The Utility of Lipids as Nanocarriers and Suitable Vehicle in Pharmaceutical Drug Delivery

Salome A. Chime¹,*, Paul A. Akpa² and Anthony A. Attama²

¹Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka 410001, Nigeria; ²Drug Delivery Research Unit, Department of Pharmaceutics University of Nigeria, Nsukka 410001, Nigeria

Abstract: Lipid based excipients have gained popularity recently in the formulation of drugs in order to improve their pharmacokinetic profiles. For drugs belonging to the Biopharmaceutics Classification System (BCS) class II and IV, lipid excipients play vital roles in improving their pharmacokinetics properties. Various nanocarriers viz: Solid lipid nanoparticles, nanostructured lipid carriers, self-nanoemulsifying drug delivery systems (SNEDDS), nanoliposomes and liquid crystal nanoparticles have been employed as delivery systems for such drugs with evident successes. Lipid-based nanotechnology have been used to control the release of drugs and have utility for drug targeting and hence, have been used for the delivery of various anticancer drugs and for colon targeting. Drugs encapsulated in lipids have enhanced stability due to the protection they enjoy in the lipid core of these nanoformulations. However, lipid excipients could be influenced by factors which could affect the physicochemical properties of lipid-based drug delivery systems (LBDDS). These factors include the liquid crystalline phase transition, lipid crystallization and polymorphism amongst others. However, some of the physicochemical properties of lipids made them useful as nanocarriers in the formulation of various nanoformulations. Lipids form vesicles of bilayer which have been used to deliver drugs and are often referred to as liposomes and nanoliposomes. This work aims at reviewing the different classes of lipid excipients used in formulating LBDDS and nanoformulations. Also, some factors that influence the properties of lipids, different polymorphic forms in lipid excipients that made them effective nanocarriers in nano-drug delivery would be discussed. Special considerations in selecting lipid excipients used in formulating various forms of nanoformulations would be discussed.

Keywords: Lipids, polymorphism, solid lipid nanoparticles, nanoliposomes, nanostructured lipid carriers, drug delivery.

1. INTRODUCTION

Commercial LBDDS have been in the market since 1981 [1] and since then, their use continuously increases, because of the advantages they offer which include their ability to facilitate the absorption of drugs that are poorly water-soluble, they can be designed such that drug release may be controlled or targeted to specific sites of the body, they have capacity to ameliorate some side effects of drugs and they are capable of encapsulating hydrophilic and lipophilic drugs. Generally, the use of LBDDS lead to better disease management [2-4]. LBDDS may be designed in order to meet particular desired goal(s), they may be formulated as controlled release preparations [5], normal release dosage forms, targeted drug delivery systems, parenteral formulations, ocular delivery systems [6], intra vaginal [7], intra nasal [8], rectal and transdermal delivery among others [9-11]. They are often prepared using natural, synthetic and semi-synthetic lipids. LBDDS such as nanoemulsions, nanoliposomes, lipid nanoparticles, micellar solutions, nanostructured lipid carriers, self-emulsifying lipid formulations, dry emulsions, solid dispersions, drug lipid conjugates and solid-liquid compacts have been developed and utilized for the delivery of drugs belonging to BCS class II and IV [12, 13].

Lipid excipients are abundantly distributed in nature and are biodegradable. They are classified as GRAS (generally regarded as safe) and can be used as an excipient in different formulations [14]. Generally, most lipid carriers are highly stable in different formulations, their ability to contain or entrap drugs are high especially when modified properly, and there is possibility to encapsulate hydrophilic and lipophilic drugs [15]. Most pharmaceutical-grade lipid excipients are compatible with most drugs and other excipients and this enhances the stability of LBDDS. Lipid excipients can be used to formulate liquid, semi-solid and solid dosage forms and these attributes make them most attractive [1] hence, there is need to study the physicochemical properties as well as some formulation considerations in LBDDS in order to ensure the stability and efficacy of these formulations. Be-
cause of its GRAS status, lipids are promising carriers for the formulation of pharmaceuticals, nutraceuticals, diagnostics and vaccines [3, 16].

Molecular structures of lipids play distinct and vital roles in deducing their phase behaviour. The P value (critical packing parameter) is employed for the formation of liquid crystal nanostructures [17]. Lipid excipients are affected by so many factors which influence the physicochemical properties of LBDDS viz: liquid crystalline phase transition, lipid crystallization and polymorphism among others. This work aims at reviewing the different classes of lipid excipients used in formulating LBDDS, the factors that influence the properties of lipids, different polymorphic forms in lipid excipients, their applications as nanocarriers, advantages and disadvantages. Also, advances in LBDDS would be discussed with greater emphasis on special considerations and guidelines in the preparation of lipid based formulations (LBFs). The factors that influence the absorption of drugs from LBFs would also be reviewed in this work.

2. LIPIDS AND CLASSIFICATIONS

Lipids are group of organic compounds found in plants, animals and microorganisms, they are one of the three large classes of foods and form major components of all living cells [18]. Lipids are compounds that are superabundant and occupy the functionality and buildup of cells in living things. They are also constituents of foods and nutrition and are major component of unsaturated fatty acids (ω-3, ω-6 and ω-9), linoleic, oleic acid and α-linolenic. Lipids may also be defined as any molecule of intermediate molecular weight (100-5000 mw.) that contain a large portion of aliphatic or aromatic hydrocarbons [19]. They are organic compounds made up of hydrocarbons necessary for the functionality and structures of living cells. They are mainly soluble in non-polar solvents viz: chloroform, ether and are relatively not water soluble. It is a composite word encompassing hydrocarbon-based molecules, which can be natural or synthetic, aliphatic or aromatic, cyclic or acyclic, saturated or unsaturated. Typically, lipid molecules are predominantly hydrophobic, but contain some hydrophilic components viz: hydroxyl, phosphate ester, carboxyl and amines. This makes lipid a group of amphipathic molecules with both hydrophobic and hydrophilic portions that can self-assemble into various colloid structures in physiological conditions [10].

Lipids can be classified based on their chemical composition as follows:

- Homolipids: These are fatty acids esters with different alcohols viz: cerides (waxes), glycerides (fats, oils) and sterides [20].
- Heterolipids: These include the phospholipids, glycolipids, and sulfolipids. Two main classes of phospholipids that occur naturally and could be used in pharmaceuticals are the phosphosphingos lipids and phosphoglycerides also known as lecithin.
- Complex lipids: These are mainly the lipoproteins and chylomicrons [20].

