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THE STABILITY OF ORAL LIQUIDS

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Many types of formulations both aqueous and non-aqueous are included among those which can be classified as oral liquids. Included in this group are syrups, suspensions, emulsions, colloids, mouthwashes, elixirs, and soft gelatin capsules. It will not be possible to cover in detail all the different formulations or factors which will effect their stability; however, those discussed should have some applicability to all systems. It is safe to say that, as a class of formulations, oral liquids are generally more complex in their composition than parenterals and, therefore, more interactions can occur which might affect the stability of the product. Not only is it necessary to consider the solution stability of the drug substance, but also the effects upon stability caused by such things as suspending agents, colorants, flavors and sweetening agents need to be addressed.

The stability of a product is described by observations which can be grouped into four areas. These are chemical stability, physical stability, microbiological integrity and elegance. The first three are measurable characteristics while the last is qualitative and usually subject to individual variance. Included in this latter category are color, feel, odor, and taste.

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There is no way of knowing, a priori, whether or not a given formulation will have any specific stability problem and, if there is, in which area the instability will occur. By performing appropriate preformulation studies on the drug substance substance, considerable information on both the chemical and physical stability can be obtained. Information such as pH stability profiles as a function of temperature, pH solubility profiles as a function of temperature, pH partitioning profiles, pKa, particle size distribution, surface area analysis and crystallogaphic characteristics are useful information for the formulation chemist.

In this regard, both pH solubility and pH stability are indispensable when it comes to formulating liquid dosage forms. An expression can be written for the solubility of a polyprotic compound as a function of pH (Eq. 1).

$$S_{m,j} = \sum_{j=o}^{m} \frac{H^j}{Y_o} \left[\prod_{\alpha=o}^{j} \frac{1}{K_\alpha} \left(1 + Y_o \sum_{i=1}^{m} \frac{1}{H^i Y_i} \prod_{t=1}^{i} K_t \right) \right] \left\{ H_{m-j}A \right\}$$

where:

m = number of equilibrium constants

y_i = activity coefficient for species i and Y_o is the most protonated species

H = hydrogen ion activity

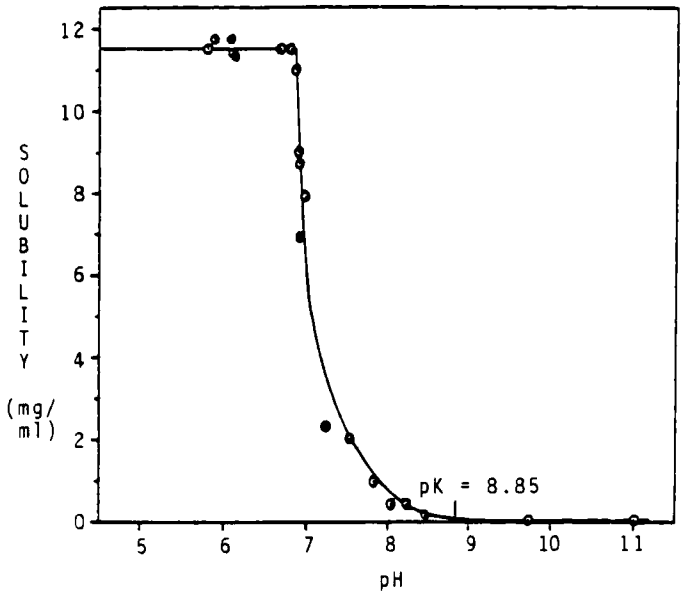
K = equilibrium constant, $K_o = 1$

$\{H_{m-j}A\}$ = Activity of species $H_{m-j}A$ (maximum solubility of species $H_{m-j}A$)

