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VOLUME 1

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PREFACE

Considerable progress has been made during the last one or two decades in the field of pharmaceutics, and yet there is still very little literature dealing specifically with this area of knowledge. Undoubtedly this is because pharmaceutics embraces a wide range of disciplines, and much information of value to the pharmacist appears in journals having no obvious connection with pharmacy. The aim of this new series is to concentrate on areas of specific interest to the pharmacist; for example, it will consider the physical aspects of pharmaceutics, pharmaceutical microbiology and the influence of formulation on product stability and efficacy. Medicinal chemistry and pharmacology will not be included since these subjects are already well catered for in the literature.

The articles will be an appraisal of a subject rather than a mere factual abstraction of the literature, and may not refer to the most recent papers on a topic unless they are adjudged to be of significant importance. The authors are expert in their field and are encouraged to include the results of their experience so that their articles may contain hitherto unpublished information. Inevitably, this means inviting reviews from those who are already heavily committed and the success of the series will depend on their generous co-operation. This is particularly so as the intention is to explore a subject in both depth and breadth, but some reviews will focus attention on relatively narrow fields of current importance.

The Editors are indebted to the contributors to the present volume for the time and labour they have devoted to their reviews and to the publishers for their patience and meticulous presentation of the material.

Chelsea College of Science & Technology
June 1964

H. S. BEAN
A. H. BECKETT
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CONTENTS

CONTRIBUTORS TO VOLUME I	v
PREFACE	vii

RHEOLOGY

Alfred N. Martin, Gilbert S. Banker and A. H. C. Chun

I. THEORETICAL CONSIDERATIONS	2
II. INSTRUMENTATION	25
III. APPLICATIONS AND PRACTICE	47
REFERENCES	80

SOLUBILITY IN SYSTEMS CONTAINING SURFACE-ACTIVE AGENTS

B. A. Mulley

I. INTRODUCTION	87
II. MICELLE FORMATION AND PHYSICAL METHODS OF INVESTIGATION OF MICELLAR SOLUTIONS	90
III. THEORY AND MECHANISM OF SOLUBILIZATION	120
IV. MEASUREMENT OF SOLUBILITY AND METHODS OF REPRESENTING SOLUBILITY DATA	129
V. PHASE EQUILIBRIA IN SYSTEMS CONTAINING SURFACE-ACTIVE AGENTS	132
VI. SOME FACTORS IN THE FORMULATION OF PHARMACEUTICAL PRODUCTS CONTAINING SOLUBILIZED MATERIALS	151
VII. REVIEW OF PHARMACEUTICAL PRODUCTS	165
VIII. TABLE OF SOLUBILITIES	185
REFERENCES	190

PRESERVATION OF EMULSIONS AGAINST MICROBIAL ATTACK

Doreen L. Wedderburn

I. INTRODUCTION	195
II. THE NEED FOR PRESERVATION	199
III. INFLUENCE OF SPECIFIC FACTORS ON PRESERVATIVES	212
IV. MECHANISM OF ACTION OF PRESERVATIVES	222

V. INTERACTION BETWEEN EMULSION INGREDIENTS AND PRESERVATIVES	225
VI. PREDICTION OF PRESERVATIVE EFFICIENCY	245
VII. CONFIRMATORY TESTS FOR PRESERVATIVE EFFECTIVENESS	256
VIII. THE SAFE USE OF PRESERVATIVES	261
REFERENCES	264

