

# Benefits Of Using The Right Carrier For Solid Dispersion Systems

As early as the 1960's, the first solid dispersion technique had improved the bioavailability of poorly-water soluble drugs. Almost 50 years on and significant advances of solid dispersion knowledge, the technique still only has a few commercial examples to name. This could set to change because current solid dispersion strategies and new raw materials may have overcome previous limitations which may offer genuine solutions for formulators. This article focuses on the latest generation of solid dispersions which are made up of the poorly-water soluble drug, non-soluble adsorbent carrier; and a polymer, surfactant or emulsifier (Figure 1). Technically, this is an amorphous solid suspension as opposed to a true solid solution yet it offers a workable compromise.

Even with the latest Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) converting a solid dispersion powder into the ideal oral solid dosage form can also poses a great

challenge to formulators. Selecting a suitable adsorbent non-soluble carrier is equally as important as the choice of solubilizer in order to maintain bioavailability. (Figure 2)

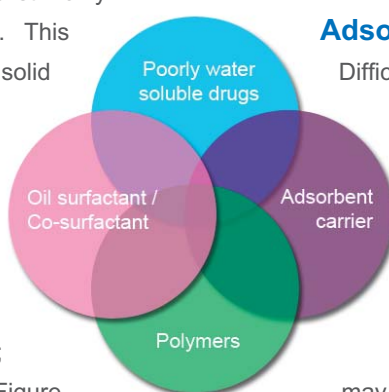


Figure 1. Basic components of adsorbent based Amorphous Solid Dispersion

## Adsorbent Carrier Challenges

Difficult to process powders (pulverization, poor compressibility, poor flow, scale-up) and amorphous stability (conversion of amorphous forms back to crystalline form) are the major problems associated with commercialization of this technology. Solid powders with low particle size have poor flowability and may stick to the tableting machines making it difficult to handle. The amorphization achieved by solid dispersion may have stability problems due to temperature or moisture stress during storage. Undoubtedly, the physical and chemical properties of the carrier will impact the bioavailability. (Figure 3)

Figure 2. Three methods to apply adsorbent carriers in different solid dispersions

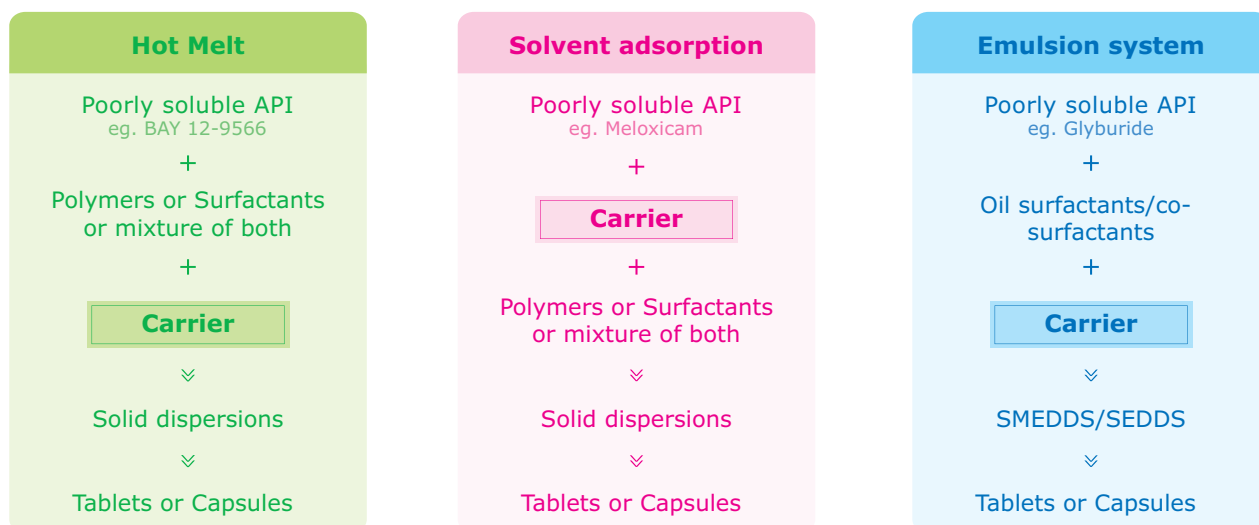


Figure 3. Suitable Properties of a Carrier for Solid Dispersions

- ☑ Drug loading capacity
- ☑ Flow index
- ☑ Compressibility index
- ☑ Surface area/adsorption capacity
- ☑ Ability to protect drug from moisture

### Silicate based Carriers

Calcium silicates, colloidal silica and magnesium aluminometasilicates have been used in several solid dispersion preparations. Some of these are very promising and may lead to scale-up and future commercial preparations.

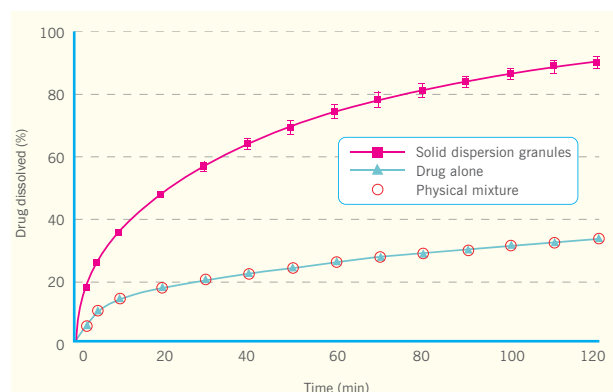
### Hot Melt Granulation

In developing a solid dispersion system for the drug BAY 12-9566, Gupta *et al.*,<sup>1</sup> prepared ternary dispersion granules using hot-melt granulation. First, the candidate drug BAY 12-9566 was added to a molten solid dispersion carrier, Gelucire® 50/13 maintaining a temperature of 90°C. Neusilin® US2 was preheated to 80°C in a granulator for 15 min with stirring at 300 rpm. The molten mixture was then added drop-wise over a period of one minute to Neusilin® with continued stirring. Hot melt granulation was performed at an increased stirring speed of 600 rpm for one more minute to obtain ternary dispersion granules of drug, Gelucire® 50/13 and Neusilin® US2. The dispersion granules were allowed to come to room temperature by air cooling followed by sieving through mesh #18 BSS. The free flowing granules of the dispersion were processed into tablets.

