FACTORS INFLUENCING THE SELECTION OF SUSPENDING AGENTS

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When developing a suspension form of a drug, the formulator is faced with a number of problems. One of these is choosing the right suspension vehicle for his formula. In many cases, the choice of the vehicle is governed by what has been used in previous suspension products or by what has been described in the literature as having been tried and found useful, however usually in specific applications. This practice of following the dictates of convention does provide a starting point, but it has often led to the failure of many suspension systems. The reason for this is the complex nature of suspension systems. Higuchi (1), in his discussion of the physico-chemical aspects of suspension formulation, points out the difficulties one might expect when relating experimental data with suspension performance.

The formulator encounters a great number of variables when working with suspensions. There are, for instance, the physical properties of the particle, such as the size, shape and density, the density of the vehicle, the volume ratio of the two phases, the extent of particle flocculation, the flow characteristics of the suspension and, probably more important, the flow characteristics of the suspension vehicle. In addition, the variables which influence the chemical stability of the suspension must be considered. Because of these many variables, it seems unlikely that a vehicle used satisfactorily in one suspension formula could be equally as effective in another, unless the physical and chemical properties of both happened to be the same. For this reason, each suspension formula should be considered separately, depending upon the rheological and physico-chemical requirements of the formula.

This paper presents a method for evaluating suspension vehicles relevant to specific suspension formulas. The method is based on the rheological requirements of good suspension vehicles and the factors which influence the selection of the most effective vehicle. Also, a check-list is

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proposed for formulating suspensions with the minimum of phase separation.

RHEOLOGICAL REQUIREMENTS

From a practical viewpoint, a good suspension vehicle is one which is both "thick" enough to suspend particles and "thin" enough to shake and pour easily. The balancing of these two requirements is difficult and has long been one of the more perplexing problems in the formulation of suspensions. In order to gain a better understanding of the rheological requirements of a good suspension vehicle, the conditions under which the vehicle should be thick and those under which it should be thin will be considered briefly.

When a suspension is at rest the particles tend to settle under the influence of gravity. The vehicle, then, should be thick so as to prevent or retard the movement of the particles. When the suspension is shaken and then poured, the vehicle should be thin to permit these operations to be done with ease. We are concerned, therefore, with two conditions involving the magnitudes of shearing stress to which the suspension is subjected after it is prepared (2, 3): namely (1) the low shearing stresses accompanying the settling of the particles, and (2) the higher shearing stresses caused by shaking and pouring the suspension.

The shearing stresses resulting from particle sedimentation are usually of a low order. For small, spherical particles whose density differs only slightly from that of the vehicle, these stresses can be calculated from basic principles. The total force (F_T) of a particle of radius r, volume V_s, and density ρ_s, suspended in a vehicle of density ρ_v, is related to the upward (F_u) and downward (F_d) forces acting upon the particle. Hence,

$$F_T = F_d - F_u = V_s\rho_s g - V_s\rho_v g \tag{1}$$

or

$$F_T = 4/3\ \pi\ rg\ (\rho_s - \rho_v) \tag{2}$$

where g is the gravitational constant. In terms of shearing stress (τ, the force per unit area), the equation becomes

$$\tau = {}^1/_3\ rg\ (\rho_s - \rho_v) \tag{3}$$

Plots of shearing stress against particle radius for various differences in densities between the particle and vehicle are shown in Fig. 1. It can be seen that for particles usually found in suspension the shearing stresses are small (< 20 dynes/cm.^{2}). Consequently, the rates of shear resulting from the movement of these particles through the vehicle are proportionately small, depending upon the viscosity of the suspension.

The higher shearing stresses induced by shaking and pouring the suspension may vary markedly. They depend upon the force applied, the size and shape of the container and the air space in the container. No precise measurements have been made of these shearing stresses but they are believed to be approximately 100 to 600 dynes/cm.^{2} and 25 to 150 dynes/cm.^{2} for shaking and pouring, respectively.

