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"SELF EMULSIFYING DRUG DELIVERY SYSTEM-A REVIEW"

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ABSTRACT

Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. The primary mechanism of action, which leads to improved bioavailability, is usually avoidance, or partial avoidance, of the slow dissolution process, which limits the bioavailability of hydrophobic drugs from solid dosage forms. The unique feature of this delivery system is the ability to self-emulsify, that is, their ability to form micro emulsions or oil-in-water emulsions when diluted in the aqueous phase because of the gentle agitation of the gastrointestinal tract.

KEYWORDS: Self emulsifying drug delivery system, bioavalability, lipophilic drug, cosolvent.

INTRODUCTION

The oral route is the most common administration route for majority of drugs. But more than 40% of drugs exhibit poor aqueous solubility, resulting in low bioavailability, high intra and inter subject variability, and a lack of dose proportionality by oral route. To improve the oral bioavailability of lipophilic drugs, self-emulsifying drug delivery systems (SEDDS) have emerged.[2] SEDDS are isotropic mixtures of oil, surfactants, solvents and co solvents. The principal characteristic of these systems is their ability to form fine oil in water (o/w) emulsions or micro emulsions upon mild agitation following dilution by an aqueous phase through the gastrointestinal tract for lipophilic drugs. SEDDS may be a promising strategy to improve the rate and extent of oral absorption.[4] The need for increased folds in bioavailability of oral lipophilic drugs led to studies on self-emulsifying drug delivery system. Drugs which have low solubility in aqueous medium but high permeability have

given rise to self-emulsifying drug delivery systems. Self-emulsifying drug delivery systems are also known as SEDDS. They are isotropic mixtures of drug, oil, solid or liquid surfactants and hydrophilic solvents or co-solvents.[6] The first marketed SEDDS is cyclosporine and it was found to have higher bioavailability than the conventional drug. Self-emulsifying drug delivery systems in research or development include formulations of drugs. Self-emulsifying drug delivery system can be administered orally via soft or hard gelatin capsules. When they get diluted in aqueous medium, due to the gentle churning of gastrointestinal fluids they form relatively fine oil-in-water emulsions.[7] This is the process of self-emulsification. Emulsions are liquid dosage forms which consist of two immiscible phases; where one is a dispersed phase is dispersed into the other phase, dispersion medium, and stability is maintained with the help of an emulsifying agent. The process of self-emulsification can be better explained with the ouzo effect which occurs in anise-flavored liquors where an oil-in-water emulsion is formed when the anise comes in contact with water. They are used to improve oral absorption of highly lipophilic drugs which have low aqueous solubility. The future of self-emulsifying drug delivery system in the pharmaceutical market is almost guaranteed because studied show that about 40% of drug compounds newly produced are hydrophobic in nature. This shows that studies relating to self-emulsifying drug delivery system would continue and more drugs will be formulated as SEDDS.[14] The bioavailability of hydrophobic drugs is enhanced by the presence of fatty acids, e.g. intake of lipid-rich meals with drugs, lipid-based drug delivery systems are formulated form poor water-soluble drugs that are administered orally. Under the lipid formulation classification systems, Type III formulations form the self (micro) emulsifying drug delivery systems which are clear isotropic mixtures of oils, hydrophilic solvents, poor water-soluble drugs and hydrophilic surfactants. These self-emulsifying drug delivery systems help to protect the drug from metabolism such as chemical or enzymatic hydrolysis along the GIT till it reaches the intestine where it is absorbed. It also solubilizes the drugs and increases the bioavailability. SEDDS are easily manufactured and cheap. This is an advantage for developing countries.[16]

Table no. 01: Marketed Preparation of SEDDS.[16]

Brand Name	Generic Drug	Dosage Forms	Manufacturer
Convulse	Valproic acid	Soft gelatin capsule	Gerot Pharmazeutika
Norvir	Ritonavir	soft gelatin capsule	Abbvie, Abbot
Neoral	Cyclosporine	Soft gelatin capsule	Novartis
Solufen	Ibuprofen	Hard gelatin capsule	Sanofi- Aventis
Depakene	Valproic acid	Soft gelatin capsule	Abbvie
Prometruim	Progesterone	Soft gelatin capsule	Virtus
Lipirex	Fenofibrate	Hard gelatin capsule	Sanofi- Aventis

