Interaction of Nonionic Hydrophilic Polymers with Phenols I

Interaction of Phenol and Hydroxyphenols with Certain Macromolecules

By B. N. KABADI* and E. ROY HAMMARLUND

There have been numerous studies of the interactions of certain phenols with nonionic macromolecules—particularly those dealing with a loss of antimicrobial properties of the phenols when combined with nonionic polymers. Relatively little attention, however, has been given to the possible disruption of the solubilizing and stabilizing properties of the polymers themselves when in combination with certain phenols. Miscibility titration studies were made by interacting the following polymers: PEG, PPG, PVP, and methylcellulose with the following phenols: catechol, pyrogallol, resorcinol, hydroquinone, tannic acid, and phenol. Photometric turbidimetric titration studies of interacting polyoxyethylene ethers, polyoxyethylene monostearates, and polysorbates with tannic acid were also carried out. Dextrose altered the complexing tendency of tannic acid by decreasing the solubility of tannic acid in PEG 6000 and increasing its solubility in PVP. Since tannic acid was found to interact strongly with nonionic hydrophilic polymers, its possible influence upon the stability of various pharmaceutical formulations containing nonionic hydrophilic polymers should not be overlooked.

INVESTIGATION has indicated that phenolic materials interfere with various nonionic hydrophilic polymers which are employed frequently in pharmaceutical and cosmetic formulations as solubilizing, stabilizing, or emulsifying agents (1–6). The interactions of various nonionic hydrophilic polymers and phenols have been the concern of many further studies (7–14), usually undertaken to explore the mechanisms of the various interactions and thereby make possible the prediction of their probable occurrence. Most prior work has focused upon the interference of the complex with the antimicrobial properties of the phenol rather than upon its interference with the solubilizing and stabilizing properties of the polymer. The present inquiry investigated the nature of the inactivation of certain nonionic polymers by various widely occurring hydroxyphenols which may be found in many pharmaceutical formulations that contain plant products. Methods employed were visual turbidimetric titration and photometric turbidimetric titration. Results are presented in the form of phase diagrams.

EXPERIMENTAL

Materials.—The nonionic polymers used were: polyethylene glycol (PEG) 1500, 1540, 4000, 6000, and 20,000; polyvinylpyrrolidone (PVP); polypropylene glycol (PPG) 400 and 1200; polysorbate 20, 40, 60, and 80;[1] polyoxyethylene monostearate;[2] polyoxyethylene ethers;[3] alkyl phenoxy polyethoxy ethanol;[4] methylcellulose 15 cps. All polymers were commercial samples. The phenols employed were phenol, resorcinol, tannic acid, catechol, pyrogallol (all reagent grade), and hydroquinone (technical grade).

Visual Turbidimetric Titration Method.—The experimental technique was similar in principle to that used by Higuchi and co-workers (11, 12), Ahsan et al. (15), Marcus et al. (16), and Karabinos et al. (17) in their studies of the interaction of phenols with macromolecules. One to 10 ml. of the polymer solutions was added to a series of 50-ml. tubes and each volume was adjusted to 10 ml. with distilled water. The phenol solution was added dropwise to the continuously stirred polymer solution until a distinct turbidity marked the end point of the titration. The same operation was repeated on each tube containing various dilutions of the polymer solutions.

The phenol and hydroxyphenol solutions were 6% w/v and the tannic acid solution was 1% w/v, except for the methylcellulose titration in which 0.1% tannic acid was used. The concentrations of the polymer solutions were: polyethylene glycol[5] 1500, 1540, 4000, 6000, and 20,000, 20.0% w/v; polyvinylpyrrolidone,[6] 4.0% w/v; methylcellulose, 15 cps., 1.0% w/v; polypropylene glycol,[7] 1200, 0.2% w/v; and polypropylene glycol,[7] 400, 20.0% w/v.
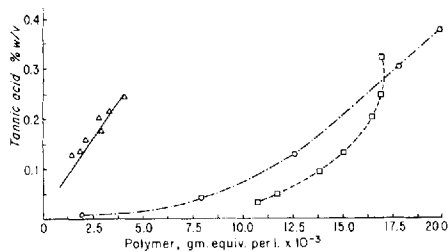
From the concentration and volume of the poly-

