International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.7, pp 515-528, 2017

Self-Micro Emulsifying Drug Delivery System: A Vital Approach for Bioavailability Enhancement

Ravinder Verma, Vineet Mittal & Deepak Kaushik*

Department of Pharmaceutical Sciences, Maharshi Dayanand University.Rohtak-124001, India

Abstract : In modern drug discovery techniques, about 40% of active moieties exhibit poorly water soluble which and present a major challenge to modern drug delivery system results in low oral bioavailability. Sekf-Micro Emulsifying Drug Delivery System (SMEDDS) is a unique feasible approach to solve low oral bioavailability problem which is associated with hydrophobic drugs due to their unparalleled potential. Recently, SMEDDS has been focused much more attention because of solving problems related to oral bioavailability, inter and intra-subject variability and lack of does proportionality of hydrophobic drugs. This drug delivery system has important application on BCSII and IV class drugs for improving their low aqueous solubility. This review is useful in knowledge of formulation excipients with their role, transportation of lipids, evalution parameters, recent advancements and recent research work.

Introduction

In the treatment of many chronic diseases oral route is the major route of drug delivery. But oral delivery of lipophilic drug is major challenge because of low aqueous solubility. So, solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Most of the BCS class II drugs have poor aqueous solubility and high permeability which results in poor oral bioavailability, high intra and inter-subject variability and lack of dose proportionality of hydrophobic drugs[1-2]. Thus, for such moieties, absorption rate from gastrointestinal (GI) lumen is controlled by dissolution. For enhancing dissolution rate of drug, alteration of physiochemical properties like particle size reduction and salt formation of compound may be one approach. But,these methods have their own limitations. For instance, salt formation of neutral compounds is not feasible, salts that are formed may convert back to their original acid or base forms and can results into aggregation in gastrointestinal tract (GIT), synthesis of weak acids and weak base may not always be practical. Particle size reduction may be desirable where handling difficulties and poor wettability are experienced for very fine powders. To overcome these drawbacks, various other formulation strategies have been adopted including use of cyclodextrins, nanoparticles and permeation enhancers [3].

In recent years, considerable attention has been given tolipid based formulation napproaches because they avoid slow rate of dissolution of lipohilic drugs.Self-dispersing lipid based formulations (SDLBFs) are classified in two categories–

1. Self-Micro Emulsifying Drug Delivery System (SMEDDS)
2. Self-Emulsifying Drug Delivery System (SEDDS)

SMEDDS are homogenous and isotropic mixture of drug, oil, surfactant, co-surfactant, co-solvent. SMEDDS are used to solve problems such as low aqueous solubility, low permeability, high molecular weight, pre-systemic first pass-effect, enzymatic degradation, gastric irritation, enhance bioavailability and stability of drug[4-5].While, SEDDS are isotropic mixture of natural or synthetic oils, solid or liquid surfactants. One or more hydrophilic solvents and co-solvents/surfactants can be present in formulation. They spread in aqueous media such as physiological fluids (present in GIT) which forms o/w type emulsion or micro-emulsion due to gastric and intestine motility during digestion which is necessary for self-emulsification. These are classified in following in following three categories: (i) Self-Emulsifying Formulations (SEFs) which have 200nm-5µm droplet size, turbid appearance, hydrophilic-lipohilic balance (HLB) value greater than 12. (ii) Self-Micro Emulsifying Formulations (SMEFs) which have >200nm droplet size, optical clear to transculent appearance, HLB value less than 12. (iii) Self-Nano Emulsifying Formulations (SNEFs) have >100nm droplet size, optical clear and HLB value greater than 12 [6].

The Emulsification Process

Self-emulsification is a phenomenon which has been widely exploited commercially in formulations of emulsifiable concentrates of herbicides and pesticides. Concentrates of crop-sprays are to be diluted by the user, such as farmers or house-hold gardeners, allowing very hydrophobic compounds to be transported efficiently. In contrast, SMEDDS, using excipients acceptable for oral administration to humans, have not been widely exploited and knowledge about their physicochemical principles is therefore limited.

Mechanism of Self-Emulsification

Self-emulsification process is related to the free energy. According to theory of Reiss (1975), emulsification occurs when the entropy change that favours dispersion is greater than energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative. The free energy of formation of microemulsion, is directly proportional to the energy required to create new surface between the two desired phases and can be described by the equation (1)

$$\Delta G = \Sigma N \pi r2 \sigma \ldots\ldots\ldots (1)$$

Where, ΔG is the free energy associated with the process, N is the number of droplets of radius r and σ represents the interfacial energy. After a certain time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. Emulsifying agents are added to stabilize emulsion which reduces the interfacial energy, as well as provide a barrier to avoid coalescence [7].In case of SMEDDS, spontaneous/rapid emulsification takes place due to very low or positive or even negative free energy of formation. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/non-ionic surfactant) to water. Self-emulsification occurs due to penetration of water into the Liquid Crystalline (LC) phase that is formed at the oil/surfactant-water interface in which water can penetrate by gentle agitation during self-emulsification. After water penetration to a certain limit, it results in disruption of the interface which leads to formation of droplet. This LC phase is considered to be responsible for the high stability of nanoemulsion against coalescence [8].

Components used in SMEDDS

The selection of excipients isvery critical because of pharmaceutical acceptability of excipients and the toxicity issues of the components used. There is a great restriction as which excipients to be used. Early studies showed that the self emulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self emulsification occurs. Important parameters for excipients are solubility of drug in the formulation as such and upon dispersion (for SMEDDS), the rate of digestion (for formulation susceptible to digestion) and possibly, the solubilization capacity of the digested Formulation [21].

