

The Properties and Application of New Emulsifying and Thickening Agents

By D. J. McHugh

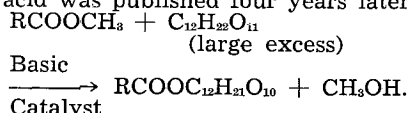
(A paper presented at the Adelaide Meeting, A.N.Z.A.A.S., August, 1958)

New raw materials for use in the preparation of pharmaceuticals are continually appearing. Some of these, which can be used as emulsifying, wetting or thickening agents, are described briefly below, together with some examples of their applications.

Sugar Detergents

Sucrose is a chemical which is available in large quantities at a reasonably stable and low price, and the presence of eight hydroxyl groups within the molecule makes it quite reactive chemically. In spite of this, sucrose has been relatively neglected as a starting material for organic synthesis. The possibility of forming surface-active compounds from sucrose by esterification with fatty acids has been realised for some time, but progress was hindered by the lack of control of the esterification, all eight hydroxyl groups being esterified by classical methods such as the use of pyridine and an acid chloride.

In 1952, the Sugar Research Foundation of New York supported a project at Foster D. Snell Inc. for an attempt to esterify sucrose with fatty acids and the following process using sucrose and the methyl ester of a fatty acid was published four years later.¹



Among the difficulties which had to be overcome was the finding of a basic catalyst which would cause a reasonably rapid alcoholysis without causing too much degradation to the sucrose; a solvent to dissolve the very hydrophilic sucrose and the very lipophilic methyl esters of fatty acids was also required. The process finally evolved used dimethylformamide as solvent and potassium carbonate as catalyst. The use of an excess of sucrose gives the monoester and if the diester is desired, two moles of methyl ester of fatty acid are employed for one mole of sucrose. In the monoester, structural studies have shown that the ester linkage is predominantly on the 6 position of glucose.^{1,2} It has been assumed that if a second fatty acid group is attached, it will probably be on the 6 position of fructose.³

In the manufacture of sugar esters, the sucrose must compete in price with the petrochemical ethylene oxide, which can also be reacted with fatty acids to form non-ionic surfactants. In the United States, ethylene oxide is about twice as expensive as sucrose and in other countries the ratio is even higher.

The sucrose esters, when pure, are reported to be colourless, odourless and virtually tasteless. The compounds are solids which usually soften at about 40° C. and are pourable liquids at 80-90° C. Most anionic detergents become less soluble in water with increasing temperature and cannot be used in really hot water; however, the sucrose esters become more soluble as the temperature of the water increases. A most important feature of these substances is their reported complete safety and freedom from toxicity when ingested. Experiments with sucrose palmitate have shown that it breaks down into glucose, fructose and fatty acid in the intestinal wall.⁴ In the food, cosmetic and pharmaceutical industries, the sucrose esters have been suggested as emulsifiers and detergents.

The sugar esters are good detergents and, either built or unbuilt, compare favourably with present detergents, such as sodium dodecylbenzene sulphonate. The foaming tendencies of the sucrose esters decrease as the length of the fatty acid radical increases; sucrose mono-

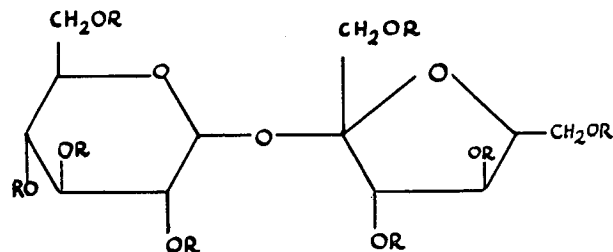
laurate gives a moderate foam, while the monostearate is essentially non-foaming. The wetting properties also decrease as the hydrocarbon chain becomes longer, the monoesters being in general fair wetting agents. Their lack of taste and very low order of irritation make the sugar esters suitable for use in toothpastes and shampoos; for example, a 10 per cent. solution of sucrose monostearate applied to the eyes does not sting or smart.

