Amorphization of Pharmaceuticals by co-grinding with Neusilin®

Amorphization of crystalline drugs can be achieved through several methods. The most common method is melting and solidification by rapid cooling over liquid nitrogen or slow cooling at room temperature. Other methods for drug amorphization include milling, solvent evaporation, spray drying, and lyophilization. Solid state amorphization can be achieved through high energy milling or co-grinding drugs with excipients leading to micronized particles with particle size distributions at submicron levels. These amorphous forms are in a higher energetic state compared to its crystalline counterpart and therefore, provide an advantage in terms of solubility, dissolution and bioavailability. Such amorphized forms of crystalline drugs leads to a marked improvement in their dissolution rates and bioavailability.

In a previous report, we discussed solid dispersion methods using Neusilin® as an adsorption carrier to improve dissolution and bioavailabilty of poorly water soluble drugs. In this report, we present a much simpler method of co-grinding drugs with Neusilin® to overcome limitations to scale-up with solid dispersion methods. Poor water solubility is a major bottle neck for the nearly 40% of new chemical entities (NCE's) launched world-wide and co-grinding option with Neusilin® is a welcome method to overcome this hurdle. The scope of this technical paper is not to cover the entire pros and cons of co-grinding poorly water soluble drugs with excipients but to highlight the application of Neusilin®, a synthetic form of Magnesium Aluminometasilicate as an excipient for co-grinding.

Table 1. Approaches to improve bioavailability of poorly water soluble drugs

Methods	Advantages	Limitations
Co-grinding / Milling	Simple, Scalable, grinding with suitable materials prevent re-crystallization Improves wettability, solubility, dissolution Improves stability	Low temperature or Cryo- grinding required for faster amorphization and temperature sensitive actives
Solid dispersion (Hot melt, Solvent evaporation, SMEDDS)	Results in colloidal particles with small particle size Improves wettability, solubility, dissolution Improves stability	Degradation of API at higher molten temperatures Scale up

Conventional milling

For practical formulation reasons, milling crystalline drugs may be the easiest route to induce amorphization or transformations to other crystal polymorphs. However, milling, although can bring about particle size reduction or convert the crystalline state of a drug to amorphous state, stability of these formulations are at greater risk due to partial amorphization, milling temperatures, etc. Milling usually results in high energetic particles which tend to revert back to crystalline forms unless high amount of surfactant or stabilizer is added to the formulation. These could in turn reduce the solubility and dissolution. Jet milling or ball milling can also introduce moisture which produces clumps in the mixture leading to handling problems and poor yield.

Co-grinding with excipients

A number of successes have been reported by co-grinding crystalline drugs with excipients. The common excipients that have been used for co-grinding are polyvinylpyrrolidone, microcrystalline cellulose, cyclodextrins and various silicates including Neusilin®. The examples of drugs that showed improvement in dissolution and or solubility drugs after co-grinding with excipients include sulfathiazole, indomethacin, aspirin, ketoprofen, naproxen progesterone, glebenclamide and new chemical entities.

Case studies

1.Indomethacin with Neusilin US2

Indomethacin is a non-steroidal anti-inflammatory drug that reduces fever, pain and inflammation. It is a crystalline and poorly water soluble drug and the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. Co-grinding indomethacin with Neusilin®US2 in the ratio 1:5 at 75% RH for 5 days at room temperature in a rolling jar mill consisting of a cylindrical porcelain jar and zirconia balls resulted in complete amorphization (Fig 1,2).

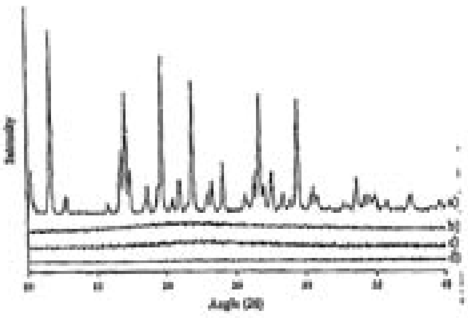

Fig 1. Powder X-ray diffraction scans of a) crystalline indomethacin, b) amorphous indomethacin (melt –quenched), c) amorphous

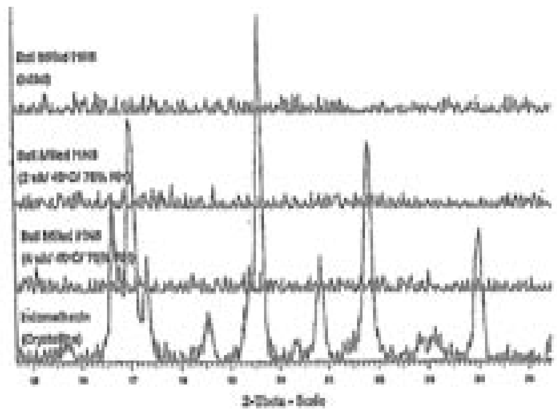

Fig 2. XPD spectra of ball milled powder of indomethacin before and after storage up to 4 weeks at 40°C, 75% RH. Ref: Gupta et al., 2003

Solubility and dissolution profiles were evaluated using powders in a USP type II dissolution apparatus. Dissolution profiles of indomethacin co-ground with Neusilin US2 initially and at 1 to 3 months of storage at 40°C/75% RH showed a slight increase in the maximum transient concentration (MTC) from the initial sample to the sample stored for 1 month. Further storage for 2 months did not change the MTC. The maximum sustained concentration (MSC) at the start was 13 times higher than the solubility of crystalline indomethacin and increased with storage time (Fig 3).

