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EXCIPIENTS USED IN SELF NANOEMULSIFYING DRUG DELIVERY SYSTEMS

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ABSTRACT

Out of newly discovered drugs most of the drugs are found to be lipophilic and are poorly water soluble, which leads to poor oral bioavailability. Currently a number of technologies are available to deal with poor solubility, dissolution rate and bioavailability of insoluble drugs. Recently more attention has been focused on lipid based formulations with particular emphasis on self emulsifying drug delivery systems (SEDDS). These are isotropic mixtures of oil, surfactants, and co-solvents or co-surfactants. The principal characteristic of these systems is their ability to form fine oil in water emulsion or microemulsion upon dilution followed by mild agitation with the aqueous fluids which presents drug in solubilized form, and the small size of droplets formed provides large interfacial surface area for drug absorption. For lipophilic drugs which exhibits dissolution rate limited absorption, SEDDS are promising approach to improve the rate and extent of oral absorption.

KEYWORDS: Emulsion, microemulsion, lipophilic and SEDDS.

INTRODUCTION

The oral route is the major route for chronic drug therapy, majority of the drugs are frequently administered through oral route, but approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is complicated for the reason that of their low bioavailability, high intra and inter subject variability and not have dose linearity. To overcome these problems, a variety of strategies have been developed including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions, and self emulsifying drug delivery systems etc,[1,2] Self-nanoemulsifying drug delivery systems are defined as isotropic mixture of oils,

surfactants and co-surfactants that distribute readily in the GI tract, and the digestive motility of stomach and intestine provide sufficient agitation enough for spontaneous formation of fine oil-in-water nanoemulsions. They typically produce nanoemulsions in the size range of 20-200 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. 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 results in more reproducible blood–time profiles. They are traditionally designed for the oral route. They can be given in hard or soft gelatin capsules.[3,4,5]

ADVANTAGES OF SMEDDS.[6-9]

1. Enhanced oral bioavailability enabling reduction in dose.
2. More consistent temporal profiles of drug absorption.
3. Selective targeting of drug towards specific absorption window in GIT.
4. Protection of drug from the gut environment.
5. Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved.[10]
6. The dose ranging from less than 25 mg to greater than 2000 mg can be administered by using these systems.
7. Fine oil droplets of these SEDDS would pass rapidly and encourage extensive distribution of the drug all the way through the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
8. These offer large interfacial area for partitioning of the drug between oil and water.

DISADVANTAGES OF SMEDDS.[11-14]

1. One of the obstacles for the development of SMEDDS and other lipid-based formulations is the lack of good predicative in vitro models for assessment of the formulations.
2. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
3. This in vitro model needs further development and validation before its strength can be evaluated.

4. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model.
5. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.
6. Moreover, volatile co solvents in the conventional self-microemulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
7. The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.

EXCIPIENTS USED IN SEDDS.[15]

The self-emulsification process is specific to the nature of the oil–surfactant pair. The process also depends on the oil nature, the surfactant concentration and the oil/surfactant ratio, and the temperature at which self-emulsification occurs.

Oils

The oil represents the most important excipient in the SEDDS formulation. Both long-chain triglyceride (LCT) and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used in the design of SEDDS. 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 inefficiency of self-emulsification markedly reduced their use in SEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages. Nowadays, MCTs are largely replaced by novel semisynthetic MCT derivatives, which can be defined as amphiphilic compounds exhibiting surfactant properties. MCT are medium-chain fatty acid esters of glycerol. Medium-chain fatty acids are fatty acids containing 6 to 12 carbon atoms. The medium-chain fatty acid fraction used commercially is mainly comprised of the eight-carbon caprylic or octanoic acid, and the 10-carbon capric or decanoic acid. The caprylic- and capric-rich mixture is finally re-esterified to glycerol to produce MCTs that are mainly glycerol esters of caproic (C6), caprylic (C8), capric (C10), and lauric acid (C12). Unlike most natural oils of animal or vegetable origin, MCT is stable and resistant to oxidation owing mainly to the saturation of the medium-chain fatty acids.MCT is rapidly absorbed

from the small intestine, and is therefore considered to facilitate the uptake of some lipophilic drugs when ingested.

Medium-chain fatty acids are transported into hepatocytes and converted to medium-chain fatty acyl CoA esters. These are transported into mitochondria, where they are metabolized to acetoacetate and beta-hydroxybutyrate. These may be further metabolized in the liver to carbon dioxide, water, and energy and may enter some other metabolic pathways in the liver or be transported by the systemic circulation to other tissues, where they undergo metabolism and mainly produce CO2, H2O, and energy. Very little ingested MCT is deposited in the body as fat.

