Interaction of Chitosan, a Natural Polymer Used in Nanodrug/gene Delivery, with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

M Shahbazi, M Hamidi, P Peymani

Citation

M Shahbazi, M Hamidi, P Peymani. *Interaction of Chitosan, a Natural Polymer Used in Nanodrug/gene Delivery, with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*. The Internet Journal of Nanotechnology. 2007 Volume 2 Number 2.

Abstract

Chitosan is one of the most important natural polymers used as a dietary weight-loss supplement in world, especially in Japan and china. The binding of bile acids to dietary fibers like chitosan in the small intestine has been proposed as a main mechanism for the reduction of blood cholesterol levels. In this article we suggest the possibility that chitosan at high dose reduces the gastrointestinal absorption of water-insoluble drugs like non-steroidal anti-inflammatory drugs such as indomethacin and piroxicam, but not water-soluble drugs, by diminishing the surfactant-like effect of bile acids. A beneficial effect of chitosan as a food supplement is the reduction of plasma cholesterol and triglycerides due to its ability to bind dietary lipids in the stomach before they are absorbed through the digestive system into the bloodstream and also interruption of the enterohepatic bile acid circulation that is base of interaction of this supplement with NSAIDs when use together. In the present study, we examined the effect of chitosan on the gastrointestinal absorption profiles of the water-insoluble drugs. This study provides an idea that chitosan can interfere with the intestinal absorption of NSAIDs via direct binding to NSAIDs or decreasing the dissolution of these drugs within GI lumen due to fecal excretion of bile acids.

INTRODUCTION

Chitosan is a semi-synthetic polymer formed by alkaline deacetylation of chitin, a natural polysaccharide obtained from crustaceans such as lobster and shrimp, and has often better properties than much more expensive synthetic polymers ([1,2]). The main advantage of this polymer over chitin is that it is soluble in dilute acid solutions through protonation of amine groups ([3]). Chitosan was proved to have the best chelating properties among other natural polymers [4] because of complex formation of amino groups of chitosan NH2, in which nitrogen is a donor of electron pairs, although hydroxyl groups can also participate in complex formation. Chitosan is also known to inhibit the absorption and enterohepatic circulation of bile acids, leading to the decrease of plasma cholesterol levels accompanied by an increase in compensatory oxidative synthesis of the bile acids from hepatic cholesterol([5]). Recently, chitosan due to its promising properties it has received great attention in both medical and pharmaceutical field as well as in food science and in cosmetic formulations. Various favourable intrinsic properties of chitosan include:

- Well-established biocompatibility for uses in various medical applications (6);
- Penetration enhancement through biological barriers via opening the epithelial tight-junctions (7);
- Biodegradability by the action of certain human enzymes, especially lysozyme (8);
- Bioadhesion due to its positive charges (9).

These and other advantages have been provided the impetus to use this cationic polymer as promising carrier system for various drugs and other bioactive agents, in particular proteins/peptides and genes. But one of the main problems when chitosan is used as a supplement or a carrier is possibility of interaction between this polymer with other drugs that is used a little time before or after consumption of chitosan.

The aim of this study is to clarify the interaction of chitosan on the gastrointestinal absorption of drugs by evaluating alterations in plasma concentration–time profiles after oral administration of the NSAIDs such as indomethacin and

ibuprofen as water-insoluble drugs.

NSAIDS-CHITOSAN INTERACTION

Non-steroidal anti-inflammatory agents, while belonging to a variety of chemical groups, exert three major types of pharmacological effects, including analgesia, anti-inflammation, and antipyretic effects which are all linked to their primary action, the inhibition of an enzyme known as arachidonate cyclooxygenase (COX) which is presented extensively throughout the body as two subtypes of COX-1 and COX-2. This inhibition is not only responsible for the above-mentioned effects of these agents, but is also associated with their side effects such as gastric mucosal damage and renal toxicity. Substantial evidences suggest that sparing COX-1 is advantageous in avoidance of the majority of the side effects observed with these drugs.