Emulsions containing sugar monoesters combined with Arlacels or glyceryl monostearate have been successfully prepared. Since the sucrose monoesters are o/w emulsifiers and the corresponding diesters usually w/o emulsifiers, it is possible to prepare stable emulsions containing both types of sugar esters; in fact, emulsions made with a mixture of the two are more stable than those made with either alone. Sugar esters are reputed to contribute a soft, velvety feel to emulsions in which they are incorporated.³ The fact that some non-ionic emulsifiers inhibit the action of phenolic preservatives such as the p-hydroxybenzoates has been reported in the literature several times; it had been hoped that the sucrose esters might not suffer from this disadvantage, but a quite recent report indicates that sucrose monopalmitate inhibits the action of p-hydroxybenzoates and quaternary ammonium compounds.⁵ However, sorbic acid, benzoic acid and phenyl mercuric nitrate were still effective in the presence of this sugar ester.

In aged or other persons whose liver no longer produces adequate quantities of emulsifying agents, the digestion of fat becomes inefficient. It has been shown, at the Sinai Hospital of Baltimore, that people who otherwise could not digest fat can do so efficiently with a little sugar ester in the diet.⁴

The sucrose monoesters have been used to solubilise fat-soluble vitamins; for example, one part of Vitamin A Acetate can be solubilised by twelve parts of sucrose monolaurate or twenty parts of sucrose monopalmitate.⁶ Sucrose esters are, therefore, useful in such applications if materials containing polyoxyethylene chains (such as Tweens) are considered unsuitable; in addition, such aqueous solutions containing sucrose esters are very stable and do not exhibit cloud formation when warmed.

A different type of sugar derivative which shows promise as an emulsifier or detergent has been developed by Dow Chemical; these are the fatty esters of octabis-(2-hydroxypropyl)-sucrose (known as Hyprose SP80), which is made by reaction of propylene oxide with sucrose and has the following formula—



where R = C₃H₆OH

The eight reactive hydroxyl groups allow as many as eight moles of fatty acids to be esterified with one of Hyprose SP80. Toxicological studies made so far show the esters as suitable for use in food packaging mate-

rial and to warrant further study for application in food and cosmetic products.⁷

Carbopol 934

Carbopol 934⁸ is a synthetic polymer described by the manufacturers as carboxy polymethylene. It is supplied as a finely divided white powder which readily disperses in water to yield a low viscosity acid solution. When neutralised with an appropriate alkaline substance, the solution is transformed into a clear stable gel, so that Carbopol 934 finds many applications as a thickening and suspending agent.

The advantages of Carbopol 934 are:

(1) Its thickening efficiency, only low concentrations being required to give considerable increases in viscosity (Fig. 1).⁹

