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Strategies to Overcome the Solubility Issue of Drug

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ABSTRACT

The oral hydrophobic drugs delivery are the biggest challenges due to insolubility in the aqueous vehicle of these components. Self-emulsifying drug delivery system is classified to self-nanoemulsifying drug delivery system (SNEDDS) and self-micro emulsifying drug delivery system (SMEDDS). Self-micro emulsifying drug delivery systems has ability to increase the solubility and bioavailability of low water soluble drugs. The real mechanism of this system is not until now understood, to increase solubility as well as bioavailability of poorly water soluble drugs but it has recommended self- emulsification happens while entropy change favoring dispersion is more than energy necessary to enlarge dispersion surface area. Therefore by decreasing the droplet size increasing the surface area, hence increase the solubility as well as bioavailability of drugs. There are several formulation factors effect on efficacy of oral absorption of lipophilic drugs such as, amount of surfactant, oil, ratio of oil and surfactant, droplet size and charge, polarity of emulsion and some of specific pharmaceutical inactive ingredients. The aim of surfactant used in SMEDDS formulation to reduce the interfacial tensions among both phases (O/W) and improve the flow ability of drugs in GIT environments.

1. Introduction

SMEDDS defined as an isotropic admixture of surfactants, co-solvents and oils, which can formulated to increase the oral absorption of hydrophobic active ingredients and there formulation components. The hard and soft gelatin capsules of SMEDDS are available, which is after administration with the help of mild agitation of gastrointestinal fluid, form a fine and stable oil in water (o/w) type of emulsion. Delivery of drug is an important factor, mainly when lipophilic active agents administered from different routes. Over years, micro emulsion drug delivery have involved main attention as potential active ingredient delivery vehicle [1]. The interest for these delivery system is to enhance the bioavailability, permeability, administration and increase shelf life [2]. Another main property which prepared micro emulsion is an appropriate medium for pharmaceutical purpose, it is capacity to incorporate different drugs with hydrophobic nature [3]. Micro emulsions at the first time discovered in 1943 by Hoar and Schulman, who defined a thermodynamically constancy translucent system compounded of two immiscible liquids with the aid of surfactant [4]. Some oil based formulations afford protection against abiotic factors that are dangerous to condidia, for example oil based formulation can protect the candidia against inhalation damage and dangerous effect of UVray [5]. Micro emulsion is on important vehicle for carrying and solubilization of poorly water soluble active component in the field of cosmetics, food and also pharmaceutical ingredients [6]. Recently improvement in biotechnology, enhanced the discovery of novel drugs, hence most of these drugs are insoluble in water, and result is low dissolution in GIT and poor bioavailability. However micro emulsions are an outstanding solvents for solubilization and transportation of poorly water soluble drugs and unsolvable active mixtures [7]. Micro emulsion is disperses system, inert structure and in the range of Nano droplets which is stabilized by surfactants. The solubilization capability is an important factor in formulation of SMEDDS, but the talent of these medium which are used as a carriers more important to transport the drug to the place of action (cells, skin, guts). The main interest is for those drugs which are insoluble in aqueous system or has poor permeability. Absorption of drugs from micro emulsion system related to, partition coefficient of active agent among two immiscible vehicle, the present of active ingredient in the interface site of absorption, components of formulation and droplet size [8]. Oral delivery route is the common and easy route for application of different dosage forms, but challenges are, delivery of macromolecules, such as peptides and protein [9]. In last few decades, many approaches has been applied to enhance oral bioavailability of such drugs for their suitable efficacy such as absorption enhancers, enzymes inhibitors, chemical adjustments, micro emulsions, liposome as a carrier, solid liquid nanoparticles, polymers with multifunctional effect and different active agent delivery systems[10]. Recently (SMEDDS) self-emulsifying drug delivery system gained a broadly pharmaceutical attention as a possible carrier for delivery of peptides and proteins. In modern drug discovery there are number of techniques to increase drug solubility and improve bioavailability, hence there are many poorly water soluble and water insoluble drugs, presently more than 50% of novel pharmacologically active molecules are hydrophobic and shows low solubility in water. For improvement of solubility and bioavailability of those drugs, the following methods are applicable: pH change, salt formation, complex with β – cyclodextrine, micro emulsion and etc. SMEDDS consist of oil and surfactant which (some time needed to add co surfactant) form an emulsion with the help of water [11].

