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SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Oral route is the main route of drug administration in many diseases. Major problem in oral route of drug administration is bioavailability which mainly results from poor aqueous solubility. This leads to lack of dose uniformity and high intrasubject/intersubject variability. It is found that 40% of active substances are poorly water-soluble. Various technologies are developed to overcome this problem, like solid dispersion or cyclodextrin complex formation. Much attention has been given to lipid-based formulation with particular emphasis on self-micro emulsifying drug delivery system to improve the oral bioavailability of lipophilic drugs. It requires small amount of dose and also drugs can be protected from hostile environment in gut.

Self micro emulsifying drug delivery systems are specialized form of delivery system in which drug is encapsulated in a lipid base with or without pharmaceutical acceptable surfactant.

KEY WORD

Bioavailability, lipophilic drug, self micro emulsifying drug delivery system, surfactant.

INTRODUCTION

Self micro emulsifying drug delivery system (SMEDDS) or self micro emulsifying oil formulation (SEOF) is defined as isotropic mixture of oil and surfactants or alternatively one or more hydrophilic solvents and co-solvents[1,2]. 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 drug delivery systems (SMEDDS)]. 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[3] 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.

SMEDDS can be formulated to give sustained release dosage form by adding polymeric matrix, which is not ionizable at physiological pH and after ingestion in contact with GI fluid forms a gelled polymer making it possible to release the micro emulsified active agent in a continuous and sustained

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matter by diffusion[4]. Bases of self micro emulsifying system have been formulated using medium chain triglyceride oils and non-ionic surfactant which are acceptable for oral ingestion [5]. The lipophillic (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.

It should be noted that water-in-oil version of SMEDDS has also been investigated. 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.

COMPOSITION

1) Oil
2) Surfactant
3) Co solvent / Co surfactant
4) Others components

OILS

The oil represents the most important excipient in the SMEDDS formulation. Indeed it can solubilize relevant amount of the poorly water soluble drug. Both long-chain triglyceride (LCT) and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used in the design of SMEDDS[6].

E.g. - Corn oil, olive oil, soybean oil, hydrolyzed corn oil.

SURFACTANT

Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows,

1 Anionic surfactants
2 Cationic surfactants
3 Ampholytic surfactants
4 Nonionic surfactants

1: Anionic Surfactants, where the hydrophilic group carries a negative charge such as carboxyl ($RCOO^-$), sulphonate (RSO_3^-) or sulphate ($ROSO_3^-$).
Examples: Potassium laurate, sodium lauryl sulphate.
2: Cationic surfactants, where the hydrophilic group carries a positive charge.
Example: quaternary ammonium halide.
3: Ampholytic surfactants (also called zwitterionic surfactants) contain both a negative and a positive charge.
Example: sulfobetaines.
4: Nonionic surfactants, where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH_2CH_2O).
Examples: Sorbitan esters (Spans), polysorbates (Tweens).

Nonionic surfactants with high hydrophilic-lipophilic balance (HLB) values are used in formulation of SMEDDS. The usual surfactant strength ranges between 30-60% w/w of the formulation in order to form a stable SMEDDS. Surfactants having a high HLB and hydrophilicity assist 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 amount of hydrophobic drug compounds[6].

COSOLVENTS

Organic solvents such as ethanol, propylene glycol (PG) and polyethylene glycol (PEG) are suitable for oral delivery and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base[7]. These

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solvents can even act as co surfactants in micro emulsion systems. Alternately alcohols and other volatile cosolvents have the disadvantage of evaporating into the shells of the soft gelatin or hard sealed gelatin capsules in conventional SMEDDS leading to drug precipitation.

OTHER COMPONENTS

Other components might be pH adjusters, flavors, and antioxidant agents. Indeed a characteristic of lipid products, particularly those with unsaturated lipids show peroxide formation with oxidation. Free radicals such as $ROO^{\cdot}$, $RO^{\cdot}$, and $^{\cdot}OH$ can damage the drug and induce toxicity. Lipid peroxides may also be formed due to auto-oxidation, which increases with unsaturation level of the lipid molecule. Hydrolysis of the lipid may be accelerated due to the pH of the solution or from processing energy such as ultrasonic radiation. Lipophilic antioxidants (e.g. α-tocopherol, propyl gallate, ascorbyl palmitate or BHT) may therefore be required to stabilize the oily content of the SMEDDS.

FORMULATION OF SMEDDS

Drugs with low aqueous solubility present a major challenge during formulation as their high hydrophobicity prevents them from being dissolved in most approved solvents. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents, such as ethanol, PG and PEG may also contribute to the improvement of drug solubility in the lipid vehicle[8]. With a large variety of liquid or waxy excipients available ranging from oils through lipids, hydrophobic and hydrophilic surfactant to water soluble co solvent, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixture which disperse to give fine colloidal emulsions[9]. The following should be considered in the formulation of a SMEDDS.

1: The solubility of the drug in different oil, surfactants and co solvents

2: The selection of oil, surfactant and co solvent based on the solubility of the drug

3: Preparation of the phase diagram.