VISCOSITY VS. CONCENTRATION OF VARIOUS MATERIALS

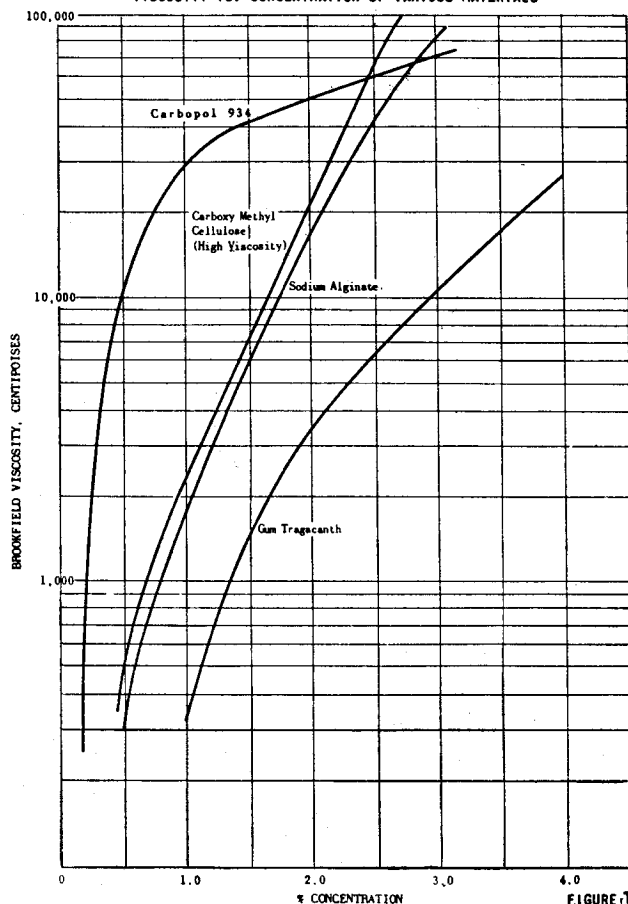


FIGURE 1

(2) Its uniformity, enabling a greater assurance of reproducibility than can be obtained using natural gums.

(3) Low variation of viscosity at different temperatures. For example, as the temperature rises from 20° C. to 40° C., the viscosity of 1% Carbopol drops by 6%, while that of 2.5% sodium carboxymethylcellulose (high viscosity) falls by 50%.⁹

(4) Its resistance to ageing and its resistance to degradation by bacterial or fungal attack.

(5) Its compatibility with appreciable quantities of ethanol and glycerin.

On the subject of compatibility, it might be mentioned that, while the polymer is compatible with many organic and insoluble inorganic compounds used in pharmacy, excessive concentrations of monovalent salts cause a drop in viscosity, and this drop is even more rapid in the presence of di- and trivalent salts. This disadvantage can be partly overcome by increasing the concentration of Carbopol 934, although the resulting gels are usually no longer clear.

In preparing formulations based on Carbopol 934, the polymer should first be dispersed by adding it slowly to water, using moderate to high speed agitation. The amount of alkali needed for neutralisation to the desired

pH is then added with slow speed stirring to avoid the production of air entrainment in the viscous mucilage. The pH necessary to achieve full viscosity and the effect of using different alkalis for 1% Carbopol, are shown in

VISCOSITY VS. pH IN CARBOPOL 934

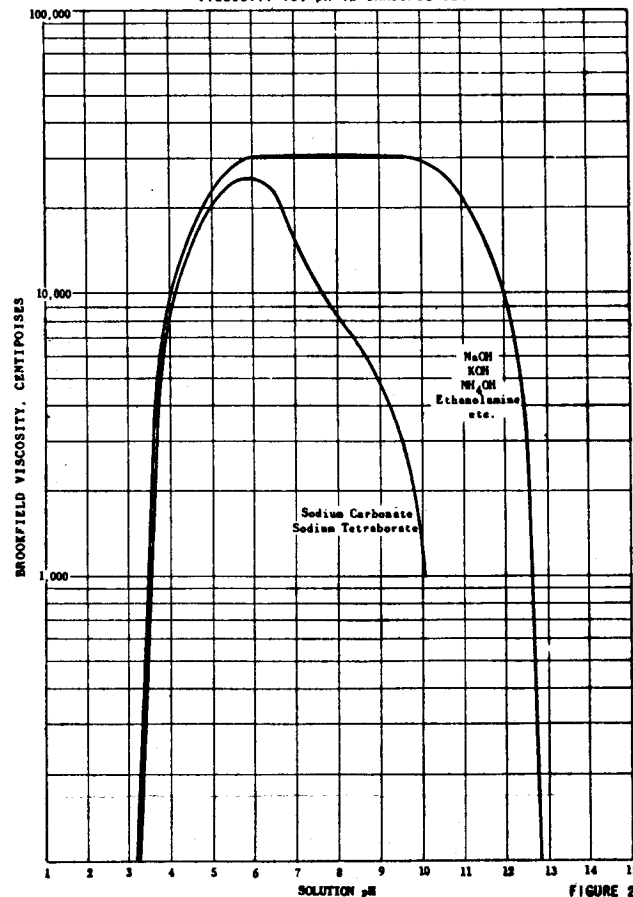


FIGURE 2

figure 2. It has recently been found that solutions of Carbopol 934 show a drop in viscosity when continually exposed to light; this can be overcome by the addition of a small percentage of ethylenediamine-tetra-acetic acid, which seems to indicate that trace metals act as catalysts in the degradation of Carbopol.¹⁰

Carbopol 934 Salts are physiologically inert and can be used in both internal and external preparations.

