Mechano-Chemical Activation and Stabilization of APIs by Co-Milling

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INTRODUCTION

Poor drug dissolution and solubility are often the cause for low bioavailability. Counteracting can include physical modifications of active ingredients by increasing the surface area, solubility and wettability of powder particles with focus on particle size reduction and specific surface area increase or - on the other hand – with focus on the generation of the amorphous state [1]. During milling both the size reduction as well as the induced transition of a crystalline to an amorphous compound can be conducted at the same time.

The aim of this work is to study the influence of general milling parameters like stressing energy (SE) and stressing number (SN) on particle size reduction and mechano-chemical activation (MCA) by vibration milling using a small scale mill. As feed particles lactose monohydrate, itraconazole (ITZ), a BSC II class antifungal drug and a blend of itraconazole and HPMC (1:3) were used.

MATERIALS AND METHODS

Prismalac 40 (Lactose monohydrate, Meggle Pharma AG, Germany) and Pharmacoat 603 (HPMC – Hydroxypropyl Methylcellulose - Shin-Etsu Chemical Co Ltd., Japan) were used as received. Itraconazole (ITR) was kindly donated by Micromacinazione SA (Switzerland).

Small scale vibrational mill

The milling process was performed in a vibrational mill, Retsch MM301 (Retsch GmbH, D), which was equipped with two steel jars layered with zirconium oxide, each one with a capacity of V_{GC} = 30 ml. The grinding media consists of yttrium-stabilized zirconium oxide (ZrO_2) beads with different diameters but identical filling ratio of φ_{GM} = 0.14. The jars with the grinding media can be vibrated horizontally.

Variation of Stressing Energy (SE) and Stressing Number (SN) – Milling parameters

Following parameters were chosen for the variation of SE and SN:

- Grinding media diameter d_{GM}: 3, 5 and 10 mm
- Grinding media mass m_{GM} = 0.09, 0.41 and 3.81 g
- Mill frequency n: 10, 20 and 30 Hz
- Milling time t_G: 2, 4, 8, 16, 30, 60 and 90 min.
- Filling ratio φ_{GM} = const. = 0.14
- Grinding chamber/beads velocity v_{GC}: measured with a high speed camera (0.53 – 1.66 m/s)

Calculations

The calculations for the stressing energy (SE), stressing number (SN) and specific energy provided by the beads ($E_{m,P}$) are based on theories developed for stirred media milling [2] and can be adapted to vibrational milling as follows:

$$SE = \frac{m_{GM} \cdot v_{GC}^2}{2}$$

$$SN = 2 \cdot n \cdot t_G \cdot \frac{V_{GC} \cdot \varphi_{GM} \cdot (1-\varepsilon)}{\frac{\pi}{6} \cdot d_{GM}^3} \cdot P_S \cdot K$$

$$E_{m,P} = \sum_{t_G=0}^{90} \frac{SN_{tot,t_G} \cdot \overline{SE}}{m_{P,tot,t_G}}$$

Ps [-] = Probability that a particle is caught and sufficiently stressed
ε [-] = Porosity of the grinding media
K [-] = Correction factor for product distribution inside grinding chamber

Analytics

A HELOS/KF laser diffractometer with a Rodos dispersion unit (Sympatec GmbH, Germany) was used for particle size measurements and a TM3030Plus (Hitachi Ltd, Japan) scanning electron microscope to study the morphology. The same instrument was used for chemical characterisation (energy-dispersive x-ray spectroscopy). The determination of crystallinity of different compounds was carried out with a D2 Phaser x-ray powder diffractometer (Bruker AXS GmbH, Germany). A cobalt kα radiation source with λ_{Coka} = 1.78 Å was used. The range of 2θ is from 5 to 40 ° with an increment of 0.34°. 1'200 steps were performed with a step time of 1.3 s and a rotation of 15 rpm. For evaluation the Diffrac.Evaluation® software from Bruker was used.

RESULTS AND DISCUSSION

Figure 1 shows SN as a function of SE for all experiments. The data points represent combinations of SN and SE required to produce a median particle size of x_{50} = 25 µm. At small stressing energies, the curve tends towards infinity; if the provided stressing energy of the beads is smaller than the minimal stressing energy necessary for particle breakage, no size reduction can take place although the particle is stressed several times. On the other hand, at high stress intensities, the curve shows another asymptotic behaviour: At very high stressing energies each feed particle must be stressed at least once. This corresponds to experiences with stirred media mills [2] and the same effect has been observed for amorphization, which also depends on SE and SN in the same manner.

