SYMPOSIUM

FINE PARTICLES IN PHARMACEUTICAL PRACTICE

CLINICAL AND PHARMACEUTICAL ASPECTS

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Introduction

While the fundamental factors required to explain the effects of particle size were first investigated in the last century, the technology of particle size is much more advanced in some industries, for example, the manufacture of paints, cement and ink, than in others; which, as yet, must include pharmacy. Scant attention has hitherto been paid to particle size effects, whether in official reference books or in text books of pharmacy, and a relatively insignificant research effort has been applied to this and related topics in pharmacy. The effects on therapeutic efficiency and on presentation, stability and control procedures has now been recognised.

The commonly accepted criterion for a dose, namely an amount by weight of a drug, is not the only factor necessary to ensure a consistent pharmacological response; the size of the particles of some drugs has a considerable bearing on their efficacy. In one instance at least, that of griseofulvin, control of fineness has led to a dosage scheme half of that formerly required.

The significance of the fineness of small particles in pharmacy can be conveniently considered from clinical, pharmaceutical, manufacturing and control aspects. In this review, those aspects of pharmacy in which the effects of solid particle size is important will be discussed.

Clinical Aspects

The infinitely complex biochemical system that we are seeking to influence by administering drugs comprises factors too numerous to allow their inter-relationship to be followed adequately. At this early stage in the understanding of the effects of particle size, we can only feel our way empirically towards the more effective presentation of drugs.

(Reviews and theoretical treatments of drug absorption and distribution have been made by Teorell, 1937, and Wagner, 1961).

Oral Therapy

Drugs absorbed in solution for systemic effect. Drugs are normally absorbed in solution from the gut. The absorption process can be rapid enough to make the solution rate of the drug the rate-determining step in the therapeutic process; limitation of absorption at this point is confined to drugs of low solubility.

There are many examples of drugs whose particle size influences their uptake from the gut. Corticosteroids and their relatively insoluble esters taken orally in tablets have been reported to give variable clinical results;

although a varying rate of disintegration was thought at the time to be the explanation, it is now accepted that the difference among preparations was due to differences in particle size.

Sulphur is practically insoluble in water; most of the dose of powdered sulphur given orally passes through the bowel unchanged (Wild, 1911), and only 10 per cent of the dose given to dogs was absorbed (Denis and Reed, 1927). Orally administered colloidal sulphur is rapidly and completely absorbed, to give peak urinary levels of sulphur compounds within 2 hr. Powdered sulphur (100 mesh) is poorly absorbed, the peak occurring 8 to 16 hr. after ingestion, at which time it is probably undergoing chemical modification in contact with the intestinal flora of the lower bowel (Maillard, 1911, Greengard and Woolley, 1940). A macabre demonstration of the efficient absorption of colloidal sulphur was obtained when concentrates of a water from Graham Springs, Kentucky, containing colloidal sulphur taken orally in large doses, caused intoxication and death within 5 min., indicating that the absorption of sulphur in this form is exceedingly rapid.

Sulphur, therefore, is an example of a drug whose particle size has a profound effect on efficiency of absorption, and may also modify the processes by which absorption occurs and can even lead to toxic effects.

Sulphonamides, in general, have a limited solubility in water. The greater efficiency of micro-crystalline sulphadiazine, each crystal approximately 1/350th the mass of normal crystalline material, has been demonstrated by Rheinhold, Phillips and Flippin (1945), and the marked influence of the effects of food or fasting state of the subject on uptake of the micro-crystalline form but not, apparently, of the control crystalline material noted. The importance of checking the effects of particle size on absorption under various conditions of fasting and food intake, and the need to arrange for doses to be given in precise relationship to food intake, should be recognised when planning such experiments.

The efficiency of absorption of the antibiotic griseofulvin depends on particle size, and a direct relationship between the logarithm of the specific surface and absorbability has been established (Atkinson, Bedford, Child and Tomich, 1962). The work, greatly aided by the availability of a precise method for assaying the drug in blood samples, led to appreciable savings in treatment cost, this being one of the justifiable reasons for doing research in this field.

Conflicting pharmacological responses can be obtained unless due attention is paid to the fineness of drug particles.

