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Novel Approaches for Lipid Based Drug Delivery System: An Updated Review

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Abstract

In designing a new drug, considering the preferred route of administration, various requirements must be fulfilled. Active molecules pharmacokinetics should be reliable with a valuable drug profile as well as well-tolerated. Associated with the old/traditional of method of drug delivery are several limitation ranging from first-pass effect, low tolerance, minimal bioavailability, fluctuation of plasma drug concentration which result to less or no desired effect produced. This call for the demand for a more efficient drug administration technique. Over the past 20 years, nanotechnologies have provided alternative and complementary solutions to those of an exclusively pharmaceutical chemical nature since scientists and clinicians invested in the optimization of materials and methods capable of regulating effective drug delivery at the nanometer scale.

Among the many drug delivery carriers, lipid nano vesicular ones successfully support clinical candidates approaching such problems as insolubility, biodegradation, and difficulty in overcoming the skin and biological barriers such as the blood–brain one. In this review, the authors discussed the structure, the biochemical composition, and the drug delivery applications of lipid nanovesicular carriers, namely, niosomes, proniosomes, ethosomes, transferosomes, pharmacosomes, ufasomes, phytosomes, catanionic vesicles, and extracellular vesicles.

Keywords: lipid vesicles, biocompatible, biodegradable, bioavailability, lipidsniosomes, proniosomes, ethosomes, transferosomes, pharmacosomes, ufasomes, phytosomes, extracellular vesicles

Introduction

Drug delivery technique utilizes elegant chemical substances capable of crossing different animal system barriers to deliver a drug compound to a target tissue or cell in order to produce a needed therapeutic effect. The popular techniques for drug delivery follows the traditional means of administering drugs which includes; oral delivery, submucosal (tissues having mucosal lining such as mouth, anus, vagina, nose etc.) topical and intra-muscular. Dosing is preferred in the conventional delivery method as it enhance immediate release (IR) as soon as it get into systemic circulation [1].

Treatment related factors ranging from rate of drug administration and target site delivery as well as time frame of drug treatment have all been devised and improved for the past two decades.

General Routes of DDS

1. Through the vein (Intravenous)
2. Via anus (Rectal)
3. Under skin (Subcutaneous)
4. Administered in the muscles (Intramuscular)
5. Under the tongue or between cheeks (Sublingual/ buccal)

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Associated with the old system of drug delivery are several limitations ranging from first-pass effect, low tolerance, minimal bioavailability, fluctuation of plasma drug concentration which result to less or no desired effect produced. Hence, these call for innovative means for drug delivering techniques to match current medical challenges.

In these modern days, many significant efforts have been applied to use the potentials of lipid-based drug delivery systems, as it provides the suitable means of site specific as well as time controlled delivery of drugs with different molecular weight, either small or large, and also the bioactive agents [1, 2]. Poorly water-soluble drugs are challenging for the formulation scientists with regard to solubility and bioavailability. Lipid-based drug delivery systems (LBDDS) have shown the effective size dependent properties so they have attracted a lot of attention. Also LBBDS have taken the lead because of obvious advantages of higher degree of biocompatibility and versatility. These systems are commercially viable to formulate pharmaceuticals for topical, oral, pulmonary, or parenteral delivery. Lipid formulations can be modified in various ways to meet a wide range of product requirements as per the disease condition, route of administration, and also cost product stability, toxicity, and efficacy. Lipid-based carriers are safe and efficient hence they have been proved to be attractive candidates for the formulation of pharmaceuticals, as well as vaccines, diagnostics, and nutraceuticals [3-5]. Hence, lipid-based drug delivery (LBDD) systems have gained much importance in the recent years due to their ability to improve

Lipid Formulation Classification System

The lipid formulation classification system (LFC) was introduced as a working model in 2000 and an extra "type" offormulation was added in 2006 [6-8]. In recent years the LFCs have been discussed more widely within the pharmaceutical industry to seek a consensus which can be adopted as a framework for comparing the performance of lipid-based formulations. The main purpose of the LFCs is to enable in vivo studies to be interpreted more readily and subsequently to facilitate the identification of the most appropriate formulations for specific drugs, that is, with reference to their physiochemical properties [9-10].

Table 1: The lipid formulation classification system: characteristic features, advantages, and disadvantages of the four essential types of "lipid" formulations

Formulation Type	Material	Characteristics	Advantages
Type I	Oils without surfactants (e.g., tri-, di-, and monoglycerides)	Nondispersing requires digestion	Generally recognized as safe(GRAS) status; simple; and excellent capsule compatibility
Type II	Oils and water insoluble surfactants	SEDDS formed without water-solublecomponents	Unlikely to lose solvent capacity on dispersion
Type III	Oils, surfactants, and cosolvents (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS formed with water-soluble components	Clear or almost cleardispersion, drug absorption without digestion
Type IV	Water-soluble surfactants andcosolvents	Formulation disperses typically to form a micellarsolution	Formulation has good solvent capacity for many drugs

Points to Be Considered for the Formulation

Solubility: While the lipids (fatty acid derivatives) are the core ingredient of the formulation, one or more surfactants, as well as perhaps a hydrophilic cosolvent, may be required to aid solubilization and to improve dispersion properties. Surfactants are categorized by their hydrophilic-lipophilic balance (HLB) number, with a low value (≤10) corresponding to greater lipophilicity and a higher value (≥10)

corresponding to higher hydrophilicity. As a guideline as a starting point for formulation design, most of the lipids used in these oral formulations have a known "required HLB" value (generally available from the vendors), which corresponds to the optimal HLB for the surfactant blend necessary to emulsify the oil in water. Various emulsifiers can be used for the various formulations depending on their HLB values as depicted in Table [11–13].

