conjugated metabolites with increasing drug dose. The present study differs from earlier ones (4, 9, 10) by not showing any dose-excretion correlation, and by yielding per cent excretion values substantially higher than those of Posner *et al.*, considered less than comprehensive, but lower than those of Huang *et al.*, believed to include normal urinary contaminants.

The reported results (Table I) could not be expected to show a definite correlation between drug excretion and such clinical parameters as diagnosis, drug response, or mental status of the patients; this group of patients was selected only to establish the spread of urinary excretion over a large range of chronic doses. The population sample, though small, included members of the three major ethnic groups with the most diverse psychiatric diagnoses. However, preliminary data on the correlation between side effects of drug therapy and urinary drug metabolism were recently reported for the initial phases of drug administration (19) as well as for drug-induced skin hyperpigmentation (22, 23).

The method is currently being used to study the time required to reach a steady excretion rate, to determine the effect of simultaneously administered compounds on the biotransformations and urinary excretion of chlorpromazine, and to elucidate species differences in chlorpromazine metabolism.

When studying the urinary drug excretion in mental patients, a number of factors not readily controlled in a normal hospital setting may affect the reproducibility of the chemical results. They are variations in diet, and intake of food and liquids. Most patients were found to increase their urinary output by a factor of 2 or 3 under chronic administration; the volumes eventually became reasonably stable at this higher level. Large fluctuations in consecutive 24-hr. specimens tended to yield erratic results. Therefore, rigorous surveillance of controllable parameters like drug intake (preferably in liquid form) and of 24-hr. urine collections cannot be overemphasized.

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Solubility of Parabens in Syrup Vehicles

By ANTHONY N. PARUTA* and BHOGILAL B. SHETH

The solubilities of methyl, ethyl, propyl, butyl, and benzylparabens have been determined in sucrose vehicles of varying concentration. These syrup vehicles possess dielectric constants less than pure water, their respective dielectric constants decreasing with increasing sucrose concentration. The effect of both the concentration of sucrose added and the dielectric constant upon the solubility of the subject compounds is presented. The solubilities of these materials were seen to change to a relatively small degree with increasing sucrose concentration. Although these changes in solubility are minute, they would appear to be positive in character. The only definitive change noted was for benzylparaben where a relatively large change in solubility was noted.

The general use and application of sucrose solutions of varying concentration for liquid pharmaceuticals is still widespread. In an effort to continue (1, 2) to determine the solvency characteristics of these media, the present study was undertaken. It was felt judicious that a study of a set of solutes of varying polar character be undertaken so that the effect of methyl, ethyl, etc., groups upon the solubility in common dissolution media could be studied. In this way, a tendency or characteristic effect of substituent groups could be delineated implying an effect that has been termed "solute polarity."

It has been found that relatively dramatic

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solubility effects occurred with the xanthine drugs, antipyrine, and several derivatives in syrup vehicles (2). In these cases, both increased and decreased solubility was noted with increasing sucrose concentration up to simple syrup. The parabens find wide use as preservatives in pharmaceutical liquid preparations as well as syrup vehicles, and it was felt desirable to determine their solubility in these vehicles. It was thought that if solubility effects, especially decreased solubility, occurred as extensively as with materials previously studied, the possibility of untoward effects such as preservative precipitation may occur.

EXPERIMENTAL

Materials.—The solutes used in this study were used directly as supplied by the manufacturer. The methyl and propylparabens were obtained from the Nepera Chemical Co. The ethyl and benzylparabens were obtained from Heyden Chemical Corp., lots 113 and 59, respectively. Butylparaben was obtained from Eastman Kodak, catalog No. EK 4574. Syrup vehicles were prepared from commercial granulated sugar and deionized or distilled water. Mixtures of absolute ethanol and either deionized or distilled water were used for dielectric constant calibration.

Equipment.—A WTW DK-06 multidekameter was used for dielectric constant determinations, a Bantam (mixed resin bed) demineralizer for producing deionized water. A Bausch & Lomb 505 spectrophotometer was used to determine sample absorbance and a water bath and attendent temperature controller was used for equilibration at 25°.