Oils

Lipids are important component in SMEDDS because they are responsible for fluidization of intestinal cell membrane, solubilization of hydrophobic drugs, enhancing in dissolution rate and solubility in GI fluids, protection of drug from chemical and enzymatic degradation[9-10]. Oil is important for maximum solubilizing

capacity for the selected drug candidate and formation of nanoemulsion in the formulation. Triglycerides are highly lipophilic oily molecules and the solvent capacity of drugs is common function of effective concentration in ester groups, the medium chain triglycerides (MCT) molecules having higher solvent capacity and capability for resistance against oxidation as compare to long chain triglycerides (LCT). In present, the MCT have been replaced by novel semi-synthetic MCT is important to influencing water solubility of poorly soluble drugs and oil phases are modified by vegetable oils, digestible or non-digestible oils and fats such as olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil, hydrogenated oil for better solubility [11]. These are used in concentration of 40-80%. Modified and hydrolysed vegetable oils are preferred because they show more solubility potential, form good self-emulsification system with large number of surfactant and approved for oral administration. They offer physiological and formulation advantages and their degraded product resembles with natural end product of intestinal digestion. Isopropyl myristate, capmul MCM, maisine 35-1, labrafil M 1944 CS, capmul MCM C-8, lauroglycol 90, paceol, capmul PG-8 etc. are mainly used oils in SMEDDS [12-15].

Surfactants

Surfactants playimportant roles such as enhancing solubility of hydrophobic drug in oil, dispersion of liquid vechle in GIT fluids, improving bioavailability by increasing permeability, avoiding precipitation of drug in GI lumen and prolonging existence of drug moiety in soluble form, which results in effective absorption. But, a few surfactants are orally acceptable. They concentrate at oil-water interface and internal phase in emulsion and make more stable micro-emulsion. Combination of ionic and non-ionic is very effective for improving degree/area of micro-emulsion region. Anionic and non-ionic surfactant mixtures are responsible for synergetic effect in Critical Micelle Concentration. High amount of surfactant may cause GI irritation. So, 30-60% surfactant is used to form stable system. There is relationship between concentration of surfactant and droplet size, by increasing surfactant concentration, droplet size decreases. In some cases, mean droplet size may increase by increasing surfactant conc. [4, 12]. Attempts have been made to rationalize surfactant behavior in terms of the hydrophile-lipophile balance (HLB) and the critical packing parameter (CPP). Both approaches can be a useful guide forthe surfactant selection. The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is well known that low HLB (3-6) surfactants are preferred for the formation of w/o microemulsions whereas high HLB surfactants are preferred for the formation of o/w microemulsion systems. In contrast, the CPP relates the ability of surfactants to form particular aggregates to the geometry of the molecule itself. Isaraelachvili explained the analysis of film curvature for surfactant association leading to microemulsion formation. According to him, the packing ratio provides a direct measure of HLB. The o/w structure are favored if the effective polar part is more bulky then the hydrophobic part ($P<1$), and the interface curves spontaneously toward water (positive curvature). When the interface curves in the opposite direction ($p>1$, negative curvature) results in formation of w/o structures. At zero curvature, when the HLB balanced ($P\sim1$), either bicontinuous or lamellar structures may form according to the rigidity of the film [16]. Surfactants obtained from natural sources are expected to more safe than synthetic, recommended for Self Dispersed Lipid formulation(SDLF) but they have limited self-emulsification capacity.Span 20, span 80, cremophor EL, cremophor RH 40, tween 85, tween 20, labrasol, solutol HS15 are used as surfactants in SMEDDS[17].

Co-surfactants

High concentration of surfactant is required to reduce interfacial tension sufficiently, which can cause gastric irritation. So, co-surfactants of HLB value 10-14 are added to reduce their concentration. They are added in combination with surfactants to provide sufficient flexibility to interfacial film, to dissolve large amount of either lipophilic drug or hydrophilic surfactant in lipid base, to decrease interface of oil/water. In absence of co-surfactant, surfactants produce highly rigid film and results in production of micro-emulsion over limited range of concentration [18-20].However, it is not compulsory to use them with non-ionic surfactant in micro-emulsion. The selection of surfactant and co-surfactant is crucial not only to the formation of SMEDDS, but also to solubilization of the drug in the SMEDDS. Such as PEG, hexanol, ethanol, transcutol HP, akoline MCM are mainly used co-surfactants in SMEDDS.

Co-solvents

Ethanol, polyethylene glycol, propylene glycol, transcutol are mainly used organic solvents for oral dosage form. They help in dissolving large amount of surfactant or drug in lipid base, to assist the dispersion

process, to decrease amount of surfactant in formulation and can perform action of co-surfactant in micro-emulsion system. Alcohol and other volatile solvents migrate into soft gelatin capsule shell and causes precipitation of lipophilic drug. But, lipophilic drug of alcohol free products have limited dissolution ability. Low molecular weight solvents are incompatible with capsule shell. So, proper solvent should be selected. Propylene glycol, dimethyl isosorbide, mannitol, isopropanol, sorbitol, glycerol are commonly used co-solvents in SMEDDS [21].

Biopharmaceutical Aspects

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs is well known. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms including:

1. Alterations (reduction) in gastric transit time, thereby slowing delivery to the absorption site and increasing the time available for dissolution,
2. Increases in effective luminal drug solubility- The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), which results in the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract,
3. Changes in the biochemical barrier function of the GI tract- It is known that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and thus reduce the extent of enterocyte-based metabolism.
4. Changes in the physical barrier function of the GI tract- Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties [22-23].

Transportation of drug via lymphatic system

There is increasing in number of lipophilic drug candidates which results in development of number of formulation approaches to support absorption of compounds with very low water solubility and high lipophilicity. The GIT is richly supplied with both lymphatic and blood vessels. So, material or drugs that are absorbed across the small intestinal epithelial cells can potentially enter either lymphatic or blood capillaries. The majority of drugs or materials are transported into blood capillaries due to high flow rate(500-fold) higher than that of intestinal lymph. Lymphatic system occurs in all body except central nervous system. When drug is highly lipophilic (logP>5) and have high solubility in triglycerides (>50mg/ml) [24-25] lymphatic transportation will take place via diffusion of drug across intestinal enterocytes and binds with enterocyte lipoproteins to form chylomicrons. These chylomicrons associatewith drug moiety which enhances intestinal lymphatic transport and leads to changes in drug disposition and finally alteration of pharmacological actions of poorly soluble drugs. Drug-lipoprotein association enters into thoracic duct via mensentric lymph duct and finally enters into systemic circulation at junction of left jugular and left subclavian veins. This anatomy results in avoiding first pass metabolism of highly lipophillic drugs. Additionally, toxicity profiles of drugs can be altered because of drug concentration and persistence in lymphatic system and systemic circulation will be affected by the dynamics of intestinal lymphatic transport [26-27].

