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RECENT PATENT REVIEW ON SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Self-Microemulsifying Drug Delivery Systems (SMEDDS) are isotropous mixtures of oil, wetting agent and co surfactants, and a drug that forms an oil-in-water micro emulsion upon light agitation SMEDDS are of specific worth in with water. increasing the absorption of oleophilic medicine taken orally. SMEDDS unfold without delay within the gastrointestinal tract, and also the biological process motility of the abdomen and also the bowel offer the agitation necessary for self-emulsification. A SMEDDS primarily based dose type was with success developed and shows potential for application within the delivery of poorly water soluble medicine. In this literary criticism, we are going to discuss regarding SMEDDS & patents. due to their suitability for delivery and delivery of drug for systemic effect. **KEYWORDS**- Smedds, Bcs, Solid Carrier, Patents.

INTRODUCTION

Approximately, one third of the drugs emerging from drug discovery programs are poorly water soluble, presenting several problems when the pharmaceutical scientist developing formulations of such active pharmaceutical ingredients (API). Conventional oral dosage forms for poorly water soluble drugs present the drug in a solid form to the gastrointestinal tract which means the drug has to dissolve in the GI fluids before it can be absorbed. Thus, their rate and extent of absorption is largely dependent on the rate of dissolution. The formulation technique plays an important role in overcoming this short coming of poorly

water soluble drugs. According to the Biopharmaceutical Classification System (BCS), two classes of drugs show poor aqueous solubility namely BCS II and BCS IV. BCS II drugs possess poor aqueous solubility but have good permeation properties. BCS class IV drugs are poorly water soluble and poorly permeable. Developing a formulation for a class IV drug is nearly impossible unless the dose necessary is very small. Most of the times, such drugs are withdrawn at its lead optimization stage of drug discovery and reworked to improve its physicochemical properties. Developing a formulation for a drug belonging to BCS II is often challenging as it requires improved dissolution characteristics. Popular formulation techniques used for delivering a poorly water soluble drug include: (a) micronized crystalline solids (b) amorphous formulation or solid solutions and (c) lipid based formulations. When particles of drug are milled to smaller particle sizes, there is an increase in surface area resulting in an increased dissolution of the drug. Micronization using an air jet mill will yield particles in the size range of 2-5 µm using a new technique NanoCrystal®, which employs high-speed attrition process, particles can be reduced in nanometer ranges. Such powders can be processed into tablets and capsules.^[1] Solid dispersions can be defined as a "dispersion of one or more active ingredient in an inert excipient or matrix" where in the active ingredient exists in a finely crystalline, solubilized or amorphous state.^[2] When solid dispersions are exposed to aqueous media, the matrix dissolves and releases the drug as very fine colloidal particles.

ADVANTAGES

1. Enhanced oral bioavailability (enabling dose reduction)^[3]

2. More consistent temporal profiles of drug absorption^[4]

3. Selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut^[5, 6]

DISADVANTAGES

1. Chemical instabilities of drugs and high surfactant concentrations.

2. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.

3. Moreover, volatile co solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

Lipid Formulation Classification System^[8]

The Lipid Formulation Classification System was introduced as a working model in 2000, and an extra 'type' of formulation was added in 2006. The main purpose of the Lipid Formulation Classification System is to enable in vivo studies to be interpreted more readily and, subsequently, to facilitate the identification of the most appropriate formulations for specific drugs (i.e. with reference to their physicochemical properties). Table 1 shows the fundamental differences between types I, II, III and IV formulations. Briefly Type I formulations are oils which require to be digested. Type II formulations are water-insoluble self-emulsifying drug delivery systems (SEDDS), Type III systems are SEDDS or selfmicroemulsifying drug delivery systems (SMEDDS) which contain some water-soluble surfactants and/or co-solvents (Type IIIA) or a greater proportion of water soluble components (Type IIIB). Table 1 includes an additional category (Type IV) to represent formulations which contain predominantly hydrophilic the recent trend towards surfactants and co-solvents. The advantage of blending a surfactant with a co-solvent to give a Type IV formulation is that the surfactant offers much greater good solvent capacity on dilution (as a micellar solution) than the co-solvent alone.