1.1 Mechanism of self-Emulsification

According to Reiss, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion.[1] The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation: In emulsification process the free energy (ÄG) associated is given by the equation.[4]:

$$\triangle G = \sum N i \pi r 2 \sigma$$

Where, ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and σ represents the interfacial energy.[6] The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.[12] The specificity of surfactant combination required to allow spontaneous emulsification may be associated with a minimization of the phase inversion temperature, there by increasing the ease of emulsion.[13] Phase studies are also necessary for liquid crystal formation in self –emulsification.[18] These indicate that good formulations are usually operating close to a phase inversion region and in a region of enhanced close to a phase inversion region and in a region of enhanced aqueous solubilization.[29]

1.2 Advantage of self-emulsifying dru1g delivery system:

1. Protection of sensitive drug substance.[5]
2. More consistent drug absorption.[5]
3. Protection of drug from gut environment.[5]
4. High drug loading efficiency.[7]
5. Quick Onset of Action.[7]
6. Reduction in the Drug Dose.[7]
7. Ease of Manufacture & Scale-up.[7]
8. Improvement in oral bioavailability Inter-subject and Intra-subject variability and food effects.[7]
9. Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.[10]
10. No influence of lipid digestion process.[10]
11. Increased drug loading capacity.[10]
12. High drug solubilization capacity.[10]

13. Good thermodynamic stability.[10]
14. Protect the drug from enzymatic hydrolysis.[15]
15. Improvement in oral bioavailability.[15]
16. Reduce the intrasubject and intersubjective variability and food effects.[15]
17. Useful for drug targeting toward specific absorption window.[20]
18. Control of delivery profile.[20]

1.3 Disadvantage of self - emulsifying drug delivery system

1. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.[5]
2. This in vitro model needs further development and validation before its strength can be evaluated.[11]
3. 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.[11]
4. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations approximately 30-60%) which GIT.[18]
5. Lack of in vitro model for assessment of the formulations.[20]
6. Chemical instabilities of drugs and high surfactant concentrations.[26]
7. Moreover, volatile co solvents in the conventional self-Emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsule, resulting in the precipitation of the lipophilic drugs.[26]
8. These formulations potentially are dependent on digestion prior to release the drug.[29]

2. Types of SEDDS

On the basis of the water solubility of components,

SEDDS can be classified as

A) Non-water soluble Component Systems

These systems are isotropic mixtures of lipids & lipophilic surfactants having HLB value less than 12 that self- emulsify to form fine oil in water emulsion in aqueous medium. Self-emulsification is generally obtained at a surfactant level above 25% w/w.[1] But at a surfactant level of 50-60% w/w the emulsification process may be compromised by formation of viscous liquid crystalline gels at the oil/water interface.[4] This system is also known as Type-II SEDDS according to lipid formulation classification System (LFCS) Poorly water

soluble drugs can be incorporated in SEDDS & encapsulated in capsules (hard or soft gelatin) to produce convenient single unit dosage forms.[13]

These systems offer advantages

- They are able to generate large interfacial areas which cause efficient partitioning of drug between oil droplets and the aqueous phase.[14]
- They can overcome the slow dissolution step typically observed with solid dosage forms.[14]

B) Water soluble component system

These systems are formulated by using hydrophilic surfactants with HLB more than 12 & co solvents such as Ethanol, Propylene Glycol & Polyethylene glycols Type III SEDDS are commonly known as self -micro-emulsifying drug delivery systems (SMEDDS).[28] Type III formulations can be further divided into type III A & Type III B formulations in order to identify more hydrophilic forms. In Type IIIB, the content of hydrophilic surfactants and co solvents is increased and lipid content is reduced.[29] The distinction between SEDDS & SMEDDS formulation is commonly based on particle size and optical clarity of resultant dispersion. Thus SEDDS formulations typically provide opaque dispersions with particle size greater than 100 nm while SMEDDS disperse to give small droplets with particle size less than 100 nm and provide optically clear or slightly opalescent dispersions. SEDDS may be solid or liquid in nature and they may be formulated into tablets, capsules, pellets, solid dispersions, microspheres, nanoparticles or dry emulsions.[30]

3. Factors affecting the efficiency of oral absorption

These factors also determine the drug's ability to self-emulsify.