Lipids, however, can be classified in different ways based on their sources, chemical structure, and functions. The lipid maps structure database (LMSD) recorded above 30,000 unique lipid structures classified into eight main classes as shown in Fig. (1) [21, 22].

3. PHYSICOCHEMICAL PROPERTIES OF LIPIDS

The physical properties of most lipids are largely dependent on the characteristics of the alkyl chain of the fatty acids including the content of saturated or unsaturated fatty acids, cis or trans configuration and chain size. The melting point of lipids increases with an increase in chain length and decreases with increased unsaturation [23]. The presence of cis-double bonds largely decreases the melting point and the bent chains packing. Trans fatty acids have melting points much closer to those of the corresponding saturates [24]. The triacylglycerol composition determines to a large extent the physical properties of most lipids and also influences their structure and stability [23, 25]. The factors that influence the properties of lipids used in drug delivery and their effect on LBFs are discussed below. These factors can influence the stability, drug release, absorption, permeation, drug entrapment and the bioavailability of the LBFs.

3.1. Gel-liquid Crystalline Phase Behavior

Lipids can exist in a frozen gel state or liquid crystalline state depending on the temperature. Transitions between the gel and liquid-crystalline phases can be monitored using different techniques which include: nuclear magnetic resonance (NMR), electron spin resonance, fluorescence (ESRF) and differential scanning calorimetry (DSC) [26].

Lipids undergo phase changes in response to temperature; some lipids e.g. phospholipids have specific phase transition temperature (Tm), also called the melting temperature, between the gel and liquid crystalline states according to their fatty acid compositions [27]. The melting transition is accompanied by enthalpy and volume changes. Controlling the transition temperature of lipids is crucial for lipid vesicles drug delivery, as this could affect the stability and overall bioavailability of the incorporated drug(s).

The phase transition temperature of phospholipids is a temperature at which it transits from gel to liquid crystalline state. This property is influenced by the nature of the polar head group, the length of the hydrocarbon chains and the degree of saturation of the hydrocarbon chains. Phospholipids with longer hydrocarbon chains have higher Tm than those with shorter chains [27]. High saturation in the hydrocarbon chains increases the Tm in phospholipids with the same head group and length of the aliphatic chain. The purity of the lipid also affects Tm. The lower the purity of phospholipids, the wider the range of Tm hence, naturally occurring phospholipids are usually mixtures of components having different length hydrocarbon chains. Such mixtures would usually be expected to produce broad ill-defined transitions, unlike the synthetic phospholipids which have definite Tm. Tm of some phospholipids are shown in Table 1. When choosing the phospholipids as carrier materials, many factors must be taken into comprehensive consideration to select a kind of phospholipid with appropriate Tm [27].

The isobaric heat capacity and the volume expansion of lipids with temperature have proportional relationships for
different lipids. This correlation has been analyzed in terms of a proportional relationship between the enthalpy (ΔH) and volume changes (ΔV) in the melting transition, with similar proportional factors for different systems. The explanation of this fact could be that ΔH and ΔV are mainly due to the “melting” of the individual lipid molecules. In other words, the main phase transition would be driven by intrinsic structural changes within the lipid molecules [26, 28, 29].

In the formulation of lipid nanoparticles, lipid microparticles and most lipospheres, melt-homogenization is done well before the melting point of the lipid, for the melted lipid has high mobility. Emulsions form faster at high temperatures, because of higher mobility which could enhance the encapsulation efficiency of the nanoparticles.

3.2. Lipid Polymorphism

The molecular structures of lipids play definitive roles in the determination of their phase behaviour. The critical packing parameter (P) (Eq. 1) is employed in order to determine the nanostructures of formed liquid crystals.

\[ P = \frac{V}{aL} \]  

where P is critical packing parameter, V is the hydrophobic chain volume, a is the cross-sectional area of the polar head group, and L is the hydrophobic chain length [17, 30].

The value of P is important in the self-assembled nanostructures and is influenced by temperature and solvent conditions. When P = 1, lamellar liquid crystalline structures form. When P < 1, oil-in-water self-assembled structures form, such as normal micelles (L1), normal cubic structure (V1), and normal hexagonal phases (H1). When P > 1, water-in-oil self-assembled structures form, such as reversed micelles (L2), reversed cubic structure (V2), and reversed hexagonal structure (H2) [17].

Table 1. Phase transition temperature (Tm) of some phospholipids [27].

<table>
<thead>
<tr>
<th>Phospholipid</th>
<th>Tm (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean phosphatidylcholine (SPC)</td>
<td>-20 to -30</td>
</tr>
<tr>
<td>Dimyristoyl phosphatidylcholine DMPC</td>
<td>23</td>
</tr>
<tr>
<td>Hydrogenated soybean phosphatidylcholine (HSPC)</td>
<td>52</td>
</tr>
<tr>
<td>Egg sphingomyelin (ESM)</td>
<td>Ca. 40</td>
</tr>
<tr>
<td>Egg phosphatidylcholine (EPC)</td>
<td>-5 to -15</td>
</tr>
<tr>
<td>Dioleoyl phosphatidylcholine (DOPC)</td>
<td>-22</td>
</tr>
<tr>
<td>Dipalmitoyl phosphatidylcholine (DPPC)</td>
<td>41</td>
</tr>
<tr>
<td>Dioleoyl phosphatidylserine (DOPS)</td>
<td>-10</td>
</tr>
<tr>
<td>Dipalmitoyl phosphatidylserine (DPPS)</td>
<td>51</td>
</tr>
<tr>
<td>Distearoyl phosphatidylcholine (DSPC)</td>
<td>55</td>
</tr>
<tr>
<td>Dipalmitoyl phosphatidylglycerol (DPPG)</td>
<td>41</td>
</tr>
<tr>
<td>Dioleoyl phosphatidylglycerol (DOPG)</td>
<td>-18</td>
</tr>
<tr>
<td>Distearoyl phosphatidylglycerol (DSPG)</td>
<td>55</td>
</tr>
<tr>
<td>Dioleoyl phosphatidylethanolamine (DOPE)</td>
<td>-16</td>
</tr>
<tr>
<td>Dimyristoyl phosphatidylserine (DMPS)</td>
<td>38</td>
</tr>
<tr>
<td>Dipalmitoyl phosphatidylethanolamine (DPPE)</td>
<td>60</td>
</tr>
<tr>
<td>Dimyristoyl phosphatidylethanolamine (DMPE)</td>
<td>50</td>
</tr>
<tr>
<td>Dimyristoyl phosphatidylglycerol (DMPG)</td>
<td>23</td>
</tr>
</tbody>
</table>
Polymorphism is the ability of lipids to exist in varying structures on hydration [26, 27]. It is the behavior of lipids that influences their long-range order, i.e., how they aggregate. The structure may appear as pairs of layers that face each other (lamellar phase), sphere of lipid molecules (micelles), tubular arrangement (hexagonal), or maybe in form of cubes (cubic phases) as shown in Fig. (2). More complicated aggregations such as rhombohedra, tetragonal and orthorhombic phases have also been observed. The different phases of the aggregation may be affected by the ratio of lipids present, hydration, pressure, temperature and ionic strength [31]. Techniques employed in the study of polymorphism in lipids include the X-ray diffraction, Phosphorus-31 NMR (nuclear magnetic resonance) spectroscopy, proton nuclear magnetic resonance (proton NMR, hydrogen-1 NMR) and freeze-fracture procedures [26].