The physiological effects of *p*-hydroxypropiophenone (PHP) in animals were in dispute for a time. Whether the substance had oestrogenic activity or alternatively an inhibitory action on the secretion of gonadotrophic hormone was the problem. Impurities in certain samples were thought to explain the conflicting results, but the contradiction was finally resolved only when careful experiments were conducted on rats with samples of PHP specially prepared in a range of crystal sizes (Foglia, Penhos and Montuori, 1955). Although an initial preparation of PHP did not provoke oestrus or inhibit the action of the pituitary in rats, even

when administered in high doses for a long time, the same powder reduced to crystals of 2,000μ^3 or less produced the typical effects of an oestrogen. These small crystals when reconverted to larger ones (3,000 to 10,000μ^3) became inactive.

Drugs absorbed as solid particles. Bacteria pass through the wall of the alimentary tract, and particulate material can do likewise. Resin particles, 1–5 μ in diameter passed through the mucous membrane of the tonsil, pharynx and small intestine of the calf (Payne, Sansom, Garner, Thomson and Miles, 1960). Little of the dose was absorbed, but the factors governing such absorption have not yet been studied in detail.

Drugs acting locally in lumen of gut. Some drugs, administered orally, are required to exert their action within the lumen of the gut, e.g., anthelmintics, amoebicides, contrast agents and some antibiotics and sulphonamides.

Attempts to improve the efficiency of anthelmintics by reducing the particle size have led to conflicting possibilities. Although the primary objectives of higher solution rate for the drug in the gut and improved dispersion of the solid particles can be achieved, the consequences of the concommitant increased rate of absorption (and hence removal) from the gut must be borne in mind (Swales and Collier, 1940). Improvement in clinical efficiency may not result from increased solution rate; indeed, particle size reduction can reduce the efficacy of these drugs. Toxicity from the absorbed drug can become important when the particle size of the drugs intended to act within the gut is reduced.

Improved *in vivo* anthelmintic action of small particle phenothiazine is well established (Kingsbury, 1958); particles with equivalent sphere diameters less than 10 μ are desired, whereas particles greater than 20 μ in diameter have little anthelmintic action. Similar results have been obtained with bephenium hydroxynaphthoate and bephenium embonate, for which it appears that 30 μ is the limiting diameter for good anthelmintic effect (Newman and Axon, 1961). Presumably these insoluble salts of bephenium were chosen to minimise the absorption from the gut that might occur with more soluble salts.

A drug evaluated for use orally in the veterinary field is 4,4′-dinitrocarbanilide, for which particles of 3 to 5 μ have been shown to be less effective than those under 1 μ in diameter (Merck).

Barium sulphate for radiography of the alimentary canal should be fine but it is possible for extremely small particles to give rise to unexpected results. Small particle barium sulphate administered as an enema can enter intestinal glands and may be the cause of barium granulomas (Sasson, 1960). Similarly, silica gel particles have been shown to produce intestinal nodules in rats, and it seems likely that particle size of the silica will determine the extent of this occurrence (Desai, Burkman and Salisbury, 1958).

Parenteral Therapy

The fineness of the particles of an injected drug can influence the rate of absorption from the injection site, and this has been recognised for

zinc insulin in the British Pharmacopoeia, although the physical nature of the insulin is also highly important. Amorphous zinc insulin produces a rapid effect, whereas crystalline zinc insulin in suspension produces a prolonged effect, particularly if care be taken to ensure that a substantial proportion of the crystals are longer than 5 μ (Hallas Møller, 1954).

Particle size of procaine penicillin is important in injectable suspensions, the extent of the effect depending on the nature of the vehicle used. Arachis oil, as a gel with aluminium stearate, prepared so as effectively to coat the procaine penicillin particles with a hydrophobic protective layer, gives prolonged blood levels with small particles of procaine penicillin, preferably below 5 μ (Buckwalter and Dickison, 1958). On the other hand presentation of procaine penicillin in extremely small particles in an aqueous suspension could have the opposite effect of increasing the rate of uptake of antibiotic from the site of injection.

The particle size of drugs in solution for injection containing high concentrations of solid may influence blood levels by modifying viscosity and thereby minimising spread of the injection in the muscle (Ober, Vincent, Simon and Frederick, 1958).

The relationship between crystal size and oestrogenic activity of *p*-hydroxypropiophenone mentioned earlier, applies equally to the same compound injected subcutaneously (Foglia, Penhos and Montuori, 1955).

Modification of the release of drugs from injected suspensions by control of particle size has been applied to drugs that cannot readily be prepared in crystalline form (Organon). To obtain particles of the required size, the drugs (adrenocorticotrophic, gonadotrophic and thyrotropic hormones, testosterone and heparin) were first compressed to glassy solids by the application of high pressures and subsequently reduced in size by milling and graded by sifting.

