Solubility of the Xanthines, Antipyrine, and Several Derivatives in Syrup Vehicles

By ANTHONY N. PARUTA and BHOGILAL B. SHETH

The solubilities of the xanthine drugs, antipyrine, aminopyrine, and 4-aminoantipyrine in sucrose solutions of varying concentration have been determined. The effect of "additive" concentration, sucrose, upon the solubility of subject materials is rather dramatic, either increases or decreases in solubility being noted. The path or rate of change of solubility with increasing sucrose concentration are seen in some cases to be of a complex functionality and may indicate a combination of mechanisms. Since the dielectric constants of these sucrose vehicles were also known, the solubility as a function of the dielectric constant is also considered.

SYRUP VEHICLES still find wide use in the pharmaceutical field in liquid preparations, and in a continued effort (1) to study the characteristics of these dissolution media, this study was undertaken. The primary objective of this study was to determine if a given solute would have the same magnitude of solubility in water and simple syrup. If the solubilities were found to differ, it was felt important to determine the rate of change of solubility with sucrose concentration. Thus, syrup vehicles at concentrations intermediate to simple syrup were also tested. The solubilities of the xanthines, antipyrine, aminopyrine (4-dimethyl aminoantipyrine), and 4-aminoantipyrine in syrup vehicles at various concentration levels up to saturation have been determined.

Since it was known that the dielectric constants of sucrose solutions (1) decreased with increasing concentration, this was felt to be another parameter in which solubility could be expressed. It is implied that the usefulness of the dielectric constant resides in the expression of polarity of a given dissolution media. The dielectric constants of sucrose solutions have been determined previously (1), by other workers (2, 3), and have been repeated in this study. One main purpose of studying dielectric constants of saturated solutions of solutes was to observe if the magnitude of solubility could be correlated with the change in dielectric constant of the syrup vehicle used.

These sucrose solutions can also be considered as media in which the activity of water has been decreased by the additive, sucrose, and this may also effect the magnitude of solubility. It is possible that both decreased and increased solubility can occur and the operative mechanism being decreased dielectric constant, decreased activity, or a combination of these. It is obvious that as the sucrose concentration is increased, the water concentration is decreased; however, it is the author's view that these vehicles are *per se* dissolution media. The dependence of increased or decreased solubility probably resides in the nature of the solute and the solvent system. Whereas increased solubility had been noted in a previous study (1), both increased and decreased solubility have been found in this study.

Previous work (4–7) had indicated that the asymptotic portion of the solubility curve would have to be extended past the dielectric constant value for pure water in order to achieve decreased solubility. The results of this study show that significant solubility decreases can occur with a solvent system having dielectric constant values less than pure water.

EXPERIMENTAL

Materials.—Caffeine U.S.P. (Nepera Chemical Co.), theophylline U.S.P. (Matheson, Coleman and Bell, 7094 Tx 450), theobromine alkaloid N.F. (Penick NBT 4092), antipyrine N.F. (Penick NBT 3710), aminopyrine N.F. (Penick NBT 2376), and 4-aminoantipyrine (Eastman-Kodak white label—6902). These materials were used directly as received from the manufacturer.

Equipment.—Constant-temperature bath, Bausch & Lomb spectronic 505, WTW Multidekameter DK-06, Bantam demineralizer, BD-1, with mixed resin bed.

Solubility Determinations.—Solubility determinations were made as described previously (4–7). Equilibration time was found to be 72 hr. and all determinations made at 25° ± 0.1°. Some difficulty was encountered in pipeting samples of simple syrup due to high viscosity and these samples show a somewhat larger variation since 1-ml. samples were used in contrast to 5-ml. samples for all other syrup vehicles. After appropriate dilutions, all samples were assayed spectrophotometrically.

Dielectric Constant Determinations.—Dielectric constant determinations were done at 25° on a WTW Multidekameter, DK-06. A calibration curve was prepared from absolute ethanol and water. One advantage of this instrument is that the cali-

Received February 21, 1966, from the Pharmaceutical Research and Development Laboratories, Warner-Lambert Research Institute, Morris Plains, N. J. 07950.
Accepted for publication June 8, 1966.
Presented to the Basic Pharmaceutics Section, A.PH.A. Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.

