DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(7), 933-951 (1986)

STRATEGIES FOR FORMULATION AND EVALUATION OF EMULSIONS AND SUSPENSIONS: SOME THERMODYNAMIC CONSIDERATIONS

Norman Weiner
College of Pharmacy
University of Michigan
Ann Arbor, Michigan 48109, USA

ABSTRACT

The difficulties in the development of reasonably stable emulsions and suspensions and the problems associated with the evaluation of such products are, for the most part, related to their non-equilibrium state. A conceptual understanding of the thermodynamics of these dispersions, particularly their surface and/or interfacial free energy, will facilitate successful formulation of such disperse systems. A strategy that fails to utilize surface behavior to stabilize thermodynamically unstable formulations is unlikely to be productive whereas a strategy based on an appreciation of the surface properties of the system is much more likely to succeed. Stability testing of liquid disperse systems is one of the most difficult problems faced by pharmaceutical and cosmetic chemists. The scientist is often asked to predict the shelf-life of a product or choose between experimental formulations based on estimates of how well they will hold up with time. While there are no standardized tests available to determine stability, a conceptual understanding of the

0363-9045/86/1207-0933$3.50/0

thermodynamics of these systems, particularly their interfacial properties, can provide some insight into the expected types of instability, and equally important into the most sensible tests for predicting shelf-life.

INTRODUCTION

The majority of cosmetic products and many pharmaceutical products may be classified as emulsions and suspensions. These liquid disperse systems are extremely complex and the method of manufacture, formulation approach, component materials selection, effect of environmental factors such as temperature and holding-time profoundly affect the degree of variability in the product's performance, stability characteristics and a host of other variables. Although disperse systems are prevalent in almost all industrial settings where a liquid product is involved, it seems somewhat surprising that, in most cases, such products are formulated on a "trial and error" basis, with little or no theoretical input. Admittedly, many theories dealing with disperse systems have little apparent practical value, but there is a large body of available knowledge that, when used properly, enables the formulator to prepare better products more efficiently and evaluate them in a more systematic and realistic manner.

The problems or challenges, (depending upon perspective), in working with disperse systems are for the most part related to their non-equilibrium state. Since an almost infinite number of non-equilibrium states are possible, each slight variation in product design and/or processing can lead to a different non-equilibrium product. Although these differences may not seem apparent initially, long-term stability may be affected. Of equal importance, the product is continuously seeking to reach thermodynamic equilibrium. In practical terms, thermodynamic equilibrium is synonymous with a completely coalesced emulsion or a settled, non-redispersible suspension. Thermodynamics "tells" us that this final state is inevitable, and the task of the formulator is to merely delay its occurrence. A stable emulsion is a thermodynamic anomaly with the possible exception of microemulsions (1). Basically, the formulator must seek, in a thermodynamic sense, to formulate the system in order to make the product as independent of processing variables as possible and to introduce the necessary energy barriers to delay thermodynamic equilibrium for the desired shelf-life of the product. The concept of equilibrium coupled with an understanding of free energy, particularly surface and/or interfacial free energy, is the basic framework which links all of the disperse systems of interest.

INTERFACIAL FREE ENERGY CONSIDERATIONS

An interface is defined as a boundary between two phases. With suspensions the solid/liquid interface is of primary interest, and with emulsions the liquid/liquid interface is of primary concern. Of course, other interfaces such as the liquid/gas (foams) or solid/gas (wetting problems) interfaces may also come into play. The most important and fundamental property of any interface is that it possesses a positive free energy (2). Essentially, this means that the molecules at the interface are in a higher energy state than if they were located in the bulk phase (see Fig. 1).

The greater the preference of the molecule of interest for the bulk as compared to the interface, the higher the interfacial free energy.