I. The solubility and dose of the drug- Unless a drug exhibits extremely good solubility in any one or more components, which make up the SEDDS formulations, most importantly the oil phase, drugs that are administered in high dose are not suitable for SEDDS. Drugs that have low solubility in water and oils and exhibit limited solubility with log P values having an estimate of 2 are more difficult to deliver by SEDDS. The solubility of the drug in the oil phase determines the ability of SEDDS to keep the drug in solubilized form.[4]

II. The concentration of surfactant or co-surfactant- Precipitation may occur if the surfactant or co-surfactant contributes greatly to the solubilization of drug as this leads to low capacity of surfactant or co-surfactant to act as solvent due to the dilution of SEDDS.[12]

III. The polarity of emulsion- The polarity of the emulsion depends on the polarity of the lipophilic phase and this controls the release of drugs from the emulsions.[15]

IV. The size, polarity and charge of the droplet- Factors that control the polarity of the droplet include hydrophilic-lipophilic balance, molecular weight of the micronized drug, and the degree of unsaturation and chain length of fatty acid.[18]

V. The temperature at which self-emulsification occurs.[21]

4. Process of Self-Emulsification

4.1. Self nano emulsifying drug delivery system (SNEDDS)

These are Nano emulsions formed from SEDDS. Self-nano emulsifying drug delivery systems are heterogeneous dispersions of two immiscible liquids which have a mean droplet size that falls within the nano metric scale (20-200nm). Self-emulsifying drug delivery systems are important for increasing the solubility of drugs.[1] Self -micro emulsifying drug delivery system (SMEDDS). They form micro emulsions when in contact with water. The emulsions formed from SMEDDS have a mean droplet size that falls within the micrometric scale which ranges between 2-100nm.[4] The main difference between common emulsions and micro emulsions is the mean droplet size. SMEDDS are thermodynamically stable. They form optically transparent emulsions. Because of the small droplet size, surface area for absorption and dispersion are increased significantly and it easily penetrates the gastrointestinal tract and can be absorbed.[14]

Types of Nanoemulsion (SNEDDS)

Water in oil (W/O) Nano-emulsion: In Which Droplet of Water was dispersed in Continuous Phase oil.[14]

Oil in water (O/W) Nano-emulsion In Which Oil droplet was dispersed in Continuous Phase Water. Bi-continuous Nano- emulsion In which Surfactant was Soluble in Both Oil as well as water Phase, and droplet was dispersed in both Oil as well as water phase.[14]

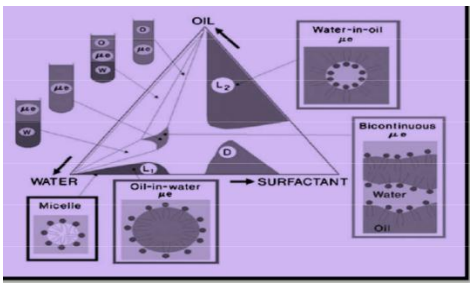


Fig: Psedoternary phase diagram.

4.2 Self- micro emulsifying drug delivery system (SMEDDS)

They form micro - emulsions when in contact with water. The emulsions formed from SMEDDS have a mean droplet size that falls within the micrometric scale which ranges between 2-100nm.[15] The main difference between common emulsions and micro emulsions is the mean droplet size. SMEDDS are thermodynamically stable.[16] They form optically transparent emulsions.[29] Because of the small droplet size, surface area for absorption and dispersion are increased significantly and it easily penetrates the gastrointestinal tract and can be absorbed.[30]

5. Composition of SEDDSS

The self-emulsification process is specific to the factors affecting self-emulsification and all factors should be considered in the selection of excipients.[1]

- Drug or Active Pharmaceutical Ingredient
- Natural or synthetic oils.
- Solid or liquid surfactants.
- One or more hydrophilic solvents/co-solvents.[12]

The self –emulsifying process is depends on

- The nature of oil – surfactant pair.
- The surfactant concentration.
- The temperature at which emulsification occurs.[13]

5.1 Drug/active pharmaceutical ingredient

According to the Biopharmaceutical classification system (BCS), there are four classes of drugs based on solubility (ability of a solute dissolve in a solvent) and permeability (contact between a solute and solvent to form a solution). These classes include.

a. Class I- High solubility and high permeability.

