Filtration Rates of Pharmaceutical Suspension Systems

A. DAKKURI * and B. ECANOW ‡×

Abstract ☐ This study was undertaken to find if a correlation exists between the filtration rate and the H_u/H_0 ratio. For this purpose, flocculated and coagulated structures of sulfamerazine were used. Suspension settling profiles and filtration rates, using additives and additive-free sulfamerazine suspensions, were studied. A straight-line correlation was found. Effects of filter bed parameters on refiltration rates were studied, and a relationship was found by the use of the Kozeny–Carman equation. A straight-line relationship existed between the H_u/H_0 ratio and the filtration rate exhibited by the different suspension aggregates.

Keyphrases ☐ Suspensions—settling profiles and filtration rates, flocculated and coagulated structures of sulfamerazine, effects of filter bed parameters on refiltration rates ☐ Filtration rate—pharmaceutical suspensions, sulfamerazine, correlation with ratio of final to initial suspension settling height ☐ Sulfamerazine—flocculated and coagulated suspension structures, settling profiles and filtration rates

There are several parameters for following the aggregation and deaggregation of suspended particles: (*a*) rate of settling, (*b*) sediment height ratio, (*c*) filtration of the suspension and refiltration of the filtrate through the formed filter bed, (*d*) height of the consolidated filter bed, and (*e*) turbidity of the supernate (1, 2). Each method has its advantages and disadvantages. Few, if any, pharmaceutical suspensions have been studied utilizing the filtration or refiltration rate. The structures of these suspensions have been determined employing electrokinetic measurements, the H_u/H_0 ratio, and other empirical procedures (3, 4).

The present study was undertaken to find if a correlation exists between the filtration rate and the H_u/H_0 ratio. Flocculated and coagulated structures of sulfamerazine were used. A flocculated system is considered to consist of an open network structure formed by aggregated particles. At the other extreme is the dense structure, consisting of closely packed particles that exist in a coagulated system.

EXPERIMENTAL

Materials—Sulfamerazine USP, Calcomites grade[1], was used. Dioctyl sodium sulfosuccinate[2] (I) was obtained commercially. Aluminum chloride hexahydrate and sodium chloride were reagent grade.

General Procedure—Sulfamerazine was mixed with 50 ml of distilled water for 10 min using a magnetic stirrer. The agitation intensity was then decreased, and 25 ml of I solution was added. Stirring was continued for 15 more min; then 20 ml of aluminum chloride solution was added together with sufficient water to yield a final volume of 100 ml, and the suspension was stirred for another 2.5 min. The latter interval and the lower agitation intensity were chosen to minimize disruption of flocs, which may occur at high shear rates.

The final concentrations of the additives in the suspensions are indicated in the text. The volumes of the solutions were replaced by equivalent volumes of water when settling profiles and filtration rates of additive-free suspensions were studied. Sodium chlo-

ride was used in lieu of aluminum chloride to determine its effect on sulfamerazine particles coated with I.

Filtration Process—Each suspension was transferred into a sulfur adsorption tube of 130-ml capacity with a fritted-glass disk (30 mm in diameter). The tube was described previously (5). The intervals required to collect 10, 40, and 50 ml of filtrate were recorded. The 50-ml filtrate was then immediately poured back into the funnel, and the intervals required to collect the same volumes of refiltrate were also observed. The time, in seconds, required to collect the last 40 ml of the 50-ml refiltrate was designated as refiltration time 10–50.

Subsidence Rate and Sediment Height—In another series of experiments, the suspension was transferred into a 100-ml glass-stoppered graduated cylinder. The sediment height (volume) was determined every minute, or more frequently, for the first 15 min, and then the time lapse between readings was increased.

RESULTS AND DISCUSSION

Settling Profiles and Filtration Rates of Additive-Free Sulfamerazine Suspensions—The ultimate height, H_u, to which a suspension settles without agitation is a function of the concentration of the solid phase, C (6). The sediment volume is reported in terms of the H_u/H_0 ratio, where H_0 is the initial height of the suspension (7). The rate of settling of sulfa suspensions in concentrations of 1, 2, 3, 4, and 5% is observed. Plotting the sediment height *versus* time shows that these suspensions behave in accordance with the Type I curve (8). They show a coarse appearance when set aside to settle, and the coarseness decreases as C increases. Such an appearance is ascribed to aggregation affected by van der Waals' forces and hydrophobic bonds.

