INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM: SOLIDIFICATION TECHNIQUES, DOSAGE FORM AND EVALUATION.

Wagh M.P*, Sodnar Kiran*, Misal Kailas, Ingle Vaibhav, Kamdi Sanjay, Muzammil Husain
Department of Pharmaceutics, MVP's College of Pharmacy, Gangapur Road, Nasik (02), Pune University, Maharashtra, India.

ARTICLE INFO

Article history
Received 24/03/2017
Available online
12/04/2017

Keywords
Self-Microemulsifying Drug Delivery System,
Solid Self-Emulsifying Drug Delivery Systems,
Microemulsion,
Co-Surfactants,
Lipid Based Drug Delivery System,
Spray Drying.

ABSTRACT

Low aqueous solubility is attributed to the low oral bioavailability is a major problem for formulation scientist as most of recent drugs are lipophilic in nature and their lower solubility and dissolution is a major limitation for their successful formulation. Nowadays much more attention has been given on Self-microemulsifying drug delivery systems (SMEDDS) mainly used to improve the bioavailability of hydrophobic drugs. SMEDDS are mainly formulated in a liquid dosage form, which possess some disadvantages. In order to minimize those disadvantages it become necessity to convert it into an solid form .Accordingly, solid SMEDDS (S-SMEDDS), prepared by solidification of liquid/semisolid self-emulsifying (SE) ingredients into powders, have gained popularity. This article emphasizes on the recent advances in the study of S-SMEDDS, mainly the solidification techniques and the development of the solid SE dosage forms. Moreover, the existing problems and the possible future research direction in this field are also mentioned over here.

Corresponding author
Wagh M. P.
NDMVP Samaj's College of Pharmacy,
Shivajinagar, Gangapur Road, Nashik-422002, Maharashtra, India.
kirankumarsodnar@gmail.com

*Please cite this article in press as **Wagh M. P** et al. Self-Microemulsifying Drug Delivery System: Solidification Techniques, Dosage Form and Evaluation.. Indo American Journal of Pharmaceutical Research.2017:7(03).*

INTODUCTION [1]

The oral route is the most popular route among all the route of administration. Nearly 35 to 40% of newly launched drugs possess low aqueous solubility which leads to their poor dissolution and thereby low bioavailability. For these drugs absorption rate from gastrointestinal tract is mainly governed by dissolution and improvement in solubility may lead to enhanced bioavailability. There are various techniques use for improve the bioavailability of those drug like salt formation, pH change, β-cyclodextrin complex, microemulsion etc. Self-microemulsifying drug delivery (SMEDDS) is the one of the method for the improvement of oral bioavailability. SMEDDS are class of emulsion that has received particular attention as a means of enhancing oral bioavailability of poorly absorbed drugs. These systems are isotropic mixture of oil and surfactant (sometimes with added co surfactant) that form emulsion on mixing with water with little or no energy input.

These systems can spontaneously form fine (oil in water) emulsion upon mild agitation when diluted with aqueous media. The emulsion formed from SEDDS having particle size from a few nanometers to several microns. The formulations forming transparent emulsions with oil droplets ranging from 100 to 250 nm are termed as 'Self-micro emulsifying drug delivery systems' (SMEDDS). Self microemulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. These are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion and solubility effect of surfactants.

ADVANTAGES OF SMEEDS

- Fine oil droplets of these SMEDDS would pass rapidly and encourage extensive distribution of the drug all the way through the GI tract.
- While compare with oily solutions, these SMEDDS are afford a large interfacial area for partitioning of the drug between oil and water.
- For lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.
- 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 SMEDDS [2]

- Due to high conc. Of surfactant it produces GI irritation.
- Volatile co solvents may migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.

Suitable Drug Candidate for SMEDDS

Lipophilic drug compounds that exhibit dissolution-rate-limited absorption, SEDDS can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, use of SEDDS can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs. These systems can help in solving the under-mentioned problems of all the categories of BCS class drugs,[3]

Table.1.BCS class and there problem.

