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INFLUENCE OF DISPERSION METHOD ON PARTICLE SIZE AND DISSOLUTION OF GRISEOFULVIN-SILICON DIOXIDE TRITURATIONS

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ABSTRACT

Dissolution rate and particle size distribution of griseofulvin were determined after simple blending or solvent deposition using colloidal silicon dioxide. Griseofulvin deaggregation in simple blends and microparticulate drug dispersion in solvent deposited samples, both determinants of drug dissolution rate, were a function of silicon dioxide content. Solvent deposited samples scored impressively highly initial dissolution rates compared to corresponding simple blends. However, dissolution data thereafter were not encouraging. Drug particle size enlargment in griseofulvin rich samples and incomplete drug recovery from silicon dioxide rich samples were notable drawbacks in solvent deposition systems. Viscosity effects of silicon dioxide dispersion on griseofulvin dissolution were demonstrated. Simple blending with silicon dioxide was recommended as a means of promoting disso-

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lution rate of griseofulvin. Limitation of average particle size data determined by methods which do not discriminate between drug and insoluble carrier is discussed.

INTRODUCTION

Many powdered pharmaceutical drugs show reluctance to dissolute in aqueous media for reasons such as hydrophobicity, poor wettability, aggregation and lack of ionisation at physiologic pH. Various physical approaches have been attempted to tackle this biopharmaceutical problem, ranging from simple measures such as drug micronization to more sophisticated methods involving drug dispersion, as molecules or microcrystals in a powdered inert carrier (1). Water soluble and later on, insoluble hydrophilic carriers have been put to use. Appropriate terminology such as solid solution and solid dispersion define the final state of subdivision of the drug in the carrier (2,3). Similarly, terms such as eutectics (1) and coprecipitates (4) indicate possible methods of preparation of the drug-carrier system. Adsorbates and minuscular forms refer specifically to solvent deposition systems in which the drug is dispersed on the surface of an insoluble microparticulate adsorbent carrier (5,6). Among the advantages of insoluble carriers advocating their use, is drug release in an unbound absorbable state (5).

In solvent deposition systems, improvement in drug dissolution is anticipated as a result of the decrease in particle size serving to increase the thermodynamic activity of the drug. However, reported dissolution data have not always supported the above speculations. Particularly provoking are cases reporting poor dissolution quality of solvent deposited samples inspite of a low drug-carrier ratio (7,8). Factors such as drug instability, solvent migration and drug entrapment proved operative in these situations.

The aim of the present study was to investigate drug release potentials of griseofulvin-colloidal silicon dioxide triturations prepared by simple blending or solvent deposition. Investigational tools included dissolution rate monitoring and particle sizing. Dialysis, adsorption and viscosity data were collected to aid in interpretation of dissolution profiles. Silicon dioxide, a microparticulate adsorbent frequently used in solvent deposition systems, has been praised by some and condemned by others (5,8,9). In view of its unique surface properties, this pharmaceutical adjuvant appeared worthy of further study.

EXPERIMENTAL

Materials- Griseofulvin[1] and colloidal silicon dioxide[2] were used as supplied. Ethanol 95% was spectroscopic grade and chloroform[3] was analytical grade.

Methods-Sample preparation- For the simple blends, ingredients equivalent to ten dissolution samples were sieved using a 0.2 mm aperture wire sieve and mixed. The mixtures were resieved and tumbled for 15 minutes in a bottle. Simple blends were prepared at drug-carrier ratios of 10:1, 1:1, 1:20 and 1:50. For the solvent deposited samples, griseofulvin equivalent to ten dissolution samples was dissolved in chloroform in a glass morter. Silicon dioxide was added while stirring forming a thin gel. Evaporation of solvent was effected by stirring at room temperature. The resulting powder was sieved and remixed by bottle tumbling. Samples of 10:1, 1:1 and 1:20 drug-carrier ratios were prepared.

