Acta Poloniae Pharmaceutica – Drug Research, Vol. 69 No. 2 pp. 179–191, 2012 ISSN 0001-6837
Polish Pharmaceutical Society

EMULSION FORMING DRUG DELIVERY SYSTEM FOR LIPOPHILIC DRUGS

JYOTI WADHWA*, ANROOP NAIR and RACHNA KUMRIA

M.M. College of Pharmacy, M.M. University, Mullana (Ambala), Haryana, India

Abstract: In the recent years, there is a growing interest in the lipid-based formulations for delivery of lipophilic drugs. Due to their potential as therapeutic agents, preferably these lipid soluble drugs are incorporated into inert lipid carriers such as oils, surfactant dispersions, emulsions, liposomes etc. Among them, emulsion forming drug delivery systems appear to be a unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the BCS class II drugs. Self-emulsifying formulations are ideally isotropic mixtures of oils, surfactants and co-solvents that emulsify to form fine oil in water emulsions when introduced in aqueous media. Fine oil droplets would pass rapidly from stomach and promote wide distribution of drug throughout the GI tract, thereby overcome the slow dissolution step typically observed with solid dosage forms. Recent advances in drug carrier technologies have promulgated the development of novel drug carriers such as control release self-emulsifying pellets, microspheres, tablets, capsules etc. that have boosted the use of "self-emulsification" in drug delivery. This article reviews the different types of formulations and excipients used in emulsion forming drug delivery system to enhance the bioavailability of lipophilic drugs.

Keywords: lipid based formulations, emulsion forming drug delivery system, self-emulsification

The advances in combinatorial chemistry has lead to tremendous increase in the number of poorly water soluble drugs, and currently, more than 40% of new pharmacologically active chemical entities are lipophilic and exhibit poor aqueous solubility. However, the oral delivery of lipophilic drugs presents a significant challenge to pharmaceutical scientists due to their inherent low aqueous solubility, which generally leads to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality (1). Many formulation approaches are presently being employed to tackle the formulation challenges of biopharmaceutical class II (BCS) drugs, either by pre-dissolving the compound in a suitable solvent and subsequently filling the formulation into capsules (2) or by formulating as solid solution using water-soluble polymers (3). Nevertheless, these approaches can probably resolve the issue related to initial dissolution of drug molecules in aqueous environment within the GI tract to certain extent. However, major limitations like drug precipitation during dispersion of formulation in the GI tract or drug crystallization in the polymer matrix remain unresolved. Therefore, in case of such formulations, the assessment of physical stability using techniques such as differential scanning calorimetry or X-ray crystallography is necessary.

Various formulation approaches including carrier technology offer an intelligent approach for enhancing the solubility of poorly soluble drug molecules. Improvement in oral bioavailability of these molecules utilizing lipid based formulations has received much attention in the recent past. Lipids are perhaps one of the most versatile excipient classes currently available, provide the formulator a great potential option for improving and controlling the absorption of lipophilic drugs, where typical formulation approaches failed, or when the drug itself is oil (i.e., Dronabinol, ethyl icosapentate). Moreover, with such formulations, there is lower potential for precipitation of lipophilic drug molecules during dilution in the GI tract, as partitioning kinetics will favor the drug to be remained in the lipid droplets (4).

A review on the literature denotes that the application of carrier technology is not limited to the scientific interest in oral lipid-based formulations but reinforces the promise and versatility in addressing the issues related to oral delivery of several poorly soluble drug molecules. New approaches, such as self-emulsification systems, have also found

* Corresponding author: e-mail: jyotiwadhwa29@gmail.com; phone no.: 091-08059930171

its way in enhancing the solubility of poorly soluble drugs and have several advantages as well. Introduction of this novel concept on self-emulsification and the recent advances in polymer science lead to new applications of self-emulsifying lipid based formulations in several drug delivery aspects including drug targeting. The present article is an attempt to review the potential applications and comprehensive knowledge of emulsion forming drug delivery system (EFDDS) in enhancing the bioavailability of lipophilic drugs by means of various dosage forms. Current developments in the design and development of self-microemulsifying and self-nanoemulsifying formulations have also been highlighted.

SELF-EMULSIFICATION: BASIC CONCEPTS

The mixture of oil, surfactant, co-surfactant, and co-solvents (absence of external phase water) forms a transparent isotropic solution, which emulsify under gentle agitation similar to those which would be encountered in GI tract and is referred as the self-emulsifying formulation (SEF). It has been recognized that this formulation when administered orally undergo spontaneous emulsification in aqueous GI fluids. This emulsified oil (triglycerides) stimulates bile secretion and drug containing oil droplets are further emulsified by bile salts. Lipid droplets are then metabolized by lipases and co-lipases, secreted from the salivary gland, gastric mucosa and pancreas, which also hydrolyze the triglycerides into di- and monoglycerides and free fatty acids. Further, solubilization of these molecules occurs during the passage through the GI tract and eventually forms a range of emulsion droplets, vesicular structures and mixed micelles containing bile salts, phospholipids and cholesterol (5). The chylomicron synthesis takes place into lymphatics which ensures the enhancement of drug absorption. The bioavailability enhancing property of self-emulsifying formulations has been mainly associated with a number of *in vivo* properties including:

- The inhibition of cellular efflux mechanisms, which keep drugs out of the circulation.
- Reduction of first-pass drug metabolism in the liver due to association of certain lipidic excipients with selective drug uptake into the lymphatic transport system.
- The formation of fine dispersions and micellar suspensions to prevent precipitation and recrystallization of the drug compound.
- The ability of certain lipid compounds and their metabolites to initiate changes in the GI fluid in favor of improved drug absorption (6).

EFDDS are usually formulated as simple emulsions, however, SEFs are prepared using surfactants of HLB < 12 while self-microemulsifying formulations (SMEFs) and self-nanoemulsifying formulations (SNEFs) with surfactants of HLB > 12. These formulations possess high stability and improved dissolution (for poorly soluble drugs) due to enhancement in surface area on dispersion.

Table 1. Comparative features of all self emulsifying formulations.