When the different conditions of shearing stress are understood, it becomes readily apparent why a good suspension vehicle should be both thick and thin. Also, it is obvious that in formulating suspensions with the minimum of phase separation the conditions of low rates of shear should be of prime concern. This is where measurements of the rheological behavior of suspension vehicles should be made. The higher rates of shear should also be considered, but the measurement of these conditions is unnecessary as long as the suspension can be shaken and poured with ease.

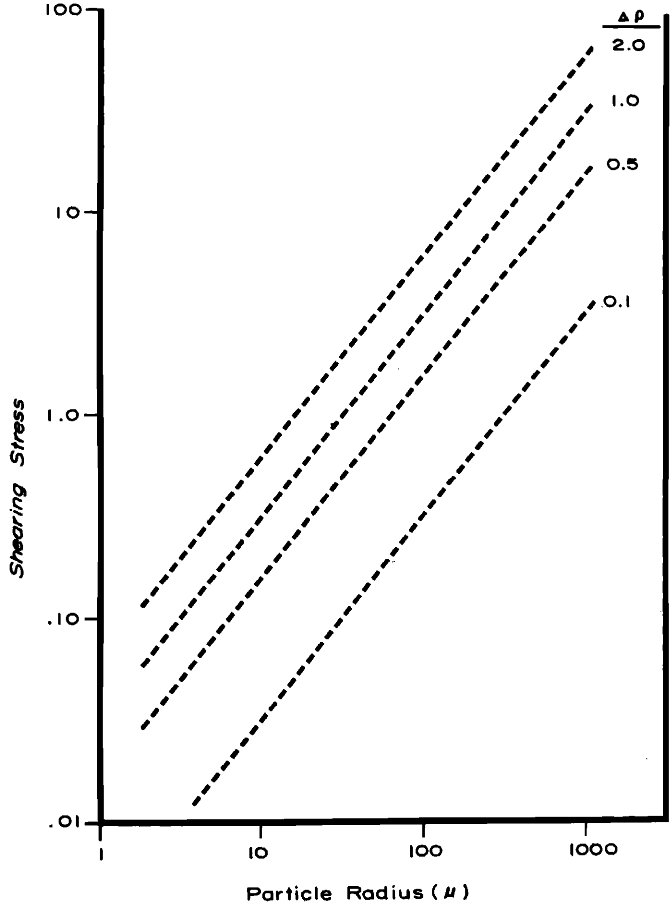

Figure 1.—Shearing stresses of particles (spheres) settling under the influence of gravity.

In summarizing the first portion of the discussion, we can say that the rheological requirement of a good suspension vehicle is (1) that it have infinitely high viscosity at low rates of shear or under the conditions when particle sedimentation would occur and (2) that it have low viscosity at the higher rates of shear or when the suspension is shaken and poured. With this in mind, it is possible to construct a hypothetical flow curve of shearing stress against rate of shear of a suspension vehicle having the desired rheological properties. In doing so, however, we find that such a curve would be similar to that of ideal plastic flow. This is shown in Fig. 2.

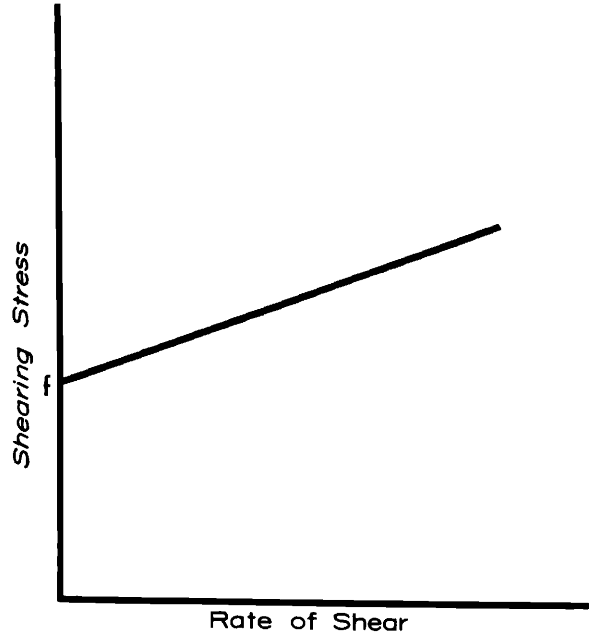

Figure 2.—Flow curve of ideal plastic flow.