Ternary phase diagram

Ternary phase diagram is useful for determination of best emulsification region of oil, surfactant and co-surfactant combinations. The apex of the triangle represents ternary phase diagram of surfactant, co-surfactant and oil. Mainly, dilution and water titration methods are used to plot ternary phase diagram.

1. Dilution Method:

Ternary mixtures with varying compositions of surfactant, co-surfactant and oil will be required. The surfactant conc. ranges 30 to 75% (w/w), oil conc. ranges 25 to 75% and co-surfactant conc. ranges 0 to 30% (w/w). The total of surfactant, co-surfactant and oil conc. always added to 100% for every mixture. The ratios of excipients are evaluated for nanoemulsion formation by diluting with required amount of mixtures with appropriate double distilled water. The area of nanoemulsion formation in ternary phase diagram will identified for the respective system in which nanoemulsion with desirable globule size will be obtain [28].

2. Water Titration Method:

Pseudo-ternary phase diagram is constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature. Oil phase and Smixs (surfactant: co-surfactant ratio)are prepared by using ranges from 9:1 to 1:9 and weighed in screw-cap glass tubes and vortexed. Then titrate each mixture slowly with aliquots of distilled water and stir at room temperature to achieve equilibrium. Visual inspection is done for transparency. When equilibrium is achieved, then mixture is further titrated with aliquots of distilled water until turbidity is not obtained in the mixture. Clear and isotropic sample is noted to be within the micro-emulsion region. Based on the results, appropriate percentage of oil, surfactant and co-surfactant is selected, correlated in the phase diagram and is used for preparation of SMEDDS formulation [29].

General method for preparation of SMEDDS

The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents may also contribute for improvement of drug solubility in the lipid vehicle. In formulation of SMEDDS following steps are performed: - Solubility study or screening of the drug in different oils, surfactants and co-solvents,- Selection of oil, surfactant and co-solvent based on the solubility and emulsification tests,- Construction of the Pseudo ternary phase diagram, Preparation of SMEDDS formulation by dissolving the drug in selected proportion of oil, surfactant andco-solvent [30-31].

Factors influencing SMEDDS formulation

Different factors affecting SMEDDS formulations are discussed below which are following:

Polarity of lipophilic phase: This factor governs drug release from emulsion. Polarity of droplet is depends on HLB value, chain length and degree of unsaturation of FA, molecular weight of micronized FA [15].

Nature and dose of the drug: Formulation of high dose is not suitable for SMEDDS unless they have good solubility in at least one component of formulation. Drugs having limited solubility in lipids are difficult to deliver by SMEDDS [32].

Charge on droplet of emulsion: Many physiological studies show that apical potential of absorptive cells, as well as all other cells in body, is negatively charged mucosal solution in lumen. Mainly negative charge is present in formulation which causes electrostatic repulsive force. Charge may be positive in some formulations [32].

Equilibrium solubility measurement: It is done to anticipate potential cases of precipitation in the gut. Pouton's study found that formulation in which crystallization occurs may take 5 days to reach equilibrium and drug can remain for 24 hours in supersaturated state after initial emulsification process [32].

Advantage of SMEDDS

SMEDDS have numerous advantages which are discussed below:

Ability to deliver macromolecules: This system is capable to deliver macromolecules such as peptides, hormones, enzyme substrate/inhibitor and provide protection from enzymatic degradation in GIT [4].

Enhancement of oral bioavailability enabling reduction in dose and reduction in inter/intra-subject variability: Slow dissolution rate is limiting factor for low oral bioavailability of poorly water soluble drugs. This system provides drug in pre-dissolved form, enhance surface area for absorption and avoid pre-systemic first pass effect which results in enhancement of oral bioavailability of drug and reduction in inter/intra-subject variability of poorly aqueous soluble drugs [5-6].

Enhance drug loading capacity: Formulation components provide high solubility of drug which results in high drug loading capacity of the formulation [6].

No effect of lipid digestion process: This delivery system is unaffected from action of pancreatic lipases and bile salts (process called lipolysis) because of self-emulsified form of the formulation [6].

Easy to formulate formulation: SMEDDS can be formulated easily as liquid, solid or semi-solid dosage form.

Protection of drug from biodegradation: Many formulations are degraded in physiological fluids/system due to change in the pH around the drug. Such as acidic pH in stomach leads to enzymatic or hydrolytic degradation etc. SMEDDS formulation prevents drug from biodegradation by forming barrier between degrading environment and the drug which is formed due to liquid crystalline phase [6].

Controlled Release formulation: Addition of polymer in the composition of SMEDDS provides prolong/control release of drug [32].

Characterization & evaluation of SMEDDS

Visual evaluation is the primary means of self-micro emulsification assessment. The efficiency of self-micro emulsification can be estimated by determining the rate of micro emulsification, droplet size distribution and turbidity measurement. Various evaluation parameters used in SMEDDS are following:

Droplet size: Droplet size of the micro-emulsion is determined by Photon Correlation Spectroscopy (PCS) or Scanning Electron Microscopy (SEM).Droplet size of the emulsion is a crucial factor because it determines the rate and extent of drug release as well as absorption [1].

Refractive index and percent transmission: Refractive index and percent transmittance proves transparency and stability of formulation on dilution. Colour occurs on dilution due to presence of synthetic oil and polyosorbate derivatives. Transparency decreases with increase in oil droplet size. The refractive index is measured by refractometer and percent transmittance is measured at specific wavelength utilizing UV-Vis spectrophotometer keeping distilled water as clear. Detailing indicates transmittance >85 percent is transparent in nature [33].

Electroconductivity test: This test is useful in determination of type of emulsion either o/w or w/o type. SMEDDS system contains ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the electroconductive nature of system due to presence of non-ionic surfactants which is measured by electroconductometer [34].

Dispersibility test: To 500 ml of water 1 ml of the formulation is added in standard USP dissolution apparatus at 37±0.5°C. A standard stainless steel dissolution paddle rotating at 50 r.p.m. provides gentle agitation. In-vitro study of the formulation is evaluated from such a dispersion using a suitable grading system. Grading system can be based upon the arrangement of a micro-emulsion (o/w or w/o), micro-emulsion gel or emulgel [35].