Table 2: Emulsifiers used in lipid-based formulations

Common name/type	Examples
Low HLB (<10) emulsifier	
Phosphatidylcholine and phosphatidylcholine/solvent mixtures	Phosphatidylcholine, phosphatidylcholine in propylene glycol, phosphatidylcholine in medium chain triglycerides, and phosphatidylcholine in safflower oil/ethanol
Unsaturated polyglycolized glycerides	Oleoyl macrogolglycerides, linoleoyl macrogolglycerides
Sorbitan esters	Sorbitan monooleate, sorbitan monostearate, sorbitan monolaurate, and sorbitan monopalmitate
High HLB (>10) emulsifier	
Polyoxyethylene sorbitan esters	Polysorbate 20, polysorbate 40 , polysorbate 60, and polysorbate 80
Polyoxyl castor oil derivatives Polyoxyethylene	Polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil
polyoxypropylene block copolymer	Poloxamer 188, poloxamer 407
Saturated polyglycolized glycerides	Lauroyl macrogolglycerides, stearoyl macrogolglycerides

Dispersion:
Formulationsthatexhibitsufficientsolubility of the drug candidate should be examined for emulsification and dispersion properties in aqueous vehicles. A preliminary screening can be carried out by microscopic observation of the formulation when mixed with water. Vigorous mixing, accompanied by diffusion and stranding mechanisms, occurring at the water/formulation interface is indicative of an efficient emulsification. Absence of drug precipitate after complete mixing of the formulation with aqueous medium is another requirement. Particle size measurement of emulsion droplets by laser light scattering or other techniques is useful to select promising formulations [12-13].

Digestion: The actions of intestinal lipases can have aprofound effect on the behaviour of lipid-based formulationsin the GI tract and must be considered in their design. Ithas long been recognized that nondispersible but digestiblelipids such as triglycerides can be metabolized by lipases tomono-/diglycerides and fatty acids which will emulsify anyremaining oil. Thus, the presence of high amounts of surfactants may be unnecessary to assure creation of the requisite small particle sizes and large surface areas for drug release [14].

Absorption: Efficient absorption of the drug by theintestinal mucosal cells is of course the ultimate goal of any oral lipid-based formulation [13]. First the components are dispersed to formlipid droplets (for type I formulations) or emulsion droplets(for types II-III), followed by lipolysis and solubilization ofthe digestion products by bile acids, forming colloidal mixedmicelles. It is believed that drug then partitions from theemulsion oil droplets and bile salt mixed micelles to beabsorbed by the mucosal cells of the intestinal wall.

Advantages of LBDDS [15]

1. Drug release in controlled and targeted way.
2. Pharmaceutical stability.
3. High and enhanced drug content (compared to other carriers).

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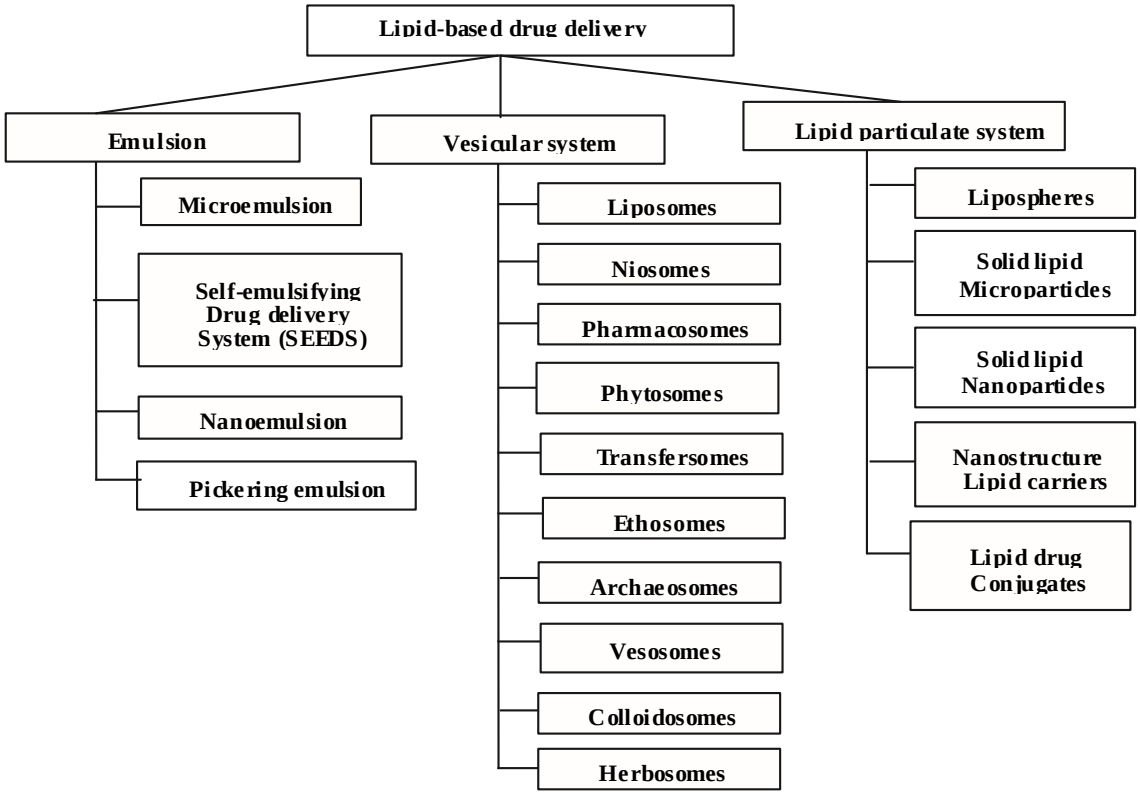
Feasibilities of carrying both lipophilic and hydrophilic drugs.
Biodegradable and biocompatible.

