

Self Micro Emulsifying Drug Delivery System - A Capsulization

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Abstract

The aim of the present work is to emphasize about the importance and to make a capsule review on self micro emulsifying drug delivery system. Oral route of drug administration has been the most prominent way of drug delivery system, because of its ability to prepare the formulation in an economical way, easy to administer, does not require any specific storage condition compared with parenteral route of administration. Some products also have the disadvantage of poor solubility of drugs which cause low dissolution rate resulting in low bioavailability. As classified under the BCS, the Class II drugs have low solubility. Many technologies are available to improve the solubility of the drugs such as micronization, dispersion, alteration of pH, conversion into salt forms, etc. Self micro emulsifying drug delivery system is new into these category which ensure improved bioavailability of the drugs and thereby decreases the dosing frequency, the amount to administer and also has the ability to target selective.

Keywords- Drug delivery, emulsification, improved bioavailability, SMEDDS, solvents, surfactants,

1. INTRODUCTION

Self Emulsifying Drug Delivery system (SMEDDS) is a new approach to improve the solubility of poorly soluble drugs. It can be ideally called as an isotropic mixture. Drugs which are lipophilic in nature can be formulated in this lipid based drug delivery system [1]. SMEDDS improves solubility thereby increases dissolution rate and bioavailability of drugs. Drug, oil, surfactant, solvent and co-solvent are the components of SMEDDS. It forms small droplets due to agitation. The size of the droplet is 10-100nm. Absorption of drug is improved by small droplets due to its ability to increase the interfacial surface area. In this system, the drug is dissolved in oil, solvent or surfactant [2]. Co-solvents are used when required. Once it enters into the stomach it forms micro emulsion due to mild agitation. Agitation is caused by the digestive motility and intestine. SMEDDS is available as different dosage forms such as capsules, tablets, suppositories and topical preparations [3, 4].

2. ADVANTAGES OF SMEDDS [5-7]

- ✓ Enhances oral bioavailability
- ✓ Delivers peptides, protein
- ✓ Available in both liquid and solid dosage form
- ✓ Poorly water soluble drugs can be used
- ✓ Improve patient compliance
- ✓ The drug is protected by oil droplets
- ✓ Drugs will not be affected by presence of food
- ✓ Has reproducible drug absorption profile
- ✓ Gives prolonged release due to use of appropriate polymer

2.1. Limitations Of SMEDDS [8, 9]

- ✓ Lack of *in-vitro* models for evaluation
- ✓ Dissolution test cannot be completely relied on, because this formulation depends on digestion
- ✓ It causes GIT irritation due to the excess amount of surfactant
- ✓ Use of co-solvents can destroy the soft gelatin capsule shells

3. FACTORS AFFECTING SMEDDS [10, 11]

3.1. Dose of drug: The drugs which have low solubility at high dose are not suitable for SMEDDS. The drugs required to administer at high dose should possess good solubility in the components used at least in oil phase.

3.2. Solubility of drug: The drug should be highly soluble which influences its bioavailability. The incorporation of surfactants and co-surfactants at high concentration can cause risk of precipitation.

3.4. Polarity of lipid phase: Release of drug is highly influenced by polarity of lipid phase. High polarity value increases the rate of release.

3.5. Droplet size and charge: Smaller the droplet size and larger the surface area increases absorption and if the droplet is positively charged the drugs can penetrate into the physiological barrier in deep leads to improved bioavailability.

4. FORMULATION OF SMEDDS

The following should be considered in the formulation of a SMEDDS [12].

- The solubility of the drug in different oil, surfactants and co-solvents
- The selection of oil, surfactant and co-solvent based on the solubility of the drug
- Preparation of the phase diagram
- The preparation of SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co-solvent

The components of SMEDDS are [13-17]

4.1. Oil

Oil is the prime excipient in SMEDDS. It can easily solubilise and increase the absorption of lipophilic drug. Oil can reduce self emulsification time and increases the intestinal lymphatic transport of lipophilic drugs. Modified or hydrolyzed vegetable oils are used in SMEDDS for the success of preparation.