BCS Class	Problem
Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilization, enzymatic degradation, gut wall efflux and bioavailability

Mechanism of self-emulsification [4]

The mechanism by which self-emulsification occurs is not yet well understood. Nevertheless, it has been suggested that self-emulsification takes place when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of a conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases. The two phases of the emulsion tend to separate with time to reduce the interfacial area and thus the free energy of the system. The conventional emulsifying agent stabilizes emulsion resulting from aqueous dilution by forming a monolayer around the emulsion droplets, reducing the interfacial energy and forming a barrier to coalescence. Thus the main driving force of SMEDDS is ultra-low interfacial tension, which is achieved by using two or more emulsifier in combination, but sometime single nonionic surfactant may work.

Excipients used in SMEDDS [5]

Self-emulsification has been shown to be specific to the nature of the oil/surfactant pair; the surfactant concentration and oil/surfactant ratio; and the temperature at which self-emulsification occurs. Hence only very specific pharmaceutical excipient combinations could lead to efficient self-emulsifying systems an Example of such excipients are mentioned below.

Oils [5-6]

Oil mainly represents one of the most important excipients in the SEDDS formulation not only because it can solubilize marked amounts of the lipophilic drug or facilitate self-emulsification but also it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Novel semi-synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.

Surfactant [6]

Non-ionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g. Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). Emulsifiers derived from natural sources are expected to be safer the synthetic once. The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. A large quantity of surfactant may irritate the GIT and it can be proved that the Non-ionic surfactants are to be less toxic as comp aired to ionic surfactants. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation.

Co-solvent [6,8]

Co-solvents like ethanol, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role as co-surfactant in the microemulsion systems. Alcohol-free self-emulsifying micro-emulsions have also described in the literature.

Table 2.Example of oils ,surfactant and co-surfactant.

Oils	Surfactants	Co-surfactant /Co-solvent
Cotton seed oil Soybean oil Corn oil Sunflower oil Sesame oil Peanut oil Labrafac Labrafil Castor oil Capryol90 Capmul	Polysorbate 20 (Tween 20) Polysorbate 80 (Tween 80) Labrasol Polyoxy - 40 - hydrogenated castor oil(Cremophor RH40) D-alpha Tocopheryl polyethylene glycol 1000 succinate Span 20 Span 80	Ethanol Polypylene glycol Polyethylene Glycol

Solid Self-Emulsifying Drug Delivery Systems [6-8]

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid ingredients into powders by different solidification techniques. Such powders, which refer to SE dry emulsions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SMEDDS are directly filled without any solidifying excipient. To some extent, S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS are the sum of the corresponding properties of both SMEDDS and solid dosage forms.

Advantage of S-SMEDDS over Liquid SMEDDS

- Low production cost.
- Convenience of process control.
- High stability and reproducibility.
- Better patient compliance etc.

Solidification Techniques for Transforming Liquid/ Semisolid SMEDDS to S-SMEDDS

Capsule Filling With Liquid and Semisolid Self-Microemulsifying Formulations [12-15]

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. it is a four step process:

i. Heating of the semisolid excipient to at least 20°C above its melting point.
ii. Incorporation of the active substances (with stirring).
iii. Capsule filling with the molten mixture and
iv. Cooling to room temperature.

For liquid formulations, it involves a two-step process:

- filling of the formulation into the capsules
- sealing of the body and cap of the capsule, either by banding or by microspray sealing

Advantages

- Simplicity of manufacturing;
- Suitability for low dose of highly potent drugs and
- High drug loading potential

Disadvantage

- Volatile co-solvents may migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

Spray drying [15-18]

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) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. Critical parameter that affects the spray drying process yield of liquid formulation

- The atomizer,
- Inlet and outlet temperature,
- airflow pattern
- drying chamber design

Adsorption to solid carriers[19-24]

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers Solid carriers can be microporous inorganic substances, high surface- area colloidal inorganic adsorbent substances, cross-linked

polymers or nanoparticle adsorbents example-

- silica,
- silicates,
- magnesium trisilicate,
- magnesium hydroxide,
- talcum, crospovidone,
- cross-linked sodium carboxymethyl cellulose and
- crosslinked polymethyl methacrylate

Melt granulation [24-28]

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.

Advantages

- One-step operation
- Liquid addition and the subsequent drying phase are omitted compared with conventional wet granulation
- It is also a good alternative to the use of solvent.
- The main parameters that control the granulation process are
- Impeller speed.
- Mixing time.
- Binder particle size and
- Viscosity of the binder.

