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BETA-CYCLODEXTRIN COMPLEX, SOLID DISPERSION AND SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): AN APPROACH TO ENHANCE THE SOLUBILITY OF POORLY SOLUBLE DRUG

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ABSTRACT

The present focuses on enhancement the solubility of poorly soluble drug (BCS 11 drug) of β-cyclodextirn, solid dispersion and self emulsifying drug delivery system. The ability of β-cyclodextrin , solid dispersion and SEEDS to improve oral bioavailability of poorly water soluble drug. B-cyclodextrin is cyclic oligosaccharides with a hydrophobic cavity and hydrophilic surface. The basic physiochemical characteristics of β-CD had been discovered, including their ability to solubilize and stabilize drugs. Cyclodextrin also effects on drug solubility and bioavailability and drug release from formulation. Cyclodextrin application in the design of various novel drug delivery systems (Liposome, Microsphere etc). Solid dispersion composed of two components the drug and polymer matrix. Solid dispersion have been improving the dissolution rate and hence the bioavailability of drugs. Numerous method are existing to prepare the solid dispersion such as melting method, solvent evaporation method etc. SEDDS are isotropic mixture of oil, surfactant, co-surfactant and co-solvent. The ability of these systems to form fine o/w emulsion & microemulsion upon mild agitation following dilution by an aqueous phase through the gastrointestinal tract for lipophilic drug which display dissolution rate limited absorption. The development of β-cyclodextrin, solid dispersion & SEDDS has been suggested in relief.

KEYWORDS: Poorly soluble drug, β-cyclodextrin, Solid dispersion & Self emulsifying drug delivery system, Techniques, Lipid based formulation, Bioavailability, Dissolution.

INTRODUCTION

Solubility: Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent. The solubility of a substance fundamentally depends on the physical and chemical properties of the solute and solvent as well as on temperature, pressure and the PH of the solution. The extent of the solubility of a substance in a specific solvent is measured as the saturation concentration, where adding more solute does not increase the concentration of the solution and begins to precipitate the excess amount of solute. The solubility of a substance is an entirely different property from the rate of solution, which is how fast it dissolves.

ROLE OF SOLUBILITY AND DISSOLUTION

Among all newly discovered chemical entites about 40%drugs are lipophilic and fail to reach market due to their poor aqueous solubility. For orally administered drugs solubility is one of the rates limiting parameters to achieve their desired concentration in systemic circulation for pharmacological response(Kumar et al., 2011). Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the in vivo efficacy (Mohanachandran et al., 2010).

Therefore, the improvement of drug solubility thereby its oral bioavailability remains one of most challenging aspects of drug development process especially for oral drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water soluble drug. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form (Pinnamaneni et al., 2003).

CYCLODEXTRIN BASED SOLID DISPERSION TECHNIQUE

Cyclodextrins are a family of compounds consists of glucose monomers arranged in a donut shape ring. They are non-reducing, crystalline cyclic oligosaccharides which proximate a truncated core generating a hydrophilic outer surface and a lipophilic interior cavity that offers interaction with appropriately sized molecules to result in the formation of inclusion complex. Cyclodextrin are able to form host-guest complexes with hydrophobic molecules have found a number of applications in a wide range of fields. They are novel excipients having glucopyranose units that exhibit amphoteric properties of a lipophilic central cavity

and a hydrophilic outer surface (Ali et al., 2012 and Sejtli et al., 1988). CDs are homologous group of cyclic glucans consisting of α-1, 4 bound glucose units. They are obtained by the action of cyclodextrin glucanotransferase (CGTase) on starch or similar substrates to prodeuce a mixture of cyclodextrins comprised of 6, 7 and 8 glucose units (α, β and ϒ-cyclodextrin, respectively).

Advantage of cyclodextrin based solid dispersion technique

- CDs help in improving the aqueous solubility of many poorly soluble drugs.
- CDs enhances the dissolution thus helps in enhancing bioavailability of drugs.
- Cyclodextrin complexes improve the chemical, physical and thermal stability of drugs.
- Cyclodextrin inclusion complexes help in ameliorating the irritancy of the drug moiety that irritates the stomach, skin or eye.
- Cyclodextrin cloak the unpleasant odour and bitter taste of drugs.
- Complexing oily and sticky substances with CDs into microcrystalline or amorphous powders help in improving the material handling properties.
- Formulation of modified release preparations.
- Cyclodextrin helps in decreasing the toxic effects associated with drugs.
- CDs have also been used in the novel pharmaceutical applications.

