mg. iodochlorhydroxyquin per Gm.

$$\text{of ointment} = \frac{A}{K \times \text{Gm. of sample}}$$

where A = absorbance at 650 mμ, and K = absorbance index in terms of mg. of drug per 100 ml. of sample solution.

Absorbance Index.—Prepare three standard solutions of iodochlorhydroxyquin reference standard in methyl cellosolve to contain approximately 30, 50, and 70 mg. per 100 ml. Develop the color for each standard as follows. Add a 3-ml. aliquot to a 25-ml. volumetric flask and add 17 ml. of methyl cellosolve. Add 2 ml. of the iron reagent, dilute to volume with methyl cellosolve, and mix thoroughly. Prepare a reagent blank by diluting 2 ml. of the iron reagent to 25 ml. with methyl cellosolve. Determine the absorbance at 650 mμ using the 1-cm. cells and the reagent blank solution in the reference cell. Calculate the absorbance index K by the equation $K = A/c$, where c is the concentration of standard in mg. per 100 ml. and A is the observed absorbance for the corresponding colored solution. Table II shows the results for three such standards using the Beckman DU spectrophotometer.

TABLE II.—DETERMINATION OF ABSORBANCE INDEX ($K = A/c$)

Concn. c, mg. per 100 ml.	Absorbance A	Absorbance Index K
34.8	0.218	0.00626
52.0	0.320	0.00615
69.5	0.427	0.00614

CONCLUSIONS

The U.S.P. method for iodochlorhydroxyquin in ointment preparations presents many difficulties. It is practically impossible to obtain a precipitate free of ointment base materials from an acetone extract of most ointment preparations.

The method described in this paper offers several advantages over the official method in that it is simple, rapid, reproducible, and accurate. The color formed by the reaction of ferric ion and iodochlorhydroxyquin in methyl cellosolve has been shown to be stable over a period of at least 1.5 hours. The application of the assay to two different types of ointment bases was demonstrated.

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Technical Articles

Preparation of Parenteral Dispersions

By THOMAS J. MACEK

Parenteral dispersions of medicinal products may take the form of parenteral colloids, parenteral emulsions, or parenteral suspensions. The paper defines these categories and discusses problems of manufacture and stability and illustrates with practical examples.

THE TERM "dispersion" is very general and may have several meanings. A simple solution of a salt or sugar in water can be considered an aqueous dispersion. As such, it occupies a position at one end of a scale describing various states of matter. Heterogeneous admixtures of a liquid and relatively large fragments of another immiscible liquid or solid, on the other hand, are described as emulsions or suspensions and occupy a place at the opposite end of that scale. The state of matter between these two extremes, and more particularly when the dispersed phase consists of particles between 1 and 100 mμ in size is that intermediate range called the "colloidal state." This region frequently is subdivided further by the term "colloidal solution" or "sol" as in the case of a solution of gelatin or of silver iodide, and colloidal dispersions, as in the case of colloidal gold having solids suspended in the submicron form. The term "hydrosol" is employed when the solvent is water, and the term "aerosol" refers to a colloidal dispersion in air or another gas.

Actually, the line of demarcation between a true solution and the colloidal state is not really very sharp. Solids dissolve in a liquid such as water when there is complete or near complete intermingling of solute and solvent molecules or ions. The ionic bonds of salts such as exist between Na^+ and Cl^- must be fractured in the process of dissolving, the energy being derived from the polarity of the solvent. At best, solute to solute and solvent to solvent bonds have to be broken and new solute to solvent bonds formed. If the forces—such as

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hydrogen bonding—between these new associations are great, solubility is favored. In that special situation where these forces are equal or cancel previously existing forces between individual particles of solute and individual particles of solvent, there is a free intermingling and we have a case of an ideal or perfect solution. On the other hand, the forces between the dissimilar particles much more frequently are not as great as the forces between the similar individual components; hence solubility will not be favored, but dispersion may occur. The dispersion may assume colloidal or suspension proportions, sometimes followed by precipitation or flocculation or both.