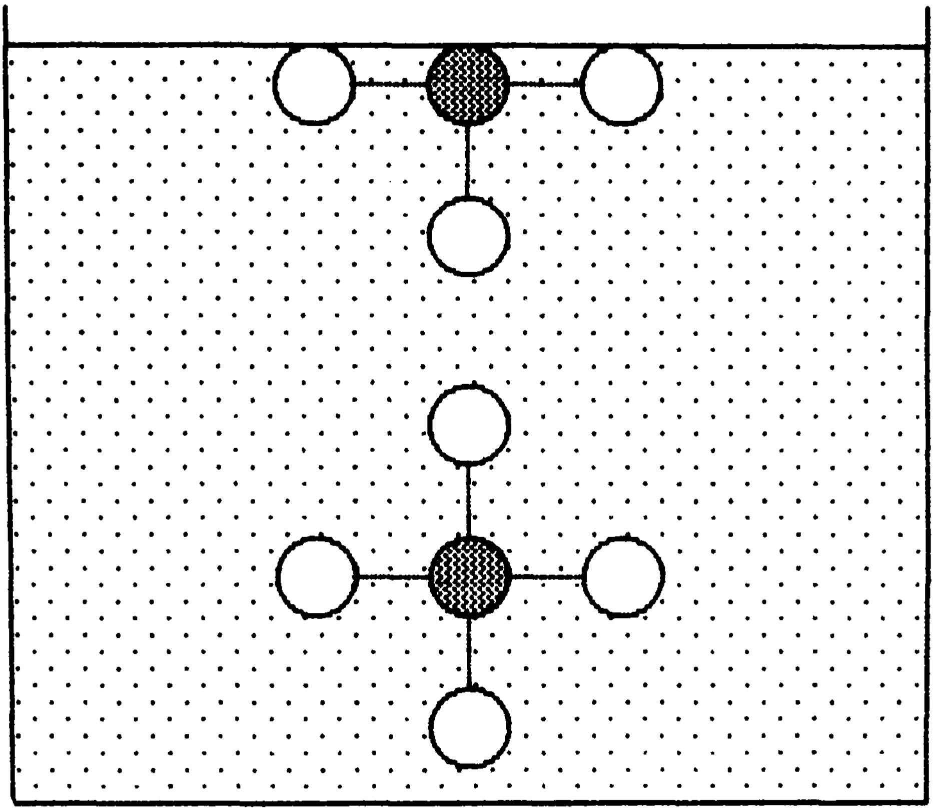

Figure 1

Diagramatic representation of the derivation of positive free energy of interfaces. (●) Molecule of interest; (O) Surrounding molecules. Note that the molecule of interest at the surface is in a higher energy state than the molecule of interest in the bulk phase because the former is being pulled down by its neighbor and there is no upward force to equalize it.

Although interfacial free energies cannot be measured directly, interfacial tension values (which can be obtained experimentally), give reasonably good approximations. As a rule, accurate interfacial and surface tension measurements are very difficult to obtain since impurities in the system and instrument wetting problems introduce large errors (3). Since most of the surfactant systems used in industry are either mixtures of surfactants or contain significant amounts of impurities, surface or interfacial tension values associated with these systems have little meaning. Most often, these measurements are carried out without purpose since there is usually no apparent relationship between surface or interfacial tension and the formulation parameter of concern, e.g., emulsifier or solubilizer efficiency (4). Surface or interfacial tension should simply be looked upon as a mathematical approximation of surface or interfacial free energy. The principal problem for formulators is "nature's" continuous attempt to reduce this positive interfacial free energy value to zero, (true equilibrium), by various means. One method is simply to reduce the amount of interface, i.e., a two-fold reduction of the amount of interface results in a similar reduction in the interfacial free energy of the product. For example, when emulsion droplets collide, they can either bounce away or coalesce into larger droplets which ultimately leads to the destruction of the emulsion. The latter event will result in a reduction of interfacial free energy, and unless barriers are placed in the way, will occur with each collision. Thus, in the absence of an emulsifying agent, oil and water will separate almost instantaneously. Most often, compounders are not changing the ultimate thermodynamic fate of the product by altering the formulation, (or even the processing), but are merely changing the thermodynamic path, which in practical terms, means increasing the shelf-life of the product.

