radioactivity in whole milk was 19.4% (±10.2) in the goats and 6.2% in the cow of the total radioactivity in whole milk.

SUMMARY AND CONCLUSIONS

1. Whole body retention studies of TI*BA in four adult lactating goats showed a two-component system—one with a biological half-life of 13.5 hr. and the second of 423 hr.

2. Excretion studies in five adult lactating goats and one cow showed that the primary route of excretion was *via* the kidney. For the goats, 76, 12, and 3%, respectively, of the administered dose was excreted in the urine, milk, and feces. Corresponding values for the cow were: 57.5, 12.2, and 11.4%.

3. Distribution studies, 8 hr. after oral administration of TI*BA to goats, indicated TIBA and/or its metabolites were located in the kidney, heart, thyroid, blood, spleen, G.I. tract, liver, fat, lean, and brain. The G.I. tract contained 41% of the administered dose at 8 hr. The average relative concentration of radioactivity in the thyroid was 28 times the average blood concentration. Thyroid uptake occurred for 5 days after oral TIBA administration.

4. Metabolite studies of the urine indicated TIBA and nine metabolites. Four of the metabolites were identified as 2,5-DIBA, 2,3-DIBA, OIBA, and iodide ion. In the 6–18 hr. urine sample of the cow, TIBA accounted for 28% of the radioactivity while the predominate metabolite, 2,5-DIBA, accounted for 45% of the radioactivity. In goats, 21% of the radioactivity in the accumulated 0–8 hr. urine sample was attributable to 2,5-DIBA while 55% was TIBA. The remaining (24%, goat and 27%, cow) metabolites in the urine are explained as representing iodide ion and conjugated forms of OIBA, 2,3-DIBA, 2,5-DIBA, and TIBA.

5. Milk analyses indicated iodide ion as the predominant (82.8–100.0%) metabolite. Eighty-one percent of the radioactivity within the milk was nonprotein bound in the goat while 94% was nonprotein bound in the cow. The two unknowns in skim milk ranged from 0% up to 17.2% of the radioactivity in the milk of goats and was 1.8% of the cow's milk.

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Keyphrases

2,3,5 Triiodobenzoic acid (TIBA)
Metabolic fate, TIBA-lactating cow, goats
Thyroid uptake—TIBA
Excretion, TIBA-urine, milk, feces
Scintillation counting-whole body
Column chromatography—TIBA identification
Thick-layer chromatography—component identification

Complexing Behavior of Starches with Certain Pharmaceuticals

By ZEYAD MANSOUR and EARL P. GUTH

A study has been made of the complexing behavior of a number of starches and starch fractions with benzoic acid, *p*-hydroxybenzoic acid, sorbic acid, and other selected molecules in aqueous solutions at 30°. By means of the solubility method of analysis it was found that the low molecular weight polymer, amylose, is the main complexing component of starch. The starches showed different affinities for the same drug according to their content of amylose. A correlation of these complexes to those of "starch-alcohols" and "starch-iodine" was made.

STARCH has a multitude of applications in many areas of our life; *e.g.*, foods, drug therapy, and many industries. It has a long history of usefulness in medicine and pharmacy. Its use, however, has been entirely empirical. It is described as a protective, an adsorbent, and as a diluent in texts on pharmacology, with no explanation of the mode of action. Starch appears

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to be quite effective in "drying-up" dermatitis lesions where there is a watery exudate; as a consequence, starch is found as a component in such pharmaceuticals as dusting powders, pastes, ointments, emulsions, and aerosols. The importance of starch inclusion in these products has not been questioned. Starch has also been used in the manufacturing of compressed tablets as a disintegrator, as a diluent, and as an excipient.

Although vast numbers of researches have been published on the physical and chemical properties of the various species of starch, very little work has been published regarding the possible involvement of the properties of starch regarding the stability and availability of the drug when included in a pharmaceutical preparation.

Guth and Goudah (1) reported a study of the complexing behavior of potato and arrowroot starches with a number of pharmaceutical compounds most of which are used as preservatives. By means of the solubility method of analysis it was found that starches form complexes in solution with benzoic acid with a number of its derivatives. All the complexing drugs were polar organic molecules, and the mechanism of interaction was believed to be a combination of inclusion formation and attractive forces like hydrogen bonding and dipole–dipole interactions.

In this work further investigation was undertaken to determine the affinities of various starches for a drug molecule, and the affinity of each of the starch fractions, amylose and amylopectin, for the drug. Dry starch adsorption of fatty acids and fatty alcohols from their methanol solutions was also investigated.

