THE PREPARATION AND PROPERTIES OF ARABIC ACID AND ITS SALTS

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Table of Contents

INTRODUCTION

Gum arabic has been one of the most widely used emulsifying agents known, although its low viscosity has always been a problem. The strong point in its favor is its ability to produce a strong film, because a fairly large quantity can be used without making an emulsion too viscous; the strength of a film being partially dependent on the amount of film former present. When compared with other gum type agents, it ranks lowest in viscosity. (1)

A factor to be considered when acacia is used, is the variation in quality and physical properties from lot to lot. As will be seen later in the experimental work, there are variations in the viscosity of the solution of the gum. Since these difficulties arise when acacia is used, it was decided to ascertain whether the replacement of acacia by arabic acid or one of its salts would solve these difficulties.

The problem, briefly stated, was to study the physicochemical and pharmaceutical properties of arabic acid and to study the effect of cations or mixtures of cations on arabic acid.

For this purpose, the following course of action was followed, arabic acid solution was obtained in a very pure form. Since arabic acid solutions deteriorate on standing and since different concentrations of arabic acid could be more readily prepared from a solid form, the arabic acid solution was converted to a powdered form without changing its chemical and physical properties. Thirdly, an investigation of the physicochemical properties of the acid and its salts was carried out, and finally, possible pharmaceutical applications for the acid and salts were studied.

In order to obtain a complete picture of arabic acid, the following discussion describes the work which has already been done on the compound.

CONSTITUTION

Arabic acid is obtained from gum arabic, which consists of the potassium, calcium, and magnesium salts of arabic acid along with some tannins, oxidases, and foreign matter. This arabic acid was first mentioned by Neubauer in 1854. Upon analysis he found that the hydrogen and oxygen was present in the same ratio as found in water. (2) In 1868 Scheibler obtained arabinose from arabic acid by decomposition. (2) The presence of arabinose has been confirmed by others. (3)

Also among the early workers on arabic acid was O'Sullivan. He obtained an acid on sulfuric acid hydrolysis which he called -arabinosic acid. The acid, he claimed was very stable resisting the action of sulfuric acid for several hours. The moleculær formula was given as $C_{23}H_{38}O_{22}$. He arrived at this formula by the removal of 12 $C_6H_{12}O_6$ molecules from the original formula which he determined to be $C_{89}H_{142}O_{74}$. The sugars he found were arabinose and galactose. (4)

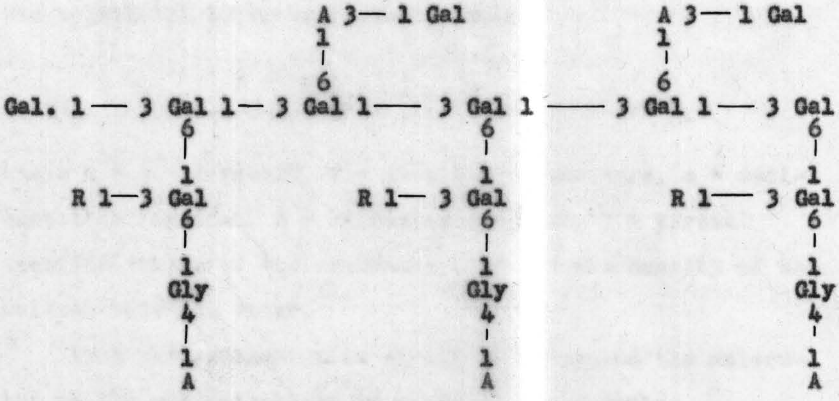
Butler and Cretcher obtained amorphous aldobionic acid on hydrolysis of gum arabic with sulfuric acid. Hydrolysis was continued until polarimetric readings remained relatively constant. Analysis showed the formula for aldobionic acid to be $C_{12}H_{20}O_{12}$. The components of this acid were d-glycuronic acid and galactose. These workers further stated that aldobionic acid was identical with O'Sullivan's arabinosic acid, since the analytical figures for the latter correspond as well for $C_{12}H_{20}O_{12}$ as for $C_{23}H_{38}O_{22}$. (5) From the amount of iodine consumed on oxidation and the amount of carbon dioxide liberated on boiling with 12 per cent hydrochloric acid as well as the percentage of calcium found in the calcium salt, the aldobionic acid corresponds to a compound containing one free aldehyde and one free carboxyl group.

These workers also determined by titration of arabic acid with alkali in hot and cold solution that arabic acid exists to the extent of about 22 per cent as the lactone. It has been determined that only traces of lactone exist in the gum itself.

Heidelberger and Kendall obtained aldobionic acid in the crystalline form. Besides confirming the work of Butler and Cretcher, they also concluded that the glycuronic acid was linked to galactose by either a 1,3 or a 1,6 linkage. (6) Challinor, Haworth, and Hirst confirmed the work of Heidelberger and Kendall and also showed that the linkage was 1,6. (7) Levene and Tipson demonstrated the β-glycosidic linkage in the acid. (8)

A considerable amount of work was done by Smith and Jackson on the structure of arabic acid. It was found that on autohydrolysis several sugars and degraded arabic acid were contained in the molecule. In their first work l-arabinose, l-rhamnose, and 3-d-galactosido l-arabinose were characterized. (9, 5, 10) The degraded arabic acid appeared to be the basic nucleus of the acid, and it was made up of galactose and glycuronic acid. (11) Hydrolysis of the methyl ester of the methylated degraded arabic acid yielded 2:3:4:6 tetramethyl galactose (1 molecular proportion), 2:3:4 trimethyl galactose (5 molecular proportions), and 2:4 dimethyl galactose (3 molecular proportions), and 2:3:4 trimethyl glycuronic acid (3 molecular proportions). The identification of these methylated derivatives shows that 1:6 and 1:3 glycosidic linkages are present in degraded arabic acid, and that the sugar units all of which have pyranose rings are joined in a branched chain type of structure probably having four terminal or end residues. (11) Graded hydrolysis of methylated degraded arabic acid gave a hexamethyl-6-β-glucuronosidogalactose which suggested that the terminal groups of the degraded acid were made up of this compound. (12, 13) The formation of 3-galactosidogalactose by prolonged autohydrolysis of degraded arabic acid proved that some of the galactose units are joined by 1:3 links. (14) The identification of the hydrolyzed products of methylated arabic acid demonstrated the branched chain structure of arabic acid and also showed that the labile sugar residues are joined to the nucleus of degraded arabic acid in the form of l-arabofuranose, l-rhamnopyranose, and 3-galactopyranosido-l-arabofuranose. The presence of a 1:4 linkage was also proved to be present. (15)

Hirst has set up the following structure which he believes may be that for the repeating unit of arabic acid. (16)



Gal = d-galactopyranose

Gly = d-glycuronic acid

R = l-rhamnopyranose

A = l-arabofuranose

The numbers indicate the linkages between the component compounds.

PHYSICAL CONSTANTS

Molecular Weight

The mean molecular weight of the gum has been determined using three different methods. One method by which the molecular weights were obtained was based on the measurements of rate of sedimentation in the centrifugal field and rate of diffusion, another was obtained from sedimentation equilibrium determinations, and the third was obtained by the osmotic pressure method. In the first case the molecular weight was calculated by means of the formula:

$$M = \frac{R\,T\,s}{D\,(1 - V\rho)}$$

where R = gas constant, T = absolute temperature, s = sedimentation constant, D = diffusion constant, V = partial specific volume of the substance, and ρ = the density of the solvent which is water.

From the sedimentation equilibrium method the molecular weight was calculated by means of the formula:

$$M = \frac{2\,R\,T\,\log\,(c_2/c_1\,)}{1 - V\rho\,)\,\omega^2(x_2^2 - x_1^2\,)}$$

where c_1 and c_2 are the concentrations at the distances x_1 and x_2 from the center of rotation and ω is the angular velocity of the centrifuge rotor. (17)

From osmotic pressure measurements the molecular weight was calculated by means of the formula:

$$P\,v = \frac{g}{M}\,R\,T$$

where P = osmotic pressure, v = volume of the solution, g = weight of the solute, and M = molecular weight.

The molecular weights obtained from the first method using the acid gum were 279,000 and 319,000. The difference in these two values was due to different diffusion constants obtained by different means of calculation. Values obtained using sodium gum were 247,000 and 267,000. The latter values are in close agreement with the values obtained by Oakly for electrodialyzed gum. They were 245,000 - 286,000. (18) This is surprising since the former gives the weight average whereas the latter method gives a number average. By the sedimentation equilibrium method a mean value of 307,000 was obtained.

Equivalent Weight

Values for equivalent weights vary between 1000 to 1400 in the literature. Saverborn reported an equivalent weight of 1314 and 1309 obtained by titration of the acid at room temperature using bromthymol blue as the indicator. (17) 982 and 997 were the values obtained from titrations after heating the mixture of solution and standard alkali at 100°C. for half an hour. (17) The values 1318 and 1308 were obtained by a determination of the sodium content of the sodium salt. (19) Tiebackx gave a figure of 1210 as the equivalent weight. (20) Briggs gave 1175 as the equivalent weight. (21) Thomas and Murray reported an equivalent weight of 1177. (22) Lactone formation as discussed above may account for the different results obtained.

Optical Rotation

Razukin has reported the specific rotation of arabic acid as -27.86° for a 2 per cent concentration at 25° C. (23)

Thomas and Murray have reported a value of -24.3° for a 1 per cent concentration at 25° C. (22) Smith has reported a -28° for a 2 per cent concentration at 20° C. (9)

pH Titrations

Upon titration the acid behaves like a monobasic acid although there is more than one acid group present.. (21, 22) Briggs has given an explanation for this phenomena. He states that the acid hydrogens must be so far apart in the molecule that the ionization on one group has no intramolecular influence upon the tendency of the other groups to ionize. Another possibility he gives; that every ionizable hydrogen present has a dissociation constant somewhat different from every other one and that these constants for the various acid groups are rather uniformly distributed throughout the buffer range of the acid. (21) The pH of a one per cent arabic acid solution has been reported by Thomas and Murray to be 2.7. (22) Briggs reported an approximate pH value of 2 for a 5 to 10 per cent solution of arabic acid. (21) Both determinations were made potentiometrically.

Dissociation Constant

Amy gives a value determined at 22° C. of 2.0×10^{-4}. (24) The dissociation constant determined by Briggs for 50 to 100 grams of arabic acid per liter was 1×10^{-3} and at infinite dilution (extrapolation value) it was 2×10^{-7}. The author explained this difference by making the assumption that a reversible peptization of the micella occurs at high dilutions, and that this is accompanied by a marked decrease in the dissociation tendency of the acidic groups on the micella. (21)

Viscosity Determinations

To be discussed in Part II of this thesis.

PHARMACOLOGY

Very little work has been described in the literature for arabic acid. Since gum arabic consists of the salts of arabic acid, a discussion of the pharmacology of gum arabic is also included.

Czerny in his work on animals concluded that a considerable amount of acacia could be injected into normal animals without apparent injury. (25) Erlanger and Gasser cite a series of cases in which acacia-glucose solutions were administered. Distinct improvement was shown after the patients have been in shock. (26) Gross evidence of toxicity was not seen by Huffman following the intravenous injection of solutions of acacia and sodium chloride in cases of shock. The blood pressure increased, pulse rate decreased, the respiration deepened and the general condition of the patient improved.

Injurious effects on the kidney were not seen, and chemical changes of a harmful nature in the blood were not apparent. Physico-chemical changes in the blood did not lead to harmful alterations in the physiological processes. About 6 days were required to rid the blood of acacia. Pathological changes resulting from the acacia were not demonstrated at necropsy. These results were obtained from about 200 cases in which acacia and saline were given. (27)

Bayliss also observed that acacia was effective in replacing blood lost unless the blood loss amounted to more than 70 per cent of the blood volume. He found that acacia does not produce anaphylaxis, hemolysis, or agglutination of blood corpuscles in man. (28) Matill found that a 3 per cent acacia solution with a 30 - 40 per cent glucose solution was capable of maintaining blood volume in spite of a marked glucose diuresis. A six per cent acacia solution also prevented the diuresis. (29) Butt, et al have found that the administration of acacia results in a short temporary increase in the colloid osmotic pressure, a decrease in the total serum protein concentration but practically no change in serum albumin. (30)

Although there has been much evidence in favor of acacia there has also been much evidence against its use for intravenous injection. Andersch and Gibson produced evidence of acacia toxicity. They found, that after injection of 10 cc. of a 30 per cent solution, the acacia disappeared from the blood in two to three days and that 50 per cent of it had been taken up by the liver and was removed quite slowly. Some was also found in the spleen and bile. Upon histological examination it was found that the liver cells had been affected producing large vacuoles in the cells, although the Kupfer cells were not damaged. It was stated that it may be the reticulo-endothelial system which is responsible for the retention of the gum. This work was done on rabbits. (31) Liver injury was also shown by Erickson and Heckel. (32) Hanzlik, et al noted disturbances in the acid-base balance of the blood on intravenous injection. (33) Karsner and Hanzlik found that a one per cent acacia solution caused agglutination of human, cat, and guinea pig blood in vitro. The acacia also caused hemolysis. (34)

Jackson and Frayser in a study of the effect of acacia on the blood found that plasma and blood volumes were increased after acacia was given intravenously to dogs with a proportionately greater decrease in the total proteins. Plasma volume returned to normal quickly, but protein regeneration was delayed. They likewise found acacia in the liver and spleen. Hemoglobin, cell volume, and red blood corpuscle count decreased markedly and regenerated slowly. The white blood corpuscle count showed no appreciable change. This meant that intravenous injection in case of nephrosis would be contra-indicated since the serum protein level is an important consideration in nephrosis. (35)

The only mention of arabic acid was in a report by Schwartze and co-workers who studied the action of acacia and arabic acid in salt solution on the blood. They found that agglutination occured, and that the sedimentation rate was greatly increased in many of the cases in which these substances were used. (36)

Acacia is no longer used as a blood substitute, because blood plasma and whole blood are available to such an extent that the use of acacia is unnecessary.

A method of preparation for salts of arabic acid with anesthetic bases has been described. The bases used were cocaine, tropacocaine, stovain, novacain and analgous compounds. It was stated that the duration of anesthesia was three times as long with the arabic acid salts of the bases as with the chloride salts and that the toxic symptoms were lower. (37)

PREPARATION OF ARABIC ACID

This will be discussed in Part I of this thesis.

This portion of the report has been divided into three sections. The first portion deals with the preparation of the arabic acid solution. The second portion discusses the conversion of the arabic acid solution to the powdered form, and third, the preparation of the salts of arabic acid is described.

ARABIC ACID SOLUTION

Until recently, the only method for the preparation of arabic acid which had been reported was what might be generally called the acid-alcoholic precipitation method. (4, 17,20,21,22,38,39) The earliest method was described by Graham in which he obtained arabic acid with 0.1 per cent ash content by dialyzing a 20 per cent solution of gum arabic with 4 or 5 per cent hydrochloric acid for 5 days. (22) O'Sullivan obtained arabic acid by adding to a solution of the gum, 2 to 3 times the amount of hydrochloric acid equivalent to the metallic ions present and removed the chlorides by precipitation of the arabic acid with alcohol. This procedure was repeated 3 to 4 times. (4)

A method used in the present investigation was that as described by Saverborn. (17) The acid was prepared by acidifying a 20 percent aqueous solution of gum arabic with hydrochloric acid and precipitating the acidified gum in 3 volumes of alcohol. After three precipitations the gum was again dissolved in water and dialyzed for one to two days. The ash content was reported to be reduced to 0.05 per cent. Briggs reported an ash content of 0.05 per cent after only one precipitation, but he electrodialyzed the solution for one week. (22) Holler and Frankfurt used acetic acid instead of hydrochloric acid in the preparation. (39)

Another method has been recently described which makes use of ion-exchange resins to remove metallic ions. (40) A column made up of Amberlite IR-100 was used. A 0.1 per cent ash content was reported. This method was also utilized in the present investigation.

The cationic type resins which can be used to remove metallic ions possess reactive acid groups. These acid groups may be either carboxylic, phenolic, or sulfonic in character. Of the three the sulfonic acid group is the strongest. Two of the resins used in the research work were IRC-200 and IR-120. Both of these resins have a sulfonic acid group as its reactive group. The IR-100 mentioned above also has a sulfonic acid group as its reactive group. IR-120 has 4 times the capacity of IR-100 and is also the most stable of the resins of this type. (41)

Experimental Procedure

Alcohol Precipitation Method

Arabic acid was prepared by acidifying one liter of a 20 per cent solution of gum arabic (Penick Co.) with varying quantities of hydrochloric acid. Smaller quantities of hydrochloric acid were used in the beginning than stated in the literature in order to find the minimum amount necessary to obtain an arabic acid solution with an ash content of 0.05 per cent or less. The acidified solution was then poured into three volumes of 95 per cent ethyl alcohol with rapid stirring. The alcohol was then decanted off the white gummy precipitate. The precipitate was dissolved in water, acidified again and reprecipitated three or four times. The solution was then dialyzed for 24 hours. Table I shows the work done and the results obtained. Although larger quantities of HCl were used than given in the literature, no ash content values were obtainedd as low as stated in the literature.

Another check on the purity of the compound were the equivalent weight determinations. These were carried out by titration with .1040 N. sodium hydroxide using bromthymol blue as the indicator. The values obtained ranged from 1300-1600 with an average value of 1370. These values are high when compared with reported values given previously.

Since the goal was to obtain arabic acid with an ash content of 0.05 per cent or less, the method given above would be unsatisfactory. The procedure was also tedious, and only small batches could be prepared at one time. It was also noted that a considerable amount of sedimentation occurred in the solution on standing.

Table I

	Amount of HCl used in moles	Number of precipitations	Per cent Ash
1	0.05	3	1.25
2	0.07	3	0.6
3	0.1	3	0.53
4	0.3 mole added first with 0.2 mole added after 1st precipitation	3	0.31
5	Same as above	3	0.24
6	0.3 mole first with 0.2 mole added after 1st and 2nd precipitation	3	0.13
7	0.3 mole added first with 0.2 mole added after each of three succeeding precipitations	4	0.06
8	"		0.07
9	"		0.04
10	0.6 mole	4	0.06
11	"		0.16
12	"		0.16
13	"		0.06
14	0.8 mole	4	0.08
15	"		0.07

Ion-exchange Method

IRC-200, a hydrogen activated resin, was chosen; and a small column was set up containing approximately 400 gms. of resin. 1600 cc. of a 3 per cent solution of acacia was passed through the column. The ash content of the solution after passage through the column was 0.04 per cent, which was in the range desired. The acacia solution was poured through in increments of 1600 cc. to determine the maximum amount which could be put through the column before the ash content would rise. 3 batches were put through before the ash content went above the maximum standard set. A 5 gallon batch of arabic acid solution made up of one gallon batches which had been prepared, had an ash content of 0.019 per cent and an equivalent weight of 1203.

