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Review Article

Lipid Based Drug Delivery Systems: Past, Present and Future Perspectives in Improving Drug Bioavailability

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ABSTRACT

Low oral bioavailability is due to low aqueous solubility of drugs is a growing challenge in the evolution of new pharmaceutical products. Lipid based formulations such as microemulsion, nanoemulsion, self-emulsifying drug delivery system (SEDDS), self-microemulsifying drug delivery system (SMEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS) used to improve the oral bioavailability of BCS-II drugs were surveyed in many studies as an efficient approach for improving the bioavailability and dissolution rate. This review article focuses on the following topics. First, it presents an overview of lipid-based drug delivery systems and excipients involved in improving the solubility and bioavailability of poorly water-soluble drugs. Second, the article reviews selection of components in lipid-based drug delivery systems for oral use with their characteristics. Third, it brings a detailed description of the processing techniques necessary to obtain lipid-based formulation for oral delivery, along with brief discussion of their strategies to enhance the bioavailability and characterization perspectives.

Keywords: Lipid-based drug delivery system (LBDDS), BCS class II drugs, Bioavailability, Self-emulsifying drug delivery system, Self-microemulsifying drug delivery system, Self-nano emulsifying drug delivery system

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INTRODUCTION

In the pharmaceutical field increasing in number of poorly water-soluble drug candidates results in development for advanced drug delivery systems that able to increase bioavailability. These drug candidates are class-II drugs according to Biopharmaceutics Classification System (BCS) (low solubility, high permeability), and thus solubility or dissolution rate in gastrointestinal tract are the limiting steps for drug absorption [1]. BCS class-IV drugs (low solubility, low permeability) still need to dissolve in gastrointestinal tract before drug is absorbed. Lipid based formulations generally utilizes two principles to increase bioavailability of BCS class-II and IV compounds [2]. The first principle includes solid dosage forms where dissolution rate is enhanced by either increasing the surface area (e.g., nanoparticles) or by stabilising an amorphous or molecular form of compound. The second principle covers formulation approaches using lipid and surfactant excipients to create formulations where the compound in the solution [3]. In last decade lipids have gained much interest as carriers for the delivery of drugs with poor water solubility. In this context, the objective is to outline the pharmacokinetic aspects and *invitro* processing steps occurring after administration of lipid-based formulation with concept and methodologies in development [4].

Table 1: Various work done upon lipid-based drug delivery system:

Author name, year	Tittle& Journal	Methodology	Results	Reference
Manoj Aswar et al., (2020).	Self – microemulsifying drug delivery system of curcumin attenuates depression in olfactory bulbectomized rats. Science Direct Heliyon.	Depression was induced by bilateral olfactory bulbectomy and animals were accidentally into 8 groups, control vehicle 10ml/kg, pure curcumin- 10, 20, 40mg/kg and curcumin SMEDDS- 10,20mg/kg of respective treatment, behavioural parameters such as open field test (OFT) ambulation were count and passive avoidance response (PAR) were evaluated	In OFT, increased central area frequency, peripheral frequency, central area duration & decreased and grooming were recorded with an increased ambulation counts. In PAR, reduction in number of trails and serum cortisol level was also found to be decreased in the test groups.	[5]
Mitali H. Patel et al., (2019)	Novel drug delivery Approach- SMEDDS for enhancing oral bioavailability of Asenapine Maleate American Association of Pharmaceutical Scientists.	Asenapine Maleate (AM) using Capryol 90, Cremophor EL, and Transcutol HP by spontaneous emulsification method. Confocal and flow cytometry showed cellular uptake of curcumin-6 solution.	AM-SMEDDS showed globule size and zeta potential of 21.1+ 1.2 nm & -19.3+1.8mV distributed by transmission electron microscopy. The relative bioavailability of AM – SMEDDS was found to be 3.53 times greater than Asenapine suspension.	[6[
Monika P et al., (2018)	Development and characterization of SMEDDS of Rosavastatin GSC Biological and Pharmaceutical Sciences.	To enhance solubility and dissolution rate of Rosuvastatin by formulating as a SMEDDS were prepared by using Castor oil & sesame oil, Tween 80, PEG 200 were further evaluated for drug content, thermodynamic stability and in vitro drug release.	Among all formulations the drug release for F2 formulation was 99.70% in 120min. The selected optimized F2 formulation was characterized by using FTIR spectroscopy, scanning electron microscopy and globule size.	[7]
Yunrong Zhang et al.,	Characterization and evaluation of	The formulation of the SMEDDS Capryol 90 (oil),	TG-SMEDDS showed significantly higher C_{max} &	[8]

(2017)	SMEDDS containing Tectorigenin, an isofalvone with low aqueous solubility and poor permeability Drug Delivery.	Cremophor RH 40, (emulsifier) and Transcutol HP (co-emulsifier) showed a significant increase in solubility. TG-SMEDDS remained stable at room temperature for at least 3 months showed excellent dissolution than 90% of TG was released within 5min.	AUC values, TG and absolute oral bioavailability of TG-SMEDDS was 56.33%.	
Ankita V et al.,(2016)	Development of SMEDDS for oral delivery of poorly water soluble nutraceuticals. Drug Delivery and Industrial Pharmacy.	Bioactive agents- vitamin A, vitaminK2, coenzyme Q10, quercitin and trans-resveratrol contained a 1:1 mixture (w/w) of capmul MCM NF & captex 355 EP/NF as hydrophobic lipid and Tween80 as hydrophillic surfactant. The solubility values 500, 12,8, 56 and 87mg. Formulations of nutraceuticals were prepared and filled into hard gelatine capsule.	Invitro dispersion testing using 250mL of 0.001N HCL in USP dissolution appratus-II. The dispersion test showed that all SMEDDS containing nutraceuticals dispersed to form microemulsion after disintegration of capsule shells with globule size in the range 25 to200nm.	[9]
Lan Wu et al.,(2015)	SMEDDS of novel medicative compound against depressive: a preparation and bioavailability study in rats - (2015) American Association of Pharmaceutical Scientist Pharmacy Technology.	SMEDDS has composition of castor oil (24.5%), Cremphor EL (40.8%), Transcutol HP (2.7%). The drug concentration in plasma samples using the high performance liquid chromatography-electrospray tandem mass spectroscopy (HPLC-MS/MS) method.	The droplet size of micro emulsion formed by the optimized formulation storing at 25^{o}C. Droplet size formed by optimized formulation was 26.08±1.68nm, zeta potential -2.76Mv. The oral bioavailability of AJS-SMEDDS was increased by 3.4 and 3.9 fold respectively.	[10]
Jyotsana R et al., (2014)	Formulation and development of SMEDDS of pioglitazone hydrochloride. Asian journal of Pharmaceutics	It is aimed to improve the dissolution of poorly water soluble antidiabetic drug formulating in SMEDDS with Capmul MCM C8B, Cremophor RH40 & Tween80, Trancutol P phase after screening various vehicles. The prepared and formulation were evaluated for self emulsifying ability and phase diagram were constructed.	The optimised system possessed mean of globule size of 122.2nm, zeta potential -22.9mv, drug content 99.66±0.6%, drug release in hydrochloric acid buffer pH-2 was found to be 99.35±0.38%. More than threefold increase in dissolution characteristics of pioglitazone HCL in SMEDDS.	[11]
Shailesh T et al., (2012)	Preparation and characterisation of SMEDDS of Olmesartan Medoxomil for bioavailability improvement. Hindawi publishing Corporation	Olmesartan Medoxomil is an antihypertensive drug agent with absolute bioavailability of only 26% due to poor aqueous solubility was to enhance the absorption of OLM. The solubility of OLM in oils (Acrysol EL 135), surfactant (Tween80), co-surfactant (Transcutol P).	The optimized formulation S2 contained OLM (20mg) which shows small partical size, maximum solubility, less emulsification time, good optical clarity, and invitro release.	[12]