Rectal Therapy

Particle size can influence the absorption of drugs administered in rectal suppositories. Maximum rate of transfer from the oily suppository vehicle to the aqueous mucosal fluids can be achieved by choosing a vehicle in which the drug has a low solubility and also by using a dispersion of fine particles to ensure that saturation is maintained in the melted suppository (Reigelman and Crowell, 1958).

Topical Treatment

Many ointments contain dispersed particles of drug that exert their effect by solution in the base and transfer by partition to the skin or wound exudate.

The processes involved in securing therapeutic effect when such ointments are applied to the skin are: (i) solution of drug in base; (ii) diffusion of drug through base to skin; (iii) transfer of drug from base to skin; (iv) diffusion of drug through skin.

Maximum possible concentration of the drug in solution in the base at the ointment-skin interface is desirable, to encourage transfer of the

drug from the ointment to the skin. Maintenance of maximum concentration in the ointment at the interface depends on the relative rates of processes (i) and (ii) compared with processes (iii) and (iv). Presentation of the drug in fine particles in the ointment base minimises the possibility that solution and diffusion processes in the base will limit the clinical response. That this is so can be appreciated when it is remembered that corticosteroid ointments containing as little as 0·01 per cent w/w of dispersed drug are now being used.

Increased inhibitory effects have been demonstrated for ammoniated mercury and yellow oxide of mercury when present as small particles in standard ointment bases (MacDonald and Himelick, 1948). Similarly, the activity of calomel ointment has been shown to depend on the particle size of the dispersed drug.

The treatment of superficial burns with sulphathiazole in microcrystalline form gives higher rates of solution, improved dispersion and freedom from clumping or caking on the burn (Sharr, Ferguson and Nova, 1942). The same type of concentrated sulphathiazole magma of fine particles gave much improved results in impetigo contagiosa when compared with conventional dusting powders or ointments containing the same drug (Harris, 1943).

Some ointments, such as those containing calamine or zinc oxide, are required to provide protective and reflective properties. For these the reflective properties will depend on the particle size of the dispersed material, although for these preparations in particular the effect is not of great practical importance; thus calamine, being cheap, is not normally used at limiting concentrations.

Respiratory Tract Therapy

Treatment of the respiratory tract with aerosols containing solid particles is well established, especially for corticosteroids. The drug may be required to act in the trachea, bronchioles or alveoli. The mass of an individual particle largely determines how far down the orobronchial tree it will travel. Careful formulation is therefore needed if the steroid is to penetrate to the desired site and exert maximum and consistent effect. For clay dusts, maximum retention in the upper respiratory tract occurs when particles are 5 μ or more in diameter but particles less than 1 μ in diameter are not retained. On the other hand, satisfactory retention in the alveoli was achieved with much smaller particles, thus providing a basis for selective distribution of drugs according to particle size.

For xylocaine used in a pressurised aerosol, particles of about 5 μ diameter best ensure deposition on the mucosa throughout most of the tracheobronchial tree. Deposition on the pharyngeal mucosa occurs with larger particles, or in the alveoli if smaller particles are used (Tomashefski, Nelson and Christoforidis, 1962).

Pharmaceutical Aspects

The pharmacist is the person best fitted to co-ordinate and interpret all the observations about particle size of drugs that can be collected.

There are, however, certain features, for example, particle size, of particular types of products that he alone will have to consider, assessing their significance and, if necessary, taking steps to control them.

Powders

The need to control the particle size of substances of limited solubility in aerosols, insufflations, dusting powders, and so on, can be forecast from results obtained with insecticides, which offer many instances of its importance.

Thus the toxicity of Paris Green particles to the Mexican leaf beetle has been shown to depend on particle size; Paris Green with an average particle diameter of 1·1 μ caused higher mortalities than did particles of average diameter 12 μ which were more effective than particles of diameter 22 μ. It was apparent that, for clear-cut results, it was important to ensure that each sample contained a narrow distribution of size of particles (McGovran, Cassil and Mayer, 1940).

Some substances are presented as powders to be made into extemporaneous solutions or suspensions by the clinician or pharmacist. Clearly there is a need for such products to behave uniformly and disperse readily in the shortest possible time. The character of the film of saturated solution at the solid-liquid interface largely determines dispersion and solution characteristics. For solids whose saturated solutions are of a syrupy consistency, too great a reduction in particle size is to be avoided, because the interfacial film of dissolving drug can cause the particles to adhere together, which will greatly reduce solution rate. Insoluble components, such as procaine penicillin, suitably dispersed as fine particles along with the more water-soluble components, such as streptomycin sulphate, minimise these difficulties.