The calculated porosity of the sediment (9) is shown in Table I, and the high values indicate the presence of a loose structure. The percent difference between the extreme values is about half that calculated using data reported by Steinour (10, 11). A straight line is obtained when H_u/H_0 is plotted *versus* C on log–log paper. A similar relationship is also exhibited by sulfamerazine–trichlorotrifluoroethane suspensions where flotation rather than settling occurs (12).

Filtration of the suspension and, in particular, refiltration of the filtrate through an already formed sediment or filter bed have proved to be accurate and readily reproducible measures of the state of aggregation (2). However, the suspension must be prepared under controlled conditions to minimize disruption of the
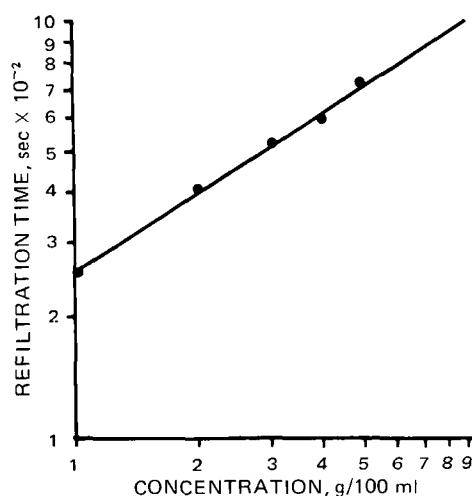

Figure 1—*Refiltration time 10–50, time required to collect the last 40 ml of the first 50 ml of refiltrate, of sulfamerazine suspensions.*

Table I—Parameters of Sulfamerazine Suspensions

Sulfamer-azine Concentration, % w/v	Sediment Volume, ml	Sediment Porosity	Refiltration Time 10–50[a], sec
1	20	0.964	247
2	33	0.956	415
3	45	0.952	523
4	54	0.947	589
5	66	0.946	722

[a]Time required to collect the last 40 ml of the first 50 ml of re-filtrate.

structure and, consequently, to obtain reproducible results.

In Table I, refiltration time 10–50 is given for sulfa suspensions with no additives. This parameter is preferred to the time required to collect the first 50 ml of refiltrate because it allows sufficient time for the filter bed to reform if it is disturbed by the addition of the filtrate. A straight line is also obtained when refiltration time 10–50 is plotted against C on log–log paper; the slope of the line is 0.666 (Fig. 1). When H_u/H_0 is plotted versus C on log–log paper, the slope is 0.723.

The two slopes, that for t_{ref} versus C and H_u/H_0 versus C on a log–log grid, are of nearly similar magnitude. This similarity may lead to the conclusion that the factors controlling the structures of both the filter bed and the sediment are the same. Thus, this similarity suggests the close relationship between the two methods, i.e., refiltration and settling, for studying the suspension structure.

Relationship between Initial Settling Rate and Initial Filtration Time—The initial settling rate is the slope of the straight-line component (constant-rate zone) of a settling curve obtained by plotting subsidence level versus time; it represents the maximum subsidence rate. Initial filtration time 0–10 is the interval required to collect the first 10 ml of filtrate. Since the suspension structures in the initial stages of the two processes are comparable, it was of interest to find if a correlation exists between these parameters.

Steinour (10) described the dependence of the subsidence rate, S, on the velocity of sedimentation of isolated spheres, V_s, and the volume fractions occupied by the liquid, E, and solid phase, $1 - E$, as:

$$S \propto \frac{E^3}{1-E} V_s \qquad \text{(Eq. 1)}$$

However, since hindered settling (2, 3) is absent in suspensions of

Table II—Effect of I on Refiltration Time 10–50, Thickness of Filter Bed, and H_u/H_0 Ratio of 5% Sulfamerazine Suspension

I Concentration, % w/v	Refiltration Time 10–50 min	Refiltration Time 10–50 sec	Thickness of Filter Bed, cm	H_u/H_0 Ratio
0.00	14	12	4.0	0.66
0.025×10^{-2}	13	55	4.0	0.65
0.25×10^{-2}	18	50	4.0	0.59
2.5×10^{-2}	23	35	3.3	0.52
7.5×10^{-2}	42	15	2.7	0.36
12.5×10^{-2}	59	5	2.2	0.215
17.5×10^{-2}	77	—	2.1	0.212
25×10^{-2}	82	40	2.1	0.207
32.5×10^{-2}	85	40	1.9	0.190

low concentrations, as in the present suspensions, V_s may be assumed to be constant. Furthermore, $1 - E$ is proportional to C. Consequently, $(E^3/s) \propto C$.

