Adsorption and Desorption of Indomethacin on Cellulose-like Biopolymers: Chitin and Chitosan

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The adsorption–desorption effect of cellulose-like biopolymers such as chitin and chitosan, and microcrystalline cellulose on indomethacin was investigated. The adsorptive capacity was ranked in the order: chitosan > chitin > microcrystalline cellulose. All the adsorption isotherms were found to follow Langmuir and Freundlich equations. However, chitosan–acetate gel powders and chitosan powders with pre-added acetic acid and methanol did not follow these equations, due to gel formations that led to more adsorption of indomethacin on the interlayer space of the gel. The strong adsorption of chitosan might result in difficult desorption of indomethacin.

Keywords chitin; chitosan; microcrystalline cellulose; adsorption; desorption

Introduction

It is well known that the coadministration of a soluble drug and an insoluble excipient might result in a decrease in drug bioavailability due to the drug–excipient interaction or drug adsorption on the excipient.[1,2] Thus, the selection of a suitable excipient to incorporate with drugs is a prerequisite for a formulation design. Drug–excipient interaction or adsorption always occurs from the drying mixing process of various solids, or from the interfacing between the drug solution and the solid excipients during manufacturing processes, or after disintegration of dosage forms in the GI tract. The adsorption phenomenon is one of the drug interactions. Most adsorption mechanisms can be classified as either physical adsorption or chemisorption.[3] The extent of adsorption depends on the properties of the solute and the adsorbent used.

Recently, cellulose-like biopolymeric polysaccharides such as chitin and chitosan (Chart 1) have been used for immediate-release or sustained-release preparations by pharmaceutical scientists[4–8] because they have good biocompatibility, biodegradable and low toxicity. On the other hand, chitin and chitosan are also found to be powerful chelating agents for transition metal ions,[9–11] and to be strong adsorbents for dyes, bromine and iodine.[12–15] However, there seems to be no attention devoted to studying the adsorption and desorption of drugs onto either of them.

As part of a preformulation study, this work was conducted to determine the adsorption affinity of indomethacin on microcrystalline cellulose, chitin and chitosan.

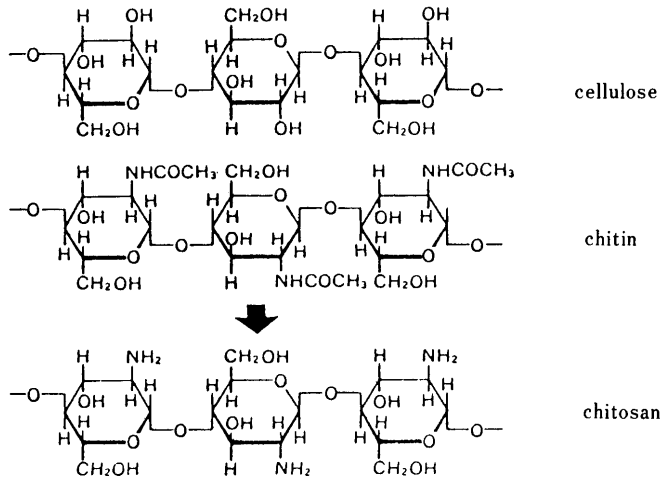

Chart 1. Chemical Structure of Cellulose, Chitin and Chitosan

Experimental

Materials Chitosan (Flonac N) with 89.3% deacetylation was obtained from Katakura Chikkarin Co., Tokyo, Japan. Chitin from Crab Shells was purchased from Nakalai Tesque, Inc., Kyoto, Japan. Microcrystalline cellulose (Avicel PH 101) was supplied by Asahi Kasei Co., Tokyo, Japan. Chitin, chitosan and microcrystalline cellulose were each previously milled and passed through a 150 mesh screen. Indomethacin was purchased from Sumitomo Chem. Co., Osaka, Japan. All the other reagents are pharmaceutical grade.

Preparation of Chitosan–Acetate Gel Powders Chitosan–acetate gels were made from a 2% solution of chitosan in 2% acetic acid. The gel was poured onto a glass plate to allow acetic acid to evaporate, a film was formed. The film was taken off and vacuum-dried at 40 °C for 2 d, then was micronized and passed through a 150 mesh sieve for use.