Self-emulsifying formulations (SEFs)	Self-microemulsifying formulations (SMEFs)	Self-nanoemulsifying formulations (SNEFs)
Isotropic mixture of the drug compound, surfactant, cosurfactant and lipid phase which emulsify under conditions of gentle agitation, when come in contact with gastro-intestinal fluid.		
• Oil droplet size in the dispersion ranges from 200 nm to 5 μm. • Appearance of dispersion is turbid. • Formulations formed using surfactants of HLB < 12.	• Oil droplet size in the dispersion is less than 200 nm. • Appearance of dispersion is optically clear to translucent. • Formulations formed using surfactants of HLB > 12.	• Oil droplet size in the dispersion ranges from less than 100 nm (small polydispersity index). • Appearance of dispersion is optically clear. • Formulations formed using surfactants of HLB > 12.
All these formulations have high solubilizing and dispersibility capacity		
• Thermodynamically stable in physiological conditions. • Development may require characterization of ternary phase diagram.	• Thermodynamically stable in physiological conditions. • Development may require characterization of pseudo ternary phase diagram.	• No phase separation during storage. • Development may require characterization of pseudo ternary phase diagram.

Therefore, their absorption is independent of bile secretion and ensures a rapid transport of poorly soluble drugs into the blood. Further, these preparations have few distinct features associated with improved drug delivery properties. The comparative features of reported systems are illustrated in Table 1.

EXCIPIENTS FOR SELF-EMULSIFYING FORMULATIONS

Studies have revealed that self-emulsification process is highly specific to the nature of the oil/surfactant pair used; surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self-emulsifying therapeutic systems. Various major components used in the EFDDS are discussed below:

Oils

Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-microemulsification markedly reduces their use in SEFs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEFs owing to their biocompatibility. Natural di- and triglycerides are widely used excipients susceptible to degradation (major pathway to release the drug component from EFDDS based formulations). Recently, medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as Gelucire (Gattefosse Corporation, Westwood, N.J.). These excipients form good emulsification systems due to their potential for higher fluidity, better solubilizing potential and self-emulsification ability. Digestible or non- digestible oils and fats such as olive oil, corn oil, soyabean oil, palm oil and animal fats could be used as oil phases in EFDDS (7).

Surfactants

Screening of the surfactants can be empirically done according to its hydrophilic lipophilic balance, as well as the critical packing parameter. Non-ionic surfactants are frequently selected for fabrication of EFDDS due to their lower toxicity and typically possess low critical micelle concentration, compared to their ionic counterparts (8). Surfactants with high HLB value are generally used in the formulation of EFDDS including: Gelucire (HLB 10), polysorbate 80, sorbitan monooleate (Span 80), poloxamers, cremophor EL, sodium lauryl sulfate and hexadecyltrimethylammonium bromide and bis-2-ethylhexyl sulfosuccinate. Moreover, fatty alcohols such as lauryl, cetyl and stearyl, glyceryl and fatty acid esters are employed among the most well-known surfactants (9).

Naturally occurring surfactants are also recommended for SEFs; among them lecithin is most commonly employed due to its excellent biocompatibility. Its major component is phosphatidylcholine, which has an amphiphilic structure and has low solubility in water. To obtain stable SEFs, the surfactant concentration generally utilized is in the range of 30 to 60% w/w. However, one should remember that the usage of greater amount of surfactant concentration (~60%) may likely cause moderate reversible changes in intestinal wall permeability or irritation of GI tract.

The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self-emulsifying performance. The surface active agents are amphiphilic by nature, and they are therefore usually able to dissolve and even solubilize relatively greater amount of hydrophobic drug. The later is of prime importance for preventing precipitation within the GI lumen and for prolonged existence of drug molecules in soluble form, which is vital for effective absorption (10).

Recent investigations indicated that the digestion of surfactants has an impact on the performance of SEFs due to change in solubilization environment, which in due course causes precipitation of poorly water-soluble drugs (11–13). In addition, very little is known about the formation of degradation products of surfactants and their interactions with fatty acids and endogenous lipids like bile salts, phospholipids and dietary lipids. This might play an important role in maintaining the poorly water-soluble drug in solution and the requisite building of mixed micelles might be compromised (13).

Taking into account all these findings it is apparent that knowledge of possible inhibitory effects of non-ionic surfactants on triglyceride digestion is crucial for the rational development of lipid-based formulations. Moreover, the susceptibility of the surfactants themselves towards degradation by pancreatic enzymes is a crucial factor to be considered during formulation development.

Co-surfactants/Co-solvents

For a formulation to be self-emulsifying, a co-surfactant is often included in the formulation to

Table 2. Applications of formulations included in emulsion forming drug delivery system.

Dosage forms	Drug(s)	Oil	Surfactant(s)	Co-surfactant/ cosolvent	Inference/Application
Tablet	Diclofenac	Goat fat	Tween 65	-	Batches with higher Tween 65: goat fat content ratios yielded better release rates (16).
	CoQ10	Lemon oil	Cremophor EL	Capmul MCM-C8	Cumulative percent of CoQ10 released within 8 h ranged from 40.6% to 90% (17).
Powder	Griseofulvin	Castor oil	Capmul GMO-50,	Myvacet 9-45	The mean AUC and *C*max after oral administration of GRIS-PEG formulation in rats were 1.28 and 1.15 fold higher, respectively, compared to SEFS (20).
	Dexibuprofen	Transcutol P, Labrasol	Labrafac CC	Capryol 90	AUC of solid SEFS was about two fold higher than that of dexibuprofen powder (21).
	Vitamin E	Palm oil	Tween	Span	AUC: SEFS > soft gelatin capsule (50).
	Halofantrine	Soybean oil: Maisine	Cremophor EL	Absolute ethanol	The self emulsifying formulations of halofantrine improved the oral bioavailability significantly (~6–8 fold) relative to previous data of the solid halofantrine HCl tablet formulation (51).
Pellets	Nimesulide	Mono- and di-glycerides	Polysorbate 80	-	Bioavailability: Pellets > Emulsions (23).
	Diazepam	C18 mono and di-glycerides	Solutol HS15	-	Significant improvement in the *in vitro* dissolution of diazepam compared to the release from the non-emulsifying formulation (25).
	Progesterone	Captex 355, Capmul MCM	Solutol HS 15	-	Solubilization capacity strongly depends on the concentration of endogenously secreted materials such as bile salts and phospholipids (37).
	Nitrendipine (NTD)	Miglyol 812	Cremophor RH40 and Tween 80 (2:1)	Transcutol P	AUC of NTD of SE pellets showed 1.6-fold greater than the conventional tablets and were comparable with the liquid SEFs (39).
	Silymarin	Miglyol 812	Tween 80	Propylene glycol	Phytotherapic extract (silymarin) in self emulsifying pellets enhance the oral bioavailability of its main active compounds (52).
	Piroxicam	Lauroglycol 90	Cremophor EL	Transcutol HP	Piroxicam release was significantly enhanced with respect to pure drug (53).
Controlled release self emulsifying pellets	Methyl and Propyl Paraben	Mono- and diglycerides of capric and caprylic acids	Tween 80	Ethanol and glycerol	Water-soluble polymer can refine the control of the *in vitro* release of drug from such pellets (27).
	Vinpocetine	Peanut oil, mono- and di-glycerides	Croscarmellose sodium, Microcrystalline cellulose	Polysorbate 80	Bi-layered pellets resulted in plasma levels 2.4 fold higher than the physical mixture (28).
	Compritol and Precirol	Mono- and di-glycerides	Glyceryl palmito-stearate	Glyceryl behenate	The lipophilic binders may exhibit a relatively complex behavior, i.e., melting and crystallization, polymorphism, physical modifications (54).