Triturations were assayed spectrophotometrically for content uniformity. An amount equivalent to 20 mg of griseofulvin was dispersed in alcohol 50%. An aliquot was filtered[4], diluted with the same solvent and measured[5] at λ_{max}, 295 nm.

Dissolution Study- The stirrer motor[6] rotating at 50 and 125 rpm drove a stirrer blade (4 x 1 cm), which was centrally placed 2.5 cm above the lowermost base of a one-liter flask. A sample equivalent to 20 mg of griseofulving was introduced. The dissolution medium was either 0.1N HCl or phosphate buffer (0.15M, pH 7.4), both containing 0.02% polysorbate 80. Samples were withdrawn by a syringe fitted with a 0.45 um membrane

filter and were analyzed by UV spectrophotometry at 295 nm. For this system, the absorbance value of silicon dioxide dispersions in the concentrations used was negligible.

Particle Sizing- was carried out using an electronic particle counter[7] with 1% w/v aqueous NaCl previously saturated with griseofulvin as the electrolyte.

Viscosity measurment- were made using a capillary Ostwald viscometer, on samples withdrawn from different parts of the dissolution flask, during agitation, following withdrawl of the last dissolution sample.

Adsorption- Silicon dioxide dispersions 0.17-0.34% in 0.1N HCl were shaken for 24 hours at 37° in presence of 0.5-1.0 mg% griseofulvin. Samples were analyzed spectrophotometrically.

Dialysis- Dialysis bags[8] containing 10 ml of silicon dioxide dispersion were immersed for different time periods, at 37°, in 30 ml of griseofulvin solution. Concentrations used were the same as under adsorption. Griseofulvin concentration outside the bags was determined.

Microscopic examination- samples mounted in 0.1N HCl containing 0.02% polysorbate 80 were examined.

RESULTS

Dissolution data obtained are given in Table I. Counting data were used to construct histograms (Fig. 2) and to calculate average particle size

TABLE I
Dissolution Data of Griseofulvin-Silicon Dioxide Triturations.

Method	Ratio[a]	pH	Revolutions, rpm	Percentage dissoluted minutes 5	10	20	30	60	90	Sample
Simple blending	Drug	1.2	50	2	4	7	12	22	31	1
	Drug[b]			5	8	16	21	35	44	2
	10: 1			3	6	11	18	29	36	3
	1: 1			16	22	39	47	53	55	4
	1:20			26	29	36	39	43	44	5
	1:50			23	29	34	37	40	41	6
	Drug		125	18	28	39	45	51	56	7
	1: 1			37	47	54	57	62	64[d]	8
	1:20			33	43	50	51	54	56	9
	1:50			32	39	43	44	47	47	10
	Drug	7.4	50	2	4	7	12	16	17	11
	1: 1			20	24	32	34	39	42	12
	1:20			21	27	34	37	39	40	13
Solvent deposition	Drug[c]	1.2	50	1	2	5	8	16	22	14
	10: 1			12	14	17	18	22	26	15
	1: 1			27	29	34	36	38	41	16
	1:20			42	56	56	56	56	56	17
	Drug[c]		125	24	29	36	38	42	45	18
	10: 1			26	31	40	43	47	48	19
	1: 1			38	42	46	49	51	52	20
	1: 1	7.4	50	19	25	30	32	35	37	21

[a] Ratio of griseofulvin to silicon dioxide
[b] The dissolution medium contained 20 mg of silicon dioxide equivalent to the 1:1 simple blend.
[c] Deposited from chloroform in absence of silicon dioxide.
[d] Corresponds to 12.8 mg of griseofulvin/700 ml of dissolution fluid. Equilbrium solubility of griseofulvin in 0.02% Tween 80 in 0.1N HCl was 21 mg/700 ml.

(Table II). Viscosity measurements indicated an increase in viscosity of the dissolution medium in the region below the stirrer, in presence of 400 mg of silicon dioxide per 700 ml. Adsorption data indicated no uptake of griseofulvin molecules by silicon dioxide in aqueous medium. Similarly, the rate of dialysis of griseofulvin was unaffected by silicon dioxide. Griseofulvin particles, 20-30 um, were a microscopic feature in the 1:1 and 10:1 solvent deposited samples as well as in griseofulvin deposited in absence of carrier.

