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PARTICLE AGGREGATION STATES AND AEROSOL CLOGGING

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ABSTRACT

The clogging tendencies of different concentrations of sulfamerazine suspensions composed of suspended particles in the dispersed, coagulated, and flocculated states were studied. The dispersed suspension system showed clogging at the 10 to 15 percent solids level, while the coagulated system clogged between 5 and 10 percent, and the flocculated system clogged between the 20 and 25 percent sulfamerazine concentration. The greater the extent of coagulation of the solid particles, the lower the concentration at which clogging occurs. In the flocculated system, the particles are loosely packed in a network-meshed structure and a cake does not form. The propellant systems used were selected for their value in this theoretical study.

INTRODUCTION

A pharmaceutical suspension is defined as a preparation containing a finely divided undissolved drug in a liquid vehicle. When such a dosage form is to be dispensed as an aerosol delivery system, there is the possibility of the orifice becoming clogged. In this study we consider the effect of the nature of aggregation of the

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suspension system on the clogging potential of the aerosol delivery system. The solvent systems selected for this study were of theoretical interest rather than for possible commercial value.

Insoluble particles dispersed in a liquid medium have large specific surface areas rendering the suspension system thermodynamically unstable. The particles tend to settle and form aggregates which results in a system having greater thermodynamic stability since there is a reduction in surface area and thus a reduction in surface free energy. We define a dispersed system as consisting of primary particles behaving as independent entities in a dispersion medium. The settling process in general is relatively slow with each particle settling separately. We also define two types of aggregation: coagulation and flocculation. In a coagulated system the aggregated particles including absorbed surface films are in surface contact with each other and each aggregate of particles (coagulum) acts as a unit. The particles are held together by film-film bonds. Coagulated suspensions tend to form caked systems which can be difficult, if not impossible, to redisperse. In a flocculated system the aggregated particles are held together by one of several mechanisms: adsorption bridging, chemical bridging, or long-range van der Waals forces (secondary minimums). The particles settle out as a "floc", a loosely packed aggregate having a network-like structure. The sediment is readily redispersible to the original suspension form. The distinctions among these systems have been described by Ecanow et al.[1].

The "no spray" malfunctioning of an aerosol is seldom due to failure of the valve itself, but may be attributed to one or a combination of the following causes: propellant not added; propellant leakage; valve gaskets that have become swollen and blocked due to solvent effect; solid particle in the housing, stem, or actuator orifice (in the case of solvent-based formulations); and blockage of housing, stem actuator orifice or dip tube (in the case of powder-based formulations)[2]. In this study the clogging tendencies of different concentrations of sulfamerazine suspensions composed of suspended particles in the dispersed, coagulated, and flocculated states are reported. Also of interest was the effect of the non-polar propellant, Freon 11, on controlled aggregated suspension systems.

EXPERIMENTAL

Materials: Sulfamerazine (Sigma Chemical Company) powder was USP grade and ranged in particle size from 5 to 20μ. Dioctyl sodium sulfosuccinate (DSS) (Fisher Scientific Company), USP, was employed as the surfactant and aluminum chloride (Mallinckrodt Chemical Works), USP, served as the flocculating agent. Trichloromonofluoromethane (Freon 11) (Matheson Gas Products) and compressed air were used as the aerosol propellant. All other chemicals were reagent grade and were used without further treatment.

Aerosol accessories included: aerosol bottle valves, 6B Bottle Valve, stem assembly 31-0300, housing 07-1901--.080 orifice, dip tube 90-2010, cup 12-6450, plastic actuators, 01-1410--.018 orifice, and

polyethylene tubing (Precision Valve Corp.) and four ounce plastic coated aerosol bottles, Boston Round (Mold AC-10556) (Owens-Illinois).

Preparation of Suspension Systems. Sulfamerazine dispersed suspensions and coagulated systems were prepared in the following concentrations (percent, w/v) of sulfamerazine: 2, 5, 10, 15, 20, 25, 30, 35. Each system contained DSS at a concentration of one-tenth that of the sulfamerazine content. For the flocculated systems, in addition to sulfamerazine and DSS, each system contained aluminum chloride at a concentration of one-twentieth that of the sulfamerazine content.

The suspensions were prepared by adding the calculated amount of sulfamerazine powder to a glass mortar and adding the appropriate volume of a 5 percent solution of DSS to the mortar. The mixture was then transferred to a 100-mL cylindrical graduate with the aid of additional rinsings of the mortar using distilled water. Sufficient water was added to bring the volume to the mark. For the flocculated suspensions, the appropriate volume of 20 percent aluminum chloride solution was added to the graduate prior to filling the graduate to the mark with distilled water. After the cylinder was filled to volume, it was capped with a glass stopper, inverted, and agitated sufficiently to ensure thorough mixing and to assure the formation of a uniform initial suspension of the sulfamerazine powder.