$S_{m,j}$ = total concentration of all species of compound A in solution, i.e.,

$$S_{m,j} = \sum_{j=o}^{m} [H_{m-j}A]$$

FIGURE 1. pH-SOLUBILITY PROFILE OF AMINE*



*S.F.Kramer & G.L.Flynn, J.Pharm.Sci.,61,1897 (1972)
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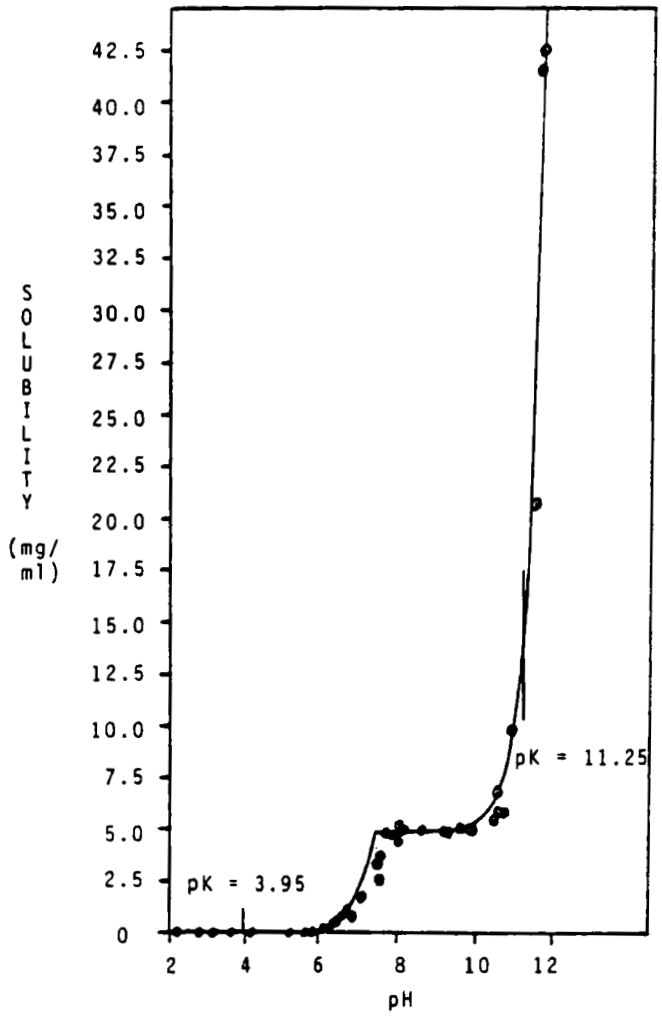
This expression is completely general and can be applied to any compound regardless the number of replaceable protons. It can be seen that the total solubility is a function of the hydrogen ion concentration, the ionization constants and the intrinsic solubility of the individual species. In Fig. 1 a pH solubility profile is shown for a monoprotic secondary amine [1].

It can be seen that as the pH increases above a value of 6.8 there is a rapid decrease in the solubility. This is due to the fact that the protonated species is charged and more soluble in aqueous media than the uncharged free base species. The curve in this figure was calculated using Eq. 1 without activity coefficient corrections.

Another example of pH solubility profile [2] is shown in Fig. 2.

In this case the compound is a diprotic acid where the dissociation of each proton increases the charge on the molecule

FIG. 2 pH-SOLUBILITY PROFILE OF A DIPROTIC ACID*



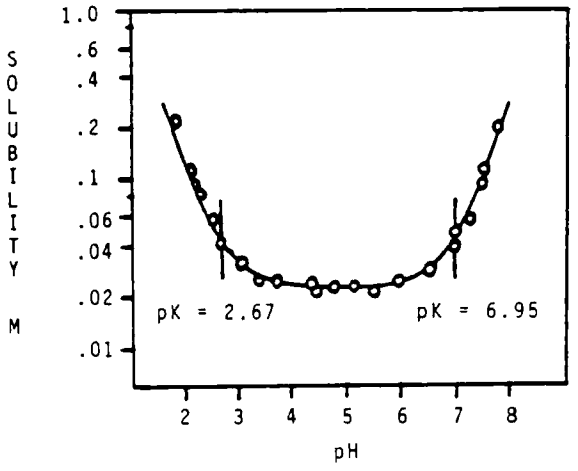
*W. H. Streng, Unpublished Data

and, therefore, the solubility increases with an increase in pH. The curve in this figure was calculated using Eq. 1.

Finally, Fig. 3 is the pH solubility profile of a compound having two acid functional groups, a carboxylic acid, and a primary amine [3].

According to this figure at low pH and at high pH the solubility of the compound increases. The reason for this is because

FIGURE 3. pH-SOLUBILITY PROFILE OF AMPICILLIN AT 37°C



*A.Tsuii, E.Nakashima, A.Hamano & T.Yamana, J.Pharm.Sci., 67, 1059 (1978)

there is a molecule having both a positive and negative charge (zwitterion) formed when the first proton is removed from the molecule. It is important, therefore, to know the pH solubility profile of the drug substance in order to formulate in regions where slight shifts in the pH will not result in precipitates forming in the case of solutions, or where the drug will not be solubilized in the case of suspensions.