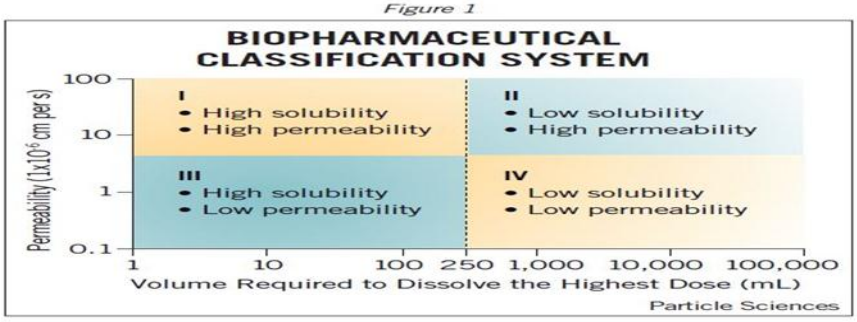
b. Class II- Low solubility and high permeability.

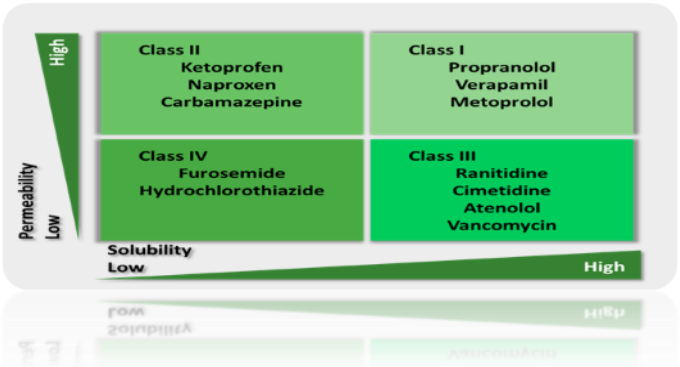
C. Class III- High solubility and low permeability.

D. Class IV- Low solubility and low permeability.[5]

The class II drugs which have low solubility and high permeability are used in the formulation of SEDDS.[11]

Figure 1





5.2 Oil

Oil is by far the most important excipient. It is responsible for facilitating the process of self-emulsification. Because of the importance of oil in SEDDS, they are also called self-emulsifying oil formulations.[1] It helps in the solubilizing lipophilic drugs. Natural or synthetic oils can be used in self-emulsifying drug delivery system.[5] They increase the fragments of lipophilic drugs that pass through the intestinal lymphatic system; this increases the absorption from gastrointestinal tract depending on the nature of triglyceride. Different degrees of saturation of low chain triglyceride (LCT) and Medium chain triglyceride (MCT), monoglycerides, diglycerides have been used in the formulations of SEDDS.[7] Semi synthetic medium chain triglycerides are novel compounds. They are defined as compounds having both hydrophilic and lipophilic properties as well as having surfactant properties.[15] Novel semi-synthetic medium chain triglycerides are amphilic compounds and they are rapidly replacing the regular MCT oils. Oils affect the bioavailability of oral lipophilic drugs by increasing the intestinal lymphatic permeability, solubility in gastric and intestinal fluids, protecting the drug from metabolism and increasing the rate of dissolution. Generally, a higher concentration of surfactants like cremophor RH40 is required when using low chain

triglycerides to form micro-emulsions compared to medium chain triglycerides. Hydrolyzed vegetable oils are widely used since they form a good emulsification system with vast number of approved orally administered surfactants.[16] They also show better drug solubility properties. Comestible oils are not usually selected because their ability to dissolve large quantities of lipophilic drugs is poor. Hydrolyzed oils provide more advantages and their degraded products are almost similar to the natural end products of digestion. Some oils that can be used in the composition of SEDDS include.

