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PHYSICO-CHEMICAL PROPERTIES OF PARTICULATE MATTER

BY

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ABSTRACT

In dealing with particulate matter, it is important to distinguish between properties on the microscopic level and attribute bulk properties. It is the latter with which the practitioner is concerned, but knowledge of the former is of utmost importance.

The attribute properties of particulate matter in the manufacturing of solid state pharmaceutics are blending propensity, compressibility, powder flow, apparent density and compression potential.

INTRODUCTION

In the typical scheme of R & D, one usually begins ones work on a very small scale and then later attempts scale-up. It is advantageous to obtain as much information regarding the parameters that are important in scale-up as possible. This is sometimes not possible, but often small scale experimentation will give information which is valuable in the change of scale.

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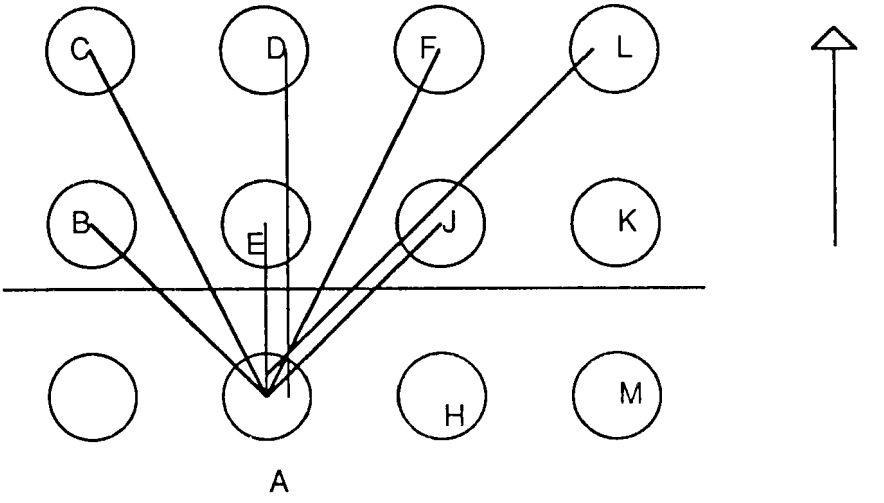

Fig. 1. Schematic of cohesive stress.

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For example, the amount of granulating fluid necessary to wet granulate a product is smaller than proportional amounts calculated from laboratory batches. The aim in this writing is to assess predictable properties of solids.

The properties which will be discussed are cohesion, and its influence on blending and flow, micromeritics, crystallization and finally the influence of water on some select properties.

COHESION

Of the mentioned properties, blending propensity and powder flow are directly linked to the cohesive force or the cohesive stress exterted between the particles in the bed. The concept of cohesion is best explained by Fig. 1, which is somewhat simplified.

The cohesive force is proportional to the mass ($\rho\pi d^3$) of the particle (e.g., A in the figure) and inversely proportional to the distance squared. ρ is the true density of spheres of diameter, d. If the spheres are touching each other, then the distance is a multiple of d. And, if summed over all the

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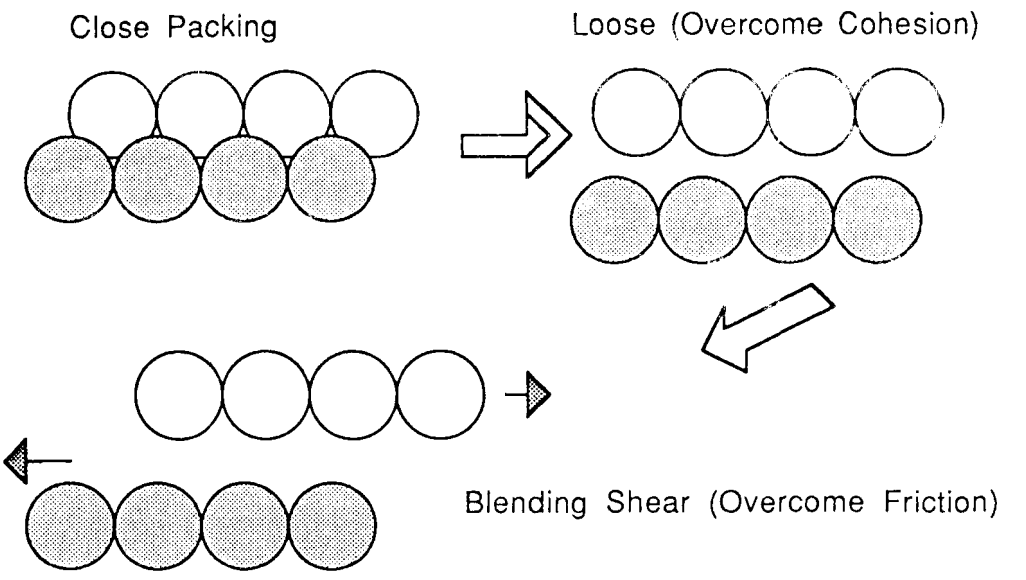

Fig. 2. Effect of cohesion and friction on the blending process.

particles above the line, the total upward force on the particle is

$$\text{Force} = (\rho\pi d^3)/(Bd^2) = q'd$$

where B is a number (a type, Madelung constant). The stress (i.e. the force per area) is then:

$$\tau = q'd/(\pi d^2) = q/d$$

i.e. the cohesive stress increases with decreasing diameter. It, of course, increases with closer packing, and it is a well known fact that fine powders stored in drums frequently cake, particularly in the bottom, where the force from the powder above have compressed the particles to closer distances.

Cohesive stress, in some shape, manner and form, is part of the strength of a tablet, once it is formed; although, as shall be seen shortly, the elastic limit is a more important factor in the creation of the tablet.

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BLENDING

In blending, which in Fig. 2 is simplified as binary blending, cohesion directly plays a role because interparticulate friction will have to be overcome. Overcoming the interparticulate friction is achieved by applying a sufficient blending stress. The first step involves bed expansion[1] which is then followed by the movement of layers of particles and later by the movement of individual particles relative to these layers, and other particles.

Extensive blending theories have been developed for non-cohesive blending[2]. The degree of blending during a blending process is characterized by the standard deviation of assays of samples taken at N parts of the mixer. In present day validation, the sample size is frequently that of the dosage form, but this often creates a bias because of the physics of the thief with which the sample is taken. Larger samples can rationally be used and (a) either the entire sample assayed (the best method) or (b) a representative "completely" blended subsample taken and the total amount obtained by proportionation. The standard deviation between larger samples will have to be adjusted to that of the smaller sample.

