Physical and Chemical Study of Simvastatin Inclusion Complexes

Rédai Emőke[1], Tőkés B.[2], Kiss A.[3], Sipos Emese[1], Ciurba Adriana[1], Todoran Nicoleta[1]

[1] Pharmaceutical Technology Department, Faculty of Pharmacy, University of Medicine and Pharmacy Tîrgu Mureş
[2] Physical Chemistry Department, Faculty of Pharmacy, University of Medicine and Pharmacy Tîrgu Mureş
[3] Organic Chemistry Department, Institute of Chemistry, Faculty of Science and Technology, University of Debrecen

Background: Simvastatin is an inhibitor of hydroxy-methyl-glutaryl-coenzyme A reductase, used in the treatment of hypercholesterolemia.
Aim: To enhance his bioavailability through inclusion complexation, as host molecule hydroxypropyl-b-cyclodextrin had been used. The objective of this study is to present our results of the study of some simvastatin and hydroxypropil-β-cyclodextrin (HPβCD) inclusion complexes. We analyzed the products by phase solubility study, dissolution test and Fourier-transformed Infrared Spectroscopy (FT-IR).
Methods: Complexes were prepared by kneading molecular ratios of 1:1 and 1:2 and compared also with physical mixtures. Solubility studies were performed in the presence of various HPβCD concentrations and the stability constant was calculated.
The inclusion complexation was evaluated by dissolution and Fourier transformed infrared spectroscopy.
Results: When compared with the pure drug, the dissolution of simvastatin is improved in the presence of β-cyclodextrin derivates, depending on the complex preparation method.
Conclusions: The solubility of simvastatin increases as a function of HPβCD concentration. FT-IR study suggests the presence of intermolecular hydrogen bonds between simvastatin and HPβCD in inclusion complex.

Keywords: simvastatin, hydroxypropyl-β-cyclodextrin, inclusion complex, bioavailability

Introduction

Simvastatin is a cholesterol-lowering agent that is derived from a fermentation product of Aspergillus terreus. Simvastatin (Figure 1) is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyses the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. However, it is practically insoluble in water and poorly absorbed from the gastrointestinal tract [1]. Therefore, it is very important to enhance the solubility, thus to increase its bioavailability.

The objective of this study is to present our results of the study of some simvastatin and hydroxypropil-β-cyclodextrin (HPβCD) inclusion complexes. We analyzed the products by phase solubility study, dissolution test and Fourier-transformed Infrared Spectroscopy (FT-IR).

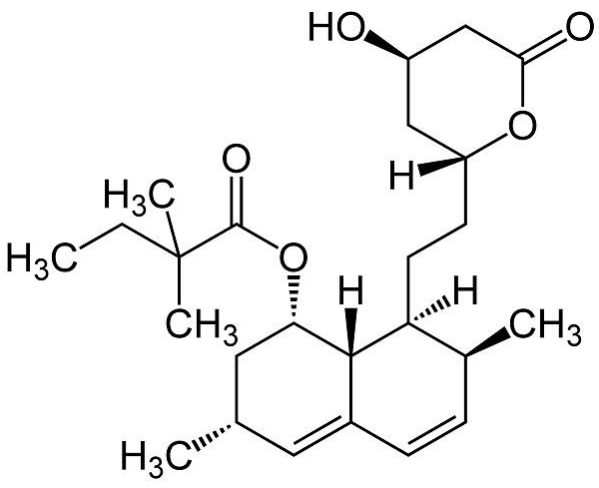

Fig. 1. Simvastatin structure

Material and method

Simvastatin, was kindly offered by Labormed Pharma (Bucureşti, Romania), hydroxypropil-β-cyclodextrin by Cyclolab R&D Ltd (Budapest, Hungary). Potassium dhydrogen phosphate was supplied by Penta (Praga, Czech Republic), di-potassium hydrogen phosphate by Lachner (Praga, Czech Republic). Solvents meet the requirements of the Romanian Pharmacopoeia Xth edition.

We obtained products with hydroxypropil-β-cyclodextrin (HPβCD) by mixing (FH) and kneading (GH) in different (1:1 and 1:2) molecular ratios. For kneading, we used ethanol 50^{c} in equal amount with the sum of simvastatin (SIM) and hydroxypropil-β-cyclodextrin mass. The product was dried at 50 °C by full evaporation of the solvent, than it was pulverized to an average size of 200 µm (Retsch AS 200 sieve).

