

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. Although, several different methods are available to produce amorphous drugs, ball milling appears to be the most practical method to amorphization.

In this newsletter, we introduce published articles by Gupta and Bhal *et al*; wherein dissolution of indomethacin was markedly improved by co-grinding with **Neusilin®** US2. 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).

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).

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.

Other drug candidates viz. ketoprofen, naproxen, and progesterone showed complete amorphization and stability on milling indicate that **Neusilin®** US2 is an excellent media for amorphization of a large number of BCS class II poorly water soluble crystalline drugs.

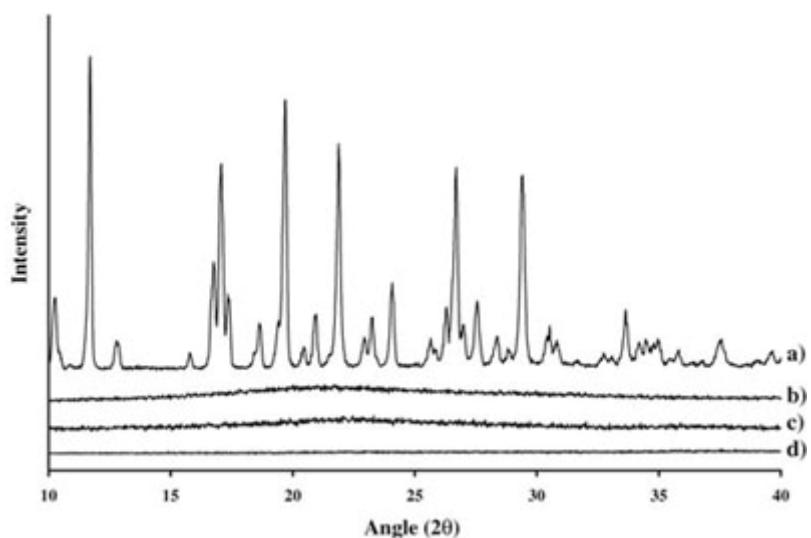


Fig 1. Powder X-ray diffraction scans of a) crystalline indomethacin, b) Amorphous indomethacin (melt –quenched), c) amorphous indomethacin (co-ground at 75% RH with Neusilin US2 in the ratio 1:5 for 5 days), d) Neusilin US2.

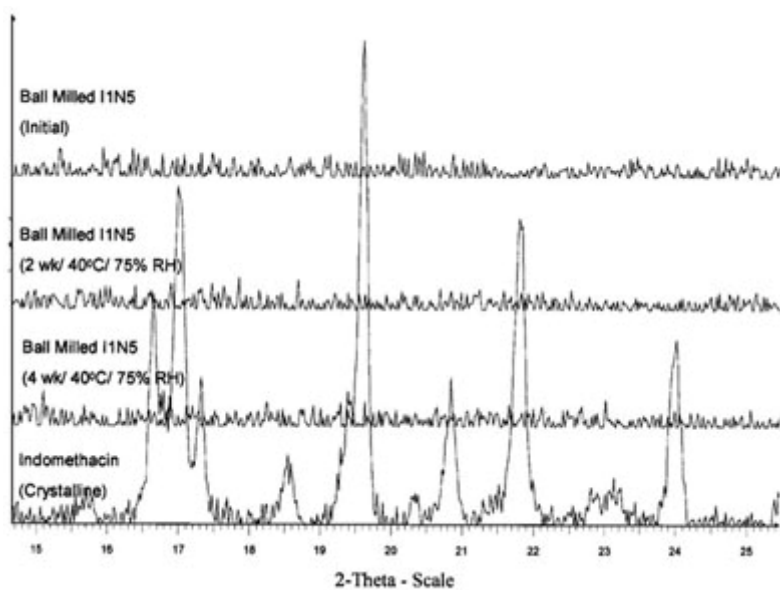


Fig 2. XPD spectra of ball milled powder of indomethacin before and after storage up to 4 weeks at 40°C, 75% RH.

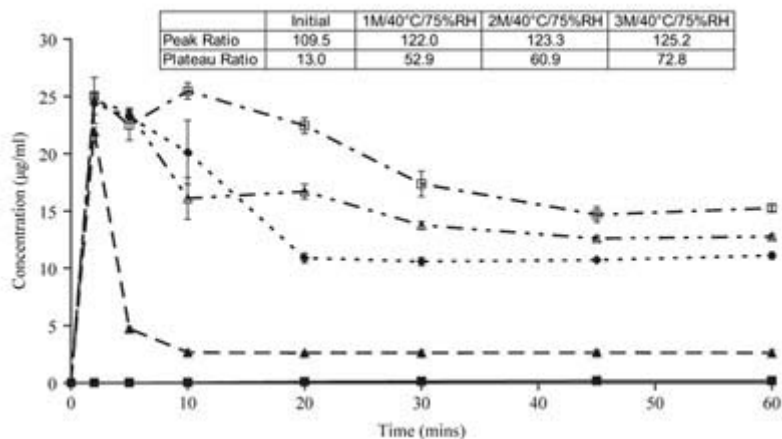


Fig 3. Dissolution profiles (n=3) of indomethacin co-ground with Neusilin US2 (1:5 w/w) in 0.1 N HCl (900 ml) : closed triangle- initial; closed diamond – 1 month at 40°C, 75% RH, open triangle-2 months at 40°C, 75% RH, open square- 3 months at 40°C, 75% RH, Closed square – crystalline indomethacin.

Key advantages of incorporating Neusilin® US2:

- ◆ Complete amorphization of crystalline poorly water soluble drugs is possible by co-grinding with Neusilin® US2 at room temperature
- ◆ 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

Neusilin® US2 is a synthetic amorphous form of Magnesium aluminometasilicate. It has good flow and compressibility properties. Large amounts of API can be loaded on to Neusilin® because of its highly porous nature, high specific surface area of 300 m²/g and high adsorption capacity.

References

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