	Journal Pharmaceutics			
Xinru Li et al., (2010)	Development of Silymarin SMEDDS with enhancing oral bioavailability. American Association of pharmaceutical Science and Technology.	The optical formulation with the SMEDDS and solubilising ability consist of 10% w/w of ethyl linoleate, 30% Cremophor EL, and 60% ethyl alcohol.	The release of silymarin from SMEDDS faster than that from commercial silymarin in hard capsule. The bioavailability result indicate that the oral absorption of silymarin SMEDDS about 2.2 fold.	[13]
Ajeet K et al., (2009)	Oral bioavailability enhancement of Exemestane from SMEDDS. American Association of pharmaceutical Science and Technology	Solubility of exemestane was determined in various vehicles. Ternary phases diagrams were plotted to identify the efficient self emulsification region	The release of Exemestane from SMEDDS capsule was studied using dissolution apparatus in different dissolution media and compared the release of Exmestane from the conventional table. Oral absorption of Exemestane from SMEDDS from resulted is about 2.9 fold increased in bioavailability compared with the suspension	[14]
Ashok R et al., (2007)	Preparation and invivo evolution of SMEDDS containing Fenofibrate. American Association of pharmaceutical scientists .	The optimized formulation for invitro dissolution and pharmacodynamic studies was composed of Labrafac CM10 (31.5%), Tween80 (47.3%), and polyethlene glycol 400 (12.7%). SMEDDS formulation showed complete release in 15mins compared with plain drug which showed limited dissolution rate.	Comparative pharmacodynamic evaluation was investigated in terms of lipid lowering efficacy, using a Triton-induced hyperchlestrolemia model in rats. SMEDDS formulation reduced serum lipid levels in phase 1 and 2of the Triton test, as compared to plain fenofibrate.	[15]

Advantages of Lipid-based Drug Delivery System:

- Drug release is controlled and in targeted manner.
- Pharmaceutical stability.
- High drug content.
- Feasibility of carrying both lipophilic and hydrophilic drug.
- Lipids and developed formulation are bio-degradable and biocompatible in nature.
- Excipients adaptable.
- Formulation flexible.
- Low-risk profile.
- Improved oral bioavailability.
- Lipids provide sufficient protection of drugs that are sensitive to gastric environment or undergo enzymatic degradation.
- They dispense a hydrophobic environment to delay the release of the loaded drug.
- Ability to improve physical stability of pharmaceuticals [16].

Disadvantages of Lipid-based drug delivery system:

- Difficulty in assessment of physicochemical properties.
- Provocation mainly in stability & manufacturing.
- Finite solubility of some poorly water-soluble drugs in lipids.
- Pre-absorptive gastrointestinal processing.
- Absence of predictive *in-vitro* and *in-vivo* testing methodologies [17].

Lipid based drug delivery system (LBDDS) Classification: According to lipid formulation classification system (^{LFCS}) are divided into four groups (I–IV), enables differentiation among various systems hiding behind the term lipid-based delivery [18]. Class-I systems include simple oil solutions without surfactants, containing mono-, di-, and/or tri-glycerides. Systems of Class-II contain lipophilic surfactants in addition to the oil phase in

order to increase the solubilisation capacity of systems for incorporated drugs to facilitate the stability of the emulsion formed upon dilution [19]. These LBDDS are known as SEDDS. The addition of hydrophilic components (surfactants and/or co-solvents) to the oil phase creates SMEDDS, which belong to Class III system. The most hydrophilic group are belonging to Class-IV system that are only composed of hydrophilic surfactants and hydrophilic co-solvents, which form colloidal micellar dispersion upon dilution with aqueous media.

Table 2: Lipid formulation classification system by Pouton[20]:

Classes	I	II	IIIa	IIIb	IV
Glycerides mono-di-, tri-glycerides	100	40-80	40-80	< 20	0
Lipophilic surfactants (HLB < 12)	0	20-60	20-40	0	0-20
Hydrophilic surfactants (HLB>12)	0	0	0-40	20-50	20-80
Co-solvents	0	0	0-40	20-50	0-80

FORMULATION

The choice of excipients for formulating poorly water-soluble drugs in lipid formulations is:
(a) lipids: synthetic or natural lipids, (b) surfactants: non-ionic- lipophilic or hydrophilic surfactants, (c) hydrophilic solvents: better dispersion and to increase solvent capacity, (d) co-solvents: reducing the viscosity of formulation and facilitate dispersion. The excipient selection has an impaction on drug loading [21], dispersion characteristics, and solubilisation of drug and importantly on stability. The lipids present in lipid-based formulations are:

A) Lipids: Lipids are naturally occurring oils and fats; these are composed with triglycerides and fatty acids of having chain lengths with degree of unsaturation. Lipids are classified according to their chemical structure, polarity, characteristics and degree of interaction with water [22]. Resistance of lipid phase highly influence of drug release in which higher polarity indicate the drug release to aqueous phase. Glyceride fractions of natural lipid oils are used to reduce the oxidation preparation. Hydrophilic forms solid formulation illustrates low bioavailability as their absorption is dissolution and capacity limited due to poor solubility [23]. Oil has main role in solubilising the lipophilic drug (or) facilitates self emulsification. Non digestible lipids such as mineral oil. e.g. liquid paraffin and sucrose polyesters, essentially remain unabsorbed in intestinal lumen and even reduce drug absorption. Digestive lipids comprise dietary lipids such as glycosides, fatty acids, phospholipids, cholesterol esters as well as various synthetic derivatives [24]. Thus rate and extent of digestion, colloidal phases formed and pharmacological effects of digestion products represent potential factors influencing release of API from the vehicle and its absorption [25].