Types of Lipid-Based Drug Delivery Systems [15]



Various Lipid Based Drug Delivery System

Micelles: Micelles are therapeutic agent or a carrier to deliver a poorly water soluble drug having size of around 5-100 nm range. It consists of surfactants having a hydrophilic head and a lipophilic tail [14]. The drug is associated with the hydrophobic block of the co-polymer which is orientated toward the interior of the micelles while the hydrophilic blocks form an external shell. For applications by the oral route, pH-sensitive polymeric micelles are particularly interesting. These micelles are usually composed of block co-polymers with PEG as the hydrophilic part and a polymer derived from acrylic acid as the hydrophobic part. Such polymers self-aggregate at low pH, this protecting an encapsulated drug in the acid environment of the stomach, but dissociate at higher pH to allow drug release in the intestine. One such polymer is the PEG-bpoly(alkyl acrylate-co-methacrylic acid) [15].

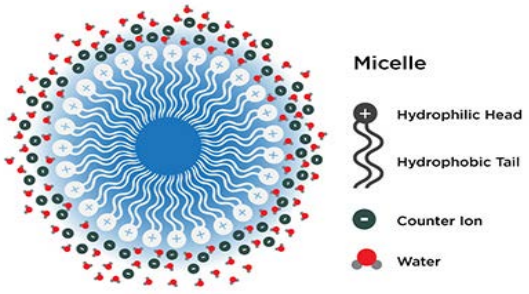


Figure 1: Micelle

Liposome: Liposomes are closed concentric bilayer membranes consisting of water-insoluble polar lipids. They are spherical vesicles (typically 50-500 nm in diameter), consisting of a lipid bilayer sustained through hydrophobic interactions that allow them to carry hydrophobic

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and hydrophilic molecules [16]. The amphiphilic feature of liposomes explains why they are widely used to increase the penetration of hydrophilic molecules (in the aqueous core) and/or lipophilic molecules (within the membrane bilayer) [17]. They can encapsulate biomolecules and drugs for targeted delivery while protecting their bioactivity [18]. They are made up of phospholipids enclosing hydrophilic core 19 and were discovered by Bangham and co-workers in the 1960s [20]. A liposome surface decorated with PEG (PEGylated) can significantly improve the half-life of liposomes (>200 nm) in systemic circulation. Furthermore, the PEGylation approach can help to facilitate liposomal drug delivery by reducing multidrug resistance due to the over-expression of drug efflux transporter pumps such as Pglycoprotein [21]. Phospholipid vesicles demonstrate high biocompatibility, low toxicity, biodegradability, and can be produced on a large scale [22-23].

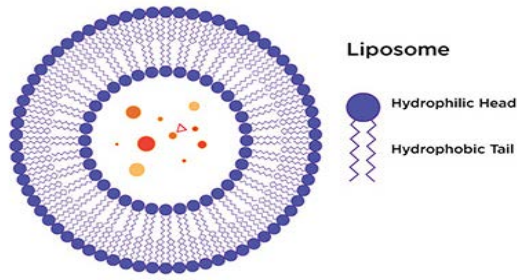

Figure 2: Liposome

Cholesterol is sometimes added to themembranes of the liposomes for the purpose ofincreasing their stability and the rigidity of thelipid bilayer, reducing their permeability andinhibition of phospholipid acyl chaincrystallization by modulating the bilayer fluidity.Phytosterols have been recently used as asubstitute of cholesterol in the formulation ofliposomes since cholesterol may cause healthproblems especially for consumers who aresuffering from hypercholesterolemia[24].

Alcohol and surfactant are added to liposomes torender them more elastic transformable andflexible. They are composed of lipids andsofteners (sodium cholate). This property ofelasticity offers liposomes better skin permeationability [25].

Liposomes have the ability to cross any cellmembrane, the addition of other components totheir surface to enhance their effectiveness isinteresting in such a way, liposomes can includemultiple brain cell membrane-targeting agents ontheir surface, enabling a specific interaction withtarget cells by molecular recognitionmechanisms, and hence, improving the transportof the encapsulated Growth Factors through theBBB. RMP-7 is a molecule with the ability toincrease the permeability of the BBB, whenconjugated with liposomes enhances delivery ofGFs [26].

Small-sized liposomes enhance transitivity, butlarge-sized liposomes show a higher cell affinitycompared with smaller ones. It therefore appearsthat large particles have a higher retention [27].

Classification of Liposomes: Liposomes can be categorized into different groups depending on their structural association, size and lamellarity, small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), double bilayer vesicles (DBVs), oligolamellar vesicles (OLVs), multi-lamellar vesicles (MLVs), giant unilamellar vesicles (GUVs), and multivesicular vesicles (MVV) [1,24,28].