Adsorption Measurement A certain amount of pH 8.0 indomethacin phosphate buffer solution was added to the stoppered conical flasks containing 0.5 g of each micronized adsorbent (chitin, chitosan, Avicel or chitosan-gel powder). Another adsorption study was also performed: one milliliter of 2% acetic acid solution and 5 ml of methanol were added to the flask in which an indomethacin solution and 0.5 g of chitosan had previously existed. The flask was protected from light and shaken in a water bath shaker for 48 h at 37 °C with 200 revolutions. After equilibrium, samples were withdrawn and filtered through a 0.2 μm membrane filter. The equilibrium concentration of indomethacin was determined with a spectrophotometer (VUIDEC-320, Jasco Co., Tokyo, Japan) at 320 nm. The data shown in the figure indicates averages of three experimental runs, and the results were reproducible.

Analysis of Adsorption Data The basic equations used to described adsorption from a solution by adsorbents are the Freundlich equation and the Langmuir equation,[3] as follows:

$$X/M = KC_{eq}^{1/N} \qquad \text{Freundlich equation}$$

$$\frac{C_{eq}}{X/M} = \frac{1}{K_1K_2} + \frac{C_{eq}}{K_2} \qquad \text{Langmuir equation}$$

where X is the amount of indomethacin adsorbed by a mass of adsorbent, M; C_{eq} is the equilibrium concentration of indomethacin; K is a constant for relative adsorptive capacity, and N is an affinity constant. K_1 is the adsorption coefficient; K_2 is the limiting adsorptive capacity, and K_1K_2 is used as a measure of the relative affinity of indomethacin to the adsorbent.

Desorption Measurements One gram of chitosan powder preadsorbed indomethacin was poured to fill a glass tube, then glass wool was inserted on both sides of it. The elution procedure was carried out with a fraction collector. The flow rate of the eluting medium (pH 8.0 phosphate buffer solution) was 1 ml/min. The amount of indomethacin desorbed was assayed spectrophotometrically at 320 nm. Each elution was performed on three separate samples to obtain an average value.

Results and Discussion

Adsorption Study The results for the adsorption of indomethacin on chitin, chitosan and microcrystalline cel-

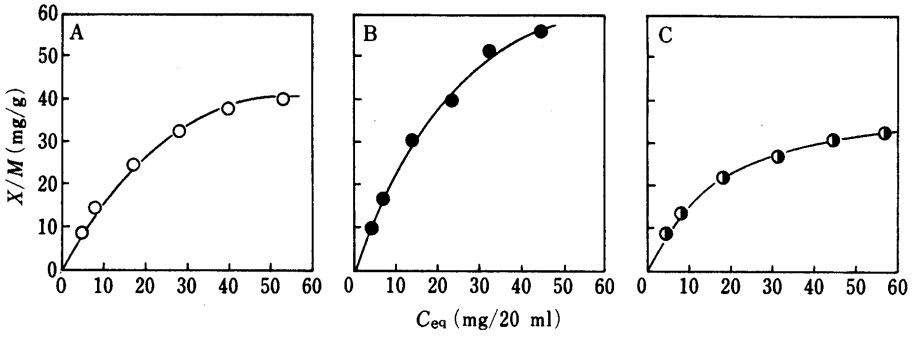

Fig. 1. Adsorption Isotherms of Indomethacin on Chitin (A), Chitosan (B) and Microcrystalline Cellulose (C) in pH 8.0 Phosphate Buffer Solution at 37 °C

TABLE I. Summary of Constants Obtained from Linear Plots of Langmuir and Freundlich Equations for Indomethacin

Adsorbents	Langmuir constants			Freundlich constants		
	K_2	K_1K_2	r	K	N	r
Chitin	56.818	2.570	0.9989	4.160	1.615	0.9848
Chitosan	97.656	2.890	0.9911	4.279	1.449	0.9891
Avicel	41.079	2.530	0.9974	3.834	1.938	0.9791

Note: K_2 and K_1K_2 represent adsorptive capacity and affinity constant for the Langmuir equation, respectively; K and N are relative adsorption capacity and affinity constant for Freundlich equation, respectively; r: correlation coefficient of linear plot.