B) Triglycerides: These are most commonly used lipid-based drug delivery excipients. In this ester groups are present majorly with fatty acid triesters of glycerol. The pure triglycerides are mainly present in refined vegetable oils. When compared with long chain glycerides, medium chain glycerides show complete digestion and also high solvent capacity [26]. Long chain fatty acids and mono-glycerides are re-esterified to triglycerides within intestinal cell, and secreted from intestinal cell by exocytosis into lymph vessels by resynthesized triglycerides accumulation within Golgi apparatus. Chylomicrons are formed by addition of phospholipids and proteins. These chylomicrons in Golgi vesicles are secreted into intercellular spaces by exocytosis, and then travel through the lamina propria to lymphatics [27].

C) Mixed Glycerides: Mixed glycerides are obtained by partial hydrolysis of vegetable oils. The starting material (triglyceride) and extent of hydrolysis determine the chemical composition of mixed glycerides produced [28]. Medium-chain mixed glycerides is not susceptible to oxidation, having greater solvent capacity, and promote emulsification.

D) Surfactants: Surfactants are mainly used to improve the bioavailability. Where glycerides containing fatty acid (Cremophor® EL) exhibits ethoxylation and increases the hydrophilicity, and also bioavailability. Surfactants can improve drug dissolution, enhance intestinal epithelial permeability and also increase tight junction permeability [29]. Surfactant in formulation plays a predominant role to increase absorption of lipophilic drugs.

E) Co-surfactants: Co-surfactants with HLB (value-10-14) is used along with surfactant for

lowering the oil phase tension, interface would expand to form fine dispersed droplets. Fluid interfacial film is to achieve the addition of co-surfactant. Co-surfactant enhance the fluidity of interface and thereby increasing the entropy of system [30].

F) Water-insoluble surfactants: These are the group of lipid excipients having intermediate hydrophilic lipophilic balance (HLB of 8–12) that adsorb at oil/water interfaces are hydrophilic in nature forms self emulsification[31]. Oleate esters such as polyoxyethylene sorbitan trioleate (Tween-85), polyoxyethylene glyceryl trioleate (Tagot TO) are examples of water-insoluble surfactants having HLB values are between based on the degree of ethoxylation, these are soluble in water and forms dispersion[32].

G) Water-soluble surfactants: These are most commonly used surfactants in formulation of self emulsifying drug delivery systems. These are water soluble having HLB value of 12, low concentration of this forms micellar solutions in pure water above their critical micellar concentration. Alcohols can be react with ethylene oxide to produce alkyl ether ethoxylate, which is commonly used surfactant. e.g., cetostearyl alcohol ethoxylate (cetomacrogol)[33]. Cremophor RH40 and RH60 (ethoxylated hydrogenated castor oil), this enhances the absorption by inhibiting the efflux pump.

H) Co-solvents: co-solvents are the purpose of solubilising the drugs and triglyceride in the composition. This enables dissolution of large quantities either hydrophilic surfactant or drug in lipid base[34]. They even act as co-surfactants in microemulsions. Some limitations are includes-immiscibility of some co-solvents with oils, incompatibilities of low molecular weight solvents and precipitation of solubilised drug from solvent due to loss of solvent capacity[35]. Other volatile co-solvents exhibit evaporation especially in hard gelatin and soft gelatin capsules in conventional SEDDS leading to precipitation, so that alcohol free formulations have been designed [36].

I) Additives: This are to protect the formulation from oxidation, various lipid soluble anti-oxidants such as α-tocopherol, β-carotene, propylgallate, butylated hydroxyl toluene (BHT) or butylated hydroxyanisole (BHA) can be used [37].

Factors affecting bioavailability of lipid-based formulations:

i) Lipid dissolution: I lipid digestion consists of three sequential steps: (i) the dispersion of fat globules to yield a fine emulsion, (ii) the synthetic hydrolysis of fatty acid esters at the emulsion-water interface, and (iii) the elution and dispersion of insoluble lipid products for later absorption. The API assembles at surface of absorptive epithelium by enterocytes [38]. Certain drugs and surfactants reduce the activity of efflux transporters in GI-wall and increase the fraction of drug absorbed [39]. Because they interplay between P-gp and CYP3A4 activity, this mechanism may decrease intracellular metabolism. Non-digestible lipids, including mineral oils, sucrose polyesters and others, are not absorbed from gut lumen [40].

ii) Role of lipids improvement in bioavailability: The bioavailability of some drugs is increased when it is co-administered with food. BCS class-I drugs are not affected by presence or absence of food, but class II drugs have an altered absorption when it is co-administered with food. Such increasing in bioavailability attributed to solubility, permeability and interference of efflux transporters in presence of food. The lipid component of food has vital role in absorption of lipophilic drugs leading to improving in oral bioavailability [41]. This has capacity of high fat meal to stimulate biliary and pancreatic secretions to decrease metabolism and efflux activity and also increase in intestinal wall permeability to prolongation of gastrointestinal tract (GIT) residence time and transport via lymphatic system. This is similar to lipoproteins with drug molecules improves intestinal lymphatic transport and leads to changes in drug disposition and finally changes in kinetics of the pharmacological actions of poorly soluble drugs.

iii) Mean emulsion droplet diameter: The mean emulsion droplet diameter is parameter indicating the grade of self-emulsifying formulations. The droplet size of SEDDS upon thin with aqueous media is principally influenced by type and concentration of emulsifier. The higher concentration of emulsifier, its shows smaller emulsion droplet and the faster the drug release [42]. Two techniques are commonly used to determine the term emulsion droplet diameter. low angle laser light diffraction is applied for emulsions with droplet sizes > 1μ and quasi-elastic light scattering for investigations of submicron dispersions.

iv) Lipophilicity of the API: Highly hydrophobic drugs (log P > 6) can be taken up into the lymphatic system by partitioning into chylomicrons in the mesentery vein which has been demonstrated to be crucial for the absorption of the anti-malaria compound [43]. Therefore, more highly lipophilic retinoids are known as transported in the intestinal lymph after oral administration.

