International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Recent Advances in Improving the Bioavailability of Hydrophobic / Lipophilic Drugs and their Delivery via Self-Emulsifying Formulations

Amiya Ranjan Dash

Utkal University, Bhubaneswar, Odisha, India

Abstract: ***Formulations based on emulsions for enhancing hydrophobic and lipophilic drug delivery and its bioavailability have attracted a lot of interest. As potential therapeutic agents, they are integrated with inert oils, emulsions, surfactant solubility, liposomes, etc.; drug delivering systems that use emulsion formations have emerged as a unique and commercially achievable accession to override the issue of less oral bioavailability in connection with hydrophobic and lipophilic drugs. As an ideal isotropic oil mixture of surfactants and co-solvents, it self-emulsifies and forms fine oil in water emulsions when acquainted with aqueous material. As droplets rapidly pass through the stomach, fine oil promotes the vast spread of the drug all over the GI (gastrointestinal tract) and conquers the slow disintegration commonly seen in solid drug forms. The current status of advancement in technologies for drug carrying has promulgated the expansion of innovative drug carriers for the controlled release of self-emulsifying pellets, tablets, capsules, microspheres, etc., which got a boost for drug delivery usage with self-emulsification. The present review article includes various kinds of formulations based on the size of particles and excipients utilized in emulsion formation for drug delivery mechanisms and the increase in the bioavailability of lipophilic/hydrophobic drugs in the present time.***

Keywords: self-emulsifying drug delivery systems, lipophilic drug bioavailability, emulsion-based formulations, gastrointestinal drug absorption, controlled release carriers

1. Introduction

The improvements in combinatorial chemistry show an enormous rise in a variety of less water-soluble drugs. At least forty novel pharmacologically active lipophilic/hydrophobic moieties exhibit very low aqueous solubility. Nevertheless, a unique challenge regarding drugs is presented to pharmaceutical scientists: orally administrated drugs have innate low aqueous solubility, leading to inadequate oral bioavailability with higher inter- and intra-subject changeability and scarcity of dose proportionality. Numerous formulation perspectives are currently being applied to handle challenges related to formulations of biopharmaceutical class system (BCS) drugs; this includes compound pre-dissolution in suitable solvents followed by capsule filing with this formulation, or as solid solution formulations that utilize water-soluble polymers. Although these perspectives will help resolve the matter related to the primary dissolution of drug matter in a liquid phase inside the GI tract up to specific proportions, momentous restrictions such as the precipitation issue of drug molecules in the dispersal of formulations during the crystallization of drugs in the polymer-based matrix are still unsolved. For the same reasons, assessment of physical stability is critical and has been evaluated using techniques such as X-ray crystallography or differential scanning calorimetry. Several formulation modes, such as carrier technology, provide an innovative methodology for enhancing solubility in drug molecules with low solubilities. Advancements in oral drug molecule bioavailability use lipid-based formulations that have now become attraction points. Perhaps the most adaptable excipient class members presently available are lipids, providing a strong eventuality as a formulator in improving and controlling the lipophilic drug's absorption where ordinary formulation methods failed or when the drug molecule itself is an oil molecule (i.e., Dronabinol, ethylicosapentate). In addition, with a low affinity for precipitation of lipophilic drugs in the GI tract during dilution, such formulations will favor partitioning kinetics in the lipid droplets to be retained. The literature review indicates that the application of carrier technology is a perspective of scientific interest in lipid-based oral formulations and strengthens the ambidexterity in addressing the issues complementary to oral drug delivery of poorly soluble molecules. Novel methods such as self-emulsification modes have also intensified the solubility of inadequately soluble drugs and have some advantages. The introduction of this self-emulsification concept and present-day advances in polymer science have led to application advancements with lipid-based self-emulsifying formulations in various drug delivery views comprising drug targeting. This article endeavors to review the far-reaching awareness of emulsion-forming drug delivery systems (DOS) for the bioavailability enhancement of hydrophobic/lipophilic drugs by cherishing numerous formulations. The present-day architectural innovations and the advancement of self-nano-emulsifying and self-micro-emulsifying formulations have also been considered. Thus, this review's main focus is on improving the bioavailability or solubility of hydrophobic/lipophilic drugs via self-emulsifying formulations (SEF).