Melt Extrusion/Extrusion Spheronization [29-32]

The extrusion–spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve a momogenious powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). In the wet masses comprising SES (polysorbate 80 and mono-/di-glycerides), lactose, water and MCC, the relative quantities of SES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets. Studies suggested that the maximum quantity of this SES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight. Generally, the higher the water level, the longer the disintegration time. The rheological properties of wet masses may be measured by an extrusion capillary.

Advantages

- Melt extrusion is a solvent-free process
- high drug loading up to 60%
- content uniformity
- converting material with plastic properties into a product of uniform shape and density
- uniforme size product

Dosage Form Development of S-SMEDDS

Dry emulsions [32-35]

Dry emulsions are powders dosage form, in which emulsion spontaneously occurs *in vivo* or after exposure to an aqueous solution this solves the stability problems associated with classic emulsions (*e.g.* phase separation, and contamination by microorganisms) during storage and also helps avoid the use of harmful or toxic organic solvents .Dry emulsions may be redispersed in water before use. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier like lactose or maltodextrins. Dry emulsions can be obtained by rotary evaporation, freeze-drying or spray drying. The technique of spray drying is more frequently used in preparation of dry emulsions. The O/W emulsion was formulated and then spray-dried to remove the aqueous phase. Dry emulsions can be used for further preparation of tablets and capsules.

The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, vegetable oil, and a pH-responsive polymer, with lyophilization used.

Self -Microemulsifying Capsule [33]

After administration of capsules containing conventional liquid SME formulations, microemulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SME formulation. With the similar purpose, the supersaturable SMEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state *in vivo*. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects. 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). As an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self-micro emulsification upon mixing with water and nevertheless oral administration of SME capsules has been found to enhance patient compliance.

Self-Emulsifying Sustained/Controlled-Release Tablets [33,35]

SE tablets are mainly prepared as they are stable than the available dosage forms. Sustained action can be produced by using suitable polymer or combination of polymer. Furosemide prepared as SMEDDS floating tablets is used for treatment of edema and cardiac heart failure with controlled release.in order to reduce significantly the amount of solidifying excipients required for transformation of SMEDDS into solid dosage forms, a gelled SMEDDS has been developed by Patil *et al*. 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 slowing down of the drug release. SE tablets are of great utility in obviating adverse effect, as disclosed by Schwarz in a patent. Inclusion of indomethacin (or other hydrophobic NSAID), for example, into SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. Polyethylene oxide successfully illustrated its suitability for controlled-release matrices. The resultant SE tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet.

Self-Emulsifying Beads [36]

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 is 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 is a potential carriers for solidification of SES.

loading efficiency is mainely governed by Geometrical features likewise

- pore architecture of PPB
- bead size

Self- Micro Emulsifying Implants [37]

Research into SME implants has greatly enhanced the utility and application of S-SMEDDS. As an example, 1, 3-bis (2-chloroethyl)-1-nitrosourea is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. In order to enhance its stability compared with that released from poly (d,l-lactide-co-glycolide) (PLGA) wafer implants, SMES was formulated. Such wafers had higher *in vitro* antitumor activity and were less susceptible to hydrolysis.

Self- Micro Emulsifying Suppositories [38]

Some investigators proved that S-SMEDDS could increase not only GI adsorption but also rectal/vaginal adsorption (46). For example Glycyrrhizin, which is given by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SME suppositories.

Evaluation of SMEDDS

Self Emulsification efficiency [38-39]

The self emulsification time is determined by using USP dissolution apparatus II at 50 r/ min, where 0.5 g of SMEDDS formulations is introduced into 250 ml of 0.1N HCL or 0.5% SLS solution. The time for emulsification at room temperature is indicated as self emulsification time for the formulation.

Droplet size Analysis & Particle size Measurements [40]

Photon correlation Spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques are used to determine droplet size of emulsion. A number of equipments are available for measurement of particle size viz. Particle Size Analyzer, Mastersizer, Zetasizer etc which are able to measure sizes between 10 and 5000 nm. In many instances nanometric size range of particle is retained even after 100 times dilution with water which indicates the system's compatibility with excess water.