An ideal plastic fluid is unique in that it will flow only after the applied shearing stress exceeds a minimum value. This minimum shearing stress is called the yield stress of the fluid and is indicated by the intercept *f* on the stress axis (Fig. 2). When referring to dispersed systems, yield stress may be defined as the resistive force of a fluid which prevents or retards the motion of particles in the fluid.

It is obvious that a suspension vehicle with ideal plastic behavior is most desirable. In addition to fulfilling the viscosity requirements, it possesses a yield stress which has been found to contribute to the suspension quality of the vehicle. The search for such a vehicle would be fruitless, however, since ideal plastic behavior is seldom, if ever, found among the suspension vehicles used in pharmacy and the cosmetic industry. Nevertheless, we can adopt the unique features of ideal plastic flow as criteria by which to evaluate suspension vehicles. Any approach to this type of flow behavior, therefore, could be considered a step toward attaining the ideal suspension vehicle.

In Fig. 3 are shown the flow curves of three suspension vehicles which differ in type of flow: (A) a pseudoplastic vehicle; (B) a thixotropic vehicle; and (C) a Bingham plastic vehicle. The curve for ideal plastic flow is included merely for comparison. It can be seen that the flow curve of vehicle C, the Bingham plastic, most closely approximates that of the ideal plastic. Thus, according to our criteria, the Bingham plastic vehicle C should be the best of the three. The thixotropic vehicle B should be rated second, and the pseudoplastic vehicle A last. There may be some question as to whether vehicle C or vehicle B should be placed first, because of the relative positions of the flow curves and the presence of a hysteresis loop (in vehicle B) which has been considered important for good suspension properties (4). The reason for this disagreement may be based on the interpretation of the thixotropic flow curve.

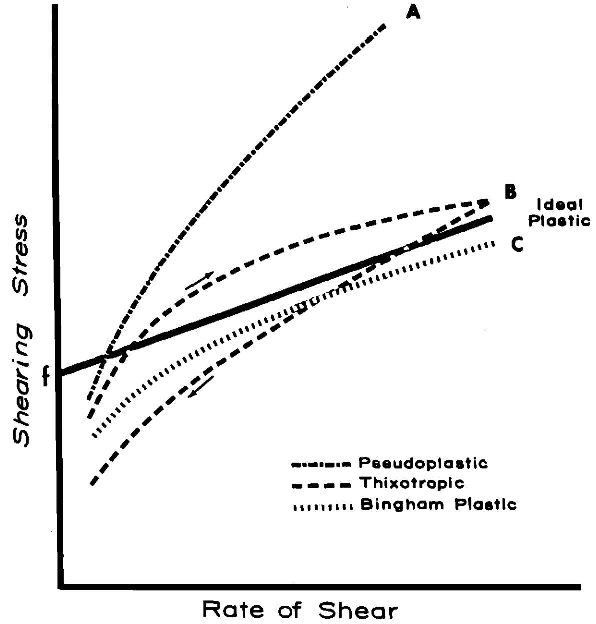

Figure 3.—Typical flow curves of non-Newtonian suspension vehicles.

Thixotropic flow is described by two flow curves, an upcurve and a downcurve. The two curves meet at a point of maximum shear. The upcurve describes the breakdown of internal structure as the vehicle is being sheared up to the maximum value. The downcurve, on the other hand, represents the flow characteristics of the vehicle after it has been subjected to maximum shear. In determining the suspension quality of the vehicle, we are concerned mainly with the conditions soon after the maximum shear has been applied, since this is when the particles begin to settle. If we assume, therefore, that the maximum shear described in the flow curves corresponds to the high shear of mixing during preparation of the suspension or to the shear induced by shaking and pouring the suspension during its use, it seems reasonable to consider only the downcurve for the measure of suspension quality.