From the equivalent weight and ash content values which were obtained, it was seen that the method would be suitable, and therefore, a large column containing 6 pounds of IR-120 (Na activated) was set up. The resin was changed to a hydrogen activated resin by putting through a 10 per cent solution of hydrochloric acid and then rinsing the column with distilled water.

Upon experimentation it was found that it was possible to put through 10 gallons of a 7 per cent acacia solution before regeneration was necessary. In order to have a good margin of safety only 5 gallons of acacia solution was put through each time, and then regeneration of the column was carried out. Table II shows the ash content of numerous batches of arabic acid by the ion-exchange process.

Table II

Batches	Ash Content
L-I, B-I	.019%
L-II, B-I	.05
B-II	.05
B-III	.05
L-III, B-I	.04
B-II	.03
B-III	.04
B-IV	.05

The acacia used came in 25 pound lots. Three different lots were used as indicated in the table.

Regeneration of the column was carried out by putting through a 10 per cent solution of hydrochloric acid and then washing the column several times with distilled water until the water coming through the column tested 4 parts per million as sodium chloride on the Barnstead Purity meter. This reading was the same for the distilled water obtained from the tap.

PREPARATION OF THE POWDER

Some attempts have been made to obtain arabic acid in the dry powdered state, but no successful methods have been reported. (9,24,22,3) It was noted by Thomas and Murray that arabic acid on drying either with alcohol or by heating under vacuum renders it practically insoluble in water. (22) Amy also states that when arabic acid was dehydrated it was converted to an insoluble acid which he called meta-gummic or meta-arabic acid. (24) He also stated that when alkali was added the acid swelled and dissolved. On the other hand Smith appeared to have obtained a soluble product by drying the alcohol-precipitated acid under vacuum.(9) Carrington, et al dried an arabic acid solution under vacuum at 50° C. and apparently were able to dissolve it again. (3)

Experimental Procedure

An investigation was carried out on methods of obtaining arabic acid in the dried form. Arabic acid precipitated from solution with 95 per cent alcohol was dried in a vacuum oven at 50° C. The product obtained was insoluble in water. Alcohol precipitated arabic acid was dried under vacuum at room temperature (24°). The product was also insoluble in water although the powder did hydrate to some extent. Two arabic acid solutions were dried under vacuum; one at 50° C. and one at room temperature. The former was insoluble in water, but the latter was soluble. Although this procedure resulted in a soluble product, the method would not be feasible because of the length of time required to evaporate the solution to dryness, and the quantity which could be made at one time would be small. For this reason the spray-drier was considered as a possible method for obtaining the powder.

The spray-drier subjects the solution to drying temperatures for a very brief period of time. Drying is almost instantaneous. Consequently, no changes occur in the compound which would make it insoluble. The spray-drier has been described previously by Sidney Riegelman. (42)

Spray-drying of the arabic acid was carried out at 400° F. Approximately 8 hours were required to spray-dry 5 gallons of solution. Table III shows the yields which were obtained by this process. The per cent yields were quite low, because so much of the arabic acid remains on the walls of the spray-drier.

The arabic acid obtained from the spray-drying process was a fine white powder with a starch-like texture. It went into solution more slowly than acacia, because it has a tendency to clump together more readily than acacia. This was probably due to the extreme fineness of the powder.

Table III

Batches	Per cent yield
L-I, B-I	34%
L-II, B-I	40%
B-II	50%
B-III	--
L-III, B-I	40%
B-II	50%
B-III	80%
B-IV	80%

SALTS OF ARABIC ACID

Inorganic

Krantz and Gordon have prepared several salts of arabic acid. They prepared the sodium salt by addition of sodium carbonate to a solution of acacia to precipitate out the calcium ions. The solution was filtered and the filtrate was evaporated to dryness on a water bath. The magnesium salt was prepared by adding an excess amount of magnesium carbonate to arabic acid, filtering, and evaporating to dryness over a water bath. The ferric salt was prepared by adding ferric chloride solution drop by drop to a 20 per cent acacia solution until a gel of uniform reddish brown color and stiff consistency was obtained. Preparation of the lead arabate was attained by treating an acacia solution with a solution of lead subacetate until a precipitate was no longer obtainable. The precipitate was washed free of soluble lead salts and dried to constant weight at 100°C. (38)

The sodium, potassium, lithium, and calcium salts have been prepared by neutralization of arabic acid with the hydroxides of the metal desired. The salts were dried in vacuo at 70° C. (21) In a similar manner others have prepared the sodium salt. (17,22)

In this project only the sodium salt was prepared in the powdered form. All the other salts were kept in solution for viscosity determinations described in Part II of this thesis.

Experimental and Results

Sodium Arabate--An arabic acid solution was neutralized with 0.5 N. sodium hydroxide to a pH between 7 and 8. This solution was then spray-dried at 400°F. 85 x 10^{-4} equivalents of sodium hydroxide were needed to neutralize 10 grams of arabic acid.

.0085 40
.340 Gms.

The powder obtained was white and of a fine texture. The powder was soluble in water, and its solution had a pH of 7.

Potassium Arabate--The arabic acid solution was raised to pH 7 with 0.5 N. potassium hydroxide. The amount used was equivalent to the amount of sodium hydroxide needed to prepare the sodium salt.

Calcium Arabate--0.25 grams of calcium hydroxide was added to approximately 100 cc. of a 10 per cent solution of arabic acid. The amount of calcium was slightly in excess, and this excess was filtered off from the solution. 0.213 grams of calcium hydroxide is the exact amount needed to neutralize exactly 10 grams of arabic acid.

Magnesium Arabate--0.4 gram of magnesium carbonate was added to 50 cc. of a 20 per cent solution of arabic acid and the excess filtered off.

Zinc Arabate--In this case zinc chloride was used. 0.58 gram of zinc chloride, which was the exact amount needed to completely react with 10 grams of arabic acid, was used. Hydrochloric acid is also present in the solution giving it a low pH.

Ferric Arabate--Although ferric chloride added to gum arabic will produce a gel, the addition of ferric chloride to arabic acid will not produce a gel unless the pH of the arabic acid solution has been raised to 5 with sodium hydroxide solution.

10 grams of arabic acid in 25 cc. of water was raised to pH 5 with 0.5 N. sodium hydroxide. Then 4 cc. of a 20 per cent ferric chloride solution was added. A very stiff

gel was formed. The amount of ferric chloride added was equivalent to the amount of sodium hydroxide needed for neutralization of the arabic acid. The solution also contains some sodium chloride.

The gel on heating became fluid, but on cooling it returned to its original consistency.

Aluminum Arabate--A 20 per cent solution of arabic was raised to a pH of 7 with 0.5 N. sodium hydroxide. 25×10^{-4} equivalents of aluminum chloride in the form of a 20 per cent solution wereadded. Then more 0.5 N. sodium hydroxide was added to raise the pH to 7. After this addition a gel was formed. No gel would form below pH 7. Sodium chloride is present in the solution.

An attempt was made to prepare the gel by adding sufficient sodium hydroxide solution to compensate for the lowering of the pH of the aluminum chloride solution before addition of the aluminum chloride. This brought the pH of the arabic acid solution above pH 8 and no gel formed.

This aluminum arabate gel prepared by the procedure first given also became fluid on heating, but returned to its original consistency on cooling.

Organic

Organic salts of anesthetic bases have been prepared by Erhardt who mixed an alcoholic solution of the base with an aqueous solution of the arabic acid until the solution showed an alkaline reaction. The solution was then concentrated and shaken with ether for several hours. The solutions were separated, and the solution containing the salt was evaporated to dryness. (37)

As in the case of the inorganic salts, no attempt was made to obtain the organic salts in the dry state.

Experimental and Results

Trimethyl Benzyl Arabate--A 38 per cent technical grade trimethyl benzyl hydroxide was used. 22.3×10^{-3} equivalents of the compound were added to 50 cc. of a 20 per cent solution of arabic acid. This raised the pH of the solution to 7.

Butylamine Hydroarabate--85×10^{-4} equivalents of butylamine were added to 10 grams of arabic acid in 50 cc. of water to raise the pH to 7.

Ethylenediamine Hydroarabate--42.5×10^{-4} equivalents of ethylenediamine were added to 50 cc. of a 20 per cent solution of arabic acid. The amount added indicated that salt formation occurred on both amino groups.

Diethylenetriamine Hydroarabate--Since there are three amino groups present on the diethylenetriamine molecule, 28.3×10^{-4} equivalents of diethylenetriamine would be expected to be used, but in this case 56.6×10^{-4} equivalents were needed. This indicates that salt formation occurred on two of the amino groups.

Triethylenetetramine Hydroarabate--In this case 21.2 x 10^{-4} equivalents of triethylenetetramine would be expected to be used. Actually 42.5 equivalents were used to raise the pH to 7 thus indicating salt formation on two of the amino groups.

Attempted Preparation of the Salts of Dodecylamine and Octadecylamine--These two compounds are insoluble in water and therefore could not be prepared by the methods used for the other amines. 2.2 grams of the hydrochloride salt of octadecylamine was heated with 10 grams of sodium arabate in 50 cc. of water. A cream colored soapy solution resulted. Since it appeared that no reaction occurred no attempt was made to prepare a salt of dodecylamine.

In order to determine whether changes of any significance occurred in the spray-drying of the arabic acid, several physical measurements were made both before and after spray-drying of the arabic acid. The first portion of this section of the thesis gives the results of these measurements.

Following this a thermostability study on the spray-dried arabic acid powder is presented.

Since data obtained from viscosity and surface tension measurements are of definite value when determining the merit of a compound as an emulsifying or suspending agent, therefore, the third and fourth portions of this section deal with the results obtained on the effect of cations and heat on the viscosity of arabic acid solutions, and surface tension measurements of organic salts of arabic acid.

It was observed that an aluminum arabate solution appeared to have properties of dilatancy. The final portion of this section gives a description of the test made and the results obtained.

PHYSICAL CONSTANTS FOR ARABIC ACID

The following measurements were made to determine the effect of spray-drying on the arabic acid.

Viscosity

In order to study the effect of spray-drying on the arabic acid, viscosity curves were made both before and after spray-drying. The curves in Fig. 1 and 2 show the results obtained. No appreciable change in viscosity was noted in any of the batches. All viscosity determinations were made at 30° C., since this was the most convenient temperature to maintain both summer and winter. The Fenske viscosimeter, a modification of the Ostwald viscosimeter, was used. The reason for plotting specific viscosity (η sp)/concentration against concentration will be discussed later.

In the course of the research project three different lots of acacia were used, and it was noted that the viscosity of the arabic acid varied from one lot to another; although each batch within a lot remained quite consistent as shown by the viscosity determinations in Fig. 1 and 2.

In order to determine whether the difference in viscosity was due to the process of preparation or to the acacia itself; viscosity determinations were made on the acacia from the different lots. From the results as shown in Fig. 3, it may be seen that the acacia itself varied in viscosity. The curves in Fig. 3 show also that the charge on the acacia molecules was not a factor in the difference in viscosity. The effect of charge on the viscosity is discussed under the viscosity study.

Equivalent Weight

Determinations were made before and after spray-drying.

Figure 1

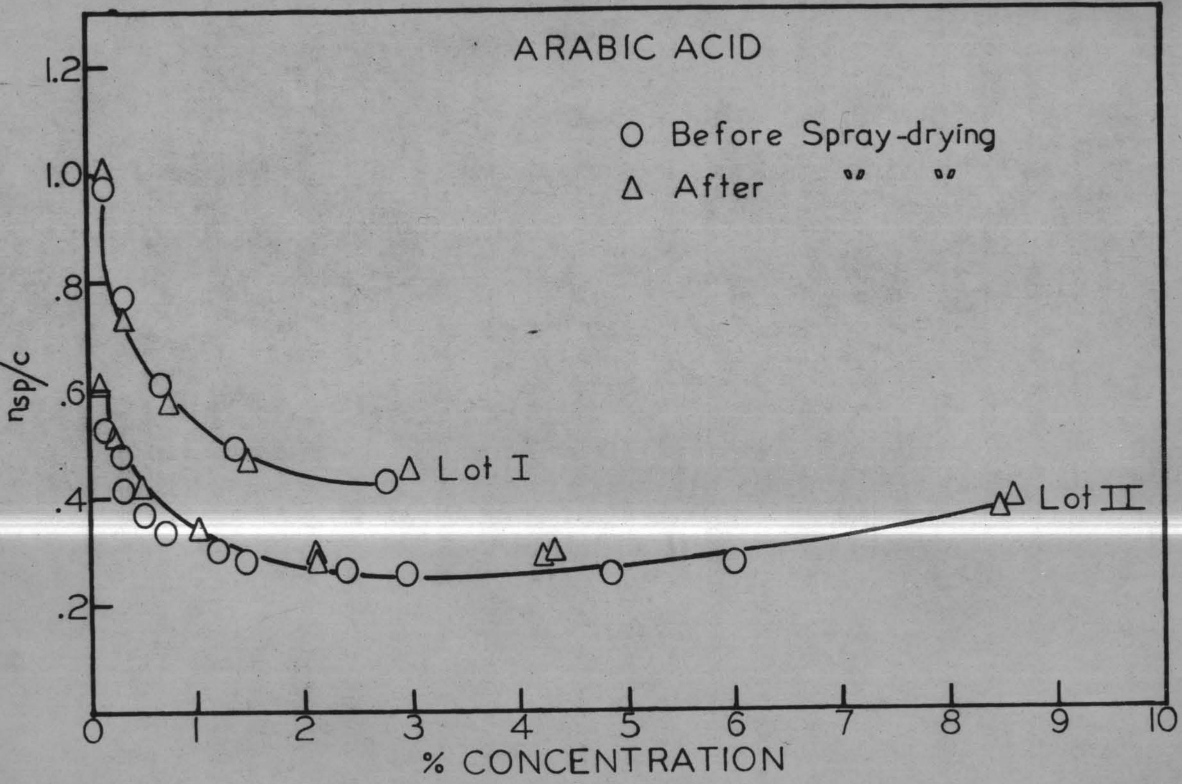
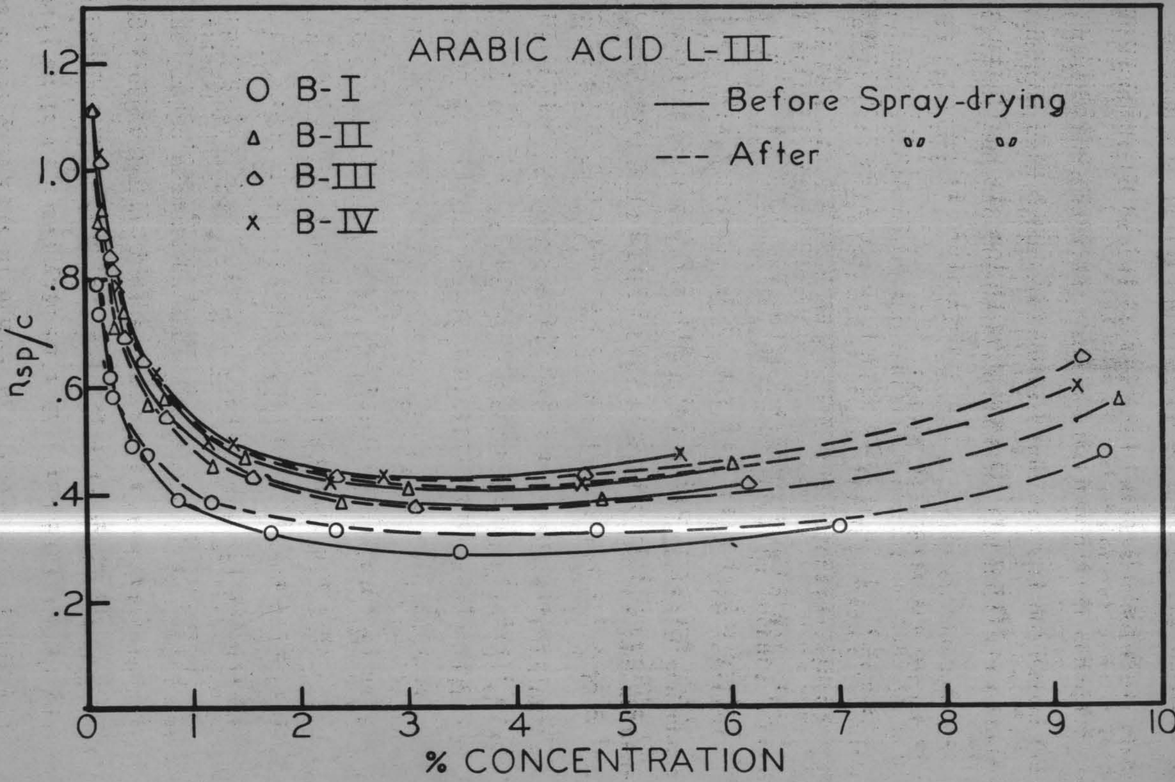

ARABIC ACID
O Before Spray-drying
Δ After " "
Δ Lot I
Δ Lot II
η_{sp}/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 2


ARABIC ACID L-III
O B-I
Δ B-II
◇ B-III
x B-IV
—— Before Spray-drying
--- After " "
η_{sp}/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Batches prepared from Lot III are shown in Table IV. The data given in the table show that no significant change occurred in the equivalent weight and thus no change in the number of free carboxylic acid groups. The differences which were noted may have been due to lactone formation discussed previously in this thesis.

