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Studies on the Complex Interaction of Acacia and Sodium Alginate with Certain Preservatives (Spectrophotometric Studies)

Chong Hak Woo, Shin Keun Kim and Shin Hong Min*

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禹鍾鶴・金信根・閔信弘 : Acacia 및 Sodium Alginate와 數種의 防腐劑와의 Complex Interaction에 關한 硏究

乳化劑 또는 懸濁化劑로 쓰이고 있는 hydrophilic polymer의 一種인 acacia 및 sodium alginate와 防腐劑와의 interaction에 關한 硏究로서 Higuchi 氏等의 solubility method를 實驗方法으로 하여 考察하였다.

acacia는 溶液中에서 或種의 interaction을 하나 o-hydroxybenzoic acid 및 p-hydroxybenzoic acid의 methyl, ethyl, propyl, butyl ester와는 그러한 interaction이 없다. sodium alginate는 butyl-p-hydroxybenzoate 및 o-hydroxybenzoic acid를 除外한 本實驗에 使用한 防腐劑와는 溶液內에서 interaction을 나타내었다.

防腐劑의 初濃度와 acacia 및 sodium alginate를 加하여 一定時間 反應시켜 平衡에 到達했을때의 防腐劑의 濃度와의 比인 K 値는 acacia 및 sodium alginate의 濃度와 函數關係에 있음을 發見하였다.

In recent years the study of interaction of macromolecules such as polyethers, nonionic surfactants, nonionic hydrophilic polymers with various pharmaceuticals has been grown rapidly. These macromolecules are employed frequently in pharmaceutical and cosmetic formulations as solubilizing, stabilizing or emulsifying agents. Although they are considered to be chemically inert, many of them interact with drug molecules.

These complex formations may result in incompatibility of these additives with some pharm

* College of Pharmacy, Seoul National University,

aceuticals as well as the reductions of drug effect, especially in the case of preservatives, antimicrobial activity.[1]

Investigation of the interactions of PVP and polyethers with preservatives and sulfadrugs was carried out by Higuchi *et. al.*[2-4]

Pisano[5], Patel[6-8], Kostenbauder[9-13], Ahsan[14,15], Blaug[16,17], Goodhart[18], and Kabadi[19] reported the study of interactions of Tween, Span, PEG, CMC, gelatin and tragacanth with pharmaceuticals.

The complex formation of hydrocolloids[20-22] with anti-histamines, polysaccharides, alkaloids and dextrin[23-25] and that of starch[26] with preservatives was also reported.

These studies prompted us to study about acacia and sodium alginate which are currently employed to a great extent as emulsifying and suspending agents in pharmaceuticals.

The object of this study is to investigate the general nature of the interaction between acacia and methyl-p-hydroxybenzoate, ethyl-p-hydroxybenzoate, propyl-p-hydroxybenzoate, butyl-p-hydroxybenzoate, benzoic acid, o-hydroxybenzoic acid and sorbic acid, and that between sodium alginate and these preservatives respectively.

EXPERIMENTAL

Reagents.—Emulsifying agents: acacia, powdered, U.S.P.′ and sodium alginate, N.F.
Preservatives: benzoic acid, m.p. 120—121°. o-hydroxybenzoic acid, m.p. 158°; sorbic acid, m.p. 133°; methyl-p-hydroxybenzoate, m.p. 126—127°; ethyl-p-hydroxybenzoate, m.p. 116—117°; propyl-p-hydroxybenzoate, m.p. 96°; butyl-p-hydroxybenzoate, m.p. 68—69°.

Equipments.—Constant temperature water bath equipped with a mechanical stirrer, Carl-Zeiss spectrophotometer, 1 cm. quartz cell, 100 ml. glass-stoppered bottle.

PROCEDURE

Preparation of acacia and sodium alginate solution:

A. Acacia solution.—Acacia, powdered, U.S.P., was dissoloved in redistilled water, boiled for a few minutes at 100°, allowed to stand for one day and boiled for a few minutes again. This procedure was repeated for three times and then filtered.

B. Sodium alginate solution.—Sodium alginate, N.F., was dissolved in redistilled water, allowed to stand for over night, after vigorous agitation, and filtered.

Solubility study

The solubility method of Higuchi and Lach[27] was used to study the interaction. In a 100 ml. bottle appropriate quantities of the drug together with varying amounts of acacia and sodium alginate solutions were weighed. The bottles were closed, then agitated in a constant temperature water bath with mechanical stirrer for 24 hours at 30°, and allowed to stand for overnight to complete their equilibrium state. After that, a suitable aliquot of the solution was removed, filtered and appropriately diluted with the same solvent used to prepare the

original solution for spectrophotometric analysis. At 5% of acacia and 0.5% of sodium alginate they showed high degree of viscosity. To avoid any error due to the viscosity of the solution, each pipet was calibrated to deliver all of its contents by washing the pipet several times with redistilled water or 0.05 N hydrochloric acid.