Assuming that a sample the size as the dosage form is taken, then the relative standard deviation, σ, obtained is a function of blending time, t, by the following equation:

$$\ln[(\sigma-\sigma_\infty)/(\sigma_0-\sigma_\infty)\ ] = -kt$$

where σ_0 is the relative standard deviation at time zero and σ_∞ is the final relative standard deviation given by:

$$\sigma_\infty = 100[(1-x)/(xN)]^{1/2}$$

x is the fraction of drug and N is the number of particles in the mixture. The initial relative standard deviation, σ_0, is given by

$$\sigma_0 = 100[(1-x)(x)]^{1/2}$$

k is a blending rate constant, which is maximum at x = 0.5 (where it equals k_{50}) and depends on x (where $x < 0.5$) by:

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$$k = k_{50}\, x \qquad x < 0.5$$
$$k = k_{50}\, (1-x) \qquad x > 0.5$$

When x is small ($0.01 < x < 0.1$), then preblending is resorted to. The amount of preblend, B, [3] is optimally:

$$B = x^{1/2}$$

In order to conform with the USP, blending must be continued until the relative standard deviation is less than 6% when comparing10 samples each of a size equivalent to the unit dose.

Non-cohesive blending rate constants are a function of particle size, and particularly of the relative particle size of the two blended fractions. This is demonstrated in Fig. 3.

It is assumed, for the moment, that the two ingredients, A and B, that are being blended, each individually, are monodisperse, i.e. all the A particles have the same size, d_A, and all the B particles have the same size, d_B. However, d_A need not equal d_B. A, for instance, could be 30/40 mesh and B could be 10/20 mesh.

The most rapid blending occurs when $d_A = d_B$. Rapid blending also occurs when $d_A < d_B$ and is so much smaller that it will percolate (the first situation shown in Fig. 3). When it cannot percolate then blending rates are small, and the segregation potential large. In the case of percolating powders, the segregation potential becomes large if there is more A present than will fit in the interstices between B spheres (i.e. the B spheres are now suspended in a bed of fine A spheres). The lowest segregation potential occurs when there is just enough of A to fit in the interstices of B, and this occurs[4] at the maximum apparent density of the binary system of A and B.

An example[5] of this is shown in Fig. 4.

In cohesive blending high intensity mixers must be utilized, to assure that aggregates (caused by the cohesion) are broken up. This is accomplished by guiding all the powder through an area (impeller area) where the shear is large.

In cohesive blending, the random mixing equations do not necessarily hold, and when mixing is performed between a fine and a coarse powder, then ordered mixing occurs. Here small particles adhere to larger ones, and will not segregate due to cohesion. This is also accomplished by wet granulation.

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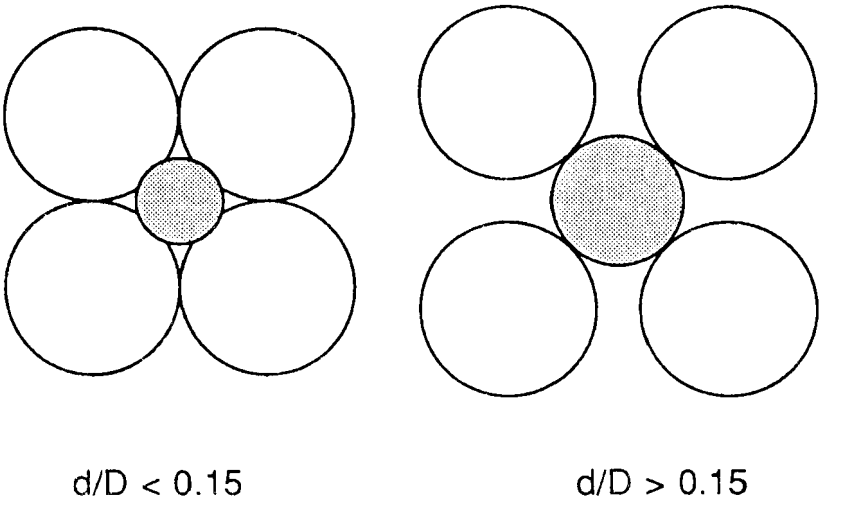

Fig. 3. Percolation.

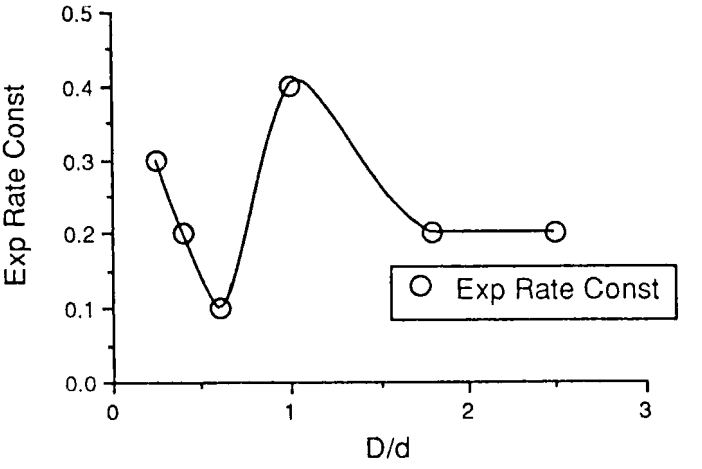

Fig. 4. Effect of diameter ratio of two powders on the non-cohesive blending rate constant.

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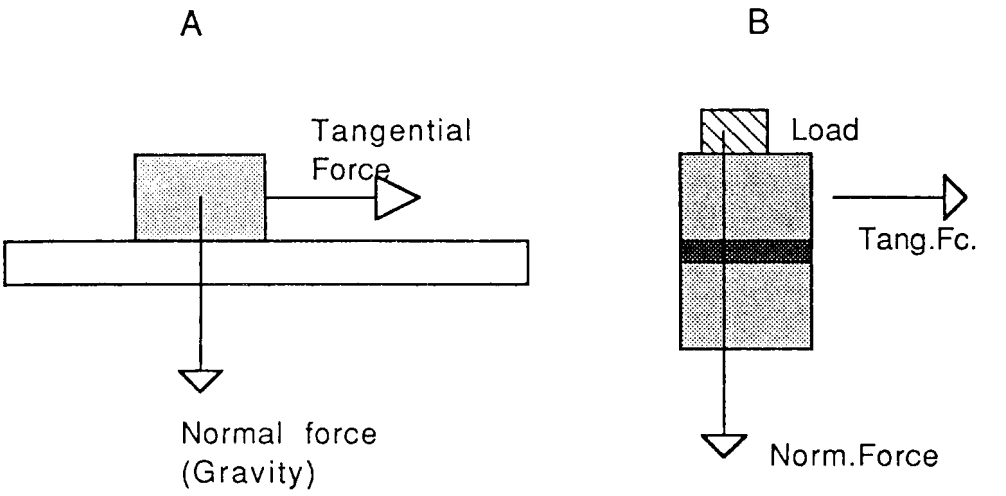

Fig. 5. Definition of internal friction.