Table IV

Batch No.	Equivalent weights Before	 After
1.	1279	1297
2.	1215	1291
3.	1299	1300
4.	1177	1300

Optical Rotation

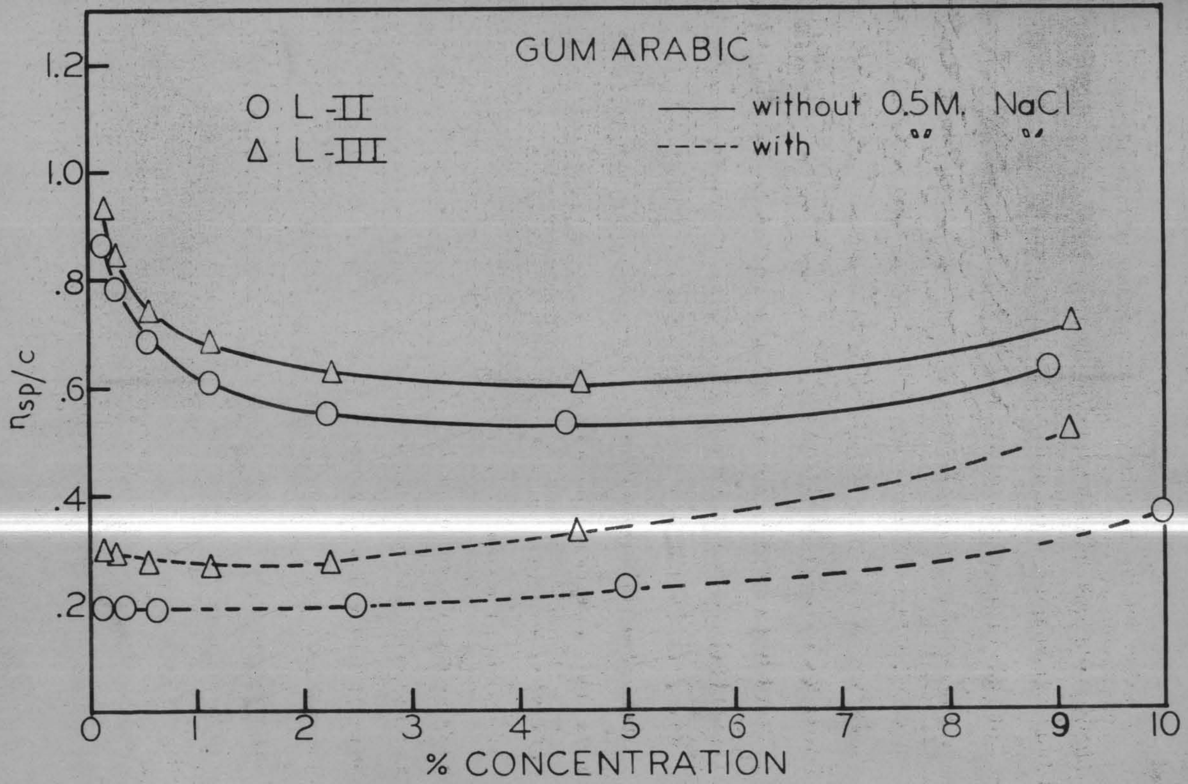
The literature value for the specific rotation was given as -27.86° for a 2 per cent solution . (23) The value obtained for spray-dried arabic acid was -27.44° for a 2.001 per cent solution at 24° C.

pH Titrations

Curves were made as a confirmation of results obtained by others and as a check on arabic acid prepared by the spray-drying method.

All measurements were made on a Beckman pH meter at room temperature (29° C.), and the titrations were made with .1040 N.

Figure 3


GUM ARABIC
○ L-II
△ L-III
—— without 0.5M. NaCl
----- with " "
1.2
1.0
.8
.6
.4
.2
η_{sp}/c
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

sodium hydroxide solution.

5 cc. of an 18.3 per cent solution of arabic acid was used in the first titration. This amount would be equivalent to .915 grams of arabic acid. The titration curve is shown in Fig. 4 and is in agreement with results reported in the literature.

In the second titration one gram of spray-dried arabic acid was used. The titration curve for the spray-dried arabic acid is shown in Fig. 5 and is also in agreement with results reported and with the curve obtained before spray-drying.

It may be noted from the curves that the point of inflection is at pH 7 in both cases.

THERMOSTABILITY STUDY OF ARABIC ACID

In order to determine the value of having the arabic acid in the dry state, a study of its stability to heat was made.

Experimental and Results

Spray-dried arabic acid was heated in an oven at various temperatures and intervals of time. Equivalent weight, solubility, and weight loss determinations were used as a criteria of possible changes which may have occurred on heating. The equivalent weight determinations were made by ti-

Figure 4

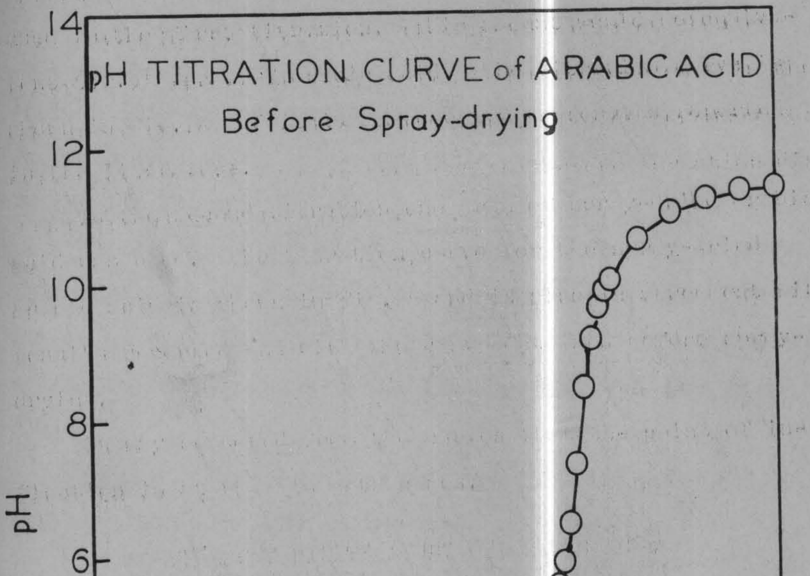
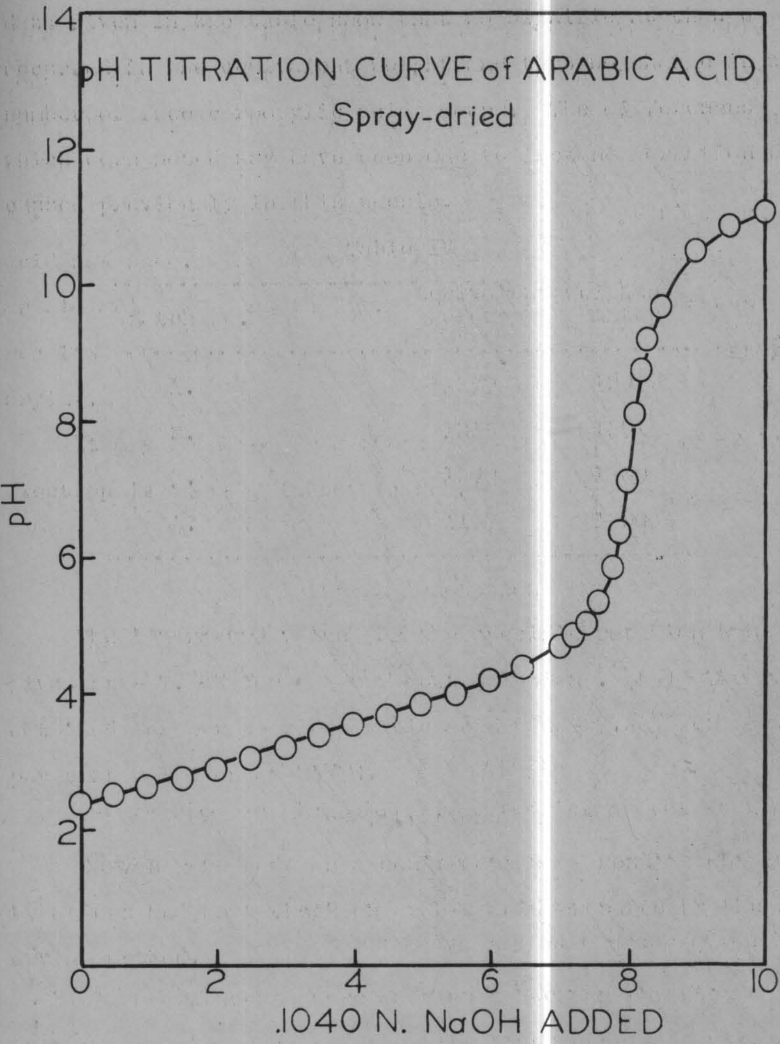

pH TITRATION CURVE of ARABIC ACID
Before Spray-drying
pH
14
12
10
8
6
4
2
0
2
4
6
8
10
.1040 N. NaOH ADDED

Figure 5


pH TITRATION CURVE of ARABIC ACID
Spray-dried
pH
.1040 N. NaOH ADDED
14
12
10
8
6
4
2
0
2
4
6
8
10

trations of samples with .1040 N. sodium hydroxide using bromthymol blue as the indicator. The equivalent weight of the arabic acid before heating was 1178. Table V gives the results obtained.

Table V

Temp.	Time	Equiv. Wt.	Weight loss	Solubility
80° C.	5 min.	1178		soluble
	20 "	"		"
	75 "	"		"
	24 hours	"		"
100° C.	1 hour		1.1%	soluble
125° C.	1 hour		0.8%	soluble
125° C.	24 hours		1.54%	insoluble brown colored powder

Conclusions

The compound was quite stable in the dry state except at high temperatures over a long period of time.

VISCOSITY STUDY

One important factor in the stability of emulsions and suspensions is the viscosity of the preparation. As stated in the introductory portion of this thesis, gum arabic solutions have a low viscosity; but it was thought that the polyvalent salts of arabic acid may have a higher viscosity by linking two or more molecules of the acid together and thus increase the size of the molecule.

Viscosity may be defined as the force per unit area (dynes/sq. cm.) required to maintain a unit difference in velocity between two parallel layers one cm. apart. The equation which is the basis of the capillary tube method for determining co-efficients of viscosity was first derived by J. Poiseuille and is given below.

$$\eta = \frac{\pi P r^4 t}{8vl}$$

where η = viscosity, P = driving pressure, r = radius of capillary tube, t = time, v = velocity, and l = length of the capillary tube. Since the pressure at any time is equal to $hg\rho$ and since h, g, r, v, l, and π are constants the equation reduces to:

$$\eta_1/\eta_2 = \rho_1 t_1/\rho_2 t_2$$

where ρ_1 = the density of the solution, and ρ_2 = the density of the solvent.

The unit of viscosity is the poise which is equal to one dyne sec./cm.^{2}. Viscosity may also be expressed in centipoises which are 1/100 of a poise.

One form in which viscosity of solutions may be expressed is specific viscosity, which is the relative increase of the viscosity of the solution over that of the solvent and is due to the presence of dissolved material. It is calculated by the following formula:

$$\eta_{sp} = \frac{\eta - \eta_0}{\eta_0}$$

where η_{sp} is the specific viscosity, η = the viscosity of the solution, and η_0 = the viscosity of the solvent. (43)

Another expression for viscosity is intrinsic viscosity $[\eta]$. This value is equal to the η_{sp}/c(concentration) at infinite dilution and is obtained when η_{sp} / c is plotted against concentration. The curve obtained is linear in many cases and can be extrapolated to zero concentration to obtain the value for intrinsic viscosity.

Intrinsic viscosity is roughly directly proportional to the molecular weight of long chain molecules and the following equation has been developed:

$$[\eta] = KM^a$$

where M = molecular weight (average) of the compound, and K and a are constants which differ from one type of compound to another. (44)

Effect of Cations on the Viscosity of Arabic Acid Solutions

It has been noted by investigators that colloidal solutions which contain charged colloidal particles exhibit a peculiar type of curve when the specific viscosity/concentration is plotted against concentration. This peculiarity of the curve is attributed to the charge on the molecule. The charge on lyophilic colloids is due to some group on the molecule such as the carboxyl group and is dependent on the degree of dissociation and consequently on pH. The influence of the charge on the viscosity is a phenomenon very typical of this group of macromolecules. It is clear that in the presence of charges the skein will not assume its statistically most probable form but will have a less dense form through the interaction of the charged spots (mutual repulsion) or a more compact form if positive and negative charges are present simultaneously. As a result, the viscosity which is sensitive to the form of the skein, is one of the most important aids in the investigation of systems with charged macromolecules. If there are only charged spots of one sign on the molecule, then the molecule will be relatively spread out. If charged spots of both signs are present, then the molecule will be more compact than corresponds to the most probable state. Since this remodelling of the skein depends on the interaction of the charged spots, but also on the extension of the ion atmosphere around each charged spot. The shape of the molecule will, therefore, also depend on the concentration and nature of the indifferent electrolytes in the solution, since these determine the thickness of the ion atmosphere.

The colloids may be divided according to the nature and sign of the charge of the ionogenic groups and may be divided into three categories as follows:

a. Colloids with acid character which carry only acid groups such as COO^-, OSO_3^-, OPO_3H^-.

b. Colloids with basic character which carry only basic groups such as $-NH_3^+$, $-NH-O(NH_2)_2^+$.

c. Colloids with amphoteric character which carry both types of groups. (45)

Gum arabic from which the arabic acid for the investigation was derived, is an example of the type of colloid given in (a) above. It, therefore, would be expected that a charge would exist on molecules of arabic acid and its salts as it does on gum arabic. It was with this in mind that the investigation which follows was carried out.

When specific viscosity/concentration is plotted against concentration, Kruyt and Bungenberg De Jong have observed for agar solutions and other colloids that as the concentration is decreased the curve decreases to a minimum, then at low concentrations a rapid rise occurs again. An example of this type of curve may be found in the gum arabic curve in Fig. 6. This rapid rise at low concentrations has been attributed by Kruyt and Bungenberg De Jong to the charge on the molecule which affects the viscosity to a larger extent at low concentrations. They called the viscosity due to the charge the electroviscous effect. It was also noted by them that electrolytes added to the colloidal solutions will suppress this charge resulting in a curve which is linear. For colloidal solutions with a negative charge the addition of an electrolyte with a divalent cation will result in a greater suppression of the charge, and a trivalent cation would suppress it still further. Suppression of the charge results in a more compact molecule, therefore, some of the water surrounding the molecule is squeezed out, resulting in less hydration and consequent lowered viscosity.

Self-suppression of the charge by the colloidal particles at a higher concentration has been given as the explanation for the minimum in the curve discussed above. (48)

Experimental and Results

The Fenske viscosimeter used in the study differs from the Ostwald viscosimeter in that the capillary tube is on an angle instead of straight up and down. This decreases the velocity of the solution as it passes through the tube and thus reduces the error resulting, when the energy used in overcoming viscosity is changed to kinetic energy. A correction term for the error known as the Hagenbach-Couette correction is obtained from the following equation:

$$\text{Correction term} = \frac{d(v/t)}{\pi^2 Pr^4}$$

Viscosity determinations were made at various concentrations on gum arabic, arabic acid, and its salts. The salts on which determinations were made were the sodium, potassium, calcium, magnesium, zinc, ferric, aluminum, trimethyl benzyl, butylamine, ethylenediamine, diethylenetriamine, and triethylenetetramine salts of arabic acid. Preparation of these salts has already been described in Part I of this thesis. Determinations were also made on these solutions in the presence of 0.5 M. sodium chloride and 0.5 M. calcium chloride. The solutions were filtered with a sintered glass funnel before the determinations were made. The Westphal balance was used to obtain the specific gravity of the solutions. All determinations were made in a constant temperature bath set at 30°C. Curves were made of the determinations with specific viscosity/concentration plotted against concentration.

Determinations were made on a sodium arabate solution with sodium chloride concentrations of 0.1, 0.5, and 1.0 M. added. This was done to find the most suitable concentration of sodium chloride to give a curve which could be readily extrapolated to zero. The 0.5 M. concentration appeared to be the best and was therefore used as stated above.

The curves are shown in Fig. 7.

Since $\ln\eta/c$ is identical with η_{sp}/c as specific viscosity approaches zero, $\ln\eta/c$ may also be plotted against concentration as shown for sodium arabate in Fig. 8. An extrapolation of the curve obtained when sodium chloride was used should give the same value when η_{sp}/c is plotted against c.

It may be noted from the curves in Fig. 9 and Fig. 10 that a considerable difference exists in the viscosity curves of sodium arabate and arabic acid without the presence of salt, but in the presence of salt the viscosity was the same. One possible explanation is that the higher viscosity of the sodium arabate was due to the higher charge on the molecule. Carboxyl colloids lose their negative charge quite readily at a low pH, but in the region of neutrality ionization is practically complete, thus the charge would be high. (45) The gum arabic curve (Fig. 6) without added salt was found to be between that of arabic acid and sodium arabate as might be expected from the above explanation, since gum arabic has a pH of 5. This would be between the pH 7 of the sodium arabate and the pH 2.4 of arabic acid, therefore, the amount of ionization should be between that of the sodium arabate and arabic acid. Of course, the fact that gum arabic is a mixture of potassium, calcium, and magnesium salts may also be a factor. The potassium salt curves in Fig. 11 are of the same magnitude and appearance as the sodium salt which was expected.

It might be expected that the curves for the divalent salts of calcium, magnesium, and zinc in Fig. 12, 13 and 14 would show a higher viscosity than the monovalent salts, but this was not found to be true. In the case of the divalent salts the curves made without salt were much lower than the monovalent arabic acid salts and also did not display the rapid rise in viscosity as shown by the monovalent salts and by arabic acid at low concentrations. Apparently, instead of an intermolecular attraction linking the carboxyl groups of two molecules, an intramolecular attraction occurred linking two carboxyl groups on one molecule thus making the molecule more compact resulting in less hydration and lowered viscosity. It was noted that the curves for the zinc salt were somewhat lower than the curves for the calcium and magnesium salts. This probably was due to the fact that zinc chloride was used to prepare the zinc salt. The pH of the solution would be lower than the other two salts as a result of the hydrochloric acid formed. There would then be a suppression of charge because of the lowered pH resulting in a lower viscosity.

The trivalent salts might be expected to have a high viscosity. This was found to be true as shown from the curves for ferric and aluminum arabate in Fig. 15 and 16. The viscosity of the ferric arabate rises very rapidly in the region between 8 and 9 per cent. The aluminum arabate viscosity does not rise as rapidly but does have a high viscosity in the region of 20 per cent (see Fig. 24). The curves for both compounds decrease very rapidly at low concentrations with the curves ending up much lower than that of any of the other salts. An explanation for the results obtained is that the aluminum and ferric ion have a tendency to pull carboxyl groups toward them, and in the case of a concentrated arabic acid solution the tendency was toward an intermolecular attraction with an increase in the size of the molecule resulting in increased hydration and higher viscosity. In dilute solution with less molecules present, the tendency is apparently toward an intramolecular attraction resulting in a more compact molecule, less hydration and low viscosity.

