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Drug Phospholipid Complexation as an Effcient Lipophilic Nan approach for Delivery of BCS Class III/IV Drugs.

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ABSTRACT: One of the best methods for increasing the BA of oral poorly absorbed plant parts is through the use of phospholipid (PL) complexes. However, the PLs are to blame for the drug's slow breakdown and stickiness. Drug phospholipid complex (DPC) maintained the complexed state with PLs while enhancing the permeability and solubility of BCS class III/IV drugs, thereby increasing their oral bioavailability (BA). In contrast to BCS class IV drugs, which in both cases either solubility or permeability can ultimately lower the BA of drug candidates, BCS class III drugs are highly soluble and less permeable, allowing them to excrete out of the system with partial absorption. To get around this issue, we looked at how PL complexation with the drug and lipid nanocarrier (LNC) can improve total BA and modulate the permeability of BCS class III/IV drugs. The effectiveness of drugs delivered through the mouth could be enhanced by nanomedicine. Oral administration of certain vitamins and anticancer drugs can benefit from improved solubility, chemical stability, epithelium permeability and BA, half-life, nidus targeting, and fewer side effects by using LNC. Self-emulsifying drug delivery systems (SEDDSs), nanoemulsions (NE), microemulsions (ME), solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are all examples of these LNCs. DPC leads as an efficient LNC with more lipophilic properties and the potential to modulate the BA of drugs that are less permeable.

KEYWORDS: Drug phospholipid complexation, BCS Class III/IV, Lipid Nanocarrier, Oral delivery, Permeation enhancement.

I. INTRODUCTION

Most of the drugs are ingested orally and its BA and pharmacokinetics profile are altogether affected by their capacity to break up in a fluid medium. Oral medication administration is the most common method because it has a high rate of patient compliance and is also economical. However, oral dosage forms cannot be made because of their low BA. The primary factors that contribute to medicines' poor oral BA are poor plasma membrane permeation coefficient and poor solubility [1]. This is because PL complexes have gained more attention and become effective strategies among others that have been studied till now for the improvement of poorly absorbed drug's oral BA. The majority of studies have demonstrated that PLs have significance in improving the drug's aqueous solubility and intestinal epithelial permeation. The sticky nature of PLs, on the other hand, causes the PL complex to tend to cluster and agglomerate. Even though the PL complex may help pharmaceuticals dissolve better when compared to free drugs, this disadvantage makes it harder for drugs to dissolve and be absorbed through the mouth [2]. As a result, the selection of the appropriate carriers needs to spread the PL complex and enhance the drug's absorption. PLs, are the main building blocks of cell membranes. The primary PL was found in 1847 by a French drug specialist and scientist named Theodore Nicolas Gobley in the chicken egg yolk's phosphatidylcholine [3]. Lipid-based drug delivery systems (LDDS) has unique characteristics that can be altered by varying the proportions of non-APIs and lipid excipients. Most lipid drug conveyance frameworks are efficacious as medication wholesalers because of their high security, huge transporter limit, capacity to integrate hydrophilic and hydrophobic substances, and an assortment of conveyance techniques, including oral, skin, parenteral, and pneumonic courses. As conveyance frameworks for prescriptions with low water dissolvability, lipids stand out. The headway of lipid-integrated formulations for drug transport has been assisted by their capacity with facilitating oral BA [5]. The lipophobic head contains the adversely charged phosphate bunch, which may likewise incorporate

