Abstract

Charles University, Faculty of Pharmacy in Hradec Králové

Training workplace:	Department of Pharmaceutical Technology
Doctoral Degree program:	Pharmaceutical Technology
Candidate:	Mgr. Chiazor Ugo Ogadah
Supervisor:	Assoc. Prof. PharmDr. Barbora Vraníková, Ph.D.
Advisor:	Assoc. Prof. PharmDr. Zdeňka Šklubalová, Ph.D.
Title of Doctoral Thesis:	Development of liquisolid systems for colon targeting

Colon-targeted drug delivery holds significant promise for the local treatment of colonic ailments or the systemic delivery of drugs. Nevertheless, the success is challenged by the physiological barriers within the gastrointestinal tract. Improving the solubility of the drug prior to targeting will circumvent the rate-limiting step of dissolution and enhance absorption and oral bioavailability. Additionally, retaining the formulation at the target site will optimize the dose and improve the therapeutic efficacy. Therefore, the aim of this thesis was to develop a drug delivery system that will potentially allow the targeting a poorly water-soluble drug, cyclosporine A (CyA), to the colon.

In the first part of the experiments, the preformulation studies related to improving the solubility and dissolution rate of the CyA by the formulation of liquisolid systems (LSS) or interactive mixtures by co-milling was performed. This included the selection of suitable carrier and evaluation of its milling properties as well as the selection of non-volatile solvent for the solubilization of CyA. The carrier, Neusilin® US2 (NEU) emerged as the most suitable one due to its large specific surface area, high flowable liquid retention potential and acceptable milling behaviour. Solubility studies were performed and further, LSS were prepared and evaluated for drug release in different biorelevant media of pH 1.6, 6.5 and 7.8, respectively, which confirmed Transcutol® HP (TRC-HP) as the most suitable solvent. By comparison of NEU-based LSS and co-milled formulations with functionalized calcium carbonate based ones, NEU exhibited better carrier properties regarding its efficiency in loading higher concentration solutions of CyA as well as by co-milling, due to its high surface area and pore volume. Ultimately, the LSS demonstrated superiority to the co-milled formulations, as the release of CyA was significantly improved from LSS.

To develop a mucoadhesive matrix core for the adequate prolonged release of drug and increased residence time of the dosage form at the target site in the colon, several mucoadhesive polymers were characterized by measuring their rheological properties in different biorelevant media. Subsequently, the swelling and drug release of matrix tablets prepared from selected polymers were studied, using a model freely soluble drug, theophylline. The polymers showing promising controlled release properties, hydroxypropyl methyl cellulose (HPMC) and guar gum (GG) were selected and their mucoadhesion properties was determined by estimation of adhesion force needed to detach the tablet from the mucin layer. Finally, the influence of the LSS carrier, NEU on the swelling and mucoadhesive properties of the matrix systems incorporating each of the selected polymers above was investigated. However, the details of the NEU influence on mucoadhesion were not completely clarified in this thesis and a more detailed study is necessary in future.

In summary, the acceptable excipients for development of a suitable colon-targeted dosage form for improving CyA solubility were achieved. The formulation of LSS proves to be a better approach for improving CyA solubility and drug release over co-milling. The polymers with suitable swelling, drug release and mucoadhesion properties necessary for the matrix core with prolonged release were confirmed. However, the influence of the LSS carrier on the polymer matrix behaviour and drug release requires future studies.