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Review Article

Particle Size of Drugs and Its Relationship to Absorption and Activity

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THE PARTICLE SIZE of a drug is not a new consideration. Down through the ages the state of subdivision of a drug was and still is a primary factor to be considered in the preparation of esthetical, elegant, and stable dosage forms (1–11). With the evolvement of physical pharmacy, pharmaceutical scientists and medical practitioners have begun to look more critically at this property in an effort to not only learn of its effect in physical systems, but also to gain insight into the influence of particle size in biological systems. This article treats primarily the recent information of the biopharmaceutics (12) of the particle size of drugs.

Several review articles treating particle size in different context have been published since 1963: (*a*) "Effect of Particle Size on Dissolution and Gastrointestinal (GI) Absorption Rates of Pharmaceuticals," in March 1963, by Levy (13); (*b*) "Pharmaceutical Aspects of Fine Particles and Their Evaluation," in September 1963, by Lees (14) (no references were listed); (*c*) "Particle Size in Relation to Formulation," in July 1964, by Dare (15) (partial list of references was presented); (*d*) "Importance of Particle Size in Pharmaceutical Practice," in November 1966, by Lamy (1); (*e*) "Importance of Particle Size in Pharmaceuticals" in February 1967, by Renoz (16). The latter two are not comprehensive reviews but were written for the purpose of calling this property to the attention of the hospital pharmacist and Belgium industrial pharmacist, respectively. Some of the more important principles and considerations discussed in these reviews are worth reiterating here since neither of these articles was published in this journal. From this writer's experience, some are not readily accessible to every library. All are in English, however, except Renoz's (16), which is in French.

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Clinical Aspects—GI—(*a*) Absorption from particulate matter usually results after the drug is in the dissolved state. If the dissolution rate is the rate-limiting step; *i.e.*, the dissolution rate is less than the diffusion rate to the site of absorption and the absorption rate itself, the particle size of the drug is of great importance in the transport from the GI tract to the site of action by way of the blood and lymph (13, 14).

(*b*) When the solubility of a drug is less than 0.1 mg./ml., its physiological availability must be considered and the effect of particle size could be paramount (8). Others claim that particle size is a factor to be considered if the solubility is 1 mg./ml. or less (15).

(*c*) Most drugs are passively absorbed and their rates of absorption are dependent upon the concentration gradients in each case; by increasing the dissolution rate in the GI tract the absorption rate is necessarily increased so long as the dissolution rate is still the limiting step (12–15). It

follows that an increase in the absorption rate results in the entrance of more drug into the blood, and usually more will reach the site of action before metabolism and excretion eliminate the active form of the drug from the body.

(*d*) If a drug is not absorbed enough to be systemically active and if the drug is not soluble enough to be used for its local action in the gut, the reduction of particle size may improve its therapeutic efficacy. A larger particle may be needed to give local action in the lower GI tract (13–15).

(*e*) Reduction of particle size can act as a "double-edged sword." The potential toxic effects due to increased concentration must always be considered in both locally acting and systemically acting drugs (13–15).

(*f*) The stability characteristics of the drug may be altered considerably by reduction of particle size. The resultant increase in surface area places more of the drug molecules in a vulnerable position for rapid degradation by the GI fluids (13–15).

Other general clinical considerations which are directly related to particle-size effects are: (*g*) Localized absorption areas in the gut—if the area of absorption of a given drug is in the stomach or upper region of the gut only, then the reduction of particle size is potentially beneficial, since more of the drug would be in solution in the absorption region. However, if the area of absorption is in the lower portion of the gut, drug absorption may be independent of particle size. After the time required to reach the site of absorption, dissolution would have occurred already when using the drug in a large or a small particle size (13–16). This factor obviously is directly related to the conveyance of the materials through the GI tract—stomach emptying time and peristaltic activity of the gut in general (12).

(*h*) pH of the contents of the GI tract—the average changes of medium pH as a drug is conveyed through the GI tract and has been discussed in a review by Wagner (12). The solubilities of weak acids and weak bases are a function of the pH of the dissolving medium, and in some cases the availability of drug will be independent of particle size due to a dissolution in one compartment and a subsequent precipitation in another. For example, a weak organic base drug would be solubilized rapidly in the form of the amine acid salt in the pH of the stomach, but as the drug passes into the duodenum and small intestines the free base would be precipitated in the contents. Since the large and small particles are each dissolved rapidly and reprecipitated before any appreciable absorption can occur, the absorption rate is independent of the initial particle size (13). A weak acid drug would lend itself to particle-size consideration. In solution, it is largely in the undissociated form in the stomach, and absorption can occur. It would be very insoluble in this pH, however, and a smaller particle could improve the dissolution rate and the availability of the drug for absorption. After the weak acid drug passes into the duodenum and small intestines, it would be much more soluble due to salt formation, but at the same time it would be highly ionic in character. Thus, the availability for absorption is greater, but its ionic character would make the absorption rate less since only a small fraction of the drug molecules are in the undissociated state (12, 13). It is appropriate to mention at this point that the pH at the site of absorption may be different from the pH of the GI lumen contents, and absorption from an ionic solution may not be as limited as the pH-partition theory would indicate.