4: The preparation of SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co solvent[10].

TERNARY DAIGRAM

The use of pseudo ternary diagrams is not recent. This technique was mainly used to map the micro emulsion areas (composition ranges)[11]. Pseudo ternary phase diagram is used to map the optimal composition range for three key excipients according to the resulting droplet size following self-emulsification, stability upon dilution and viscosity.

CONSTRUCTION OF PHASE DIAGRAM

A Titration method is employed to construct phase diagram. Mixture of oil with surfactant is prepared at different ratios (e.g. 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) into different vials. A small amount of water in 5 % (w /w) increments is added into the vials. Following each water addition the mixture in vials is centrifuged for 2 to 3 minute and is incubated at 25°c for 48 hrs with gentle shaking. The resulting mixture is evaluated by visual and microscopy observation. For phase diagram the micro emulsion is the region of clear and isotropic solution[12]. Coarse emulsion is the region of cloudy dispersion.

GENERAL PREPARATION METHOD OF SMEDDS

The appropriate quantity of lipid and surfactant are melted together in a crucible at 40 to 60°c. The

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drug is added and stirred thoroughly. The mixture is injected drop wise into a stirred solvent using a syringe fitted with an 18G needle at a stirring speed approx of 1000 rpm. The SMEDDS is filtered out from the solvent with aid of a filter paper (Whatman no-1) and then dried for 72 hrs in desiccator[12].

MECHANISAM 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. 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:

$$DG = S N Pr^2 s$$

Where,

DG is the free energy associated with the process (ignoring the free energy of mixing),

N is the number of droplets of radius r and S represents the interfacial energy[13].

The two phases of emulsion tend to separate with time to reduce the interfacial area. The emulsion is stabilized by emulsifying agents who form a monolayer on emulsion droplets and hence reduce the interfacial energy as well as provide a barrier to prevent coalescence. In the case of self emulsifying systems the free energy required to form the emulsion is either very low or positive or negative (then the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions[14].

EVALUATION OF SMEDDS

The primary means of self micro emulsification assessment is visual evaluation. The efficiency of self micro emulsification could be estimated by determining the rate of micro emulsification, droplet size distribution and turbidity measurement [15].

STABILITY STUDIES

The physical stability of a Lipid based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient affecting not only formulation performance but also visual appearance. In addition, incompatibilities between the formulation and the gelatin capsule shell can lead to brittleness or deformation delayed disintegration or incomplete release of drug[16].

1.Heating cooling cycle: Six cycles between refrigerators temperature (4°C) and (45°C) with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

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

3. Freeze thaw cycle: Three freeze thaw cycles for the formulations. Those formulations pass this test show good stability with no phase separation, creaming or cracking.

DISPERSABILITY TEST

The efficiency of self emulsification of oral nano or micro emulsic.. .s assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation is added to 500 ml of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle

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rotating at 50 rpm provides gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system[16].

Grade A: Rapidly forming (within 1 min) nanoemulsion having a clear or bluish appearance.

Grade B: Rapidly forming slightly less clear having a bluish white appearance.

Grade C: Fine milky emulsion that forms within 2 min.

Grade D: Dull grayish white emulsion having slightly oily appearance that is slow to emulsify.

Grade E: Formulation exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SMEDDS formulation.

BIOAVAILABILITY STUDY

Based on the self emulsification properties, particle size data and stability of micro emulsion the formulation is selected for bioavailability studies[16]. The in vivo study is performed to quantify the drug after administration of the formulation. The plasma profiles of the drug in experimental animals following oral administration of the conventional tablet and SMEDDS form are compared. Pharmacokinetic parameters of the maximum plasma concentration (*C*max) and the corresponding time (*T*max) for the drug following oral administration are calculated. The area under the concentration–time curve (AUC0→24 h) is estimated according to the linear trapezoidal rule. The relative bioavailability (BA) of SMEDDS form to the conventional table is calculated using the following Equation

Relative BA *(%)* = (AUC test / AUC reference) X (Dose reference / Dose test)

TURBIDIMETRIC EVALUTION

This is done to identify efficient self emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. Nephelo turbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature and the increase in turbidity is measured using a turbidometer. However, since the time required for complete emulsification is too short it is not possible to monitor the rate of change of turbidity (rate of emulsification)[17].

VISCOSITY DETERMINATION

The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. Therefore, it should be easily pourable into capsules and such system should not be too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield Viscometer. This viscosity determination confirms whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosity then it is w/o type of the system[17].

DROPLET SIZE AND PARTICAL SIZE MEASUREMENT

This is a crucial factor in self micro emulsification performance because it determines the rate and extent of drug release as well as the stability of the micro emulsion[17]. The droplet size of the micro emulsion is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) which can measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle after external standardization with spherical

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

REFRACTIVE INDEX AND PERCENT TRANMISSION

Refractive index and percent transmittance proves the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it is compared with water. The percent transmittance of the system is measured at particular wavelength using UV-Vis spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water and formulation has percent transmittance > 99 percent then formulation has transparent nature[17].