Dielectric Constant Determination.—The dielectric constants were determined by the use of a WTW multidekameter DK-06. Calibration curves were prepared from condenser readings and known dielectric constants (3) using ethanol–water mixtures. The dielectric constant values obtained for the syrup vehicles prepared gave excellent agreement with values of previous workers (4, 5). The accuracy of these determinations is about ±0.3 of a dielectric constant unit.

Solubility Determinations.—The protocol used in solubility determinations has been described previously (1, 2). Seventy-two hours was the time determined for equilibration at 25° ± 0.1°. All solubility runs were done at least four times, however, seven replicates were needed for the propyl and butylparabens in order to delineate the range of the magnitude of solubility for each given sucrose vehicle. Methylparaben caused some experimental difficulty since nonfilterable suspensions formed in syrup vehicles. It was found that allowing the methylparaben samples to lie quiescent in the water bath for several hours, clear samples were readily obtained.

RESULTS AND DISCUSSION

In Fig. 1, the solubility of methylparaben in mg./ml. *versus* both the concentration and the di-

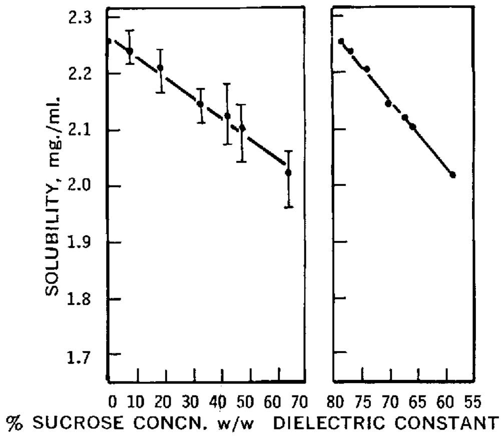

Fig. 1.—A plot of the solubility of methylparaben in mg./ml. at 25° as a function of sucrose concentration and dielectric constants.

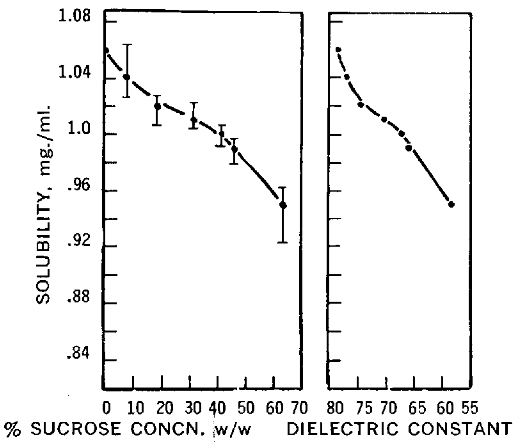

Fig. 2.—A plot of the solubility of ethylparaben in mg./ml. at 25° as a function of sucrose concentration and dielectric constants.

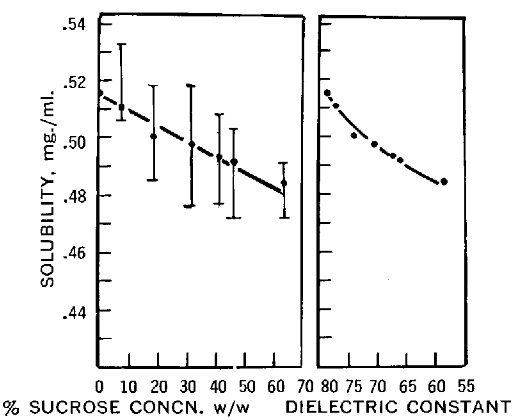

Fig. 3.—A plot of the solubility of propylparaben in mg./ml. at 25° as a function of sucrose concentration and dielectric constants.

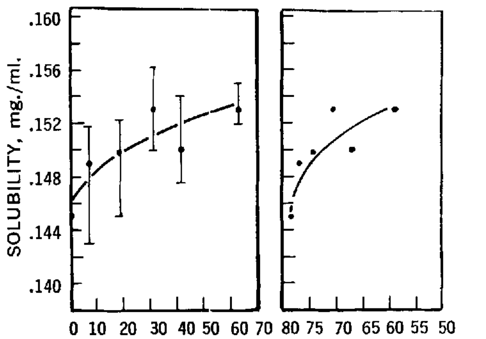

Fig. 4.—A plot of the solubility of butylparaben in mg./ml. at 25° as a function of sucrose concentration and dielectric constants.