DISCUSSION

Griseofulvin, without formulation aids exhibited poor dissolution at a low agitation rate irrespective of the pH of the medium (samples 1 & 11), due to clumping together of the hydrophobic micronized particles (10). Increasing the agitation brought about partial deaggregation and, consequently, a faster dissolution rate (sample 7). A simple remedy for the problem of aggregation proved to be blending with silicon dioxide (sample 1-13). Aqueous dispersions of the hydrophilic carrier did not hinder aggregation of griseofulvin particles; hence, the nonimpressive dissolution profile of sample 2 compared to sample 4. Intimate mixing of griseofulvin with silicon dioxide proved to be a requisite for deaggregation and consequently, improvment of initial dissolution rates (samples 3-6 and samples 8-10, data at 5 minutes). However, the amounts disso-

luted at 90 minutes (same samples) were inversly proportional to the silica content of the samples; thus implicating silicon dioxide in supression of griseofulvin dissolution. In exploring possible contributing factors, adsorption and dialysis data indicated that silicon dioxide did not adsorb nor bind griseofulvin in an aqueous medium, in accordance with a previous report (8). Viscosity measurements, however, suggested that silicon dioxide could have supressed griseofulvin dissolution through viscosity effects. Dissolution of griseofulvin is probably diffusion controlled, and hence, susceptible to viscosity effects (11).

Dissolution profiles of solvent deposited samples gave further insight into silicon dioxide potential to alter griseofulvin dissolution. During the process of solvent deposition, the initial drug particle characteristics are sacrificed in view of promoting the formation of still finer particles. This is accomplished by the microparticulate dispersion of the drug on the extensive surface offered by the carrier and results in a rapid drug availability to the dissolution medium. The solvent deposited samples prepared in the present study all scored initial dissolution rates higher than corresponding simple blends (Fig. 1, data at 5 minutes). In both cases, initial dissolution rates were a function of silicon dioxide content of the sample, in agreement with

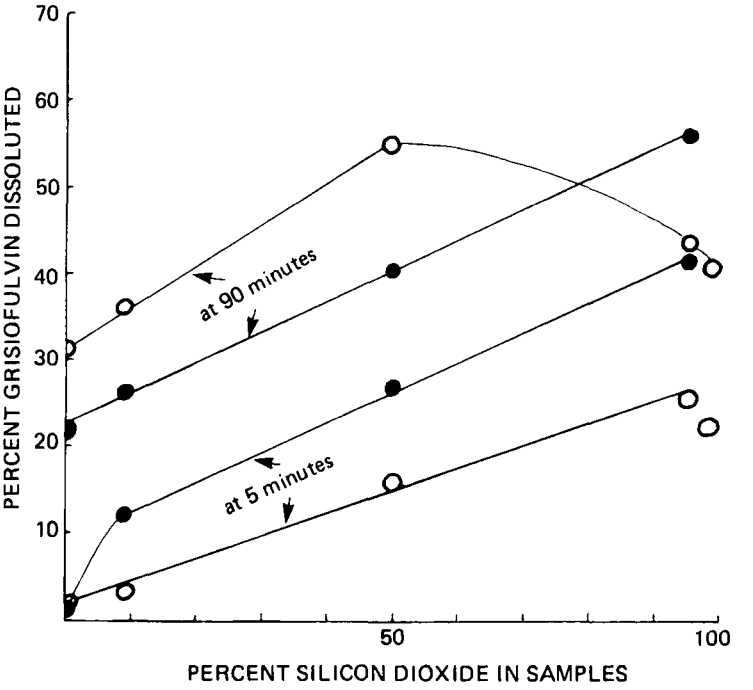

Fig. 1: Relationship between dissolution and silicon dioxide content of simple blends ○, and solvent deposited samples ●.