The upcurve may also represent the gel state of the vehicle. For many thixotropic vehicles, this state may take hours or even days to reach. Therefore, if the upcurve is used to measure suspension quality, some of the measuring would be done long after the particles have begun to settle. By this time, and if the downcurve is such that it denotes poor suspension qualities, the particles may have settled markedly. The upcurve, then, could be used as a measure of suspension quality only if the thixotropic vehicle recovers its gel state within a very short time. The flow curve of such a vehicle, however, would appear similar to that of a Bingham plastic vehicle.

Before proceeding, I would like to clarify a point. It may seem that, from my foregoing discussion, thixotropic vehicles, in general, are inferior to Bingham plastic vehicles. This is not always true. I merely wish to point out that in the specific example shown, the Bingham plastic (Fig. 3, curve *C*) appears more desirable than the thixotrope (Fig. 3, curve *B*). Certainly, if a more concentrated thixotropic vehicle was used, such that its downcurve was positioned above the flow curve of the Bingham plastic, the thixotrope would be the vehicle of choice, provided, of course, that in its gel state it is not too thick to shake and pour.

Bingham plastic flow is distinguished by the need of a finite yield stress required to initiate flow. It differs from ideal plastic flow in that after the yield stress has been exceeded, the rate of shear is not a linear function of the shearing stress. Instead, the flow curve is concave to the rate of shear axis. This is similar to pseudoplastic flow except that at low rates of shear the curve appears to intersect the stress axis, indicating the presence of a yield stress, and at higher rates of shear the slope of the curve is usually small, indicating low viscosity. Unlike the ideal plastics, Bingham plastics do exist among the suspension vehicles which have potential use in pharmaceutical and cosmetic products. There may be some difficulty in finding them, however, because of the lack of reliable methods for detecting this type of flow behavior.

MEASUREMENT OF SUSPENSION QUALITY

In the process of screening potential vehicles for suspensions, we found that yield stress was largely responsible for the suspension qualities of a vehicle. Because of this, we found it necessary to develop methods which could provide reliable measures of yield stress. These methods will not be discussed at this time, but they will be presented in a forthcoming paper (5). Nevertheless, I would like to present to you the relationship which we found useful for determining the yield stress of non-Newtonian vehicles.

I. For pseudoplastic flow:

$$\tau = AD + Be^{-kD} \tag{4}$$

II. For Bingham plastic and thixotropic flow (downcurve):

$$\tau = (2UfD)^{1/2} + f \tag{5}$$

where τ is the shearing stress, D the rate of shear, U the plastic viscosity, f the yield stress, and A, B, and k are constants. By using these relationships, we obtained reliable measures of yield stress which showed good correlations with actual performance tests using glass and nylon beads of known sizes and densities.

PHYSICO-CHEMICAL FACTORS

Having dealt with the rheological aspects of suspension formulation, let us consider some factors which may influence the performance of suspension vehicles. These factors are:

1. Concentration
2. Ionic charge
3. pH
4. Temperature
5. Compatibility with substituents normally used in suspensions.

CONCENTRATION

Quite often the suspension properties of a vehicle can be enhanced significantly by slightly increasing the concentration of the suspending agent. This effect is shown in Fig. 4 for a typical Bingham plastic vehicle. It can be seen that as much as a twofold increase in yield stress can be achieved when only an additional 15 % of the suspending agent is used. This small increase in the suspending agent concentration may be the difference between a good and a poor suspension vehicle.

The data shown in Fig. 4 could facilitate the selection of suitable concentrations of the suspending agent, if the effective settling force of the particles is known. Also, since economics, to a large degree, governs the marketability of a suspension product, this information could aid in determining the minimum amount of the agent required for effective suspending action.