Another important method that nature uses to reduce interfacial free energy is to vary the composition of the interface to make it rich in surface active material, and poor in highly polar compounds, e.g., water. This mechanism is advantageously used by introducing materials (emulsifiers) into the formulation that concentrate at the oil/water droplet interface and present barriers to droplet coalescence. The principal mechanism by which emulsifiers stabilize emulsions is not a reduction of the interfacial free energy of the system but involves the introduction of a mechanical barrier to delay the ultimate destruction of the system. It is important to note that, although the concentration of surface active emulsifier is greater at the oil/water interface than in in either of the bulk phases, most of the emulsifier molecules are in the water phase, (hydrophilic emulsifier), or in the oil phase, (hydrophobic emulsifier), and not at the emulsion droplet interface (5). Reduction of the interfacial free energy probably does help somewhat in the ease of preparing the emulsion, (since energy needs to be added to the system to prepare the product), but it is not a major factor with respect to long-term stability.

Finally, proper orientation of the molecules at the interface, (polar groups directed toward the water phase and non-polar groups directed toward the oil phase), further reduces interfacial free energy. It is extremely important for the formulator to keep in mind that throughout the processing of the formulation, (whether it be simple mixing with a stirring rod or the use of high energy shear equipment), the emulsifier molecules are continuously partitioning between the bulk phases and the interface, and changing their orientation at the interface. Moreover, when a combination of emulsifiers is used, (as is the usual case), the ratio of the hydrophilic and hydrophobic emulsifier at the interface continuously changes during the preparation of the emulsion. Since equilibrium is never established, the final configuration is very much a function of processing. Thus, choosing the correct emulsifying blend, (and other components as well), and processing the emulsion in such a manner that small changes in processing and storage variables do not result in large changes in the properties of the emulsion, are extremely important considerations.

Whereas emulsions have been used as an example of the importance of interfacial free energy, these concepts are applicable to all disperse systems. The importance of interfacial properties in determining the overall characteristics of the formulation depends to a great extent on the interface-to-bulk ratio of molecules in the disperse phase. In other words, the greater the percentage of molecules at the interface, (e.g., the smaller the particle size), the more important are the surface properties for describing the system. For example, surface properties are much more important for colloidal dispersions than for coarse suspensions. Likewise, surface properties are much more important for microemulsions than for macroemulsions. Even though the properties of products can be altered by formulation factors affecting primarily the bulk phase, e.g., addition of hydrophilic polymers to increase viscosity, interfacial properties are much more important as a determinant of the preparation's overall appearance, performance and stability. A strategy that fails to utilize surface behavior to stabilize thermodynamically unstable formulations is unlikely to be productive. For example, if one attempts to stabilize a suspension by relying entirely on minimizing the rate of settling (Stokes' Law approach), i.e., use of a small particle size and very high viscosity, the particles will ultimately settle and form a dense cake which is likely to be difficult to resuspend (6).

On the other hand, a strategy based on an appreciation of the surface properties of the system is much more likely to succeed. In the previous example, an understanding of the surface charge characteristics of the suspended particles allows formulation of the suspension so that a porous flocculated particle network is intentionally formed which can be easily redispersed (controlled flocculation approach) (7). The use of electrolytes to stabilize suspensions by this approach is based on classical electrical double layer theory. Thus, an understanding of this concept facilitates the experimental determination of the amount of electrolyte necessary to produce the surface charge resulting in the most stable suspension (8). Similarly, an understanding of this concept permits the experimental determination of the pH at which a particle containing a pH-dependent surface charge is most stable (9). In both of the above cases, the intuitive approach, (greatest surface charge = greatest degree of repulsion = greatest stability), will most likely lead to a product which will settle slowly but will not be resuspendable.

FORMULATION STRATEGIES: THERMODYNAMIC CONSIDERATIONS

A knowledge of the surface properties of the system also helps identify the various available options and the most successful strategies for preparing the best formulation. In the case of suspensions, surface properties of the system other than surface charge can be employed. Adsorption of small hydrophilic colloids or nonionic polymers provides alternate pathways to stabilize suspensions. The former increases the particle's interaction with water and the latter sterically hinders adjacent particles from entering the primary energy minimum, where they will interact in such a way as to form a non-suspendable cake. Whereas none of these strategies will provide permanent stability to the formulation, they can create a strong enough energy barrier, so that for practical purposes, the formulation can be considered stable. Similar arguments and strategies can be used for formulating emulsions and other disperse systems.