The curves for butylamine hydroarabate (Fig. 17) and sodium arabate (Fig. 10) are both of the same magnitude and appearance. This indicates that the butylamine salt must be ionized to the same extent as the sodium salt, and thus the charge must play an equally important part in the viscosity of the butylamine salt as with the monovalent salts.

The trimethyl benzyl arabate curve without salt (Fig. 18) has the same appearance as the monovalent salts but shows a lower viscosity. An explanation for this is that the trimethyl benzyl hydroxide used to prepare the salt has a positive charge on the molecule, therefore, it would be expected to suppress the negative charge of the arabic acid and thus lower the viscosity.

The curves for ethylenediamine hydroarabate (Fig. 19), diethylenetriamine hydroarabate (Fig. 20), and triethylenetetramine hydroarabate (Fig. 21) are all similar in magnitude and appearance, and these curves are also similar to the curves obtained with the divalent inorganic salts. This would indicate that the triamine and tetramine react with arabic acid the same way as ethylenediamine and that all three compounds react like the divalent salts. It may also be observed that the curves which were made without the presence of salt decrease at lower concentrations rather than increase. This may probably be due to an intramolecular attraction rather than an intermolecular attraction.

It may be noted, that sodium chloride or calcium chloride added to a solution of arabic acid or any of its salts, lowers the viscosity curves of these solutions. Calcium chloride lowered the curves to a greater extent than sodium chloride. This indicates a negative charge in each case as might be expected.

Figure 6

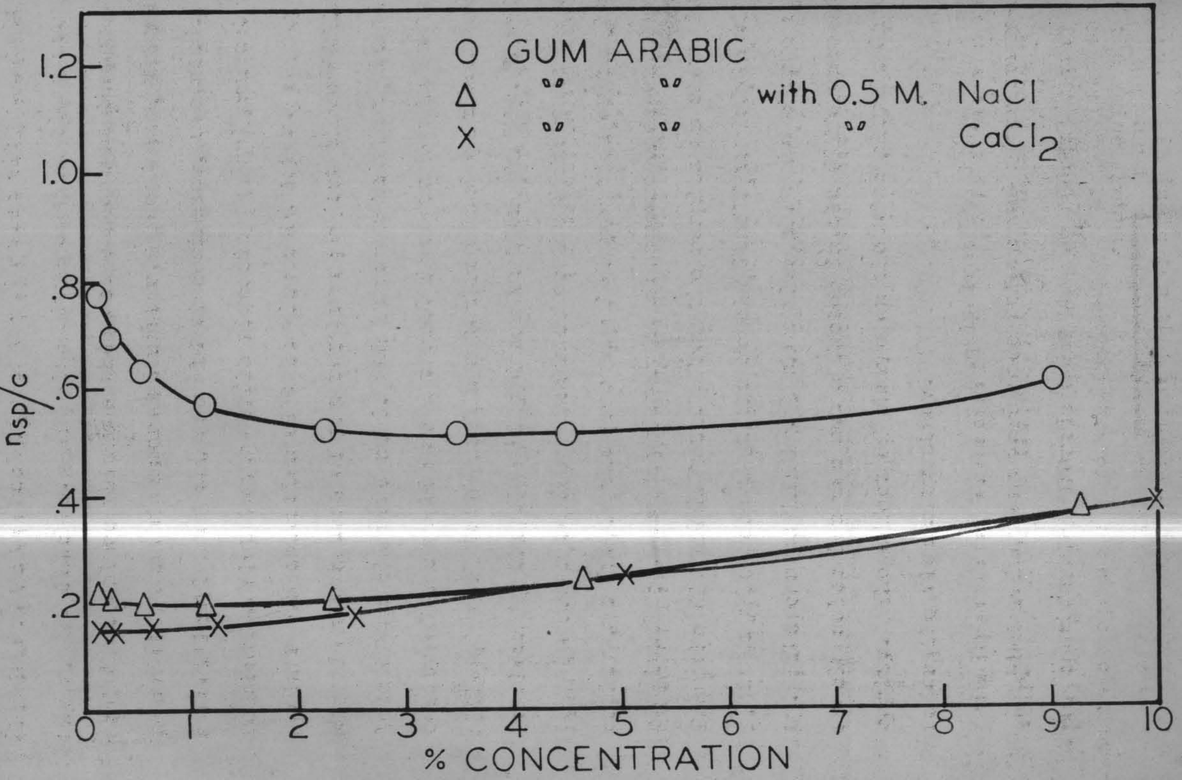

O GUM ARABIC
Δ " " with 0.5 M. NaCl
X " " " CaCl$_2$
1.2
1.0
.8
.6
.4
.2
nsp/c
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 7

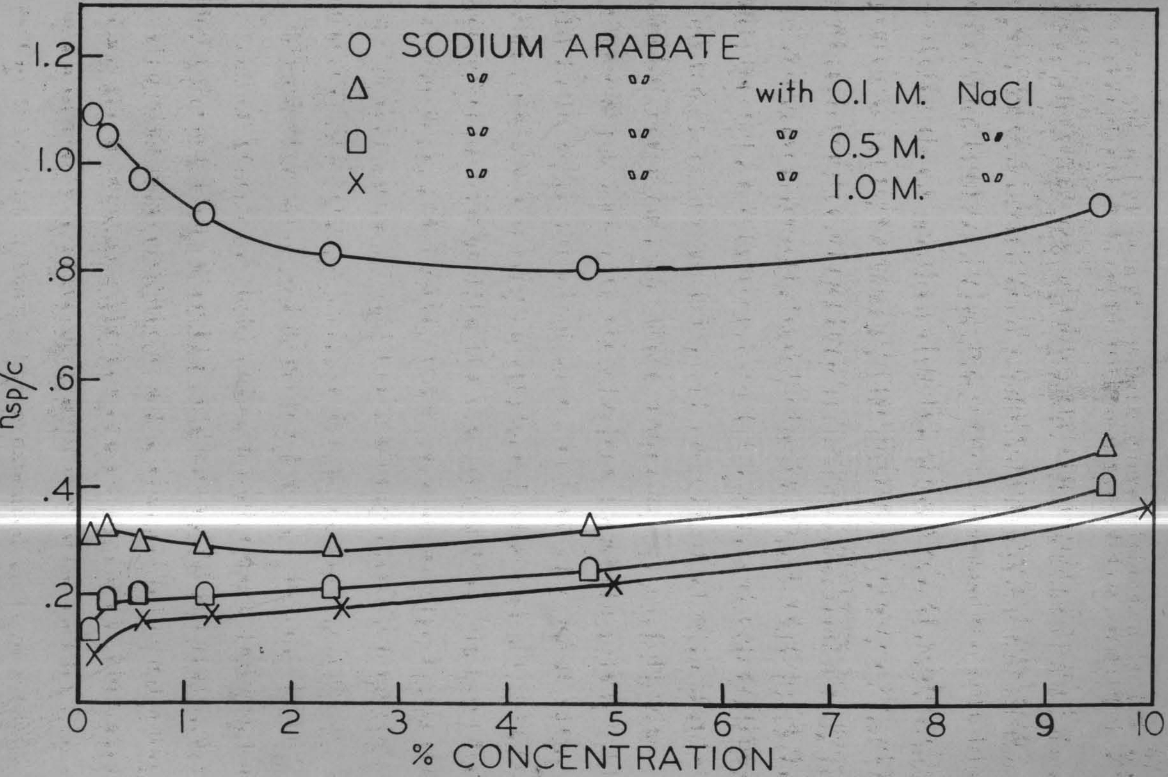

○ SODIUM ARABATE
△ " " with 0.1 M. NaCl
◻ " " " 0.5 M. "
X " " " 1.0 M. "
ηsp/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 8

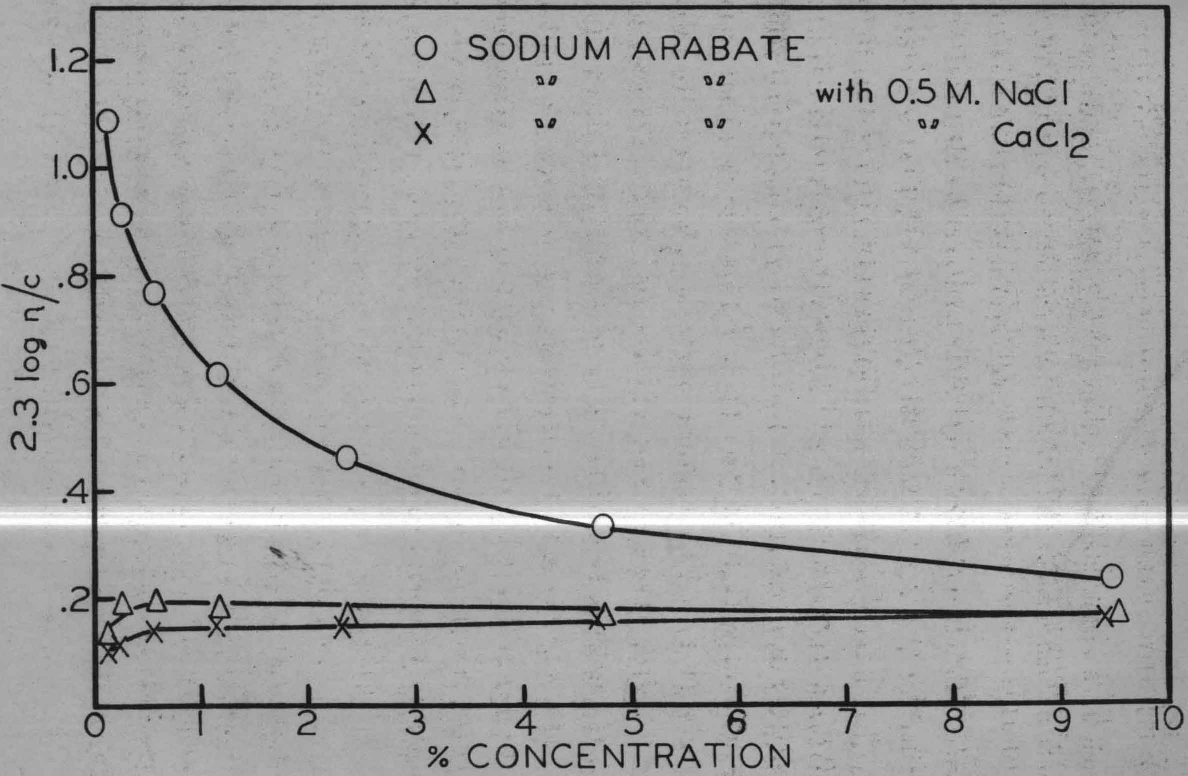

O SODIUM ARABATE
Δ " " with 0.5 M. NaCl
X " " " CaCl2
2.3 log n/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 9

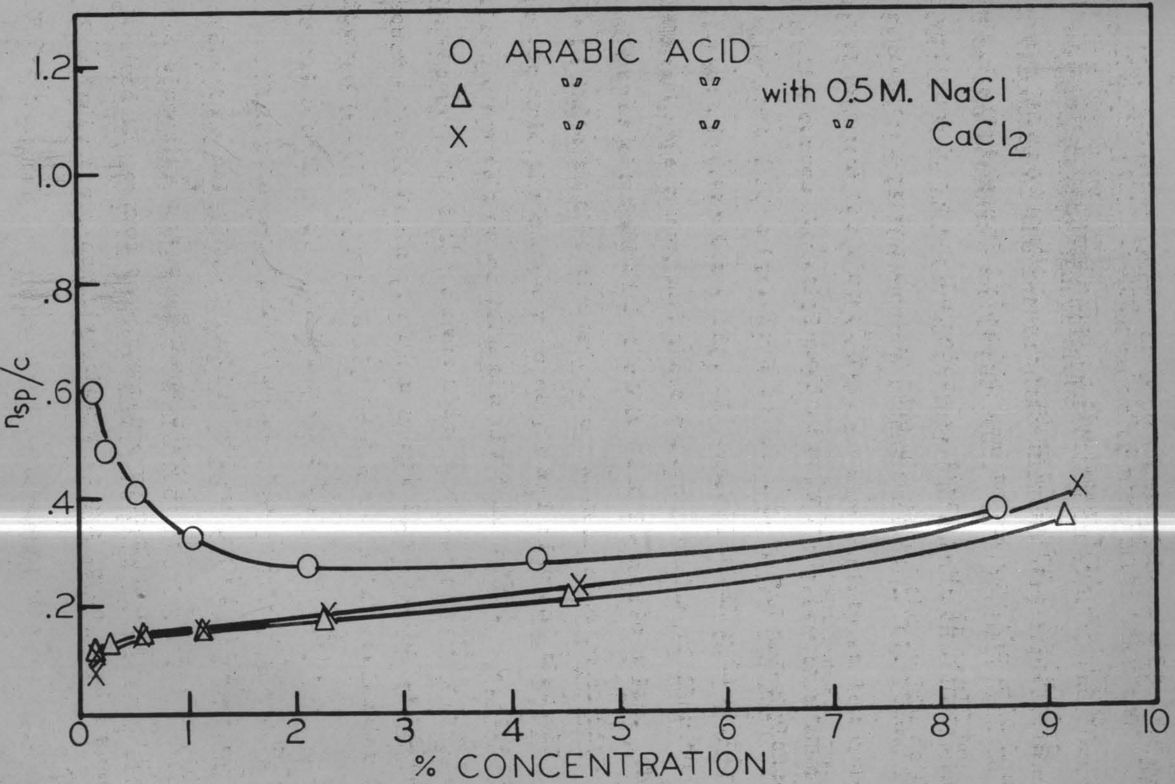

O ARABIC ACID
Δ " " with 0.5 M. NaCl
X " " " CaCl2
n_{sp}/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 10

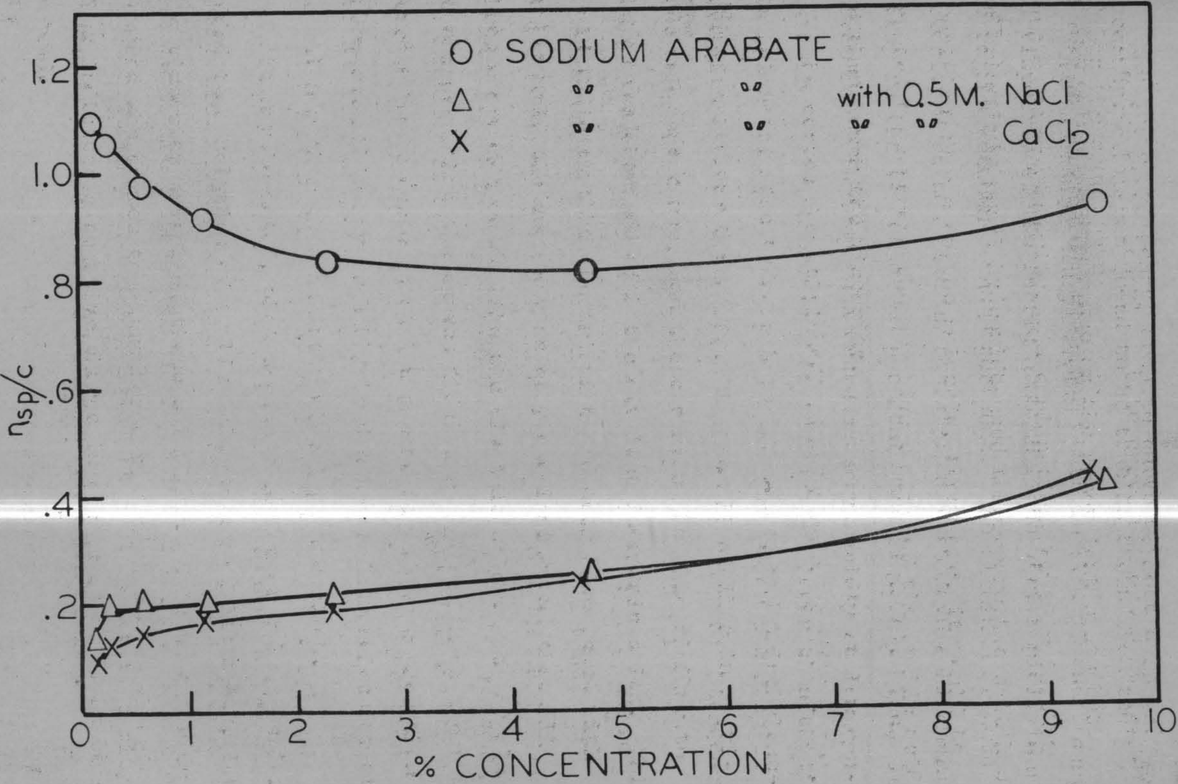

O SODIUM ARABATE
Δ " " with 0.5 M. NaCl
X " " " " CaCl2
ηsp/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 11

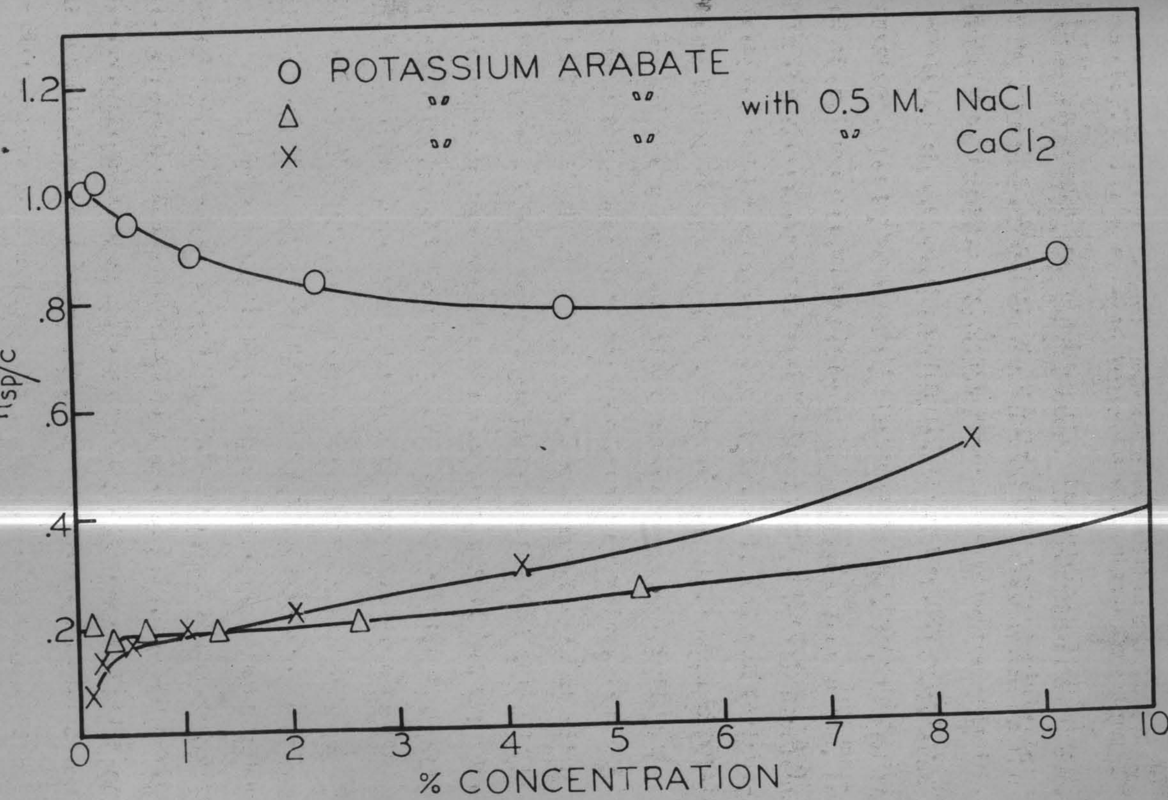

O POTASSIUM ARABATE
Δ " " with 0.5 M. NaCl
X " " " CaCl2
nsp/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 12