2. Classification of self-emulsifying drug delivery system

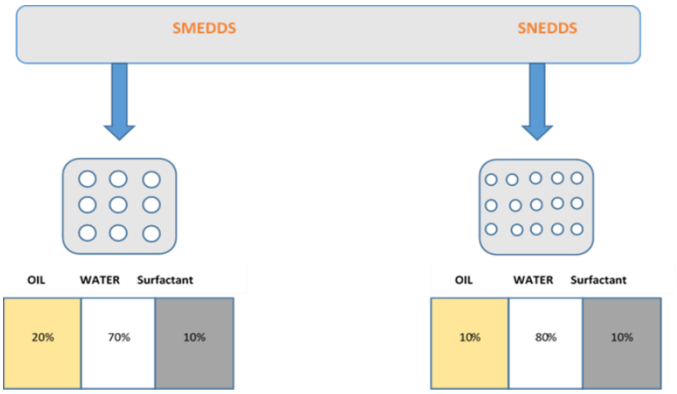

Fig.1. Dissimilar Composition of SMEDDS & SNEDDS Formulations

3. Self-emulsifying drug delivery systems

SEDDS is one of the broadly applicable drug delivery system for enhancing the bioavailability of low water soluble active ingredients, enhancement of bioavailability due to increase solubilization as well as adjustment of pharmacokinetic parameters of lipophilic medicines. The main mechanism of this system, it is ability to form a very fine oil in water (o/w) micro emulsions below slight agitation and finally dilution with water. This motility is depended to stomach and intestinal environments for providing in vivo self-emulsification [12]. The requirement for selection of appropriate vehicle for self-emulsification are: solubility of the drugs in different components and distribution of droplet which is resulting self-emulsification [13]. SEDDS are physically stable and easy manufactured. SEDDS is a possible formulation for dose active ingredients which are related to biopharmaceutical class II (low solubility and high permeability) that show low dissolution rate and incomplete absorption, SEDDS improved rate and extend of drug absorption. Among several drawback of SEDDS and lipid based formulation one of them is lack of in vitro model for evaluation of formulation. Lipid based formulation is classified as: lipid solution and nanoparticles, emulsions, micro emulsions and Nano emulsions[14].

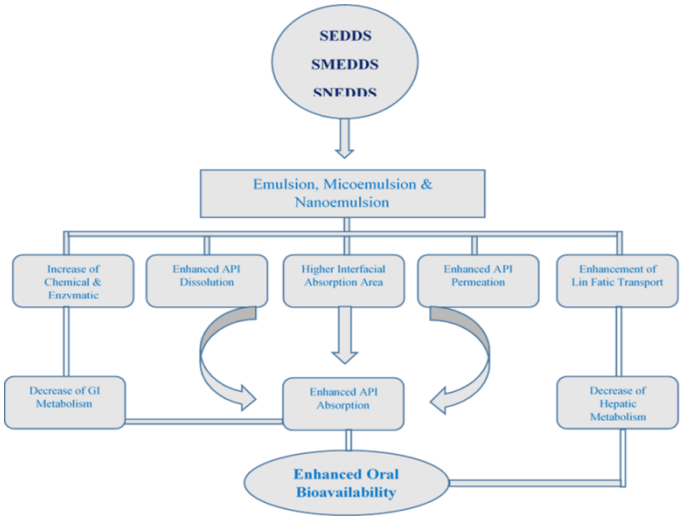

Fig.2. Comprehended Factors on Bioavailability of SMEDDS, SEDDS & SNEDDS Formulations

4. Mechanism of action of self-emulsification

Mechanism of self-emulsification of the formulation is not until now understood, but it has recommended self-emulsification happens while entropy change favoring dispersion is very than the energy necessary to enhance dispersion of surface area. Formulation of SMEDDS consist of surfactant, co- solvent and oil, surfactant forms the interfacial film while co-solvent ensures flexibility of interfacial film, hence decrease the interfacial tension. The greater bioavailability of lipophilic active agents are incorporated in SMEDDS was informed. There is a study approved in non-fasting dogs for evaluation of verbal bioavailability of a hydrophobic Naphthalene derived formulated as a SMEDDS result is greater values of C_{max} and AUC well compared with another dosage forms. Other study on the rats shown, oral bioavailability of anti-inflammatory Antazolast drug increased when this hydrophobic drugs ordered in lipid base formulation, like glyceryl oleate solution, emulsion and SMEDDS to compare with suspension formulation. A several study was conducted for diagnostic of HIV virus in human's body, formulations of HIV protease inhibitor is available as SMEDDS and elixir. Reported the higher C_{max} and C_{min} values of SMEDDS formulation is compared with elixir form [15]. After oral administration of SNEDDS, it form an emulsion with GIT fluid than it cross the mucus membrane, reach to the blood capillary and final bioavailable in the blood stream, as shown in figure 3.

