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REVIEW ARTICLE

Self Emulsifying Therapeutic System - A Review

Roshan V. Patil, Karan K. Patil, Vijay R. Mahajan*, and Avinash S. Dhake

S.M.B.T. College of Pharmacy, Nandi Hills, Dhamangaon Tal. Igatpuri, Dist. Nasik (MS), India

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ABSTRACT

Self-emulsifying therapeutic system (SETs) provide an effective and intelligent solution to the various issues related to the formulation of hydrophobic drugs with limited solubility in gastrointestinal fluid. Most of the drugs are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Due to their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophillic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs one of them is Self-Micro Emulsifying Drug Delivery Systems (SMEDDS). Today a huge problem of poorly water soluble drugs is being faced in the world. Many methods are there for increasing the solubility, but lipid technology is one of the most prominent and latest technologies. Lipid formulations always produce a fine dispersion which is useful for increasing the solubility of poorly water soluble drugs. So the main objective is to increase the solubility by various techniques related to lipid technology.

The study methodology includes different formulations which are as follows:

Oil based formulations, Triglyceride, liposomes, niosomes, lipid emulsions, emulsome, hydrogel nanoparticles, aquasomes, solid lipid nanopartciles, and nanostructure lipid carriers.

Key words: SMEDDS, Lipid/ oil based system, Self emulsifying system

INTRODUCTION

Recently synthesized drug that are being discovered are lipophillic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Because of their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophillic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. The Self-Dispersing Lipid Formulations (SDLFs) is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/lipophillic drugs and to improve the oral bioavailability of poorly absorbed drugs. The SDLFs contain oil and a surfactant mixture into which the drug is incorporated. They emulsify when mixed with aqueous environment. The selfemulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs [1, 2, 3]. After selfdispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. Bioavailability enhancement results from the finely dispersed state of the drug containing lipid globules. The large surface area enhances the dissolution. The emulsion globules are further solubilized in the gastrointestinal tract by bile fluids. The presence of surfactant causes enhanced absorption due to membrane induced permeation changes. The droplets formed are either positively charged or negatively charged. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the ileum [14]. A cationic

***Corresponding Author:** Vijay R. Mahajan**, Email:** vijaymahajan8@gmail.com

emulsion has greater bioavailability than an anionic emulsion [12,13].

The SDLFs are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion.

Potential advantages

Includes,

1. Enhanced oral bioavailability (enabling dose reduction)
2. More consistent temporal profiles of drug absorption
3. Selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut [4,5].

Drawbacks of SEDDS

1. Chemical instabilities of drugs and high surfactant concentrations.
2. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.
3. Moreover, volatile co solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

NEED FOR LIPID BASED FORMULATIONS

Generally, for a drug to show a high affinity and specificity for binding to molecular targets some degree of hydrophobic interactions is required where this hydrophobic interaction is likely to cause solubility constraints. New chemical entities (NCE) are successful as a drug candidate when there are no feasible means to deal with solubility issues. With an increasing number of poorly-water soluble NCE, it is necessary to evaluate and test these molecules to realize their genuine potential. The ability to use a drug delivery enabling technology for poorly-water soluble compounds could potentially have a tremendous impact on moving compounds successfully from discovery, through development and to the patient. In this context, application of lipid based formulations could be used for low aqueous soluble compounds and may ensure the success of the NCE.

"Lipid-based drug delivery systems" cover a wide array of formulation types, from oil solutions, emulsion and dry emulsions to Self-Emulsifying formulations (SEFs) as well as micellar systems. The absorption enhancing properties of lipid-based drug delivery systems are most often attributed to the ability of the vehicles to keep the API in solution in the gastrointestinal (GI) tract, thereby omitting the dissolution step. The absorption of the API will depend upon trafficking between different colloidal phases generated in the intestine. Lipid based drug delivery systems, and in particular self-emulsifying therapeutic systems (SETs), show great potential for enhancing oral bioavailability but have not been broadly applied, largely due to lack of general formulation guidance.

BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed [15,16]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including:

- **Alterations (reduction) in gastric transit**: Thereby slowing delivery to the absorption site and increasing the time available for dissolution.
- **Increases in effective luminal drug solubility:** The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract. However, 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 and a further increase in solubilisation capacity [17].
- **Stimulation of intestinal lymphatic transport:** For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism [18,19,20].
- **Changes in the biochemical barrier function of the GI tract:** It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism [21,22,23].
- **Changes in the physical barrier function of the GI tract:** Various combinations of lipids, lipid digestion products and surfactants have

been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs[24,25].