The co-solvent is useful to facilitate dispersion of the surfactant, which is likely to reduce variability and irritancy caused by high local concentrations of surfactant. A Type IV formulation is useful for drugs which are hydrophobic but not lipophilic, though it is necessary to bear in mind that Type IV formulations may not be well-tolerated if the drug is to be used on a chronic basis. An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase, GSK).

LFCS Type	Characteristics	Advantages	Disadvantages
	Oils without surfactants	GRAS status; simple	Formulation has poor
	Non-dispersing; requires	Excellent capsule	Solvent capacity unless
Ι	digestion	compatibility	drug is highly lipophilic
	SEDDS without water- soluble	Unlikely to lose solvent	Turbid o/w dispersion
II	components	capacity on dispersion	(particlesize0.25–2µm)
	SEDDS/SMEDDS with water	Clear oral most clear	Possible loss of solvent
TILA	seluble components	dispersion, absorption without	capacity on dispersion
IIIA	soluble components	digestion	less easily digested
	SMEDDS with water-Soluble	Clear dispersion drug	Likely loss of solvent
IIIB	components and low oil content	Absorption without digestion	capacity on dispersion

 Table 1: The lipid formulation classification system^[7,8]

Oil-free formulation based on surfactants and co-solvents	Good solvent capacity Form any drugs; disperses to micellars solution	Loss of solvent capacity on dispersion; may not be digestible
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Mechanism of Self-Emulsification

Conventional emulsions are formed by mixing two immiscible liquids namely water and oil stabilized by an emulsifying agent. When an emulsion is formed surface area expansion is created between the two phases. The emulsion is stabilized by the surfactant molecules that form a film around the internal phase droplet. In conventional emulsion formation, the excess surface free energy is dependent on the droplet size and the interfacial tension. If the emulsion is not stabilized using surfactants, the two phases will separate reducing the interfacial tension and the free energy.^[9] In case of S(M)EDDS, the free energy of formation is very low and positive or even negative which results in thermodynamic spontaneous emulsification. It has been suggested that self emulsification occurs due to penetration of water into the Liquid Crystalline (LC) phase that is formed at the oil/surfactant-water interface into which water can penetrate assisted by gentle agitation during self-emulsification. This LC phase is considered to be responsible for the high stability of the resulting nanoemulsion against coalescence.^[10, 11]

Various Major Components of Smedds

Oils

Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SMEDDS. Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-micro emulsification markedly reduces their use in SMEDDS. Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as GELUCIRE ,Other suitable oil phases are digestible or non-digestible oils and fats such as olive oil, corn oil, soya bean oil, palm oil and animal fats^[12] etc.

Surfactant

Nonionic surfactants with high Hydrophilic Lipophilic Balance (HLB) values are used in formulation of SEDDS. The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading

of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules.^[15]

Co surfactant

In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as methanol hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion.^[12, 14]

Co-solvent

Organic solvents are suitable for oral administration. Examples are ethanol, propylene glycol, and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base [13]. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents.

Surfactant	Co surfactant	Oil
Tween 80	Methanol	Soyabean oil
span 80	Ethanol	Rice bran oil
Cremophor RH 40	Caproyl 90	Groundnut oil
Labraphil M 2125	Propylene glycol	
	Glycerol	

Table 2: Component of Smedds

Biopharmaceutical Classification System

The introduction of BCS in1995 was the result of continuous effort on mathematical analysis for the elucidation of kinetics and dynamics of the drug process in gastrointestinal tract. It is used for the bioequivalence study for in vitro dissolution tests this method reduce the drug development process and reduces unnecessary exposure of the drug in volunteer person which is the normal study in BE study.^[16] BCS is scientific framework for classifying drug according to aqueous solubility and intestinal permeability.