Advantages of oils

It can solubilize relevant amounts of the poorly water-soluble drug. Facilitate self-emulsification and absorption if digestible. Increase the fraction of lipophilic drug transported via the lymphatic system, thereby increasing absorption from the GIT, depending on the molecular nature of the triglyceride.

Surfactants

Surfactants are used to improve the physical and chemical characteristics of the formulation and may be included to improve the efficacy or biological performance of the product. The properties of surfactants are such that they can alter the thermodynamic activity, solubility, diffusion, disintegration, and dissolution rate of a drug. Each of these parameters influences the rate and extent of drug absorption. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.Numerous surfactants can be used in the design of SEDDS, but the choice is limited to those which are orally suitable because safety is the major determining factor in choosing a surfactant. The most extensively used ones are non-ionic surfactants with high hydrophilic lipophilic balance values are used in the formulation. Examples of non-ionic surfactants include ethoxylated polyglycolyzed glycerides, polyoxyethylene 20 oleate (Tween 80), sorbitan mono oleate (span 80), and Brij 35. Non ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. Usually the surfactant concentration ranges between 30% and 60% w/w to form stable SEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. The surfactant involved in the formulation of

SEDDS should have a relatively high HLB and hydrophilicity, so that immediate formation of o/w droplets and rapid spreading of the formulation in the aqueous media can be achieved.

Co-Surfactants

Generally co-surfactants having HLB value of 10-14 are used. Spans, caproyl 90, capmul, alcohols, lauroglycol, diethylene glycol, transcutol, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, glycofural etc, may help to dissolve large amounts of hydrophilic surfactants or drug in the lipid base.

Medium chain length alcohols which are commonly added as co-surfactants have the effect of reducing the interfacial tension, whilst increasing the fluidity of interface there by increasing the entropy of the system. They also increase the mobility of the hydro carbon tail and also allow greater penetration of oil into this region. The alcohol present may also influence the solubility properties of aqueous and oily phases due to partitioning between these phases.

Co-Solvents[16]

Organic co-solvents and additional compounds suitable for oral administration are used to enhance the solubility of therapeutic agent or triglyceride in the composition.

Examples

Alcohols and Polyols such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols, glycerol, sorbitol, dimethyl isosorbide, polypropylene glycol and other cellulosic polymers, cyclodextrins and its derivatives.

Esters of propylene glycols having average molecular weight of about 200 to 6000 such as tetrahydrofuryl alcohol, PEG ether or methoxy PEG.

Amides such as 2-pyrrolidone, 2-piperidone, caprolactam, N-alkylpyrrolidone, N-hydroalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam.

Esters such as ethyl propionate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, ethylene oletae, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate**.**

LIST OF COSURFACTANTS

Name	Chemical name	Route of administration	Physical properties	Applications
Labrafil M 1944 CS	Oleoyl macrogol 6 glycerides (EP)	Topical, Oral	Form: liquid HLB: 4	Adsorption on to neutral carrier and powders for use in capsules, tablets.
Labrafil M 2125 CS	Oleoyl polyoxyl 6 glycerides (NF)	Topical, Oral	Form: liquid HLB: 4	Topical ointments, microemulsions and emulsions.
Capmul MCM C8	Glyceryl monocaprylate	Oral	Form: liquid or semisolid HLB: 5-6	Effective carriers and solubilizers of active compound.
Plurol oleique	Polyglycerol oleate	Oral and topical	Form: liquid HLB: 6	Bioavailability enhancer.
D-alpha tocopherol polyethylene glycol 1000 succinate	RRR-alpha tocopherol PEG 1000 succinate	Oral	Form: waxy substance HLB: 13.2	Emulsifier, drug solubiliser, absorption enhancer.

