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Review Article

Solid self-emulsifying pellets: Solubility enhancement for oral delivery of poorly soluble BCS Class II drug

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Abstract

The review focused on technique of solid self-emulsifying pellets (SEPs) for solubility enhancement of poorly water soluble drug. The oral route of administration has been and still is currently the primary route of drug delivery owing to its potential advantages compared to the other routes. The solubility enhancement process of hydrophobic drugs plays a key role in the formulation development to achieve the bioavailability and therapeutic action of the drug at the target site.[1] Around 40% of probe new drugs are characterized as belonging to class II in the BCS classification (poorly water soluble and highly permeable), giving rise to poor and erratic oral bioavailability. The solid SEPs system combines the advantages of liquid Self emulsifying drug delivery system with those of solid dosage form, which can overcome the limitations of liquid formulations and improve the storage stability and patient compliance. To enhance the dissolution and oral absorption of water insoluble drug selfmicroemulsifying pellets develop and evaluated. SEPs pellets showed a significant quicker redispersion rate than the dissolution rate of commercial tablets. The solid SEPs pellets might be an encouraging strategy to improve the oral absorption of Poorly water soluble drug and the extrusion–spheronization method is a feasible technology for the solidification of liquid SMEPs. Self microemulsifying drug delivery system (SEPs) as an effective bioavailability enhancement pharmaceutical technology has been widely used during the recent years and have some successful products in the market (e.g. Neoral®, Norvir® and Fortovase®).

Keywords: Self Emulsifying Pellets, Bioavailability, Solubility, extrusion–spheronization, Biopharmaceutical Classification.

Introduction

The oral route of administration has been and still is currently the primary route of drug delivery owing to its potential advantages compared to the other routes. The solubility enhancement process of hydrophobic drugs plays a key role in the formulation development to achieve the bioavailability and therapeutic action of the drug at the target site.[1] Around 40% of probe new drugs are characterized as belonging to class II in the BCS classification (poorly water soluble and highly permeable), giving rise to poor and erratic oral bioavailability. Therefore, dissolution controls the rate of absorption of these drugs from the gastro intestinal tract (GIT).[1,2] Hence, suitable formulations have to be produced to enhance their bioavailability. Drug solubility enhancement is one of the most important challenges in the field of pharmaceutics.[2] Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system and is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Poorly water-soluble drugs after oral administration often require high doses in order to reach therapeutic plasma concentrations. The bioavailability of an orally administered drug depends on its solubility in aqueous media over different pH ranges. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds.[3] To attain the anticipated concentration of a drug in the systemic circulation in order to exhibit the pharmacologic response, solubility of the drug plays a critical role. Key research problems faced during formulation development of various drugs owe to their low aqueous solubility.

Importance of solubility enhancement

1. Solubility is one of the important parameters to achieve preferred concentration of drug in systemic circulation for achieving required pharmacological response

2. Hydrophobic drugs frequently require high doses and need high dosage regimens to influence therapeutic plasma concentrations after administration

3. Low aqueous solubility is the main problem encountered with preparation and development of NCEs as well as for generic drugs.

4. For orally administered drugs solubility is the one of the important rate limiting parameters to reach their desired concentration in complete circulation for pharmacological response.

Biopharmaceutical Classification System Biopharmaceutical Classification System1 (BCS) guidance was provided by US

Food and Drug Administration (FDA), to improve the efficiency of drug product development process. According to which drugs are grouped into four major classes basing on their solubility and permeability.

Class I: High Permeability and High Solubility Ex: Propranolol, Metoprolol, Diltiazem, Verapamil

Class II: High Permeability and Low Solubility Ex: Ketoconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Piroxicam

Class III: Low permeability and High solubility Ex: Acyclovir, Neomycin B, Captopril, Enalaprilate, Alendronate.

Class IV: Low permeability and Low solubility Ex: Chlorthiazide, Furosemide, Tobramycin.

