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Review Article

APPROACHES TO DEVELOPMENT OF SOLID- SELF MICRON EMULSIFYING DRUG DELIVERY SYSTEM: FORMULATION TECHNIQUES AND DOSAGE FORMS – A REVIEW

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ABSTRACT

Oral route still remains the favorite route of drug administration in many diseases and till today it is the first way investigated in the development of new dosage forms. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. Solubility is one of the most important parameter to achieve desired concentration of drug in systemic circulation for therapeutic response. As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water soluble. It is a great challenge for pharmaceutical scientist to convert those molecules into orally administered formulation with sufficient bioavailability. Among the several approaches to improve oral bioavailability of these molecules, Self- micron emulsifying drug delivery system (SMEDDS) is one of the approaches usually used to improve the bioavailability of hydrophobic drugs. However, Conventional SMEDDS are mostly prepared in a liquid form, which can have some disadvantages. Accordingly, solid SMEDDS (S-SMEDDS) prepared by solidification of liquid/semisolid self-micron emulsifying (SME) ingredients into powders, have gained popularity. This article gives an overview of the recent advancements in S-SMEDDS such as development methods and the future research direction.

KEY WORDS: *Solid-Self Micron Emulsifying System, Solidification Techniques, Recent Advances and Future aspects*

INTRODUCTION:

Oral route is the easiest and most convenient route for non invasive drug administration. Oral drug delivery systems being the most cost-effective have been leading the worldwide in the drug delivery market. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties. Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy.

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The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles, such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposomes, with every formulation approach having its special advantages and limitations. Efficacy of lipophilic drug is often hindered due to their poor aqueous solubility leading to low absorption after *in vivo* administration. A part of the administered dose is absorbed and reaches the pharmacological site of action and remainder causes toxicity and undesirable side effects due to unwanted bio-distribution. Enhancement in drug efficacy and lowering of drug toxicity could be achieved through encapsulation and delivery of the drug in lipid based delivery system. The concept of drug delivery system has emerged to minimize the toxic side effects of drug, to broaden their application, to expand modes of their

administration and to solve absorption problems.

The twentieth century has witnessed a remarkable growth in drug development and the newly developed drugs are mostly lipophilic compound with poor aqueous solubility, which limits their efficacy and bioavailability. Solubilization, encapsulation, and delivery of these drugs using lipid based and biocompatible systems are likely to furnish better absorption, by way of lower dose, reduced frequency of administration, and improved therapeutic index. Over recent years, much attention has been focused on lipid micro emulsion formulations, with particular emphasis on liquid self-micro emulsifying and self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly water-soluble drugs. [1, 2, 3]

However, these delivery systems had a few limitations, such as stability, the manufacturing methods, the interaction between the filling and the capsule shell, and the storage temperature4. When the product is kept at lower temperatures, there may be some precipitation of the active ingredient and/or the excipients. Therefore, the precipitated materials should be dissolved again when warmed to room temperature or the drug will not be present in solution or as a fine emulsion droplet. Moreover, its efficiency is dependent upon a moist environment. [4]

Thus solid self microemulsifying drug delivery system (S-SMEDDS) should be carefully explored as a means of overcoming these problems. These systems require the solidification of liquid self-micron emulsifying (SME) ingredients into powders/nanoparticles which can be converted to various solid dosage forms (SME tablets, SME pellets and so on). Thus, S-SMEDDS will have combined advantages of SMEDDS such as enhanced solubility and bioavailability and with those of solid dosage forms, such as low production cost, convenience of process control, high stability and reproducibility, better patient compliance. To date, there have been studies that mainly focused on the preparation and characterization of a single, solid SME dosage form, yet relatively few that introduce S-SMEDDS in a systematic way, especially with respect to the dosage form development and preparation techniques.

NEED OF S-SMEDDS:

S-SMEDDS, one of the lipid-based drug delivery systems prepared by the incorporation of liquid excipients into powders by solidification, is a promising drug delivery system for poorly water soluble compounds as it combines the advantages of liquid SMEDDS (solubility and bioavailability enhancement) with those of solid dosage forms (high stability with various dosage forms options) [5,6]. S-SMEDDS produce oil-in-water microemulsions with droplet sizes of less than 200 nm upon mild agitation in aqueous media (such as gastrointestinal fluids) [6, 7]. These fine microemulsion droplets have the advantage of presenting the drug in a dissolved form with a large interfacial surface area for drug absorption, which results in an enhanced and more uniform and reproducible bioavailability [8].

SMEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid self micron emulsifying ingredients into powders/nanoparticles by different solidification techniques (*e.g.* adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology, and so on). Such powders/nanoparticles, which refer to self emulsifying nanoparticles [9], dry emulsions/solid dispersions, are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. self micro emulsifying capsules). Self micro emulsifying capsules also include those capsules into which liquid/semisolid SMEDDS are directly filled without any solidifying excipients. To some extent, S-SMEDDS are combinations of SMEDDS and

solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. For instance, the characterizations of self micron emulsifying pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on. In the 1990s, S-SMEDDS were usually in the form of self micron emulsifying capsules, self micron emulsifying solid dispersions and dry emulsions, but other solid self micron emulsifying dosage forms have emerged in recent years, such as self micron emulsifying pellets/tablets, self micron emulsifying microspheres/nanoparticles and self micron emulsifying suppositories/implants.

ADVANTAGES OF S-SMEDDS [10, 11]

- Low production cost
- Convenience of process control
- High stability and reproducibility
- Better patient compliance
- Spontaneous formation
- Thermodynamic stability and
- Improved solubilization of bioactive materials
- More consistent temporal profiles of drug absorption
- less drug need to be used
- For many drugs taken by mouth
- Faster release rates and it improve the drug acceptance by consumers
- Selective drug targeting toward a specific absorption window in the GI tract and
- Drug protection from the hostile environment in the gut
- Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption
- These systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles

S-SMEDDS Overcoming the Need of Liquid SMEDDS [12]

- S-SMEDDS form is more preferred than liquid SMEDDS form.
- S-SMEDDS (solid microemulsion preconcentrate) readily forms microemulsion when comes in contact with water.
- Need for outsourcing of soft gelatin capsule manufacturing at the early stage of drug product development may be avoided.
- S-SMEDDS remain solid at room temperature, yet maintains all the advantages of liquid SMEDDS.
- S-SMEDDS can be filled into hard gelatin capsules.
- S-SMEDDS is highly stable and reproducible than liquid SMEDDS.
- S-SMEDDS may even be incorporated into other solid dosage forms (e.g., fast dissolving tablets, films etc.

ADVANTAGES OF S-SMEDDS OVER EMULSION:

Microemulsions help in the improvement of drug bioavailability**,** protection against enzymatic hydrolysis and decrease toxicity. The only problem with microemulsion is poor palatability and moreover due to their water content, microemulsions cannot be encapsulated in soft and hard gelatin [11]. Hence, there is a need for delivery of lipophillic drug in S-SMEDDS.

FORMULATION OF S-SMEDDS:

Formulation components of S-SMEDDS include

- Drug
- Oil
- Surfactants/ cosurfactants
- Co solvents
- Consistency builders
- Enzyme inhibitors
- Adsorbents/solidifying agents

The selection of oil, surfactant and co solvent is based on the solubility of the drug and preparation of the phase diagram.

SELECTION OF COMPONENTS FOR S-SMEDDS

- The crucial challenges to any oral formulation design program is maintaining drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the primary absorptive site of the gut [13].
- Lipid based formulations offer a potential platform for improving oral bioavailability of drugs especially those belonging to biopharmaceutical Classification System (BCS) class II and class IV.

Class II drugs are poorly water soluble drugs with high permeability but once they are dissolved; they absorbed over the gastro-intestinal membrane, and Class IV compounds are poorly soluble with poor permeability, respectively [14]. The basic criteria for selection of components of lipid formulation are; the lipophilicity of the drug, with solubility in pharmaceutically-acceptable lipid excipients which should be sufficient to allow the entire dose of the drug to be administered in a single dosage unit.

- Since the aim of this study is to develop an oral formulation, therefore, solubility of drug in oils is more important as the ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oil phase. Thus solubility of drug in various oils (Castor oil, Olive oil, Labrafil 1944 CS, Labrafac lipophil WL 1349, Capmul MCM C-10 etc) was determined [15].
- Among physicochemical characteristics melting point and dose play a major role. Low melting point and low dose are desirable for development of lipidic systems. Drugs high melting point having with low log P values (around 2) is not suitable for S-SMEDDS.