In accordance with this concept, the terms "hydrophilic" and "hydrophobic" are used to describe the tendency of a surface, a particle, or a functional group to establish bonds of association with the solvent, water. In colloidal systems, stable colloids are always referred to as lyophilic or hydrophilic. Unstable colloids are always lyophobic or hydrophobic. They represent those that are readily flocculated by small amounts of electrolytes.

Some examples will serve to illustrate. Albumin and other proteins dissolve in water, forming hydrophilic sols. Polyvinylpyrrolidone, dextran, the carbohydrate gums, and other synthetic gums behave similarly. In spite of the large size of the protein or gum molecules, they form remarkably stable colloidal solutions. This is because of their state of hydration (the so-called watery envelope) and of their electrostatic charge. To precipitate a hydrophilic sol, one must first remove the charge. This usually is accomplished by adjusting the pH to the isoelectric point at which there is electrical neutrality. Then the watery envelope is removed by dehydration, as with alcohol or a dehydrating salt, such as ammonium sulfate. The protein or gum precipitates under these rather special conditions.

Hydrophobic sols behave quite differently. If an insoluble substance is ground long enough and fine enough in water, a hydrophobic sol may form. This colloidal state will not be very stable, however. The particles, continually in motion, bombard each other, energy is reduced in the process, and there is a great tendency toward coalescence and flocculation. Hydrophobic sols are stabilized by reducing interfacial tension which changes the energy at the particle surface. The process of transforming an insoluble substance into the colloidal state frequently is referred to as "peptization." However, even this colloidal state is easily broken by the simple addition of an electrolyte.

When the extent of the stabilization by reduction of surface forces is great enough, a hydrophobic material can be rendered seemingly water-soluble. This process is called "solubilization," or solubilization through micelle formation. It differs from hydrotropy, another solubilization process which is distinguished by the absence of colloidal material. In the latter case, solubilization is accomplished through the use of aqueous solutions of salts or organic ions, the so-called "salting in" effect, or through the use of water-diluted organic solvents or mixtures of solvents. Emulsification is distinguished from both solubilization and hydrotropy principally by the size of the dispersed phase. An emulsion generally also is opaque, whereas the other phenomena produce solutions which are transparent, at least to the naked eye. Furthermore, an emulsion comprises a dispersion of one immiscible liquid in another. When the process describes solids instead of liquids, the system is a suspension.

Over the years, numerous parenteral formulations have been developed for medicinal use which span the entire range of these different states of dispersion. Much could be said about the properties of surface-active agents, about the hydrocolloids, and about techniques and theories involved in the dispersion and emulsification processes. However, inasmuch as industrial pharmacists constantly are faced with practical problems of development and manufacture, this paper concerns itself with some practical considerations pertaining to parenteral colloids, emulsions, and suspensions. It is hoped that observations and experiences in the development of these dispersion products may prove interesting while illustrating principles and problems which are encountered when working in this field.

MATERIALS AND FACILITIES

The choice of active form of the drug for the preparation of parenteral dispersions is limited largely by pharmacological considerations. Therefore, in most cases the industrial research pharmacist is confronted with a form of a drug that is active biologically with which he must prepare safe and acceptable parenteral products. Quite often, this may be the only active form of the drug known at the time. In some cases, only insoluble forms of the drug possess desirable properties such as prolongation of activity, stability, lack of irritation, etc.