METHODS OF PREPARATION OF β-CYCLODEXTRIN

Physical blending method: A solid physical mixture of drugs and CDs are prepared simply by mechanical trituration. In laboratory scale CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. In industry scale, the preparation of physical mixture is based on extensive blending of the drug with CDs in a rapid mass granulator usually for 30 minutes. These powdered physical mixtures are then stored in the room at controlled temperatures and humidity conditions.

Solution/Solvent method: This method involves dissolving of the drug and CDs separately in to two mutually miscible solvents, mixing of both solutions to get molecular dispersion of drug and complexing agents and finally evaporating the solvent under vacuum to obtain solid poedered inclusion compound. Generally, the aqueous solution of CDs is simply added to the alcoholic solution of drugs. The resulting mixture is stirred for 24 hrs and evaporated under vacuum at 45℃. The dried mass was pulverized and passed through a 60-mess sieve. This

method is quite simple and economic both on laboratory and large scale production and is considered alternative to the spray drying technique.

Kneading method: Kneaded complexes of Etoricoxib and cyclodextrins like β CD, HP β CD and polymers like PEG6000, surfactant like Poloxamer 407 were prepared by wetting the physical mixtures in a mortar with minimum volume of Methanol-water mixture and kneading thoroughly with a pestle to obtain a paste which was then dried under vacuum at room temperature and stored in a desiccators until further evaluation. This is the most common method used to prepare the inclusion complexes and it presents very low cost of production.

Neutralization precipitation method: This methods is based on the precipitation of inclusion compounds by neutralization technique and consists of dissolving the drug in alkaline solutions like sodium/ammonium hydroxide and mixing with an aqueous solution of CDs. The resultant clear solution is then neutralized under agitation using hydrochloric acid solution till reaching the equivalence point. A white precipitating is being formed at this moment, corresponding to the formation of the inclusion compound. The precipitate is filtered and dried. Doijad et al (2007) have studied the enhancement of solubility of piroxicam by complexation with beta-cyclodextrin. Acid and alkaline susceptible drugs can undergo degradation during this process is the limitation associated with this method.

C0-Precipitation techniques: This method involves the co-precipitation of drug and CDs in a complex. In this method Required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex. However, due to low yield, risk od using organic solvents, and longer time required for the preparation in larger scale, this method is attaining little attraction in the industrial scale (Hedges et al., 1998).

Spray drying method: Spray drying is a common technique used in pharmaceutical to produce a dry powder from a liquid phase. Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β- cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer. The sufficient and efficient interaction between

drug and CDs to form a perfect complex is the added advantage of atomization/spray drying method where as thermal stress and low yield of the final product are the limitations associated with this technique.

Milling/Co-grinding technique: A solid binary inclusion compounds can be prepared by grinding and milling of the drug and CDs with the help of mechanical devices. Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. This technique is superior to other approaches from economic as well as environmental stand point in that unlike similar methods it does not require any toxic organic solvents. This method differs from the physical mixture method where simple blending is sufficient and in co-grinding it requires to achieve extensive combined attrition and impact effect on powder blend.

Microwave irradiation method: This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. Drug and cyclodextrins mixture is reacted in microwave oven to form inclusion. It is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantages of shorter reaction time and higher yield of the product (Saharan et al., 2009).

Freeze/Lyophilization drying technique

In order to get a porous, amorphous powder with high degree of interaction between drug & CD, lyophilization / freeze drying technique is considered as a suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/ freeze drying technique is considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent.

EVALUATION OF β-CYCLODEXTRIN

Drug content: Inclusion complexes were assayed for drug content by dissolving a specific amount of the complex in methanol and analyze drug content of each complex was observed at spectrophotometrically.

Inclusion efficiency: The kneaded complexes were placed in 25ml volumetric flasks. Methanol was added, mixed thoroughly and sonicated for 30min. The volume was made up to the mark with methanol. The solution was suitably diluted with the same solvent and spectrophotometrically assayed for drug content (Swami et al., 2010).