It is a drug development tool that allows estimation of the contributions of three major factors, dissolution, solubility, and intestinal permeability that affect oral absorption of drugs. BCS Class II and IV drugs, which have low solubility, provide a number of challenges for formulation scientists working on the oral delivery of drugs.[2]

The purpose of this review article is to describe the technique of Solubilization for the attainment of effective absorption with improved bioavailability. BCS class II drugs pose challenging problems in their pharmaceutical product development process because of their low solubility and dissolution rates. They require enhancement in solubility and dissolution rate in their formulation development especially solid dosage forms for formulation development of BCS class II drugs.[3]

Many strategies have been reported to overcome the problem of solubility arising for BCS class II drugs. Various techniques used for to increase solubility of hydrophobic drugs such as complexation of drugs, use of cosolvents, emulsion formation, microemulsions, micelles, polymeric micelles, pharmaceutical salts, pro-drugs, particle size reduction technologies, solid state alternation, soft gel technology, solid dispersion techniques, drug nanocrystals, nanomorph technology, and crystal engineering techniques.

Some techniques used for solubility enhancement has some drawbacks like solid dispersion technique has failed to gain popularity due to manufacturing, stability and scale-up issues. Micronization is not appropriate for drugs having a high dose number because it does not change the saturation solubility of the drug. Nanosuspension the key concern related to particle size reduction is the ultimate conversion of the high-energy polymorph to a low-energy crystalline form, which may not be therapeutically active one. Complexation method is difficult and exclusive for preparation, Reproducibility of physicochemical characteristics, difficulty in incorporating into formulation of dosage forms, scale-up of manufacturing process and Stability issues, only small dose drugs are complexed.

Biopharmaceutical aspects

Lipids affect the oral bioavailability of drugs by varying the biopharmaceutical properties such as dissolution rate and solubility in the intestinal fluids, protecting the drug from enzymatic degradation and formation of lipoproteins that enhance lymphatic absorption and distribution of the drugs. This distribution depends on triglyceride chain length, saturation degree, and the volume of lipid administered.

In addition, administration of lipophilic drugs with lipids may improve drug absorption into portal blood compared with non-lipid formulations.[4,5]

The use of lipid-based vehicles has generated significant interest as a potential formulation move toward to improve oral bioavailability of poorly water soluble drugs[6–8]. Lipid formulations are a diverse group of formulations with a wide variety of properties and usually consist of mixture of excipients, ranging from triglyceride oils through mixed glycerides, lipophilic surfactants, hydrophilic surfactants and cosolvents[9]. Lipid-based formulations can reduce the intrinsic limitations of slow and incomplete dissolution of poorly water soluble drugs by facilitating the formation of solubilized phases from which absorption takes place. The attainment of such phases will not essentially take place from the formulation itself, but on the other hand from taking the advantage of the intraluminal processing to which lipids are subjected [10]. The extent of drug absorption from lipid vehicles is significantly affected by the dispersability of the administered lipid and drug. On the other hand, because of the inherent physical instability, the large volume of the two phase emulsion, and the poor precision of dose, the use of conventional emulsions is problematic. A formulation approach for avoiding such limiting problems is the use of microemulsions or self-emulsifying drug delivery systems (SEDDS). The most famous example of a microemulsion based system is the Neoral_ formulation of Cyclosporine, which replaced Sandimmune[11]. SEDDS have shown a reasonable success in improving oral bioavailability of poorly water soluble and lipophilic drugs [12,13].

Self-Emulsifying Drug Delivery Systems has come to the fore due to its ability to enhance the bioavailability of poorly water-soluble drugs. Due to this fact, many drug candidates fail to reach the market, although they show potential pharmacodynamic activity.[14]

Self-Emulsifying Drug Delivery Systems (SEDDS) are involved in lipid formulations. These formulations consist of isotropic mixtures of drugs, which are commonly lipids or surfactants [15-18] with one or more hydrophilic co-solvents or co-emulsifiers. This system forms an emulsion immediately after slight agitation and dilution with water. These emulsions produced are a droplet size extending from a few nanometers to numerous microns. This system can be used with all BCS class drugs to help improve their solubility. SEDDS helps maintain solubility in the gastrointestinal tract by avoiding the dissolution step, which can limit the absorption rate of hydrophobic drugs. The two main factors that affect the release rate of the drug in SEDDS are the particle size and the polarity of the droplets. For the most effective formulation, it is best to keep the number of excipients to a minimum. Excipients are the backbone of SEDDS. The most frequently used excipients are lipids, surfactants and co-solvents. The best choices of excipient are those that increase drug solubility. Lipids are good for solubilizing lipophilic drugs and enhancing the transportation of lipophilic drugs [19]. Surfactants are ampiphilic, so they are able to dissolve large amounts of hydrophobic drug compounds. Co-solvents typically use high concentrations of hydrophilic surfactants. A mixture of surfactant and co-surfactant leads to formation of Self-Micro Emulsifying Drug Delivery System (SMEDDS), which ranges from droplet size between 100 and 200 nm [20]. An advantage with the use of SEDDS and SMEDDS is that tablets and capsules can be developed while sustaining good flow ability, cohesive properties, and good content uniformity. This method allows outstanding product design, performance, and manufacturability. It has not been until recently that understanding in detail the use of SEDDS and SMEDDS on drug deposition as lipid formulations.

