

# Radioisotopic Method of Evaluating Dispersed Systems II

## Suspensions

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A new method of determining the settling rates of suspensions has been studied using a specially constructed absorptiometer and a sealed source of  $\beta$ -excited characteristic X-radiation. The X-radiation source was immersed in the suspension, and the attenuation of the radiation beam, which passed vertically through a portion of the suspension column, was used to measure the suspensoid concentration in that portion of the column which was between the source and the bottom of the suspension-containing cell. The method described is suggested as a non-destructive means of determining the sedimentation rates of pharmaceutical suspensions which contain elements with a high atomic number.

THE CONVENTIONAL method of measuring the settling rate of a suspension consists of recording changes in the position of the suspension-supernatant interface as it changes with time. Changes in the system which occur prior to the appearance of a visible separation of the phases are not detectable by this method. Other methods of measuring settling rates require sampling techniques that are likely to disturb the suspension system and necessitate the manipulation of the suspension at given intervals by the investigator.

This study is concerned with the development of a nondestructive method of measuring settling rates. The method makes it possible to make determinations with a minimum of effort, continuously or after any desired period of time and reveals changes in the distribution of suspended particles which are not apparent in the observation of the interface. The method utilizes an absorptiometer and a sealed source of X-radiation.

Other absorptiometers used to measure sedimentation rates are reported in the literature (1-5). These devices use conventional X-ray machines or low energy  $\gamma$ -emitting isotopes as sources of radiation. The use of low energy  $\gamma$ -emitting isotopes is often precluded by their high cost, short half lives, and complex decay schemes which limit their usefulness where monoenergetic radiation is desirable. Sources of tube-produced X-rays are bulky and expensive.  $\beta$ -Excited characteristic radiation provides an alternative which consumes no power and has a stability that is unaffected by changes in circuitry or environment.

Characteristic X-radiation (K-radiation) is produced by the interactions of  $\beta$ -particles with the orbital electrons of a target material. It is discrete and monoenergetic for each element of the target. Many papers have been written in recent years on the design of sources of  $\beta$ -excited characteristic radiation (6-10).

Solutions were used in the first attempts to establish calibration curves because they were easier to prepare than suspensions, did not require agitation, and could be measured and quantitatively transferred with greater accuracy. The use of solutions eliminated errors which might have resulted from the settling of suspensions during individual determinations. Calibration curves were prepared by plotting the intensity of the emergent beam against the different concentrations of solution.

A method of sampling a suspension identical to the one settling in the absorptiometer was devised, so that changes in the count rate might be correlated to changes in the concentration of the suspensoid in the segment measured. The concentration of the suspensoid and the count rate were both plotted against elapsed time.

### EXPERIMENTAL

**Construction of the Apparatus.**—The six basic elements of the absorptiometer (Fig. 1) were A, the stand which supported the functional components of the apparatus; B, a rod which could be used to lower a radioactive source into the suspension system; C, a plastic cell which held the suspension; D, a lead shield; E, a probe containing the detection system; and F, the counting system (not shown).

The X-radiation source was constructed by drilling a small hole, approximately  $1/8$  in. deep at its lowest point, in the end of a 0.5-in. diam.  $\times$  31-in. long stainless steel rod. Three hundred seventy-five microcuries of  $^{90}\text{Sr}$ - $^{90}\text{Y}$  was placed in this hole and dried under an infrared lamp. The dried isotope

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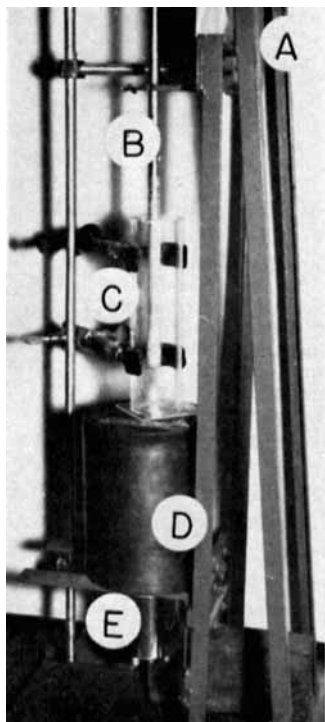


Fig. 1.—Absorptiometer. Key: A, stand; B, source-bearing rod; C, plastic cell; D, lead shield; E, probe.

was covered with an epoxy cement and the cement was allowed to dry for 24 hr., after which time smear tests were made for surface contamination. The process was repeated until the smear tests indicated the absence of any contamination on the surface of the source rod, and the formation of a watertight seal over the  $^{90}\text{Sr}$ - $^{90}\text{Y}$  source.