(*i*) The degree of agitation in the GI contents is related to particle-size effects, and this factor is subject to considerable variability within the individual depending on the physiological state during the time of administration and absorption. No suggestions are offered for the control of this variable, but the agitation intensity would affect the size of the "saturated boundary layer" on each of the drug particles and also the "effective diffusion rate" of the drug to the sites of absorption (13).

(*j*) Measurement of the effects of particle size on drug action—apparently, there is not a good way to measure the dissolution rate of a drug (dosage form) in the stomach and intestinal contents. *In vitro* measurements made in simulated gastric and in simulated intestinal fluids are not necessarily indicative of actual *in vivo* processes. The determination of blood levels is assumed to be a good criterion for drug action in most cases, and since passive excretion by way of the urine is a function of blood level, the excretion rate is usally a good criterion to use (12). In order to measure the amount of drug absorbed, the bound drug and the metabolites, as well as the unchanged drug, must be measured. Thus, with particle size controlled, the absorption, distribution, metabolism, and excretion routes of the drug should be studied first. If particle-size effects need to be determined, the blood levels and excretion rates can be used more effectively as an indirect measure of drug availability, as some function of particle size.

(*k*) Since particle absorption has been reported

(14, 15), one cannot preclude this possibility as an adverse effect in the use of extremely small, insoluble particles. The passage of bacterial cells and oil globules (in emulsified form) through the intestinal wall into the blood has been reported. Particles (globules) up to 0.5 μ are reported to pass through (14, 15). Entrance of very small particles of barium sulfate into the intestinal glands can cause granulomas (14).

Clinical Aspects—Other Than GI—In parenteral therapy, the particle size (surface area) of suspended particles injected i.m. or subcutaneously is an important factor. The absorption of the drug from particles appears to increase with an increase in the specific surface area; however, in certain vehicles where a hydrophobic protective layer is involved the absorption may be more delayed when using very small particles. This may be related to the fact that fine particles tend to cake or form gels in certain vehicles. The viscosity of suspensions increases with a decrease in particle size, and this factor may explain some of the delayed absorption using very small particles (14, 15).

In semisolid systems (ointments and suppositories), the particle size of the insoluble fraction of the drug is an important factor in obtaining the desired results. In these cases an improved dissolution rate leads to greater availability of the drug for absorption in the case of systemic effects, and for higher concentration at the area of application for a better local action (14, 15).

Inhalation therapy has been improved considerably by controlling the particle size of aerosol-generated droplets. The size of the droplet governs the deposition area in the respiratory tract (14, 15). Tables of the droplet size, ranges, and areas of condensation are presented in the aerosol chapters of Husa's and Sprowl's dispensing textbooks (17, 18).

The particle size of practically insoluble drugs in dusting powders, insufflates, and aerosols was predicted to be an important consideration in their dissolution and subsequent local action (14).

Physical and Chemical Aspects of Particle Size—The dissolution rate of drug particles has been discussed thoroughly by Levy (13) and Dare (15) in terms of the modified Noyes-Whitney (19) equation and there is no particular need for a complete discussion here. The modified Noyes-Whitney equation is:

$$\frac{dA}{dt} = KS(C_s - C) \qquad \text{(Eq. 1)}$$

where A = amount of drug in solution, t = time, K = intrinsic dissolution rate constant, S = surface area, C_s = concentration of the drug–solvent boundary on the surface of the particle which is approximately equal to the solubility of the drug in the solvent, and C = concentration of the drug in the dissolution medium at time t.

The equation is useful for the determination of the intrinsic dissolution rate at a constant surface area. It is noted by an examination of the equation that the rate of dissolution dA/dt is directly proportional to the surface area, S, and the concentration differential $(C_s - C)$. The variables which must be controlled in the determination of the intrinsic dissolution rate are surface area, agitation intensity, temperature of the system, and volume of the dissolution medium. This expression is very valuable indeed, but it falls short of expressing the dissolution rate of a multiparticulate system where agitation intensity is more difficult to control. It is even farther from simulating the conditions in the fluids of the GI tract or other tissue fluids at different administration sites.

The closest analogy of the above expression in a living system would be the subcutaneous implantation of pellets made from practically insoluble drugs which exert a therapeutic effect for several months. The change of surface area with time is small, but even in this case the absorption rate is not constant (13).

The Hixson-Crowell (20) cube root law as modified by Parrott (21) is presented:

$$Kt = W_o^{1/3} - W^{1/3} \qquad \text{(Eq. 2)}$$

where W_o = weight of solid particle initially, W = weight of solid particle at time, t, K = the product of intrinsic dissolution constant, solubility, and density.