Eg: olive oil, corn oil, soyabean oil.

4.2. Surfactant

The surface area of the drug can be increased by the use of surfactants. The most desired characteristic of a surfactant is that it should possess HLB value greater than 12. Non-ionic surfactant is the most widely used due to its less toxicity. 30-60%w/w of non-ionic surfactant is used in the preparation to obtain stable SMEDDS. The size of the droplets can be reduced by increasing the concentration of surfactant.

Eg: Tween80, span 80, capryol 90.

4.3. Solvent

Solvents are used to reduce the size of the droplets into small thereby the absorption of the drug is increased.

Eg: Ethanol, Isopropranol, Tetrahydrofuryl alcohol.

4.4. Consistency builder

Tragacanth, cetyl alcohol, stearic acid or beeswax can be added to alter the consistency of the emulsion.

4.5. Enzyme inhibitors

Enzymatic degradation of drugs can be avoided by incorporating enzyme inhibitors in the formulation of SMEDDS. Inhibitors are classified into different types based on its chemical composition such as

1) Inhibitors that are not based on amino acids. eg: P-aminobenzamidine, FK-448, Cosmostat mesylate, Sodium glycolate.

2) Amino acids and modified amino acids eg: amino bromine derivatives and n -acetylcysteine.

3) Peptides and modified peptides e.g. Bacitracin, antipain, leupeptin, amastatin.

4) Polypeptide protease inhibitors e.g. Apratinin, Bowman-Birk inhibitor, Soyabean trypsin inhibitor, Chicken egg white trypsin inhibitor.

5) Complexing agent e.g. EDTA, EGTA, 1, 10 Phenanthroline, Hydroxyquinoline.

4.6. Adsorbents/solidifying agents

S-SMEDDS can be prepared by adsorption into carrier method and extrusion spheronization technique which require solidifying agents and adsorbents in high amount. Cellulose, lactose, microcrystalline cellulose are some of the solidifying agents used in the formulation of S-SMEDDS. Stable S-SMEDDS can be obtained by using these agents in high amount and also with suitable processing properties. But many studies showed it is practically infeasible for drugs having low solubility in oil phase.

4.7. Polymers

5-40% of the SMEDDS composition weight represents the inert polymer matrix. It is unionisable at physiological pH and is used in the preparation of sustained release SMEDDS due to its ability to form matrix.

4.8. Other components

pH adjusters, flavours and antioxidants are the other components used in the SMEDDS formulation. Since it is a lipid product, the susceptibility to form peroxide is high, particularly with unsaturated lipids. As a result of oxidation, free radicals such as ROO, RO, OH can be formed which cause damage to drugs and induces toxicity. Unsaturation level of lipid molecule can be increased due to formation of lipid peroxides by auto oxidation. The other factors which effect the stability of the formulation is pH of

the solution and processing energy such as ultrasonic radiation which accelerates the hydrolysis of lipids. Lipophilic antioxidants (e.g. α -tocopherol, propyl gallate, ascorbyl palmitate or BHT) can be used to stabilize the oily content of the SMEDDS.

5. DOSAGE FORM DEVELOPMENT OF S-SMEDDS

Various dosage forms of S-SMEDDS are

- Dry emulsions
- Self-emulsifying capsules
- Self-emulsifying sustained/controlled-release tablets
- Self-emulsifying sustained/controlled-release pellets
- Self-emulsifying solid dispersions
- Self-emulsifying beads
- Self-emulsifying sustained-release microspheres
- Self-emulsifying nanoparticles
- Self-emulsifying suppositories
- Self-emulsifying implant

6. MECHANISM OF SELF EMULSIFICATION

Self emulsification process occurs, when the entropy changes [18]. The energy required to increase the surface area of the dispersion is smaller than the dispersion. The free energy of conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation

$$\delta G = \sum N_i \pi r_i^2 \sigma$$

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

σ is the interfacial energy with time

The two phases of the emulsion will tend to separate, in order to reduce the interfacial area and subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence [19, 20].

