## Abstract

Charles University, Faculty of Pharmacy in Hradec Králové

| | |
|---|---|
| Department of: | Pharmaceutical Technology |
| Candidate: | Mgr. Jana Jezerská |
| Supervisor: | doc. PharmDr. Zdeňka Šklubalová, Ph.D. |
| Consultant: | Ing. Jakub Koktan, Ph.D. |
| Title of Doctoral Thesis: | Utilization of technological procedures of milling and co-milling in the preparation of interactive mixtures |

The dissertation thesis is an annotated summary of the publication and research activities of the author, Mgr. Jana Jezerská (maiden name Brokešová). The thesis is focused on the preparation of binary interactive powder mixtures which consist of the micronized drug particles adhered onto the larger particles of an excipient (a carrier). The binary powder mixtures were prepared by mixing and/or co-milling and characterized by granulometric methods; crystallinity (thermal analysis, X-ray powder diffractometry), the flow properties (shear cell, avalanche properties) and the surface energy were evaluated as well. The dissolution rate of model drugs was estimated using a flow-through powder dissolution cell (USP-4).

The used statistical model (central composite design) enabled to establish optimal milling conditions in a ball mill (the milling speed, the milling time, the size of milling balls) for five powder carriers. Based on quadratic response surface, the prediction the response variable $x_{90}$ representing the particle size for 90% of the cumulative distribution curve was possible. A linear relationship was detected between the cohesion and energy to break an avalanche and the cohesion and specific surface area of powders by the theoretical investigation of cohesive surface properties of the binary interactive mixtures containing a cohesive model drug meloxicam and alginic acid or calcium alginate. The influence of acid-base properties of a carrier and the glass forming ability of a poorly soluble drug on the dissolution rate enhancement was demonstrated. The surface activation due to co-milling pronounced by the higher specific surface energy. Almost 50 times higher

dissolution rate of meloxicam was achieved due to the adhesion of meloxicam particles on the surface of chitosan carrier particles. In all binary mixtures prepared, the dissolution rate improvement was directly proportional to the drug/excipient mass ratio.

The measurement of surface energy by the inverse gas chromatography and the analysis of surface heterogeneity at a various nominal surface coverage $n/n_m$ are suitable methods to characterize the binary interactive powder mixtures and the interparticle interactions. The proposed difference between the experimentally detected work of cohesion and the theoretical estimation of work of adhesion as well as the work of adhesion and the work of cohesion ratio are promising indicators demonstrating the preference of drug particles adhesion to the host carrier particles and the physical stability of the prepared interactive mixture, respectively.