a previous report (8), but contrary to another (5). Inspite of a rapid initial dissolution rate, the adsorbates (samples 15 & 16) yielded less amounts in solution at 90 minutes compared to the simple blends (Fig. 1). It could be reasoned that any drug not accomodated on the carrier surface during solvent deposition tended to form larger particles in comparison to the initial micronized state. Histograms obtained confirmed this trend for the 10:1 and 1:1 drug-carrier samples (Fig.2, B,C & D) in which a considerable portion of the drug lay in the 20-30 um range, resulting in relatively slow dissolution rates. In the 1:20 drug-carrier sample,

most of the drug particles apparently were below counting level leaving only silicon dioxide aggregates to be counted; hence the close similarity between histograms E and F (Fig. 2). Although this sample (sample 17) scored understandingly the highest initial dissolution rate among all samples tested, the incomplete drug recovery during dissolution was puzzling but has been reported in similar situations (8,9).

Predictive characterisation of solvent deposition systems in terms of drug dissolution requires particle sizing. Yet, few studies have reported particle size data of such systems probably owing to some difficulty of selectively sizing the drug particles. The carrier if insoluble, may be counted along with the drug particles interfering with their sizing. The situation becomes further complicated with a carrier such as colloidal silicon dioxide existing itself as micron sized aggregates with an ultimate particle size in the submicron range. This explains the limited correlation between average particle size values and dissolution data obtained in the present study (Table II). Similarly, inspection of average particle size and dissolution data reported for griseofulvin-silicon dioxide triturations (8), fails to reveal an impressive correlation. Apart from average particle size, these authors (8) calculated width of particle size distri-

