

Worried About the Stability of Your Solid Dispersions?



Incorporate Neusilin®

Solid dispersion system has shown great promise in improving the dissolution properties of poorly water-soluble drugs. Although a significant amount of knowledge has been accumulated about solid dispersion, very few commercial examples are available to rate the technology a success. Amongst the problems, stability of amorphous solid dispersion remains one of the serious concerns to formulators. Recent publications as well as patents validate that Neusilin® keeps the drug amorphous and stable under accelerated stability conditions as well as at room temperature for up to three years. The scope of this article is to provide examples of stable solid dispersion with Neusilin® giving a very positive outlook for commercialization.

Fuji's Neusilin® comes with high specific area, increased surface adsorption, porosity, anticaking and flow enhancing properties. These features of Neusilin® allow formulators to explore solid dispersion technology to improve bioavailability and overcome problems associated with processing and stability of poorly water soluble drugs. The physical and chemical stability of the amorphous state of drug-Neusilin® complexes is well documented. Gupta *et al*¹ reported the amorphization of both acidic and basic drugs through ball milling with Neusilin®. The drugs were found to be physically stable for up to 4 weeks when stored at 40°C/75% relative humidity (RH). Vadher *et al*² reported complete amorphization

and stability of Aceclophenac-Neusilin complex for up to 4 weeks at 40°C/75% RH conditions.

Neusilin® has also been demonstrated as an excellent adsorbent carrier for solid dispersion preparation via hot melt granulation³, Self Micro-Emulsifying Drug Delivery Systems (SMEDDS)⁴ for BCS class II drugs such as meloxicam, naproxen, ketoprofen, glyburide and other highly permeable but poorly water soluble drugs. The most exciting use of Neusilin® in Hot Melt Extrusion (HME) was recently reported by Maclean *et al*⁵. HME was prepared by simple mixing of crystalline drug and Neusilin® before passing it through the extruder. The samples were recovered as amorphous powder and converted to highly stable tablets through direct compression.



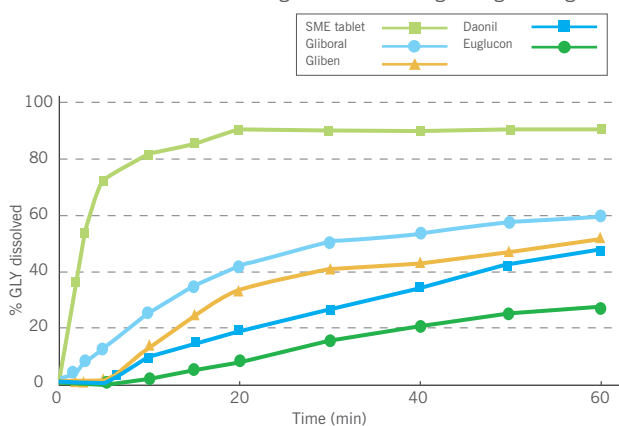
Case Study I

Production of Stable Self-Microemulsifying Drug Delivery Systems (SMEDDS) of Glyburide

Mura *et al*⁴ reported production of Glyburide SMEDDS tablets with Neusilin[®] which demonstrated increased physical and chemical stability. Glyburide, 5 mg (the therapeutic drug dose) solubilized in 0.8 ml SMEDDS was adsorbed on to 350 mg Neusilin[®] US2 or other adsorbents to obtain free flowing powder. The liquid SMEDDS consisted of Labrafac[®] Hydro WL 1219 (6%) as oil phase, Transcutol[®] (47%) as co-surfactant and Tween[®] 20 (47%) as surfactant. Briefly, the accurately weighed drug amount was dispersed into the mixture of oil, surfactant and co-surfactant. The resulting mixture was then stirred until Glyburide was completely dissolved to obtain liquid SMEDDS. Powderized SMEDDS with Neusilin[®] and AcDiSol were mixed in a tumbler mixer for 15 min. The resulting mixture was sieved in a 35 mesh ASTM screen before adding Magnesium stearate. After a short additional mixing for 2 min, the blend was tableted using a single-punch tablet press.