The determination of pH stability profiles on drug substances are obviously of importance to the formulation chemist. From these profiles intrinsic rate constants can be calculated. When the intrinsic rate constants are obtained as a function of temperature, an indication of the type of reaction can be determined through subsequent calculation of activation energy. Most reactions will follow either zero order Eq. 2, or first order, Eq. 3, kinetics.

$$\text{Zero Order} \qquad A-A_o = -k't \qquad (2)$$

$$\text{First Order} \quad \ln A/A_o = k't \tag{3}$$

$$k' = k_o + k_H [H] + k_{OH} + \sum_i k_{Bi} [B_i] \tag{4}$$

where:

A = concentration at time t

A_o = initial concentration

k' = observed rate constant

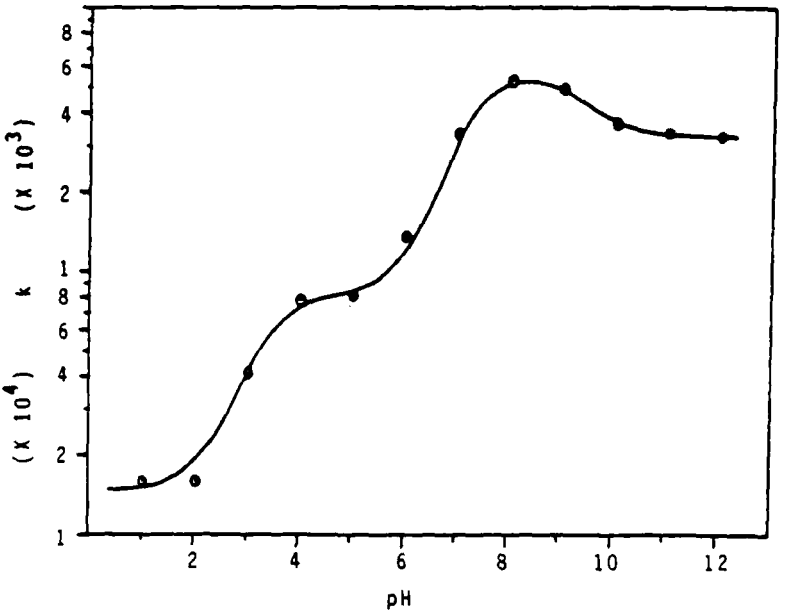
k_i = intrinsic rate constant for species i

$[x]$ = concentration of x

The generalized rate constant expression given by Eq. 4 can be solved for the individual intrinsic rate constants. Besides the hydrogen and hydroxide catalyzed ractions, it is possible to have buffer species or other excipients which also catalyze the degradation. These latter effects are included in the summation term. In addition, each species of the drug can have its own rate constant for the hydrogen and/or hydroxide catalyzed reaction. If this occurs then k_H and k_{OH} need to be expressed for the specific species.

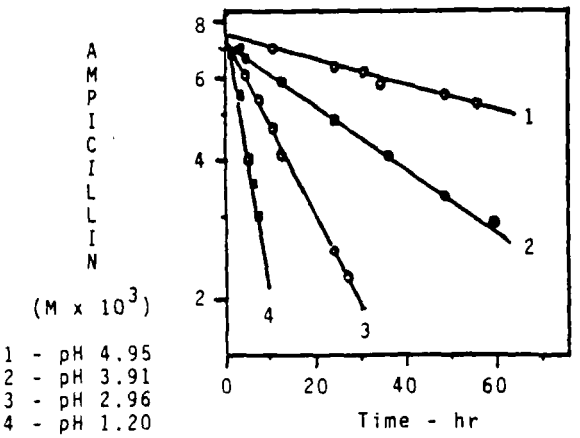
In Fig. 4 are shown the observed rate constants at 90°C for pirbuterol [4], a compound with three pKa and, therefore, four species. The data obtained at individual pH were observed to follow first order kinetics. Further work indicated the degradation to be an oxidation reaction (Ea = 8-12 Kcal/mole) and each species of pirbuterol had its own rate constant. The calculated curve is given by the solid line in the figure. Representative plots of the first order rate data obtained for ampicillin [5] are shown in Fig. 5. The linear relationship for the data is apparent in this figure indicating the reaction to be first order.

FIGURE 4. pH-STABILITY PROFILE OF PIRBUTEROL*



*P.C.Bansal & D.C.Monkhouse, J.Pharm.Sci., 66, 819 (1977)

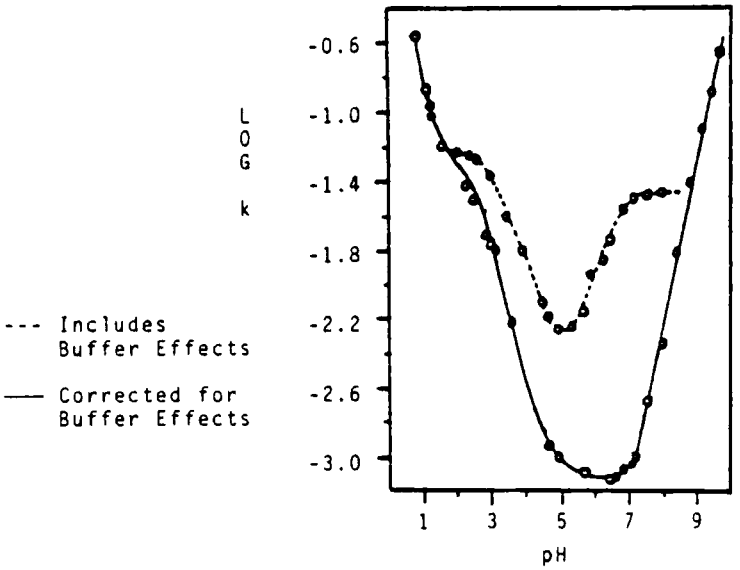
FIGURE 5. OBSERVED FIRST ORDER DEGRADATION OF AMPICILLIN AT 35°C *