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other polar gatherings. These new lipid excipients have respectable safety and regulatory characteristics [4]. The hydrophobic tail typically has chains of long fatty acids and hydrocarbons. They create a wide range of formations in the water based on their distinctive characteristics. Micelles are organized as lipid bilayers, with the lipophobic head bunch confronting the water on the two sides and the hydrophobic tails arranged against each other. More than half of the lipids in cellular membranes are composed of glycerol-containing PLs, which are the most common component of liposome formulation. From phosphatidic acid come these. PLs from soya, basically phosphatidylcholine (PC), are the most broadly utilized lipid stage parts for the creation of liposomes and phytochromes [6]. It is feasible to additionally esterify one of the Gracious gatherings of the phosphoric corrosive to different natural alcohols, like glycerol, choline, ethanolamine, serine, and inositol [7]. PLs such as Soybean phosphatidylcholine (SPC) have for quite some time been utilized in medication because of their low harmfulness, metabolic movement, biodegradability, and biocompatibility in contrast with fake other options, are a suitable candidate for the production of drug delivery systems due to their numerous characteristics. PC is miscible in both oil and water [8]. When taken orally, lipid climate is greatly assimilated. Between the phytoconstituent (PCS) group of hydroxyls and the phosphate group of another head of PC, choline, in its two polar and non-polar regions, an H-band is made. Lecithin is a fatty substance with a brownish-yellow color that is composed of phosphoric acid, PLs, and triglycerides like glycolipids. It can be found in animal or plant tissue. The chemical connection that exists between PCSs and the PC H-band has improved the physical stability of phytosomes. This works on the ingestion of hydrophilic polar PCSs, Lecithin is delivered synthetically from sunflower, cottonseed, rapeseed, eggs, milk, soybeans, and marine sources. Lecithin can lubricate and emulsify [10]. Additional reasons for limited BA include the presence of using compounds, a siphon P-GP that results in the expulsion of naked medications, and natural pH-interceded debasement. Delivery vehicles are essential for drugs to enter into GIT. PL-drug complexes (DPC), in which the absorption takes place by triglycerides [11]. The DPC is also absorbed by the body, like how enterocytes naturally absorb PLs. Two unsaturated fat chains are joined basically to a diacylglycerol (glycerol) moiety in the PL. As a result of this degradation, fatty acids are released, which lead to the PL being absorbed. The drug and diacyl glycerol combination hydrolyzes as well when taken via the oral route. Drug-diacyl glycerol is hydrolyzed in the digestive system, delivering unsaturated fats and medication monoacyl glycerol all the while, as phospholipases, explicitly phospholipase A2, are present [12]. At a pH of 1.5 or less, some hydrolysis occurs in the stomach, however, most of it starts in the duodenum, where juicy discharges from the liver, bile bladder, and following, bile salts, the micellar vehicles formed. The hormone cholecystokinin (CCK) regulates the process by which the bile must be excreted into the duodenum for these micelles to form. CCK is delivered when fatty oils and diacyl-glycerol PLs are hydrolyzed, bringing about a more noteworthy convergence of greasy acids [13]. In any case, enterocytes latently diffuse Medication monoacyl PL vesicles into cells following hydrolysis after the little hydrolysis that takes place in the stomach frequently results in the delivery of unsaturated fat. The medications' regular diglycerides and drug-monoacyl PLs are changed by compounds in the smooth endoplasmic reticulum of enterocytes into fatty oils and diacyl PLs, separately. After the chylomicron leaves the enterocyte by means of exocytosis through the basal film and joins the PL vesicle in the Golgi contraption to frame a creating chylomicron, it is shipped out of the stomach by the lacteal (lymph fine) [14]. The drug complex is conveyed into the circulatory framework by the chylomicrons at the convergence of the left subclavian vein and the thoracic channel [15].

II. ORAL DELIVERY SYSTEM

Oral administration is frequently the most efficient method when bioactive agents have preventative action and patient compliance is crucial. Rather, the harsh environment of the GIT can make oral bioactive agents less soluble, stable, and absorbed [16]. Substance and enzymatic corruption, the GI film forestalling pervasion into the foundational course, and particles with low water solvency not promptly dissolving in the GI parcel are only a couple of the variables that lessen the sum that can be consumed and also their BA [17].

The degree and rate at which a functioning build is ingested from an item and opens up at the objective site are alluded to as BA, which is a huge pharmacokinetic boundary. On proper absorption in body, vitamins and other bioactive nutrients can be effective. To expand assimilation and BA, past

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scientists have grown refined definitions that give controlled discharge during processing, shield the dynamic fixings from debasement, and further develop actual soundness [18]. Utilizing prodrugs, permeability enhancers, solid dispersion, polymeric complexes, and molecular encapsulation can increase oral BA [19]. Colloidal delivery systems have nano- or micron-sized encapsulation formulations that can also enhance oral bioactive agent BA and absorption. Drug plans in the nanometric range have preferable pharmacokinetics over those in the micrometer range because more modest transporters have viable surface regions [20]. The increased surface area improves the active agents' BA and dissolution rate.

Nanoformulations placed increment assimilation by working with enterocyte take-up. To diminish the portion, there is proof that nanocarriers structure a defensive safeguard that keeps up with their strength in the gastrointestinal plot [21]. Furthermore, a large number of synthetic compounds, including little particle drugs, cell reinforcements, supplements, nutrients, peptides, proteins, antibodies, and RNAs, can be conveyed using nanocarriers [22]. Nanocrystals, nanoparticles (polymeric, silica), dendrimers, nanotubes, liposomes, and have all improved their oral BA.

The utilization of lipid nanocarriers (LNC) can tackle the issue of low BA for poorly aqueous oral drugs. Excipients of lipid nanoparticles (LNP), such as surfactants or emulsifiers, can also improve BA [23]. Examples of these nano-delivery systems that, when administered orally, encapsulate bioactive compounds and enhance their dissolution and BA include self-emulsifying drug delivery systems (SEDDSs), nanoemulsions (NE), ME, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) (Figure 1). Improved pharmacokinetic boundaries and biocompatibility, diminished harmfulness, and simplicity of scale-up for modern creation are benefits of LNP given their lipid dissolvability and nanoparticle-like properties [24]. The enzymatic hydrolysis of the fatty oil lipid at the lipid-water interface, the scattering of the bioactive item into the ingested structure, and the scattering of fat globules into an emulsion with a high surface region are parts of their processing [25]. Using lipid-based nanosystems to encapsulate drugs or bioactive agents can also minimize the effect on absorption and subject variability because of their controlled release.

