DEFINING THE PHYSICAL FUNCTIONALITY OF EXCIPIENTS, BULK DRUGS AND FORMULATIONS

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INTRODUCTION

At present, the pharmaceutical industry tends to relate a powder's physical functionality to the size and morphology of individual particles. While the emphasis on individual particles is helpful, in reality, we are dealing with several million particle assemblages even in the smallest capsule or tablet. This means that the integrated effect of individual particles really governs physical powder handling and processing. This strongly suggests that knowledge of a pharmaceutical powder's bulk properties is essential to defining its physical functionality. This article discusses these bulk properties, their measurement, particle size effects, and interpretation in terms of indices. Finally, the correlation of these indices with such processing phenomena as tablet weight variations, capping and powder hangups in a process line is discussed.

A powder's physical functionality often determines the success or failure of pharmaceutical processing. Physical functionality of particle assemblages include:

- Cohesive bridging over hopper outlets, capsule fillers, and tableting dies.
- Adhesive hangups on container walls, press fixtures and chutes.
- Limiting flow rates into capsule, tableting dies, and formulation equipment.
- Tablet hardness and dissolution rates.
- Segregation after final mixing.
- Broken, capped and off -weight tablets.
- Effective dosage variations in aerosols.

METHODS OF MEASURING PHYSICAL FUNCTIONALITY

The most used, but not necessarily the most useful of a powder's physical properties, is particle size. Excipient specifications, bulk drugs, and formulations always indicate a particle size range. Unfortunately, powder with the same average range of particle size, may behave entirely different in the process. For example, agglomeration can make an extremely fine powder flow like a much coarser grind. Bimodal particle size mixtures sometimes flow worse than either of the mix's separate components.

In general, particle size offers at best, a broad-brush correlation to physical functionality in process or handling equipment, and often produces a false specification for bulk drugs and excipients. Attempting to interpret the surface roughness, charge, shape or porosity of individual particles in a powder that contains millions of particles is more than even high-speed computers can analyze.

The most direct way to define a powder's functionality in a process is to run the powder through the process while carefully, defining and controlling all of the variables. Unfortunately, the result is a bimodal "yes-it-works-or-no-it-doesn't-work" answer. In

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addition to the great cost in time, equipment and powder, the result provides no means of extrapolating the result to other process equipment or conditions within the same process or to other processes.

Fortunately, there are means of measuring a powder's bulk properties such as unconfined yield strength, surface internal and effective function angles, air permeability, bulk-specific weight, elastic modulus (percentage springback), and adhesion. Unfortunately, all of these properties are dependent on the solid particles' contact pressure as well as variations in particle characteristics (see Table I). The solids contact pressure through most powder processing is generated by gravitational forces, and thereby directly proportional to the bulk-specific weight of the solid, and the size of the container or equipment used Heavier powders are subject to greater solids contact pressures. Larger containers produce larger pressures.

In this article, we will quantify this mass of bulk properties data by using an indices systems described by the author [I, 2, 3]. These indices quantify bulk properties at conditions relative to bulk-specific weight and container size. In addition to the indices measured directly by the bench-size laboratory equipment (see Fig. I), and as described in the references, several additional indices derived from the measure quantities have been developed specifically for pharmaceutical applications. Table II shows these indices, their mathematical relations to the basic bulk properties, and describes the basis for selecting indices test conditions.

INDICES CORRELATION TRENDS

One of the most prevalent uses of the indices is comparing one powder with another. If the indices are the same for two powders, the behavior in handling and processing equipment will be the same. Unfortunately, no two powders are ever exactly the same, so it is useful to know the negative direction of each index, and the processes and equipment that are affected.

Arching Index AI

The Arching Index (AI) is measure a of powders tendency to bridge over hopper outlets. The negative direction for the AI generally is an increase. For example, a powder with a large AI tends to stop flow in hoppers, increase variations in tablet weight as reported by Rowlings [4], increase difficulty in filling capsules, an decrease the ability to act as a dry carrier for aerosols. There is one positive to an increased in the AI, and that is a decreased tendency to segregate by particle size.