Lead was chosen for the target material for the formation of secondary radiation because of its high atomic number and availability. A small sheet of  $1/16$ -in. lead was wrapped around the lower 3 in. of the source rod, the source itself, and the epoxy resin seal, forming a lead tube. The end of the tube was covered with another sheet of lead which had been cut to fit over it. The lead was cemented to the rod with epoxy cement so that the  $^{90}\text{Sr}$ - $^{90}\text{Y}$  source was completely surrounded by a  $1/16$ -in. cylinder of lead sheet. The portion of the source rod which would come in contact with the sample was coated by dipping it into a 5% solution of ethylcellulose (50 cps.) in methylene chloride to prevent any interaction of the metal with the sample.

Suspension-holding cells were prepared by covering the ends of 12-in.  $\times$  2.5-in.  $\times$   $1/8$ -in. wall cast acrylic tubes<sup>1</sup> with 3-in.-square sections of  $1/16$ -in. Plexiglas sheet. One end of each tube was dipped in Cadco Acrylic Adhesive No. 94,<sup>1</sup> and then the tube was placed upon the Plexiglas sheet and allowed to dry for 2 hr.

The counting system consisted of the following transistorized components<sup>2</sup>: high-voltage supply (model 40-9), amplifier (30-19), single channel

analyzer (33-10), decade scaler (49-30), mechanical timer (90-10), and scintillation probe (10-8) with a 1.5-in. diam.  $\times$  1-in. thick NaI(Tl) crystal.<sup>3</sup>

The probe was positioned under the source rod and cell and was shielded from background radiation by a  $5\frac{5}{8}$ -in. diam. hollow cylinder of lead with a  $5/8$ -in. wall. The top of this shield consisted of a 0.75-in. thick piece of lead, except for a 1.5-in. diam. hole which was cut through the top near the center of the shield. The center of this hole was placed directly beneath the source. The scintillation crystal was positioned beneath the hole, and the cell was centered over it. The source was hung in a fixed position (although it could be raised to different heights) so that it would be immersed in a suspension that was placed in the cell.

After the counting system had been calibrated with the photopeak of a  $^{137}\text{Cs}$  source for the range 0–1.0 Mev., the X-radiation spectrum of the source was determined (Fig. 2) using an analyzer window equivalent to 0.02 Mev. The spectrum revealed a characteristic radiation peak at about 0.075 Mev. and a broader bremsstrahlung energy peak at about 0.22 Mev.

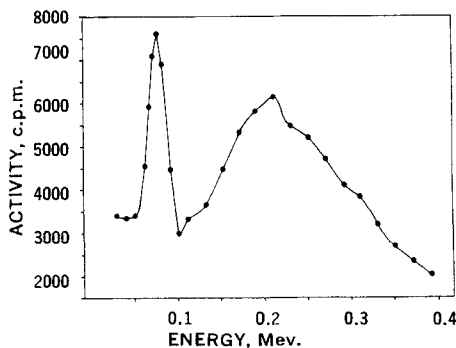


Fig. 2.—Energy spectrum of X-radiation source.

**Effects of Solute Concentration on the Transmission of the Characteristic Radiation.**—Aliquots of a 10% solution of lead acetate N.F. IX in distilled water, with 1% glacial acetic acid added as a stabilizer, were diluted to a volume of 200 ml. In every case the entire sample was placed in the cell to preclude the effects of geometry on the determinations. The samples were placed in the cell by means of a rubber tube which ran from a funnel above the apparatus to the bottom of the cell. A stopcock on the tube made it possible to regulate the flow of the sample into the cell, and prevented the collection of bubbles on the cell wall and underneath the source. The cell was emptied by suction after each determination. The few drops of sample remaining in the cell did not have any significant effect upon the concentration of the samples which were introduced later.

