IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
September 2022 Vol.:25, Issue:2

A Review on Lipid Based Oral Formulation

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 21 August 2022
Accepted: 27 August 2022
Published: 30 September 2022

Keywords: LBDDS, Solid oral dosage form, Emulsion, Vesicular system, Lipid particulate system.

ABSTRACT

Oral route of drug administration is most convenient for self-administrations and patient friendly. However some kind of drug molecules having low solubility, severe first pass metabolism and instability in GIT make oral route of drug administration difficult. To overcome these problems, novel oral lipid based nanocarrier systems comes out with most successful ways in enhancing bioavailability and other pharmacokinetic parameters. Various oral lipid based drug delivery systems like Pickering emulsion, solid-lipid nanoparticles, Nano-lipid based carrier (NLC), SMEDDS, SEDDS, Lipospheres, Liposomes etc. has been prepared and optimized. In this paper, we try to understand the author's achievement in the formulation, development and optimization of the selected drug moiety. For these some selected research papers were studied and observed a significant enhancement in its bioavailability as well as pharmacological characteristics by evaluating various parameters like particle size, Zeta, PDI, entrapment efficiency *and In-vitro, In-vivo study* etc. Finally we concluded that as compare conventional oral, or other synthetic oral drug delivery systems lipid based drug delivery system is the most promising approach for hydrophobic drugs and mostly BCS class-II & IV class of drugs and ingredients.

INTRODUCTION

The requirement for oral delivery of medicines derives from the fact that this route is patient-friendly and the most convenient for self-administration. However, the physical features of drug molecules that exhibit low solubility, severe first-pass metabolism, and instability in the gastrointestinal tract make oral distribution of therapies difficult (GIT). Furthermore, the possibility of dosage dumping as well as inter and intrasubject variability pose a threat to their potential success(1).The majority of novel compounds found or produced through drug discovery and screening methods that have therapeutic efficacy are powerful and lipophilic in nature(2,3). Because of its hydrophobic nature, the drug's solubility and absorption are limited, as is its bioavailability for therapeutic purposes when taken orally.The use of lipids and lipophilic excipients in oral administration has received a lot of interest in the last decade (4,5).

Lipids have been used as carriers in a variety of drug delivery systems, including solutions, suspensions, emulsions, and the more appealing self-emulsifying/micro emulsifying/nanoemulsifying drug delivery systems (SEDDS/SMEDDS/SNEDDS), which are designed to increase the solubility and bioavailability of drugs in BCS Classes II–IV. SEDDS, SMEDDS, and/or SNEDDS have proven to be the most successful ways in enhancing bioavailability among numerous approaches now available to insert active pharmaceutical medicines into lipid vehicles in a range of dosage forms. The primary goal of these formulation systems (SEDDS/SMEDDS/SNEDDS) is to improve the solubility of poorly water soluble medicines by forming emulsions and/or micellar systems (colloidal solutions).

Nanotechnology has become a term among scientists, and efforts to expand its uses in medical and pharmaceutical fields are underway. Lipid-based nanocarriers, polymeric nanocarriers, inorganic nanocarriers, and drug nanoparticles or nanosuspensions are all examples of nanoscale technologies. Since the development of low energy emulsification technologies such as spontaneous or self nano emulsification, there has been a resurgence of interest in nanoemulsions within the lipid-based nanocarriers category. SNEDDS are anhydrous homogeneous liquid solutions including oil, surfactant, drug, and/or cosolvents that spontaneously form transparent nanoemulsion (20–250 nm droplet size) when diluted in water with slight agitation (35).

CONVENTIONAL ORAL SOLID DOSAGE FORM (36)

The term "conventional oral solid dosage forms" refers to solid dosage forms that are taken orally by patients and are designed to deliver the medicine to the site of action quickly.

Some common conventional solid oral dosage forms are discussed in short below in table no.1;

1. Powder and granules

2. Tablets

3. Capsule

Table no.1: Conventional Oral Solid Dosage Form;

Sr. No	Solid Oral Dosage Form	Definition	Method of Preparation	Limitations
1	Powders & Granules	Powders are dry mixes of finely separated medicinal and nonmedicinal ingredients that can be used internally or externally. Powders can be given to a patient in bulk and used to generate a douche solution, or they can be separated into single dose units and packed in folded sheets or unit-of-use envelopes.	co-milling, trituration, pulverization by intervention, and levigation.	Bulk powders or granules are not an effective way to deliver powerful medications in small doses. This is due to the fact that individual dosages are often withdrawn from the bulk using a 5 ml spoon, which is prone to fill fluctuation. Powders and granules are not appropriate for the delivery of medications that are inactivated in the

				stomach; instead, enteric-coated tablets should be used. Dispensing hygroscopic or deliquescent medications is difficult with powders and granules.
2.	Tablets	Tablets are solid dosage forms containing one or more medicinal substances with or without added pharmaceutical ingredients. A particular amount of drug material is contained in each tablet. Manufacturers frequently make several tablet or capsule strengths of a particular drug accessible to provide for dosage flexibility. A tablet may be split in half (many tablets are scored or grooved for this purpose) or more than one tablet may be consumed as a recommended dose if	wet granulation, dry granulation (roll compaction or slugging), and direct compression	When drugs need to act very fast, the disintegration of the tablet and the dissolution of the drug from the tablet might be the rate-limiting step in determining the onset of drug action.