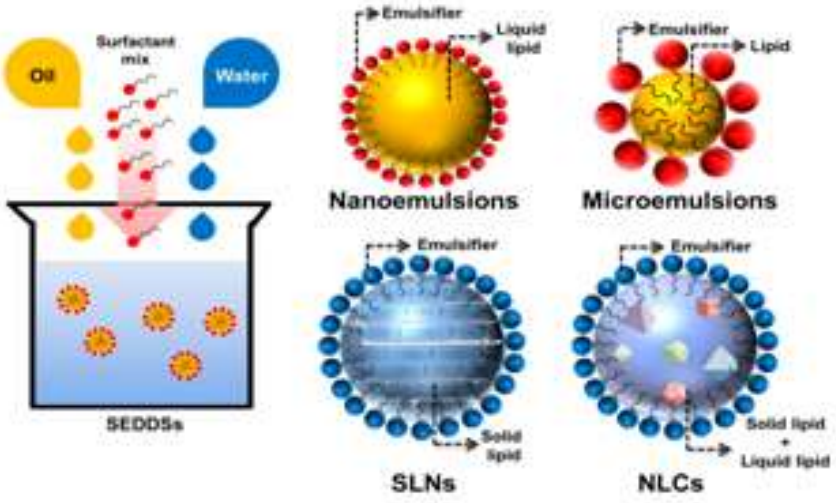

Figure 1. Lipid-based nanoparticle structures.

Through a variety of mechanisms, LNP can increase the BA of bioactive agents taken orally. First, the inclusion of lipids within LNP enhances solubility and speeds up the dissolution of lipid nanoparticles. Lipids can cause biliary and pancreatic secretion to be activated, which aids in lipid digestion [26]. Lipid nanosystems' adhesiveness prolongs the bioactive molecules' presence in the gastrointestinal tract, thereby increasing their absorption. Peyer's patches, for

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instance, deliver LNP by targeting gut-sac lymphoid tissue and allowing M cells to absorb them. Due to the avoidance of first-pass metabolism hepatic metabolism, lipids having higher solubility in triglycerides undergo lymphatic transport, which results in increased BA [27]. From the intestinal epithelium Intestinal permeability is also increased by their capacity to prevent P-glycoprotein (P-gp) efflux [28]. Previous research [29–32] has demonstrated that lipid-based nanoparticles easily penetrate the cells of the gastric and intestinal epithelium on a molecular or cellular level. Various pathways, such as clathrin-mediated endocytosis, macropinocytosis, and lipid raft-dependent endocytosis, can be involved in the transport of LNP into epithelium cells [33]. As a result, there are several ways that lipid-based delivery systems can make oral bioactive agents more bioavailable (Figure 2).

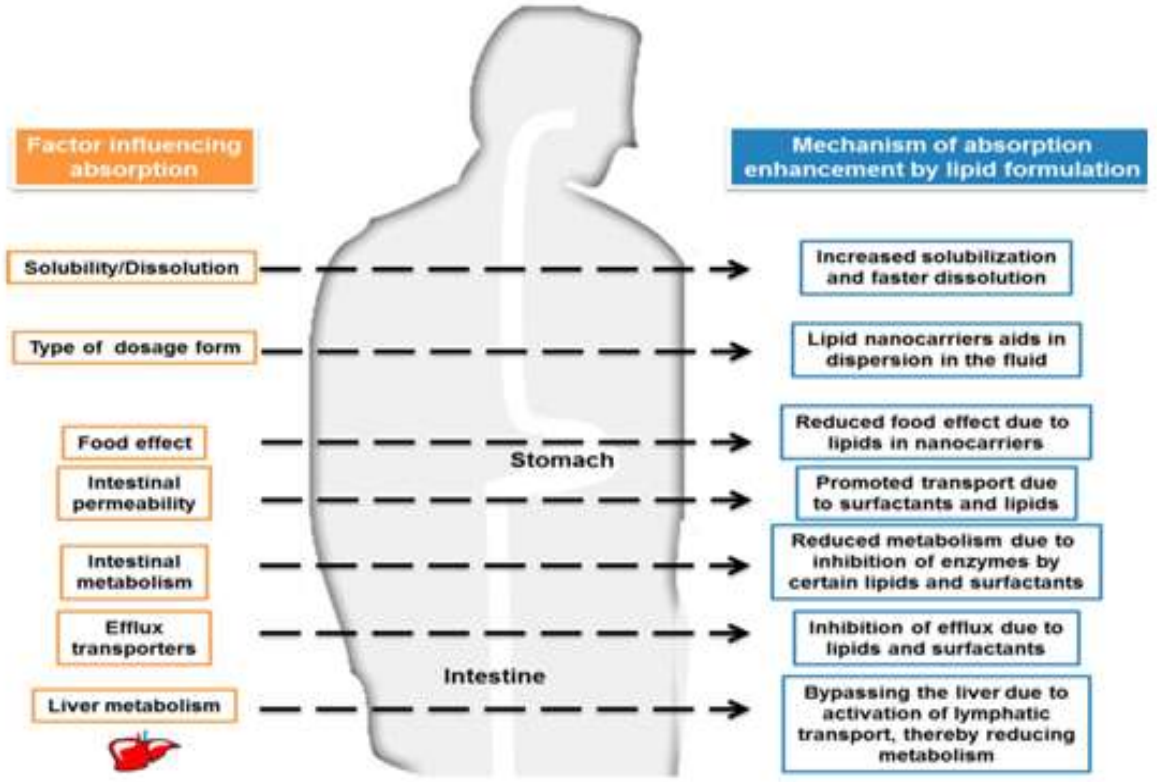

Figure 2. Lipid-based delivery systems have the potential to improve vitamin BA in a variety of ways.

