EFFECTIVE TRANSPORT PROPERTIES OF DRUG DELIVERY SYSTEMS: POROUS GRANULES AND TABLETS

Frantisek Stepanek, University of Chemistry and Technology, Prague, Czech Republic
Frantisek.Stepanek@vscht.cz
Michaela Gajdosova, University of Chemistry and Technology, Prague, Czech Republic
Marek Soltys, University of Chemistry and Technology, Prague, Czech Republic
Katerina Puncochova, University of Chemistry and Technology, Prague, Czech Republic
David Smrcka, University of Chemistry and Technology, Prague, Czech Republic
Marek Schongut, University of Chemistry and Technology, Prague, Czech Republic

Key Words: diffusion, magnetic resonance imaging, uv imaging, dissolution, pharmaceutical formulation

Solid dosage forms such as tablets, granules or capsules represent over 80% of all pharmaceutical products. Modern pharmaceutical formulations are designed so as to release the active pharmaceutical ingredient (API) at a well-defined and reproducible rate. Two main classes of dosage forms can be distinguished: rapid release formulations (which are designed to disintegrate rapidly and dissolve the API within the shortest possible time), and sustained release formulations (which are designed to release the API gradually over a prolonged period of time, typically 24 hours). In both cases, the effective transport properties of the drug carrier (granule, tablet) play a crucial role. The wetting and imbibition of gastric juices into the porous structure of the tablet determines the time-scale over which the individual drug particles will be contacted with the dissolution medium, which the diffusion of the dissolve drug substance trough the tablet structure determines the release rate. Pharmaceutical formulations typically contain not only the API particles but also several auxiliary components (excipients) such as fillers, disintegrants, binders, controlled release polymers, lubricants, surfactants, etc. The porous structure is formed hierarchically, starting with the blending of the initial powders with given particle size distributions, followed by dry or wet agglomeration into granules, which are then compressed into the final tablets. The understanding of a relationship between the material properties of the formulation, the parameters of the manufacturing process, and the effective transport properties (water permeability and drug diffusivity) of the final pharmaceutical product is therefore crucial when developing new solid dosage forms.

In this contribution, we will present our recent progress on the combination of 3D imaging methods (MRI, micro CT), spectroscopic analytical methods (UV/Vis spectrophotometry) and mathematical modeling to evaluate the effective transport properties of pharmaceutical granules and tablets. By systematically changing the manufacturing process parameters (granulation conditions, tabletting pressure) and the formulation composition (ratio of API and excipients), we have prepared a series of structutres with systematically varying drug release profiles. The rate-limiting step was identified in each case, and three limiting regimes were found: drug release limited by water transport into the tablet, drug release limited by intrinsic dissolution kinetics of the API, and drug release limited by the diffusion of API from the tablet. The knowledge of these limiting regimes then and their dependence on the formulation and processing parameters then allows rational choices to be made when designing new drug products.

References:

[1] Kašpar O., Tokárová V., Oka S., Sowrirajan K., Ramachandran R., Štěpánek F., “Combined UV/Vis and micro-tomography investigation of acetaminophen dissolution from granules”, Int. J. Pharm. 458, 272-281 (2013)
[2] Gajdošová M., Pěček D., Sarvašová N., Štěpánek F., “Effect of hydrophobic inclusions on polymer swelling kinetics studied by magnetic resonance imaging”, Int. J. Pharm., in press (2016)
[3] Punčochová K., Ewing A.V., Gajdošová M., Sarvašová N., Kazarian S.G., Beránek J., Štěpánek F., “Identifying the mechanisms of drug release from amorphous solid dispersions using MRI and ATR-FTIR spectroscopic imaging”, Int. J. Pharm. 483, 256-267 (2015)
[4] Smrčka D., Dohnal J., Štěpánek F., “Effect of process scale-up on the dissolution of granules with a high content of active pharmaceutical ingredient”, Powder Technol. 285, 88-95 (2015)