Table 2. cont.

Dosage forms	Drug(s)	Oil	Surfactant(s)	Co-surfactant/ cosolvent	Inference/Application
Beads	Loratadine	Captex 200	Cremophore EL	Capmul MCM	PPB are potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required for the solid form (55)
SMEFs	Cyclosporine	Hydrogenated castor oil, medium chain triglycerides	Polyethylene glycol	Sucrose monolaurate	Solid micellar solution exhibited significant higher C_{max} bioavailability (141% and 139%vof Sandimmune, respectively) (31).
	Itraconazole	Tocopherol acetate	Pluronic L64	Transcutol	Greatly enhanced bioavailability of itraconazole.
	Acyclovir	Sunflower oil	Tween 60	Glycerol	SMEFs increased the oral bioavailability of acyclovir by 3.5-fold compared with the pure drug solution (33).
	Exemestane	Capryol 90	Cremophore ELP	Transcutol	The relative bioavailability of exemestane of SMEFs was enhanced by 2.9 fold (56).
	Itraconazole	———	Cremophor®, HCO®-50	Phosphoric acid, transcutol, ethanol	AUC 0–24 and *C*max after oral administration of the solid SMEFs were 1.9 and 2.5 fold higher in the fasted state and 1.5 and 1.3 fold higher in the fed state, respectively, than those of the Sporanox capsule (57).
	Curcumin	Ethyl oleate	Cremorphor EL, Poloxamer 188	Propylene glycol 400, Tween 80	Solubility: SMEFs > curcumin suspension. The solubility of curcumin in SMEFs was found 21 mg/g (58).
	Nimodipine	Ethyl oleate	Labrasol, Cremophor RH 40	———	AUC and Cmax after oral administration of the solid SMEFs were 2.6 and 6.6 fold higher, respectively, compared with those of the conventional tablet (59).
	Furosemide	Myglyol 812	Caprylocaproyl macrogolglycerides, Labrasol®	polyglyceryl-6 dioleate Plurol Oleique®	Self-microemulsifying cores with completely solubilized drug (SMEFs with 1 and 5% furosemide) exhibited the fastest release profiles with pronounced initial release (44).
	Curcumin	Labrafac PG and Capryol 90	Cremophor EL and Labrasol	Propylene glycol, and polyethylene glycol 400	Bioavailability of curcumin from liquid SMEFs and SMEFs pellets was about 16-fold higher than that of unformulated curcumin (60).
	Ligusticum chuanxiong oil (VOC)	Chuanxiong oil	Tween 80	Propylene glycol	The absorption rate of VOC-SMEFs capsules was 2.53 and 1.59 times higher than that of VOC and VOC/β-cyclodextrin inclusion (β-CD), and the percent absorption was 1.55 and 28.19 times higher than that of VOC and VOC/β-CD, respectively (61).
	Coenzyme Q10 (CoQ10)	Lemon oil,	Cremophor EL	Capmul MCM-C8	The extent of dissolution for the samples stored at 40°C/75% RH was comparable (14).
	Ezetimibe	Capryol 90	Cremophor EL	Lauroglycol 9	The SNGs filled into hard gelatin capsules showed 2–3 fold increase in the dissolution rate as compared to plain drug filled capsules (63).

Table 2. cont.

Dosage forms	Drug(s)	Oil	Surfactant(s)	Co-surfactant/ cosolvent	Inference/Application
SNEFs	Cyclosporine A	Phospholipids	Chremophor RH 40,	Tween 80, Span 80	Higher AUC and Cmax with lipospheres with small diameter (45).
	Probucol	Sesame oil	Cremophor RH40	Ethanol	The bioavailability from the surfactant solution and the oil solution were slightly lower compared to the self-nanoemulsifying drug delivery system (62).
	Coenzyme Q10 (CoQ10)	Witepsol H35	Solutol HS15	Lauroglycol	Result observed from SNEDDS *vs.* reported SEFS were AUC (4.6 fold *vs.* 2.4 fold), Cmax (5.5 fold *vs.* 1.7 fold) and reduction in Tmax (2.0 fold) (46).
	Coenzyme Q10 (CoQ10)	Lemon oil	Cremophor EL	Capmul MCM-C8	The extent of dissolution for the samples stored at 40ºC/75% RH was comparable (14).
	Ezetimibe	Capryol 90	Cremophor EL	Lauroglycol 9	The SNGs filled into hard gelatin capsules showed 2–3 fold increase in the dissolution rate as compared to plain drug filled capsules (63).
Super saturable SEFs	Paclitaxel	Glyceryl dioleate, Cremophor EL	Cremophor EL	Ethanol, PEG 400	The paclitaxel S-SEFS formulation shows 10 fold higher Cmax and 5 fold higher oral bioavailability compared to orally dosed Taxol formulation (48).

increase dispersion entropy, interfacial area and to reduce the interfacial tension and free energy to a minimum (8). Owing to its amphiphilic nature, a co-surfactant accumulates substantially at the interfacial layer, increasing the fluidity of interfacial film by penetrating into the surfactant monolayer. Co-surfactants are preferably short and medium-chain alcohols such as octanol, pentanol and hexanol etc., which are known to formulate the spontaneous self-emulsifying formulation.