Such was the case at first with the insoluble derivatives of the corticosteroids. Several years elapsed before stable, biologically active, and completely water-soluble derivatives of the adrenocortical steroids were discovered. As a general rule, when biological properties are equal, it is far more desirable and economical to search out water-soluble forms of new drugs for parenteral administration than to attempt the more difficult formulation of physically less stable parenteral dispersions. In the case of methyldopa,[1] exactly this course was pursued, resulting in the development of the water-soluble and biologically active ethyl ester hydrochloride derivative specifically for parenteral use. Other well-known examples of this approach have occurred among the antibiotics. The sodium methanesulfonate of colistin provides a water-soluble parenteral. The ethanol-ammonium-magnesium complex of oxytetracycline is soluble in a propylene glycol-water vehicle employed for injection. The ethyl succinate of erythromycin has been dissolved in a polyethylene glycol vehicle for intramuscular administration. A 10% solution of the sodium succinate derivative of chloramphenicol proved useful for both intravenous and intramuscular injection. Similar examples are found among other classes of therapeutic compounds.

On the other hand, the natural oil form of vitamin K_1 proved much superior therapeutically to syn-

[1] Marketed as Aldomet by Merck and Co., Rahway, N. J.

thetic analogs of K and had to be dealt with even though water-insoluble. For reasons of stability, the insoluble salts of penicillin had to be employed to formulate ready-to-use aqueous suspensions of this antibiotic. The insoluble dibenzylethylenediamine salt of penicillin had to be used to achieve the sought-after prolongation of blood levels. And so the problems of preparing parenteral dispersions persist.

Agents which are employed to prepare and stabilize parenteral dispersions have to meet at least three principle criteria. The first is that they must be safe. This requires that they be nontoxic, nonantigenic, nonpyrogenic, nonirritating, and nonhemolytic. The second is that they must be potent dispersants and/or stabilizers so that only small amounts are required. Third, the agents should be stable, especially upon prolonged storage, and preferably under the conditions of higher temperatures which one would like to employ for positive sterilization. One might add a fourth criteria—namely, known acceptability to the federal Food and Drug Administration. Otherwise, the burden of proof of safety, which today if not attainable without considerable expenditure of time and money, rests entirely upon the user. These are very rigid specifications and rule out many agents that are perfectly satisfactory for oral use in pharmaceuticals and even in foods. A partial list of agents which have been employed in commercial parenteral products is shown in Table I.

The preparation of parenteral dispersions often presents difficult or unusual problems of manufacture because of the requirements for sterility and freedom from pyrogen contamination. In this regard, the efficiency of dispersing and mixing equipment sometimes must be comprised to achieve completely aseptic operation. The alternative is to reconstruct such equipment to withstand heat sterilizing conditions, also a job not easily accomplished. Totally enclosed systems have had to be designed for large-scale aseptic production operations. In such instances assurance was needed to show that the dispersions could be adequately mixed and kept in a state of uniform suspension throughout all preparative, transfer, and subdividing operations. This has been a task to engage the best thinking and ingenuity of both pharmacists and engineers in many industrial plants. Apart from the facilities and techniques for sterile formulation, the development and production of parenteral dispersions would not have been possible without considerable attention to the physical properties of the starting materials, particularly in dealing with suspensions.

In this regard the first gram of cortisone acetate ever produced was processed by aseptic milling with aqueous vehicle employing a glass bottle and glass beads. Milling continued until 90% of the particles were smaller than 10 μ. Although the procedures changed drastically as the scale of operation increased, the requirement for the particle size was retained and, indeed, established a standard for most of the corticosteroid suspensions that followed. Today cortisone acetate and other corticosteroids for parenteral use are crystallized using methods and facilities which produce a sterile solid having a particle size smaller than 10 μ. In addition, the crystallization of cortisone acetate is conducted in a way which produces that polymorphic form which experience has shown to be stable upon prolonged storage in aqueous suspensions. Such starting material requires no subsequent milling. It is simply suspended in a sterile aqueous vehicle by a process which lends itself readily to large-scale operation under strictly aseptic conditions.