In early years, a method for estimating both cohesion and internal friction was the so-called repose angle. When a powder is allowed to flow through a funnel, then it will deposit itself on the support below in a cone with a characteristic angle, α, the so-called repose angle. It is useful, at this point, to define the coefficient of internal friction, μ.

If a body is supported by a horizontal plane and is subjected to a downward (normal force, e.g. gravitional) force, σ, then it will take a tangential force, τ, to move it horizontally. The relation between the two forces (or stresses) is given by:

$$\tau = \mu\sigma$$

where is the frictional coefficient. The same argument holds between two planes of powder, as shown in Fig. 4B.

Early attempts to quantitate the cohesion and friction of a powder sample was by means of the so-called repose angle. (Fig. 6) From a force parallelogram[6] it can be shown that

$$mg \sin \alpha = \mu [C + mg \cos \alpha]$$

where m is the mass of the particle, and g is gravitational acceleration. The method is poorly reproducible, and suffers from being one equation with two unknowns.

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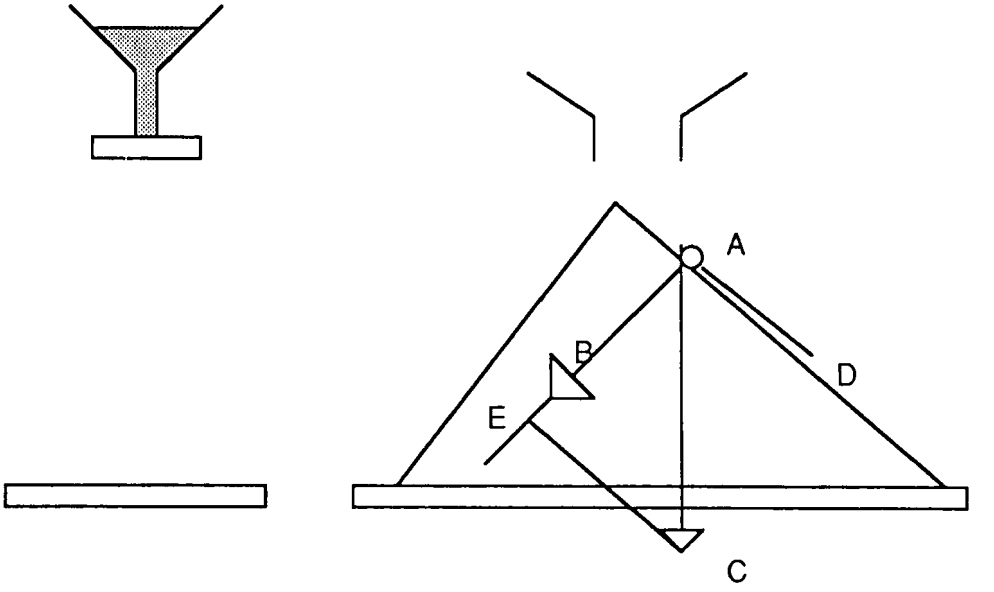

Fig. 6. Measurement of the repose angle, α.

JENIKE LOCI

A better, and a now accepted way of obtaining values of the cohesive stress is by way of Jenike shear cells. The principle of such a cell is shown in Fig. 7 and 8. The main feature is that a powder bed is sheared in a given plane. The manner in which the cohesive stress is obtained from this is by changing the normal load. The maximum load is applied first, and sequentially the load is lightened. The minimum load is, of course, the weight of the upper bed plus the ring. A typical locus has the appearance of Fig. 9

The manner in which the cohesive stress is obtained is as follows. It is tacitly assumed that the intersect with the x-axis of the locus is the tensile strength, T, of the powder, hence the locus with appropriate nomenclature would look as shown in Fig. 10. Such a plot of σ versus τ is called a yield locus (Jenike locus). The graph can be linearized by iteration to fit the following equation:

$$\ln[\tau] = (1/N)\,[\ln(\sigma+T)]$$

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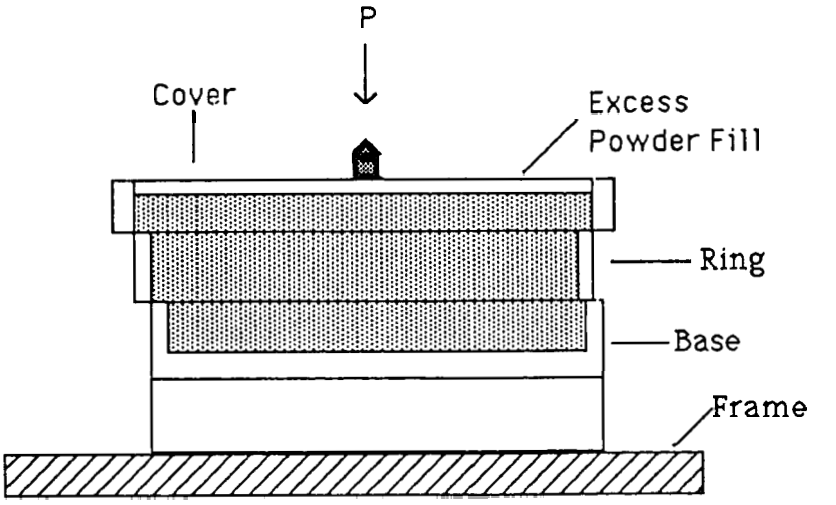

Fig. 7. Diagram of a Jenike shear cell arranged for preconsolidation.

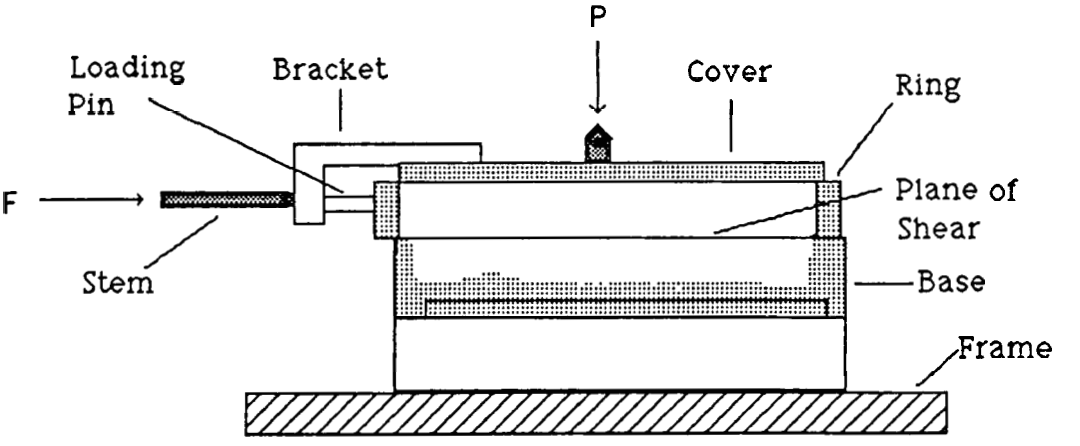

Fig. 8 Diagram of a Jenike shear cell ready for shearing.