Besides co-surfactants, some of the co-solvents such as triacetin (an acetylated derivative of glycerol), transcutol (diethylene glycol monoethylene ether), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, glycofurol (tetrahydrofurfuryl alcohol polyethylene glycol ether), etc. are suitable for dissolving of hydrophobic drug in the lipid base. Recently, polyglycolyzed glycerides (PGG) with varying fatty acid and polyethylene glycol (PEG) in combination with vegetable oils have been used for emulsification and solubilization of hydrophobic drugs (7).

PHARMACEUTICAL APPLICATIONS

Most of the investigations described so far have evaluated the pharmacokinetics of the drug in SEFs and very few investigations have demonstrated pharmacodynamic efficacy. Although pharmacokinetic studies are sufficient to establish the proof of concept for SEFs, the result of the investigation should be preferably corroborated by pharmacodynamic studies. This is particularly important for drugs such as simvastatin, atorvastatin and ezetimibe, which do not show pharmacokinetic-pharmacodynamic correlation. Although the potential of SEFs in improving oral bioavailability of lipophilic drugs has been established, an increase in the drug bioavailability needs not be translated into an increase in the pharmacodynamic effects of these drugs. Such aspects should be carefully considered while planning investigations on the SEFs. The key investigations that describe the potential of SEFs in oral drug delivery are listed in Table 2 and some of them have been discussed in the subsequent sections (14, 15).

Self-emulsifying tablets

Incorporation of lipid formulation into a solid dosage form combines the advantages of both lipid-based drug delivery systems with those of a solid dosage form, which can preferably overcomes several shortcomings of liquid formulations. Attama et al. formulated the solid self-emulsifying formulation

using goat fat and Tween for the delivery of diclofenac (16). The fatty material and surfactant were melted together and the drug was incorporated. This molten mass was then poured into plastic mould and cooled. During the processing of this formulation the authors observed that the agitation during fabrication of tablets reduced the liquification time, resulting in faster emulsification. The results demonstrated that different formulation ratios possess varying dissolution profiles at constant speed/agitation and the optimized formulation showed good release profiles with acceptable tablet properties.

Nazzal and Khan have evaluated the effect of some processing parameters (colloidal silicates – X1, magnesium stearate mixing time X2, and compression force X3) on coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEFs. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face-centered cubic design (17). Further, gelled SEFs have been developed to reduce the amount of solidifying excipients required for transformation of SEFs into solid dosage forms. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in reduced drug release (18).

SE tablets are of great use in avoiding adverse effects such as GI bleeding, as described by Schwarz in a clinical application. Incorporation of indomethacin (or other hydrophobic NSAID), for example, in SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. In this study, the SES was composed of glycerol monolaurate and TyloxapolTM (a copolymer of alkyl phenol and formaldehyde). The resultant SE tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time period compared with a non-emulsifying tablet (19).

Self-emulsifying powder formulation

To promote the bioavailability of griseofulvin (poor aqueous solubility), Capmul GMO-50, poloxamer, Myvacet were used as the lipophilic phase of the dry powder formulation. The results indicated that given formulation significantly enhanced the dissolution and bioavailability of griseofulvin (20).

Most recently, novel solid SEFs of dexibuprofen have been prepared using Aerosil 200 as a water-soluble solid carrier. Both *in vitro*/*in vivo* studies were carried out to characterize the prepared formulation and the optimization of SEF composition was carried out by assessing solubility, phase diagram, particle size, drug release studies etc. This research demonstrated that Labrafil M 1944 CS, Labrafil M 2125, Labrasol, Capryol 90 and Lauroglycol FCC had optimum solubility of dexibuprofen to formulate a self-emulsifying powder formulation with desired drug loading (21).

Self-emulsifying pellets

Pellets, as a multiple unit dosage form, have not only proven their utility for mitigating the poor and variable GI absorption of poorly soluble drugs, but also have shown the ability to reduce or eliminate the influence of food on bioavailability. Thus, it seems very appealing to combine the advantages of pellets with those of EFDDS by formulating SE pellets. Kang et al. has reported considerable differences in the solubility of simvastatin using a range of surfactants. The authors suggest that the properties of surfactants need to be considered while identifying and selecting for the formulation of self-emulsifying pellets (22).

There is another report which demonstrats the successful formulation of self-emulsifying pellets using oil (mono and diglycerides) and polysorbate 80 with varying concentration of nimesulide. The pellets were prepared by initially mixing the oil, surfactant and added to water. The prepared binder solutions were sprayed on the granules (prepared from microcrystalline cellulose (MCC) and lactose) to obtain the pellets. The *in vivo* studies have indicated a greater bioavailability with the prepared pellets compared to corresponding emulsions (23).

Tuleu et al. (24) presented comparative bioavailability study of a self-emulsifying pellet formulation of progesterone with an aqueous suspension in dogs. The results indicate the complete drug release from capsules and self-emulsifying system within 30 min and 5 min, respectively. However, in case of aqueous suspension, the drug release was very low (~50% of the dose in 60 min). Indeed, the plasma drug concentration was significantly higher when the drug was orally administered from self-emulsifying pellets and self-emulsifying solution, compared to aqueous suspension at similar dose (24).

In another attempt, three self-emulsifying pellet formulations were prepared by melting Cithrol GMS (mono and diglycerides) and solutol HS 15. To this molten blend, the drug (diazepam), dry MCC was added to obtain a suitable mass for extrusion. A dye was incorporated for assessment of self-emulsification and spin probe was added for assessing release kinetics and microenvironment of pellets. The dissolution profile indicated a rapid and complete release of drug from the non self-emulsifying GMS/MCC pellets. Nearly 90% of the drug was

released within an hour, while only 55% was released from the GMS/MCC pellets (25).