2. Emulsion Concept and Types of Emulsions

An isotropic and transparent solution from an oil mixture and co-solvent, with surfactant and co-surfactant, is emulsified with gentle agitation equivalent to that experienced in the GI tract; this is known as SEF. Spontaneous emulsification is recognized for this solution in aqueous GI fluids in the presence of oral administration. Bile secretion is stimulated by this triglyceride (emulsified oil), which further emulsifies oil droplets containing the drug. Lipases and co-lipases, secreted from various portions such as the salivary gland, pancreas, and gastric mucosa, then metabolize these lipid droplets and hydrolyze the triglycerides by forming free fatty acids and di- and mono-glycerides. Additionally, these

molecules get solubilized when they pass through the GI tract. In due course, emulsion droplets are formed in various sizes, along with mixed micelles and vesicular structures containing phospholipids, bile salts, and cholesterol. The synthesis of chylomicron occurs in lymphatics, ensuring enhanced drug absorption. The bioavailability intensifies formulations' self-emulsification characteristics primarily in connection with confident in vivo features, such as inhibiting cellular efflux mechanisms and retaining the drugs from circulation; this is because of the attachment of several lipidic excipients with a particular drug, a decrease in drug metabolism by the liver in the first pass, as well as its uptake in the lymphatic transport system. In addition, the formation of micellar suspensions and fine dispersions that restrict recrystallization and/or precipitation of drug molecules, where changes in the GI fluid begin because of the properties of several lipid components that favor upgraded drug absorption. Usually, emulsion-forming drug delivery systems (EFDDS) are prepared as simple emulsions, whereas surfactants with a hydrophilic-lipophilic balance (HLB) < 12 SEFs are formulated. Self-nano-emulsifying formulations (SNEFs) and self-micro-emulsifying for- mutations (SMEs) are acquired using surfactants of HLB > 12. Because of surface enhancement for dispersion, the formulations contain improved dissolution (drugs with poor solubility) and high stability. Due to this, independent drug absorption from bile secretion ensures a speedy shift over that of less soluble drugs in blood. Additionally, their formulations have specific, definite characteristics associated with upgraded drug delivery systems. Thus, the emulsion contains hydrophobic and hydrophilic parts.

3. Excipients for Self- Emulsifying Formulations

Based on studies, the process of self-emulsification is precise to the kind of surfac- tant/oil pair utilized, the concentration of surfactant, the ratio of oil/surfactant, and the temperature at which the self-emulsification materialized. These salient findings have been supported by the fact that only selective combinations of pharmaceutical excipients led to effective systems of self-emulsifying therapeutics. Numerous remarkable components are used in EFDDS, such as the following.

3.1 Oils

The most natural support for lipid vehicles is available from consistent edible oils. However, they have poor dissolving properties for enormous amounts of hydrophobic drugs, and limitations for superior self-micro emulsification considerably decrease their use in SEFs. Vegetable oils that are altered or hydrolyzed have a widespread role in successive SEFs attributed to their biocompatibility. Naturally occurring di- and triglycerides have been used exponentially as excipients with susceptibility for degradation (a crucial pathway for releasing drug molecules from EFDDS-based formulations). At present, triglycerides with a medium chain are being replaced by new semi-synthetic medium-chain-containing triglycerides, with molecules such as Gelucire. Robust emulsification systems are formed based on their ability for notable fluidity and the remarkable solubilizing prospect capabilities of self-emulsification. Oils and fats, such as corn, olive, palm, soya bean oils, and animal fats, either digestible or non-digestible, may be used as oil phases in EFDDS.

Digestion is vital for lipid-based formulation development. In addition, the susceptibility of surfactants towards digestion through pancreatic enzymes is an essential factor that should be considered in formulation development.

A simple mechanism/preparation of a self-emulsifying system is depicted in Figure 1, which could help the reader understand this.

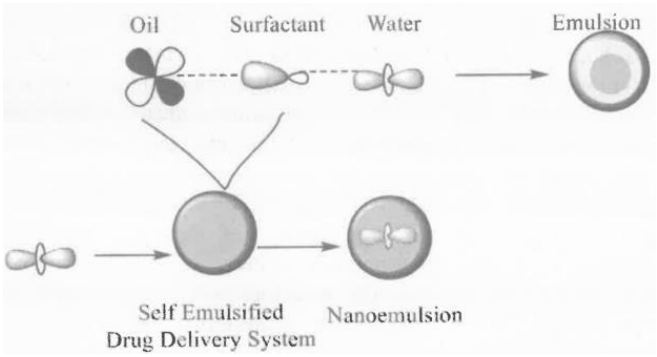

Figure I: Pictorial representation of a self-emulsified drug delivery system and nanoemulsion.