Need of Solid Self-Emulsifying Pellets SEDDS, usually formulated in the liquid form, has some disadvantages especially in the manufacturing process, thereby giving rise to

high production costs. Moreover, incompatibility problems with the capsule shell are common. Although desirable, it is difficult to incorporate an SE mixture into a solid form.[21-22] In contrast, the possible advantages of solid self-emulsifying drug delivery (S-SEDDS) have been of interest to researchers.[21] S-SEDDS provides several advantages for pellets, eliciting great interest in its development.

It is therefore suitable to combine the advantages of SEDDS with those of pellets. However, the development of SSEP is a challenge nonetheless, as high lipid loads often impair pellet formulation.[22]

Development of SSEP

It is a multiple-unit dosage form; Newton *et al*., (2001) proposed the idea of bringing together the advantages of SEDDS and pellets through the inclusion of SE mixture into micro-crystalline cellulose and the production of pellets by the E/S method.[22] Moreover, in a comparative bioavailability study carried out by Tuleu *et al*. (2004), it was observed that bioavailability was equivalent when the drug was administered to dogs in SE systems in either a liquid form or a solid pellet dosage form.[23]

- **Advantages of Pellets:** The pellets also reduce variations in gastric emptying rates and overall transit time and therefore a reduction of intra and inter-subject variability of plasma profiles is achieved. In addition, pellets reduce the problem of high local concentration of drugs and thus avoiding irritation that may be caused by certain active constituents.
- Pellets have advantages, over conventional solid dosage forms viz; flexibility in designing and developing the dosage form and improving the safety and efficacy. Because the pellets disperse freely in the gastrointestinal tract, drug absorption is increase with a subsequent reduction in peak plasma fluctuations and hence minimizing potential side effects without lowering drug bioavailability.

Techniques for pellet production:

The most extensively used techniques for pellet production in the pharmaceutical industry are extrusion/spheronization (ES), solution/suspension layering, and powder layering.

Extrusion/Spheronization (ES): The process of ES has become the method of choice in the preparation of pellet-based dosage forms since it offers many advantages over the other methods,

- Good flow properties,
- Low friability,
- Spherical shape with a narrow size distribution
- Uniform packing characteristics and
- Reproducible scalability[14]

It is therefore very attractive to combine the advantages of self-emulsifying delivery systems with pellets. Pellets are characterized for their size, shape, friability and dissolution.

Possible advantages of SSEP [24-25]

- Flexibility in development of the dosage form.
- Improving safety and efficacy of the bioactive form
- Reducing intra-and inter-subject variability of plasma profiles.
- Pellets reduce the problem of high local concentration of drugs, thus avoiding GI irritation.
- Protecting drug(s) from the gut environment
- High drug loading efficiency (up to 98%)
- Possibility of attaining better stability with pellets.

Specificity

Nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio, and temperature are a few of the factors that affect the SE process. Only very precise pharmaceutical excipients' combination leads to efficient SSEP. The efficiency with which a drug is incorporated into an SSEP depends on the particular physicochemical compatibility of the drug/ system. Hence, it is important to perform solubility studies prior to the formulation to obtain a formulation design.

Choice of excipients for self-emulsification in SSEP

Oils/lipids Oils/lipids play an important role in contributing to solubilizing lipophilic drugs in specific amounts, thereby facilitating SE of the drug and rising the fraction of lipophilic drug transported through the intestinal lymphatic system causing an increase in the absorption through GIT.[26] edible oils or Hydrolyzed vegetable can be successfully used in designing high soluble lipophilic drugs owing to their formulation and physiological properties.[16]Both long-chain and medium-chain triglyceride oils may be used for the formulation of SSEP. Surfactant

Amphiphilic surfactants can dissolve relatively high amounts of hydrophobic drugs, thereby preventing the precipitation of drugs within the GI lumen.[24]

Non-ionic surfactants with high HLB values are used in the formulation of SSEP. (e.g., Tween, cremophore, labrasol, etc.). To form a suitable SSEP, the potency of a surfactant should vary between 30% and 60% w/w of the formulation. The large quantities of surfactants used in SSEP preparation might irritate the GIT, which leads to the possible consideration of using non-ionic surfactants over ionic ones.

