TABLE II.—ABSORBANCE AS A FUNCTION OF
CHLORPHENESIN SAMPLE SIZE

Sample, mg.	A_{570}	$A_{570}/mg.^a$
0.10	0.062	0.620
0.20	0.139	0.695
0.30	0.194	0.647
0.40	0.260	0.650
0.50	0.323	0.646

^{a} Mean ± standard deviation = 0.652 ± 0.027.

TABLE III.—DETERMINATION OF CHLORPHENESIN
IN SYNTHETIC MIXTURES WITH CHLORPHENESIN-1-
CARBAMATE

Chlorphenesin, %		Recovery, %^{a}
Taken	Found	
1.96	1.95	99.5
2.91	2.98	102.4
3.85	3.81	99.0
4.76	4.63	97.3

^{a} Mean ± standard deviation = 99.6 ± 2.1.

Absorbance at 570 mμ follows Beer's law over the range 0.10 to 0.50 mg. of chlorphenesin per sample (Table II). A mean absorbance per milligram ± standard deviation of 0.652 ± 0.027 has been observed, indicating adequate precision.

Application of the method to typical synthetic mixtures of chlorphenesin and chlorphenesin-1-carbamate is shown in Table III. Over the range 2 to 5% chlorphenesin, a mean recovery ± standard deviation of 99.6 ± 2.1% has been found.

The method described is rapid, sensitive, and specific for chlorphenesin in the system studied. The range 1 to 10% chlorphenesin is covered by the method as outlined; different ranges may be accommodated by suitable changes in sample size.

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Interaction of Low Molecular Weight Polyethylene Glycols with Sorbitol Solution

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A single-phase solid material is produced when liquid polyethylene glycols and sorbitol solution U. S. P. are mixed. Various factors which influence this interaction have been explored. Temperature, components, component ratio, and soluble salts affect the rate of the interaction but do not affect the product itself. A nonspecific mechanism of dehydration of the sorbitol solution is apparently involved.

OBSERVATIONS MADE in our laboratories had shown that a waxlike solid material was produced when two widely used pharmaceutical liquids, polyethylene glycol 400 U.S.P. and sorbitol solution U.S.P., were intimately mixed. This solid substance was found to be soluble in water in all proportions and to melt in a range of 35 to 40°.

A survey of the literature indicated that this phenomenon had never been reported. This fact, in addition to the potential pharmaceutical applications of a material with such solubility and fusion characteristics, prompted further investigation.

Both sorbitol and polyethylene glycol (PEG) are ordinarily chemically inert. The oxyethylene moiety of PEG, however, is known to associate with compounds that possess an "active" hydrogen atom. This type of hydrogen bonding occurs between PEG and water, alcohol, and phenols (1). The strong tendency of PEG to form hydrogen bonds has been shown to be of pharmaceutical importance in such instances as the inactivation of salicylates (1) and a number of phenolic preservatives (2). An illustration of the extent of this association is the strong solvation of the polymer in water, which results in its complete solubilization.

A study was initiated to investigate certain variables which would provide an insight into the possible mechanism of this liquid-liquid interaction.

EXPERIMENTAL RESULTS

Procedure.—Sorbitol solution U.S.P. [containing 70% (w/w) D-sorbitol in water] and the various low molecular weight polyethylene glycols used in this investigation were maintained at 25° for at least 1 hour prior to mixing. Mixing of the components was accomplished in a 600-ml. beaker immersed in a water bath at 25 ± 0.2°. The total weight of the mixture used in all experiments was 100 Gm.

The addition of the liquid PEG to sorbitol solution results in two distinct liquid phases. Gentle stirring immediately produces a hazy cloud within the mixture. Upon continued stirring, the viscosity of the mixture gradually increases until a solid material, with no apparent liquid phase, is produced. It was noted that an increase in the rate of stirring greatly decreased the time required to solidify the mixture. Intermittent manual stirring required about 2 hours to form the solid, whereas high-speed agitation with a model F Lightnin mixer produced equivalent results in considerably shorter periods of time. The transition from the fluid to the solid state was clearly defined and gave rise to an end
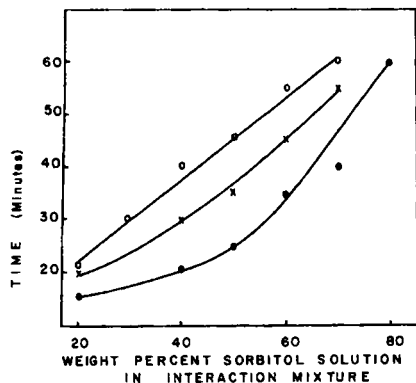
Fig. 1.— The effect of PEG molecular weight and sorbitol solution concentration on solidification time. Key: O = PEG 200; X = PEG 300; ● = PEG 400.
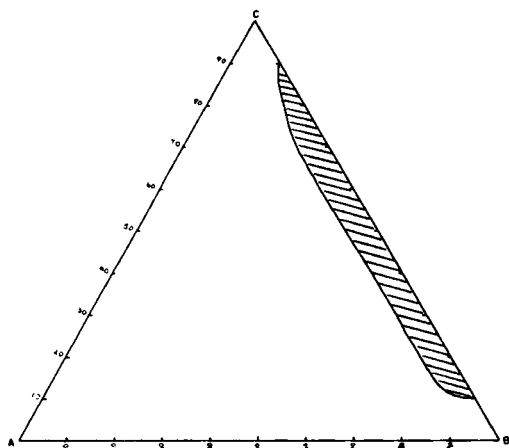

