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ORAL LIPID BASED DRUG DELIVERY SYSTEM: A REVIEW

Ritiksha Khatri, Umang Varia *, Hitesh Katariya and Krunal Detholia

Department of Pharmaceutics, Smt. S. M. Shah Pharmacy College, Ahmedabad-Mahemdabad Highway, Ahmedabad - 387130, Gujarat, India.

Keywords:

Lipid-based drug delivery system (LBDDS), Excipients, Digestion and solubilization of lipid-based formulation, Techniques, Types of lipid-based carriers

Correspondence to Author:
Mr. Umang R. Varia

Assistant Professor,
Department of Pharmaceutics,
Smt. S. M. Shah Pharmacy College,
Ahmedabad-Mahemdabad Highway,
Ahmedabad - 387130, Gujarat, India.

E-mail: umangvaria.ph@gmail.com

ABSTRACT: In the recent progressive era of pharmaceutical technology, newly investigated most of the drugs come under BCS class II and IV having low solubility as well bioavailability. The drugs are not suitable candidate for the conventional oral delivery of drug. The reason is that the drugs are not able to dissolve in aqueous environment of GI (gastrointestinal) tract. Poor water solubility of drug is challenging to deliver orally. Lipid-based drug delivery systems (LBDDS) is emerging technologies to delivered the drug orally by dissolving, dispersing or encapsulating drugs in lipidic excipient and ultimately results in improvement in bioavailability. This review focus on different types of excipients used in the formulation of LBDDS and digestion and solubilisation of lipid-based formulation in body. This review also focuses on the conversion of liquid dispersion into solid particles of lipid for oral delivery of drug. Different types of lipid-based carriers which are useful for the development of lipid-based delivery are briefly described in this article.

INTRODUCTION: Major drawbacks of intravenous administration of drug, including extravasation of blood or drugs, thrombosis and catheter infections can be prevented by administering the drug orally making the oral drug delivery most suitable and popular route of drug administration. At the same time oral administration of drug is limited due to some physico-chemical properties of drug molecule such as, poor solubility, low permeability, instability and rapid metabolism, all of the problems that directly decreases the oral bioavailability ultimately reduces the therapeutic effect of drug [1]. In the recent progressive era of pharmaceutical research and technology.

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The investigated new chemical entity (NCEs), is generally from Biopharmaceutical classification system (BCS) class II (compound having low solubility and high permeability) and IV (compound having high solubility and low permeability). From the discovered chemical entities, most of the bio actives have high molecular weight, low solubility and high permeability. These properties limit the absorption of the drug and ultimately limit oral bioavailability [1-4].

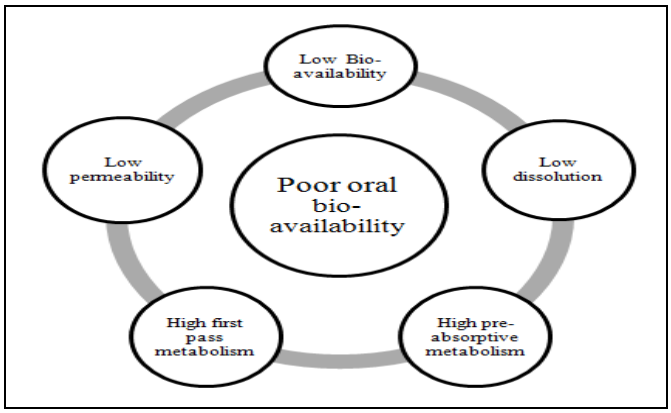


FIG. 1: CAUSES OF POOR ORAL BIOAVAILABILITY

This poor solubility not only gives low oral bio-availability but also leads to intra and inter-subject variability and lack of dose proportionality [5]. The main causes of poor bioavailability are given in **Fig. 1**. [6] Simple formulation approaches like conventional tablet, and powder-filled in the capsule are not enough to overcome these issues. Bioavailability enhancement technologies like lipid-based formulation and API particle size reduction have been developed to overcome such issue [2].

Lipid-based drug delivery system (LBDDS) is a drug delivery that gained too much attention in recent years for improvement of solubility, dissolution, and bioavailability of poorly water-soluble drugs [1]. These are improving demands to develop suitable drug carriers of lipids in order to control, localize, and improvement in drug targeting [7]. They show effective size-dependent properties and obvious advantages such as biocompatibility and bio-degradability [8]. LBDDS can also reduce the inherent limitation of slow and incomplete dissolution of poorly soluble drugs and facilitates the formation of the solubilised structure after digestion in the gastrointestinal tract (GIT), from which absorption improve, and may improve oral bioavailability of drug [7].

The lipid-based formulation may also protect active compounds from biological and enzymatic degradation, that in turn, improvement in drug potency. Lipid-based formulation system shown to reduce toxicity of various drugs by biodistribution of drug [5].

Most of the lipid drug delivery systems used as drug carriers have high drug stability, high drug carrier capacity, and feasibility of incorporating both hydrophilic and lipophilic substances as well as the feasibility of various routes of administration, including oral, topical, parenteral and pulmonary route.

An LBDDS is typically composed of lipids, and a surfactant may also contain a hydrophilic co-solvents [7]. In practice, lipid formulations are a diverse group of formulations, which have a wide range of properties.

These result from the blending of up to five classes of excipients, ranging from pure triglyceride oils, through mixed glycerides, lipophilic surfactants, hydrophilic surfactants, and water-soluble co-solvents. The simplest lipid products are those in which the drug is dissolved indigestible oil, usually a vegetable oil or a medium-chain triglyceride. The inclusion of surfactants may improve the solvent capacity of the formulations and promote their emulsification into water [3].

1.1 Common Routes of LBDDS: Different routes such as oral, parenteral, ocular, intranasal, dermal/ transdermal, and vaginal can be for the administration of the lipid-based drug delivery systems (LBDDS).

In general oral route is the most convenient route because of some properties like non-invasiveness, less expensive, and less prone to side effects, such as injection-site reactions. It is also considered as the easiest and the most preferred method of drug delivery for chronic therapies. And other routes are most commonly used to avoid first-pass metabolism and enzymatic degradation of drug or to provide targeting/ site-specific delivery of drug [8].

1.2 Lipid Formulation Classification System (LFCs): Lipid formulations are categorized in the lipid formulation classification system (LFCs) according to their formulation components: hydrophobicity, dispersibility, and digestibility. The lipid formulation classification system (LFCs) was introduced in 2000 as a working model, and in 2006, other types of formulation were added.

TABLE 1: LIPID FORMULATION CLASSIFICATION SYSTEM BY POUTON

Classes	I	II	IIIa	IIIb	IV
% Glycerides (mono-, di-, tri-glycerides)	100	40-80	40-80	< 20	0
% Lipophilic surfactants (HLB < 12)	0	20-60	20 – 40	0	0-20
%Hydrophilic surfactants (HLB > 12)	0	0	0	20-50	20-80
%Co-solvents	0	0	0 – 40	20-50	0-80
Characteristic features	Simple oil Solution	Self-emulsifying ability	Self-emulsifying ability	Self-emulsifying ability	Spontaneous formation of micellar dispersion

Advantages	GRAS (generally Recognized as safe) status Capsule compatibility	Unlikely to lose solvent capacity on dispersion	Formationof clear /opalescent dispersion; droplet size < 250 nm. No digestion needed for drug absorption	Transparent dispersion No digestion needed for drug absorption	Good solvent capacity for many drugs
Disadvantages	Poor solvent capacity for the drug with intermediate Log P value. Suitable only for lipophilic drugs limited or no dispersion requires digestion	Coarser emulsion (droplet size: 0.25-2 μm)	Likely to lose solvent capacity on dispersion less easily digested	May cause partial drug precipitation Less easily digested	Risk of drug precipitation upon dispersion may not be digestible

In the latest years, the LFCs have been discussed more widely within the pharmaceutical industry to seek a consensus that 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, *i.e.,* with reference to their physiochemical properties [5, 7, 9, 10].

1.3. Strategies of Improvement of Oral Bioavailability of Poorly Water-Soluble Drug by LBDDS:

TABLE 2: LBDDS FOR IMPROVEMENT OF ORAL BIOAVAILABILITY

Strategy	Brief Description
Extended retention in the stomach	Introduction of lipids into the GIT results in slower peristaltic action, gastric emptying, and consequently increased the retention time of its content and possibly the co-administered drug in the upper intestine, where absorption occurs. This contributes to more efficient dissolution in the upper intestine and positively influences drug absorption.
Increased solubilization	The presence of lipids in the GIT stimulates increased excretion of bile salts and endogenous bile lipids (including cholesterol and phospholipids), which facilitates the emulsification of the lipids present and drug solubilization. This leads to the formation of intestinal mixed micelles of endogenous origin and increased solubilization capacity of the GIT for the drug
Changes in the biochemical barrier	Some lipids and surfactants can reduce 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
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. Surfactants can cause fluidization of the intestinal cell membrane and opening of tight junctions, which results in increased membrane permeability
Stimulation of intestinal lymphatic transport	Lipids composed of LCT (Long-chain triglycerides) or MCT (medium-chain triglycerides) 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 [7]

1.4. Advantages of Lipid-based Drug Delivery System:

- Drug release is controlled and in a targeted manner.
- Pharmaceutical stability.
- High drug content.
- Feasibility of carrying both lipophilic and hydrophilic drug.
- Lipids and developed formulation is bio-degradable and biocompatible in nature.
- Excipients versatility.
- Formulation versatility.
- Low-risk profile
- Passive, non-invasive formation of vesicular system which is available for immediate commercialization [8].
- Improved oral bioavailability.
- Reduces plasma profile variability.
- Increases permeation when used orally.