3.3. Hexagonal Phase

Hexagonal phases in the lipid polymorphism are formed if the packing ratio of lipids is less or greater than one. Lipid membranes can form two separate hexagonal phases, or non-lamellar phases, in which long, tubular aggregates form according to the environment in which the lipids are introduced. The hexagonal I phase (H₁) is favored in detergent-in-water solutions and has a packing ratio of less than one. The micellar population in a detergent or water mixture cannot increase without an increase in the limit of detergent to water ratio. Therefore, in the presence of low amounts of water, lipids that would normally form micelles exhibit larger aggregates in the form of micellar tubules and satisfy requirements of the hydrophobic effect. These aggregates can form micelles that are fused together. These tubes exhibit polar head groups facing out, and the hydrophobic, hydrocarbon chains in the interior [31].

3.4. Hexagonal II Phase (H₂)

In this phase, the polar head groups are on the inside while the hydrophobic hydrocarbon tails on the outside in a solution (Fig. 2). The packing ratio for this phase is less than one, which is synonymous with an inverse cone packing. There are extended arrays of long tubes, as in the hexagonal I phase, and due to the nature of the polar head groups packing, aqueous channels are formed [31]. They can come together in the form of packed pipes which may leave a finite hydrophobic surface in contact with water on the outside. The packing apparently stabilizes this phase as a whole and an outer lipid single layer coats the surface of the tube to protect the hydrophobic surface from the aqueous phase. Lipids that form this phase include the phosphatidylethanolamine (PE) with unsaturated hydrocarbon chains, diphosphatidylglycerol (DPG) in the presence of calcium [31], oleyl glycerate (OG, 2,3-dihydroxypropionic acid octadec-9-enyl ester) and phytanyl glycerate [17].

For the cubic phases, the X-ray crystallographic studies revealed that it is divided into the double diamond lattice cubic phase (Pn3m), the body-centered cubic lattice cubic phase (Ia3d), and the gyroid lattice cubic phase (Ia3d) [2, 16], some of these shapes are shown in Fig. (3). Cubic phases can be used as carriers for the delivery of lipophilic, hydrophilic or amphiphilic drugs [17]. The hydrophilic drugs are normally in the polar head of lipid or in the water channels, the lipophilic drugs are normally loaded in the lipid bilayer, while the amphiphilic drugs are located normally in the interface (Fig. 3a) [32]. The hexagonal phase is made up of cylindrical micelles arranged in a hexagonal form (Fig. 3b). Unlike the cubic phase, the water channels in the hexagonal phase are closed [33] and drug distribution is similar to that in the cubic phase as shown in Fig. (3b). Recently, the
cubic and hexagonal phases have received tremendous interest because of their potential as drug delivery carriers. They have the potential for controlled release of drugs and protect sensitive drugs like peptides, proteins, and nucleic acids from degradation [17, 34-36]. They are used in preparing novel LBF termed liquid crystals, which can be administered through various routes of administration. Recently, there has been tremendous advancement in lyotropic liquid crystal mesophases, specifically cubosomes and hexosomes in lipid-based nanoparticles known as liquid crystal nanoparticles. Liquid crystal nanoparticles have recorded huge success for the delivery of hydrophobic drugs, increasing bioavailability and potency of the delivered pharmaceuticals, and it has been used to target drug to various organs of the body with minimal side effects [37].

Cubic and hexagonal phase forming lipids are nontoxic and biodegradable and examples include glyceryl monooleate (GMO, 2,3-dihydroxypropyl olate), phytantriol (PT, 3,7,11,15 tetramethyl-1,2,3-hexadecanetriol), alkyl glycerates, monolinolein, monoaetin, phosphatidylethanolamine, oleoylethanolamide, phospholipids, PEGylated phospholipids, and glycolipids [17].

3.5. Lipid Bilayer

This is a thin polar membrane consisting of two layers of lipid molecules (Figs. 2 and 3). The membranes are made up of flat sheets that form a continuous barrier around the cells. Lipid bilayer is found in the cell membrane of living organisms and some viruses. They are in membranes surrounding the cell nucleus and other cellular structures. The lipid bilayer is the barrier that keeps proteins, ions, and other molecules where they are needed and prevents them from diffusing into areas where they should not be. Lipid bilayers are ideally suited for this role because, even though they are only a few nanometers in width, they are impermeable to most water-soluble (hydrophilic) molecules [31]. They help the cells in maintaining salt concentrations and pH by pumping ions across their membranes using proteins called ion pumps, this is because they are impermeable to ions. Natural bilayers are also usually composed of phospholipids, which have a hydrophilic head and two hydrophobic tails each. If phospholipids are exposed to water, they get themselves arranged into a two-layered sheet with all of their tails pointing toward the center of the sheet. This bilayer center contains almost no water and excludes molecules like sugars or salts that dissolve in water but not in oil. This phase process is similar to the coalescing of oil droplets in water and is driven by the same force called the hydrophobic effect. Lipid tails can also affect the membrane properties, for instance by determining the phase of the bilayer. Bilayers can undergo a phase transition from solid gel phase state at lower temperatures to a fluid state at higher temperatures. The packing of lipids within the bilayer also affects its mechanical properties, like its resistance to stretching and bending. Biological membranes other than phospholipids, like cholesterol, help to strengthen the bilayer and decrease their permeability [31].