		necessary.		
3.	Capsule	Capsules are solid dosage forms in which the pharmacological component is encased in a hard or soft dissolving shell, most often made of gelatin. The capsule may be thought of as a container drug delivery method that delivers a tasteless and odorless dosage form without the requirement for a further coating process, as is often necessary with tablets.	Simply filling of preparation in capsule. Powder compositions for encapsulation should take into account the specific filling principle involved. The filling process's formulation criteria, such as lubricity, compactibility, and fluidity, are not only necessary for a successful filling operation, but they may also impact drug release from capsules. Indeed, the different filling principles may have an impact on drug release.	Iodides, bromides, and chlorides are examples of very soluble salts that should not be administered in firm gelatin capsules. Due to the creation of a high drug concentration in limited locations, their fast release may induce stomach discomfort. Both hard gelatin capsules and tablets can get stuck in the oesophagus, causing injury due to the localized high concentration of some medications (e.g., doxycycline, potassium chloride, indomethacin).

COMPLICATION ASSOCIATED WITH CONVENTIONAL ORAL FORMULATION: (37)

Oral administration is the most prevalent method of medication delivery. It is the favored method because to benefits such as non-invasiveness, patient compliance, and medication

administration simplicity. Medication solubility, mucosal permeability, and gastrointestinal tract environment stability are all factors that influence oral drug absorption. Understanding the physicochemical, biochemical, metabolic, and biological obstacles that restrict total medication bioavailability has been the focus of efforts to overcome these constraints.

To improve oral medication absorption, many pharmaceutical technologies and drug delivery systems have been investigated, including nanocarriers, micelles, cyclodextrins, and lipid-based carriers. To that purpose, the physiological and pharmacological obstacles determining drug bioavailability for the oral route of administration, as well as traditional and innovative drug delivery techniques will be discussed.

1. Biological Barriers

pH of the GI fluid: In the fasting state, the stomach pH varies, and the median basal pH for adult males is 2.18 ± 0.18. Thus, drugs with poor stability under acidic pH need to be protected in the stomach.

Smaller surface area and thicker mucus layer (thickness, 1.5 mm) of GI track: Most orally administered medications are primarily absorbed by the duodenum and jejunum in the upper parts of the GI tract. The drug absorption ability of the stomach is less than that of the intestine because of the smaller surface area and thicker mucus layer (thickness, 1.5 mm).

The **GI transit time** is also important for developing an oral dosage form.

2. Physicochemical Barriers:

Solubility and permeability, drug metabolism can also influence their oral bioavailability.

3. Metabolic and Biochemical Barriers (37)

Digestive enzymes released by the pancreas such as lipases, amylase, and peptidases, as well as chymotrypsin and trypsin produced by the intestinal flora of the colon, which are mostly present in the lower portion of the GI tract, typically stimulate intestinal metabolism. Furthermore, enzymes residing within the brush-border membrane perform first-pass metabolism on the enterocyte surface, which encompasses intracellular and brush-border metabolism. The small intestine is where brush-border metabolism takes place. Brush-border

metabolism is aided by isomaltase, alkaline phosphatase, sucrose, and other peptidases. Oral absorption may be limited by first-pass metabolism.

STRATEGIES TO IMPROVE ORAL DRUG DELIVERY: (37)

Table no.2: strategies to improve oral drug delivery

Sr. No.	Type of System	Advantages	Limitations
1.	Metabolic polymorph Co-crystal formation	Stabilization requires only a little quantity of surfactants and polymers. High-drug loading and high-energy systems that aid in drug absorption	Medicine/polymer miscibility issues, as well as excipient compatibility for a certain drug. Storage causes physical instability.
2.	Pro-drug formation	Drug solubility, lipophilicity, and transporter-mediated absorption have all improved. Possibility of achieving site-specific delivery	Screening and development of prodrugs have limitations. Linked to an increased likelihood of degradation by-product production and a lack of chemical stability. Polymorphism and disruption of solid-state crystallinity
3.	Salt formation	The most widely used method for increasing solubility and the ideal method for developing liquid formulations. Increased the drug's apparent inherent solubility, which increased the dissolving rate. Synthesis is simple, and the cost of the raw ingredient is minimal.	It's only good for medications that are mildly acidic or basic, and it's not good for neutral pharmaceuticals. After oral delivery, the medication salt is converted back into its corresponding free acid or base forms in the GI fluid. Limitations in salt screening and choosing the best salt types
4.	Micronization and	It's simple to scale up and	It's simple to scale up and quick

	nanosized drugs, e.g., Nanocrystal, Dissocubes	saves time. Because the medication is in the crystallin solid form, there is less drug degradation. Possibilities of developing a medication in various pharmacological dose forms	to get started. Because the medication is crystallin solid, it has a lower rate of deterioration. Formulating a medicine in several pharmacological dose forms is a possibility.
5.	Solid dispersion	Added to the drug's stability and protection throughout the formulation process. It also slowed agglomeration/crystallization of medicinal molecules due to molecular level dispersion and steric hindrance interactions inside the polymeric matrix, compared to standard crystal habit modification.	The high-energy amorphous medication tends to transition to a low-energy crystalline form and recrystallize. It is necessary to have miscibility between the chosen medication and polymeric matrix. A notable disadvantage is the lack of stability.
6.	pH adjustment	The simple yet effective approach for adjusting the solubility of ionizable medicines. The drug candidate is ionized to the point where the intended drug dosage can be completely dissolved. This method works for drug salts as well as the equivalent free acid or free base medications.	The impact on the drug's long-term stability. Physiological pH is distorted. The precipitation patterns and dilution incompatibility.
7.	Co-solvent	Reduced the polarity of the solvent to provide the best solubility for nonpolar	Co-solvents are only used in a small number of solvents. The possibility of precipitation after