Since interfacial free energy always has a positive value, energy has to be put into the system in order to prepare a disperse system. Theoretically, (and to a great extent, practically), enough energy can always be put into the system to overcome the thermodynamic obstacles necessary to prepare the product. Of course, the source of energy must eventually be removed, (when the plug is pulled), and thermodynamics of a closed system comes back into play. The crux of the matter is that there often are two approaches at hand to formulate products: i) the use of mechanical energy, and; ii) the use of the inherent energy of the system. The first relies on processing and the second relies on formulation factors; as a practical matter, a combination of the two is used.

As stability and other problems begin to appear with products under development, modifications in processing may be employed as one approach to solve these problems. Generally, these modifications involve the introduction of more mechanical energy into the system. Whereas this strategy may appear to alleviate the situation initially, it results in an increase in the interfacial free energy of the system and invites future stability problems. If the inherent energy of the system is not sufficient to meet the increased thermodynamic demands that processing imposes, shelf-life will likely be shortened. Modifications of the manufacturing procedure can be used to increase stability, but these modifications should result in improvements in energy barriers rather than increases in interfacial free energy. In other words, a processing change that results in a reorientation of the emulsifier film at the emulsion droplet interface so that a better barrier to coalescence is attained, or a processing change that allows a more uniform, (not necessarily smaller), droplet size to develop will likely result in a longer shelf-life.

Even under the most optimized manufacturing procedure, a disperse system will not be at thermodynamic equilibrium but will possess a positive interfacial free energy value. Each modification of the procedure will change this value, (potentially resulting in different product characteristics including stability). Since small variations in large-scale manufacture of products must be expected, (e.g., holding-time, temperature), processes must be avoided in which these small unavoidable variations result in major changes in the surface properties of the system. This situation is much more likely to occur with high energy processing. If instead, reliance is placed on lower energy processing and optimization of the system by controlling such factors as method of preparation (e.g., oil to water or water to oil ratio in the case of emulsions), rate of addition and initial location of the emulsifiers, chances of improving the product will increase (10).

The reason that the latter approach has been found to be so successful can be explained by the examination of Fig. 2 which represents hypothetical interfacial free energy pathway plots.

Point **A** represents the interfacial free energy of the product (e.g., smaller particle size will increase this value) and point **C** represents the lowest free energy state attainable (complete coalescence of the emulsion or a *cementing* of the suspension). Although thermodynamics teaches that point **C** will eventually be reached, it does not teach how long it will take or along what pathway the system will travel. The curves for Products #1 and #2 represent different pathways that can be imposed on the system as a function of processing and/or formulation. Each pathway has a different energy barrier, (e.g., it can be a function of how efficiently the emulsifier film prevents coalescence when emulsion drops collide, point **B**). Product stability could be enhanced by lowering the interfacial free energy of the product (point **A**) but the most efficient mechanism for stabilization involves increasing the value of the interfacial free energy barrier (point **B**). Actually, the stability of the