a. Corn oil.

b. Sesame oil.

c. Soybeans oil.

d. Olive oil.

e. Peanut oil.

f. Hydrogenated vegetable oil.

g. Hydrogenated soybeans oil.[30]

5.3 Surfactants

In the formulation of SEDDS, non-ionic surfactants having high value in the hydrophilic-lipophilic balance (HLB) scale are used. Non-ionic surfactants are preferred to cationic and anionic surfactants in SEDDS because they are not harmful.[2] The concentration of surfactants added to SEDDS formulation are 30%- 60%. This high concentration of surfactants leads to irritation of the gastrointestinal tract and is a drawback of SEDDS.[5] Safety is a huge criterion in choosing surfactant. The choice is restrained as very few surfactants are approved as orally acceptable.[14] No-ionic surfactants are widely recommended because they are less toxic compared to ionic surfactants but they may alter the permeability of the intestinal lumen by reversible changes. Surfactants of natural sources are usually preferred to synthetically made surfactants but the natural emulsifiers have restrained self-emulsification ability.[17] Studies show a relationship between the mean droplet size and the concentration of surfactants used. In some cases, the increase in the surfactant concentration leads to a decrease in mean droplet size as seen in SMEEDS. This is because of the stability of the oil droplets due to the positioning of surfactant molecule in oil-water interface. In other cases, an increase in surfactant concentration leads to an increase in mean droplet size. This can be explained by the disruption on the interface educed by enhanced water penetrations into oil droplets by which the increased surfactant concentration acts as a medium leading to the extrusion of oil droplets into the aqueous phase.

Surfactants employed for use in the SEDDS formulation act by various mechanisms to improve the bioavailability which include increased permeability of intestinal epithelium, reduced or inhibited p-glycoprotein drug efflux, enhanced drug dissolution and increased tight junction permeability. High quantity of surfactant can cause reversible changes in the permeability of intestinal wall. Solid or liquid surfactants maybe used in SEDDS formulation. The non-ionic group of surfactants consists of tween and span. They include.

a. Tween 20 (Poly sorbate 20).
b. Tween 80 (Poly sorbate 80).
c. Span 80 (Sorbitan mono-oleate).
d. Hydrogenated castor oil.
e. D-alpha Tocopheryl.
f. Cremophor RH40 4/6.[17]

Classification surfactant molecule

Surfactant molecule is mainly classified has four types:

- Anionic surfactants
- Cationic surfactants
- Ampholytic surfactants
- Non-ionic surfactants

1. Anionic Surfactants

The hydrophilic group carries a negative charge is known as Anionic Surfactant. The negative charged group such as carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3-).

Examples - Potassium laurate, sodium lauryl sulphate.[2]

2. Cationic surfactants

The hydrophilic group carries a positive charge is known has cationic Surfactant.

Example - quaternary ammonium halide.[5]

3. Ampholytic surfactants / Zwitter or Zwitterion

Surfactants the surfactant unit consist of both charges Positive as well as negative Charge.

Example – sulfobetaines.[14]

4. Non-ionic surfactants: The hydrophilic group carries no charge but derives its water solubility because it can contain strong polar functional groups such as hydroxyl or polyoxy ethylene (OCH2CH2O).