Co-solvents

They facilitate in the dissolution of large quantities of hydrophilic surfactants or hydrophobic drugs in the lipid base. These solvents sometimes play the role of Co-surfactant in micro-emulsion systems (e.g., ethanol, polyethylene glycol, propylene glycol, etc.).[24]

Physicochemical characterization of SSEP [24]

Assessment of SE and droplet size

The core of SSEP is SE, which is mainly assessed by the visual method. The efficiency of this process can be estimated by determining the rate of emulsification and droplet size distribution. The size of the emulsion droplet released from the SSEP is determined in water at 37°C and compared to liquid SEDDS. Then the droplet size can be measured by laser diffractometry.[27]

Crystallinity study

For confirming the drugs present in the amorphous or crystal state in the lipid carrier in SE pellets, Differential scanning calorimetry and X-Ray diffraction techniques are used.

SSEP size analysis

Size analysis is performed using a set of standard sieves of a √2 (square root) progression ranging from 500 to 2800, with 100 g of SSEPs, agitated on a sieve shaker for 20 min.

Friability testing of SSEP

Friability testing is conducted using a friability tester. A 10 g pellet sample is placed in the drum together with 10 g of glass spheres of 5 mm diameter, and rotated for 10 min at 25 rpm. Pellets are then weighed and then friability is determined.

Drug entrapment studies

Around 10 g of the drug loaded pellets from the different batches are placed in specified phosphate buffer 1000 ml conical flasks and stirred continuously using magnetic stirrers till the pellets burst completely. Aliquots are taken and the required dilutions were made with methanol and estimated by High pressure liquid chromatography (HPLC). The drug entrapment capacity is calculated using the following formula:

Drug entrapment capacity (%) = (AQ/TQ) × 100

where AQ is the actual quantity of the drug present in the SE pellets and TQ the 100% theoretical quantity of the drug that must be present in the SE pellets.

Disintegration testing of SSEP

Disintegration testing of pellets is measured using a disintegration tester, modified by the installation of a 500 µm mesh at the bottom of tubes. Six pellets are tested in distilled water at 37°C and the end point is considered as the point where no particles are present on the sieve.[26]

Dissolution testing of SSEP

Dissolution is performed using USP II apparatus, with the bath temperature being 37°C. The media to be used are selected depending on the drug present in the SSEP formulation.

Factors influencing SSEP

Polarity of the lipophilic phase

The polarity of the lipid phase is the main factor governing the drug release from SSEP. The high polarity enhances a rapid rate of release of drug into the aqueous phase. The optimum release was obtained with the formulation that had oil phase with the highest polarity.

Nature and dose of the drug in SSEP[27]

Drugs that are administered at high doses are not encouraged for SSEP unless they have extremely good solubility in at least one of the components of SSEP, mostly the lipophilic phase. The drugs that have limited or poor The model size fraction and the interquartile range are estimated from the cumulative percentage undersize curve.

The geometrical standard deviation (σg) is determined by the log-normal distribution curve.[28]

SSEP shape analysis

Shape analysis is performed using a stereomicroscope and a digital camera connected to the computer with an image analysis software image C. One thousand pellets are used and for each pellet, 36 Feret diameters are measured to calculate the mean Feret diameter. The maximum Feret diameter and Feret diameter 90° to the maximum Feret diameter are obtained and the aspect ratio is calculated as the ratio between the maximum Feret diameter and the Feret diameter 90°. solubility in water and lipids are the most difficult to be formulated by SSEP.

Drawbacks of SSEP

The main drawback in the development of SSEP and other lipid based formulations is the lack of good *in vitro* models for the assessment of SE formulations. The traditional dissolution model is not reliable, because these formulations potentially depend on digestion prior to release of the drug. To mimic this, an *in vitro* model stimulating the digestive process of the duodenum has been developed. This *in vitro* model needs further development to carry out *in vitro*/*in vivo* correlations; therefore, different prototype lipid based formulations need to be developed and tested *in vivo* in a suitable animal model. Future studies are required to address the development of the *in vitro* model.[29]

Examples of products available in the market

Several drug products intended for oral administration have been marketed utilizing lipid and surfactant based formulations. Sandimmune® and Sandimmune Neoral® (cyclosporin A, novartis), Norvir® (ritonavir), and Fortovase® (saquinavir) have been formulated in SEDDS. Lipid based formulations are recognized as a feasible approach to improving the bioavailability of poorly soluble compounds. However, to date, not many clinical studies have been published.