- The lipid-based dosage form is stable at a varying moisture content and pH.
- Lipids provide adequate protection of drugs that are sensitive to the gastric environment or undergo enzymatic degradation.
- They provide a hydrophobic environment to delay the release of the loaded drug.
- They used in the design of sustained-release beads, tablets, microemulsion, implants, and microcapsule.
- Ability to improve physical stability of pharmaceuticals [11].
- Manufacturing and scale-up are easy [12].

1.5. Disadvantages of Lipid-based Formulation:

- Complexity in physicochemical properties.
- Challenge mainly in stability & manufacturing.
- Limited solubility of some poorly water-soluble drugs in lipids.
- Pre-absorptive gastrointestinal processing.
- Lack of knowledge about the *in-vivo* behavior and influence of co-administered drugs/lipids [13].
- Lack of predictive *in-vitro* and *in-vivo* testing methodologies [8].

1.6. Guideline for Designing Lipid-based Formulation: Lipid-based formulation is to be an important tool to formulate poorly soluble drugs; the design of this formulation can be challenging.

Seven guidelines for the design of lipid-based formulation summarized below.

1. It is critical to maintaining drug solubility in the formulation, after dispersion and digestion.

2. Properties of the colloidal species formed after processing in the GI milieu are probably more important than properties of the formulation itself in enhancing absorption.

3. Higher proportion of lipids (>60%) and a lower proportion of surfactant (<30%) and co-solvent (<10%) generally leads to more robust drug solubilisation after dilution.

4. Medium-chain triglycerides may afford great drug solubility and stability in the formulation, but long-chain triglycerides facilitate the more efficient formulation of bile salt lipid colloidal species and thus may afford higher bioavailability.

5. Type IIIB SMEEDS formulation give lower droplet size after dispersion; however, they are more dependent on the surface properties employed, non-digestible surfactant generally gives higher bioavailability.

6. Dispersion of type IV formulation (Surfactant / co-solvent) is likely more efficient if two surfactants are used rather than a single one.

7. Type IV formulation may give higher drug solubility but must be designed carefully to assure that drug does not precipitate after digestion.

These guidelines are important ones to keep in mind when designing oral lipid-based formulations for poorly soluble drugs. As further experience is gained with the design and use of these formulations and the database of successful formulations grows, it is to be hoped that design of these formulations will become less of an empirical exercise and more rational in its approach [8].

2. Drug and Excipients used in LBDDS:

2.1. General Selection Criteria of Drug Candidate used in LBDDS:

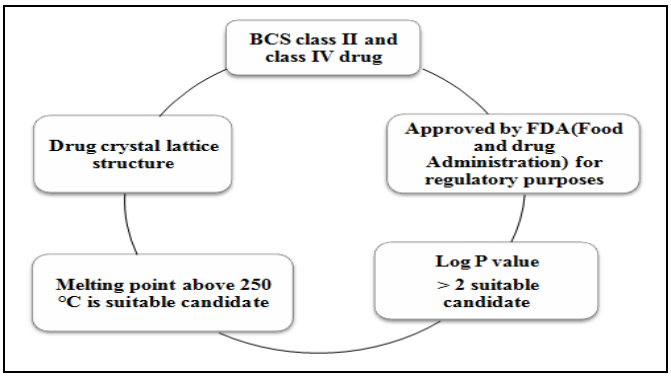


FIG. 2: SELECTION CRITERIA OF DRUG CANDIDATE IN LBDDS

2.2. Excipients for Lipid-based Formulation: When formulating LBDDS, drugs have to be incorporated into an appropriate mixture of oil(s) and surfactant(s); therefore, formulation development commonly starts with excipient election. As there are many lipid-based substances that can be used for formulating LBDDS, some general criteria for excipient selection were introduced in order to save time and cut costs.

During preliminary selection studies, a few excipients are identified as possibly appropriate for further research owing to their safety, drug solubility and stability in excipients, and some other characteristics presented in **Fig. 3**. [7]

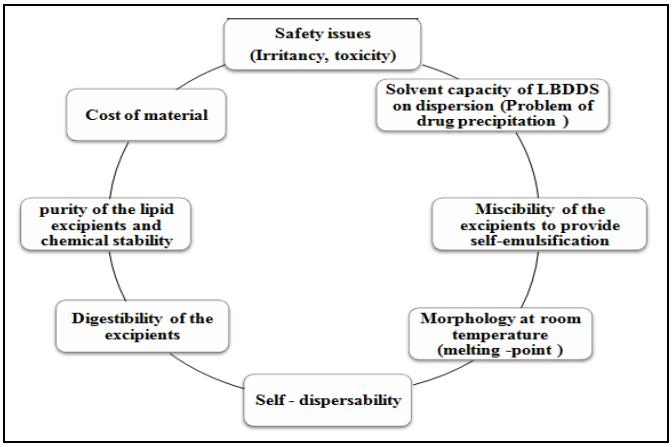


FIG. 3: SELECTION OF EXCIPIENTS USED IN LBDDS

2.2.1. Lipids: The lipid used in the preparation of LBDDS can be formulated from various non-polar components [7]. Lipids are naturally occurring oils and fats, and they are co-composed with triglycerides and fatty acids of varying chain lengths with a degree of unsaturation. The formation, stability, and properties of lipid-based formulation depends on the characteristic of the oil phase, for example, polarity, water-solubility, interfacial tension with an aqueous phase, viscosity, density, phase behavior and chemical stability [14].

Oil can solubilize the lipophilic drug in a definite amount. The oil phase highly influences the dissolution of hydrophobic drugs and may contribute to their lymphatic transport. It also influences the self-emulsifying ability of formulation and precipitation in GIT [15].

2.2.1.1. Tri-glycerides: Tri-glycerides is the most commonly used excipients in the lipid-based formulation. Tri-glycerides is one of the class of lipid, which does not show any safety issues, as they are fully digested and absorbed in the body.

Tri-glycerides further divided into three classes (1) Long Chain Triglycerides (LCT) (2) Medium Chain Triglycerides (MCT) (3) Short Chain Triglycerides (SCT). The solvent capacity for a drug is mainly decided by the effective concentration of the ester group. MCT has a higher solvent capacity than LCT [1].

TABLE 3: EXAMPLES OF GLYCERIDES USED IN THE FORMATION OF LBDDS

Class	Examples	Characteristic
Long-chain tri glycerides (LCT)	Corn oil, soybean oil, olive oil, peanut oil, sesame oil, sunflower oil, castor oil, *etc*.	GRAS status, easily ingested, digested, and absorbed, poor self-dispersing properties of LCT and generally lower loading capacity for drugs with intermediate log P values. Their advantage is generally a higher solubilizing capacity after dispersion and digestion of the formulation
Medium-chain triglycerides (MCT)	Fractionated coconut oil, palm seed oil, triglycerides of Caprylic/ capric acid Miglyol® 812, Captex® 355	MCTs exhibit a good solubilizing capacity for less lipophilic drugs and good self-dispersing ability. Semi-synthetic MCT with hydrogenated double bonds are resistant to oxidation
Mixed mono-, di- and tri-glycerides	Imwitor® 988, Imwitor® 308, Maisine® 35-1,Peceol®, Plurol, Oleique®CC49, Capryol®, Myrj®	They possess surface-active properties because of their amphiphilic nature and are effective in replacing conventionally used oils owing to their better self-dispersing ability and higher solubilizing capacity for poorly water-soluble drugs

2.2.1.2. Mixed Glycerides: Mixed glycerides are obtained by partial hydrolysis of vegetable oils. The starting material (triglyceride) and the extent of hydrolysis determine the chemical composition of the mixed glycerides produced. Medium-chain mixed glycerides is not susceptible to oxidation, have the greater solvent capacity, and promote emulsification.

These polar oily Excipients also improve solvent capacity and the dispersibility of the formulation [1].

2.2.2. Surfactant: For the proper designing of LBDDS, the selection of proper surfactants is the most important factor. Stability of lipid dispersion or lipid-based formulation to the different environment stress like pH, ionic strength, and temperature is often predominantly determined by the type and concentration of emulsifier used. It is generally acceptable that most stable emulsions are formed in the presence of surfactant combinations, in which one acts as an emulsifier and the other as a co-emulsifier, depending on their HLB values [16, 17].

TABLE 4: EXAMPLES OF SURFACTANTS ACCORDING TO THEIR HLB VALUE

HLB value	Types of surfactant
Low HLB (< 10)	Phosphatidylcholine and Phosphatidylcholine mixtures Phosphatidylcholine, mixtures in propylene glycol / MCT, ethanol glycerides Unsaturated polyglycolized (macrogolglycerides): Labrafil® M1944 CS, Labrafil® M2125CS. Sorbitan esters: Capmul®, Capmul® S, Span® 20, Span® 40. Polyethoxylated alkyl ethers: Brijs®
High HLB (> 10)	Polyoxyethylene Sorbitan esters (Polysorbate): Tweens® 20, 40, 60, 80. Polyethoxylated fatty acid ester - Myrj® 52, Solutol® HS15. Polyethoxylated alkyl ethers - Brijs® 35, 56, 78 Polyethoxylated glycerides Caprylo/caproil macrogolglycerides: Labrasol® Polyoxyl castor oil derivatives. Polyoxyl 35 castor oil: Cremophor® EL, Polyoxyl 40 hydrogenated castor oil: Cremophor® RH40. Polyoxyethylene polyoxypropylene block copolymer: Poloxamer® 188, Poloxamer® 407. Saturated polyglycolized glycerides: Lauroyl macrogolglycerides: Gelucire® 44/14, Stearoyl macrogolglycerides: Gelucire® 50/13

2.2.3. Co- Surfactants: Co-surfactants with HLB value 10-14 is used along with surfactant for lowering the interfacial tension, the interface would expand to form finely dispersed droplets. The fluid interfacial film is achieved by the addition of a co-surfactant. Co-surfactant will enhance the fluidity of the interface and thereby increasing the entropy of the system [14].