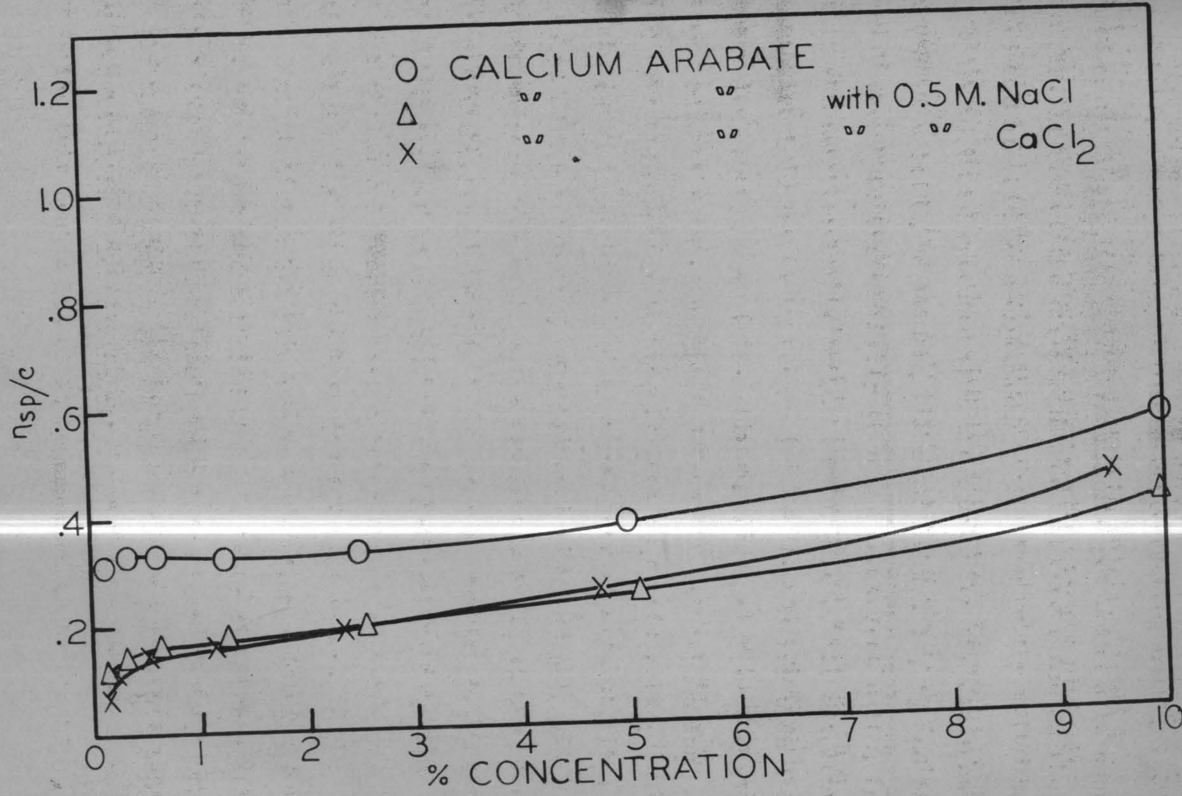

O CALCIUM ARABATE
Δ " " with 0.5 M. NaCl
X " " " " CaCl$_2$
1.2
1.0
.8
.6
.4
.2
ηsp/c
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 13

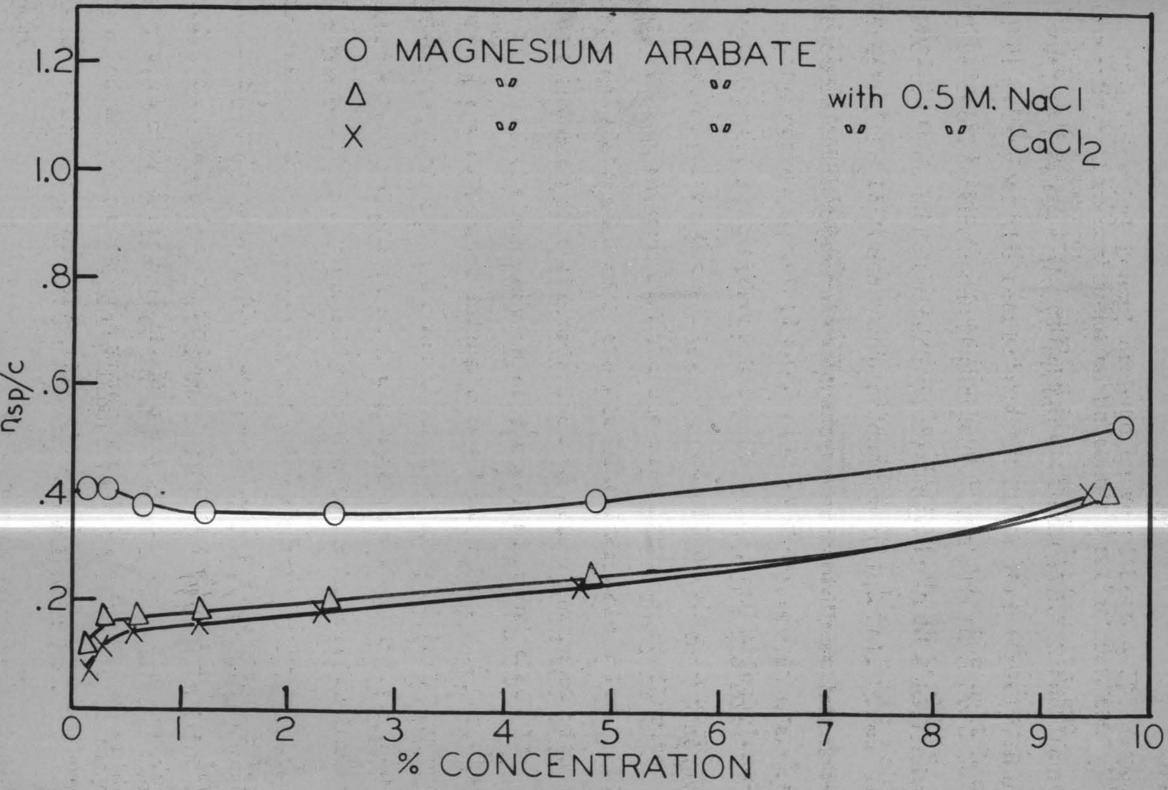

○ MAGNESIUM ARABATE
Δ " " with 0.5 M. NaCl
X " " " " $CaCl_2$
η_{sp}/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 14

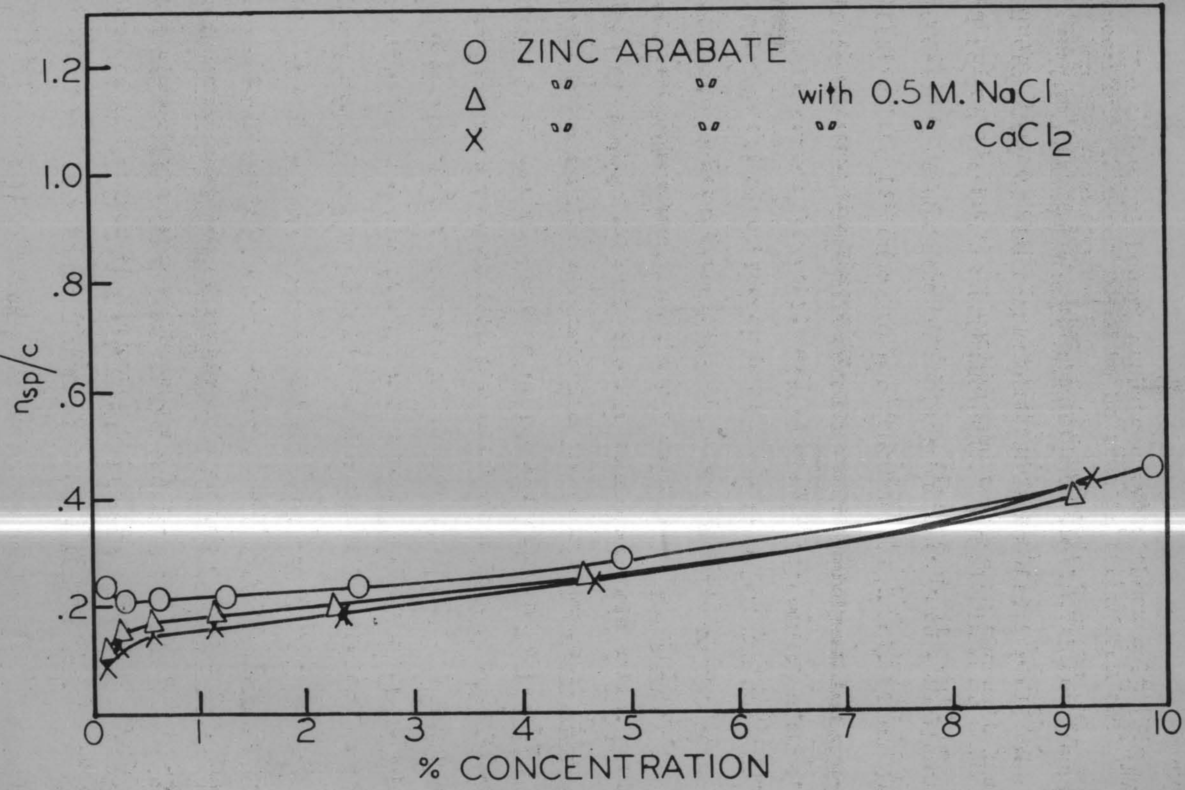

O ZINC ARABATE
Δ " " with 0.5 M. NaCl
X " " " " CaCl2
nsp/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 15

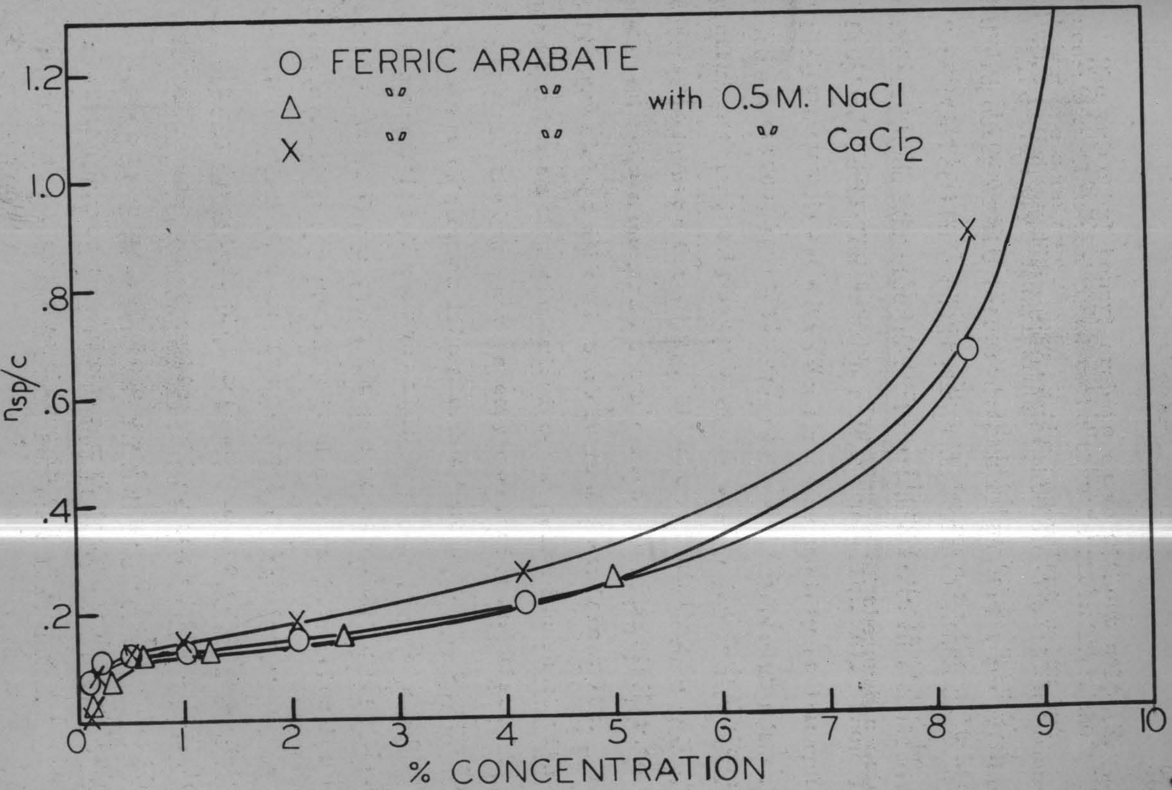

○ FERRIC ARABATE
△ " " with 0.5 M. NaCl
X " " " $CaCl_2$
η_{sp}/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 16

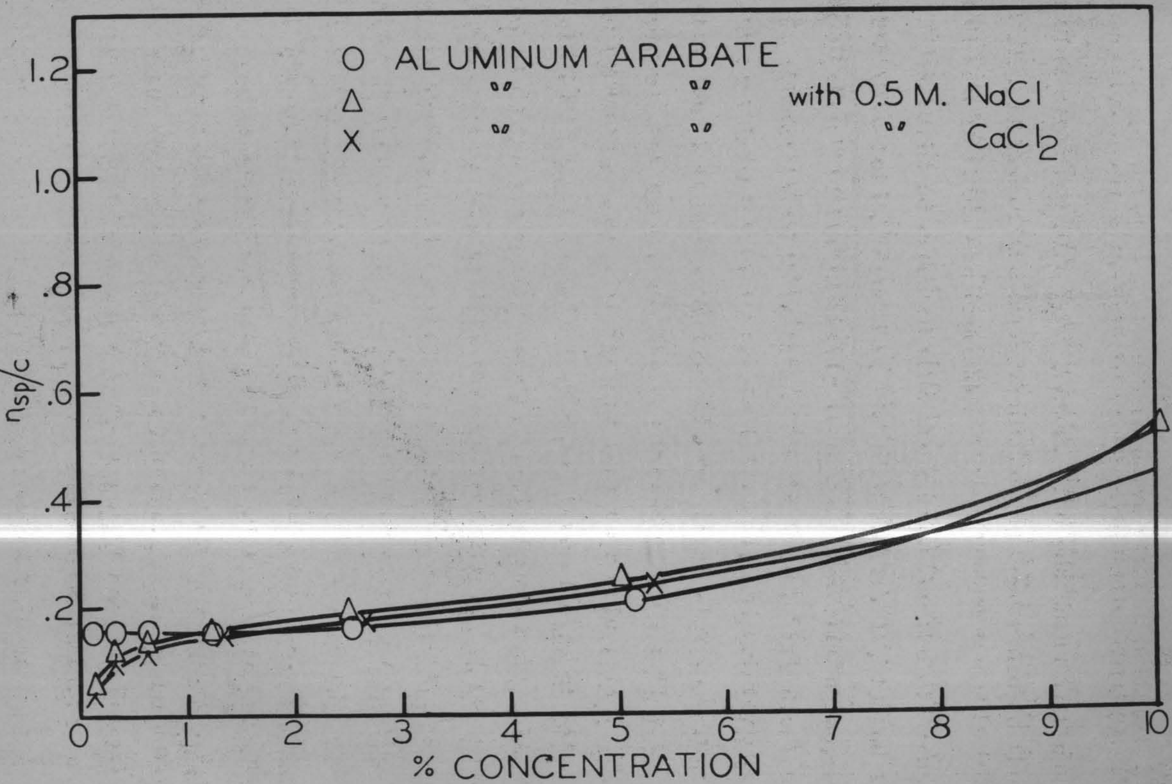

O ALUMINUM ARABATE
Δ " " with 0.5 M. NaCl
X " " " CaCl2
nsp/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 17