Reviews on starch chemistry (2, 3) show that it is now established that starch is a polymolecular system containing two components, amylose and amylopectin. The former is a linear polymer composed of α-D-glucopyranose residues linked by α-D-(1–4) glucosidic bonds. The latter, amylopectin, is the major component (75–85% in most starches) and consists of high molecular weight multibranched polysaccharide composed of α-D-glucopyranose residues linked by α-D-(1–4) glucosidic bonds. The chains normally contain 20–25 D-glucose residues and are interlinked to form a ramified or bush-like structure by means of α-D-(1–6) glucosidic linkages. Evidence regarding the manner in which the glucose units are combined in the two starch components has been obtained from methylation studies (4), from terminal group determination by periodate oxidation (5), and from hydrolysis studies (6). When a suspension of starch in cooled water is heated, the starch granules swell to several hundred times in original volume forming a viscous sol or paste. The swelling occurs at a specific temperature after which the granules undergo a complete rupture. Thus, a starch paste or sol is a collodial system in which there are highly swollen granules, free molecules of the starch, two molecular components, and empty sacs (7). Starch sols are physically unstable and tend to become less soluble on standing. This phenomenon has been termed as "retrogradation" and explained to be caused by aggregation of amylose molecules. Amylose stable form is suggested to be an α-helix (8); in retrogradation aggregates of the α-helical molecules are formed. The properties and behavior of amylose chains have been subjected to extensive investigations (9, 10). The rates of retrogradation in a given starch sol depend on the amylose percentage in the starch, on the size of the amylose molecule, and on the method in which the starch sol is prepared (11). The occurrence of amylopectin aggregates is improbable, since it was shown that amylopectin is physically stable in aqueous solutions (12).

EXPERIMENTAL

Materials—Three amylose starches, designated as amylose-A,[1] amylose-B,[2] and amylose-C,[3] are starches containing varying amounts of amylose (National Starch and Chemical Corp., Chicago). All other starches were commercially available from different sources, potato starch (Mallinckrodt Chemical), corn starch (Argo), arrowroot and rice (S. B. Penick and Co.), pure amylose, and amylopectin (amylose-free) (Calbio Chem. Co.). All other chemicals used were commercially available and of reagent grade.

Procedures—Determinations of the "Weight Average" Molecular Weights of the Starches—Light scattering measurements were applied on dilute solutions of the starches in 0.5 *M* potassium hydroxide solution. The starch solutions were prepared by stirring the starches or starch fractions in the potassium hydroxide solution while nitrogen is bubbled through the system. The turbidities of the solutions (τ) were measured indirectly by measuring the transmitted light at 430 mμ on a Beckman DU spectrophotometer and a Cary 15 recording spectrophotometer, using 1-cm. cells. The turbidity is defined by Debye (13) as the fractional decrease in the transmitted light intensity:

$$I/I_o = e^{-\tau L} \qquad \text{(Eq. 1)}$$

where I_o = the intensity of the incident beam, I = the intensity of the transmitted beam, τ = the turbidity in cm.$^{-1}$, L = the length of the scattering medium (1 cm. in this case).

The following equation was used for molecular weight determinations taken from the theoretical treatment given by Debye.

$$\tau = H \cdot M_w \cdot C \qquad \text{(Eq. 2)}$$

where τ = turbidity, cm.$^{-1}$, M_w = molecular weight

[1] Trademarked as Amioca.
[2] Trademarked as Amylon.
[3] Trademarked as Amylon VII.

of the solute, C = the concentration of the solute in Gm./cm.^{3}, H = a constant given by the following equation:

$$H = (32\pi^3/3)\,(\gamma^2 \cdot n_o^2/\lambda^4 N) \qquad \text{(Eq. 3)}$$

where γ = the refractive increment which can be considered constant if the dilution is sufficiently great, n_o = the refractive index of the solvent, N = Avogadro's number, λ = the wavelength of light.

Equation 2 is corrected to show the effect of solvent–polymer interaction and is finally written:

$$HC/\tau = \frac{1}{M_w} + 2BC \qquad \text{(Eq. 4)}$$

where B = a constant which depends on the degree of solvent–polymer interaction.

Using Eq. 3 the values of the constant H for three different starches were calculated and averaged into one constant to be used in the study. The only unknown is the refractive index increment γ. A sample determination of that value is shown in Fig. 1. The slope of the line was calculated by the least-squares method to give the value $\gamma = 0.1141$.

The average value of H was calculated to give $H = 3.71 \times 10^{-6}$. This value was used for all subsequent calculations, using Eq. 4. The values HC/τ are plotted against C (Figs. 2–4). The least-squares method was used to calculate the intercepts $(1/M_w)$.