Vesicles of bilayer have been used to deliver drugs and are often referred to as liposomes. They are usually formed from lipid bilayers enclosing varying amounts of water (Kulkarni, 2012). Liposomes can be used for oral, pulmonary, ocular, and transdermal drugs delivery and have industrial, clinical and veterinary applications [39, 40]. Lipid bi-

Fig. (3). The structure of (Pn3m) cubic phase (a), and hexagonal phase and possible drug localization in liquid crystals (b) [17, 38]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).
layers also have been used to measures the permeability of drugs across the blood-brain barrier, GIT, the skin and some cells, using the parallel artificial membrane permeability assay (PAMPA) technique [41-43].

3.6. Micelles

A micelle is a colloidal aggregate of surfactant molecules dispersed in a liquid. In aqueous solutions, they form hydrophilic "head" portions which are around the solvent phase and sequestering the hydrophobic single-tail portions. This is as a result of the packing behavior of single-tail lipids in a bilayer. This type of micelle is called a normal-phase micelle or oil-in-water micelle. The inverse micelles have the head groups at the center with the tails extending out (water-in-oil micelle). Micelles are mainly spherical (Fig. 4), however, other phases or shapes like ellipsoids, cylinders, and bilayer, also occur [31]. The size and shape of micelles are dependent on the conditions of the solution such as surfactant concentration, molecular geometry of its surfactant molecules and, ionic strength, pH and temperature. Micellization is the process of formation of micelles and is the part of phase behaviour of many lipids according to their polymorphism [31].

In the GIT, micelles influence the oral absorption of drugs by enhancing the solubility and regulating the permeability of the membranes. Micelles formed by bile acid and lecithin in the GIT have vital roles to play in the overall oral absorption of poorly water-soluble drugs, hence, they promote the dissolution of the drug in the GIT [49]. Micelles enhance drug solubility by incorporating drug molecules into the micellar phase. However, the incorporation of drugs in micelles reduce their activity, scarcely permeating the cell membrane directly. Micellar solubilization of lipophilic drugs sometimes produces such a small fraction of free drug in the GI tract that the extent of absorption is reduced [50-52].

In the GIT, bile acids form mixed micelles that solubilize lipophilic drugs, thus enhancing their oral absorption. This effect is more efficient in the fed state due to the high concentration of micellar elements, and therefore lipophilic drugs exhibit higher absorption in the fed state. An alternate pathway for intestinal absorption involves the collisional transfer to glycoalyx on enterocytes [53]. Amidon et al. [54] also proposed that micelles can help in the transport of entrapped solubilized solutes across the aqueous diffusion layer to the surface of the cell membrane, which reduce the effect of the unstirred water layer on absorption. Yano et al. [55], proposed that the absorption of poorly soluble drugs from a micellar solution is not always predicted from parameters such as the solubility or membrane permeability of the free drug, because the direct route of drug partitioning from the micelle to the cell membrane is significant when the free fraction is small. Drugs in micelles can be absorbed by direct partitioning into the intestinal membrane from the micellar phase. This alternate pathway of intestinal absorption may contribute to the enhanced absorption of poorly soluble drugs after food intake [55].

Micelles have gained huge research interest in drug delivery because of the fact that they are simple to develop, have the ability to encapsulate lipophilic drugs, and the possibility to develop and improve their moieties. They are applied largely in the medical field and maybe formulated by forming various shapes of micelle, or maybe trapped by metal nanoparticles. Micelles can be attached to some biological molecules like proteins and lipids which are greatly applied in drug delivery and specifically, in cancer therapy [52]. Nanomicelles are emerging drug delivery for different forms of drugs and have also been applied in drug targeting [52].

Polymorphism and crystallization in lipid-based formulations could however cause the generation of higher energy polymorphs during storage which could lead to drug expulsion from the matrix in lipid based nanoformulations and lipospheres [56]. Stable polymorph of materials is represented by their lowest energy state, it has the highest melting point and least aqueous solubility. The metastable form represents the higher energy state, has lower melting point and high aqueous solubility. However, the metastable forms show better bioavailability and therefore preferred in formulating drug substances [57].

3.7. Lipids Crystallization

Crystallization process involves nucleation and crystal growth. It involves aggregation of molecules which exceed a
critical size and is stable. Once a crystal nucleus has formed, it begins to grow by bringing other molecules from the adjacent liquid layer, which is continuously filled by the super-saturated liquid that is around the crystal [58]. Crystallization is mostly experienced in triglycerides (TAG) and is the system arrangement as a result of driven forces, characterized by total or partial restriction of movement caused by the physical or chemical bonds between the TAGs molecules. This results in the formation of various crystalline forms and crystals consisting of molecules arranged in fixed relatively stable patterns known as reticulates [59].

Mechanisms of nucleation are classified into primary and secondary nucleation. Primary nucleation can be homogeneous or heterogeneous; and homogeneous nucleation occurs from the junction of isolated molecular species, which form dimers, trimers and subsequently continue the accumulation process up to when a possible nucleus has been formed and depends on the temperature and supersaturation conditions [23]. The secondary nucleation is the formation of a new nucleus in the presence of existing crystals, which may occur if microscopic crystalline elements are separated from a crystalline surface that has been formed already hence, resulting in the formation of crystals that have been fractured into small stable nuclei [60, 61]. When the nuclei formed approach favorable dimensions, these elements become crystallites and their growth depends on external factors such as temperature, impurities, supersaturation, and solvents, and on internal factors (structure, links, defects). Hence, the growth rate of crystals may vary by several orders of magnitude and occur by the binding of molecules to a crystalline surface. As molecules bind to the surface of a crystal, it deactivates some molecules and there is a continuous movement of molecules on the surface of the crystal resulting in processes that determine the rate of crystal growth. Crystal growth rate varies directly to the sub-cooling and inversely with the viscosity system [23, 59]. However, nucleation and crystal growth are normally seen as separate events, however, nucleation can also occur from the exiting crystals as the crystal grows from molecular clusters [23, 62, 63].

Lipid crystallization has important implications in nanodrug delivery technology because they may affect the physical characteristics of some LBFs [64, 65]. They may also influence the growth of crystals, oil migration and coalescence of particles and emulsions [23]. Crystallization of TAGs is generally considered the most important event in lipid structuring. Crystallization of diacylglycerols (DAGs), monoglycerols (MAGs) and phospholipids are important in the quality of nanoformulations and other lipid-based drug delivery systems [61]. TAGs show different polymorphic forms and can crystallize into different polymorphs such as α, γ, β', and β- forms. After melting, recrystallization in the metastable α-polymorph makes them to undergo a polymorphic transition into the stable β-form via a metastable intermediate. The β-polymorph especially consists of a highly ordered, rigid structure with a low loading capacity of drugs and leads to drug expulsion and inability to protect or prolong the release of the encapsulated drug [66]. This phenomenon is related to the fact that β form has a higher free energy of activation for nucleation and this polymorphic transformation is an irreversible process going from the less stable to the more stable form (monotropic phase transformation). This process depends largely on temperature and time. In TAGs, the degree of homogeneity is dependent on the rate of transition. Lipids with low variability of TAGs quickly turn into the stable form β, those with a random distribution of TAGs may have the form β' indefinitely [23].