Class 1 high solubility and high permeability

Class 1 drug exhibit a high absorption number and high dissolution number .The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determing step. bioavailability and dissolution is (In vitro In vivo correlation) cannot be

expected .thus compound are highly suitable for design the sustain release and controlled release formulation .Ex-ketoprofen ,naproxen,propanolol.^[17]

Class 2 -Low solubility and high permeability

Class 2 drug have a high absorption number but low dissolution number .In vivo drug absorption is then a rate limiting step for absorption expect, at a very high number these drug exhibit variable bioavailability and need the enhancement in dissolution for increasing the bioavailability .these compounds are suitable for design SR and CR formulation.^[17]

Ex-nisoldipine, quetapine

Class 3 high solubility and low permeability

Drug permeability is the rate limiting step for drug absorption ,but the drug is solvated very quickly .these drug exhibit a high variation in the rate and extent of drug absorption .since the dissolution is rapid the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors .if the formulation does not change the permeability or gastrointestinal duration time ,then class 1 criteria can be applied.^[16]

Ex-Cimetidine, Ranitidine

Class 4 low solubility and low permeability

This drug of this class are problematic for effective oral administration .these compounds have poor bioavailability they are usually not well absorbed thorough the intestinal mucosa and high variability is expected .class 4 drug are rarely developed^[16] Ex-hydrochlorthiazide, taxol, furosemide.

Characterization and optimization of smedds

SMEDDS forms fine o/w micro emulsions with only gentle agitation, upon its introduction into aqueous media. Since the Gibbs energy required to form micro emulsion is very low, the formation is thermodynamically spontaneous. Surfactants (emulsifiers) form a layer around the emulsion droplets and reduce the interfacial energy as well as provide a mechanical barrier to coalescence. For selecting a suitable self-emulsifying vehicle, it is important to assess (a) the drug solubility in various components, (b) the area of self emulsifying region in the phase diagram, and (c) droplet size distribution following self-emulsification.^[18]

1) Solubility Studies

The solubility of drug in various oils, surfactants and co surfactants is determined by using shake flask method. An excess amount of drug is added to each vial containing 1 mL of the

selected vehicle i.e. oil, surfactant or solubilizer. After sealing, the mixture is vortexed using a cyclomixer for 10min in order to facilitate proper mixing of drug with the vehicles. Mixtures are then shaken for 72 h in an isothermal shaker maintained at $37 \cdot 1^{\circ}$ for equilibration. Equilibrated samples are centrifuged at 5,000 rpm for 15 min, followed by filtration through membrane filter (0.22 µm). The concentrations of drug are then determined by high-performance liquid chromatography (HPLC) method.^[19]

Balakrishan et al 20 determined the solubility of Coenzyme Q10 in various oils and Surfactants. After preformulation solubility studies only, oils (Labrafil M 1944 and Labrafil M 2125), surfactant (Labrasol) and co surfactant (Lauroglycol FCC and Capryol 90 were chosen. In all the formulations, the level of Coenzyme Q 10 was fixed at 6% (w/v) of the vehicle.

2) Construction of Pseudo ternary Phase Diagrams

Pseudo-ternary phase diagrams are constructed to identify the self-emulsifying regions and to optimize emulsifier to co emulsifier ratio and the concentration of oil. The micro emulsion regions in the diagrams are plotted, and the wider region indicated the better self-emulsification efficiency. Pseudo-ternary phase diagrams of oil, surfactant/ co surfactant, and water are developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios are diluted with water in a dropwise manner.^[18] For each phase diagram at a specific ratio of S/CoS, transparent and homogenous mixture of oil and S/CoS is formed by vortexing for 5 minutes. Then each mixture is titrated with water and visually observed for phase clarity and flowability. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred is derived from the weight measurements. These values are then used to determine the boundaries of the self emulsifying domain corresponding to the chosen values of oils, as well as the S/CoS mixing ratio.^[21]

Singh et al 22 prepared eight potential different combinations of surfactant, co surfactant, and oil based on the results of solubility studies which were used for the phase diagram study for Ex:emestane SMEDDS. No distinct conversion from water-in-oil (w/o) to (o/w) micro emulsion was observed. The translucent and low viscosity micro emulsion area was presented in the phase diagram marked as micro emulsion.