Fig. 2.—Ternary plot indicating critical component ratios of A, excess water; B, PEG 400; and C, sorbitol solution. (Shaded area = solid state; unshaded area = liquid state.)

point which was reproducible to within 1 minute at a given speed of mixing. Since the rate of mixing was critical in determining the end point, the Lightnin mixer was locked at a constant speed of about 1500 r.p.m. measured by a tachometer.

Effect of Composition.—Varying amounts of PEG 200, 300, or 400 were added to a sufficient quantity of sorbitol solution to prepare 100 Gm. The mixtures were treated as outlined above, and the time required to achieve a solid end point for each mixture was recorded. Figure 1 demonstrates that this time is increased with an increase in sorbitol solution concentration in the mixture. In addition, this plot indicates that the interaction rate is dependent on the ethylene oxide content of the PEG used. A decrease in the ethylene oxide content results in an increase in the time required for solidification. Mixtures containing more than 90% of either liquid component failed to solidify within 2 hours of mixing.

Solubility determinations revealed that crystalline D-sorbitol exhibited less than 1% solubility in PEG 400 with no apparent viscosity change. Excess

amounts of D-sorbitol produced suspensions of this material in the PEG with no solidification occurring even when a 50% (w/w) suspension was prepared and stirred for several hours. No changes occurred when these suspensions were stored under ambient conditions for 3 months in sealed containers. It would thus appear that water is required for the interaction to occur.

To determine the extent of the role of water in the interaction, various mixtures of water, sorbitol solution, and PEG 400 were prepared. Figure 2 illustrates the phase analysis derived from these experiments. This ternary diagram indicates that excess water above 7% results in a clear, single-phase solution, regardless of the sorbitol solution–PEG ratio present. An excess water content of between 0 and 7% resulted in the formation of a solid, provided a proper ratio of sorbitol solution–PEG existed.

There were no intermediate stages of solidification. A given mixture either remained fluid or else became a solid mass. The solid never varied in its apparent consistency. The "melting point" of the solid was between 35 and 40° in all cases.

Effect of Temperature.—Raising the temperature of the interaction mixture resulted in a significant increase in the time required for solidification. The results of one series of such experiments are depicted in Fig. 3.

Effect of Addition of Soluble Salts.—Two grams of either powdered sodium chloride or powdered calcium chloride were added to an interaction mixture consisting of 50% (w/w) of sorbitol solution and PEG 400. The mixtures were stirred under controlled conditions and the solidification point determined. In each case, the effect of the salts was observed merely as a kinetic phenomenon. Both salts significantly increased the time for solidification to occur. This is indicated in Table I. Salts, however, did not affect the solidification products, which were indistinguishable in consistency from the control samples.

Effect of Dehydration of Sorbitol Solution.—Since it appeared that the water content of the interaction mixture was critical to the formation of the solid, a series of experiments was conducted to evaluate the effect of physical and chemical dehydration on sorbitol solution. The addition of excess amounts of soluble salts to sorbitol solution resulted in the formation of a clear, rigid gel after about 1 week. Salts such as sodium chloride and sodium citrate were equally efficient in their ability to produce the gels.

Anhydrous ethyl alcohol was carefully layered on top of sorbitol solution. This resulted in the gradual solidification of the lower sorbitol layer. A clear gel resulted upon standing for 2 weeks.

Continuous heating of sorbitol solution in an open vessel at 80° produced a very hard, clear gel after 3 days.