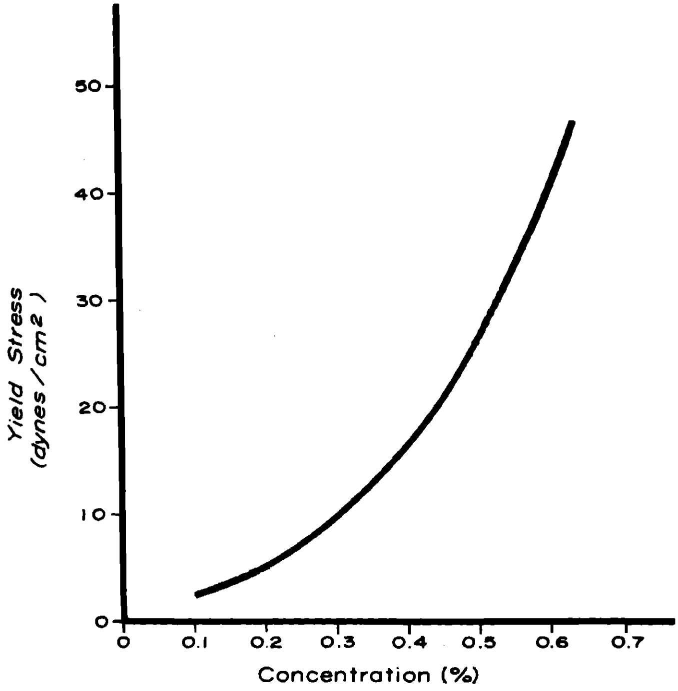

Figure 4.—Effect of concentration upon the yield stress of a Bingham plastic suspension vehicle.

Ionic Charge

It is important that the ionic charge of the suspending agent is known. Very often the use of a suspending agent and a drug of opposite charges results in unwanted effects. These effects are usually evidenced as a suspension which has settled rapidly, has decreased in drug potency or is altered in color, taste or over-all effectiveness. For this reason, the suspending agent should be one with the same charge as the drug or, preferably, one which is nonionic.

pH

In Fig. 5 is shown the effects of pH upon the yield stress of a suspension vehicle with Bingham plastic flow properties. It is evident that maximum suspension performance is achieved between pH 6 and 10. If it is necessary that the final pH of the suspension be less than 6 (or greater than 10) for reasons of drug stability, solubility or compatibility, then this vehicle should not be used. Instead, a vehicle which is not pH sensitive or one which is most effective at the desired pH should be selected.

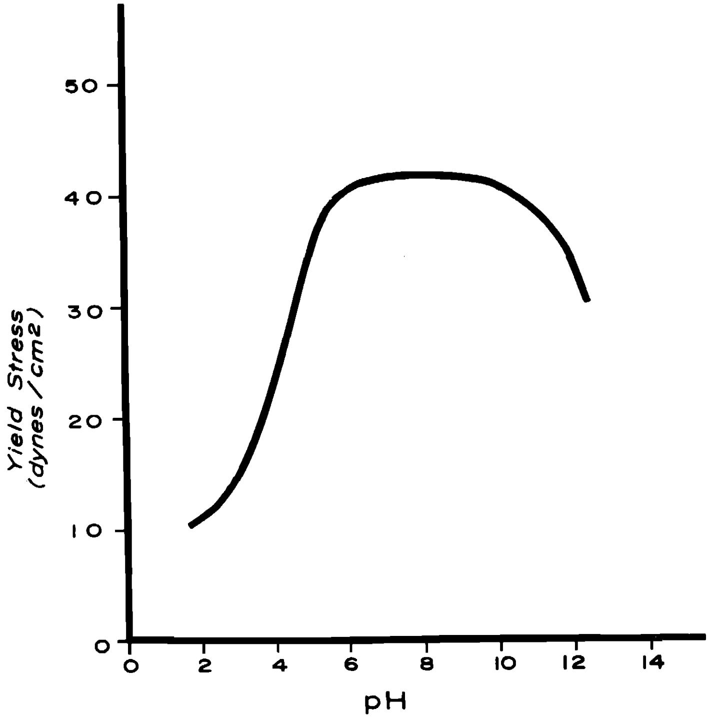

Figure 5.—Effect of pH upon the yield stress of a Bingham plastic suspension vehicle.