TABLE I.—MATERIALS USED IN PARENTERAL DISPERSIONS

Surfactants
Pluronic F-68 (polyethylene-polypropylene nonionic)
Polysorbate 80 U.S.P.[a]
Polyoxyethylene sorbitan monolaurate
Emulphor EL-620
Sorbitan trioleate[b]
Lecithin
Hydrocolloids
Sodium carboxymethylcellulose
Polyvinylpyrrolidone
Gelatin (nonantigenic)
Methylcellulose
Other
Polyethylene glycol 300
Propylene glycol
Sorbitol
Silicone antifoam
Aluminum monostearate

[a] Polyoxyethylene 20 sorbitan monooleate, marketed as Tween 80 by Atlas Powder Co., Wilmington, Del. [b] Marketed as Span 85 by Atlas Powder Co., Wilmington, Del.

The manufacture of other parenteral suspensions presents somewhat different problems. Nonetheless, detailed attention is required to specifications of crystal form and particle size in order to achieve physical and therapeutic uniformity in the final parenteral dispersions.

PARENTERAL COLLOIDS

The area of biological products provides numerous examples of parenteral dispersions in the colloidal state. These include serum albumin, fibrinogen, various immune globulins, human fibrinolysin, insulin, corticotropin, and other hydrophilic protein or peptide products derived from human blood and natural sources.

Several parenteral solutions of iron are actually colloidal dispersions of complexes of iron with carbohydrate materials. This category includes an iron-dextran complex,[2] a high molecular weight iron-carbohydrate,[3] and a saccharated iron oxide.[4]

Perhaps of greater interest, however, are those colloidal dispersions prepared by micellular solubilization involving smaller organic molecules that are essentially hydrophobic. Parenteral products in this category include a product containing water-solubilized vitamin A,[5] an aqueous dispersion of a synthetic vitamin K,[6] and an aqueous colloidal

[2] Marketed as Imferon by Lakeside Laboratories., Inc., Milwaukee, Wis.
[3] Marketed as Astrafer I. V. by Astra Pharmaceutical Products, Inc., Worcester, Mass.
[4] Marketed as Proferrin by Merck Sharp and Dohme, West Point, Pa.
[5] Marketed as Aquasol A by U. S. Vitamin and Pharmaceutical Corp., New York, N. Y.
[6] Marketed as Konakion by Hoffmann-LaRoche, Inc., Nutley, N. J.

solution of vitamin K_1[7] made using Emulphor EL-620 as solubilizing surfactant.

The theory of solubilization by micelle formation was first postulated in 1913 by McBain (1). It described the phenomenon wherein particles of a colloidal substance such as potassium stearate functioned to incorporate the insoluble materials within themselves. In the process the original solid or oil particles disappeared into the organized structure of the stable colloid. This process today has been extended to include a wide variety of surface-active agents, some of which are acceptable for parenteral dispersions.

To be effective the surfactants themselves must be soluble in water and form the proper micellular environment for solubilization. The concentration at which micelle formation begins to occur is known as the critical micelle concentration. This can be measured in various ways and has been observed to decrease as chain length of surfactant increases, regardless of its basic organic structure. Sometimes the surface-active solubilizer may have other effects which enhance its activity, such as cosolvency and specific complex formation. However, in spite of many excellent studies on solubilization which have brought about a better understanding of some of the mechanisms involved, it still is necessary to conduct empirical research to arrive at practical answers in most cases.

Some generalizations are available, however, and are worth noting. In 1949, Griffin (2) devised a hydrophile-lipophile balance (HLB) system for classifying surfactants which is helpful in selecting solubilizers. Moore and Bell (3) later listed some useful observations based upon the studies of a number of workers which are helpful in laboratory problems of solubilization. For example, it has been observed that in a homologous series of compounds the amount of solubilizer needed increases directly with the polarity, cyclization, and unsaturation of the hydrophobe and inversely with chain length. The addition of inorganic salts to a solubilized system increases the amount of nonpolar or hydrocarbon-like substances solubilized, but decreases the amount of polar substances solubilized. The more lipophilic nonionic surfactants favor maximum solubilization of low polar substances, and the more hydrophilic nonionic surfactants favor solubilization of the more polar hydrophobes.