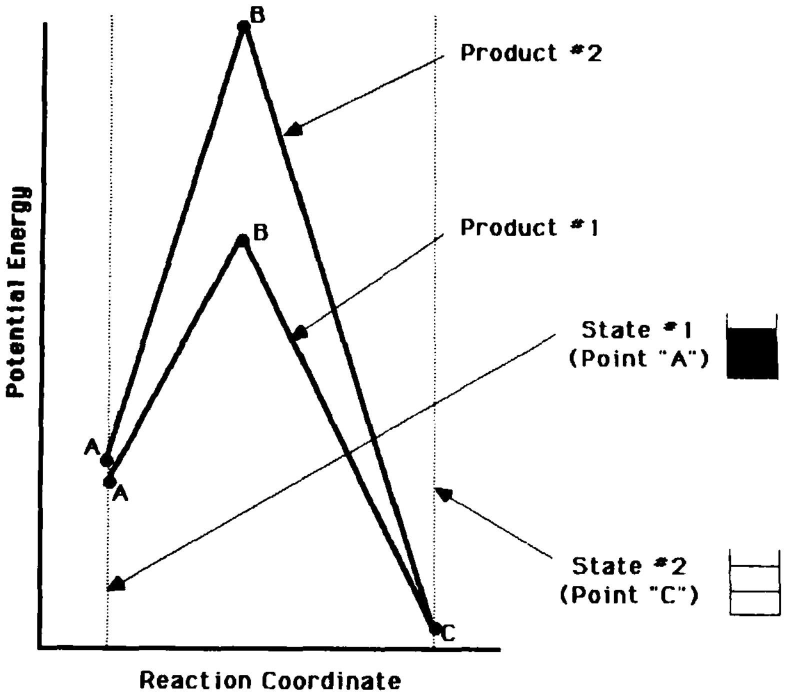

Figure 2

Hypothetical potential energy diagram demonstrating how the energy barrier affects emulsion or suspension stability. See text for detaied explanation.

system is a function of the difference in energy values between point **B** and point **A** for each product.

The curve for Product *1 might result from a strategy of attempting to improve stability by primary reliance on increasing the energy output. Note that the energy values of both products (point **A**) are nearly the same, since, as a practical matter, changes in formulation and/or processing affect point **B** to a much greater extent than their effect on point **A**. However, there is a lack of a high energy barrier for this product, (perhaps the emulsifier molecules did not have the opportunity to align properly), and there are very few thermodynamic impediments in the way for the system to reach its desired free energy, (point C), and this product will show poor shelf-life. The curve for Product *2 would result from a strategy of attempting to improve stability by optimizing the process as discussed previously. Since ample opportunity is allowed for the molecules to align in a favorable orientation, the energy barrier (point B) is strengthened leading to a formidable barrier against product instability. Another advantage to this approach is that minor changes in manufacturing procedure are less likely to change the nature of the curve. The energy barrier can be further increased by simply changing the components in the formulation, (e.g., changing the emulsifier blend or increasing its concentration). In fact, formulation changes rather than processing changes should be the preferred strategy of product improvement.

Most products generally are quite complex with respect to the number of components in the formulation. For example, emulsions usually contain at least two emulsifiers, (further complicated by their heterogeneous nature), more than one oil and other components which tend to accumulate at interfaces and affect the film. Therefore, it is not surprising that small changes in temperature, alterations in method of manufacture or in source of supply of raw materials can result in altered non-equilibrium states, which equate to altered product performance. The formulator has the responsibility to anticipate, as far as possible, which parameters are likely to affect the product and which parameters can be controlled. Generally, the more complex the formulation, the less control the formulator has.

For example, many formulators do not give enough thought to scale-up problems, particularly at the early stages of product development. In fact, expensive laboratory processing equipment is sometimes used in the formulation stage of product development that has no resemblence to production scale equipment available. There is little practical value in preparing 100 ml of a product when a completely different procedure must be used to produce larger batches. When scale-up problems are not scrutinized early on, and when a given laboratory formulation becomes final, high energy processing often is necessary to solve the problem. Such a solution rarely works satisfactorily.

EVALUATION STRATEGIES: THERMODYNAMIC CONSIDERATIONS

Of the many product types that are encountered, disperse systems are the most difficult to deal with from a stability point of view. Homogeneous dosage forms, such as solutions, are already at thermodynamic equilibrium, and chemical decomposition is usually the only concern. Accelerated stability testing is reasonably straightforward, and quantitative estimates of the rate of chemical decomposition can be obtained with a fair degree of certainty. Solid dosage forms usually have fewer stability problems than liquid disperse systems even though the solid systems, (e.g., powders), are not at thermodynamic equilibrium since the molecules have little opportunity to reorient themselves. Furthermore, solid dosage forms generally are quite stable from a chemical point of view because of the absence of an aqueous environment.