NSAIDs cause hemorrhagic mucosal injury in the gastrointestinal tract of human and experimental animals ([10], [11]). Although the exact mechanism underlying these ulcerogenic manifestations remains unknown, it is believed that a deficiency of endogenous prostaglandins (PGs) due to COX inhibition plays a crucial part in the pathogenesis of these lesions in tissues ([12]). Indeed, many studies have shown that supplementation with exogenous PGE prevents the occurrence of damage induced by these drugs in both the stomach and intestine ([13], [14]). Anionic groups in the NSAIDs and some of the physicochemical properties of these drugs such as dissolution in acidic medium in presence of bile acids was the main reason for choose of this group of drugs for evaluation of interaction with chitosan.

HYPOTHESIS AND DISCUSSION: INTERACTION OF CHITOSAN WITH GASTROINTESTINAL ABSORPTION OF NSAIDS

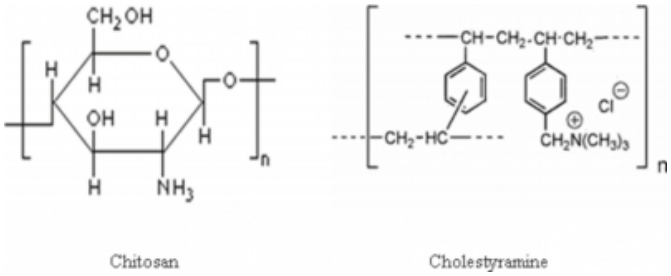
Generally, it is recognized that often a rate-limiting step when the drug is given orally as a solid form is dissolution rate of drug in the gastrointestinal tract. Coadministered drugs or foods might affect the gastrointestinal absorption of drugs with low solubility and high permeability such as NSAIDs by changing their solubility and dissolution rate in the gastrointestinal tract. For example, coadministration of high-fat meals enhances the absorption of water-insoluble drugs like griseofulvin and indomethacin by increasing the dissolution rate of these drugs. It is also reported that secretion of bile salts, pancreatic juice and digestive enzymes are increased in the presence of a high-fat meal that cause increase in bioavailability of low water soluble drugs ([15]).

Bile acids are synthesized from cholesterol in the liver and are secreted into the duodenum by enterohepatic circulation. Normally, the majority of the bile acids are reabsorbed and returned to the liver so that the bile acid level remains constant in the body. It has been proved that certain dietary fibers, drugs or polymers like cholestyramine and chitosan to reduce cholesterol levels are due to their ability to interfere with the re-absorption of bile acids via reactive groups and cause fecal excretion of these drugs. The mechanism of combining these reactive groups with bile acids in the intestine can depend on the chain length, electrical charge density, surface activity and binding capacity of polymers or fibers.

It is clinically known that cholestyramine, a commercially available anion-exchange resin therapeutically intended for lowering the plasma cholesterol levels, decreases the gastrointestinal absorption of various co-administered anionic drugs such as piroxicam, aspirin, phenylbutazone and ibuprofen via binding to these drugs. Comparing the chemical structures of chelestyramine and chitosan, it becomes evident that these molecules have some key chemical similarities, including, mainly, the presence of repeating positive charge amine groups in polymer chain that is one of the main agents of interaction between chitosan or cholestyramine with other drugs when they are coadministered. Chitosan, having cationic tertiary amine groups in its molecule (Fig. 1), has documented to reduce the absorption of fats from gastrointestinal tract by binding to anionic carboxyl groups of fatty acids, thus, interferes with emulsification of lipids and highly lipophilic agents, leading to decreased plasma cholesterol levels. Considering the above-mentioned observations on both polymers as well as their chemical similarities, there is quite a possibility that chitosan affect the gastrointestinal absorption of NSAIDs in the same manner as cholestyramine does.

Figure 1

Figure 1: amine groups in chitosan and cholestyramine can bind to anionic groups of NSAIDs to cause decreased absorption of these drugs.



The postulated role of chitosan in decreasing the absorption of these drugs can be explained by two mechanisms:

i) it is reported that enhancement of the dissolution of NSAIDs in the presence of bile acids, including sodium desoxycholate, sodium cholate, sodium glycocholate and sodium taurocholate, are due mainly to micellar solubilization. Chitosan, via disrupting the micelle formation due to the binding to bile acids, may lead to decreased solubilization effect by bile acids. Chitosan has shown to increase the fecal excretion of two bile acids, i.e., cholic acid and chenodeoxycholic acid.

ii) In addition, chitosan acts as a weak anion-exchange resin similar to cholestyramine. Therefore, the anionic NSAIDs may form non-absorbable ion-pairs with chitosan, which, in turn, can lead to reduced drug absorption through the gastrointestinal epithelial wall via modification of its physicochemical properties.