From a formulator's viewpoint, it is often found that a mixture of two or more surfactants proves better for solubilizing a compound than does one alone. In addition, a co-solvent sometimes also helps to attain a clear solubilized solution. Once a solubilizer or mixture of solubilizers shows promise, the effect should be studied over a range of ratios of solubilizer and solubilizate. And finally, a mixture of water, solubilizer, and hydrophobic solubilizate often has to be heated to obtain a solution. The optimum heating time may vary with different systems. In some cases, mixtures may show a negative solubility. In other words, their solutions may be cloudy at higher temperatures and clear at room temperature. Clarification may develop slowly in these instances and the solution therefore should be allowed to stand. Slightly opalescent solutions sometimes may be made crystal clear by rapid cooling.

Even though the list of parenteral products made by solubilization using surfactants is still small, this area of formulation offers interesting possibilities. It not only provides a means for preparing aqueous parenteral forms of hydrophobic drugs, but also provides the opportunity for stabilization of some sensitive drugs in parenteral products as well. In this regard, Riegelman (4) observed that micelles of cationic or anionic surfactants shielded certain esters against hydrolysis.

In a 5% sodium lauryl sulfate solution, the half-life of benzocaine against base-catalyzed hydrolysis was extended some eighteenfold. This is a very profound change and is worth noting. Although sodium lauryl sulfate may be unsuitable for parenteral use in these quantities, other surfactants need to be studied. The ampholyte, Emulphor EL-620, by comparison is much less toxic, and also nonhemolytic in rather substantial concentrations.

PARENTERAL EMULSIONS

Until now only two commercially-available parenteral emulsions have enjoyed extensive medical use. Both of these were specifically for intravenous administration. However, parenteral emulsions of fats, either alone or supplemented with amino acids or vitamins, attracted considerable research and clinical interest some time ago and occupied the attention of pharmacists for several years.

An emulsion of a natural vitamin K_1 in an aqueous vehicle made with a purified form of lecithin as emulsifier is described in the U.S.P. as sterile phytonadione emulsion.[8] Considerable care is taken during manufacture and testing of this parenteral to assure that all of the emulsified oil droplets conform to a rigid particle size specification in the range of 1 to 5 μ. This state of subdivision is achieved by an emulsification process involving the use of an intermediary solvent. The emulsion is sterilized by autoclaving while in bulk; it is then filtered and subdivided aseptically into the final ampul containers.

The second product is a parenteral fat emulsion[9] containing 15% cottonseed oil and 4% dextrose, with 1.2% lecithin and 0.3% of an oxyethylene-oxypropylene polymer as emulsifying agents. The product is administered in volumes of 250 to 500 ml. by intravenous infusion to supply dietary fat in debilitating diseases, post surgery, etc. Most of the dispersed droplets in this product are less than 1 μ in size and none can be greater than 5 μ. The product presumably is sterilized in the final container by autoclaving. Like sterile phytonadione emulsion, it must be protected against freezing.

Inasmuch as parenteral emulsions are intended for intravenous administration, absolute assurance of sterility is required, and sterilization in the final container by autoclaving is virtually essential.

[7] Marketed as Aquamephyton by Merck Sharp and Dohme, West Point, Pa.

[8] Marketed as Mephyton by Merck Sharp and Dohme, West Point, Pa.

[9] Marketed as Lipomul I. V. by The Upjohn Co., Kalamazoo, Mich.

Elevated temperature, however, tends to cause increased coalescence of fat globules; hence, parenteral emulsions must be designed to withstand heat sterilization. In this connection, nonantigenic gelatin has been explored for use both as an emulsifier and emulsion stabilizer for intravenous products. Unfortunately, solutions of gelatin hydrolyze upon autoclaving, and this change can result in alterations in emulsion stability. Small concentrations of methylcellulose appear to stabilize fat emulsions against separation or creaming, but one encounters a problem during autoclaving because of the insolubility of methylcellulose at elevated temperatures. Dextran also has been examined as an emulsion stabilizer.