3.2 Co-Surfactants/Co-Solvents

Frequently, a cosurfactant is added in the self-emulsifying formulations to increase interfacial area and dispersion entropy and decrease free energy at its minimum and interfacial tension [8]; on the cause of amphiphilic nature, this is substantially accumulated by a cosurfactant at an interfacial layer that increases interfacial film fluidity through surfactant monolayer penetration. Pentanol, hexanol, and octanol, like short and medium- chain alcohols, are preferred cosurfactants known to form self-emulsifying formulations spontaneously. Apart from cosurfactants, transcutol (diethylene glycol mono ethylene ether), triacetin (an acetylated derivative of glycerol), polyethene glycol, propylene glycol, propylene carbonate, glycofurol (tetrahydro furfuryl alcohol polyethene glycol ether), etc., like several co-solvents, are convenient for hydrophobic drug dissolution in lipid bases. Recently, with varying fatty acids, polyglycolyzed glycerides (PGG) and polyethene glycol (PEG) in aggregation with vegetable oils have also been reported for use in hydrophobic drug solubilization and emulsification.

Thus, the structure and stability of w/o and o/w types of emulsions

3.3 Surfactants or Emulsifiers

Based on the critical packing parameter and hydrophilic-lipophilic balance, the screen- ing of surfactants can be carried out. For the formation of EFDDS, non-ionic surfactants are often chosen because of their limited toxicity; furthermore, they have reduced critical mi- celle concentrations compared with their ionic complements. High HLB-value-containing surfactants are commonly used in forming EFDDS, including polysorbate 80, poloxamers, Gelucire (HLB 10), sorbitan monooleate (Span 80),

cremophor EL, hexadecyltrimethylammo- mum bromide, sodium lauryl sulphate, and bis2-Ethylhexyl sulfosuccinate. Additionally, fatty alcohols and famous surfactants, such as cetyl and stearyl, lauryl, glyceryl, and esters of fatty acids, are also incorporated. Surfactants occurring naturally are also endorsed for SEFs; the most commonly used surfactant is lecithin, with the due reason of the most significant biocompatibility. It has phosphatidylcholine as a fundamental component, having an amphiphilic structure and water-solubilizing properties. To get stable SEFs, the commonly used surfactant concentration is 30 to 60% w/w.

A higher surfactant concentration (~60%) may cause selective, reversible alterations in intestinal wall permeability or GI tract irritability. The subsequent hydrophilicity and higher HLB of surfactants are essential for the prompt formulation of o/w droplets and/or for the sudden spread of the formulate in an aqueous condition, yielding exceptional self-emulsifying/dispersing achievement. By nature, surface-active agents are amphiphilic and generally dissolve more remarkably than hydrophobic drugs. This property is of great importance as it prevents precipitation through the GI lumen, and drug molecules have prolonged presence in a solubilized form, an essential phase for effective absorption. Recent reports show that the surfactant digestion mechanism affects the performance of SEFs, as the dissolving environment alterations can cause precipitation of a little less water-soluble drug.

Additionally, more information is needed for degradation molecule formation from surfactants and their interaction with fatty acids and phospholipids, bile salts, and dietary lipids such as endogenous lipids. This may play a vital role in maintaining a solution with poorly water- soluble drugs, and an essential part in forming mixed micelles may be compromised. Considering all these data reported, information about the impacts of non-ionic surfactants that may show inhibition of triglyceride delivery, as reported by Hong Wang et al. A precipitation-ultrasonication method is used to prepare breviscapine nanocrystals, which are cast using water-soluble polymer mould load further into PLGA microparticles. These disc-like particles were characterized and compared with spherical particles by emulsion-solvent evaporation. Through confocal laser scanning microscopy (CLSM) and X-ray powder diffraction (XRPD), analysis of the highly dispersed breviscapine state in microparticle confirmation is carried out. The drug significantly affects the efficiency of breviscapine and its loading capacity in PLGA microparticles and liberation mechanism through loading percentage and fabrication methodology. When both template and nanocrystal methods were enforced, drug loading and encapsulation potential was enhanced by 2.4% to 15.3%, and 48.5% to 91.9%, respectively.

