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Report on the habilitation thesis of

Zdenek Grof, Ph.D.

„Mathematical modelling of pharmaceutical unit operations"

Modelling of particulate systems has become a strongly evolving field within the broader discipline of chemical engineering. Especially pharmaceutical processes have thereby shifted into the focus, where products are usually costly and quantities to be handled small while there is a high demand for precision regarding the process design as well as regarding the expected product properties. The named conditions favor the utilization of mathematical modelling in this particular area of chemical engineering, which leads to the fact that modelling in the area of pharmaceutical processes is often further progressed as in other areas of chemical engineering, where particulate processes are present. To this aspect, also the habilitation thesis of Zdenek Grof makes its contribution, which addresses modelling of pharmaceutical particulate systems covering features such as liquid/solid and particle/particle interactions as well as dissolution processes.

The habilitation thesis is written in a cumulative way comprising of two parts, a commentary part and the reprints of the thirteen underlying journal articles of which twelve are already published while the thirteens article is awaiting publication. Note, that thirteen journal articles are an appropriate number for a habilitation in this context. Thematically three different areas of mathematical modeling are addresses in the thirteen publications. In publications one to four capillary interactions in porous and particulate media, in publication five to nine particle/particle interaction and breakage and in publication ten to thirteen tablet disintegration and dissolution is addressed.

As a first area, capillary interactions in porous and particulate media is addressed. Thereby both modeling of particle/fluid interactions as part of a Discrete Element Method (DEM) coupled to Computational Fluid Dynamics (CFD) is targeted (paper one) as well as the direct modeling of the capillary interactions and of the thereby resulting gas/solid/liquid interfaces is pursued (papers two and three). A combined experimental and numerical approach is utilized thereafter to address drying in a particulate system (paper four).

As a second area particle/particle interactions and particle breakage is addressed. A focus is thereby set onto needle shaped particles as being relevant especially in pharmaceutical processes which form e.g. as a consequence of a crystallization step. In paper five a multi-element DEM is used to analyze breakage in the context of a predefined particulate stress state. It is thereby analyzed how system parameters influence the breakage process. In paper six a Population Balance Model (PBM) is utilized and it is investigated how computational modelling by e.g. DEM can be incorporated into the PBM. Paper eight addresses the DEM modeling of mixtures of spherical and needled shaped particle, while paper nine targets particle/particle interactions and breakage as arising between two parallel plates.

As the last and third area tablet disintegration and dissolution is addressed. While paper ten is an experimental investigation of dissolution, in paper eleven the aim is pursued to correlate tablet structure with resulting dissolution rates. Paper twelve addressed the drug release from so called immediate-release tablets which contain a desintegrant component. In the recent yet unpublished paper thirteen, it is aimed for the optimization of tablet configurations by relying on genetic algorithm based optimization strategies.

In summary, Zdenek Grof has been able to derive highly convincing fundamental and applied results for all three areas covered in his habilitation thesis. The individual findings are all of extremely high quality, which is reflected also by the well known and recognized journals they are published in. Individually the findings contribute towards an enhancement of understanding of granular systems, but pose also an outstanding advancement of methodology for pharmaceutical process modeling. Despite the thematical broadness of the topic, Zdenek Grof has been able to compile his results nicely into a well-structured thesis. This and the ability to combine a variety of numerical methods with state-of-the-art experimental techniques underlines the fact of Zdenek Grof to be high quality researcher.

Based on the submitted habilitation thesis and my outlined assessment I clearly recommend Zdenek Grof for a position (and title) of an Associate Professor in chemical engineering.

Harald Kruggel-Emden

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