The stability of fat emulsions is no small problem. Apart from the potential development of rancidity of the oil phase, fat emulsions are subject to adverse physical changes. Excessive shaking of parenteral fat emulsions has been observed to accelerate the rate of separation ("creaming") and to cause a greater tendency toward particle coalescence. This change probably is caused by rupture of the film of emulsifier about the particles of dispersed oil. It has been also observed that bottles half full of fat emulsion "creamed" at a faster rate upon prolonged storage than full bottles. Such change was thought to be due to decomposition of the film of emulsifying agent by oxidation.

It is apparent, then, that the preparation of parenteral emulsions is troublesome. It is made more difficult by rigid requirements regarding particle size for reasons of safety, without much latitude in the choice of emulsifiers and stabilizers and stringent requirements for stability upon exposure to both high and low temperatures.

PARENTERAL SUSPENSIONS

One of the earliest commercial parenteral suspensions was sterile bismuth subsalicylate suspension in oil. The product still is described by U.S.P. monograph and is employed as an antiprotozoal and antisyphilitic agent. Among other early parenteral suspensions were those of the estrogens, androgens, and progestational hormones, some of which still are very valuable therapeutic agents.

However, it was the discovery of the adrenocorticol stercids, of penicillin, and the broad spectrum antibiotics that gave renewed impetus to the development of new compositions and technology for the preparation of parenteral suspensions.

The method employed for preparing the first quantities of cortisone acetate was mentioned previously. Glass bead milling to reduce particle size was conducted in a portion of the vehicle containing polysorbate 80 as surfactant to facilitate wetting of the water-insoluble, hydrophobic crystals of the steroid. The wetting agent was effective in this case because it favored the replacement of the solid-air interface by a solid-liquid interface. This is the property expected of a good dispersing agent. However, this alone was insufficient to produce a physically stable suspension. Hence, there was a need for a compatible dispersion stabilizer, protective colloid, or agent to bridge the gap between the continuous phase of the aqueous vehicle and the essentially hydrophobic particles which it enveloped. For this purpose sodium carboxymethylcellulose was employed. This is a safe parenterally acceptable hydrocolloid which had an affinity for the continuous phase. It could be employed effectively in concentrations which produced only a small change in viscosity; it was stable and could be sterilized by autoclaving. In the presence of sodium carboxymethylcellulose, to a large extent the dispersed particles of steroid lost many of the properties which normally identified them as hydrophobes—namely, surface charge, water repellency, and tendency toward agglomeration. Instead they assumed some of the properties of the protective colloid and of the continuous phase. Thus, the suspension was stabilized, settling was reduced, and resuspension by shaking was readily accomplished. Sodium chloride was added to adjust isotonicity. Benzyl alcohol was employed as a preservative. This example illustrates one of the fundamental ways available to the pharmacist for preparing suitable suspensions of a hydrophobe for parenteral use—namely, dispersion using a wetting agent in conjunction with a compatible protective colloid.

A brief digression for a moment will serve to highlight another potential problem. During the period that parenteral suspensions of cortisone acetate were made by bead milling, no problems with polymorphic changes were encountered. It is apparent today that phase changes were being experienced, inasmuch as the starting solid was later shown to be a physically unstable variety in contact with water. However, if a change occurred, this happened during the course of the extended milling cycle and without evidence of significant changes in particle size. Difficulties with polymorphism were encountered when dry, premilled solid of the wrong crystal form was rapidly suspended in the aqueous vehicle by mechanical agitation and the resulting suspensions were allowed to stand undisturbed. The change to a more stable crystal form invariably was associated with crystal growth, the intermingling of these crystals, and the formation of a cake or lumpy suspension. Usually these changes occurred in the final vials so that little could be done to recover the product. The possibility of polymorphic change, therefore, should be anticipated in many parenteral suspensions of new compounds, especially of the steroid type.