LIST OF SURFACTANTS

Name	Chemical name	Physical properties	Applications
Cremophor EL	Polyoxyl 35 castor oil	HLB: 12-14 Solubility: Soluble in water, ethyl alcohol, n-isopropyl alcohol, carbon tetrachloride, ethyl acetate, chloroform, toluene, xylene, trichloro ethylene.	Solubilizer, emulsifier, suitable for production of liquid preparations.
Capmul MCM C8	Glyceryl monocaprylate	HLB: 5-6 Solubility: Partially water soluble	Increase absorption and delivery
Captex 355	Glyceryl tricaprylate/tricaprate	HLB: 7 Solubility: Soluble in most organic solvents especially 95% of ethanol.	Used as a carrier, solubilizer, lubricant, emolient, viscosity modifier.
Caprol ET	Hexaglycerol octastearate	Solubility: Soluble in many organic solvents and miscible with mineral and vegetable oils.	Emulsifier, foaming agents, solubilizer, suspending agent
Cremophor RH 40	Polyoxyl 40 hydrogenated castor oil Macrogol glycerol hydroxystearate	HLB: 14-16 Solubility: Soluble in water, ethanol, 2-propanol, n-propanol, ethyl acetate, chloroform, toluene, xylene, carbon tetrachloride	Emulsifying agent

Solutol HS	Macrogol 15 hydroxy stearate Polyoxyl 15 hydroxy stearate	HLB: 14-16 Solubility: Soluble in water, ethanol, 2-propanol, insoluble in liquid paraffin	Solubilizer, emulsifier
Span 20	Sorbitan monolaurate	HLB: 8.6 Solubility: Dispersable in hot and cold water	Emulsifier and stabilizer
Span 80	Sorbitan mono oleate	HLB: 4.3 Solubility: Soluble in ethanol, ether, aniline, toluene, dioxane, ethyl acetate, petroleum ether, carbon tetrachloride	Emulsifier and stabilizer.
Tween 20	Polyoxy ethylene sorbitan monolaurate	HLB: 16.7 Solubility: Soluble in cold water, methanol, isopropanol. Dispersable in cotton seed oil, ethylene, glycol, propylene glycol.	food additive and excipient in pharmaceutical fields.
Tween 60	Polyoxyethylene 20 sorbitan monostearate	HLB: 14.9 Solubility: Soluble in water, ethyl acetate, aniline, toluene. Insoluble in mineral and vegetable oils	Emulsifier and stabilizer
Tween 80	Polyoxyethylene 20 sorbitan monooleate	HLB: 15 Solubility: Soluble in water, ethanol, ethyl acetate, dioxane. Insoluble in mineral oil, petroleum ether	Emulsifier and suspending agent.

LIST OF COSOLVENTS USED

Name	**Chemical name**	**Physical properties**	**Applications**
Ethanol	Ethyl alcohol	Density: 0.790 Viscosity: 1.2cps Solubility: Miscible with water, acetic acid, acetone, benzene, chloroform, diethyl ether, ethylene glycol, trichloroethane, tetracholro ethylene etc,.	Used as cosolvent
Glycerol	1,2,3-propanetriol	Density: 1.26 Viscosity: 1410mpas Solubility: Miscible with water, ethanol, Insoluble in ether, benzene, chloroform	Used in urethanes, cellophane, humectants, plasticizer, lubricants, sweetener, thickening agent
PEG 4000	Polyoxyethylene oxide	Density: 1.07-1.09 Viscosity: 76-110cps Solubility: Soluble in water	Used as binder, dry lubricant, wetting agent, antidusting agent, enhancing of thermal stability of adhesive preparations.

PEG 200	polyoxyethylene	Density: 1.1239 Viscosity: 50cps Solubility: Soluble in water, methanol, diethyl ether	Used as adhesive, ceramics, lubricant, elastomers
Carbitol	Diethylene glycol monoethyl ether	Density: 0.99 Viscosity: 21-25cps Solubility: soluble in water	Solvent for dyes, resins, nitrocellulose.

LIST OF OILS USED

Name	Chemical name	Physical properties	Applications
Miglyol 812	Caprylic or capric triglyceride	Type: MCT Density: 0.94-0.95 Viscosity:27-33cps Solubility: Soluble in toluene, diethyl ether, ethyl acetate, acetone, isopropanol & ethanol.	Used in pharmaceutical, oral, parentral, topical, cosmetics.
Imwitor 742	Glycereol monocaprylate	Type: MCT Density:0.954 Viscosity: 40mpas Solubility: soluble in diethyl ether, n-hexane, ethanol, very slightly soluble in water	Used in external, vaginal, nasal and rectal preparations Adsorption promoter for active ingredient, Plasticizer in tablet coating, coemulsifier in emulsions
Caprol 90	Polypropylene glycol monocaprylate	Type: MCT Density: 0.942 Viscosity: 0.8872cps Solubility: Water insoluble	w/o surfactant, solubilizer
Acrysol K 140	Polyoxyl 40 hydrogenated castor oil	Type: MCT Density: 0.952-0.965 Viscosity: 20-40mpas Solubility: soluble in water, ethanol 2-propanol, ethyl acetate, n-propanol, chloroform, carbon tetrachloride, tolune & xylene.	Vitamin solubilizer, dissolution improver, emulsifier, moisturizer, masking agent, foam stabilizer, volatility retardment, film former, transparency improver
Acrysol EL 135	Polyoxyl 35 castor oil	Type: MCT Density: 1.05-1.06g/ml Viscosity: 600-800mpas Solubility: Forms clear mixures with fatty acids and fatty alcohols at high temperatures.	Used in parentral products
Miglyol 840	Propylene glycol dicaprylate or dicaprate	Type: MCT Density: 0.91 Viscosity: 28cps Solubility: Soluble in hexane, toluene, diethyl ether, acetone, ethyl acetate, isopropanol, ethanol 96%	Raw material for cosmetics, lubricants and lubricant additives.

