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The Science of Lysing

Micromilling and co-micromilling of small quantities of poorly water-soluble pharmaceutical API

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CONTEXT

Micromilling and co-micromilling of drugs with specific pharmaceutical excipients is an interesting approach for **increasing the solubility and the dissolution rate of poorly water-soluble compounds**. In preclinical development and early clinical formulation development, the amount of active pharmaceutical ingredient (API) available is often limited and specific process requiring micro quantities (100-200 mg) of drug for formulation screening is of high need.

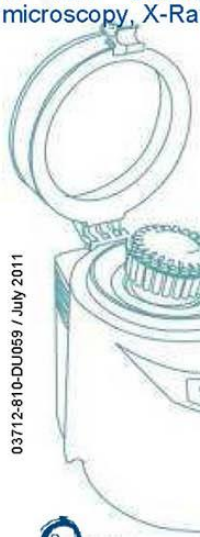
Evaluation of co-micromilling with various pharmaceutical excipients with regards to this limitation is in fact difficult to perform with classical milling equipment. In this respect the performance of Precellys24 has been studied [1].

MATERIAL

- Precellys homogenizer.
- Precellys kit: 03961-1-008 (2.8mm metal beads).
- Sample: 200 mg of Ketoprofen (as a model poorly water-soluble API) blended with various excipients (ratio 70/30) in a mortar (physical mixture).

PROTOCOL

- Precellys: 5500 rpm, 3x30sec (10s break).
- Controls made on the produces formulations include: in vitro dissolution profile, scanning electronic microscopy, X-Ray diffraction and DSC.



RESULTS

A significant increase of the Ketoprofen dissolution rate is observed after co-micromilling using various excipients, compared to non micromilled material. This increase is observed for excipients which have or do not have solubilizing properties (surfactant vs PVP derivatives) (Figure 1).

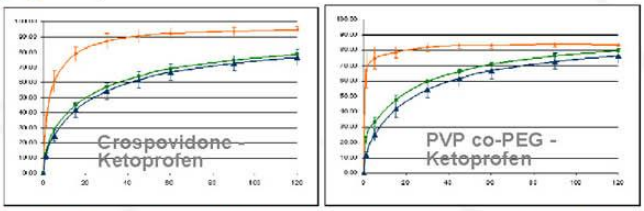


Fig. 1: Percentage of Ketoprofen released versus time (min). Co-micromilled material (orange), physical mixture (green) and ketoprofen non microzed (blue) (mean ± SEM, n=3).

Significant particle size reduction is observed for co-micromilled formulations such as Crospovidone-Ketoprofen (Figure 2). Drug dissolution following co-micronisation has been significantly improved. No amorphisation of the API was found after the process [1].

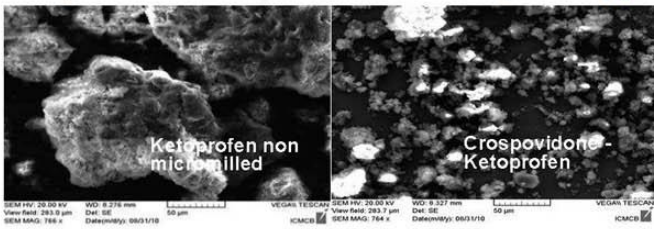


Fig. 2: Scanning electronic microscopy of non-micromilled ketoprofen and co-microlilling formulation (scale:50µm)

[1] Precellys24 as a useful screening tool in preformulation for micronisation and co-micronisation of small quantities of poorly water-soluble pharmaceutical API, A. Colin et al. 2nd Conference on Innovation in drug delivery, 3-6 October, 2010, Aix-en Provence

CONCLUSION

Precellys24 is successfully evaluated as a screening tool in preformulation for **micromilling** and **co-micromilling** of small quantities of **poorly water-soluble active pharmaceutical ingredient** (API). **Nanomilling** of API particle size down to sub-micron range can also be investigated with Precellys to help dissolve recalcitrant molecules.

Since an increasing number (around 70%) of newly developed drug candidates in pre-clinical development phases present poor water-solubility characteristics, it remains a significant challenge for pharmaceutical scientist and chemical engineers to overcome this issue.

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