Fig. 1.—Influence of several polymers on the solubility of tannic acid. Key: △, PVP; ○, PEG 6000 □, PPG 400.
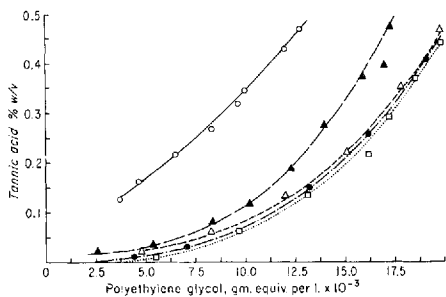
Fig. 2.—Influence of several PEGs on the solubility of tannic acid. Key: ○, PEG 20,000; ▲, PEG 1540; △, PEG 4000; ●, PEG 6000; □, PEG 1500.

Fig. 3.—Effect of dextrose on the solubility of tannic acid in PEG 6000. Key: ○, PEG 6000 in water; ●, PEG 6000 in dextrose (1 *M*).

Fig. 4.—Effect of dextrose on the solubility of tannic acid in PVP. Key: △, PVP in water; ▲, PVP in dextrose (1 *M*).

mer solutions used the corresponding number of monomer-gram equivalents of polymer per liter was calculated (except for methylcellulose) and this value was plotted *versus* the final concentration of the phenolic solution in the mixture at the end point. The effect of dextrose on the interaction of PEG 6000 and PVP with tannic acid was likewise determined. The procedure used was the same as above except that the polymers were dissolved in 1 *M* aqueous dextrose solutions instead of in water. The data thus obtained from the titrations of the various polymers and phenols are plotted in the form of phase diagrams (Figs. 1–6).

Photometric Turbidimetric Titration Method.— The nonionic polymer solution was added slowly to a constantly stirred 10-ml. volume of 0.1% w/v tannic acid solution in a 50-ml. flask. At the first sign of turbidity an aliquot solution was removed, and its absorbance was measured at 625 mμ in a Bausch & Lomb Spectronic 20 colorimeter. The 0.1% tannic acid solution was used as the blank. Following this initial reading the aliquot was returned to the titration vessel, and more polymer solution was added to the mixture in 0.2-ml. increments. Absorbance readings were repeated until the solution in the titration flask became transparent (zero absorbance) which took about 0.5 hr. This titration procedure was carried out for each of the nonionic polymers tested. The solution absorbance was plotted *versus* the total volume of the polymer solution added. Figures 7–9 show the data thus plotted.

RESULTS AND DISCUSSION

Figures 1–6 show the phase diagrams of the complexation reactions between hydroxyphenols
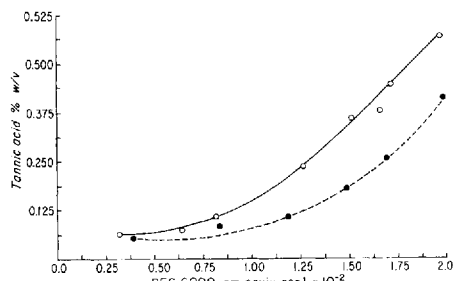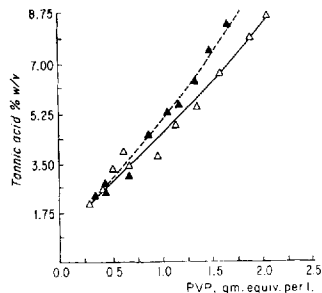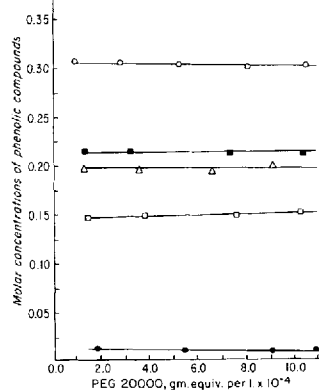