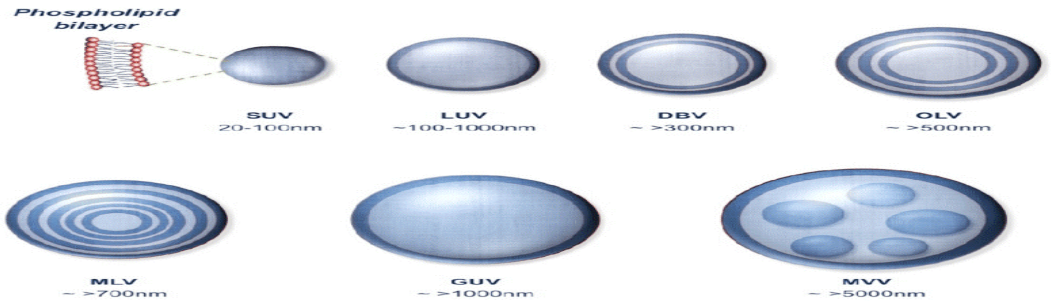

Figure 3: Different types of lipid vesicles

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Transfersomes: In order to overcome thisinability of liposomes to permeate the skin, Cevcand Blume in the 1990s developed novel lipidvesicles known as deformable/elastic/flexibleliposomes [17].Transfersomesrepresent not onlythe first generation of ultra-deformable vesicles,but also one of the most successful carriers forskin delivery. The word Transfersome derivesfrom the Latin word "transferre", which means "tocarry across", and the Greek word "soma", whichmeans "body" [22].

Transferosomes are typically below 300 nmbeing more elastic and flexible than liposomes(typically five- eight times higher), which makesthem highly suitable for skin penetration. Theyare mainly composed of phospholipids and edgeactivators. These edge activators interfere withthe bilayer and confer ultra-flexibility to thevesicles which enhance their passage throughsmall apertures of the skin. The concentration ofthe edge activator in the formulation (usuallybetween 10-20 %) is crucial and ideally includedin sub-lytic concentrations i.e. not able to causedestruction of vesicles [31-32]. Some widely usededge activators of Transfersomes are: Tween,deoxycholate, spans, sodium cholate. However,enhanced permaeation is observed withmonoterpenes as edge activator. Mixedmonoterpenes (limonene-citral mixture) couldsignificantly enhance the elasticity of MixedMonoterpenes edge-activated PEGylated TFSs(MMPTs). CLSM analyses demonstrated thatMMPTs were distributed in deep layers of theskin, indicating that MMPTs might transportdeeper through the skin than conventionalliposomes [32].

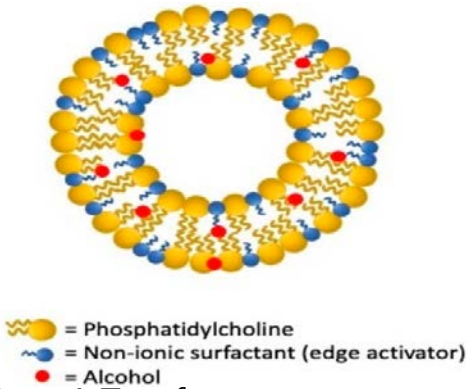

Figure 4: Transfersomes

Ethosomes: Similar to transfersomes,ethosomes can improve the penetration throughthe stratum corneum barrier due to a quickpermeation and greater transdermal flow [33].The second generation of novel vesicular drugcarriers are represented by these spherical, lipidblisters mainly composed of phospholipids,ethanol and water. The high alcohol content ofup to 45% is the main distinguishing feature fromliposomes enabling a decrease in size andelasticity when same method of preparation isused. In order to reach deeper tissues and causea systemic action the penetration of the naturalskin barrier and the magnitude of transdermalpermeation are influenced. Further adjuvantsadded to the ethosomal formulation arecholesterol to improve stability or gel markers forincreased residence time [34].

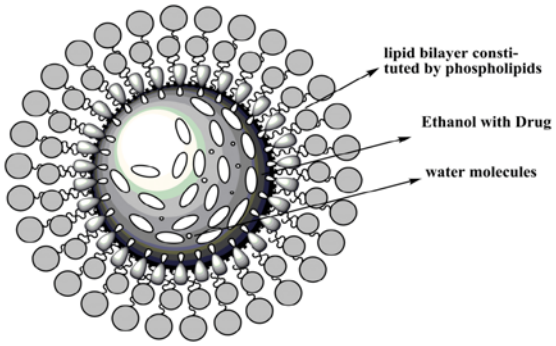

Figure 5: Ethosomes

Cubosomes: Cubosomes are nano-structurescomposed mainly of amphiphilic polar lipid.When this amphiphilic substance dissolved inwater with concentration above the criticalmicelle concentration, it forms micellaraggregations. At higher concentration, theformed micelles are forced to form cubicstructure [35].

They are liquid crystalline particles in nano sizerange (100-300 nm), usually composed of lipidssuch as (Monoolein, and phytantriol) and with orwithout stabilizer/surfactant (Poloxomer 407)[36]. They are highly stable nanoparticles formedfrom the lipid cubic phase and stabilized by apolymer-based outer layer. The bicontinuous lipidcubic phases consist of a single lipid bilayer thatfolds in a tridimensional architecture forming abicontinuous phase of lipid bilayered regions andaqueous channels [37]. The composition of thecubosome can be modified to control the

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poresizes or to include specific types of lipids. Theirouter polymer layer can be used to enhancetargeting. They are highly stable forms underphysiological conditions [38].

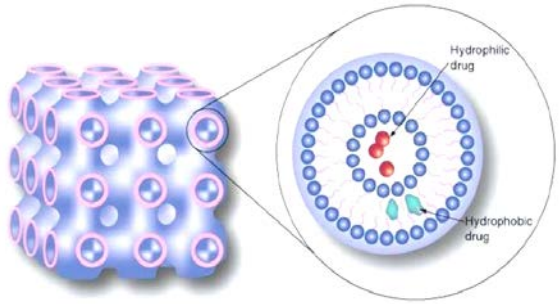

Figure 5: Cubosomes

Phytosome: Phytosomes, also known asherbosomes, are complexes of natural bioactivematerials (plant extracts or water solublephytoconstituents) and phospholipids(phosphatidylcholine, phosphatidylethanolamine,and phosphatidylserine). In fact, there is nodifference between phytosomes and liposomes.The former are liposomes loaded with phytocompounds and hence phytosomes are a specialcase of liposomes [34].