Lipid-based nano-approached formulations consist of hydrophilic solvents, emulsifiers, co-emulsifiers, and lipids. Long, medium, and short triglycerides (LCTs, MCTs, and SCTs) can be used to make a variety of lipids into LNC [34]. Lipase activity decreases with chain length, as LCTs are digested more slowly than MCTs and SCTs. In addition, the solubility of bioactive substances in LCTs and MCTs is typically superior to that of SCTs. SCTs may enable the precipitation of bioactive substances due to their diminished capacity as solvents. LCTs, on the other hand, do not suffer from the first-pass effect and absorb more through the lymphatic system than MCTs do through the portal vein [35]. Chemical stability and lipase inhibition should also be taken into account when choosing an emulsifier system [36]. The oil-water interface of LNP is thus coated with both nonionic and ionic surfactants. The most frequently utilized emulsifiers in lipid-based nanoparticles are cremophors and pluronic. Increasing the charge present on the particulate surface and preventing electrostatic aggregation can be achieved by incorporating cationic or anionic surfactants into lipid nanoparticles. When administering ionic surfactants, an important safety concern is the induction of GI irritation, which necessitates taking into account lipid nanoparticles' storage stability. Emulsifiers coated with steric structures or a high surface charge can prevent nanoparticle aggregation. When it comes to ensuring that nanoparticles remain stable over time,

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it is generally agreed that a zeta potential of >30 mV or 30 mV is preferable. It is common knowledge that the decoration of polyethylene glycol on the surface of LNP demonstrates the steric hindrance-mediated repulsion between particles. Stability in the GI environment can also be improved by employing steric repulsion and surface charge increase strategies. Particularly, some surfactants make the nanosystem more viscous, which makes it more bioadhesive and makes it stay in the gastrointestinal tract for longer [37].

One significant technique for the oral conveyance of supplement-grade fixings, like nutrients, cell reinforcements, and unsaturated fats, is the joining of bioactive specialists using LNC [38]. Many vitamins act as cofactors for enzymes, making them essential organic micronutrients. Many people around the world take vitamins and dietary supplements to avoid obesity, cardiovascular disease, osteoporosis, premature skin aging, and various cancers. Vitamins can be soluble in water or lipids. B1 (thiamine or TH), B2 (riboflavin), B3 (niacin), B5 (pantothenic corrosive), B6 (pyridoxal), B7 (biotin), B9 (folic corrosive), B12 (cyanocobalamin), and C are water-solvent nutrients. Vitamin A (retinol), D2 (ergocalciferol), and D3 (cholecalciferol) are examples of fat-soluble vitamins. Additionally, there are numerous analogs or derivatives of these vitamins, each of which has a distinct bioactivity. Due to low BA, compound shakiness, and unfortunate GI ingestion, most of the nutrients have a generally low oral BA [39]. Oral nutrients might have sporadic retention profiles, high intra-and between-subject varieties, and non-portion subordinate assimilation, all of which make oral organization testing and lead to the LNC formation that may enhance the BA of vitamins taken orally.

Pharmacokinetics of oral vitamins or BCS class III/IV drugs formulated with lipid-based nanoparticles are the focus of this review. SEDDSs, NE, microemulsions (ME), SLNs, and NLCs, as well as other LNCs used to encapsulate vitamins, are the studies that we concentrate on. The majority of the LNCs discussed are oil-in-water (o/w)-based nanosystems. Because molecules presented are aqueous cores and lipid shells covered nanovesicles with a lipid matrix rather than nanoparticles and liposomes and niosomes excluded from consideration.

III. ORAL DELIVERY OF BCS CLASS DRUGS

Due to an imbalance in their permeability and solubility properties, drugs in BCS Class III/IV had low BA. Vitamin B, for example, is a water-soluble molecule that serves as a cofactor for numerous enzymes and is one of the vitamins that the body requires. Vitamins B1, B2, B3, B5, B6, B7, B9, and B12, as well as their derivatives, make up the vitamin B group. B1, B2, B3, B6, and B12 are a few of these that play major roles in the prevention of diseases. Dehydrogenase and transketolase, for instance, are cofactors of vitamin B1 or TH; B1 deficiency is linked to polyneuritis, Alzheimer's disease, and colon cancer [40]. Flavin adenine-dinucleotide (FAD) and flavin-mononucleotide (FMN) are co-factors for flavoenzymes, a large group of oxidoreductases, and vitamin B2 is a precursor to them. Anemia, skin disorders, and mucosal disorders can all result from B2 deficiency. B3 deficiency is linked to pellagra, depression, and dementia because it is the precursor of nicotinamide-adenine dinucleotide (NAD) and NAD-phosphate (NADP). The amino acid, carbohydrate, and lipid metabolism enzymes all require vitamin B6 as a cofactor [41]. For cardiovascular disease patients, it's important to keep an eye on their B6 levels. With a corrin ring and an embedded cobalt ion, vitamin B12 has a complicated structure. This nutrient is significant for erythrocyte arrangement, nerve cell upkeep, and DNA union. Megaloblastic anemia may result from a lack of vitamin B12. Vitamin B12 is primarily found in dairy products, but it is bioavailable in milk preparations only 8 to 12 percent [42] and in tofu and cheese only 12 to 33 percent [43].