Selection of lipid-based excipients: Self emulsification is the specific nature of the oil/surfactant ratio, the surfactant concentration and

temperature at which self emulsification occurs. These components are to achieve maximum drug loading, minimal self emulsification time and droplet size in the gastric milieu for obtaining maximum absorption to reduce variation in the emulsion droplet size and to prevent or minimize drug degradation [44]. For selection of a suitable self emulsifying vehicle the following are to be: (a) The drug solubility in various components, (b) The area of self emulsifying region in the phase diagram and (c) Droplet size distribution following self-emulsification.

i) Solubility: Solubility is useful for the selection of a solvent or solvents for a particular application[45]. Solubility parameters estimate the compatibility Hildebrand solubility parameters are effective to predict the formulation characteristics.

ii) Hydrophilic-Lipophilic Balance (HLB): The HLB is an empirical formula that is used to characterize surfactants and select those appropriate for preparation of micro emulsions of a particular compound[46].

Figure1: Way of selection of lipid-based system.

iii) Partition Coefficient: The lipophilicity of a molecule related to the partition coefficient of a compound between a lipophilic and hydrophilic phase it is also an important factor in selection of excipients. Compounds with log P>4 (i.e., being more lipophilic) are dissolved in oils and the compounds with intermediate log P (log P<4) require a mixture of hydrophilic surfactants (HLB 4-12) or water-soluble co-solvents to form a self-emulsifying system with maximum solubility [47]. Compound with low log P shows highest solubility in oil phases compound with high log P does not show highest solubility in oil.

METHODOLOGY

A) Microemulsion: Microemulsion is thermodynamically stable, isotropically clear with two immiscible liquids, such as oil and water, and it maintain by interfacial film of surfactant molecules. Surfactant molecules contain both polar and non-polar group. Microemulsion and other biphasic disintegration are nano-sized diffusion comprised of oil phase, aqueous phase, and relatively large part of surfactant and co-surfactant mixture in relevant ratios[48]. Coarse emulsion, microemulsion are spontaneously formed system and possess very low interfacial tension[49]. A process of self-emulsification is initiated inclusion of large portion of surfactant and co-surfactant mixture to oil and water. It result, thermodynamically stable microemulsion is formed voluntary without input of mechanical energy [50].

Formulation of Microemulsion: Microemulsions are nano-structured vehicles have energetic structures which affect performance of topical formulation. its structural dynamics need to completely assessed[51]. Microemulsions should characterized for ternary phase diagram, phase behaviour, selection of specific microemulsion region from phase diagram, identification and assuming of microemulsion region selected for formulation development, dispersed phase droplet size and its distribution and rheological behaviour. Apart from development of microemulsion formulation needs to characterized for physical properties such as pH, surface tension and specific gravity [52].

i. Phase Behaviour: The phase behaviour of mixture and its constitution can confine with the support of the phase diagram. The phase behaviour of simple microemulsion systems with oil, surfactant, and cosurfactant are carried out with aid of ternary phase diagrams in corner of diagram represents 100%of meticulous component. They contain supplemental component as cosurfactant and/or drug where four or more components are involved, pseudo ternary diagrams are constructed a corner represents a binary mixture of two components as surfactant/cosurfactant, water/drug, or oil/drug [53].

ii. Phase Rule: The phase rule enables recognition number of variables depending on system compositions and conditions. It is depicted as,F = C

– P + 2Where, F is number of possible independent changes of state or degrees of freedom, C is number of independent chemical constituents, and P is number of phases present in system. The F value determines system to invariant, monovariant, bivariant, etc., depending upon values whether zero, 1, 2, or so on [54].

iii. Phase titration method: Microemulsions are arrange by unconstrained emulsification method (phase titration method) and portrayed with help of phase diagram. As quaternary phase diagram (four component system) is time-consuming and difficult to interpret, pseudoternary phase diagram is constructed to find out different zones counting microemulsion zone each corner of diagram represents 100% of particular components. Pseudoternary phase diagrams of oil, water, and cosurfactant/surfactants mixtures are constructed at fixed cosurfactant/surfactant weight ratios. Phase diagrams are acquire by mixing of ingredients, which should be re-weighed into glass vials and titrated with water and stirred well at room temperature. The visual inspection is used to confirm the formation of the monophasic/biphasic system[55]. The turbidity appears followed by phase separation, the samples shall be considered as biphasic. In case monophasic, clear and transparent mixtures are envision after stirring. the samples shall be marked as point in phase diagram by these points is considered as microemulsion region.

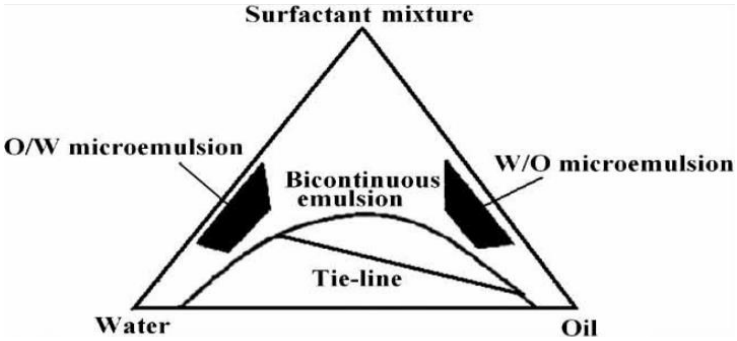

Figure 2: Pseudo ternary phase diagram.

iv. Phase inversion method: Phase inversion of the microemulsion is carried out excess of the dispersed phase or in response to temperature. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an O/W microemulsion at low temperature to a W/O microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets [56].

B) Nanoemulsions: Nanoemulsions are based upon drug delivery system comprise of emulsified oil and water systems with droplet diameter align from 50 to 1000nm. The average droplet size between 100 and 500nm as oil-in water (o/w) or water-in-oil (w/o) form, core of particle size is any oil or water form. Nanoemulsions prepared by high-low energy methods both high energy and low energy methods make stable nanoemulsions[57]. High pressure blending used for preparation of nanoemulsion by high energy emulsification low energy methods for preparation of nanoemulsions. This emulsification conducts by changing parameters such as temperature and composition affect the hydrophilic lipophilic balance (HLB) system.