3.4 Drug Loaded Nanoemulsions

On the other hand, as drug loading is increased, loading efficiency is reduced. An initial release by bursting in all microparticles has been seen that later slows down to 28 days and is further followed by erosion-acceleration phase release, which supports sustained delivery over a month for breviscapine. Stable serum drug level after intramuscular mi-croparticle injection in rats was observed even after 30 days. Therefore, nanocrystals of less-soluble drug-loaded PLGA microparticles provide a supportive way for long-term therapeutic outcome characterization desirable in vivo and in vitro accomplishment. An ap- proved safe herbal drug for several hepatic disorders is Silymarin. However, poor oral bioavail- ability is its major limitation. Silymarin-loaded nanoemulsions could be prepared using the high-pressure homogenization (HPH) method. Capryol 90 as the oil phase, Solutol HS 15 as a surfactant, and Transcutol HP as a co-surfactant were selected accordingly. Design- based quality has been employed for optimized nanoemulsions in conditions of several cycles, processing pressure, and (Smix) surfactant/co-surfactant mixture amount. Globule size, polydispersity index (PDI), zeta potential, transmittance, and percentage in vitro drug release of the optimized formulation were found as 50.02 ± 4.5 nm, 0.45 ± 0.02, -31.49 mV, 100.00 ± 2.21% and 90.00 ± 1.83%, respectively. The apparent permeability coefficient (Papp) has been enhanced by nanoemulsion, as shown in everted gut sac studies. Silymarin Papp in nanoemulsion and the oral suspension was 1.00 x 10^{-5} cm/h with a flux of 0.422 µg/cm^2/h, and 6.30 x 10^{-6} cm/h with a flux of 0254 µg/cm^2/h at 2 h, respectively. The enhancement in Silymarin are mainly based on the constituents of the emulsifier and how much hydrophobicity or hydrophilicity it has.

4. Recent Studies

4.1 Self-Stabilized Picketing Emulsion

A novel high-pressure homogenization technique for silybin oral bioavailability enhancement has been developed for silybin nanocrystal self-stabilized Pickering emulsion (SN-SSPE). The impacts of drug content and homogenization pressure on SN-SSPE formation were also evaluated. Using SEM (scanning electron micrograph), atomic force microscopy (AFM), and confocal laser scanning microscopy, the structure, size, and morphology of PE droplets were identified. Investigation of in vivo oral bioavailability and SN-SSPE release in vitro was also carried out. The results revealed that when homogenization pressure is scaled up to 100 MPa, the silybin nanocrystals' (SN-NC) particle size decreases. A stable silybin Pickering emulsion might be formed when silybin content reaches 300 mg or above; thus, surfaces of oil droplets are entirely covered by sufficient SN-NC, and a self-stabilized Pickering emulsion is formed. A core-shell arrangement composed of a core of SN-NC shell and oil was seen when the SN-SSPE emulsion droplet was 27.3 =t 3.1 jam. A stability of about 40 days or more has been recorded for SN-SSPE. SN- SSPE showed a faster in vitro release rate compared with silybin coarse powder. However, it is similar to the suspension of SN-NCS. Intragastric administration showed a 2.5-fold and 3.6-fold incremental peak concentration of SN-SSPE of silybin compared with SN-NCS and coarse powder of silybin in rats. Furthermore, there were 1.6-fold and 4.0-fold increases in the AUC of SN-SSPE concerning SN-NCS and silybin coarse powder. From the results, it has been confirmed that silybin nanocrystals could stabilize the Pickering emulsion of silybin and increase oral bioavailability. The self-stabilized Pickering emulsion of drug nanocrystals has encouraged a system for poorly soluble drugs for oral drug delivery. For a controlled drug delivery system, (PLGA) (Poly lactide-co-glycolide) microparticles

are often utilized. To formulate PLGA microparticles, standard emulsion methods have been used. However, they show less loading capacity, more precisely for poorly soluble drugs in organic solvents. A template of water-soluble polymers and nanocrystal technology was used to manufacture nanocrystal-loaded microparticles with enhanced encapsulation and drug-loading efficacy for extended breviscapine developed for protein loading into Eudragit LI00 fibers for perioral delivery. Alkaline phosphatase and horse red- dish peroxidase encapsulation lead to higher efficiency into fibers and pH-specific release. Protein bioavailability recovery has been enhanced by aqueous emulsion phase reduction and hydrophilic polymer excipient inclusion. Hannah Frizzell et al. demonstrated that protein formulation in lyophilized electrospun fibers increases therapeutic compounds' shelf life compared with aquatic storage. Thus, a novel promising dosage form of bio-therapeutics for perioral delivery has been available from the platform. In another work, designing a new octa-arginine (R8) altered with (LE) a lipid emulsion system of the lipophilic drug disulfiram (DSF) for ocular delivery was the target purpose. On corneal permeation, R8 presence and lipid emulsion particle sizing (DSF-LE1, DSF-LE2, DSF-LE3) with DSF loading and altered with R8 (DSF-LE1-R8 and DSF-LE2-R8) was formulated. There was a change in zeta potential from negative to positive values for lipid emulsions after the modification of R8.