The weight of a sphere was determined at different times and a linear relationship was obtained. This equation is useful only for the determination of the intrinsic dissolution rate constant and it is limited to those particles whose ratio of dimensions does not change as dissolution proceeds (22). The error would be even more pronounced if different dissolution rates occurred from different faces (22). There is an applicability, however, to those cylindrical particles whose heights are equal to their initial diameter (22). In general, all particles with dimensions which are in the proximity of spheres would first dissolve away those faces and edges, so that by their absence the particles can assume the shape of minimum surface (spherical). In shapes grossly different from spherical, most of the drug material will be dissolved before the spherical shape is approached, if it is possible for the final shape to be nearly spherical. Long needles and irregular

platelets are good examples of grossly different shapes from spherical. The Hixson-Crowell equation has limited applicability to *in vivo* conditions.

Dissolution rates of multiparticulate systems are the best estimate of actual *in vivo* conditions (23). The Hixson-Crowell equation was extended by Niebergall *et al.* (24) to include multiparticulate systems. Their equation is:

$$W_o^{1/3} - W^{1/3} = K''N^{1/3}t \qquad \text{(Eq. 3)}$$

where W_o, W, K'', and t have the same significance as above and where N equals the number of particles.

According to Levy (13) the determination of apparent dissolution rates is necessary since (*a*) highly irregular shaped particles do not maintain constant ratio of dimensions; (*b*) the particle-size distribution is not normal or log-normal and cannot be adequately described mathematically in many cases; (*c*) many particles exhibit different dissolution rates from the different crystal faces (anisotropic in nature); (*d*) agitation intensity is hard to control or define, and it varies with density and particle size—small particles (less than 10 μ) are not subjected to much agitation and the boundary layer is effectively larger for them; (*e*) dissolution rates need to be determined in the presence of the other ingredients of a formulation; (*f*) the functional surface area is different from the specific surface of solid drugs and this difference may be brought about by surface fissures, porosity, surface hydrophobicity, and particle aggregation—surfactants may change the effective surface of a particle.

Agitation intensity and its effect on the dissolution rate, as determined by the method of the rotating disk, has been expressed quantitatively by Levy (13).

$$R = K\ (\text{r.p.m.})^{1/2} = \text{dissolution rate/min.} \qquad \text{(Eq. 4)}$$

where K = a proportionality constant.

In a dissertation by Fincher (25) a review of physical phenomena associated with the reduction of particle size is presented. The reduction of particle size is associated with an enormous increase in specific surface area. The classic example (26) of a cube 1 cm. (10^{-2} m.) on edge being divided into smaller cubes which are 1 mμ (10^{-9} m.) on edge gives an increase in surface area of seven orders of magnitude, *i.e.*, 6×10^{-4} m.^{2}, as compared to 6×10^{3} m.^{2} Properties which play a subordinate role in determining the behavior of large particles will become increasingly important as the particle size is reduced (26).

Drug materials, upon fine subdivision, show an increase in solubility and vapor pressure and a decrease in melting point. Particle size determines color in some cases. For example, antimony changes from red to yellow as the particle size decreases. As particle size is decreased the amount of gas and other types of molecules adsorbed is increased due to the increased surface (26). This phenomenon is utilized in the treatment of flatulence, in toxin absorption in the treatment of poisoning, and in the determination of surface areas (B.E.T. method).

The mechanism of solution involves surface action and by virtue of an increased surface a given solute will dissolve more rapidly (26). Increased solubility is reported to be evident when particle size is in the submicron range. Alexander (27) found a linear relationship between the logarithm of the solubility, S, and the surface area, A, of amorphous silica: $\log S = 0.00480A - 2.043$. As will be noted, the slope is a very small positive number, but as the surface area becomes very large, the increase in solubility is significant. Higuchi (28), in a discussion of the theoretical effects of particle size on solubility noted that the increase in solubility is significant only for very small particles. Even perfect crystals, differing in size, will have different solubilities (28).

The formation of complexes has the effect of increasing molecular dimensions, increasing the charge on the molecule if the complex is soluble, and decreasing the solubility of the drug if the complex is not charged. Complexing is a function of pH, and the pH of GI contents is an important consideration here.

The advantages gained by reducing the particle size below 1 μ are far outweighed by the difficulties encountered in handling and formulating drugs into dosage forms (15). The surface energy of the particles is one property manifesting itself in a very small particle size (below about 5 μ) by their sticking to each other and the sides of the container or by their scattering asunder on contact with an agitator.

Effects of Particle Size on Clinical Response Reported Prior to 1964—Table I is an alphabetical summary of those drugs which have been studied and information published prior to June 1964 (*References 29–57*).

More Recent Reports on Particle Size and Clinical Response—Table II is an alphabetical listing of those drugs which have been studied with respect to particle size and have been reported since 1964 (*References 58–65*).