		medicines. When pH modification is inadequate, the introduction of a cosolvent can give extra solubilization for medication solutions.	dilution. It has the potential to change the pH and strength of the buffers in a medication formulation.
8.	Micelles	Its lipophilic medicines are stored in its hydrophobic core. Chemical alteration is simple, and it can respond to stimuli.	Micelles disintegrate following oral delivery due to dilution, resulting in in vivo instability below the threshold micelle concentration. Drug loading is minimal.
9.	Nanoparticles	Increased lipophilic drug solubility, improved drug stability, sustained drug delivery, drug cargo shielding from enzymatic activity, prolonged retention in the gastrointestinal tract, improved mucoadhesiveness, overcoming multidrug resistance, and the ability to target specific cells and uptake via M cells	Increased lipophilic drug solubility, improved drug stability, sustained drug delivery, drug cargo shielding from enzymatic activity, prolonged retention in the gastrointestinal tract, improved mucoadhesiveness, overcoming multidrug resistance, and the ability to target specific cells and uptake via M-cells
10.	Cyclodextrins	Excipient that is generally recognized as safe (GRAS). It's ideal for making supersaturated medication solutions. Drugs' physical and chemical stability, as well as their shelf life, should be improved.	To solubilize the medicine, a considerable quantity of cyclodextrin is required in comparison to the drug. The weak binding and dissociation of complexes in the GIT as a result of dilution. Intact drug/CD complexes are difficult to pass through the lipophilic epithelial

			membranes, resulting in limited bioavailability, particularly for BCS class III medicines.
11.	Lipid-based formulations (SLN, liposomes, SEDDS)	Non-immunogenic, biocompatible, stimulates the release of bile salts, phospholipids, and cholesterol, forming vesicles and micelles that aid medication absorption, scalable, and readily manufactured	Poor stability and short shelf life

Advantages of LBDDS (6)

1. Drug release in controlled and targeted way.
2. Pharmaceutical stability.
3. High and enhanced drug content (compared to other carriers).
4. Feasibilities of carrying both lipophilic and hydrophilic drugs.
5. Biodegradable and biocompatible.
6. Excipients versatility.

METHODS OF PREPARATIONS:

Spray Congealing:

Spray cooling is another name for this method. In this procedure, molten lipid is sprayed into a cooling chamber and congeals into spherical solid particles when it comes into contact with the cool air. Solid particles are gathered at the chamber's bottom and can be filled into firm gelatin capsules or compacted into tablets. In this spray cooling method, ultrasonic atomizers are typically utilized to generate solid particles. The melting point of the excipient, the

viscosity of the formulation, and the cooling air temperature within the chamber must all be taken into account in order for the droplets to solidify instantly(7,8).

Spray Drying:

This procedure is identical to the last one, but the temperature of the air within the atomizing chamber is different. The drug solution (drug in organic solution/water) is sprayed into a heated air chamber, where the organic solvent or water evaporates, resulting in solid drug microparticles. Solid carriers such as silicon dioxide can be employed in this method in addition to lipid excipients. Gelucire (lipid excipient) improves drug release by establishing hydrogen bonds with the active ingredient, resulting in stable amorphous drug solids in microparticles (7,8).

Adsorption onto Solid Carrier:

A liquid-lipid formulation is adsorbed onto a solid carrier such as silicon dioxide, calcium silicate, or magnesium aluminometa silicate in this simple and cost-effective (in terms of equipment investment) technique. In a blender, the liquid-lipid composition is combined with the carrier. The carrier should be chosen to have a higher capacity to adsorb the liquid formulation and acceptable flow properties following adsorption. Gentamicin and erythropoietin formulations containing caprylocaproyl polyoxyl glycerides (Labrasols) were efficiently transformed into solid intermediates with high bioavailability even after adsorption on carriers. Good content consistency and high lipid exposure are two advantages of this approach (9,10).

Melt Granulation:

It also called as pelletization. Pelletization is the process of converting a powder mix (including a medication) into granules or pellets. Pelletization is the process of converting a powder mix (including a medication) into granules or pellets(11,12). A meltable binder (molten state) is sprayed over the powder mix in the presence of high shear mixing in this approach. A "pump on" approach can be used to describe this procedure. Alternatively, the meltable binder is mixed with the powder mix, and the binder melts owing to particle friction (solid/semisolid) during high-shear mixing. The melted binder generates liquid bridges between powder particles and tiny granules, which under regulated circumstances change into spheronized pellets. 15–25 % of the lipid-based binder can be utilized, depending on the

fineness of the powder. Binder particle size, mixing duration, impeller speed, and binder viscosity on melting are the characteristics to consider during the process (13). Formulating melt agglomerates including solid diazepam dispersions improved diazepam dissolving rate (14). Lactose monohydrate was melt-agglomerated in a high-shear mixer with a meltable binder such as Gelucires 50/13 PEG 3000. Some of the lipid excipients employed in the melt granulation approach to generate self-microemulsifying systems are polyoxyl glycerides, partial glycerides or polysorbates, and lecithin (15).