Cloud point measurement: It is examined by visual perception. 0.5 ml of preconcentrate is diluted to 50ml with distilled water in glass receptacle. The specimen is warmed at the rate of 0.5º C/min. A nearby perception is shown up of scattering with increment in the temperature. The temperature at which dispersion becomes cloudy is taken as Tc. After the temperature exceeds the cloud point, the sample is cooled below Tc, and then it is heated again to check the reproducibility of the measurements [35].

Effect of different dilution media: This study is done to get to the impact of dilution on SMEDDS preconcentrate, with a specific end goal to imitate physiological dilution procedure after oral administration. In this study chosen plan is subjected to expanding dilution (i.e. 10 and 100 times) with different diluents such as double distilled water, simulated gastric liquid, simulated intestinal liquid. Visual perception is recorded [35].

Determination of percentage drug content: Take one capsule of every formulation in 100 ml volumetric flask and add 100 ml of extracting solvent. At that point, shake blend for 1 hour in mechanical shaker and keep aside for 24 h. After 24 h, separate arrangement through Whattman filter paper (0.45 µm) to collect the filtrate. Then, filtrate is investigated in UV spectrophotometer. The percent drug content is determined using absorbance by compairing with standard graph[35].

Thermodynamic stability study: The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SMEDDS formulation. SMEDDS were diluted with aqueous medium were centrifuged at 15,000 rpm for 15 min and then observed visually for phase separation. Further formulation

were subjected to freeze thaw cycles (-200ºC for 2 days followed by+400ºC for 2 days) and were observed for phase separation [35].

Zeta potential measurement: Zeta potential for micro emulsion can be determined using a suitable Zeta sizer in triplicate samples. This is used for identification of charge present on droplet which is mainly negative in SMEDDS due to presence of free FA, however, addition of cationic lipid such as oleylamine at a conc. range of 1-3%, will give cationic SMEDDS with positive n-potential value of about 35-45 mV. Zeta potential may be positive or negative on basis of oil and surfactant ratio [5, 14].

pH determination: The apparent pH of the selected micro emulsion is determined at 25°C by immersing the electrode of a digital pH meter [24].

Viscosity determination:It is measured by using Brookfield viscometer.Viscosity confirms whether system is w/o or o/w type. If system has low viscosity then it is o/w type or vice-versa [19,24].

Effect of drug loading on droplet size: Effect of drug loading on globule size of micro-emulsion is studied using optimized formulation with or without drug. The resultant SMEDDS preconcentrate 0.5 ml is diluted to 100 ml with double distilled water and the mean globule size of the subsequent small scale emulsion is measured by Motic Computerized Microscope [32].

In-vitro lipolysis study: In-vitro lipolysis is conducted to characterize formulation in intestine under condition of fed or fasting state, to access drug solubliztion and drug release in intestine. It is done by using in-vitro lipid digestion model with a pH-Stat programmed titration unit (848 Titrino in addition, Metrohm AG, Herisau, Switzerland). For every experiment, take 1 g of SMEDDS (or 0.4 g of oil) into a thermo stated response vessel and scattered in 18 ml of digestion media (50 mM Trizma maleate, 150 mM NaCl, 5 mM $CaCl_2$•2 H2O, pH 7.5) containing 5 mM NaTC (sodium taurocholate) and 1.25 mM PC. Then adjust the pH with 7.5 with 0.1 M NaOH. Start processing tests by the expansion of 1 ml of pancreatin concentrate and keep the blend at 37°C with persistently mixing. Use pH-Stat automatic titration unit to maintain pH at 7.50±0.05 by titrating with 0.1 M NaOH. Record titrant volume at predetermined time. The percentage of lipid digested is determined by amount of free fatty acids, which equals to amount of consumed NaOH [36].

$$\text{Digestion percentage} = \frac{n_{FFA} \times M_{lipid}}{m_{lipid} \times 2} \times 100 = \frac{C_{NaOH} \times V_{NaOH} \times M_{lipid}}{m_{lipid} \times 2}$$

Where, n_{FFA} = numbers of free acids generated which is product multiple of V_{NaoH} and C_{NaoH}, M_{lipid} = molecular weight of lipid,

m_{lipid} = total mass of lipid, C_{NaOH} = concentration of NaOH consumed for titration

In-vitro release study:1gm of SMEDDS is set in boiling tube containing 200 ml buffer solution. Both side of boiling tube was opened and one side of tube is tied with cellophane layer and plunged in support arrangement kept in a recepticle beneath. Upper side of the chamber is supported to hold. Measuring glass was constantly blended by stirrer and test is pulled back after sufficient time intervals in straight position and investigated by UV- Spectrophotometer. Percent medication disintegrated at distinctive time intervals is computed utilizing the lambert's beer mathematical equation[37].

In-vitro intestinal permeability study: For this study, male albino rat (250-300 g) is sacrificed with overdose of pentobarbitone. To check the intra-duodenal permeability, the duodenal part of the small intestine is isolated and taken for the in vitro diffusion study. Then this tissue is thoroughly washed with cold Ringer's solution to remove the mucous and lumen contents. Prepare equivalent dose of optimized micro-emulsions and plain drug solution were prepared. Close one side of the intestine tightly and inject formulation (1 mg/ml) into the lumen of the duodenum using a syringe and then close other side of the intestine. Then tissue is placed in a chamber of organ bath with continuous aeration at constant temperature of 37˚C. The receiver compartment is filled with 30 ml of phosphate-buffered saline (pH 5.5). After a particular time interval of 30 minutes withdraw 1ml sample and dilute to 10 ml. The absorbance is measured using a UV spectrophotometer at a 250 nm, keeping the respective blank. The percent of cumulative drug diffusion is calculated against time and plotted on a graph. Similarly, prepare suspension of plain drug and compare with the optimized formulation [38].

Bioavailability study: In-vivo study is performed to analysis drug quantitatively after administration of formulation. Tablet and SMEDDS form are compared from plasma profiles in experimental animals after oral administration. Cmax and Tmax for oral administration are calculated. Area under the Concentration-Time Curve is estimated by trapezoidal method. Relative bioavailability(BA) of tablet is calculated from below given formula [10]:

Relative BA(%) = (AUC_{test}/AUC_{ref}) x $(Dose_{ref}/Dose_{test})$

Yield of the SMEDDS:SMEDDS is filtered from the solvent and dry in the desicator and weigh to get the yield of SMEDDS formulated per batch. Percentage yield can be calculated by the formula:

% recovery = W1 / W2 + W3 * 100

Where, W1 is the weight of the SMEDDS formulated,W2 weight of the drug added, W3 is the weight of the lipid and surfactant used as the starting material [32].