Fractionation of Potato Starch to Obtain Crystalline Amylose—The method based on complexing amylose with *n*-butanol was followed in this work. A starch sol was prepared by autoclaving, as described later in the complexing study. The sol was saturated with *n*-butanol after it was removed from the autoclave. The mixture was stirred while placed in the hood until it was cooled to room temperature. The precipitate of "amylose–butanol" complex was isolated by centrifuging at 7,000 r.p.m. for 20 min. This precipitate was stirred in 500 ml. of *n*-butanol saturated water and recentrifuged as before, the precipitate was resuspended several times in distilled water and centrifuged at 10,000 r.p.m. as recommended for the removal of *n*-butanol from the complex. The amylose, thus obtained, was dried and used for preparation of amylose sols for the complexing study. Although some residual *n*-butanol was left in the amylose crystalline powder, the bubbling of nitrogen through the sols during their preparation was one of the procedures recommended for the removal of the residual *n*-butanol (14).

Complexation in Aqueous Solutions—The starch sols were prepared by autoclaving as described in a previous work (1). The required amount of starch or starch fraction to make 500 ml. of the sol was accurately weighed into a 125-ml. beaker, smoothed into a slurry with distilled water, then poured all at once into a liter beaker containing 400-ml. boiling water. The gelatinized paste was stirred and transferred to an autoclave to be heated at the pressure of 20 p.s.i. for 3 hr. The resulting sol was then stirred until cooled and distilled water added to obtain 500 ml. of the sol.

Excess quantities of the drug were added to various starch sols of different concentrations in stoppered bottles. The bottles were agitated in a constant temperature water bath at 30° until the system reached equilibrium (24–48 hr.). Aliquots of 2–3 ml. were removed from each bottle using 10-ml. hypodermic syringes kept at 30° temperature. The aliquots were filtered through a Swinny filter adapter placed on the tip of the syringe. The adapter was equipped with S&S filter paper. The filtrates were placed in tubes kept in the 30° water bath. The filtered solutions were left 20 min. in the bath. Aliquots of these were removed using pipets kept at 30° temperatures and appropriately diluted for spectrophotometric analysis. Dilution factors varied from 1:100 to 1:1000 depending on the solubility and the molar absorbancy of the drug tested. The wavelengths of maximum absorbance were determined on a Cary 15 recording spectrophotometer. Each drug showed the same wavelength of maximum absorbance in water and in the presence of starch solution. Readings of absorbance were made using proper dilution of a starch sol (without the drug) as a blank in the reference cell.

Determination of the Adsorption of Long Chain Fatty Acids and Fatty Alcohols on Dry Unruptured Potato Starch Granules—Solutions of the fatty materials were prepared in two different solvents, methanol and petroleum ether. All solutions had the same concentration (15 Gm./L.), since it was shown that adsorption of fatty acids on potato starch follows a typical Freundlich isotherm (15). Fifty grams of potato starch was placed in a bottle, 100 ml. of the fatty material solution was added. The bottles were tightly stoppered and agitated in a water bath at 30° for 24 hr. All samples were filtered and the filtrates were tested for the excess of fatty acid or fatty alcohol in solution. The starch collected on the filter papers was washed with 25 ml. of petroleum ether three times. The washed starches were transferred into clean beakers and hydrolyzed with 500 ml. of 1 *N* hydrochloric acid while heated on a steam bath and stirred slowly. A blank sample of potato starch was hydrolyzed in a similar manner. Two hours of hydrolysis showed a complete disappearance of the iodine reaction in the mixture. The mixtures were cooled and placed overnight in the refrigerator. The cold

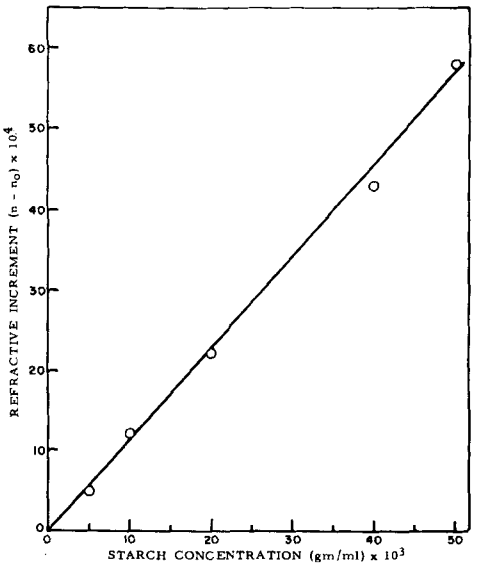

Fig. 1—Refractive index increments of potato starch solutions in 0.5 M KOH.

mixtures were than filtered through a fluted filter paper, and the beakers and the filters were repeatedly washed until the filtrates were free of hydrochloric acid as shown with methyl orange T.S. The inside and the lip of the beakers were scrubbed with small pieces of damp filter paper to pick up adherent fatty materials, and these pieces were placed in the fluted filter of each beaker. The papers were allowed to dry overnight and then were extracted in a Soxhlet extractor with petroleum ether. The solvent was removed and the amount of the fatty material was determined by weighing the dry flask containing the extracted fatty material.

