THE ADSORPTION OF SIMVASTATIN ON CHITOSANS IN AN IN VITRO PHARMACEUTICAL MODEL

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Abstract

In clinical practice for the treatment of obesity, several natural macromolecular compounds are used, whose operation is based on supporting weight loss. During the use of dietary supplements containing chitosan, disease sometimes occurs and treatment for this often comprises different therapeutic agents and antibiotics. The aim of our study was to determine the binding capacity of simvastatin to chitosan, which is found in dietary supplements promoting weight loss, depending on variable physicochemical factors in the gastrointestinal tract model.

The phenomenon of adsorption of simvastatin was investigated by a static and dynamic pharmaceutical model (according to the Modified method of Polish Pharmacopoeia IX) simulating the conditions in vitro. The amount of bound drug is used to calculate the average percentage of the adsorbed dose.

The obtained results showed that simvastatin is adsorbed by chitosan in the used pH ranges, and the binding capacity is dependent on the environmental pH, viscosity, the concentration of the drug, the type of chitosan and additional substances present in the gastrointestinal tract. The average adsorption of simvastatin in the system of chitosan-nutrients, depending on the pH of the medium, was in the range of 27 to 95%. The highest amount of adsorption was noted above pH 7 (chitosan precipitated polymer forming the emulsion-gel system), when the bioavailability of dietary supplement using chitosan was almost zero.

Key words*: simvastatin, adsorption, chitosan*

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1. Introduction

In the treatment of obesity many natural compounds whose activity is based on the capacity to absorb dietary factors are currently used. In addition to slimming drugs, patients can choose from a wide range of dietary supplements available over the counter.

On the market, there are many preparations containing hydrophilic fibres, such as glucomannan, xanthine, psyllium, agar-agar and pectin and chitosan. The mechanism of action of these dietary supplements is to increase their volume by absorbing water and filling the stomach. The result is increased satiety by coating the walls of the upper gastrointestinal tract, which hinders the absorption of glucose [1,2]. In the intestinal transit, a polymer gel is produced. which has the ability to adsorb nutrients [3,4].

There are no reported studies in the available literature on the relationship between the level of adsorption of simvastatin and the type of chitosan polymer used. The adsorption properties of chitosan may lead to a significant interaction with the active substances of the medication taken by patients. The intensity of the adsorption phenomenon may also depend on the type of chitosan and its properties.

The aim of the study was to investigate the in vitro effect of selected physicochemical factors on the ability of adsorption of various kinds of chitosans. Moreover, an assessment of the assumption that the use of formulations of chitosan is important for bioavailability of the drug substance to be administered orally was made. Finally, the study aimed to clarify the mechanism of interaction of the drug simvastatin with dietary supplements, which contains chitosan. A high adsorption capacity of the chitosan polymer may reduce the bioavailability of the drugs.

2. Materials and method

2.1. Materials

2.1.1. Chitosan

Chitosan is a deacetylated chitin, i.e. a product obtained after the removal of functional acetyl groups. The greater the degree of deacetylation, the higher the functional effect (biochemical activity) of the preparation. It occurs in the form of cations (positively charged ions) and has a high degree of deacetylation (over 85%), giving the highest functional effect. The polycationic behaviour of chitosan, resulting from the presence of protonated amino groups enables the formation of multicomplexes with derivatives carrying negative charges, such as polymers or proteins. In addition, chitosan is capable of selectively attaching to a molecule of cholesterol, fat, tumour cells, nucleic acids (DNA and RNA) [5,6].

In the present study, natural chitosans with a very high degree of deacetylation, in a range between 85% and 95%, were used (Table 1). Chitosan was treated with IR radiation before use to produce smaller molecular weight. During the test, a radiation dose from 5 to 30 kGy was applied.

Table 1. Type of chitosans and their intrinsic viscosty

Lp	Type of chitosan	Intrinsic viscosity [dm^3g^{-1}]	Ionising radiation [kGy]
1	Chito-Clear TM 1015	0.2852	0
2	Chito-Clear TM 1015	0.2545	5
3	Chito-Clear TM 1015	0.2282	10
4	Chito-Clear TM 1015	0.2057	15
5	Chito-Clear TM 1015	0.1872	20
6	Chito-Clear TM 1015	0.1576	30
7	Chitosan type 352 food grade	0.2117	0
8	Chitosan type 352 food grade	0.1949	5
9	Chitosan type 352 food grade	0.1696	10
10	Chitosan type 352 food grade	0.1639	15
11	Chitosan type 352 food grade	0.1575	20
12	Chitosan type 352 food grade	0.1497	30
13	Chitosan Huasu sample	0.7437	0
14	Chitosan Huasu sample	0.5843	5
15	Chitosan Huasu sample	0.5185	10
16	Chitosan Huasu sample	0.3717	15
17	Chitosan Huasu sample	0.3303	20
18	Chitosan Huasu sample	0.2986	30
19	Chromdiet®	0.1872	0
20	Bio-active®	0.1576	0
21	Witana®	0.1774	0

2.1.2. Simvastatin

Simvastatin (lat. Simvastatinum) is a multifunctional organic compound, a natural derivative of lovastatin, a prodrug with a molecular structure of a lactone ring, which is hydrolysed to be common with other statins with active pharmacophoric groups – chain β-hydroxycarboxylic acid. It is used as a drug, and its lipid-lowering effect has additional pleiotropic effects on the cardiovascular system through effects on endothelial function, stabilising atherosclerotic plaques, inhibiting coagulation, stimulating the fibrinolysis system and inhibiting inflammatory and immunomodulatory effects. It works by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.