X-ray Diffraction study: The X-ray diffractograms of etoricoxib and beta-cyclodextrin complex were obtained using on X-ray diffraction instrument XPERT-PRO with Ni-filtered Cu radiation, at a voltage of 45kV and current of 40 mA. The scanning speed was 2 degree/min between 5 and 50 theta. XRD study gives us the level of crystallinity in the complexes and cyclodextrin reduces crystallinity of drugs and hence enhance the solubility of poorly soluble drugs.

Differential scanning Calorimetry: DSC measurements were performed using a Mettler Toledo DSC 821 module controlled by STAR software (Mettler- Toledo GmbH, Switzerland). All accurately weighed samples were placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10 C min-1, over the temperature range of 30℃ to 300℃. An empty aluminium pan was used as reference. DSC study gives us the changes in endothermic behavior of drugs upon compexation and thus helps to detect the change in solubility behavior of drugs (Reddy et al., 2004).

Scanning electron microscopy study (SEM): The morphology of samples was studied using SEM (HITACHI S-3000N,Japan), operated at an accelerating voltage of 20Kv (lament current of 1.751 beam current of 30-40 mA and probe current of 250pA). Sample are prepared by mounting 0.5 mg of powder onto a 5mm silicon wafer a fixed via graphite tape to an aluminium stub. The powder was then sputter coated for 40 s at beam current of 38-42Ma with a 200 A^0 layer of gold/palladium alloy. SEM study is used for analysis of the surface structure of formulations and also change in behavior, by comparing with SEM of pure drug.

In vitro dissolution study: In vitro dissolution study is used to assess the drug release from cyclodextrin complexes. Generally cyclodextrin complexes equivalent to 100mg of drug is taken in the dissolution medium. A paddle type stirrer is adjusted to 100 rpm and the temperature is maintained at 37℃ ± 0.5℃. Aliquots of dissolution medium (5ml) were withdrawn at different time intervals while replacing it with the same volume of dissolution medium. The samples were analyzed for drug after suitable dilution by measuring absorbance using UV-Visible spectrophotometer. The percentage of drug dissolved at various time

intervals was calculated and plotted against time (Vilarnovo et al., 2001 and Shiralashetti et al., 2010).

SOLID DISPERSION

Poor water solubility is the major drawback for the various types of drugs and many approaches have been introduced for the solubility enhancement of such drugs (Ingle et al., 2011). Solid dispersion is one of the techniques adopted for the formulations of such drugs and various methods are used for the preparation of solid dispersion like kneading method, solvent evaporation method, supercritical method, fusion method. Solid dispersion is generally prepared with drug which is having poor aqueous solubility and hydrophilic carrier. In solid dispersion particle size of drug is reduced or a crystalline pure drug is converted into amorphous form and hence the solubility of drug is increased (Dixit et al., 2012). Polymers incorporated in solid dispersion technologies are usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility (Saffoon et al., 2011).

METHODS OF PREPARATION OF SOLID DISPERSION

Melting method: This method involves the preparation of physical mixture of a drug and a water soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. The modification in the method can be done by pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures (Dressman et al., 2000). However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

Solvent evaporation method: In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The

film is further dried to constant Weight. The main advantage of the solvent method is thermal decomposition of drugs or carrierscan be prevented because of the relatively low temperatures required for the evaporation of Organic solvents.

Melting solvent method (melt evaporation): It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5-10%(w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, It is only limited to drugs with a low therapeutic dose e.g. below 50mg.

Melt extrusion method: The drug/carrier mix is typically processed with a twin's crew extruder. The drug/carrier mix is simultaneously melted, homogenzied and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantages of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1min, which enables drugs that are somewhat thermolabile to be processed (Ingle et al., 2011). Solid dispersion by this method is composed of active ingredients and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1kg/h and the screw rate is set at 300rpm. The five temperature zones are set at100, 130,170,180 1nd 185℃ from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1min with a laboratory cutting mill and sieve to exclude particles>355 µm.

Lyophilization Technique: Lyophilization involves transfer of heat and mass to and from the product under preparation.

This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion (Patidar et al., 2010).

Melt Agglomeration Process: This technique has been used to prepare solid dispersion wherein the binder acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersion by melt agglomeration. It has been found that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedurealso results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

Electrospinning: Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulate on the surface of a pendant drop; destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The thinning down of the charged jet is limited. If the viscosity increases, the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

Super Critical Fluid (SCF) Technology: The supercritical fluid antisolvent techniques, carbon dioxide are used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization

processes: aerosol solvent extraction system, precipitation with a compressed fluid antisolvent, gas antisolvent and solution enhanced dispersion by supercritical fluids and supercritical antisolvent. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continous supercritical phase flowing concurrently (Sekhon et al., 2010). Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of the carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component).

