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RESEARCH ARTICLE

Quality Enhancement by Inclusion Complex Formation of Simvastatin Tablets

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Introduction: Simvastatin is an inhibitor of hydroxy-methyl-glutaryl-coenzyme A reductase, used in the treatment of hypercholesterolemia. To enhance its bioavailability by inclusion complexation, as host molecule randommethyl-β-cyclodextrin had been used. After evaluating the complexes we chose the kneading product in 1:2 molar ratio for incorporation of 10 mg simvastatin tablets.
Materials and methods: We prepared homogenous mixtures of the inclusion complex and some excipients. The tablets were prepared by direct compression. The tablets were evaluated in regard to: weight uniformity, thickness, diameter, hardness, friability, disintegration and dissolution profile.
Results: Weights are in the range of 196–208 mg, diameter 6.83–6.86 mm, height 3.86–4.01 mm, hardness 78.3–113.1 N, friability 0.75–1.19 %, disintegration above 15 minutes. The dissolved amounts of simvastatin from the tablets are higher compared to the dissolution of pure simvastatin, but lower than the dissolution of the complex itself. Excipients, like disintegrants and lubricants greatly influence the dissolution properties of the tablets.
Conclusions: According to our results, tablets containing inclusion complex of simvastatin exhibit better solubility, according to the dissolved amount of simvastatin, than pure drug alone. Proper physical parameters of the tablets are obtained by application of 5 % Primellose.

Keywords: simvastatin, randommethyl-β-cyclodextrin, dissolution, tablet

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Introduction

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].

By inclusion complexation of simvastatin with cyclodextrins its bioavailability can be enhanced [2]. Therefore inclusion complexes are recommended to be used in formulations to obtain proper pharmaceutical forms.

The aim of this experimental work was the obtaining of uncoated tablets containing simvastatin inclusion complex as active ingredient and to observe the influence of excipients (disintegrants and lubricants) on the tablet properties. The inclusion complexes had been characterized in a previous article [3]. The main criteria of complex selection were solubility improvement and accessible obtaining method.

The used disintegrants: Primellose is chemically cross-linked sodium carboxymethyl cellulose. About three glucose units from four x are substituted with sodium carboxymethyl groups, and some of these groups are used to form cross links. The substituent groups disrupt hydrogen bonds that bind the cellulose chains tightly together and make sodium carboxymethyl cellulose very hydrophilic. The cross-links prevent dissolution of the polymer (which would lead to formation of a viscous gel). The optimized combination of substitution and cross-linking means that Primellose rapidly absorbs water and swells, the swelling resulting in the generation of a powerful disintegrating force within the tablets. Primellose is effective in combination filler-binders such as lactose at concentrations of 2–6% [4]; Starch 1500 is a partially pregelatinized maize starch. Partial pregelatinization provides partial solubility, increased particle size, improved flow properties and compactibility.

Fillers fill out the size of the tablets, making it practical to produce and convenient for the consumer use. By

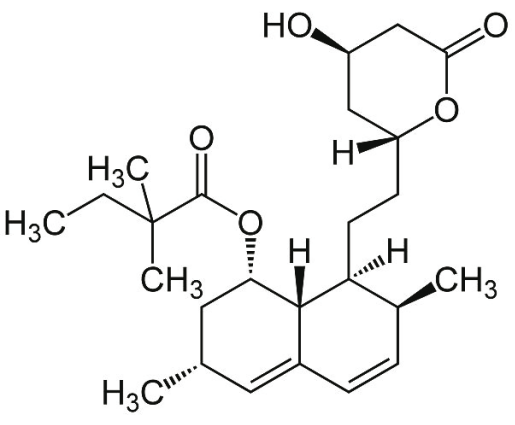

Fig. 1. Simvastatin

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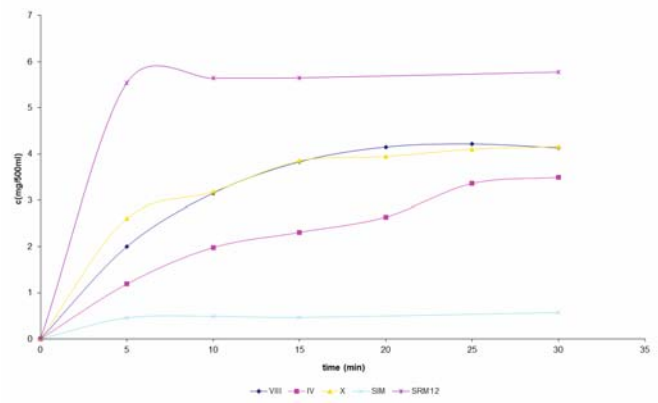