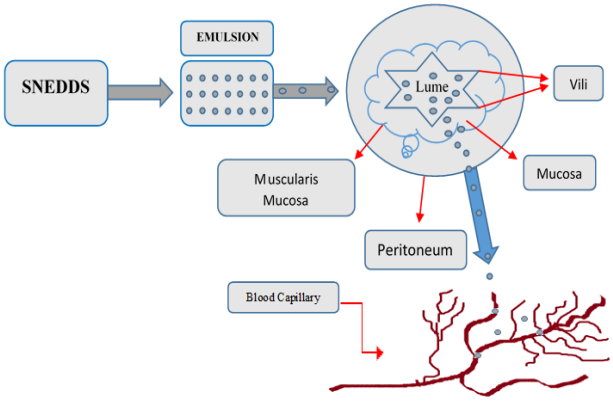

Fig. 3. Schematic Diagram of Absorption of SNEDDS Formulation

Different methods have been informed in the literatures, there is no single concept to clarify whole characteristics of micro emulsion system. The subcutaneous droplet of micro emulsion due to formation of complex film by surfactant and co-solvent at the interface of water-oil phases, therefore thermodynamic techniques of development of micro emulsion system describes, while entropy change that favor dispersion is greater than energy need to increase surface area of the dispersion, thus micro emulsion occurs. When micro-emulsion formed the free energy of formulation create the new surface between two phases as explain by equation.

$$\Delta G = \Sigma N\pi r2 \sigma$$

Therefore ΔG is free energy which is related to the process. N number of droplets, r is radius and σ is present to interfacial energy. When both phases of emulsion don't dispersed the free energy of the system will decrease. Hence emulsion stabilized by conventional surface active agents, which are forms around the emulsion droplet a mono layer, thus decrease the interfacial energy and prevent the coalescences [16].

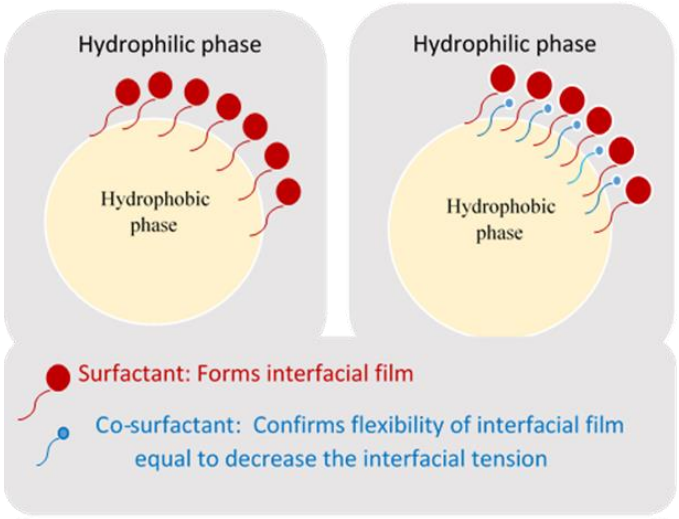

Fig.4. Mechanism of Action of Self-Emulsification

5. Formulation of SMEDDS

The SMEDDS formulation consist of oil phase, surface active agent and co-solvent. This formulation is an isotropic system usually easier to formulate than normal emulsion. In preparation of SMEDDS formulation not only temperature is an important factor but nature of the components and their relative concentration is also considered [17]. Studies have presented the self-micro emulsifying process is directly related to concentration and nature of surfactant as well as oil phase, means the ratio of surfactant and oil in a specific temperature producing self-micro emulsion [18].

5.1 Oil

For preparation of acceptable pharmaceutical SEDDS systems, it is compulsory to make this system by using nontoxic as well as safe ingredients[17]. Most of the oils and their derived produced from natural sources for example fatty acid and triglycerides, methyl esters are simply tainted by microorganism and measured to be not hurtful to the atmosphere. Manufacture of micro emulsions with mineral oil almost applicable for industrial products[19]. A suitable hydrophobic phase for pharmaceutical application is vegetable oils. Therefore the texture of micro emulsion related to the nature and sources of oil. Those oils which are broadly used such as Sunflower oil, Caster oil, Olive oil, Sesame oil and hydrogenated specific oils. Most of lipophilic active ingredients have more solubility in triglycerides, therefor average chain and extended chain triglycerides with the dissimilar grade of saturation has been applicable for solubility of lipophilic active ingredient to designed SMEDDS formulation. Original eatable oil derivation from natural sources use as a lipid medium, but it has less ability to dissolve the huge amount of lipophilic drugs, thus it reduce the application on SMEEDS[18].

