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REVIEW ARTICLE

A REVIEW ON SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM

***Ruchita Patel [1], Meghana Kamble[2], Ramesh Katedeshmukh[1], Nitin Zarikar[1], Akshada Kulkarni[1]**

[1] Shree Chanakya Education Society's, Indira College of Pharmacy, Tathwade, Pune, Maharashtra, India

[2] P. E. Society's Modern College of Pharmacy, Nigdi, Pune, Maharashtra, India.

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ABSTRACT

Self-emulsifying drug delivery system (SEDDS) is one of the most popular and commercially viable formulation approaches for enhancing solubility of poorly water soluble drugs. SEDDS are isotropic mixtures of oil, surfactant and co-surfactant which are generally present in liquid or semisolid form. Solid SEDDS are solid forms of liquid SEDDS converted into solid by suitable means. These solid SEDDS are considered more stable over liquid SEDDS, also solid forms improve handling, packaging and storage. The aim of this review is to discuss various methods of preparation of solid SEDDS and different existing drug delivery systems which incorporated solid SEDDS to obtain advantage of both the systems.

KEYWORDS: self-emulsifying, microsphere, liposphere, nanoparticles, implants, SEDDS

INTRODUCTION:

In drug discovery, about 40% of new drug candidates display low solubility in water, which leads to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Furthermore, oral delivery of numerous drugs is hindered owing to their high hydrophobicity. Therefore, producing suitable formulations is very important to improve the solubility and bioavailability of such drugs.

One of the most popular and commercially viable formulation approaches for solving these problems is self-emulsifying drug delivery systems (SEDDS). SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs.[1]SEDDS are isotropic mixtures of oil, surfactant and co-surfactant which are generally present in liquid or semisolid form. Depending on the globule size of the formed emulsion, they are further claimed as self microemulsifying drug delivery system (globule size in micrometer range) and self nanoemulsifying drug delivery syatem (globule size in nanometer range).

Traditional preparation of SEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents. However, Self Emulsifying (SE) formulations are normally prepared as liquids that produce some disadvantages, for example, high production costs, low stability and portability, low drug loading and few choices of dosage forms. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation. To address these problems, Solid SEDDS (S-SEDDS) have been investigated, as an alternative approach. Such system requires the solidification of liquid self-emulsifying (SE) ingredients into powders/nanoparticles to incorporate into various solid dosage forms (SE tablets [2,3]and SE pellets[4] and so on). Thus, S-SEDDS combine the advantages of SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance.).[5]This review throws light on various methods of preparation of solid SEDDS from liquid SEDDS and variety of drug delivery systems containing SEDDS for combined advantage of both systems.

Figure 1: Various types of solid SEDDS

*Corresponding author: Ruchita Patel | Email: ruchip14@gmail.com

SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM (S-SEDDS):

As SEDDS may exist in liquid or solid dosage form, but due to better stability as well as ease in handlingand transportation, solid SEDDS are generally preferred over liquid SEDDS. Conventional solid SEDDS are capsules, solid dispersions and dry emulsions but recently, a number of other solid SEDDS have been prepared such as pellets, microspheres, tablets, beads, implants & suppositories.

ADVANTAGES OF SELF EMULSIFYING DRUG DELIVERY SYSTEM:[6]

1. Spontaneous formation
2. Ease of manufacture
3. Thermodynamic stability
4. Improved solubilization of bioactive materials
5. More consistent temporal profiles of drug absorption
6. Greater bioavailability
7. less drug need to be used
8. For many drugs taken by mouth
9. Faster release rates and it improve the drug acceptance by consumers
10. Selective drug targeting toward a specific absorption window in the GI tract and
11. Drug protection from the hostile environment in the gut
12. Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption
13. These systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles
14. This may lower cost.

METHODS OF SOLIDIFICATION:

Solid SEDDS were developed mainly by adsorption onto solid carriers, spray drying, melt extrusion, dry emulsion, solid dispersion etc. These solid SEDDS can be converted into pellets, tablets and capsules.

