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. 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 redispersibility 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. 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). 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. 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. 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, Dilatazem, Verapamil

Class II: High Permeability and Low Solubility Ex: Ketconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Pirxicam

Class III: Low permeability and High solubility Ex: Acyclovir, Neomycin B, Captorpril, Enalaprilate, Aclondonare.

Class IV: Low permeability and Low solubility Ex: Chlorothiazide, 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 drugs6-8. 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 cosolvents9. 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 subjected10. 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 Sandimmune11. SEDDS have shown a reasonable success in improving oral bioavailability of poorly water soluble and lipophilic drugs12,13.

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 surfactants15-18 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 drugs19. Surfactants are amphiphilic, 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 nm20. 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. In
contrast, the possible advantages of solid self-emulsifying drug
delivery (S-SEDDS) have been of interest to researchers. 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.

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. 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.

Advantages of Pellets

- 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
(E/S), 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.

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

- 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,
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. Edible
oils or Hydrolyzed vegetable can be successfully used in
designing high soluble lipophilic drugs owing to their
formulation and physiological properties. 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.

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.).

Physicochemical characterization of SSEP

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
SEDS is determined in water at 37°C and compared to
liquid SEDDS. Then the droplet size can be measured by laser
diffractionometry.

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:

\[ \text{Drug entrapment capacity (\%)} = \left( \frac{AQ}{TQ} \right) \times 100 \]

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.27

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.28

The geometrical standard deviation (σg) is determined by the log-normal distribution curve.29

**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 simulating 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**

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug/LogP /BCS Class</th>
<th>Powder Carriers</th>
<th>Presentation</th>
<th>Evaluation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>Tempol Benzoate (Tb),</td>
<td>MCC 101</td>
<td>Pellets</td>
<td>Physical characterization, dissolution testing</td>
<td>Ahmed Abdalla 2006 [31]</td>
</tr>
<tr>
<td>4.</td>
<td>Piroxicam,</td>
<td>Microcrystalline Cellulose (MCC) and</td>
<td>Pellets</td>
<td><em>In vitro dissolution Test</em>,</td>
<td>E. Franceschinis et al.</td>
</tr>
</tbody>
</table>
|   | Polyvinylpyrrolidone K 90 (PVP) | Characterization | 2011  
8. | Furosemide And Propranolol | Microcrystalline cellulose, | Pellets | Physical characterization, Statistical analysis | Nikolakakis and Malamataris,2014  
9. | Model Drugs (Methyl And Propyl Parabens) | lactose and microcrystalline cellulose (MCC) | Pellets | *In vitro dissolution Test, Characterization* | M. Serratoni et al.2007  
10. | Nifedipine | microcrystalline cellulose (MCC) and a lactose monohydrate | Pellets | *In vitro dissolution Test, In-vivo study* | Z. Wang et al. 2010  

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