5.2 Surfactant

Surfactant is a molecule consist of two parts and it has dissimilar coherency for solvents. One of the coherency for polar solvents (water) and another has for Nan polar vehicles (oil). A small amount of this molecules reduce the water surface tension that is why called as surface active agent[70].

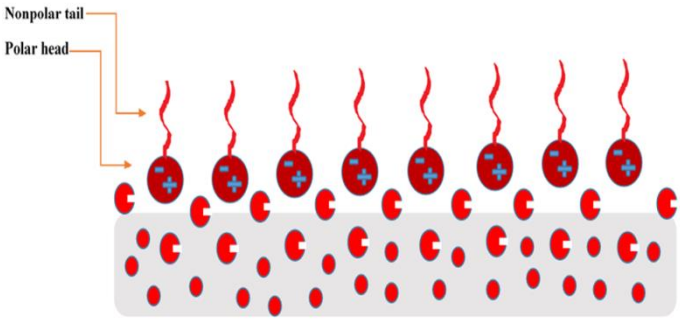

Fig. 5. Schematic Diagram of Surfactant Molecule

Surfactants are used for different purpose like stabilization of micro emulsion system. Due to surface charge surfactants classified as nonionic, cationic, anionic, zwitterionic, for stabilization and better effectiveness of micro emulsion mostly use the combination of ionic and nonionic surfactants for example Brij 35 (polyoxyethylene) Span 80 (sorbitanmonooleat) used as nonionic surfactant. Some of other surfactants like sodium dodecyl sulfate or sodium deoxy cholateincrease the solubilization ability of fats[20]. HLB or hydrophilic, lipophilic balance is an important factor for selection of surfactant. Those surfactant with less value of HLB (3-6) applicable for w/o types of formulation of micro emulsion while surfactant with high value of HLB (8-18) is suitable for stabilization of o/w micro emulsion formulation[21]. Safety is the most important factor for election of a surfactant. Surfactants are produce from natural sources as well as synthetic. The natural surface active agents are harmless than the synthetics but the limitation of these categories less self-emulsification ability. Nonionic surfactant is less toxic when compare with ionic but it may reversible variations in the intestinal membrane penetrability [22].Usually 30 to 60 % w/w concentration of surface active agent needed for stability of SMEDDS formulation, determination of surfactant concentration very important, therefore the high concentration of surfactant make irritation on GI system. Amphiphilic surfactants are able to stabilize and dissolved high amount of lipophilic active ingredient. Thus for SMEDDS formulation combination of surface active agent, co-solvent and oil with the adequate ratio, required[23].

5.3 Co-Surfactant

Most of the surfactants with single chain structure not capable to lower the interfacial tension among water and oil to form a micro emulsion, thus co-surfactant added to reduce the interfacial tension among two phase (water & oil)[24]. Usually co-surfactant is a small chain alcohols (ethanol - butanol), glycols (propylene glycol), average chain alcohols such as amines and acids. The main action of co-surfactant is, to remove gel structure or fluid crystalline arrangements and form phase of micro emulsion. The role of co-surfactant summarize by El-Nokaly: Improve the fluidity of interface, destroy the structure of gel as well as liquid crystalline which are prevent the development of micro emulsion, correct the HLB value and curving the interface by altering surfactant separating characteristic[25]. Usually HLB value of co-surfactant is 10 to 14 it used simultaneous with surfactant to reduction the interfacial tension among water and oil, although increase the loading of active ingredients in SMEDDS formulation and permits the development of micro emulsion.Suitable co-

surfactant for oral drug deliver are organic solvents like PG, PEG and ethanol, they able to stabilize large amount of active agent as well as hydrophilic surfactant in the oil phase[26].