2.2.4. Co-solvents: Co-solvents increase the solvent capacity of the formulation for drugs and aid in the dispersion of systems that contain a high proportion of water-soluble surfactants, thus enhancing the solubilization processes. Some limitations for the usage of co-solvents include; immiscibility of some co-solvents with oils, incompatibilities of low molecular weight solvents with capsule shells, and precipitation of solubilized drug from solvent due to loss of solvent capacity following dilution. The co-solvents mainly include ethanol, propylene glycol, and polyethylene glycol 400 (PEG- 400) [1, 5, 12].

2.2.5. Additives: Lipid-soluble antioxidants such as α-tocopherol, β-carotene, butylated hydroxy-toluene (BHT), butylated hydroxyanisole (BHA) or propyl gallate could potentially be included in formulations to protect either unsaturated fatty acid chains or drugs from oxidation [10].

3. Drug Absorption from Lipid-based Formulation: In general, lipid formulation can be obtained from the result of the blending of excipients such as pure triglyceride oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants, and water-soluble co-solvents. These whole system leads to increase the absorption from gastrointestinal tract by accelerating dissolution process and facilitating the formation of solubilizing phase by reducing the particle size and thereby reducing surface tension, yielding a solid-state solution within the carrier, changing drug uptake, efflux and disposition by altering enterocyte-based transport, and enhancing drug transport to the systemic circulation via the intestinal lymphatic system.

3.1. Lymphatic System: The lymphatic system plays a significant role in the transport of drugs to the systemic circulation, given its widespread drainage network throughout the body. Some of the advantages of lymphatic transport of drug are prevention of first-pass metabolism and targeting of specific diseases which are known to spread *via* lymphatics; such as certain lymphomas and HIV. Possible mechanisms by which lipids affect drug absorption, bioavailability, and disposition after oral administration are summarized in **Fig. 4**.

The promising mechanisms include:

- Assisting transcellular absorption due to increased membrane fluidity.
- Allowing paracellular transport by opening tight junctions.
- Increased intracellular concentration and residence time by surfactants due to inhibition of P gp and/or CYP450.
- Lipid stimulation of lipoprotein/ chylomicron production.

3.2. Digestion and Solubilisation: While the lipids (fatty acid derivatives) are the core ingredient of the formulation, one or more surfactants, as well as perhaps a hydrophilic co-solvent, may be required to as serve solubilization tool and to improve dispersion properties. Surfactants are categorized by their hydrophilic-lipophilic balance (HLB) value, with a low number (≤10) corresponding to greater lipophilicity and a higher number (≥10) corresponding to higher hydrophilicity. The balance between a drug's solubility in the aqueous

environment of the gastrointestinal lumen and its permeation across the lipophilic membrane of enterocyte determines its rate and extent of absorption.

After oral administration of LBDDS, the digestion of exogenous dietary triglycerides (TG) and formulation TG is initiated by gastric lipase. Concurrently, the mechanical mixing of the stomach that facilitates the generation of crude emulsion comprises of the aqueous gastric fluid and lipid digestion. Later on in the small intestine, TG is broken down to diglycerides, monoglyceride and fatty acids by pancreatic lipase in conjunction with its cofactor colipase 203; acting mainly at the sn-1 and sn-3 positions of TG to yield 2-monoglyceride and free fatty acid. Pancreatic phospholipase A2 digests the formulation-derived or biliary-derived phospholipids (PL) by hydrolyzing at the sn-2 position of PL to yield lysophosphatidylcholine and fatty acid. The exogenous lipid present in the small intestine stimulates the secretion of endogenous biliary lipids from the gall bladder, including bile salt (BS), PL and cholesterol. Earlier formed monoglycerides, fatty acids, and lysophospholipid (products of lipid digestion) are subsequently incorporated into a series of colloidal structures, including micelles and unilamellar and multi-lamellar vesicles in the presence of bile salts. The formation of lipid metabolites significantly enhances the solubilization and absorptive capacity of the small intestine for the lipid digestion products and drug (D).

In **Fig. 5**, the oil droplet in the intestine is represented in different colors to specify undigested TG in the core (orange) and digested products such as fatty acid (blue) and monoglyceride (green) on the surface of the droplet.