Carbopol 934 Salts are excellent suspending agents for solids dispersed in aqueous systems. The use of as little as 0.05% Carbopol 934 will frequently prevent caking of insoluble materials. Swafford and Nobles¹¹ demonstrated that calamine lotion, prepared using Carbopol 934 as the suspending agent, poured easily, spread smoothly, dried quickly, and had a slow rate of sedimentation. However, its appearance is not as good as a calamine lotion based on bentonite or sodium carboxymethylcellulose, the Carbopol preparation having a more granular texture. These workers also prepared a palatable kaolin-pectin suspension that did not cake appreciably within 60 days.

Thickened aqueous solutions of Carbopol are useful for the preparations of stable suspensions of many insoluble pharmaceuticals, and when faced with the problem of formulating a suspension, the advantages of Carbopol should be investigated.

When the thickening is taken a stage further, products of consistency suitable for ointment bases are obtained. Thus ointments have been prepared, with from 2-5% aqueous Carbopol salt as the base, containing such diverse compounds as ammoniated mercury, aureomycin, benzoic and salicylic acids, boric acid, benzocaine, iodine, sulphathiazole and sulphur.¹² These ointments were smooth, homogeneous, stable and resistant to biological attack; they rub in well, do not leave a greasy or sticky

feel and are removed easily with soap and water so that staining is reduced to a minimum.

Of particular interest in pharmaceutical formulation is the fact that Carbopol will thicken organic solvents such as glycerin, sorbitol and propylene glycol. Thickened glycerin could be useful in protective creams, jellies and ointments; it would also be useful as a lubricant which, coupled with the non-toxicity of the system, makes it useful for lubricating cosmetic and pharmaceutical equipment and in diagnostic and surgical instruments. The thickened glycerin is, of course, miscible with water and washes off easily. The same remarks apply to thickened sorbitol-water mixtures. The effect of temperature on the viscosities of solutions of Carbopol 934 in glycerin is much more severe than in water.

Monohydroxy alcohols (e.g., methyl, ethyl, etc.) cannot be thickened using the usual alkalies, since, although the acidic polymer is soluble, the neutralised form or salt is insoluble and so precipitation occurs (need 65% water). However, if triethylamine is used as the neutralising agent, satisfactory thickening of methanol, 80% ethanol and methyl ethyl ketone can be obtained.

Misek et al.¹³ prepared emulsions of paraffin oil, cod liver oil, benzyl benzoate and cottonseed oil using Carbopol. They used either a "wet" or "dry" technique; for the wet method the oil was placed in mortar, the Carbopol solution slowly added and the mixture passed through a hand homogeniser several times. In the dry method the Carbopol powder was distributed uniformly throughout the oil, water was added in portions, the mixture then homogenised with trituration and finally with a hand homogeniser. However, in these preparations, the actual emulsification is achieved mainly by the mechanical work in the hand homogeniser, the Carbopol acting as a stabiliser for the emulsion so formed rather than causing the emulsification itself.

Pluronics

The Pluronics¹⁴ are a series of non-ionic surface-active agents. Most chemists know that polyoxyethylene compounds are water soluble, no matter how high their molecular weight. For many years, it was generally assumed that polyoxypropylene compounds would also be water soluble. However, the fact is that at a molecular weight of about 800-900, polyoxypropylene compounds change from water soluble to water insoluble.

Investigation by the Wyandotte Chemical Corporation revealed that if water-soluble polyoxyethylene groups were added to both ends of the water-insoluble polyoxypropylene chain, a new series of surface-active agents would develop. These surfactants could have a hydrophobic base of any controlled length and any hydrophobic-hydrophilic balance, achieved by adding amounts of ethylene oxide varying from 10% to 90% of the final molecule.