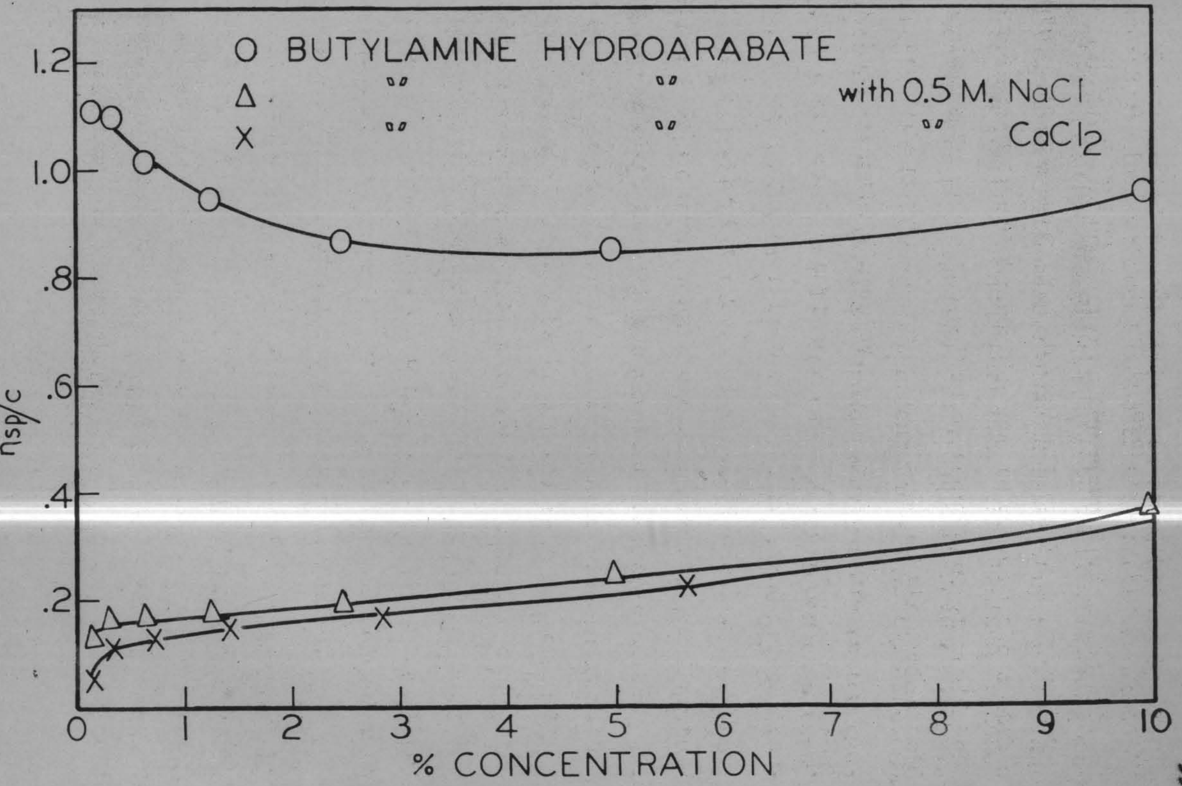

O BUTYLAMINE HYDROARABATE
Δ " " with 0.5 M. NaCl
X " " " CaCl2
ηsp/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 18

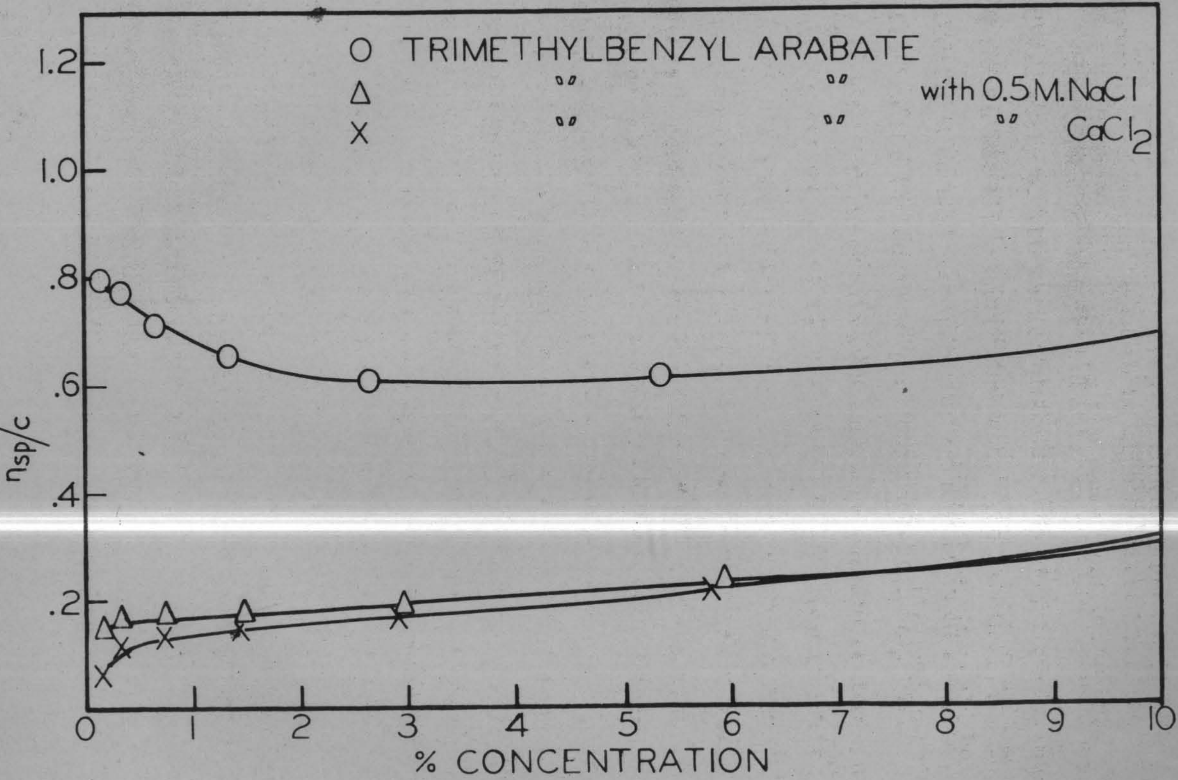

O TRIMETHYLBENZYL ARABATE
Δ " " with 0.5 M. NaCl
X " " " CaCl2
ηsp/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 19

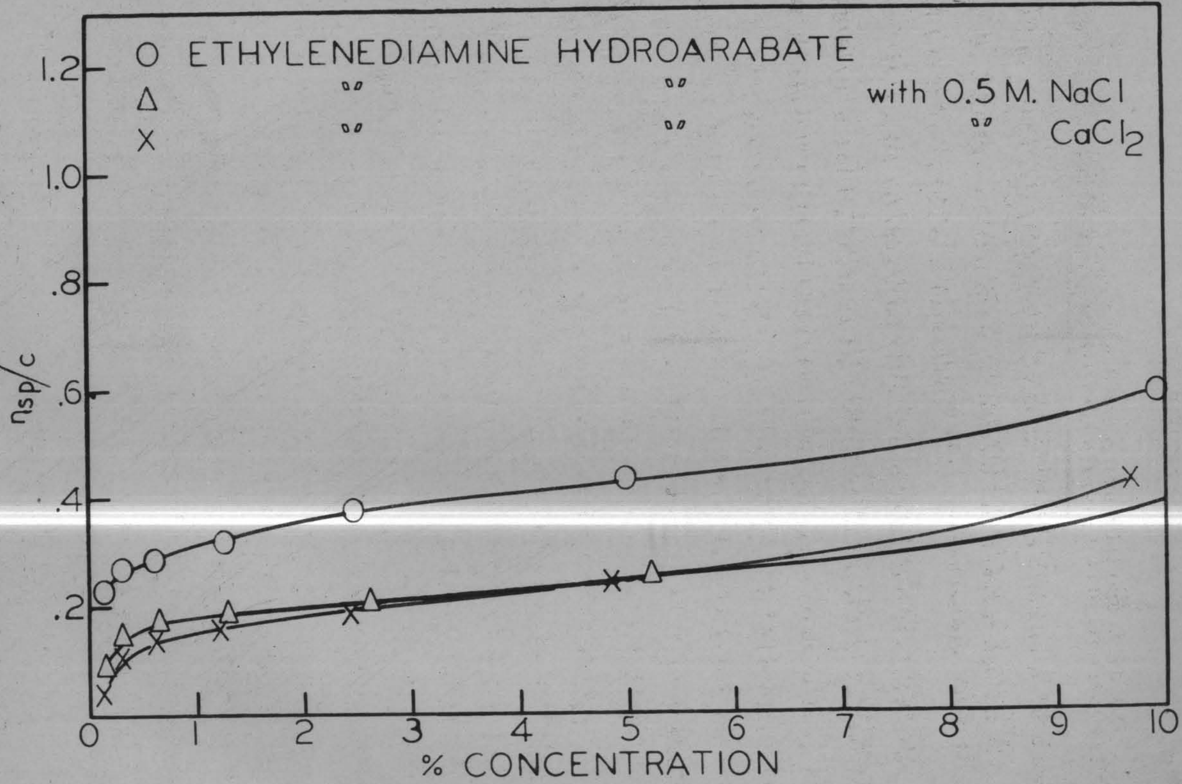
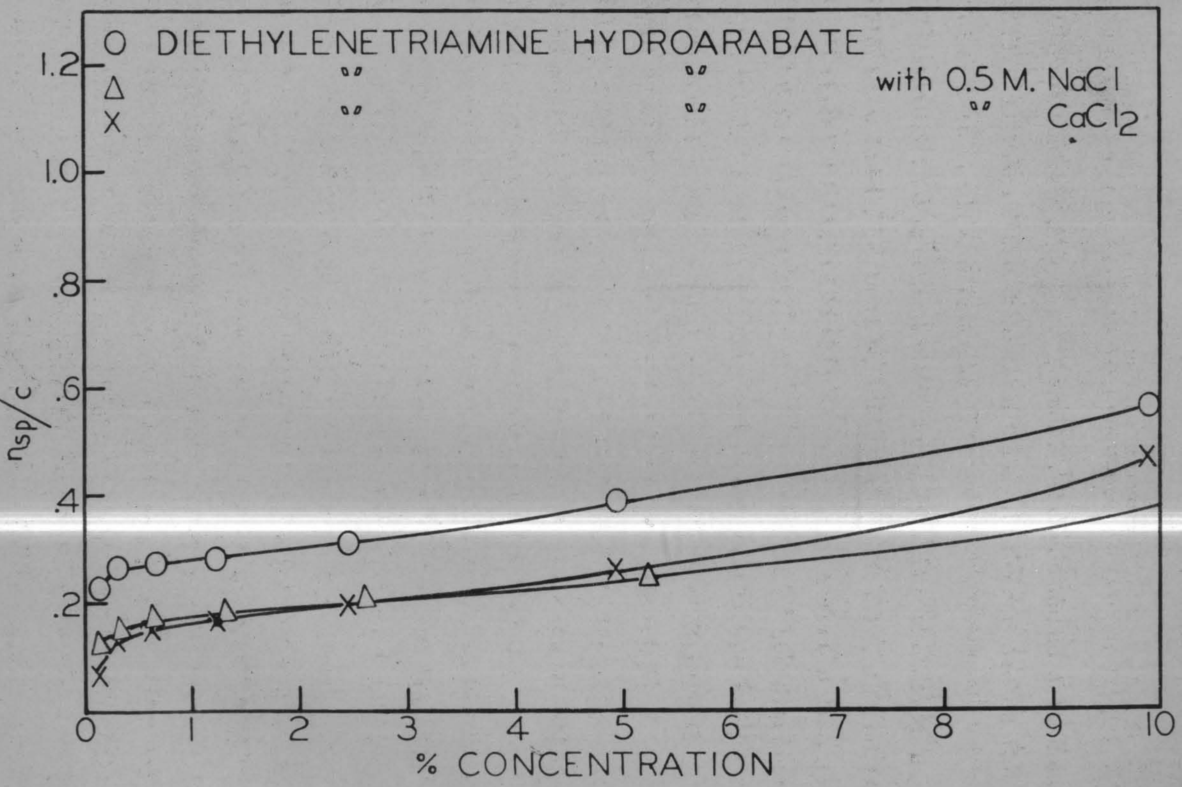
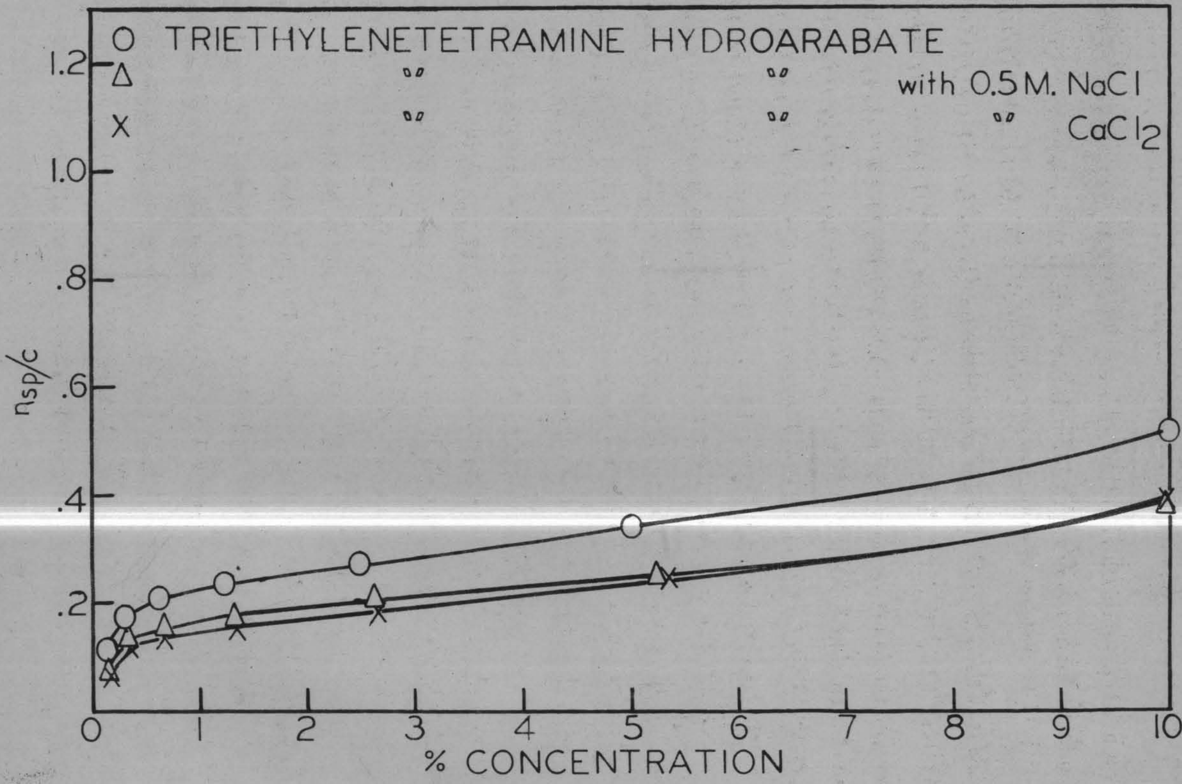

O ETHYLENEDIAMINE HYDROARABATE
Δ " " with 0.5 M. NaCl
X " " " CaCl2
1.2
1.0
.8
.6
.4
.2
nsp/c
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 20



O DIETHYLENETRIAMINE HYDROARABATE
Δ " " with 0.5 M. NaCl
X " " " CaCl2
n_{sp}/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Figure 21


O TRIETHYLENETETRAMINE HYDROARABATE
Δ " " with 0.5 M. NaCl
X " " " CaCl2
n_{sp}/c
1.2
1.0
.8
.6
.4
.2
0
1
2
3
4
5
6
7
8
9
10
% CONCENTRATION

Effect of Heat on the Viscosity of Arabic Acid Solutions

As part of the viscosity study to find an arabic acid derivative which could be more useful than gum arabic, the effect of heating on the viscosity of an arabic acid solution was studied.

It was theorized that under proper conditions of temperature and concentration an increase in the viscosity of arabic acid could be obtained. This increase would probably be due to an esterification reaction between a carboxyl group of one molecule and the hydroxyl group of another thus doubling the size of the molecule. Since the size of the molecule is a function of the viscosity, an increase in size should increase the viscosity. Such an increase would be of definite value pharmaceutically. Although gum arabic has been the emulsifying agent of choice throughout the years, the viscosity was never high enough to prevent creaming of the emulsion.

At low concentrations of arabic acid it might be expected that there would be hydrolysis of the acid, since gum arabic solutions hydrolyze on standing over a period of time. This is due to the acidity of the solution, the branched chains and the prevalence of 1,6 and 1,3 linkages in the molecule. (17) At high concentrations the amount of water present is small, and an esterification reaction would be more likely to occur.

Experimental and Results

A 40% by weight solution of arabic acid was prepared and heated for 90 minutes in a boiling water bath. It was then diluted to 9.97 per cent and the viscosity determined at 30° C. The specific viscosity/concentration (η_{sp}/c) was calculated to be 0.264, whereas a 9.27 per cent arabic acid solution which had not been heated had a η_{sp}/c of 0.647. 40% by weight solutions were also heated for periods of 15, 30, and 60 minutes. The results showed a steady decrease in viscosity with increase in time.

50% by weight solutions were then prepared and heated for the same intervals of time under the same conditions of temperature. The results also showed a steady decrease in viscosity with increasing time.

60% by weight solutions were also prepared and the same procedure was carried out except that the intervals of time were 5, 10, 15, 30, 60 and 90 minutes. The solutions heated for 30, 60, and 90 minutes contained many particles of gel, and no viscosity determinations were made on these solutions. The viscosity determinations made on the solutions heated for 5, 10, and 15 minutes showed an increase in viscosity.

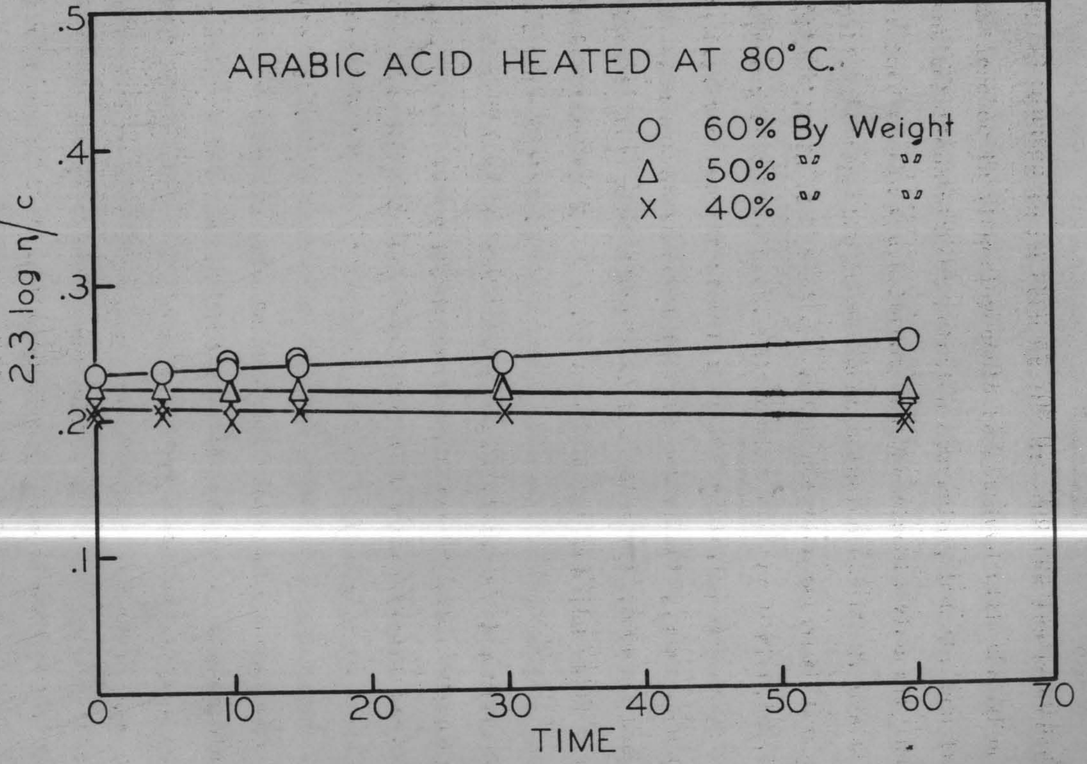
Because of the gelation which occurred, the 60 and 50 per cent solutions were heated for intervals of 5, 10, 15, and 30 minutes in an oven at 70° C. The results showed that an increase in viscosity could be obtained with the 60 per cent solutions without gelation occurring, but the results obtained were not consistent and the rise in viscosity was small. Heating the 60 per cent solution at 80° C. was then tried allowing 15 minutes for the solution to reach the temperature of the oven. Although there was a rise in viscosity, the results were not reproducible.