EVALUATION OF SOLID DISPERSION

Drug content: Solid dispersion were assayed for drug content by dissolving a specific amount of the formulation in methanol and analyzed for the drug content spectrophotometrically (Shiralashetti et al., 2010).

X-ray Diffraction Study: The X-ray diffraction of etoricoxib and beta-cyclodextrin complex were obtained using on X-ray diffraction instrument XPERT-PRO with Ni-filtered Cu radiation, at a voltage of 45kv and current of 40 mA. The scanning speed was 2 degree/min between 5 and 50 theta. XRD study gives us the level of crystallinity in the solid dispersion and solid dispersion reduces crystallinity of drugs and hence enhances the solubility of poorly soluble drugs.

Differential Scanning Calorimetry: Differential Scanning Calorimetry was performed using DSC60 Shimadzu, Japan. Accurately weighed samples (About 2 mg of ECB or its equivalent) were placed in a sealed aluminum pans, before heating under nitrogen flow (2 ml/min) at a scanning rate of 10°C/min from 25°C to 250°C. Indium oxide was placed in aluminum pan and used as a reference. The heat flow as a function of temperature is measured for the drug, polymers and solid dispersions. The glass transition temperature of the analytes was measured. Duplicate determinations were carried out for each sample.

Scanning electron microscopy: Sample of pure drug, carrier and the solid dispersion formulation were mounted onto the stubs using double-sided adhesive tape and then coated

with gold palladium alloy (150-200 Ao) using fine coat ion sputter (Joel, fine coat ion sputter, JPC-1100). The samples were subsequently analyzed under the scanning electron microscopy (SEM) for external morphology.

In vitro dissolution study: In vitro dissolution study is used to assess the drug release from cyclodextrin complexes. Generally formulation equivalent to 100mg of drug is taken in the dissolution medium. A paddle type stirrer is adjusted to 100 rpm and the temperature is maintained at 37℃ & 0.5℃. Aliquots of dissolution medium (5ml) was withdrawn at different time intervals while replacing it with the same volume of dissolution medium. The samples were analyzed for drug after suitable dilution by measuring absorbance using UV-visible spectrophotometer. The percentage of drug dissolved at various time intervals was calculated and plotted against time (Pose-vilarnovo et al., 2001).

Castro et al (2012) prepared solid dispersion of albendazole with the aim to increase dissolution of drug. The work involved the use of pluronic 188 and PEG 6000 as hydrophilic carriers. With pluronic 188 the release was 69.4% which was much more than with PEG 6000 (32.8%). The in vitro studies were carried out and were found that solid dispersion helps to improve dissolution of poorly soluble drugs. The in vivo study was also done on mice.

PHARMACEUTICAL APPLICATIONS OF SOLID DISPERSION

- To increase the solubility of poorly soluble drugs thereby enhance the dissolution rate, absorption and bioavailability.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, photo oxidation etc.
- To dispense liquid or gaseous compounds.
- To formulate a fast release priming dose in a sustained release dosage form.
- To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.
- To reduce side effects the binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex.
- To convert liquid compounds into formulations. Liquid drugs can be manufactured as solid drug formulations such as powders, capsules or tablets.

SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS)

Self emulsifying drug delivery system (SEDDS) is defined as isotropic mixture of oil and surfactants or alternatively one or more hydrophilic solvents and co-solvents. Upon mild agitation followed by dilution in aqueous media such as the gastrointestinal (GI) fluid, these systems can form fine oil in water (o/w) emulsions or micro emulsions. Self micro emulsifying formulations spread readily in the GI tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification (SEDDS) typically produce emulsion with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsion with a droplet size of less than 50 nm. When compared with emulsions which are sensitive and metastable dispersed forms, SEDDS and SMEDDS are physically stable formulations that are easy to manufacture. Bases of self micro emulsifying system have been formulated using medium chain triglyceride oils and non-ionic surfactant which are acceptable for oral ingestion. The lipophilic (poorly water soluble) drugs such as nifedipine, griseofulvin, cyclosporine, digoxin, itrconazole, carbamazepine, piroxicam, steroids, ibuprofen, diazepam, etc. are formulated in SMEDDS to improve efficacy and safety. This system can be liquid but also semisolid depending on the excipient's choice. These are traditionally designed for the oral route. These preparations can be given as soft or hard gelatin capsules for easy administration and precise dosage. In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposome with particular emphasis on self-emulsifying drug delivery systems (SEDDS).