5.4 Co-Solvent

The manufacture of ideal SEDDS need high concentration (usually more than 30 % w/w) of surface active agent. Propylene glycol, polyethylene glycol and ethanol are an organic solvents, appropriate for oral delivery and capable to dissolve great quantity of water soluble surfactant and active agent in oil phase. These solvent play role as co-surfactants in micro emulsion formulation. One of the visual limitation of alcohol and another volatile co-solvents are evaporation from the shell of soft and hard gelatin capsules, finally active agent is precipitated, in this cause alcohol free formulation designed. Hence the hydrophobic drug dissolution capacity maybe decreased[11].

6. Characterization of SMEDDS

Table 1: Characterization and evaluation of SMEDDS formulation

Visual evaluation	To maintain the self-emulsification characteristic, a few mg of formulation added in 100 ml water at 25 ^{0}C than mild stirred, formation of transparent emulsion judged as good otherwise if there is poor emulsion formation judged as bad [27].
Macroscopic assessments	Homogeneity of micro emulsion performed by macroscopic analysis. Any changes during normal storage condition (37±2 ^{0}C) such as color, transparency and phase separation was detected in micro emulsion formulation.
Differential scanning calorimetry (DSC)	It is thremo gravimetric technique used for measurement of any phase transition due to the change in temperature. It also helps to determine melting point change, interaction between drug and excipients and stability changes [28].
Fourier transform-infraredspectroscopy (FT-IR)	FTIR is used for detection of function groups. Liquid sample of SMEDDS formulation kept in sample holder and the outcome must be noted, hence any kind of physicochemical interaction will be described by applying FT-IR [29].
Droplet size measurement	Measurement of droplet size is a critical issue because it determine the micro emulsion stability, rate and extent of active ingredient release. Photon correlation spectroscopy is applicable for droplet size of micro emulsion[30].
Zeta potential	The oil droplet charge is other characteristics of SMEDDS formulation it must be determine. Hence the negative charge of SMEDDS formulation is due to being of free fatty acids [18].
Temperature stability	Temperature is directly effect on SMEDDS during storage. The effect of temperature is measured through visual assessments of SMEDDS formulation at various period of time. Hence SMEDDS are dilute with distillated water to determine temperature constancy, therefore the samples kept at three diverse temperature such as 2 to 8 ^{0}C refrigerator, room temperature, and absorbed any variations such as flocculation phase separation or precipitation[31].
Centrifugation	Centrifugation is done for 5 minutes at 3000 rpm. Observed phase separation of formulation. Only those formulations are stable which not shown phase separation are. For estimation of metastable systems, SMEDDS formulation should be optimized, hence formulation of SMEDDS was diluted with distillated water than micro emulsion at 1000 rpm for 15 minutes at 0 ^{0}C centrifuged, finally detected any changes in consistency of micro emulsion [31].
Dispersibility test	For dispersibility assessment, rate, extent and efficacy of the self-emulsifying system is evaluated by using USP XX11 standard dissolution type-II apparatus with speed of 50 rpm. One ml for each formulation placed in 500 ml of water at 37 ± 1^{0}C. For visual assessment of formulation applying the following grad system: **Grade A**: Rapid forming Nano emulsion in one minute, it have a clear appearance. **Grade B**: Rapid forming, little clear emulsion, it have a white appearance. **Grade C**: Within two minute formed a fine and milky emulsion. **Grade D**: Within two minute form dull, dark white emulsion with oily appearance [32].

7. Physicochemical characteristics for selection of drug

Most of pharmaceutical active ingredients are low water soluble with different physicochemical properties, such lipophilic drug is Cinnarizine which is a good candidate for SMEDDS formulation[33]. That is important to identify the drug concern, it has significant effect on SMEDDS formulation. The physiochemical properties such as molecular weight and structure, droplet size, pKa, log p and existence of ionizable groups which are effected on SMEDDS formulation. Potent drug is a best candidates for SMEDDS[34].

8. Application of self-emulsifying drug delivery system

Enhancement in solubility detected if an active agent is loaded in SMEDDS formulation, enhance the solubility of BCS class-II medicines (low solubility high permeability). When interaction between mixture of oil and water occurs a fine droplet of o/w emulsion formed, these droplet will convey the active component in dissolved form to the small intestinal membrane and freely available for absorption. Hence increase bioavailability of many drugs which are formulated as a SMEDDS[35]. Number of the drugs which are formulated as a SNEDDS such as:

8.1 Anti-Coagulant

Rivaroxaban is anti-coagulant agent, this drug is used the treatment of pulmonary embolism and vein thrombosis. Anti-coagulant drugs like Heparin, Vitamin K, Fawarin due to insufficient clinical effect and toxicity, not broadly used. Rivaroxaban is an effective factor Xa (FXa) inhibitor, it doesn't need a cofactor for action. Due to this advantage Rivaroxaban has widely used. The poor solubility of Rivaroxaban in aqueous vehicle shows indirect changes among fasted and fed state