ZETA POTENTIAL MEASUREMENT

This is used to identify the charge of the droplets. In conventional SMEDDS, the charge on an oil droplet is negative due to presence of free fatty acids[17].

YIELD OF THE SMEDDS

The SMEDDS formed is filtered from the solvent, dried in the desiccators and weighed to get the yield of the SMEDDS formulated per batch. Percentage yield can be calculated by formula[17]

$$\% \text{ recovery} = \frac{W1}{W2+W3} \times 100$$

Where

W1 is the weight of the SMEDDS formulated.

W2 weight of the drug added.

W3 is the weight of the lipid and surfactant used as the starting material.

DRUG ENCAPSULATION EFFICIENCY

The quantities of the drugs theoretically contained in the SMEDDS were compared with the quantity actually obtained, from the drug content studies i.e. the quantity loaded into the SMEDDS formulated. To get the drug encapsulation efficiency equation used for calculation is[17],

$$EE\ (\%) = \frac{ADC}{TDC} \times 100$$

Where

ADC is the actual drug content.

TDC is the theoretical drug content.

FACTORS AFFECTING SMEDDS

1. ***CONCENTRATION OF DRUG***: Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase[6].

2. ***SOLUBILITY OF DRUG:*** The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oily phase. If the surfactant and co-surfactant contribute to a greater extent for solubilisation then there is risk of precipitation[10].

3. ***POLARITY OF LIPID PHASE:*** The polarity of lipid phase is one of the factors that govern the release of the drug from the micro-emulsion. HLB, chain length, degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets.

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ADVANTAGES OF SMEDDS

1. Enhanced oral bioavailability enabling reduction in dose[18].
2. More consistent temporal profiles of drug absorption[2].
3. Selective targeting of drug(s) towards specific absorption window in GIT[2].
4. Protection of drug(s) from the hostile environment in gut[9].
5. Reduced variability including food effects[13].
6. Protection of sensitive drug substances.
7. Liquid or solid dosage forms.
8. In SMEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore increase in AUC i.e. bioavailability and C max is observed with many drugs when presented in SMEDDS[16].
9. Fine oil droplets empty rapidly from the stomach and promote wide distribution of drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall[9].
10. Ease of manufacture and scale up is one of the most important advantage that make SMEDDS unique when compared to other drug delivery system like solid dispersion, liposomes, nanoparticles etc.
11. SMEDDS has potential to deliver peptides that are processed to enzymatic hydrolysis in GIT.
12. When polymer is incorporated in composition of SMEDDS it gives prolonged release of medicament[5].
13. SMEDDS formulation is composed of lipids, surfactants and co-solvents. The system has the ability to form an oil-on-water emulsion when dispersed by an aqueous phase under gentle agitation. SMEDDS present drugs in a small droplet size and well-proportioned distribution and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered to the lymphatic system, can bypass first pass metabolism. Thus SMEDDS protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism.

DRAWBACK OF SMEDDS

One of the obstacles for the development of self micro emulsifying drug delivery systems (SMEDDS) and other lipid-based formulations is the lack of good predicative in vitro models for assessment of the formulation. Traditional dissolution methods do not work because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, in vitro model simulating the digestive processes of the duodenum has been developed. This in vitro model needs further development and validation before its strength can be evaluated. Further development will be based on in-vitro in-vivo correlations and therefore different prototype lipid based formulations need to be developed and tested in vivo in a suitable animal model[19].

APPLICATION

1. ***SUPERSATURABLE SMEDDS (S-SMEDDS):*** The high surfactant level typically present in SMEDDS formulation can lead to GI side effects and a new class of supersaturable formulations including supersaturable SMEDDS. (S-SMEDDS) formulations have been designed and developed to reduce the surfactant side effects and achieve rapid absorption of poorly soluble drugs[20].

2. ***SOLID SMEDDS:*** SMEDDS are normally prepared as liquid dosage forms that can be administrated in soft gelatin capsules, which have

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some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SMEDDS has been prepared by the process of extrusion / spheronization to provide a good in vitro drug release (100% within 30 min, $T_{50\%}$ at 13 min). The same dose of progesterone (16 mg) in pellets and in the SEDDS liquid formulation resulted in similar AUC, C_{max} and T_{max} values[21].

FUTURE TREND

In relation to formulation development of poorly soluble drugs in the future there are now techniques being used to convert liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules which can then be further processed into conventional 'powder-fill' Capsules or even compressed into tablets. Hot melt granulation is a technique for producing granules or pellets and by using a waxy solubilizing agent as a binding agent up to 25% solubilizing agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents products for converting liquids into powders which can then be processed into powder fill capsules or tablets. However, to obtain solids with suitable processing properties the ratio of SMEDDS to solidifying excipients must be very high which seems to be practically non-feasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of SMEDDS in solid dosage forms will be significantly reduced if SMEDDS is gelled. Colloidal silicon dioxide (Aerosol 200) is selected as a gelling agent for the oil based systems which may serve the dual purpose of reducing the amount of solidifying excipients required and aiding in slowing drug release[21]

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