Differential spectrometry was used to measure the intensity of the characteristic radiation passing through each sample. No corrections were made for background radiation, which was not large enough to have an appreciable effect upon the results. The attenuation of the radiation beam

<sup>1</sup> Supplied through the courtesy of J. Brammer, Cadillac Plastic Co., Indianapolis, Ind.

<sup>2</sup> Radiation Instrument Development Laboratories, Inc., Melrose Park, Ill.

<sup>3</sup> Model 6D4F5, The Harshaw Chemical Co., Cleveland, Ohio.

by the solution was determined by subtracting the count rate of the beam through each sample from the count rate of the beam through distilled water. Each determination consisted of 70,000 counts. The logarithm attenuation of the radiation was plotted against the logarithm of the solute concentration.

**Determination of the Settling Rate of Suspensions.**—One cell, prepared exactly as the original cell which was used in the absorptiometer, was used for each solids concentration determination. An aqueous suspension consisting of 0.15% carboxymethylcellulose 7 MSP.,<sup>4</sup> 5.0% bismuth subcarbonate, 0.5% amaranth solution, 0.025% methylparaben, and 0.005% propylparaben was used. Two hundred milliliters of the suspension was placed in each of the cells. At time periods approximately corresponding to those in which absorptiometer measurements of 1 min. were made, the suspension above the segment or strata of interest was removed from the sample cell. This was accomplished with a J-tipped glass tube (6-mm. O.D. × 2-mm. wall) which was connected with plastic tubing to a collection flask. A low level of suction was applied to the J-tube using a water aspirator, so that the suspension was withdrawn to the proper level without disrupting the suspension below it. The volume of the suspension remaining in the cell (100 ml.) corresponded to the volume of suspension in the absorptiometer which occupied the space between the source rod and the bottom of the suspension-containing cell.

A magnetic stirrer was used to disperse the solids in that portion of the suspension which remained in the cell, so that any aliquot of the suspension there would contain the same percentage of suspensoid. Four 10-ml. aliquots were removed by pipet and centrifuged in 16 × 125 mm. tared test tubes. The supernatant was decanted, and the suspensoid was dried to constant weight at 100°.

## RESULTS AND DISCUSSION

Calibration curves made for lead acetate solutions with a 2-in. radiation path showed a log-log relationship between concentration and radiation attenuation (Fig. 3). The equation for the calibration curve was found using the least squares calculation, and is  $Y = 1.598 + 1.186 X$ , where  $X$  and  $Y$  represent log percentage concentration and log attenuated radiation, respectively.

Similar plots were made with the source at several different heights. When the source-to-probe distance approached 1 in., the relationship between the variables became obscure, and as the distance approached 3 in., the length of time required for each count became excessively long.

The results of a sedimentation study performed with the apparatus are shown in Fig. 4. Both the weight of bismuth subcarbonate in the lower half of the column of suspension and the intensity of radiation passing through it had a log-log relationship to the period of elapsed time. The equations for the line which could be drawn when the two variables were plotted against time were:  $Y = 3.614 - 0.065 X$ , and  $Z = 2.794 + 0.115 X$ , where  $X$ ,  $Y$ , and  $Z$  represent log elapsed time in hours, log count rate in counts per minute, and log sediment weight in milligrams, respectively.

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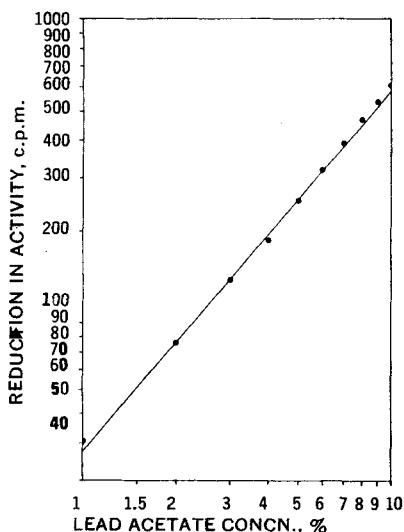


Fig. 3.—Log-log plot of radiation attenuation by lead acetate solutions.

The quantification of settling rates in this study was limited by practical considerations to suspension systems that separated into two phases within a short period of time. Preliminary experiments with several common pharmaceutical suspensions, however, clearly demonstrated the ability of the apparatus to detect the settling of some suspensions long before the appearance of a suspension-supernatant interface.

