promise for the patients in future as a means of safer convenient, novel approach to drug delivery and also researcher to turn focus on development of such drug delivery systems which will lead establishment of this revolutionary concept in targeting drug delivery.

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