RESULTS

Molecular Weight Determination—Figure 1 shows a sample determination of the refractive index increment for a series of dilute potato starch solutions. The constant γ is the slope of the line of $(n - n_o)$ *versus* (C) where n_o is the refractive index of the solvent (0.5 M KOH), n is the refractive index of the solution using light source of 430-mμ wavelength, and C is the concentration of the starch solution.

Figures 2–4 are those of HC/τ plotted against C as given by Debye (Eq. 4). The least-squares method was used to calculate the intercepts $(1/M_w)$, and Table I shows the values of the molecular weights obtained.

Complexation in aqueous solutions—Figures 5–7 represent the solubility behavior of benzoic acid, *p*-hydroxybenzoic acid, and sorbic acid in the presence of various concentrations of the starches in aqueous solutions at 30°. Figures 8 and 9 represent the solubility behavior of a number of organic molecules in the presence of potato starch aqueous solutions at 30°. Figure 10 shows the same plots on Figs. 8 and 9 plotted on the same ordinate scale to compare the slopes.

Table II shows the unruptured starch granules adsorption of fatty acids and fatty alcohols. Figure 11 shows the amounts of fatty materials adsorbed per 1 Gm. of potato starch plotted against the number of carbons of the fatty chain.

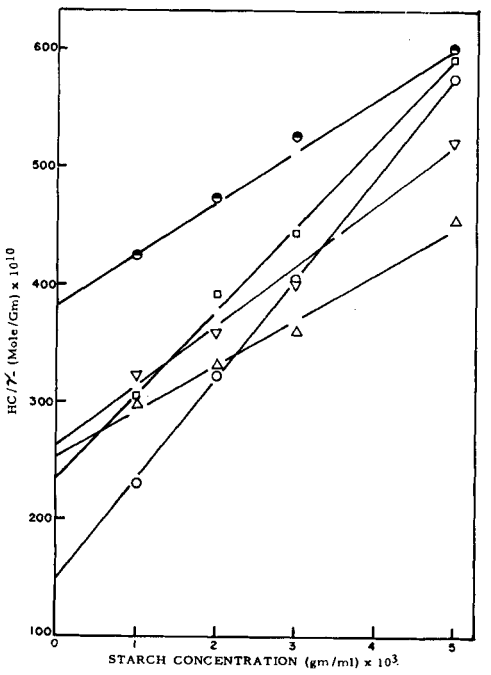

Fig. 2—Debye equation plots of turbidimetric data of various starches. Key: ◓, corn; □, amylose-A; ○, amylopectin; ▽, potato starch; △, arrowroot.

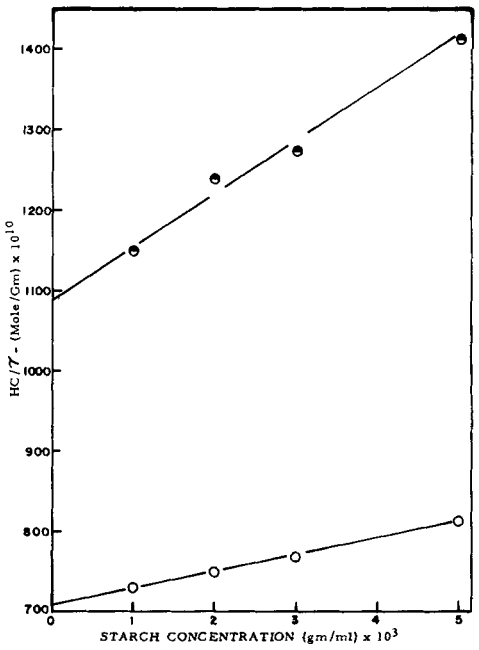

Fig. 3—Debye equation plots of turbidimetric data of rice starch and amylose-B starch. Key: ◓, amylose-B; ○, rice starch.

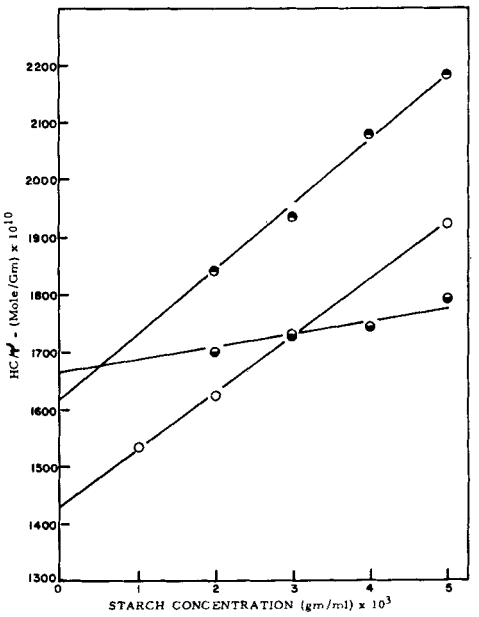

Fig. 4—Debye equation plots of turbidimetric data of several starches. Key: ◓, amylose (potato); ○, amylose-C; ◒, commercial amylose.