TABLE I.—SUMMARY OF THE AVERAGE SOLUBILITY AND THE SOLUBILITY RANGE OF THE VARIOUS SOLUTES STUDIED IN WATER AND SYRUP VEHICLES

Solvent	Av. Solubility, mg./ml.					
	Antipyrine	4-Amino-antipyrine	Amino-pyrine	Caffeine	Theophylline	Theobromine
Water	670 ± 15	410 ± 10	48 ± 3	21 ± 1	8.0 ± 0.3	0.56 ± 0.02
7.5% w/w sucrose	605 ± 20	390 ± 10	42 ± 2	...	8.2 ± 0.3	...
18.5% w/w sucrose	500 ± 20	340 ± 10	36 ± 2	19 ± 1	8.3 ± 0.2	0.66 ± 0.05
31.5% w/w sucrose	380 ± 20	305 ± 10	30 ± 2	17 ± 1	8.3 ± 0.3	0.70 ± 0.03
41.5% w/w sucrose	...	250 ± 10	24 ± 2	...	8.2 ± 0.3	...
46% w/w sucrose	280 ± 20	205 ± 15	19 ± 2	14 ± 1	7.9 ± 0.3	0.70 ± 0.03
63.5% w/w sucrose	185 ± 20	140 ± 20	16 ± 2	10 ± 1	6.2 ± 0.5	0.83 ± 0.03

TABLE II.—SUMMARY OF THE AVERAGE SOLUBILITY RATIOS, $\frac{\text{SOLUBILITY IN SYRUP}}{\text{SOLUBILITY IN WATER}}$, FOR THE VARIOUS SOLUTES STUDIED

Solute	Av. Solubility Ratio, $\frac{\text{mg./ml. Syrup}}{\text{mg./ml. Water}}$
Caffeine	0.48
Theophylline	0.83
Theobromine	1.40
Antipyrine	0.28
Aminopyrine	0.32
4-Aminoantipyrine	0.38

bration curve is linear and although minor day to day variations are noted, the calibration curves are virtually a family of parallel lines. The error in the measurement of dielectric constants is ±0.3 dielectric constant units. Deionized water was used throughout this study as distilled water seemed to cause slight aberrations in the calibration curves, possibly due to ionic contaminants.

RESULTS AND DISCUSSION

The solubilities of the solutes under consideration in this study in water and the various syrup vehicles used are given in Table I. The average value given expresses the average of at least six determinations and in some cases, *i.e.*, theophylline and theobromine, 8–12 determinations were made. The range of the determined solubility in mg./ml. is also shown in this table for the lowest and highest solubility noted over the number of runs made.

The average solubility ratios, the solubility in mg./ml. of simple syrup/solubility in mg./ml. of water, for the solutes studied are given in Table II. In all cases, significant changes in the magnitude of solubility were noted in going from water to simple syrup.

The solubility of caffeine in mg./ml. *versus* either sucrose concentration or dielectric constants is given in Fig. 1. For caffeine it is observed that the solubility decreases dramatically, the magnitude of solubility being about 0.5 in syrup relative to pure water. The path or rate of change in solubility is a smooth nonlinear function when plotted *versus* sucrose concentration; however, approximate linearity is observed on a dielectric constant basis. The rate of change for this parameter is about 0.55 mg./dielectric constant unit. The representation of data on a dielectric constant basis simply "squeezes in" the x-axis, and the solubility curve retains the approximate shape noted on the concentration basis.

In the case of aminopyrine and antipyrine it is also observed that the solubilities decrease dramatically with either increasing sucrose concentration or decreasing dielectric constant. The data have been plotted and are shown in Figs. 2 and 3. Both solubility curves are essentially smooth nonlinear functions, and the ratio of the solubility in syrup relative to water for aminopyrine and antipyrine are 0.32 and 0.28, respectively.

