Vol 7 | Issue 1 | 2017 | 16-28.

International Journal of Advanced Pharmaceutics

e-ISSN 2249 – 7706
print-ISSN 2249– 7714

www.ijapjournal.com

Review Article

SELF-MICROEMULSIFYING: A NEW APPROACH OF LIPID BASED DRUG DELIVERY SYSTEMS

Md. Mehdi Hasan*[1], Md.Mizanur Rahman[2], Mahbub Hasan[2], S.M. Nazrul Islam[3], Masum Al Hasan[1], Harun Ar Rashid[1]

[1]Department of Pharmacy, Faculty of Health science, Northern University Bangladesh, Dhaka -1205, Bangladesh.
[2]Department of Pharmacy, Stamford University Bangladesh, Dhaka-1217, Bangladesh.
[3]Department of Pharmaceutical Sciences, School of Health & life sciences, North South University, Dhaka-1229, Bangladesh.

Access this article online

Home page: http://ijapjournal.com/

DOI: http://dx.doi.org/10.21276/ijap.2017.7.1.3

Quick Response code

Received:25.10.16 **Revised**:22.11.16 **Accepted**:09.12.16

Corresponding Author
Md. Mehdi Hasan
Department of Pharmacy, Faculty of Health science, Northern University Bangladesh, Dhaka -1205, Bangladesh.
Email:- mehdinub@yahoo.com

ABSTRACT

Solubility is one of the key factor in drug formulation in order to ensure better bioavailability. As 40% of new drugs are poorly soluble, it has become a matter of concern and challenge for the formulation scientists with regard to solubility and bioavailability. Though formulation approaches like solid dispersions, complexation, pH modification exist, but there are areas of further research and development for better approaches. Lipid-based drug delivery systems (LBDDS) are one of the emerging technologies designed to address such challenges in recent time. These systems have shown great promise which can lead to increased solubilization and absorption, resulting in enhanced bioavailability. This review provides a comprehensive understandings of Lipid-based drug delivery systems especially for oral delivery, from both physicochemical and biopharmaceutical perspectives. This review also focuses on advanced techniques and processes, along with a brief discussion of various lipid excipients and their characterization.

Keywords: Bioavailability, Lipid based drug delivery system, Lymphatic transport and Self micro-emulsifying drug, Drug absorption Lipid excipients, Surfactant, Evaluation, Zeta potential.

INTRODUCTION

Administration of drug by oral route is the most effective and acceptable route as it has better therapeutic efficacy, low cost and good patient compliance. Though lipid based administration has its own unique advantages, it also has few drawbacks like extravasation of drug or blood, catheter infections, thrombosis etc. Such issues can be prevented by introducing oral administration. Nonetheless, oral administration is limited by problems related to physico-chemical properties of the drug, including poor solubility, low permeability, instability, and rapid metabolism, all of which decrease oral bioavailability [1]. With the advent of drug design, various molecules have been created that have a potential for therapeutic action. But most of the newly discovered chemical entities are of high molecular weight and belong to biopharmaceutical classification system (BCS) – II, with poor aqueous solubility and high membrane permeability. Hence these two characteristics limit the bioavailability of orally-administered drugs [2].

These drugs have low solubility which leads to low dissolution and limits absorption. This poor solubility not only gives low oral bioavailability but also leads to high inter- and intra-subject variability

and lack of dose proportionality. Also, some of these drugs have enhanced bioavailability when co-administered along with food, e.g., halofantrine and danazol. In order to formulate such drugs in a safe and efficacious form, a balance must be maintained between bioavailability, toxicity and disposition within the body. Various techniques like microniza-tion, complexation with cyclodextrins, solid dispersions, permea-tion enhancers and surfactants have been reported to overcome some solubility and permeability issues [3].

In the last decade lipids have gained much interest as carriers for the delivery of drugs with poor water solubility.

The availability of novel lipid excipients with acceptable regulatory and safety profiles coupled with their ability to enhance oral bioavailability has helped in the development of lipid based formulations as a means for drug delivery. Lipid-based drug delivery (LBDD) systems have gained much importance in the recent years due to their ability to improve the solubility and bioavailability of drugs with poor water solubility [4]. The absorption of drug from lipid based formulation depends on numerous factors, including particle size, degree of emulsification, rate of dispersion and precipitation of drug upon dispersion. Lipid-based formulations may include oil solution or suspensions, emulsions, self-micro or self-nano emulsifying drug delivery systems (SMEDDS/SNEDDS). Some of the drugs that are successfully marketed as lipid based formulations include efavirenz (Sustivas), saquinavir (Fortovases), ritonavir (Nor-virs), clofazamine (Lamprenes). An appropriate selection of lipid vehicles, formulation strategies and rational delivery system design can lead to the success of lipid based drug delivery systems [5].A water-insoluble drug can be formulated as a lipid-based formulation when the drug itself is an oil-like substance (e.g., ethyl icosapentate, tocopherol nicotinate, teprenone, indomethacin far-nesil and dronabinol), or when conventional formulation approaches like granulation or soluble liquids in capsules do not enhance the oral bioavailability [6]. A variety of lipid-based systems composed of simple oil solutions to complex mixtures of oils, co-solvents, surfactants and co-surfactants can be obtained based on the type of excipients and formulation variables. Indeed, these systems can be converted to solid intermediates (powders, granules and pellets) by various techniques and can be filled in hard gelatin capsules or can be compressed into tablets after blending with suitable tableting excipients [4]. The availability of novel lipid excipients with acceptable regulatory and safety profiles coupled with their ability to enhance oral bioavailability has helped in the development of lipid based formulations as a means for drug delivery. Which has gained much importance in the recent years due to their ability to improve the solubility and bioavailability of drugs with poor water solubility. An appropriate selection of lipid vehicles, formulation strategies and rational delivery system design can lead to the success of lipid based drug delivery systems.

DRUG ABSORPTION

In practice, lipid formulations can be obtained as a result of blending of excipients such as pure triglyceride oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants and water-soluble co-solvents10. these systems increase absorption from the gastrointestinal tract by accelerating the dissolution process, facilitating the formation of solubilized phases by reduc-tion of particle size to the molecular level, yielding a solid-state solution within the carrier, changing drug uptake, efflux and disposition by altering enterocyte-based transport [7] and enhancing drug transport to the systemic circulation via intestinal lymphatic system.

