THE INFLUENCE OF DIFFERENT KINDS OF CHITOSAN ON BIOAVAILABILITY OF ANTI-INFLAMMATORY DRUGS

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Abstract
Chitosan as a dietary supplement has been used in the treatment of obesity due to its capability of binding bioactive compounds. A molecule of a cationic polymer, such as chitosan, may bind acid drugs. The aim of the study was to determine the binding capability of Ketoprofen and Naproxen sodium salt by chitosans contained in weight-loss supplements. The drug absorption was investigated by means of a dynamic method in a biopharmaceutical model imitating in vitro conditions including the required level of nutrients. Mean absorption of drugs by chitosan ranged from 92% to 96% depending on the environmental pH. The highest absorption rate was observed at above pH 7. Concluding, the studies confirmed that the investigated drugs interact with chitosan, what leads to decrease in their amount and affects the bioavailability of the drugs.

Key words: *naproxen sodium salt; ketoprofen; chitosan; absorption.*

1. Introduction

The combinations of polymers and biopolymers with biologically active small-molecule compounds have become the subject of extensive investigations recently. A small molecular weight active substance when combined with a polymer often presents a modified action. On the other hand, the use of improper polymers may lead to drug-polymer incompatibility. Especially important are interactions in the form of absorption and formation of complex bonds diminishing the effect of the drug. Chitosan, due to its capacity of binding lipids, cholesterol, fatty acids, triglycerides, bile acids, has been used in the treatment of obesity. It is an effective source of soluble fibre. It does not undergo digestion; it dissolves in the acid environment of the stomach, where it binds many molecules of water, forming a stable absorption gel. A molecule of a cationic polymer, such as chitosan, is capable of binding acid drugs [1, 2].

For this reason the study was undertaken to explain the mechanism of interactions of anti-inflammatory drugs: Naproxen sodium salt and Ketoprofen with dietary supplements containing chitosan.

2. Materials and method

Natural chitosans with deacetylation of 85% to 95%, degraded by 5 to 30 kGy radiation dose were used in the study. Also, dietary supplements containing chitosan were used (Vitana®, Hitec Nutrition®, Chromdiet®, Bio-Active Tech-Food Trading®). The absorption of the drugs was investigated by means of a dynamic method in a biopharmaceutical model imitating the conditions in vitro. The amount of drug absorbed by chitosan was calculated from the concentration of the investigated drug prior to and after sorption. The calculated amounts of bound drug were used to calculate mean percentage of absorbed dose. 0.03 g portions of chitosan were weighed and put to 5 ml glass centrifuge vials and next 2 ml of 0.05 N HCl were added to achieve pH 2 of the solution, what corresponds to natural fasting gastric pH.

Next the drugs were added to the vials: Ketoprofen at the doses of 0.05 g and 0.1 g and Naproxen sodium at 0.22 g. Next 0.2 n Na_2CO_3 was added to the vials to achieve pH 6.4 (corresponding to the duodenal pH) and stirred for 0.5 hour (300 r.p.m.). The solution was alkalized with sodium carbonate to achieve pH 7.0 - 7.6, corresponding to the pH of the intestinal juice. The samples were then incubated at 37 °C in a shaker (300 r.p.m.) for 2.5 hours, after which the samples were brought to room temperature and centrifuged (2100 × g) for 20 minutes. The vials were then left for 30 minutes to stabilize and next, depending on the kind of investigated drug, certain amount of the solution was collected from over the sediment and determined spectrophotometrically. Viscosity investigations were performed according to the method described in the report by *Roberts G.A.F. and Domszy J.G.: Determination of the viscosimetric constants for chitosan. Int. J. Biol. Macromol. 4, 374, 1982*

3. Results and discussion

3.1. The effect of the radiation degradation on essential viscosity of chitosans

The analysis of the effect of radiation degradation rate on essential viscosity shows that a decrease in mean molecular weight of chitosan causes a decrease of this parameter (***Table 1***).

The highest decrease in viscosity-average molecular weight under the effect of an increased dose of degradation radiation (0 - 30 kGy) was observed in case of Huasu chitosan and it was 680 kDa.

The lowest change in the mass was observed for Chito Clear TM 1015, and it was 81 kDa. The remaining chitosans demonstrated a moderate decrease in mass with an increased dose of degradation radiation 0 – 30 kGy (***Figure 1***).

3.2. Ketoprofen and Naproxen sodium binding by degraded and non-degraded chitosans

Examination of absorption of the investigated drugs: Ketoprofen and Naproxen sodium confirm that the amount of bounded drug depends on the degradation rate of chitosan and its origin.