Examples- Sorbitan esters (Spans), polysorbates (Tween 20).[29]

5.4 Co-surfactant

Co-surfactant is similar function to surfactant unit.[2] Co-surfactant was added along with surfactant unit or combination of surfactant unit to able to increases the ability Surfactant to improving water solubility of poorly water soluble drug.[14] The co-surfactant are. Single chain Surfactant unit are able to prevent the Interfacial Fluidity.[15] The co-surfactant molecule is come into contact with surfactant, oil and water it can separated by Monomolecular Layer of surfactant molecule.[16] The Monomolecular Layer of Surfactant molecule is known as Liquid Crystal formation layer.[17] The most important application of co-surfactant in self Nano-emulsifying Drug Delivery system (SNEDDS) is to prevent interfacial tension between oil and water interface. Co-surfactant like Ethanol, Methanol, Pentanol, Glycol, Propylene Glycol.[26]

5.5 Co-solvents

Co-solvents are solvents that help in dissolving immiscible phases (oil/aqueous) in a formulation.[5] They dissolve either large amounts of hydrophilic surfactants or the hydrophobic drug in oil phase. One or more hydrophilic solvents maybe used. Co-solvents can also be referred as co-surfactants depending on their use in a formulation.[19] Because high concentration of surfactants is required in SEDDS formulations, usually above 30%, which causes irritation in the gastrointestinal tract, co-surfactants are employed to reduce the concentration of surfactants.[21] Both surfactants and co-surfactants work together to reduce the interfacial tension to a negligible negative value.[22] When this value is achieved, the interface expands to form droplets that are finely dispersed, surfactants and co-surfactants are later adsorbed until the bulk condition is exhausted enough to make a positive interfacial tension. This is called spontaneous emulsification and it forms the emulsions. In self-emulsifying drug delivery system, organic solvents that are approved for oral administration such as polyethylene glycol, ethanol and propylene glycol can act as co-surfactants dissolving large quantities of either the drug in oil base or the hydrophilic surfactant. Studies show that there are alcohol-free self -emulsifying emulsions. These alcohol-free SEDDS systems have advantages over the other formulations because in capsule dosage forms, alcohol and volatile

solvents migrate to the soft or hard gelatin capsule shell causing precipitation of lipophilic drug. In alcohol-free formulation systems, lipophilic drug dissolution is limited. Proper choice should be considered in the selection of excipients. Some co-solvents that are included:

a. Ethanol.

b. Propylene glycol.

c. Poly ethylene glycol (PEG).

d. Glycerin.[30]

5.6 Viscosity enhancers

Viscosity enhancers are components that added to self-emulsifying drug delivery systems to alter the viscosity of the formulations. Some examples of viscosity enhancers include;

a. Tragacanth.

b. Beeswax.

c. Acetyl alcohol.

d. Stearic acids.[17]

5.7 Antioxidants

In SEDDS formulations, antioxidants of lipophilic nature are added to stabilize the oil phase of the formulations. Examples include;

a. Tocopherol.

b. Ascorbic palmitate.

c. Propyl gallate.[17]

5.8 Polymers

Inert polymers which are non- ionizable at physiological pH present 5% to 40% w/w are able to form matrix. When added to SEDDS formulation, it prevents precipitation by formulating super saturable SEDDS. Polymers include;

a. Hydroxyl propyl methyl cellulose.

b. Ethyl cellulose (EC).[17]

6. Development of Solid Self-Emulsifying Drug Delivery Systems

One of the advantages of self-emulsifying drug delivery systems is that it can be formulated as liquid dosage forms as well as solid dosage forms. Usually, all the ingredients used in self-emulsifying drug delivery systems are usually in liquid forms, e.g., oils, liquid surfactants and

co-solvents, because of this, most SEDDS are in liquid state which can pose some disadvantages like precipitation, low stability and high costs.[1]

Solid self- emulsifying drug delivery systems (S-SEDDS) are now manufactured and have gained popularity because they eliminate all the disadvantages that come with the liquid dosage forms of SEDDS. For the preparation of solid emulsifying drug delivery systems, the liquid dosage forms are solidified to create solid dosage forms. The merits of SEDDS and the advantages of solid dosage forms are merged together to form solid self- emulsifying drug delivery systems.[15]

6.1 Solidification techniques used in the transformation of liquid SEDDS to solid SEDDS

6.1.1 Capsule filling with liquid and semi-solid self-emulsification formulations

This is the most common and easiest solidification techniques. It involves the filling of liquid or semi-solid self-emulsifying formulations into hard or soft capsule shells. For liquid self-emulsification formulations, a technology technique is used which is called Liquid- Ores technology which used osmotic properties where the layer expands when it comes in contact with water and is pumped into the hard or soft gelatin capsules.