1. ADSORPTION ON SOLID CARRIERS:

a. PHYSICAL ADSORPTION:

These solid carriers have property to absorb liquid/semisolid formulation as self-emulsifying system (SES). It is a simple procedure, where SES is incorporated into a free flowing powder material which has adsorption quality. The mixture is uniformly adsorbed by mixing in a blender. This solid mixture is filled into capsule or added to more excipient for compression into tablets. The above mixture was solidified to powder forms using three kinds of adsorbents: microporous calcium silicate (FloriteTMRE); magnesium aluminum silicate (NeusilinTMUS2) and silicon dioxide (SylysiaTM 320).[7]

b. SPRAY DRYING:

In this technique first the prepared formulation containing oil, surfactant, drug, solid carrier etc, is sprayed into a drying chamber through a nozzle. The volatile vehicles first evaporate leaving behind small solid particles. These particles are then filled into capsules or compressed into tablets. [5]

2. MELT EXTRUSION:

This formulation technique depends on the property of the plastic mass material which can be easily extruded and spheronised with pressure. Here there is no need for addition of liquid form of excipient but a constant temperature and pressure need to be maintained.[8]

DOSAGE FORMS OF S-SEDDS

CONVENTIONAL DOSAGE FORMS:

1. SELF-EMULSIFYING CAPSULES:

After administration of capsules containing conventional liquid SE formulations, microemulsion droplets are formed and subsequently get dispersed in the GI tract to reach sites of absorption. Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on).[9]

Various researchers have converted liquid SEDDS to solid SEDDS and packed them in capsules. Nekkanti*et al* converted liquid SEDDS of candesartan by adsorbing onto MCC and colloidal silicon dioxide as solid carriers. They concluded from the results that solubility of candesartan was improved. [10]

In another work liquid SNEDDS of glimepiride was converted into solid SNEDDS by spray drying using Aerosil 200 as solid carrier. [11]

2. SELF-EMULSIFYING TABLETS:

The liquid SEDDS are first adsorbed on to solid carriers and then compressed into tablets after adding tablet excipients. The newest advance in the research field of SE tablet is the SE osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SES. Auther developed this system for carvedilol has outstanding features such as stable plasma concentrations and controllable drug release rate, allowing a bioavailability of 156.78% relative to commercial carvedilol tablets.[9]

Preparation of self-emulsifying tablet of diclofenac was formulated by Attama *et al* using goat fats and tween 80. [12]

3. SELF-EMULSIFYING PELLETS:

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it is very appealing to combine the advantages of pellets with those of SEDDS by SE pellets.[9]

Self-emulsifying pellets are prepared by extrusion/ spheronization and wet granulation methods. In extrusion/spheronization and wet granulation a solid carrier is required along with SEDDS. MCC and lactose are most commonly used. Self-emulsifying pellets prepared by extrusion/ spheronization technique have been reported for diazepam [13], nitrendipine[14], and progesterone[15], aceclofenac[16].Franceschini*et al* prepared self-emulsifying pellets of nimesulide as model drug by wet granulation technique. [17]

ADVANCES IN CONVENTIONAL DOSAGE FORMS USING SOLID SEDDS:

1. SELF-EMULSIFYING BEADS:

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated loading SES into the microchannels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structures are typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. This research concluded that PPB were potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB. [18]

Floating alginate beads containing self-emulsifying drug delivery system (SEDDS) of Tetrahydrocurcumin (THC) were developed by Sriraksa*et al.* to increase drug solubility and prolong gastric residence time. The release profile of the optimized THC-SEDDS floating alginate beads indicated a significant increase in the dissolution rate of tetrahydrocurcumin and provided a controlled release of tetrahydrocurcumin over an 8 h period in a simulated gastric fluid. [19]

2. SUPERSATURABLE SELF-EMULSIFYING SYSTEM:

The supersaturatable self-emulsifying drug delivery system represents a new thermodynamically stable formulation approach wherein it is designed to contain a reduced amount of surfactant and a water-soluble polymer (precipitation inhibitor or supersaturated promoter) to prevent precipitation of the drug by generating and maintaining a supersaturated state *in-vivo*.