The analysis of the effect of intrinsic viscosity on the capability of absorption of the investigated drugs by chitosans reveals an increase in the amount of absorbed drug.

Table 1. *The value of essential intrinsic viscosity and the viscosity of average molecular weight in investigated chitosans and chitosan preparations.*

Kind of Chitosan	Dose of degradation radiation	Essential intrinsic viscosity [η], $dm^3\ g^{-1}$	Viscosity-average molecular weight $M_{[\eta]}$, kDa
Chito ClearTM 1015	0	0.5100	725
	5	0.4172	584
	30	0.2550	344
Chitosan 652	0	0.3132	429
	5	0.2725	369
	30	0.1615	210
Chitosan 343	0	0.6402	925
	5	0.4588	647
	30	0.2700	366
Chitosan 352	0	0.2117	282
	5	0.1949	258
	30	0.1497	194
Chitosan HUASU	0	0.7437	1087
	5	0.5843	839
	30	0.2986	407
Vitana®	Sample	0.1774	229
Chromadiet®	Sample	0.1872	242
Chitosan Nutrisearch®	Sample	0.1576	205
Bio-Active®	Sample	0.1576	205

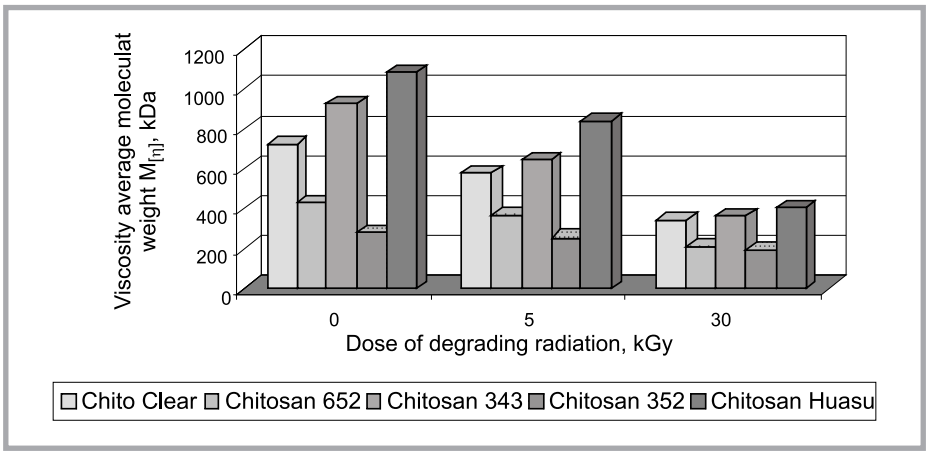

Figure 1. *The value of viscosity average molecular weight in studies chitosans and chitosan preparations.*

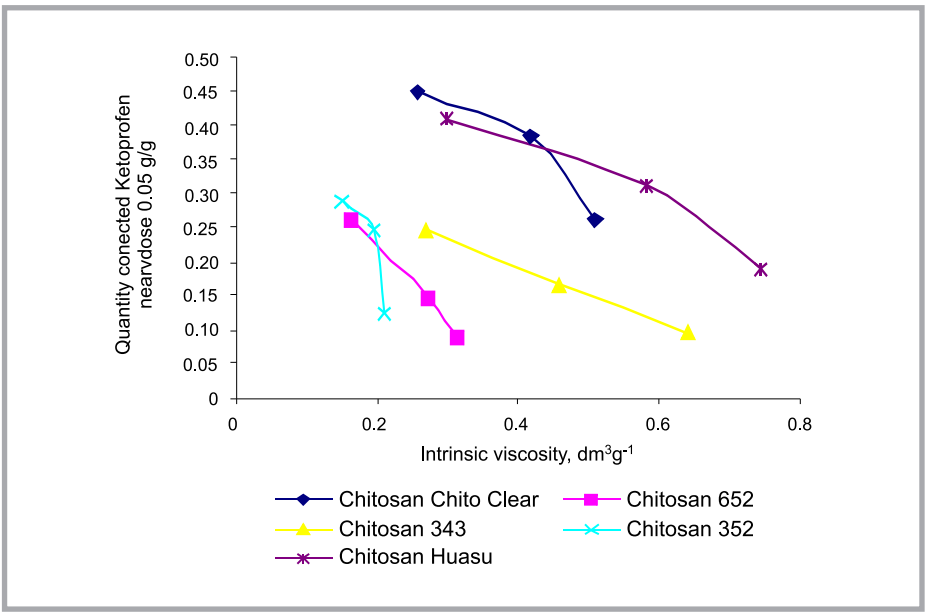

Figure 2. *The graph illustrating the dependence between binding the Ketoprofen near dose 0.05 g in relation to essential intrinsic viscosity [η].*

In case of Ketoprofen the amount of absorbed drug decreases with an increase in intrinsic viscosity for all the investigated chitosans. In case of Naproxen sodium the absorption of drug increases with increased viscosity for Chito Clear and Huasu chitosans, and decreases in case of chitosans 652, 343, 352.