Other adsorbents considered were Aeroperl[®] 300, Aerosil[®] 200 and 380, Aerosil[®] R972, Zeopharm[®] 177 and 5170. Aerosil[®] 380, R972, 200 and Zeopharm[®] 177 were rejected due to poor flow and compaction properties after adsorption of SMEDDS. Although Aeroperl[®] 300 and Zeopharm[®] 5170 showed better flow properties than Neusilin[®] US2, they practically showed no compacting propensity and needed additional filler binders which increased overall tablet weight (1,255 mg for Neusilin[®] vs 1,615 mg for Aeroperl[®] 300) without any improvement in tablet characteristics. Glyburide SMEDDS tablets with Neusilin[®] allowed 90% of the drugs to be dissolved after only 20 min, while the commercial formulations containing the same drug dosage reached values ranging from 30-60% dissolved after 60 min (Fig 1).

Fig 1. Dissolution curves of Glyburide-SMEDDS tablets with Neusilin[®] and commercial drugs with same drug dosage (5 mg)

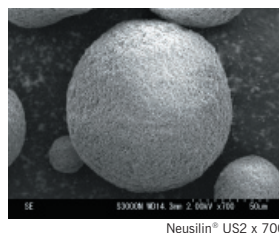


Stability Studies

Glyburide SMEDDS tablets with Neusilin[®] were stored in closed glass containers at 25°C and 60% RH for up to six months to test the physical and chemical stability. The tablet characteristics, particularly the tablet hardness and disintegration time did not change appreciably for the tested storage period. The drug dissolution profile after the storage period remain unchanged in terms of both % dissolved drug and dissolution efficiency with respect to that of fresh tablets ($P > 0.05$). Furthermore, the drug content remained almost constant during the whole of storage period. The results indicate that there was no degradation of drugs either through oxidation or hydrolysis thus confirming the stability of Glyburide-SMEDDS tablets with Neusilin[®].

Case Study II

Production of Stable Powderized Solid Lipid Nanoparticles (SLN) of Carvedilol Phosphate



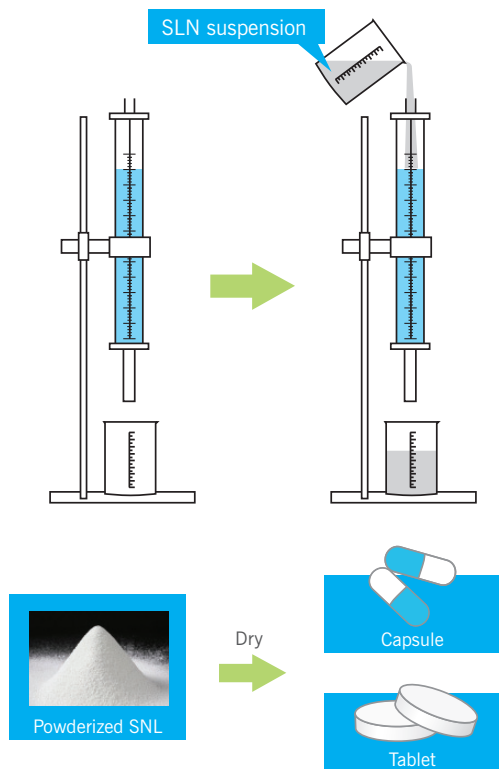
Chakraborty *et al*⁶ used Neusilin[®] to improve the stability and physical properties of solid lipid nanoparticles (SLN). In an aqueous nanodispersion, SLN have a tendency to undergo particle aggregation during accelerated stability storage

conditions due to the gelation phenomenon. The normal route to improve stability is through lyophilization of the aqueous form. Lyophilization, apart from being costly, is also a difficult technique to optimize as the rate of freezing governs the structure and properties of the lipid crystals that ultimately determine the drug retention capacity during storage. Other bottle necks include high levels of surfactants on the external phase of SLN which can be toxic to the mucosal lining of the GIT as well as leaching of drugs during long term storage resulting in reduced drug loading efficiency.