Zhang N. *et al.* prepared supersaturatable self-microemulsifying drug delivery system (S-SMEDDS) of Carbamazepine (CBZ).The results showed that the presence of a small amount of polymeric precipitation inhibitor (PVP) effectively sustained supersaturated state by retarding precipitation kinetics. Supersaturable SMEDDS formulation with precipitation inhibitor decreased impairment to cells due to a lower surfactant level compared to SMEDDS. The absorption of supersaturable SMEDDS *in-vivo* resulted in about 5-fold increase in bioavailability compared with the commercial tablet and the reproducibility of plasma concentration profiles intra-individual was improved remarkably.[20]

3. GELLED SELF-EMULSIFYING SYSTEM FOR EXTENDED RELEASE:

Gelled self-emulsifying drug delivery system containing ketoprofen as an intermediate in the development of sustained release solid dosage form was developed by Patil *et al*. Silicon dioxide was used as a gelling agent to aid in solidification and retardation of drug release. The authers studied effect of concentrations of cosurfactant and gelling agent on emulsification process and in vitro drug diffusion. Results showed that liquid crystal phase viscosity increased significantly with increasing amount of silicon dioxide, which in turn caused an increase in average droplet size of resultant emulsion and slower drug diffusion.[21]

Another gelled self-emulsifying system of felodipine was developed by same authers using Aerosil 200 as gelling agent. The gelled self-emulsifying system was further encased within the hydrophobic Gelucire® 43/01 (GEL) coat to extend the release of felodipine.[22]

4. SELF-EMULSIFYING MICROSPHERE:

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumor suppression, and antibacterial, and antithrombotic activity. With ZTO as an oil phase, You *et al*. prepared solid SE sustained-release microspheres using the quasi-emulsion-solvent-diffusion method involving spherical crystallization. The ZTO release behaviour was controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation, and the

plasma concentration time-profiles after oral administration to rabbits showed a bioavailability of 135.6% compared with the conventional liquid SEDDS. [23]

5. SELF-EMULSIFYING LIPOSPHERE:

A poorly water soluble drug, piroxicam, was incorporated into self-emulsifying lipospheres consisting of a mixture of a homolipid from Capra hircus and Tween 65. Various solid self-emulsifying lipospheres were formulated having different ratios of the homolipid and Tween 65 to contain piroxicam. The self-emulsifyinglipospheres were evaluated using the following parameters: particle size, absolute drug content, and dissolution profile. The pharmacodynamics of the drug from the lipospheres were also evaluated using anti nociceptive activity on albino mice. Results showed that the self-emulsifying lipospheres containing 4:11 ratio of the homolipid and Tween 65 gave the best performance in terms of anti-inflammatory effect, particle size, and dissolution. [24]

6. SELF-EMULSIFYING NANOPARTICLES:

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%.

Yunxia*et al* prepared self emulsifyingnanoparticle of 5-fluorouracil (5-FU) and antisense EGFR (epidermal growth factor receptor) plasmids by sonication emulsion diffusion evaporation method. The 5-FU release activity from such nanoparticles was found to be sustained for as long as three weeks.[25]

Trickler*et al.* developed a novel nanoparticle drug delivery system consisting of chitosan and glycerylmonooleate for the delivery of paclitaxel. The self-emulsifying property of glycerylmonooleate enhanced the solubility of paclitaxel and provided a foundation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of paclitaxel. These advantages allow the use of lower doses of paclitaxel to achieve an efficacious therapeutic window, thus minimizing the adverse side effects associated with chemotherapeutics like paclitaxel. [26]

7. SELF-EMULSIFYING IMPLANTS:

Self-emulsifying implants has greatly enhanced the utility and application of S-SEDDS.

Chae*et al* prepared self-emulsifying implants of 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine, BCNU) in form of flat, smooth surfaced wafer by compression molding. The release of carmustine was prolonged upto 7 days. The improvement of antitumor activity and reduction in susceptibility to hydrolysis were observed. [27]

8. SELF-EMULSIFYING SOLID DISPERSIONS:

Although solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling.

Self-emulsifying solid dispersions were reported for phenacetin and progesterone [9], Isradipine[28] and diacerein[29].

CONCLUSION:

Solid SEDDS is more stable than liquid SEDDS. If solid SEDDS form of drug is used instead of plain drug in existing commercially available dosage form, there will be improvement in solubility and not much modification would be needed in manufacturing process.

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