Fig. 2. In vitro dissolution studies

increasing the bulk volume, the fillers make possible the final product to have a proper volume for patient handling.

Tablettose® 100 is the brand-name for an agglomerated α-lactose-monohydrate. Especially designed for direct-compression, it combines the flowability of coarse lactose and the good compressibility of fine milled lactose.

Corn starch has many functional properties including binding, disintegration, absorption, and bulking for pharmaceutical and nutraceutical applications including wet and dry granulation, tableting and body powders.

Materials and methods

Simvastatin (SIM) was kindly offered by Labormed Pharma (Bucharest, Romania), randommethyl-β-cyclodextrin (RAMEB) by Cyclolab R&D Ltd (Budapest, Hungary). Potassium dhydrogen phosphate was supplied by Penta (Prague, Czech Republic), di-potassium hydrogen phosphate by Lachner (Prague, Czech Republic), Starch 1500 by Colorcon (Dartford, United Kingdom), Primellose by DFE Pharma (Goch, Germany), Tablettose 100 by Meggle GmbH (Wasserburg, Germany), Corn starch by Agrana (Aschach, Austria), magnesium stearate by Peter Greven (Vonlo, The Netherlands), talc by Luzenac Pharma (Spain). Solvents meet the requirements of the European Pharmacopoeia VIIth edition.

The inclusion complex was prepared by kneading in 1:2 molar ratio. For this purpose, we used ethanol 50c in equal amount with the sum of simvastatin (SIM) and randommethyl-β-cyclodextrin mass. The product (SRM12) was dried at 50°C by full evaporation of the solvent, and then it was pulverized to an average size of 200 μm (Retsch AS 200 sieve).

There were prepared three formulations by direct compression, containing two different superdisintegrants (Starch 1500 and Primellose), Tablettose 100 or corn starch as filler, magnesium stearate or talc as lubricant.

Weight variation test: Twenty tablets were taken determining their weights individually and collectively using a digital weighting balance. The average weight of one tablet was determined from the gross worked of mass collective weight. According to the European Pharmacopoeia not more than 2 of the individual masses deviate from the average mass by more than 7.5 % and none deviates by more than twice this percentage.

Hardness test, height and diameter: Hardness, height and diameter of the tablets were determined using Pharmatest 3 in1 Hardness, Diameter and Thickness Tester.

Friability test: Ten tablets from each batch were examined for friability using Electrolab, Automated Friabilator EF-2, India. The equipment was run for 4 minutes at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated.

%Friability = (Loss in weight/Initial weight) × 100

In vitro disintegration time: The disintegration test was performed using an USP disintegration apparatus, with distilled water at 37 ± 0.5°C. Time required to obtain complete disintegration of six tablets were recorded and average was reported.

The dissolution profile: It was obtained using an Erweka DT dissolution tester with paddle. For these studies there were taken 10 mg simvastatin and the tablets in 500 ml dissolution media, operating at 37 ± 1°C, stirring on a speed of 100 rpm. 5 ml aliquot was withdrawn at 5, 10, 15, 20, 25, 30 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.

Composition of the intestinal juice used as dissolution media: 11.94 g dipotassium hydrogen phosphate anhydride, 7.1 g potassium dihydrogen phosphate, adding distilled water to 1000 ml (pH = 7).

Dissolution profile modeling: The drug-release kinetics was fitted to first-order, Probit, Logistic, Weibull, Gompertz and Korsmeyer–Peppas models. The best fit model was chosen by R2 (determination coefficient) and MSE (Medium Square Error).

Results

The results concerning the weight uniformity, hardness, diameter and thickness test and friability are shown in Table II. The disintegration times in minutes are given in Table III. In vitro dissolution studies are shown in Figure 2. The parameters of best fit model are given in Table IV.