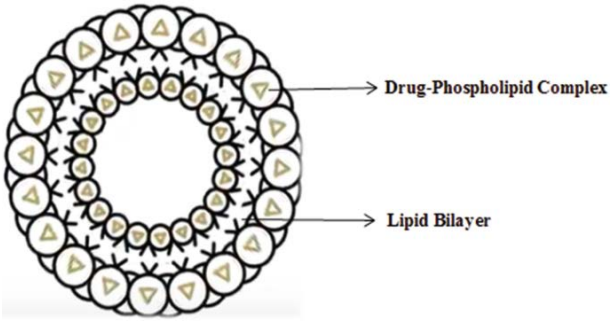

Figure 6: Phytosome

Niosomes: Niosomes have a multi-thin-layervesicular structure and contain basically non-ionic surfactants, a hydration medium, and lipids suchas cholesterol [38].Niosomes are a hydrated mixture of cholesteroland nonionic surfactants such as alkyl-ether,esters, and amides. Also called non-ionic surfactant vesicles. They have great advantages,such as low cost, high stability, wide availabilityof nonionic surfactants, and mild storageconditions. Niosomes are similar to liposomesbut the bilayers are formed by non-ionic surfactants. Compared with liposomes,Niosomes have greater stability over a longperiod of time. Liposomes and Niosomes are notable to transport into deeper skin, but Ethosomeshave the capability to reach the deep skin layer[28].Niosomes have already conquered the cosmeticindustry and are now being explored todetermine the potential for further commercialapplications [34].

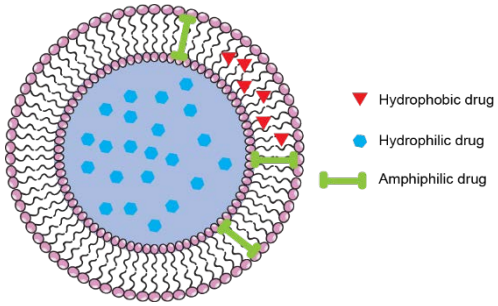

Figure 7: Niosomes

Solid-Lipid Nanoparticles: Solid lipidnanoparticles (SLNs) are lipid-based DDSs thatrepresent an evolution of emulsions; the oil of thefat emulsion is replaced by solid lipids [40].SLNs are formulated with lipids or lipid mixtureswhich are in a solid state at room and also atbody temperature [41]. Their solid lipid coreprovides the opportunity for solubilizing Essentialoils (stearic acid and palmitic acid; triglycerides,such as tristearin and tripalmitin; partialglycerides, such as glycerylbehenate andglycerylpalmitostearate;) and protect themagainst degradation [24]. These EOs arephysiological substances which are classified as“Generally Recognized as Safe” (GRAS) category[41]. Compritol®888 ATO, Precirol® ATO5, cetylalcohol, cetylpalmitate, glycerylmonostearate,trimyristin/Dynasan®114, tristearin/Dynasan®118, stearic acid, Imwitor®900 are brand namesused in formulation of SLNs[42].

SLNs is (around 10 to 200 nm) and narrow sizerange (100 to 200 nm) permits them to crosstight endothelial cells of the blood- brain-barrier(BBB) also in the digestion. It escapes from thereticuloendothelial system and bypass the liver[43]. The average diameter of SLNs is in thesubmicron range from 50 to 1000 nm.

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SLNs formulations for various application routeshave been developed such as parenteral, oral,dermal, ocular, pulmonary, and rectal andsystematically also characterized in in-vitro andin-vivo studies [43].

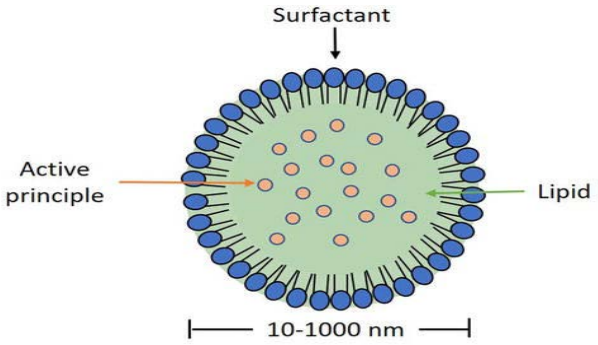

Figure 8: Solid-Lipid Nanoparticles

Nanostructured Lipid Carriers: NLCs are considered to be an upgraded versionof SLNs, where the compact arrangement of theuniformly structured solid lipids has beenreplaced with an unstructured lipid matrixestablished by blending both solid and liquidlipids, which eventually provide more space forloading drug candidates [45]. NLCs offer specialadvantages: sustained release, goodbiocompatibility and biodegradableproperties [46].The development of a nanoparticulate lipid carrierwith a certain nanostructure in order to increasethe payload and prevent drug expulsion [47].This could be comprehended in three ways: (1)the imperfect type, (2) the multiple type, and (3)the amorphous type [48-49].