Wang et al. (26) demonstrated that the extrusion/spheronization technique is a large-scale production method to prepare solid SE pellets from the liquid SEFS and to improve oral absorption. The authors prepared the liquid self-emulsifying (SE) pellets of hydrophobic drug (nitrendipine) to improve the formulation stability and solubilization capacity and the system was optimized based on equilibrium solubility, pseudo-ternary phase diagram and supersaturation studies. Further, the liquid SEFs were solidified with adsorbents (porous silicon dioxide and crospovidone), MCC and lactose to form powder with fine flowability. The AUC of nitrendipine from the SE pellets showed ~2 fold greater than the conventional tablets and were comparable with the liquid SEFs (26).

The above studies indicated that the self-emulsifying pellets can be prepared by several approaches; possess higher stability and potential to enhance the solubility, higher dissolution rate and bioavailability of several hydrophobic drugs.

Controlled release self-emulsifying pellets

Serratoni et al. (27) have observed that the release of methyl and propyl parabens from pellet formulations could be controlled by incorporating into self-emulsifying systems, containing water soluble plasticizer and talc. Formulations were prepared by mixing oil and surfactant. The prepared mixture was mixed with damp mass of MCC and lactose monohydrate and water, and then added to the prepared wet mass for extrusion-spheronization to obtain pellets. These pellets were initially coated with hydrophilic polymers (ethylcellulose) and subsequently by aqueous solution of hydroxypropylmethylcellulose in a fluid bed coater. Results obtained from *in vitro* study reveal that the presence of self-emulsifying system enhanced drug release of both model drugs, while the film coating considerably reduced the drug release from pellets made with just water, lactose and MCC (27).

In another study (28), two types of bi-layered pellets containing vinpocetine (model drug) were prepared and evaluated: type I with the self-emulsifying system internally and the inert matrix externally, whereas in type II formulation the internal and external materials were reversed. Formulation were prepared in two steps, in the first step the oil-surfactant mixture was added to water to form self-emulsifying systems and in the next stage this mixture was loaded into MCC and lactose to form extrusion-spheronization mass for pellets. Results reveal that type I pellets release 90% of vinpocetine within 30 min while the same quantity was released within 20 min from type II pellets. However, the physical mixture could release ~25% of drug in 60 min. Although both types of pellets demonstrated adequate morphological and technological characteristics, pellets type II revealed an improved drug solubility and *in vivo* bioavailability. These investigations proved that the development by co-extrusion/spheronization of a solid dosage form containing a self-emulsifying system is a promising approach for the formulation of drug compounds with poor aqueous solubility (28).

Self-emulsifying beads

In an attempt, Patil and Paradkar formulated an isotropic formulation of loratadine, consisted of Captex 200, Cremophore EL and Capmul MCM. SES was loaded to polypropylene beads (PPB) using solvent evaporation method. Formulations were optimized for loading efficiency and *in vitro* drug release by evaluating their geometrical features like bead size and pores architecture. Results indicate that the polypropylene beads are potential carriers for solidification of SES, with sufficiently high SES of PPB ratios required for the solid form. The resuls also signified that the self-emulsifying beads can be formulated as a solid dosage form with minimum amount of solidifying agents (29).

Self-emulsifying microemulsion

Trull et al. examined the absorption of cyclosporine from Sandimmune Neoral [cyclosporine A (CsA), Novartis] and Sandimmune formulations in liver transplanted patients with external biliary diversion *via* a T-tube placed in the bile duct. The observed inverse correlation between the volume of bile drainage and cyclosporine absorption from Sandimmune Neoral, and the negligible absorption from the crude emulsion, indicated that the absorption of cyclosporine was less dependent on bile levels in the intestine when administered as the self-microemulsion formulation (30).

Drewe et al. (31) investigated the absorption of cyclosporine A from three experimental formulations using Sandimmune as reference in fasting healthy volunteers. Two of the experimental formulations were microemulsions with relatively fast and slow *in vitro* release. The microemulsions were formulated using polyethylene glycol, hydrogenated castor oil, medium chain triglycerides and low molecular weight glycols. The formulation was a solid micellar solution with fast *in vitro* release composed of sucrose monolaurate and propylene glycol. The fast releasing microemulsion and the fast releas-

ing solid micellar solution exhibited significantly higher C_{max} (141% and 139% of Sandimmune, respectively), however; the slow releasing microemulsion was equivalent to Sandimmune with respect to C_{max} and bioavailability (31).

To examine the influence of bile salts and mucin layers on the permeability of ibuprofen, self-emulsifying microemulsion formulation were designed and evaluated in isolated intestinal membrane of rat using chamber method. The authors observed that microemulsion is released in mucin layer without mixed micelle formation by bile, thereafter the drug permeates the intestinal membrane (32).

Self-emulsifying formulation of itraconazole has been formulated by Hong et al. (33) using Transcutol, Pluronic L64 and tocopherol acetate. The AUC and C_{max} after oral administration of SEFs in rats were found to be 3.7- and 2.8-folds higher, respectively, compared with those of Sporanox. From this observation it can be concluded that the self-emulsifying formulation could be useful for drugs which show much higher absorption and least affected by food intake. They also abolish the requirement of bile salts for SEFs that formed microemulsion in the stomach, because the formulation was sufficiently solubilized by itself (33).

Self-emulsifying sustained-release microspheres

Zedoary turmeric oil (a traditional Chinese medicine) exhibits potent pharmacological actions including tumor suppression, and antibacterial, and antithrombotic activity. You et al. prepared solid SE sustained-release microspheres of zedoary turmeric oil (oil phase) using the quasi-emulsion-solvent-diffusion method involving spherical crystallization. The zedoary turmeric oil release behavior of the formulation was controlled by altering the ratio of hydroxypropylmethylcellulose acetate succinate to Aerosil 200. The plasma concentration time-profiles after oral administration to rabbits showed a bioavailability of 135.6% compared with the conventional liquid SEDDS (34).

Self-emulsifying implants

Research into SE implants has greatly increased the use and application of solid self-emulsifying drug delivery system (S-SEDDS). For instance, 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. Its effectiveness was hindered by its short half life. In order to enhance its stability, SES was formulated with tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolyzed glyceride). Then, the self-emulsified BCNU was fabricated into wafers with a flat and smooth surface by compression moulding. The release profile was compared with a wafer implant fabricated with poly(d,l-lactide-co-glycolide). The results indicate that the SES increased the *in vitro* half-life of BCNU up to 130 min compared with 45 min with intact BCNU. The *in vitro* release of BCNU from SE PLGA wafers was prolonged up to 7 days and likely to have higher *in vitro* anti-tumor activity and were less susceptible to hydrolysis than wafers without SES (35).