Formulation of Nanoemulsions: Nanoemulsions are produce by using oils, surfactants, co-surfactant and aqueous phase for solubility drug in many phases. As nanoemulsion are non-equilibrated systems and arrange involves in large amount of energy or surfactants. High energy and low energy methods are used in formulation because process may be artificial. The producing nanoemulsion costs more energy than required to produce macroemulsion. Surfactant help lower the surface tensions between oil and water [58].

i. Phase Inversion Temperature (PIT) Method: This method employs temperature dependent solubility of non-ionic surfactants such as polyethoxyalated surfactants to adjust their affinities for water and oil as function of temperature. This occurrence forms basis of nanoemulsion fabrication using PIT method. At intermediate temperature (also termed HLB temperature), the non-ionic surfactant has similar accord for aqueous and oily phase and ternary system has especially low interfacial tension (10^{-2}, 10^{-5}mNm $^{-1}$)[59]. It observed attribute of nanoemulsion are mainly dependent on the structure of the surfactant at HLB temperature (bicontinuous or lamellar) and surfactant/oil ratio. PIT method is useful for fabricating o/w emulsions.

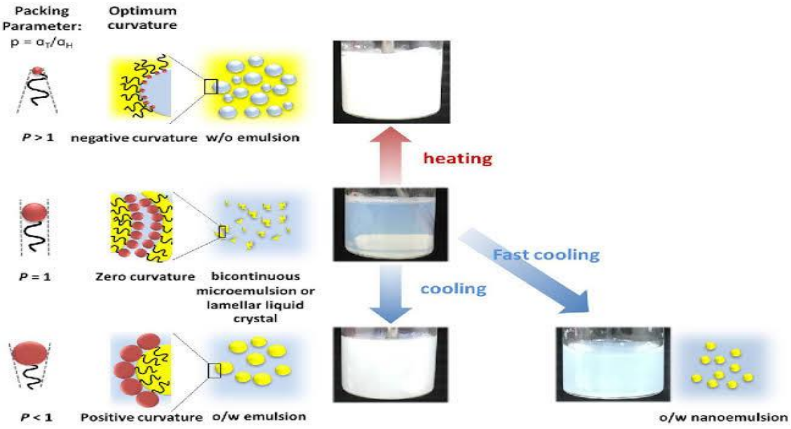

Figure 3: Phase inversion temperature method of nanoemulsion preparation.

ii. Phase Inversion Constitution Method (self nanoemulsification method): This method bring about nanoemulsions at room temperature without use of any organic solvent observe kinetically stable nanoemulsions with small droplet size (~50nm) generated by makeup of water into solution of surfactant in oil with gentle stirring at constant temperature[60].

C) Self-emulsifying drug delivery system (SEDDS): Self emulsifying drug delivery system is lipid based formulations that are isotropic mixtures of natural or synthetic oils, solid or liquid surfactant and co-surfactant susceptibility to aqueous media. (eg., gastrointestinal fluids), were self emulsification to form o/w nanoemulsion or microemulsion with droplet size between 20 to 200nm.

i.Phase diagram of SEDDS: A phase diagram of lipid expression for given API is individually by varying the ratio of drug, oil, and surfactant due to impact of physico-chemical properties of drugs such as intrinsic polarity and surface activity. phase studies are performed by diluting a mixture of oil-surfactant sequent with increasing amounts of water[61].

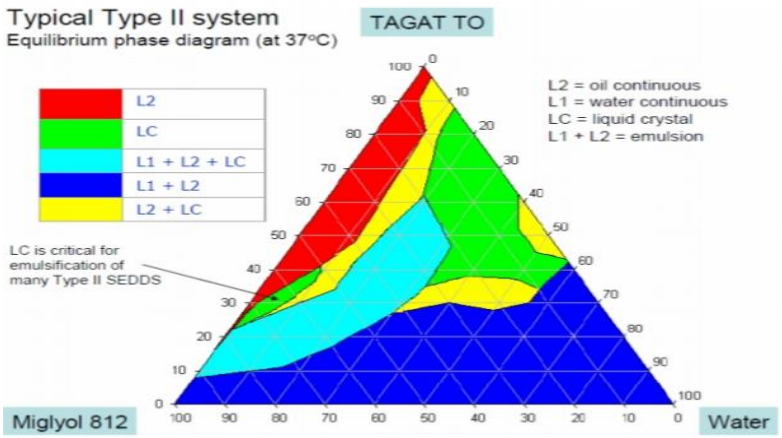

Figure 4: Phase diagram of SEDDS.

Characterization Techniques:

A. Size analysis: (i) Physical analysis: Lipid are higher chemical composition and melting points are opposed to single melting point. DSC used for thermal behaviour of excipients like melting, crystallization, solid to solid transition temperature [62].

(ii) Chemical analysis: Composition of lipid based excipients i.e., ester, others and distribution of fatty acid is assayed by HPLC and GC methods [63].

B. X-ray diffraction (XRD): X-ray diffraction patterns of sample of the drug and formulation are scanned by X-ray diffractometer from diffraction

angle (20) 5 to 500. Diffraction pattern of drug and LBDSS were obtained [64].

C. Dispersibility Test: The efficiency of self-emulsification of micro or nanoemulsion is assessed using a standard USP XXII dissolution apparatus-II. A standard stainless steel dissolution paddle rotating at 50 rpm provide gentle agitation[65]. The in vitro performance of formulations assessed using the following grading system: Grade A- it is forming (within 1 min) nanoemulsion, which shows clear or bluish aspect, Grade B- it is forming, slightly less clear emulsion, which shows bluish white aspect, Grade C- it form fine milky emulsion within 2 min, Grade D- it is dull, greyish white emulsion shows slightly oily aspect that slow to emulsify (longer- 2min), Grade E- it exhibiting either poor or minimal emulsification with large oil globules present on surface. Grade A and Grade B will remain as nanoemulsion when dispersed in GIT. Whereas formulation falling Grade C could be recommend as SEDDS formulation [66].

D. Solubilization: The balance between a drug's solubility in aqueous environment of gastrointestinal lumen and permeation across the lipophilic membrane of enterocytes determines rate and extent of drug absorption. Formulations in gastric lipase initiates the digestion of exogenous dietary triglyceride (TG), This TG broke down into diglyceride, monoglyceride and fatty acids by pancreatic lipase together with its co-factor colipase203.And TG to produce 2-monoglyceride and free fatty acid. The presence of exogenous lipids in the small intestine stimulates the secretion of endogenous biliary lipids from the gall bladder, including bile salt (BS), PL and cholesterol[67].

E. *Invitro* studies: *In vitro* evaluation of lipid-based drug delivery systems can be use for lipid digestion model sit is necessary to design an in vitro dissolution testing method. This can be termed as "simulated lipolysis release testing", as described. The instrument used for studying enzymatic hydrolysis of lipids as pH-stat titrationsystem, showed in Fig. 5. The basic principle of this system maintaining a constant pH during a reaction which releases or consumes hydrogen ions. Any deviation is found, it is compensated by the reagent addition.