The effect of the particle size on sulfisoxazole blood levels in dogs was studied by Fincher *et al.* (58), and statistical analyses were performed on the data taken at 0.5, 1, 2, 4, 8, and 12 hr. after

TABLE I—ALPHABETICAL SUMMARY OF DRUGS THAT HAVE BEEN STUDIED IN BIOLOGICAL SYSTEMS WITH RESPECT TO PARTICLE SIZE—STUDIES REPORTED UP TO JULY 1964

Name of Drug	Biological System Used	Particle Size or SSA Range	Method Used to Det. Particle Size of SSA	Criterion Used, Hours of Sampling	Clinical Effect of Reduced Particle Size (Increase SSA)	Dosage Form	Ref.
Aspirin	—	20, 120 mesh, solution	Sieve	Blood level	Increased	Cachet, solution	15
Calomel	Humans	USP (2–50 μ) 0.8 μ, max. (colloidal)	—	Antiseptic action	Increased	Ointment	44, 45
Chloramphenicol	Bacteria	11–60 μ	—	Zones of inhibition	Increased	Ointment	55–57
Chloramphenicol	Rabbits	50–800 μ	Sieve	Blood levels	Increased rates	—	33
Bishydroxycoumarin	Humans	Fine and larger	—	Hemophilia	Increased	Tablets	53
Griseofulvin	Humans	0.4–2.5 m.² per g. (0.8–11.4 μ)	Instrument[b]	Blood levels (4, 8, 12)	Increased absorption	Tablets	29, 30
Griseofulvin	Rats	Common powd. + micronized	—	Serum level (2, 4, 8, 12)	Increased Increased Increased	Suspension Suspension + surfactants Suspension in corn oil	31
Griseofulvin	—	Common powd. + micronized	—	—	—	—	32
p-Hydroxypropiophenone	Humans	Large and small	Microscope	Estrogenic activity	Increased	—	49
Mercury	Rats and rabbits	Smaller particles	—	Wet kidney content	Increased	—	48
Phenolphthalein	Humans	USP and colloidal	—	Purgative	Increased	—	43
Phenothiazine	Lambs	1–10 μ	Instrument[b]	Worm counts in abomasa and intestine (small)	Increased	—	38, 39
Phenothiazine	Moth larvas	4 and 45 μ	—	Toxicity effects	Increased	—	52
Phenothiazine	Sheep	—	—	Nematodes in large intestine	Decreased	—	40, 41
Procaine Penicillin	Humans	5–60 μ	—	Serum levels	Increased Decreased	Suspension in water Suspension in oil	50
Spironolactone	—	Common and micronized	—	Serum levels	Increased	Capsules	51
Sulfadiazine	Humans	Common powd. in tablets, microcrystalline, micronized	—	Plasma levels + urine excretion	Increased	Tablets susp.	35
Sulfadiazine	Humans	Common powd. + micronized	—	Serum levels (1, 2, 4, 6, 24)	Increased	Suspension	34
Sulfaethidole	Rabbits	68–274 μ	Sieve	Blood levels	Increased	—	36
Sulfathiazole	Humans	50–100 mesh and eutectic mixture with urea	—	—	Increased with eutectic	Suspension	37
Sulfur	Humans	Elemental and colloidal	—	Excretion	Increased	—	46
Tetracycline hydrochloride	Humans	1.00 μ–0.95 cm. pellet	Sieve	—	No effect	—	42
Tolbutamide[a]	—	—	—	—	—	—	54
Vitamin A	Humans (infants)	1–2 μ	Microscope	—	Increased	Emulsion	47

[a] See Table II, last item. [b] Fisher subsieve sizer.

oral administration of the drug in capsules. Perhaps, for a better picture of particle-size effect, it would have been better to administer the drug particles in a freshly prepared suspension, since capsules have been known to delay the availability of the drug for absorption up to 30 min., or even more. This fact may explain some of the higher degree of variation at the 0.5-hr. study. The changes of blood level with particle size at each of the times studied can be expressed in semilogarithmic function:

$$\log M = aP + b \qquad \text{(Eq. 5)}$$

where M = blood level in mg. %, P = particle diameter, and a and b are constants representing the slope and intercept, respectively.

The slope of the time constant lines changes from a negative to a positive value between 4 and 8 hr. after administration indicating that blood levels are higher for larger than for smaller particles after about 6 hr. A linear plot of the slope of each time constant line $(d \log M)/dP$, as a function of time, t, in hours produced a *straight* line whose equation is:

$$\frac{d \log M \times 10^3}{dP} = a_1 t + b_1 \qquad \text{(Eq. 6)}$$

where a_1 and b_1 are the slope and intercept equal to 0.781 and −4.32, respectively, for sulfisoxazole. The factor 10^3 was introduced for the convenience of plotting whole numbers. Integration of this equation between limits of yields:

$$10^3 \log \frac{M_2}{M_1} = (a_1 t + b_1) \cdot (P_2 - P_1) \qquad \text{(Eq. 7)}$$

If P_1, T, P_2, and M_1 are known, one can calculate with Eq. 7 the blood level resulting from P_2 at a given time. The proportion of dose absorbed did

TABLE II—ALPHABETICAL SUMMARY OF DRUGS THAT HAVE BEEN STUDIED IN BIOLOGICAL SYSTEMS WITH RESPECT TO PARTICLE SIZE—STUDIES REPORTED SINCE JUNE 1964