Conclusion

They can be orally administered easily, as they do not result in GI irritation; moreover, controlled/ sustained release of drug is achievable through SE pellets However, research is still in its nascent stage and further studies are required before more solid SE dosage forms come out in the market. Possible areas of future insight are human bioavailability studies – *in vitro*/*in vivo* correlation. It can be concluded that SSEP substantially improves the solubility/dissolution of poor water soluble drugs. SEDDS or SSEP is better to conventional liquid SEDDS in that it reduces production costs, simplifies the industrial manufacturing process, and improves patient compliance.

Table 1: List of drugs that have been formulated into solid self-emulsifying coarse powder, granules and pellets presented in chronological order.

Study	Drug/LogP /BCS Class	Powder Carriers	Presentation	Evaluation	Reference
1.	Carvedilol	MCC PH 101	Pellets	*In vitro dissolution Test,* Characterization of CAR-SEDDS	A. Avachat et.al 2015 [30]
2.	Tempol Benzoate (Tb),	MCC 101	Pellets	Physical characterization, dissolution testing	Ahmed Abdalla2006 [31]
3.	Repaglinide	MCC Lactose	Pellets	Physical characterization, dissolution testing	Desai et.al 2013 [32]
4.	Piroxicam,	Microcrystalline Cellulose (MCC) and	Pellets	*In vitro dissolution Test,*	E. Franceschinis et al.

		Polyvinylpyrrolidone K 90 (PVP)		Characterization	2011 [33]
5.	Sirolimus	Microcrystalline cellulose (Avicel PH-101 Lactose (Foremost 315WG)	Pellets	Characterization , Pharmacokinetic study,	X. Hu et al. 2012 [34]
6.	Bifendate	MCC, lactose, and mannitol	Pellets	*In vitro dissolution Test, In-vivo*	X. Yanyu et al.2012 [35]
7.	-	Microcrystalline cellulose, lactose monohydrate	Pellets	Physical characterization, ***Statistical analysis***	John Michael Newton et.al2007[36]
8.	Furosemide And Propranolol	Microcrystalline cellulose,	Pellets	Physical characterization, ***Statistical analysis***	Nikolakakis and Malamataris,2014 [37]
9.	Model Drugs (Methyl And Propyl Parabens)	lactose and microcrystalline cellulose (MCC)	Pellets	*In vitro dissolution Test,* Characterization	M. Serratoni et al.2007[38]
10.	Nitrendipine	microcrystalline cellulose (MCC) and a lactose monohydrate	Pellets	*In vitro dissolution Test, In-vivo study*	Z. Wang et al. 2010 [39]

References:

1. FDA. Draft-guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies or immediate release solid oral dosage forms containing certain active moieties/active ingredient based on a Biopharmaceutic Classification System, US Department of Health, Food and Drug Administration, Center for Drug Evaluation and Research BP2, January; 1999.

2. Christopher V , Parimalakrishnan S, Jeganathan NS, Anbazhagan S. Techniques to Enhance Solubility of Hydrophobic Drugs: An Overview, Asian J Pharmaceutics, 2016; 10 (2):67-75

3. Ramesh V, Meenakshi N, Jyothirmayee M, Bullebbai, SK, Noorjahan G, Rajeswari, G, Nagesh Babu and Madhav D. Enhancement of Solubility, Dissolution rate and Bioavailability of BCS Class II Drugs, S. Int J Pharma And Chemical Research, 2016; 2(2):24-32.