Zeta Potential Determination [39,41]

The stability of emulsion is directly related to the charge present on mobile surface, which is termed as zeta potential. Zetasizer, Mastersizer etc. are often used to determine zeta potential. The Zetasizer uses light scattering techniques to determine globule size, zeta potential and molecular weight of nanoparticulate systems. The instrument determines size and zeta potential for optimization of stability and shelf life and speeding up the formulation development The SEDDS formulation is generally diluted in a ratio of 1: 2500 (v/v) with distilled water with constant stirring for determination of zeta potential.

Conductivity measurements [50]

Conductivity measurements are able to determine point of aqueous phase addition where the system changes from oil continuous to water continuous phase.it also helps in management of phase inversion or percolation phenomena.

Refractive Index (R.I.) & Percent transmittance [44-45]

Refractive Index & percent transmittance are determined to check the transparency of formulation. Refractive Index of the formulation is measured by refractometer by placing drop of solution on slide & then compare it with water (R.I = 1.333). The percent transmittance of the formulation is measured at a particular wavelength using UV spectrophotometer by using distilled water as blank. [6] If R.I. of formulation is similar to that of water & formulation having percent transmittance is greater than 99%, then the formulation are transparent in nature.

Thermodynamic Stability Studies [45-47]

The physical stability of a formulation is very important for its performance as it can be adversely affected by precipitation of the drug in excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. Also the incompatibilities between formulation & gelatin shell of capsule (if formulation filled in capsule) may cause brittleness, softness and delayed disintegration or incomplete release of drug. The following cycles are carried out for these studies.

Heating cooling cycle [46]

Six cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (45°C) with exposure at each temperature for not less than 48 hours are carried. Those formulations, which are stable, are then subjected to centrifugation test.

Centrifugation [47]

Formulations which pass the heating cooling cycle are centrifuged at 3500 r/ min for 30 min. Those formulations that doesn't show any phase separation are taken for the freeze thaw stress test.

Freeze thaw stress cycle [48]

Three freeze thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than 48hours. Those formulations which pass this test show good stability with no phase separation, cracking or creaming. The formulations that pass this test are then further taken for dispersibility test for assessment of self emulsification efficiency.

CONCLUSION

Self-microemulsifying drug delivery system is a very promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SMEDDSs.S-SMEDDS evoked as improvements or alternatives of conventional liquid SMEDDS, S-SMEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SMEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable. . With future development of this technology, SMEDDSs will continue to enable novel applications in drug delivery.

ABBREVIATIONS

SMEDDS	- SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM
S	- SMEDDS- SOLID SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM
RI	- REFRACTIVE INDEX
DLS	- DYANAMIC LIGHT SCATTERING.

ACKNOWLEDGEMENT

The authors express their gratitude to MVP college of pharmacy Nasik. I am really thankful to my friends and family for encouraging me for this review. My special thanks to my respected guide Dr.Milind Wagh And My Colleagues Sanjay, Kailas , Nikhil, Vishal, Atul, Rohit, Prashant etc.