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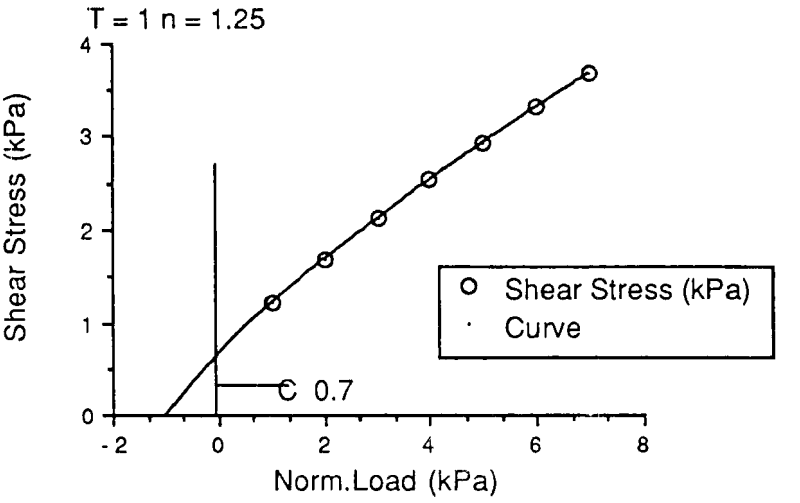

Fig. 9. Typical Jenike locus for cohesive material.

With an iterant value of T = 1 kPa, the following data in column 3 and the data in Fig. 10 result.

If C and T are interdependent, then iteration should involve only one iterant, and knowledge of the functionality. The early assumption by Ashton[7], 1965 that was made was that C = 2 T since one forms two surfaces when one pulls the bed apart, each with cohesion, C.

Crooks et al.[8] and Hiestand[9] (1974) showed that the propor-tionality between C and T can range from 0.2 to 4. It is therefore more logical to treat the data, as a first approximation, assuming that

$$C = \eta T$$

and assume η to be unknown. Geoffroy and Carstensen published data[10] for the four different substances at several mesh cuts and proposed as a best general relation between C and T that of:

$$C = \alpha T^{\beta} \qquad \text{or} \qquad \ln[C] = \beta \ln[T] + \ln[\alpha]$$

where α and ß are constants. This is demonstrated for lactose in Fig. 11.

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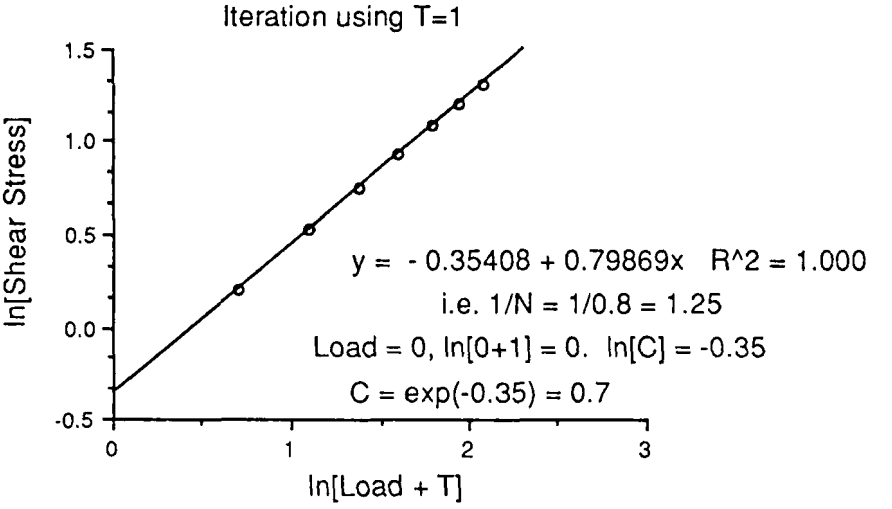

Fig. 10. Data from Fig. 9 treated by the equation $\ln[\tau] = (1/n)\ln[\sigma+1]$. i.e. using T=1 as an iterant.

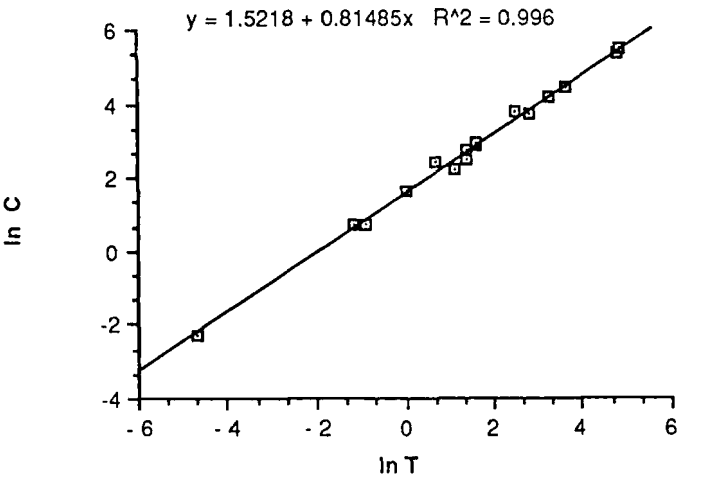

Fig. 11. ln T vs ln C for lactose (45 μm) at all preconsolidation loads. (All iterated T values (and corresponding C values) for Lactose (45 μm) at all preconsolidation loads. The slope = ß and intercept = ln α.

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Table I. Fit of $C = \alpha T^{\beta}$ for various substances, regardless of particle size.

Excipient	ß	SEM
Lactose	0.70	0.03
A-Tab	0.83	0.03
NaCl	0.83	0.03
Tri-Tab	0.74	0.02

It is worthwhile to note that the loci are a function of:

1. consolidation pressure (apparent density)
2. particle size
3. material

The four materials used were lactose, A-Tab (anhydrous dicalcium phosphate), sodium chloride, and Tri-Tab (tricalcium phosphate). Four particle sizes were used. (1/2 as is, 1/2 milled and sieved) Four preconsolidation pressures were used per particle size. Each locus was repeated four times.

The values of β found are shown in Table I. It is noted that they are fairly dependent on theparticle size and the material, with an average of about 0.77.