Name of Drug	Biological System Used	Particle Size or SSA Range	Method Used to Det. Particle Size of SSA	Criterion Used, Hours of Sampling	Clinical Effect of Reduced Particle Size	Dosage Form	Ref.
Amphotericin	Dog Mice Humans	Not known	—	Toxicity; therapeutic effect	Increased Increased	Parenteral	64
Fluocinolone acetonide	Humans	Coarse and micronized	—	Vasoconstriction	Increased	Ointments	60
Lime	Alfalfa	8–10 mesh 10–20 mesh 20–30 mesh 30–50 mesh 5–100 mesh 100 − + mesh	Sieve	Rate of growth	Increased to 50 mesh	Fertilizer	62
Medroxyprogesterone acetate	Humans	Common (1.2 m.²) and micronized (7.4 m.²) before tableting	—	Urinary excretion (8 hr.)	Increased	Tablets	59
Nitrofurantoin	Dogs	50–60 mesh 200–325 mesh micronized	Sieve	Emesis	Increased	Capsule	63
Nitrofurantoin	Rat	50–80 mesh 80–200 mesh 200–micronized	Sieve	Urinary excretion	Increased	Suspension	63
Nitrofurantoin	Humans	Same as above	Sieve	Urinary excretion	Increased	Capsules	63
Potassium dihydrogen phosphate	Rats	10–50 mesh	Sieve	Cariostatic action	Increased to 20–30 mesh	Diet	61
Sulfisoxazole	Dogs	1.7, 39, and 95 μ	Electronic counter[a]	Blood levels (0.5, 1, 2, 4, 8, 12)	Increased	Capsule	58
Tolbutamide	Humans	6.60, 36.9, 63.1, and 98.6 cm.² per dose of 5 g.	Calculations	Urinary excretion (every 2–12 hr. then every 12 hr.)	Increased	Tablet and capsules	65

[a] Coulter, Coulter Electronics, Franklin Park, Ill.

not change with particle size, but the smaller particles gave quick and higher blood levels which declined rapidly (58). With very insoluble drugs, such as griseofulvin, the absorbed proportion of the dose is increased with a decrease in particle size (29–32).

Smith *et al.* (59) compared the urinary excretion of micronized and nonmicronized medroxyprogesterone acetate after oral administration of tablets, each containing 10 mg. of the drug plus 0.05 mg. of ethinyl estradiol. A crossover testing procedure was used. One tablet of nonmicronized drug was compared with one-half tablet of micronized drug and one tablet of nonmicronized was compared to one tablet of micronized. An average of 2.23 times as much micronized drug was excreted as compared to the nonmicronized in a period of 8 hr. The specific surface area (SSA) of the micronized and nonmicronized was reported to be, before tableting, 7.4 and 1.2 m.²/g., respectively (59), but the method of determination of the SSA was not given. The effect of tableting on the SSA is not known here. Methods for determination of the apparent or effective surface area after incorporation in a tablet or other dosage form are needed in order to obtain meaningful SSA *versus* availability results. One-point determination, evident in the above studies (59), may be justified in some cases, but one still wonders what happened before and after the end point used.

A comparison of the effect of micronized and coarse fluocinolone acetonide particles on the degree of vasoconstriction was done by Barrett *et al.* (60). The coarse particles were partially milled in a triple roller mill during preparation, and the resultant particle size is open to question. White soft paraffin was the base used for the studies and two percentages of the drug were used, *viz.*, 0.025 and 0.01%. In both concentrations, the micronized form produced about two times the effects of the coarse. Ten subjects were used for each test and the ointment was applied to the flexor aspect of the forearm for 16 hr., was washed away, and the degree of vasoconstriction was read 1.5 hr. later.

It is interesting to note that the particle size of potassium dihydrogen phosphate had an effect on the cariostatic activity in rats when fed in their diets (61). The best size for cariostatic action was found to be in the 20–30 mesh range. Since the solubility of KH_2PO_4 is 1 part in about 4.5 parts of water, one wonders how particle size could possibly have any effect on tooth decay except that the larger particles may fracture the teeth more on chewing.

Another interesting study was performed by fertilizing alfalfa with limes of different mesh size (62). In the calcitic form no differences in alfalfa growth were noted with all particle sizes, but with the dolomitic form of particles above 30 mesh did not produce accelerated growth as compared to the control. Below 30 mesh the particles size had no increased effect.

Paul *et al.* (63) studied the relationship of the particle size of nitrofurantoin to emesis in dogs, urinary excretion in rats, dogs, and humans. Twenty dogs were used for each of the emesis studies, four rats and 15 humans were used in the urinary excretion studies for each crystal size. The range of crystal sizes studied was 50–400 mesh. Since the larger crystals caused less emesis in dogs and the smaller crystals gave higher blood levels, an optimum crystal size range was reached, which gave the highest blood levels with minimum nausea. A plot of the percent of dose excreted in the rat as a function of time gave excellent curves, which were very similar to those obtained by Fincher *et al.* (58). The smooth shape of the curves presented is indicative of a well planned and thorough study. No statistical analyses were performed on their (63) data, but in physiological systems 10–15 determinations can give useful data and show the expected results with the degree of variability known.

Bennett *et al.* (64) studied the toxicity and therapeutic effect of the particle size of amphotericin B after injection into the dog, mouse, and man. As the particle size increased, the toxicity level decreased but the therapeutic effect also decreased. The writer did not have access to the original article, and possibly some mistake in transmitting the abstract data has been made, but an i.v. injection was reportedly used which is unusual, if not undesirable in any circumstances.