CONTEMPORARY TRENDS IN HEAT STERILIZATION

G. R. Wilkinson and L. C. Baker

I. HISTORICAL	270
II. TIME AND TEMPERATURE RELATIONSHIPS	270
III. MECHANISM OF KILL	272
IV. DETERMINATION OF THE EFFICIENCY OF STERILIZATION	273
V. CRITICISM OF STERILITY TESTS	274
VI. THERMODYNAMIC CONSIDERATIONS	275
VII. INACTIVATION OF VIRUSES	275
VIII. STERILIZATION AT SUB-ATMOSPHERIC PRESSURES	275
IX. MATERIALS OF PHARMACEUTICAL INTEREST REQUIRING STERILIZATION	276
X. BASIS OF AUTOCLAVE DESIGN	276
XI. STEAM	277
XII. EFFECT OF AIR DURING STERILIZATION AND ITS REMOVAL	279
XIII. PROTECTION AGAINST UNDUE PRESSURE	281
XIV. COOLING THE LOAD WITHIN AN AUTOCLAVE	281
XV. STERILIZATION OF FABRICS	284
XVI. VACUUM-ASSISTED AUTOCLAVES FOR FABRICS	284
XVII. METHODS OF OBTAINING VACUUM WITHIN AUTOCLAVES	285
XVIII. CONTROL SYSTEMS FOR AUTOCLAVES	286
XIX. CONTROLLING THE STERILIZING PERIOD AND INTEGRATION OF TIME AND TEMPERATURE	289
XX. TYPES OF INTEGRATOR	291
XXI. METHODS OF OPERATING AUTOCLAVE VALVES	293
XXII. FURTHER TYPE OF CONTROLLER	293
XXIII. PROBLEMS ASSOCIATED WITH CERTAIN LOADS	294
XXIV. FILTERS	295
XXV. CARE OF AUTOCLAVES	295
XXVI. STEAM PRESSURE REDUCING VALVES FOR AUTOCLAVES	297

XXVII. TESTING THE BEHAVIOUR OF AUTOCLAVES	298
XXVIII. DESIGN	304
XXIX. STEAM SUPPLY	305
XXX. CONTROL SYSTEMS	306
XXXI. AUTOCLAVE ROOM	308
XXXII. NOISE OUTPUT	309
XXXIII. HEAT OUTPUT	310
XXXIV. HOT-AIR STERILIZATION	311
REFERENCES	313
AUTHOR INDEX	315
SUBJECT INDEX	323

RHEOLOGY

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I. Theoretical Considerations	2
A. Flow Characteristics of Newtonian Liquids	2
B. Flow Characteristics of Non-Newtonian Materials	8
C. Rheological Structure	15
D. A Need for Sound Instrumentation	22
II. Instrumentation	25
A. Capillary Instruments	27
B. Parallel Plate Instruments	30
C. Falling and Rising Body Apparatus	32
D. Rotational Instruments	37
E. Industrial Viscometers	47
III. Applications and Practice	47
A. Introduction	47
B. Factors Affecting Rheological Properties	53
C. Rheology and Product Design	60
D. Rheology and Pharmaceutical Processing	75
E. Biological Applications	78
References	80

According to Fischer (1948) the term rheology was suggested in 1929 by Bingham and Crawford to describe that branch of science which deals with the deformation and flow of matter.

The flow characteristics of matter can be discussed in terms of a limited number of flow classes; and the complex materials of interest to the pharmaceutical chemist can be described with reference to these idealized types of deformation and flow. In the first section we shall consider Newtonian flow, plastic flow, pseudoplastic flow, dilatancy and thixotropy.

¹ 1962-1963 Gustavus A. Pfeiffer Research Fellow. The senior author wishes to thank the American Foundation for Pharmaceutical Education for the support which permitted him to complete part of the manuscript while studying and carrying out research in Paris, France.

The various instruments, both empirical and those founded on a theoretical basis, which have been designed for the measurement of rheological properties will be surveyed under Section II.

Finally, some applications of rheology to various pharmaceutical systems will be considered in Section III.

I. THEORETICAL CONSIDERATIONS

The isothermal flow of simple liquids can be described by a single value, the absolute viscosity. The rheological properties of heterogeneous dispersions are more complex and must be expressed by a quantity which depends on the time and on the speed at which the material is deformed. Most alarming, the rheological characteristics may also be a function of the previous treatment which the material has undergone.

A. FLOW CHARACTERISTICS OF NEWTONIAN LIQUIDS

We begin with a review of the properties of those materials which follow Newton's law of viscous flow. This class includes liquids such as water, glycerin and chloroform; true solutions such as syrups; and very dilute colloidal systems. Most dispersions, including pharmaceutical emulsions, suspensions and semi-solids, fail to follow Newton's equation of flow; they will be considered in a later section.

Newton recognized that the higher was the flow-resistance or viscosity of a liquid, the greater was the force required to cause the liquid to flow. The force per unit area, F , imposed on the liquid is called the shearing stress. The velocity gradient of the liquid produced by this force is referred to as the rate of shear. It is ordinarily written in differential form as dv/dr , where dv is the infinitesimal velocity of the planes of liquid, and dr is the infinitesimal distance of separation of the planes. The symbol G is frequently used for the rate of shear.