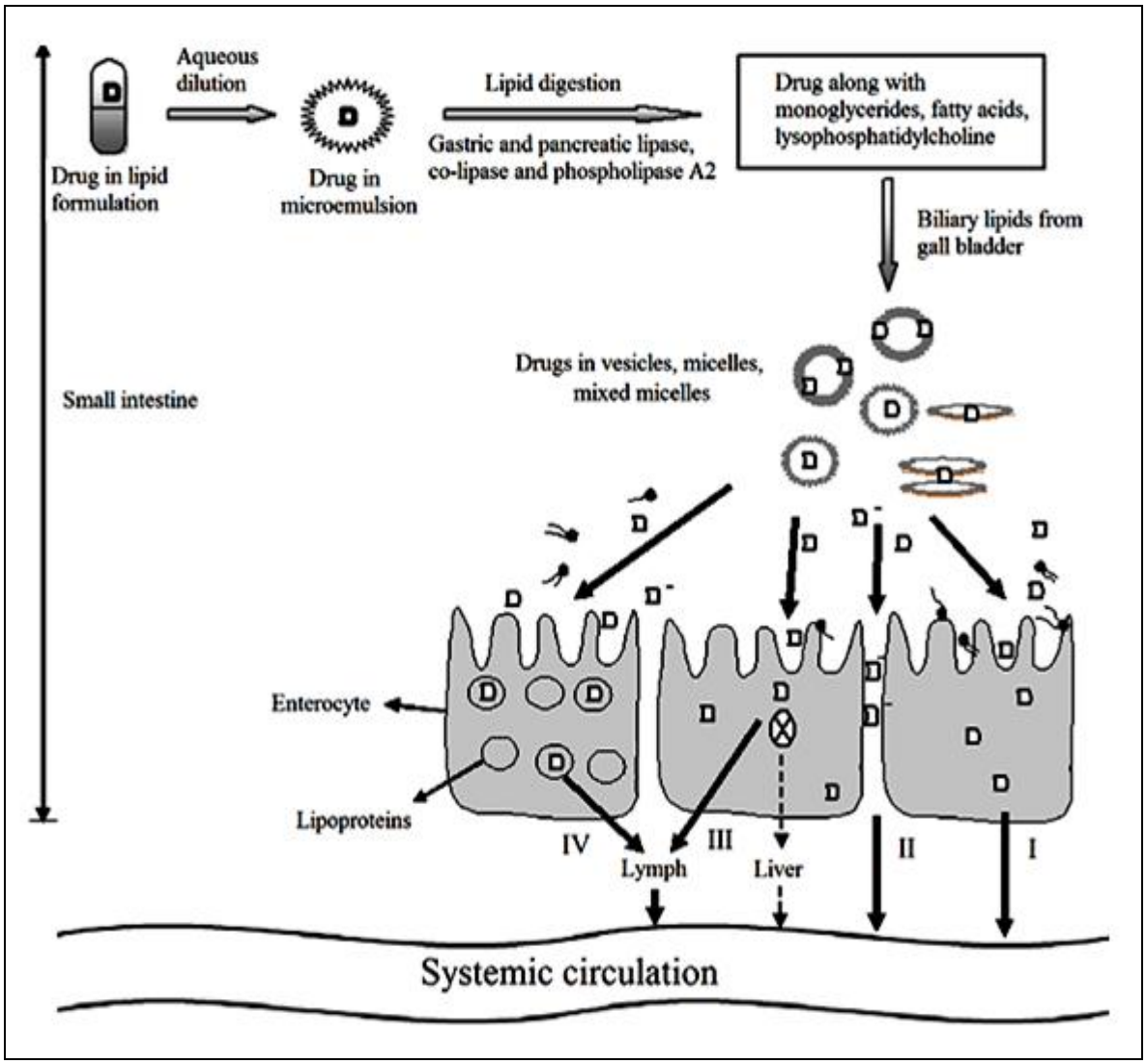


FIG. 4: SCHEMATIC DIAGRAM OF MECHANISMS OF INTESTINAL DRUG TRANSPORT FROM LBDDS

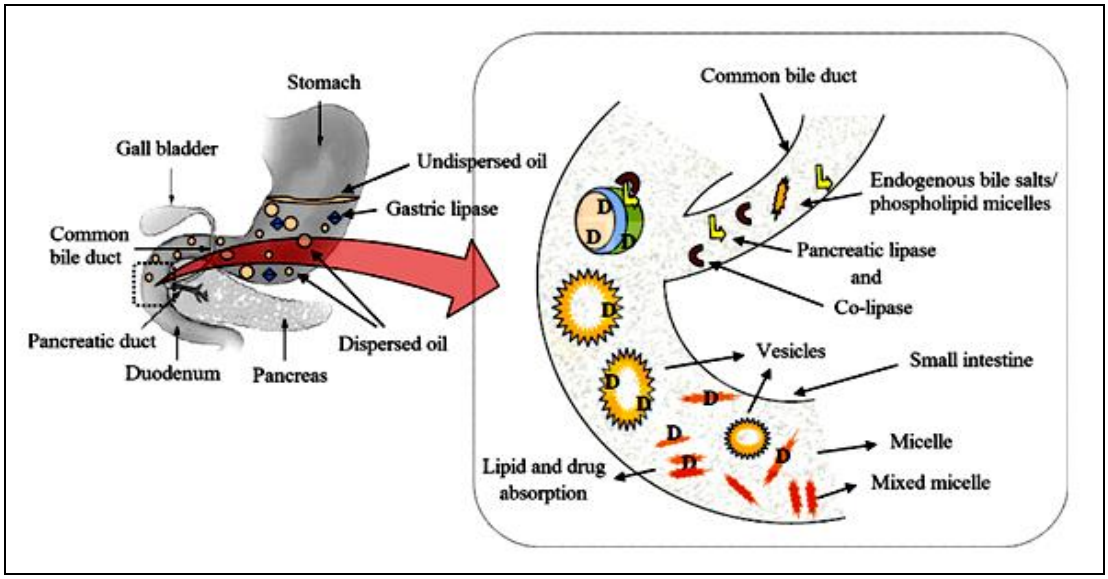


FIG. 5: REPRESENTATION OF LIPID DIGESTION AND DRUG SOLUBILISATION PROCESS IN THE SMALL INTESTINE

3.3. The Role of Lipids in Enhancement of Bioavailability: Bioavailability is increased in some drugs when administered with food. However, the drugs that belong to BCS class I had a negligible effect with the presence or in the absence of food. But class II drugs have an altered absorption when co-administered with food. The believed reason for such enhanced bioavailability might be attributed to solubility, permeability, and inhibition of efflux transporters in the presence of food. Some of the drugs like griseofulvin, halofantrine, danazol, troglitazone and atovaquone, when administered along with food that shows enhanced bioavailability. A document entitled "Food-Effect Bioavailability and Fed Bioequivalence" was issued by the FDA in December 2002. The US FDA suggested high-fat meals for food-effect studies because such fatty meals (800–1000 cal, 50%-65% fat, 25%-30% carbohydrates, and 15%-20% proteins) affect GI physiology and maximize drug transfer into the systemic circulation.

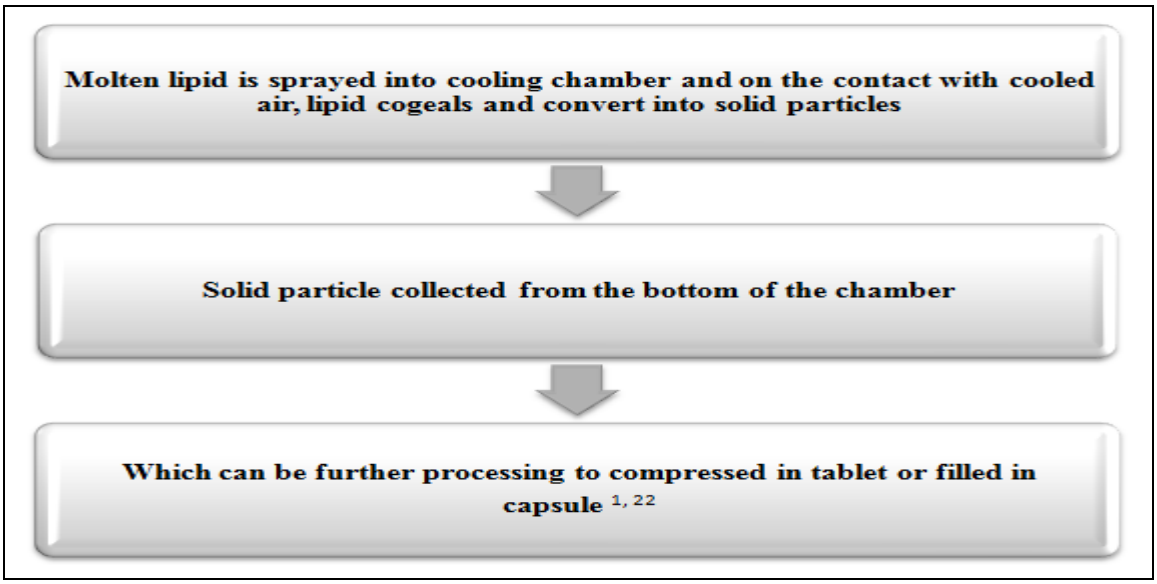
In particular, it is the lipid component of the food that mainly responsible for the absorption of the lipophilic drug as well as enhanced oral bioavailability of the drug. This can be explained by the ability of a high-fat meal to stimulate biliary and pancreatic secretions, to reduce metabolism and efflux activity, to increase intestinal wall permeability, and to a prolongation of the gastrointestinal tract (GIT) residence time and transport via the lymphatic system. Triglycerides and long-chain fatty acids play a vital role in prolonging gastric residence time. Also, a high-fat meal elevates the TG-rich lipoproteins that react with drug molecules. This association of lipoproteins with drug molecules enhances intestinal lymphatic transport and leads to changes in drug disposition and finally changes the kinetics of the pharmacological actions of poorly soluble drugs. Such type of food effects on the drug that may leads to serious concern about sub-therapeutic plasma drug concentration effect when co administered without food. Such food effect is also a serious problem for the drugs that having a narrow therapeutic index, where increased bioavailability may lead to serious unpleasant effects. Hence, control or/and monitoring of food intake is necessary when dosing such drugs.

Food-dependent bioavailability can be significantly reduced through formulating the drug as a lipid-based formulation, which can improve solubility as well as dissolution characteristic of lipophilic drug and facilitate solubilized species, from which absorption occur. Therefore lipid-based formulations can be used to reduce the dose of the drug while at the same time enhancing its oral bioavailability [2, 18, 19, 20, 21].

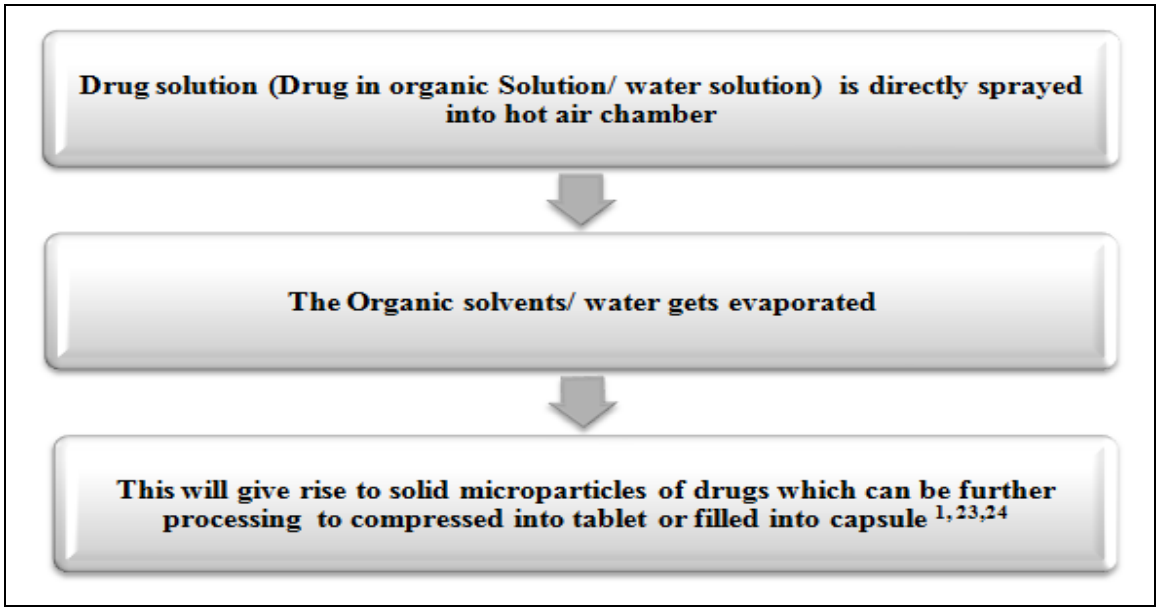
4. Conversion of Liquid Lipid Dispersion into Solid Particle for Oral Delivery:

1. Spray Congealing (Spray Cooling)
2. Spray Drying
3. Adsorption onto a solid carrier
4. Melt-granulation (Pelletization)

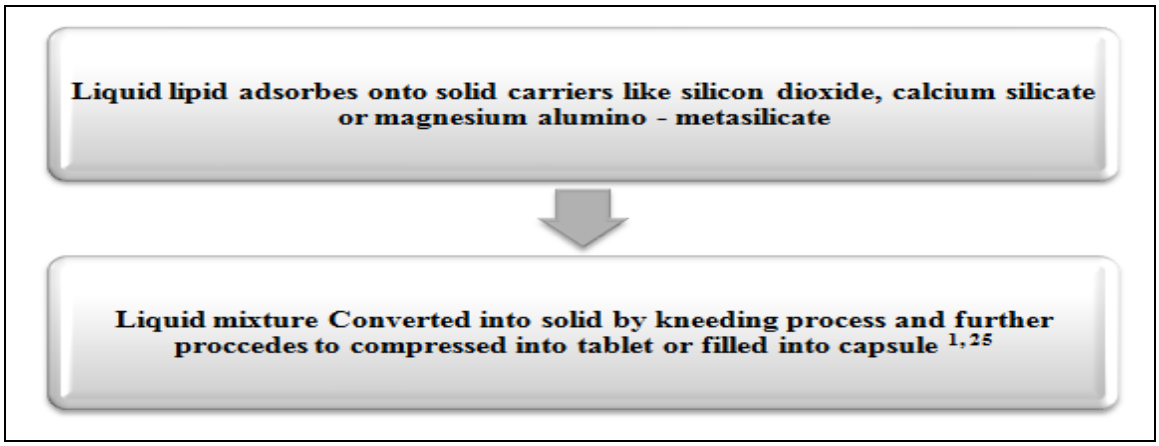
4.1. Spray Congealing (Spray Drying):