Lymphatic system

The lymphatic system plays an important role in the transport of drugs to the systemic circulation, given its extensive drainage network throughout the body. Some of the advantages of lymphatic transport of drug are avoidance of first-pass metabolism and targeting of specific diseases which are known to spread via lymphatics, such as certain lymphomas and HIV. Salt or ester formation: Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents [8]. Possible mechanisms by which lipids affect drug absorption, bioavailability and disposition after oral administration are summarized in Fig. 1. The promising mechanisms include: I facilitating transcellular absorption due to increased membrane fluidity; II, allowing paracellular transport by opening tight junctions; III, increased intracellular concentration and residence time by surfac-tants due to inhibition of P-gp and/or CYP450; IV, lipid stimula-tion of lipoprotein/ chylomicron production [9].

Digestion and solubilization

The balance between a drug's solubility in the aqueous environ-ment of the gastrointestinal lumen and its permeation across the lipophilic membrane of enterocytes determines its rate and extent of absorption. After oral administration of lipid-based formulations, gastric lipase initiates the digestion of exogenous dietary triglyceride (TG) and formulation TG. Simultaneously, the mechanical mixing (propulsion, grinding and retropulsion) of the stomach facilitates formation of a crude emulsion (comprised of aqueous gastric fluid and lipid

digestion products). The easy accessibility and higher surface area makes the nose a potentially viable drug delivery organ. Pharmaceutical product development is a crucial task which is directly dependent on its therapeutic objectives [10]. Later in the small intestine, TG is broken down to diglyceride, monoglyceride and fatty acids by pancreatic lipase together with its cofactor co-lipase203, acting primarily at the sn-1 and sn-3 positions of TG to produce 2-monoglyceride and free fatty acid [11].

Pancreatic phospholipase A2 digests the formulation-derived or biliary-derived phospholipids (PL) by hydrolyzing at the sn-2 position of PL to yield lysophosphatidylcholine and fatty acid. The 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. Previously formed monoglycerides, fatty acids, and lysophospholipid (products of lipid digestion) are subsequently incorporated into a series of colloidal structures, including micelles and unilamellar and multi-lamellar vesicles in the presence of bile salts. The solubilization and absorptive capacity of the small intestine for lipid digestion products and drugs (D) is significantly enhanced due to these formed lipid metabolites**.** In Fig. 2, the oil droplet in the intestine is represented in different colors to indicate undigested TG in the core (orange) and digested products such as fatty acid (blue) and monoglyceride (green) on the surface of the droplet.

The role of lipids in enhancement of bioavailability

The bioavailability of some of the drugs is increased when co-administered with food [12]. However, many drug molecules have negligible interaction with food. A situation in which use of, or exposure to, a violate product is not likely to cause adverse health consequences. [13]. BCS class I drugs are not affected by the presence or absence of food, but class II drugs have an altered absorption when co-administered with food. The reason for such enhanced bioavailability might be attributed to solubility, permeability and inhibition of efflux transporters in the presence of food. Some of the drugs which show enhanced bioavailability when administered along with food are griseofulvin, halofan-trine, danazol, troglitazone and atovaquone. A guidance document entitled "Food-Effect Bioavailability and Fed Bioequi-valence" was issued by FDA in December 2002. The US FDA recommended high fat meals for food-effect studies because such fatty meals (800–1000 cal, 50%–65% fat, 25%–30% carbohydrates and 15%–20% proteins) affect GI physiology and maximize drug transfer into the systemic circulation.

In particular, it is the lipid component of the food that plays a vital role in the absorption of lipophilic drug, [14] leading to enhanced oral bioavailability. This can be explained by the ability of a high fat meal to stimulate biliary and pancreatic secretions, to decrease metabolism and efflux activity, to increase intestinal wall permeability, and to a prolongation of gastrointestinal tract (GIT) residence time and transport via lymphatic system. Triglycerides and long chain fatty acids play a major role in prolonging the GIT residence time. Also, a high fat meal elevates the TG-rich lipoproteins which react with drug molecules. This association of lipoproteins with drug molecules enhances intestinal lymphatic transport and leads to changes in drug disposition and finally changes the kinetics of the pharmacological actions of poorly soluble drugs [15]. This food effect on drug absorption leads to a serious concern about the sub-therapeutic plasma drug concentra-tion when co-administered without food. Such food effect is also a serious problem for drugs with a narrow therapeutic index, where increased bioavailability may lead to serious untoward effects. Hence, control or/and monitoring of food intake is required when dosing such drugs.

However, food-dependent bioavailability can be significantly reduced by formulating the drug as a lipid-based formulation, which can increase the solubility and dissolution of lipophilic drugs and facilitate the formation of solubilized species, from which absorption occurs. Hence, lipid-based formulations can be used to reduce the dose of drug while simultaneously enhancing its oral bioavailability.

Lipid excipients

A wide range of lipid excipients are available from excipient suppliers. Since these lipids affect the absorption process, it is necessary to know the characteristics of various excipients. The factors that determine the choice of excipients for lipid-based formulations include miscibility; solvent capacity; self-dispersibility and ability to promote self-dispersion of the formulation; digest-ibility and fate of digested products; regulatory issues – irritancy, toxicity, purity, chemical stability; capsule compatibility; melting point, and cost.

For preparing lipid-based formulations, dietary oils composed of medium and long chain triglycerides, along with various solvents and surfactants are frequently chosen. Many lipids are amphiphilic in nature, having a lipophilic portion (fatty acid) and a hydrophilic portion. The melting point increases as the fatty acid chain length increases, but it decreases with the increase in the unsaturation of the fatty acid and also increases the susceptibility to oxidation [4]. A list of solubilizing agents used in lipid-based formulations is mentioned in Table 1.

Classification of lipid excipients

Triglycerides

The most common excipients used in lipid based drug delivery are triglyceride vegetable oils. The problem is how to deliver drugs right where we need it [16]This is one class of lipid which does not present any safety issues, since they are fully digested and absorbed. Triglycerides can be further classified as long chain triglycerides (LCT), medium chain triglycerides (MCT) and short chain triglycerides (SCT). The capacity as a solvent for drugs is mainly decided by the effective concentration of ester groups. MCT have a higher solvent capacity than LCT and are less prone to oxidation [17]. Oils from different vegetable sources have different proportions of each fatty acid. The composition of fatty acids found in various lipid excipients are presented in Table 2. D-α-Tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS) is derived from vegetable tocopherols. It is water soluble and acts as absorption enhancer for poorly water-soluble drugs. Pure triglycerides are presented in refined vegetable oils.

