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METHODOLOGIES FOR DEVELOPING s-SEDDS

The use of solid self-emulsifying drug delivery systems is growing in popularity as they offer advantages over liquids, such as the ease with which they can be incorporated into tablets and other solid oral dosage forms, their stability and ease of manufacture. John K Tillotson, RPh, PhD, looks at the various methods available for manufacturing these systems and explores the possibilities of optimising these methods in the future.

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.

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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, improved stability, and specific dosage form characteristics such as sustained-release or abuse-deterrence. 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.[1]

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

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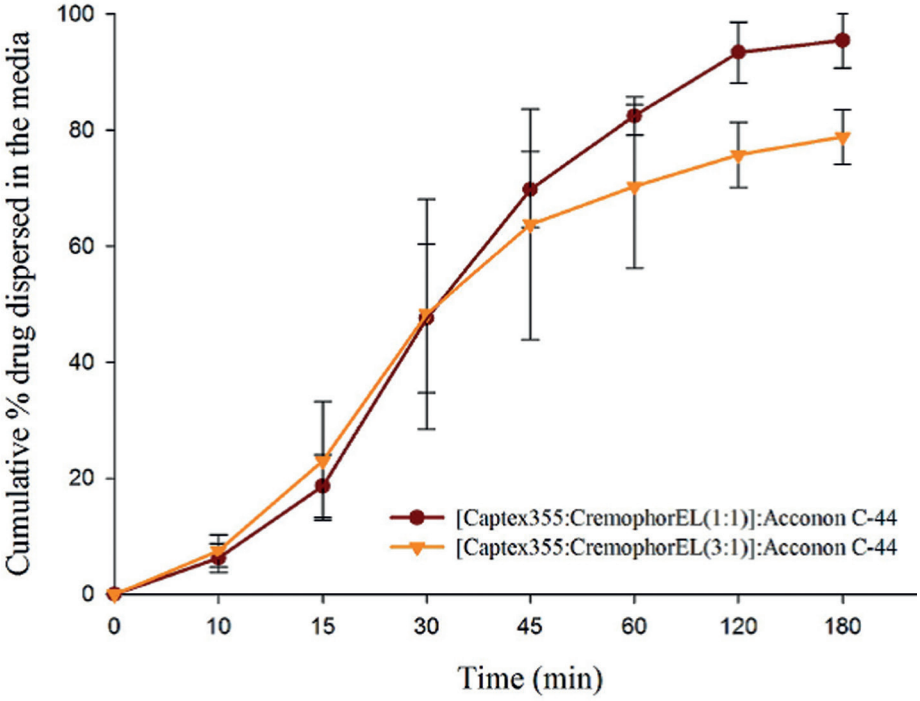

Figure 1: Dissolution of probucol from s-SEDDS.

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 monocaprylocaprate could not be suitably solidified by the lauroyl macrogolglyceride. Additionally, the addition of an ethoxylated castor 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