Aerosol Preparation and Test for Clogging. Aerosol delivery systems were prepared from the sulfamerazine suspensions. Each suspension was

shaken thoroughly to form a homogeneous dispersion. Where a cake had formed, the cake was redispersed with the aid of a glass stirring rod. Twenty-five milliliters of the dispersed suspension was transferred to a plastic coated aerosol bottle. This was followed by the addition of 25 mL of Freon 11 propellant. After the valve was inspected visually for any defects, it was positioned over the aerosol bottle and crimped in place with a bottle crimper. The pressure in the bottle was brought to 22 psi with filtered compressed air. The actuator was then affixed to the valve. The entire process was conducted inside a laboratory fume hood to minimize any potential hazards associated with propellant vapors.

The dispersed and flocculated suspension systems were tested for clogging immediately after the aerosol bottle was filled. The flocculated suspension systems were also tested for clogging after standing 24 hours. The coagulated suspension systems were allowed to settle for 24 hour before being tested for clogging. In testing an aerosol for clogging, the aerosol was first shaken thoroughly for 15 seconds. The actuator button was then pressed and the contents were sprayed into a beaker while the aerosol bottle was held firmly in a position perpendicular to the floor. The inability of an aerosol system to spray was recorded as a clogged system. When clogging occurred during the first 15 seconds of spraying, the valve and actuator were replaced by new units. This minimized the possibility of a "no spray" situation being attributable to a defective valve. Clogging data for the different suspension systems are recorded in Table 1. If the contents of the bottle were completely emptied, the system was considered to be a non-clogging suspension.

TABLE 1

Clogging Data for Suspension Systems

Suspension Concentration % w/v	Number of Clogged Aerosols* Dispersed System	Coagulated System	Flocculated System
2	0	1	0
5	0	1	0
10	1	12	1
15	10	11	2
20	12	12	0
25	12	12	12
30	12	12	12
35	12	12	12

* Out of a total of 12 trials. A system was assumed to cause clogging when at least 10 units of the 12 tested clogged.

DISCUSSION

The objective of this study was to observe the effect of the state of aggregation of sulfamerazine suspensions on the cloggability of aerosol delivery systems under the conditions described in the experimental section. Clogging, of course, can occur anywhere along the route of flow of the suspension with propellant. However, the most likely causes of valve clogging are: swollen and blocked valve gaskets due to the effect of the solvent and/or an accumulation of solid particles in the housing, stem or actuator orifices. The likelihood of a swollen valve gasket in this experiment was remote since the solvent was not in contact with the valve for a long period of time.

According to the data in Table 1, the dispersed suspension system demonstrated clogging at the 10 to 15 percent solids level, whereas the coagulated system clogged between 5 and 10 percent, and the flocculated system showed clogging at some concentration between 20 and 25 percent sulfamerazine concentration. The smallest of the aerosol orifices is that of the actuator which is about 450 μ in diameter. The particle size range of the sulfamerazine powder is between 5 and 20 μ. Thus, as the powder aggregate size increases, at some concentration of the sulfamerazine suspension an aggregate will be formed of sufficient size to clog the actuator orifice.

In the dispersed suspension at the 2 to 10 percent solids level, sulfamerazine exists as discrete particles of small size coated with a layer of DSS. As the concentration of drug increases, the particles tend to form a coagulated system by film-film bonding. At the 15 percent level the coagula are sufficiently large to cause clogging. Shaking the system does not redisperse the coagula into smaller particles. In the coagulated system the large coagula remain in the aggregated state and are not redispersed by shaking into smaller units because of the relatively strong film-film bonds formed during the 24 hour settling period. Thus, clogging occurs at a lower solids level than in the dispersed system. In the flocculated system, however, the particles are loosely packed in a network-meshed structure and do not tightly bond to each other. A cake does not form and any sediment is readily redispersed to form the original suspension as a result of turbulent flow caused by 15 seconds of shaking prior to spraying. Since large floccules or coagula do not form, clogging does not occur

until the solids level reaches 20-25 percent. For the flocculated system the same results were obtained whether the test for clogging was performed immediately or after a 24-hour standing period.

In preliminary experiments it was noted that when Freon 11 was employed as the sole propellant, the aluminum-surfactant flocculating agent dissolved in the Freon resulting in a complete disruption of the suspension. Therefore, only sufficient Freon propellant was incorporated into the aqueous suspension system which did not adversely affect the suspension. The propellant component of the aerosol was then supplemented with compressed air to a pressure of 22 psi. The effect of a non-polar propellant on a controlled aqueous aggregated suspension in an aerosol delivery system was thus observed.

It would appear from this study that when a suspension is to be formulated in an aerosol delivery system, the particles should be in the flocculated state to minimize the possibility of clogging of the aerosol valve. It is recognized that other solvent systems may show a different relationship between aggregation state and clogging. Other systems will be the subject of further study.

REFERENCES

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