1 - pH 4.95
2 - pH 3.91
3 - pH 2.96
4 - pH 1.20

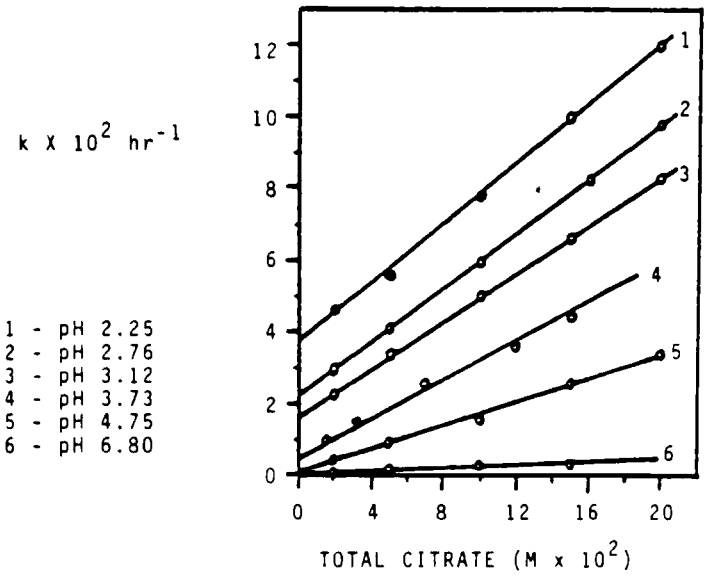
*J.P.Hou & J.W.Poole, J.Pharm.Sci.,58,447(1969)

FIGURE 6. pH-STABILITY PROFILES OF AMPICILLIN AT 35°C*



*J.P.Hou & J.W.Poole, J.Pharm.Sci., 58, 447 (1969)

FIGURE 7. CITRIC BUFFER CATALYTIC EFFECT ON AMPICILLIN AT 35°C*



*J.P.Hou & J.W.Poole, J.Pharm.Sci., 58, 447 (1969)

In Fig. 6 the pH stability profile for ampicillin at 35°C is shown. The broken line in this figure represents data which included a buffer effect, while the solid line has been adjusted for zero buffer concentration. Plots of the observed rate constants versus concentration of citrate buffer, Fig. 7, resulted in linear curves for solutions having a pH between 2.25 and 6.80, indicating that the citrate buffer catalyzed the reaction.

The activation energies for the oxidation degradations were determined using the Arrhenius equation, Eq. 5.

$$\frac{d \ln k}{d (1/T)} = \frac{Ea}{R} \qquad (5)$$

$$k = A_f \, e^{-Ea/RT}$$

where:

k = rate constant

T = absolute temperature (°K)

E_a = activation energy

R = gas law constant (8.314 joules/mole-deg)
(1.987cal/mole-deg)

A_f = pre-exponential factor (frequency factor)

The rate constants used in this equation should be the intrinsic rate constants; however, frequently the observed rate constants are used with reasonably good results. Typical activation energies for different types of reactions are shown in Table 1.

From this table it can be seen that if a low activation energy is obtained in the Arrhenius calculation then the reaction

is most likely oxidative of photolytic, whereas intermediate energies are frequently a dehydration or solvolytic reaction. High activation energies are associated with polymorphic transformations. From the temperature relationship shown by the Arrhenius equation it can be seen that when there is a low activation energy, there will be little change in the observed rate constants with temperature, whereas reactions involving high activation energies will result in large changes in the rate constants with temperture.

What do the rate constants mean to the formulating chemist? In Table 2 the relationship between the rate constant and the time for the drug to degrade to 90% of its initial value (t90) are given for both zero order and first order reactions. According to this table for a zero order reaction, a rate constant of 5×10^{-4} would be needed to have a five year shelf life, while a rate constant of 5×10^{-5} would be required for a first order reaction. The formulating chemist should also look at the pH stability profile along with the pH solubility profile in order to select the optimum pH for formulating the oral liquid dosage form.

In the same way that pH solubility data is needed for formulating solutions and suspensions, pH partitioning profiles are important when formulating emulsions and systems containing micelles. If there is a change in pH it is possible that the drug substance will redistribute itself between the phases in a deleterious manner. The formulating chemist should, therefore, look at the partitioning profile and the pH stability profile to select the optimum pH with these types of dosage forms.