Branched-chain a-keto acid dehydrogenase, transketolase, a-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and TH serve as cofactors for enzymes involved in carbohydrate metabolisms in its diphosphate form and are essential for the health of all living things. These enzymes are a component of the pathways that produce ATP, NADPH, and ribose-5-phosphate. These substances are crucial for the production of energy in the cell as well as the future production of amino acids, nucleic acids, and fatty acids. When this mineral is lacking, there are numerous negative effects on people and the environment. TH is an analyte and plays a major role in clinical, ecological, and veterinary studies, and has prompted numerous analytical methodologies for their detection. TH deficiencies may affect alligators, birds, and a variety of

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livestock species, it may cause muscle weakness and failure of the reproductive system in valuable fish like lake trout and Atlantic salmon [50]. TH presents basic analytical techniques due to its unusual properties, many of which were discovered in early research in the 1940s. Some anticancer drugs are required for developing the formulation of an effective treatment against such disease, but due to its physical characteristics related to its solubility or permeability showed a hindrance in BA. These caveats must be recognized when developing new techniques, and readers are encouraged to look to previous excellence [57-58]. 5-Fluorouracil (5-FU) is a drug in the BCS class III that is only sparingly soluble and has poor permeability, which limits its BA. 5-FU is a type of cytotoxic chemotherapy that is used to treat a variety of cancers, particularly colorectal, stomach, breast, and pancreatic cancer. 5-FU has constraints in less maintenance in the human body an outcome it shows a quick end rate.

IV. PL BASED APPROACHES FOR DRUG DELIVERY

There are various approaches used as a LDDS or incorporated the PL complex in that described system for oral drug delivery. The included system with advantageous behavior are as follows:

LIPID NANOPARTICLES

As oral vehicles for the transport of drugs, lipophilic nano-drug delivery systems like SEDDSs, nano-emulsion, micro-emulsion, SLNs, and NLCs have the potential to increase BA and solubility. As a result, a lot of researchers have looked into how LNC affects pharmacological action, side effects from conventional formulations, and patient and consumer compliance. LNP administered orally can be absorbed in a variety of ways (Figure 4). Bio-API, PC, surfactants, hydrophilic solvents, and co-solvents are the components of lipid nanoparticles and also inert and non-toxic in nature [59].

SEDDSs

SEDDSs are LNCs frequently used to improve oral absorption of vitamins. It consists of oil, emulsifier, co-emulsifier, solubilizer, and API that is anhydrous and isotropic. Under gentle agitation, it forms spontaneously o/w NE or ME with below 300 nm droplet size. The API is available as nanosized oil droplets and their unique capacity to assemble in the GI fluid, and the high interfacial surface area modulates its aqueous solubility [60].

Self-nano-emulsifying drug delivery systems (SNEDDSs) and self-micro-emulsifying drug delivery systems (SMEDDSs) are the two categories of SEDDs. The droplet diameter of SNEDDSs is typically below 100 nm, and they are typically opaque or translucent. After being taken orally, SMEDDSs form transparent microemulsion that are thermodynamically stable [61]. SEDDS's BA is affected by the ingredients, droplet diameter, digestibility of the lipids, and lipophilicity of the API. For the preparation of SEDDS and for enhancing BA, selecting the appropriate excipients is crucial. SEDDSs are typically constructed with surfactants and lipids that are generally acknowledged to be safe (GRAS). Low-energy emulsification, and the composition method, and solvent-displacement are all used to make SEDDSs [62].

Because conventional emulsions require water, they must be consumed in large quantities to ensure the therapeutic absorption of bioactive agents. During long-term storage, this large amount of aqueous content may enhance hydrolysis and precipitation, decreasing stability and absorption taking place orally. SEDDSs are emulsion preconcentrate delivery systems that do not contain any water in their formulation. With good patient compliance, the issues with conventional emulsions can be resolved. Improved physicochemical stability, the possibility of filling capsules with the vehicle, and increased patient acceptability are all advantages of using SEDDSs for oral dosage [63]. Nanoemulsion formation is thermodynamically spontaneous because self-assembly does not require the input of free energy (Go). In particular, the swelling of the liquid crystalline phase that forms between the oil and water phases makes it possible for an interface between the oil droplets and the external phase to spontaneously form [64]. SEDDSs can cause bile to be secreted into the lumen by increasing the lipids total amount in the gastrointestinal tract. In the presence of lipids and emulsifiers, the elevated levels of cholesterol, PLs, and bile salts create a lipid-rich environment that encourages the formation of emulsion droplets. As a result, the micelles contain poorly miscible drugs that are initially dissolved in SEDDSs. The formation of micelles is an essential step in enhancing solubility and absorption.