TABLE I.—EFFECT OF SALT ON INTERACTION RATE

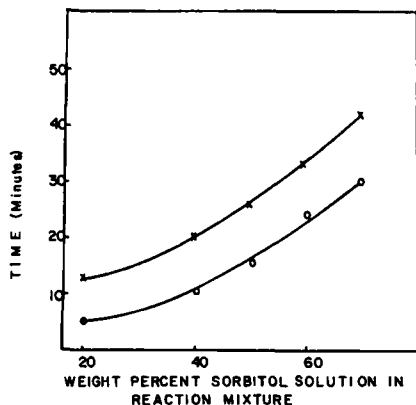| Salt	Time Required to Reach End Point, Min.
Sodium chloride	32
Calcium chloride	35
Control (no salt)	15

Fig. 3.—The effect of temperature on solidification time of PEG 400 and sorbitol solution mixtures. Key: O = 25°; X = 30°.
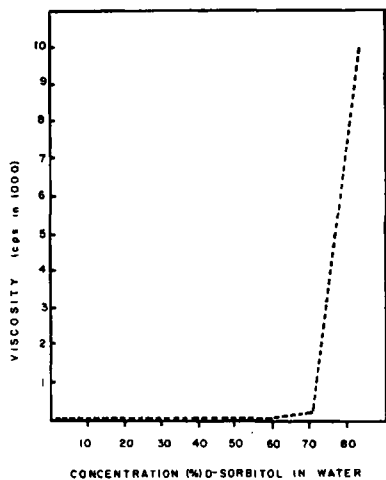

Fig. 4.—Viscosity of sorbitol solutions *versus* D-sorbitol concentration.

DISCUSSION

A study of the data indicated that a nonspecific mechanism seemed to be involved in the formation of the solidified mixture. This conclusion was based on the apparent similarity in properties of the solid obtained under the wide range of experimental conditions described. A possible explanation is that low molecular weight polyethylene glycols, mixed with sorbitol solution, produce a dehydration effect on the solution which results in a polymeric material consisting of associated molecules of sorbitol. The formation of this polymer and its dispersion throughout the system could conceivably result in an extremely rigid state possessing a high internal fluidity.

The transition from the liquid to the solid state occurred over a fairly narrow concentration range of water in the system. This is in consonance with the fact that the viscosity of sorbitol solution is nearly independent of sorbitol concentration up to 70%

(w/w). Immediately beyond this concentration a fiftyfold increase in viscosity occurs over a 13% concentration range (from 70 to 83%) (3). This unusual rheological behavior is depicted in Fig. 4.

Density data available on solutions of different concentrations of D-sorbitol in water also indicate that beyond the 70% concentration marked deviation from linearity occurs. This is indicative of a reduced molar volume and association of molecules in the system. In view of these considerations, a slight dehydration of 70% sorbitol solution would result in a disproportionate increase in the viscosity. This contention is borne out by the results obtained with those experiments where dehydration of the sorbitol solution was accomplished by physical and chemical means, *viz.*, salts, ethyl alcohol, and evaporation at elevated temperatures.

The proposed mechanism is supported by the data obtained with the PEG–sorbitol solution experiments. As indicated in Fig. 1, the reduction of sorbitol solution content in a system resulted in a decrease in the time required for the solid to form. The decrease in time is directly related to the decrease in the water content of the mixtures with lower sorbitol solution content. A relatively smaller amount of water, therefore, needs to be removed by the correspondingly larger amounts of PEG to induce solidification.

Figure 1 also shows that the time required for solidification is dependent on the molecular weight of the PEG used. The affinity of polyethylene glycol for water is related to its ethylene oxide content. By the same token, the rate at which it is capable of dehydrating a material is equally dependent on the ethylene oxide content. This is in agreement with the order of interaction time evidenced in Fig. 1.

The effect of temperature (Fig. 3) is likewise related to the dehydration effect. The association of water with the oxyethylene moiety of PEG is critically temperature dependent (1). The bonding of water to this polymer will be considerably weakened with increasing temperature, and the affinity of this moiety for water will be correspondingly decreased. The expected decrease in interaction rate with increasing temperature is demonstrated in Fig. 3.

The prolonged reaction time observed with the addition of salts to the PEG–sorbitol solution mixture (Table I) may possibly be attributed to two factors acting in concert. (*a*) The addition of salts to sorbitol solution results in an increased viscosity. This increased viscosity may be responsible for a slower rate of mixing with PEG and therefore a slower rate of interaction. (*b*) The rate of dehydration of the sorbitol solution by the PEG will be dependent upon the thermodynamic activity of the water in the sorbitol solution. The addition of salts will decrease this activity and therefore prolong this interaction time.

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