3) Droplet Size Measurement

Properly diluted samples of self-emulsifying systems are used for droplet size analysis using Photon Correlation Spectroscopy. Average droplet size and polydispersity index are determined and the data obtained are further treated with regression analysis28. Measurements are obtained in duplicate at an angle of 90°. The diluted emulsions are also allowed to stand for 12 h at room temperature to assess dilution stability.^[19]

4) Zeta Potential Measurement

In disperse systems, electrical charges are developed by several mechanisms at the interface between the dispersed phase and the aqueous medium. The two most common mechanisms are the ionization of surface functional groups and the specific adsorption of ions. Theses electrical charges play an important role in determining the interaction between the particles of the dispersed phase and the resultant physical stability of the system, particularly for those in the colloidal size range. The potential between the tightly bound surface liquid layer (shear plane) of the particle and the bulk phase of the solution is called as zeta potential. The measurement of the zeta potential tells about the stability.^[23] For o/w emulsions with low electrolyte content in the aqueous phase, a zeta potential of 30 mV is found to be sufficient to establish an energy maximum to ensure emulsion stability.

5) Refractive Index and Percent Transmittance

The refractive index of the system was measured by an Abbe refractometer by placing 1 drop of solution on the slide. The percent transmittance of the system was measured at 650 nm using UV spectrophotometer keeping distilled water as a blank. Ghosh et al 24 measured the refractive index of acyclovir system and it was found similar to the water (1.333). In addition, the developed system showed percent transmittance > 99%. The refractive index and percent transmittance data prove the transparency of the system.

Dosage forms from self emulsifying system

1) Self emulsifying capsule

It is a capsules containing liquid or semisolid form of self emulsifying system. The GIT, the capsules get dispersed to SES uniformly in the fluid to micron size, enhancing bioavailability. Second type of self emulsifying capsule is solid SES filled into capsule.

2) Self emulsifying tablets

S.Nazzal et al 25 developed self-nanoemulsified tablet dosage form of Ubiquinone. The main objectives of this study were to study effect of formulation ingredients on the release rate of

Ubiquinone and to evaluate an optimized self nanoemulsified tablets formulation. The first prepared self nanoemulsion system containing Ubiquinone was prepared as nanoemulsion; this nanoemulsion was adsorbed by granular materials and then compressed to form tablets. The optimized formulation of coenzyme Q10 self-nanoemulsified tablet dissolution profile showed that 80-90% drug release took place in 45 minute.

3) Self emulsifying pellets

E. Franceschinis et al 26 developed a method of producing first developed a binder solution containing an oil (mono self-emulsifying pellets by wet granulation. Here they and diglycerides), polysorbate 80 and model drug nimesulide in different proportion. This oil surfactant mixture was stirred then added to water to form Self- emulsifying system. Second step was to prepare granules from microcrystalline cellulose and lactose in a granulator. These binder solutions were sprayed on to the granules and pellets increasing the speed of the granulator. Pellets were able to generate significantly smaller droplets with were formed by respect to corresponding emulsions.

4) Self emulsifying beads

Self emulsifying system can be formulated as a solid dosage form by using less excipient. Patil and Paradkar discovered that deposition of SES into microporous polystyrene beads was done by solvent evaporation. Porous polystyrene beads with complex internal void structures were typically produced by copolymerising styrene and divinyl benzene. It is inert and stable over a wide range of pH, temperature and humidity. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB.^[27]

5) Self emulsifying microsphere

You et al. formulated solid SE sustained-release microspheres using the quasi-emulsion solvent diffusion method for the spherical crystallization technique. Zedoary turmeric oil release behavior could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration time profiles were achieved after oral administration of such microspheres into rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS.^[28]

6) Self emulsifying nanoparticle

Nanoparticle technology can be applied to the formulation of self emulsifying nanoparticle. One of the solvent was injection, in this method the prepared molten lipid mass contained lipid, surfactant and drug. This lipid molten mass was injected drop wise into a non solvent system. This is filtered and dried to get nanoparticles. By this method 100 nm size particle with 70-75% drug loading efficiency was obtained.^[29]

Second technique is sonication emulsion diffusion evaporation; by this method co-load 5-flurouracil and antisense EGFR (epidermal growth factor receptor) plasmids into biodegradable PLGA/O-CMC nanoparticles. The mixture of PLGA (poly-lactide-coglycolide) and O-CMC (O-carboxmethyl-chitosan) had a SE effect, with no additional surfactant required.^[30]

Trickler et al.31 developed a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX). These chitosan/ GMO nanoparticles, with bioadhesive properties increased cellular association and was prepared by multiple emulsion (o/w/o) solvent evaporation methods.