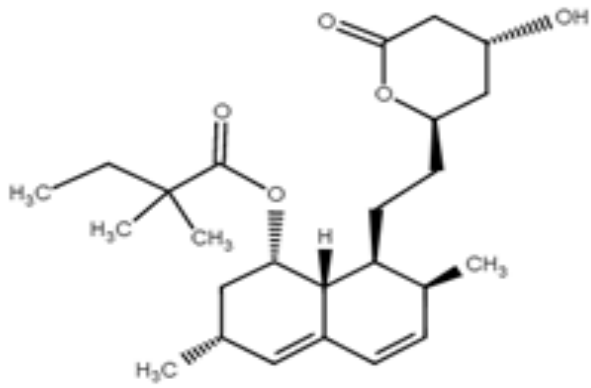

Figure 1. Simvastatin

2.2. Method

2.2.1. Investigation of Simvastatin adsorption process on the chitosans probes

The adsorption of simvastatin was analysed by a static-dynamic method in the concentration range of generally ingested single doses, using a pharmaceutical model of the gastrointestinal tract based on the modification of Polish Pharmacopoeia test [7–11].

The study was conducted in a shaking water bath, maintaining conditions to closely resemble those in the gastrointestinal tract, with an amplitude of vibration imitating peristaltic movements (300 rpm) and the process temperature (37°C).

For centrifugation, 2 ml of the appropriate solutions of chitosan was dispensed into 5 ml vials and the pH was adjusted to 2 (0.05 M HCl), which is suitable for fasting gastric pH. The volume of solution used corresponded to 0.03 g chitosan (the dose used as a slimming supplement). Then, into 5 ml vials, an amount of medicinal substance corresponding to 0.125 g of simvastatin (dose in therapeutic treatments) was added and shaken (300 rpm) for 2 hours. The contents of test tubes were then adjusted with 0.1 M Na_2CO_3 to pH 7.0–7.6, which corresponds to the pH of the intestinal tract and colon. Samples were incubated at 37°C with shaking (300 rpm) for 2.5 hours.

The tested system was brought to room temperature and centrifuged in a centrifuge (2100x g) for 20 minutes and was then allowed to stabilise for 0.5 hours. Subsequently, 1.5 ml of the supernatant was collected in clear tubes and spectrophotometrically determined (λ = nm) in 1 cm quartz cuvettes and using a standard curve determined from the concentration of the determined drug.

3. Results and discussion

3.1. The impact of intrinsic viscosities and viscosity-average molecular weights for the the adsorption of simvastatin on chitosans

Analysis of the effect of the radiation dose degradation that affects the viscosity of the material obtained for the simvastatin adsorption capacity on chitosans shows that the reduction in the intrinsic viscosity of chitosan increases the quantity of the bound drug (Table 2 and Fig. 2).

Table 2. The results of the simvastatin adsorption process on chitosan surfaces

Lp.	Type of chitosan	The average amount of bound antibiotic [mg]	The average amount of antibiotic bound by 1 g of chitosan [g]	Standard deviation DS [g]	Relative standard deviation RDS [%]
1	Chito-Clear TM 1015	7.99	266.62	0.003	1.91
2	Chito-Clear TM 1015 (5)	7.83	261.12	0.034	2.18
3	Chito-Clear TM 1015 (10)	6.92	230.87	0.021	4.12
4	Chito-Clear TM (15)	9.11	303.88	0.015	2.15
5	Chito-Clear TM 1015 (20)	6.22	207.48	0.034	4.62
6	Chito-Clear TM 1015 (20)	7.41	247.26	0.017	3.61
7	Chitosan type 352 food grade	6.86	228.91	0.014	2.32
8	Chitosan type 352 food grade (5)	6.18	206.13	0.033	4.81
9	Chitosan type 352 food grade (10)	7.19	239.83	0.018	3.34
10	Chitosan type 352 food grade (15)	6.11	203.79	0.017	2.86
11	Chitosan type 352 food grade (20)	7.90	263.66	0.016	3.37
12	Chitosan type 352 food grade (30)	2.96	98.74	0.677	2.81
13	Chitosan type 652 sample	6.31	210.62	0.483	3.30
14	Chitosan type 652 (5)	7.20	240.18	0.434	4.83
15	Chitosan type 652(10)	7.40	246.91	0.016	2.85
16	Chitosan type 652 (15)	7.09	236.42	0.15	2.16
17	Chitosan type 652(20)	7.82	260.85	0.055	2.84
18	Chitosan type 652(30)	2.60	86.82	0.017	2.26
19	Chromdiet®	7.43	247.66	0.19	2.55
20	Bio – active®	7.59	253.00	0.29	3.82
21	Witana®	7.98	266.00	0.34	4.26