TEMPERATURE

A good suspension vehicle should not be affected by temperatures normally experienced by suspension products. At high temperatures, i.e., up to 60°C., the vehicle should not become so thin that it permits the particles to settle rapidly. Also, the vehicle should be able to recover its original consistency after being subjected to repeated freeze-thaw cycles.

COMPATIBILITY

The suspension vehicle should be compatible with every ingredient used in the suspension formula. That is, in addition to the drug(s), it should not be affected by the agents used to sweeten, color and flavor the product or by any other substance in the preparation.

CHECK-LIST FOR SUSPENSION FORMULATION

This check-list is presented to serve as a guide in the development of suspension products. The step-by-step procedures of the check-list could enable the formulator to exercise better judgment in selecting the most suitable suspending agent, and, also, the most effective concentration of the agent for his formula. In doing so, he can minimize the trial and error procedures of suspension formulation.

To make full use of the check-list the formulator should have prior knowledge of the physical and chemical properties of the drug he is to suspend. Also, he should be cognizant of the possible effects of the other ingredients in his formula, even though they may be present in small amounts. With this knowledge he will be forewarned of whatever effects each ingredient may have upon the rheological properties of the suspension vehicle. I would like to emphasize that this check-list is based on experiences gained with aqueous suspensions. There is reason to believe, however, that it might also apply to non-aqueous suspensions, provided that the same physico-chemical factors, either whole or in part, are inherent in these systems as well.

In light of the foregoing discussion the following procedure for formulating suspensions is suggested:

1. *Determine the ionic character of the drug (s).*

2. *Determine the ionic character of each of the other ingredients in the formula.* Whenever possible, use nonionic ingredients.

3. *Determine the density of the drug and the size of the largest particle to be suspended.*

On the basis of the information gained from steps 1 to 3, select the suspending agent(s) best suited to the formula. Since yield stress is an important and necessary factor in good suspending action, it is advisable, also, to choose the agent with this property.

4. *Determine the resulting density of the suspension medium,* after incorporating the suspending agent and the bulk ingredients, e.g., sucrose, sorbitol, etc. in the formula.

5. *Determine the sedimentation force of the particles.* From equation 3.

6. *Select the suspending agent and the concentration of the agent on the basis of the yield stress requirements of the formula.* In order to prepare a suspension with the minimum of phase separation the yield stress of the vehicle must be in excess of the sedimentation force of the particles. This excess should be sufficient to account for the unpredictable effects associated with concentrated suspension systems. It should also counteract the effects of vibration and temperature variation incurred during transit and storage of the suspension. There is no precise, calculable method by which these effects may be corrected for, but it is possible, quite satisfactorily, to offset them by using several times the required yield stress of the suspension system.

7. *After selecting the suspending agent and establishing the concentration of the agent to be used, formulate the suspension medium.* Check the rheological behavior of the medium before adding the powdered drug to

be sure that the desired properties are still present. If, for instance, upon the addition of sucrose to a suspension vehicle, there is a decrease in yield stress, more suspending agent should be added to make up for the loss. If, on the other hand, an increase in viscosity is shown when sucrose is added, the suspension may be formulated as such as long as the yield stress remains unaffected and the product is not too thick.

In general, the rheological behavior of the suspension should be checked at the various stages of formulation, particularly after the addition of each ingredient. If there is no significant change in rheological behavior, or if the rheological properties of the suspension can be restored to their original state without further change, this is an indication that the suspension may have good shelf-life stability.

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