Mixed glycerides and polar oils

Mixed glycerides are obtained by partial hydrolysis of vegetable oils. The starting material (triglyceride) and the extent of hydro-lysis determine the chemical composition of the mixed glycerides produced. Medium chain mixed glycerides are not susceptible to oxidation, have greater solvent capacity and promote emulsifica-tion. These polar oily excipients also improve solvent capacity and the dispersibility of the formulation. Sorbitan trioleate (Span 85) is an example of polar oils. Apart from this, oleic acid is also used in a number of commercial products [18].

Cosolvents

In order to enhance the solubilization process, most marketed drug products use cosolvents [18]. The popular cosolvents used include ethanol, glycerol, propylene glycol and polyethylene glycols (PEG)-400. The reason for their use can be attributed to an increase in the solvent capacity of the formulation for drugs and to aid the dispersion of systems which contain a high proportion of water soluble surfactants. However, there are several practical limits related to these cosolvents, including precipitation of the solubilized drug from the solvent due to loss of the solvent capacity following dilution, immiscibility of some cosolvents with oils, and incompatibilities of low molecular weight solvents with capsule shells [19].

Water-insoluble surfactants

A group of lipid excipients with intermediate hydrophilic-lipophilic balance (HLB of 8–12) that adsorb at oil–water interfaces are available. Depending on the degree of ethoxylation, these have a finite solubility in water. They can form emulsions if subjected to shear and are sometimes referred as being ‘disper-sible’ in water. These substances can form micelles but are unable to self-emulsify due to their insufficiently hydrophilic nature. Oleate esters such as polyoxyethylene (20) sorbitan trioleate (Tween-85) and polyoxyethylene (20) glyceryl trioleate (Tagot-TO) are typical examples of water-insoluble surfactants whose HLB values are between 11 and 11.5. However, a blend of Tween-80 and Span-80 with average HLB value of 11 is not similar to Tween-85 in function. The former consists of both water-soluble and water-insoluble molecules, but the later consists of predominantly of water-insoluble molecules [20],

Water-soluble surfactants

These are the most commonly used surfactants for the formulation of self-emulsifying drug delivery systems. The materials with HLB value of approximately 12 or greater can form micellar solutions at low concentrations by dissolving in pure water above their critical micellar concentration. These materials can be synthesized by mixing polyethylene glycols (PEG) with hydro-lyzed vegetable oils. Alternatively, alcohols can be made to react with ethyleneoxide to produce alkyl ether ethoxylate, which is a commonly used surfactant (e.g., cetostearyl alcohol ethoxylate ‘cetomacrogol’). A reaction of sorbitan esters with ethylene oxide produces polysorbates (predominantly ether ethoxylates) [21].

Cremophor RH40 and RH60 (ethoxylated hydrogenated castor oil) are examples of this type which are obtained from hydro-genation of materials derived from vegetable oils. Cremophor EL (ethoxylated castor oil), which is not hydrogenated is also widely used. Cremophor is known to enhance the absorption by inhibiting the efflux pumps, but the mechanism of inhibition is not yet determined [22]. This might be attributed to a non-specific conformational change due to penetration of the surfactant molecules into the membrane, adsorption on to the surface of the efflux pumps, or interaction of molecules with intracellular domains of efflux pump.

1. Additives

In order to protect the formulation from oxidation, various lipid soluble anti-oxidants such as α-tocopherol, β-carotene, propyl gallate, butylated hydroxyl toluene (BHT) or butylated hydro-xyanisole (BHA) can be used.

2. Characterization of lipid systems

a. Physical analysis

Analysis of the thermal behavior of lipids during formulation is of primary importance, since lipid excipients have complex chemical compositions that lead to broad melting ranges. Various thermal properties of lipids including crystallization temperature, melting point, glass transition temperature and determination of solid fat content of the excipient versus temperature can be evaluated using differential scanning calorimetry (DSC). The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, etc [23].The organization of the lipid during heating or cooling can be assessed by hot-stage microscopy. Crystallinity of a lipid excipient can be confirmed by X-ray diffraction (XRD).

b. Chemical analysis

High performance liquid chromatography (HPLC) and gas chro-matography (GC) can be used to determine the exact composition of ethers, esters and fatty acid distribution. Other chemical indices are also available: the molecular weight of fatty acids can be determined from their saponification value; the saturation of hydrocarbon chains can be measured using an iodine-based assay; oxidative changes can be determined by measuring peroxides; free fatty acids can be measured from acid content; and free hydroxyl groups can be determined by measuring hydroxyl group content. emulsification and dispersion properties of the lipid excipients, leading to altered solubilization capacity in vivo. Hence, the digestibility of the lipid excipients must be considered when selecting lipid-based formulations [24,25]. To assess such effects and predict in vivo behavior, dissolution testing in biorelevant media can be helpful. The effectiveness of self-emulsifying formulations can be determined by dispersion testing (emulsifica-tion capacity and particle size). Photon correlation spectroscopy (PCS) or laser light diffraction can be used to measure the particle size, and visual observation can be helpful to predict emulsification capacity.

c. Analysis of physiological effects of excipients

Lipid-based excipients are known to enhance the oral absorption of drugs by affecting various physiological processes. These include stimulating bile flow and pancreatic juice secretion, prolonging gastric emptying, increasing the membrane fluidity, opening of tight junctions, promoting lymphatic transport of drugs, thus avoiding first pass metabolism, and inhibiting efflux transporters. In order to assess these effects various in vitro models are available, including intestinal microsomes, Caco-2 cells, everted gut sac, Using chamber, and in situ perfusion assays [26].

d. Regulatory status of lipid excipients

Not all excipients are inert substances, and some may be toxic at increased concentrations. In the Code of Federal Regulations, the FDA has published a list of substances that are generally recognized as safe (GRAS). Apart from this, it also maintains a list of inactive ingredients for excipients entitled Inactive Ingre-dient Guide (IIG) that are approved and can be incorporated in marketed products. This guide provides the list of maximum amount allowed for excipients, which can be used for a specific route of administration. Once an inactive ingredient has been approved for a product through a particular route of administra-tion, it can be used in any new drug formulation and does not require extensive review. The formulator can take the information from both GRAS and IIG when developing a new formulation. Currently, the FDA does not have any process or mechanism to evaluate the safety of excipients individually. Instead, the exci-pients are reviewed and approved as 'components' of the drug or biological product in the application. Since excipients play an integral part in the formulation and cannot be reviewed separately from the drug formulation, the regulatory process is appropriate from a scientific standpoint.