Figure 2 shows that filtration time 0–10 is a linear function of C. Thus, $t_{fil} \propto (E^3/S)$. When t_{fil} is plotted against E^3/S (Fig. 3), a straight line is obtained in conformity with this relationship.

Effect of Filter Bed Parameters on Refiltration Rate—The refiltration rate is more indicative of the type of structure of the filter bed than is the filtration rate. During refiltration time 40–50, the compression rate in the filter bed is negligible. Therefore, if it is assumed that all parameters, except e and L, of the Kozeny–Carman equation (13–16) are constant, it can be reduced to:

$$Q = \frac{1}{k} \frac{e^3}{L} \qquad \text{(Eq. 2)}$$

where Q is the refiltration rate in milliliters per second, e is porosity, and L is the thickness of the filter bed in centimeters; k is a constant that includes all other parameters in the original equation.

A linear relationship is obtained when refiltration rate 40–50 is plotted against e^3/L (Fig. 4). Thus, it appears that Eq. 2 expresses the dependence of the refiltration rate on the bed parameters in the studied suspensions.

Effect of I on Settling and Filtration Rates—Table II lists the refiltration time 10–50 of 5% sulfa suspensions treated with I. The variation among the determinations within concentration groups is 3–5%. Being a surfactant, I disperses the hydrophobic sulfa into smaller aggregates and/or primary particles. As the concentration of I increases, the hydrophobicity decreases and a finer dispersion of particles is produced. The extent to which secondary particles are broken into primary entities influences the packing
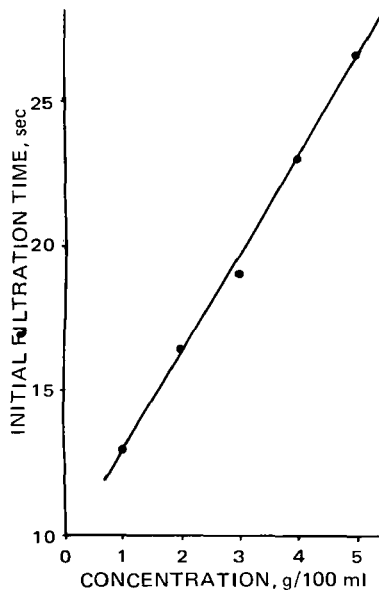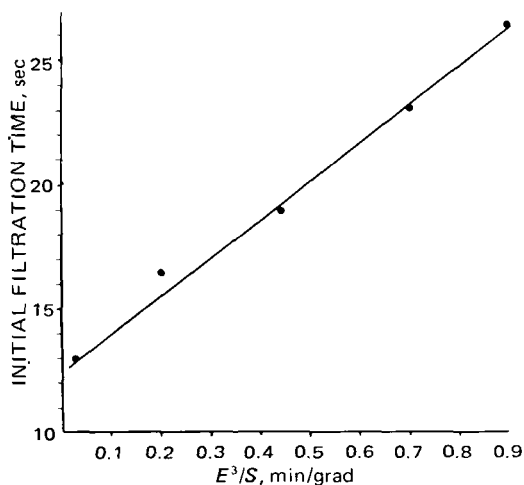

Figure 2—Initial filtration time, time required to collect the first 10 ml of filtrate, of sulfamerazine suspension at various concentrations.