Recent advancements in SMEDDS

The recent advancements in SMEDDS are discussed below:

Self-emulsifying sustained/controlled-release tablets: Numerous potent drugs have low oral bioavailability because of their poor aqueous solubility or pre-systemic metabolism. Carvedilol drug have low bioavailability, low solubility and pre-systemic metabolism. The novel Self-Emulsifying Osmotic Pump Tablet (SEOPT)containing carvedilol has many advantages [29].

Dry emulsions: These are powdered solid dosage forms which spontaneously emulsify with the addition of water in formulation. They can be obtained by emulsifiable glass system, freeze dying, and spray drying. Myers developed Lipid based surfactant free emulsifiable glass system [4-6,29].

Capsules: s-SMEDDS filled into capsule shells which are prepared by various techniques. Physical incompatibility of liquid SMEDDS can be prevented with the capsule shell by this dosage form. In case of semi-solid excipients used in the formulation, then they are first melted and filled into capsules. Contents of the capsule solidify at room temperature [5].

Tablets: Eutectic based self-emulsifying tablets were formulated by Nazzal et al. which inhibit irreversible precipitation of the drug within the formulation. Drug and suitable semi-solid oil was used in the formulation in combination. Using the melting point depression method the oil phase containing the drug melts at body temperature producing emulsion droplets in the nanometer size range. During formulation of these tablets maltodextrin, modified povidone, and microcrystalline cellulose (MCC) were used as additional excipients(carrier) [5].

Solid dispersions: manufacturing and stability problems associated with solid dispersions reduced due to availability of self-dispersing waxy semi-solid excipients. Gelucire 44/14 and Gelucire 50/02 are used for this purpose because these are semisolid excipients and can be directly filled into capsules in molten state. Absorption of drug is improved when gelucire is used as a carrier in solid dispersions because gelucire high surface activity [5].

Beads: Porous polystyrene beads for delivering SEFs were used by Patil et al. The formulation is poured into microchannels of the bead through capillary action. Copolymerization of styrene and divinyl benzene is done to prepare the beads [4].

Sustained-release microspheres: Quasi-emulsion-solvent-diffusion method was used to prepare sustained release microspheres of Zedoary turmeric oil (traditional Chinese medicine). The microspheres were prepared by using HPMC acetate succinate and Aerosil 200 [4].

Nanoparticles: Solvent injection technique, sonication emulsion-diffusion-evaporation can be used for development of SNEFs. Drug and excipients are melted together and injected into a non-solvent solution. Nanoparticles can be separated by centrifugation and lyophilization. Goat fat and Tween 65 was used for development of SNEFs. Glyceryl monooleate (GMO) has self-emulsifying property was used with chitosan for

preparation of paclitaxel nanoparticles. Chitosan acts as bio-adhesive for nanoparticles, while 100% drug incorporation was achieved because of self-emulsifying property of GMO [4-6, 39].

Implants: Self-emulsified 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine, BCNU) was incorporated into PLGA water and used as an implant. SEDDS formulation decreased exposure of BCNU from the aqueous media and its stability and shelf-life increased. The formulation comprised of tributyrin, cremophor RH 40, labrafil MC 1944 and BCNU [39].

Suppositories: C6-C18 FA glycerol ester and C6-C8 FA macrogol esters were used in formulation of glycerrhizin self-emulsifying suppositories. Formulation reported good drug absorption which is indicated by high plasma drug levels when delivered via rectal/vaginal route [12].

Self-microemulsifying mouth dissolving film(SMMDF): SMDDF was developed by Xiao L et al. for inadequately water soluble drug. In this, indomethacin was produced by fusing self-microemulsifying segments with solid carrier(MCC, low-substituted HPMC and hypromellose). Measurement units were planned according to criteria of Chinese Pharmacopeia 2010 for consistency parameters. He found that SMMDDF is another promising dose structure, demonstrating remarkable attributes of accommodation, rapid action and improvement in oral bioavailabilty of poorly water soluble drug [35].

Self-microemulsifying floating dosage form: The main problem regarding the low bioavailability is low solubility, pre-systemic metabolism, eradicate absorption of drug throughout theGIT. Floating system increases residence time of drug in the stomach and develop prolonged-release forms. The novel floating dosage form of Furosemide (FUR) to enhance its solubility by formulating SMEDDS of FUR, followed by its adsorption onto a mixture of high functionality excipient, matrix forming polymers (HPMC K4M and HPMC E50 LV) and a gas-generating agent ($NaHCO_3$) to achieve a buoyant matrix with a controlled release profile [4].

Positively charged self-emulsifying drug delivery system: One of the most commonly problems faced by the formulation scientists has been to find methods of improving the oral bioavailability of poorly water-soluble drugs. This positively charged SEDDS yields several fold increase in the bioavailability than the negatively charge. Cationic lipidsare used in this type of system. Example- Positively charged Meloxicam SEDDS were prepared by using oil components (ethyl oleate, sunflower oil and arachis oil), cationic lipid (oleylamine) and surfactants (combination of tween80 and span80) [4].

Self-double-emulsifying drug delivery system (SDEDDS): SDEDDS can spontaneously emulsify to water-in-oil-in-water (w/o/w) double emulsions in the mixed aqueous gastrointestinal environment, with drugs enclosed(encapsulated) in internal phase which is water of double emulsions. SDEDDS were used to improve oral absorption of pidotimod, a peptide-like drug with high solubility and low permeability [4].

Supersaturatable self-emulsifying drug delivery system (S-SEDDS):T, Higuchii. proposed the potential for supersaturated drug formulations for improvement of drug absorption. PVP and water soluble cellulosic polymers such as HPMC, methylcellulose, hydroxyl propyl methylcellulose phthalate are useful in generating a supersaturatable state with number of poorly water soluble drug. A high payload S-SEDDS was explored to enhance the oral bioavailability of silybin, a poorly water-soluble drug candidate, employing HPMC as a precipitation inhibitor [4].