There are no 100% assurances that a compound will be chemically stable in a formulation even though it is formulated at the optimum pH according to its pH stability profile. This is because

TABLE 1 : Activation Energies

Type	Ea (Kcal/mole)	Ref.
Pyrolysis	50 - 70	1
Solid Phase Polymorphic Transformation (Sulfathiazole)	56	2
Dehydration (Theophylline)	33	3
Solvolysis	10 - 30	1
Oxidation (Ascorbic Acid)	8 - 12	4
Photolysis	2 - 3	1

Reference:

1. Garrett, Adv. Pharm. Sci., 11, 1 (1967)
2. Shami et al., J.Pharm.Sci., 61, 1318 (1972)
3. Shefter, Fung and Mok, ibid., 62, 791 (1973)
4. Blang and Hajratwala, ibid., 61, 556

TABLE 2 : Relationship Between k and t_{90} for Zero and First Order Reaction.

k(Fraction/d)	t_{90}	k (d^{-1})	t_{90}
1×10^{-1}	9 d	1×10^{-2}	10 d
1×10^{-2}	90 d	1×10^{-3}	105 d
5×10^{-3}	180 d	5×10^{-4}	210 d
3×10^{-3}	300 d	3×10^{-4}	315 d
2×10^{-3}	450 d	2×10^{-4}	527 d
1×10^{-3}	2.5 yr	1×10^{-4}	2.9 yr
8×10^{-4}	3.1 yr	8×10^{-5}	3.6 yr
6×10^{-4}	4.1 yr	6×10^{-5}	4.8 yr
5×10^{-4}	4.9 yr	5×10^{-5}	5.8 yr

TABLE 3 : Rate of Interaction of Amines With Sugars*

Sugar:	Galactose > Dextrose > Lactose
Type of Amine:	Primary > Secondary > Tertiary

* K.T. Koshy, R.N. Duvall, A.E. Troup, and J.W. Pyles, J.Pharm.Sci., 54, 549 (1965)

* R.N. Duvall, K.T. Koshy, and J.W. Pyles, J.Pharm. Sci., 54, 607 (1965)

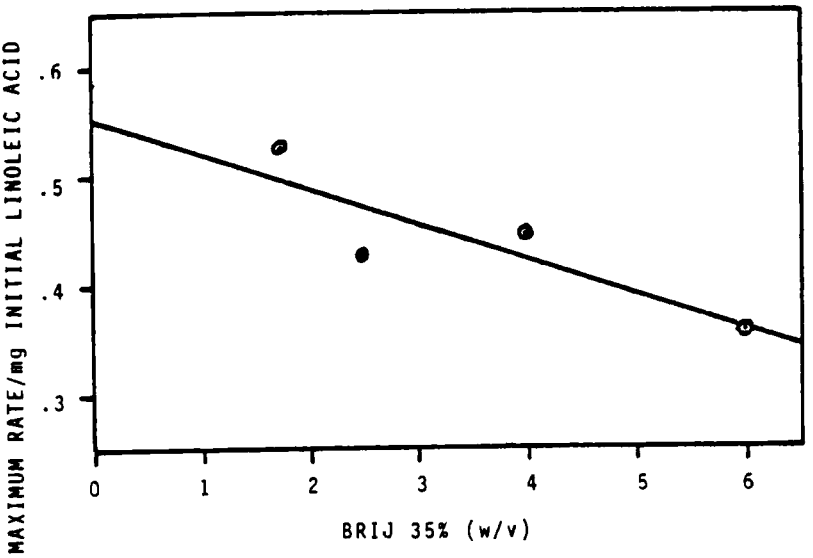
the excipients which are added to the formulation (sweetening agents, coloring agents, preservatives) can interact with the drug substance. Studies have shown [6,7] that amines react with sugar to give a brown degradation product. The degradation rate is dependent upon both the sugar used and the types of amine.

In Table 3 these relative rates are shown in which galactose promoted browning faster than the other sugars used and the primary amines were more interactive.

Problems can be encountered in the use of surfactants in liquid dosage forms. The solvolysis of sodium alkyl sulfates by hydrochloric acid was found to be faster above the critical micelle concentration [8]. Also, increasing the length of the alkyl chain increased the rate. Further, while the initial rate for the auto-oxidation of linoleic acid in non-ionic surfactant decreases with an increase in surfactant, Fig. 8, the initial rate is directly proportional to the initial micellar concentration of linoleic acid, Fig. 9, [9]. From this information it was concluded that the micelles were the site of oxidation in solubilized systems of this type.