The solubility of 4-aminoantipyrine in the syrup vehicles studied is given in Fig. 4. Again, the experimental solubilities are plotted in mg./ml. of solution for both increasing sucrose concentration and decreasing dielectric constants. In this case, it is observed that an essentially sigmoidal solubility curve is obtained, and a significant change in the solubility occurs. The ratio of the solubility in syrup relative to water for this solute was found to be about 0.38.

The effect of substituents, solubility ratios, and magnitudes of solubility will be discussed later in this communication with respect to the antipyrine derivatives.

In the case of theobromine, an increase in solubility is found with increasing sucrose concentration or decreasing dielectric constants. The ex-

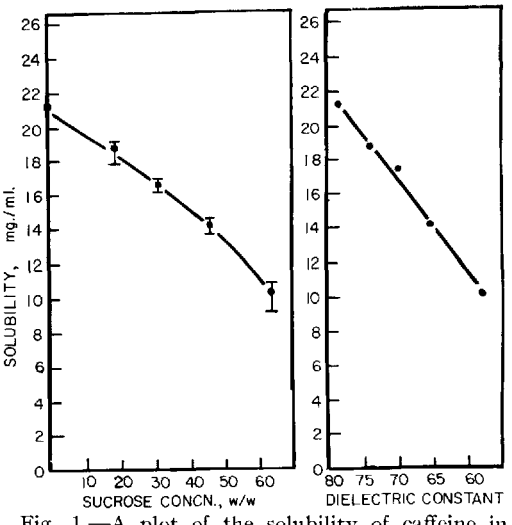

Fig. 1.—A plot of the solubility of caffeine in mg./ml. at 25° as a function of both sucrose concentration and dielectric constants.

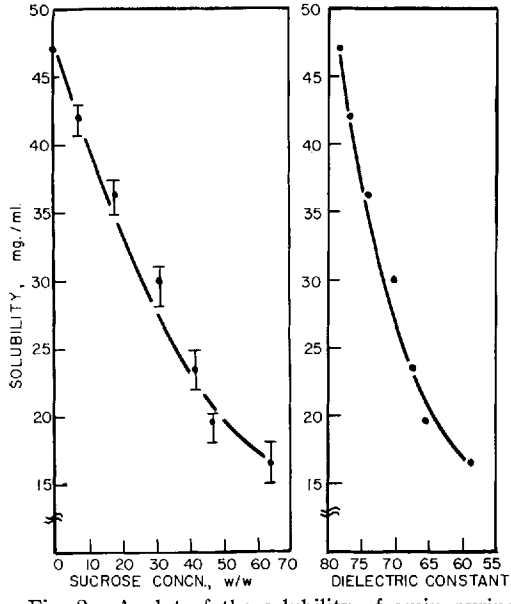

Fig. 2.—A plot of the solubility of aminopyrine in mg./ml. at 25° as a function of both sucrose concentration and dielectric constants.

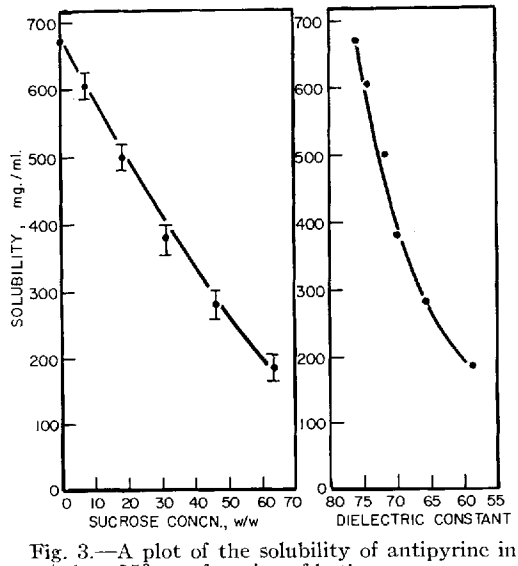

Fig. 3.—A plot of the solubility of antipyrine in mg./ml. at 25° as a function of both sucrose concentration and dielectric constants.

perimental data obtained were plotted in the usual fashion and are shown in Fig. 5. In this case, the solubility ratio has a value greater than unity, the solubility in syrup relative to water having a value of about 1.4. However, as noted in the case of 4-aminoantipyrine, the path of change is essentially sigmoidal but opposite in direction.