Recent research works on SMEDDS

The recent research work reported on SMEDDS is summarized in **Table 1**.

Table 1: Recent research work on SMEDDS [40-63]

Sr. No.	Drug	Oil	Surfactant	Co-surfactant	Type	Carrier	Reference
1.	Nisolidipine	Capmul MCM (13.04%)	Labrasol (36.96%)	Cremophor EL (34.78%)	SMEDDS	-	40
2.	Losartan	Capmul MCM (24%)	Cremophor EL (37.5%)	Transcutol HP (37.5%)	Cationic Solid-SMEDDS	Stearyl amine (1%)	41

3.	Oxyresverat-rol	Capryol 90	Cremophor RH 40	Tween 80	SMEDDS	-	42
4.	Nelfinavirm esylate	Maisine 35-1	Tween 80	Transcutol HP	-	-	43
5.	Glyburide	Capryol 90	Tween 20	Transcutol HP	S-SMEDDS	-	44
6.	Aciclovir	Crodamol GTCC (10%)	Labrasol (60-70%)	Plurol oleique CC 497/ Glycerol (20-30%)	SMEDDS	-	45
7.	Felodipine	Miglyol 812	Tween 80, Cremophor RH 40	Transcutol P	Solid-SMEDDS	Silicon dioixde and crospovi done	46
8.	Pueraria Flavones	Crodamol GT CC, Maisine - 35	Cremophor RH 40	1,2propylene glycol and poly ethylene glycol 6000	SMEDDS	-	47
9.	Prednisolon e	Capmul MCM C8, Capmul PG12 NF	Tween 20	Propylene Glycol	SMEDDS	-	48
10.	Dronedaron e	Capmul MCM	Labrafil M 1944 CS	Kolliphor EL	SMEDDS	-	49
11.	Curcumin	Ethyl oleate (30%)	Kolliphor RH 40	Transcutol HP (17.5%)	Plug tablet	Talcum (1%)	50
12.	Atorvastatin calcium	Capmul MCM (7.16%)	Tween 20 (48.25%	Tetraglycol (44 .59%)	SMEDDS	-	51
13.	Lurasidone HCl	Capmul MCM (18%)	Cremophor RH 40 (14%)	Soluphopr P (68%)	SMEDDS	-	52
14.	Atorvastatin	Isopropyl myristate	Lectin/toco pheryl polyethylen e glycol succinate	Ethanol	Solid- SE dispersible tablets	MC KG 802	53
15.	Resveratol	Ethyl oleate, castor oil, olive oil	Tween 80, triton X-100,	PEG 400, glycerol, glycol ether	-	-	54
16.	Bleomycin, ifosamide	Isopropyl myristate	Kolliphor RH 40 and labrasol	Capryol 90, Transcutol HP	Cremophor RH 40	-	55
17.	Rosuvastati n calcium	Maiscine, capryol 90	Tween 20	Lutrol E400	Solid-SNEDDS	Aerosil 200	56
18.	Telmisartan	Castor oil	Tween 20	Propylene Glycol	SMEDDS	-	57
19.	Fenofibrate	Labrafil M 1944CS	Labrasol	Capryol PGMC	SMEDDS	-	58
20.	PEG-30-dipolyhydro xystearate	Capmul MCM	Cithrol DPHS	Kolliphor HS 15	SMEDDS	-	59
21.	Leuprolein oleate	Capmul MCM (10%)	Propylene Glycol (30%)	Captex 355 (30%)	SMEDDS	-	60
23.	Celastrol (10% w/w)	Ethyl oleate (25%)	OP-10 (60%)	Transcutol HP (15%)	SMEDDS	-	61

24.	Fenofibrate	Lauroglycol FCC (60%)	Solutol HS 15 (27%)	Transcutol HP (13%)	SMEDDS	-	62
25.	Cloprodgrel	Paecol	Kolliphor RH 60	Transcutol HP	Solid-SMEDDS	HPMC	63

Future perspective

SMEDDS can be effective solution form to overcome the issue of poorly water soluble drugs with low solubility in GIT fluids. Role of intestinal lipid processing on solubilization behavior of Lipid Based Formulation (LBF) is better understood by using combinations of in-vitro dispersion and digestion methodology. This in-situ emulsion formation system that has high stability which can be taken as emulsion prefix as a formulation. In future, development in SMEDDS will remove all problems associated with delivery of poorly soluble drugs. Numerous potent drugs have low oral bioavailability because of their poor aqueous solubility or pre-systemic metabolism. However, more research is required to elucidate in the field of the novel self-emulsifying osmotic pump tablet (SEOPT) formulations needs to be more exploitation. This technology needs to be extensive and continuous comparison in regarding proper designing of in- vitro model to correlate data of in-vivo experiment to actual in-vivo experience in foreseeable future. There is still a long way to go, however, before more SMEDDS formulations appear on the market.

Conclusion:

For the solubility dissolution, bioavailability and getting best therapeutics effect of poorly soluble drug Self emulsifying drug delivery system is the best solution. Various lipid-based SMEDDS for oral lymphatic delivery of drugs are being researched and developed. This is the method suited for lipophilic drugs where resulting emulsification gives faster dissolution rates, absorption and avoids pre-systemic first pass effect, enzymatic degradation, and gastric irritation. This technology is suitable for all BCS class drugs mostly for class II and IV. However, a few disadvantages of the technology are stability, method of manufacturing formulation, lack of data base regarding solubility of excipients in the drugs. SMEDDS needs to be further exploitation such as studies about human bioavailability and development of *in- vitro/in-vivo* data correlation. There is still long way to go ahead before more SMEDDS products needs to come in the market.