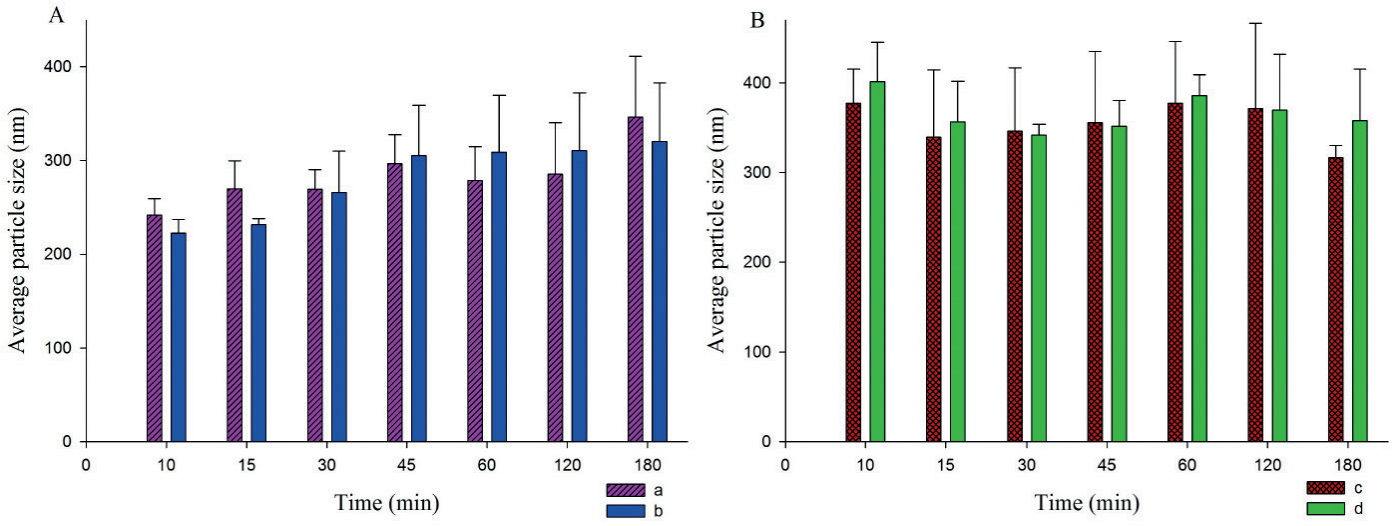

Figure 2: Average emulsion globule size for (A) 1:1 Captex 355 EP/NF:Cremophor EL, and (B) 3:1 Captex 355 EP/NF:Cremophor EL [(a) without probucol, (b) with probucol, (c) without probucol, (d) with probucol.][2]

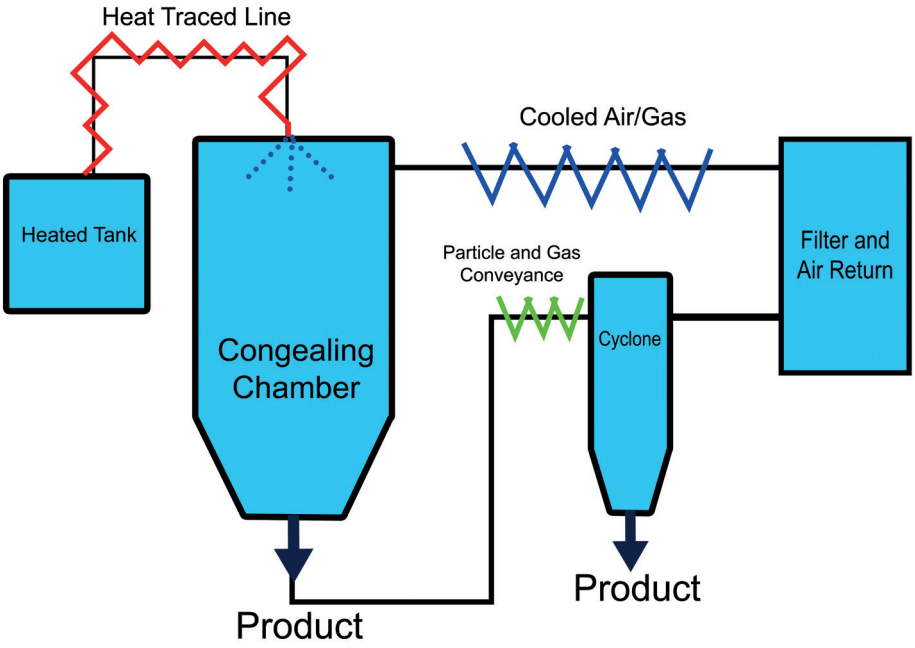

Figure 3: Schematic of a spray-congealing system.

- The ease with which the pre-concentrate is released by the substrate
- The ability of the substrate to maintain flow characteristics after SEDDS deposition
- The ability of the substrate to maintain compaction characteristics after SEDDS deposition, especially for tableted dosage forms.

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.[3] 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.[4]

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 presences 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.[5]

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.[6]

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.[7]

The structure ultimately obtained is a function of the active and the pre-concentrate lipids, as well as the manufacturing unit operation. The type of API distribution in the lipid can have a profound effect on release characteristics, as an active-enriched shell will likely release more rapidly; while in contrast, an active-enriched core may lead to diffusion-based sustained release.