Analysis of the average molecular weight viscosity assays showed that the values for chitosan varied depending on the degree of degradation of radiation of the polymer that is adequate for the intrinsic viscosity. The test results show that simvastatin is adsorbed

onto chitosan in the pH ranges used, and the binding ability of chitosan varies with type and its degradation

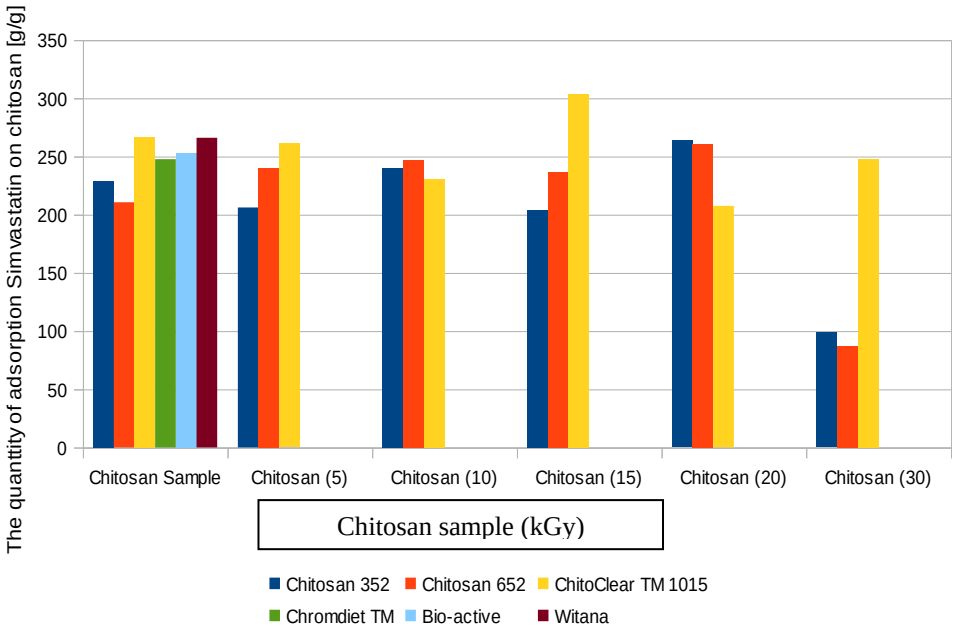

Figure 2. The binding of simvastatin by different types of chitosan according to the degradation in radiation (kGy) and food supplements containing chitosan

The results of the measurement of the adsorption process of simvastatin by chitosan contained in the preparations used, generally available over the counter as dietary supplements, confirmed the hypothesis that the adsorption would have wide variations for individual preparations. Simvastatin is bound in preparations containing chitosans with an intrinsic viscosity between 0.14 and 0.34 (dm^3g^{-1}), and absorption between 0.34 and 0.54 (dm^3g^{-1}) was the weakest and it was growing after crossing the border 0.54 to 0.74 (dm^3g^{-1}).

The binding of simvastatin by the various dietary supplements showed similar values, but was much higher in comparison with the adsorption of the drug by the various manufacturers of chitosans. Chitosan contained in the drug formulations has the ability to bind almost 95% of the administered dose of the drug, which significantly affected the bioavailability of simvastatin used.

The fact that the lowest value of the adsorption at pH 6.4 can be explained by the chemical properties of chitosan whose cationic character was shown only at pH >6.7, and this may have electrostatic voltage and an ability to demonstrate adsorption in relation to medicinal substances [12].

At a pH above 7.6 (pH of the intestines filled with ingesta), the average adsorption at the highest dose of the drug on chitosan was in the range of 27.0% to 95.0%.

4. Conclusion

In the available literature, there are many reports regarding the study of chitosan adsorption properties and the potential for using chitosan as a carrier of active substances. However, there are no studies on the interaction of preparations containing different chitosan variants with the active substances of the simultaneously concomitant drugs [13,14].

The growth of the adsorption of simvastatin on the polymer with increasing pH from 7.6 to 8.0 can be explained by the swelling properties of chitosan, which forms a conglomerate present in the form of an emulsion system.

On the basis of the above considerations, it can be concluded that between the tested drug and polymer is an antagonistic interaction, consisting of the adsorption of the drug on the chitosan polymer, which reduces the drug's bioavailability and therapeutic concentration.

5. References

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