The value of α, however, was found to be a function of particle size as shown in Fig. 12. These findings are compatible with the theories of Cheng et al. (1968).[11]

POWDER FLOW

The rate with which a powder will exit a tube of a certain diameter (or enter a cylinder of such a diameter) is denoted the flow rate of the powder, given the geometry of the flow constraint. This influences (a) the rate with which a powder will transfer from a powder hopper to a feed frame and (b) how a powder will enter a tablet die.

It has been shown[12] that powder flow through a funnel are a function of particle size by a parabolic relationship. This is shown in Fig. 13, which is reproduced from data published by Carr[13].

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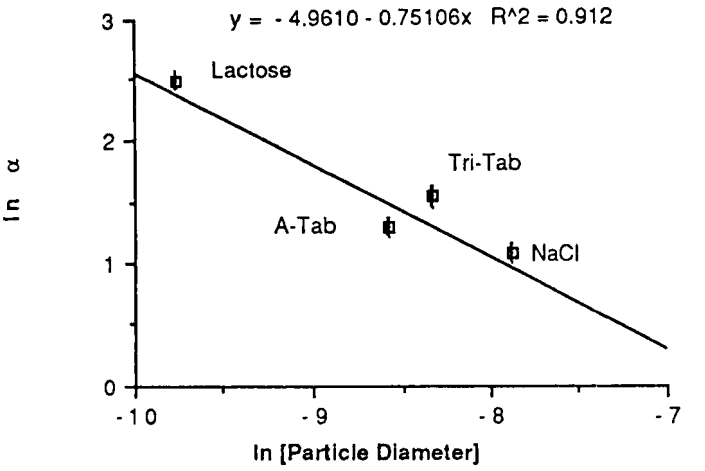

Fig. 12. ln α vs ln [particle diameter] for the four lubricated materials. These data can be averaged since no differences could be shown at various lubricant concentrations.

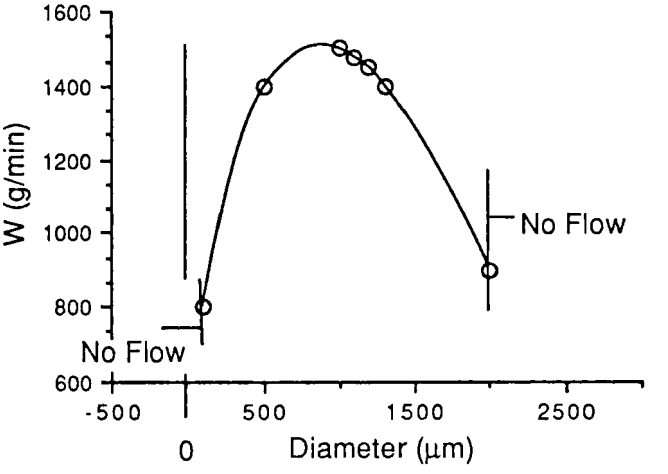

Fig. 13. Flow rate as a function of particle diameter. Graph constructed from data published by Carr.

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It is noted that at a certain lower limit there is no flow. This is due to the fact that the cohesive forces suffice, when acting over the diameter of the efflux tube, to offset the gravitational forces[14].

In fact the flow is a function of the diameter of the efflux tube , D, by the following equation:

$$W = f D^{2.5}$$

where f is a constant.

Above a certain diameter, flow is no longer possible either, and that is due to the particles meshing and forming a geometrically (althought not statically) stable bridge. This usually happens when the particle diameter is close to 1/10 of the efflux diameter, D. Danish and Parrott[15] have suggested that the reduced diameter, d/D, be used in descriptive flow, and this suggestion is quite sound.

It is noted that flow when measured through a funnel might apply to the flow from a hopper into a feed frame, but will not duplicate the situation of flow of powder from the feed frame into the die. This latter is denoted dynamic flow and has been discussed and measured by Laughlin et al.[16]

Flow is also affected by surface smoothness, and particle shape. In the treatment above, it has been assumed that the particles could be approximated by spheres. This, of course, is only approximately true for wet granulated materials, and far from truth where actual powders are concerned.

Two approaches have been used in describing the effect of surface roughness and surface shape. The first approach is (akin to that taken of Ridgway and Rupp[17]), where particles are assumed to be isometric, i.e. they can be described by an equation of the following type:

$$A = \Gamma v$$

where A is the surface area of the particle, v is its volume and Γ is the shape factor. This can be extended to a monodisperse powder mass by the appropriate introduction of the number of particles in one gram of powder.

Many factors, such as bulk density, repose angle and flow rates are functions of the shape factor. For instance, smoother and rounder particles will flow more faster.

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Another approach has recently been proposed in the pharmaceutical sciences, i.e. that of description by fractal geometry[18]. Here the surface area, A, is assumed to be a function of the particle diameter, d, in a certain range of particles (d_{min} to d_{max}) by a relation:

$$a = kd^n$$

where for a sphere, of course, $k = \pi$ and $n = 2$. This, of course, can be determined experimentally by correlating surface areas with diameters.

MICROMERITICS

Surface areas and particle sizes are of importance in pharmacy, partly due to factors already mentioned. The cohesion, as mentioned, is a function of the fineness of the powder.

Surface areas are usually determined by gas adsorption (nitrogen or krypton), and in this it is assumed that the isotherm is a BET[19] isotherm. Moisture isotherms are also of importance, since (e.g. in the case of montmorillonite and of microcrystalline cellulose) the two figures can differ by several orders of magnitude. In this case there is the possibility of moisture penetrating the particle and positioning itself in molecular interstices.

Surface areas are important because dissolution of drug substances, in its basic sense, is a function of surface area, by the Noyes-Whitney equation:

$$dM/dt = -kA(S-C)$$

where C is concentration at time, t, S is solubility, M is mass not dissolved, A is surface area, and k is the intrinsic dissolution rate constant. For particulate dissolution, the Hixson-Crowell equation holds:

$$1 - (M/M_0)^{1/3} = (2kS/(\rho d_0))\ t$$

where ρ is density and d_0 is the inital particle diameter. It is seen again, that the smaller the diameter (the larger the

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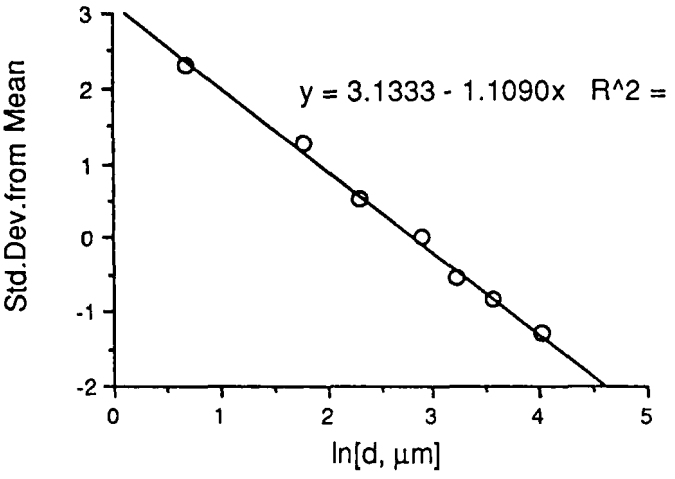

Fig. 14. Log-probit plot of oversize distribution of griseofulvin. Graph constructed from data published by Matthews and Rhodes (1967)

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specific surface area), the more rapid the dissolution. The Hixson-Crowell equation strictly speaking only holds for monodisperse populations and under sink conditions (C< 0.15S), but Brooke[20] and Carstensen and Patel[21] have shown it to hold for log-normal particle distributions and Patel and Carstensen[22] have shown it to hold for non-sink conditions.