Stability testing of liquid disperse systems is one of the most difficult problems faced by formulators (11). The scientist is often asked to predict the shelf-life of a product or choose between experimental formulations based on estimates of how well they will hold up with time. There are no standardized tests available to determine stability, and quite often, there is uncertainty as to what type of stability is being investigated. Once again, a conceptual understanding of the thermodynamics of these systems, particularly their interfacial properties, can provide some insight into the expected types of instability, and equally important into the most sensible tests for predicting shelf-life.

The first order of priority for solving stability problems of disperse systems is to define clearly the type or types of stability of concern. Categorizing stability as either physical or chemical is not sufficient. The various groups that are concerned with the product (product development, production, analytical, marketing, etc.) must have a clear and precise reference frame of stability. For example, with respect to emulsions, various types of stability problems can occur. Creaming (a reversible separation of the emulsion into dilute and concentrated regions) may even be tolerable under certain circumstances. The rate of creaming, (if not complicated by other factors), is predictable, and since the various factors which influence creaming (droplet size, density differences between phases and viscosity) are known, there are many strategies available to alleviate creaming problems successfully. Coalescence (an irreversible destruction of the emulsion) is intolerable to all groups concerned and is a function of the strength of the emulsifier film at the droplet interface, i.e., the interfacial free energy barrier shown in Fig. 2. The factors affecting coalescence, flocculation and creaming are very different (12), and accelerated stability testing for coalescence is, at best, difficult and risky. Various other types of stability problems can also occur, such as phase inversion, changes in rheological characteristics, (as a result of creaming, coalescence or other factors), various changes in physical properties due to water evaporation, flocculation of the droplets, microbial contamination and chemical decomposition, to name a few. The various types of emulsion instabilities require different testing procedures and have different degrees of reliability for making shelf-life predictions. Similar arguments can be made for other disperse systems, such as suspensions.

An understanding of the factors that lead to stability problems can help determine which methods of testing are most likely to yield information applicable to the estimation of the product's shelf-life. Stability tests commonly stress the system to limits beyond which the product will ever encounter. Typical examples of stress tests include exposure of the product to high temperatures (13) and large gravitational forces (14). It is important to understand whether these tests are being performed because the product is expected to encounter these conditions or because, even though these conditions will never be approached, the results will help predict shelf-life at more moderate conditions.

For example, accelerated stability testing to determine rates of creaming by the use of centrifugation can be performed if it is assumed that the factors which control creaming (droplet size and viscosity) remain constant during the life of the product. More importantly, the testing procedure itself should not produce changes in the emulsion that affect the creaming rate, e.g., high speed centrifugation may result in a weakening of the emulsifier film leading to coalescence (15). With respect to predictive testing for coalescence of an emulsion or non-reversible settling of a suspension, there is little evidence that pushing the system far beyond what it will encounter in the marketplace yields any reliable information useful for shelf-life predictions. Moreover, overstressing the system creates the risk of "throwing away" formulations that would be perfectly acceptable under realistic conditions.

High temperature testing (>25°C) is almost universally used for both emulsions and suspensions. Various laboratories store their products at temperatures ranging from 4°C (refrigerator temperature) to 50°C (or perhaps even higher). The temperatures used in heat-cool cycling are also quite varied, often without regard for the nature of the product. What will the increase in temperature likely do to the properties of the systems under study?

For emulsions, higher temperatures will dramatically alter the nature of the interfacial film, especially if nonionic emulsifiers are used. The principal mechanism for stability in these systems is the hydration of the polyoxyethylene groups of the emulsifier molecules (16). The choice of the emulsifier blend to be used, (whether determined by the HLB or other methods), is based on their interfacial properties at room temperature. At higher temperatures, where the stability tests are being run, the emulsifiers are much less hydrated, their HLB values are completely different, and, in fact, they can be considered as different molecules. Thus, if one expects the product to be exposed to a temperature of 45°C for an extended period of time or for short durations, (shipping and warehouse storage), studies at 45-50°C, (long term and heat-cool cycling), are quite justified. A study of a product at these temperatures determines: 1) How is the emulsion holding up at this higher temperature, and; 2) Is the damage reversible or irreversible when the product is brought back to room temperature? If temperatures higher than the system will ever encounter are used, even in short-term heat-cool cycling, there is a risk of irreversibly damaging the product so that when it is brought back to room temperature, the emulsion can not heal. This is particularly true if higher temperatures cause large changes in the physical properties of the product, such as viscosity. These changes can be irreversible if the changes result from the precipitation or breakdown of polymers in the dispersion.