This is the basis of the Pluronics which can be represented by the following simplified structure:



The Pluronic Grid (fig. 3) illustrates the possible molecular range obtainable; it offers a wide choice of carefully-controlled surface-active agents. They range in molecular weight from 1,000 to over 11,000; they have a controlled hydrophilic-hydrophobic balance varying from materials that are almost water insoluble to materials that have no cloud point—even in boiling water. Because of the wide range of molecular weights obtainable in the Pluronics—and because of complete freedom in controlling the hydrophilic-hydrophobic balance—many properties of the Pluronics can be plotted as trends across the Grid (fig. 3). By observing these trends the formulator can select from the Grid, the Pluronic having the best balance of properties for his particular application. After only a few laboratory tests, he can narrow this area down to the best Pluronic for his formulation.

To simplify the naming of the Pluronics, they are identified by a letter (L, P or F) and a two-digit number. The letter indicates the physical form of the particular Pluronic; L for liquid, P for paste, F for flake. The first digit identifies the arbitrary molecular weight

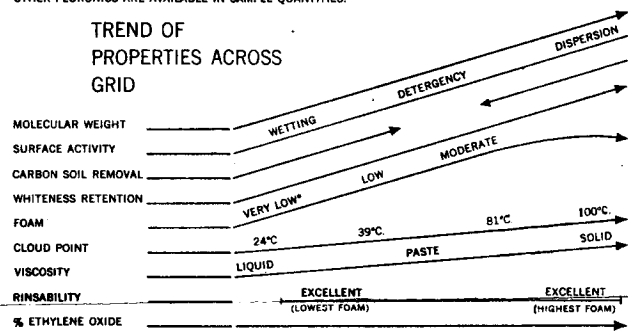
ranges of the hydrophobic base, as indicated by the column to the left of the Grid. The second digit suggests the approximate per cent. of the ethylene oxide in the total molecule. Pluronic L64 is a liquid having a hydrophobic base molecular weight of 1501-1800, and 40% of the total molecule is ethylene oxide.

PLURONIC GRID

MOLECULAR WEIGHT OF POLYOXYPROPYLENE HYDROPHOBIC BASE (FIRST DIGIT)	% POLYOXYETHYLENE (HYDROPHILIC UNIT) IN TOTAL MOLECULE									
	(SECOND DIGIT)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	
	%	0	10	20	30	40	50	60	70	80
2101-2500	(8)	L81			L84	P85				F88
1801-2100	(7)		L72			P75				F77
1501-1800	(6)	L61	L62	L63	L64	P65	P66			F68
1201-1500	(5)									
1001-1200	(4)		L42	L43	L44		P45			
801-1000	(3)			L31	L33	L35				F38

PLURONICS L61, L62, L64, L44, P75, AND F68 ARE COMMERCIALLY AVAILABLE.
OTHER PLURONICS ARE AVAILABLE IN SAMPLE QUANTITIES.

TREND OF PROPERTIES ACROSS GRID



EMULSIFICATION—ALL PLURONICS HAVE FOUND APPLICATIONS AS EMULSIFYING AGENTS.
*ABOUT 10% PLURONIC L61 (BASED ON THE TOTAL WEIGHT OF PLURONIC) EFFECTIVELY REDUCES THE FOAMING OF THE OTHER PLURONICS.

The Pluronics are generally odourless, and while the liquid ones have some taste, F68 is practically tasteless, a property rather unusual in a non-ionic surfactant. Since the molecules are composed of ether linkages they have a high chemical stability and are not precipitated by metallic ions. The Pluronics are relatively non-hygroscopic and pick up only a small percentage of moisture in atmospheres of high humidity. As with most other non-ionics, the liquid Pluronics have reverse solubility in water, becoming less soluble as the temperature increases. All the Pluronics are readily soluble in polar solvents such as acetone and alcohol.

Toxicological and dermatological studies have been carried out extensively on Pluronic F68 and have shown this material to be quite safe for internal or external use. Preliminary tests have shown that L44, L62 and L64 are not primary irritants or sensitizers when applied to human skin.

The Pluronics are used mainly for their detergent and wetting properties, and so find an outlet in formulated detergents; they have been suggested for use in shampoos and toothpaste and as solubilisers for antibiotics and vitamins. Another interesting application is their use as iodophors.