Supercritical Fluid-Based Method:

To make solid dispersions, this approach coats medication particles with lipids. By increasing the temperature and pressure, the medication and lipid-based excipients are dissolved in an organic solvent and supercritical fluid (carbon dioxide)(16,17).A steady drop in pressure and temperature aids the coating process by lowering the solubility of the coating material in the fluid, allowing it to precipitate onto the drug particles and create a coating. This approach takes into account the solubility of the formulation components in the supercritical fluid as well as the stability of the material during the procedure (18,19).

Other Formulation Tools:

A simple and effective diagnostic test is the analysis of drug solubilization in bile salt-lecithin mixed micelles. In rare circumstances, spectrophotometry or HPLC can be used to determine drug solubilization directly. This method can quickly determine if a medicine is likely to be soluble in the gut lumen. The solubility enhancement ratio of steroids is an excellent example of how the octanol water partition coefficient alone cannot predict solubilization. As computational power improves, molecular dynamics modelling may become a helpful formulation tool. Similar methods and partitioning experiments might be used to investigate the structure of lipid formulations(20).

CLASSIFICATION OF LIPID BASED DRUG DELIVERY SYSTEM (21)

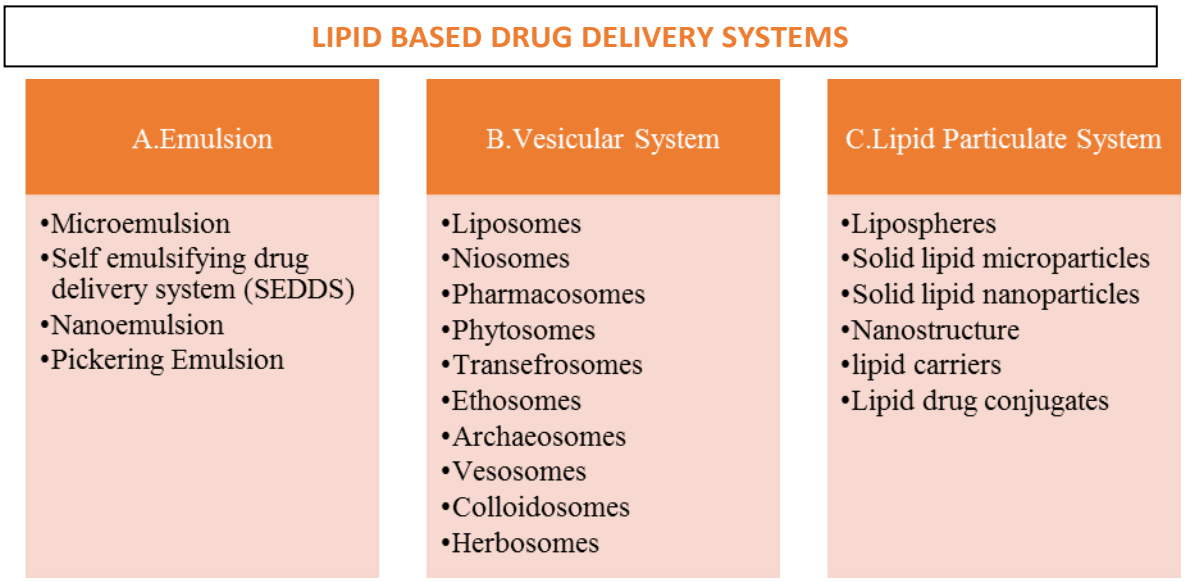

Figure no.1: classification of lipid based drug delivery system.

PICKERING EMULSION:

Pickering emulsions are emulsions without surfactants that are stabilized by solid particles. Pickering emulsions exhibit good physical stability, notably great resistance to coalescence, thanks to the practically irreversible adsorption of solid particles at the oil-water interface, which creates an efficient steric barrier. The majority of Pickering emulsion research has been done on model systems based on synthetic, inorganic materials, but the information gained suggests a wide range of possible applications in food, cosmetics, and medicines. The increased number of linked scientific publications in recent years demonstrates that food-grade particles are gaining popularity. The major goal of Pickering emulsion research is to improve emulsion physical stability. Additionally, better chemical stability and enhanced usefulness (e.g., unique texture, targeted administration in the gastrointestinal system) have been reported. Pickering emulsions may also be an appealing option for cosmetic and medicinal applications where surfactants frequently have unwanted effects (e.g. irritancy and hemolytic activity.(22)

To improve the oral bioavailability of puerarin, an oral drug nanocrystals self-stabilized Pickering emulsion (NSSPE) was developed by **(Zhang *et al.*, 2018)**, which used nanocrystals of a poorly soluble ingredient from Puerariae Radix called puerarin as solid particle stabilizers and Ligusticum chuanxiong essential oil as the main oil phase. During a