Advantages of SEDDS

1. High drug solubilization capacity.
2. Good thermodynamic stability.
3. Protect the drug from enzymatic hydrolysis.
4. Improvement in oral bioavailability.
5. Improve drug loading capacity.
6. Reduce the intrasubject and intersubject variability and food effects.
7. Useful for drug targeting toward specific absorption window.
8. Control of delivery profile.

NEED OF SEDDS

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that pre dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favour the drug remaining in the lipid droplets. Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favour a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.

COMPOSITION OF SEDDS

Oils: Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.

Table 1. Oils used in marketed SEDDS

Type of oil	Marketed Product	Drug
Corn oil	Depakene capsule	Valporic acid
Olive oil	Sandimmune oral solution	Cyclosporine
Sesame oil	Marinol soft gelatin capsule	Dronabinol
Soya bean oil	Accutane soft gelatin capsule	Isotretinoin
Peanut oil	Prometrium soft gelatin capsule	Progesterone
Bees wax	Vesanoid soft gelatin capsule	Tretinoin
Hydrogenated soya bean oil	Accutane soft gelatin capsule	Isotretinoin

Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties (Shukla et al., 2010). Novel semi-synthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride (MCT) oils in the SEDDS.

Surfactant: Nonionic surfactants with high hydrophilic– lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore etc.). 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.

Table 2. Surfactant used in marketed SEDDS

Surfactant	Marketed Product	Drug
Span 80, Tween 80	Gengraf soft gelatin capsule	Cyclosporine
Tween 20	Targretin Hard gelatin Capsule	Bexarotene
Cremophor RH 40	BCNU self emulsifying implant	Carmustine
Labrafill M 1944 CS	Sandimmune oral solution	Cyclosporine

In some cases, increasing the surfactant concentration could lead to droplets with similar mean droplet size, this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface (Karim et al., 1994). On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract (Shukla et al., 2010).

Co-Surfactant: Generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion. However, for many non-ionic surfactants it is not compulsory/mandatory to use co-surfactant in microemulsion. The selection of co-surfactant and surfactant is crucial not only to form the formation of microemulson, but also to

solubilization in microemulasions. Other variables such as the chemical nature of oil, salinity and temperature are also expected to influence the curvature of the interfacial film (Vandana et al., 2003). Organic solvents like ethanol, propyleneglycol, polyethylene glycol suitable for oral administration may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co surfactant in the microemulsion systems. Such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. But the drugs in the alcohol free formulations may exhibit limited solubility. Hence, proper choice has to be made during selection of components.

Co-Solvent: Co-solvent like diethylene glycol monoethyle ether, propylene glycol, polyethylene glycol, polyoxyethlene, propylene carbonate, tetrahydro furfuryl alcohol polyehthylene glycol ether, etc, may help to dissolve large amount of hydrophilic surfactant or the hydrophobic drug in the lipid base. The physical state of these excipients at ambient room temperature is determined by their molecular weight. PEG ranging from 200 to 600 in molecular weight is liquid at ambint room temperature where those possessing molecular weight of 1000 or greater exit as thermo softening semi solid. Polymeric liquid and semi-solid excipients, most of which are glycolic in nature and relatively non-toxic, are used as solvents for formulating poorly water-soluble drugs. These excipients can be used alone or in combination with other lipid excipients to improve the overall solubilizing power of the formulation. However, their pronounced water miscibility can compromise formulation performance due to uncontrolled precipitation of the drug substance Following dilution in the aqueous contents of the GIT this typically results in dose-dependent bioavailability enhancement.