4. Khoo S M , Humberstone A J, Portr C J, Edwards G A, Charman WN. Formulation design and bioavailability assessment of lipidic self emulsifying formulations of halofantrine. Int J Pharm, 1998; 167:155 164. https://doi.org/10.1016/S0378-5173(98)00054-4

5. Franceschinis E, Voinovich D, Grassi M, Perissutti B, Filipovic Grcic J, Martinac A. Self emulsifying pellets prepared by wet granulation in high shear mixer: Influence of formulation variables and preliminary study on the in vitro absorption. Int J Pharm, 2005; 291:87 97. https://doi.org/10.1016/j.ijpharm.2004.07.046

6. Chakrabarti S, Belpaire FM. Bioavailability of phenytoin in lipid containing dosage forms in rates, J. Pharm. Pharmacol, 1978; 30:330-331. https://doi.org/10.1111/j.2042-7158.1978.tb13247.x

7. Tokumura T , Tsushima Y, Tatsuuishi K, Kayano M, Machida Y, Nagai T.Enhancement of the oral bioavailability of cinnarizine in oleic acid in beagle dogs, J. Pharm. Sci, 1987; 76:286-288. https://doi.org/10.1002/jps.2600760404

8. Trull AK,. Tan KKC, Tan L, Alexander GJM., Jamieson NV.Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion, Br. J. Clin. Pharmacol, 1995; 39:627-631. https://doi.org/10.1111/j.1365-2125.1995.tb05722.x

9. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems, Eur. J. Pharm. Sci, 2000; 11:93-98. https://doi.org/10.1016/S0928-0987(00)00167-6

10. Humberstone AJ, Charman WN. Lipid-based vehicles for the oral delivery of poorly water soluble drugs, Adv. Drug Del. Rev, 1997; 25:103-128. https://doi.org/10.1016/S0169-409X(96)00494-2

11. Vonderscher J, Meinzer A. Rational for the development of Sand immune, Neoral. Transplant Proc, 1994; 26:2925-2927.

12. Tuleu C, Newton M, Rose J, Euler D, Saklatvala R, Clarke A, Booth S. 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,2004; 93:1495-1502. https://doi.org/10.1002/jps.20068

13. Shui-Mei Khoo, Humberstone AJ, Porter CJH, Edwards GA, Charman WN. Formulation and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine, Int. J. Pharm. Sci , 1998; 167:155-164. https://doi.org/10.1016/S0378-5173(98)00054-4

14. Ahmed A, Sandra K, Mäder K. A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: Characterization, dissolution, in vitro digestion and incorporation into solid pellets, European journal of Pharmaceutical sciences, 2008; 35:457-464. https://doi.org/10.1016/j.ejps.2008.09.006

15. Iqbal R, Rizvi SA, Shamsi SA. Glycine-based polymeric surfacants with varied polar head group: I. synthesis, characterization, and application in micellar electrokinetic chromatography. Electrophoresis, 2005; 26:4127-4137. https://doi.org/10.1002/elps.200500361

16. Rizvi SA, Shi L, Lundberg D, Menger FM. Unusual aqueous-phase behavior of cationic amphiphiles with hydrogen-bonding headgroups. Langmuir, 2008; 24:673-677. https://doi.org/10.1021/la7037608

17. Menger FM, Shi L, Rizvi SA. Self-assembling systems: mining a rich vein. J Colloid Interface Sci, 2010; 344: 241-246. https://doi.org/10.1016/j.jcis.2010.01.031

18. Akbay C, Hoyos Y, Hooper E, Arslan H, Rizvi SA. Cationic gemini surfactants as pseudostationary phases in micellar electrokinetic chromatography. Part I: effect of head group. J. Chromatogr A, 2010; 1217:5279- 5287. https://doi.org/10.1016/j.chroma.2010.05.055

19. Kohli K, Chopra S, Dhar D, Arora S, Khar RK . Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discovery Today, 2010; 15:958-965. https://doi.org/10.1016/j.drudis.2010.08.007

20. Tang B, Cheng G, Gu JC, Xu CH. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discovery Today, 2008; 13:606-612. https://doi.org/10.1016/j.drudis.2008.04.006

21. Serratoni M, Newton M, Booth S, Clarke A. Controlled drug release from pellets containing water insoluble drugs dissolved in a self emulsifying system. Eur J Pharm Biopharm, 2007; 65:94-98. https://doi.org/10.1016/j.ejpb.2006.07.011

22. Newton M, PeterssonJ, Podczeck F,Clarke A, Booth S. The influence of formulation variables on the properties of pellets containing a Self-Emulsifying mixture J Pharm Sci, 2001; 90:987-995. https://doi.org/10.1002/jps.1051

23. Tuleu C, Newton M, Rose J, Euler D, Saklatvala R, Clarke A, Booth S, 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,2004; 93:1495-1502. https://doi.org/10.1002/jps.20068