The rate of shear is directly proportional to the shearing stress, and accordingly the relationship may be written:

$$F \propto \frac{dv}{dr} \quad (1)$$

Changing this proportionality to an equality by introducing a constant, η , equation (1) becomes:

$$F = \eta G \quad (2)$$

or

$$\eta = \frac{F}{G} \quad (3)$$

where F is the shearing stress, η is the coefficient of viscosity, ordinarily called by the shortened term, viscosity, and $G = dv/dr$ is the rate of shear.

The unit of viscosity is the poise or dyne sec/cm². A more convenient unit of viscosity is the centipoise, 100 centipoises being equal to one poise. The centipoise is abbreviated cP. Kinematic viscosity is sometimes used in industry. It is the viscosity defined in equation (3), divided by the density of the liquid, and is expressed in the units of stokes (s) or centistokes (cs).

1. Analysis of Newtonian Materials

The viscosity of Newtonian liquids is ordinarily determined by means of capillary viscometers and rotational viscometers, although a number of other types of instruments are also available.

a. *Capillary viscometers.* The viscosity of a Newtonian material is measured by noting the time required for the liquid to flow from one mark to another in a capillary tube suspended vertically in a constant temperature device. The technique and the apparatus are familiar to most workers in the pharmaceutical sciences; several capillary instruments are described in Section II of this chapter. A number of monographs are available which give detailed instruction in the use of capillary viscometers (Barr, 1931; Cannon and Fenske, 1938; Cannon, 1950; Markwood, 1951; A.S.T.M. Standards, 1952).

The capillary viscometer is not particularly useful for a detailed rheological study. The rheologist is in the habit of plotting the rate of shear G versus the shearing stress F , in the analysis of the flow of materials, because such a graph can provide valuable information. The simple capillary viscometer, unfortunately, cannot be used to obtain such a plot. It affords only one mean value of head pressure, corresponding to the shearing stress, and consequently yields only one point on a flow curve. For this reason the capillary viscometer is known as a "one-point instrument". Multiple-head capillary viscometers have been designed to provide data for several points on the flow curve (Krieger and Maron, 1951), but they require the use of complex equations and do not provide the precision and reproducibility of simple capillary viscometers (Hamlow, 1958).

b. *Rotational viscometers.* The rotational viscometer probably lends itself better than do the other apparatus to the theoretical treatment of both Newtonian and non-Newtonian materials. Although various types of rotational instruments will be discussed in the section on apparatus, a description of the Stormer viscometer will be introduced at this point to assist in discussing the flow curve of a Newtonian liquid.

Rotational viscometers may be classified broadly into several types,

the revolving-cup or Couette type and the revolving-bob or Searle type being the most well known. The Couette instrument has been used extensively in industry in the form of the MacMichael viscometer (Fig. 31). A refinement of this apparatus was described by Green (1949) and a modification was reported by Samyn and Mattocks (1957).

The Searle type is represented by the commercially available Stormer viscometer (Fig. 27). It is simple in design and operation, inexpensive, and, when modified as suggested by Fischer (1950), it can be used for the

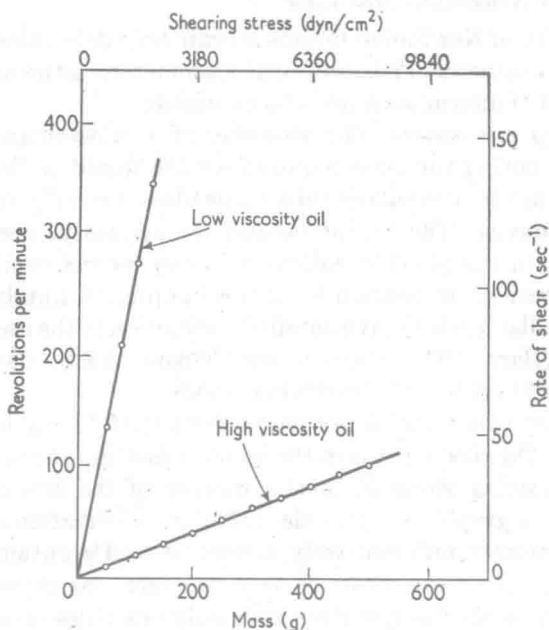


FIG. 1. Flow curves for Newtonian liquids analysed in a Stormer viscometer.

analysis of non-Newtonian as well as Newtonian materials. When a Newtonian liquid is placed in the cup of the viscometer and weights of increasing mass are successively added to the weight hanger, data are obtained which yield the curve shown in Fig. 1. This kind of graph is often referred to as a rheogram. When the Stormer viscometer is used to obtain the data for the rheogram the rate of shear is expressed in revolutions per minute (r.p.m.) and the shearing stress is given in terms of the mass in grams suspended from the weight hanger. The results may also be converted into shear-rate units of sec⁻¹ and shear-stress units of dyn/cm² as seen in the figure.