Conflict Of Interest

Authors have declare no conflict of interest

REFERENCES

1. N.S,Barakat.Enhanced Oral bioavailability of Etodolac by SEDDS: *In vitro* and *in vivo* evaluation. J. Pharm. Pharmacol.2010,62 :173-180.
2. M.E. Perlman, S.B. Murdande, M.J. Gumkowski,*et al*. Development of a self emulsifying formulation that reduces the food effects fortorcetrapib. Int. J. Pharm,2008, 351: 15-22.
3. Kumar Ajay, Sharma Surabhi Kamble, Ravindra, Self Emulsifying Drug Delivery System (Sedds), International Journal of Pharmacy and Pharmaceutical Sciences,4, 2010.
4. Attama A.A and Mpamaugo V.E.,Pharmacodynamics of piroxicam from self-emulsifying lipospheres formulated with homolipids extracted from Capra hircus. Drug Deliv .2006;13:133-137.
5. Jannin V. et al.,Approaches for the development of solid and semi-solid lipid-based formulations. Adv .Drug .Deliv. Rev. 2008; 60:734-746.
6. Sharma V, Singh J, Gill B, Harikumar SL. SMEDDS: A novel approach for lipophilic drugs. International Journal of Pharmaceutical sciences and Research. 2012; 3(8): 2441- 2450.
7. Sunitha R, Satya Sireesha D, Aparna M L V. Novel self emulsifying drug delivery system an approach to enhance bioavailability of poorly water soluble drugs. International Journal of Research in Pharmacy and Chemistry. 2011; 2(4): 828-838.
8. Taksande JB, Trivedi RV, Mahore JG. Self-emulsifying drug delivery systems: Hitherto and recent advances. International Journal of Research in Ayurvedic & Pharmacy. 2011; 2(4): 1087-1095.
9. Tang B, Cheng G, Gu J, Xu C. Development of Solid self-emulsifying drug delivery systems: preparation techniques and dosage form. Drug Discovery Today. 2008; 13: 606-612.
10. Toorisaka E, Hashida M, Kamiya N et al., An entericcoated dry emulsion formulation for oral insulin delivery. Journal of Control Release. 2005; 107: 91-96.
11. T.Yi, J. Wan, H. Xu, et al. A new solid self micro emulsifying formulation prepared by Spray drying to improve the oral bioavailability of poorly water soluble drugs. Eur. J. Pharm. Biopharm., 2008, 70: 439-444.
12. Y. D. Yan, J. A. Kim, M. K. Kwak, *et al*. Enhanced oral bioavailability of curcumin via a solid lipid based self emulsifying drug delivery system using a spray drying technique. Biol. Pharm. Bull., 2011, 34: 1179-1186.
13. P. Balkrishan, B.J. Lee, D.H. Oh, *et al*. Enhanced Oral bioavailability of Dexibuprofen by a novel solid self emulsifying drug delivery system (SEDDS). Eur. J. Pharm. Biopharm., 2009, 72: 539-545.
14. N. Passerini, B. Albertini, B. Perissutti, *et al*.Evaluation of melt granulation and ultrasonic Spray congealing techniques to enhance dissolution of praziquantel. Int. J. Pharm., 2006, 318: 92-102.
15. C. Cavallari, L. Rodriquez, B. Albertini, *et al*. Thermal and Fractal analysis of diclofenac/Gelucire 50/13 micro particles obtained by ultrasound-assisted atomization. J. Pharm. Sci., 2005, 94:1124-1134.
16. E. Mehuys, J. P. Remon, A. Korst, *et al*. Human bioavailability of propranolol from a matrix-in-cylinder system with HPMC – Gelucire R Core. J Control Rel., 2005, 107: 523-536.
17. A. Abdalla, K. Mader. Preparation and characterization of self-emulsifying pellet formation. Eur. J. Pharm. Biopharm., 2007, 66: 220-226.
18. Jannin, V. et al. (2008) Approaches for the development of solid and semi-solid lipid-based formulations. Adv. Drug. Deliv. Rev. 60, 734–746 16 Dong, L. et al. (2000) A novel osmotic delivery system: L-OROS SOFTCAP. Proceedings of the International Symposium on Controlled Release of Bioactive Materials, July, Paris (CD ROM).
19. Dong,L. et al. (2001) L-OROS HARDCAP: a new osmotic delivery system for controlled release of liquid formulation. Proceedings of the International Symposium on Controlled Release of Bioactive Materials, June, San Diego (CD-ROM)
20. Cole, E.T. et al. (2008) Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. Adv. Drug.Deliv. Rev. 60, 747–756
21. Ito, Y. et al. (2005) Oral solid gentamicin preparation using emulsifier and adsorbent. J. Control Release 105, 23–31
22. Fabio, C. and Elisabetta, C. Pharmaceutical composition comprising a water/oil/ water double microemulsion incorporated in a solid support. WO2003/013421
23. Boltri,L. et al. (1997) Enhancement and modification of etoposide release from crospovidone particles loaded with oil-surfactant blends. Pharm. Dev. Technol. 2, 373–381.
24. Venkatesan, N. et al. (2005) Liquid filled nanoparticles as a drug delivery tool for protein therapeutics. Biomaterials 26, 7154–7163.
25. Seo, A. et al. (2003) The preparation of agglomerates containing solid dispersions ofdiazepam by melt agglomeration in a high shear mixer. Int. J. Pharm. 259, 161–171.
26. Gupta, M.K. et al. (2001) Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. Pharm. Dev. Technol. 6, 563–572.
27. Gupta, M.K. et al. (2002) Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. Pharm. Res. 19, 1663–1672.
28. Verreck, G. and Brewster, M.E. (2004) Melt extrusion-based dosage forms: excipients and processing conditions for pharmaceutical formulations. Bull. Tech. Gattefosse.97, 85–95.
29. Newton, M. et al. (2001)The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture. J. Pharm. Sci. 90, 987–995.
30. Newton, J.M. et al. (2005) Formulation variables on pellets containing selfemulsifying systems. Pharm. Tech. Eur. 17, 29–33.

