
PHARMACEUTICAL DOSAGE FORMS

Disperse Systems

In Three Volumes

VOLUME 1

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EDITED BY

Herbert A. Lieberman

H. H. Lieberman Associates, Inc.
Livingston, New Jersey

Martin M. Rieger

M. & A. Rieger Associates
Morris Plains, New Jersey

Gilbert S. Banker

University of Iowa
Iowa City, Iowa

Marcel Dekker, Inc.

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Viscosity-Imparting Agents in Disperse Systems

Joel L. Zatz

Rutgers—The State University of New Jersey, Piscataway, New Jersey

Joseph J. Berry

Bristol-Myers Squibb Company, New Brunswick, New Jersey

Daniel A. Alderman

The Dow Chemical Company, Midland, Michigan

I. INTRODUCTION

Polymers are used in suspensions, emulsions, and other dispersions, primarily to minimize or control sedimentation. The rheological character given to disperse systems also plays a role in maintaining pharmaceutical preparations at their application site. For example, highly fluid skin lotions may run, whereas viscous preparations tend to remain in place for longer time periods. A related application is in ophthalmic preparations, for which polymers are used to enhance drug retention.

In addition to their effect on dispersion rheology, polymers may also play a role in determining the flocculation state of suspended particles. By virtue of their surface activity, some polymers can directly improve emulsion stability; the ability of acacia to function as an emulsifier is well known.

Various substances have been used over the years to build viscosity in aqueous drug systems. Included are such familiar compounds as sucrose and other sugars, and polyols such as glycerin. These materials suffer from two major disadvantages. They are needed in high concentration to produce significant viscosity changes, and their aqueous solutions are newtonian in nature (see Chap. 5).

On the other hand, only small amounts of many polymers (depending on chemistry and molecular weight) are needed to bring the viscosity of an aqueous preparation to almost any desired value. Furthermore, most polymer solutions or dispersions are nonnewtonian; in addition to being pseudoplastic, they may exhibit a yield point or thixotropy. These properties are advantageous in combining sedimentation resistance with processing ease. This point is explained further in Section III.

The nonnewtonian nature of polymer solutions makes it difficult to compare the properties of different polymers. Viscosity is a function of shear rate and, quite often, shear history, so that the numerical value of viscosity that is measured is a function of the method and conditions of measurement. Typically, manufacturers quote viscosity figures obtained from a single measurement at relatively high shear; this is insufficient to characterize a nonnewtonian material, particularly since its application to sedimentation control will take place under quiescent (low-shear) conditions.

As a consequence, the viscosity data provided by raw material suppliers is useful in only a very general way. Such data can show, for example, that certain polymer grades yield more viscous solutions than other grades made by the same manufacturer. However, it is extremely difficult to compare data on different polymers supplied by different manufacturers. It is not uncommon to find that two polymers, the solutions of which have nearly the same quoted viscosity value, affect a disperse system in markedly different ways.

Within a polymer family, an increase in molecular weight results in an increase in molecular asymmetry; hence, in viscosity. Different viscosity grades, based on a difference in average molecular weight, are described in several ways. With methylcellulose, the viscosity of a 2% aqueous solution measured in a standard manner is provided. Polyethylene glycols are described in terms of average molecular weight, whereas designations, such as low, medium, and high, are used in connection with viscosity grades of carboxymethylcellulose. All aqueous systems containing polymers require a preservative. Many polymers of natural origin are attacked directly by microorganisms. Cellulose derivatives are degraded by cellulases, enzymes that may be produced by microbial agents. Even if the polymer chosen is totally resistant to bacteria and molds, the aqueous medium may allow growth, and a preservative is still necessary.

Certain inorganic agents are also used as viscosity builders. Examples are colloidal magnesium aluminum silicate (Veegum) and microcrystalline silica. These substances do not support bacterial or mold growth and are relatively inert from a physiological standpoint.

II. POLYMER SOLUTION RHEOLOGY

Typically, polymer solutions are nonnewtonian. The three most commonly observed behaviors for polymer solutions are plastic, pseudoplastic, and thixotropic. Plastic systems flow only after a critical shear stress is exceeded (yield value). In pseudoplastic or shear-thinning systems, the viscosity decreases with increasing rates of shear. Thixotropy is the case in which a plastic or pseudoplastic system exhibits a time-dependent recovery, resulting in a hysteresis loop if shear stress is alternatively increased and decreased.

The type of rheological behavior, as well as the magnitude of the viscosity, is a critical factor determining the usefulness of a particular polymer for each potential application. For example, pseudoplasticity, the existence of a yield point, and some degree of thixotropy are useful characteristics for a polymer used as a suspending agent. Thus, xanthan gum, which has a yield value and is highly pseudoplastic, was a more effective retardant of creaming in mineral oil-in-water emulsions than either methylcellulose or carboxymethylcellulose [1], despite that comparisons were made at concentrations yielding the same range of measured viscosity values. Thus, it is not possible to evaluate polymer usefulness on the basis of a single viscosity value measured under arbitrary conditions.

The situation is complicated because rheological characteristics of polymer solutions may vary, depending on the concentration and degree of substitution. For example, solutions of medium- and high-viscosity grades of carboxymethylcellulose that are not highly substituted tend to exhibit thixotropic behavior, whereas more highly substituted grades are pseudoplastic.

It is sometimes advantageous to combine viscosity builders with different properties. The addition of xanthan gum to dispersions of magnesium aluminum silicate reduced the extent to which the viscosity of the latter increased over time [2]. Magnesium aluminum silicate is highly thixotropic in dispersions by itself; this was reduced by the gum. In addition, steady-shear measurements suggested synergy between the two materials in both viscosity and yield value.

Viscoelastic properties of the same materials were investigated by oscillatory shear [3]. The storage modulus G' was essentially independent of frequency for 1 and 3% clay dispersions containing no gum. The addition of gum shifted the behavior, and the data for the combined materials contained some of the rheological characteristics of each of the pure substances. The results were interpreted in terms of a reduction in structural rigidity of the clay and an increase in flexibility.

A recent study evaluated combinations of magnesium aluminum silicate with three carbomers [4]. The data suggested enhancement of the structure (yield value) in comparison with the properties of the two substances taken separately.

Specialized applications require specific rheological characteristics. For example, viscoelastic substances are used in eye surgery to prevent mechanical damage to sensitive tissues and avoid adhesions [5]. Polymer solutions are used in cataract, corneal, and glaucoma surgery. Among the agents employed are sodium hyaluronate, hydroxypropyl methylcellulose and chondroitin sulfate.

Power law relations are frequently used to describe the behavior of pseudoplastic polymer solutions. As part of a research program on natural polymer properties, the effects of concentration and temperature on the behavior of guar gum dispersions were evaluated [6]. A plot of the logarithm of shear rate was a linear function of the logarithm of shear stress and the following equation was applied to each flow curve:

$$v = a\sigma^b$$

where

v = shear rate

σ = shear stress

a and b are constants

The power constant b was directly proportional to gum concentration and inversely related to temperature. From the data, the authors were able to formulate a single empirical equation that permitted calculation of shear rate from shear stress, concentration, and temperature over a relatively wide range of values.

III. SEDIMENTATION CONTROL IN DISPERSE SYSTEMS

The control of sedimentation is of primary importance in maintaining the integrity of a disperse system. Stokes' law [7] defines the sedimentation rate of a sphere in a fluid as

$$V = \frac{2r^2(d_s - d_l)g}{9\eta}$$

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