six-month storage period at 4, 25, and 40 degrees Celsius, the appearance of emulsions, the size and zeta potential of droplets, and the concentration of puerarin in the emulsified layer were studied. The stability of centrifugation at 4000 g was also investigated. A scanning electron microscope (SEM), confocal laser scanning microscopy (CLSM), a fluorescence microscope (FM), and differential scanning calorimetry were used to examine the microstructure of emulsion droplets (DSC). In rats, the in vivo oral bioavailability of puerarin NSSPE was studied. After centrifugation at 4000 g for 15 minutes or storage for six months at 4, 25, and 40 degrees Celsius, the appearances of puerarin NSSPE remained unchanged. The puerarin NSSPE exhibited a stable core-shell structure of emulsion droplets created by the adsorption of puerarin nanocrystals on the surface of oil droplets of mixed oil of Ligusticum chuanxiong essential oil and Labrafil M 1944 CS (9:1, v/v) as shown by SEM, CLSM, FM, and DSC. The bioavailability of puerarin NSSPE in comparison to puerarin coarse powder suspension, nanocrystal suspension, and surfactant emulsion was 262.43%, 155.92%, and 223.65%, respectively. All of these findings suggested that puerarin nanocrystals could stabilize Pickering emulsion of Ligusticum chuanxiong essential oil without the use of any other stabilizers, and Pickering emulsion could improve puerarin oral bioavailability, implying that the drug nanocrystal self-stabilized Pickering emulsion could be a promising oral drug delivery system for Traditional Chinese Medicine containing poorly soluble ingredients and volatile oils.(23)

SOLID LIPID NANOPARTICLES:

Solid Lipid nanoparticles are the novel nano formulation and an alternative carrier to colloidal or other Conventional systems. for the controlled and targeted delivery. This are 50-1000 nm in size and are formulate by using biocompatible and biodegradable materials which having capacity to incorporate the lipophilic as well as hydrophilic drugs. SLN achieved a great choice over other conventional formulations, because of its better drug stability, high drug loading capacity, Negligible use of organic solvent.(24)

Gilani, S. J. *et al.* (2021) study on Apigenin (APG) solid lipid nanoparticle asan alternative preparation for rheumatoid arthritis. There are several synthetic NSAIDs, glucocorticoids and biological drugs that are commonly used to treat arthritis, but this synthetic drugs sometime shows severe life threatening side effects. Apigenin is an bioactive compound is poorly water soluble compound and having wide range of pharmacological activities. The author in this study prepared the apigenin loaded solid lipid nanoparticle. For the preparation an author

select the Glyceryl mono stearate as a solid lipid because of its high compatibility and better drug entrapment efficiency, and d-∝ -Tocopheryl/ polyethylene glycol 1000 succinate (TPGS) as a surfactant, this TPG plays an important note in drug loading and particle size of SLN's.

The main objective of the study is that to enhance the drug release, to study the permeation and mucoadhesive study. To achieve this aim, the Apigenin SLN is further coated with 0.1% w/v chitosan (APG – CH- SLN) and shows better result in the drug release, permeation and mucoadhesive study, but increase in particle size, PDI, Zeta.

The formula can be optimized by using 3 level Box- Beckman design by GMS, TPGS, and sonication time as independent variables and particle size and entrapment efficiency as dependent variable.

The APG- SLN were prepared by melt emulsification and ultra-sonication method with slide modification and subjected to further characterization. It shows higher antioxidant activity with APG- SLN and pure APG. Finally author observed a marked enhancement in the anti-arthritic as well as biochemical parameters by using Paw Edema Study, Writhing Study on rat model.(24)

Nano-lipid Carriers (NLCs):

Nano-lipid carriers (NLCs) were designed to fix the drawbacks of SLNs. An organized structure of SLNs was replaced with an unstructured matrix comprised of a combination of solid and liquid lipids to increase carrier characteristics. The drug is immobilized by a hybrid particle core, which prevents it from escaping from the carrier. Furthermore, compared to SLNs, the fluidity of oil droplets improves drug loading capacity. It's also been proposed that having a liquid lipid helps emulsification because heat energy is dispersed more uniformly throughout the melted lipid. Three types of NLCs may be recognized based on how pharmaceuticals are encapsulated in NLCs. An unsatisfactory crystal model (NLC type I) is made up of a variety of lipids in various shapes, and an ordered structure cannot be obtained. A framework with flaws allows active agents to be encapsulated. It is made by combining a little amount of oils with solid lipids. Combining particular kinds of lipids like hydroxy octacosanyl hydroxy stearate and isopropyl myristate results in an amorphous model (NLC type II). Because these lipids do not recrystallize, drug evacuation is prevented. Because they are converted into the polymorphic form, lipids remain solid. To boost the loading capacity of

agents with greater solubility in liquid lipids than in solid ones, a multiple model (NLC type III) is developed. A small compartment of oil is produced in a matrix of solid lipids during the formulation process. The release mechanism is restricted because the oil contains more medicine and there is a barrier in the form of solid lipids encapsulating oil droplets (Muller et al., 2002a). Figure 10.1 depicts the NLC type schemes.(25)

Using glyceryl monostearate and Capmul MCM C8 as solid and liquid lipids, **Shah, N. V. *et al.* (2016)** attempted to manufacture Raloxifene (RLX) loaded NLCs using the solvent diffusion approach. The influence of two independent variable, the solid lipid to liquid lipid ratio and the stabilizer concentration, on the entrapment efficiency of manufactured NLCs was investigated using a complete 3*2 factorial design. When the liquid lipid percentage in the formulation was raised from 5% w/w to 15% w/w, statistical analysis revealed a significant increase in entrapment efficiency. The change of RLX from crystalline to amorphous form was demonstrated by solid-state characterization investigations (DSC and XRD) in the optimized formulation NLC-8. The optimized formulation had an average particle size of 32.50 5.12 nm and a zeta potential of 12.8 3.2 mV, indicating high stability of NLC dispersion. In vitro release testing revealed burst release during the first 8 hours, followed by steady release for the next 36 hours. Smooth surface discrete spherical nano sized particles were verified using TEM. To get a definitive conclusion, an in vivo pharmacokinetic investigation was conducted, which revealed that improved NLCs formulations had 3.75-fold higher bioavailability than plain drug solution. These findings indicated that NLCs have the potential to significantly increase the oral bioavailability of poorly soluble RLX.(26)