Because they have enhanced lymphatic transport, inhibit P-gp-mediated efflux, and have minimal first-pass effects, SEDDSs increase BA

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with the increase in the stability of bioactive agents in the GI environment [65]. SEDDSs have several additional advantages, including their ease of oral administration, reduced intersubject variability and food effects, rapid onset of action, the ability to use lower doses, and ease of manufacturing [62]. However, one drawback of SEDDSs is that they must be administered via gelatin capsules, either soft or hard. The material in the container shell may be contrary to the excipients, prompting precipitation of the dynamic fixings, the requirement for capacity at low temperatures, and the utilization of explicit planning techniques [66]. The process of converting liquid SEDDSs into solid ones can solve this issue. As a result, methods like freeze drying, spray drying, granulation, and adsorption to carriers can be used to make forms that are easier to handle and transport and more stable.

Notwithstanding their jobs as bioactive specialists in SEDDSs, a few nutrients and their subsidiaries can be utilized as excipients in the nanocarriers to help retention [67]. Some drugs and actives have low BA primarily due to P-gp-mediated efflux. P-gp appears to be counteracted by vitamin E and D-tocopheryl polyethylene glycol succinate (TPGS) utilized as a surfactant in LNP to enhance intestinal transport due to its potent anti-P-gp activity [68].

NANOEMULSIONS

An emulsifier system stabilizes heterogeneous mixtures of oil and aqueous medium to form NE. The emulsified mixture is transparent, isotropic, and kinetically stable because it does not coalesce or flocculate during long-term storage. To enhance oral absorption, drugs can be infused into the oil cores of NE before administration. Estrasorb®, Flexogan®, and Restasis® are three examples of NE that have received approval from the Food and Drug Administration of the United States [81]. NE are advantageous over food systems and can encapsulate drugs as well as vitamins and nutrients; The incorporation of lipids, high physical stability, simple texture modification, and rapid GI digestibility are major abilities among these benefits [82].

In most cases, natural or GRAS components are used to make NE. In NE, surfactants or cosurfactants like proteins like caseinate, whey protein isolate, polysaccharides like Arabic gum and modified starch, PLs like egg and soybean lecithin, and non-ionic surfactants like Span and Tween are used to reduce toxicity and improve stability [83]. The most common method for making NE is high-pressure homogenization. Complete dispersivity can be achieved by employing electrostatically stabilized, rapidly diffusing, and low molecular weight emulsifiers. Utilizing a microfluidizer, a sonicator, and low-energy approaches are the other methods utilized to create stable NE [84]. Due to their larger surface area and smaller droplet size, they are superior to conventional emulsions as oral absorption carriers for bioactive compounds. They are therefore simple to interact with the gastrointestinal tract's biological components. NE, according to reports, increase BA by increasing solubility, extending stomach time, promoting lymphatic absorption, reducing efflux transporter effects, and preventing metabolism [85]. Vitamins, particularly those that are fat-soluble, can be encased in the oil core of liquid droplets to protect them from chemical and enzymatic degradation before being consumed.

MICROEMULSIONS

The coarse droplets in conventional emulsions strongly scatter light, rendering them optically opaque or turbid due to their diameters that are comparable to the wavelength of light (hundreds of nanometers). NE are comparable to conventional emulsions because their droplets range in size from 10 to 100 nm. Since the isolated oil and fluid stages have a lower complete free energy than the emulsified oil and water, traditional (coarse) emulsions as well as NE are thermodynamically temperamental [84]. On the other hand, ME are thermodynamically stable systems with lower free energy than the phase-separated components. Accordingly, they normally structure suddenly or with little energy input [86]. The characteristics of these three types of emulsions are examined in Table 1.

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Table 1. Oral absorption of vitamin-loaded SEDDSs with their characteristics.

Vitamin	Average Size	Model Animals	Outcomes Offered by Nanoparticles	Reference
Vitamins A and K2	25–200 nm	None	Good dispersity to form microemulsions	Shah et al. [69]
Vitamin A	Unknown	Rat	An increased bioavailability of 1.4-fold compared to control	Taha et al. [70]
Lutein	337 nm	Thoracic lymph-cannulated rat	An increased bioavailability of 2.5-fold compared to control	Sato et al. [71]
Lutein	92 nm	Rabbit	An increased bioavailability of 11.8-fold compared to control	Shanmugam et al. [72]
Seocalcitol	29 nm	Rat	A 45% relative bioavailability was achieved	Grove et al. [73]
α-tocopherol	Unknown	Human	An increased bioavailability of 2.2-fold compared to commercial capsules	Iulianto et al. [74]
Tocotrienols	1.5–10.6 μm	Human	An increased bioavailability of 2–3-fold compared to control	Yap and Yuen [75]
Tocotrienols	Unknown	Human	Improvement of arterial compliance and oral bioavailability compared to placebo	Rasool et al. [76]
Tocotrienols	211 nm	Rat	An increased bioavailability of 3–7-fold compared to commercial capsules	Alqahtani et al. [77]
γ-tocotrienol	117 nm	Fed rat	An increased bioavailability of 2-fold compared to commercial capsules	Alqahtani et al. [78]
TPGS350 and TPGS1000	11–62 nm	Rat	An increased bioavailability of 3-fold compared to γ-tocotrienol SEDDSs	Abu-Fayyad et al. [79]
Vitamin K1	82–263 nm	Human	An increased bioavailability of 1.7-fold compared to commercial tablets	El-Say et al. [80]

Based on the molecular structure of the surfactants, ME could be spherical, elliptical, or worm-like in shape. They are typically optically transparent. Ternary-phase diagrams provide a means of characterizing the various microemulsion domains. To create ME, three fundamental constituents are two immiscible liquids and a surfactant. Oil and water are typically used as immiscible liquid pairs in ME and are shown in a ternary phase diagram. The ternary phase diagram is the only place where stable and transparent ME can form. In comparison to NE, stable ME require a significant number of emulsifiers.