DSF-LE1-R8 fabricates the strongest mucoadhesion from different compositions of mucoadhesion studied. R8 altered lipid emulsion (DSF-LE1-R8) with nano-sized particles showed ocular distribution in vivo and corneal penetration in vitro, with high permeability, and the most significant DDC amount distribution in visual tissues. More homogeneous fluorescence was displayed by LE1-R8 when LE1-R8 was labelled with Coumarin-6 and deep penetration in the cornea compared with other formulations at different time frames. Furthermore, LE-R8 could be transported across the corneal epithelium apart from its paracellular routes by using transcellular ways because of an induced update on a cause of R8 modification and confirmation received by using confocal laser scanning microscopy. It was also reported that DSF-LE1-R8 exhibits a marked anti-cataract effect from evaluation. Hence, nano-sized particles with R8 alterations in lipid emulsions were proposed as a significant ocular delivery method to enhance penetration in the cornea and DSF visual delivery. Capsule designing with insulin-like hydrophilic drugs for the preservation of its biological activity and stability through double emulsion methodology and its entrapment into biodegradable microcapsules in the following manner. with xanthan and chitosan gum complexes containing shells was devotedly investigated by Mutaliyeva et al. Several formation factors such as biopolymer and oil type, stabilizer, and its concentration, aqueous solution when CBD-piperine-PNL has been orally administered, indicated as the most potent screened formulation. Similar data was found during THC-piperine-PNL-based pharmacokinetic experiments, showing a 9.3-fold increment in AUC compared with the THC solution. The synthesized Piperine-PNL can synchronize piperine with THC or CBD delivery to the enterocyte site. The bioavailability of CBD and THC has increased due to this co-localization and the effect on pre-enterocyte and enterocyte levels during the absorption process. The further amplification in THC and CBD absorption is incorporated by piperine into PNL. It plays a role in phase I and phase II metabolism inhibition by piperine with an addition to P-gp and phase I metabolism by PNL. These offbeat results put forward the way for piperine-PNL to deliver less soluble, highly metabolized drugs that cannot be orally administered at present.

4.2 Nano Lipospheres Formulation

In pomegranate, ellagic acid is a predominantly bioactive compound with low bioavail- ability. A food-grade system from self-nano emulsification has developed that enhanced the dissolving and absorption of ellagic acid. Pseudo-turning phase images and solubility assays have revealed that the components are suitable for formulation. The optimal formulation has been achieved with polyethylene glycol, polysorbate, and capric triacylglycerol/caprylic at 45/45/10 wt.%. A fine nanoemulsion was yielded from controlled stirring and optimized formulation, with an average droplet size of 120 nm. With the formulation, the ellagic acid dissolution was remarkably increased. Based on the pharmacokinetics study carried out in rats, ellagic acid's bioavailability was 3.2 and 6,6-tbld higher compared with its aqueous suspensions and pomegranate extract. A novel strategy has been devel- oped to deliver ellagic acid with a self-nano-emulsifying method for developing dietary supplement products and ellagic acid-containing functional foods. The most rapidly growing therapeutic segment is biologies, but it has limitations of low stability. It has an alternative delivery system for personal administration; however, it has particular physio- logical challenges that prompt protein susceptibility and function loss. Protein formulation in biomaterials, such as electrospun fiber, can resize these barriers. Still, optimization of such platforms is required for protein stability and maintenance of bioactivity during the formulation process. An emulsion electrospinning method has been phase internal content, volume fraction, regime mixing, and time were also evaluated. The complex's effects on the emulsion formation process, characteristics, and stability of resultant emulsions were interrogated using interfacial charge (zeta-potential) and the size distribution (DLS). The prepared capsules were analyzed using size distribution, zeta potential, and microscopic characterizations. Insulin release kinetics was monitored through UV-vis spectroscopy, and reports suggested that sustainability enhancement was progressive.