Rathole Index

The Rathole Index (RI) is a measure of a powder's tendency to stay on container walls. The negative direction for the RI is an increase. A large RI indicates a greater tendency for a powder to hang up at container walls, and to form agglomerates, which will decrease a powder's effectiveness as a aerosol carrier. The positive for an increased RI is an increase in tablet strength, or a decrease in pressure to achieve an acceptable tablet strength. With less pressure required to make tablets, the tablet will have greater porosity, which will reduce the tendency for tablet capping, and cause faster tablet dissolution rates.

Flow Rate Index

The Flow Rate Index (FRI) is a measure of a powder's limiting flow rate through a container after deaeration. The negative direction for the FRI is a decrease. A smaller FRI portends increased variability in tablet weight as reported by Rowlings [4], and an increased tendency for tablet capping. The FRI is also useful for correlating particle sizes, and size distribution if the mean particle size remains constant. A lower FRI indicates a smaller particle size or a wider size distribution if the mean size remains unchanged.

Feed Density Index

The Feed Density Index (FDI) is a measure of a powder's density at the outlet. There is no positive or negative direction for the FDI; however, it is useful to note that as the FDI decreases, feeder speeds need to increase to provide the same gravimetric rate. As the FDI increases, the particle-specific gravity is also likely increasing. If the particle-specific gravity is constant (e.g. the same chemical composition), then the increase is associated with a wider particle size distribution or a less cohesive powder.

Bin Density Index

The Bin Density Index (BDI) is a measure of a powder's density in a container. As with the FDI, there is no definite negative direction associated with the BDI. The trends predicted are similar to the FDI, except this index has little sensitivity to variations in powder cohesion, and a decease in the FDI means the bin or hopper will hold less weight.

Hopper Index

The Hopper Index (HI) is a measure of half angle required to produce flow at the walls in a conical hopper. The negative direction for the HI is a decrease. A smaller HI indicates the need for steeper hopper angles to eliminate ratholing-type hangups in containers, less uniform tablet compression from the top of the tablet to the bottom, and a greater force to remove the tablet from the die, which increases a tablet tendency to break when ejected from the die.

Chute Index and Adhesion Index

The Chute Index (Cl) and Adhesion Index (ADI) are measures of a powder's tendency to stick to walls and chutes at impact points. An increase in either the Cl or the ADI are definite negatives, and indicates a greater tendency for a powder to stick to container walls, augers, belts, pneumatic conveying bins, tablet press guides, tablet dies, and aerosol dispensing equipment. With increases in either index, there is the expectation of greater tablet and capsule weight variations, difficulties in keeping tablet dies clean and problems in dry cleanout of processing equipment.

Compressibility Index

The Compressibility Index (COM and β) is a measure of a powder's compression tendency. The usual negative direction for the COM and β Index is an increase, which indicates greater tablet and capsule fill weight variation, less uniform density in tablets, and a greater tendency for capping. On the positive side, an increased COM and β produces greater porosity, which suggest a faster dissolution rate.

Tablet Strength Index

The Tablet Strength Index (TSI) indicates whether or not tablet made from a certain product will survive handling. The larger the TSI, the greater the tablet strength is likely to be at a given pressing force.

SIMULATED APPLICATION OF INDICES DATA

This section uses actual indices test data (see Table Ill) from a bimodal sucrose mixture, containing coarse and fines, to simulate a formulation problem, discuss typical processing decisions based on the indices, and provide guidelines for establishing indices limiting values on which to base decisions. While the limiting values provided are a good approximation for industry evaluation, establishing precise limiting values depends on the experience with and type of processing equipment used. Once this is done, the indices provide an accurate prediction of a powder's behavior in the specific equipment.

Table Ill shows the indices measured for a bimodal distribution of sucrose. The coarse fraction is closely sized at about 400 micrometers, and the fine fraction in sized at minus 10 micrometers. The table shows the results at various percentages by weight of the fine fraction.

Handling unmixed ingredients

The 0% (all coarse) and 100% (all fines) test results in Table Ill show the how the raw, unmixed ingredients of sucrose will handle.

Coarse component

Because the coarse component is closely sized, there will be few, if any, segregation problems. The powder is free-flowing (AI<90 mm and RI<250 mm), and will feed accurately with volumetric feeders (FRI>100 Kg/min and COM<.04, β <.013). Almost any handling system will work satisfactorily with this component. There is one potential problem with water soluble particles that may give some concern. If this coarse sucrose is conveyed pneumatically in high humidity air or allowed to sit for an hour or two so as to pick up moisture as little as 0.01%, the Arching Index and Ratholing Index after time consolidation may increase significantly to about 370 and 3000 respectively. In this case any storage hopper should be designed for flow along the walls. For example, a conical hopper at a 70-degree slope angle (HI=20 degrees) would be required for this component, or a one-dimensional convergence hopper with a racetrack cross-section (Fig 2) and a 55 to 45-degree slope angle.

