## Project summary

Aim of the project is development of drug delivery systems and technologies that will enhance controlled release of active substances. Project started with support and contribution of two participants: Galenika a.d. and Hemofarm a.d. Project had several parts. Each part of project started with characterization of drug substance and excipients. These were followed with different ways of drug solubility enhancement and bioavailability enhancement. Furthermore, control of drug release from drug delivery systems was another important issue. In each part of the project, mathematical models were applied, with the aim to allow mechanistical understanding of inflluence of formulation factors and/or process on product quality characteristics. That was the way to implement actual Qualiy by Desing concept in pharmaceutical development.Project was divided in following phases (1) identification of optimal condition for solid dispersion formation with the aim to enhance drug solubility; optimization of spray drying process with maximal yield and best powder characteristics (with respect to particle size and specific particle surface); (2) identification of optimal conditions for solid dispersion forming, obtained solid dispersions were used in tablet and capsule preparation. Process optimization in order to retain desired drug polymorphic form; (3) development and optimization of fluid-bed hot melt granulation; (4) application of mathematical models in prediction of drug stability; (5) in silico modelling of gastrointestinal absorption of poorly water soluble drugs; (6) preparation of self(micro)emulsifying systems; identification of optimal drug/oil/emulsifier ratio for self-emulsifying system; (7) development of extended release tablets with application of QbD concept (8) 3D printing application in solid dosage forms, (9) preparation and defence of PhD thesis.

## Sažetak projekta

Predmet istraživanja projekta je razvoj proizvoda (nosača lekovitih supstanci) i tehnologija koji će omogućiti željeno (kontrolisano) oslobađanje lekovitih supstanci. Ispitivane model supstance birane su (a) u skladu sa interesom iskazanim od strane Participanta; (b) u skladu sa činjenicom da nema dovoljno literaturnih podataka o formulaciji čvrstih farmaceutskih oblika sa njima. Projekat je započeo uz podršku i učešće dva participanta, Galenike a.d. i Hemofarma a.d. Projekat je realizovan kroz nekoliko istraživačkih celina. Na početku svakog dela istraživanja, okarakterisana je lekovita supstanca i ekscipijensi. Zatim su se, u svakoj celini projekta, primenjivali različiti pristupi poboljšanju rastvorljivosti i bioraspoloživosti lekovitih supstanci, sa jedne strane, kao i kontroli brzine oslobađanja leka iz proizvoda (nosača), sa druge strane. U svakoj od faza istraživanja, bile su primenjene matematičke metode, koje su omogućile mehanističko razumevanje uticaja faktora formulacije i/ili procesa na karakteristike proizvoda, i na taj način doprinele aktuelnom Quality by Design konceptu farmaceutskog razvoja leka. Faze u projektu bi se mogle grupisati na sledeći način: (1) identifikacija optimalnih uslova za formiranje čvrstih disperzija koji će poboljšati rastvorljivost lekovite supstance; optimizacija uslova procesa sušenja raspršivanjem u kojima se dobija najveći prinos i najbolje karakteristike praška (u pogledu veličine čestica, specifične površine i sl); (2) identifikacija optimalnih uslova za formiranje čvrste disperzije lek-poloksamer, kao i upotreba nastale čvrste disperzije u izradi tableta i kapsula. Optimizacija procesa u pogledu održanja željenog polimorfnog oblika lekovite supstance u proizvodu, (3) razvijanje i optimizacija postupka granulacije topljenjem u fluidizirajućem sloju, (4) predviđanje roka trajanja farmaceutskih oblika primenom matematičkih metoda, (5) in silico modelovanje gastrointestinalne resorpcije teško rastvornih supstanci, (6) izrada samo(mikro)emulgujućih sistema; identifikacija optimalnog odnosa lekovita supstanca/ulje/emulgator u kojoj nastaje samo(mikro)emulgujući terapijski sistem. Nastali terapijski sistem je pokazao brže oslobađanje lekovite supstance, i posledično, poboljšanje bioraspoloživosti leka. (7) ispitivanje faktora koji utiču na oslobađanje lako rastvorne lekovite supstance iz tableta sa produženim oslobađanjem leka, (8) primena tehnologije 3D štampe u formulaciji čvrstih farmaceutskih oblika, (9) prijavljivanje i odbrana doktorskih disertacija.

## Selected results/Odabrani rezultati

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