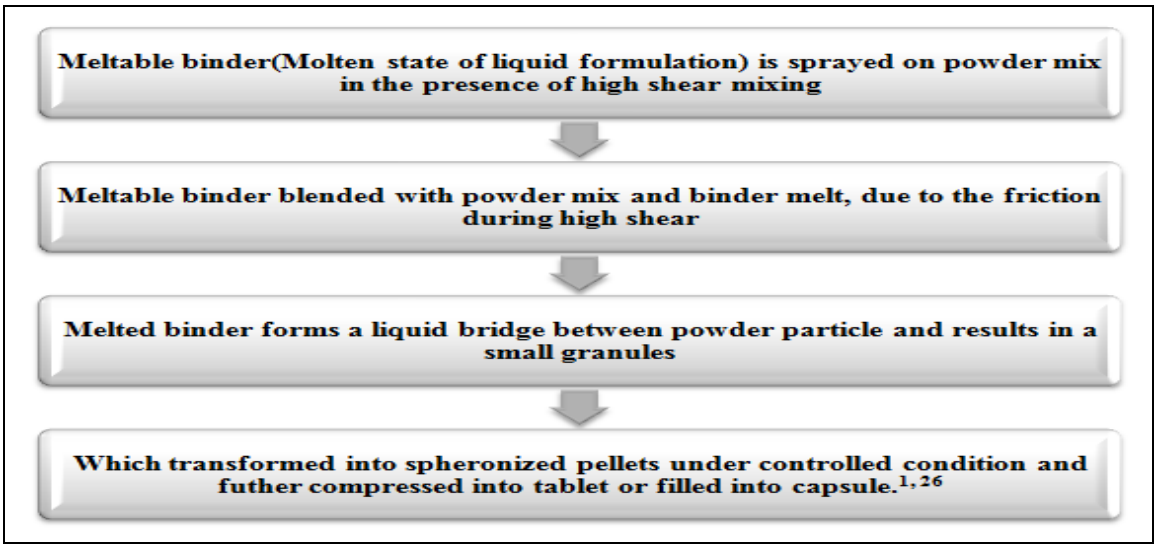
4.2. Spray Drying:



4.3. Adsorption onto Solid Carrier:



4.4. Melt Granulation (Pellatization):



5. Types of Lipid-based Drug Delivery System:

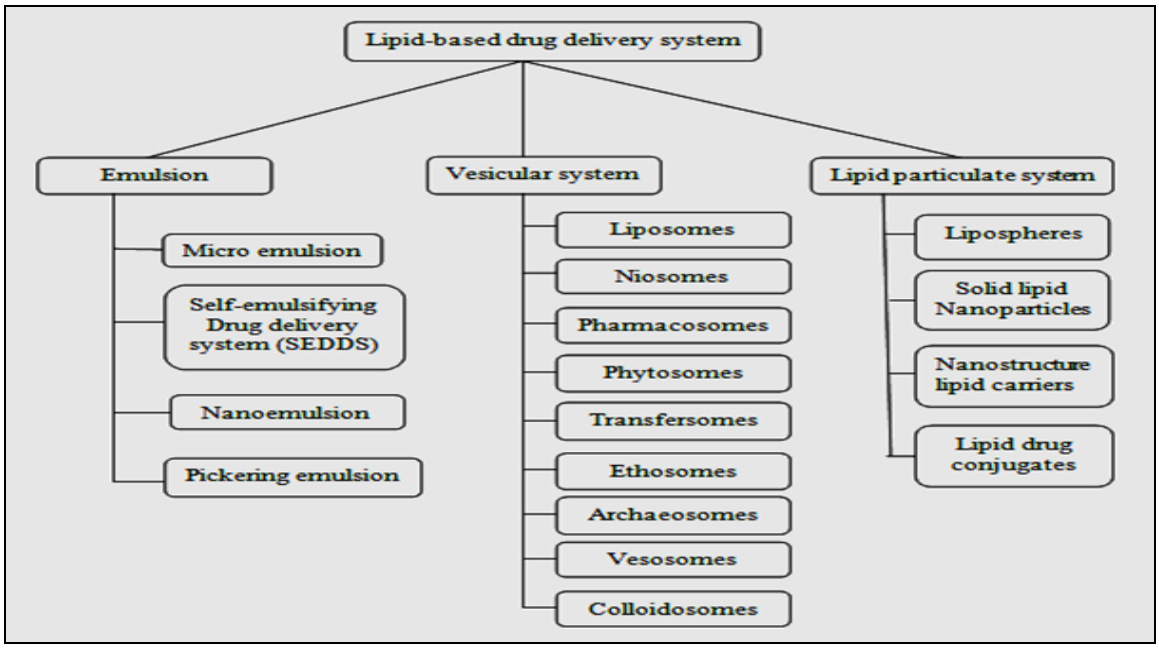


FIG. 6: CLASSIFICATION OF LIPID BASED DRUG DELIVERY SYSTEM

5.1. Micro-Emulsion: Hoar and Schulman introduced the concept of micro-emulsion firstly in 1940. They titrated a milky emulsion with hexanol to produce a single-phase clear solution. In 1959, Schulman and co-workers consequently coined the term of microemulsion [9]. Micro-emulsion is a transparent, thermodynamically stable system that consists of water, oil, and surfactant/ Co-surfactant [11, 27]. As compared with the ordinary emulsion, this micro-emulsion formed by simple mixing of the ingredients and care should be taken to avoid high shear environment, which can cause phase separation.

Droplets of micro-emulsion have a smaller particle size (10-200 nm) as compared with the ordinary emulsion have a particle size in the range of (1-20 μm). The emulsion consists of usually spherical shaped droplets whereas, micro-emulsion normally has a structure like micelles or continuous bilayer structured [27]. The existence of microdomains of different polarity within the same single-phase solution enables both water-soluble and oil-soluble materials to be solubilized, and at the same time if this is so desired. Furthermore, it is also possible to incorporate amphiphilic drugs into the micro-emulsion [12].

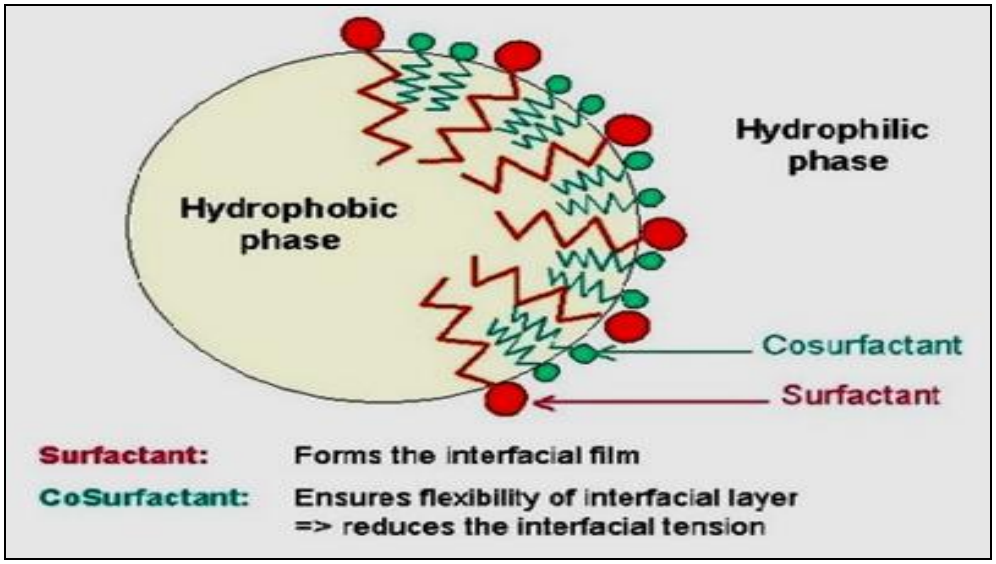


FIG. 7: SCHEMATIC REPRESENTATION OF MICRO-EMULSION

Micro-emulsion have huge application in the different fields like pharmaceuticals, biotechnology, cosmetics, analytical applications, environmental remediation and detoxification, coatings and textile finishing [28].

5.2. Self-Emulsifying Drug Delivery System (SEDDS): Pouton reported for the first time self-emulsifying drug delivery system to deliver poorly water-soluble drugs *via* Miglyol 812 (M812, medium-chain triglyceride, MCT) and Tween 85 (T85, polyoxyethylene-20-sorbitan trioleate) incorporation to enhance both solubility and bioavailability [29]. Self-emulsifying drug delivery system (SEDDS) is the thermodynamically stable isotropic mixtures of oil, surfactant, and co-surfactant, which spontaneously form an emulsion when it's in contact with aqueous fluid in the GI tract. Depending upon the particle size of emulsion droplet, it is classified as a self-micro emulsifying drug delivery system (SMEDDS), particle size ranges between 100 and 250 nm, and Self nano-emulsifying drug delivery system (SNEDDS), particle size ranges between less than 100nm. SMEDDS are a widely used system to solubilize hydrophobic drugs by partitioning into two phases (oil phase and aqueous phase), which leads to enhance bioavailability [29, 30].