Self-Microemulsifying Drug Delivery Systems (SMEDDS):

SMEDDS (Type III B systems) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or one or more hydrophilic solvents and co-solvents/surfactants that have ability to form fine oil -in-water (o/w) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SMEDDS have large quantities of co-solvents but contain less quantity of oil. These formulations have high risk of drug precipitation. Most of the marketed lipid formulations belong to Type III [27]. SMEDDS have gained lots of importance due to clarity, high solubilisation capacity, thermodynamic stability, simple preparation method and ability to be filter [28].They can increase oral bioavailability and eliminate food effects [29].

Some authors refer to the type IIIB formulations as self-nanoemulsifying drug delivery systems (SNEDDS). SNEDDS spontaneously form transparent oil-in-water emulsion of approximately less than 100 nm in size upon dilution with water.

Lipid based formulation are useful for Biopharmaceutical classification system BCS Class II and IV. Druglipophilicity (logP) is useful for design of lipidic system.High logP of drug (greater than 4) is desirable. Low melting point and low dose of drug is

desirable for formulation of SMEDDS.

Biopharmaceutical aspects of SMEDDS: Mechanism for increase in absorption of drug by SMEDDS:

- In vivo solubilization of drug - Presence of lipid in gastrointestinal tract (GIT) stimulates secretion of bile salt and biliary lipid such as phospholipids and cholesterol, leads to formation of intestinal mixed micelles. This causes enhancement in solubilization capacity of GIT. Addition to lipid from formulation causes further increase in solubilization capacity. gut wall. Thus increase in permeability of drug.
- Reduced metabolism and efflux activity of drug- Certain surfactant and lipid show reduction in activity of efflux transporters in the gut wall thus increase in absorption of drug.eg. Labrasol, Cremophore EL.

Lipid digestion and drug solubilization in GIT:

Gastric lipase helps in digestion of lipid. Peristalsis and gastric emptying aids in emulsification before it entre in duodenum. In the small intestine pancreatic lipase converts dietary glycerides to diglycerides, monoglycerides and fatty acid. The presence of exogenous lipid in small intestine stimulates secretion of bile salt, phospholipid and cholesterol. This leads to formation of intestinal mixed micelle. It causes increase in drug solubilization.

Circulatory uptake of drug:

Fatty acid and monoglycerides digestion products

- Increase in gastric residence time of drug are resynthesised into triglycerides and assembled – Lipid in the GIT causes delay in gastric emptying. This enables better dissolution of drug and improves drug absorption.
- Promotion of intestinal lymphatic transport of drug – Lipid enhances the lymphatic transport of lipophilic drug and enhances bioavailability via reduction in first pass metabolism. In to colloidal lipoprotein within endoplasmic reticulum. These lipoproteins are exocytosed across the basolateral membrane of the enterocytes and entre the mesenteric lymph vessel due to their size which causes easy diffusion through vascular endothelium. Highly lipophillic drug therefore access intestinal lymph via association with developing lipoprotein [30].

Advantages of SMEDDS:

1. Affecting intestinal permeability – Lipid Improvement in oral bioavailability- SMEDDS can change the physical barrier function of present the drug to GIT in solubilized and micro emulsified form and increase in specific surface area enable more efficient drug transport through the intestine leading to improved bioavailability. Oil phase can work not only as a carrier but also a 'shield' to protect the attack and degradation from enzymes.

2. P-glycoprotein is a type of combined protein existing in normal cells. It expels the drugs out of the cells as a self-biological defense and can reduce the drugs absorption. A drugs incorporated in SMEDDS can inhibit the activity of P-glycoprotein which results in an enhancement of oral absorption.

3. Ease of manufacture and scale-up- SMEDDS require very simple and economical equipments like simple mixer with agitator and volumetric liquid filling equipment.

4. Reduction in inter-subject and intra-subject variability in absorption and food effects- The performance of SMEDDS is independent of food.

5. Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT- SMEDDS deliver peptides, hormones, enzyme substrates and inhibitors and gives protection from enzymatic hydrolysis.

Disadvantages of SMEDDS [31]:

a. *In vitro* model needs further development and validation before its strength can be evaluated.

b. Chemical instabilities of drugs and high % of surfactant may irritate GIT.

c. Co solvents can migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation drugs.

d. The precipitation tendency of the drug on dilution may be high due to the dilution effect of the hydrophilic solvent.

e. Formulations containing several excipients become more challenging to validate.

Excipient for SMEDDS Formulations: Oils:

Oil solubilizes the hydrophobic drug and aids in self-emulsification. Lipid has a tendency to increase the fraction of drug transported via intestinal lymphatic system and thus increasing lipophilic drug absorption from the GI tract. The molecular structure of oil is responsible for emulsification property of oil [32]. Table 3 gives idea about commonly used oil in SMEDDS.

Surfactants:

Surfactants are important components of SMEDDS systems as they are responsible for forming a stable emulsion upon dilution and stabilize the internal phase in an emulsion. A surfactant with an HLB value of more than 12 is necessary in SMEDDS. Surfactants used in lipid based drug delivery are usually polyethoxylated lipid derivative. .For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration [33].

Emulsifiers of natural origin are not widely used because of their poor self-emulsification property [34]. Nonionic surfactants are less toxic than ionic.

Surfactant and possess good emulsion stability

Usually the surfactant concentration ranges between 30 and 60% w/w to form stable SMEDDS. Extremely small droplet size produced in case of SMEDDS promotes rapid gastric emptying and low local concentration of surfactant, thereby reducing the gastric irritation. 23 Increase in surfactant concentration causes a decrease in droplet size thus surfactant molecules stabilizes at the oil-water interface [35] and if surfactant concentration is less then it causes enhanced water penetration into oil droplets leading to breakdown of oil droplets [36].