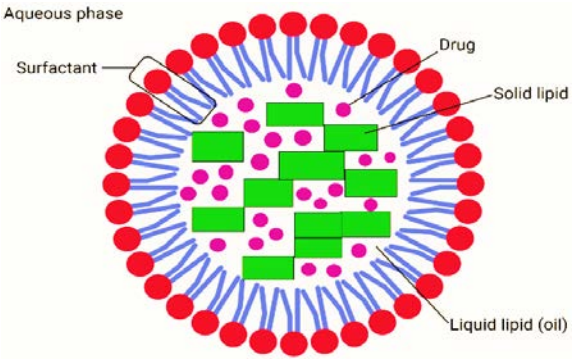

Figure 9: Nanostructured Lipid Carriers

Lipid Drug Conjugates (LDC): SLN are useful for the incorporation of lipophilicdrugs. Due to partitioning effects during theproduction process, only highly potent hydrophilicdrugs which are effective in low concentrations(e.g. LHRH or EPO) can be firmly incorporated inthe solid lipid matrix. In order to overcome thislimitation, the so- called LDC nanoparticles withdrug loading capacities of up to 33% have beendeveloped at the turn of the millennium. Here, aninsoluble drug-lipid conjugate bulk is preparedeither by salt formation with a fatty acid, i.e. lipiddrug bioconjugates through grafting of thecarboxylic groups of the fatty acids (e.g., stearicacid, oleic acid) with the functional groups (e.g.,amine group) of drug molecules or by covalentlinking (e.g. to esters or ethers). In the saltformation process, the free drug base and fattyacid are dissolved in a suitable solvent. Thesolvent is then consequently evaporated underreduced pressure. For the covalent linking, thedrug (salt) and a fatty alcohol react in presenceof a catalyst and the LDC bulk is then purified byrecrystallization [42, 47].

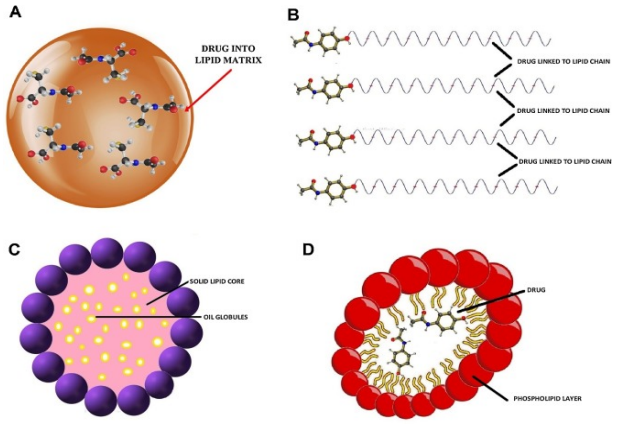

Figure 10: Lipid Drug Conjugates

Nanoemulsions: Nanoemulsions are fine emulsions, either waterin oil or oil in water, prepared by using twoimmiscible phases, with the help of one or moresuitable surfactants. The range of the dropletsize of these forms varies approximatelybetween a few to 200 nanometers, which makesthem appear in a transparent-to-milky-whiteappearance to the naked eye [38].These novel formulations enhance drug deliverywhen given orally, parenterally and dermally. Incontrast to microemulsions, nanoemulsionsdiluted with water remain stable

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without changingthe droplet size distribution; this stability isinfluenced by changes in temperature and pH[21]. Lesser toxic formulation, kinetically stablesystems, targeting applications, and aestheticfeatures forced the pharmaceutical researchersto work on nano-emulsion [50].

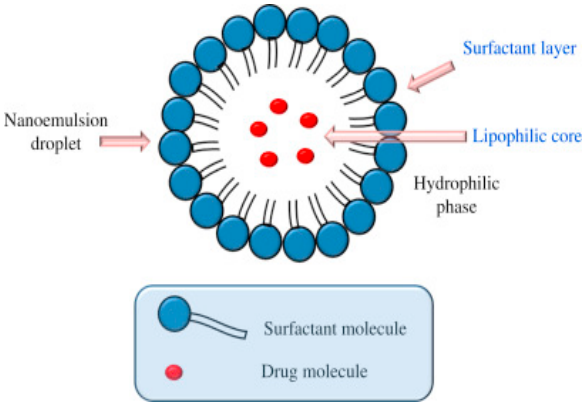

Figure 11: Nanoemulsion

Self-Emulsifying Drug DeliverySystem (SEDDS): In 1943, Hoar and Schulman hypothesized theexistence of microscopic emulsion-like structuresin a transparent mixture of oil, alcohol, water anda cationic surfactant. About fifteen years later,the presence in these systems of small emulsion like structures was confirmed by electronmicroscopy and coined the term "Microemulsion" to define a system consisting of water,oil and surfactants, which is a transparent,optically isotropic and thermodynamic stableNewtonian non-viscous liquid [51].

A readily dispersible isotopic mixture of oil, drug,surfactant, and co-surfactant, which forms an oil-in-water emulsion with a droplet size below 1000nm in the presence of agitation, is called a selfmicro/nanoemulsifying drug-delivery system[52]. Self-emulsifying drug-delivery systems(SEDDSs) enhance the bioavailability of APIswith low water solubility. SMEDDSs(microemulsifying) are different from SNEDDSs(nanoemulsifying) only in terms of droplet size.Compared with SMEDDSs, SNEDDSs aremoreeffective in enhancement of bioavailabilitybecause of the high interface surface area fordrug absorption due to the nanosized droplets.All components reach the GIT, which provides asuitable environment for the emulsificationprocess, whereas preparations of SLNs, NLCs,and liposomes need external energy. Differentparameters affect the SEDDS properties such assize, bioavailability, and drug release [28].

Formulation Approaches for LBDDS

Spray Congealing. This is also referred to as spray cooling.In this method, molten lipid is sprayed into a cooling chamberand, on contact with the cool air, congeals into spherical solidparticles. The solid particles are collected from the bottom ofthe chamber, which can be filled into hard gelatin capsules orcompressed into tablets. Ultrasonic atomizers are frequentlyused to produce solid particles in this spray cooling process.The parameters to be considered are the melting point of theexcipient, the viscosity of the formulation, and the cooling airtemperature inside the chamber to allow instant solidificationof the droplets.