The solubility of theophylline presented in the usual fashion is given in Fig. 6. The solubility curve goes through a maxima and the equilibrium solubility in simple syrup finally fell to a lower value than the solubility in pure water. The solubility in simple syrup relative to water had a value of about 0.8. The maximum solubility at about 20–30% w/w sucrose represents about an 8% increase in solubility.

Mechanistically, it is felt that the additive decreases the activity of water by causing a statistically reduced number of hydrogen bonding sites which would ordinarily be available to the solute in the absence of the additive. It would seem then that any additive capable of interferring with, reducing

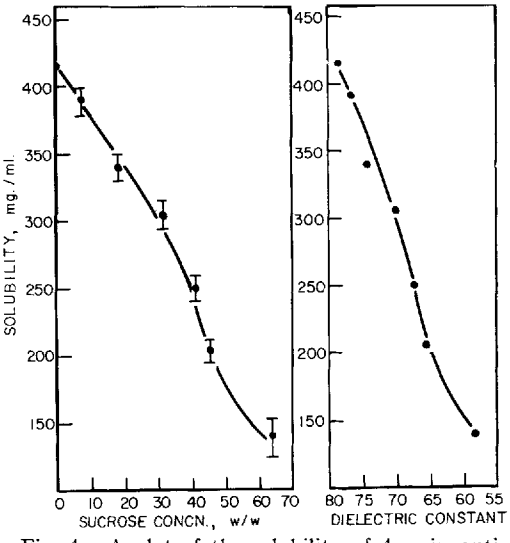

Fig. 4.—A plot of the solubility of 4-aminoantipyrine in mg./ml. at 25° as a function of both sucrose concentration and dielectric constants.

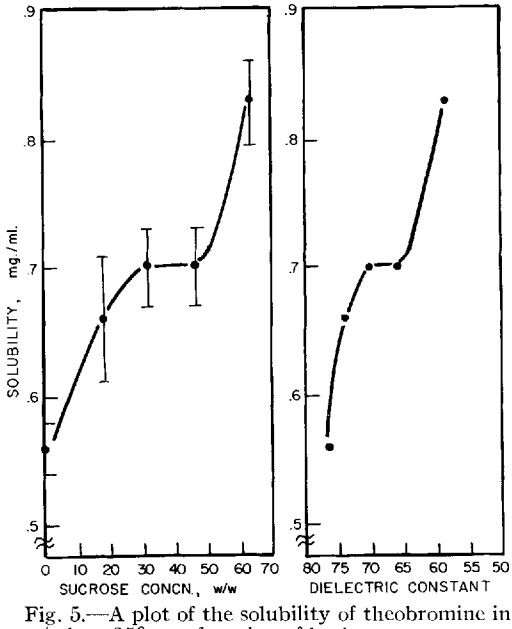

Fig. 5.—A plot of the solubility of theobromine in mg./ml. at 25° as a function of both sucrose concentration and dielectric constants.

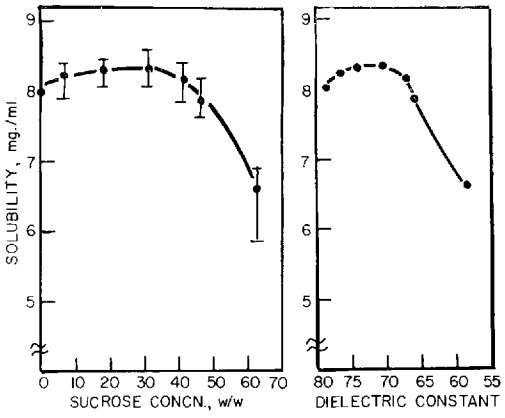

Fig. 6.—A plot of the solubility of theophylline in mg./ml. at 25° as a function of both sucrose concentration and dielectric constants.