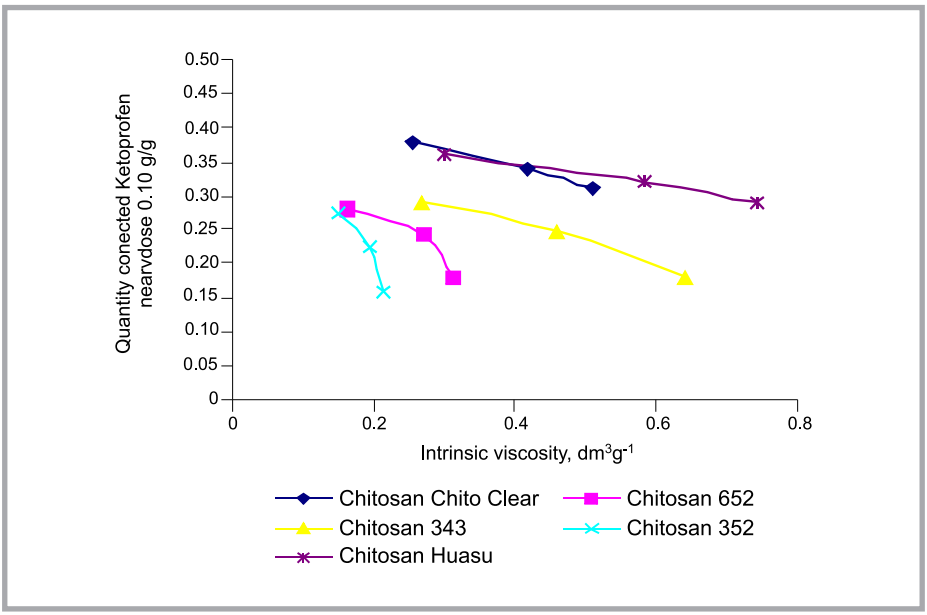

Figure 3. *he graph illustrating dependence between binding the Ketoprofen near dose 0.1 g in relation to essential intrinsic viscosity [η].*

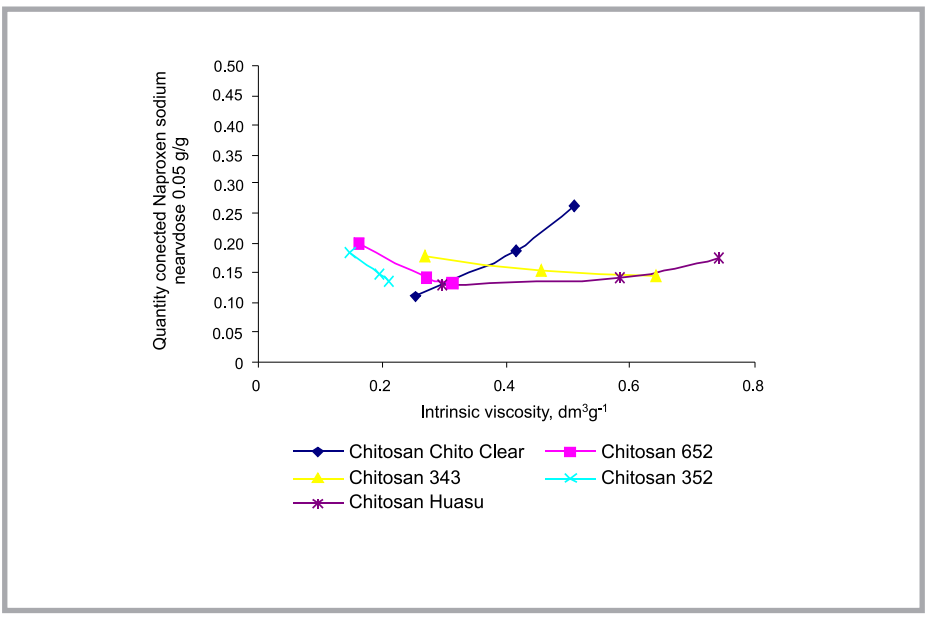

Figure 4. *The graph illustrating the dependence between binding the Naproxen sodium near dose 0.05 g in relation to essential intrinsic viscosity [η].*