The plot obtained when a Newtonian material is analysed is linear and

passes through the origin of the graph. The slopes of the lines, shown in Fig. 1, are a measure of the reciprocal of viscosity. This is seen by rearranging equation (2) to:

$$G = \frac{1}{\eta} F \quad (4)$$

or

$$\frac{1}{\eta} = \frac{G}{F} \quad (5)$$

When a rotational viscometer is employed, equation (4) assumes the form:

$$\Omega = \frac{1}{\eta} \frac{T}{4\pi h} \left(\frac{1}{R_b^2} - \frac{1}{R_c^2} \right) \quad (6)$$

where T is the torque in dyn cm required to maintain an angular velocity of Ω radians/sec, R_b is the radius of the bob in cm, R_c is the inside radius of the cup and h is the depth to which the bob is immersed in the liquid. Equation (6) can be used to compute the viscosity when the angular velocity and the torque are known. However, a correction must be made for the "end-effect" which is due to the resistance produced by the liquid touching the bottom of the submerged bob. It is more convenient to combine the fixed quantities of equation (6), together with certain conversion factors, to arrive at an instrumental constant, K_v . Equation (6) then reduced to the simple formula,

$$\eta = K_v \frac{w}{v} \quad (7)$$

where η is the viscosity in poises, w is the driving weight in grams, and v is the velocity of rotation of the bob in r.p.m. The constant, K_v , may be determined by using a standardized liquid in the viscometer. Standardized oils may be obtained for this purpose from the National Bureau of Standards in Washington, D.C. In the United States the certified viscosity standards are specially prepared and are standardized against water at 20.0°C in a capillary viscometer (Swindells, 1947). The method of the National Bureau of Standards compares closely with the standardization procedure described by Cannon (Swindells *et al.*, 1954).

2. Viscosity Coefficients of Dilute Colloidal Dispersions

The particles in colloidal sols are widely separated and do not interact to any significant extent. They simply raise the viscosity in proportion to their concentration in the dispersion. However, when the concentration of the particles in suspension is high, the frequent collision and

mutual interference of the particles lead to non-Newtonian behaviour such as plasticity, pseudoplasticity, and dilatancy. At this point we shall discuss the Newtonian viscosity of dilute colloidal dispersions, in which particle interaction may be disregarded.

Einstein (1906, 1911) derived an equation,

$$\eta = \eta_0(1 + 2.5\phi) \quad (8)$$

relating the viscosity, η , of a dilute colloidal suspension to the volume fraction, ϕ , of the particles in the mixture. The volume fraction, ϕ , is the volume of the particles per unit volume of suspension. The volume of the particles is obtained from the mass and the true density of the particles. The quantity, η_0 , is the viscosity of the dispersion medium or solvent. The equation is strictly applicable only to systems in which the particles are perfect spheres which do not interact with one another. It also may be used to describe dilute true solutions in which the particles are the molecules or ions of the solute. Broughton and Windebank (1938) and Eirich *et al.* (1936) have made experimental verification of the Einstein equation.

In order to employ equation (8) at higher concentrations various modifications must be made, one of which is applicable to suspensions of rigid spheres in moderate concentration showing no Brownian motion (Guth and Simha, 1936). The equation is written:

$$\eta = \eta_0(1 + 2.5\phi + 14.1\phi^2) \quad (9)$$

where the symbols have the same meaning as those in equation (8). Vand (1948) and Robinson (1949) have also derived formulas which apply at higher concentrations. It will be observed that no terms defining the size, shape and interaction of the particles appear in these equations. In hydrophilic colloidal systems the swollen, flexible particles of irregular geometry make a greater contribution to the viscosity than is accounted for by their concentration alone. Interaction of lyophilic particles with one another and with the solvent molecules also contribute greatly to deviations from the simpler equations, and still more elaborate treatments are required to account for these effects. These complications will be considered in later sections of the chapter.