In a unique approach, Carvedilol phosphate SLN was converted to a free flowing powder by adsorbing on to Neusilin[®] US2. SLN suspension was prepared by solvent emulsification evaporation technique. For detailed method of preparation, please refer to the original publication by Chakraborty *et al*⁶. The SLN suspension was converted to a powder using the following method. A 2 ml glass syringe after removing the plunger was fixed to a burette holder and 50 mg of Neusilin[®] US2 was packed into it by gentle tapping. The nanodispersion was then allowed to drop gently on the top surface of the column and the eluent was collected. The process was repeated until saturation point of the adsorbent.

Fresh lots of Neusilin® US2 were used to cover one batch of SLN suspension. SLN saturated Neusilin® US2 was later dried at room temperature for 24h to obtain Adsorbed Lipid Nanoparticles (ALN).

Fig 2. Schematic representation of converting SLN to ALN (adapted from Chakraborty *et al*⁶)



Stability Studies

The drug release profile of SLN and corresponding ALN for initial and 3 months after storage at room temperature are shown in Fig 3 and 4. The rate of drug release of SLN and ALN in 0.1 N HCl was found to be higher than the release in pH 6.8 sodium phosphate buffer.

Fig 3. Drug release profiles in 0.1 N HCl

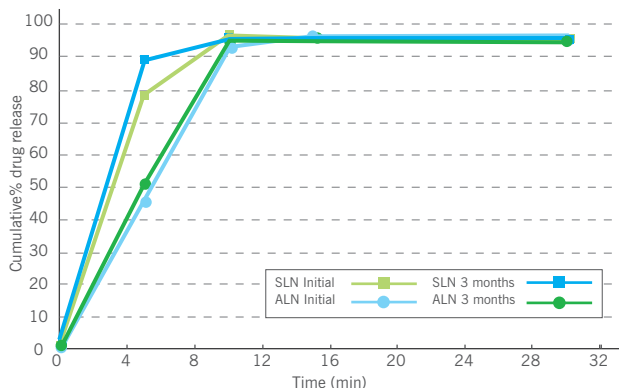
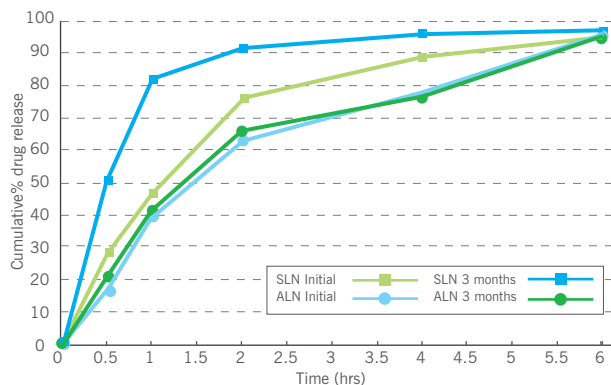


Fig 4. Drug release profiles in pH 6.8 sodium phosphate buffer



The stability studies under room temperature for 3 months showed no significant changes in the drug content, particle size and dissolution profile of ALN as well as the pH of the SLN. However, a significant decrease in drug loading efficiency, from initial 94% to 62% after 3 months storage of SLN was observed. On the other hand, no significant changes in dissolution profile or drug loading efficiency was observed in case of ALN indicating improved stability of the powdered solid lipid nanoparticles of Carvedilol phosphate with Neusilin®.

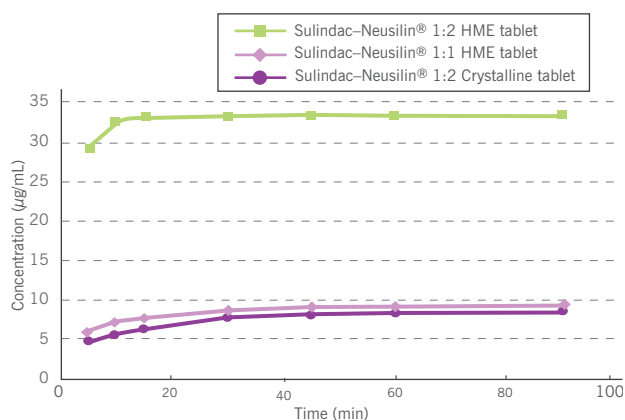
Case Study III

Manufacture of Stable Sulindac-Neusilin® Amorphous Drug Complex using Hot Melt Extrusion (HME)