Self-microemulsifying formulations

Self-microemulsifying formulations (SMEFs) have attracted a lot of attention in recent days. In an attempt to combine the advantages of SMEFs with those of solid dosage forms and overcome the shortcomings of liquid formulations, increasing attention has been focused on solid self-(micro)emulsifying formulations. Their thermotropic stability and the high drug loading efficiency make them a promising system for low aqueous soluble drugs giving particles with small size (36). SMEFs are usually filled in soft gelatin capsules, but can also be transformed into granules, pellets, powders for dry filled capsules or tablet preparations (17, 27, 37, 38). Cyclosporine A has been commercially available as Neoral®, that triggers much more attention. Many poorly water-soluble drugs such as acyclovir, asarone, atorvastatin, and fenofibrate have been reported to improve their oral bioavailability by formulating into SMEDDS (39–41).

Postolache et al. compared the bioavailability of a non-self-microemulsifying formulation of cyclosporine, which is semisolid opaque oily suspension with SMEFs. The results showed that the non-self microemulsifying formulation was bioinequivalent with the SMEFs. They observed its significantly low absorption and demonstrated that *in vivo* the non-self-microemulsifying capsules are not totally interchangeable compared with the self-microemulsifying capsules (42).

Catarzi et al. (43) reported the comparative impact of Transcutol and Neusilin® US2 on self-microemulsifying formulation. Formulation was prepared by continuous stirring of Tween 20 and Labrafac Hydro WL (oil phase) and then added distilled water to Glyburide solubilized in Transcutol (43). They found that the Neusilin-SMEDDS formulation results in hard tablets with low tablet weight, due to Neusilin®'s physical characteristics. Moreover, Neusilin® SMEDDS tablets had similar disintegration times compared to Aeroperl®. The dissolution profile obtained from the tablets showed

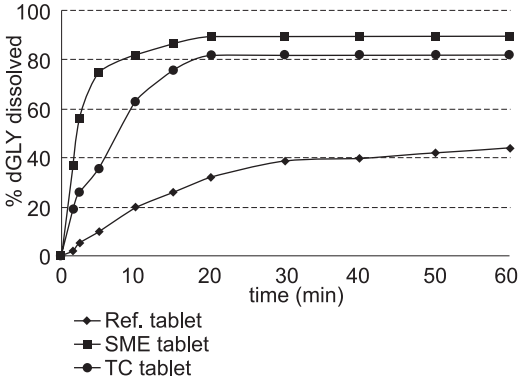

Figure 1. Glyburide (GLY) dissolution profile from the different tablet formulations.
(Ref. tablet – commercial GLY formulation; SME tablet – Glyburide SME formulation consisting of Labrafac Hydro® as oil phase, Tween 20 as surfactant and Transcutol® as co-surfactant; TC tablet – Glyburide formulation consisting of Transcutol (TC)

improved profile when compared to Glyburide alone, as shown in given Fig.1.

Reports also suggests that self-microemulsifying formulations having composition similar to microcapsules with Ca-pectinate shell would be a potential approach to enhance permeability and solubility of BCS class II drugs (44).

Self-nanoemulsifying formulations

The classical lipid nanoparticles that have been proposed for drug delivery are composed of solid lipids. A distinct advantage of self-nanoemulsifying formulations (SNEFs) over polymeric nanoparticles is the former being formulated with lipid matrix, made from physiologically tolerated lipid components, which decrease acute and chronic toxicity.

Nazzal et al. developed self-nanoemulsified tablet dosage form of ubiquinone to optimize the effect of formulation ingredients on the release rate of drug. Ubiquinone nanoemulsion was adsorbed by granular materials and then compressed to tablets. They found that 80–90% drug release took place in 45 min from the optimized formulation (14).

In an approach, Bekerman developed cyclosporine lipid nanoparticles (lipospheres) consisted of phospholipids, Span 80, Tween 80, Tricaprin, and Cremophor RH 40. The cyclosporin dispersions systems prepared have particle size range of 25 nm to 400 nm and the maximum oral bioavailability was observed for particles with low size (25 nm diameter) (45).

Nepal et al. found that the surfactant–cosurfactant blend (Witepsol® H35 and Solutol® HS15, 1:4) brought sufficient reduction in free energy of the system to resist thermodynamic instability of the nanoemulsion as well as provided sufficient mechanical barrier to coalescence of oil droplets (46).

Recently, Koynova suggested that nanosized self-emulsifying lipid vesicles for the inclusion of lipophilic dietary supplements can be a good alternative to avoid the problems associated with the liposome preparations such as colloidal instability, sterilization, and non-reproducibility between batches (47).

Supersaturable self-emulsifying formulation

Supersaturation represents a potent means to enhance absorption, by generating and maintaining a supersaturated state in the intestine. Such formulations contain reduced amount of surfactant(s) and polymeric precipitation inhibitor (e.g., water-soluble cellulosic polymers, such as HPMC), and maintain a supersaturated state of the drug in the body. Literature suggests that directly supersaturating a system with a drug during manufacture adds a risk of recrystallization of the product. Various ways to inhibit recrystallization have been identified and used. Among these, thermodynamic "freezing" inside a polymer is one possibility: at storage conditions, the drug is mobilized by thermodynamic changes in the polymeric structure. To avoid risk of direct supersaturation, the following strategies can be employed:

- Evaporation of a drug solvent from the system.
- Activation of thermodynamically "frozen" drug-supersaturated islands by hydration.

A complete knowledge of these processes, especially in multi component formulations, is worthy of further intensified research. Recently, Ping Gao investigated the mechanism responsible for the enhanced intestinal absorption of hydrophobic drugs from S-SEFs formulations containing hydroxypropylmethylcellulose. The authors suggest that it is probably due to enhanced permeation of drug to the enterocyte brush border region through aqueous pathway by mimicking, or equilibrating with, the bile acid /bile acid mixed micelle pathway (48).