Nelson *et al.* (65) administered doses of tolbutamide to normal humans in the form of a cylindrical disk (6.60 cm.^{2}) and three granules having initial surface areas of 36.9, 63.1, and 98.6 cm.^{2}/0.5-g. dose. The granules were administered in hard gelatin capsules. Urinary collections were made at intervals of 2 hr. for the first 12 hr. and at 12-hr. intervals up to 60 hr. Each test was performed three times and the average percent of dose excretions for the metabolite gave linear correlation with the surface area of the dose. Their conclusion was that the surface area of a tolbutamide dose can have a significant effect on the extent and the rate of availability.

Recent Studies of Effect of Particle Size on Release of Drugs From Dosage Forms In Vitro—The effect of salicylic acid particles on its diffusion rate from some ointment bases was studied by Kucera and Veber (66). Their exact results are not known to the author since a translation was not available. From the abstract, two grades of salicylic acid were used in the studies—one was the official form and the other was sodium salicylate. The diffusion of both samples was very low from hydrophobic bases, but, from hydrophilic bases the rate of diffusion of the sodium salicylate was very marked (66). This appears to be a study of insoluble drug *versus* a soluble form.

The interdependence of the displacement factor and particle size in suppositories was studied by Adel (67). By reduction of the particle size the value of the displacement factor is decreased. A particle greater than 150 μ should not be used in suppositories based on their conclusion from a study of the displacement factor.

The increase of the dissolution rate of drugs by preparation of solid solutions and/or eutectic mixtures of the drug and urea was attributed to the availability of the drug from such solutions and/or mixtures in a very fine state of subdivision (68–71).

The factors influencing drug release from a prolonged-action matrix were reviewed by Lazarus *et al.*, and the particle size of the drug was one of the primary considerations (72).

The theoretical effect of the distribution of the particle size in a diffusion-controlled process was studied by Higuchi, Rowe, and Hiestand (73). The change of particle-size distribution with time is shown. As dissolution proceeds the smaller particles dissolved very rapidly, leaving only the larger particles in the distribution. The assumptions are (*a*) the dissolution rate is diffusion controlled; (*b*) the diffusion layer thickness is always the same for all particles of the same size and is equal to or greater than the radius; (c) the concentration change in the "sink" is negligible at all times; (*d*) the effective particle shape approximates a sphere.

The dissolution of a single particle is expressed in terms of the particle diameter, a, at any given time, t.

$$a^2 = a_o^2 - \frac{2D\Delta Ct}{\rho} \qquad \text{(Eq. 8)}$$

where a_o = initial diameter, D = Fick's law diffusion rate constant, C = concentration of the dissolved solid, ρ = particle density.

The total dissolution rate of a powder with log-normal distribution is expressed as a function of the number of particles and the mass mean radius of the particles in the distribution. For a detailed discussion and equations see *Reference 73*.

Their theory was tested using micronized methylprednisolone, and a reasonably close agreement was obtained. The differences were believed to be due to the combined effects of agitation, sedimentation, particle shapes, and the variation of solubility with particle size.

Discussion of General Information Relating to Particle-Size Effect on Drug Absorption

and Activity—It has been noted by Dayton *et al.* (74) that with certain drugs their plasma level decline is dependent on the dose; when giving probenecid, diphenylhydantoin, phenylbutazone, and two analogs of phenylbutazone and biscoumacetate to dogs in larger doses, their rate of plasma disappearance was decreased. This phenomenon was not attributed to plasma protein binding, but was found to be caused by a special case of self-inhibition of metabolism. It is pertinent to note in this case that if particle-size reduction leads to a larger percentage of the dose being absorbed, a higher dose is the result, and a longer duration of action would be expected. This discovery also emphasizes the need for knowledge of metabolic processes prior to a study of particle-size effects.

In a review by Levine and Pelikan (75), these writers discussed the mechanisms of drug absorption and excretion. The molecular size, shape, electrical charge, and degree of polarity are properties of the drug molecule that affect its absorption. The properties of the living membrane are not only dependent on the properties of its constituents, but also on their arrangement. A living membrane is in dynamic equilibrium. Changes occur in living membranes when the pH or other environmental factors change. Consequently, when the amount of drug absorbed is directly proportional to the initial concentration, this does not necessarily prove simple diffusion as the total mechanism. Dose effects are indicated in the case of benzomethamine. A plot of the amount of drug absorbed in 3 hr. *versus* the amount of benzomethamine in GI loop gives three straight lines of different slopes. The size of the dose determines which method is used in the absorption process. The middle-sized dose gave the most rapid absorption rate (75). This "dose-effect" is another reason why the absorption rate of the drug must be studied before performing particle-size studies. If particle-size reduction produces a higher dose, which in turn induces another absorption process, the results may be interpreted in the wrong manner.