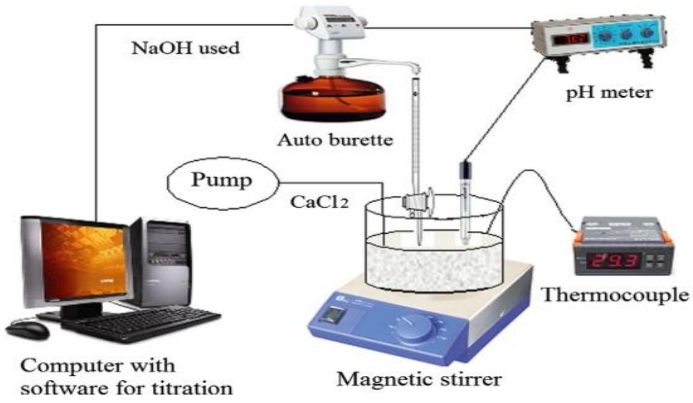

Figure 5: pH- stat titration system.

The model consists of temperature-controlled vessel (37°C), which consist of intestinal fluid, composed of digestion buffer, bile salt (BS) and phosphor lipid (PL). lipid-based formulation is addition and to initiate the digestion process of pancreatic lipase and co-lipase were added. It results in liberation of fatty acids, causing a transient drop in pH. This drop in pH is quantified by a pH electrode [68]. The pH electrode is coupled to pH-stat meter controller and auto burette. An equimolar quantity of sodium hydroxide is added to titrate the release of fatty acids by auto burette to prevent a change in pH of digestion medium from pre-set pH value. By quantifying the rate of sodium hydroxide addition and considering the stoichiometric relationship between fatty acids and sodium hydroxide. Results shows that all three parameters have an impact on initial rate of hydrolysis, whereas subsequent stages were affected by calcium concentration and lipase activity. An in vitro lipid digestion model was developed by Christensen and co-workers. The transfer of lipophilic drugs from fractionated coconut oil and sesame oil to the aqueous phase was studied [69].

Novel Lipid Based Formulations:

The carrier systems that have been most extensively studied to control the release of the incorporated substances are:

a) Nanoemulsion.
b) Solid lipid nanoparticles (SLNs).

c) Self-emulsifying drug delivery systems (SEDDS).

a) Nanoemulsion: Nanoemulsions are novel drug delivery system consists of emulsified oil and water systems with droplet diameters fluctuate from 50 to 1000nm. The extend droplet size is between 100 to 500nm as oil-in-water (o/w) or water-in-oil (w/o) forms core of particle size is either oil or water respectively. The surfactant type and concentration in aqueous phase provides good stability in opposite to coalescence. Many types of oils-natural semi-synthetic and synthetic used in formulation of nanoemulsion. Nanoemulsion has capacity to dissolve large quantities of low soluble drugs along their compatibility and ability to protect drug from hydrolysis and enzymatic degradation. The major advantage of nanoemulsion drug delivery includes drug loading, drug enhancement solubility and bioavailability, and controlled drug release[70].

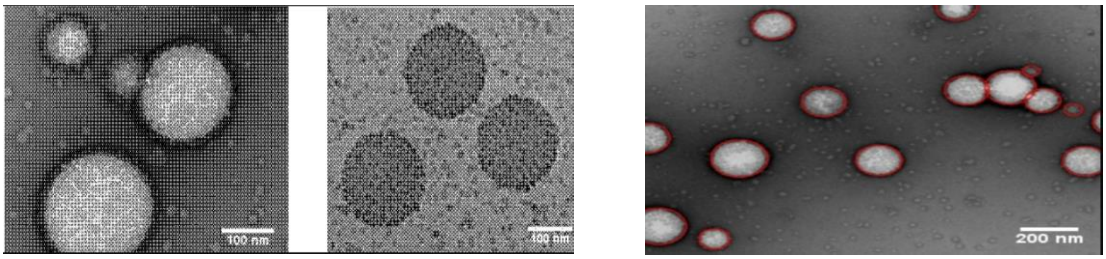

Figure6:A silicate particle stabilized oil in water nanoemulsion using negative stain.

b) Solid lipid nanoparticles: SLNs are submicron size ranges from (50–1000 nm) and built a lipidic matrix being solid at room temperature. They represent an alternative drug carrier system to liposomes and polymeric nanoparticles. SLNs has various advantages while avoiding some of their disadvantages: (i) The lipids used are similar to physiological lipids to reduce toxicity, (ii) SLNs are physic chemically stable and produced easily on large industrial scale. (iii) Raw materials and production costs are relatively low. There is important limitation that drugs are incorporated into SLN's and it has lipophilic high entrapment efficiency [71]. So, SLNs has studied for parenteral, oral, and topical administration.

c) Selfemulsifying drug delivery system: SEDDS are easily prepared and physically stable isotropic mixtures of oil, surfactants, co-surfactants and emulsifiable drug substance are administered vice voce in soft or hard gelatin capsules. Whereas SMEDDS readily diffuse in GI-tract, the motility in stomach and intestine allows for emulsification. Self-emulsifying properties are conferred by selection of lipid/surfactant pair as well as optimum ratio of lipid and surfactant. The lipid droplets formed in self-emulsifying formulations may facilitate drug absorption which is directly, independent from the bile salt mediated mixed micelle transport system [72].

Strategies to inflate bioavailability of orally administered poorly water-soluble drugs: It's suggested that to improve poorly water-soluble drugs primarily higher due to solubilization capacity. The lipid droplets formed upon dispersion of self-emulsifying LBDDS may directly ease drug absorption of bile salt–mediated mixed micelle transport system. Other mechanisms are involve protection of drug inside the lipid droplets from chemical and enzymatic degradation, localization into aqueous environment changes in gastrointestinal membrane permeability, and advancement of lymphatic drug transport [73]. Besides solubilisation capacity and droplet size of dispersions formed, the self-emulsifying ability also depends on functionality of excipients, thus influences drug absorption process.

Table3: Strategies of LBDDS for increasing bioavailability of drug:

Strategy	Brief explanation
Prolong retention in stomach	The GIT shows slower peristaltic action and gastric emptying, also increased in retention time of content and co-administration of drug in the upper intestine, whereas absorption occurs [74]. This dissolution rate in upper intestine and positively influences drug absorption.
Increased solubilisation	lipids in GIT stimulates increased excretion of bile salts and endogenous bile lipids (including cholesterol and phospholipids), which ease the emulsification of lipids and drug solubilisation [75]. This leads to formation of intestinal mixed micelles of endogenous origin and increased solubilisation capacity of GIT for drug.
Changes biochemical barrier	Some lipids and surfactants can reduce activity of intestinal secretion vectors

Changes physical barrier	in gastrointestinal wall (such as P-glycoprotein) and inhibit metabolic activity It act as promoters of intestinal absorption to increased membrane permeability [76]. Surfactants can occur fluidization of intestinal cell membrane and aperture of tight junctions, which shows in increased membrane permeability.