MARKETED FORMULATIONS

The turning point for development of the oral lipid and surfactant based formulations of poorly soluble drugs was the introduction to the market of several drug products intended for oral administration, utilizing lipid and surfactant based formulations. Sandimmune®, Sandimmune Neoral®, Norvir® (ritonavir), and Fortovase® (saquinavir) have been formulated as self-emulsifying formulations (SEFs).

Table 3. List of selected commercially available lipid-based formulations for oral administration.

Drug	Trade name/ Company	Type of formulation	Excipients	**Indication**
Cyclosporin A	Neoral (Novartis)	Soft gelatin capsule	di-α-tocopherol, corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil, (cremophor RH40)	Immuno-suppressant
	Sandimmune (Novartis)	Soft gelatin capsule	Corn oil, polyoxyglycerol ethylated linoleic glycerides (Labrafil M-2125CS)	
	Gengraf (Abbott)	Hard gelatin capsule	Polyethylene glycol NF, polyoxyl 35 castor oil NF, propylene glycol, polysorbiton 80	
Ritonavir	Norvir (Abbott)	Soft gelatin capsule	Oleic acid, BHT, ethanol, polyoxyl 35, castor oil	HIV antiviral
Sanquinavir	Fortovase (Roche)	Soft gelatin capsule	Medium-chain povidone, mono-diglycerides, dl-α-tocopherol	HIV antiviral
Lopinavir and Ritonavir	Kaletra (Abbott)	Soft gelatin capsule	Acesulfame potassium, alcohol, citric acid, glycerin, high fructose corn syrup, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol.	HIV-1 antiviral
Tipranavir	Aptivus (Boehringer Ingelheim)	Soft gelatin capsule	alcohol, polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.	HIV-1 antiviral
Amprenavir	Agenerase (GlaxoSmithKline)	Soft gelatin capsule	(+)-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400, and propylene glycol	HIV antiviral
Valproic acid	Convulex (Pharmacia)	Soft gelatin capsule	Cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch)	Antiepileptic
Bexarotene	Targretin (Ligand)	Soft gelatin capsule	Polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF	Antineoplastic
Calcitriol	Rocaltrol (Roche)	Soft gelatin capsule	Fractionated triglyceride of coconut oil, parabens (methyl and propyl) and sorbitol	Calcium regulator
Tretinoin	Vesanoid (Roche)	Soft gelatin capsule	soybean oil, butylated hydroxyanisole, edetate disodium, methylparaben, propylparaben	Acute promyelocytic leukemia

The Sandimmune and Sandimmune Neoral formulations of CsA are perhaps the best known examples of a marketed lipid and surfactant based systems and the pharmacokinetic has been studied and reviewed extensively (49). This formulation disperses, when diluted with water, into a polydisperse oil-in-water macroemulsion. In 1994, a new self-microemulsifying formulation (Sandimmune Neoral), referred as Neoral, was introduced, which emulsifies spontaneously into a microemulsion with a particle size smaller than 100 nm.

Another formulation marketed as an amorphous, semi-solid dispersion was 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 excipients 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. However, in 2006, Fortovase was removed from the market due to lack of demand; however, saquinavir is still available as 200 mg and 500 mg Invirase hard gelatin capsules. Table 3 enlists selected commercially available self-emulsifying formulations along with their characteristics.

CONCLUSIONS

Emulsion forming drug delivery system is certainly a revolutionary and promising approach to be used as effective drug delivery vehicles for wide range of drugs. This review indicates the significance of EFDDS as a promising formulation approach to overcome the problems of low bioavailability associated with poorly water soluble drugs. Extensive research in this field have produced several formulations, which are available in the market. A wide description about the formulation excipients, formulation techniques adopted, significance of various controlled release formulations etc. are incorporated in this review. The overall conclusion from this review suggests that the solid SEFs has the flexibility to develop into different solid dosage forms for oral and parentral route. Further, the efficiency of these systems is rather case-specific and is dependent on the composition of the formulation used. Developmental efforts and innovative formulation strategies have enabled a high degree of functional integration into a simplified system construction. More formulations with better clinical efficiency are anticipated.

REFERENCES

1. Stegemanna S., Leveillerb F.: Eur. J. Pharm. Sci. 31, 249 (2007).
2. Cole E.T., Cade D., Benameur H.: Adv. Drug Deliv. Rev. 60, 747 (2008).
3. Fatouros D.G., Mullertz A.: Expert Opin Drug Metab Toxicol. 4, 65 (2008).
4. Jie S., Minjie S., Qineng P., Zhi Y., Wen I.: Nanotechnology 21, 100 (2009).
5. Porter C.J., Charman W.N.: Adv. Drug Deliv. Rev. 50, 127 (2001).
6. Porter C.J., Trevaskis N.L., Charman W.N.: Nat. Rev. Drug Discov. 6, 231 (2007).
7. Bose S., Kulkarni P.K.: Indian. J. Pharm. Educ. 36, 184 (2002)
8. Shafiq S., Shakeel F., Talegaonkar S., Ahmad F.J., Khar R.K., Ali M.: Eur. J. Pharm. Biopharm. 66, 227 (2007).
9. Larsen A., Jannin V., Mullertz A.: Pharmaceutical surfactants in biorelevant media: impact on lipolysis and solubility of a poorly soluble model compound: Danazol. Proceedings 5th World Meeting in Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, March 27–30; Geneva, Switzerland. 2006.
10. Farah N., Laforet J.P., Denis J.: Pharm. Res. 11, 202 (1994).
11. Cuiné J.F., Charman W., Pouton C., Edwards G.A., Porter C.J.H.: Pharm. Res. 24, 748 (2007).
12. Cuiné J.F., Mcevoy C.L., Charman W.N., Pouton C.W., Edwards G.A., Benameur H., Porter C.J.H.: J. Pharm. Sci. 97, 995 (2008).
13. Fernandez S., Chevrier S., Ritter N., Mahler B., Demarne F., Carrière F., Jannin V.: Pharm. Res. 26, 1901 (2009).
14. Nazzal S., Smalyukh I.I., Lavrentovich O.D., Khan M.A.: Int. J. Pharm. 235, 247 (2002).
15. Newton J.M., Pinto M.R., Podczeck, F.: Eur. J. Pharm. Sci. 30, 333 (2007).
16. Attama A.A.: Int. J. Pharm. 262, 23 (2003).
17. Nazzal S., Khan M.A.: Int. J. Pharm. 315, 110 (2006).
18. Patil P.: AAPS Pharm. Sci. Tech. 5, 34 (2004).
19. Schwarz J, inventor. US patent application 20030072798. April 17, (2003).
20. Arida A.I., Moawia M.A., Hantash A.J.H.A.I.A., Moawia M.A., Hantash A.J.H.: Chem. Pharm. Bull. 55, 1713 (2007).
21. Balakrishnan P., Lee B.J., Lee Y.I., Woo J.S., Yong C.S., Choi H.G.: Int. J. Pharm. 374, 66 (2009).
22. Kang B.K., Lee J.S., Chon S.K., Jeong S.Y., Yuk S.H., Khang G., Lee H.B., Cho S.H.: Int. J. Pharm. 274, 65 (2004).
23. Franceschinis E., Voinovich D., Grassi M., Perissutti Filipovic-Grcic B.J., Martinac A., Meriani-Merlo F.: Int. J. Pharm. 291, 87 (2005).
24. Tuleu C., Newton M., Rose J., Euler D., Saklatala R., et al.: J. Pharm. Sci. 93, 1495 (2004).
25. Abdalla A., Mader K.: Eur. J. Pharm. Sci. 66, 220 (2007).
26. Wang Z., Sun J., Wang Y., Liu X., Liu Y., Fu Q., Meng P., He Z.: Int. J. Pharm. 383, 1 (2010).
27. Serratoni M., Newton M.: Eur. J. Pharm. Biopharm. 65, 94 (2007).
28. Iosio T., Voinovich D, Grassi M., Pinto J.F., Perissutti B., Zacchigna M., Quintavalle U., Serdoz F.: J. Pharm. Biopharm. 69, 686 (2008).