Descriptively, particles sizes are log-normally distributed. An example of this is shown in Fig. 14, which is constructed from data published by Matthews and Rhodes[23].

Carstensen and Patel[24] have shown that milled monodisperse powders become log-normal in the milling step. Rodriguez and Carstensen[25] have shown that thermal recrystallization leads to distribution functions which, although not quite log normal, are quite close to that pattern. Lai and Carstensen[26] has shown it to hold for different crystal habits.

CRYSTALLIZATION, MORPHOLOGY AND HABIT

The final polish of a drug substance in its synthesis is a purification, usually in the form of a recrystallization. It is important to drug manufacturers to realize that any change in

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synthesis can give rise to morphological, habit and micromeritic changes that can greatly affect the machinability of the drug substance. Changes as subtle as a 5% percent of ethanol in a recrystallization can change the particle size distribution and the surface characteristics of a drug to an extent that makes previous pharmaceutical manufacturing procedures useless. It is therefore important, in drug development, to have drug substance of the "final" form, fairly early in the development scheme.

Crystallization always takes place from a supersatureated solution. The random movement of molecules will occasionally form configurations that are identical to those in a crystal, and if these configurations are sufficiently large, then the assembly will grow voluntarily, and the critical configuration is denoted a nucleus.

The reason for this is that when a configuration is created, then the Gibbs energy (G over-all and μ per volume) is proportional to the volume (and is negative, since it was voluntary), but the surface energy (interfacial energy being denoted σ) is positive, so that one may write:

$$\Delta G = 6\sigma d^2 - d^3\mu.$$

This function, as can readily be seen by differentiation, has a maximum at

$$d = 4(\sigma/\mu)$$

and the total curve has the appearance as shown in Fig. 15.

The particle size distribution is a function of nucleation (J) rates and crystal growth rates (G) both of which are a function of supersaturation (C-S), where C is the supersaturated concentration and S is the solubility. They are often of the form:

$$dJ/dt = j\ (C-S)^{1/2}$$

$$dG/dt = g\ A\ (C-S)^2.$$

where A is surface area. If the supersaturation is large, then nucleation is often much more rapid than growth, so that a lot

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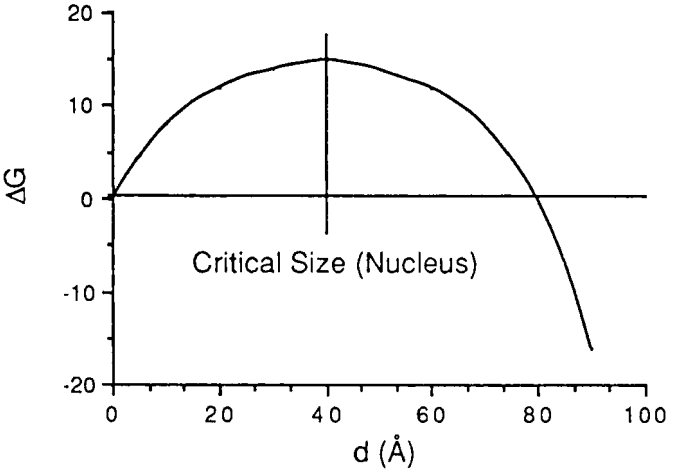

Fig. 15. Gibbs energy changes during nucleation.

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of crystals are being formed. Since the total mass, M, of crystals formed is

$$M = V(C\text{-}S)$$

where V is the volume of the liquid, it follows that in such a case the mass of each crystal is small. This happens in reprecipitation (where one solvent is added to the solution of the drug in another solvent), so that such a procedure produces a fine product, often giving rise to pharmaceutical manufacturing difficulties.

In thermal recrystallization, however, the liquid is cooled at a certain rate, and (C-S) is first small, and then rises. Hence growth is larger in relation to nucleus formation, and as crystals grow, the supersaturation ratio decreases, so that there will be fewer crystals, each weighing more.

As mentioned earlier, changes in the purification step can have disastrous effects on machinability of the drug. For example, changing from recrystallization to reprecipitation usually is of such a serious nature.

As much as pharmaceuticists are bound to not changing procedures drastically, companies seem rather laxadacical about changes in syntheses. Here the cost arguments seem to be one-sided, and cost savings in synthesis can be far offset by

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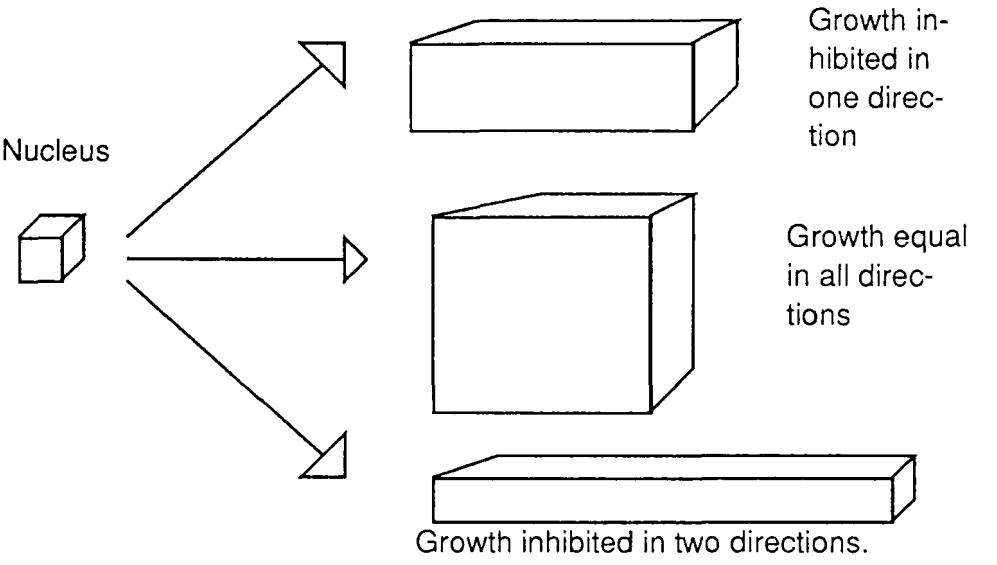

Fig. 16. Crystal habits.

the cost of the changes they necessitate in pharmaceutical production. They often also delay the filing and approval of NDA's.