[36]. Hence several methods are applied to solve low solubility of BCS class II drugs, such as, application of liposome, niosomes and nanoparticles as a carrier, solid dispersion, Nano suspension and complexation with cyclodexrin is the other techniques to improve solubility [37]. SNEDDS or self-nanoemulsifying drug delivery system is a novel solubilization method which is enhance the solubility as well as bioavailability of BCS class II drugs, therefore Rivaroxaban is formulated as SNEDDS tablet, thus increase the oral solubility and bioavailability [38].

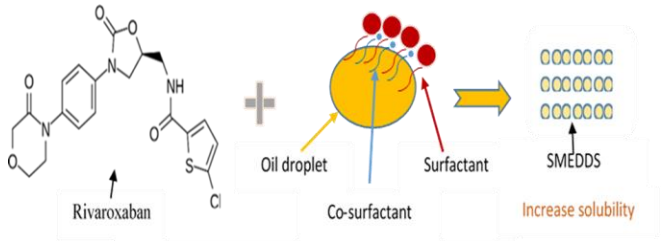

Fig. 6. Schematic Diagram of SMEDDS Formulation of Rivaroxaban

8.2 Benign Prostatic Hyperplasia (BPH)

Finasteride is synthetic 4-aza-3-oxosteroid complex, used in management of prostatic hyperplasia and male pattern baldness [39]. The drug mechanism includes: prevention of 5α-reductase enzyme which change testosterone to di-hydro testosterone. However testosterone metabolites are 17b-diol-glucuronide and ostanediol glucuronide, uncontrolled cellular increaseconducting to enlarge the prostate size due to increase the serum concentration and physical compression of urethra and mechanical abstraction of the bladder outlet, cases stroma smooth muscle tone, called as prostatic hyperplasia [40-41]. FDA considered by its low water solubility and it has 63% absolute bioavailability. It undergoes wide metabolism with liver and inactive metabolites which are easily eliminate of the body among the bile and urine. The excretion half-life of Finasteride is 4.7 to 7.1 hours, with multiple drug doses slow accumulation may occur [42]. The popular pharmaceutical products of FSD are capsules, tablets, granules, sachets, powders, and chewable tablet. These dosage formssuggest several advantage for patient as well as physicians like stability, accurately measure dose, easy to package and transport and unusual characteristics of the drugs such as fast dissolving and uncontrolled release. [43-44]. FSD drug formulated as self-nanoemulsifying drug delivery system to increase the solubility, rate and extend of dissolution, absorption and bioavailability. For optimization of SNEDDS formulation the most appropriate oil, surface active agent and co-surfactant have been nominated. Anise oil used as an oil phase, tween 80 like a surface active agent and methanol used as a co-surfactant in formulation of FSD [43-45].

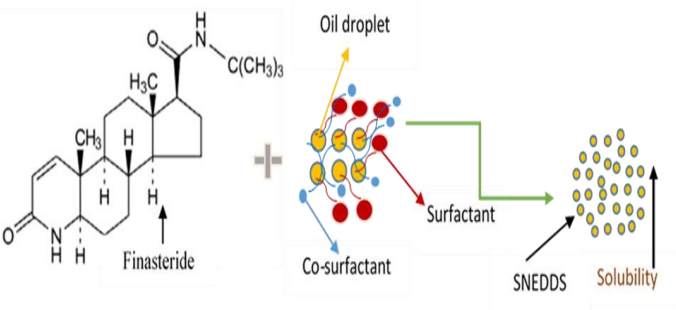

Fig. 7. Categorical Diagram of SNEDDS Formulation of Finasteride

8.3 Anti Hyperlipidemic Agent

Fenofibrate is related to fibrate class, it mostly used to decrease the cholesterol levels in patient as risk of cardiovascular disease. Fenofibrate reduce the LDL and VLDL and decrease HDL and decreasing triglyceride level [46]. Finofebrate is applied with statins to treat hyperlipidemia, the main said effect is muscle damage and FDA approved the use of combination of statins with fenofibrate [47]. Fenofibrate is BCS class II with low solubility and high permeability, prepared as a SMEDDS with different oil, surface active agent and co-surfactant to improve solubility, absorption and bioavailability [48].