Table 3. Commonly used co-emulsifiers, co-surfactants or solubilizer

General class	Examples	Acceptability
Short chain alcohols	Ethanol, benzyl alcohol	P/O/T/Oc/M
Alkane diols and triols	Propylene glycol	P/O/T/Oc/M
Polyethylene glycols	PEG 400	P/O/T/Oc/M
Alkane diols and triols	Glycerol	P/O/T/Oc/M
Glycol ethers	Diethyleneglycol monoethylether (transcutol)	O/T

M: Mucosal; O: Oral; Oc: Ocular; P: Parenteral; PEG: Polyethylene glycol; T: Topical (dermal).

Examples

- Alcohols and Polyols: Such as ethanol, isopropranol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, hydroxyprpyl methyl cellulose.
- Esters of propylene glycols having average molecular weight of about 200 to 6000 such as tetrahydrofuryl alcohol, PEG ether or methoxy PEG.

METHODS OF PREPARATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM

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. In parallel with the advances in capsule technology proceeding, liquid-Oros technology (Alza Corporation) has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SE 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. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The liquid/semisolid lipophilic vehicles compatible with hard capsules were listed by.60 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: 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.

Adsorption to solid carriers: Free flowing powders may be obtained from liquid SE 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 30. 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. SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be microporous 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.

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. The melt granulation process was usually used for adsorbing SES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium aluminometa silicate) (Seo et al., 2003, Gupta et al., 2001).

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 36. 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:

a) Dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder

b) Extrusion into a spaghetti-like extrudate

c) Spheronization from the extrudate to spheroids of uniform size

d) Drying Sifting to achieve the desired size distribution and coating (optional).

e) Applying extrusion-spheroniation, SEM pellets of diazepam and progesterone and bi-layered cohesive SEM pellets have been prepared

Construction of Pseudo ternary phase diagram: The phase diagrams of ternary systems (oil phase, surfactant phase and aqueous phase) were constructed using aqueous titration or spontaneous emulsification method. Optimized surfactant was dissolved in oil phase in ratios of 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1.5:1, 1:1, 0.66:1, 0.43:1 & 0.25:1 in glass vials at room temperature. Each ratio of surfactant and oil phase was then titrated drop by drop continuously with distilled water using micropipette by vortex mixing till it turned turbid. The phase behavior of each ternary system during titration was observed minutely. The percentage composition of the component in each ternary system was determined and the observed results were plotted on triangular co-ordinates to construct the phase diagrams.

EVALUTION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM

Droplet size: Droplet size measured by dynamic light scattering technique andproperly diluted samples of self emulsifying systems is 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 analysis. Measurements are obtained in duplicate at an angle of 90°. The diluted emulsions are also allowed standing for 12 h at room temperature to assess dilution stability.

Zeta potential: It determines the charge on droplets. Zeta potential helps to predict the stability and flocculation effect in emulsion system. If the zeta potential falls below a certain level, colloid will aggregate due to attractive forces. High zeta potential maintains a stable system. Sample was placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment.

Viscosity determination: SEDDS formulations are subjected to sonication prior to estimation of viscosity determination. For this study the formulated SEDDS (50g) was diluted to 50ml with media (double distilled water). The viscosities of the resulting micro-emulsions were determined by zeta sizer nano-ZS Malvern instrument (Date and Nagarsenker, 2006).

Drug content: S-SEDDS are assayed for drug content by dissolving a specific amount of the complexes in methanol and analyzed for the drug content spectrophotometrically (Shiralashetti et al., 2010).

Dispersibility test: The efficiency of self-emulsification of oral micro/nanoemulsion is assessed using a standard USP dissolution apparatus II (Pouton CW, 1985; Shefiq et al., 2007; Tuleu et al., 2004).One milliliter of each formulation is added to 500 mL of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm tends to provide gentle agitation. The *in vitro* performance of the formulations is visually assessed from such dispersion, using a suitable grading system. A grading system has been reported to be based upon the formation of a microemulsion (o/w or w/o), microemulsion gel, emulsion or emu gel. The mode to characterize the type of formulation on the basis of this grading system and the type of dispersion formed on water dilution.

Scanning electron microscopy study (SEM): Some amount of optimized formulations was mounted on the stub. This specimen was then sputter coated with gold particles and observed with a SEM (JSM-5610, JEOL, Japan) at an accelerating voltage of 10 kV. Surfaces of powder were photographed.SEM study is used for analysis of the surface of formulations also change in behavior, by comparing with SEM of pure drug (Shiralashetti et al., 2010).