Captex 300	Glyceryl caprylate caprate	Type: MCT Density: 0.92-0.96 Viscosity: 20-25cps Solubility: Soluble at 50%w/w at room temperature in vitamin E acetate, Spanish rosymary oil, eucalyptus oil, menthol	Carrier, Solubilizer, Lubricant, Emollient, Energy Source, Viscosity Modifier.
Transcutol P	Highly purified dithylene glycol monoethyl ether EP/NF	Type: MCT Density: 0.991 Viscosity: 3.5cps Solubility: Soluble in water	Increases drug permeation, penetration, drug depot effect.
Maisine 35-1	Glycerol monolinoleate EP/NF	Type: MCT Density: 0.94 Solubility: Insoluble in water freely soluble in methylene chloride	Human pharmaceutical products and veterinary products including animal food products.
Ethyl oleate	9-octadecenoic acid	Type: MCT Density: 0.871 Viscosity: 5.15cps Solubility: Insoluble in cold water and hot water. Miscible with vegetable oils, mineral oils, alcohol.	Used as a solvent for pharmaceutical purposes.
Hydrogenated castor oil	Hydroxystearic acid	Type: LCT Density: 0.895 Viscosity: 98-130cps Solubility: Insoluble in water Miscible with ethyl alcohol.	Wax polish, hard durable thermosetting polymer use, manufacture of greases and lubricants, hydrodynamic waxes, rubbers.
Corn oil	Corn oil	Type: LCT Density: 0.914-0.921 Viscosity: 28.7cps Solubility: Soluble in ether, chloroform, insoluble in water	Chemicals, and insecticides, paint, and varnish, printing ink, rubber substitutes, rust preventive
Olive oil	Triglycerides of fatty acids	Type: LCT Density: 0.915-0.918 Viscosity: 43.2cps	Increase elasticity of arteries, reduces skin cancer upon uv exposure, and helps to prevent alzeihmers disease.
Cotton seed oil	Cotton seed oil	Type: LCT Density: 0.915-0.921 Viscosity: 37.9cps Solubility: Insoluble in water Soluble in ether.	Lowers risk of developing heart disease and reduces the LDL in the blood. Gossypol which is present in it helps to inhibit the growth of neck and head tumours.
Soybean oil	Soybean oil	Type: LCT Density: 0.992 Viscosity: 35.4cps Solubility: Miscible with non polar organic solvents	β-sitosterol present in it appears to block absorption of cholesterol and may reduce high cholesterol levels.
Sesame oil	Triglyceride of fatty acids	Type: LCT Density: 0.918	Solvent, lubricant, known to increase the plasma

		Viscosity: 35.4cps Solubility: Soluble in alcohol, miscible with ether, chloroform, mineral oils, vegetables	tocopherol and vitamin E which are known to prevent the cancer and heart disease.
Linseed oil		Type: LCT Density: 0.932 Viscosity: 22.2cps Solubility: Insoluble in water	Used for treating arthritis, anxiety, benign prostatic hyperplasia, high blood pressure, diabetes.
Peanut oil	Peanut oil	Density: 0.912-0.920 Viscosity: 40mpas Solubility: Very slightly soluble in alcohol, miscible with ether, chloroform, carbon disulphide.	Used to lower cholesterol, and prevent heart disease. Decrease appetite and aid as weight loss, used as solvent and vehicle.