Phase solubility study was performed using the Higuchi and Connors method [2]. Excess amount of simvastatin was added to the aqueous solution containing various concentration of HPBCD (0, 2, 6, 8 and 10 mM/l) and the shaken at 25 °C for 24 hours. After the equilibrium state was reached, the samples were withdrawn and filtered through a 0,45 µm methyl-ethyl-cellulose membrane filter and suitably diluted. The drug concentration was determined spectrophotometrically (Jenway UV/VIS Spectrophotometer) at 240 nm. The phase solubility diagram was

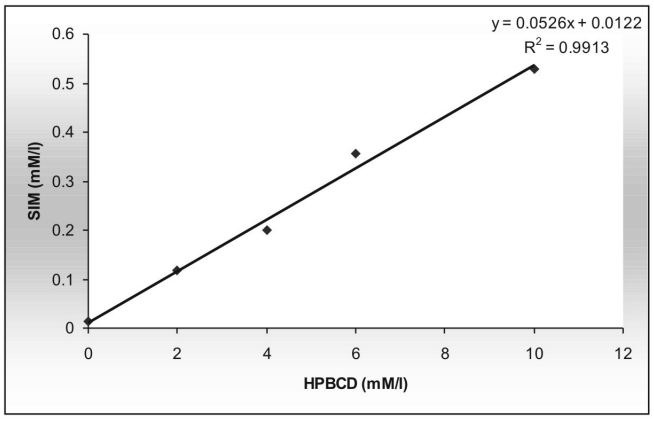

Fig. 2. Phase solubility diagram

constructed by plotting the total dissolved drug concentration against the total HPβCD one. The apparent complexation constant was calculated from phase solubility slope, where the intercept is the intrinsic solubility (σ) of drug in the absence of HPβCD:

$$K_{1:1} = \frac{slope}{\sigma(1 - slope)}$$

The dissolution profile was obtained using an Erweka DT dissolution tester with paddle. 10 mg simvastatin and samples equivalent to 10 mg simvastatin were taken for dissolution studies in 500 ml dissolution media, maintained at the temperature 37±1 °C at a stirring speed of 100 rpm. 5 ml aliquot was withdrawn at 5, 10, 15, 30, 60, 90, 120 minutes, replaced with the same amount of dissolution media. The samples were estimated for amount of simvastatin dissolved by measuring the absorbance in UV at 239 nm. Dissolution studies were performed in triplicate.

The composition of the gastric and intestinal juice used as dissolution media: artificial gastric juice: 0.35 g sodium chloride, 94.0 g hydrochloric acid 1 N completed to 1000 ml with distilled water (pH = 1.1); artificial intestinal juice: 11.94 g dipotassium hydrogen phosphate anhydride, 7.1 g potassium dihydrogen phosphate, adding distilled water to 1000 ml (pH =7).

Fourier-transformed infrared (FT-IR) spectra were obtained by a Perkin Elmer 16 PC FT-IR spectrometer. A resolution of 1 cm^{-1} was used and 8 scans were co-added for each spectrum at 450–4400 cm^{-1}.

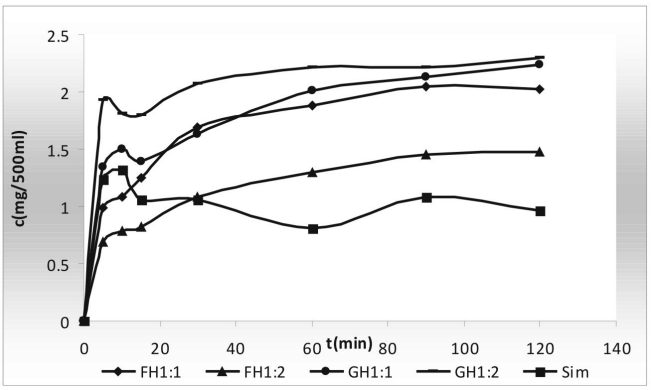

Fig. 3. Dissolution profiles in artificial gastric juice

Results

The phase solubility diagram can be seen in Figure 2. The apparent complexation constants (K1:1) calculated from phase solubility diagram was 4084 M-1.

