The term oral controlled release (CR) dosage forms covers a heterogeneous group of formulations intended to reduce the dosing frequency while improving the efficacy, safety and tolerability of an oral drug product. Current technologies to produce oral CR formulations are intended to alter the timing and control of drug release in a pre-determined fashion and/or to target drug release to selective sites in the gastrointestinal (GI) tract. An oral CR formulation thus represents much more than a means to increase patient compliance and moreover, presents the unique chance to optimize the clinical properties of a drug candidate. For these reasons, oral CR dosage forms maintain an important position in the area of pharmaceutical product development. However, beside the chance of improving efficacy, safety and tolerability of a drug, oral CR formulations can also result in severe risks for the patients, particularly in cases where the drug release mechanism is not robust in GI conditions. Unwanted effects that have been described in the literature during the last decades range from “dose dumping” to subtherapeutic plasma levels.

To develop an oral CR formulation with an optimal risk-benefit ratio, it is of utmost importance to estimate the robustness of *in vivo* drug release in early stages of product development by applying predictive *in vivo, in vitro* and/or *in silico* tools. Independent of which of these tools is used, it should reflect both the dosing conditions and the relevant physiological intra- and interindividual variability that can affect *in vivo* drug release drug release of the dosage form.

Over the last half century, various techniques have been established to monitor gastrointestinal transit of oral dosage forms. Even if there is still a lot of information lacking, through the use of these techniques we gained essential knowledge on the critical impacts that can affect *in vivo* drug release from oral CR formulations. This enormous gain in scientific findings on human GI physiology in turn resulted in a significant change in the tools that are nowadays applied to enable a better prediction of the *in vivo* performance of oral CR dosage forms. This is particularly true for *in vitro* and *in silico* tools. Whereas in the past, *in vitro* and *in silico* models for establishing a correlation with *in vivo* data were designed subsequent to the respective bioavailability studies, the new physiologically-based models are intended to be used in a prospective rather than a retrospective way.

The present talk will discuss several new approaches for predicting the *in vivo* performance of oral CR formulations. The focus will be set on physiologically based *in vitro* models that taking into account the aspects of human GI physiology that are relevant to *in vivo* drug release.