Varying concentrations of acacia, sodium alginate and other preservatives used here were as follows;

Acacia, 1, 2, 3, 4, and 5 w/v%; sodium alginate, 0.1, 0.2, 0.3, 0.4 and 0.5 w/v%; methyl-p-hydroxybenzoate, 0.05 w/v%; ethyl-p-hydroxy benzoate, 0.05 w/v%; propyl-p-hydroxybenzoate, 0.02 w/v%; butyl-p-hydroxybenzoate, 0.005 w/v%; benzoic acid, 0.15 w/v%; o-hydroxybenzoic acid, 0.05 w/v%; and sorbic acid, 0.05 w/v%.

All esters were dissolved in redistilled water and benzoic acid, o-hydroxybenzoic acid and sorbic acid in 0.05 N hydrochloric acid to suppress ionization. Blank test was also carried out without addition of acacia and sodium alginate solutions.

Method of Analysis

The spectrophotometric analysis method was employed to determine the concentrations of the drugs at the following wave lengths; benzoic acid, 274 mu; o-hydroxybenzoic acid, 301 mu; sorbic acid, 263 mu; methyl-p-hydroxybenzoate, 255 mu; ethyl-p-hydroxybenzoate, 256 mu; propyl-p-hydroxybenzoate, 255 mu and butyl-p-hydroxybenzoate 255 mu.

At dilution of 0.0005%, the effect of acacia and sodium alginate on the absorbance of the drugs was negligible.

RESULTS AND DISCUSSIONS

Comparative binding tendencies of preservatives by acacia and sodium alginate are given in Table I.

Table I.—Comparative Binding Tendencies of Preservatives by Acacia and Sodium Alginate

Preservatives	Preservatives	5% Acacia		0.5% Sodium Alginate	
	Concn. × 10^{-5} Molar	% Bound	K*	% Bound	K*
Methyl-p-hydroxybenzoate	16.43	No Interaction		4.71	1.049
Ethyl-p-hydroxybenzoate	15.04	No Interaction		3.36	1.038
Propyl-p-hydroxybenzoate	5.55	No Interaction		3.37	1.035
Butyl-P-hydroxybenzoate	1.29	No Interaction		No Interaction	
Benzoic Acid	61.42	16.31	1.195	10.89	1.122
o-Hydroxybenzoic Acid	18.10	No Interaction		No Interaction	
Sorbic Acid	22.30	2.12	1.022	3.30	1.034

K* refers to the ratio of (total drug)/(unbound drug).

Acacia.—Data for the binding tendencies of p-hydroxybenzoic acid esters are presented in Fig. 1. As shown in this graph, the results indicate that preservatives of p-hydroxybenzoates, i.e., methyl-p-hydroxybenzoate, ethyl-p-hydroxybenzoate, propyl-p-hydroxybenzoate and butyl-p-hydroxybenzoate do not interact with 5% acacia in aqueous solution. But in benzoic acid,

and sorbic acid, they show the association with acacia. Among three free acids, only o-hydroxybenzoic acid does not interact with this gum.

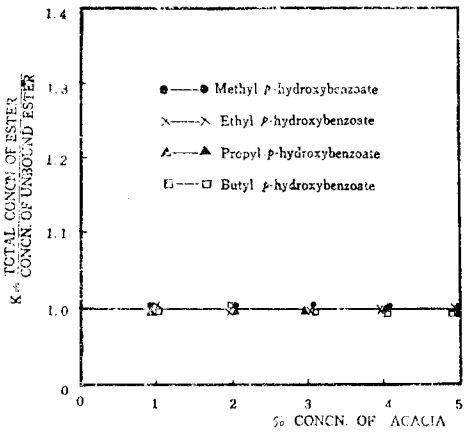

Fig. 1. Binding of methyl-p-hydroxybenzoate and Butyl-p-hydroxybenzoate benzoate. Propyl p-hydroxybenzoate and Butyl-p-hydroxybenzoate by Acacia at 30°.

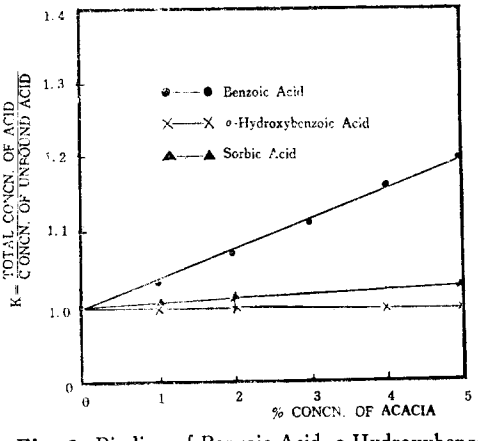

Fig. 2. Binding of Benzoic Acid, o-Hydroxybenzoic Acid and Sorbic Acid by Acacia at 30°.