References-

1. Rahman M.A., Hussain A., Hussain M.S., Mirza M.A. and Iqbal Z., Role of excipients in successful development of SMEDDS/SEDDS, Drug Dev Ind Pharm, 2013, 39(7), 1-19.
2. Gursoy R.N.and Benita S., Self-emulsifying drug delivery systems for improved oral delivery of lipophilic drugs, Biomed Pharmacother, 2004, 58, 173-182.
3. Potphode V.R., Deshmukh A.S. and Mahajan V.R., Self-micro emulsifying drug delivery system: an approach for enhancement of bioavailability of poorly water soluble drugs. Asian J Pharm Tech, 2016, 6 (3), 159-168.
4. Ingle L.M., Wankhade V.P., Udasi T.A. and Tapar K.K., New approaches for development and characterization of SMEDDS, Int J Pharm Sci Res, 2013, 3(1), 7-14.
5. Agrawal S., Giri T.K., Tripathi D.K. and Alexander A., A review on novel therapeutic strategies for enhancement of solubility for hydrophobic drugs through lipid and surfactant based SMEDDS: a novel approach, Am J Drug Disc Dev, 2012, 1-41.
6. Chaus H.A., Chopade V.V.and Chaudhri P.D., Self-emulsifying drug delivery system: a review, Int J Pharm and Chem Sci, 2013, 2, 34-44.
7. Pandya B.D., Shah S.H.and Shah N., Bioavailability enhancement of poorly water soluble drugs by SMEDDS: a review, JPSER, 2015, 5, 187-206.
8. Ganesh K., SMEDDS o/w microemulsion for BCS II drugs: an approach to enhance oral bioavailability, Int J Pharm Sci,2011, 3(3), 1-3.
9. Reddy S., Katyayani T., Navatha T.and Ramya G., Review on self-microemulsifying drug delivery systems, Int J Pharm Res Pharm Sci,2011, 2(3), 382-392.
10. Pooja M., Rajni B.and Nimrata S., Lipid based SMEDDS for lipophilic drugs: a acquainted review, IRJP, 2011, 2(12), 75-80.

11. Savale S.K.,A review-self nanoemulsifying drug delivery system (SNEDDS). Int J Res Pharm and Nano Sci, 2015, 4(6), 385 - 397.
12. Shah I., Development and characterization of o/w nano-emulsions form self-microemulsifying mixture-thesis, 2011, 1-25.
13. Khan A., Khan H., Mohamad T.andRasul A., Basics of SMEDDS, J Pharm and alternative medicine, 2012, 13-20.
14. Thakare P., Mogal V., Borase P., Dusane J.and Kshirsagar H., A review on self-emulsifying drug delivery system, Pharm and bio evaluations, 2016, 3 (2), 140-153.
15. Parmar B., Patel U., Bhimani B. and Sanghavi K., SMEDDS: a dominant dosage form which improve bioavailability, Am J Pharm Tech Res, 2012, 2(4), 54-72.
16. Patel M.J., Patel S.S., Patel N.M. and Patel M.M., A self-microemulsifying drug delivery system (SMEDDS),Int J Pharm Sci Rev and Res, 2010, 4(3), 29-35.
17. Jinalbahen B.and Patel M., Self-microemulsifying drug delivery system: a review, World J Pharm and Pharma Sci, 2016, 2, 2215-2232.
18. Prachi S., PrajapatiS.K., Shipra S.andAli A., A review on SMEDDS: an approach to enhance oral bioavailability of poorly water soluble drugs, Int Res J Pharm, 2016, 1-6.
19. Kumar A.andNanda A., Novel approaches of SMEDDS, J Chem Pharma, 2016, 8(7), 149-157.
20. Drasika C., Self-emulsifying drug delivery system: a capsulization, J Pharm Sci Res,2016, 8(2), 121-124.
21. Nigade P.M., Patil S.and Tiwari S, Self emulsifying drug delivery system (SEDDS): a review, IJPBS, 2012,2(2), 42-52.
22. Sanghi D.K.and Tiwle R., A review on (SMEDDS) self micro-emulsifying drug delivery system, IJPDT, 2015, 5(1): 20-26.
23. Dahan A.andHoffman 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, 2008 129, 1–10.
24. Reddy L.H.V. and Murthy R.S.R., Lymphatic transport of orally administered drugs, Ind J experimental biotech, 2012, 40: 1097-1109.
25. Trevaskis NL et al. / Advanced drug delivery reviews, Am J Pharm Sci, 2008, 60, 202-216.
26. Kim H., Kim Y.and Lee J., Liposomal formulations for enhanced lymphatic drug delivery,Am J Pharm Sci,2013, 3(4), 96-103.
27. Kalepu S., Manthina M.and Padavala V., Oral lipid based drug delivery systems- an overview, Acta Pharmacetica Sinica B, 2013, 3(6), 361-372.
28. Gadhave A., Determination of hydrophilic-lipophilic balance value, Int J Sci and Res, 2014, 3(4), 2319-7064.
29. Bragagni M., Mennini N., Maestrelli F., Cirri M. andMura P.,Comparative study of liposomes, transfersomes and ethosomes as carriers for improving topical delivery of celecoxib, Int J Pharm Sci, 2012, 6, 202-210.
30. Vilas P.C., Nayan G., Bhusahan R. and Sunil P., A review on self-emulsifying drug delivery system, Pharm Sci Monitor, 2013, 4, 3628-3648.
31. Chandra A., Abblu K. and Hyma P., Formulation and evaluation of telmisartan self-emulsifying drug delivery system, Int J Pharm Sci,2014, 6, 120-125.
32. Parul J., Geeta A. and Amanpreet K., Bioavailability enhancement of poorly water soluble drugs by SMEDDS: a review, J Drug Del & Therapeutics, 2013, 3(1), 98-109.
33. Shodhganga.inflibnet.ac.in/bitstream/10603/9096/7/07_chapter%204-b.pdf
34. Pandya B.D., Shah S.H. and Shah N., Bioavailability enhancement of poorlywater soluble drugs by SMEDDS: a review. JPSER, 2015, 5: 187-206.
35. Talele S.G. and Gudsoorkar V.R., Novel approaches for solidification of SMEDDS, J Pharm BioSci, 2015, 4, 90-101.
36. Khamkar G.S., Self-emulsifying drug delivery system o/w microemulsion for BCS II drugs: an approach to enhance oral bioavailability, Int J Pharm Sci, 2011, 3, 1-3.
37. Ghosh P.K., Majithiya R.J., Umrethia M.L. and Murthy R.S.R.,Design and development of micro-emulsion drug delivery system of acyclovir for improvement of oral bioavailability, American Association of Pharmaceutical Scientists 7, 2006, E1- E6.
38. Deokate U.A., Shinde N.and Bhingare U., Novel approaches for development and characterization of SMEDDS: review. Int J Curr Pharm Res, 2012,5(4), 5-12.