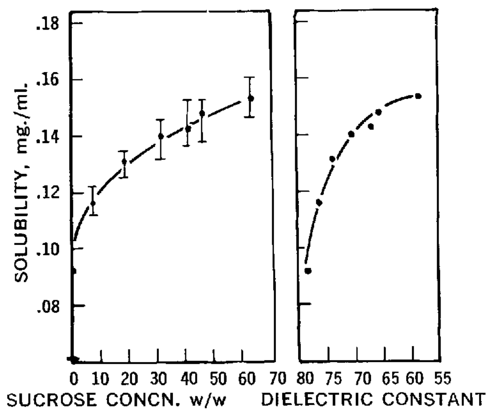

Fig. 5.—A plot of the solubility of benzylparaben in mg./ml. at 25° as a function of sucrose concentration and dielectric constants.

electric constant of the syrup vehicles is shown. The solubility is seen to decrease as a function of both increased sucrose concentration and decreased dielectric constant. The rate of change is approximately linear having values of about −0.1 mg./10% w/w sucrose and about −0.1 mg./10 dielectric constant units. The solubility of methylparaben in simple syrup relative to water has a value of about 0.9. The variation in solubility in mg./ml. in Fig. 1 and subsequent figures is shown as a vertical line through the point of the average value. The variation is shown as the highest and lowest solubility in mg./ml. over the number of runs for pure water or any particular syrup vehicle. The variation has only been shown on the sucrose concentration axis, since once the nature of the curve has been defined on this basis, the dielectric constant scale retains the same shape, accentuated to some degree due to the "squeezing-in" on a shorter x-axis scale. The latter is especially true in the case of ethylparaben shown in Fig. 2. Again the solubility in mg./ml. is plotted in the usual fashion. In this case, an approximately sigmoidally disposed and decreasing solubility curve is observed. The solubility ratio, the solubility in simple syrup relative to water has a value of about 0.9. Repetitive runs in the 20–40% w/w sucrose range showed small variation and it is felt that the curve shown is a true reflection of the solubility pattern. It should also be pointed out that the solubility curve on a dielectric constant basis accents the sigmoidal nature of this curve.

In Figs. 3 and 4, the solubility curves obtained for the propyl and butylparabens, plotted in the usual fashion, are shown. As can be seen from these plots, the variation of solubility over a number of runs is quite wide, and this is due to the very low solubility of these materials. It would seem that one can only simply describe these solubility curves in approximately quantitative terms. Thus, the solubility of propylparaben decreases

Table I.—Summary of the Average Solubility in mg./ml. for the Parabens in the Systems Noted

System	Solubility, mg./ml.				
	Methylparaben	Ethylparaben	Propylparaben	Butylparaben	Benzylparaben
Water	2.26	1.06	0.516	0.145	0.092
7.5% w/w sucrose	2.24	1.04	0.510	0.149	0.116
18.5% w/w sucrose	2.21	1.02	0.500	0.150	0.131
31.5% w/w sucrose	2.15	1.01	0.497	0.153	0.140
41.5% w/w sucrose	2.12	1.00	0.493	0.150	0.143
46% w/w sucrose	2.11	0.99	0.491	...	0.149
63.5% w/w sucrose	2.02	0.95	0.484	0.153	0.153
Solubility ratio: mg./ml. syrup / mg./ml. water	0.89	0.90	0.94	1.06	1.7

Table II.—Summary of the Solubility Ratios (mg./ml. Syrup/mg./ml. Water) Found for the Paraben Derivatives

	Run, No.							
	1	2	3	4	5	6	7	Av.
Methylparaben	0.89	0.91	0.92	0.86	0.91	0.88	...	0.90
Ethylparaben	0.93	0.89	0.89	0.91	0.87	0.89	...	0.90
Propylparaben	0.90	0.93	0.95	0.96	0.97	0.93	0.93	0.94
Butylparaben	1.04	1.03	1.06	1.09	1.05	1.04	1.06	1.05
Benzylparaben	1.7	1.4	1.7	1.9	1.6	...	...	1.67