TABLE I—"WEIGHT AVERAGE" MOLECULAR WEIGHTS (M_w) AS CALCULATED FROM TURBIDIMETRIC DATA BY LEAST-SQUARES METHOD

Starch	Mw
Amylopectin	6.719×10^7
Amylose-A	4.288×10^7
Potato	3.959×10^7
Arrowroot	3.807×10^7
Corn	2.626×10^7
Rice	1.411×10^7
Amylose-B	9.195×10^6
Amylose-C	6.991×10^6
Amylose (fractionated)	6.171×10^5
Amylose (commercial)	6.004×10^5

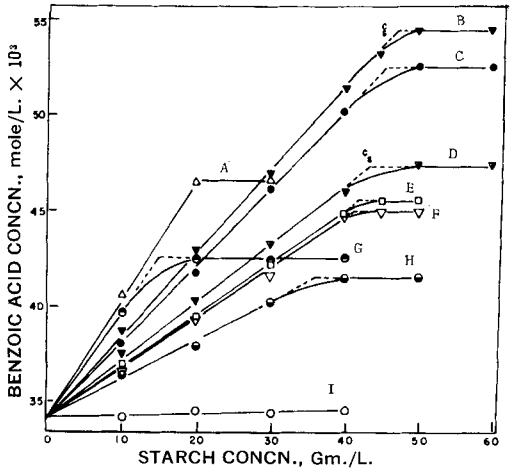

Fig. 5—Effect of various concentrations of starches on the apparent solubility of benzoic acid at 30°. Key: A, amylose; B, amylose-C; C, amylose-B; D, rice; E, corn; F, arrowroot; G, amylose-A; H, potato starch; I, amylopectin.

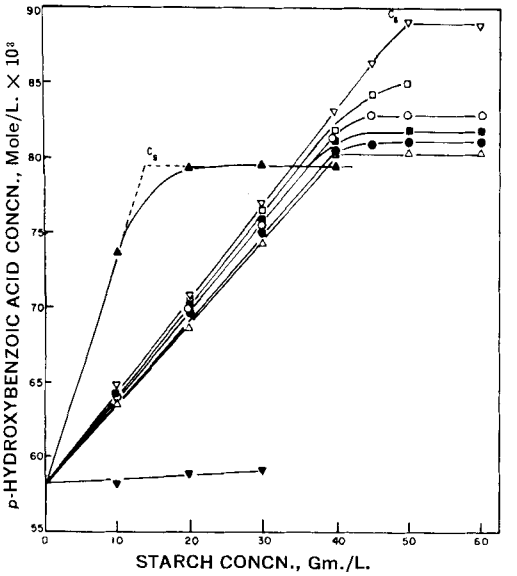

Fig. 6—Effect of various concentrations of starches on the apparent solubility of p-hydroxybenzoic acid, at 30°. Key: ▽, amylose-C; □, amylose-B; ○, rice; ■, corn; ●, arrowroot; ▲, amylose-A; △, potato; ▼, amylopectin.

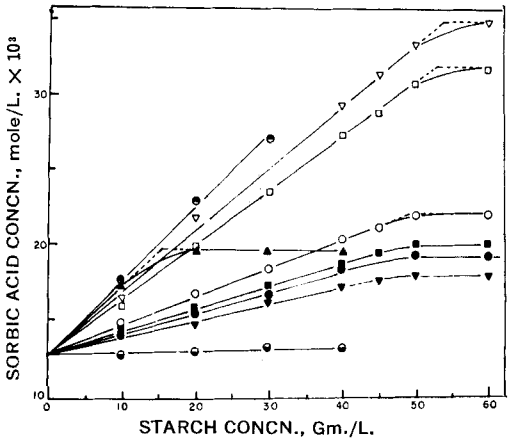

Fig. 7—Effect of various concentrations of starches on the apparent solubility of sorbic acid at 30°. Key: ◒, amylose (fractioned); ▽, amylose-C; □, amylose-B; ▲, amylose-A; ○, rice; ■, corn; ●, arrowroot; ▼, potato; ◒, amylopectin.

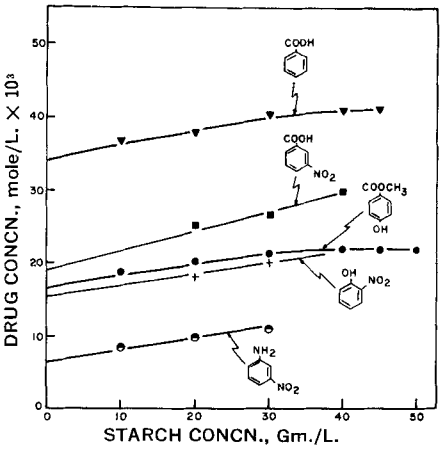

Fig. 8—Effect of various concentrations of potato starch on the apparent solubilities of several organic acids in water at 30°.