4.3 W/O/W Double Emulsion Formulation

Sesamol, the phenolic compound and degradative product of sesamolin, has poor bioavailability but is recognized for its anti-inflammatory properties. An attempt was made to increase its bioavailability through mixed phosphatidylcholine micelles encapsulation. Sesamol solubilization and entrapment can be seen in PCS (phosphatidylcholine mixed micelles), having a 3.0 nm particle size with 96% efficiency. PCS showed lower comparative fluorescence intensity when it was compared with free sesamol. PCS cellular uptake, bioaccessibility, and transport across cell monolayer was 1,2-fold, 8.58%, and 1.5 times improved compared with FS. By using lipoxygenase inhibition and an LPS-treated RAW 264.7 cell line, the FS

and impact of PCS regarding its anti-inflammatory action were studied. The iNOS protein expression downregulation (27%), ROS (32%), NO (20%), and inhibition of lipoxygenase with 31.24 µM (IC5Q) were affected by PCS in comparison to FS. Omid Shamsara et al. loaded piroxicam (PX) into multi-layered oil-water emulsions and stabilized using the complexes of P-lactoglobulin (β-L) and pectin, in which homogenized sunflower oil was used as a primary emulsion with a β-L solution containing PX. These droplets get stabilized by a subordinate layer of pectin. The low-methoxyl sunflower pectin (LMSP), low-methoxyl citrus pectin (LMCP), high-methoxyl apple pectin (HMAP), and high-methoxyl citrus pectin (HMCP), were respectively utilized to produce emulsion droplets with a secondary or double layer. Creaming stability, PX entrapping efficiency (%), and droplet mean size of emulsion (D43) have been determined. Trend or PX release was examined and used for the zero-order kinetic experiment. The output of such experimental work has suggested that citrus pectins with NaCl and β-L/high-methoxyl-apple-stabilized emulsions were found with maximum stability, with good PX loading capacity compared with stabilized emulsions by a β-L complex of pectin in the absence of NaCl. The mean droplet size of double-layered emulsions increased at a high pectin fraction and reduced by a low β-L fraction.

A potent bioactive molecule such as betulinic acid (BA) is recognized for therapeutic action. Yet, it has limited efficacy because of poor solubility and low bioavailability. Harwansh and coworkers developed BA-loaded nanoemulsions with increased hepatoprotective activity and bioavailability. Using the BA-NE1 procedure, the nanoemulsion was formulated containing surfactants such as labrasol, olive oil, aqueous phase, and co-surfactant, such as plural isostearate, in the convenient ratio optimized. Its characterization was done through several parameters, such as the size of the droplet, refractive index, zeta potential, FTIR, UV-spectrophotometry, TEM, and stability studies. A droplet size of about 150.3 nm with negative zeta potential such as —10.2 mV of this emulsion was evaluated. Pharmacokinetic limits such as Cmax (96.29 ngmL~"l), AUCO-t oo (2540.35 nghmL"[1]), the elimination half- life (11.35 h), Tmax (12.32 h), and relative bioavailability (440.48%F) were also investigated and compared with BA. The hepatic serum marker levels and antioxidant enzymes con- cerning CC14-intoxicated groups (** $p < 0.05$ and *** $p < 0.01$) were significantly restored by BA-NE1. Accordingly, the study also reveals that the BA-loaded nanoemulsion could improve hepatoprotective activity because of increased solubilization and enhanced oral bioavailability. There is an advanced formulation with better biocompatibility, stability, and higher loading of hydrophobic drugs in submicron emulsions (SEs) from sterilization with an autoclave. To increase the targeting and uptake of tumor cells, SEs get altered by target moieties and a positive charge. Cationic DocSEs (DocCSEs), docetaxel-loaded SEs (DocSEs), and peptide-RLT-modified DocCSEs targeted by low-density lipoprotein receptor (LDLR) were formulated. A particle size of 182.2 db 10 nm and loading efficiency of docetaxel (Doc) 98% with a zeta potential of 39.62 ± 2.41 mV was reported for optimized RLT-DocCSEs. They showed 96 h of sustained release and were found stable for 2 months at 4 degrees Celsius. Significantly more cell apoptosis and RLT-DocCSEs have caused inhibition of cells compared with DocCSEs and DocSEs. RLT-DocCSEs showed greater cellular uptake with slow elimination from DocCSEs and DocSEs.