31. Newton, J.M. et al. (2005) The rheological properties of self-emulsifying systems, water and microcrystalline cellulose. Eur. J. Pharm. Sci. 26, 176–183.
32. Tuleu, C. et al. (2004) Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of progesterone. J. Pharm. Sci. 93, 1495–1502.
33. Itoh K. et al. Improvement of physicochemical properties of N-4472 part I.formulation design by using self-microemulsifying system.Int.J.Pharm .2002; 238:153-160.
34. Gao P. and Morozowich W.,Development of supersaturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs. ExpertOpin.Drug.Discov 2006; 3:97- 110.
35. Gao P. et al: Development of a supersaturable SEDDS (S-SEDDS) formulation of paclitaxel with improved oral bioavailability. J. Pharm. Sci .2003;92:2386-2398.
36. Li P. et al.,Development and characterization of a solid microemulsion preconcentrate system for oral delivery of poorly water soluble drugs.Controlled Release Society Annual Meeting, Long Beach, C.A, 2007;sss June.
37. Li P. et al.,Novartis Pharmaceuticals Corp. Spontaneously dispersible pharmaceutical compositions.WO2006/050123.
38. Ito Y. et al.,Preparation and evaluation of oral solid heparin using emulsifier and adsorbent for in vitro and in vivo studies. Int. J. Pharm .2006;317:114-119.
39. Joseph.,Solid self-emulsifying dosage form for improved delivery of poorly soluble hydrophobic compounds and the process for preparation thereof. US Patent 20030072798.
40. Wei L.L. et al., Investigations of a novel self-emulsifying osmotic pump tablet containing carvedilol. DrugDev Ind .Pharm. 2007;33:990-998.
41. Kim, J.Y. and Ku, Y.S. (2000) Enhanced absorption of indomethacin after oral or rectal administration of a self-emulsifying system containing indomethacin to rats. Int. J. Pharm. 194, 81–89.
42. Takada,K. and Murakami,M. Glycyrrhizin preparations for transmucosal absorption. US Pat 6890547.
43. Chae, G.S. et al. (2005) Enhancement of the stability of BCNU using self-emulsifying drug delivery systems (SEDDS) and in vitro antitumor activity of self-emulsified BCNU-loaded PLGA wafer. Int. J. Pharm. 301, 6–14.
44. Loomis, G.L. Bioresorbable compositions for implantable prostheses. US Pat 6403758.
45. S. Shafiq, F. Shakeel, S. Talegaonkar, *et al*. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur. J. Pharm. Biopharm., 2007, 66: 227-243.
46. Y. G. Bachhav, V. B. Patravale. SMEDDS of glyburide: formulation, *in vitro* evaluation, and stability studies. AAPS Pharm. Sci. Tech., 2009, 10: 482-487.
47. S. Shafiq-un-Nabi, F. Shakeel, S. Talegaonkar, *et al*. Formulation Development and Optimization using nanoemulsion technique: A Technical Note. AAPS Pharm. Sci. Tech., 2007, 8: E1-E6.
48. P.A.Patel, G.M.Chaulang, A. Akolkotkar , *et al*. Self Emulsifying Drug delivery system: A Review. Res. J Pharm and Tech., 2008, 1: 313- 323.
49. B. Singh, S. Bandyopadhyay, R. Kapil, *et al*. Self Emulsifying Drug Delivery System: Formulation, Development, Characterization and Applications. Critical Review in Therapeutic Drug Carrier Systems, 2009, 26: 427–521.
50. Constantinides PP, Pharm Res.1995, 12,1561-7.