Technique of solid Smedds development

Solid SEDDS were developed mainly by adsorption of solid carriers, spray drying, melt extrusion, dry emulsion, solid dispersion etc. These solid SEDDS can be converted into pellets, tablets and capsules.

i) Solid carriers

These solid carriers have property to absorb liquid/semisolid formulation as self emulsifying system (SES). It is a simple procedure, where SES is incorporated into a free flowing powder material adsorbed by mixing in a blender. This solid mixture is filled into capsule or added to more excipient before compression into tablets.^[27] The above mixture was solidified to powder forms using three kinds of adsorbents: microporous calcium silicate (FloriteTM RE); magnesium aluminum silicate (NeusilinTMUS2) and silicon dioxide (SylysiaTM 320).^[28]

ii) Spray Drying

In this technique first the prepared formulation containing oil, surfactant, drug, solid carrier etc, is sprayed into a drying chamber through a nozzle. The volatile vehicles first evaporate leaving behind small solid particles. These particles are then filled into capsules or compressed into tablets.

iii) Melt extrusion

This formulation technique depends on the property of the plastic mass material which can be easily extruded and speronised with pressure. Here there is no need for addition of liquid form of excipient but a constant temperature and pressure need to be maintained.^[29]

iv) Dry Emulsion

It is mainly O/W emulsion, which is then converted into solid form by spray drying/solid carrier/ freeze drying.^[30,33]

Recent Patent Review on Self Emulsifying Drug Delivery System

Table: 3 Recent Patents on Smedds

Title	Patent number	Date	Information
Modafinil	7,749,540	July 6 ,2010	Particle-forming compositions of modafinil compounds, and aqueous compositions of particles, wherein the particles comprise a modafinil compound, are disclosed, along with methods of their preparation, and their use in the treatment of diseases
Naproxen	7,736,666	June15, 2010	The present invention claims and discloses a Pharmaceutical composition suitable for oral administration, in form of an emulsion pre concentrate, comprising a compound of formula one or more surfactants; optionally an oil or semi-solid fat; said composition forming an in-situ oil-in- water emulsion upon contact with aqueous media such as gastrointestinal fluids.
Method for designing	US2009124670 (A1)	2009	This study was aimed to prepare and develop a stable

formulation of			formulation for self-
self-emulsifying			emulsifying drug delivery
preparation			system to enhance the
(2009)			solubility, release rate, and
			oral absorption of the poorly-
			soluble drug, carvedilol
			A fibrate self-emulsifying
			oral formulation with
			improved bioavailability
			when compared to
Self-emulsifying			commercially available
formulations of			formulations containing a
femolibrate and/or			therapeutically effective dose
demissatives with	11970222702	A mil 4 2006	of fenofibrate, combinations
improved oral	03/02233/02	April 4,2006	thereof, one or more
hipproved of al			surfactants and optionally
ond/or reduced			one or more stabilizers useful
food affact (2006			in the treatment of
1000 effect (2000			hypercholesterolaemia or
			hypertriglyceridaemia in
			mammals in the fed or fasted
			state.
			The present invention relates
		2007	to phaemaceutical
			formulation of salts, ester,
Self-	US 2007/0104740 A1		polymorphic, and
microemulsifying			peudopolymorphic forms
drug delivery			which are self micro
systems of a HIV			emulsifying drug delivery
protease inhibitor			systems and comprise as
[2007]			carrier a lipophilic phase ,one
			or more surfactant ,a
			hydrophilic solvent and a
			nuclation inhibitor.
		2001	Self-emulsifying ibuprofen
	US 6221391		solution and soft gelatin
Self-emulsifving			capsule for use therewith this
ibuprofen solution			invention relates to a self-
(2001)			emulsifying solution of
(/			ibuproten suitable for
			encapsulation into a soft
			gelatin capsule (2001)

CONCLUSION

In this article some basics of SMEDDS are discussed. SMEDDS is known to improve dissolution characteristics of a poorly water soluble drug since they maintain the drug in a solubilized state in the GI tract. As a conclusive note we can say that SMEDDS can be potentially used for delivering a poorly water soluble drug. Self-Micro Emulsifying Drug

Delivery Systems appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophillic drugs. As there is increase in oral drug absorption of BCS II class drugs, so we can say it is one of the method for enhancing oral bioavailability of drug.

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