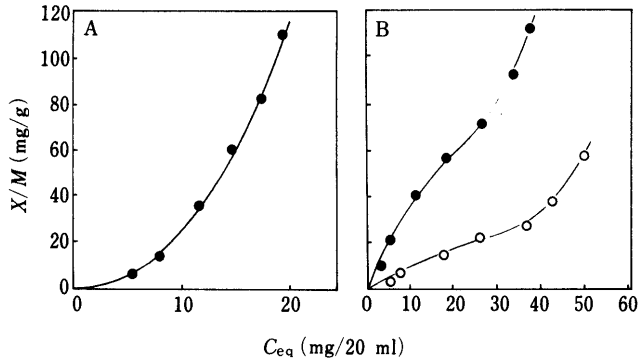

Fig. 2. Adsorption Isotherms of Indomethacin on Chitosan–Acetate Gel Powders (A) and Chitosan Powders Pre-added with Acetic Acid and Methanol (B) in pH 8.0 Phosphate Buffer Solution

Key: ●, 37 °C; ○, 25 °C.

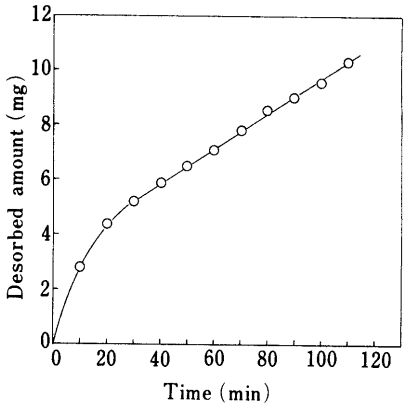

Fig. 3. The Amount of Indomethacin Desorbed from Chitosan Powders at 37 °C in pH 8.0 Phosphate Buffer Solution

lulose are shown in Fig. 1. Table I shows constants obtained from the different isotherms as well as the correlation coefficient of linear plots for indomethacin. It clearly indicates that the adsorption behavior of indomethacin on these three excipients followed Freundlich and Langmuir types of isotherms, since the r values obtained from the linear plots of the respective isotherms were >0.9. It is evident that the amounts of drug adsorbed increased in the following order: chitosan > chitin > microcrystalline cellulose. The presence of a polar amino group in chitosan, and the swelling of chitosan particles may explain why the largest amount of drug was absorbed on chitosan. On the other hand, isotherms of indomethacin adsorbed on the chitosan–acetate gel powder or chitosan powder pre-added with acetic acid and methanol at 25 °C and 37 °C exhibited different patterns, as shown in Fig. 2. A concave pattern was found in these adsorption isotherms. If adsorption follows the assumptions of Langmuir equation, a sharp initial increase in the amount adsorbed with the increase of equilibrium concentration of the solute was expressed by a convex curve.[3] Thus, in this study, the adsorption behavior of indomethacin on chitosan–acetate gel powder or chitosan powder previously mixed with acetic acid and methanol did not follow the Langmuir equation. We also found that the amounts of indomethacin adsorbed on these powders was larger than that of indomethacin adsorbed on chitosan powder. This might be attributed to the finding that the chitosan–acetate gel powder had previously swollen in the solution to form swollen chitosan and an excess number of molecules of indomethacin were captured in the molecular network of swollen chitosan. This suggests that the adsorption and encapsulation phenomena of indomethacin might simultaneously occur on chitosan–acetate gel powder, leading to a large adsorbed amount and different adsorption behavior. Methanol and temperature perhaps influenced the adsorption behavior of indomethacin by increasing the solubility of indomethacin.

Desorption Study Desorption refers to the release of a solute from an adsorbent. Figure 3 shows the desorption behavior of indomethacin from chitosan. The desorption data indicates that the initial desorption rate increased with elution time, then maintained constant after 30 min. The tight bounding might be attributed to the drug interaction between indomethacin (carbonyl and carboxyl groups) and chitosan (amino group) in a phosphate buffer solution. The desorption phenomenon of chitosan played an important role in drug bioavailability. If chitosan was commonly used as an additive in a convenient dosage form, the adsorption of a drug onto chitosan occurred first

in the GI tract. If adsorption was strong, incomplete desorption of a drug from chitosan might result in poor drug availability. On the other hand, the phenomenon of strong adsorption and weak desorption of chitosan might be used to design a controlled-release dosage form, which could maintain the drug release rate and improve a drug's bioavailability.

In summary, the adsorptive–desorptive phenomena of indomethacin on chitin, chitosan and microcrystalline cellulose was worthy of attention for a formulation study.

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