A constant temperature bath set at 80° C. was then tried. Five minutes were allowed for the solutions to reach the temperature of the bath. As before the results still were not reproducible.

It was thought that the inconsistent results were due to lack of uniformity in heating, therefore, the Erlenmeyer flasks which had been used were replaced by test tubes. This was done to allow for more uniform heating of the arabic acid.

Another factor which had not previously been taken into consideration was uniformity in the mixing of the arabic acid with the water. As a result of the above two changes the data became more reproducible. A plot was made of the results for 40, 50 and 60 per cent with 2.3 log η/c as the ordinate and time as the abscissa. The curves in Fig. 22 shows a linear rise and fall in viscosity with time dependent on the concentration.

Figure 22


ARABIC ACID HEATED AT 80° C.
○ 60% By Weight
△ 50% " "
X 40% " "
2.3 log η/c
.5
.4
.3
.2
.1
0
10
20
30
40
50
60
70
TIME

Conclusions

The procedure does show promise that a rise in viscosity can be obtained, but the rise isn't sufficiently high to be of value. If the arabic acid solution could be prepared at a still higher concentration, there could conceivably be a two to three-fold rise in viscosity.

SURFACE TENSION MEASUREMENTS

Since data obtained from surface tension measurements are also of definite value in determining the worth of a compound as an emulsifying agent, surface tension measurements were made on the organic salts of arabic acid.

For stability and greater ease of emulsification it is necessary to have a low interfacial tension at the interface between the aqueous phase and the oil phase. For example, an interfacial tension of ten dynes requires considerable amount of energy to bring about emulsification. Emulsification will take place on vigorous shaking with an interfacial tension of 5 dynes; while in the case of an interfacial tension of one dyne, emulsification will take place with little agitation. The tension at the interface may be calculated from Antonoff's Rule which states that the interfacial tension is equal to the difference in surface tension of the two liquids. (43)

The surface tension at any interface is a force causing globules to coalesce, resulting in larger oil or water globules and possible breaking of the emulsion. The substances used as emulsifying agents collect at the interface and aid in lowering the interfacial tension. Gum arabic, an emulsifying agent which is soluble in the aqueous phase, does not lower the surface tension of the aqueous phase to any extent, therefore, the measurements given below were made with the possibility that the organic salts in solution would have a lower surface tension.

Experimental and Results

All measurements were made with the Cenco-du Nuoy Tensiometer at the temperatures shown in the table. Calibration of the instrument was made using a one gram weight. The average reading on the scale for the one gram weight was 58.47. The circumference of the ring used was 6.010 cm. The constant for the instrument was determined by the following equation:

$$K = \frac{M g}{2 L S}$$

where M = the weight added, g = 980.3, L = circumference of ring, and S = scale reading. The constant as determined by the above equation was 1.395. It was multiplied by the scale reading obtained for the various solutions to change the values to dynes/cm. No corrections were made for temperature and other factors. Table VI shows the results obtained. The determinations were made on 10 per cent solutions, the preparation of which is given in Part I of this thesis.

Table VI

Name of Compound	Average Observed Reading	Surface Tension	Temp.
Arabic Acid	40.2	56.04	23° C.
Trimethyl Benzyl Arabate	36.2	50.50	23° C.
Diethylenetriamine Hydroarabate	36.3	50.63	22° C.
Triethylenetetramine Hydroarabate	37.9	52.87	23° C.
Butylamine Hydroarabate	37.7	52.59	22° C.
Ethylenediamine Hydroarabate	37.4	52.17	22° C.

Conclusions

As seen from the table there was some lowering of surface tension in the case of the organic salts, but the difference was not too significant.

TEST FOR DILATANCY IN ALUMINUM ARABATE

It was observed in the preparation of aluminum arabate solutions for viscosity determinations given in the previous section, that a 20 per cent aluminum arabate gel appeared to be stiffer and more viscous when stirred rapidly, therefore, determinations were made to ascertain whether the compound has dilatant properties.

Dilatancy is defined as the property of certain suspensions in which the resistance to flow increases at a greater rate than the increase in rate of flow. A classic example of dilatancy is shown by quicksand or wet sea sand. If the surface is struck sharply, the sand is rigid and solid; but slow, sustained stirring causes the sand to flow. Directly opposite in character is thixotropy, in which a suspension loses part of its consistency when agitated but regains its original consistency when allowed to rest. This is in contrast to Newtonian flow in which the rate of shear is directly proportional to shearing force. (1)

A rotational type viscosimeter is one means of studying these types of phenomena. Typical examples are the Couette and MacMichael viscosimeter.

The MacMichael viscosimeter, which was used for the test, consists of a spindle plunger assembly supported by a wire. This plunger dips into the sample which is contained in a rotatable cup. When the cup is rotated, the spindle plunger assembly is subjected, through the sample, to rotational forces which are related to the viscous properties of the sample. The assembly continues to rotate until the torsional reaction of the wire suspension just balances the torque exerted by the cup through the sample. Then, a dynamic equilibrium results and the force is measured in MacMichael units. By calibration of the wire used with a suitable standard, the MacMichael units may be converted to centipoises. The following equation is used for the conversion;

$$K = \frac{\eta HN}{M^{o}}$$

where K = the constant, η = viscosity in centipoises, H = depth of submergence of the plunger, N = number of revolutions of the cup per minute, and M^{o} = deflection in MacMichael degrees. After K has been determined with a compound of known viscosity, the formula is then used to solve for the viscosity of the compound desired.

$$\eta = \frac{KM^{o}}{HN}$$

In order to determine whether a suspension is Newtonian or dilatant, a plot is made of deflection vs. revolutions per minute. If the suspension is Newtonian, the curve will be linear and pass through the origin. A suspension which has dilatant properties will give a curve which shows a rapid increase in deflection with a small increase in rate of flow. (1)

Experimental and Results

A #30 wire was used on the MacMichael viscosimeter. Calibrations were made with glycerol at 25° C. The specific gravity was 1.25, and the viscosity for glycerol of this specific gravity was 366. (46) The K values were determined at 3 different rates of shear, and the results are shown in Table VII. The depth of submergence or H value was 4 cm.

Table VII

M°	RPM.	K
10	25.3	3700
15	36.6	3570
18	44.5	3610

The K value which was used in the calculation of the viscosities was 3600 an average of the K values in Table VII.

Determinations were then made on a 20 per cent aluminum arabate solution at several different rates of shear. A plot of deflection vs RPM or rate of shear is shown in Fig. 23.

The linear curve shown indicates that the gel is not dilatant but has thixotropic properties.

The curve shown in Fig. 24 illustrates the effect of rate of shear on the viscosity. The curve also illustrates its thixotropic properties.

Figure 23. Curve obtained for aluminum arabate gel with a MacMichael viscosimeter.

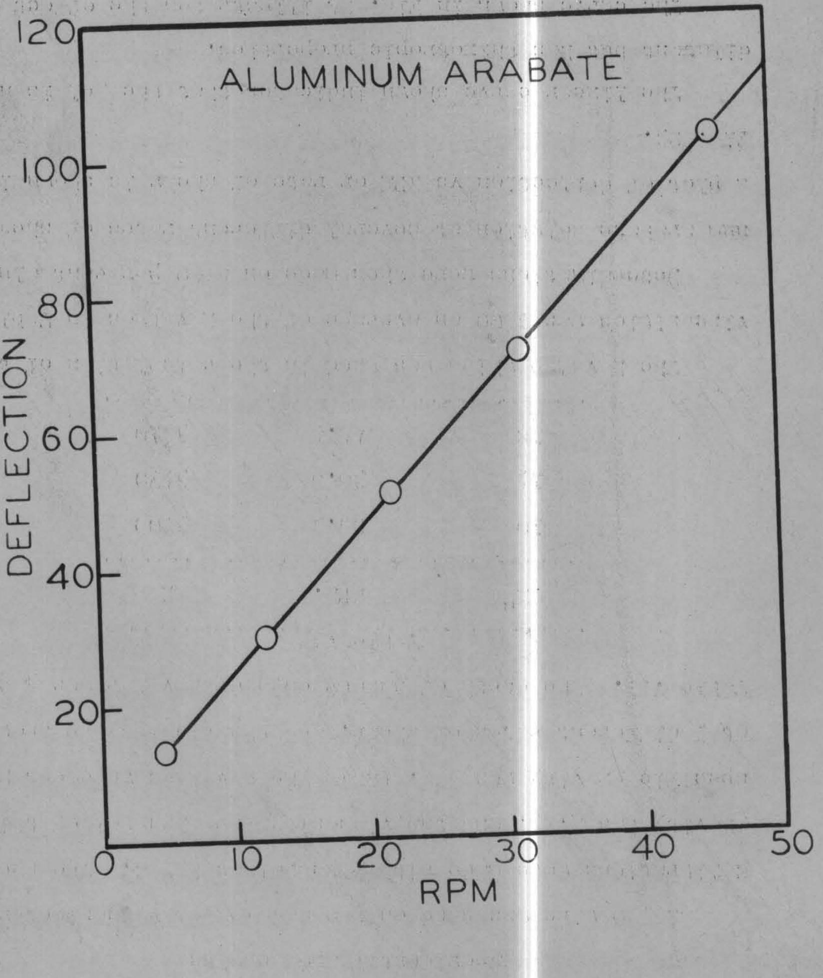
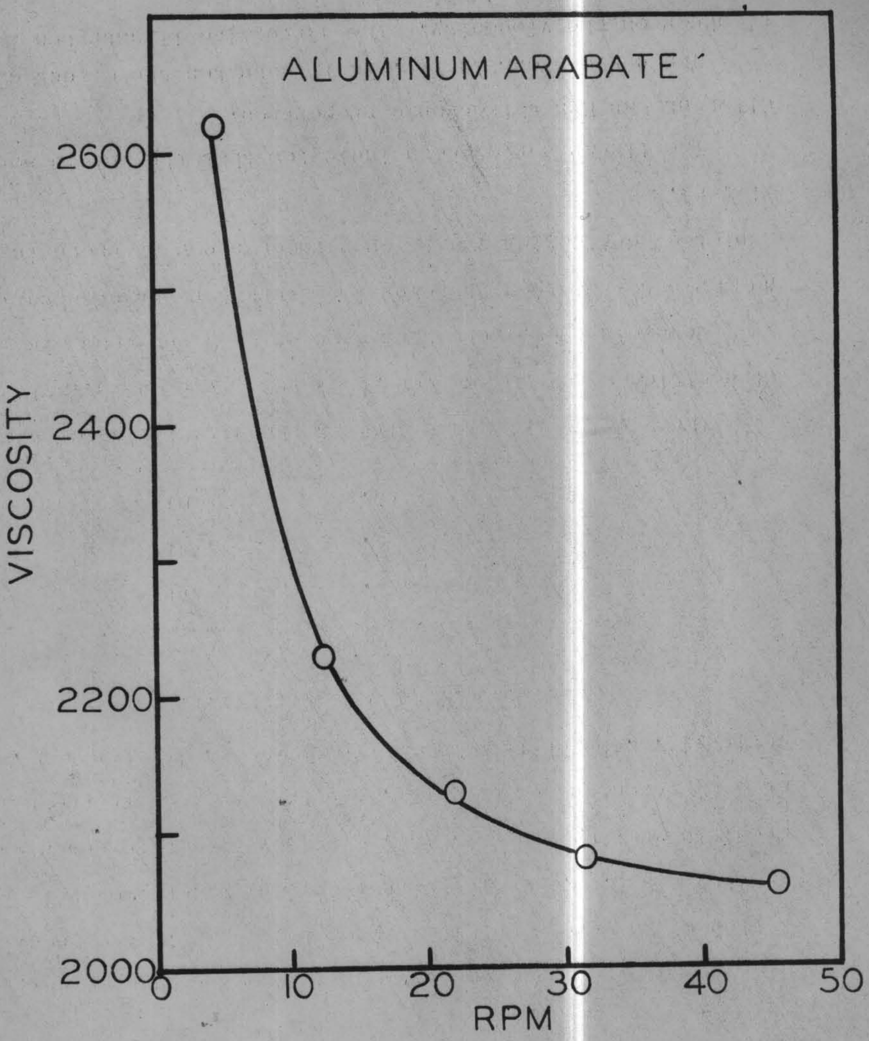


Figure 24. Curve obtained with a MacMichael viscosimeter.



From the data obtained in the viscosity study and surface tension measurements given in the preceding sectinn of this thesis, several conclusions applicable to pharmaceutical emulsions are implied.

First of all, in the viscosity study it was shown that the arabic acid solution had the lowest viscosity of any of the solutions considered, therefore, one might conclude that emulsions prepared with arabic acid as the emulsifying agent would cream very readily; for according to Stoke's law, the viscosity is a factor in the rate of creaming of an emulsion or the rate of settling of particles in a suspension.

Next, in order of increasing viscosity, were the solutions of the divalent inorganic salts and the organic salts containing two, three, and four amino groups. Emulsions made with these salts would be expected to cream at a slower rate than the arabic acid emulsions but would have a higher creaming rate than emulsions made with gum arabic; since gum arabic solutions have a higher viscosity than the solutions of the salts stated above.

Following this were the solutions of the monovalent inorganic salts and the organic salts of compounds to which one carboxyl group could be attached. These solutions had a higher viscosity than the gum arabic solutions, and therefore, emulsions prepared with these salts would be expected to have a lower creaming rate than any of the salts already mentioned.

The solutions of the trivalent inorganic salts had the highest viscosity of all the solutions prepared at concentrations above 8 to 10 per cent, but at low concentrations the viscosity was lower than the solutions of any of the other salts. From this data, the creaming rate would be expected to be very low at the higher concentrations and very high at the lower concentrations. At the higher concentrations solutions of these salts may well serve as suspending agents.

It may also be noted from the curves in the preceding section, that the presence of salts and, in particular, divalent salts decrease the viscosity of the solutions. From these results, it may be concluded that the presence of any salts in an emulsion or suspension would produce a small decrease in the efficiency of the substances as an emulsifying agent or suspending agent, but the presence of divalent salts would cause a large decrease in the efficiency of the substances.

Secondly, from the data obtained from the surface tension measurements one might expect that there should be less creaming in the emulsions prepared from the organic salts than those prepared from the inorganic salts or arabic acid itself. Since according to Stoke's law the particle size of the oil globules in an oil in water emulsion is a factor in the rate of creaming of an emulsion, and since surface tension is a factor in the particle size; the lower surface tension of the organic salts solutions should indicate a smaller particle size for the oil globules of the emulsions prepared with the organic salts.

No work of a pharmaceutical nature has been reported with the exception of Krantz and Gordon, who have reported the preparation of emulsions with arabic acid, sodium arabate, ferric arabate, and lead arabate. They stated that stable oil in water emulsions were formed in each case with the exception of the lead salt from which no emulsion could be prepared. (38)

In a discussion which follows, the results of a preliminary pharmaceutical investigation on arabic acid and its salts are given.

Experimental and Results

Emulsions

In a preliminary study several emulsions were prepared with a mortar and pestle using the 4:2:1 method (Continental Method). The oil used was U.S.P. heavy mineral oil. In each case 10 cc. of water was added to the primary emulsion. The following emulsifying agents were used; acacia, arabic acid, sodium arabate, and arabic acid neutralized with sodium hydroxide solution. This latter emulsion was prepared by using 0.5 N. sodium hydroxide solution as the aqueous phase. A sufficient quantity of the base was added to neutralize the arabic acid. After preparation the emulsions were allowed to stand in bottles at room temperature to study their stability.

These emulsions were observed under a microscope to determine whether there was any difference in size of the globules of oil. The emulsion prepared with arabic acid neutralized with sodium hydroxide appeared to have the smallest and most uniform globules. In order of increasing size; arabic acid was second, and sodium arabate and acacia were third having about the same size globules.

The emulsions were also observed for mold growth. After three days mold growth was observed in the acacia emulsion, but none in the others. After eight days mold growth was also observed in the sodium arabate emulsion. After three months mold growth appeared in the arabic acid emulsion, but none was noted in the emulsion prepared from arabic acid neutralized with sodium hydroxide.

Observations on creaming of the emulsions were likewise made. After 3 days some creaming had occurred in the acacia emulsion, and after eight days creaming had occurred in all four emulsions studied. The greatest amount of creaming was seen in the acacia emulsion with sodium arabate second, arabic acid third, and arabic acid neutralized with sodium hydroxide showed the least creaming.

The emulsions listed above along with other emulsions were then prepared. The compounds used included besides those above; ethylenediamine, trimethyl benzyl hydroxide, diethylenetriamine, triethylenetetramine, dodecylamine, and octadecylamine. These compounds were added to the mineral oil in amounts necessary to neutralize the arabic acid which was also added to the oil. These substances were thoroughly mixed with the oil before the water was added. The emulsion prepared from arabic acid neutralized with sodium hydroxide had a pH of 10 instead of 7 as in the emulsion made previously. Only the primary emulsions were made.

Examination of the oil globule size showed that the emulsions prepared with dodecylamine, octadecylamine, diethylenetriamine, and trimethyl benzyl hydroxide had very small oil globules. Comparatively large oil globules were observed in the other emulsions.

