

Physical and Chemical Study of Lovastatin Inclusion Complexes. Bioavailability Improvement

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Background: Lovastatin is an inhibitor of hydroxy-methyl-glutaryl-coenzyme A reductase, used in the treatment of hypercholesterolemia. To enhance its bioavailability through inclusion complexation, as host molecule hydroxypropyl- β -cyclodextrin had been used.

Methods: Complexes were prepared by kneading in molecular ratio 1:1 and compared also with a physical mixture in molecular ratio 1:1. The complex was studied by performing dissolution tests and differential scanning calorimetry.

Results: Mixing the drug with the host molecule the soluble amounts were increased to 1.55 mg in artificial gastric juice and 2.99 mg in artificial intestinal juice. Kneading also improved the solubility of lovastatin to 1.94 mg in artificial gastric juice and 2.78 mg in artificial intestinal juice. In the thermograms a sharp endotherm peak was observed at the same position of lovastatin.

Conclusions: Dissolution studies showed an improvement of the drug release both in artificial gastric and intestinal juice. The sharp endotherm peak on the DSC curves indicates the untrapped lovastatin.

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

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Introduction

Among the recently used hypolipemians, hydroxymethyl-glutaryl coenzyme A inhibitors, named statins, are the most used in the treatment of dyslipidemia. The basic structure of lovastatin (Figure 1) is a substituted decalin ring. This ring has a hydroxyglutaric acid chain, making the structure similar to the endogenous substrate of HMG CoA reductase. After oral administration, the inactive parent lactone is hydrolyzed to the corresponding hydroxyacid form. Lovastatin is insoluble in water [1].

The bioavailability of lovastatin is about 5%, roughly 95% of the molecule bonds to plasma proteins, and its main side effects are myopathy and increase of hepatic transaminase levels.

Its poor water solubility leads to inadequate dissolution in gastrointestinal fluids. Low aqueous solubility can be enhanced by association with cyclodextrins, which leads to bioavailability improvement [2].

Lovastatin and hydroxypropyl- β -cyclodextrin inclusion complex had been prepared by kneading and coevaporation methods and studied with different methods (DSC, XRD, FTIR and dissolution studies) [3]. For kneading the authors used mixture of water and methanol. Complexation is greatly influenced by solvents, the properties of the complex vary depending on preparation.

The objective of this study is to present our results of the study of some lovastatin and hydroxypropyl- β -cyclodextrin (HP β CD) inclusion complexes. We analyzed the products, obtained by kneading with ethanol and water in 1:1 molecular ratio, by dissolution test and thermoanalysis.

Material and methods

Lovastatin was kindly offered by Labormed Pharma (Bucharest, Romania), hydroxypropyl- β -cyclodextrin by Cyclolab R&D Ltd (Budapest, Hungary). The solvents met the requirements of the Romanian Pharmacopoeia Xth edition.

We obtained the inclusion complexes with hydroxypropyl- β -cyclodextrin by kneading in 1:1 molecular ratio and a physical mixture in the same ratio. Hydroxypropyl- β -cyclodextrin contained 7.01 % water, therefore we calculated all the amounts reported to the contained humidity. For kneading, we used ethanol 50c in equal amount with the sum of lovastatin and hydroxypropyl- β -cyclodextrin mass. The product was dried at 60°C to the full evaporation of the solvent, then it was pulverized to an average size of 100 μ m (Retsch AS 200 sieve).

The dissolution profile was obtained using a Pharmatest dissolution tester with six test station with paddle. Ten mg lovastatin and samples equivalent to 10 mg lovastatin were taken for dissolution studies in 900 ml dissolution

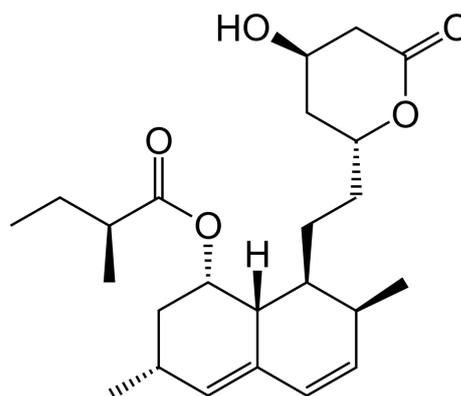


Fig. 1. Lovastatin structure

Table I. Dissolution in artificial gastric and intestinal juice (Lovastatin, PM 1:1, KP 1:1, means and standard deviations)