An iodophor is a compound which greatly increases the solubility of and tends to stabilise iodine in aqueous systems. Surface-active agents have been known to be iodophors for some time; they increase the solubility of iodine above the normal water solubility by incorporating the element in molecular aggregates called micelles. The micelles are formed in the bulk of the solution when a definite concentration of the surface-active agent has been exceeded. Unlike miscible solvents such as alcohol, the effect of surfactants becomes pronounced in relatively dilute solution of the surfactants, whereas miscible dilute solutions have little effect on solubility unless used in high concentration.

The Pluronic will dissolve iodine, more rapidly in the presence of 2% acid, and the resulting concentrate can be diluted with water to give product of any desired concentration.¹⁵ Such solutions are claimed to be better than the usual type of iodine preparation because they eliminate the irritation and staining of alcoholic solutions of iodine or aqueous solutions of potassium iodide and iodine.¹⁶ A recent U.S. patent¹⁵ describes the use of Pluronic F68 to solubilise iodine in oral lozenges, the product being non-toxic and composed of the usual components of lozenges. Also described is a dry germicidal composition of Pluronic F68, iodine and a solid diluent. Such a product has value in that it can be carried more easily than a liquid and is simply dissolved in water before use. The composition is non-toxic dermatologically and is claimed to lose no iodine by vaporisation.

Polyox Resins

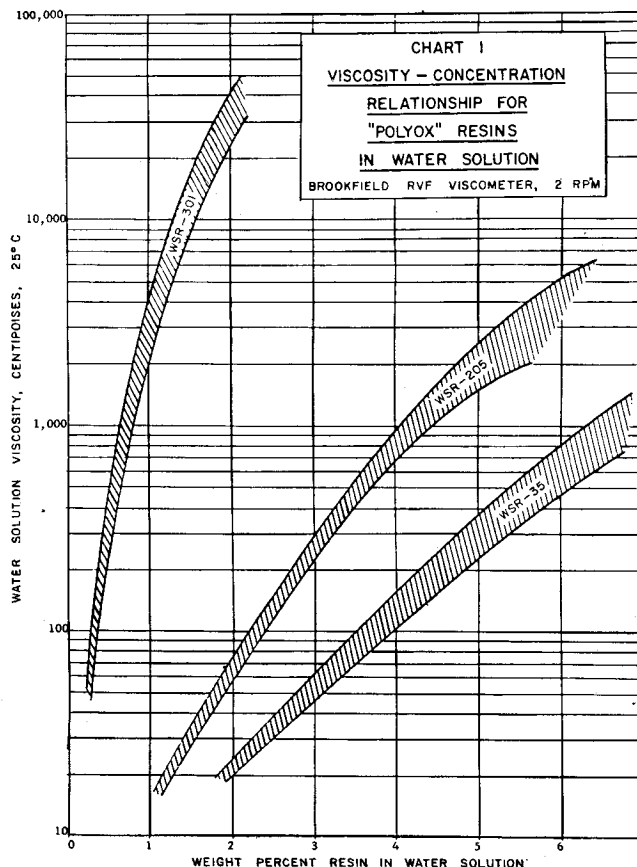
Polyethylene glycols and their derivatives are now well known for their use in cosmetic and pharmaceutical products. The liquid polyethylene glycols of molecular weight 200-700, are commonly used as humectants and coupling agents for water-insoluble organic compounds. The higher polymers of molecular weight 1,000-20,000 serve as water-soluble waxes and are used in ointment bases.

Recently it has been found that with the aid of special catalyst systems it is possible to prepare ethylene oxide polymers of extremely high molecular weight.¹⁷ The products are of a resinous nature, commercial material ranging in molecular weight from about 100,000 to about 4 million. These materials, unlike the lower molecular weight products, increase the viscosity of water in very low concentrations, and so can probably be used in applications requiring thickening, suspending, emulsifying and film-forming properties.

These Polyox resins,¹⁸ as they are called, are soluble in water, chloroform and the lower alcohols if they contain 10% water, as well as some other organic solvents; they thicken both aqueous and organic solvents, in which they are soluble. When dissolved in water the resins form slightly cloudy, moderately alkaline solutions, and if desired they can be clarified by lowering the pH to 5.5 when the small amount of salt present in the resin is solubilised, but this treatment is not recommended if subsequent solution stability is required for long periods of storage. Approximate viscosity-concentration curves for the various grades are shown in fig. 4.