SELF-EMULSIFYING THERAPEUTIC SYSTEM (SETS)

SETs are pre-concentrates or anhydrous forms of emulsions. These systems are an anhydrous isotropic mixture of oils, surfactant(s) and drug, which when introduced into the aqueous phase under gentle agitation, spontaneously form o/w emulsion (droplet size between 100 and 300 nm) while self-micro emulsifying formulations (SMEFs) form transparent micro-emulsions with a droplet size of less than 50 nm. Formulations based on SETs contain co-emulsifier or co-surfactant and/or solubilizer in order to facilitate emulsification and improvedrug incorporation in SETs. Within the human body, the required agitation is provided by digestive motility of the GI tract (GIT).

SETs are usually formulated as simple emulsions or self-emulsifying formulations (SEFs) making use of surfactants with an HLB value of less than 12. Self-micro-emulsifying formulations (SMEFs) and self-nano emulsifying formulations (SNEFs), on the other hand, are formulated using surfactants with an HLB value of more than 12. These formulations possess high stability and improved dissolution due to enhanced surface area upon dispersion.

Formulation considerations and potential components

A thorough understanding of the spontaneous emulsification process, the physiochemical and biological properties of components used for fabrication of SETs, is essential for formulation of effective SETs. Factors influencing the phenomenon of self-emulsification include:

- The physiological nature and concentration of oily phase, surfactant, co-emulsifier or co-surfactant and solubilizer;
- The ratio of each component, especially oil to surfactant ratio;
- The temperature and pH of the aqueous phase where emulsification would occur;
- Physicochemical properties of the drug, such as hydrophilicity/ lipophilicity, pKa and polarity.

Oil phase

Oil phase has great importance while formulating SEFs, as the physicochemical properties of the oil (e.g. molecular volume, polarity and viscosity) significantly affect the spontaneity of the emulsification process, the droplet size of emulsion (o/w), drug solubility and biological fate of both the emulsion and drug. Oil phase represents one of the most important excipients in SEFs as it solubilizes the lipophilic drug, facilitates self-emulsification, and increases the fraction of lipophilic drug transported through the intestinal lymphatic system. This in turn increases the absorption from the GIT. However, the absorption is dependent upon the molecular nature of the triglyceride.

It is difficult for a single oil component to have optimum properties with respect to emulsification and drug delivery. In certain cases, using a mixture of oils can also be used to attain optimum properties of the oily phase. Vitamin E (D-α-tocopherol) is increasingly being used as an oily phase in SEFs owing to its ability to solubilize drugs that are difficult to solubilize using conventional oil components, for example paclitaxel, itroconazole and saquinavir

Surfactants

The choice of surfactant is critical for the formulation of SEFs. The properties of surfactants such as HLB value, cloud point, viscosity and affinity for oil phase, all have a strong influence on the emulsification process and droplet size. There is a direct relationship between the droplet size and concentration of surfactant being used. Increasing the surfactant concentration may lead to droplets with smaller mean droplet size. This could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand, in a few cases the mean droplet size was found to increase with greater surfactant concentrations . This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by increased surfactant concentration, leading to ejection of oil droplets into the aqueous phase.

Surfactants used in these formulations improve the bioavailability of the drug. This can be attributed to different mechanisms including improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and inhibited P-glycoprotein drug efflux. However, a large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the gastrointestinal tract. However, formulation effect and effect of surfactant concentration on GIT

mucosa should ideally be investigated in each case.

Several compounds exhibiting surfactant properties may be employed for the formulation of self-emulsifying systems. However, the list of such surfactants is limited. The most widely recommended non-ionic surfactants such as polysorbates (e.g., Tween® 80) and polyethylene glycol derivatives (e.g., Cremophor® EL) possess HLB in the 2 to 18 range. These may be used in combination with lipid excipients to promote self-emulsification or micro-emulsification. High HLB value and hydrophilicity are desirable characteristics of the surfactants for an immediate formation of o/w droplets and rapid spreading of the formulation in the aqueous environment.

Co-solvents

Usually an effective SEF requires a high concentration of surfactant. Accordingly, co-solvents such as ethanol, propylene glycol and polyethylene glycol are required to facilitate the dissolution of large quantities of hydrophilic surfactant. These co-solvents sometimes play the role of the cosurfactant in the microemulsion system. On the other hand, alcohol and other volatile co-solvents have the drawback of evaporating into the shell of soft or hard gelatin capsules, leading to precipitation of the drug.