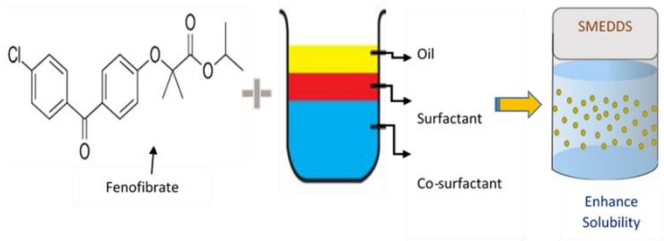

Fig. 8. Diagram of SMEDDS Formulation of Fenofibrate

8.4 Anti Hypertension

Candesartan is a prodrug, used for treatment hypertension and heart failure [49]. This prodrug is easily and totally activated through ester hydrolysis and change to active form of candesartan when absorbed from GIT route [50]. Condesartan is very effective and particular non peptide type-1 angiotensin (AT_1) receptor antagonist. Condesartancilexetil have low bioavailability (15%) as well as solubility and efflux by p-glycoprotein of intestinal cells and metabolized by cytochrome P 450 3A4 [50-51]. For increasing the solubility and bioavailability, candesartan formulated as a solid dispersion [52]. However candesartancilexetil is formulated as SNEDDS with p-glycoprotein and cytochrome P3A4 inhibitor to improve the solubility and oral delivery. In last decade SEDDS are widely considered to increase oral bioavailability of low water soluble active ingredients by increasing their solubility. Hence other main effects of SEDDS is opening the tight junction, therefore candesartan cilexetil is formulated as self-Nano-emulsifying drug delivery system to enhance bioavailability. Candesartan cilexetil formulated with peppermint oil 55%, chromophore RH40 25% and labrasol 20% it exhibited the great emulsification features [53].

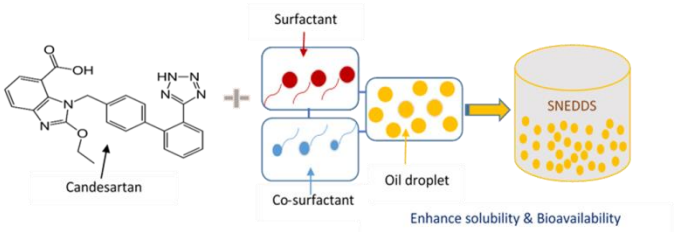

Fig. 9. Diagram of SNEDDS Formulation of Candesartan

8.5 Anti-Oxidant (Multi Effect)

Thymoquinone is with multi effect such as anti-oxidant, cardio protective, hepato protective, neuro protective, antidiabetic, anti-inflammatory and anti-carcinogenic [54]. Although, high dose of TQ is needed due to low solubility and bioavailability for treatment of hepatic disorders. The solubility

of TQ is reported at room temperature is less than, 1.0mg/ml [55]. The low solubility of TQ outcome is, less in-vitro dissolution rate such as poor oral bioavailability. The main therapeutic effect of TQ is antioxidant effect [56]. Recently researchers much consideration for development of nanotechnology delivery system, like micro emulsion, Nano emulsion, polymer nanoparticle, liposomes, niosomes, solid-lipid nanoparticles, self-micro emulsifying and self-nanoemulsifying drug delivery systems, to enhance the bioactive natural mixtures, nutraceuticals bioavailability, therapeutic ability and minimize adverse effects [57]. TQ is formulated as SNEDDS and showed considerably increase in oral bioavailability when compared with Thymoquinone suspension. The enhancement of oral bioavailability of Thymoquinone as SNEDDS formulation is related to Nano sized droplets and existence of capryol-90 and tween-20 as solubilizer [58].

*8.6 Anti-Oxidant(*Quercetin*)*

Quercetin is a flavonoid, plant is the natural sources. It presence in eatable fruits and vegetables. The hepatoprotective effect of quercetin is reported [59]. It shows different pharmacological effect such as anti-proliferative, anti-inflammatory, and antiviral [60]. The result of poor oral bioavailability is related to low solubility in aqueous medium and metabolized by gut microorganisms. Therefor Quercetin is formulated as SNEDDS to increase dissolution rate and improve bioavailability [61].