Spray Drying. This method is somewhat similar topreceding one but differs in the temperature of the air insidethe atomizing chamber. In this method, the drug solution(drug in organic solution/water) is sprayed into a hot airchamber, where the organic solvent or water evaporates giving rise to solid microparticles of drug. During this process,along with the lipid excipients, solid carriers like silicondioxide can be used. Gelucire (lipid excipient) enhances thedrug release process by forming hydrogen bonds with theactive substance, leading to the formation of stable solids ofamorphous drug in microparticles [17, 18].

Adsorption onto Solid Carrier. This is a simple andeconomical process (in the context of equipment investment)in which a liquid-lipid formulation is adsorbed onto solidcarrier like silicon dioxide, calcium silicate, or magnesiumalumina metasilicate. The liquid-lipid formulation is addedto the carrier by mixing in a blender. The carrier must beselected such that it must have greater ability to adsorbthe liquid formulation and must have good flow property after adsorption. Gentamicin and erythropoietin withcaprylocaproyl polyoxylglycerides (Labrasols) formulationswere successfully converted into solid intermediates whosebioavailability was maintained even after adsorption oncarriers. Advantages of this method include good contentuniformity and high lipid exposure [19–21].

Melt Granulation. This is also referred to as pelletization,which transforms a powder mix (with drug) into granules orpellets [22–24]. In this method a melt able binder (moltenstate) is sprayed onto the powder mix in presence of highshear mixing. This process can be referred to as a "pumpon" technique. Alternatively, the melt able binder is blendedwith powder mix and, due to the friction of particles(solid/semisolid) during the high-shear mixing, the bindermelts. The melted binder forms liquid bridges between powder particles and forms small granules which transform intospheronized pellets under controlled conditions. Dependingon the fineness of the powder, 15%–25% of the lipid-basedbinder can be used. The parameters to be considered duringthe process are binder particle size, mixing time, impellerspeed, and viscosity of the binder on melting [25]. The dissolution rate of diazepam was enhanced by formulating meltagglomerates containing solid dispersions of diazepam [26-27].

Supercritical Fluid-Based Method. This method useslipids for coating drug particles to produce solid dispersions.In this method, the drug and lipid-based excipients aredissolved in an organic solvent and supercritical fluid (carbondioxide) by elevating the temperature and pressure [28, 29].The coating process is facilitated by a gradual reduction inpressure and temperature in order to reduce the solubility ofthe coating material in the fluid and hence precipitate ontothe drug particles to form a coating [30, 31]. The solubilityof the formulation components in the supercritical fluid andstability of the substance during the process are importantconsiderations of this method[32].

Characterization of Lipid-Based DrugDelivery Systems

Appearance. The appearance can be checked in graduatedglass cylinder or transparent glass container for its uniformityand colour at equilibrium [33].

Color, Odor, and Taste. These characteristics are especially important in orally administered formulation. Variations in taste, especially of active constituents, can oftenbe accredited to changes in particle size, crystal habit, andsubsequent particle dissolution. Changes in color, odor, andtaste can also indicate chemical instability [34].

Density. Specific gravity or density of the formulation isan essential parameter. A decrease in density often indicatesthe entrapment air within the structure of the formulation.Density measurements at a given temperature can be madeusing high precision hydrometers [34].

pH Value. The pH value of aqueous formulation shouldbe taken at a given temperature using pH meter and onlyafter settling equilibrium has been reached, to minimize "pHdrift" and electrode surface coating with suspended particles.Electrolyte should not be added to the external phase of theformulation to stabilize the pH, because neutral electrolytesdisturb the physical stability of the suspension [34].

Self-Dispersion and Sizing of Dispersions. Assessment ofthe dispersion rate and resultant particle size of lipid-basedsystems is desirable so attention has been given to measuringdispersion rate. The particle size measurement can be performed by optical microscope using a compound microscopefor the particles with measurement within microns. Particlesize analyzer can be used for the measurement of the particlesize.

Droplet Size and Surface Charge (Zeta Potential). Thedroplet size distribution of microemulsion vesicles can bedetermined by either electron microscopy or light-scatteringtechnique. The dynamic light-scattering measurements aretaken at 90∘ in a dynamic light-scattering spectrophotometerwhich uses a neon laser of wavelength 632 nm. The dataprocessing is done in the built-in computer with the instrument. Recently, with respect to the importance of particle sizedistribution in terms of particle characterization and productphysical stability testing, there has been interest in newerlight-scattering methods for particle detection called photoncorrelation spectroscopy (PCS).The surface charge is determined using a zeta potentialanalyzer by measuring the zeta potential (ZP) of the preparations. ZP characterizes the surface charge of particles and thusit gives information about repulsive forces between particlesand droplets. To obtain stable nanoemulsions by preventingflocculation and coalescence of the Nano droplets, ZP shouldtypically reach a value above 30 mV [34].

Viscosity Measurement. Brookfield type rotary viscometer can be used to measure the viscosity of lipid-basedformulations of several compositions at different shear ratesat different temperatures. The samples for the measurementare to be immersed in it before testing and the sample temperature must be maintained at 37 ± 0.2∘C by a thermo bath.The viscometer should be properly calibrated to measurethe apparent viscosity of the suspension at equilibrium ata given temperature to establish suspension reproducibility.Apparent viscosity, like pH, is an exponential term, andtherefore the log-apparent viscosity is a suitable way ofreporting the results [34].