The flow properties of powders depend on particle size, shape and density (Train, 1960). Reduction in particle size results in poorer flow properties, which means that blending and mechanical subdivision of fine powders is usually difficult. Griseofulvin and procaine penicillin are particularly troublesome to feed to mills or to fill into vials in small amounts mechanically at high speed.

Extremely fine powders with high specific surface areas can adsorb relatively large quantities of water. Synthetic silicates can adsorb three to four times their weight of water and yet behave as dry free flowing powders (Johns Mansville Celite Division, 1960).

Tablets

The fineness of a drug affects the likelihood of obtaining a satisfactory distribution of drug in each dose of powder or tablet preparation. Train (1960) has calculated that if a blend of two powders in equal amounts is required to be made such that there are 997 chances out of every 1,000 that either component will be within ± 10 per cent of the true concentration, that is, actually between 45 to 55 per cent concentration, 800 particles must be present in each dose. If the permissible limits are set at ± 1 per

cent of the intended value of 50 per cent, then 80,000 particles per dose would be required, and for a drug present at a nominal concentration of 1 per cent at least eight million particles per dose would be needed to maintain the desired limits of ± 1 per cent of the stated content.

The apparent intensity in colour of a powder depends on its particle size; indeed for coloured drugs, presented as uncoated tablets, it may be necessary to place some control on the particle size to avoid too much variation in colour from batch to batch.

Pharmacists use colour to make products more attractive to patients. Dyes adsorbed on aluminium salts as lakes are gaining in popularity for colouring coated or uncoated tablets. The lake should be in the form of fine particles to achieve uniform dispersion of colour. Different batches of coloured powder mixtures will vary in colour if the particle size of the highly coloured components are not controlled. Samples of carbon black with specific surfaces ranging from one to tenfold showed a similar difference in tinting strength when tested by a standard method (Herdan, 1960).

Presentation of finely powdered substances in tablet form requires the tablets to disintegrate so as to provide the original powder for solution. The criterion for a satisfactory conventional tablet is that the blood levels of drug obtained should be the same as those obtained by administration of an aqueous suspension or, say, of cachets containing an equivalent dose as a powder.

Suspensions

The viscosity of suspensions with high solid : liquid ratios depends on the particle size of the dispersed solid. Smoluchowski (1916) claimed that viscosity depends on, among other things, particle diameter and increases with decreasing particle size: this effect was confirmed by Kruyt (1922), for sulphur sols by Oden (1931), for ultramarine particles of around 5 μ diameter by Pryce Jones (1947) and for suspensions of metal carbonates and sulphates (10 to 40 μ range in diameter) in water by Ward and Kammermeyer (1940).

The relative viscosity of suspensions increases as the size ratio of the dispersed powder decreases, at least for suspensions containing more than 25 per cent of solid by volume. Styrene-butadiene latices consisting of spherical polymer particles have been examined; the conditions required for minimum viscosity were that the distribution of latex particle size should be as wide as possible and that the mass of the larger particles should comprise about 75 per cent of the total mass of the particles. This conclusion is in agreement with theoretical calculations showing that a minimum void volume is obtained when approximately 70 per cent of the mass of the particles is contributed by the larger of two particles. The degree of anisotropy of the particles in suspension may mask the effect of the size ratio of the powder; this is particularly so for particles of highly irregular shapes (Ward and Whitmore, 1950). A pharmaceutical system in which anisotropy of the particles masks the effect of size ratio is Injection of Propyliodone, B.P., particularly the aqueous injection, which

contains 50 per cent w/v solid material prepared by milling needle crystals of propyliodone.

Adjustment of particle characteristics in a suspension can enable a minimum viscosity to be obtained, but such a system will not necessarily exhibit minimum thixotropy.

Particle Size and Solubility

The solubility of small solid particles in a liquid depends on their size. Small particles are in equilibrium with higher concentrations of solute than are larger particles.

The relationship between the solubility of amorphous silica and its particle size has been determined and shown to be expressed by

$$\log S = 4{\cdot}80 \times 10^{-4} A - 2{\cdot}043$$

where S = solubility per cent at 25°; and A = specific surface $m.^2/g.$ (Alexander, 1957).