Fig. 5.—Effect of PEG 20,000 on the apparent solubility of phenol and polyhydroxy phenols. Key: ○, pyrogallol; ■, catechol; △, hydroquinone; □, resorcinol; ●, phenol.
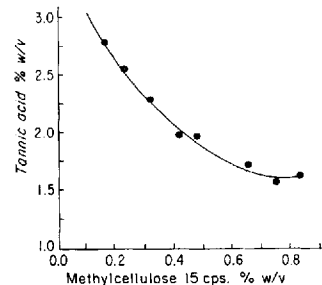

Fig. 6.—Influence of methylcellulose on the solubility of tannic acid.

and various hydrophilic polymers. In all these diagrams the points at low concentrations were less precise due to difficulty in discerning the end point. A heterogeneous system consisting of the white, oily complex dispersed throughout the aqueous phase existed at concentrations above any given curve. The mixtures were clear below each curve. The graphs in Figs. 1–5 have positive slopes which indicate that the insoluble complex was solubilized by an excess of uncomplexed polymer solution. In Fig. 6 the negative slope in the phase diagram of the methylcellulose was identical to that obtained from the interaction between phenol and PPG 1200 by Guttman and Higuchi (11). Likewise, the graph was similar to those which show interaction between phenol and certain surfactants below their critical micelle concentrations (CMC) (15, 16). For precipitation to occur, any decrease in the concentration of one reactant requires a corresponding increase in the concentration of the other. The negative slopes in this type of phase separation appear to be characteristic of polymers with negative temperature coefficients of solubility.
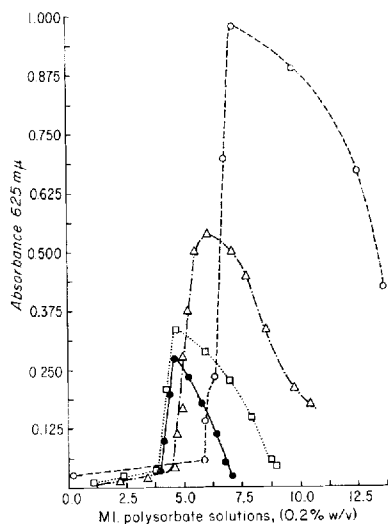
Since dextrose occurs as one of the products of

tannic acid hydrolysis, its effect on the solubility of tannic acid in hydrophilic polymers was studied (Figs. 3 and 4). Dextrose was found to decrease the solubility of tannic acid in PEG 6000 and to increase the solubility of tannic acid in PVP.

The order of phenolic concentrations required for precipitation by PEG 20,000 (Fig. 5) was found to be phenol < resorcinol < hydroquinone < catechol < pyrogallol. Guttman and Higuchi (11) reported the sequence with PVP to be resorcinol < hydroquinone < phenol < catechol. No simple explanation appears to be evident for the discordant position of phenol in these two series.

In Figs. 7 and 8 there is a sharp increase in absorbance at a critical polymer concentration for all of the systems. This is due undoubtedly to a sudden increase in aggregation of the tannin–polysorbate complex above the CMC of the surfactant solutions. The absorbance reached a maximum and then began to decrease as the oily complex which formed became solubilized in the excess of polymer solution. A rapid decrease in the absorbance of the system resulted. Although the concentration of the surfactant at the point of the sudden increase in absorbance differs from its CMC values, the marked change in turbidity may be related to micelle formation in the complex system.

Figure 7 shows that each of the polysorbates produced a turbidity upon the addition of tannin. Figure 8 shows the absorbance breaks at different fixed concentrations of polysorbate 20 upon titration with tannic acid solution. Because of the marked differences between the graphs of the separate polysorbates, the photometric turbidimetric titration method employing tannic acid was found to be a useful method for distinguishing qualitatively between these surfactants. However, with a series of polyoxyethylene ethers having the same aliphatic chain length but with different size glycol chain lengths, there appeared to be no correlation between the concentration of the surfactants at their absorbance discontinuities and the monomer content of the surfactants.