Important structural properties of lipid crystals such as morphology, number and size distribution, and spatial distribution are directly influenced by nucleation behavior. Challenges encountered in control of the crystallization of lipids is a clarification of how a particular polymorph nucleate in comparison with others [65]. However, the Ostwald step rule could be employed in studying multiple polymorphic forms when they are crystallized from vapor, solution, and melt phases. According to this rule, less stable polymorphs crystallize much faster than more stable forms when the driving force for crystallization is supplied by decreasing the temperature. Also, less stable forms stepwise transform to more stable forms during the storage processes after crystallization and the kinetic behaviour of polymorphic nucleation of various lipids and drug materials follow this rule [67, 68]. However, the Ostwald step rule may not be used when complex systems are involved, hence other detailed studies should be applied. The metastable and stable polymorphs of lipids are generally influenced by variation in temperature, like the heating rate, cooling rate, and thermal thawing (tempering). These effects are paramount in pharmaceutical and biomedical applications [65].

The factors that may influence the crystallization of lipids are summarized below:

i. **Thermal thawing**: “cooling-heating-cooling cycle” called thermal thawing can produce optimal polymorphic forms through melt-mediated or solid-state transformation. Such a process is often called tempering [65].

ii. **Additives**: Some additives or materials have been used to modify the crystallization behaviour of TAGs. Saturated phospholipids increase the crystallization temperature of the TAGs by several degrees compared to soybean phospholipids. The crystallization behaviour is not simple because of the solidification of the phospholipid chains prior to triglyceride crystallization. For most TAGs, egg lecithin also induce crystallization at higher temperatures than natural soybean lecithin [65, 69]. Generally, modification, control and stabilization of the crystallization and polymorphic transitions in lipids can be carried out using three methods which can be applied individually or in combination depending on the case and these include: removal, addition or fractionation of minor lipids in fat bases, the use of nucleating agents to modulate the process of crystallization (seeding) and dynamic control of the crystallization in lipid systems through the use of emulsifiers [23].

- The crystalline modification in lipids may be achieved by physicochemical changes provided by processes such as hydrogenation, inter-esterification, fractionation and blending, as well as the use of specific time and temperature protocols [70]. Lipids like DAGs, MAGs, free fatty acids, phospholipids and sterols with an amphiphilic structure, have been considered molecular agents that affect crystallization. In some cases, their presence can en-
hance crystallization, while, in some systems, there is the effect of inhibition [61]. Phospholipids crystallize at higher temperatures compared to TAGs, and they can act as crystallization nuclei. High concentrations of polar phospholipids, such as lysophosphatidylethanolamine and phosphatidylserine, are related to slow nucleation rates, whereas, for rapid nucleation, low concentrations of these compounds and significant levels of phosphatidylcholine are observed. Lipid crystallization may be enhanced by the addition of nucleating agents (seeding). These are solid material with properties of nucleation agents - or crystallization seeds. The incorporation of crystallization seeds into lipids may evoke two effects associated with the control of crystallization which are the availability of numerous additional nuclei (known as ready-made nuclei) and surfaces for crystal growth. Also, nucleating agents promote some specific polymorphic forms. Active nucleation agents with specific crystal habit may induce crystallization of lipids in the desirable polymorphic forms, as the information for the crystalline packing is provided by the seeds that control this process [61, 71]. The crystallization agents used in the seeding technique consist of saturated or unsaturated TAGs [23].

- Emulsifying agents with different hydrophobic properties may influence the rate of crystallization of lipids by either enhancing or retarding crystallization, as well as the polymorphic transitions. These compounds promote changes in the surface properties of lipids, resulting in changes related to the size and morphology of crystals and crystalline density [23, 72]. Emulsifiers may form heteronuclei, accelerating crystallization through the direct catalytic action as impurities. During crystal growth, the emulsifiers would be adsorbed on the surface of the crystals and would change the rate of incorporation of TAGs and the crystal morphology. Also, TAGs and emulsifiers may cocrystallize because of the similarity between their chemical structures. Thus, the structural dissimilarity would also entail delay on the nucleation and possible crystal growth inhibition [23, 72]. According to this mechanism, the emulsifiers are associated with the TAG molecules by their hydrophobic groups, especially through acyl-acyl interactions. The acyl group of emulsifiers determines its functionality in relation to TAGs. Garti [72] and Miskandar [73] proposed three emulsifier actions on lipid crystallization as: Limited miscibility between the emulsifiers molecules and TAGs, in this situation, the emulsifier acts as an impurity and the interaction results in imperfect crystals, which can promote or slow down the crystal growth and polymorphic transitions, according to the compatibility of the hydrophobic chains in their structures; the second is high degree of miscibility between emulsifiers and TAGs, which may enhance the formation of molecular compounds; and thirdly, total immiscibility between emulsifiers and TAGs, here emulsifiers can act as crystallization seeds and microstructural modifiers [23]. The selectivity of these additives such as dynamic controllers of polymorphic transitions in lipids has been explained by their ability to create hydrogen bonds with neighboring TAGs, by a process known as Button Syndrome. Here, the presence of a specific emulsifier does not dictate the formation of a given polymorph but influences the dynamics of the molecules and their ease to undergo configuration changes. In this process, the emulsifiers can modulate the polymorphic transformations in the solid-state or through the liquid state, and the temperature program controls the physical state of the crystals during the polymorphic transition and the extent of the mobility of the molecules, thus regulating the rate of polymorphic transformation [74]. Typical emulsifiers in controlling crystallization include the fatty esters and polyesters from saccharose, sorbitan esters of fatty acids, natural lecithin and chemically modified lecithin, and polyglycerol polyricinoleate [23, 75].