The higher solubility of small particles, and the fact that solutions are in equilibrium with one size of particle only, must be borne in mind during experimentation (Higuchi, Rowe and Hiestand, 1963).

Phenolphthalein is an example of a drug for which the colloidal form has been shown to have a greater solubility than the crystalline form and also to be more active in producing its specific effect of bowel evacuation (Fantus and Dyniewicz, 1935).

Noyes and Whitney (1897) conducted a simple and elegant experiment on the rate of solution of benzoic acid and lead chloride and concluded that the rate at which a solid substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution. They regarded the solids as being surrounded by an infinitely thin film of saturated solution and the process of solution being the dispersion of this film of saturated solution throughout the bulk of solvent.

The greater the available surface the greater the proportion of saturated film, hence the greater the solubility rate. Wilhelm, Conklin and Sauer (1941) calculated an effective diffusion film thickness of 0·016 mm. for sodium chloride crystals in specified conditions of agitation.

The different concentrations of solute in equilibrium with small and large particles of suspended solid results in migration of solute by diffusion from the "atmosphere" surrounding small particles to those of larger particles, the net result being that larger particles tend to grow in size at the expense of the smaller. This, the Ostwald effect (Ostwald, 1900), can cause the specific surface of powders in liquid suspensions to change on storage.

For each solid there will be a maximum size, depending on the composition of the suspending fluid, above which the effect will not be detectable. For gypsum the effect disappeared for particles above 5 μ diameter (Jones and Partington, 1951). The tendency for sulphadiazine crystals to grow in aqueous suspension has been examined mathematically (Hasegawa and Nagai, 1958).

Recent advances in instrumentation have led to improved methods for examining crystal growth and methods sensitive to less than 0·1 μ have been applied to methyl prednisolone (Higuchi and Lau, 1962).

Stability of Fine Particle Drugs

Reduction in particle size can cause faster deterioration of a solid drug stored in the "dry" state. The toxic components of pyrethrum deteriorate most rapidly upon exposure to light and air when the insecticide is finely ground. A measure of protection against the effect of light was obtained by coating pyrethrum particles with tannic acid, titanium dioxide or an antioxidant (Smith, 1936).

The decomposition of aspirin in the solid state has been investigated. A mechanism for this deterioration has been postulated, involving an initial adsorption of a water layer on the particle surface and diffusion of aspirin, with subsequent hydrolysis in the surface solution. Particle size is therefore likely to affect the decomposition (Leeson and Mattocks, 1958).

Manufacturing Aspects

Chemists and physicists both need to contribute their specialised fundamental understanding of natural phenomena towards the more efficient working of production processes. We are better equipped to understand what is going on in the manufacturing plant than in the human body.

Milling

Pharmacists frequently mill powders; the hazards involved in such processes must be kept in mind and suitable precautions taken. Atmospheric dusts of fine powders may explode violently given the proper concentration of solid and a source of ignition which the powder itself may provide by virtue of static electrical charge. The rate of the explosive reaction depends on the particle size of the solid phase. The relative inflammability of potato starch increases slowly as the particle size is reduced from 100 μ to 40 μ in diameter, but below this size the hazard rises steeply. For oat and corn dust and wheat flour inflammability hazards appear to be maximal just below diameters of 40 μ (Boyle and Llewellyn, 1950).

The ability of a powder to sustain an explosive reaction can be measured in the laboratory, and a classification for a particular powder may be obtained by submitting samples to the Safety in Mines Research Establishment, H.M. Factory Inspectorate, Ministry of Labour and National Service, Harper Hill, Buxton, Derbyshire.

For many pharmaceutical purposes it is important that the bulk density of a powder preparation should not fluctuate too widely. Dr. Heywood, in his conjoint paper, refers to the relationship between the size and packing of particles and the effect on the bulk density of a powder. Pharmacists experienced in the devices of production sometimes utilise the principles of inter-particle packing by subjecting to a further size reduction a proportion of a batch of powder with an unacceptable low bulk density

finally reblending with the remainder of the batch to yield a mixture of increased bulk density.

The influence of the type of mill and the conditions of their operation on the particle size of powdered materials is outside the scope of this review.

Polymorphic Solids

The process of reducing solids to fine particles can modify crystalline structure, which in turn can influence both solubility and rate of solution. For example, methyl prednisolone in one physical form is 1·8 times as soluble as another physically more stable form (Higuchi, Lau, Higuchi and Shell, 1963). The several forms of oestradiol, barbiturates and aluminium trihydroxides are readily interconvertible by apparently innocuous grinding techniques (Smakula, Gori and Wotiz, 1957, Cleverly and Williams, 1959, and Yamaguchi and Sakamoto, 1959). The infra-red spectra of steroids, benzoic acid and carbohydrates have been shown to change according to the method adopted for preparing the sample for examination (Roberts, 1957, Farmer, 1955, and Barker, Bourne, Weigel and Whiffen, 1956).