The shapes of the titration curves of the polyoxyethylene ethers were nearly identical to those of the polysorbates which are shown in Figs. 7 and 8—although the sudden absorption increase at some critical point was not so sharp with the ethers as with the polysorbates. Moreover, aqueous solutions of polyoxyethylene ethers (No. 30, 42, 52, and 72) were too turbid initially to determine

Fig. 7.—Photometric turbidimetric titration curves of polysorbates interacted with tannic acid. Key: O, polysorbate 20; △, polysorbate 40; □, polysorbate 60; ●, polysorbate 80.
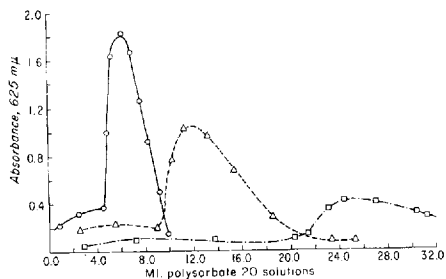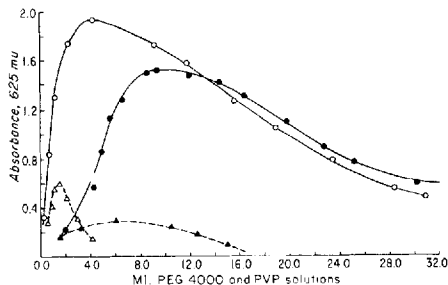

Fig. 8.—Photometric turbidimetric titration of tannic acid with various concentrations of polysorbate 20. Key: O, 0.4% w/v; △, 0.2% w/v; □, 0.1% w/v.

Fig. 9.—Photometric turbidimetric titration of tannic acid with PEG 4000 and PVP. Key: O, 0.2% w/v PEG 4000; ●, 0.5% w/v PEG 4000; △, 0.4% w/v PVP; ▲, 0.6% w/v PVP.

any further change in their absorbance properties. The polyoxyethylene monostearates and alkyl phenoxy polyethoxy ethanol did not show any abrupt increase in absorbance at a critical point above their CMC because they produced uniformly turbid mixtures. This was due possibly to a lack of purity of the commercial products. Polyethylene glycol and PVP polymers, which do not exhibit a CMC, gave smooth curves as expected without any breaks. Their graphs are shown in Fig. 9.

Although the interaction or binding of tannin as such may not necessarily be detrimental to pharmaceutical products, the fact that tannin occurs in numerous pharmaceutical formulations of natural origin could cause frequent unexpected incompatibilities if surfactants were added or whenever these products were mixed with other preparations containing surfactants. The decrease in the concentration of the stabilizers or solubilizers through their binding with tannin will obviously decrease the effective concentration of the stabilizing agent which may lead to the ultimate breakdown of some liquid pharmaceutical products. Except by complete separation of the ingredients, the only way that this incompatability may be overcome is by the addition of excess dispersing agent (18). Allawala and Riegelman (19) have pointed out that for

optimum conditions of preservative effectiveness, the ratio of phenol to surfactant should be at a minimum. Therefore, in preserved tannin-containing pharmaceuticals this incompatibility with surfactants should be considered.

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Interaction of Nonionic Hydrophilic Polymers with Phenols II

Interaction of Phenol and Hydroxyphenols with Certain Polyethylene Glycols

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The general nature of the interaction between phenol and PEG was investigated utilizing equilibrium dialysis through a cellophane membrane and NMR analysis of the insoluble complexes. Equilibrium dialysis experiments indicated that there was no correlation between the binding of phenols and the increase in acidity associated with the addition of hydroxyl groups on the phenol nucleus. An increase in temperature was found to decrease the degree of binding of phenol with PEG. NMR data indicated that for high molecular weight PEG's complexed with phenol and *p*-chlorophenol, the insoluble, oily complexes contained two ETO base moles to each cosolute molecule.

ALTHOUGH THE interactions of nonionic polymers, e.g., polyvinyl pyrrolidone (PVP)

and polysorbate 80, with various phenolic derivatives have been investigated rather extensively, the analogous reactions of polyethylene glycols (PEG) with phenols have received much less attention (1-4). Higuchi and co-workers (5, 6) have studied the interaction of PEG's and barbiturates and iodine in potassium iodide solution. They demonstrated that at a high cosolute concentration a complex formed which had a stoichiometric ratio of 2 base moles of ethylene oxide units (ETO) of the glycol to each cosolute molecule.

Various attempts to determine the mechanism of such interactions and the stoichiometric relationships of the complexes formed by interaction