24. Natarajan J, Vivekananda R Novel solid self-emulsifying pellets: An approach for enhanced oral delivery of poorly soluble drug International Journal of Health & Allied Sciences, International J of health and allied sciences, 2013; 2(2):63-68. https://doi.org/10.4103/2278-344X.115678

25. Gursoy RN, Benita S. Self emulsifying drug delivery systems (SEDDS for improved oral delivery of lipophilic drugs. Biomed Pharmacother, 2004; 58:173-182. https://doi.org/10.1016/j.biopha.2004.02.001

26. Patel PA, Chaulang GM, Akolkotkar A, Mutha SS, Handicap SR , Bhosale AV. Self emulsifying drug delivery systems: A Review. Res J Pharm Technol, 2008; 1:313-323.

27. Halbaut L. Oxidative stability of semi-solid excipient mixtures with corn oil and its implication in the degradation of vitamin A. Int J Pharm, 1997; 147:31-40. https://doi.org/10.1016/S0378-5173(96)04789-8

28. Bouwman AM, Bosma JC, Vonk P, Wesselingh JH, Frijlink HW. Which shape factor(s) best describe granules? Powder Technology, 2004; 146:66-72.

https://doi.org/10.1016/j.powtec.2004.04.044

29. .Hauss DJ, Fogal SE, Ficorilli JV, Price CA, Roy T, Jayaraj AA. Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor. J Pharm Sci, 1998; 87:164-169. https://doi.org/10.1021/js970300n

30. Vikas B, Amelia A. Formulation and characterization of self emulsifing pellets of carvedilol Brazilian Journal of Pharmaceutical Science, 2015; 51(3):663-671 https://doi.org/10.1590/S1984-82502015000300018

31. Ahmed A, Preparation and characterization of self-emulsifying pellets formulation, European journal of pharmaceutics and biopharmaceutic, 2006; 66(2):220-226 https://doi.org/10.1016/j.ejpb.2006.11.015

32. Desai NS, Narsenker M S, Design and Evaluation of Self-Nanoemulsifying Pellets of AAPS PharmSciTech, 2013; 14(3):994-1003. https://doi.org/10.1208/s12249-013-9990-9

33. Franceschinis E , Bortoletto C , Perissutti B, Dal Zotto M , Voinovich D, Realdon N. Self-emulsifying pellets in a lab-scale high shear mixer: Formulation and production design Powder Technology, 2011;207:113-118. https://doi.org/10.1016/j.powtec.2010.10.016

34. Xiongwei H, Chen L, Dingxiong C, Jing Z, Zhihong L, Wei W, Hongtao S . Sirolimus solid self-micro emulsifying pellets: Formulation development, characterization and bioavailability evaluation International Journal of Pharmaceutics, 2012; 438:123- 133. https://doi.org/10.1016/j.ijpharm.2012.07.055

35. Xiao Y, Wang S, Chen Y, Ping Q, Self-emulsifying bifendate pellets: Preparation, characterization and oral bioavailability in rats Drug Development and Industrial Pharmacy,2013; 39(5):724-32. https://doi.org/10.3109/03639045.2012.689766

36. Newtona JM, Pintoa MR, Fridrun P.The preparation of pellets containing a surfactant or a mixture of mono- and di-glycerides by extrusion/spheronization, European journal of pharmaceutical sciences, 2007; 30:333-342. https://doi.org/10.1016/j.ejps.2006.11.020

37. Ioannis N, Stavros M Self-Emulsifying Pellets: Relations Between Kinetic Parameters of Drug Release and Emulsion Reconstitution-Influence of Formulation Variables, Drug Delivery and Pharmaceutical Technology, Journal of Pharmaceutical Sciences, 2014; 103:1453-1465. https://doi.org/10.1002/jps.23919

38. Mauro S , Michael N, Steven B, Ashley C, Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system, European Journal of Pharmaceutics and Bio pharmaceutics, 2007; 65:94-98. https://doi.org/10.1016/j.ejpb.2006.07.011

39. Zhiyuan W, Jin S, Yongjun W, Xiaohong L, Yanhua L, Qiang F, Ping M, Zhonggui H. Solid self-emulsifying nitrendipine pellets: Preparation and in vitro/in vivo evaluation, International Journal of Pharmaceutics, 2010; 383:1-6. https://doi.org/10.1016/j.ijpharm.2009.08.014