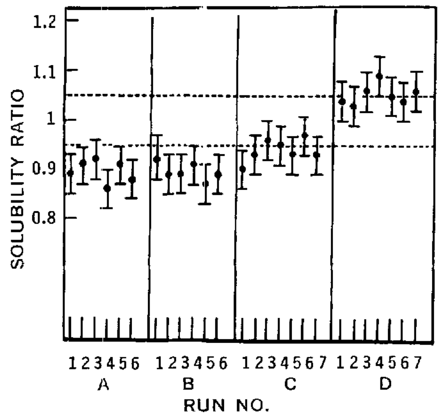

Fig. 6.—A plot of the solubility ratios for the *n*-alkyl parabens over repetitive runs including the determined variation. Key: A, methylparaben; B, ethylparaben; C, propylparaben; D, butylparaben.

slightly and has a solubility ratio of about 0.94. Butylparaben, on the other hand, increases slightly, the solubility ratio having a value of 1.06.

For both propyl and butylparaben, a nonlinear solubility curve has been drawn through the points of average value. Since the experimental values varied to such a large extent, the nature of the curve is considered arbitrary.

In Fig. 5, the solubility of benzylparaben in mg./ml. is plotted in the usual manner. For this derivative, having very low solubility in water, the solubility is seen to increase to a rather large extent, the solubility ratio having a value of about 1.7.

The average solubility in mg./ml. for each of the parabens studied in the syrup vehicles noted is given in Table I.

Although the solubility effects in syrup vehicles for the parabens are small, there is good consistency in the solubility ratios over a set of multiple runs. The value for independent solubility ratios for the number of runs stated is given in Table II.

The dielectric constants of the syrup vehicles were known, and it would be desirable to note any changes in this parameter for the saturated solutions of the parabens. The dielectric constants of the saturated solutions were measured at 25° on the DK-06 dekameter. As was found previously (2) no discernible patterns of change were found for the parabens. The dielectric constants for the saturated solutions, however, did follow the solubility curve and no sudden changes or aberrations in these values were noted for the range studied.

The solvency characteristics of sucrose vehicles can be viewed in two ways, the first being the decrease in the activity of water. With increasing sucrose concentration less water is available to interact with solute molecules, causing dissolution.

Second, the dielectric constants of syrup vehicles decrease with increasing sucrose concentration, implying decreased "polarity" of the dissolution media. The solubility of any given solute may then increase or decrease according to the mechanism or combination of mechanisms operative. The increase or decrease in solubility probably depends upon the nature of the solute and the original magnitude of the solubility in water.

It would be well to consider that a noted change in solubility should be outside or greater than 5%. In other words, it is presumed that a direction of change can only be classified as positively increased or decreased when all the data on repetitive runs fall outside this 5% limit.

In this regard, the solubility ratios for the *n*-alkyl parabens over repetitive runs (Table II) have been plotted in Fig. 6 using the largest variation observed for the solubility in simple syrup for each of the parabens.

The line unity represents 100% of solubility (of the value in water) and the dashed lines are the 5% limit described above. The vertical lines through the average data points represent the determined variation.

From the spread of values for the methyl and ethylparabens, it would seem that the solubility of these materials is affected to a very slight degree, *i.e.*, about 5%. For propyl and butylparabens, the descriptive term of "essentially linear" would apply, especially in view of the wide variation of solubility in the vehicles studied.

The only definitive change observed in the magnitude of solubility was for the benzylparaben where an average increase of about 70% in solubility was observed.

These results are perhaps not completely unexpected since the solubility parameter values given by Martin (6) are quite close to one another. This would indicate that the asymptotic right-handed portion of the solubility distribution curve over a small portion of the dielectric range (syrup vehicles ϵ = 60–75) for the parabens are very close to one another. This would be especially true in solvent systems such as sucrose in water relative to a hydroalcoholic solvent system where it might be expected that discriminatory differences in solubility would occur.

In conclusion, the solubility effects noted with the parabens of general interest are slight or nonexistent in contrast to previously noted effects with other materials (2).

Since large solubility effects have been noted for the xanthines and antipyrine (2) and small or no effect was noted for the parabens, it is felt judicious to continue this type of work. In this regard, the solubility of acetanilide and several derivatives are presently being studied in syrup vehicles.

The parabens are an important class of materials in pharmacy. Future work on the dielectric solubility profiles of these materials is presently under way and the authors' results will be given in a future communication.

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