It should be mentioned, at this venture, that differences in shape and surface characteristics of particles of different batches of the same drug substance can be due to either (a) crystal habit or (b) morphology.

The solubilities of the various crystal habits do not differ greatly, whereas solubilities of different polymorphs can vary a great deal.

YIELD STRENGTHS (ELASTICITY)

Cohesion plays a part in the bonding in a tablet, and the formation of a plug in a capsule, but in the case of the former, it is the elastic limit of the material which is of importance. This limit must be exceeded in the tableting process for a compact to result.

It is difficult to determine, directly, the elastic limit of small particles, but easier (and more practical) as well, is the determination of a Heckel plot. Below the critical capping

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pressure, a tablet will become thinner asr the maxium applied pressure, P, increases.

The apparent density, ρ', of the tablet is the mass (determined by the tablet weight) divided by its volume (which can be calculated from its dimensions). For a flat tablet it is the thickness multiplied by the tablet cross-sectional area. If the true density is denoted ρ, then the fraction of voids or porosity, ε, is given by:

$$\varepsilon = 1 - (\rho'/\rho)$$

Then, by simple geometry it is possible to convert thickness into porosity, and a plot of the natural logarithm of porosity versus applied pressure is linear at high pressures, and is denoted an Athy-Heckel plot. However, in the pharmaceutical range, pressures of the magnitude necessary to achieve linearity are not reached (and are above the critical capping pressure). In essense this means that it is, in the pharmaceutical range, not possible to remove all the voids. Carstensen and Geoffroy[27] (Fig. 17) have shown that the correct plotting mode is one where

$$-\ln[(1/\{(1-\varepsilon)-J\}] = aP + b$$

where J is an iterant and where a and b are constants dependent on the material being compressed. It can be shown[28] that

$$a = 1/(3\phi)$$

where ϕ is the yield strength of the material.

EFFECTS OF MOISTURE

There are several types of moisture encountered in solid pharmaceuticals. Sorbed moisture, usually adhering to a BET isotherm, is the most common type. It is of importance because cohesion is greatly affected by amounts of sorbed moisture. This is one reason why shear cell work should be carried out in carefully controlled relative humidity areas, and

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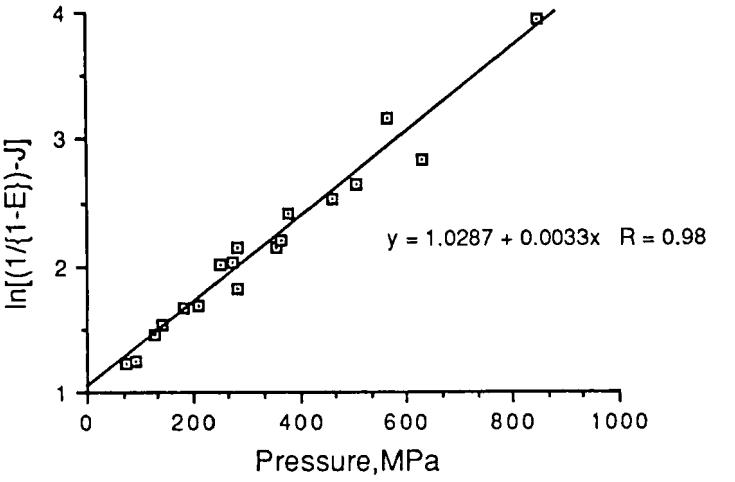

Fig. 17a) Data treated according to the modified Athy-Heckel equation. Material: 10% APAP in dicalcium phosphate dihydrate (DiTab), using J = 1.07.

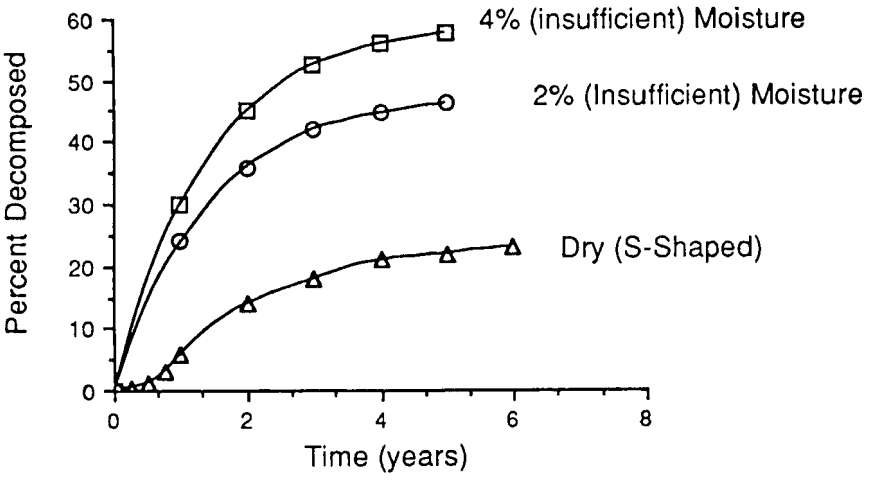

Fig. 17b) Decomposition of a fairly unstable drug in the presence and absence of water. The dry decomposition can be either by Prout-Tompkins or by Bawn kinetics.

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why equilibration of powder with the surroundings is important.

The blocking point in Fig. 14 could theoretically allow calculation of the cohesion in the powder, but it is so poorly reproducible because of the difficulty in controlling the amount of moisture sorbed to the funnel, that it cannot serve that purpose. From a practical point of view, often one can carry out an operation on a dry day and not on a moist day (or vice versa).

Stability of solids is also affected by this property. When a solid drug substance is (virtually) anhydrous, then it will either decompose by a Prout-Tompkins[29] scheme or by a Bawn scheme[30]. The decomposition in the presence of water in a certain range is governed by Leeson-Mattocks kinetics which dictate that the decay is zero order with a rate constant, k_o, of:

$$k_o = SkV.$$

where V is the volume of water present, k is the solution first order decomposition rate constant, and S is the solubility. As water is used up, V will decrease, and hence the curves will often appear as in Fig. 17 when carried out far enough. Above 90% retained, they will, however, be linear, and the slopes are then given by:

$$\text{Slope} = (Sk)(V-V^*)$$

where V* is the amount of "bound" water. Bound water can, for instance, be water of crystallization.