Excipients used in solid snedds

Name	Description	Physical properties
Magnesium aluminium silicate	It is a blend of colloidal montmorillonite and saponite. Four types are available based on viscosity as IA, IB, IC, IIA.	Moisture content: 6-9.98% Density: 2.418 Solubility: Insoluble in alcohols, water and organic solvents.
Magnesium trisilicate	It is a compound of Mgo and SiO_2 with varying degrees of water.it is odourless, tasteless fine white coloured powder.	Moisture content: 17-23%w/w at 25^0C Solubility: Practically insoluble in diethyl ether, ethanol, and water.
Bentonite	Crystalline clay like material and available as odorless, cream to grayish fine powder.	Moisture content: 5-12% Solubility: Insoluble in ethanol, fixed oils, glycerin, water, propanol
Sodium carboxy methyl cellulose	Occurs as white, odorless, granular powder.	Moisture content: <10% Density: 0.52 Solubility: Insoluble in ethanol (95%), acetone, ether, toluene.
Crospovidone	It is a synthetic croslinked homopolymer of N-Vinyl-2-pyrrolidinone.	Moisture content: App60% Density: 1.22 Solubility: Insoluble in water and most organic solvents.
Polymethyl methacarylate	It is the aqueous dispersion of an anionic copolymer designed for use of enteric coated solid dosage forms.	Moisture content: 0.22% Density: 1.058-1.068 Solubility: soluble in water
Talc	It is very fine, white to grayish white, odorless, impalpable, which adheres readily to skin.	Moisture content: 0.23% Density: 2.7-2.8 Solubility: Insoluble in water, solvents dilute acids and alkalies.
Lactose	It occurs as white to off white crystalline powder.	Moisture content: NMT 1% Density: 1.5 Solubility: Soluble in water, sparingly soluble in ethanol 995%), ether.

Lecithin	It forms viscous semiliquids to powders depending on free fatty acid content	Moisture content: <1% Density: 0.97(liquids) 0.5 (powders) Solubility: Soluble in aliphatic and aromatic hydrocarbons, mineral oils, fatty acids. Insoluble in cold vegetable animal oils, polar solvents and water.
Silicon dioxide	It is light, loose, bluish white colored, odorless, tasteless, nongritty amorphous powder.	Moisture content: <3% Density: 0.029-0.042 Solubility: Insoluble in organic solvents, water, acids. Soluble in hot solutions of alkali hydroxide.
Microcrystalline cellulose	It is partially depolymerized cellulose that occurs as white, tasteless, odorless.	Moisture content: <5%w/w Density: 0.337 Solubility: Insoluble in water, ethanol, ether, mineral acids. Slightly soluble in sodium hydroxide.
Magnesium hydroxide	It is odorless, inorganic white powder occurring naturally called as brucite.	Moisture content: 30% Density: 2.36 Solubility: Slightly soluble in water and alcohol.
Zeolite	It is a mineral from the group of water aluminosilicates of alkali and alkaline earth elements with tetrahedral structural frame that includes cavities, occupied by cations and water molecules.	Density: 1.535 Solubility: Insoluble in water.
Nanotubes	They are tiny tubes that can comprise several concentric walls with a graphite structure. Their diameter ranges from 1 to 60 nanometers, and their length can reach several tens of microns	Density: 2.1 Solubility: Carbon nanotubes are soluble in water and organic solvents.
Carbon nanohorns	They are available in single walled; double walled and multi-walled forms, bundled and unbundled, with tube lengths from 5 to 30 nanometers (nm) and specific surface area (SSA) in the 50 to 500 m 2 /g range.	Density: 2.27 Solubility: Soluble in chloroform, methylene chloride, and tetrahydro-furan
Charcoal	Fine, black, tasteless, odorless powder free from grittiness.	Moisture content: 4% Density: 0.203 Solubility: Insoluble in water.

Construction of the pseudo ternary phase diagram.[15]

The pseudo ternary diagrams are mainly used to map the microemulsion areas (composition ranges). The surfactant and co-surfactant were mixed in different weight ratios (1:2, 1:1, 2:1, 3:1, 4:1, 5:1, and 6:1) to give different S_{mix}. For each diagram, the oil and the S_{mix} were mixed in different weight ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) and titrated with water by a drop wise addition under gentle agitation. End point in these titrations was determined where the solution becomes transparent gel or cloudy or turbid. The concentrations of water, oil and S_{mix} at the end point were derived from the weight measurements. These values were used to determine the boundaries of the micro/nanoemulsion domain by constructing phase diagrams using TRIPLOT V 4 software. Phase diagrams were constructed to identify the good region where the self-emulsification occurs.