SOLID SELF MICROEMULSIFYING DRUG DELIVEERY SYSTEM (SMEDDS):

In recent years, lipid-based preparations have received a lot of interest, with a particular focus on the self-micro emulsifying drug-delivery system (SMEDDS). Poor bioavailability is a major hurdle in developing an oral dose form. Because a medicine cannot be absorbed via the GI tract until it is in the solution form, reduced aqueous solubility is one of the key difficulties for bioavailability in this context. Aqueous solubility is a problem for many chemical compounds with notable and favorable pharmacological effects. Furthermore, almost 30% of widely marketed medicinal entities and nearly 50% of new drug compounds accessible for product manufacture are lipophilic in nature and lack aqueous phase solubility. Class II medications, according to the biopharmaceutical categorization system (BCS), have

low solubility but high permeability. Class IV medicines, on the other hand, have lower solubility and permeability when utilized to distribute across the GI membrane. Both kinds of medicines, however, have an uneven absorption pattern and limited oral bioavailability. However, numerous strategies are thought to promote medication solubility and absorption, including solid dispersions, crystal habit adjustment, particle size reduction, solid solution production, and salt synthesis. In addition, a variety of additional ways are being used such as supercritical fluid technique, incorporation of emulsifiers, solubilizing agents, cosolvent, and numerous other excipients to increase bioactive solubility.(27)

In recent years, lipid-based carrier systems have gained popularity as a way to improve the bioavailability of medications that are less soluble in water. The main purpose of this formulation is to keep the lipophilic chemicals in solution throughout the gastrointestinal system. Furthermore, lipid-based carriers come in a variety of forms, including emulsions, microemulsions, solutions, suspensions, self-emulsifying drug delivery systems (SEDDS), and dry emulsions. SEDDS's ability to incorporate lipophilic drugs (e.g., cyclosporine A in microemulsion) was previously reported. Unlike lipophilic compounds, which have limited absorption, the SEDDS is focusing more on designing these medications for oral delivery (Shah et al., 1994). *Pouton et al* also presented a simple lipid formulation classification system in the year 2000. (LFCS). *Pouton et al* modified it again in the year 2006. The SEDDS (type II) has been described in LFCS as an isotropic combination of oil and/or surfactant (s). However, when this mix comes into contact with the aqueous phase in the gastrointestinal domain, it generates an oil-in-water (O/W) emulsion spontaneously after only a little agitation. In addition, the word SEDDS has been shortened to SMEDDS and self-nanoemulsifying drug-delivery system (SNEDDS), sometimes known as type IIIA or IIIB.(27)

In this study **Singh, Dilpreet *et al.* (2020)** describe significant improvement in biopharmaceutical properties of Canagliflozin an Antidiabetic BCS class-2 drug in solid SMEDDs formulation.

For this an author select the optimized concentration of Lauroglycol FCC (Nonionic water insoluble surfactant) 320mg, Tween-80 (Nonionic surfactants) 1200mg & Transcutol P (Skin permeation enhancer) 480mg. This all ingredients were mixed under stirring to form homogenous blend then Canagliflozin was incorporated into it to form liquid SMEDDS. This liquid SMEDDS was spray dried using hydrophobic adsorbent Neusilin US2 with objective

to attain stable and acceptable nano-particulate formulation and to overcome the limitation of conventional adsorption technique.

The main aim of the study is to enhance oral bioavailability and antidiabetic activity of CF2 and it can be proved by studying various biopharmaceutical and antidiabetic attributes. The results shows that after oral administration of optimized solid SMEDDS in rats has relative bioavailability (%) is 172.54+- 24.56, it quit better than other marketed preparation.

UGE study can also conducted for T2DM in rats to compare excretion levels of glucose treated with various CF2 loaded formulation. Control and diabetic group observed with negligible and minimal glucose excretion resp. Authors observation on tested formulation indicated moderate glucose excretion due to poor aqueous solubility and permeability. However, solid SMEDDS formulation facilitated enhanced urinary glucose concentration through kidney ($P<0.05$) as compare to pure drug and marketed product. The urine volume was also observed to be enhanced and found directly proportional to urine glucose concentration in diabetics rats.