Recently, with some steroids, particularly the highly water-insoluble tertiary-butylacetate esters of hydrocortisone and prednisolone, it was possible to replace sodium carboxymethyl cellulose in the aqueous vehicle with sorbitol. This additive functioned as a suspension aid by increasing the density of the aqueous vehicle rather than as a protective colloid. The rate of settling of the suspended solid was readily decreased as the density of the aqueous phase increased by addition of graded increments of sorbitol.

The preparation of aqueous parenteral suspensions of procaine penicillin both in the ready-made and dry-mix forms presented some very different and interesting dispersion problems. Where concentration of suspended solids did not exceed 5% in the case of the corticosteroids, the problem now was one of preparing essentially fluid, syringeable, and injectable suspensions containing up to about 35% solids. Without effective dispersing agents, it

was very difficult even to wet this much solid adequately with the limited volume of water. Surfactants such as lecithin and Pluronic F-68, which proved very effective for purposes of wetting, produced highly dispersed suspension systems exhibiting extremely poor physical stability. Such systems settled slowly but ultimately sedimented to a very dense cake which was exceedingly difficult to resuspend. When viewed under the microscope, disperse suspensions of this type were seen to consist of individual particles, each in random and haphazard motion in relation to others having no apparent association between themselves. The dispersion could be likened to a suspension of sea sand in a bottle of water. Each particle was free to move in any direction at any speed even after colliding with another. When gravity sedimentation occurred, the volume occupied by the solid was small. The dense cake which formed, however, was resuspended again only by peeling a thin layer of particles off the top, one after another, until finally all solid was resuspended.

With procaine penicillin dispersions, it was found that not enough protective colloid could be added to improve adequately the sedimentation properties without also significantly altering their viscosity, flow, syringeability, and other physical properties, usually in an undesirable way. This is not to say that hydrocolloids, like sodium carboxymethylcellulose or gelatin, did not produce a favorable result in aqueous suspensions of procaine penicillin. If the products had been for oral use where high viscosity was not of great importance, they probably would have been quite acceptable. Indeed, the addition of gums is a common way of stabilizing oral suspensions. However, in the parenteral suspension the properties sought included a high degree of product fluidity, little or no foaming, quick restoration with water when in the dry form, a rapid break from the surface of the siliconed vial, a thin suspension for easy syringeability, and a product with good injectability through small bore hypodermic needles. Such properties could not be achieved readily in suspensions of high solids content by the classic method of using a protective colloid alone in conjunction with a wetting agent. Some other method for suspension stabilization had to be found. In this connection partial flocculation by the addition of selected inorganic ions proved to be highly successful.

Flocculation of the dispersed solid was achieved in increasing magnitude by monovalent, divalent, and trivalent ions, respectively. Indeed, flocculation of procaine penicillin dispersions by the addition of even very small amounts of trivalent aluminum, as the chloride, would occur to such an extent that the suspensions acquired an unsightly, nonuniform appearance. However, such suspensions could always be resuspended by gentle shaking. In practice, a partially flocculated dispersion made with monosodium citrate proved most practical. A small amount of the protective colloid, or the use of sorbitol to increase vehicle density, also proved of benefit.

According to Michaels and Bolger (5), in the partially flocculated system, the floc, or the associated colony of a number of particles, becomes the basic flow unit in low shear processes such as gravity sedimentation. These flocs can be regarded as rigid spheres which tend to cluster together in weak aggregates. The aggregates grow by collision, are broken down by low shear forces such as gentle shaking or by flow through a small orifice of a hypodermic syringe or needle, yet they are able to reform easily the extended networks which give the suspension its structural properties with virtually no increase in viscosity. The partially flocculated suspension will settle rapidly, but to a high sedimentation volume and is easily resuspendable. Most important from our standpoint, they can be produced easily under sterile conditions, using materials which are fully acceptable for parenteral formulation.

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