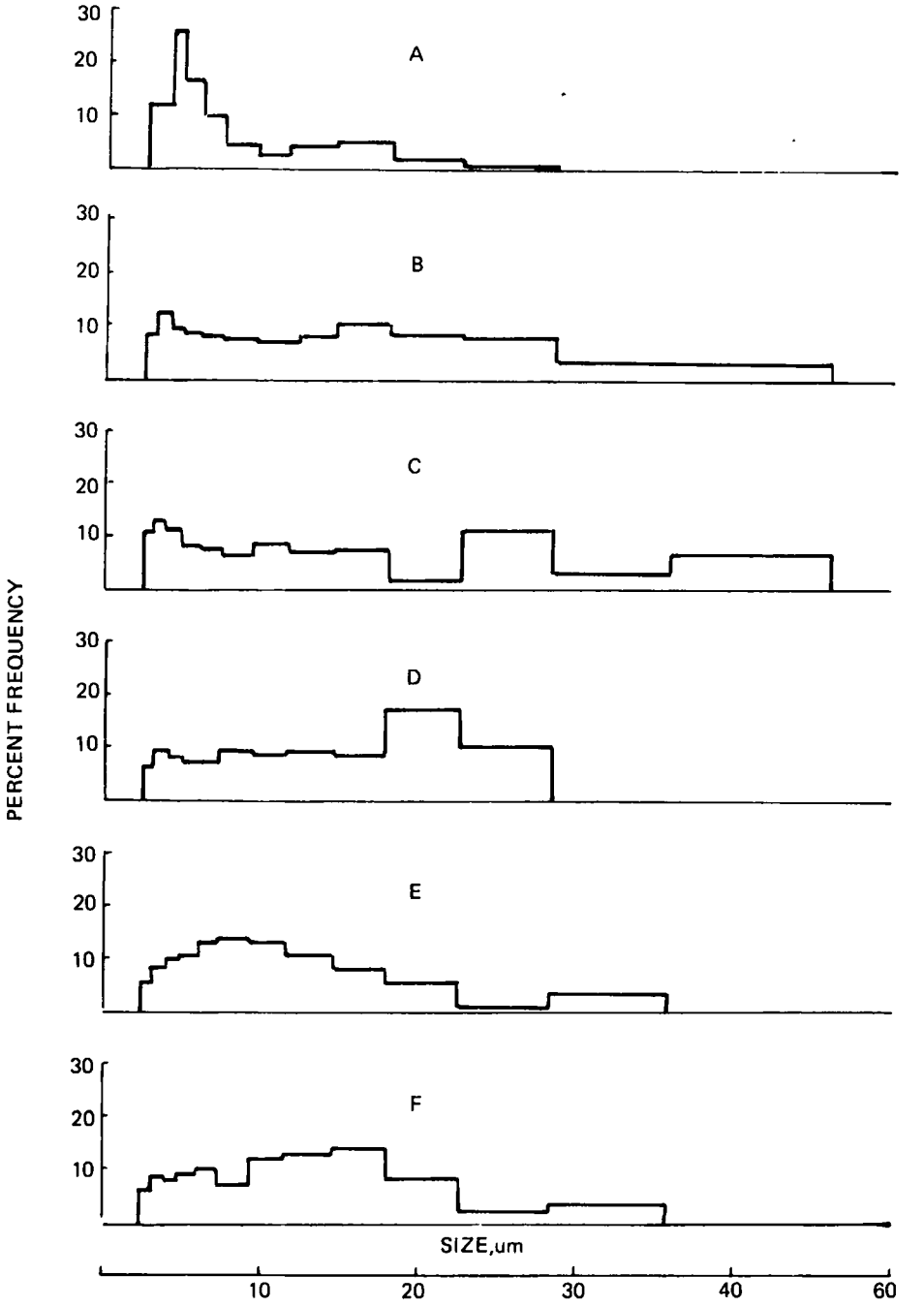

Fig. 2: Particle size distribution of griseofulvin particles released into eletrolyte from the original powder (A); from the solvent deposited samples, without silica (B); 10:1 drug-carrier adsorbate (C); 1:1 adsorbate (D); 1:20 adsorbate (E); and from silica (F).

TABLE II
Average Particle Size Data for Griseofulvin-Silicon Dioxide Triturations

Sample	d_g [a] um	d_{sn} [b]	Percent dissoluted after 90 minutes
Griseofulvin	4.7	11.15	31
Griseofulvin[c]	8.6	15.26	22
Sample 15	7.6	16.01	26
Sample 16	10.5	14.90	41
Sample 17	7.8	12.05	56
Silicon dioxide	9.5	12.96	
Silicon dioxide[d]	11.8	18.53	

[a] Geometric mean diameter, obtained from log-probability plot of weight percent oversize versus particle size.

[b] Surface-number mean diameter calculated from frequency data using the equation $d_{sn} = \left[\frac{\sum (nd)^2}{\sum n}\right]^{1/2}$

[c] Sample 14

[d] Wetted with chloroform, dried at room temperature and passed through a 0.2 mm aperture sieve.

bution as a measure of change in particle size distribution in silicon dioxide triturations brought about by ball milling or solvent deposition.

In conclusion, data obtained in the present study permitted assessment of solvent deposition versus simple blending with colloidal silicon dioxide as means of producing fast dissolving griseofulvin triturations. Drug particle enlargment in griseofulvin rich samples and incomplete drug recovery from silicon dioxide rich samples were notable drawbacks in the solvent deposited samples prepared. Simple blending with silicon dioxide

at a 1:1 ratio yielded encouraging results in terms of powder dissolution quality. A study has been initiated to assess the bioavailability in man of tablets prepared from these simple blends.

FOOTNOTES

[1]Micronized griseofulvin, Glaxo Laboratories, LTD.

[2]Aerosil 200, Degussa, Frankfurt A. Maine

[3]Mallinckrodt Inc.St.Louis, Missouri.

[4]HAWG, 0.45 u filter, Millipore Filter Corp., Beford, Mass., USA.

[5]Unicam SP 1800 Spectrophotometer.

[6]Hurst MFG Corp., Princeton, Ind.

[7]Coulter counter, Coultronics, France SA, 100 um aperture tube.

[8]Dialyzer tubing, Fischer Scientific Co., catalog No. 8-667-D.

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