Dissolution profiles of BAY 12-9566 from dispersion granules were determined using a USP Type II apparatus at 75 rpm. Dissolution profile of the ternary dispersion granule when compared to drug alone and that from the physical mixture of an equal amount of drug, Gelucire® 50/13 and Neusilin® US2 showed considerable enhancement. Drug dissolution profile showed an increase of 60% to reach 90% over a period of 2 hours (Figure 4).

Although it is widely accepted that the high-energy amorphous state of the drug in solid dispersions tends to revert to low-energy crystalline form on storage, dispersion granules with Neusilin stored at 40°C/75% RH, showed

Figure 4. Comparison of dissolution profiles of BAY 12-9566 in 0.1 N HCl, 1% SLS using USP Type II apparatus at 75 rpm. Drug dissolution profile from solid dispersion granules; corresponding physical mixture and drug alone. N=3, bar represent standard deviation – ref: Gupta *et al.*, 2001



improved physical stability of amorphous state<sup>2,3</sup>.

Neusilin® has been demonstrated as an excellent adsorbent carrier with several other BCS class II drugs such as meloxicam<sup>4</sup>, naproxen, ketoprofen and other highly permeable but poorly water soluble drugs.

### Self-Microemulsifying Drug Delivery Systems (SMEDDS)

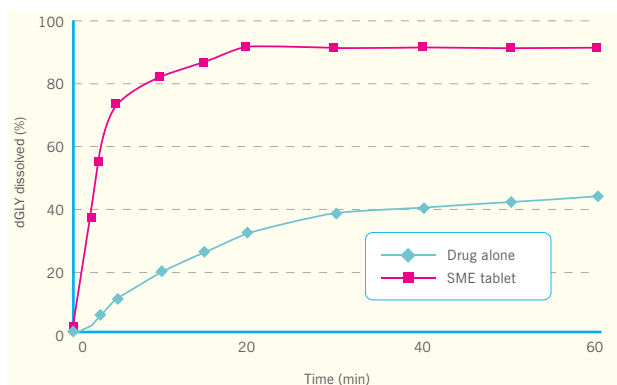
SMEDDS is useful particularly if the formulation process does not require a hot-melt step. Silicate based adsorbent carriers have also been successfully demonstrated with SMEDDS. For example, capsules and tablets of Piroxicam and Ketoprofen prepared with SMEDDS (Labrasol®/ Labrafil®)-Zeopharm® showed better dissolution when compared to that of an SMEDDS preparation with Neusilin®<sup>5</sup>. However, in another example with Glyburide, a silicate carrier such as Aerosil® was excluded because it did not give the desired Flow Index. Zeopharm® 5170 and Aeroperl® had the lower Flow Index when compared to Neusilin® after SMEDDS adsorption. Despite this, Table 1 shows that the Neusilin-SMEDDS formulation resulted in

Table 1. Composition and properties of SMEDDS tablets - adapted from Catarzi *et al.*, 2008

	Neusilin®	Aeroperl®	Zeopharm®
Glyburide (mg)	5	5	5
Self-microemulsifying formulation (mL)	800	800	800
Adsorbent (mg)	350	350	350
Sodium Carboxymethyl Cellulose (mg)	-	400	400
Croscarmellose Sodium (mg)	95	50	50
Magnesium Stearate (mg)	5	10	10
Tablet weight (mg)	1,255	1,615	1,615
Hardness (N)	50	30	10
Disintegration time (min)	9-12	8-13	-

the hardest tablets with lowest tablet weight. This is only possible because of Neusilin®'s physical characteristics. Furthermore, Neusilin® SMEDDS tablets had similar disintegration times compare to Aeroperl®. The dissolution profile obtained from the final tablets showed improved profile when compared to Glyburide alone<sup>6</sup>. (Figure 5)

Figure 5. Dissolution profile of Glyburide SMEDDS tablets - adapted from Catarzi *et al.*, 2008



## Outlook

Solid dispersions remain attractive because 40% of promising NCEs launched in the US market are poorly water soluble drugs. Fuji's Neusilin® US2 and other excipients with similar physico-chemical properties (high specific surface area, surface adsorption, porosity, anticaking and flow enhancing properties) allow formulators to explore solid dispersion technology (again) to improve bioavailability and overcome problems associated with processing and stability of poorly water soluble drugs. An additional advantage of Neusilin® as a carrier for solid dispersion is that unlike other silicates which are either acidic or alkaline in their surface properties, Neusilin® is neutral. This may overcome incompatibility problems with the candidate drug leading to more stable formulations.

Lastly, amorphous solid dispersion stability issues need to be addressed in more detail to successfully commercialize solid dispersion technology. There are positive indications so far in that Neusilin® US2 maintained the amorphization and in-turn, bioavailability for at least 4 weeks at 40°C/75% RH. Stability studies of amorphous BCS class II drugs after ball milling with Neusilin® US2 were found physically stable after storage of 3 to 6 months at 40°C/75% RH.

## References:

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