Figure 3—Relationship between initial filtration time (time required to collect the first 10 ml of filtrate) and E^3/S of sulfamerazine suspensions, where E is the volume fraction of suspension occupied by the liquid phase and S is the rate of subsidence as determined from the slope of the straight-line component of a settling curve obtained by plotting subsidence level versus time.
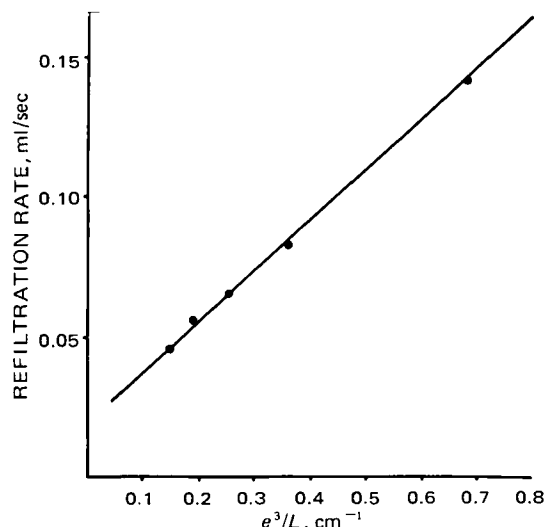
Figure 4—*Relationship between porosity of the filter bed, e, its thickness, L, in centimeters, and the refiltration rate of sulfamerazine suspensions. The refiltration rate is calculated using the refiltration time required to collect the last 10 ml of the first 50 ml of refiltrate.*

characteristics of the filter bed, and this effect is reflected on the refiltration rate.

As the particles settle, geometrical rearrangements take place and the interparticle pores are occupied by smaller particles. Therefore, the liquid has to travel through a closely packed sediment. In addition, the coalescence of the hydrated adsorbed layers covering the particles results in a denser bed (17, 18). These effects increase with an increasing surfactant concentration. Figure 5 shows a linear relationship between the refiltration time and the I concentration up to 17.5×10^{-2}%; a plateau is then approached. It is possible that a monolayer is formed at this particular concentration, whereas at higher concentrations a multilayer may start forming.

Table II also shows the thickness of the filter bed and H_u/H_0 ratio for the same suspensions. Both parameters apparently decrease with an increasing concentration of I up to 12.5×10^{-2}%. No significant change is observed at higher concentrations. The decrease is accompanied by an increased tendency to form a dense and smooth bed, which may be attributed to an increase in the availability of I for adsorption at the interface.

Effect of Aluminum Chloride on Filtration Behavior of I-Coated Sulfamerazine Suspensions—A flocculated structure is formed, due to interaction of Al^{+3} with the negatively charged particles, when aluminum chloride is added to suspended sulfa parti-
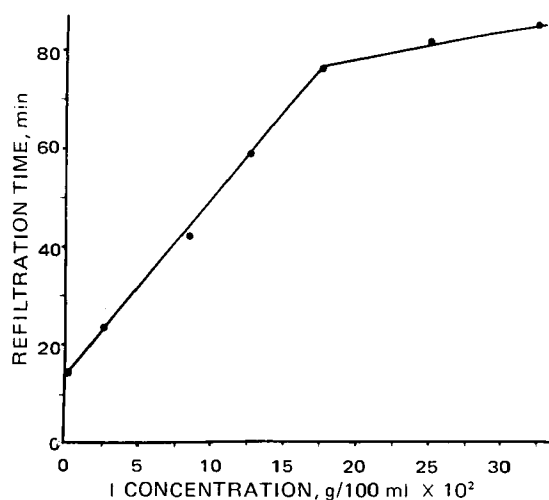
Table III—Effect of Aluminum Chloride on Refiltration Time 10–50 of 5% Sulfamerazine Suspensions Containing I

I Concentration, % w/v	Aluminum Chloride Concentration, % w/v	Refiltration Time 10–50	
		min	sec
0.025 × 10⁻²	0.00	13	55
	0.02	14	15
	0.04	14	2
	0.10	14	20
0.25 × 10⁻²	0.00	18	50
	0.02	18	35
	0.04	18	28
	0.10	18	24
25 × 10⁻²	0.00	82	40
	0.10	49	38
	0.20	50	43

cles coated with I (19). Flocculation takes place instantaneously. But the coagulation process affected by indifferent salts acting on the diffuse double layer of colloidal particles may take a prolonged time to become manifest (20, 21). Due to the open network structure present in a flocculated system, the filtration rate is expected to be higher than that obtained with a coagulated sediment.