For the semi-solid self-emulsifying formulations, the semi-solids are heated to a temperature twenty degrees above their melting point. The molten mixture is placed in the capsule shell with a stirrer. The capsule is capped and left to cool.[16]

6.1.2 Spray drying: All the ingredients, that is, excipients, drug and solid carriers are mixed and solubilized. The solubilized mixture is put in a spray dryer and atomization of droplets occurs. The water phase in the emulsion evaporates and the particles formed are dried in the drying chamber. The particles are collected and used for the formulations of self -emulsifying tablets and capsules.[18]

Adsorption to solid carriers: The adsorption to solid carrier technique is another simple technique for preparation of self-emulsifying powders. It requires the mixing of liquid self-emulsifying formulations and solid carriers in a blender. The resultant can further be used in the formulation of self-emulsifying tablets and capsules. Liquid self-emulsifying formulations easily adhere to the solid carriers. The solid carriers that are used include cross-linked

polymers, such as cross-linked sodium carboxyl methyl cellulose, cross-linked povidone, or nano-particles absorbents such as charcoal, bamboo charcoal, porous silicon dioxide.[20]

Melt granulation: Unlike wet granulation, the binding agent used in melt granulation melts at low temperature and is used to form powder agglomeration.[25] It has more advantages than wet granulation. It is also known as "one-step" technique.[26]

Melt-extrusion/extrusion spheronization: This is a solvent-free technique. The extrusion-spheronization includes drying of the ingredients, that is, drugs and excipients, addition of a liquid binder to wet the mixture.[28] The mixture is then extrudated with pressure and controlled temperature. The spheronization occurs when the extrudate form spheroids of same size. These spheroids are dried and may be coated. The melt extrusion/extrusion spheronization technique is used in the pharmaceutical industry. Self -emulsifying pellets of Diazepam and progesterone were manufactured with the melt-extrusion/extrusion-spheronization technique.[30]

7 Dosage Forms of Self- Emulsifying Drug Delivery System

7.1 Self- emulsifying capsules

These are typical liquid self-emulsifying formulations encapsulated in soft or hard gelatin capsules shells. When administered, they spontaneously form fine droplets of micro emulsions. These micro-emulsions are dispersed in the gastrointestinal tract and improve intestinal absorption. Irrefutable limitations in this dosage form which cause decrease in drug absorption is the irreversible phase separation of micro-emulsion which may take place.

In cases where this may occur, the anionic surfactant, sodium dodecyl sulphate is added to the self-emulsifying formulations to improve absorption. A small quantity of polymer is used in the formulation to formulate super-saturable SEDDS to prevent precipitation of drug ensuring a supersaturated state is generated and maintained in vivo. These formulations have a decreased amount of surfactant so the side effects relating to the gastrointestinal tract are minimized.

Apart from filling in liquid formulations in capsules, the liquid self- emulsifying formulations can also be filled in solid or semi-solid state by combining the liquid with a solid carrier. Oral SEDDS capsules were found to have a higher patient compliance than injections as it was seen in Low Molecular Weight Heparin (LMWH) which was usually administered by

parenteral route. The LMWH was merged with solid carrier absorbents and placed into hard capsule shells. This technique was also applied to Gentamicin which is usually administered in topical or parenteral route. Gentamicin self- emulsifying capsules were formulated.[4]

7.2 Dry emulsions

Dry emulsions are oil-in-water emulsions that use techniques like spray drying, rotatory evaporation freeze drying or solid carrier adsorption to get converted into actual powders. They are solid dosage forms. Before use, these powders maybe re-dispersed into water. Dry emulsions are powders that undergo self-emulsification in vivo or when they make contact with aqueous solution.