CONCLUSION

Lipid based drug delivery system (LBDDS) has wide scope in terms of solubility and bioavailability enhancement. Low water solubility of drug from BCS class II and IV leads to poor oral bioavailability. Improvement in oral bioavailability of drug by formulating in lipid-based formulation is one of the most common method in current days. Digestion of lipid-based system and direct absorption from lymphatic system allows lipid-based delivery most likely to improvement in bioavailability is achieved. Various characterizations were done to improve effectively of lipid based systems.

REFERENCES

1. Anette M et al. New prespectives on lipid and surfactant-based drug delivery system for oral delivery of poorly soluble drugs. JPP Journal of pharmacy and pharmacology 2010; (62): 1622-1636.
2. Sandeep K et al. Oral lipid-based drug delivery systems- an overview. Acta Pharmaceutica Sinica B 2013;3(6):361-372.
3. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. European Journal Pharmacy Science 2006;29:278–87.
4. O'Driscoll CM, Graffin BT. Biopharmaceutical challenge associated with drugs with low solubility, the potential impact of lipid-based formulations. Advance Drug Delivery2008; (60): 617-624.
5. Manoj A et al. Self micro emulsifying drug delivery system of curcumin attenuates depression in olfactory bulbectomized rats. Science Direct Heliyon 2020.
6. Mitali H Patel et al. Novel drug delivery approach self micro emulsifying drug delivery system for enhancing oral bioavailability of Asenapine Maleate. AAPS Pharmacy Science Technology 2019: 20-44.
7. Mounika P et al. Development and characterization of self microemulsifying drug delivery system of Rosavastatin. GSC Biological and Pharmaceutical Sciences 2018; 1: 1-10.
8. Yunrong Z et al. Characterisation and evaluation of a self-micro emulsifying drug delivery system containing tectorigenin, an isoflavone low aqueous solubility and poor permeability. Drug delivery 2017; 24(1): 632-640.
9. Ankita V Shah et al. Development of self microemulsiying drug delivery system for oral delivery of poorly water-soluble nutraceuticals. Drug development and industrial pharmacy 2016; 16(09): 34-42
10. Lan Wu et al. A self micro emulsifying drug delivery system for a novel medicative compound against depression: a preparation and bioavailability study in rats. AAPS Pharmacy Science and Technology 2015;6 :1-5.
11. Jyotsana RM et al. Formulation and development of self micro emulsifying drug delivery system of pioglitazone hydrochloride. Asian Journal of pharmacy 2014;8:10-18.
12. Shailesh T. Prajapti, Harsh A. Joshi. Preparation and characterisation of self microemulsifying drug delivery system of Olmesartan Medoxomil for bioavailability improvement. Hindawi Publishing Corporation journal of pharamceutics 2012; 9:1-10.
13. Xinru Li et al. Development of silymarin self micro emulsigying drug delivery system with enhanced oral bioavailability. American Association of Pharmaceutical Scientists 2010; 11: 1121-1127.
14. Ajeet K. Singh et al. Oral bioavailabilty enhancement of Exemestane from self microemulsifying drug delivery system; American Association of pharmaceutical scientists 2009;10(3):1-10.
15. Ashok R Patel and Pradeep R Vavia. Preparation and in vivo evaluation of SMEDDS containing Fenofibrate. American Association of pharmaceutical scientists 2007; 9(3):110-118.
16. Gershanik T, Benita S. Self dispersing lipid formulations for improving oral absorption of lipopholic drugs. European Journal Pharmacy Biopharmaceutical 2000;50:179-188.
17. Ritiksha Khatri et al. Oral lipid based drug delivery system, International journal of pharmaceutical science and research 2014; 5(4): 2074-82
18. Pouton WC and Porter JHC. Formulation of lipid-based delivery systems for oral administration. Advance Drug DeliveryRev 2008;60:625–637.
19. Nanjwade BK et al. Function of lipids for enhancement of oral bioavailability of poorly water soluble drugs. Science Pharmacy 2017;79:705-727.