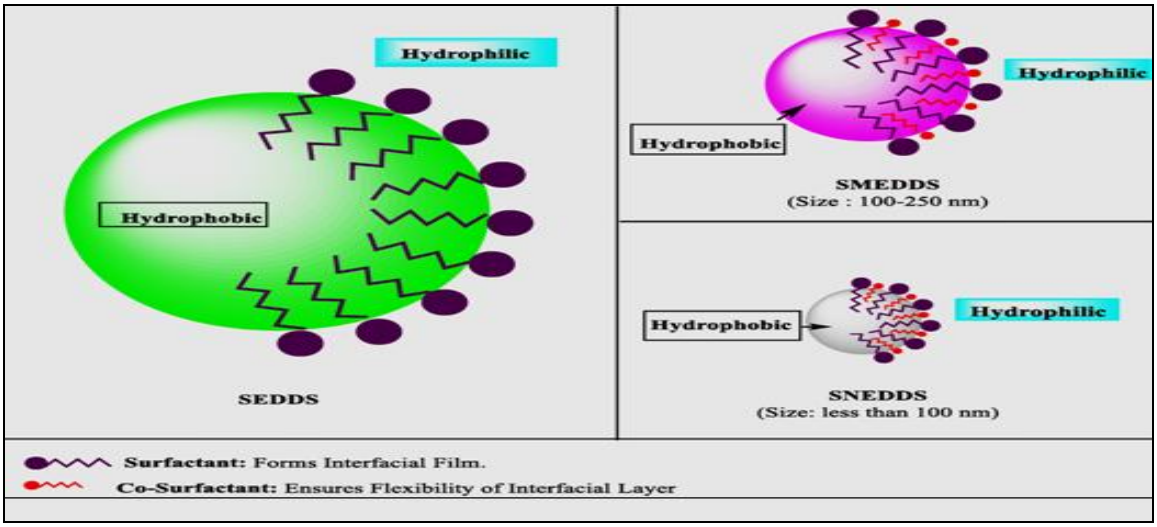


FIG. 8: SCHEMATIC REPRESENTATION OF SEDDS, SMEDDS AND SNEDDS

The advantages of this system include enhanced oral bioavailability, reduction of dose and its frequency, most consistency plasma level profile curve, selective targeting of drug and protection of drug against the harsh environment of GIT and environment in gut [12].

5.3. Nano-emulsion: Nano-emulsion primarily made up of the oil and water phase and stabilized by surfactant or alcohol.

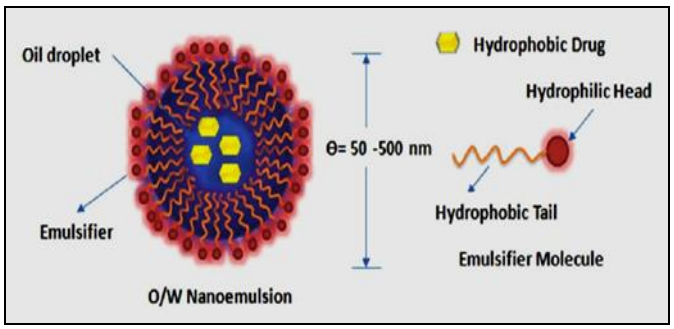


FIG. 9: SCHEMATIC REPRESENTATION OF NANOEMULSION

Nano-emulsions are oil-in-water (O/W) type of emulsion with a mean droplet size is between 100 to 500 nm. The particles can exist in oil-in-water (O/W) and water-in-oill (W/O) forms, where the core of the particle is either oil or water, respectively [27]. These nano-emulsions are meta-stable and diluted with water without changing the droplet size of nanoemulsion [11]. The stability of nanoemulsion is influenced by various factors such as temperature and pH [27]. Nano-emulsions are biodegradable as well biocompatible in nature, easy to scale up, used for lipophilic drugs. Surfactant and ingredients used in the formulation of nano-emulsion which are approved by generally recognized as a safe (GRAS), regulatory authorities [31]. Due to their large surface area, they provide excellent drug release patterns. Nano-emulsion delivered through varieties of routes such as parenteral, ocular, oral, pulmonary, and dermal [32].

5.4. Pickering Emulsion: Pickering emulsion is a type of O/W type of emulsion in which stability is achieved by solid particles present at the interface of two phases, thereby reduction in the surface energy of system [33].

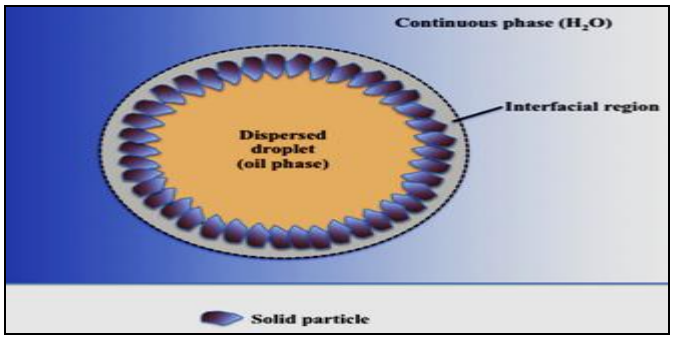


FIG. 10: SCHEMATIC DIAGRAM OF PICKERING EMULSION

A solid particle used is silica, calcium carbonate, titanium dioxide, latex, and many more. Added solid particles will bind to the surface of interface and prevent droplets from coalescing, thus forming more stable emulsion comparing with conventional emulsion [11]. Various properties such as hydro-phobicity, shape, and size of particle can have an effect on the stability of the Pickering emulsion [12].

5.5. Liposomes: Liposomes were firstly discovered by Bangham and colleagues in the early 1960s [12].

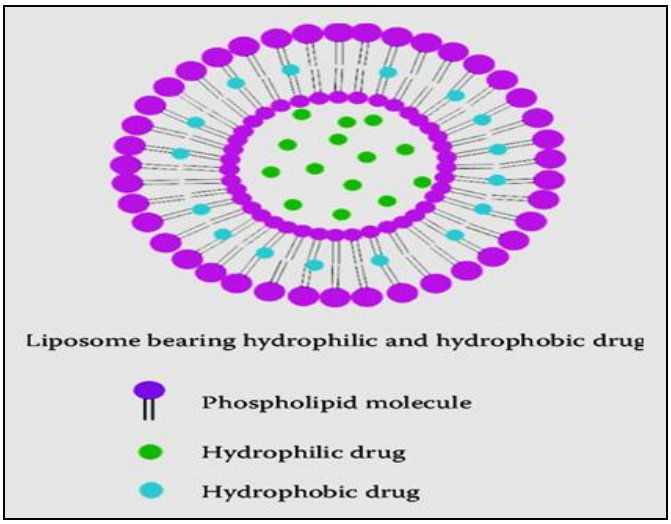


FIG. 11: SCHEMATIC REPRESENTATION OF LIPOSOME

Liposomes are artificial vesicles composed of a lipid bilayer made up of phospholipids and cholesterol with particle diameter varying from 0.01 and 100 μm. There are a number of components used in the formation of liposomes; among them, phospholipids and cholesterol are main ingredients [4]. The amphiphilic natures of phospholipids have capabilities to enclose both lipophilic and hydrophilic drugs in the structure of liposome [32]. It has drawbacks like a tendency to taken up by the body's reticular endothelial system (RES), physically unstable system, cost-effective [11].

Liposomes basically classified into three basic types depending on their size and number of bilayer; (1) multilamellar vesicles (MLVs) (2) small unilamellar vesicles (SUVs) (3) large unilamellar vesicles (LUVs). Liposomes can be used for oral, ocular, pulmonary, and transdermal delivery of drugs. Anti-tumour and antimicrobial agents, chelating agents, peptide hormones, enzymes, other proteins, vaccines, and genetic

materials have been incorporated into the aqueous or lipid phases of liposomes [32].

5.6. Niosomes: Niosomes is also known as anon-ionic surfactant vesicle widely studies as an alternative of liposomes. Niosomes are vesicles composed of mainly non-ionic bilayer, forming surfactant size ranges from 10 to 100 nm. They are structurally similar to liposomes but contain a synthetic non-ionic surfactant in contrast to natural phospholipids present in the liposomes.

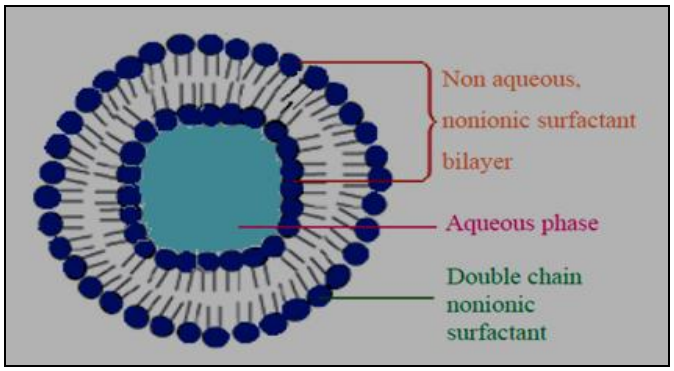


FIG. 12: SCHEMATIC REPRESENTATIONS OF NIOSOMES

The two main components of Niosomes are cholesterol, which gives integrity, rigidity, and shape to the structure and non-ionic surfactant like Span 60, Span 40, Span 20, Span 80, Tween 20, Tween 40, Tween 60 and Tween 80 [4, 32]. Non-ionic surfactants are less costly and chemically stable as compared to phospholipids. Niosomes is similar to liposome in functionality and improvement in bioavailability of the drug, also used to target the drug to a specific organ. However, over liposomes, Niosomes are most preferred because of its chemical stability and economy. The limitations of Niosomes include Physical instability during storage, fusion, and leakage may lead to hydrolysis of encapsulated drugs, which affect the shelf life of the drug. Antigen and small molecules mainly encapsulated in Niosomes [32]. Niosomes successfully used for oral administration of protein and peptides and both hydrophilic and hydrophobic drugs can be embedded in niosome vesicles [31, 40].