In rotator evaporation technique, mineral oils and sucrose are used to obtain glass emulsions in the form of dry foams. Surfactants are not required in this technique. Spray-drying technique is mostly used in the formulations of dry emulsions. Currently, dry emulsions were prepared by spreading liquid self -emulsifying formulations on a glass plate and left to dry and further mixed to powders. This dry emulsion technology neglects the use of toxic organic solvents and eradicates all the stability problems associated with a typical emulsion like creaming, phase separation, micro-organism contamination during storage. For the oil phase of dry emulsion formulations, medium chain triglycerides (MCT) are used. Dry emulsions can be used to further the formulation of tablets and capsules.[10]

7.3 Self- emulsifying solid dispersion

Although stability is the main interest in the manufacturing process, they are used to increase the rate of dissolution and also the bioavailability of drugs that are poorly soluble in water. A technique that is commonly used for the preparation of self-emulsifying solid dispersion is the hot-melt granulation. Self- emulsifying solid dispersions may be filled in capsules in the molten form.[10]

7.4 Self- emulsifying sustained-release tablets

The self-emulsifying tablets have been successfully formulated. The aim was to create self-emulsifying tablets that would not require a large amount of solid excipients, and for this, a gelling agent called colloidal silicon dioxide was introduced. The gelling agent helped to minimize the amount of solid excipients required for the formulations of self-emulsifying tablets and also to cause slow or sustained release of drug, hence the name.

Indomethacin is a hydrophobic non-steroidal anti-inflammatory drug (NSAID). Application of Indomethacin self-emulsifying tablets could increase permeability through gastrointestinal mucosa to avoid bleeding. A new technology is introduced in self-emulsifying tablets involving the use of osmotic pump as carriers.[11]

7.5 Self-emulsifying sustained-release pellets

Pellets have a lot of advantages such as ease of dispersion in gastrointestinal tract, flexible manufacturing environment. Therefore, the need to merge the good characteristics of pellets with the characteristics of SEDDS led to the formulation of self-emulsifying sustained release pellets. Self-emulsifying pellets were prepared using the extrusion/spheronization.[11]

7.6 Self-emulsifying nanoparticles

Self-emulsifying nanoparticles have been formulated by a technique which involves the melting of drug, lipid and surfactants together, the mixture is injected in a stirred solvent drop wise. The resulting nanoparticles were filtered and dried. The technique employed in self-emulsifying nanoparticles is known as the solvent injection technique. A second technique is called sonication emulsion-diffusion-evaporation.[19]

7.7 Self-emulsifying suppositories

Some studies have shown that solid self-emulsifying drug delivery systems which can increase gastrointestinal absorption also have the properties to increase rectal and vaginal absorption. Example; Glycyrrhizin would give a better therapeutic value of chronic hepatic disease when administered as self-emulsifying suppositories.[19]

7.8 Self-emulsifying implants

Self-emulsifying implants have shown advancement in solid self-emulsifying drug delivery systems. Co-polymers that have a hydrophilic region and about 2 functional groups that can be cross-linked are used in the manufacture of self-emulsifying implants. These co-polymers are used as sealants. Carmusine, a chemotherapeutic agent has a short half-life and is used for brain tumors. Self-emulsifying carmusine or bis chloroethyl nitorosourea was formulated by compression molding to form wafer-like implants.[26]

8 Applications

A. 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.[17] A high content of liquid SEDDS can be loaded (up to 70%) onto a carrier, which not only maintains good flow ability but also enables the production of tablets with good cohesive properties and good content uniformity in both capsules and tablets.[18] This clearly expands the options available to the formulator.[19]

B. Enhancement of solubility

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of Class-II drug (Low solubility/high permeability).[19] A SMEDDS formulation of a poorly water soluble drug, candesartan cilexetil was formulated for directly filling in hard gelatin capsules for oral administration.[20] The results from the study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like candesartan.[21]

9. CONCLUSION

This review paper studies on self-emulsifying drug delivery systems emphasizing on its main advantage;

1. To improve the bioavailability of poor water-soluble drugs.
2. SEDDS also improve the solubility and absorption of the lipophilic drug as well as intestinal permeability.
3. There are several marketed products of SEDDS in the market of which most are in capsule dosage forms. Solid self- emulsifying drug delivery systems are preferred to liquid formulations because the disadvantages of liquid SE formulations are eliminated. SEDDS are used for drugs with low solubility and high permeability.

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