Based on this study an author concluded that ratified spray dried lipid based formulation of CF2 as one of the promising alternatives for oral delivery with suitable translational potential. (28)

SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS):

An isotropic combination of oil, surfactant, co-surfactant, and the drug material is termed as a self-emulsifying drug delivery system (SEDDS). When mixed with water, the system produces fine colloidal droplets with a large surface area. This often speeds up lipid formulation digestion, enhances absorption, and lowers dietary impact and inter-subject variability. Because the free energy required to generate the microemulsion is either minimal and positive or negative, the self-emulsification process happens spontaneously. The lipid/surfactant pair, the surfactant concentration, and the lipid/surfactant ratio all play a role in the self-emulsification process. Only certain combinations, however, can result in an effective self-emulsifying system. This formulation strategy is ideal for drug compounds with acceptable solubility in lipid/surfactant blends. The addition of surfactants in the formulations leads to a more uniform and consistent bioavailability, as observed with cyclosporine, making the SEDDS preferable to lipid solutions.(29)

The possibility of employing SEDDS as an efficient approach for the oral distribution of hydrophobic nevirapine was noted by **Chudasama, A. *et al.* (2011)**. SEDDS might be a useful formulation strategy for enhancing oral bioavailability of medications with low water solubility, as almost 40% of pharmaceuticals are hydrophobic. For oral delivery, a SEDDS comprising the weakly water-soluble medication nevirapine was developed. Solubility studies, pseudo-ternary phase diagram building, and droplet size analyses were used to determine the components and their ratio ranges for the formulation of SEDDS. The optimal SEDDS formulation had 8.56 % Caprylic acid as oil, 74.50 % Soluphor P as surfactant, and 16.93 % Transcutol P as cosurfactant, resulting in adequate drug loading, quick self-emulsification in aqueous medium, and droplet sizes in the microemulsion range. The created nevirapine SEDDS formulation has higher diffusion and intestinal permeability than the commercial solution, according to our findings. The findings revealed that the produced nevirapine SEDDS might generate a tiny microemulsion, potentially enhancing drug accumulation in Peyer's patch and lymphatic transport. The new formulation should be a welcome addition to the clinical arsenal for attaining higher therapeutic concentrations of nevirapine in lymphoid organs and successful viral load reduction in HIV infected patients.(30)

LIPOSPHERE:

Lipospheres are a fat-based encapsulating method used to deliver bioactive substances via parenteral and topical routes (1–12). Lipospheres are solid microparticles that disperse in water and have a diameter of 0.1 to 100 mm. These are made up of a solid hydrophobic fat core (triglycerides) that is stabilized by phospholipid molecules embedded in the surface. The bioactive chemical is dissolved or disseminated in the solid fat matrix in the interior core. The liposphere system has been utilized to administer anti-inflammatory chemicals, local anesthetics, antibiotics, and anticancer medicines under controlled conditions. They've also been utilized effectively as vaccine and adjuvant carriers (2–5). Lipospheres have recently been employed for peptide delivery and oral medication administration (10,11). There have been reports of similar systems based on solid fats and phospholipids (13,14). When phospholipid is utilized, solid lipid nanospheres are basically nanosized lipospheres (14).

Lipospheres offer various benefits over emulsions, liposomes, and microspheres as delivery mechanisms. Better physical stability, low cost of ingredients, ease of preparation and scale-up, high dispersibility in an aqueous medium, high entrapment of hydrophobic drugs,

controlled particle size, and extended release of entrapped drug after a single injection, which can last from a few hours to several days, are just a few of the benefits of using liposphères.(31)

An **Rasul, A. *et al.* (2021)** developed and improved controlled release liposphères (LS) made of safe biocompatible behenic acid (BA) was done to improve patient compliance against chronic diabetes, as well as to overcome the shortcomings of standard medication delivery systems. The Box-Behnken design (BBD) was used to statistically assess the influence of formulation factors on percentage yield (Y1), entrapment efficiency (Y2), and SG-release (Y3) from saxagliptin (SG) loaded LS, and the optimized LS was compared to a commercially available SG brand. DSC and FTIR compatibility studies revealed that no formulation components interact with SG, although p-XRD showed a minor transition of the crystalline drug to its amorphous form during the encapsulation procedure. The LS was simply formed as a spherical, free flowing smooth surface with a zeta potential of -32 mV and a size range of 11-20 m. The data collected for Y1 (30-80%), Y2 (30-70%), and Y3 (40-90%) demonstrated the best match using a quadratic model. In comparison to the commercial brand of SG (99:66 2:97 ng/mL and 3:55 2:18 h), the pharmacokinetics investigation of LS revealed a substantially lower C-max of SG (75:63 3:85) with a suitably high T-max (10.53 h). Higher levels of half-life, mean residence time (MRT), and AUC0-24 for SG released from LS were most likely responsible for the increased bioavailability of SG. Finally, the new strategy of SG-loaded LS was successful in maintaining plasma SG levels for a long period without raising C-max, resulting in effective chronic diabetes control. (32)

LIPOSOMES:

Oral liposomes have showed potential as a delivery system for a variety of medicinal compounds. Liposomes can protect labile peptides in the GI tract and improve lipophilic agent solubility by forming mixed micelle structures with bile salts, however research on the relevance of oral liposomes for low-permeability nonpeptidic medicines is limited. In addition, the impact of liposomal features such as lipid composition, size, surface charge, L/D ratio, and PEGylation on in vivo oral bioavailability of medicines have not been thoroughly studied. In this context, we endeavored to investigate the impact of various formulation characteristics on oral absorption of Dox, a low permeability hydrophilic medication, with the goal of determining the best formulation qualities for improved oral bioavailability.(33)

In this study, **Daeihamed, M. *et al.* (2017)**the effects of liposome characteristics on oral absorption of doxorubicin (Dox), as a hydrophilic low-permeability drug, were investigated.

Several Doxorubicin loaded liposomes were produced using the transmembrane ammonium sulphate gradient technique. (The Dox aglycone metabolite was made by moderate acid hydrolysis of Dox, which involved heating the medication dissolved in 2 mL of 1% HCl solution at 65°C for 6 hours. The product was cleaned, dried, and dissolved in DMSO again. Liquid chromatography–mass spectrometry was used to validate the metabolite's production.) To create unilamellar vesicles of the necessary size, the vesicles were prepared using a thin-film hydration process then shrunk using an extrusion technique.