The effect of molecular size on the diffusion coefficient was considered by Wurster (76). The conclusion was that a large increase in molecular size would be necessary to get an appreciable increase in the diffusion coefficient. The charge on a particle (molecule) can increase the effective molecular size much greater than the physical dimensions *per se*, and can decrease the diffusion process through a biological membrane (77). The diffusion through an aqueous medium would be facilitated, however. Water is, apparently, able to pass through the pores of living membranes easily, but charged ions encounter some difficulty even though some ions may be pulled through by "solvent drag." When a molecule is lipid soluble, this greatly increases the permeability of a substance, *i.e.*, in effect the size of the pores of the membrane increases greatly (75, 77).

Reduction of the particle size of purified cellulose from 74 × 16 μ to 100 mesh had the effect of reducing the "lag-time" of the digestion by rumen cellulolytic bacteria *in vitro*, from 12 to 6 hr. (78).

Time and space will not permit a detailed discussion of other aspects of particle-size studies, but the study of particle size and its effect on drug absorption and action can be divided into several phases each of which is not without its problems. It is assumed that some knowledge of the drug's metabolism and excretion is already accomplished. The phases will be outlined in the order in which they are likely to be encountered, and a few pertinent references given.

Phase I—The aquisition of monosized particles in the range of desired studies. This is usually not feasible nor possible, and a narrow particle-size distribution is the next best possibility (25, 68–71, 79, 80).

Phase II—Characterization of the particles with regard to crystal shape, form, and habit. This is normally done by use of X-ray diffraction, microscopy, and other physical property studies, and it should be checked after formulations are prepared.

Phase III—Selection of the best method for particle-size analysis and determination of the particle-size distribution or specific surface area (2, 25, 81, 82).

Phase IV—Selection of the best dosage form and animal to administer the particles for the purposes of the study.

Phase V—Determination of the effective particle size after incorporation into the dosage form. Phase II may have to be repeated if a character change occurs during the production procedures (13).

Phase VI—Selection of an appropriate criterion to use in the evaluation of the effects of particle size (29–65).

Phase VII—Design of the animal experimentation procedures, including proposed statistical analyses to be performed (29–65).

Phase VIII—The experiment and data analysis.

In vitro dissolution rates may precede animal studies, but unless positive correlation is established with *in vivo* results, they cannot be the sole initial factor for estimation of biological avail-

ability. If a correlation is established, they may be used as the criterion in subsequent batches of the same drug and dosage form. Methods for the determination of dissolution rates *in vitro* have been devised, and in some cases, correlated with *in vivo* studies (13, 68–71, 73, 82–88).

The significance of particle-size effects on the therapeutic response of drugs will be reflected in the new revisions of the official compendia of this country and others (16, 89–91). Effective particle-size limits will probably be an established procedure for those drugs which are practically insoluble. If the particle size of other drugs, which are not so insoluble, can influence the needed therapeutic response, their particle size may also need to be controlled.

The effect of particle size on formulation procedures, as such, are not necessarily a part of this article but a few references are compiled for the benefit of the readers' interest (1–11, 13–16, 66, 67–73, 82–84, 92–111).

A recent discussion of the increase in solubility of small particles (spherical only) has been presented by Smolen and Kildsig (112). The thermodynamic equation—relating vapor pressure to the change of free energy—is the basis for their derivation of another equation which relates solubility to particle size:

$$dG = dNRT \ln \frac{P}{P_o} \qquad \text{(Eq. 9)}$$

where G = surface free energy, P = vapor pressure of a small particle, P_o = vapor pressure of pure drug, N = number of moles of substance in the bulk of drug material.

In Eq. 9, they (112) substituted γdA for dG, $(4\pi r^2)/V$ for dN, and $8\pi r dr$ for dA and obtained

$$RT \ln \frac{P}{P_o} - \frac{2\gamma V}{r} \qquad \text{(Eq. 10)}$$

where V = molar volume, γ = surface energy, r = radius of particle, A = surface area.

Since the same relationship applies using the solubilities, S and S_o, in place of P and P_o, respectively, Eq. 10 can be written

$$\log \frac{S}{S_o} = \frac{2\gamma V}{2.303\, RTr} \qquad \text{(Eq. 11)}$$

The greater solubility of smaller particles is a consequence of a larger molar free energy.

Model of Possible Particle-Size (SSA) Effects on Absorption Rate of a Drug—Consider a system composed of a segment of GI lumen in which a single drug particle is placed. Let

- C_s = concentration of the drug at saturation in the GI fluid (the concentration of the saturated boundary layer)
- C_m = concentration at the membrane site of absorption
- C_b = concentration in the blood (the other side of the membrane site of absorption)
- A_o = initial surface area of the particle at the time of its entrance into the GI segment
- t_o = initial time the particle enters the segment
- A = surface area of the particle at the time it leaves the GI segment
- t = time the particle leaves the GI segment
- a_o = total amount of drug dissolved at the time it enters the GI segment
- a = amount of drug dissolved at the time it leaves the segment
- f_a = agitation intensity factor
- x = mean distance from the center of the lumen to the wall of the lumen—the expected mean location of the particle
- N = total number of particles
- a_T = total amount of drug dissolved in the segment
- $a_{\text{tot.}}$ = total amount of drug dissolved in all segments

The assumptions are (*a*) passive diffusion is the absorption process; (*b*) the rate of absorption is limited by the dissolution rate of the particle.