Experience with the absorptiometer revealed inadequacies of the counting system which might be corrected in subsequent models of the prototype apparatus. An automatic means of recording data, such as a count rate meter used in conjunction with a chart paper recorder, is suggested. Such a device would not require the presence of an operator and might be calibrated to read the concentration

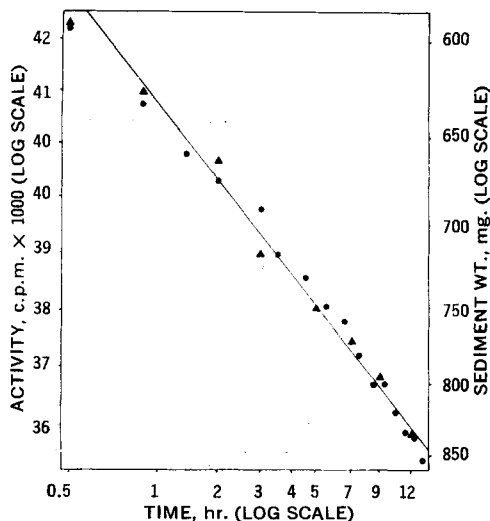


Fig. 4.—Sedimentation of bismuth subcarbonate. Log-log plots of activity and sediment weights vs. time. Key: ●, activity; ▲, sediment weight.

of the suspensoid directly. Null-balance instrumentation might increase the sensitivity and accuracy of the determinations.

The use of a vertical radiation beam worked well in this preliminary study of the apparatus, for it made adjustment of the radiation beam path possible without necessitating the construction of a watertight cell with movable walls. The major disadvantage of this arrangement seems to be the time and labor required for calibration, which consisted of sampling the suspension at different time intervals and relating the concentration of the suspension at any given time to the intensity of the radiation beam which passed through it. An apparatus which utilized a horizontal beam might be calibrated with samples of the same suspension in different concentrations, and thereby eliminate the need of waiting for the suspension to settle.

Salts of heavy metals were chosen purposely for suspensions and solutions used in this study, for this method will have its greatest application in the evaluation of preparations containing these materials. Obviously the change in the concentration of the suspensoid will become more and more difficult to detect as the atomic number and density of the suspensoid approach those of the vehicle. To optimize the detection of small changes in suspensoid concentration, the absorption of X-radiation might be made selective for some element in the suspensoid by constructing a characteristic radiation source (through choice of a target material of the proper atomic number) which has an energy that just exceeds the critical absorption edge of the element in question. An alternative might be to use a  $\beta$ -emitting isotope as a source of radiation, and to determine the concentration of suspensoid by measuring the characteristic radiation emitted by one of its elemental constituents.

## SUMMARY

Studies have been carried out to investigate the feasibility of a new approach to the determination of settling rates of pharmaceutical suspensions. This approach consists of passing a beam of characteristic radiation vertically through a column of suspension and measuring the attenuation of the beam by the suspension at the bottom of the column, to find the concentration of suspensoid there as it changes with time.

An apparatus has been constructed which utilizes the characteristic X-ray produced by the bombardment of lead foil with a  $^{90}\text{Sr}$ - $^{90}\text{Y}$  source. The concentrations of dissolved and suspended metal salts have been found with this apparatus. The relationship between concentration and intensity of radiation was studied, and the relationship was shown to be useful for studying the sedimentation of heavy metal salts. Changes in the design of the apparatus which may extend its utility further are suggested.

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# Drug Standards

## Spectrophotometric Assay for Potassium Guaiacolsulfonate N.F.

By RICHARD DABROWSKI and D. M. PATEL

A spectrophotometric assay method for potassium guaiacolsulfonate (KGS), which is applicable to both solid and complex liquid dosage forms, was devised. This method led to the establishment of the fact that commercial KGS is a hemihydrate.

The N.F. Revision Committee has adopted this method for the new N.F. XII.

POTASSIUM guaiacolsulfonate (KGS) is determined by oxidation with hot nitric acid followed by gravimetric determination of the

sulfate produced (1). Consistently low results have been obtained in this laboratory, due probably to incomplete oxidation. The ichthammol procedure (2) gave better results, but the assay is tedious and time-consuming. A simpler method is required for routine industrial control.

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