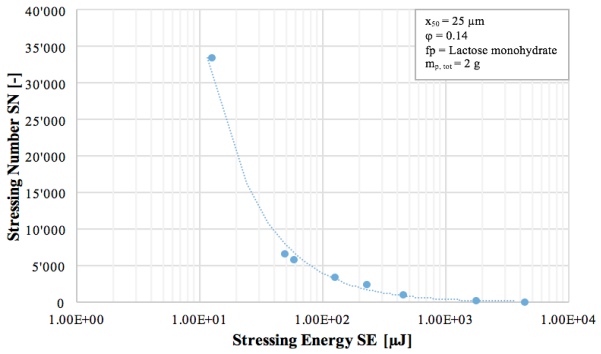

Figure 1 Stressing energy and stressing number which are required for x_{50} = 25 µm – each data point represents a different experiment

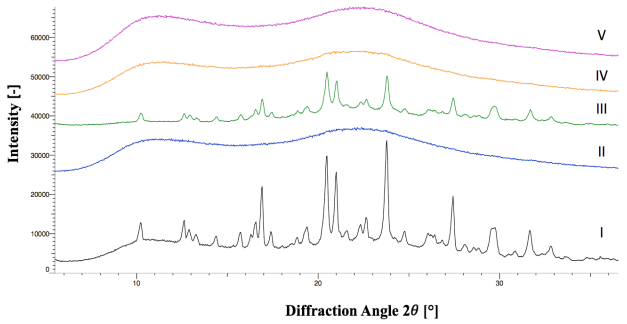

Figure 2 I: Physical mixture ITR/HPMC (1:3); II SE = 124 µJ / SN = 25056 ITR/HPMC (1:3); III SE = 124 µJ / SN = 25056 (100 % ITR) IV SE = 565 µJ / SN = 4700 ITR/HPMC (1:3); SE = 4380 µJ / SN = 192 ITR/HPMC (1:3)

When particles are stressed between two surfaces, energy is transferred/loaded to the particle. This energy causes a stress field in the particle. Now it has to be distinguished between a) the cases when the stressing energy SE is high enough to cause a particle breakage or b) when SE is too small. In cases a) size reduction occurs. In the other case b) the energy is stored in the particle and disturbs its crystalline structure. With every contact providing a too low energy for particle breakage, the crystalline structure is changed increasingly until it is fully amorphous.

The higher chemical potential and free energy of the amorphous state of a drug compared to the crystalline form is responsible for its higher apparent solubility but also for a decrease in stability. Incorporation of amorphous drugs into the network of polymers hinders their molecular mobility. This lowers the chemical potential of the amorphous drug and prevents devitrification thereby preserving stability of the amorphous state [3].

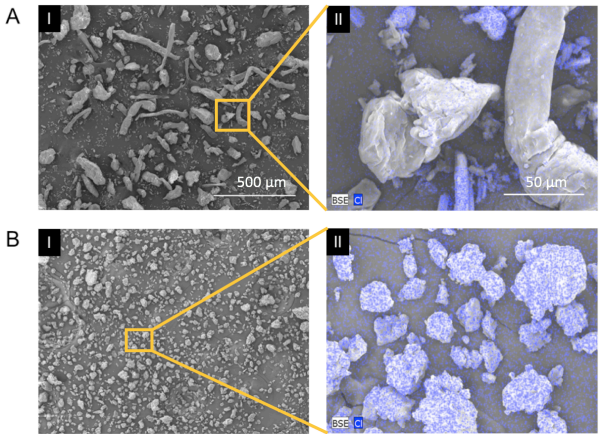

Figure 3. A Physical mixture at t_G = 0 min; B t_G = 30 min; I 100x magnification; II 1000x magnification

This is proven by the results of this work. The XRD results in Figure 2 shows that by adding HPMC as a carrier an amorphous solid dispersion can be obtained after 30 min of milling with the 3 mm beads at 30 Hz (see curve II).

Only slight amorphization was detected without carrier but the same parameter setting (see curve III). Furthermore, by increasing the bead size – hence increasing SE – the milling time can be reduced – reducing SN – to get an amorphous solid dispersion (see curve IV and V). The SEM/EDS results in Figure 3 show that at the beginning almost no API particles (blue dots indicate chloride in the itraconazole particles) are incorporated into HPMC polymer particles. However, after 30 min of milling the majority of API particles is integrated into HPMC.

CONCLUSION

Particle size reduction of API depends on SE and SN, whereas same results can be obtained for high SE and low SN or vice versa. At the same time MCA occurs depending also on SE and SN. Milling of API together with polymers lead to a solid dispersion with improved stability. In conclusion, the influence of major milling parameters on particle size reduction, MCA and stabilization can be applied to different mills by adopting the underlying stressing model.

ACKNOWLEDGEMENT

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