Thus surfactant is also responsible for total solubility of the drug in SMEDDS, preventing drug precipitation upon aqueous dilution and keep the drug in solubilized form in GI tract. [35] **Table 4** gives idea about commonly used surfactant in SMEDDS.

Co-surfactant:

Co-surfactant is added to lower the interfacial tension between the oil and water phase, fluidize the hydrocarbon region of the interfacial-film, and to influence the film curvature [37].The role of a Co-surfactant is to:

a.Increase the fluidity of the interface.

b.Destroy liquid crystalline or gel structure which would prevent the formation of micro emulsion.

c.Adjust HLB value and spontaneous curvature of the interface by changing surfactant partitioning characteristic [38]. **Table 5** gives idea about commonly used co-surfactant in SMEDDS.

Other components:

Other components might be pH adjusters, flavors, and antioxidant agents. Lipid peroxides may be formed due to auto-oxidation, which increases with unsaturation level of the lipid. So lipophilic antioxidants may be required. eg. α-tocopherol, propyl gallate, ascorbyl palmitate or BHT.

Formulation of SMEDDS:

The synthetic hydrophilic oils and surfactants provides good solubility to hydrophobic drugs than conventional vegetable oils. Ethanol, PG and PEG also contribute for the improvement of drug solubility in lipid vehicle.

The following points should be considered in the formulation of a SMEDDS -

Find solubility of the drug in different oil, surfactants and cosurfactant:

Determine solubility by adding excess amount of drug in small vials containing 2 ml of selected oil, surfactant and cosurfactant separately. The drug was mixed with glass rod for 30 min, and then the vials kept for sonication about 2 hours. The vials are tightly stopper and continuously stirred for 72 hours in orbital shaking incubator at 250C.Then centrifuged at 3500 rpm for 20 min. The 1ml supernatants are separated and dissolve in methanol or alcohol and solubility is quantified by UV-spectrophotometer at specific wavelength after appropriate dilution with methanol or alcohol. But after dilution the solutions are not clear. So oils should be diluted with 66% v/v chloroform in methanol and surfactant should be diluted with 7% v/v chloroform in methanol [39].

Select oil, surfactant and co solvent based on the solubility of the drug.

Select ratio of surfactant to cosurfactant:

The emulsifying effect is good if the ratio of the surfactant to the co-surfactant is higher than 1:2.5 but stability properties are inferior at this ratio. Fixing the surfactant/co-surfactant ratio at 1:1 is a better choice for the stability of SMEDDS [40].

Construction of Phase Diagram:

Phase diagrams were constructed to obtain the proportion of components that can result in maximum microemulsion existence area. Chemix software can be used for this. These diagrams were constructed with oil, surfactant/co-surfactant (Smix) and water (pseudo-ternary phase diagram) by using water titration method at room temperature. The procedure consists of preparing solutions of different ratio of surfactant to cosurfactant by weight such as 1:1, 2:1, 3:1 etc. These solutions then vortexed for 5 min and placed at 50°C for 1 hour so that an isotropic mixture can be obtained. Each of these solutions was then used for preparing a mixture containing oil and Smix (mixture of surfactant and co-surfactant) in the following ratios by weight: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4,7:3, 8:2, 9:1 and after preparation vortexed for 5 min followed by placing in oven at 50°C for 1 hour.

All the mixtures then placed at room temperature for 24 hour. Water from 5% to 95% of the mixture added at 10-15 min interval to each of the mixture under stirring on magnetic stirrer. After each addition the mixtures were observed for their appearance (turbid or clear). Turbidity of the samples would indicate formation of a coarse emulsion, whereas a clear isotropic solution, would indicates the formation of a microemulsion. The formation of microemulsion regions was monitored visually for turbidity–transparency– turbidity.

Preparation of SMEDDS:

From the ternary phase diagram ratio of

surfactant to co-surfactant was optimized. Then by varying ratio of oil to Smix, different formulations were prepared with and without drug. Formulations were prepared by preparing optimized ratio of Smix first, for this surfactant and co-surfactant were accurately weighed and then vortexed for 5-10 min. After that Smix was placed in oven at 50°C for 1 h. Oil with different ratio was added to Smix then these formulations were vortexed for 5-10 min and placed in oven at 50°C for 1 h so that an isotropic mixture was formed. Drug was loaded to these isotropic formulations at the end and vortexed by vortex shaker until clear solution was obtained [41].

Mechanism of self-emulsification:

When the entropy change is greater than the energy required to increase the surface area, then self-emulsification takes place. Free energy of formation is very low and positive or even negative which results in spontaneous emulsification in case of SMEDDS. For emulsification to take place, it is important for the interfacial structure to no resistance against surface shearing. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/non-ionic surfactant) to water. This is followed by solubilization within the oil phase, as a result of aqueous penetration through the interface. This occur upto the solubilization limit attained close to the interphase. Aqueous penetration will lead to the formation of the dispersed liquid crystal (LC) phase.

Lastly, everything that is near with the interface will be liquid crystal, the actual amount of which depends upon the emulsifier concentration in the binary mixture. Hence, following gentle agitation of the self-emulsifying system, water rapidly penetrates into the aqueous cores leading to interface disruption and droplet formation. This LC phase is considered to be responsible for the high stability of the resulting microemulsion against coalescence [42].

Evaluation of SMEDD: Thermodynamic stability studies:

Freeze thawing is employed to evaluate the stability of formulations. The formulations are subjected to 3 to 4 freeze -thaw cycles, which include freezing at –4°C for 24 hours followed by thawing at 40°C for 24 hours. Centrifugation is performed at 3000 rpm for 5 minutes. The formulations are then observed for phase separation. Only formulations that are stable to phase separation are selected for further studies [43].

Dispersibility test:

The efficiency of self-emulsification SMEDDSs checked using a standard USP dissolution apparatus. 1ml of each formulation added to 500 ml of water at 37 ± 0.5˚C. A standard stainless steel dissolution paddle rotating at 50 rpm provides gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system: Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance. Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance. Grade C: Fine milky emulsion that is formed within 2 min. Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min). Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT, while formulation falling in Grade C could be recommend for SMEDDS formulation [44].

Turbidimetric evaluation:

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of self-emulsifying system is added to fixed quantity of suitable medium (generally 0.1 M HCl) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity.