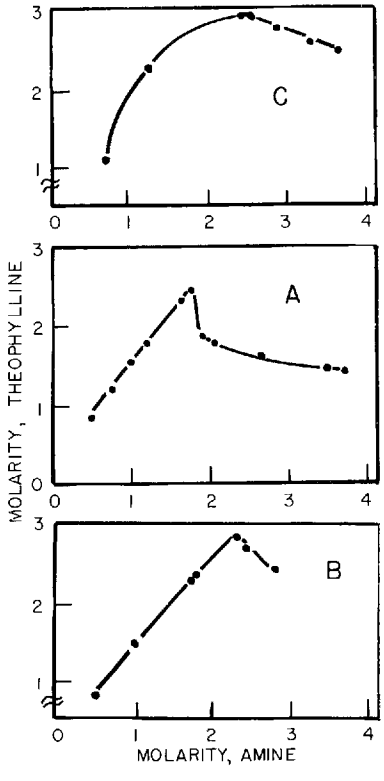

Fig. 7.—A plot of the solubility of theophylline as a function of added amine in amine–water mixtures. Key: A, monomethylamine; B, monoethylamine; C, monopropylamine.

the number, or tying up hydrogen bonding sites disturbs or shifts the equilibrium to the left, thereby decreasing the magnitude of solubility.

However, increased solubility was also found in this study, and this may be due to the decreased polarity of the syrup vehicles as measured by the dielectric constant. It is probable that a combination of mechanisms are operative. From this study, and others presently underway, it would seem that the nature of the solubility curve for a given solute in syrup vehicles depends strongly upon the original magnitude of solubility in pure water.

On the dielectric constant basis, maximum solubility is seen to occur in the dielectric constant range of 70–75. Some data (8) were available in which the solubility of theophylline had been studied in alkylamine solutions. Although the authors, Leuallan and Osol, were apparently determining the "complex" formation of theophylline and amines and solubilization therefrom, their data have been reanalyzed to apply the dielectric constant concept. The data have been replotted and shown in Fig. 7.

In the presence of monomethylamine, a maxima appears in the solubility curve at about 1.8 Gm. moles amine/L. of water. In this case and in other solubility curves presented for the amines, it has been assumed that the dielectric constant variation is linear with respect to the weight/weight composition notation. In other words, the decrease in dielectric constant from pure water to any amine concentration is proportional to the weight of the added amine. For monomethylamine, the peak solubility occurs at a dielectric constant value of about 75 which agrees with the span of 70–75 noted in the syrup vehicles. In the case of monoethyl and monopropylamines, also shown in Fig. 7, peak solubility occurs at dielectric constant values of about 71 and 68, respectively. These values concur with the range of 70–75 found in syrup vehicles. It should also be noted that the peak dielectric constants in these amine systems decrease with increasing size of the *n*-alkyl substitution.

The above data have been summarized in Table III using dielectric constant values from the literature (9). The approximate correlation of peak solubility dielectric constants for some of the amine–theophylline systems and theophylline–syrup systems is considered to be fair. The remaining theophylline–amine systems were also analyzed; however, no conclusion could be drawn from the data within the above context. Furthermore, it may be instructive to note, that both the amine and sucrose can be considered as "additives" having an approximately common effect on the solubility of theophylline. It is also rather surprising that irrespective of the possible formation of a more soluble "amine compound" or just simply adding sucrose, the peak solubility dielectric constants are to a fair degree correlatable.

Table III.—Summary of the Peak Solubility Dielectric Constants Found for Several Theophylline–Amine Systems[a]

Amine	ϵ^b Amine	Dielectric Constant Range	Peak Solubility Dielectric Constant
Monomethylamine	9.4	78.5–69.7	74.6
Monoethylamine	7.9	77.0–69.6	71.2
Monopropylamine	~5.0	75.5–62.5	68.0

[a] Data from *Reference 8*. [b] *Reference 9*.

DIELECTRIC CONSTANTS

After sample withdrawal for those solutes, the saturated solutions were tested in the dekameter at 25°, by a circulating water bath, relative to their dielectric constant values.