In case of self-emulsifying system, the free energy required to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously. Emulsification requires very little input energy, which involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing.

In earlier work it was suggested that the case of emulsification could be associated with the ease by which water penetrates into the various liquid crystal or phases get formed on the surface of the droplet. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the interface formation between the oil and aqueous continuous phases, followed by the solubilisation of water within the oil phase owing to aqueous penetration

through the interface, which occurs until the solubilisation limit is reached close to the interface [21]. Further aqueous penetration will result in the formation of the dispersed liquid crystalline phase.

As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self emulsification process causes interface disruption and droplet formation [22]. A combination of particle size analysis and low frequency dielectric spectroscopy was used to examine self-emulsifying properties of a series of Imwitor 742 (a mixture of mono and diglycerides of Caprylic acids/Tween 80) systems, which provided evidence that the formation of the emulsion may be associated with liquid crystal formation, although the relationship was clearly complex.

The presence of the drug may alter the emulsion characteristics, possibly by interacting with the liquid crystal phase. The droplet structure can pass from a reversed spherical droplet to a reversed rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase or other structures until, after appropriate dilution, a spherical droplet will be formed again.

7. BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of poorly water soluble drugs is well known. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including [23]

- a) Delivery to the absorption site and time available for dissolution increases by altering gastric transit.
- b) Luminal drug solubility increases. Secretion of bile salts (BS), endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of intestinal mixed micelles and increases the solubilisation capacity by presence of lipids in GI tract. However, further solubilisation capacity can be increased by intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures
- c) For highly lipophilic drugs, lipids may increase the extent of lymphatic transport and enhance bioavailability of the drug directly or indirectly via a reduction in first-pass metabolism. Absorption of hydrophilic drugs through lymphatic (chylomicron) is less and in spite it may diffuse directly into the portal supply. Emulsion can be used to increase the dissolution rate and thereby improve the absorption of drugs
- d) Changes in the biochemical barrier function of the GI tract reduce the extent of enterocyte based metabolism since certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p glycoprotein efflux pump.
- e) By changing the physical barrier function of the GI tract. Various combinations of lipids, lipid digestion products and surfactants can be used to enhance permeability properties. The bioavailability of the majority of poorly water-soluble,

and in particular, lipophilic drugs is not mainly affected by passive intestinal permeability.

8. SMEDDS – THE NEED OF THE HOUR

Poorly water soluble drugs can be delivered orally by pre-dissolving the compounds in appropriate solvent and fill the formulation into capsules. The initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract can be overcome by this approach. The main problem is that the formulation may disperse in the GI tract which produces precipitation of drugs in the solution, It occurs mostly with hydrophilic solvents (e.g. polyethylene glycol). Occurrence of precipitation on dilution in the GIT can be avoided by dissolving the components in lipid vehicle. Water-soluble polymer can be used to aid solubility of the drug compound. For example, polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. Crystallisation of the polymer matrix due to thermodynamically stable state is one of the problems in this type of formulation that affects the physical stability of the product which can be studied by Differential scanning calorimetry or X-ray crystallography. SMEDDS are novel approach to enhance the solubility, bioavailability and protect the drug from gastric environment which gives better systemic absorption of drugs.

9. METHODS OF PREPARATION [24, 25]

9.1. Spray drying

In this method, all the excipients are mixed together. The formulation is atomized into small droplets. The droplets are introduced into the drying chamber, the temperature and airflow is maintained as per required. Further it can be prepared as capsules/ tablets.

9.2. Adsorption into carrier

In this method the liquids are mixed with the excipients. The powdered mixture is filled into capsules or it can be formulated as tablets. The benefit of this technique is it ensures content uniformity.