- Polymorphic matchings also influence additives; they act as a template to promote the nucleation of lipid crystals. Additives may selectively promote the nucleation of specific polymorphic forms, this may occur because of polymorphic matching between the template crystals and the lipid crystals [65]. The similarity in molecular shape between the additives and the fatty acid compositions of lipids is quality attribute of crystallization modifiers. For long-chain saturated fatty acid, an additive having a similar acyl chain structure may affect crystallization more than those containing short-chain or unsaturated fatty acid moieties [76]. The concentration of additive also is of importance because there may be a critical concentration of the additive, as determined by the solubility of the additive in the supercooled liquid of the lipids at crystallization temperature (Tc). When the concentration of the additive is lower than the solubility limit, it may not crystallize prior to the lipid during cooling, it may even limit the formation of crystal nuclei of the lipid through attractive molecular interactions between the additive and the lipid molecules, due to the similarity in molecular shape (de-clustering) [63, 77]. Contrarily, additive with low solubility may crystallize prior to the lipid when the concentration of the additive exceeds its solubility limit. Here, the additive functions as a “template” enhancing crystallization (templating) as shown in Fig. (5) [65, 78].

iii. Application of shear: Shear application has been known to increase the rate of polymorphic crystallization and transformation of lipids. It influences the aggregation of nanocrystals of the crystal network [65]. This may be because of increased rates of heat and mass transfer which enhances nucleation. This transformation may be facilitated by a huge increase in surface area compared to the volume of nanocrystals.

iv. Ultrasound: Ultrasound waves can be utilized in characterizing the physical properties of lipid crystals such as solid fat content (SFC) and to control the crystallization of lipids a process known as sonocrystallization [17, 79-81]. Sonocrystallization influences crystal size, and morphology in pure TAGs and the rate of polymorphic crystallization. Application of high-intensity ultrasound (HIU) was studied by Martini et al. and the observations made were that HIU induced primary and secondary nucleation of lipid crystals, generating smaller crystals amongst others [65].

v. Pressure: High pressure may promote lipid crystallization in the emulsion and decreased undesirable effects like grain growth of lipid crystals that occur after crystallization [65].
In addition, factors such as formulation, cooling rate, crystallization heat and level of agitation affect the number and type of crystals formed. However, as lipids are complex mixtures of TAGs, at a certain temperature, different polymorphic forms and liquid oil can coexist [64].

Table 2 summarizes the different crystal behaviors of some natural lipids. Lipids that are prone to crystallization in the form of β₁ include the soybean, peanut, canola, corn and olive oils and lard [25]. For cocoa butter, there are six polymorphic forms, as a result of its TAG composition, where symmetrical monounsaturated TAGs are prevalent. The characteristic classification of polymorphs of cocoa butter is based on the Roman numbering system (I to VI), in which form I is the less stable one and form VI is most stable. Also, a combination of these crystal modifications is often seen [23, 82].

4. LIPID FORMULATIONS

Lipid formulations are typically composed of lipids and surfactants, and may also contain a hydrophilic co-solvent. According to the lipid formulation classification system (LFCS) [83, 84], these systems are divided into four groups (I-IV), depending on their composition and the possible influence of dilution and digestion on their ability to prevent drug precipitation. These classes allow for proper clarity among the individual groups and help in explanation and data comparison. Class I is made up of oil solutions without surfactants and having mono-, di-, and/or tri-glycerides. Class II systems contain lipophilic surfactants and the oil phase. Class III systems consist of the hydrophilic components (surfactants and/or co-solvents) added to the oil phase and yield self micro emulsifying drug delivery system (SMEDDS). Group of class IV is a highly hydrophilic group. They are systems composed of hydrophilic surfactants and hydrophilic co-solvents, which form colloidal micellar dispersion upon dilution with aqueous media [83, 85].

4.1. Advances in Lipid-based Drug Delivery Systems

Lipid-based drug delivery systems are broadly grouped into four and they include the solid lipid particulate dosage forms, emulsion-based systems, solid lipid tablets, and vesicular systems. Modifications from these four types include: lipospheres, solid lipid nanoparticles (SLNs), nano structured lipid carriers (NLC), lipid drug conjugate nanoparticles (LDC), self-emulsifying formulations (SEFs), Pickering
emulsions, dry emulsions, micro and nano-emulsions, solidified reverse micellar solution (SRMS) based tablets, liposomes, herbosomes, cryptosomes and transferosomes amongst others [3, 86, 87]. Fig. (6) summarizes the advances made so far in LBFs, for further readings we refer the readers to our previous work [3].

4.2. Guidelines for Design of Lipid-based Formulations

Guidelines for the design of LBFs were recently outlined by Porter et al., [88] and include the following [89]:

- It is important to maintain drug solubility in the formulation, after dispersion, and for improved absorption, the characteristics of the colloidal materials formed in the gastro-intestinal milieu are more important than the properties of the formulation itself.
- Higher proportions of lipid (>60%) and lower proportions of surfactant (<30%) and cosurfactants (<10%) give improved drug solubilization after dilution.
- Medium-chain triglycerides may afford greater drug solubility and stability in the formulation, however, long-chain triglycerides facilitate the formation of bile salt and lipid colloidal species, thus may afford higher bioavailability.
- SMEDDS belonging to Type IIIB gives lower droplet sizes after dispersion. This property depends largely on the surfactant used. Nondigestible surfactants give higher bioavailability generally.
- The dispersion of type IV formulations (surfactant/cosolvent) is likely more efficient if two surfactants are used rather than a single one.
- Type IV formulations may give higher drug solubility but must be designed carefully to assure that the drug does not precipitate after dispersion.

Knowledge of these guidelines is important in the design of oral LBFs for drugs belonging to BCS class II and IV in order to ensure that all the formulation parameters are correct. This will finally lead to the formulation of stable products.

4.3. General Routes of LBDDS

Lipid-based drug delivery systems (LBDDS) can be administered by oral, parenteral, ocular, intranasal, dermal/transdermal, rectal and vaginal routes [7, 8]. However, the oral route is the most preferred route because of the properties like non-invasiveness, less expensive, and less prone to side effects, such as injection-site reactions. It is the easiest and the most convenient method of drug delivery when the patient is on a long term therapy. However, various useful guidelines regarding the convenient routes and formulation strategies are useful before deciding on the final application route [89-91].

4.4. Factors Affecting the Bioavailability of Lipid-based Drugs

4.4.1. Lipid Digestion

If the drug possesses a high affinity for the lipid vehicle, it can be assumed that the active pharmaceutical ingredient (API) moves apparently together with the vehicle in the GI tract. Lipid vehicles control the absorption rate of drugs and lipid digestion in the GI consists of three consecutive steps:

- Dispersion of fat globules into fine emulsion
- Enzymatic hydrolysis of fatty acid esters at the emulsion-water interface
- Dispersion of insoluble lipid products for absorption.