5.7. Pharmacosomes: Pharmacosomes are the colloidal dispersion of drugs covalently bonded to lipids. As the whole system is made up of linking a drug (pharmakon) to a carrier (soma), so it termed as a Pharmacosomes. Depending upon the chemical nature of drug and lipid complex, they may exist as ultra-fine vesicular, micellar, or hexagonal aggregates. They are an effective carrier for targeting and controlled release of the drug.

Pharmacosomes are also capable of entrapped hydrophilic and hydrophobic drugs. For the development of vesicular pharmacosomes, surface and bulk interaction of lipids with the drug is important criteria. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH_2, *etc*.) could be esterified to the lipid, with or without spacer chain that strongly results in an amphiphilic compound, that will facilitate membrane, tissue, or cell wall transfer in the organism. The whole system acquired hydrophilic and lipophilic properties, thus acquired amphiphilic character, ultimately reduces interfacial tension and exhibits mesomorphic behavior [32].

5.8. Phytosomes: Phytosomes also referred to as Herbosomes. The term phytosome is derived from two words ‘phyto’, meaning ‘plants’, and ‘somes’ meaning ‘cell-like structure’.

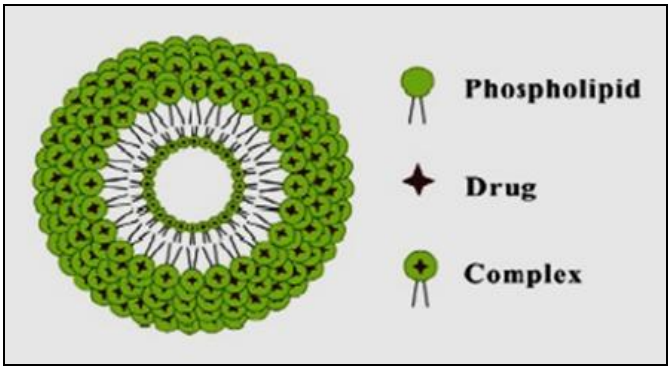


FIG. 13: SCHEMATIC REPRESENTATION OF PHYTOSOMES

These are lipidic vesicles manufactured by the reaction of a stoichiometric amount of phospholipids with standardized extract, or polyphenolic constitute like flavonoids, tannins, *etc*. in an aprotic solvent [11, 32, 35]. When treated with water, phytosome assumes a micellar and forming liposome like structure. Phytosomes are better absorbed than conventional herbal extract. Phytosomes also improve the bioavailability and permeation of drugs through cell membranes. The active ingredients of herbal extract protected from destruction by gut bacteria and digestive secretion [12]. Herbosomes gained too much importance in the field of pharmaceuticals, cosmeceuticals, and

nutraceuticals for the formulation of solution, creams, lotions, gels, and emulsion [32].

5.9. Transfersomes: Transfersomes meaning carrying the body, 'transferred' meaning 'take across' and 'soma' meaning 'body'. Transfersomes is an artificial vesicle designed the same as a cell vesicle, thus suitably controlling and targeting drug. Transfersomes was developed to take advantage of phospholipids vesicles for the transdermal delivery of drug [12].

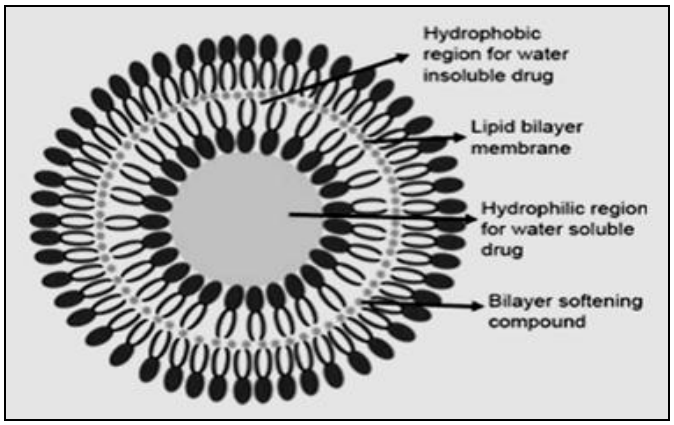


FIG. 14: SCHEMATIC REPRESENTATIONS OF TRANSFERSOMES

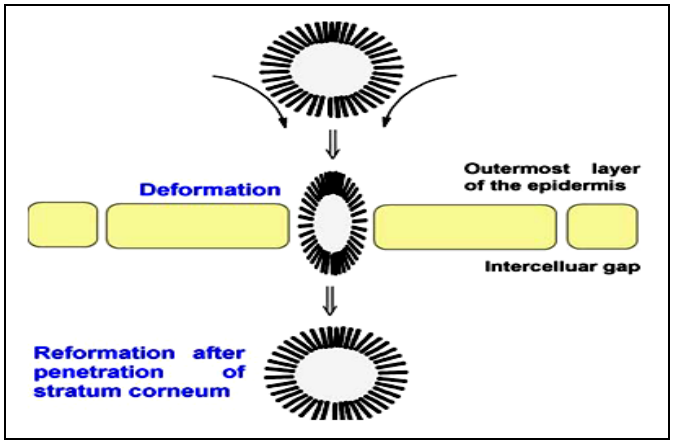


FIG. 15: MECHANISM OF TRANSFERSOMES PENETRATION THROUGH SKIN

Transfersomes were developed to take an advantage of phospholipids vesicles for the transdermal delivery of drug [12]. These system mainly composed of phospholipids, surfactant and water and can be used impart deeper permeation to the dermal layer of skin compared with conventional liposomes. These artificial vesicles contains phospholipids and an amphiphilic group like Tween 20, Tween 60, Tween 80, Sodium cholate, sodium deoxycholate, Span 60, Span 63, Span 80 or dipotassium glycyrrhizinate this provide vesicle elasticity and deformability to the system. They have the capacity to carry both hydrophilic and lipophilic drugs. Transfersomes Diameter ranges from 10 to 100 nm. And they can penetrate through skin membrane by transepidermal water gradient activity and in the presence of high water content, results in spontaneous migration of the drug-loaded vesicles through skin barrier [36, 37].

5.10. Ethosomes: Ethosomes are soft, malleable vesicles for the transdermal delivery of active ingredients. Ethosomes are vesicular systems mainly comprises of phospholipids, and the hydroalcoholic mixture contains the active ingredient in the core of system. Hydro-alcoholic mixture generally contains 20-30% of alcohol, which act as a permeation enhancer and permeates through skin membrane rapidly as compare with other vesicular systems of delivery.

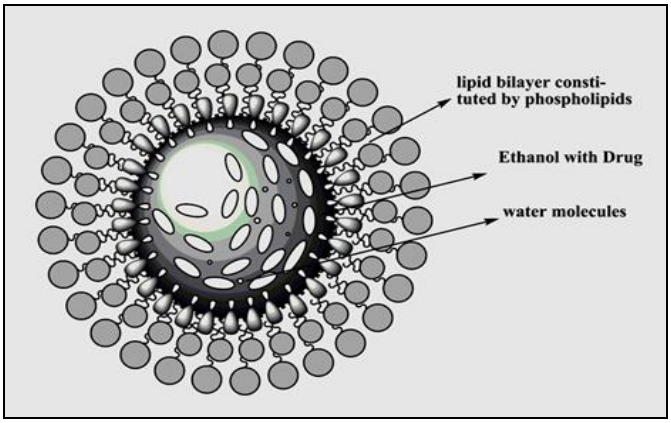


FIG. 16: STRUCTURE OF ETHOSOMES, EMBODYING ETHANOL AND DRUG MOLECULE

Ethosomes can encapsulate drug molecules with hydrophilic, lipophilic or amphiphilic nature. Ethosomes drug delivery is non-invasive and delivers the drug to the deep stratum corneum of the skin and to the systemic circulation. 11, 12, 38

5.11. Archaeosomes: Archaeosomes are archebacteria lipids containing vesicular systems. These are made up of one or more of the fully saturated bipolar tetraether lipids, which are less sensitive to oxidative stress, high temperature, and alkaline pH. Archaeosomes are the same as liposomes and size range of 200 nm, which are prepared from ether lipids extracted from various archaeobacteria. It has been demonstrated that the incorporation of polyethylene glycol and Coenzyme Q10 into archaeosomes can alter the

tissue distribution profiles of intravenously administered vesicles.

It had also reported that intravenous and oral delivery of nanometric-sized archaeosomes to an animal model was well tolerated with no apparent toxicity [12, 32].

5.12. Vesosomes: Vesosomes are vesicular structure consists of one or more bilayers enclosing aqueous core that contain unilamellar vesicles as an internal compartment and contains the drug. Vesosomes are multicompartment structures which have distinct inner compartment separated from external membrane. Unilamellar vesicles contain drug inside the core. Every compartment of vesosome can encapsulate the different types of material and have different bilayer compositions. Vesosome could entrap both colloidal particles and biological macromolecules relatively efficiently [12, 32].

