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A Review on Self Emulsifying Drug Delivery System



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ABSTRACT

Self-emulsifying drug delivery systems, which mainly isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, must be used for the developed of formulations in order to improve the oral absorption of highly lipophilic drug compounds and easy to orally administered in soft or hard gelatin capsules. These systems formation of fine emulsions or microemulsions in a gastrointestinal tract with mild agitation provided by gastric mobility. No. of parameters like surfactant concentration, oil/surfactant ratio, the polarity of the emulsion, droplet size and charge plays a significant role in oral absorption of the drug from SEDDS. In this formulation enhanced bioavailability because to increase the solubility of the drug and minimizes the gastric irritation. The truth that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will be continuing, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future. Self-emulsifying lipid oral formulations improved the bioavailability of poorly water soluble & highly permeable compound. The bioavailability enhancing property has been associated with a number of in vivo properties of lipid formulation.



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INTRODUCTION:-

Self-emulsifying drug delivery formulations simply binary systems of lipophilic phase and drug, or lipophilic phase, surfactant, and drug. The formation of a SEDDS requires co-surfactant to generate a microemulsion. SEDDS formulations characterize by in vitro lipid droplet sizes of 200 nm–5 μ m and the dispersion has a turbid appearance. Self-emulsifying drug delivery systems are mixtures of oils and surfactants, ideally isotropic, and occasionally containing co-solvents, which emulsify suddenly to produce fine O/W emulsions when introduced into the aqueous phase under gentle agitation. Recently, SEDDS containing medium chain triglyceride oils and non-ionic surfactants, the latter being not as much of toxic. Upon per oral administration, these systems form fine emulsions or microemulsions in the gastrointestinal tract (GIT) with mild agitation provided by gastric mobility.

ADVANTAGES OF DELIVERY SYSTEM:-

- ✓ Quick Onset of Action.
- ✓ Reduction in the Drug Dose.
- ✓ Ease of Manufacture & Scale-up Improvement in oral bioavailability.
- ✓ Inter-subject and Intra-subject variability and food effects.
- ✓ Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.
- ✓ No influence of lipid digestion process.
- ✓ Increased drug loading capacity.

DISADVANTAGES OF DELIVERY SYSTEM:-

- ✓ Traditional dissolution methods do not work because these formulations potentially are dependent on digestion prior to the release of the drug.
- ✓ 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 necessary to developed and tested in vivo in a suitable animal model.

✓ The drawbacks of this system include chemical instabilities/incompatibility of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

MECHANISM OF SELF EMULSIFICATION:-

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:

$$DG = S N \pi r^2 s$$

Where,

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

N = number of droplets;

r = radius of droplets and

S = interfacial energy.

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.

USE OF EXCIPIENT IN SEDDS:-

Pharmaceutically accepted excipients and the toxicity issues of the components are markers of the selection of excipients. There is a huge restriction as which excipients to be used. Early studies opened to the self-emulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-emulsification occurs.

Important parameter for excipients

- The solubility of drug in the formulation as such and upon dispersion for (SEDDS),
- The rate of digestion (for formulations susceptible to digestion) and possibly,
- The solubilization capacity of the digested Formulation.

EXCIPIENTS:-

SURFACTANTS:-

Several compounds exhibiting surfactant properties may be employed for the development of self-emulsifying systems, but the choice is limited as very few surfactants are orally used or accepted. The most widely recommended the non-ionic surfactants which is having high hydrophilic-lipophilic balance (HLB). Safety is a major determining factor in choosing a surfactant the four main groups of surfactants are defined as following,

- Anionic surfactants
- Cationic surfactant
- Ampholytic surfactants
- Nonionic surfactants

Anionic Surfactants: - Where the hydrophilic group carries a negative charge such as carboxyl (RCOO⁻), sulphonate (RSO₃⁻) or sulfate (ROSO₃⁻). Examples: Potassium laurate, sodium lauryl sulfate.

Cationic surfactants: - Where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

Ampholytic surfactants: - (Also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

Nonionic surfactants: -Where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene. Examples: Sorbitan esters (Spans), poly - sorbates (Tweens)

CO-SOLVENTS:-

The production of an optimum SEDDS requires comparatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant reduced by the incorporation of co-surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even negative value. At this value, the interface would expand to form fine dispersed droplets, and subsequently, adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. On the other hand, the use of co-surfactant in self-emulsifying systems is not compulsory for many non-ionic surfactants. The selection of surfactant and co-surfactant is vital not only to the formation of SEDDS but also to solubilization of the drug in the SEDDS.

METHOD OF PREPARATION:-

A) Solidification techniques for transforming liquid/semisolid:-

Various solidification techniques are as listed below;

1) 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. For semisolid formulations, it is a fourstep process:

- A) Heating of the semisolid excipient to at least 20°C above its melting point.
- B) Incorporation of the active substances (with stirring).
- C) Capsule filling with the melt cooling to room temperature. For liquid formulations, it involves a two-step process.
- D) Filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing.