EVALUATION OF THE HYPOTHESIS

Little information is known about the relationship of the physico-chemical properties of chitosan preparations and their potential of interaction with bile acids and triglycerides thus the aim of this study is to clearly demonstrate the effect of chitosan on the gastrointestinal absorption of drugs via affect on bile acids excretion by evaluating alterations in plasma concentration–time profiles after oral administration of the water-insoluble drugs like ibuprofen in rats. To understand chitosan affecting on the plasma concentration–time profiles of ibuprofen after oral administration, we will examine its effect on the absorption profiles of ibuprofen after administration of the solid formulation of this drug.

Experimental Protocols for determination of chitosan affect on absorption of ibuprofen are including: One day before examination, 12 rats under anesthesia by intraperitoneal injection of sodium pentobarbital (25 mg/kg) will cannulate with polyethylene tubes into the right jugular vein for blood sampling. Rats will divide in two equivalent groups, Volunteers from group A that will receive ibuprofen and chitosan solution but volunteers in group B will receive only oral ibuprofen without chitosan and then we will evaluate concentration of this drug in plasma of two groups and compare them together.

The rats of Group A, will be fast for 12 h before the experiments and will receive an oral administration of chitosan solution at a constant doses dissolved in 5% acetic acid solution. Fifteen minutes after administration of chitosan, ibuprofen will administer orally. Blood samples (0.2 ml) were collected at designated intervals (10, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, 480, 540 and 600 min after the oral administration of drug). Plasma samples were obtained by centrifugation of blood samples at 4000g for 10 min at 4 °C. Plasma samples were stored at -30 °C until analysis. This procedure also should be done for group B but they will not receive chitosan solution.

For Analysis of Drug, concentrations of ibuprofen in plasma will be determined by high performance liquid chromatography (HPLC). The apparatus will be use for HPLC was a Waters system (USA) equipped with a UV detector (Model 746, Waters, USA) consisting of a pump (Model 600, Waters, USA). The column will be use for analysis of ibuprofen is a C_{18}, Waters, USA (particle size, 5 µm; 250 ×4.6 mm I.D).

For data analysis, the standard curve for drug will be measurement over an appropriate range for calculations of plasma drug concentrations, and the within-day and between- day coefficients of variation for this assay will be calculate. Then in each rat Concentration–time profile will analyze individually and the maximum concentration (Cmax) and the time to reach Cmax (Tmax) will be obtained from the observed data and at the end all of data in both of groups will be compare.

CONCLUSION

There are no previous publications on investigation of interaction between chitosan and NSAIDs. Chitosan, when co-administered, as a supplement food or drug delivery vehicle, with NSAIDs, might affect the gastrointestinal absorption of these drugs, particularly those with low solubility and high permeability such as ibuprofen and

piroxicam by binding to their anionic groups and/or changing their solubility and dissolution rate in the gastrointestinal tract. This study will provide a more detailed understanding of the origin and characteristics of the interactions between bile salts and chitosan, which may prove useful in the design of supplements, drugs or functional foods that can reduce cholesterol levels.

CORRESPONDENCE TO

Department of Pharmaceutics, Faculty of Pharmacy, Shiraz University of Medical Sciences, P.O. Box 71345-1583, Shiraz, Iran. Tel: +98 9171119323 Fax: +98-711-2426070
E-mail address: shahbazym@sums.ac.ir

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Author Information

Mohammad Ali Shahbazi
Department of Pharmaceutics, Faculty of Pharmacy, Shiraz University of Medical Sciences

Mehrdad Hamidi
Department of Pharmaceutics, Faculty of Pharmacy, Shiraz University of Medical Sciences

Payam Peymani
Department of Pharmaceutics, Faculty of Pharmacy, Shiraz University of Medical Sciences