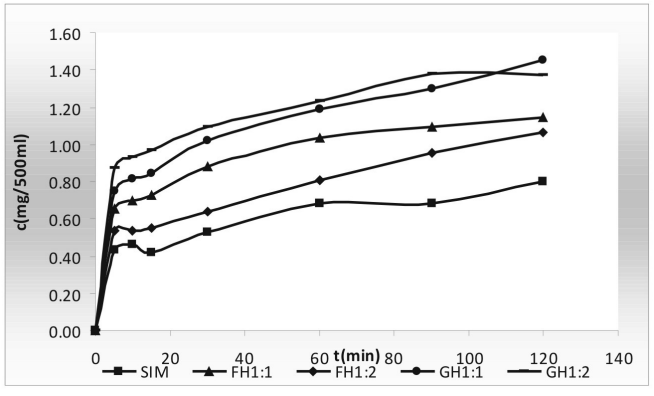

Fig. 4. Dissolution profiles in artificial intestinal juice

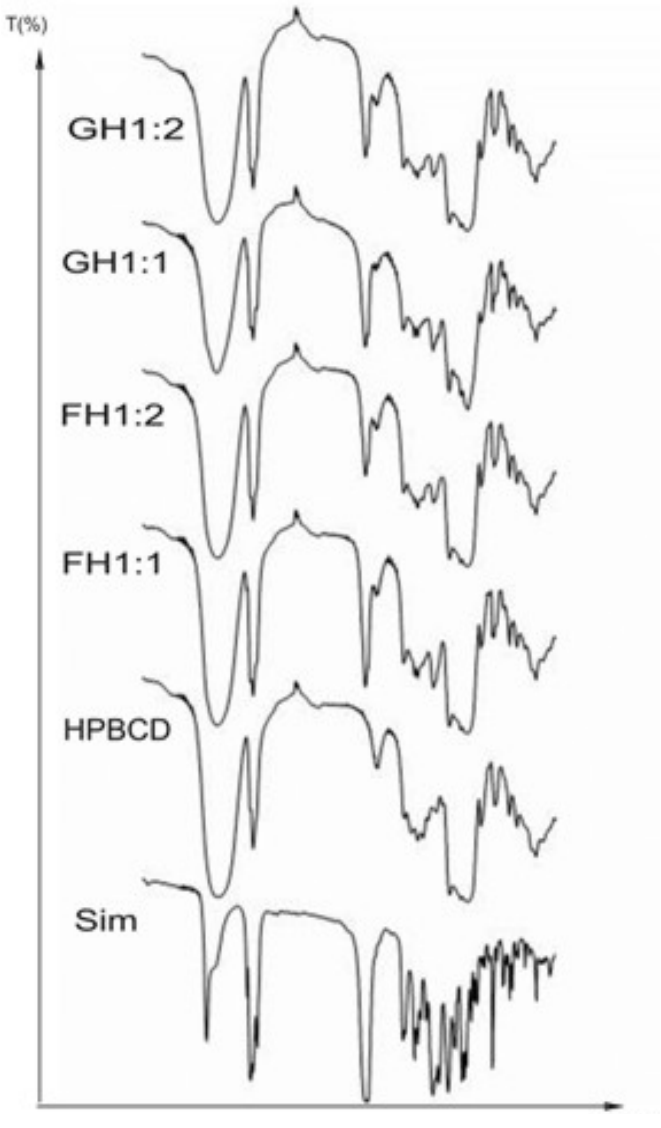

Fig. 5. FT-IR spectra of simvastatin and products

The dissolved amounts of simvastatin were calculated for the physical mixture (PM) and kneading product (KP) based on the calibration curve. Dissolution curves are presented in Figure 3. in artificial gastric juice and Figure 4. in artificial intestinal juice.

The FT-IR spectra can be seen in Figure 5.

Discussions

The phase solubility diagram of drug in the presence of various HPβCD concentrations at 25 °C was linear, A_L type of Higuchi and Connors [2].

When compared with the pure drug, the dissolution of simvastatin is improved in the presence of β-cyclodextrin derivates, depending on the complex preparation method [3].

The FT-IR spectra of simvastatin point to the presence of the following peaks: 3549 cm^{-1} (free O–H stretching vibration), 3011, 2968, and 2871 cm^{-1} (C–H stretching vibrations), 1712 cm^{-1} (stretching vibration of ester and lactone carbonyl functional group) and the FT-IR spectra of HPβCD contain absorption bands at 3404 cm^{-1} (for O–H stretching vibrations) and 2928 cm^{-1} (for C–H stretching vibrations). The characteristic absorption peaks of the carbonyl group of simvastatin at 1700–1800 cm^{-1} have not disappeared from the spectrum of the products.

Conclusions

The phase solubility diagram suggests a 1:1 stoichio-metry of the complexes over the concentration range (0–10 mM) investigated. The solubility of simvastatin increases as a function of HPβCD concentration.

Aqueous solubility and dissolution studies indicated that the dissolution rates were increased in GH 1:1 and GH 1:2 products compared with the physical mixtures and drug alone.

FT-IR study suggests the presence of intermolecular hydrogen bonds between simvastatin and HPβCD in inclusion complex. The absorption peaks of simvastatin at 3549 cm^{-1} 3011, 2968, and 2871 cm^{-1} disappeared from the spectrum of the inclusion complex. This is probably due to the inclusion complexation of drug into the HPβCD cavity.

References

1. Stancu C, Sima A – Statins: mechanism of action and effects, J Cell Mol Med, 2001, 5: 378-387.
2. T. Higuchi, K.A. Connors - Phase-solubility techniques, Adv. Anal. Chem. Instrum., 1965, 4:117–212.
3. Seoung W, Min-Soo K, Jeong-Soo K – Preparation and characterization of simvastatin/hydroxypropyl-b-cyclodextrin inclusion complex using supercritical antisolvent (SAS) process, Eur J Pharm Biopharm, 2007, 65:125-136.