Gastric juice		Lovastatin			PM1:1			KP1:1		
Time (min)	Average (mg/900ml) A	Standard deviation		Average (mg/900ml) A	Standard deviation		Average (mg/900ml) A	Standard deviation		
5	1.21	0.37		1.35	0.20		2.01	0.43		
10	1.57	0.58		1.02	0.58		1.83	0.11		
15	1.15	0.59		1.62	0.33		1.65	0.25		
30	0.96	0.08		1.55	0.03		1.88	0.21		
60	1.09	0.31		1.67	0.14		1.72	0.12		
90	1.07	0.05		1.85	0.10		2.15	0.08		
120	1.11	0.22		1.78	0.11		2.35	0.06		
	Overall Average	1.16	SD of means ±0.03	Overall Average	1.55	SD of means ±0.10	Overall Average	1.94	SD of means ±0.12	

Intestinal juice		Lovastatin			PM1:1			KP1:1		
Time (min)	Average (mg/900ml) A	Standard deviation		Average (mg/900ml) A	Standard deviation		Average (mg/900ml) A	Standard deviation		
5	1.24	0.01		2.89	0.19		2.57	0.36		
10	1.13	0.17		2.72	0.45		2.55	0.53		
15	1.25	0.11		2.86	0.19		2.43	0.20		
30	1.14	0.15		2.78	0.21		2.77	0.18		
60	1.36	0.12		3.38	0.11		2.73	0.62		
90	1.15	0.12		3.33	0.35		3.31	0.29		
120	1.24	0.17		2.97	0.24		3.09	0.23		
	Overall Average	1.21	SD of means ±0.03	Overall Average	2.99	SD of means ±0.11	Overall Average	2.78	SD of means ±0.09	

media, maintained at $37\pm 1^\circ\text{C}$ at a stirring speed of 100 rpm. Five 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 the amount of lovastatin dissolved by measuring the absorbance in UV at 240 nm [5]. Dissolution studies were performed in triplicate. The composition of the gastric and intestinal juice used as dissolution media were: artificial gastric juice: 0.35 g sodium chloride, 94.0 g hydrochloric acid 1 N, 0.5 g glycine completed to 1000 ml with distilled water (pH=1.1); artificial intestinal juice: 14.4 g dipotassium hydrogen phosphate anhydride, 7.1 g potassium dihydrogen phosphate, adding distilled water to 1000 ml (pH=7).

A Mettler Toledo Star System was used for differential scanning calorimetry (DSC). The samples were weighed accurately in crimped aluminum pans and heated, from

25°C to 300°C at a scanning rate of $5^\circ\text{C}/\text{minutes}$ under dry nitrogen flow [4,5].

Results

The dissolved amounts of lovastatin were calculated for the physical mixture (PM) and kneading product (KP) based on the calibration curve. The means and standard deviations of the dissolved amount of lovastatin are presented in Table I. Dissolution curves are presented in Figures 2 and 3.

The DSC scans of lovastatin, hydroxypropyl- β -cyclodextrin, physical mixture 1:1 and kneading product 1:1 can be seen in Figure 4.

Discussions

When compared with the pure drug, the dissolution of lovastatin is improved in the presence of β -cyclodextrin