Aqueous phase

The droplet size and stability of W/O emulsion is influenced by the nature of aqueous phase where SETs is designed to be introduced. Hence, the pH and ionic content of aqueous phase is of prime importance when designing SETs. The physiological milieu has a diverse pH range varying from a pH of 1.2 (stomach) to around 7.4 (blood and intestine). In addition to plain water, ringer's solution, simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8) and phosphate buffer saline can be used as aqueous phase to evaluate spontaneous emulsification of SETs.

Drug

It is important to bear in mind that the therapeutic agent of interest can also have a significant impact on the various aspects of SETs, such as phase behavior and emulsion droplet size. Physiochemical properties of the drug, such as log P, pKa, molecular structure and weight, presence of ionizable groups and their quantity all have considerable impact on the performance of SETs.

Evaluation of SMEDDS

1. Visual assessment may provide important information about the self-emulsifying property of the SMEDDS and about the resulting dispersion [6, 8, 9]. Estimation of the increased drug dissolution and absorption from large surface area afforded by the emulsion. Inhibit gastric motility by oil / lipid phase of emulsion allows more time for dissolution and absorption of drug from lipid phase. Fatty acids are distributed between other aqueous solution emulsion droplets and the micelles (formed by bile salt) Monoglycerides along with water insoluble components such as vitamins, lipophillic drugs are moved into the micelles, which diffuse through gut content to intestinal mucosa. Short chain fatty acids along with hydrophilic drug are diffused directly to portal supply, while longer fatty acids are utilized in chylomicron formation. Once monoglycerides along with lipophillic drugs are transported into intestinal mucosa, chylomicron synthesis takes place and are released into lymphatic's efficiency of the self-emulsification can be done by evaluating the rate of emulsification and particle size distribution [10]. Turbidity measurement to identify efficient self-emulsifying can be done to establish whether the dispersion has reached equilibrium rapidly and in reproducible time [6].

2. Droplet polarity and droplet size are important emulsion characteristics. Polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion and concentration of the emulsifier. A combination of small droplets and their appropriate polarity (lower partition coefficient o/w of the drug) permit acceptable rate of release of the drug. Polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophillic drug [6, 7].

3. Size of the emulsion droplet is very important factor in self emulsification / dispersion performance, since it determine the rate and extent of drug release and absorption [6, 9]. The Coulter nanosizer, which automatically performs photon correlation analysis on scattered light, can be used to provide comparative measure of mean particle size for such system. This instrument detects dynamic changes in laser light scattering intensity, which occurs when particle oscillates due to Brownian movement. This technique is used when particle size range is less than 3μm; a size range for a SMEDDS is 10 to 200 nm [6].

4. For sustained release characteristic, dissolution study is carried out for SEMDDS. Drugs known to be insoluble at acidic pH can be made fully available when it is incorporated in SMEDDS [7].

MARKETED FORMULATIONS

The successful commercialization of oral lipid- and surfactant-based formulations of poorly

soluble drugs in the market has encouraged researchers to explore the field further. Sandimmune®, Sandimmune Neoral®, Norvir® (ritonavir), and Fortovase® (saquinavir) have been formulated as SEFs. The Sandimmune® and Sandimmune Neoral® formulations of CsA are perhaps the best known examples of marketed lipid and surfactant based systems and the pharmacokinetic has been studied and reviewed extensively (Ritschel, 1996). When diluted with water, these form a polydispersed oil-in-water macro/microemulsion.

Another formulation marketed as an amorphous, semi-solid dispersion was the hard gelatin capsule of ritonavir (Norvir®). However, unexpected precipitation of amorphous ritonavir as a less soluble crystalline form in the excipient matrix negatively impacted both the drug dissolution rate and bioavailability, leading to a temporary withdrawal of the product from the market in 1998. Norvir® was reintroduced in 1999 after reformulation as a thermodynamically stable solution containing 100 mg of ritonavir solubilized in a self-emulsifying excipient delivered in soft gelatin capsules.

Saquinavir was first introduced in 1996 as a solid oral dosage form (Invirase®) and subsequently, as a self-emulsifying lipid-based formulation in a soft gelatin capsule (Fortovase®) containing 200 mg of saquinavir. In 2006, Fortovase® was removed from the market due to lack of demand. Saquinavir is still available as 200 mg and 500 mg Invirase hard gelatin capsules. Table II lists selected commercially available self-emulsifying formulations along with their characteristics.

CONCLUSION

The majority of new chemical entities and many existing drug molecules are poorly soluble. The oral delivery of poorly soluble drugs from solid oral dosage form continues to encounter significant formulation obstacles, such as decreased bioavailability, increased chances of food effects, incomplete release and high inter-patient variability. Oral SETs are a promising formulation approach to overcome these problems of poorly water soluble drugs.

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