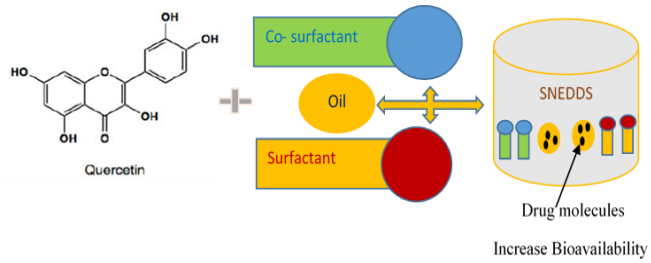

Fig. 10. Diagram of Quercetin SNEDDS Delivery System

*8.7 Anti Hyperlipidemic Agent(*Rosuvastatine calcium*)*

Rosuvastatine calcium is effected on low density lipoprotein (LDL), it mostly used to decrease the cholesterol levels in patient at risk of cardiovascular sickness [46]. The absolute bioavailability of rosuvastatine is around 20% and C_{max} is achieved 3 to 5 hr. It bounded 88% with plasma protein (albumin) [62]. Rosuvastatine calcium is formulated as SNEDDS to enhance its solubility and bioavailability. Rosuvastatine incorporated with different oil to find out the maximum solubility, hence rosuvastatine in essential oil showed high solubility when compare with other oils. Researchers improved diverse self-emulsifying design of rosuvastatine based on solubility data, thus the best SNEDDS formulation with higher ability of emulsification of rosuvastatine is used, Cinnamon oil 30%, Labrasol 60% and Campul MCMC8 10%, and the droplet size was less than 200 nm [63].

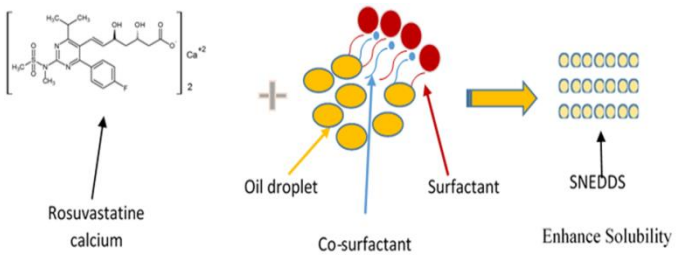

Fig. 11. Diagram of SNEDDS Formulation of Rosuvastatine

*8.8 Anti Hyperlipidemic Agent(*Gemfibrozil*)*

Gemfibrozil is benzene derivative of valeric acid, it used in hyperlipidemia and hyper glyceridemia. Gemfibrozil is reduce the amount of triglyceride, very low density lipoprotein (VLDL) and enhance high density lipoprotein in the serum [64]. The main side effect of Gemfibrozil some gastrointestinal symptoms are observed. Gemfibrozil is low soluble in water about 0.01mg/ml. Gemfibrozil is related to BCS class II (low solubility- high permeability) with high dose 250mg administrated. The low bioavailability is depend to poor solubility and limited dissolution rate [65]. Among the several techniques for enhancing the solubility, SNEDDS is considered to extent of drug absorption [66-67]. Formulation of Gemfibrozil as SNEDDS increase the oral bioavailability and drug solubilization (dissolved in oil phase), due to small droplet size around 20-200 nm, reduce the food effect [68]. SNEDDS formulation play role of bio enhancers due to certain kind of surfactant like Chromophore, by facilitating transcellular and paracellular improved the bioavailability of drug [69].

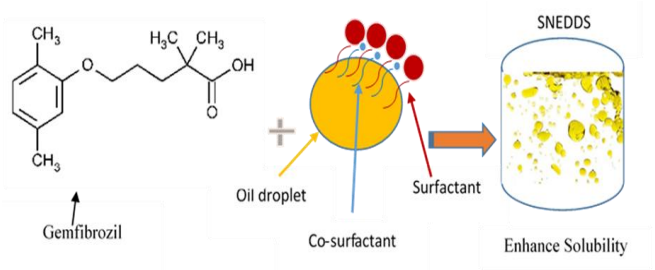

Fig. 12. Composition of Gemfibrozil SNEDDS

9. Conclusion

For hydrophobic pharmaceutical active ingredients, which have incomplete absorption, self-emulsifying drug delivery system are verified to be promising policy to enhance solubility and bioavailability of active component. Now a day the oral delivery of lipophilic medicines are not a hard job, because it can formulated as self-micro emulsifying delivery. Some problems are related with numerous active agents such as producing gastrointestinal irritation, having great first pass metabolism, little half-life and constancy. These problems are solved when incorporated drug in SMEDDS. In the future, novel progress technology will assist SMEDDS to resolve more difficulties related with other routes of running along with oral route.

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