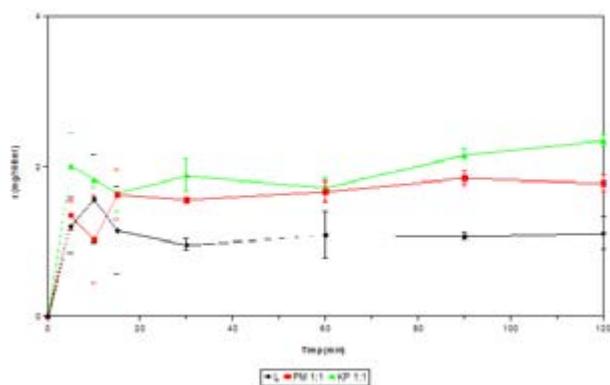


Fig. 2. Dissolution profiles in artificial gastric juice

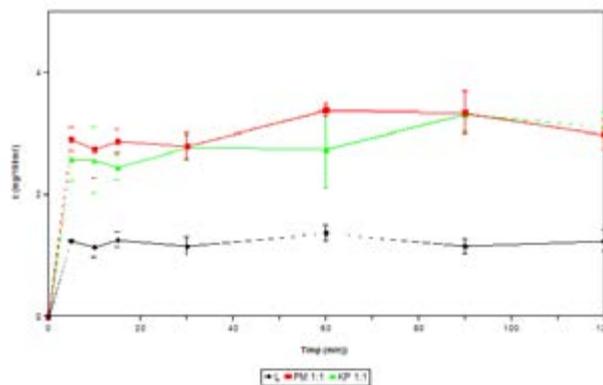


Fig. 3. Dissolution profiles in artificial intestinal juice

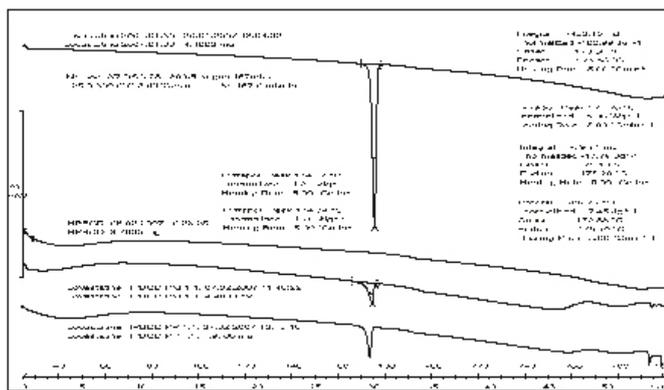


Fig. 4. DSC curves of lovastatin, HP β CD, PM 1:1, KP 1:1

derivates, as proved by Süle, Szente and Csempesz in their work for β -cyclodextrin, and randomly methylated β -cyclodextrin. In ternary systems with polyvinyl-pyrrolidone solubility can further be increased. Both in binary and ternary systems a significant increase in the immersion enthalpy values could be detected, which indicates that the complexes exhibit a fairly hydrophilic character [5,6,7]. Complexes of lovastatin and β -cyclodextrin were prepared by kneading and included in osmotic pump tablets. Dissolution studies showed that the amount of β -cyclodextrin has a pronounced influence on the extent of the release profiles [8]. Another possibility to enhance the bioavailability of lovastatin is by dry-emulsion containing Phosal 53MCT and Tween 80 [9].

Our results confirmed that solubility improves in binary systems with hydroxypropyl- β -cyclodextrin. The inclusion complex prepared by kneading method showed an improvement of *in vitro* drug release, an approximately 3 fold increase. The *in vitro* drug release of the physical mixture improved too. Dissolution was fast in all cases, after 5 minutes only measurement fluctuations could be observed.

The complexation method influences the dissolution of the drug, as seen in the work of Seoung Min-Soo, Jeong-Soo in the case of simvastatin [10]. Kneading (with water ethanol mixture) is more effective than mixing the two components (lovastatin and hydroxypropyl- β -cyclodextrin).

According to the dissolution test results in artificial gastric juice, an overall average of 1.16 mg lovastatin and in artificial intestinal juice an overall average of 1.21 mg lovastatin was dissolved. Mixing the drug with the host molecule increased the soluble amount to 1.55 mg in artificial gastric juice and 2.99 mg in artificial intestinal juice. Kneading also improved the solubility of lovastatin to 1.94 mg in artificial gastric juice and 2.78 mg in artificial intestinal juice. The pH of the dissolution medium influences

the dissolution, at pH=7 (intestinal juice) the dissolved amount increases.

Lovastatin showed a melting endotherm at 174°C with enthalpy of fusion (ΔH) 102.99 J/g. In the thermogram of the hydroxypropyl- β -cyclodextrin, the endothermic peak near 100°C was caused by loss of water from hydroxypropyl- β -cyclodextrin molecules. In the thermogram of physical mixture and kneading product, a sharp endotherm was observed at the same position of lovastatin with enthalpy of fusions of 17.79 J/g for PM1:1 and 17.45 J/g for KP1:1, thus indicating the presence of its untrapped extent. The area of the endotherm peak is directly proportional to this amount.

Conclusions

Our results presented in this paper prove that, in some conditions, profound interactions take place between lovastatin and hydroxypropyl- β -cyclodextrin. Their produces are, in general, inclusion or/and intermolecular complexes. These interactions manifest in dissolution studies as well, which show an improvement of the drug release both in artificial gastric and intestinal juice (an approximately 3 fold increase). DSC method also confirms the formation of a complex in the solid state. The disappearance of different thermal phenomena of guest molecules in conditions of complex formation is considered as a proof of a real inclusion compound rise. A sharp endothermic peak at the same position as that of lovastatin indicates the presence of some remained untrapped lovastatin amount in the studied process.

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