Viscosity values are influenced by the technique used in preparing the resin solutions, and if maximum viscosity is desired, unusually violent or very high-speed agitation during the dissolving process should be avoided, since this breaks apart the longest molecules and causes a permanent loss in viscosity. Solution viscosities are relatively unaffected by the presence of small amounts of neutral dissolved salts, but the resins can be salted out of water and the solution undergoes a drop in viscosity by the addition of larger quantities.¹⁹ Viscosities decrease as the temperature is raised, but to a lesser degree than for solutions of most other water-soluble thickening agents. Upon ageing, a slow, permanent loss of viscosity may occur in solutions of Polyox resins; with solutions of pH5 (or more acid solutions) the change of viscosity is more pronounced. For this reason, viscosity stability should be checked in specific formulations. Aqueous solutions of Polyox resins have almost no surface activity; their solutions have a rosy consistency which ranges from a maximum with the higher viscosity grades of resin to a much less apparent degree of stringiness in the lower viscosity grades. When substantial thickening action is required without the stringy characteristic, higher concentrations of WSR-205 are preferable to lower concentrations of WSR-301 to obtain the same thickening action.

A rather unexpected property of these gums is that they are not compatible with non-ionic surfactants which contain ethylene oxide. However, they are compatible with the non-ionic sucrose esters as well as with cationic and anionic surfactants, including soaps.



Preliminary results of toxicological studies have been sufficiently promising to warrant the evaluation of Polyox resins in products for external use, but further studies are necessary.

Polyox resins exhibit a high degree of flexibility and strength, and a few suggested uses are—

1. As a film former and binder in calamine lotions.
2. As a tablet binder, that is, to use them as granulating agents, especially in conjunction with gum acacia.
3. As a tablet coating.
4. In protective hand lotions, since they have excellent film-forming ability and are resistant to oils and greases.
5. In rubbing alcohol compounds, since they impart excellent lubricity.
6. As thickening and suspending agents in the preparation of products for external use.

References

1. Osipow, Snell, York and Finchler, "Ind. Eng. Chem.," 1956, 48, 1459.
2. York, Finchler, Osipow and Snell, XII International Congress of Pure and Applied Chemistry, Zurich, Switzerland, July 21-27, 1955.
3. Osipow, "J. Soc. Cosmetic Chemists," 1956, 7, 251.
4. Hass, "Manuf. Chem.," 1958, 29, 153.
5. Wedderburn, "J. Soc. Cosmetic Chemists," 1958, 9, 215.
6. Mima, "Bull. Pharm. Soc., Japan," 1957, 5, 496.
7. "Chem. Eng. News," 1957, 35, 90.
8. A product of B. F. Goodrich Chem. Co., Cleveland, Ohio, U.S.A.
9. "Carbopol 934," Service Bulletin GC-20, B. F. Goodrich Chem. Co., Cleveland 15, Ohio.
10. Schwarz and Levy, "J. Amer. Pharm. Assoc.," 1958, 47, 442.
11. Swafford and Nobles, "J. Amer. Pharm. Assoc. (Pract. Pharm. Ed.)," 1955, 16, 171.
12. Streeter, Caver and Nobles, *ibid.*, 1955, 16, 671.
13. Misek, Powers, Ruggiero and Skauen, "J. Amer. Pharm. Assoc.," 1956, 45, 56.
14. A product of Wyandotte Chemicals, Wyandotte, Michigan, U.S.A.
15. U.S. Patent 2,759,869.
16. Cantor, Most and Shelanski, "J. Soc. Cosmetic Chemists," 1956, 7, 419.
17. Hill, Bailey and Fitzpatrick, "Ind. Eng. Chem.," 1958, 50, 5.
18. A product of Union Carbide Chemicals Co., New York, U.S.A.
19. Osipow and Berger, "Drug Cos. Ind.," 1958, 82, 167.