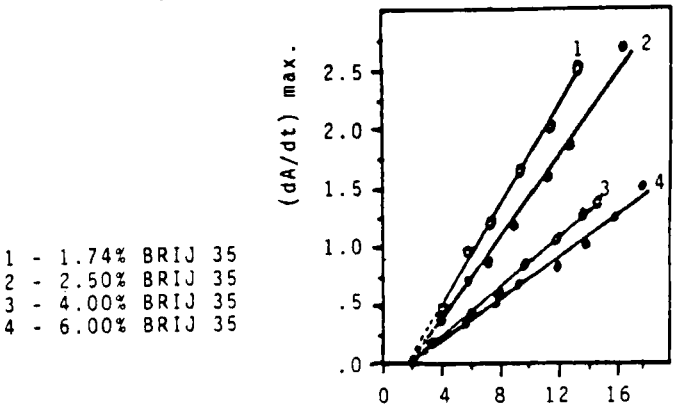
The physical stability of liquid formulations involves such things as the formation of precipitates, formation of less solu-

FIGURE 8. VARIATION OF MAXIMUM OXIDATION RATE/mg INITIAL LINOLEIC ACID WITH BRIJ 35 CONCENTRATION*



*J.Swarbrick & C.T.Rhodes, J.Pharm.Sci., 54, 903 (1965)

FIGURE 9. MAXIMUM RATE OF CONCENTRATION CHANGE AS A FUNCTION OF INITIAL MICELLAR LINOLEIC ACID CONCENTRATION*



*J.Swarbrick & C.T.Rhodes, J.Pharm.Sci., 54, 903 (1965)

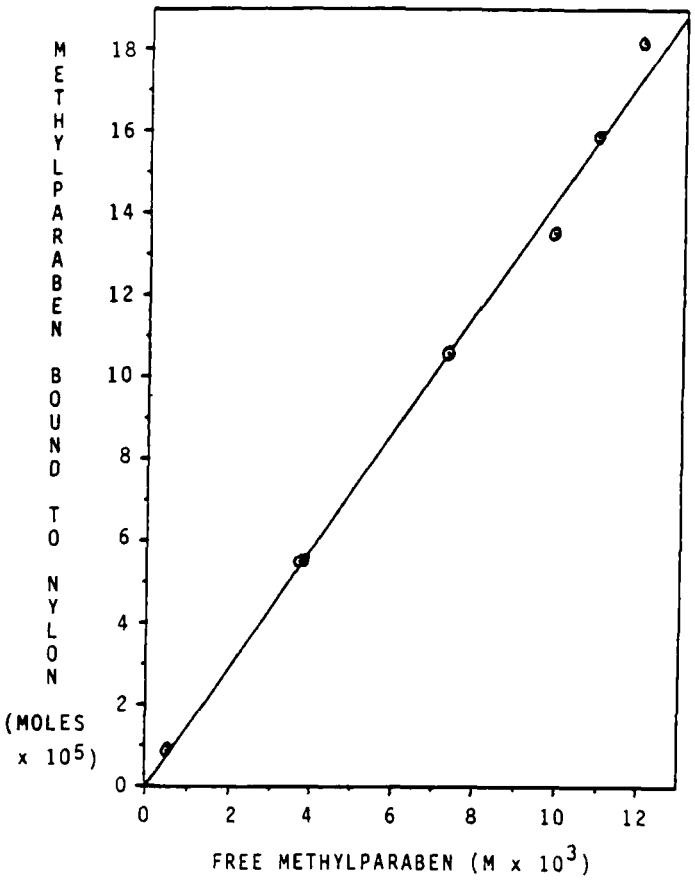
ble polymorphs, adsorption of the drug substance onto surfaces, migration into or out of a soft gelatin capsule formation of insoluble solvates, changes in the particle size distribution and separation of emulsions. When using sugar as a sweetening agent, a floc may develop depending on the sugar used. In addition, some dyes have been found to precipitate when used at high concentration.

The formation of less soluble polymorphs has been well documented in the literature and can be a significant problem. It has been observed [10] that theophylline suspensions can undergo a polymorphic change in suspensions...starting with micronized anhydrous crystals, a needle-like crystal will form which is a hydrate. Different dissolution behavior has been observed when using drug substances having different solvation [11]. The rate of change from one polymorph to a second was studied in great detail for succinylsulfathiazole in suspensions [12,13]. This work showed catalytic effects to the transformation caused by several surfactants, coloring agents, and glycerin. It was also observed that methylcellulose retarded the transformation.

Particle size distribution in suspension can change with time due to the equilibrium established between the solid and liquid phases. Smaller particles are more energetic than larger ones and will have a tendency to dissolve more rapidly than the larger particles. Conversely, the larger crystals will tend to increase in size. Emulsions are also unstable systems and, as such, can break down. In view of the energetics of emulsions to coalesce, the relative stability to withstand the stresses of handling, transport and storage must be determined.