EVALUATION OF SMEDDS.[17-20]

Thermodynamic stability studies

The physical stability of a lipid based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipients matrix. In addition, poor formulation physical stability leads to phase separation of the excipients, affecting not only formulation performance but also visual appearance.

Heating cooling cycle: Six cycles between refrigerator temperature 4^0C and 45^0C with storage at each temperature of not less than 48 hours is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

Centrifugation: Passed formulations are centrifuged thaw cycles between 21^0C and $+25^0$C with storage at each temperature for not less than 48 hours is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Droplet Size Analysis Particle Size Measurements: The droplet size of the emulsions is determined by photon correlation spectroscopy using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external

standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water.

Phase separation and stability study of microemulsion

Each SNEDDS formulation (100 µl) was added to a glass beaker containing 300 ml double distilled water and 0.1N hydrochloric acid solution at 37 ^{0}C. Emulsion was stored for a period of 24 hrs and observed for phase separation and precipitation of the drug, if any. The observations were made after 2, 4, 6, 8, 12 and 24 hrs.

Drug content: Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

Robustness to dilution: Robustness to dilution was studied by diluting the formulation with 100 times volumes of various dissolution media. The diluted emulsions were stored for 12 hours and observed for any signs of phase separation or drug precipitation.

Zeta potential: It is a technique which is used to measure the surface charge properties and further the long term physical stability of emulsions and the instrument used is Zetasizer. The measurements were carried out with diluted emulsion formulations and its values were determined from the electrophoretic mobility of the oil droplets. The minimum zeta potential of +/-20mv is desirable.

SOLID STATE CHARACTERIZATION.[21,22,23]

Differential scanning calorimetry: Samples of drug alone and its physical mixture with additives were accurately weighed, encapsulated and hermetically sealed in flat bottomed aluminium pan with crimped on lid. The pans were positioned on sample pan holder. The samples were heated in an atmosphere of nitrogen over a temperature range from 30 to 250^{0}C with a constant heating rate. Thermogram, transition temperature range, the onset of peak transition and maximum peak of transition were recorded. Two replicates were made for each DSC thermogram using an empty sealed aluminium pan as reference and indium as instrument calibration standard.

Transmission electron microscope: The emulsion globules were visualized by transmission electron microscope and their morphology and structure were studied. Samples were dried

on carbon coated grid and negatively stained with aqueous solution of phosphotungstic acid. After drying the specimen was viewed under the microscope.

Friability testing of pellets: Friability testing was conducted using a friability tester. The pellets sample was placed into drum together with glass spheres and rotated for 10min ay 25rpm. Pellets were then reweighed and friability was calculated according to,

$$\text{Friability} = m_b - m_a / m_b$$

Where m_a and $m_b$are masses of pellets after and before testing and the result is mean of three runs.

Disintegration testing of pellets: This test is done by using a disintegrating tester. Six pellets were tested in distilledwater at 37 C And the endpoint was taken at the point at which no particles were present in the sieve.

Fourier transform infrared (FTIR) spectroscopy: FTIR spectra are mainly used to determine if there is any interaction between the drug and any of the excipients used. The existence of an interaction is detected by the disappearance of an important functional group of the drug. It is performed using a FTIR spectroscope fitted with a single cuvette or a single bounce diamond at 45^0 that internally reflected incident light, providing a sampling area 1mm in diameter with a sampling depth of several microns. A small amount of the sample was directly scanned for absorbance over a range from 4,000 to 400 wave numbers.

Scanning electron microscope: Both the surface and cross section morphology of the solid pellets were observed by a scanning electron microscope. Prior to examination, the samples were fixed on a brass stub using double sided tape and gold coated in vacuum by a sputter coater. The photographs were taken at an excitation voltage of 10kV.

Powder x-ray diffraction: powder x-ray diffraction of samples was evaluated by diffractometer over 2θ range at a scan rate of 3^0 per minute, where the tube anode was copper monochromatized with a graphite crystal. The pattern was collected at 40kV of tube voltage and 60mA of tube current in step scan mode. In order to exclude interference of the non-pareli cores with the x-ray diffraction analysis, the solid samples were prepared with inert polyvinylchloride beads as a substrate and crushed to collect the powder. To prepare the physical mixtures, blank solid SNEDDS powder containing 40% of liquid SNEDDS was

mixed with drug powder to stimulate one of the solid SNEDDS formulations that contained 40% liquid SNEDDS in the coating layer and drug in liquid SNEDDS.

CONCLUSION

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDS, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs**.**

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