For suspensions, higher temperatures will dramatically alter the solubility of the suspended drug. During heat-cool cycling, the saturated layer around the suspended particles will change resulting in a greater tendency for aggregation of particles, particularly in suspensions in which particle size is not uniform. Higher temperatures will also affect a number of other parameters, such as the stabilizing efficiency of polymer additives which depends on hydration, a very temperature dependent phenomenon. Once again, questions arise, "What factors are temperature dependent in the formulation? Which are reversible when the temperature is lowered? Is this study realistic enough to help predict shelf-life?" Finally, one should keep in mind that that a product which appears to be the best one at room temperature may perform poorly over the range of temperatures and other conditions it will encounter. Perhaps the use of dual emulsifiers and preservatives commonly found in emulsion systems allows the system the needed flexibility to perform well over the range of conditions encountered during its lifetime.

Protocols for stability testing should have flexibility that takes into consideration special properties of the product that may prove troublesome as well as special conditions the product may encounter. For example, if controlled flocculation is the strategy that is used to stabilize a suspension, one must make certain that the energy barrier, (responsible for stabilizing the product), is great enough to protect the product from destabilizing factors, such as the vibration caused by shipping. Thus, testing of this type of product should include use of a reciprocating shaker. Sun-screen emulsions that may be left in the glove compartment of a car and attain temperatures of 70-80°C is another example of a product that requires special testing.

CONCLUSION

In conclusion, formulators spend much time and energy designing product formulations and exhaustively testing these products. Formulation chemists are not (and probably never will be) in a position to sit at their desk and, based on theoretical concepts, design a product which is certain to meet all of the desired specifications. However, as formulators, we are in a position to use a combination of theoretical concepts, experience and common sense so that the formulation of products doomed to failure and the evaluation of products with tests that have no validity can both be avoided .

REFERENCES

(1) L.J. Osipow, *J. Soc. Cosmet. Chem.*, **14**, 277 (1963).

(2) A.W. Adamson, *Physical Chemistry of Surfaces*, 2nd Ed., (Interscience, 1960), p. 1.

(3) N.D. Weiner and G.L. Flynn, *Chem. Pharm. Bull.*, **22**, 2480 (1974).

(4) P. Becher, *Emulsions Theory and Practice*, 2nd Ed., (Reinhold, 1965), p. 105.

(5) T.J. Lin, *J. Soc. Cosmet. Chem.*, **30**, 167 (1979).

(6) E.N. Hiestand, *J. Pharm. Sci.*, **53**, 1 (1964).

(7) A.N. Martin, *J. Pharm. Sci.*, **50**, 513 (1961).

(8) W. Schneider, S. Stravchansky and A. Martin, *Am. J. Pharm. Ed.*, **42**, 280 (1978).

(9) D.N. Shah, R. Feldkamp, J.L. White and S.L. Hem, *J. Pharm. Sci.*, **71**, 266 (1981).

(10) T.J. Lin, H. Kurihara and H. Ohta, *J. Soc. Cosmet. Chem.*, **26**, 121 (1975).

(11) G. Zografi, *J. Soc. Cosmet. Chem.*, **33**, 345 (1982).

(12) S.R. Reddy and H.S. Fogler, *J. Colloid Interf. Sci.*, **82**, 128 (1981).

(13) P. Sherman, *Soap, Perfumery and Cosmetics*, **44**, 693 (1971).

(14) L. Lachman, H.A. Lieberman and J.L. Kanig, *Theory and Practice of Industrial Pharmacy*, (Lea and Febiger, 1970), p 484.

(15) P. Sherman, *Emulsion Science*, (Academic Press, 1968), Chapter 2.

(16) R.G. Laughlin, *J. Soc. Cosmet. Chem.*, **32**, 371 (1981).