The microbiological integrity of oral liquids is of importance, and many of the oral liquids have favorable mediums for growth of molds and bacteria. The propensity of a formulation to support microbial growth is an area that needs to be studied.

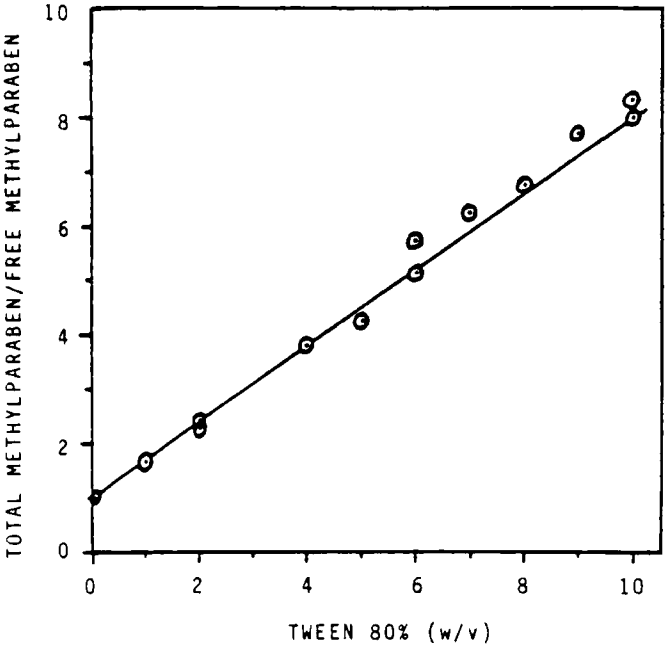
FIGURE 10. BINDING OF METHYLPARABEN TO NYLON*



*N.K.Patel & H.B.Kostenbauder, J.Am.Pharm.Assoc., Sci.Ed., 47, 289 (1958)

Little is known at this time concerning the microbiological integrity of products and the need for microbiological testing. Preservatives have been shown to bind to macromolecules [14]. The binding of methyl p-hydroxybenzoate to nylon was found to be dependent upon the size of the nylon membrane and the concentration of free paraben, Fig. 10. It was also shown that methyl p-hydroxybenzoate would complex with Tween 80 varying directly with the amount of free paraben and the concentration of Tween 80, Fig. 11. Similar results were reported for propyl p-hydroxy-

FIGURE 11. BINDING OF METHYLPARABEN BY TWEEN 80*

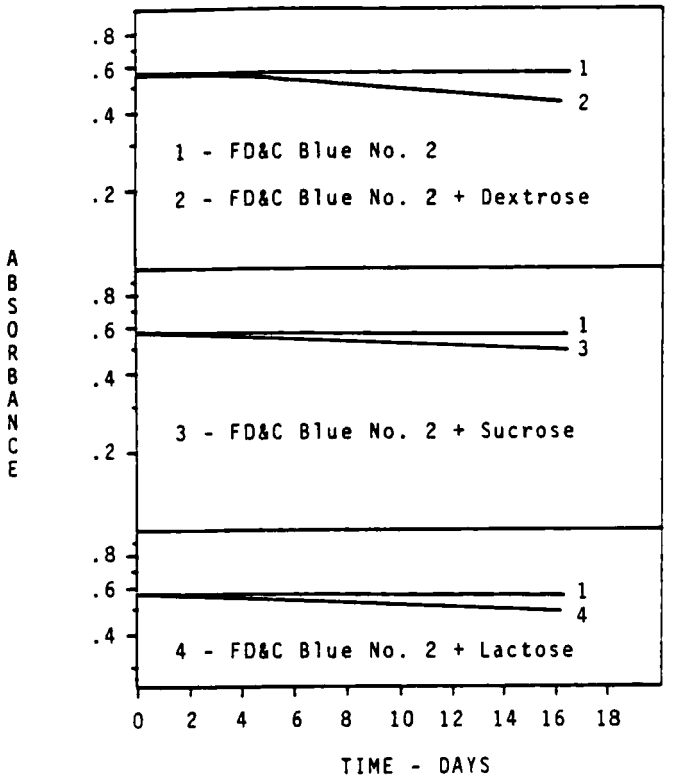


*N.K.Patel & H.B.Kostenbauder, J.Am.Pharm.Assoc., Sci.Ed., 47, 289 (1958)

benzoate. When dealing with biphasic systems it is important to be aware that bacteriostatic agents can partition between the phases in such a way that they can become ineffective.