20. PoutonW.C. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. European Journal. Pharmacy science 2006;29:278–287.
21. Tejeswari N et al. Lipid based drug delivery system for enhancing oral bioavailability- A Contemporary Review; Journal of global trends in pharmaceutical sciences 2014; 5(4): 2074-2082.
22. Kim HJ et al. Preparation and in vitro evaluation of self micro emulsifying drug delivery systems containing idebenone. Drug Dev Ind Pharm 2000; 26: 523–529.
23. Pouton CW, Porter CJH. Formulation of lipid based delivery systems for oral administration. Advance Drug Deliv Rev.2008; 60: 625–37.
24. Humbertone AJ, Charman WN. Lipid based vehicles for the oral delivery of poorly water soluble drugs. Adv Drug Delivery Rev 1997; 25: 103-28.
25. Wilson CG, Mahony BO. The behaviour of fats and oils in the upper G.I Tract; Bull Tech Gattefosse 1997; 90: 13-18.
26. Cao Y, Marra M, Anderson BD. Predictive relationships for the effects of triglyceride ester concentration and water up take on solubility and partitioning of small molecules into lipid vehicles. J Pharm Sci 2004; 93:2768–79.
27. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharm Res 2004; 21:201–30.
28. Lindmark T et al. Mechanism of absorption enhancement by medium chain fatty acids in intestinal epithelial Caco-2 monolayer. Journal Pharmacol ExpTher 1995;60:625-637.
29. Lawrence MJ, Rees GD. Micro emulsion-based media as novel drug delivery systems. Advance Drug Delivery Re 2000;45:89–121.
30. Warkerly MG et al. Self emulsification of vegetable oil-non-ionic surfactant mixture; Proposed mechanism of action. ACS Symp Series 1986;11:242-55.
31. Pouton CW. formulation of self emulsifying drug delivery system. Advance Drug Delivery Rev 1997;25:47-58.
32. Schick MJ. Surfactant Science Series. New York: Marcel Dekkar 1987: 23.
33. Strickley RG. Solubilising excipients in oral and injectable formulations. Pharm Res 2004; 21:201–230.
34. Cole ET et al. Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. Advance Drug Delivery Rev 2008;60:747–56.
35. Yalkowsky SH. Solubility and solubilisation in aqueous media (ACS Professional Reference Books). American Chemical Society 1999: 1-480.
36. Gibson L. Lipid based excipients for oral drug delivery. New York; Informa Healthcare 2007:33-61.
37. Embleton JK, Pouton CW. Structure and function of gastrointestinal lipases. Advance Drug Delivery Rev 1997; 25: 15–32.
38. Shah NH et al. Self-emulsifying drug delivery systems (SEDDS) with poly glycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. International Journal Pharm 1994;106:15–23.
39. Charman SA et al. Self emulsifying drug delivery system; Formulations and biopharmaceutical evaluation of an investigational lipophilic compound. Pharma Res 1992;9: 87-93.
40. Strickley RG. Currently Marketed oral lipid based dosage form. Drugs products and excipients 2007;1-31.
41. Armstrong NA, James KC. Drug release from lipid-based dosage forms. Int J Pharm 1980; 6:195–204.
42. Swenson ES, Curatolo WJ. Intestinal permeability enhancement for proteins, peptides and other polar drugs; mechanisms and potential toxicity. Advance drug delivery Rev 1992;8:89-92.
43. Osborne DW et al. Alcohol-free microemulsion. J Dispersion Sci Technol, 1988;9:415-423.
44. Aungst BJ et al. Amphiphilic vehicles improve the oral bioavailability of a poorly soluble HIV protease inhibitor at high dose. International Journal of Pharmacy 1997;156:79-88.
45. Szuts EZ, Harosi FI. Solubility of retinoids in water; Arch Biochem Biophys, 1991;87:297-304.
46. Charman WN, Stella VJ. Estimating the maximal potential for intestinal lymphatic transport of lipophilic drug molecules. International Journal of Pharmacy 1986;340:175-178.
47. Eccleston GM. Microemulsions, Encyclopedia of pharmaceutical technology, Marcel Dekkar; NewYork, 1992;9:375-421.
48. Attwood D. Microemulsions. colloidal drug delivery systems. Marcel Dekkar, New York 1994;31-71.
49. Griffin BT, O'Driscoll CM. A comparison of intestinal lymphatic transport and systemic bioavailability of saquinavir from three lipid based formulations in the anaesthetised rat model. Journal Pharm Pharmacol 2006;58:917–25.
50. Kaur J et al. Microemulsions: A potential novel drug delivery system. International Journal Pharmacy Medical Res 2014;2:15-20.

51. Muzaffar F et al. Review on microemulsion as futuristic drug delivery. International Journal Pharmacy Science 2013;5:39-53.
52. Yogi J et al. Microemulsion as advanced topical drug delivery: A review. International Journal Pharm Res Bio Science 2015;4:320-40.
53. Verma A et al. Topical gels as drug delivery systems: A review. International Journal Pharm Science Rev Res 2013;23:374-82.
54. Ritika A et al. Microemulsion system in role of expedient vehicle for dermal applications. Journal Drug Delivery Ther 2012;2:23-8.
55. Patel RM et al. Investigating the effect of vehicle on in vitro skin permeation of ketoconazole applied in o/w microemulsions. Acta Pharm Sci 2010;5:65-77.
56. Porter CJH et al. Lymphatic transport of halofantrine in the triple cannulated anesthetized rat model: Effect of lipid vehicle dispersion. Journal Pharm Science 1996; 85:351–356.
57. Hauss DJ. Lipid-based systems for oral drug delivery: Enhancing the bioavailability of poorly water-soluble drugs. Am Pharm Rev 2002;5:22–28.
58. Stella V et al. Enhancement of bioavailability of a hydrophobic amine antimalarial by formulation with oleic acid in a soft gelatin capsule. Journal Pharm Science 1978;67:1375–1377.
59. Tokumura T et al. Enhancement of oral bioavailability of cinnarizine in oleic acid in beagle dogs. Journal Pharm Science 1987;76:286–288.
60. Lalitachuhan et al. Microemulsion- A new vista of novel delivery system. Pharmaco other 2019;2:37-44.
61. Jannin V et al. Approaches for the development of solid and semi-solid lipid-based formulations. Advance Drug Delivery Rev 2008;15:734–746.
62. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and self-microemulsifying drug delivery systems. European Journal Pharmacy Science 2000;11:93-8.
63. Bora DK et al. Formulation and evaluation of self microemulsifying drug delivery system of low solubility drug for enhanced solubility and dissolution. Asian Journal of Biomedical and Pharmaceutical Sciences 2013;2:7-14.
64. Bagwe RP et al. Improved drug delivery using microemulsions. Crit Rev Ther Drug Carrier Syst 2001;18:77-140.
65. Mehnert W, Mader K. Solid lipid nanoparticles: production, characterization and applications. Advance Drug DeliveryRev 2001;47:165–196.
66. Pramod K et al. An overview of lipid based formulation for oral drug delivery. Drug Inv Today 2010;2:390-5.
67. Zangen berg NH et al. A dynamic in vitro lipolysis model I. Controlling the rat of lipolysis by continuous addition of calcium. European Journal Pharm Science 2013;14:115–22.
68. Zangen berg NH et al. A dynamic in vitro lipolysis model II: evaluation of the model. European Pharm Science 2001;14:237–44.
69. Zeng XM et al. The controlled delivery of drugs to the lung. Int J Pharm 1995; 124: 149–164.
70. Zur MA et al. Solid lipid nanoparticles (SLN) for controlled release drug delivery- Drug release and release mechanism. European Journal Pharmacy Biopharm 1998;45:149-155.
71. Constantinides P. Lipid microemulsion for improving drug dissolution and oral absorption; physical and biopharmaceutical aspects. Pharm Res:1995;12:1561-1572.
72. Jannin V et al. Approaches for the developments of solid and semi-solid lipid based formulations. Advance Drug Delivery Rev 2008;60:734-746.
73. Rajesh BV et al. Lipid based self-emulsifying drug delivery system (SEDDS) for poorly water-soluble drugs: A review. Journal Global Pharma Technology 2010;2:47–55.
74. Gupta RN et al. Singh. Enhancement of oral bioavailability of lipophilic drugs from self-micro emulsifying drug delivery systems (SMEDDS). International Journal Drug Delivery Res 2009;1:10–18.
75. Mohsin K et al. Lipid based self-emulsifying formulations for poorly water soluble drugs- an excellent opportunity. Industrial Journal Pharm Edu. Res 2012;46: 88–96.
76. Porter HJC et al. Lipids and lipid based formulations: optimizing the oral delivery of lipophillic drugs. Nat Rev Drug Discov 2007;6:231-248.