It had been hoped that, as the concentration of a given solute would increase or decrease, the dielectric constant of that sample would increase or decrease proportionally relative to the dielectric constant value of the syrup vehicle. In other words, the 10 mg./ml. of caffeine in simple syrup should affect the dielectric constant of simple syrup to a lesser extent than the 19 mg./ml. of caffeine in the 20% w/w syrup vehicle. This was not found to be the case in general, and no apparent conclusion could be observed from these data. The dielectric constants of the saturated solutions did, however, follow the shape of the solubility curve, but there was no general pattern in incremental increases or decreases relative to the syrup vehicles themselves. It should be noted that these determinations are over a relatively short dielectric constant span and overlapping small incremental changes with the error involved and day-to-day calibration variation are too close to delincate any patterns of change.

There was a notable exception to the above, that being the case of the highly water-soluble antipyrine, and this is shown in Fig. 8. In this figure the solubility curve and the Δ-dielectric constant curve for the saturated solutions (difference between the dielectric constant of saturated solution and the syrup vehicle) cross each other and are approximately mirror images. In this case then, as the solubility of antipyrine decreases in the syrup vehicles going to simple syrup there is proportionately less effect on the dielectric constant of the syrup vehicle itself. The very high solubility of antipyrine relative to the other solutes studied is probably the main factor in this type of analysis.

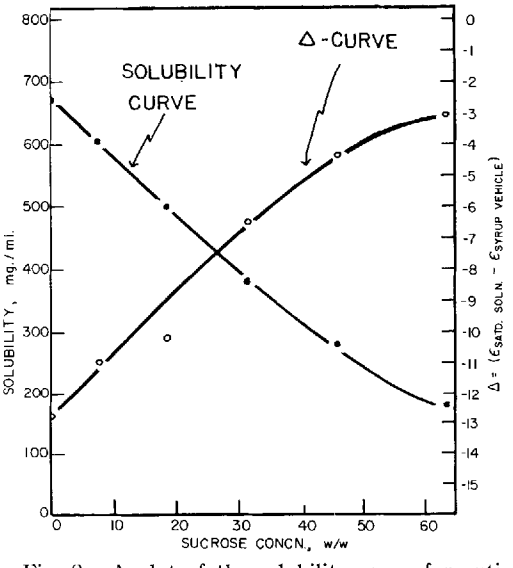

Fig. 8.—A plot of the solubility curve for antipyrine in syrup vehicles and the dielectric constant difference (Δ-curve) between saturated solutions of antipyrine and the syrup vehicles used.

PREDICTION OF SOLUBILITY CHANGE

The data on antipyrine and its derivatives may be considered from an alternate approach. Antipyrine and two derivatives, the 4-amino and 4-dimethyl amino, were studied in order to find the effect of substituent groups relative to solubility effects. In Table IV, the average determined solubility in water and simple syrup is listed. By allowing the solubility of the aminopyrine in water and simple syrup to be represented by unity, the ratios of solubility of the other solutes in the same solvent system were calculated. As can be seen from the table, these ratios are fairly constant irrespective of the solvent system. By taking the difference between the solubility in water and the solubility in syrup a delta value (Δ) is obtained. If the Δ value is divided by the original solubility, the percentage decrease in solubility can be calculated. These values are shown in the final column of this table. The percentage decrease is also seen to be fairly constant. It would seem that the derivative effects for these solutes are relatively constant and predictive solubility is a possibility, at least for the range and systems studied.

In other words, in so far as the approximate rule is valid, only the solubility of antipyrine in syrup need be determined; and the solubility of the derivatives in syrup can be approximately calculated from the ratios in pure water.

Although this type of analysis could be done for antipyrine and its derivatives, the xanthines could not be viewed in the same fashion since the solubility curves obtained were more complex and they are essentially positional isomers, with caffeine containing an extra methyl group in the 1-position.