HYGROSCOPICITY

When a substance is subjected to a moist atmosphere, then it may take up moisture in one of several ways. Moisture will condense on the particles, if the equilibrium water vapor pressure of the solid as a whole is smaller than that of the atmosphere.

This is shown in Fig. 18.

It is noted from Fig. 18, that the moisture uptake rate is proportional to the difference between the moisture vapor pressure in the atmosphere, and the equilibrium pressure over

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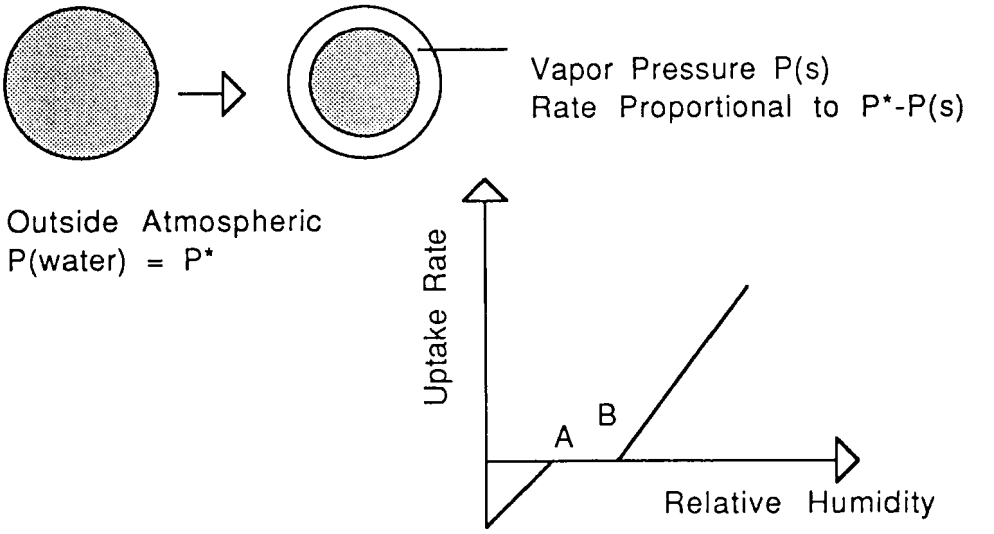

Fig. 18. Moisture uptake by a solid.

the solid. Beyond point B, this corresponds to the condensated layer containing dissolved solid. If, for instance relative humidities beyond B in Fig. 18 are used, then the rate of condensation is linearly related to the relative humidity in the atmosphere. At point B the uptake rate is zero, and this coincides with the relative humidity over a saturated solution of the compound. At lower relative humidities moisture will not be picked up nor given off, unless the compound is a hydrate. If it is a hydrate with an equilibrium RH-range of AB, then it will start dehydrating at relative humidities below A.

SUMMARY

Various microscopic properties of particulate solids have been described, and their relationship to technological parameters are outlined. Novel forms of the Warren-Springs equation and of the Athy-Heckel equation are presented, with experimental data substantiating them.

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REFERENCES

[1]Carstensen , J.T., (1973) Theory of Pharmaceutical Systems, Vol. II, Disperse Systems, Academic Press, N.Y., p.171.

[2]Rippie, E.G., Olsen, J.L., and Faiman, M.D., (1964), J. Pharm. Sci., **53**, 1360.

[3]Carstensen, J.T., and Rhodes, C.T., (1984), Drug. Dev. and Ind. Pharm., **10**, 1017.

[4]Carstensen, J.T., (1977) Pharmaceutics of Solids and Solid Dosage Forms, Wiley, N.Y., pg. 139-140.

[5]Carstensen, J.T., and Patel, M., (1977), Powder Tech., **17**, 273.

[6]Carstensen, J.T., (1980), Solid Pharmaceutics, Mechanical Properties and Rate Phenomena, Academic Press, N.Y., pg. 94-97.

[7]Ashton, M.D., Cheng, D.C.H., Farley, R., and Valentin, F.H.H., (1965) Rheol. Acta, **4**, 206.

[8]Crooks, M.J., Ho, R., and Bagster, D.F.,(1977) Drug Dev. Ind. Pharm., **3**, 291.

[9]Hiestand, E.N., and Peot, C.B., (1974), J. Pharm. Sci., **63**, 605.

[10]Geoffroy, J.M., and Carstensen, J.T., (1992) Powder Tech., in press.

[11]Cheng, D.C.H., Farley, R., and Valentin, F.H.H. (1968) Tripartite Meeting of Chemical Engineers, Montreal, Canada.

[12]Carstensen, J.T., and Chan, P.L., (1977), J. Pharm. Sci., **66**, 1235.

[13]Carr, R.L. (1956), Chem. Eng., **72**, Jan. pg. 163, Feb. p. 108.

[14]Carstensen, J.T., (1980), Solid Pharmaceutics, Mechanical Properties and Rate Phenomena, Academic Press, N.Y., pg. 99.

[15]Danish, F.Q., and Parrott. E.L. (1971), J. Pharm. Sci., **60**, 550.

[16]Laughlin, S., and Carstensen, J.T. (1979), Powder Tech., **23**, 79.

[17]Ridgway, K., and Rupp, R (1969), J. Pharm. Pharmacol., **21**, 30S.

[18]Farin, D., and Avnir, D., (1992), J. Pharm. Sci., **81**, 54.

[19]Brunauer, S., Emmett, P.H., and Teller, E., (1938), JACS, **60**, 309.

[20]Brooke, D., (1975) J. Pharm. Sci. **64**, 1409.

[21]Carstensen, J.T., and Patel, M. ((1975), J. Pharm. Sci., **64**, 1770.

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[22]Patel, M., and Carstensen, J.T., (1975), J. Pharm. Sci., **64**, 1651.
[23]Matthews, B. A., and Rhodes, C.T., (1967), J. Pharm. Sci. **56**, 839.
[24]Carstensen, J.T., and Patel. M., (1974), J. Pharm. Sci., **63**, 1494.
[25]Rodriguez, N., and Carstensen, J.T., (1986), J. Pharm. Sci., **75**, 552.
[26]Lai,T., Y-F., and Carstensen, J.T., (1978), Int. J. Pharm., **1**, 33.
[27]Carstensen, J.T., Dellamonica, C., and Geoffroy, J.-M., (1990) Powder Tech. **67**, 10.
[28]Heckel, R.W., (1961) Trans. Metall. Soc., AIME, **221**, 671 and 1001.
[29]Prout, E., and Tompkins, F., (1944), Trans. Faraday Soc., **40**, 448.
[30]Bawn, C.E.H., (1955) in "Chemistry of the Solid State", Ed. Garner, W.E., Butterworths, London, England, pg. 254 ff.

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