PHASE DIAGRAMS:

Pseudo ternary phase diagram is used to map the optimal composition range for three key excipients according to the resulting droplet size following self emulsification, stability upon dilution and viscosity. Phase diagrams are useful tools to determine the number and types of phases, the wt% of each phase and the composition of each phase at a given temperature and composition of the system. These diagrams are three-dimensional but are illustrated in two-dimensions for ease of drawing and interpretation. On the basis of the solubility study of drug, oil, surfactants, co-surfactants and aqueous phase were used for construction of phase diagram. Oil, surfactant, and co-surfactant are grouped in four different combinations for phase studies. Surfactant and co-surfactant (Smix) in each group were mixed in different weight ratio. These Smix ratios are chosen in increasing concentration of surfactant with respect to co-surfactant and in increasing concentration of co surfactant with respect to surfactant for detail study of the phase diagram for formulation of micro emulsion. For each phase diagram, oil, and specific Smix ratio are mixed thoroughly in different weight ratio in different glass vials. Different combination of oils and Smix were made so those maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagrams. Pseudo-ternary phase diagram was developed using aqueous titration method. Slow titration with aqueous phase is done to each weight ratio of oil and Smix and visual observation is carried out for transparent and easily flowable o/w micro emulsion. The physical state of the micro emulsion was marked on a pseudo-three-component phase diagram with one axis representing aqueous phase, the other representing oil and the third representing a mixture of surfactant and co-surfactant at fixed weight ratios (Smix ratio) [16].

EFFECT OF DRUG ON PHASE DIAGRAM:

The formulation amount of drug was added to the boundary formulations of the self microemulsifying domain of ternary phase diagrams. The self-micron-emulsifying performance was visually assessed after infinite dilution using purified water [15].

MECHANISM OF SELF-EMULSIFICATION:

Self emulsification occurs, when the entropy change occurs**,** dispersion is greater than the energy required to increase the energy required to increase the surface area of the dispersion [17]. The free energy of conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation.

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

Where:

ΔG is the free energy associated with the process (ignoring the free energy of mixing),

N is the number of droplets of radius r,

σ is interfacial energy with time

The two phases of the emulsion will tend to separate, in order to reduce the interfacial area and subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence [18]. In case of self-emulsifying system, the free energy required to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously [19]. Emulsification require very little input energy, involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing [20]. In earlier work it was suggested that the case of emulsification could be associated with the ease by which water penetrates into the various liquid crystal or phases get formed on the surface of the droplet [21]. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the interface formation between the oil and aqueous continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, which occurs until the solubilization limit is reached close to the interface [22]. Further aqueous penetration will result in the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self emulsification process causes interface disruption and droplet formation. A combination of particle size analysis and low frequency dielectric spectroscopy was used to examine self-emulsifying properties of a series of Imwitor 742 (a mixture of mono-and diglycerides of Caprylic acids/Tween 80) systems, which provided evidence that the formation of the emulsion may be associated with liquid crystal formation, although the relationship was clearly complex .[23] The presence of the drug may alter the emulsion characteristics, possibly by interacting with the liquid crystal phase.

DESIGN OF S-SMEDDS FORMULATION

A series of SMEDDS formulations were prepared using various oil, surfactant and co surfactant. In all the formulations, the level of drug was kept constant. The amount of SMEDDS should be such that it should solubilize the drug (single dose) completely. The drug was added in the mixture. Then the components were mixed by gentle stirring and mixing, and heated at 37˚C.The mixture was stored at room temperature until used. So, prepared SMEDDS was the concentrate of oil, surfactant, co-surfactant and drug. Based upon the above results liquid SMEDDS is optimized which are further converted to Solid SMEDDS (Tablet) by adsorbing it on to adsorbent carriers like Neusilin US2, Fujicalin etc and various formulations were prepared [15].

SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/SEMISOLID SMEDDS TO S-SMEDDS

- **Capsule filling with liquid and semisolid self-emulsifying formulations:**

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process:

- Heating of the semisolid excipient to at least 200C above its melting point;
- Incorporation of the active substances (with stirring);
- Capsule filling with the molten mixture and
- Cooling to room temperature.

For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by microspray sealing [24]. In parallel with the advances in capsule technology proceeding, liquid-oros technology has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SME formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation through an orifice in the hard or soft capsule. [25] A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The advantages of capsule filling are simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading (up to 50% (w/w)) potential.

