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ABSTRACT

Obtaining technology, physico-chemical and biopharmaceutical study of statin inclusion complexes

Statins (or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. Statins exhibit action beyond lipid-lowering activity in the prevention of atherosclerosis. Statins have rare but severe adverse effects, particularly muscle damage.

Simvastatin and lovastatin are BCS Class II drugs having low solubility and therefore low oral bioavailability (5%). Low aqueous solubility of the drug leads to inadequate dissolution and hence poor absorption, distribution and target organ delivery. Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy.

The rate of absorption can be increased using various techniques, which include solvent disposition, cosolvents, salt formation, pH control, co-grinding, and solid dispersions. The usage of carriers like PEG, PVP, cyclodextrins HPMC, has been proved to enhance the dissolution of poorly soluble drugs.

Cyclodextrins are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability.

The aim of the present work was to improve the solubility and dissolution rate of simvastatin and lovastatin using cyclodextrins, to study the obtained binary mixtures and to prove the formation of inclusion complexes.

We prepared binary mixtures of **lovastatin** and hydroxypropyl-β-cyclodextrin by mixing and grinding with ethanol in a molecular ratio 1:1.

Binary mixtures of **simvastatin** were obtained with β-cyclodextrin by mixing and grinding with ethanol in molecular ratios 1:1 and 1:2, with hydroxypropyl-β-cyclodextrin by mixing and grinding with ethanol in molecular ratios 1:1 and 1:2, with random methyl-β-cyclodextrin by mixing, grinding with ethanol and co-evaporation from methanol and water, methanol and ethanol, respectively in molecular ratios 1:1 and 1:2.

Preliminary analysis by molecular modelation demonstrated, that inclusion complexation is energically benefic (the energy of inclusion complex is lower than the sum of the two substances). The influence of cyclodextrins on the solubility of lovastatin and simvastatin was

verified by the increase of absorption in UV of aqueus dispersions. Hydroxypropyl-β-cyclodextrin and random methyl-β-cyclodextrin showed the highest solubility enhancement.

The mixtures were analyzed with different methods, like Fourier transformed infrared absorption spectrometry, differential scanning calorimetry, dissolution studies, thin layer chromatography and determination of stability constant by the method of Higuchi and Connors.

Lovastatin containing inclusion complex of hydroxypropyl-β-cyclodextrin in 1:1 molecular ratio obtained by kneading possess the highest solubility (LPM11). The best fit model to describe the dissolution profiles is Korsmeyer-Peppas one.

Thermal analysis of lovastatin products marks the presence of uncomplexed active drug. The amount of free lovastatin is given by the complexation rate.

Thin layer chromatography of simvastatin, cyclodextrins, products and in situ mixtures by the changes in R_f values is a strong argument for complex formation.

The solubility of simvastatin increased with increasing cyclodextrin concentration indicating the formation of soluble complex with 1:1 stoichiometry. Stability constant for random methyl-β-cyclodextrin inclusion complex was 4049 M^{-1}, for hydroxypropyl-β-cyclodextrin 4084 M^{-1}, respectively. The obtained values can be correlated with sigmoidal models such as Logistic and Gompertz models with determination coefficients of 0.985-0.998.

Dissolution testing in artificial gastric and intestinal juice of simavastatin RAMEB products showed the highest solubility increase in the case of kneading and co-evaporation products from water ethanol mixture in 1:2 molecular ratio (SRM12 and SRC112). Also kneading products proved to have the best solubility among hydroxypropyl-β-cyclodextrin simvastatin products both in in artificial gastric and intestinal juice. β-cyclodextrin containing products indicate that kneading is an efficient method for solubility enhancement.

Dissolution profile analysis reveals that the eliberation of simvastatin and lovastatin from the inclusion complexes fits the semi-empiric Korsmeyer-Peppas model, the exponent ``n`` indicating liberation mechanism directed by Fickian diffusion.

Fourier transformed infrared absorption spectrometry certifies the formation of partial simvastatin inclusion complexes by the disappearance of the characteristic band except one, at 1712 cm^{-1} assigned to a carbonyl group double band for all three cyclodextrins.

Differential scanning calorimetry is used to confirm inclusion complex formation by the comparative analysis of DSC curves. The lack of melting peak of simvastatin indicates complex formation.

Furthermore, to find an appropriate application of simvastatin inclusion complexes, we choose tablets, as a pharmaceutical form to embed one of our products (SRM12). The main criteria of complex selection were solubility improvement and accessible obtaining method. The

complex associated with disintegrant (Primellose), filler and glidants (talc and magnesium stearate) pressed into a conventional tablet provides better dissolution, than pure simvastatin. The physical parameters of 5 % Primellose containing tablets comply with the requirements of European Pharmacopoeia. The dissolution of simvastatin is influenced by the disintegants and lubricants and can be described by the Korsemeyer Peppas model. The n parameter of this model permits a more profound elucidation of the liberation mechanism. The fact that $n < 0.5$ indicates a Fickian transport.

Keywords: lovastatin, simvastatin, cyclodextrin, solubility enhancement, dissolution, FTIR, DSC