Differential scanning calorimetry: Thermal properties of drug, placebo, and solid SMEDDS formulations were investigated using a Perkin-Elmer DSC-7 differential scanning calorimeter/TAC-7 thermal analysis controller with an intracooler-2 cooling system (Perkin-Elmer Instruments, USA). About 3 to 5 mg of product was placed in perforated aluminum sealed 50-µl pans, and the heat runs for each sample was set from 40°C to 200°C at 5°C/min, under an inert environment using nitrogen. The apparatus was calibrated using pure metals like indium with known melting points and heat of fusion (ΔHfusion). DSC study gives us the changes in endothermic behavior (Endothermic peaks) of drugs upon formulation and thus helps to detect the change in solubility behavior of drugs.

Morphological Studies: The SEDDS globules are observed by transmission electron microscope. Sample is visualized by drying it on carbon-coated grid and stained negatively with aqueous solution of phosphotungstic acid. After drying the phosphotungstic acid, the sample was observed under TEM.

In vitro dissolution study: In vitro dissolution study is used to assess the drug release from cyclodextrin complexes. Generally formulation equivalent to 100 mg of drug is taken in the dissolution medium. A paddle type stirrer is adjusted to100rpm and the temperature is maintained at 37℃ ± 0.5℃. Aliquots of dissolution medium (5ml) was withdrawn at different

time intervals while replacing it with the same volume of dissolution medium. The samples were analyzed for drug suitable dilution by measuring absorbance using UV-Visible spectrophotometer. The percentage of drug dissolved at various time intervals was calculated and plotted against time solid SEDDS with the aim to improve oral bioavailability using gelatin as solid carrier. The method adopted for the preparation was spray drying. The liquid SEDDS was composed of labrafil M 1944 CS/labrasol/transcutol HP (12.5/80/7.5%) with 2% w/v flubiprofen. After the analysis it was found that gelatin is good carrier for enhancement of dissolution and oral bioavailability.solid SEEDS of poorly soluble drug. The liquid SEDDS consisted of labrafec-hydro, tween 20, trancutol and drug. After analysis Neusilin US2 was be found as the most suitable adsorbent. The developed tablets showed the advantages of SEDDS as great increase in dissolution were observed.

APPLICATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM

Solid self-emulsifying drug systems: Solid self-emulsifying drug delivery used for the development of tablets using a liquid SEDDS for a poorly water-soluble drug. A high content of liquid SEDDS can be loaded (up to 70%) onto a carrier, which not only maintains good flowability but also enables the production of tablets with good cohesive properties and good content uniformity in both capsules and tablets. This clearly expands the options available to the formulator.

Enhancement of solubility: If drug is incorporated in SEDDS, it increases them solubility because it circumvents the dissolution step in case of Class-II drug (Low solubility/high permeability). A SMEDDS formulation of a poorly water soluble drug, was formulated for directly filling in hard gelatin capsules for oral administration. The results from the study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds.

Protection against biodegradation: SEDDS have ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and protect these from enzymatic degradation.

Supersaturable SEDDS (S-SEDDS): The high surfactant level typically present in SEDDS formulations can lead to GI side-effects and a new class of supersaturable formulations, including supersaturable SEDDS (S-SEDDS) formulations, have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble

drugs. The S-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturationis intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier. The S-SEDDS formulations contain a reduced level of surfactant and a polymeric precipitation inhibit or to yield and stabilize a drug in a temporarily supersaturated state. Hydroxypropyl methylcellulose (HPMC) and related cellulose polymers are well recognized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time periods

CONCLUSION

The enhancements of oral bioavailability of poorly water soluble drugs remain one of the most important challenging aspects of drug development. Beta-Cyclodextrin based drug delivery systems currently developed have shown a marketed increase in drug loading capacity which is very important from a pharmaceutical point of view. They are also beneficial in improving the aqueous solubility of poorly water soluble molecules, to protect degradable substances, to obtain sustained delivery systems or to design innovative drug carriers. 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 SEDDSs, 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. SEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs. Since the concept of solid dispersion technology was introduced in 1960s, great progresses have been made in solid dispersion technology as solid dispersion offers a variety of opportunities. A single solid dispersion method cannot be universally accepted for a variety of drug materials. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method. The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. Most of the solid dispersion work is in lab-scale setups; therefore the manufacturing process requires enough knowledge to scale up to the commercial scale.

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