DISCUSSION

Using the light scattering method "weight average" molecular weights of the various starches were obtained. These molecular weights count the various molecules in the polymolecular starch system according to their masses. Each of the starch fractions, amylose and amylopectin, is known to be a polymolecular system consisting of a number of subfractions (16). Thus, the molecular weight of a given starch as obtained in this work can be considered a mean value which accounts for all the polymolecular components of that starch according to their respective masses. The amyloses showed the lowest molecular weights, and amylopectin the highest. As the rest of the starches are heterogeneous systems, the molecular weight values varied according to the starch content of low molecular weight amylose and according to the sizes of the amylose and amylopectin fraction. In each starch the two polymer fractions (and even their subfractions) contributed to the value of (M_w) according to their percentage and weight distribution.

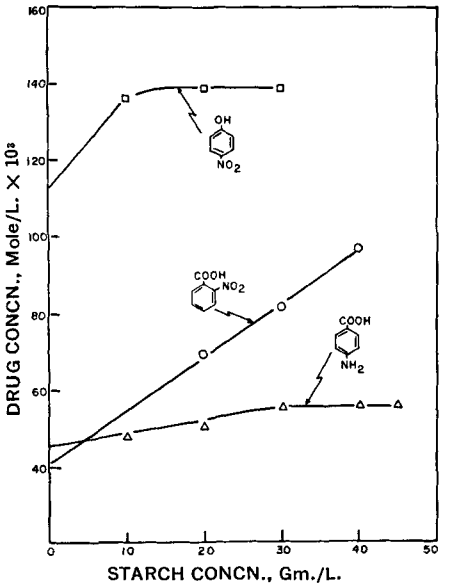

Fig. 9—Effect of various concentrations of potato starch on the apparent solubilities of several organic acids at 30°.

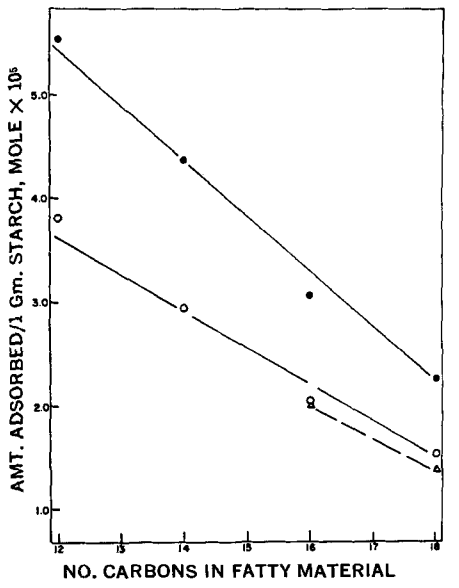

Fig. 11—Dry starch adsorption of several fatty acids and fatty alcohols from methanol or petroleum ether solutions. Key: ●, saturated fatty acids in methanol; O, fatty acids in petroleum ether; △, alcohols in petroleum ether.

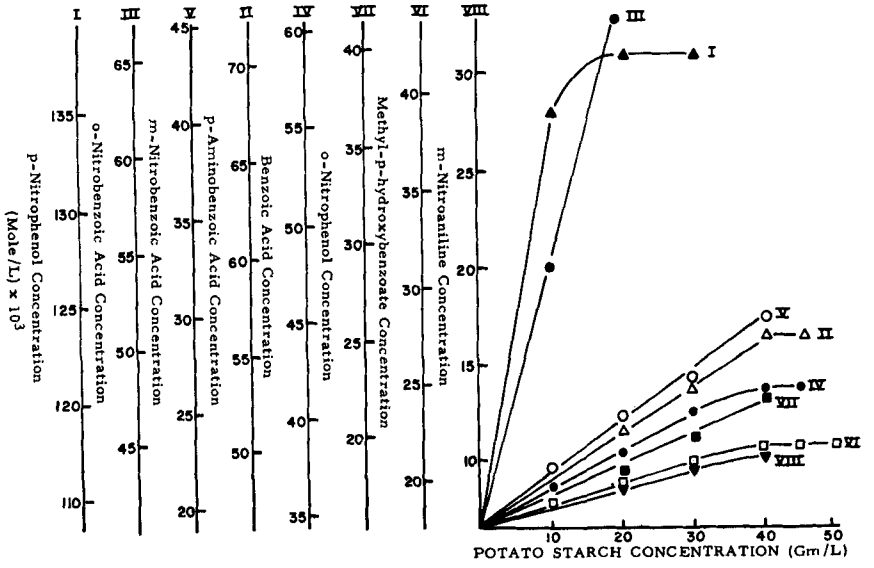

Fig. 10—Solubility behavior of a number of organic compounds in the presence of potato starch.