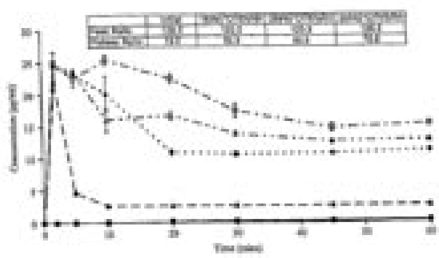

Fig 3. Dissolution profiles (n=3) of indomethacin co-ground with Neusilin US2 (1:5 w/w) in O.1 N HCl (900 ml) : - initial; – 1 month at 40°C, 75% RH, - 2 months at 40°C,▲ 75% RH,◆ - 3 months at 40°C, 75% RH□ – crystalline indomethacin. Ref: Bahl et al., 2008 ■

Amorphous solids of Indomethacin co-ground with Neusilin US2 (1:4 and 1:5) at 75% RH was physically stable for 3 to 6 months when stored at 40°C and 75% RH. A further investigation of pore volumes and pore diameters for the initial and stored samples revealed no difference suggesting that there is no further deposition or depletion of drug from the pores of Neusilin US2 during storage.

2.Aceclofenac with Neusilin US2

Aceclofenac is a non-steroidal analgesic, antipyretic and anti-inflammatory drug belonging to poorly water soluble BCS class II drug. Co-grinding aceclofenac with Neusilin® US2 in the ratio 1:5 at 25°C for 20 h using a modified ball mill resulted in complete amorphization.

In vitro drug dissolution studies carried out for neat drug, 5 h and 20 h after co-grinding showed faster dissolution rates when compared to crystalline aceclofenac. Co –ground mixture of aceclofenac/Neusilin® US2 showed 103 % dissolution within 3 h when compared to 92% at the end of 8 h (Fig 4).

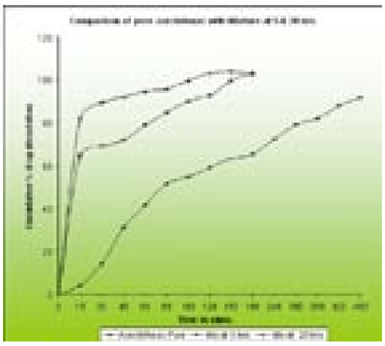

Fig 4. Dissolution profile of Aceclofenac (pure drug) and co-ground mixture with Neusilin® collected at 5 and 20 h interval.

The initial drug dissolution rate was also faster with 20 h co-ground sample than 5 h ground sample indicating complete amorphization with extended grinding. The extended time could be related to the melting point of drug. As a general rule when grinding at room temperature, higher the melting point would require longer milling times. Amorphization can be done in less time if milling is carried out well below the glass transition temperature (Tg) of the corresponding liquid state.

The amorphous co-ground mixture of Aceclofenac and Neusilin® was found physically stable during storage at 40°C/75% RH for up to 4 weeks (Fig 5). XRD, DSC and FITR analysis confirmed the amorphous state of Aceclofenac after 4 week stability period with no reversion to crystalline state.

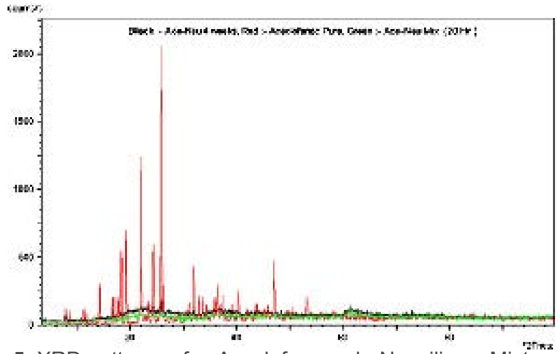

Fig.5. XRD patterns of a. Aceclofencac, b. Neusilin, c. Mixture at 20 h and d. Mixture after four weeks storage at 40°C, 75% RH.

Ball milling of other drug candidates, ketoprofen and nanoprexn, both carboxylic acid containing drugs as well as progesterone which does not contain a proton donating group showed complete amorphization on milling with Neusilin.

Stability mechanism:

It is believed that several potential interactions between the drug and surface of Neusilin® makes the co-ground mixtures physically stable during storage. pH could be a major factor affecting the stability. Neusilin US2 is pH neutral when compared to other silicates and can have a broad range of compatibility. In case of slightly acidic drugs, co-grinding with alkaline grade of Neusilin® like FL2 or FH2 will be the preferred choice. The FL2 and FH2 has a pH range of 8-10 and has been found efficient in maintaining stability of slightly acidic drugs like Quinapril hydrochloride.

Presence of silanol rings on the surface of Neusilin® makes it a potential proton donor as well as proton acceptor. Hydrogen bonding between silanols and drug as well as interaction between the drug and metal ions on the surface of Neuslin® are suggested stabilizing mechanisms of indomethacin, aceclofenac and other carboxylic acid containing drugs.

Conclusion:

Neusilin® can be successfully used to develop amorphous solids of crystalline poorly water soluble drugs by co-grinding methods. Amorphization leads to improved solubility and dissolution times.

Table 2.

Key advantages of incorporating Neusilin US2:

Complete amorphization of crystalline poorly water soluble drugs is possible by co-grinding with Neusilin US2

Shorter amorphization time due to large surface area

Amorphization leads to better dissolution and enhances bioavailability.

Process simple and scalable

Physically stable and the amorphized drug do not revert back to crystalline forms.

References

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