The titration method, which makes use of the physicochemical properties and thermodynamic stability of ME, permits the spontaneous formation of emulsions through emulsification with low energy. Enhanced solubilization, anti-degradation effect, and GI transport are some of the advantages of orally given ME for the delivery of nutrients and drugs [87]. ME contain a lot of surfactants, which make the GI membrane more fluid and, as a result, more permeable [88]. An oral microemulsion formulation containing cyclosporine A that has been approved by the FDA in the United States is Neoral®. Coenzyme Q10, lutein, and carotenoids are just a few examples of vitamins and nutraceuticals that benefit from the solubilization and BA of ME [89].

SOLID LIPID NANOPARTICLES (SLNS)

Due to their lack of many of the drawbacks of microcapsules and conventional colloidal carrier systems, SLNs are receiving more attention from the food and pharmaceutical industries [90]. Melt-emulsified lipids make up SLNs, which are solid in the body and at room temperature. As a result, they are lipid crystals in colloidal nanosystems. Due to the unique properties of their particle structure, SLNs are suitable for industrial-scale production and have the meritious effect of controlled release [91]. They also have improved stability and BA. Solid lipids like triglycerides, glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate, wax, fatty acids, and cholesterol are added to SLNs to create stable nanosystems [92]. Melt micro emulsification, cold homogenization, or melt homogenization are all methods of manufacturing SLNs. The most common method is hot homogenization because, to

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produce small particles, the solid lipids must first be melted into a liquid state. For heat-sensitive drugs or bioactive, cold homogenization may be used.

The action of gastric lipases initiates oral SLN digestion in the stomach. A crude emulsion is produced when gastric fluid and SLNs are mechanically mixed [93]. SLNs are then further digested by intestinal fluids. SLN particles can enter the intervillous space and adhere to GI mucus due to their small size. Because they make the membrane less fluid, the emulsifiers that cover the surface of SLNs make it possible for more water to be absorbed. Chemically labile API safeguarded and the drug or vitamin's release is prolonged by the solid state of the LNP matrix. To make application easier, SLNs can also be packed into pellets or capsules [69].

NANOSTRUCTURED LIPID CARRIERS (NLCS)

Before using SLNs for the oral delivery, few limitations need to be addressed. The bioactive agent only has a small loading area because of the densely packed solid lipid matrix. Additionally, particulate aggregation and gelation during storage may result in the drug or bioactive agent being expunged from the nanoparticle. For some oral SLNs, the drugs' "burst escape" can make them more toxic. As a result, additional research is required to enhance SLN formulations. Liquid incorporation into the crystalline matrix of lipid may lead to an increase in core imperfections known as "lattice defects," which in turn may lead to an increase in the active ingredients' entrapment [70].

LNP of the second generation (NLCs) are made up of a mixture of liquid/solid lipids. The physical stability of these carriers has improved. In addition, the proportion of liquid to solid lipids in NLCs can be easily altered to alter the release of Bio-API.

NLCs can be delivered in a few different planning stages. Examples of these include membrane extrusion, high-pressure homogenization, solvent evaporation, emulsification-solvent diffusion, solvent injection, phase inversion, microemulsion, multiple emulsion, sonication, and others [94]. High-pressure homogenization is liked to different techniques since it doesn't need a dissolvable and has developed over numerous long periods of purpose in the drug business.

NLCs are useful for improving GI absorption through lymphatic uptake via M cells due to surpassing hepatic metabolism especially. NLCs promote absorption by increasing carrier transport through the stagnant layer (between the brush border of enterocytes and the bulk fluid of the intestinal tract) [71]. Surfactants on the shells of NLCs additionally repress P-gp efflux. NLCs can be loaded with certain lipophilic drugs to improve GI transport. The BA of NLCs of etoposide, iloperidone, silymarin, and tamoxifen has been found to increase by 3.5 times, 8.3 times, 2.5 times, and 2.7 times, respectively [72]. Coenzyme Q10, for example, can be made more bioavailable through the use of NLCs as carriers [95].

V. ORAL BA MODULATION OF BCS CLASS DRUGS USING LNC

Vitamin deficiency can cause drastic effects and even contribute to some diseases. Vitamin deficiency prevention and treatment have made significant progress over the past few decades, but they are far from satisfactory. Vitamin oral formulations typically lack BA and frequently have negative effects. For vitamins that are taken orally, LNC can address many of these issues. LNC, in particular, has greater solubility, stability, and bioactivity in addition to allowing for the modulation of specific ligand size, surface charge, ingredients, and targeting.