TABLE II—POTATO STARCH ADSORPTION OF FATTY ACIDS AND FATTY ALCOHOLS IN PETROLEUM ETHER OR IN METHANOL

Fatty Acid or Alcohol	Total Amt. Adsorbed per 1-Gm. Dry Starch, mole × 10⁵	
	Petroleum Ether Solution	Methanol Solutions
Stearic acid	1.51	2.26
Stearyl alcohol	1.35	...
Oleic acid	1.37	2.07
Palmitic acid	2.03	3.06
Myristic acid	2.94	4.36
Lauric acid	3.80	5.54
Cetyl alcohol	2.01	...

The solubility method for determining interactions between starch and the selected drugs indicated complex formation evidenced by an increase of the solubility of the drug with the increase of a given starch concentration. The phase diagrams of benzoic acid, *p*-hydroxybenzoic acid, and sorbic acid in the presence of various starches and starch fractions can be explained briefly by (*a*) pure amylopectin showed little or no interaction with the three drugs. (*b*) The various starches showed complexation represented by a linear increase of the solubility of the drug with the increase of a given starch concentration up to a certain limit where no more drug could be detected in the solution. The limit can be called the saturation concentration of the complex (C_S), at which the turbidity of the

solution was notably increased and the "starch-drug" complex precipitated out of the solution. (*c*) Amylose sols showed a high uptake of the complexing drug into solution. In sols containing more than 20 Gm./L. of amylose a cake-like product precipitated out of the solution. This precipitate was successfully centrifuged at 7,000 r.p.m. A similar precipitation occurred in potato starch when the complexing drug was *p*-nitrophenol or *p*-aminobenzoic acid (Fig. 9).

It can be said in summary that when the same solid drug was added to the solutions of the various starches (each being a polymolecular system of its own), the amounts of the drug that entered the solution before precipitating the complex were dependent on the type of the starch. These amounts can be calculated by subtracting the amount of drug in water at 30° (C_o) from the total drug in the system at the plateau region (C_s). It must be noted that these values (C_s-C_o) for the same drug decreased with the increase of the "weight average" molecular weight of the starch.

These values varied from one starch to the other for the same complexing drug. The lower the average molecular weight of the starch the greater the amount of the complexing drug needed to reach the plateau region. Such a relationship can only be explained when one understands that the lower the molecular weight of a starch the richer the starch in amylose, thus the precipitation of an amylose complex from the system at the plateau region is influenced by the average molecular weight of the starch which can be considered related to the amylose content of the starch. (*d*) Finally, one can recognize that the low molecular weight polymer, amylose, is the main complexing component of starch with the drug. The amylose tendency to crystallize in a complex form with the drugs tested is noted to be far stronger than that of amylopectin.

The complexing of potato starch sols with selected molecules occurs with wide variance as seen in Figs. 8–10. It appears at first that the tendency of drugs to complex with the starch matches their solubility, *i.e.*, the higher the solubility of a drug the higher its tendency to complex; however, arranging the tendencies for complexing, as given by the slopes of the lines on Fig. 10, in a decreasing order shows that those tendencies do not match the solubilities in water (Table III). The effect of groups, like nitro or amino, in increasing the tendency to complex is noted. For example, the water solubility of *p*-aminobenzoic acid is higher than that of *o*-nitrobenzoic acid but the latter has a higher tendency to complex with starch than the former.

TABLE III—SOLUBILITY RELATIVE TO COMPLEXING TENDENCY OF DRUG MOLECULES

Decreasing Order of Solubility in Water	Decreasing Order of Tendency to Complex[a]
I	I
II	III
III	V
IV	II
V	IV
VI	VII
VII	VI
VIII	VIII

[a] I = *p*-nitrophenol, II = *p*-aminobenzoic acid, III = *o*-nitrobenzoic acid, IV = benzoic acid, V = *m*-nitrobenzoic acid, VI = methyl-*p*-hydroxybenzoate, VII = *o*-nitrophenol, VIII = *m*-nitroaniline.

Correlations of the complexes reported in this work with those of "amylose-alcohols" used for the fractionation of starch and "amylose-iodine" can be made after extensive X-ray studies as reported in the cases of "amylose-fatty acids" complexes (19). A general similarity is noted in the behavior of the complexes reported in this work with those of "alcohols-amylose," and those reported by Whistler (20) that are obtained with nitrobenzene, pyridine, 2-heptanone, and many other water soluble compounds possessing groups capable of hydrogen bonding and used for the fractionation of starch. Such similarity in the complexing behavior makes one assume that the complexing takes the same route and mechanism as that of "starch-iodine" and "starch *n*-butanol" complexes, which are explained to be consisting of an entrapment of the "guest" molecule in the α-helical structure of amylose with a supplementary stabilization by dipole–dipole interactions (21).