39. Mahapatra A.K., Murthy P.N., Swadeep B.and Swain R.P., Self-emulsifying drug delivery systems (SEDDS): an update from formulation development to therapeutic strategies, Int J Pharm Tech Res, 2014, 6, 546-568.
40. Nekkanti V., Rueda J., Wang Z.and Betageri GV. Comparative evaluationof proliposomes andself micro-emulsifying drug delivery system for improved oral bioavailability of nisoldipine. IntJ Pharm, 2016,505 (1-2),79-88.
41. Venu M.K.and Kishan V., Cationic solid self micro-emulsifying drug delivery systems of losartan, J Drug Del Sci and Tech, 2016, 35, 190-199.
42. Sangsen Y., Iwattanawongsa K., Sritularak B., Graidist P.and Iwattanapatapee R.,Influence of surfactan ts in self-microemulsifying formulations on enhancing the oral bioavailability of oxyres- veratrol : studies in caco-cells and in vivo, Int J Pharm, 2016,498 (1-2),294-303.
43. Kamboj S.and Rana V., Quality by design based development to reduce effect of food on nelfinavir mesylate, Int J Pharm, 2016, 501, 311-325.
44. Macriza C., Development and characterizationof fast dissolving tablet formulations of glyburides based on solid self micro-emulsifying drug delivery systems, Eur J Pharm Bio, 2016, 104, 1929-1935.
45. Jankovi J., Djekic., Dobrii V.and Primorac M,Evaluation of critical formulation parameters in designan d differentiation of self-microemulsifying drug delivery systems for oral delivery of acyclovir, Int J Pharm, 2016 , 497(1-2),301-11.
46. Jing B., Ang R., Heng X., Hao J.and Tang S.,Enhanced oral bioavailability of felodipine by the novel solid selfmicroemulsifying tablets, Drug Dev Ind Pharm, 2016, 42(3),506-512.
47. Guan Q., Zhang G., Sun S., Fan H., Sun C.and Zhang S,Enhanced theoral bioavailability of puerariaflav ones by thenovel solid selfmicroemulsifying drug delivery systems (SMEDDS) dropping pills,Biol Phar m Bull, 2016 , 39(5),762-769.
48. Bansode S.T., Kshirsagar S.J., Madgulkar A.R., Bhalekar M.R.and Bandivadekar M.M.,Designanddeve lopment of SMEDDS for colon-specific drug delivery, Drug Dev Ind Pharm. 2016;42(4),611-623.
49. Han S., Jung S., Jang S., Son M., Kim B.M.and Kang M.J., Reduced food-effect on the intestinalabsorptionof dronedarone by self-microemulsifying drug delivery system, BiolPharm Bulletin, 2015, 38 (7),1026-32.
50. Yuanrui H., Rui T.and Wenjing H., A novel plug-controlled colon-specific pulsatile capsule with tablet of curcumin loaded SMEDDS, Carbohy polym, 2015, 49, 2218-2223.
51. Yeom D.W., Song S., Kim S.R., Lee G., Kang H., Lee S.and Choi W, Development and optimi- zation ofself-microemulsifying drug delivery systems (SMEDDS) for atorvastatin calcium byusing D-optimal mixture design,Int J Nanomed, 2015 , 10, 3865-77.
52. Foram J.and Vaishali L., Solubility enhancement of lurasidone hydrochloride by preparing SMEDDS, Int J Pharm, 2015, 7, 283-288.
53. Rania A.H., Ishak, and Rihab O., Lectin/TGPS-based spray-dried self-microemulsifying drug delivery systems: In vitro pulmonary deposition and cytotoxicity,Int J Pharm 2015, 485, 249-260.
54. Chen Y., Zhang H., Yang H.and Sun H., Improved antioxidant capacity of optimization of SMEDDS of resveratrol, Molecules, 2015, 21167-21177.
55. Zoltan U., Azin K.K., Miklos V.and Eszter R., The enhanced inhibitory effect of different antitumor agents in self-emulsifying drug delivery systems on human cervical cancer HeLa cells, Molecules 2015, 20, 13226-13239.
56. Nilesh N.K., Nisharani S.R. and Govind M., Development and characterization of solid selfmicro-emulsifying formulation of rosuvastatin calcium for improved bioavailability, Tropical J Pharm Res, 2015, 14(4), 575-582.
57. Jaiswal P., Aggarwal G., Harikumar S.L.and Singh K.,Development of a self-microemulsifying drug delivery system and solid-selfmicroemulsifying drug delivery system of telmisartan, Int JPharm Investig, 2014,4(4),195-206.
58. Weng T., Qi J., Lu Y., Wang K., Tian Z., Hu K., Yin Z.and Wu W., Role of a lipid-based nanodelivery systems on oral bioavailability enhancement of fenofibrate, a BCS II drug: comparison with fastrelease formulations, J Nanobiotech, 2014, 12,39-43.
59. Tamer H., Handrik M., Karsten H., Novel semisolid SNEDDS on PEG-30-dipolyhydroxystearate: development and characterization, Int J Pharm 2014, 477, 506-518.
60. Hintzen F., Perera G., Hauptstein S., Mller C., Affleur F. and BernkopA., In vivo evaluation ofan oral self-microemulsifying drug delivery system SMEDDS for leuprorelin, Int J Pharm, 2014, 472(1-2), 20-26.

61. Qi X., Qin J., Ma N., Chou X. and Wu Z.,Solid self-microemulsifying dispersible tablets of celastrol: fo rmulation development, charaterization and bioavailability evaluation, Int J Pharm,2014, 472(1-2),40-7.
62. Cho D.and Park J., In vitro and in vivo evaluation of a self-microemulsifying drug delivery sys- tem for the poorly soluble drug fenofibrate, Arch Pharm Res, 2014, 37(2),193-203.
63. Kim D., Kwon M.S., Mousaf A.M., Balakrishnan P., Park J.H., Kim D.S., Park J., Kim J.O.and Choi H.G., Comparison of a solid SMEDDS and solid dispersion for enhanced stability and bio- availability of clopidogrel napadisilate, Carbohydr Polym, 2014, 114,365-74.

*****