***In-Vitro* Studies.** In vitro evaluation of lipid-based drugdelivery systems can be done with the use of lipid digestionmodels. In order to assess the performance of an excipientduring formulation development and to predict in vivoperformance, it is necessary to design an in vitro dissolutiontesting method. This can be termed as "simulated lipolysisrelease testing" [35]. The basic principle on which this systemworks requires maintaining a constant pH during a reactionwhich releases or consumes hydrogen ions. If any deviation isfound, it is compensated by the reagent addition. The modelconsists of a temperature-controlled vessel (37 ± 1∘C), whichcontains a model intestinal fluid, composed of digestionbuffer, bile salt (BS), and phospholipid (PL). Into this modela fluid lipid-based formulation is added and to initiate thedigestion process pancreatic lipase and colipase were added.As the digestion process starts it results in the liberationof fatty acids, causing a transient drop in pH. This drop in pH is quantified by a pH electrode. The pH electrode iscoupled with a pH-stat meter controller and auto burette.An equimolar quantity of sodium hydroxide is added totitrate the liberated fatty acids by the auto burette, so as toprevent a change in pH of the digestion medium from apreset pH value. By quantifying the rate of sodium hydroxideaddition and considering the stoichiometric relationshipbetween fatty acids and sodium hydroxide, the extent ofdigestion can be quantized. During the digestion process,samples can be withdrawn and separated into a poorlydispersed oil phase, highly dispersed aqueous phase, andprecipitated pellet phase by centrifugation. Quantification ofdrug in the highly dispersed aqueous phase indicates thatdrug has not precipitated, from which an assumption can bemade with respect to in vivo performance of the lipid-basedformulation.

In Vivo Studies. The impact of excipients on the bioavailability and pharmacokinetic profile of drugs can be estimatedby designing appropriate in vivo studies. A detailed studyof intestinal lymphatic absorption is required, since lipidbased formulations enhance bioavailability by improving theintestinal uptake of drug. Due to insufficient clinical dataand differences in methods and animal models used, studiesrelated to the drug transport by lymphatic system havebecome difficult [36].

In Vitro-In Vivo Correlation (IVIVC). In vitro-in vivocorrelation will help to maximize the development potentialand commercialization of lipid-based formulations. A shortened drug development period and improved product qualitycould be achieved by developing a model that correlatesthe in vitro and in vivo data. Determining the solubility,dissolution, lipolysis of the lipid excipient, and intestinalmembrane techniques (isolated animal tissue and cell culturemodels) are various in vitro techniques that can be used toassess lipid-based formulations [37]. Such techniques provideinformation about specific aspects of the formulation only.But it is important to know the in vivo interaction andperformance of these systems. Similar to that of in vivoenterocytes, Caco-2 cells produce and secrete chylomicronson exposure to lipids. More study has to be carried out onthe choice of the most suitable in vivo model for assessing thelipid-based formulations.

Applications

- So far, the design of successful lipid-based delivery systems has been based largely upon empirical experiences. Systematic physicochemical investigations of structure and stability do not only help to speed up the development of new and improved formulations, but may also aid in the understanding of the complex mechanisms governing the interaction between the lipid carriers and the living cells. Hence they sought to be safe, efficient, and specific carriers for gene and drug delivery.

- LBDDS can be used to deliver various types of drugs from new chemical entities to more recent new developments for proteins and peptides, nucleic acids (DNA, siRNA), and cellular site specific delivery [38–40].
- The utility of lipid-based formulations to enhance the absorption of poorly water-soluble, lipophilic drugs has been recognized for many years. Lipids are perhaps one of the most versatile excipients classes currently available, providing the formulator with many potential options for improving and controlling the absorption of poorly water-soluble drugs. These formulation options include lipid suspensions, solutions, emulsions, microemulsions, mixed micelles, SEDDS, SMEDDS, thixotropic vehicles, thermosoftening matrices, and liposomes.
- Lipid-based formulations, which are by no means arecent technological innovation, have not only proventheir utility for mitigating the poor and variable gastrointestinal absorption of poorly soluble, lipophilicdrugs, but also, in many cases, have shown the abilityto reduce or eliminate the influence of food on theabsorption of these drugs. Despite these realities,marketed oral drug products employing lipid-basedformulations are currently outnumbered 25 to1 byconventional formulations. Some of the commerciallyavailable lipid-based formulations.

Future Prospects

More consideration needs to be paid to the characteristicsof various lipid formulations available, so that guidelinesand experimental methods can be established that allowidentification of candidate formulations at an early stage.Methods need to be sought for tracking the solubilisation state of the drug in vivo, and there is a need for in vitromethods for predicting the dynamic changes, which areexpected to take place in the gut. Attention to the physicaland chemical stability of drugs within lipid systems and theinteractions of lipid systems with the components of capsuleshells will also be required. Whilst these present challengesthere is a great potential in the use of lipid formulations.The priority for future research should be to conduct humanbioavailability studies and to conduct more basic studies onthe mechanisms of action of this fascinating and diversegroup of formulations.

Conclusion

Lipid-based drug delivery systems provide the vast array ofpossibilities to formulations as they potentially increase thebioavailability of number of poorly soluble drugs along withthe formulations of physiologically well tolerated class. Thedevelopment of these systems requires proper understandingof the physicochemical nature of the compound as wellas the lipid excipients and gastrointestinal digestion. Oneof the major challenges of lipid excipients and deliverysystems is the varying range of compounds they contain.Proper characterization and evaluation of these deliverysystems, their stability, classification, and regulatory issuesconsequently affect the number of these formulations. On the way of conclusion, the prospect of these delivery systemslooks promising.

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