Table III shows the effect of various concentrations of aluminum chloride on the refiltration time of suspensions containing different amounts of I. It is apparent that the salt does not exert a noticeable effect on the refiltration time at very low surfactant concentrations (<0.25 × 10⁻²%). At these concentrations, the amount adsorbed is rather small, causing few, if any, bridges to be formed between particles. However, at 0.25% I, the addition of 0.1 or 0.2% aluminum chloride results in about a 40% decrease in the refiltration time. The refiltration time of surfactant-free suspensions at 0.1 and 0.2% aluminum chloride does not differ from that obtained in the absence of the aluminum salt. This result indicates that the flocculated structure, obtained in the presence of both dioctyl sulfosuccinate and Al^{+3} ions, is due to chemical bridging through interaction between the two ions.

The H_u/H_0 ratio of 5% sulfa suspensions coated with 0.25% I to which various concentrations of aluminum chloride are added is reported in Table IV. The increase in the ratio for the last two systems in the table corresponds to the decrease in refiltration time. This finding is a further indication of the correlation existing between the two parameters.

Effect of Sodium Chloride on Sulfamerazine Suspensions Containing I—Filtration times 10–50 and 40–50 of suspensions

Figure 5—*Effect of I on refiltration time 10–50 of 5% sulfamerazine suspension.*
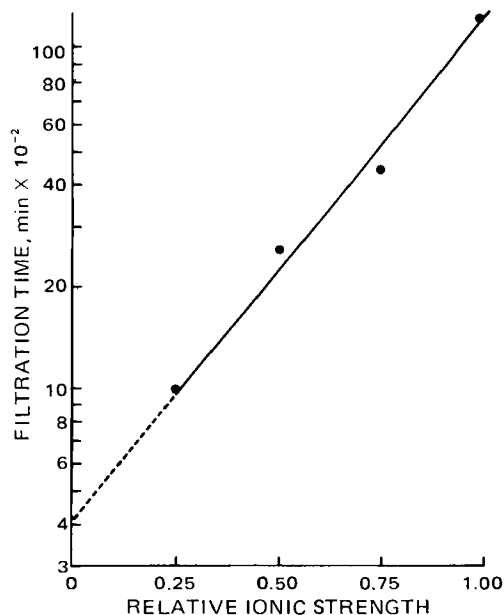

Figure 6—*Effect of relative ionic strength contributed by sodium chloride on filtration time 10–50 of 5% sulfamerazine suspensions in the presence of 0.25% I.*

Table IV—Effect of Aluminum Chloride on the Sediment Height Ratio of 5% Sulfamerazine Suspensions Containing 0.25% I

Aluminum Chloride Concentration, % w/v	H_u/H_o Ratio
0.00	0.20
0.02	0.19
0.04	0.35
0.06	0.40
0.08	0.40
0.10	0.40
0.20	0.40

Table V—Effect of Sodium Chloride on the Filtration Time of 5% Sulfamerazine Suspensions Containing 0.25% I

Relative Ionic Strength[a]	Filtration Time 10–50, min	Filtration Time 40–50, min
1.00[b]	1274	832
0.75	432	220
0.50	270	131
0.25	100	39
0.00	41	15

[a] Contributed by sodium chloride only. [b] At 0.29% NaCl.

containing 0.25% I and various concentrations of sodium chloride are shown in Table V. The highest concentration used (0.29%) corresponds to 0.2% $AlCl_3 \cdot 6H_2O$ with respect to ionic strength. The data show that the filtration rate decreases as sodium chloride concentration increases. Probably, I is partially salted out of solution as sodium chloride is added, and an excess amount of the surfactant is then available for adsorption onto the sulfa particles. Consequently, the sediment is expected to become denser as the amount adsorbed increases and a lower filtration rate is observed.

Increased filtration time with increased availability of surfactant has already been demonstrated (Fig. 5). In contrast, formation of an open network structure consisting of large clusters of particles is anticipated if the electrolyte is acting on the diffuse double layer of the negatively charged particles, and the filtration rate is expected to increase with an increasing salt concentration. However, the data indicate the opposite effect. Figure 6 shows that there is a steady increase in filtration time 10–50 as the ionic strength is increased.

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