Droplet Size:

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for determination of the emulsion droplet size.

Viscosity Measurement:

The Rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of emulsion and if a high viscosity then it is w/o emulsion [45].

Zeta potential measurement:

In conventional SMEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids. The SMEDDS diluted with a ratio 1:2500 (v/v) with distilled water and mixed with magnetic stirrer. Zeta-potential of the resulting microemulsion was determined using the Zetasizer (Malvern instrument, Australia [46].

***In vitro* release:**

The quantitative *in vitro* release test is performed in 900 ml purified distilled water, which is based on USP XXIV dissolution method. SMEDDS is placed in dialysis bag during the release period to compare the release profile with conventional tablet. 10 ml of sample solution is withdrawn at predetermined time intervals, filtered through a 0.45µ membrane filter, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium is replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals was calculated using the Beer Lamberts equation [47].

Applications:

Improvement in Solubility and bioavailability:

SMEDDS have the ability to present the drug to GIT in 1 - 100 nm globule size improves dissolution and bioavailability of drug for which water is a rate limiting step. Because of the fine oil droplets empty rapidly from the stomach and causes wide distribution of the drug through the intestinal tract and thereby reducing irritation due to drugs. SMEDDS enhance the bioavailability enabling reduction in dose of the drug [48].

Protection against Biodegradation:

Many drugs are degraded in physiological system, may be because of acidic PH in stomach, enzymatic degradation. Such drugs when presented in the form of SMEDDS can be well protected from these degradation processes as liquid crystalline phase might be act as a barrier.

Recent trends in SMEDDS:

1.Self-emulsifying sustained/controlled -release tablets.
2.Self-emulsifying capsule.
3.Self-emulsifying suppositories.
4.Self-emulsifying sustained/controlled release pellets.

- Self-emulsifying beads.
- Self-emulsifying sustained-release microspheres.
- Positively charged self-emulsifying drug delivery system.
- Supersaturatable self-emulsifying drug delivery system (S-SEDDS).
- Self-micro emulsifying floating dosage form.
- Self-micro emulsifying mouth dissolving films (SMMDF)
- Self-double-emulsifying drug delivery

Table 1. Solubilizing excipients used in commercially available Lipid-based oral formulations

Water-insoluble	**Triglycerides**	**Surfactants**
Bees wax, Oleic acid, Soy fatty acids, D-a-Tocopherol (vitamin E), Corn oil mono-di-triglycerides, Medium chain (C8/C10) mono and diglycerides, Propylene glycol esters of fatty acids.	*Long-chain triglycerides* Hydrogenated soyabean oil, Hydrogenated vegetable oil, Corn oil, Olive oil, Soyabean oil, Pea nut oil, Sesame oil. *Median-chain triglycerides* Caprylic/capric triglycerides derived from coconut oil or palm seed oil	Polysorbate 20 (tween 20), Polysorbate 80 (tween 80), Sorbitanmonolaurate (Span20), D-a -Tocopheryl PEG 1000 succinate (TPGS), Glycerylmonooleate, Polyoxyl 35 castor oil (cremophor EL), Polyoxyl 40 hydrogenated castor oil (cremophor RH40), Polyoxyl 60 hydrogenated castor oil (cremophor RH60), PEG 300 oleic glycerides (Labrafil® M-1944CS), PEG 300 linoleic glycerides (Labrafil® M-2125CS), PEG 400 caprylic/capric Glycerides

Table 2. Composition of fatty acids found in lipid-based excipients

Fatty acid chain length (number of carbons)	**Common name**	**Melting temperature (°C)**
8	Caprylic acid	16.5
10	Capric acid	31.6
12	Lauric acid	44.8
14	Myristic acid	54.4
16	Palmitic acid	62.9
18	Stearic acid	70.1
18	Oleic acid	16.0
18	Linoleic acid	—5.0
18	y-Linoleic acid	—11.0

18	Ricinoleic acid	6.0
20	Arachidic acid	76.1
22	Behenic acid	80.0

Table 3. List of oils that can be used in SMEDDS

Class	Example
Triglyceride vegetable oils	
1)Triglycerides of long chain fatty acids	Miglyol 812, Captex 355,
2)Triglycerides of medium chain fatty acids	Labrafac
Vegetable oils derivatives	Hydrogenated cottonseed oil
1)Hydrogenated vegetable oil	Capmul MCM
2)Mixed Partial Glycerides	Labrafil 1944CS, Labrafil M
3)Polyoxylglycerides/	2125CS, Labrasol, Gelucire 44/14.
Macro golglycerides	Cremophor EL, Cremophor
4) Ethoxylated glycerides	RH40 ,Cremophor RH60.
5) Polyalcohol esters of fatty	Plurol OleiqueCC497,Capryol, & J.
acids	Oleic acid, Myristic acid,
Fatty acids	Caprylic acid,
Ethanol ester	Capric acid.
Soybean oil, peanut oil, corn oil	Ethyl oleate.

Table 4. List of surfactants that can be used in SMEDDS

Chemical or Common Name	Trade name	HLB
Polyoxyethylene 20	Polysorbate 20	16.7
sorbitan monolaurate	lauric glycerides	14
PEG 1500	Gelucire 44/ 14	
PEG 400 capric/caprylic	Labrasol	14
glycerides	Polysorbate 80	15
Polyoxyethylene 20	CremophorEL	12-14
sorbitan monooleate	Cremophor RH40	14-16
Polyoxyl 35 castor oil	Cremophor RH 40	14 -16
Polyoxyl 40 hydrogenated castor oil	Cremophor RH 60	14-18
Polyoxyl 40 hydrogenated castor oil	Brij 35	13.7
Polyoxyl 60 hydrogenated castor oil	Labrafil Ml 2125,	4
Polyoxyethylene lauryl ether	M1944	
Unsaturated polyglycolized glycerides	Gelucire 44/14,	13-14
Saturated polyglycolized glycerides	50/13	
PEG-8 Caprylic/Capric glycerides	Labrasol	14
PEG-8 Capiylic/Capric glycerides	Labrafac®CM10	10
Polyoxyl 40 stearate	Myrij 52	16.9

Table 5. List of co-surfactants that can be used in SMEDDS

Co-surfactant
PEG 200,400,600
Propylene glycol
Ethanol
Transcutol P
Lauroglycol FCC
Lutrol E400

Figure 1. Schematic diagram of mechanisms of intestinal drug transport from lipid-based formulations.

