POVZETEK

Zdravilno učinkovino omeprazol uvrščamo med predstavnike inhibitorje protonske črpalke (IPČ) in je nestabilna farmacevtska substanca, saj pri povišani temperaturi, vlagi in svetlobi razpada in ga je zato potrebno shranjevati v zrakotesnih vsebnikih, zaščitenega pred svetlobo ter pri nižji temperaturi. Prav tako je omeprazol v vodnih raztopinah z nizkim pH, v prisotnosti pomožnih snovi ali učinkovin, ki imajo kisle funkcionalne skupine, nestabilen. Zaradi slabe topnosti v vodi in fizikalno-kemične nestabilnosti predstavlja izziv pri izdelavi formulacije v farmacevtski industriji.

Ibuprofen spada v skupino nesteroidnih antirevmatičnih zdravil (NSAR), ki zaradi svojega farmakološkega delovanja povzroča pri kroničnem jemanju resne neželene učinke kot so npr.: razjede zgornjih prebavil, krvavitve in perforacije. Učinkovina ibuprofen ima kemijske lastnosti šibke kisline in je slabo vodotopna. Ker je s sočasnim jemanjem NSAR in IPČ zdravila dokazana manjša pojavnost omenjenih neželenih učinkov, sem želel v magistrski nalogi z izvedbo neizotermičnega in izotermičnega (pospešenega) testiranja preveriti stabilnost binarne zmesi učinkovin in napovedati reakcijsko kinetiko na podlagi HPLC analize razpadnih produktov obremenjenih vzorcev, ki sem jih vzorčil po določenih časovnih terminih.

S stabilnostno indikativno HPLC metodo za določevanje sorodnih substanc omeprazola v učinkovini, sem potrdil ugotovitve navedene v strokovnih člankih o nestabilnosti omeprazola pri povišani temperaturi in relativni vlagi.

Rezultati sorodnih substanc obremenjenih vzorcev binarnih zmesi so pokazali povečan razpad omeprazola v prisotnosti ibuprofena pri povišani temperaturi in relativni vlagi. Še večjo vsebnost sorodnih substanc omeprazola sem določil v binarnih zmeseh z vsebnostjo ibuprofena, kot jo predpostavljam v modelnih formulacijah. S postopkom linearnega neizotermičnega testiranja stabilnosti sem določil katere nečistote nastajajo med prvimi in kakšen je njihov trend naraščanja. Ker se med stabilnostnim testiranjem binarna zmes obarva značilno rdeče barve, sem določil katera nečistota povzroči takšno spremembo videza.

V nadaljevanju sem z LC-MS analizo kvalitativno ovrednotil razpadne produkte, ki so se v zmeseh pojavili prvi in katerih obseg razpada je bil največji. Na podlagi znanih dejstev kompatibilnostne študije sem zasnoval modelne formulacije - fiksno kombinacijo obeh

učinkovin skupaj s pomožno substanco, ki zmes učinkovin stabilizira, ter modelno formulacijo, ki v procesu priprave vključuje farmacevtsko tehnološki proces polizdelka, s čimer sem želel doseči stabilno formulacijo.

Z rezultati stabilnostnega testiranja sem ugotovil, da je modelna formulacija, ki vsebuje pelete omeprazola in granulat ibuprofena obloženega z eudragitno oblogo najbolj stabilna. Manj stabilna je bila formulacija s peletami omeprazola in s PVA obloženim granulatom ibuprofena. Najmanj stabilni pa sta bili modelni formulaciji s peletami omeprazola in neobloženim granulatom ibuprofena z MgO ter formulacija s peletami omeprazola in neobloženim granulatom ibuprofena ter smukcem, kar je bila posledica kemijskih in fizikalnih nekompatibilnosti med učinkovinama in pomožno snovjo.

Ključne besede: omeprazol, ibuprofen, fiksna kombinacija, neizotermično testiranje, reakcijska kinetika, modelna formulacija

ABSTRACT

Active pharmaceutical ingredient (API) omeprazole is a drug of the proton pump inhibitor (PPI) class and is considered a sensitive pharmaceutical substance depending on many factors such as elevated temperature, moisture and light. Therefore omeprazole should be stored in airtight containers, protected from light and at a lower temperature. The compound is very unstable especially in aqueous solutions with low pH value and less stable in presence of excipients or active substances with acidic functional groups. Due to low solubility in water and physical-chemical instability omeprazole represents a challenge for designing a pharmaceutical formulation.

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) which long-term use may cause serious unwanted side-effects due to pharmacological actions such as ulceration, bleeding and perforation of gastrointestinal tract. Active ingredient of ibuprofen is a weak acid and is relatively insoluble in water. Because scientifically proven facts have shown that concomitant use of NSAID and PPI causes less unwanted side-effects, the purpose of the thesis was to study stability and to predict chemical kinetics of binary mixtures of both active compounds using nonisothermal and isothermal (accelerated) stability tests. The related substances of omeprazole were determined by a High-Performance Liquid Chromatography (HPLC) method after fixed time intervals.

A stability-indicating HPLC method for related substances of omeprazole in API was used to confirm the results of instability of omeprazole published in articles at elevated temperature and relative humidity.

The results of related substances of tested samples indicated that omeprazole is unstable in presence of ibuprofen at higher temperature and relative humidity. The concentration of related substances was even higher in binary mixtures which were formulated in the ratio as presumed in model formulations. Using linear nonisothermal stability testing I determined the impurity profile which were detected first and their increasing trend. Due to obvious red coloration of binary mixture during stability testing, the impurity which caused changed appearance was determined.

In addition, LC-MS analysis was used to identify degradation products which appeared first and were among the most abundant. On the basis of known facts of compatibility studies, the model formulations – fixed combinations of two active compounds, were designed containing

one excipient or using a pharmaceutical technological process of semi-product to determine which would assure better stability of compounds in binary mixture.

By use of stability testing it was confirmed that model formulation which contains omeprazole pellets with *Eudragit*® coated ibuprofen granulate is the most stable followed by the formulation which contains omeprazole pellets with *PVA* coated ibuprofen granulate. Due to chemical and physical incompatibilities between API-s and excipients formulation which contains omeprazole pellets with ibuprofen granulate and MgO and model formulation which contains omeprazole pellets and ibuprofen granulate and talcum are presumed to be the least stable.

Key words: omeprazole, ibuprofen, fixed combination, nonisothermal testing, reaction kinetic, model formulation