Lipid-based drug delivery (LBDD) is an effective method of improving the solubility of BCS Class II and Class IV compounds and the permeability of certain BCS Class III and Class IV compounds. Typically, LBDD systems are formulated by dissolving the therapeutic compound in one or more lipids to form a pre-concentrate. Subsequently, this pre-concentrate forms a drug containing oil-in-water emulsion in the gastrointestinal (GI) tract through the actions of enzymes and bile salts or by self-emulsification of the lipid components.

Traditionally, the employed lipids have been liquid at room temperature. Recently, it has become of greater interest to develop solid LBDD pre-concentrates which can offer certain advantages over liquids, most specifically ease of incorporation into tablets and other solid oral dosage forms, their stability and ease of manufacture.

The formulation of solid LBDD pre-concentrates is not a trivial process as attention needs to be paid to the physical state of both the therapeutic compound and the pre-concentrate lipids, as well as the dispersion of the solid pre-concentrate into an oil-in-water emulsion in the GI tract, in order to ensure drug delivery.

**METHODS OF MANUFACTURING S-SEDDS**

There are many methods available for the preparation of solid self-emulsifying drug delivery systems (s-SEDDS) including filling capsules with semi-solids, adsorption of the SEDDS pre-concentrate onto suitable substrates, congealing and nanoparticle formation.

**Semi-Solid Capsule Filling**

In this method of s-SEDDS manufacturing, there is a combination of SEDDS pre-concentrate components, which are liquid at room temperature with a solidifying agent, which is normally a lipid surfactant or co-surfactant that is solid at room temperature.

The components are brought together in the liquid state and filled into capsules and other solid oral dosage forms, their stability and ease of manufacture.

**“The formulation of solid LBDD pre-concentrates is not a trivial process as attention needs to be paid to the physical state of both the therapeutic compound and the pre-concentrate lipids.”**

**Dr John K. Tillotson**

Pharmaceutical Technical Business Director (Americas)

T: +1 616 990 4726

E: jtillotson@abiteccorp.com

**ABITEC Corporation**

501 W 1st Ave

Columbus

OH 43215

United States

www.abiteccorp.com
allowed to solidify. A typical approach is
to bring together the liquid pre-concentrate
components with the solidifying agent under
heat in order to create a continuous liquid
phase of all materials.

The active pharmaceutical ingredient
(API) is then dissolved in the hot pre-
concentrate, and subsequently, the hot pre-
concentrate is then filled into capsules. As
the hot pre-concentrate cools, the solidifying
agent comes out of its molten state and
incorporates the liquid pre-concentrate
components into a solid form or semi-solid
form, which contains the active.

Selection of the proportion and type
of pre-concentrate components is very
important for two reasons:

- The components must be selected in a
  manner allowing for re-solidification of
  the pre-concentrate upon cooling
- Solid / semi-solid pre-concentrate should
disperse into, preferably, a micro-emulsion
upon contact with aqueous media.

For example, it was found that for
a probucol formulation a combination
of a solid lauroyl macrogolglyceride,
medium chain triglyceride and an
ethoxylated castor oil were suitable for
solidification, dissolution and emulsifying
characteristics (see Figure 1).²

In the same study, propylene
glycol monocaprylate and glycerol
monocaprylooctanoate could not be suitably
solidified by the lauroyl macrogolglyceride.
Additionally, the addition of an ethoxylated
caster oil as a co-surfactant was necessary
to provide for adequate active dissolution
and emulsion formation in the aqueous
environment.

Substrate Adsorption
The objective of this method of
manufacturing is to deposit a liquid SEDDS
pre-concentrate onto a suitable carrier in
order to produce a free-flowing, SEDDS-
containing powder, which can be employed
for subsequent unit operations such as
tableting. These SEDDS powder systems
may be prepared by various methods
including direct mixing, high-shear
granulation, vacuum deposition and
fluid-bed layering/granulation.

As with any SEDDS system, it is
important to optimise the pre-concentrate
components, such as primary and secondary
solubilisers, surfactants and co-surfactants
to achieve maximum drug loading in the
pre-concentrate as well as suitable emulsion
characteristics such as emulsion globule size.
Once an optimal SEDDS pre-concentrate is
developed, it can be applied to a substrate as
described above.

Election of the substrate is also
important, as well as the interaction of
the substrate with the pre-concentrate.
The most important characteristics of the
substrate are:

- The extent to which the liquid pre-
  concentrate can be absorbed by the substrate

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Figure 1: Dissolution of probucol from s-SEDDS.

Figure 2: Average emulsion globule size for (A) 1:1 Captex 355 EP/NF:Cremophor EL, and (B) 3:1 Captex 355 EP/NF:Cremophor EL
([a] without probucol, [b] with probucol, [c] without probucol, [d] with probucol).²
onto water soluble substrates may only the deposition of SEDDS pre-concentrate lactose; however, this may result in a tacky, soluble substrates, such as mannitol or drug release. From the carrier. This results in incomplete concentrate is not always readily released and small pore size of the silica, the pre-concentrate for s-SEDDS. As in the aforementioned study, silica substrates release from the s-SEDDS. As in the spray-congealing, similar to the development of a liquid SEDDS pre-concentrate, requires formulation optimisation towards maximising drug solubility and achieving the desired emulsion characteristics.