In vitro and *in vivo* experiments were conducted to determine the impact of various liposomal formulation parameters (main lipid composition, particle size, L/D molar ratio, PEG density, and potential magnitude) on Dox oral absorption as a low-permeability nonpeptidic medication. Oral absorption was not improved by increasing phospholipid fluidity. In terms of particle size, as compared to 120nm particles, increasing particle size to 400 and 800 nm or further reducing liposomal size to 80 nm resulted in a significant drop in Dox oral bioavailability. For the first time, the effects of potential magnitude and L/D molar ratio on oral absorption were established. The findings demonstrated that a slight rise in potential will aid oral absorption the most, and that oral absorption of Dox-loaded liposomes is notably L/D dependent. Liposomes with an L/D molar ratio of 10 and a primary lipid of DSPC, 25–30% Chol, and a lesser proportion (5%) of positively charged lipid significantly enhanced Dox oral bioavailability. The internalization and transport of the optimal liposomes in Caco-2 cells was greater than that of the solution, suggesting that endocytosis is an energy-dependent process involving caveolae- and clathrin-dependent endocytosis.(34)

SUMMARY:

Table no.3: Summary

Sr. no.	LBDDS	Chemotherapeutic Agent	Lipid used	Method of preparation	Observation	Reference
1.	Pickering Emulsion	Puerarin (Puerariae Radix)	Ligusticum chuanxiong essential oil	High pressure homogenization method	Self- stabilized Pickering emulsion by hydrophilic Puerarin with Ligusticum chuanxiong essential oil as lipid shows improved oral bioavailability of Puerarin.	**Zhang et al., 2018** (23)
2.	Solid Lipid Nanoparticles	Apigenin (APG)	Glyceryl mono stearate (GMS)	Melt Emulsification And Ultra-Sonication Method	Solid lipid nanoparticle by using glyceryl monostearate as solid lipid and Apigenin as active ingredient was prepared by melt emulsification and ultra-sonication method. It shows significant enhancement in pharmacokinetic study and comes as an alternative to synthetic oral delivery systems.	**Gilani, S. J. et al. (2021)** (24)
3.	Nano-lipid Carriers (NLCs)	Raloxifene (RLX)	Glyceryl monostearate and Capmul MCM C8	Solvent diffusion method	It was observed that improved NLCs formulations had 3.75-fold higher bioavailability than plain drug solution. These findings indicated	**Shah, N. V. et al. (2016)** (26)

					that NLCs have the potential to significantly increase the oral bioavailability of poorly soluble Raloxifene (RLX)	
4.	SMEDDS	Canagliflozin	Lauroglycol FCC (also act as co-surfactant)	Spray dry method	It was observed that mark enhancement in biopharmaceutical properties of Canagliflozin in solid SMEDD preparation.	**Singh, Dilpreet et al. (2020)** (28)
5.	SEDDS	Nevirapine	Caprylic acid	Melt Emulsification	Nevirapine in SEDDS shows higher *ex-vivo* intestinal permeability than the marketed conventional suspension.	**Chudasama, A. et al. (2011**) (30)
6.	Lipospheres	Saxagliptin	Behenic acid	Hot Emulsion Congealing Technique	In comparison to the commercial brand of SG (99:66 2:97 ng/mL and 3:55 2:18 h), the pharmacokinetics investigation of LS revealed a substantially lower Cmax of SG (75:63 3:85) with a suitably high Tmax (10.53 h). Higher levels of half-life, mean residence time (MRT), and AUC0-24 for SG released from LS were most likely responsible	**Rasul, A. et al. (2021)** (32)

					for the increased bioavailability of SG. Finally, the new strategy of SG-loaded LS was successful in maintaining plasma Saxagliptin levels for a long period without raising C-max, resulting in effective chronic diabetes control	
7.	Liposomes	Doxorubicin	Distearoylphosphatidylcholine, phosphatidylcholine, ;dipalmitoylphosphatidylcholine, 1,2-dioleoyl-3-trimethylammonium-propan, distearoylphosphatidylglycerol, distearoylphosphatidylethanolamine PEG 2000,	Transmembrane ammonium sulfate gradient method. vesicles were prepared by thin-film hydration method and downsized by extrusion technique	Liposomes containing Distearoylphosphatidylcholine (DSPC) as the major lipid, Cholesterol, and 5% positively charged lipid, with an L/D molar ratio of 10, significantly enhanced Doxorubicine oral bioavailability.	**Daeihamed, M. et al. (2017)** (34)

CONCLUSION:

As stated in this review, a substantial amount of study has been completed. Lipid based nanocarrier as well tolerated carrier has been concluded. For both research and clinical application, lipid based nanomedicine has demonstrated significant therapeutic promise to treat a number of disorders. The parameters such as particle size, shape and entrapment efficiency as well as drug release behavior pattern may be customized using physicochemical characteristics of drug and lipids. The quality, stability and release kinetics of product are all controlled by formulation's characterization. Because of their reduced size, these lipids based drug delivery systems and there derivatives conjugated with hydrophobic drug moieties have been discovered to have a longar circulation duration in blood and less absorption by the reticuloendothelial system (RES).

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