The stability of dyes are dependent upon the excipients used in the formulation. FD&C Blue No. 2 was found to fade more rapidly in the presence of several sugars (sorbitol, mannitol, dextrose, sucrose, lactose) [15]. In Fig. 12 several of these are shown. In addition, it appeared as though trace amounts of impurities also contributed to the fadings, Fig. 13. It was also found that the non-ionic surfactants Pluronic F-68 promoted the fading of FD&C Blue No. 2, Fig. 14 [16]. From the temperature dependence of the rate constants shown in Fig. 14 the activation

FIGURE 12. COLOR FADING - FD&C BLUE No. 2 - SUGAR*

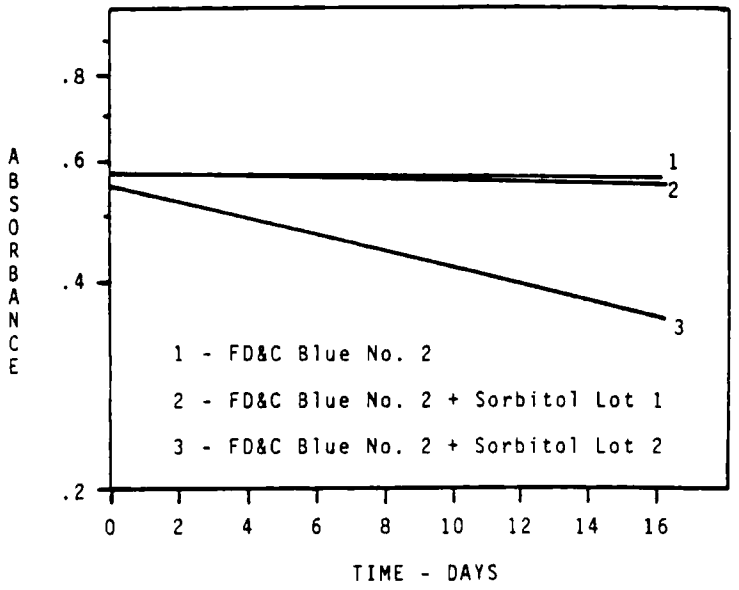


*R.Kuramoto, L.Lachman & J.Cooper, J.Am.Pharm.Assoc., Sci.Ed., 47, 175 (1958)

energy was determined to be 22.7 Kcal/mole in the presence of the surfactant.

Elegance of a product is basically a subjective evaluation and includes those properties which involves the senses. It is important to know under what conditions changes can occur in order to minimize their effect. Not only will some dyes fade or change color with time, as mentioned, but sometimes small amounts of degradation (<1%) of the drug substance can introduce color changes. In addition, some antioxidants become colored when they

FIGURE 13. COLOR FADING -
FD&C BLUE No. 2 - SORBITOL LOT VARIATION*

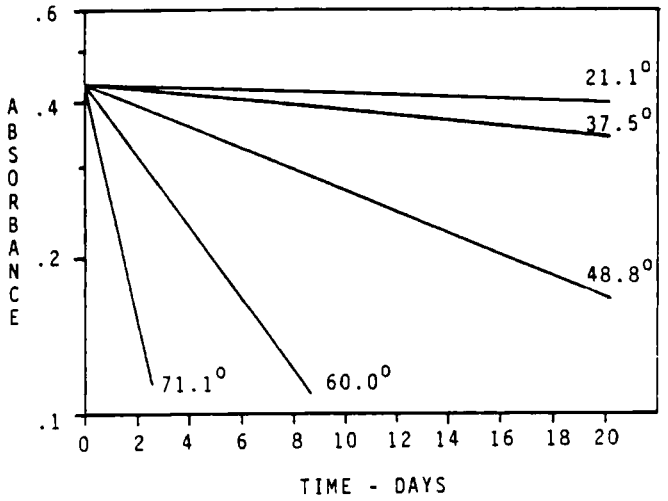


*R.Kuramoto, L.Lachman & J.Cooper,
J.Am.Pharm.Assoc., Sci.Ed., 47, 175 (1958)

are oxidized and will thus effect the appearance of the product. Another problem which can occur with biphasic formulations is the partitioning or transfer of the dyes and flavors from one phase into the other phase.

The prediction of the chemical stability down to 90-95% of potency of the drug substance (for purposes of shelf life prediction) can usually be made using standard kinetic procedures. It is, however, much more difficult predicting the shelf life when there are physical instabilities, microbiological difficulties or changes in the elegance of the formulations and, at times, it cannot be done. The job of a formulating chemist is,

FIGURE 14. COLOR FADING - FD&C BLUE No. 2 - PLURONIC F-68 SYSTEM*



*M.W.Scott, A.J.Goudie & A.J.Huetteman, J.Am.Pharm.Assoc., Sci.Ed., 49, 467 (1960)

therefore, a mixed bag in which both an intuitive understanding of the system as well as good preformulation studies need to be combined in order to arrive at a marketable commodity.

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4. P.C. Bansal and D.C. Monkhouse, J. Pharm. Sci., 66, 819 (1977).

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