This study is the first in a series of investigations of the solubility of various solutes in syrup vehicles and has shown that both decreases and increases in solubility are possible with this additive. Furthermore, it seems that the path in syrup vehicles in certain systems has a complex functionality. It must be pointed out that this work deals only with one highly water soluble material, *i.e.*, sucrose, and conclusions attendant to this must be viewed for the

TABLE IV.—SUMMARY OF THE SOLUBILITIES AND SOLUBILITY RATIOS OF ANTIPYRINE AND SEVERAL DERIVATIVES IN WATER AND SIMPLE SYRUP

Substance	Solubility, mg./ml.		Solubility Ratio		Δ mg./ml.	% Decrease = Δ/Soly. in Water
	Water	Simple Syrup	Water	Syrup		
Antipyrine	670	185	14.0	11.6	485	72
4-Aminoantipyrine	411	141	8.6	8.8	270	66
4-Dimethylamino-antipyrine	48	16	1	1	32	67

range and the system studied. It would be interesting to note the effect of additives, especially other sugar moieties, upon the solubility of various solutes.

Whether the dielectric concept, or activity concept mechanisms, or a combination of these are strictly involved cannot be completely delineated in this work. Although the fair correlation given for theophylline has some basis in dielectric constants, no sweeping involvement of dielectric constants for all their systems is apparent. In addition, the observations made may eventually show a very strong solute nature and solvent system dependence. Studies attendant to these points are being carried out in these laboratories and will be the subject of future communications.

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Solubilizing Properties of Bile Salt Solutions II

Effect of Inorganic Electrolyte, Lipids, and a Mixed Bile Salt System on Solubilization of Glutethimide, Griseofulvin, and Hexestrol

By THEODORE R. BATES*, MILO GIBALDI†, and JOSEPH L. KANIG

Studies of the influence of inorganic electrolyte on the solubilization of griseofulvin, glutethimide, and hexestrol in four individual bile salt solutions at 37° showed that sodium chloride had little effect on the solubility of the former two drugs but significantly increased the solubility of hexestrol. Based on these findings the possible location of the drug molecules within the micelle is considered. A mixed bile salt system was found to possess a significantly lower critical micelle concentration (CMC) than any of the individual bile salts previously studied. However, the affinities of this mixed micellar system for the drugs were comparable with those obtained with individual bile salts. The addition of lipids to the mixed bile salt system resulted in a decrease in hexestrol solubility but had little effect on griseofulvin and glutethimide solubility. The biological implications of the results obtained in the present communication are explored, and a mechanism for the role of dietary lipids and bile salts in the absorption of drugs is proposed.

BORGSTRÖM (1) has proposed a theory for the fate of ingested triglycerides prior to absorption. According to this theory, the breakdown products of pancreatic lipolysis (*i.e.*, 1- and 2-monoglycerides and fatty acids) are solubilized by bile salt micelles, present in the upper segment of the small intestine, prior to their absorption across the intestinal mucosa. In connection with this theory of fat absorption, several *in vitro* investigations have appeared in the literature demonstrating the marked micellar solubilizing properties of conjugated bile salts for fatty acids and monoglycerides (2–5). There has also been *in vivo* and *in vitro* evidence that the intestinal mucosa is capable of uptaking fatty acids and monoglycerides from a mixed micellar solution composed of these substances and conjugated bile salts (6–8).

In a previous communication (9) the effects of bile salt concentration and type, and temperature on the micellar solubilizing properties of bile salt solutions for the relatively water-insoluble drugs, griseofulvin, glutethimide, and hexestrol were reported. This report proposed that bile salts play a role in the dissolution step of the intestinal absorption mechanism for water-insoluble drugs.

In the present communication the results of findings on the influence of a mixed bile salt system, inorganic electrolyte concentration, and pancreatic lipolytic products and bile components on the degree of micellar solubilization of griseofulvin, glutethimide, and hexestrol are presented.

Received April 21, 1966, from the College of Pharmacy, Columbia University, New York, N. Y. 10023.
Accepted for publication July 6, 1966.
Previous paper: Bates, T. R., Gibaldi, M., and Kanig, J. L., *J. Pharm. Sci.*, **55**, 191(1966).
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