Analytical Considerations

Much that is relevant to analytical control methods is contained in the conjoint paper by Dr. Heywood. The analyst has a vital role to play in helping to devise and choose methods of determining particle size so as to control adequately particular characteristics as required.

The specific surface (air permeability) of griseofulvin has been found to correlate with blood levels and this variable is convenient to use for control purposes. Methods of determining specific surface area by air permeability, although not a measure of total surface area, can usually be expected to be adequate for drugs designed for oral use. Indeed, other methods, for example those involving nitrogen absorption, may measure powder surface not readily available for dissolution in an aqueous system; thus fissures and minute faults in crystals are measured by nitrogen absorption, but not by air permeability.

The possibility should always be considered that two powdered samples of a drug with identical specific surface areas but with entirely different distributions of particle size may give different rates of absorption from the alimentary canal.

Table I sets out comparative dissolution rates for two "theoretical" powders with the same specific surfaces. The rate of solution expressed per unit area of particle surface is assumed to be identical for large and small particles. Dose A comprises one hundred particles of 10μ in radius, Dose B contains one oversize particle, $40\,\mu$ in radius, with a sufficient number of a calculated second size to satisfy the requirements that the specific surfaces of both samples should be virtually identical.

Thus, a sample of a drug with particles of different sizes will dissolve more slowly than the same dose of drug containing particles of one size only, each sample having the same initial specific surface area. In

practice this means that, for oral use, drugs of controlled specific surface should preferably have a minimum distribution of particle size.

The influence of distribution of particle size on efficiency of absorption from the gut will be maximal for drugs given in large doses and absorbed solely in the upper parts of the alimentary tract. This effect was found not to be significant for griseofulvin, which is absorbed throughout the gastrointestinal tract (Atkinson, Bedford, Child and Tomich, 1962),but this is not true of other drugs. Crystals of phenothiazine have been seen in the faeces of sheep (Gordon, 1956). If, for the drug used as an example in the table above, the physiological conditions were such that particles of 10 μ radius were the largest that could be dissolved before the drug passed the "zone of absorption" in the gut, dose B would be only 75 per cent as effective as dose A.

TABLE I

Dose	Number of particles (spheres)	Particle radius (microns)	Total relative surface area per dose	Total relative weight per dose	Relative weight remaining after dissolution of increments of radius (μ)						
					−1	−2	−3	−4	−6	−8	−10
A	100	10	10,000	100,000	72,900	51,200	34,300	21,600	6,400	800	0
B	1	40	1,600	64,000	59,330	54,880	50,650	46,660	39,310	32,750	27,000
	457	429	8,412	36,090	16,280	5,487	981	0	0	0	0
			10,012	100,090	75,610	60,367	51,631	46,660	39,310	32,750	27,000

Control of particle size may be required for other reasons, such as to avoid needle blockage with injectable suspensions or to ensure reproducibility of viscosity in a suspension. For the former requirement it is usually adequate to supplement the determination of specific surface by a simple test for oversize particles, for example, by sifting an appropriate weight of powder as a suspension in a non-solvent liquid through, say, a 325 or 250 mesh sieve and examining the residue, if any, under the microscope.

Control of fine particle characteristics for suspension products containing high solid-liquid ratios can become complicated if an attempt be made to measure mean size, size distribution and degree of anisotropy of the particles and then relate these to ultimate effect on the suspension. The relationship between the three variates is complex and not fully understood; it is probably different for every suspension. In these circumstances the quality of the fine particle powder may best be controlled by setting up an empirical test embodying the essential features of the product system (omitting stabilisers, preservatives and so on, but including wetting agents, if used) and measuring viscosity directly in the manner used for the final product.

Conclusion

Particle size is important in many branches of pharmacy, so much so for some drugs, the marginally soluble ones, that it will not be inapt to consider the subject as a new technology. It has as much claim to this as rheology, in America the term "micromeritics" has already appeared.

To understand the significance of the many effects of fine particles requires explanations in physico-chemical terms. Examination of the effects of fine particles in pharmaceutical systems can provide fruitful and rewarding subjects for research.

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