B) Spray drying:-

Essentially, 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) prepared into tablet pattern and the drying chamber design are selected according to the drying characteristic the product and powder specification

C) 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 the addition of the liquid onto carriers by mixing in a blender.

D) 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.

E) 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 product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions.

EVALUATION:-

A) Thermodynamic stability studies:-

The physical stability of a lipid –based formulation is also essential to its performance, which can be adversely affected by precipitation of the drug in the excipient medium. In addition, poor formulation physical stability can be lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance also. In addition, incompatibilities between the

formulation and the gelatin capsules shell must be brittleness or deformation, delayed disintegration, or improper release of the drug.

a) Heating cooling cycle:- Six cycles between refrigerator temperature 40°C and 45°C with storage at each temperature not less than 48 hr is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

b) Centrifugation:- Passed formulations are centrifuged thaw cycles between 21 °C and +25 °C with storage at temperature for not less than 48 hr at 3500 rpm for 30 min. Those formulations that do not show any phase separation or significant changes are taken for the freeze-thaw stress test.

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

B) Dispersibility test:-

The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP XXII dissolution apparatus II. One milliliter of each formulation was added to 500 mL of water at $37 \pm 0.5^{\circ}\text{C}$. A standard stainless steel dissolution paddle rotating at 50 rpm provided mild agitation. The in vitro performance of the formulations is visually assessed using the following Grading system:

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

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

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

Grade D: Dull, a grayish white emulsion having a slightly oily appearance that is slow to emulsify (longer than 2 min).

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 recommended for SEDDS formulation.

C) Turbidimetric Evaluation:-

Nephelo/turbidimetric evaluation is done to monitor the growth of emulsification. A fixed quantity of Self-emulsifying system is added to fixed quantity of suitable medium generally (0.1N hydrochloric acid) under continuous stirring (50 rpm) on the magnetic plate at room temperature, and the raise 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),

D) Viscosity Determination:-

The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. The rheological properties of the microemulsion are evaluated by Brookfield viscometer using the different spindle and rpm. This viscosities determination confirm whether the system is w/o or o/w. If the system has low viscosity then it is o/w type of the system and if high viscosities then it is w/o type of the system.

E) Droplet Size Analysis /Particle Size Measurements:-

The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyzes the fluctuations in light scattering due to the Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm.

APPLICATIONS:-

Improvement in Solubility and bioavailability:-

If the drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in of BCS Class-II drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic (log P 0.979) non-steroidal anti-inflammatory drug is a drug of choice for the sustained release formulation having high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained

release formulations. This formulation enhanced bioavailability due to increasing the solubility of the drug and minimizes the gastric irritation. Also, incorporation of gelling agent in SEDDS sustained the release of Ketoprofen. In SEDDS, 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 SEDDS

Protection against Biodegradation:-

The ability of self-emulsifying drug delivery system to overcome degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in a physiological system, may be because of acidic pH in stomach, enzymatic degradation or hydrolyte. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as a liquid crystalline phase in SEDDS might be an act as a barrier between degradation environment and the drug. Ex: - Acetylsalicylic acid (Log P = 1.2, M_w=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an HCL environment. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the Galacticles Oral Lipid Matrix

Controlling the release of drug:-

Different formulation approaches that have been required to achieve sustained release, increase the bioavailability and decrease the gastric irritation of ketoprofen include preparation of matrix pellets of nanocrystalline ketoprofen, sustained release ketoprofen microparticles and floating oral ketoprofen systems and transdermal systems of ketoprofen. Preparation and stabilization of nano-crystalline or improved solubility forms of the drug may pose processing, stability, and economic problems. This problem can be successfully overcome when Ketoprofen is presented in SEDDS formulation. This formulation enhanced bioavailability due to increasing the solubility of the drug and minimizes the gastric irritation. Also, incorporation of gelling agent in SEDDS sustained the release of Ketoprofen.

Marketed examples:-

Type of delivery system	Drug
SEDDS(Gelled)	Ketoprofen
SEDDS	Carvedilol
SMEDDS	Simvastatin
Self- emulsifying tablet	Diclofenac sodium
Self- emulsifying pallets	Methyl and propyl parabens
SGC	Cyclosporine
SGC	Ritonavir

CONCLUSION:-

From the above review, we can conclude that Self-emulsifying drug delivery systems are the 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 significantly improve oral bioavailability. The SMEDDs formulation can be optimized for the delivery of hydrophobic compounds with drug loading; minimum surfactant concentration and proper infinite dilution can be achieved without drug precipitation. SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and Traditional preparation of SEDDs involves the dissolution of drugs in oils and their blending with suitable solubilizing agents.

With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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