Under these conditions, the absorption rate is equal to the dissolution rate of the particle, and $C_s >>>> C_m > C_b$. The dissolution rate, da/dt, is a function of the effective surface area of the particle at any time, t, the agitation intensity factor, $f_a(C_s - C_m)$—which includes the solubility effect and the time the particle remains in the segment. It is represented by the equation:

$$\frac{da}{dt} = R_1 (A_o - A)(C_s - C_m) f_a \qquad \text{(Eq. 12)}$$

The mean distance between the center of the lumen need not be considered if the steady-state is reached in a negligible amount of time. R_1 is a proportionality constant. The change in surface area $(A_o - A)$ decreases with time and approaches zero as a limit. The concentration gradient $(C_s - C_m)$ is approximately equal to C_s, a constant, since C_m is reduced to a minimum by the blood sink under the conditions existing. The agitation is assumed to be constant in a given segment of the GI tract. This factor may fluctuate considerably in a biological system in a given segment, but one has no control over this variable

except to assign it an average value which is assumed to be constant.

With the above considerations, the constants, R_1, $(C_s - C_m)$, and f_a, may be combined into one constant, K, the dissolution rate constant in the fluids of the GI segment. Substitution gives[1]

$$\frac{da}{dt} = K(A_o - A) \qquad \text{(Eq. 13)}$$

on rearrangement one obtains

$$da = K(A_o - A)dt \qquad \text{(Eq. 14)}$$

The integral of equation between the limits of t_o and t gives the total amount of drug dissolved in the segment.

$$\int_a^{a_o} da = K \int_t^{t_o} (A_o - A)dt \qquad \text{(Eq. 15)}$$

$$a_o - a = K(A_o - A)(t_o - t) \qquad \text{(Eq. 16)}$$

Since $a_o = 0$ at $t_o = 0$, one can write

$$-a = K(A_o - A)(-t) \qquad \text{(Eq. 17)}$$

Multiplying through by -1, one obtains:

$$a = K(A_o - A)t \qquad \text{(Eq. 18)}$$

With the assumptions made at the onset of this discussion, the amount of drug dissolved from a unit particle during the time it remains in the GI segment in question is a function of the change in surface area. In order to obtain the amount of drug, a_T dissolved from N particles of the same size, the equation would be

$$a_T = NK(A_o - A)t \qquad \text{(Eq. 19)}$$

If the particles are not monosized, the size distribution must be considered. In a log-normal distribution, the initial area of the mass median particle, as suggested by Higuchi *et al.* (73), would be a good estimate of the A_0 value, even though the number of particles would change to some extent with time (73). The more narrow the particle-size distribution, the better the estimate of the mass median particle area.

If a drug is absorbed from more than one segment of the GI tract, each having a different dissolution medium, then each set of constants would have to be determined separately. The total amount of drug dissolved in the GI tract, $a_{\text{tot.}}$, is found by the sum of the a_T values in each GI segment

$$a_{\text{tot.}} = \sum N_i K_i (A_{o_i} - A_i)t_i \qquad \text{(Eq. 20)}$$

where i refers to any GI segment. The stomach, duodenum, and segments of the small intestine, whose medium content is different from the others, could be used as hypothetical segments. It is recognized that, due to duodenal and intestinal secretions, there is a gradual change in any one segment (12), and an average content must be determined. It is also recognized that the emptying time of the stomach and the motility of other segments may be quite variable. The average time the particles remain in a given segment must be determined. Also, the change in the surface area of the particle in any given segment is not an easy determination. X-rays have been used to study movements of particles, but the size or surface-area determination would be a more difficult task. The values of each element of the equation would have to be based on the means of 10 to 15 determinations, especially where physiological variables are involved.

A word about averages. A treatment of a given disease or an abnormal condition is analogous to the make-up of our society. Our society is not made up of averages, but it is made up of individuals who deviate considerably from the mean. Furthermore, the things which are important to our lives at any given time period are not made up of averages, but they are made of those which serve to fulfil the needs of the individual at the time period in question. Thus, average behavior of biological systems under study are good guidelines, but they are not necessarily the all-important answer in an individual system.

Lest anyone get the idea that particle-size control and knowledge of the particle size are the answer to all the ills of dosage form production and drug availability for absorption, the author has this to add: particle size is like a wrench in the tool box. If it is needed to accomplish the goal, then by all means it should be used. If it is not needed, then it should be left in the tool box of knowledge until the occasion arises where it can contribute. In formulation and production one would suspect that particle size is considered regularly. In the case of its effect on drug availability, its use may be less frequent. However, where the consideration of particle size is essential, its effect should be known.

[1] Since the modified Noyes-Whitney equation indicates that the dissolution rate is proportional to the surface area, it is represented in this way in Eq. 13. If the effect of $(A_o - A)$ is some function of $(A_o - A)$ raised to some power e, *i.e.*, $(A_o - A)^e$, the equation would be linear as a log-log function.

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Keyphrases

Particle size, drugs—review
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