9.3. Melt agglomeration

Powder agglomeration can be obtained by melt granulation. It is obtained by using binder which melts at low temperature.

9.4. Melt extrusion

It is a solvent free method. In this process, the raw material which has plastic properties converts into a product with uniform density and shape; it is obtained by forcing the raw material into a die. This process is carried out under controlled pressure, temperature and proper flow of product. The advantage of this method is high drug loading and content uniformity.

10. EVALUATION [26, 27]

10.1. Visual assessment: The prepared SMEDDS is evaluated for its appearance after dilution with water and the preparation which shows clear, isotropic and transparent solution indicates micro emulsion.

10.2. Particle size: Determination of size of the droplet is an important part in the characterization of emulsion

because absorption and drug release efficiency is dependent on the droplet size. The particle size can be determined by using photon correlation, it is based on the principle of dynamic changes in laser light scattering intensity due to Brownian movement of particles. Droplet size is affected by the nature and concentration of surfactant. Before analysing the prepared emulsion, it should be diluted with water

10.3. Zeta potential: It is used to determine the stability of the formulation. Zeta potential analyzer or Zeta meter system is used to measure the zeta potential value. Higher value indicates good stability.

10.4. Cloud point determination: Cloud point is defined as the temperature above which the transparent solution changes into cloudy solution. It is determined by gradually increasing the temperature of water bath in which the emulsion placed and measured spectrophotometrically. Cloud point depends on the nature of drug and components.

10.5. Refractive index: It is used to determine the stability of the formulation. It can be measured by using refractometers. Co-surfactant and globule sizes are the two factors which affect the refractive index.

10.6. Thermo stability: Freeze thawing can be used to study the stability of the formulation. The product should be maintained at -4°C or 40°C of temperature for 24 hours. Then it should undergo centrifugation at 3000rpm for 5minutes. At the end of the process the product is observed for phase separation. Product stability is indicated by absence of phase separation.

10.7. Self emulsification and precipitation assessment: 200ml of 0.1N HCL or purified water can be used as buffer solution. 37°C temperature should be maintained with 60rpm for 24hours. Few ml of the emulsion was added into the buffer solution. The appearance of the solution was checked visually and the solution was categorised as clear, turbid and transparent.

10.8. Viscosity: Thickness of the emulsion is an important parameter while filling into capsules. Viscosity of the emulsion is checked by using Brook field viscometer. The emulsion type can be identified with the values. If the viscosity is low it confirms O/W and high indicates W/O type emulsion.

10.9. Polydispersibility index: Particle homogeneity can be analysed by calculating polydispersibility index. The values can differ from 0.0 to 1.0. The formulation is homogeneous if the value is near to 0.

10.10. % Transmittance: Transparency of the formulation is detected by Abbes Refractometer. A small amount of the emulsion placed on the slide is compared with water. Colorimetry and UV spectrometry can be used to measure the % transmittance.

10.11. Electro conductivity study: Electro conductivity of emulsion can be checked by electro conductometer. Electro conductivity is used to confirm the formulation is O/W or W/O based on the values.

High value - O/W

Low value - W/O

10.12. In vitro dissolution study: After filling the micro emulsion into hard gelatin capsule, the amount of drug released from the formulation can be estimated by using USP apparatus type 1 and 2 by maintaining the temperature at 37°C for 100 rpm. The sample should be withdrawn periodically and analysed by using UV spectrophotometer at appropriate wavelength.

11. CONCLUSION

Self micro emulsifying drug delivery system is one of the promising technologies to deliver the drugs in spite of low solubility. The bioavailability of the drugs can be achieved with low dose due to its high loading capacity. This system of drug delivery is easy to prepare and low in cost.

ACKNOWLEDGEMENT

The authors are grateful to the management of Sri Ramachandra University for their constant support and encouragement.

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