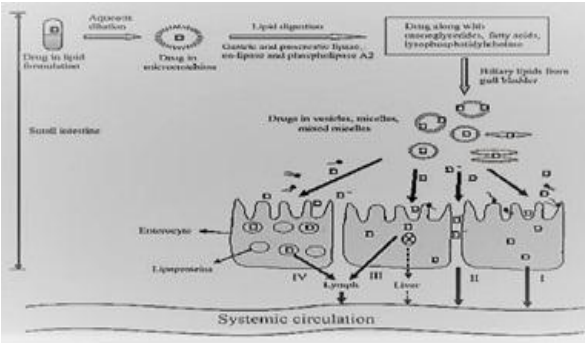
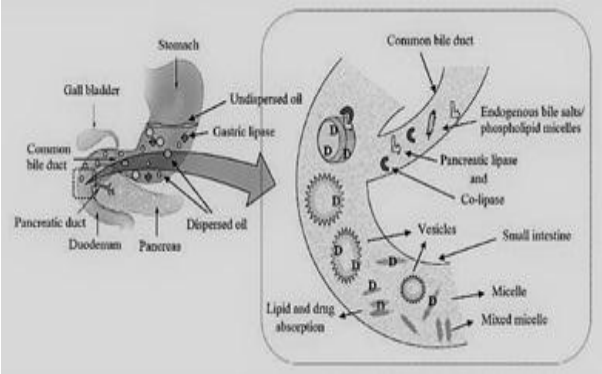


Figure 2. Lipid digestion and drug solubilization process in the small intestine.



CONCLUSION

With successful commercialization of various lipid based drugs in recent years, these systems have proved their possibilities in the future. A few limitations of the technology such as the stability of lipid-based formulations, manufacturing methods, the lack of a database considering the solubility of drugs in lipids, indicate that development of proper regulatory guidelines for lipid-based formulations still need to be addressed in depth to advance the technology. Newly developed formulation techniques haverectified these issues to some extent but there are areas for improvement which demands further detailed research. There is a lack of enough study to correlate the data obtained in vitro studies to the actual in vivo experience. This review has given a summery and characterization of the various aspects of lipid based formulations which will be helpful for the advancement of the technology to obtain safer, more stable and efficacious drug products.

ACKNOWLEDGEMENT

The authors wish to thank Harun Or Rashid , Basel University , Basel, Switzerland, for providing their support to our research work.

CONFLICT OF INTEREST:

The authors declare that they have no conflicts of interest.

REFERENCES

1. Roger E, Lagarce F, Benoit JP. Development and characterization of a novel lipid nanocapsule formulation of Sn38 for oral administration. *Eur J Pharm Biopharm*, 79, 2011, 181–8.
2. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation in vitro drug product dissolution and in vivo bioavailability. *Pharm Res*, 12, 1995, 413–420.
3. Aungst BJ. Novel formulation strategies for improving oral bioavail- ability of drugs with poor membrane permeation or pre-systemic metabolism. *J Pharm Sci*, 82, 1993, 979–87.
4. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. *Adv Drug Deliv Rev*, 60, 2008, 734–46.
5. Dahan A, Hoffman A. Rationalizing the selection of oral lipid based drug delivery systems by an in vitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs. *J Control Release*, 129 2008, 1–10.
6. Gibson L. Lipid-based excipients for oral drug delivery. In: Hauss DJ, editor. Oral lipid-based formulations: enhancing the bioavailability of poorly water soluble drugs. New York: Informa Healthcare, 2007, 33–61.
7. Wilson CG, Mahony BO. The behavior of fats and oils in the upper G. I. Tract. *Bull Tech Gattefosse*, 90, 1997, 13–8.
8. Rashid HA, Faisal KS, Bhyian MHU, Alam MJ, Hasan MM . Mixture design experiment on dissolution of pioglitazone hcl solid dispersion as affected by hydrophilic polymers interaction .*International Journal of Biopharmaceutics*, 7(1), 2016, 17-23.
9. Driscoll CMO. Lipid based formulations for intestinal lymphatic delivery. *Eur J Pharm Sci*, 15, 2002, 405–15.
10. Hasan MM, Rahman MM, Kabir AKL, Gosh AK, Hasan MM, Karim SM, Rashid Ha. Contemporary investigation on nasal spray drug delivery system.*International Journal of Pharmacy & Therapeutics*, 7(4), 2016, 184-200.
11. Erlanson-Albertsson C. Pancreatic colipase. Structural and physiolo- gical aspects. *Biochim Biophys Acta*, 1125, 1992, 1–7.