Multiple SEDDS pre-concentrate formulations containing rosuvastatin were deposited onto colloidal silicon dioxide by mixing, followed by dissolution tests.

Of 12 s-SEDDS formulations tested only one provided adequate drug loading, particle size and acceptable drug release. This highlights one of the primary difficulties with this manufacturing methodology — obtaining adequate drug release from the s-SEDDS. As in the aforementioned study, silica substrates are often chosen for this application, as they can absorb large amounts of oil. However, due to the hydrophobicity and small pore size of the silica, the pre-concentrate is not always readily released from the carrier. This results in incomplete drug release.

Additionally, it is possible to adsorb lipid pre-concentrates onto the surface of water soluble substrates, such as mannitol or lactose; however, this may result in a tacky, non-free-flowing powder. For this reason, the deposition of SEDDS pre-concentrate onto water soluble substrates may only be suitable for low-dose actives, requiring less pre-concentrate for dissolution of the active, leading to a lower pre-concentrate proportion in the s-SEDDS.

**Spray-Congealing**

In spray-congealing, a molten lipid system carrying an active is sprayed into an expansion chamber where the molten material re-solidifies at the lower temperature to produce an active carrying multi-particulate s-SEDDS (Figure 3). Essentially, the molten lipid matrix is the pre-concentrate for s-SEDDS prepared in this manner.

The particle size distribution of the multi-particulate is determined by nozzle diameter and air pressure brought into the nozzle during spraying. Alternatively, in certain systems, a rotary disc which receives the molten material from a nozzle can control the particle size of the multi-particulates by controlling the rotational velocity of the disc.

The objective of an s-SEDDS prepared by congealing is to maintain the active in the amorphous state (if possible) during and after processing. For this reason, it is preferable to match the melting point of the active with the melting point of lipid pre-concentrate components.

In practice, this is not always possible, as the lipids tend to have lower melting points than many actives. This does not preclude employing spray-congealing as a unit operation for improving the solubility of actives. In fact, in an s-SEDDS for glibenclamide prepared by spray-congealing, despite the presence of crystalline glibenclamide in the final s-SEDDS multi-particulate, a five-fold increase in the dissolution rate of glibenclamide was obtained from the s-SEDDS as compared with the raw active.

This indicates that spray-congealing can provide significant increases in dissolution rate even when some of the active remains in the crystal state after processing. Additionally, as the components of the molten pre-concentrate are solubilising lipids, the active can dissolve into the molten lipid matrix rather than melt entirely. The development of a pre-concentrate blend for s-SEDDS for spray-congealing, similar to the development of a liquid SEDDS pre-concentrate, requires formulation optimisation towards maximising drug solubility and achieving the desired emulsion characteristics.

**Solid Lipid Nanoparticles**

Solid lipid nanoparticles (SLN) s-SEDDS are very small multi-particulate systems typically with a size of 100–200 nm. There are several manufacturing methods for producing SLN s-SEDDS, including high-shear homogenisation, high-pressure homogenisation (HPH) and solvent emulsiﬁcation/evaporation.

The most common of these is HPH, wherein a lipid matrix (containing API) is pushed through a very narrow gap (several microns) under high pressure (100-2000 bar) to create nanoparticles from the resulting high shear forces generated in this process. In hot HPH (Figure 4, left-hand side), the homogenisation is carried out at temperatures above the melting-point of the lipid pre-concentrate; and therefore, it is the homogenisation of an emulsion. In cold HPH (Figure 4, right-hand side), the conditions are controlled (refrigeration) such that the heat generated by the process is well below the melt point of the excipients present. It is noted that for both hot and cold HPH, the active must first be incorporated into the molten pre-concentrate lipids. One major advantage of cold HPH is that it can be employed to process heat labile actives.

s-SEDDS SLNs can be administered by multiple routes including peroral, transdermal, parenteral, intraocular, inhalation and transfollicular.

There are three basic models proposed for the incorporation of actives into manufactured s-SEDDS SLNs:

- Homogeneous matrix
- Active-enriched shell
- Active-enriched core.
CONCLUSION

While liquid SEDDS systems have been more commonly employed in the pharmaceutical industry, there are many advantages to s-SEDDS formulations. These include improved stability, ease of manufacture and the ability to formulate modified release characteristics.

While there are many techniques to manufacture s-SEDDS resulting in products with varying functionalities and applications, the optimisation of the pre-concentrate lipid components is the same as for liquid SEDDS: optimisation is based upon maximising drug solubility and loading as well as the final emulsion characteristics of the pre-concentrate.

While the concept of s-SEDDS has been around for quite some time, further research and optimisation of these formulations must be realised, in order for this dosage form to be more readily accepted and employed in marketed pharmaceutical products.

REFERENCES


About the Author

John Tillotson’s research areas include functional lipids, SEDDS system development and direct compression tableting.