# Improvement of solubility of disperse materials by the means of the mechanochemical treatment

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### Introduction

The solubility of drug is very important factor that determines its applicability, since solubility may act as rate-limiting step in absorption and therefore may affect the bioavailability of the drug. Therefore, it is important to identify ways over which solubility improvement can be accomplished. Our goal was to improve the solubility of the Verapamil<sup>®</sup> (VHCl) by the mechanochemical treatment. Same treatment was applied to the pure Verapamil hydrochloride (pVHCl), which is an active substance in VHCl, in order to resolve what physicochemical properties are correlated with the solubility improvement, since Verapamil<sup>®</sup> contains excipients that can mask the effects of mechanochemical treatment.

### Experiment

Verapamil<sup>®</sup> (VHCl) and pVHCl have been ball milled in planetary mill, keeping the milling time in the range of few minutes to the several hours. Influence of mechanochemical parameters and surfactants on the physicochemical properties was examined using a XRD, FE SEM technique and Malvern's Master Sizer instrument for particle size distribution. Finally, solubility of verapamil hydrochloride was correlated with the particle size, structural and morphological characteristics of the drug via UV-VIS Cintra 101 spectrometer.

#### Results

Both VHCl and pVHCl absorb radiation in the UV and visible light regions (**Fig. 1a**). Intense, and better defined absorption at  $\lambda$ =229 nm was used for calibration and determination of dissolution concentrations of the commercial Verapamil<sup>®</sup> drug formulation (**Fig. 1b**). After milling, particle size distribution of the milled VHCl was measured (**Fig. 2a**) and peaks maxima were correlated with the time at which maxima of the dissolution concentration were observed (**Fig. 2b**)

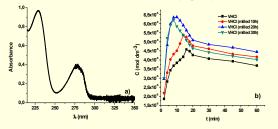
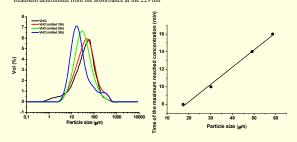
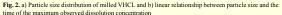


Fig. 1. a) UV-VIS spectrum of the VHCL and b) dissolution curves of VHCL after mechanochemical treatment determined from the absorbance at the 229 nm





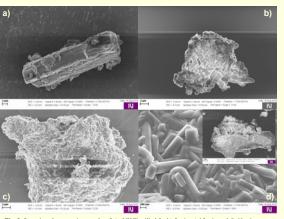


Fig. 3. Scanning electron micrographs of a) pVHCl milled for b) 5 min, c) 15 min and d) 60 min.

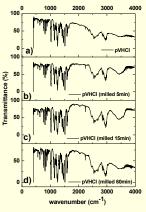


Fig. 5. IR spectra of mechanically activated a) pVHCl milled for b) 5 min, c) 15 min and d) 60 min

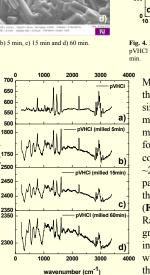


Fig. 6. Raman spectra of mechanically activated a) pVHCl milled for b) 5 min, c) 15 min and d) 60 min.

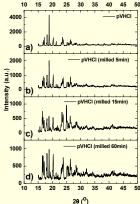


Fig. 4. Difractograms of mechanically activated a) pVHCl milled for b) 5 min, c) 15 min and d) 60 min.

Milling of the pVHCL leads to the reduction of the particle sizes and changes of the morphology (Fig. 3). Prolonged milling (t>60 min) leads to the formation of agglomerates composed of pVHCl particles ~200 nm wide. Reduction of particle sizes is accompanied by the structure amorphization (Fig. 4). As evidenced by Raman spectrometry (Fig. 6), greatest changes are noticeable in the region 300-1600 cm<sup>-1</sup>, while IC measurements showed that treated samples have only

<sup>d a)</sup> increased amount of adsorbed water (**Fig. 5**).

#### Conclusions

Mechanochemical treatment leads to the reduction of the particles sizes of the examined samples
This treatment induces the changes of the morphology and, in the cases of the prolonged milling time, the formation of the nanoscale particles is viable

•At the same time, particle size reduction is accompanied by the amorphization i.e. structural disorder; this is corroborated by Raman spectrometry, while, other than increased amount of the adsorbed water, there are no new bonds created as a result of milling (as evidenced by IC measurements).

•Solubility and kinetics of the solubility of VHCl can be successfully investigated by applying UV-Vis spectrometry

• There is linear relationship between particle sizes and the time at which maxima of the dissolution concentrations are achieved

• Reduction of particle sizes to the nanometer scale, the amorphization of the crystalline structure as well as increased dissolution rate imply that mechanochemical treatment can be successfully applied for the improvement of solubility of disperse materials.