Maclean *et al*⁵ reported a break-through utilization of Neusilin® in HME. The group succeeded in preparing a stable amorphous drug complex without any addition of polymers, waxes or plasticizers normally associated with HME. Blends of Sulindac-Neusilin® in 1:1 and 1:2 (w/w ratio) were prepared by mixing the components and charging them to the Brabender single-screw volumetric feeder that fed directly into the extruder hopper at 5% feed rate. The material was then extruded using a Prism PharmaLab 16 mm twin-screw extruder (25:1 L/D). The screw speed was set to 50 rpm for the duration of extrusion process. Conversion of the crystalline to amorphous complex was observed when HME was conducted at a temperature of 200°C, which is above the melting point of Sulindac. The sample was recovered as powder from the HME apparatus thus avoiding a fair amount of downstream processing. The powder was then compressed into 100, 200 and 500 mg tablets. Sulindac-Neusilin® 1:2

HME tablets showed 100% release in 90 min as against 9% release of crystalline Sulindac-Neusilin® tablets of the same ratio (Fig 5).

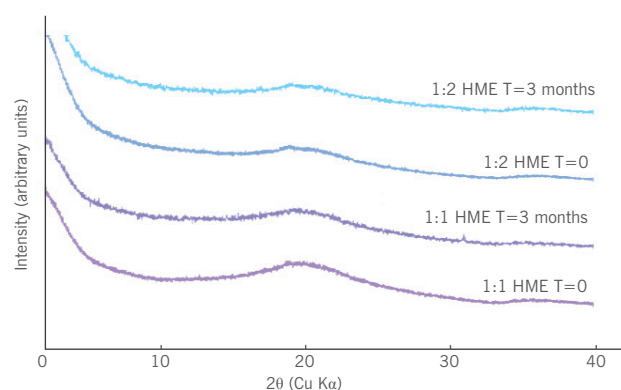
Fig 5. Dissolution profiles of HME Sulindac-Neusilin® tablets



Stability Studies

The HME samples remained amorphous after 3 months of storage at 40°C/75% RH (Fig 6). The 1:2 Sulindac-Neusilin® samples were found to remain amorphous for more than 17 months at ambient conditions. The HPLC analysis during and after the storage period showed no chemical degradation thus confirming the physical and chemical stability of amorphous phase. It is significant to note that amorphous Sulindac without the presence of polymers can crystallize in 24 h at ambient conditions and in about 2 weeks in the presence of 1:1 ratio of Sulindac-Polyvinylpyrrolidone⁵.

Fig 6. XRPD data of Sulindac-Neusilin® HME samples stored at 40°C/75% RH. All samples remained amorphous for 3 months.



Outlook

The three examples published by independent research groups clearly demonstrate that a combination of drug with Neusilin® remain stable for relatively long period of storage under accelerated as well as ambient conditions. Literature reveals that the status-quo is true for a broad class of acidic drugs as well as non-acidic drugs. Neusilin® is available in

neutral and alkaline form with different particle size, bulk density and adsorption capacity to suit a variety of APIs. Commercialization of stable amorphous drug complexes with Neusilin® is not a big hurdle anymore with availability of techniques like SMEDDS and HME.

Fuji Chemical Industry Co., Ltd. based in Toyama, Japan manufacture Neusilin® using its spray dry technology. Neusilin® is a totally synthetic, amorphous form of Magnesium Aluminometasilicate (MAS) that can be used both in pharmaceutical and cosmetic preparations. Neusilin® has been in the Japanese market for over 50 years and over 500 drug formulations in Japan alone is testimony to its multifunctional capabilities. Fuji also manufactures other unique excipients, Fujicalin® (dibasic calcium phosphate anhydrous) and F-MELT® (an excipient system for oral disintegrating tablets).

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