Discussion

In order to find the most suitable formulation from the technological point of view several different disintegrants were used, in the initial formulation phase. RAMEB is a powder with poor flow properties and sticking tendency. At direct compression RAMEB behaved as a powerful binder. Since its relatively big amount in the tablets (36%), superdisintegrants (Starch 1500 and Primellose) were needed in order to achieve a good disintegration [5]. Talc may be used in 1–10 % in the composition of tablets, associated or not with magnesium stearate. The platy nature of talc, the slipperiness that results from its crystalline

Table I. Composition of tablets

Ingridients (mg)	Formulation code		
	IV	VIII	X
SRM12	72.2	72.2	72.2
Starch 1500	112.8		
Primellose		10	12
Tablettose 100		102.8	
Corn starch			95.8
Magnesium stearate		5	10
Talcum	15	10	10
Final weight (mg/tablet)		200	

Table III. Disintegration times

Disintegration time (min)	IV	VIII	X
	12	7	6

Table II. Weight uniformity, hardness, diameter, thickness and friability test results

Parameter	Formulation code		
	IV	VIII	X
Weight (mg) ± S_{abs}	198.15 ± 1.7	200.6 ± 2.28	199.65 ± 1.46
Hardness (N) ± S_{abs}	113.1 ± 8.5	94.5 ± 9.7	78.3 ± 8.1
Diameter (mm) ± S_{abs}	6.84 ± 0.01	6.84 ± 0.01	6.85 ± 0.01
Thickness (mm) ± S_{abs}	3.95 ± 0.03	3.93 ± 0.05	3.91 ± 0.03
Friability (%)	0.749	0.985	1.189

structure, its softness and hydrophobicity all contribute to its performance as a glidant and lubricant in tableting. The effectiveness of talc glidant activity is dependent upon particle size compatibility between the talc and other powders in the formulation, improves direct compression tablet formulation disintegration behavior. Talc can effectively be used in combination with magnesium stearate for better disintegration and dissolution properties [6].

All batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability, disintegration. All above properties and values were close to boundary of standard limit. All the tablets maintained hardness in the range 78.3–113.1 N. The loss in total weight of the tablets due to the friability was in the range of 0.75–1.19 %. Formulation X, probably, due to the 6 % Primellose content, has lower hardness and friability over 1 %. Oral tablets normally have hardness higher than 40 N.

The result in vitro disintegration were within the prescribe limit and comply with the criteria for uncoated tablets, values were within 6–12 minutes [7].

Dissolved amount of simvastatin from the tablets were between the dissolvent quantity of pure simvastatin (10%) and the inclusion complex (60%). The type of used disintegrant influences the dissolution profile as well as the amount of it. Primellose confers better dissolution than Starch 1500. Phenomenom could be explained with the most adventagous chemical structure of the previous disintegrant. Unfortunately, the amount of talcum influences negatively the dissolution of simvastatin, formulation IV containing the greatest amount, possesses the lowest quantity of dissolved simvastatin. Fillers have less influence on dissolution.

The best fit model proved to be the empiric Korsmeyer–Peppas (determination coefficients 0.968–0.985).

Conclusions

From our studies can be concluded that solubility of simavastatin can be improved by inclusion complex formation with randommethyl-β-cyclodextrin in 1:2 molecular ratio by kneading. 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 the more profound elucidation of the liberation mechanism. The fact that n <0.5 indicates a Fickian transport.

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Table IV. Parameters of Korsmeyer-Peppas model

Formulation code	SRM12		SIM		IV		VIII		X	
param	kKP	n	kKP	n	kKP	n	kKP	n	kKP	n
	53.818	0.020	2.566	0.262	5.030	0.600	13.374	0.357	18.005	0.258
R2	0.998		0.956		0.982		0.968		0.985	
MSE	0.915		0.649		1.802		3.020		1.776	

Equation of model $F = kK_p t^n$, where kK_P – Peppas constant (release constant incorporating structural and geometric characteristics of the drug-dosage form); n is the diffusional exponent (indicating the drug-release mechanism)