Sodium alginate.—The results of complex reaction of sodium alginate with preservatives are plotted in Figs. 3 and 4. Methyl-p-hydroxybenzoate, ethyl-p-hydroxybenzoate and propyl-p-hydroxybenzoate which do not react with acacia undergo complex formation with sodium alginate.

The magnitude of interaction decrease in general with the increase of molecular weight of the parabens. However butyl-p-hydroxybenzoate and o-hydroxybenzoic acid showed nearly no complexation.

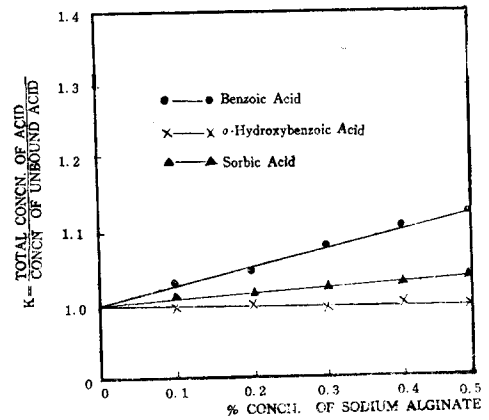

Fig. 3. Binding of Methyl-p-hydroxybenzoate. Ethyl p-hydroxybenzoate. Propyl p-hydroxy benzoate and Bytyl-p-hydroxybenzoate by Sodium Alginate at 30°.

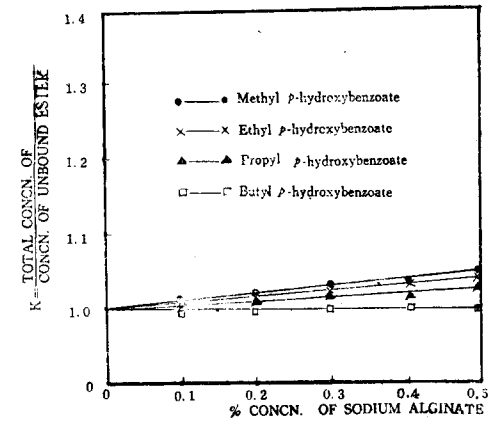

Fig. 4. Binding of Benzoic Acid, o-Hydroxybenzoic Acid and Sorbic Acid by Sodium Alginate at 30°.

It would appear that increase of the length of the alkyl group produce an inhibition of complex formation. The longer length of the ester chain may, therefore, produce steric hindrance which prevents the ester molecule from aligning itself in a position for complex formation of the polymer that can afford optimum binding between two molecules in this experiment. Although no clear-cut mechanism of binding of polymers by preservatives is not completely known at the present time the hydrogen bonding appears to play a substantial role in this complexing reaction. As the results indicate, o-hydroxybenzoic acid shows nearly no interaction with acacia and sodium alginate. This phenomenon may be resulted from that its hydrogen bonding ability[28] has been decreased owing to *ortho* position of carboxyl to hydroxyl group. All of diagrams in Figs. 2, 3 and 4 show that the value K, a ratio of the total drug concentratration in solution to the concentration of the unbound preservatives is a function of the concentration of acacia and sodium alginate.

SUMMARY

The certain interaction phenomena of acacia and sodium alginate with some preservatives such as benzoic acid, o-hydroxybenzoic acid, sorbic acid, methyl-p-hydroxybenzoate, ethyl-p-hydroxybenzoate, propyl-p-hydroxybenzoate and butyl-p-hydroxybenzoate which are extensively used as preservatives were reported by authors using Higuchi's solubility method, Results of this experiments indicated that acacia exhibits a high degree of reaction with benzoic acid, less with sorbic acid, but o-hydroxybenzoic acid and the esters of p-hydroxybenzoic acid showed no interaction with acacia.

Most of preservatives studied here combined with sodium alginate and the magnitude of interaction with the esters of p-hydroxybenzoic acid decreased with the increase of carbon chain of alkyl group. It is postulated that hydrogen bonding and inclusion formation are responsible for the interaction observed. No evidence of complex formation was detected between sodium alginate and butyl-p-hydroxybenzoate and o-hydroxybenzoic acid respectively. Data are reported to show the value K, the ratio of the total preservatives concentration in solution to the concentration of the unbound preservatives as a function of the concentration of acacia and sodium alginate.

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