The API which accumulates at the surface of the absorptive epithelium is taken up by enterocytes [1]. Some drugs and surfactants are known to reduce the activity of efflux transporters in the GI wall and increase the fraction of drug absorbed as well. Mineral oils are non-digestible lipids and hence not absorbed from the gut lumen. These lipids remain in the gastrointestinal lumen and entrap the lipophilic drug within the oil leading to reduction in the absorption of such drugs. Therefore, lipids that are not affected by surfactants are preferred as vehicles for lipid delivery systems and typical examples of such lipids are medium-chain monoglycerides, fatty acids, and monoesters of fatty acids [1].

4.4.2. Droplet Diameter

The mean diameter of the emulsion droplet is indicative of the quality of formulations. The droplet size of SEDDS upon dilution with aqueous media is primarily affected by the nature of the emulsifier and its concentration. Emulsion droplet size is inversely proportional to the concentration of emulsifier and the smaller the size of the emulsion droplet, the faster the drug release. Two techniques used to determine the mean emulsion droplet diameter are the low angle laser light diffraction which is used for emulsions with droplet sizes of >1μm and quasi-elastic light scattering used for submicron dispersions [92, 93].

Emulsion droplet diameter is a very important factor in the prediction of the in-vivo performance of undigested lipid-based formulations, such as long-chain triglycerides e.g. cyclosporine (Neoral® versus Sandimmune®) [94]. However, this may not be applicable to predigested lipids like the medium-chain monoglycerides and propylene glycol monoester of C8-C10 fatty acids [1].

For lipospheres, the particle size also affects the bioavailability of formulated drug and also determines the site of administration of the drug formulations. The small particle size of lipospheres (520 μm) is hypothesized to be well tolerated by single cell contact, while large particle size (450 μm) are much more reactive due to van der Waals attractive forces [95].

4.4.3. Lipophilicity of the API

Highly hydrophobic drugs (log P > 6) can be taken up into the lymphatic system by partitioning into chylomicrons in the mesentery vein which has been demonstrated to be crucial for the absorption of the anti-malaria compound halofantrine [96, 97]. After oral administration, highly lipophilic retinoids are also known to be transported in the intestinal lymph [1].

4.4.4. Type of Lipids

The nature or type of lipids is important because digestible lipids may influence absorption in a manner different
from that of non-digestible lipids. For these lipids, the lower the melting point of the fatty acid, the higher the amount of drug absorbed [1]. Commonly used digestible lipid vehicles may be grouped into the following [1]:

- Fatty acids: These include the capric acid, oleic acid, myristic acid, caprylic acid
- Ethyl esters: Ethyl oleate
- Triglycerides of long-chain fatty acids: Corn oil, soybean oil, peanut oil
- Triglycerides of medium-chain fatty acids: Miglyol® 812, Softisan® 154, Captex® 355, Labrafac®

**4.4.5. Drug Release**

The characteristics of the drug and the lipid carrier play an important role in controlling drug release and absorption from LBFs. The nature or type of LBFs is also important e.g. For SEDDS or emulsified form, the pathway of the drug absorption, droplet size of the emulsion in the GIT, type of surfactants, the metabolic pathway of the lipids and the changes in gastric motility due to presence of lipids may influence drug release and absorption [1]. The influence of lipids on the absorption of drugs from LBFs are discussed further below.

**5. INFLUENCE OF LIPIDS ON THE ABSORPTION OF DRUGS FROM LIPID-BASED NANOFORMULATIONS**

**5.1. Extended Retention in the Stomach**

The presence of lipids in the GIT slows the peristaltic action and gastric emptying. There is an increase in the retention time of the GIT content including drug in the upper intestine, where absorption occurs. This leads to proper dissolution in this region and enhanced absorption of drugs [85, 98].

**5.2. Changes in the Biochemical Barrier**

Lipids and surfactants may lower the activity of intestinal secretion vectors in the gastrointestinal wall (such as P-glycoprotein) and inhibit metabolic activity in the enterocytes and lumen of the GIT (e.g., cytochromes), which contributes to enhanced absorption of drugs that are substrates for these enzymes or transporters [85, 98].

**5.3. Changes in the Physical Barrier**

Various combinations of lipids and/or surfactants and their digestion products may act as promoters of intestinal absorption due to increased membrane permeability. Surfac-
5.4. Stimulation of Intestinal Lymphatic Transport

Lipids composed of long-chain triglycerides (LCT) or medium-chain triglycerides (MCT) are differently transported in the body; whereas MCT is directly transported by the portal blood to the systemic circulation, LCT stimulates the formation of lipoproteins, which facilitates their lymphatic transport. LBDDS containing LCT are therefore likely to enhance the lymphatic transport of a lipophilic drug substance, and thus they can also affect the extent of the first-pass metabolism as the intestinal lymph circulation bypasses the liver [85, 98].

5.5. Digestion of Triglycerides

Intestinal absorption after digestion of LBFs undergoes three basic processes including fat globules dispersion of the ingested lipids to give coarse emulsion with high surface area, enzymatic hydrolysis of the fatty acid glycerol esters (primarily triglyceride lipids) at the oil/water interface and the dispersion of the lipid digestion products into forms that are absorbable [1]. Salivary glands secrete lingual lipase and gastric mucosa secretes gastric lipase, which initiate triglyceride (TG) hydrolysis to the corresponding diglyceride (DG) and fatty acid (FA) within the stomach. The optimum pH ranges for lingual and gastric lipase from 3 to 6, and MCT are hydrolyzed at a faster rate than LCT [99]. TG is preferentially hydrolyzed by pancreatic lipase, an interfacial enzyme, which preferentially acts at the surface of emulsified TG droplets to quantitatively convert TG into the corresponding 2-monoglyceride (MG) and two fatty acids (FA). Optimum activity is observed when olate is the fatty acid, and it decreases towards shorter chain triacylglycerols and soluble carboxyl esters substrates. Bile salts at concentrations usually present in the duodenum inhibit the binding of pancreatic lipase at the oil-water interface. Further classes of biliary-derived lipids are the phospholipids (e.g., phosphatidylcholine, PC) playing an important role as solubilizers for lipid digestion products. Prior to absorption, PC is hydrolyzed by phospholipase A2 to lysophosphatidylcholine (lyso-PC), with the majority of PC present in the intestine secreted in bile (with only modest dietary influence [1, 100]).