<u>Fine powder component</u>

Since the fine powder is cohesive (AI= 390>100 and RI=3290>300), there will be little or no segregation tendency. The large AI and RI requires that any hopper storing or handling this powder produces flow along the walls. For a conical hopper, this means an outlet in excess of 390 mm (AI=390 mm) combined with a hopper slope of 76 degrees (14 degrees measured from the vertical). With a one-dimensional convergence hopper similar to that shown in Fig. 2, the outlet size can be reduced to 200 mm and the slope can be reduced by 20 to 30 degrees. To develop any significant flow rate from a feed or storage hopper, air permeation is necessary at the appropriate position and at an appropriate controlled air injection rate to achieve the desired powder discharge rate [6]. This is necessary because FRI < 100 Kg/min.

Fine powder will very likely build up on chutes (CI = 88>60), and will require a loose fitting, flexible elastomer chute liner at impact points to break adhesion and keep the powder flowing.

Mixing the ingredients

Because of the finer component's cohesive nature (AI=390>100 and RI=3290>300), a high shear mixer will be required to mix the coarse and fine components. There will be a great tendency for the fine component to accumulate and cake on the mixer's walls and moving parts, especially at impact points (CI=88>60 and AD =50>20). The fine component may also collect as a fine coating on non-impacted surfaces and affect subsequent batch consistencies if the mixer is not thoroughly cleaned between batches (FRI<100 and ADI>10). The mixer will tend to form agglomerates of the fine fraction when high concentrations of fines are added to one part of the mixer (AI>200 and RI>2000). Adding the fines slowly to the coarse while mixing will help.

Handling after mixing

The proper handling procedure and equipment used after mixing depends highly on the percent of fines in the mixture. If the fines fraction is 20% or less, the mixture will handle much like the pure coarse component. If the mixture is 50% fines or greater the mixture will handle much like 100% fines, except for the tendency to adhere to equipment surfaces. There is one significant difference, however. A significant potential for segregation exists in the minus 50% fines mixture (AI<100). Any feed or storage hopper should provide flow at the walls and produce a first-in/first-out flow pattern to remix any segregated portion that resulted from filling the hopper. This slope angle for a conical hopper must exceed 75 degrees from the horizontal, or 15 degrees from the vertical (HI=20 to 15 degrees). Again, an alternate one-dimensional hopper would have slope angles of between 35 and 45 degrees to produce first-in/first-out flow patterns (HI≥15 degrees) at 50% fines or greater.

Tableting

As far as tableting is concerned, the fines need to be greater than 20%, but there is no reason to increase fines above 50% (TSI is essentially unchanged at 50, 70 and 100% fines tableting). Capping is a likely problem at or above 50% fines (FRI<50). Tablet weight variations are likely at 50% fines or greater (AI>100 and COM>.3, β>.05). Powder buildup on the press will likely start at somewhat above 70% fines (CI>60 and ADI>25). Feeding the press will be difficult at 50% fines or greater and bridging and limiting feed rates [6] are problems unless special feed hoppers are used, such as a one-dimensional hopper with a racetrack configuration [5] (AI>100 and FRI<100).

The conclusion is that tableting can be successful in the bimodal sucrose mixture, but only in a narrow range of about 40% fines content. More data is required to find a precise range for the example given.

This data base indicates that above 50% fines, there is a tendency for the powder to agglomerate (RI>2000). This could be used to advantage if the process involved a rotating drum or light compaction in a roll press that would purposely form agglomerates. Agglomeration decreases the AI while the RI and TSI remain essentially unchanged. This could generally increase the percentage of fines allowed in the mixture entering the tablet press.

Capsule tilling

Capsule filling requires a free-flowing powder (AI<100) without significant flow rate limits (FRI>200). This generally restricts the percentage fines to 20% or less. However, near 20% there will likely be weight variations because of the mixture's compressibility (COM>.1 β>.03). The greatest potential problem is fines and coarse segregation (AI<100) that results in non-uniform weights (FDI range from 849 to 862), or chemical variations, if the chemistry of the two components are different. It's important to run additional tests to quantify segregation. These tests should simulate handling before capsule filling. The FRI provides an excellent way to quantify segregation because of the correlation with percent fines. In the range of 0 to 20% fines, the FRI varies monotonically from 4560 to 155.