4.4 Polymeric Emulsifier Containing Formulation

Polyethylene glycol (PEG), lactide (LA), and £-caprolactone (CL) were derived as amphiphilic bioresorbable copolymers studied for their emulsification and degradation properties. With monomethoxy PEG, lipophilic 20 wt.% PCL, PLACL block, PLA, and 80 wt.% PEG (hydrophilic) block comprising polymers were formulated with the LA and/or CL ring-opening polymerization process. These emulsifiers have analogous capa- bilities for stabilizing squalane/water interfaces in emulsification as they possess equivalent hydrophilic-lipophilic balance (HLB) values. Polymer degradation within the emulsion and in the aqueous phase at 37 degrees Celsius to mimic conditions of the human body was carried out. According to the result, the polymer degradability was found to cause instability in the emulsion. In addition, emulsion polymer matrices exhibit lower degradative rates than in an aqueous phase from corresponding polymers. The characteristics in phannaceutical applications are of keen interest, particularly for sustained delivery mechanism designing. A study aimed to develop a re-dispersible dry emulsion that contains simvastatin, a model drug with lipophilic, low water solubility properties; they used a fluid bed coating methodology. This represented manufacturing of dry-emulsion-mode-formulated pellets, in which a dry emulsion layer was applied to a neutral core. As an oily phase, 1-oleoyl-rac-glycerol, a preliminary formulated material, was selected because of its higher drug solubility and potent bioavailability possibilities. Tween 20, mannitol, and HPMC were used as solid surfactants and carriers. The experimental design was used more specifically for mixture design to get the optimal formulation composition. The initial responses used as formulation optimization parameters were the stability and ability to reconstitute the emulsion. On optimization, the formulation represented slender-sized droplet distribution at reconstitution, high strength, satisfactory drug encapsulation, and an increase in dissolution possessions as compared with a pure drug and a non-lipid-based tablet. Uniform morphological data for the functional layer and separated droplets with simvastatin and uniform distribution of size and coated pellets with a circular shape were derived from image analysis using Raman spectroscopy and scanning electron microscopy. The work revealed the evidential design concept of re-dispersible dry emulsions using the fluid bed layer technique.

4.5 Nano-Precipitation/Dry Formulations

From another work, nanoemulsion from surfactant-free Pickering formulations can liberate a drug with enhanced oral bioavailability at specific pH. By using the nano-precipitation method, magnesium hydroxide-based stabilizing nanoparticles were obtained. The Mg(OH)2 nanoparticles stabilized oil-in-water Pickering nanoemulsions were prepared using a high-energy procedure and sonication probe. The effect of all formulating proper- ties, composition, and the Mg(OH)2 nanoparticles' size on the physicochemical parameters of Pickering nanoemulsions was explored with experimental processes. By using trans- mission electron

microscopy and DLS, the formation was characterized. Moreover, the Mg(OH)2 was solubilized in an acid medium as an advantage that leads to nanoemulsion destabilization and oral release of active components. It is revealed from the acid-releasing work (pH = 1.2) that an increase in release is due to the loading of nanodroplets with the saturation of concentration. At pH = 6.8 (an alkaline media), ibuprofen is significantly released from saturated nanoemulsions in an acid medium. These nanoemulsions not only prompt drug bioavailability but also protect patients from acid medicine side effects through the basic features of hydroxides. Additionally, hydroxides increase pH when present in the stomach; enhancing the release of ibuprofen is greatly affected by pH for solubility.

The drug atorvastatin calcium (ATV) is less bioavailable. A dry emulsion method was orally utilized with lyophilized disintegrating tablet development to improve its dissolution in vitro and performance in vivo. Under proper homogenization, the emulsions were formulated using a collapse protectant (glycine) as an aqueous phase, 4% alginate/gelatin-containing mannitol, and synperonic PE/P 84 (surfactant) as an oil phase. The impact of the emulsion formulation parameters was investigated for the prepared tablets' friability, in vitro dissolution, and disintegration time for tablets to the drug. The outcomes revealed the important impact of matrix emulsifier types and the former on disintegration time. From a study of in vitro dissolution, the ATV rate of dissolution was enhanced from lyophilized-dry-emulsion-tablets (LDET) in comparison with a plain drug. Optimized ATV- loaded LDET was studied for DSC and XRD, and the results proved drug presence in the amorphous form. From the SEM images, the intact, non-collapsible, porous-structured LDET was seen to have a complete ATV crystallinity loss. When high-fatty rats were administrated with ATV-loaded LDET, the serum and tissue levels were found to be significantly decreased. The polymers that have grown extensively in the last decades are known to be smart polymers because of their extensive uses for drug targets with controlled drug delivery methods. Based on this concept, Chekuri Ashok et al. used Albizia lebbeck L. seed polysaccharide (ALPS) to design and make the preparation of smart releasing emulsion (o/w).