29. Patil P., Vandana P., Paradkar A.: Acta Pharm. 7, 111 (2007).
30. Trull A.K., Tan K.K., Tan L., Alexander G.J., Jamieson N.V.: Br. J. Clin. Pharmacol. 39 627 (1995).
31. Drewe J., Meier R., Vonderscher J.: Br. J. Clin. Pharmacol. 34, 60 (1992).
32. Araya H., Mikio, T., Masahiro H.: Drug. Metab. Pharmacokinet. 21, 45 (2006).
33. Hong J.Y., Kim J.K., Song Y.K., Park J.S., Kim C.K.: J. Control. Release 110, 332 (2006).
34. You J.: Colloid. Surf. B. 48, 35 (2006).
35. Chae G.S., Lee, J.S., Kim S.H.: Int. J. Pharm. 301, 6 (2005).
36. Jannin V., Musakhanian J., Marchaud D.: Adv. Drug Deliv. Rev. 60, 734 (2007).
37. Abdalla A., Klein S., Mader K.: Eur. J. Pharm. Sci. 35, 457 (2008).
38. Tan A., Simovic S., Davey A.K., Rades T., Prestidge C.A.: J. Control. Release 134, 62 (2009).
39. Wang L., Cui F.D., Sunada H.: Pharm. Bull. 54, 37 (2006).
40. Shen H., Zhong M.: J. Pharm. Pharmacol. 58, 1183 (2006).
41. Patel A.R., Vavia P.R.: AAPS J. 9, E344 (2007).
42. Postolache P., Petrescu O., Dorneanu V.: Eur. Rev. Med. Pharmacol. Sci. 6, 127 (2002).
43. Catarzi F., Valleri M., Cirri M., Mura P.: in 6th World Meeting On Pharmaceutics, Biopharma. Pharma.Techno. Barcelona, Spain, April 7–10 (2008).
44. Zvonar A., Berginc K., Kristl A., Gasperlin M.: Int. J. Pharm. 388, 151 (2010).
45. Bekerman T., Golenser J., Domb A.: J. Pharm. Sci. 93, 1264 (2004).
46. Nepal P.R., Han H.K., Choi H.K.: Eur. J. Pharm. Sci. 39, 224 (2010).
47. Koynova R., Mariana T.: Biochim. Biophys. Acta. 1798, 646 (2010).
48. Gao P., Morozowich W.: Expert Opin. Drug Deliv. 3, 97 (2006).
49. Ritschel W.A.: Methods Find. Exp. Clin. Pharmacol. 13, 205 (1996).
50. Julianto T., Yuen K.H., Noor A.M.: Int. J. Pharm. 200, 53 (2000).
51. Khoo S.M., Porter, C.J., Edwards G.A., Charman W.N.: Pharm. Sci. 1, 614 (1999).
52. Iosio T., Voinovich D., Grassi M., Pinto J.F., Perissutti B., Serdoz F., Hasaa D. et al.: Phytomedicine (in press).
53. Franceschinis E., Bortoletto C., Perissutti B., Zotto M.D.D., Voinovich D.: Powder Tech. (accepted manuscript) (2010).
54. Hamdani J., Moës A. J., Amighi K.: Int. J. Pharm. 260, 47 (2003).
55. Patil, P., Paradkar, A.: AAPS Pharm. Sci. Tech. 7, 10.1208/0pt07012 (2006).
56. Singh A.K., Chaurasiya A., Awasthi A., Mishra G., Asati D.: AAPS Pharm. Sci.Tech. 10, 906 (2009).
57. Woo J.S., Song Y.K., Hong J.Y., Limd S.J., Kim C.K.: Eur. J. Pharm. Sci. 33, 159 (2008).
58. Cui J., Yu B., Zhao Yu., Zhu W., Li H., Lou H., Zhai G.: Int. J. Pharm. 371, 148 (2009).
59. Yi T., Wan J., Xu H., Yang X.: Eur. J. Pharm. Biopharm. 70, 439 (2008).
60. Setthacheewakul S., Mahattanadul S., Phadoongsombut N., Pichayakorn W., Wiwattanapatapee R.: Eur. J. Pharm. Biopharm. 76, 475 (2010).
61. Yao G., Li Y.: Biomed. Pharmacother. (in press) (2010).
62. Nielsen F.S., Gibault E., Ljusberg-Wahrer H.: J. Pharm. Sci. 96, 876 (2007).
63. Dixit R.P., Nagarsenker M.S.: Eur. J. Pharm. Sci. 35, 183 (2008).

Received: 22. 12. 2010