5.6. Physical Chemistry, Absorption and Solubilization of Lipid Digestion Products

Bile plays a key role in solubilization of lipid digestion products and poorly water-soluble drugs [101]. Expulsion of bile is brought about by the contraction of gall bladder initiated by cholecystokinin and relaxation of the sphincter of Oddi. The peak flow occurs at approximately 30 min after the ingestion of a meal. Typical concentrations of bile salts in the fasted intestine are 4-6 mM compared with postprandial concentrations of 10-20 mM [99]. The inclusion of the lipidic components decreases the critical micelle concentration (CMC) and increases the size and solubilization capacity of the micelles, e.g., the inclusion of lecithin and MG decreases the CMC of mixed micellar systems to values less than 1 mM. Therefore, it is likely that the CMC of mixed bile salt systems present in the intestine is surpassed even in the fasted state. Although the specific mechanisms of absorption of the lipid digestion products have not been elucidated yet, the common role of the intestinal mixed micellar phase to solubilize these poorly water-soluble compounds and to provide a concentration gradient for the absorption of lipids and presumably of drugs solubilized in this phase is generally accepted. Micelles are not absorbed intact, and lipids are suggested to be absorbed from a monomolecular intermicellar phase. The dissociation of monomolecular lipids from the mixed micellar phase prior to absorption may be stimulated by a microclimate of lower pH at the intestinal absorptive site [1].

5.7. Lipids and Intestinal Permeability

Composition of the mixed micellar phase can modify the intestinal permeability of poorly water-soluble drugs through three basic mechanisms. The presence of lipid digestion products and bile salts may alter the intrinsic permeability of the intestinal membrane, causing increased absorption through paracellular or transcellular routes. Also, the solubilization of lipophilic drugs within bile salt mixed micelles may enhance diffusion through the aqueous diffusion layer, thereby improving absorption. Finally, drug solubilization may reduce the inter-micellar free fraction of drug, which could reduce drug absorption [1].

6. PREPARATION OF LIPID-BASED NANO CARRIERS

Lipid-based nanocarriers may often be prepared by combining different ratios of different lipids (e.g. medium-chain triglycerides and lecithin) [2-5], in order to cause disorder in the crystal arrangement of the individual lipids and increase the amorphous nature of the lipids, thereby creating spaces for drug encapsulation. These lipid matrices which may be termed structured lipid matrices (molecularly structured) may be utilized as nanomaterials in the formulation of various lipid-based nano drug delivery systems.

Nanocarriers, based on molecularly structured lipids may be prepared by the fusion method [5, 7]. Here, the individual lipids are melted together and stirred with a homogenizer until the uniform melt is obtained. Reverse micellar based nanocarriers have also been formulated according to this method [5].

7. CHARACTERIZATION OF LIPID NANOCARRIERS USED IN PHARMACEUTICAL DRUG DELIVERY

7.1. Lipids Nanocarriers are often Characterized by Different Methods viz:

7.1.1. Differential Scanning Calorimetric Analysis (DSC)

Melting transitions and changes in the heat capacity of lipid nanocarriers are often evaluated by DSC [7, 66, 102, 103]. DSC is also used to study the crystal behavior of the lipid nanocarriers and the influence of additives on the crystal habits.

7.1.2. Small Angle X-ray Diffraction Analysis (SAXD)

This is employed in the analysis of the long range order of the lipid nanocarriers crystal structures. This obtains the
interlayer spacing which is the separation between a particular set of planes of the crystal lattice structure [66].

7.1.3. Wide Angle X-ray Diffraction Analysis (WAXD)

WAXD analysis of lipid nanocarriers provides information on the crystalline state of the matrices. The spacing of the structure of cells, preferred orientation and crystal arrangement including the ratio of the crystalline properties to the non-crystalline properties are revealed by WAXD [66, 102, 103].

7.1.4. Transmission Electron Microscopy (TEM) and Photon Correlation Spectroscopy

TEM analysis is utilized in the evaluation of different layers in the lipid nanocarriers. Also, the photon correlation spectroscopy (PCS) measurements may be performed with a Zetasizer in order to study the size of the nanocarriers [102, 103].

8. MECHANISM OF LIPIDS AS NANOCARRIERS AND SUITABLE VEHICLE IN DRUG DELIVERY

Recently, there is a growing interest in lipid-based nanoformulations and lipids as nanocarriers because of the advantages they offer over polymeric nanocarriers as discussed earlier [14]. Lipid nanocarriers are produced in such a way that drug localization in the nanostructures is enhanced and maximized. By disrupting the nanostructure of the individual lipids, various lipids with varying structures are combined such that when drugs are incorporated in them, the drugs are localized in their amorphous structures and hence, high entrapment efficiency is often recorded. Therefore, for good drug entrapment in lipid nanocarriers, amorphous lipids are often used [11-14].

Lipid nanocarriers including NLC, SLNs, micelles, nanoliposomes, nanolipid crystals basically entrap the drug in their inner core. For NLC and SLN, the drug is entrapped in their inner fat core, hence, these drugs are shielded away from the environmental factors that can cause degradation. The inner core are often stabilized by layers of solid lipid that stabilize the formulations [3, 16]. Therefore, stable formulations are produced and because of this arrangement, modifications may be done on the outer layers of the nanocarriers in order to control the rate and site of drug release.

CONCLUSION

Lipid-based drug delivery has recorded tremendous success and could be used for the delivery of drugs topically, orally, pulmonary and parenterally. Lipid excipients have great potential for use in formulating various nanoparticles of different drugs and have GRAS status. However, guidelines for the formulation of various LBDDS should be adhered to in order to continually ensure the safety, efficacy and stability of these formulations. Also, the right choice of lipids and other additives should be adequately made before the formulation of lipid-based formulations as these would ensure greater success. Knowledge of the specific behavior of individual lipids employed as a carrier in LBFs would ensure the production of stable formulations with enhanced stability over time. Adequate preformulation studies and a good literature review should be done before the proper formulation so that the final goal of formulating stable LBFs for improved delivery of drugs could be achieved.

CURRENT & FUTURE DEVELOPMENTS

Currently, lipids have found application in nanopharmaceuticals and nutraceuticals. They have also been applied as nanomaterials for different diagnostic purposes. The future application of lipid nanomaterials would focus on applications of nanolipid-based drug delivery for targeting different cells, organs and body tissues for effective treatment of various ailments. Also, modifications of lipid-based nanocarriers with some pH-sensitive polymers for effective targeting of drugs to body tissues especially, in the treatment of various body cancers, would be focused on.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We appreciate Prof. Anthony A. Attama for all his input that led to the success of this work.

REFERENCES


The Utility of Lipids as Nanocarriers and Suitable Vehicle

Current Nanomaterials, 2019, Vol. 4, No. 3

173