5. Conclusions

The bioavailability and solubility of hydrophobic and lipophilic drugs is an issue for their oral administration, which is resolved using self-emulsifying formulations to a certain extent. Thus, this review article deals with emulsion-formulation-based drug delivery and improving the bioavailability of hydrophobic and lipophilic drugs. The dispersion or loading efficacy of the drug into emulsions depends upon the emulsion's constituents, such as oil, surfactants, and co-surfactants. In this regard, the nanoemulsions have been found effective for target drug delivery and improving the bioavailability of poorly water-soluble drugs. The present scenario of progression in technologies for drug carrying has broadcast the expansion of innovative drug carriers for the target release of self-emulsifying pellets, tablets, capsules, and microspheres, which has improved drug delivery with self-emulsification. Thus, the present review article will help readers working in the field of emulsion-based drug deliver}' with the increased bioavailability of lipophilic/hydrophobic drugs at the current time.

References

[1] Stegemanna. S.; Leveillerb, F. When poor solubility becomes an issue: From early stage to proof of concept. Eur. J. Pharm. Sci. **2007**, 31. 249. CrossRef] [PubMed]
[2] Bwart Coie. I.; Dominique. C.: Hassan, 11. Challenges and opportunities in encapsulating liquid and semisolid formulations into capsules for oral administration. Adv. Drug Deliv. Rev. 2008. 60. 747.
[3] Fatouros. D.G.; Mutlertz, A. In Vitro Lipid Digestion Models in Design of Drug Delivery Systems for Enhancing Oral Bioavailability. Expert Opin. Drug Metab. loxicol. 2008. 4. 65.
[4] Jie. S.; Minjie. S.:Qineng. P.; /hi. Y.; Wen. I. Incorporating liquid lipid in lipid nanoparticles for ocular drug deliver)' enhancement.Nanotcchnology 2009. 21. 100.
[5] Porter. C.J.: (.'barman, W.N. In vitro assessment of oral lipid based formulations. Adv. Drug Deliv. Rev. 2001.50. 127. [Cros;,Rcf][PubMcdJ
[6] Christopher Porter, J.H.: Natalie Trevaskis. L.; William Charman, N. l.ipids and lipid-hased formulations: Optimi/ing the oral delivery oflipophilie drugs. Nat. Rev. Drug Disco v. 2007. 6. 231.
[7] Bose. S.; Kulkarni. P.K. Preparation and in vitro evaluation of ibuprofen spherical agglomerates. Indian J. Pharm. liduc. 2002. 36. 184.
[8] Shafiq. S.: Shakeel. F.: Talegaonkar, S.: Ahmad, F.J.; Khar. R.K.; Ali, M. Nanoemulsions as vehicles for transdermal delivery of aceclofenac. Eur. J. Pharm. Biopharm. 2007. 66. 227
[9] Larsen. A.: Jannin. V.: Mullertz, A. Pharmaceutical surfactants in biorelevant media: Impact on lipolysis and solubility of a poorly soluble model compound: Dana/.ol. In Proceedings of" (he 5th World Meeting in Pharmaceutics, Biophannaceutics and Pharmaceutical Technology, Geneva. Switzerland, 2 March 2006.
[10] Panayiotis Constantimdes, P. Lipid Microeirmlsions for Improving Drug Dissolution and Or;il Absorption: Physical and Biopharmaccutical Aspects. Pharm. Re*. 1995, 12. 1561-1572.
[11] Sachin. A.: Roshan, (i.: Yuvraj. R.: Beny. B. Lipid Based Drug Delivery System: An Approach to Knhmicc Bioavaitability of Poorly Water Soluble Drugs. Int. J. Phar. Pharm. Res. 2020. 19, 93 714.
[12] Devalapally, II.: Sitchenko, S.; Zhou, F.: McDade. J.: Golovcrda, G.: Owen, A.; Hidalgo, l.J. Evaluation of a nanocmulsion formulation strategy for oral bioavailability enhancement of danazol in rals and dogs. J. Pharm. Sci. 2013. 102. 3808-3815.
[13] Fernando/, S.; Chcvrier. S.: Riticr. N.: Mahler, B.: Demarne, K: Carrirc, F.: Jannin. V. In vitro gastrointestinal lipolysis of four formulations of piroxicam and cinnarizine with the self-emulsifying excipients Labrasol® and Gelucire® 44/14. Pharm. Res. 2009. 26. 1901.
[14] Nazzal. S.; Smalyukh. I.I.; Lavrentovich, O.D.; Khan. M.A. Preparation and in vitro characterization of a

euteclic based semisolid self-nano emulsified drug delivery system. 1m. J. Pharm. 2002. 235. 247 265.

[15] Halbaut, L: Berbe. C.; del Pozo. A. An investigation into physical and chemical properties of semi-solid selfemulsifying systems for hard gelatin capsules. Int. J. Pharm. 1996. 130. 203-212.