- **Spray drying:**

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification. [26]

- **Adsorption to solid carriers:**

Free flowing powders may be obtained from liquid self micro-emulsifying formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. For an instance a formulation of Liquid SMEDDS was made which is converted to Solid SMEDDS using Malto dextrin as a solid carrier. SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. [27] Solid carriers can be micro porous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked Polymers or Nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum crospovidone, cross-linked sodium carboxymethyl cellulose and cross linked polymethyl methacrylate. Cross-linked polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation. Nanoparticle adsorbents comprise porous silicon dioxide (Sylysia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal. [28]

- **Melt granulation:**

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a ‘one-step’ operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders. Thereinto, Gelucire1, a family of vehicles derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is able to further increase

the dissolution rate compared with PEG usually used before, probably owing to its SME property.[29] Other lipid-based excipients evaluated for melt granulation to create solid SMES include lecithin, partial glycerides, or polysorbates. The melt granulation process was usually used for adsorbing SMES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium alumina meta silicate). [30, 31]

- **Melt extrusion/extrusion Spheronization:**

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions. [32] The size of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets). The extrusion spheronization process requires the following steps: Dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). In the wet masses comprising SMES (Polysorbate 80 and mono-/di-glycerides), lactose, water and MCC, the relative quantities of SMES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets. Studies suggested that the maximum quantity of this SMES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight. Generally, the higher the water level, the longer the disintegration time. [33]. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SMES containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to provide complete characterization of how well it can be processed by extrusion-spheronization. [34] Applying extrusion-spheronization, SME pellets of diazepam and progesterone and bi-layered cohesive SME pellets have been prepared [35, 36].

DOSAGE FORM DEVELOPMENT OF S-SMEDDS

- **Dry emulsions:**

Dry emulsions are powders from which emulsion spontaneously occurs *in vivo* or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation [37] , freeze-drying [38] or spray drying [39,40). Myers and Shively obtained solid state glass emulsions in the form of dry 'foam' by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant. In freeze-drying, a slow cooling rate and the addition of amorphous cryoprotectants have the best stabilizing effects, while heat treatment before thawing decreases the stabilizing effects. The technique of spray drying is more frequently used in preparation of dry emulsions [41]. The O/W emulsion was formulated and then spray-dried to remove the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, a vegetable oil, and a pH-responsive polymer, with lyophilization used.

- **Self- micron emulsifying capsules:**

After administration of capsules containing conventional liquid SME formulations, microemulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium

dodecyl sulfate was added into the SME formulation [42]. With the similar purpose, the supersaturable SMEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state *in vivo*. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects [43, 44]. Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on). As an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self-micro emulsification upon mixing with water [45,46]. Oral administration of SME capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo embolism was clinically available only via the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules. LMWH was dispersed in SMEDDS and thereafter the mixture was solidified to powders using three kinds of adsorbents: micro porous calcium silicate; magnesium aluminum silicate and silicon dioxide. Eventually these solids were filled into hard capsules [47]. In another study, such adsorbents were also applied to prepare SME tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms.

- **Self- micron emulsifying sustained/controlled-release tablets:**

Combinations of lipids and surfactants have presented great potential of preparing SME tablets that have been widely researched. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SMEDDS has been developed, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release. SE tablets are of great utility in obviating adverse effect for example; SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. The resultant SME tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet [48]. The newest advance in the research field of SME tablet is the SME osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SMES. This system has outstanding features such as stable plasma concentrations and controllable drug release rate, allowing a bioavailability of 156.78% relative to commercial carvedilol tablets [49].

- **Self- micro emulsifying sustained/controlled-release pellets:**

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability [50]. Thus, it is very appealing to combine the advantages of pellets with those of SMEDDS by SME pellets.

- **Self- micron emulsifying solid dispersions:**

Although solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed. Excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling. SME excipients like Gelucire1 44/14, Gelucire150/02, Labrasol1, Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field [51,52,53,54].

- **Self- micron emulsifying suppositories:**

Some investigators proved that S-SMEDDS could increase not only GI adsorption but also rectal/vaginal adsorption . For example

Glycyrrhizin, which is given by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SME suppositories.[55]

• **Self- micron emulsifying implants:**

Research into SME implants has greatly enhanced the utility and application of S-SMEDDS. As an example, 1,3- bis(2-chloroethyl)-1- nitrosourea is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. In order to enhance its stability compared with that released from poly (d,l-lactide-co-glycolide) (PLGA) wafer implants, SMES was formulated. Such wafers had higher *in vitro* antitumor activity and were less susceptible to hydrolysis. [56]

CONCLUSION:

S-SMEDDS are a promising approach for the formulation of drugs with poor aqueous solubility. The oral delivery of lipophilic drugs can be made possible by S-SMEDDS, which have been shown to substantially improve oral bioavailability. As mentioned above, numerous studies have confirmed that S-SMEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs. As improvements or alternatives of conventional liquid SMEDDS, S-SMEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SMEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable. There is still a long way to go, however, before more solid SME dosage forms (except for SME capsules) appear on the market. Because there exist some fields of S-SMEDDS to be further exploited, such as studies about human bioavailability and correlation of *in vitro/in vivo*.

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