The LNP known as SEDDSs are the most commonly used ones for increasing vitamin absorption through the mouth. Nanosystems are attractive for the engineering of nanomedicines with distinct physicochemical properties due to their self-assembly, which greatly simplifies formulation optimization. Vitamin A, vitamin K2, coenzyme Q10, resveratrol, and quercetin—five nutraceuticals with poor water solubility—were examined in previous research [73]. The formulations for filling gelatin capsules were improved by the researchers. All formulations containing nutrients spontaneously dispersed to form ME with droplet diameters ranging from 25 to 200 nm, according to a dispersion test. For instance, the average diameter of vitamin K2-loaded nanocarriers was approximately 40 nm. As a result, developing formulations of this kind is a practical strategy for increasing the oral absorption of nutraceuticals with low solubility.

NE and ME are various strategies used to chip away at the dissolvability and GI transport of supplements [96]. Nanoemulsion-formed nutrients have better actual soundness in plasma and

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electrolyte scatterings [97]. The group led by Dr. McClements at the University of Massachusetts carried out several experiments to ascertain how the oil matrix of various NE affected beta-carotene's GI diffusion and how this affected the GI bioaccessibility of the provitamin A beta-carotene [98]. NE made with LCTs, MCTs, or orange oil as the carrier oils were used to measure bioaccessibility across a GI membrane using an in vitro model that simulated the gastric and intestinal phases. The nanoemulsion's bioaccessibility was significantly affected by the kind of oil it contained. Orange oil had near-zero bioaccessibility because it was unable to form mixed micelles that soluble-carotene. However, due to the low bioaccessibility of MCTs (2%) and the high bioaccessibility of LCTs, the mixed micelles containing MCTs were insufficient to solubilize beta-carotene.

Due to their biocompatibility with the lipid matrix, which is made up of triglycerides, fatty acids, or glycerol esters, and their ease of degradation in vivo, some studies have looked into the possibility of using SLNs as oral delivery systems for vitamins and their analogs. Astaxanthin is a carotenoid that is found in abundance in salmon, shellfish, and shrimp. It is more effective than vitamin E and beta-carotene at fighting a variety of cancers and cardiovascular conditions [99]. However, its use in oral formulations has been restricted due to its low solubility in water, sensitivity to light, and oxygen-induced decomposition. As a result, researchers have entrapped astaxanthin in SLNs made of Tween 20 and glycerol esters [100]. The average diameter of these SLNs ranged from 163 to 167 nm, and approximately 89 percent of them were encapsulated. In simulated GI juices, the findings demonstrated that SLNs prolonged astaxanthin release.

Dacarbazine is an anticancer medication that is light-sensitive and has very low oral absorption [101]. Almousallam and others [102] utilized TPGS-coated NLCs to enhance dacarbazine absorption. The nanoformulations have a diameter of 155 nm, and these NLCs contained approximately 99 percent of this medication. Sulforaphane, a natural anti-cancer agent derived from broccoli, cauliflower, and cabbage, was encapsulated previously using TPGS-coated NLCs to improve oral BA [103]. The drug is released in vitro in two phases: 50% released within the first two hours and up to 30 hours of sustained release. Sulforaphane is effective against cancers of the pancreas, breast, liver, melanoma, and prostate [104]. The encapsulation efficiency was 85% and the particle diameter was 145 nm. The permeability coefficient increased from 0.67 ± 1.04 to 4.82 ± 1.04 cm/min when NLC loading was measured in vitro during intestinal transport. In addition, the in vivo pharmacokinetics of rats revealed that NLCs increased oral BA five times more than the control suspension. To further enhance the dissolution and oral BA of ferulic acid based on PL complex (FAPLC-MD) without destroying the complexation state of ferulic acid and PLs, this compound was developed. The Tmax also increased from 2.5 to 7.5 hours when NLCs released sulforaphane continuously. However, the low melting point of this lipid is what causes PC to be so sticky. These are sticky at room temperature. It has non-flowing aggregation and agglomeration characteristics that cause poor dissolution and low oral absorption. Pentaerythritol serves as the dispersion carrier when the matrix dispersion material is added in these instances. Pentaerythritol is a carrier for dispersion. They described pentaerythritol as a matrix dispersion and dissolution enhancer. The pentaerythritol improves oral BA, increases ferulic acid dissolution, and reduces the adhesive nature of the PL complex. the sum of pentaerythritol, PL, and ferulic acid (1:2:5). The 1:2 proportion keeps up with the respectability of GIT and forestalls its debasement by GIT. BA and drug release are both enhanced by these appropriate interactions [105].

VI. CONCLUSION

The various techniques or approaches for the modulation of permeability and BA characteristics of BCS class III/IV drugs, including vitamins and anticancer drugs, are reviewed and discussed in the current study. Enhance the PL complex-based drug delivery system's dissolution and oral BA without destroying the drug and PLs' complexation state. However, the low melting point of this lipid is what causes PC to be so sticky. These are sticky at room temperature. It has non-flowing aggregation and agglomeration characteristics that cause poor dissolution and low oral absorption. This strategy also includes SEDDS, NLC, SLN, and nanoemulsion, all of which have an advantage over the drug's total BA. BCS class III/IV drug's BA and drug release are both enhanced by these appropriate interactions.

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