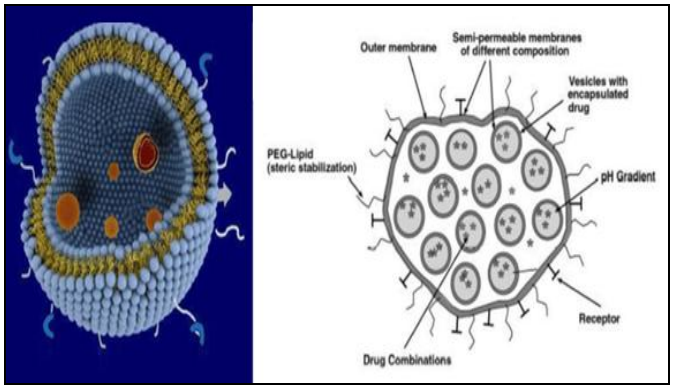


FIG. 17: STRUCTURE OF VESOSOMES

5.13. Colloidosomes: Colloidosomes are microcapsules whose shell consists of densely packed colloidal particles. Their physical properties, such as permeability, mechanical strength, and biocompatibility, can be precisely controlled through the proper choice of colloids and preparation conditions for their assembly. The high degree of control over their physical properties makes colloidosomes attractive structures for encapsulation and controlled release of materials ranging from fragrances and active ingredients to molecules produced by living cells. Colloidosomes are hollow, elastic shells whose permeability and elasticity can be controlled.

It is a novel class of microcapsules whose shell consists of coagulated or fused colloidal particles at the interface of emulsion droplet. Colloidosomes can be fabricated as rigid porous superstructures to enhance the viability of the cells. They may also be used for the following range of therapeutic and pharmaceutical applications: Drug/protein delivery carrier, controlled and sustained drug release, for enhanced drug solubilization, in tumour therapy, antimicrobial, antifungal, antiviral, could be used in cosmetics and dermatology ocular drug delivery, brain delivery, DNA delivery and in enzyme immobilization. However, a major problem in the colloidosomes manufacture is the poor yield of particles. If the shell locking is inefficient, the colloidosomes simply coalesce and fall apart on transfer into the water; a large proportion of the colloidosomes are normally lost during the transfer from organic to water medium [32].

5.14. Liposphere: Liposphere were first reported as a particulate dispersion of solid spherical particles of diameter ranges from 0.2 to 100 μm consisting of solid lipophilic core like triglycerides or fatty acids derivatives, stabilized by monolayer of phospholipids. Inner core contains drug dissolved or dispersed in a hydrophobic core.

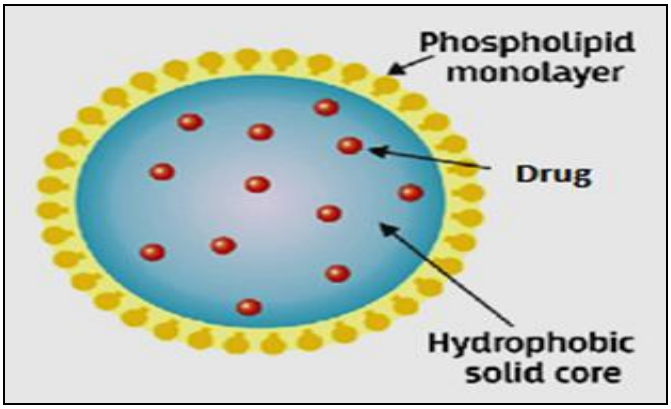


FIG. 18: SCHEMATIC REPRESENTATION OF LIPOSPHERE

Liposphere is a new type of fat-based encapsulated system formulated for the development of parenteral and topical delivery of drugs or bioactive. The lipospheres are microdroplet and solid at room temperature. The combination of the solid inner core with phospholipid exterior confers several advantages on the lipospheres and PNL compared with conventional microspheres and micro-particles, including high dispersibility in an aqueous medium, and a release rate for the entrapped substance that is controlled by phospholipid coating and carrier.

There are also many advantages over the dispersion based delivery systems. Lipospheres have increased stability as compared to emulsion-based systems, including vesicles and liposomes, and are more effectively dispersed than most suspension based systems. Further, the substance to be delivered does not have to be soluble in the vehicle since it can be dispersed in the solid carrier.

Lipospheres also have a lower risk of the reaction of substance to be delivered with the vehicle than in the emulsion system because the vehicle is a solid material. Moreover, the release rate of substance from the lipospheres can be manipulated by altering either or both the inner solid vesicle or the outer phospholipid layer. Lipospheres are also easier to prepare than vesicles such as liposomes and are inherently more stable [32, 39].

5.15. Solid-Lipid Microparticles: Polymeric microspheres have been tested successfully as sustained release drug delivery systems; however, their safety still remains uncertain, which leads to the development of solid lipid microparticles (SLMs). Lipid microspheres known as lipospheres are composed of a solid hydrophobic fat core (triglycerides) stabilized by a layer of phospholipid molecules embedded on their surface. These fat-based encapsulation systems contain the bioactive compound in the internal core, dissolved or dispersed in the solid fat matrix.

5.16. Solid Lipid Nanoparticles (SLNs): SLNs were firstly developed in 1990 as an alternative carrier of tradition lipid based formulation like liposomes, nanoemulsion, and polymeric particles [32, 46]. SLNs are particulate systems with particle size ranges from 50-1000 nm. They are derived from the oil in water emulsion, by replacing liquid oil by solid lipids [27].

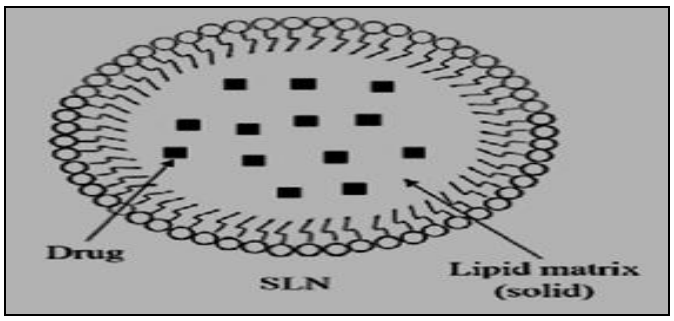


FIG. 19: SCHEMATIC REPRESENTATION OF SOLID LIPID NANOPARTICLE (SLN)

The SLNs are sub-micron colloidal carriers which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. Advantages of SLN are the use of physiological lipids, the avoidance of organic solvents, a potential wide application spectrum (dermal, per oral, intravenous), and the high-pressure homogenization as an established production method. Potential disadvantages such as poor drug loading capacity, particle growing, unpredictable gelation tendency, drug expulsion after polymeric transition during storage, and relatively high water content of the dispersions (70-99.9%) have been observed [12].

5.17. Nanostructured Lipid Carriers (NLCs): Nanostructured lipid carriers were developed in 1999 to overcome the issues related to SLNs *i.e.* low drug loading capacity due to perfect crystalline structure, expulsion of drug, physical instability of system, unwanted particle growth and gelation tendency may overcome by formulating NLCs. NLC comprises of solid lipid, liquid lipid, and surfactant in the system. Additional liquid lipid is advantageous to NLCs system it will provide better drug loading capacity, the stability of system and improvement of drug solubility in the lipidic matrix. The three types of NLC include The imperfect type, amorphous type, and multiple types [32, 41, 42, 43, 44].

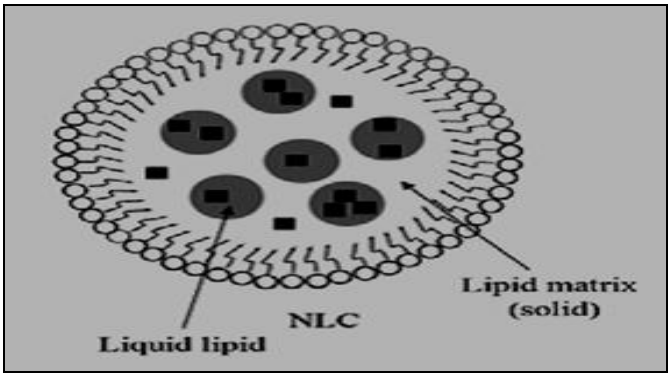


FIG. 20: SCHEMATIC REPRESENTATION OF NANOSTRUCTURED LIPID CARRIER (NLCS)

5.18. Lipid Drug Conjugates (LDC): Lipid drug conjugates were developed especially for the hydrophilic drug molecules, wherein an insoluble drug-lipid conjugate bulk is synthetically prepared either by salt formation (for example, with a fatty acid) or by covalent linking (for example, to the esters or ethers). Lipid drug conjugates bulk is then

homogenized in the presence of a stabilizer in water using high-pressure homogenization. A major problem of SLNs is the low capacity of loading hydrophilic drugs due to partitioning effects during the production process. In order to overcome this limitation, LDC nanoparticles with drug loading capacities of up to 30% have been developed. Such matrices may have potential applications in brain targeting of hydrophilic drugs in serious protozoal infections [32].

6. Characterization of LBDDS:

- Appearance
- Color, odor, taste
- Density
- pH value
- Self- dispersion and sizing of dispersion
- Droplet size and surface charge (Zeta Potential)
- Viscosity measurement
- *In-vitro* studies
- *In-vivo* studies
- *In-vitro – in-vivo* correlation
- Equilibrium phase behavior [5, 8].

CONCLUSION: Low water solubility of the drug from BCS class II and IV is extensively recognized as a reason for poor oral bioavailability. The improvement in oral bioavailability of drug by formulating in the lipid-based formulation is principally focused by a research scientist. However, the proper knowledge of drug and excipient used in the formulation is necessary to develop any lipid-based formulation. Digestion of lipid-based system and direct absorption from the lymphatic system allows lipid-based delivery most promising.

As well as improvement in bioavailability is achieved. Various techniques used to improve the stability of lipid dispersion. Wide verities of carrier available for the encapsulation of the drug, drug may be hydrophilic, lipophilic, or both.

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CONFLICTS OF INTEREST: We declare that there is no conflict of interest regarding this review article.

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