Beginning with the Einstein equation several viscosity coefficients, frequently encountered in the literature, may be defined.

a. *Relative viscosity.* This coefficient, abbreviated η_r , is defined as the ratio of the viscosity of the dispersion to that of the solvent. When relative viscosity is used, the Einstein equation is written as

$$\eta_r = \frac{\eta}{\eta_0} = 1 + 2.5\phi \quad (10)$$

in which the ratio η/η_0 is, by definition, the relative viscosity.

b. *Specific viscosity*. This term is defined as the relative increase in viscosity of the dispersion over that of the solvent alone, or:

$$\eta_{sp} = \frac{\eta - \eta_0}{\eta_0} = \frac{\eta}{\eta_0} - 1 \quad (11)$$

Notice that the specific viscosity, η_{sp} , is equal to the relative viscosity minus unity. Using specific viscosity, the Einstein equation becomes:

$$\eta_{sp} = \frac{\eta}{\eta_0} - 1 = 2.5\phi \quad (12)$$

Now, since volume fraction, ϕ , is directly proportional to concentration, equation (12) may be rewritten in the form:

$$\eta_{sp} = kc \quad (13)$$

in which k is a constant. The equation shows that specific viscosity is directly proportional to the particle concentration in a dilute colloidal dispersion. The concentration, c , is ordinarily expressed as grams of dispersed phase (particles) per 100 ml of total dispersion. For real systems at finite concentrations the equation is ordinarily written as a power series:

$$\eta_{sp} = \alpha c + \beta c^2 + \dots \quad (14)$$

where α and β are constants that must be determined by experimentation.

c. *Reduced viscosity*. We now define a reduced viscosity, namely η_{sp}/c . It may be obtained from equation (14) by dividing both sides through by the concentration:

$$\frac{\eta_{sp}}{c} = \alpha + \beta c + \dots \quad (15)$$

d. *Intrinsic viscosity*. When the reduced viscosity is determined at various concentrations and the results are plotted as shown in Fig. 2, the resulting line can be extrapolated to $c = 0$ to obtain the intercept, α . The intercept is known as the intrinsic viscosity and is given the symbol $[\eta]$. The intrinsic viscosity is an important quantity in polymer science, for it is used to obtain the average molecular weight of high polymers. The average molecular weight \bar{M} is related to the intrinsic viscosity by the expression:

$$[\eta] = K\bar{M}^a \quad (16)$$

where K and a are constants for a series of polymers and must be obtained

from separate experiments with the given polymer-solvent system. The constant, α , ordinarily has a value of unity or close to unity.

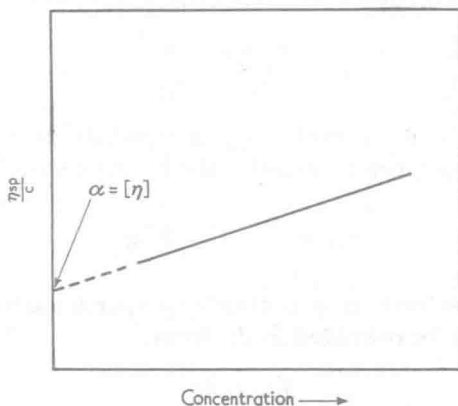


FIG. 2. Intrinsic viscosity of a high polymer.

B. FLOW CHARACTERISTICS OF NON-NEWTONIAN MATERIALS

Concentrated heterogeneous dispersions, including colloidal dispersions, emulsions, suspensions and ointments, comprise a class of systems whose flow do not follow the simple Newtonian relationship. Characteristic consistency curves or rheograms are obtained for the various types of flow, plastic, pseudoplastic and dilatant, when non-Newtonian materials are analysed in a suitable viscometer.

1. Plastic Flow

The characteristic properties of materials which exhibit plastic flow are depicted in the rheogram of Fig. 3. Such materials are called Bingham bodies in honour of E. C. Bingham who first studied their properties (Reiner, 1943). The curve is linear over most of its length, corresponding to that of a Newtonian fluid. However, the curve does not pass through the origin; instead, its linear portion intersects the horizontal axis at a point known as the yield value, f . Contrary to a Newtonian liquid that yields under the slightest force, a Bingham body fails to flow until a definite shearing stress, the yield value, is exceeded. The yield value is thought to result mainly from a network of floccules which is broken down as the material begins to flow.

Materials which show pure plastic flow are few. A suspension of zinc oxide in mineral oil serves as a simple example of a Bingham body. Certain paints, printing inks and firm jellies also fall in this class.