After a two week period no creaming was noted in the emulsions prepared from the following agents; octadecylamine, dodecylamine, diethylenetriamine, and trimethyl benzyl hydroxide. These emulsions were more viscous than the others which may explain the lack of creaming. All the other emulsions had creamed within a day from the time in which they were prepared.

Ointment Bases

Because of the viscousness and consistency of the emulsions, it was thought that the primary emulsions could be utilized as ointment bases. Application of a layer of the emulsions in which dodecylamine, octadecylamine, diethylenetriamine, and trimethyl benzyl hydroxide to the skin, produced a flexible film after drying for a few minutes. The films adhered well to the skin and were still intact after one hour. The films could be washed off with water. 10 per cent sulfur triturated with the emulsions produced a smooth ointment.

Suspending Agent

Precipitated sulfur in 10 per cent concentration was triturated with a 10 per cent solution of acacia, arabic acid, and sodium arabate. Neither the arabic acid nor the sodium arabate proved to be any more effective than acacia as a suspending agent.

Mucilages

The mucilages of acacia, arabic acid, and sodium arabate were prepared according to the U.S.P. XIII formula for Mucilage of Acacia but omitting the preservative, benzoic acid. After ten days mold growth appeared in the sodium arabate mucilage and in about the same time the odor of fermentation was detected in the mucilage of acacia although there was no evidence of mold growth at the time. After 3 months mold growth or fermentation had not appeared in the arabic acid mucilage.

Syrups

Syrup of acacia, arabic acid, and sodium arabate were prepared according to the N.F. VIII formula. The syrups were placed in bottles previously boiled in water. The preparations were allowed to stand at room temperature. After six months no mold growth was noted in either of the preparations, but in the syrup of acacia there were indications of fermentation.

Conclusions

Although the investigation was only of a preliminary nature, the following conclusions may be drawn:

a. Arabic acid preparations are less prone to mold growth than preparations made from acacia.

b. The primary emulsions prepared from octadecylamine, dodecylamine, diethylenetriamine, and trimethyl benzyl hydroxide may be useful as ointment bases, and the films formed on the skin could serve as a means of retaining a medicament on the skin.

d. Emulsions of almost any pH may be prepared with the arabic acid.

e. As might be expected, a correlation may be noted between surface tension, globule size and stability. The agents with the lowest surface tension, produced emulsions with the smallest oil globules and the greatest stability.

This part of the thesis contains research work done which was unrelated to the purpose of the project, but nevertheless represents interesting ideas and theories of possible work which could be done on arabic acid.

The first portion deals with the possible use of arabic acid and sodium arabate as chromatographic adsorbents. In the second portion a quantitative method for the determination of arabic acid is described.

ATTEMPTED USE OF ARABIC ACID AND SODIUM ARABATE AS CHROMATOGRAPHIC ADSORBENTS

It was thought that arabic acid and sodium arabate might be of value as chromatographic adsorbents with the compounds having an action like ion-exchange resins. Theoretically an organic acid would pass through an arabic acid column and be collected in the first few fractions but would be held on a sodium arabate column almost indefinitely. The acid would be held on the column by the changing of a hydrogen ion for a sodium ion. A basic compound would be held on the column by the arabic acid but would pass through a sodium arabate column. Thus by using various combinations of arabic acid and sodium arabate the fraction in which an acidic or basic compound would be collected could be regulated at will be varying the quantities of the arabic acid and sodium arabate.

Experimental and Results

A column 1 cm. by 4 cm. containing arabic acid was set up. 10 mg. of succinic acid in 1 cc. of n-butanol was put on the column. Elutions were made with 20% n-butanol in chloroform. Three cc. fractions were collected, and each fraction was titrated with .0077 N. sodium hydroxide.

A sodium arabate column with the same dimensions as above was prepared, and the same procedure as given for the arabic acid column was carried out.

From the results given in Table VIII and IX it may be seen that the succinic acid passed through immediately in both cases.

Table VIII

Arabic Acid Column

Fraction no.	cc. .0077 N. NaOH
1	11.4
2	7.7
3	0.6
4	0.3
5	0.3
6	0.3
7	0.2
8	0.2
9	0.2
10	0.2

Table IX

Sodium Arabate Column

Fraction no.	cc. .0077 N. NaOH
1	12.5
2	6.0
3	1.6
4	0.5
5	0.5
6	0.3
7	0.3
8	0.2
9	0.2
10	0.2

Conclusions

It is apparent that the procedure as given would be of no value. Since arabic acid and sodium arabate are soluble only in water, the presence of a small amount of water may aid in bringing about the desired exchange reaction; although the presence of the water may make the arabic acid and sodium arabate too gummy to allow the passage of any substance through the column.

TITRATION OF ARABIC ACID WITH CEEPRYN SOLUTION

The method involves coacervation which occurs when two hydrophilic sols with opposite charges come in contact with each other. This results in the formation of droplets or aggregates. It is believed that the shells of tightly bound water molecules surrounding the particles prevent them from coalescing, but the electrostatic attraction of their opposite charges holds a number of particles together in the form of a droplet, which may be microscopic or macroscopic in size. (43,45) Cetyl pyridinium chloride or "Ceepryn" which is a bacteriocidal agent is also a surface active agent and thus has a relatively low surface tension value. Since arabic acid has a relatively high surface tension value, it was assumed that the titration could be followed by surface tension measurements with a tensiometer. It was thought that the end point, that is, the point at which the Ceepryn had completely reacted with the arabic acid would be detectable from the surface tension measurements. It was reasoned that at the end point the arabic acid would be completely removed from the solution and only excess Ceepryn would be measured.

Experimental

It was observed that the addition of arabic acid solution to a Ceepryn solution resulted in the formation of a white precipitate which disappeared on further addition of arabic acid solution. Because of this observation, an attempt was made to titrate the Ceepryn solution with arabic acid.

A 100 cc. sample of a 1:10,000 solution of Ceepryn was titrated with 0.509% arabic acid while taking surface tension measurements at intervals during the titration. The DuNuoy Interfacial tensiometer was used for the measurements. A small amount of solution was poured from the beaker into a watch glass for the measurements and then returned to the beaker after each measurement was made. The ring was rinsed and flamed after each measurement.

The change in surface tension occurred too rapidly in this case therefore, a 1:1000 Ceepryn solution was tried. This time the change insurface tension was too slow and required a large amount of arabic acid solution to reach the end point. A 0.1% solution of arabic acid was then used to titrate a 100 cc. sample of 1:10,000 Ceepryn solution. Better results were obtained in this instance, but when the surface tension was plotted against amount of arabic acid used the curves obtained were not consistent. The actual surface tension was not calculated, but the readings taken on the tensiometer were used.

The procedure was then reversed, and the arabic acid was titrated with the Ceepryn solution using the same method as given above. A 50 cc. sample of a 0.1% arabic acid solution was titrated with 1:1000 Ceepryn solution after having first used a 1:10,000 dilution with poor results. In this case the curves and end points shown on the curves were consistent. The end point was considered to be the point at which the curve and straight line intersected. Varying concentrations of arabic acid were then titrated with the 1:1000 Ceepryn solution. The curves in Fig. 25 show typical curves obtained at various dilutions when the surface tension was plotted against the amount of Ceepryn added.

Higher concentrations of arabic acid above 0.1 gm. were titrated with a 1:100 Ceepryn solution. A plot was then made with weight of arabic acid titrated vs. amount of Ceepryn solution needed to obtain an end point. Two curves were made, one for the concentrations of arabic acid titrated with the 1:1000 Ceepryn solution and one for the concentrations titrated with the 1:100 Ceepryn solution. In both cases the curves were linear as shown in Fig. 26. except when the concentration of arabic acid went above 0.5 gm.

Conclusions

1. The titration appears to be a good semi-quantitative method for the determination of arabic acid although the procedure is somewhat tedious.

2. An unknown quantity of cetyl pyridinium chloride could also be determined by this method.

Figure 25. Typical examples of curves obtained when arabic acid is titrated with Ceepryn.

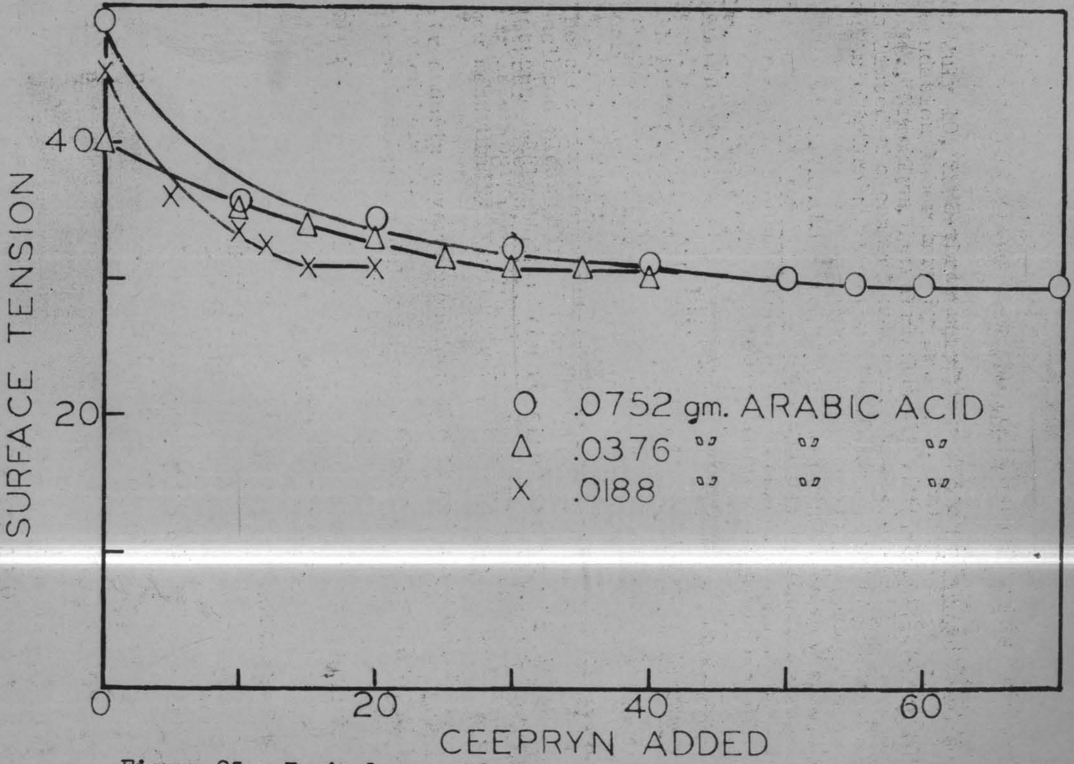
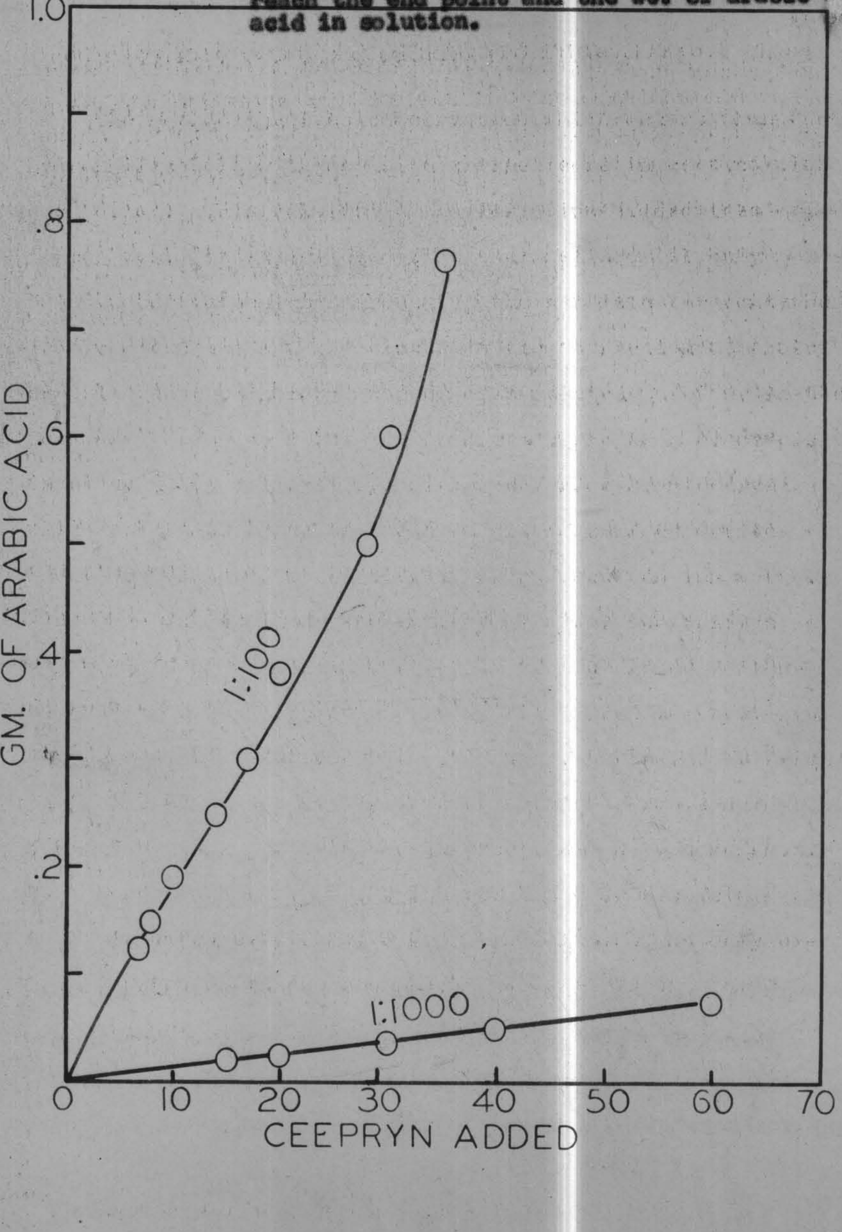


Figure 25. Typical examples of curves obtained when arabic acid is titrated with Ceepryn.

Figure 26. Illustration of proportionality between the amount of Ceepryn solution added to reach the end point and the wt. of arabic acid in solution.



SUMMARY

Gum arabic which consists mainly of the potassium, calcium, and magnesium salts of arabic acid has been one of the most widely used emulsifying agents, even though it has presented difficulties because of the low viscosity and the variation in viscosity of its solutions. For these reasons, arabic acid and numerous salts were prepared and studied to determine their value in pharmaceutical technology.

Arabic acid, which has not previously been prepared in a dry state, was obtained in a dry, powdered form without changing its physical or chemical properties.

The procedure for its preparation which was adopted after other methods had proved unsuccessful was as follows. The arabic acid solution was prepared by putting a seven per cent gum arabic solution through a hydrogen-activated ion-exchange resin column to remove the cations. The solution was then run through a spray-drier to obtain arabic acid in the powdered form. The results of viscosity determinations, equivalent weight determinations, optical rotation measurements, and pH titrations showed that no significant change had occurred in the arabic acid molecule on spray-drying.

Thermostability studies made on the arabic acid powder proved it to be stable to heat except at high temperature for a long period of time.

The preparation of the sodium, potassium, calcium, magnesium, zinc, ferric, aluminum, butylamine, trimethyl benzyl, ethylenediamine, diethylenetramine, and triethylenetetramine salts of arabic acid is described. Only the sodium salt was obtained in the powdered form. All the other salts were allowed to remain in solution. An attempted preparation of the octadecylamine and dodecylamine salts was unsuccessful.

Since data obtained from viscosity determinations and surface tension measurements are of definite value in determining the merit of a substance as an emulsifying agent, surface tension measurements and viscosity determinations were made on arabic acid and its salts.

Since the colloidal particles of arabic acid contain a negative charge, and since this charge has a definite effect on the viscosity; theref ore, a study of its effect on the viscosity of the solutions was made. From the results obtained the following conclusions were drawn;

a. The low viscosity of the arabic acid solution was due to the low pH which suppressed the charge resulting in a more compact molecule and less hydration.

b. The higher viscosity exhibited by the solutions of the monovalent inorganic salts was due to a high charge resulting from an almost complete dissociation at a pH of 7.

c. The solutions of the divalent inorganic salts had a low viscosity as a result of an intramolecular attraction of the carboxylic acid groups. This makes the molecule more compact resulting in less hydration.

d. The solutions of the trivalent inorganic salts had a very high viscosity at high concentrations and a very low viscosity at low concentrations. An explanation for the high viscosity is that an intermolecular attraction linking two or more molecules together, whereas at low concentrations an intramolecular attraction occurs.

e. The solutions of the butylamine and trimethyl benzyl salts both have similar curves, and both of these curves were similar in magnitude and appearance as that of the monovalent inorganic salts.

f. The solutions of the ethylenediamine, diethylenetriamine, and triethylenetetramine salts of arabic acid had similar curves both in magnitude and appearance, and these curves were similar to the divalent inorganic salts. It therefore was concluded that the attraction was intramolecular and that only two of the amino groups of the triamine and tetramine reacted.

As part of the viscosity study, arabic acid solutions were heated to observe the effect of heat on the viscosity of an arabic acid solution. The study showed that at high concentrations it was possible to obtain an increase in viscosity, but at low concentrations the viscosity decreased.

Surface tension measurements made on solutions of the organic salts of arabic acid showed no large difference in surface tension between the salts and arabic acid.

It was observed in the preparation of aluminum arabate for viscosity determinations that a 20 per cent solution appeared to have properties of dilatancy, but determinations made on a MacMichael viscosimeter showed that the aluminum arabate gel had thixotropic properties rather than dilatant properties.

A preliminary pharmaceutical investigation which was carried out showed the possibilities of some of the organic salts as emulsifying agents, and that the primary emulsions made with these salts may possibly be used as ointment bases. A correlation was noted between the surface tension, oil globule size, and stability of the emulsions prepared.

Arabic acid and sodium arabate were used to prepare other pharmaceuticals in which gum arabic has ordinarily been used. It was found that the arabic acid preparations were less prone to mold growth than gum arabic.

Two analytical applications for arabic acid are described.

An attempt was made to use arabic acid and sodium arabate as chromatographic adsorbents, but this proved to be unsuccessful.

A semi-quantitative titration method for the determination of arabic acid was developed. The titration was carried out using cetyl pyridinium chloride or "Ceepryn" with surface tension measurements used to determine the end point. It was found that the amount of cetyl pyridinium chloride needed to obtain an end point was directly proportional to the amount of arabic acid in solution. This method may also be used to determine an unknown quantity of cetyl pyridinium chloride.

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