Ultimately, the formulation of s-SEDDS SLNs is optimised on the same basis as other s-SEDDS formulations by optimising API solubility and loading with the desired characteristics of the final emulsion.

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.

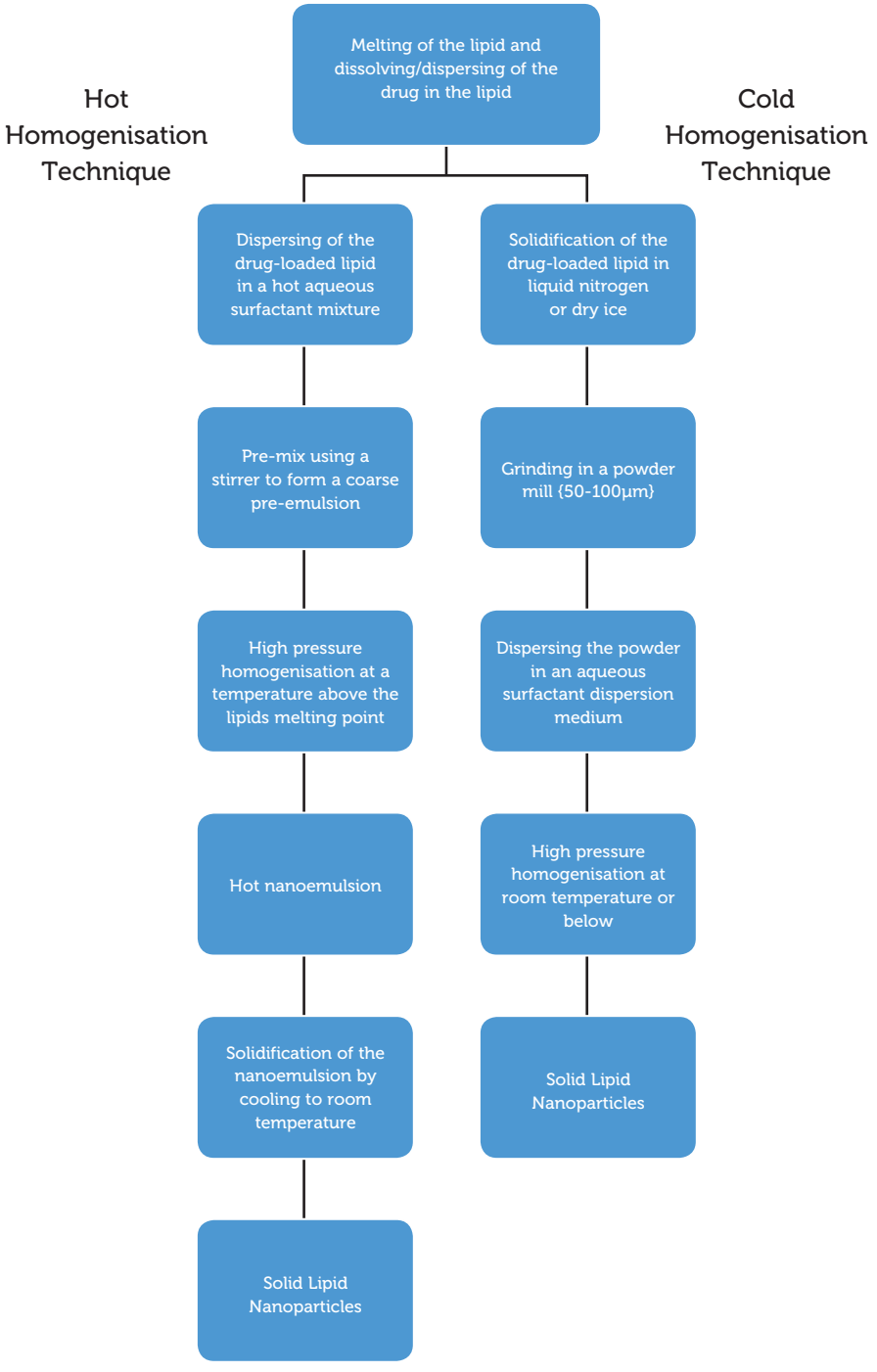

Figure 4: Schematic of SLN production by hot and cold HPH.[6]

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ABOUT THE AUTHOR

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