The adsorption affinity of starch is demonstrated in the case of the unruptured starch granules interacting with fatty acids and fatty alcohols. The affinity was decreased with the increase of the hydrophobic chain of the fatty material. Starch affinity for a given fatty material in methanol solution was higher than its affinity for the same material in a petroleum ether solution of the same concentration. This cannot be explained easily. One must notice that the starch used contained 10–12% water. It is conceivable that the fatty acid can be carried into the granule polymers by an exchange process between the water content and the organic solvent; thus, the polarity of the solvent proved to be of value.

It is important to appreciate that the understanding of the many applications of a fundamental phenomenon, like starch complexation can help the pharmaceutial compounder to predict any unfavorable incompatibilities. A drug complexed with starch might differ from the free drug with respect to solubility, diffusivity, partition coefficient, and ability to penetrate biological membranes. A drug pharmacological effectiveness might be altered if the drug is bound in such a complex; when the complex dissociates by the hydrolysis of the macromolecular polysaccharide at some stage in the body, the drug can then be available for its usual absorption and effect. In this respect the availability of a drug for external therapeutic treatment and its effectiveness should be investigated when the drug is included in a starch paste, sol, or any base containing polysaccharides in general.

With the fundamental understanding of the high affinity of starch for molecules varying from phenols and alcohols to weak carboxylic acids, the pharmaceutical compounder should investigate the effects of the complexation of the various drugs introduced in very small quantities in a tablet containing starch, especially when starch paste or polysaccharide excipients increase the magnitude of the complexation in the wet granulation technique. In general, the possible interactions between starch and many organic molecules found in small concentration dosage forms where starch is used as a pharmaceutical adjunct, must be considered carefully. The complexation of the starch with a preservative like benzoic acid, for example, is expected to decrease its preservative activity.

Finally, drug complexation with starch can be a useful method of retarding absorption of a very irritant drug that might complex with starch and thereby reduce its toxicity. Starch has been used in this sense as an antidote for iodine poisoning. In a similar manner, the starch complexing affinity could explain the possible binding to bacterial excretion products in certain dermatitis conditions, thus providing the rationale of the wide use of starch as anti-irritant in dusting powders.

As the precipitation and isolation of "amylose-drug" complex is possible, a highly important question about the stability of a drug enclosed in such a complex form should not remain long unanswered. The nature of these complexes appear to suggest their possible use in a sustained dosage form, since the release of the drug from the complex is possibly caused by the enzymatic hydrolysis of the macromolecule.

SUMMARY AND CONCLUSION

Amylopectin (amylose-free) was found to have very little interaction for benzoic acid, *p*-hydroxybenzoic acid, and sorbic acid, while amylose was found to produce complexes rapidly. Potato starch, arrowroot starch, corn starch, rice starch, and a number of commercial starches rich in amylose were all found to complex with the three drugs tested. A number of selected pharmaceuticals showed interaction with potato starch sols, and in many cases, depending on the solubility of the pharmaceutical, the complex precipitated off the solution after reaching a saturation concentration.

Unruptured potato starch granules were found to adsorb fatty acids and fatty alcohols from methanol or petroleum ether solutions.

A correlation of the appearance and behavior of these complexes with those of "amylose-alcohols" used for the fractionation of starch, and with those of "amylose-iodine" reported in the literature, make one assume that the drug-starch complexing takes the same route and may be the same mechanism as that of "starch-iodine" and "starch-alcohols" complexes.

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Keyphrases

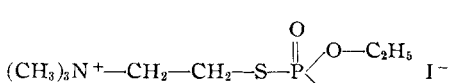
Complexes–starch
Starch starch–fraction sols–complexing behavior
Fatty acids–starch affinity
Molecular weight determination–starches
Spectrophotometry turbidity analysis
Solubility–complex formation analysis

Kinetics and Mechanism of Degradation of Echothiophate Iodide in Aqueous Solution

By ANWAR HUSSAIN, P. SCHURMAN, V. PETER, and G. MILOSOVICH

The degradation of echothiophate iodide was found to occur by two different mechanisms depending on the pH of the solution. In alkaline media (pH range 9.5–12), the major reaction was S-P bond cleavage to yield (2-mercaptoethyl)trimethylammonium iodide. This reaction was found to be first order with respect to the concentration of the compound and first order with respect to hydroxyl ion concentration. In weakly acidic media (pH range 2.4–5), the loss of 1 mole of ethanol through C—O bond cleavage was the predominant reaction. The rate of this reaction was also found to be first order with respect to the concentration of echothiophate iodide. The reaction rate constants and the energies of activation were determined for the two reactions and the degradation products were isolated and characterized.

ALTHOUGH ECHOTHIOPHATE IODIDE (I), a potent long-acting cholinesterase inhibitor, has been recognized in the USP (1) to be unstable in aqueous solution, the chemical degradation of the compound has not been thoroughly investigated. However, it is known that I



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