12. Hasan MM, Moniruzzaman M, Rashid HA et al. A key approach to care pharmaceutical products and recalls. *International Journal of Pharmacy Practice & Drug Research*, 6(2), 2016, 63-70.
13. Winstanley PA, Orme MLE. The effects of food on drug bioavail- ability. *Br J Clin Pharmacol*, 28, 1989, 621–8.
14. Hunt JN, Knox MT. A relation between the chain length of fatty acids and the slowing of gastric emptying. *J Physiol*, 194, 1968, 327–36.
15. Gershkovich P, Hoffman A. Effect of a high-fat meal on absorption and disposition of lipophilic compounds: the importance of degree of association with triglyceride-rich lipoproteins. *Eur J Pharm Sci*, 32, 2007, 24–32.
16. Hasan MM, Uddin F, Islam MM, Hasan M, Banik K, Islam MA, Hashid HA. Nanotechnology drug delivery system: tools in advance pharmaceutical & human health care .International Journal Of Biopharmaceutics, 7(2), 2016, 90-99.
17. Kaukonen AM, Boyd BJ, Porter CJ, Charman WN. Drug solubiliza- tion behavior during in vitro digestion of simple triglyceride lipid solution formulations. *Pharm Res*, 21, 2004, 245–53.
18. Strickley RG. Currently marketed oral lipid-based dosage forms: drugs products and excipients. In: Hauss DJ, editor. Oral lipid-based formulations: enhancing the bioavailability of poorly water soluble drugs. New York: Informa Healthcare, 1–31, 2007.
19. Cole ET, Cade D, Benameur H. Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. *Adv Drug Deliv Rev*, 60, 2008, 747–56.
20. Wakerly MG, Pouton CW, Meakin BJ, Morton FS. Self-emulsification of vegetable oil-non-ionic surfactant mixture: a proposed mechanism of action. *ACS Symp Ser*, 311, 1986, 242–55.
21. Rowe RC, Sheskey PJ, Owen SC, editors. Handbook of pharmaceu- tical excipients. 5th Ed. Washington DC: American Pharmaceutical Association and London: The Pharmaceutical Press; 2006, p. 1–918.
22. Grove M, Mullertz A, Pedersen GP, Nielsen JL. Bioavailability of seocalcitol III. Administration of lipid-based formulations to minipigs in the fasted and fed state. *Eur J Pharm Sci*, 31, 2007, 8–15.
23. Jannat E, Arif AA, Hasan MM, Zarziz AB, Rashid HA. Granulation techniques & its updated modules. *The Pharma Innovation Journal*, 5(10), 2016, 134-141
24. Yap SP, Yuen KH. Influence of lipolysis and droplet size on *tocotrienol absorption from self-emulsifying formulations. Int J Pharm*, 281, 2004, 67–78.
25. Sek L, Porter CJ, Charman WN. Characterisation and quantification of medium chain and long chain triglycerides and their in vitro diges- tionproducts, by HPTLC coupled with in situ densitometric analysis. *J Pharm Biomed Anal*, 25, 2001, 651–61.
26. Martignoni M, de Kanter R, Grossi P, Mahnke A, Saturno G, Monshonwer M, et al. An in vivo and in vitro comparison of CYP induction in rat liver and intestine using slices and quantitative RT- PCR. *Chem–Biol Interact*, 151, 2004, 1–11.
27. Pouton CW, Porter CHJ: Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. *Advanced Drug Delivery Reviews*, 60(6), 2008, 625-637.
28. Mohsin K, et al: Lipid based self-emulsifying formulation for poorly water soluble drug-An excellent opportunity. *Indian journal of pharmaceutical education and research*, 46(2), 2012, 88-96.
29. Rane SS, Anderson BD: What determines drug solubility in lipid vehicles: Is it predictable? *Advanced Drug Delivery Reviews*, 60(6), 2008, 638-656.
30. Sarpal K, et al: Self-emulsifying drug delivery systems: A strategy to improve oral Bioavailability. *Current research and information on pharmaceuticals sciences*, 11(3), 2010, 42-49.
31. Khan BA: et al. Basics of Self Micro Emulsifying Drug Delivery System. *Journal of Pharmacy and Alternative Medicine*, 1, 2010, 13-19.
32. Kimura M. et al. Relationship between the molecular- structures and emulsification properties of edible oils. *Bioscience, biotechnology and biochemistry*, 58(7), 1994, 1258-1261.
33. Hasan MM, Rashid HA, Chadni SH, Alam MJ, Hasna R, Islam MM. Gastroretentive: an innovative drug delivery system. *International Journal of Biological & Pharmaceutical Research*, 7(5), 2016, 262-272.
34. Constantinides P. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. *Pharmaceutical research*, 12(11), 1995, 1561-1572.
35. Patil P, Shrivastava SK: Formulation, evaluation and optimization of fast dissolving oral film of selective antihypertensive drug. *World Journal of Pharmacy and Pharmaceutical Sciences*, 3(8), 2014, 996- 1060.
36. Pouton C: Formulation of self-emulsifying drug delivery systems. Advanced Drug Delivery Reviews, 25(1), 1997, 47-58.
37. Ozawa K et al: Oil-induced structural change in nonionic microemulsions. *Journal of Dispersion Science and Technology*, 22(1), 1986, 119-124.
38. Nokaly EI, Ravey J. Solubilization by nonionic surfactant in the HLB Temperature Range. In: Micellization, solubilization and Microemulsions, Plennum press, New York 1991; 2:901-911.

39. Linda C, et al. Computational prediction of drug solubility in lipid based formulation excipients, *pharm Res*, 30(12), 2013, 3225-3237.
40. Bora D, Borude P, Bhise K:Formulation and Evaluation of Self microemulsifying drug delivery systems of low solubility drug for enhanced solubility and dissolution. *Asian journal of biochemical and pharmaceutical sciences*, 2(15), 2012, 7-14.
41. Pathak C et al. A review on self microemulsifying drug delivery system. *Pharma science monitor-An international journal of pharmaceutical sciences*, 4(1), 2013, 3628-3648.
42. Wakerly et al. Self-emulsification of vegetable oil-non-ionic surfactant mixtures. *ACS Symp. Series*, 311, 1986, 242-55.
43. Shukla P et al. A review on self micro emulsifying drug delivery system: an approach to enhance the oral bioavailability of poorly water soluble drugs. *international research journal of pharmacy*, 3(9), 2012, 1-6.
44. Yeole S et al. A Review - Self-Micro Emulsifying Drug Delivery Systems (SMEDDSs). *Indo American Journal of Pharmaceutical Research*, 3(4), 2013, 3031-3043.
45. Parmar B et al. SMEDDS: A Dominant Dosage Form Which Improve Bioavailability. *American Journal of PharmTech Research*, 2(4), 2012, 54-72.
46. Atef E, Belmonte AA: Formulation and in-vitro and in-vivo characterization of a Phenytoin self-emulsifying drug delivery system. *European Journal of Pharmaceutical Sciences*, 2008; 35: 257-26
47. Julianto T, et al, Improved Bioavailability of Vitamin E with a Self Emulsifying Formulation. *Int J Pharm*, 200, 2000, 53-57.
48. Shinde G, et al, Self microemulsifying drug delivery system: a novel approach for hydrophobic drugs. *International journal of pharmaceutical sciences*, 3(1), 2011, 988-1005.

Cite this article:
Md. Mehdi Hasan, Md.Mizanur Rahman, Mahbub Hasan, S.M. Nazrul Islam, Masum Al Hasan, Harun Ar Rashid. Self-microemulsifying: A New Approach of Lipid Based Drug Delivery Systems. ***International Journal of Advanced Pharmaceutics*.** 2017; 7(1):16-28. DOI: **http://dx.doi.org/10.21276/ijap.2017.7.1.3**