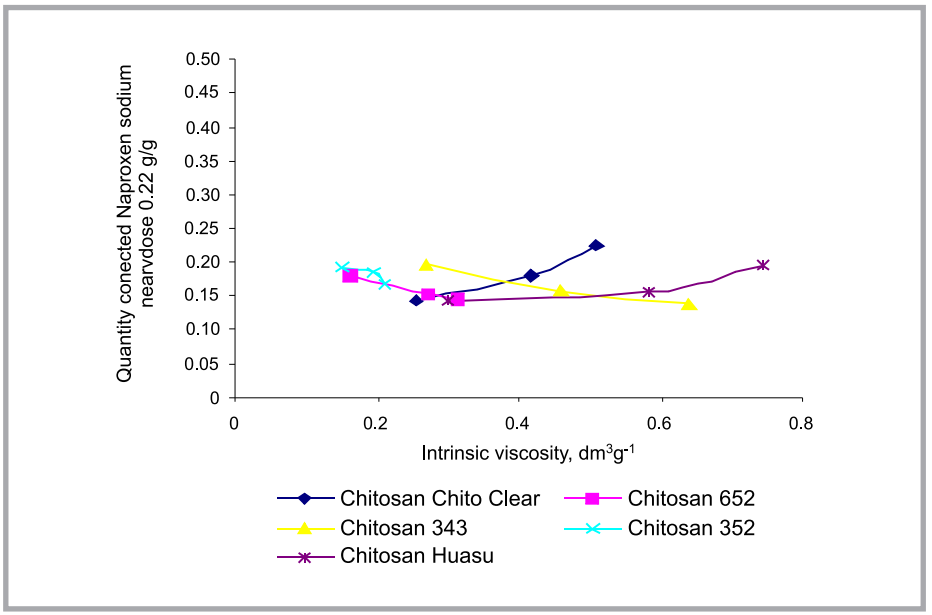

Figure 5. *The graph illustrating the dependence of binding the Naproxen sodium near dose 0.22 g in relation to essential intrinsic viscosity [η].*

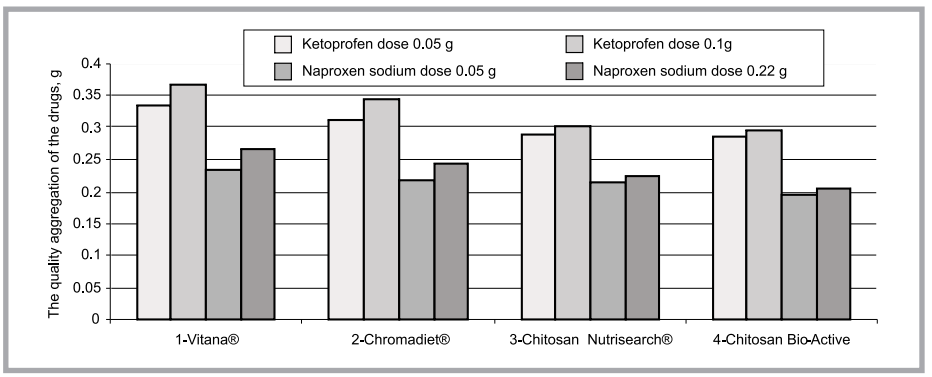

Figure 6. *The amount of Ketoprofen and Naproxen sodium bound by 1 g of chitosans present in dietary supplements.*

The analysis of viscosity-average molecular weights demonstrated that absorption of individual drugs increases with decrease in molecular weight of all the investigated chitosans. The decrease in molecular weight induces lower strength of the polymer chain and the capability of formation of larger branches in the polymer network.

The binding of Ketoprofen and Naproxen sodium by chitosans contained in dietary supplements confirms the hypothesis of aggregative character of chitosan in relation

to these drugs. The highest amounts of drug are bound by chitosan contained in Vitana® dietary supplement (***Figure 6***).

The investigated chitosans contained in dietary supplements available on the weight-loosing products market are capable of binding on an average of 0.062 – 0.450 g of Ketoprofen and 0.1328 – 0.265 g of Naproxen sodium per 1 g of chitosan . The highest absorption rate was observed at pH above 7.

Standard deviation ranged from 0.006 to 0.042 and the determined relativity coefficient ranged form 0.048% to 4.34%, what confirms high accuracy of measurements [7].

4. Conclusion

In conclusion, the studies have shown that there is an interaction between drugs and chitosan, what decreases their quantity and affects the bioavailability of these drugs. At pH above 7.6, corresponding to the environment of the intestinal contents, the mean absorption for the highest dose of the drug on chitosan ranged from 92% to 96%, what is associated with an increased essential surface of the polymer and its sorption capability. Basing on the above considerations, it can be stated that the investigated drug and polymer interact antagonistically in the form of absorption of drugs from this group on a polymer such as chitosan.

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