Dry aerosol carrier choice

A dry aerosol carrier must be free-flowing with no tendency to agglomerate (AI<80 and RI<250). It should also be fine enough to fluidize (FRI<100) and yet be closely sized (FRI>10) with no significant tendency to adhere to equipment surfaces (ADI<4).

INDICES REPEATABILITY

The question always arises as to the precision of indices measurements. This is best addressed in Table IV. Tests on a single sample of diatomite (swimming pool filter media), suggests high repeatability. Deviations greater than these are caused by variations in the powder itself, such and those caused by particle size segregation during processing or handling before a test; by chemical changes; by fines agglomeration; by moisture changes (with powder, even .1% or less moisture change can be significant); or by sample precompaction that results from bumping the test cell during loading.

CONCLUSION

The indices approach allows researchers to reduce multiple powder properties data to a few precise numbers and then quantify indices cutoff values for a given process. This eliminates or at least reduces costly full-scale, trial-and-error formulation runs because the researcher know the powder's functionality.

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TABLE I
Basic Bulk Properties of Powders

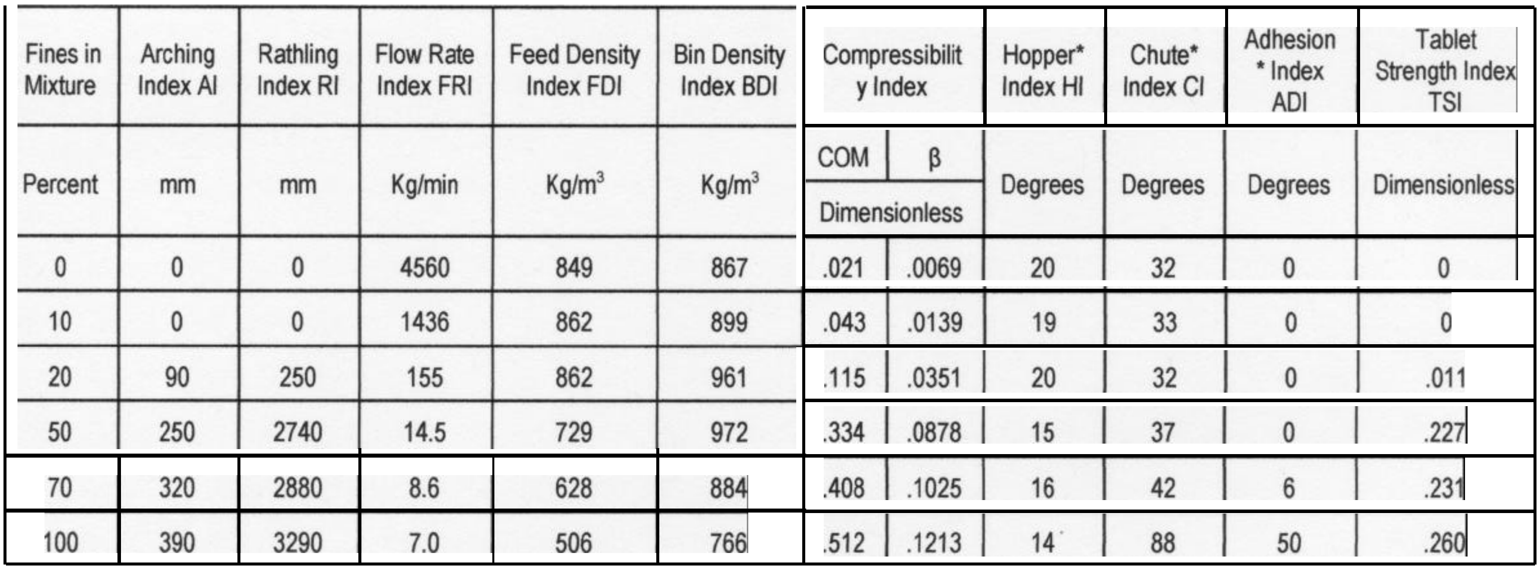
Symbol	Units	Name and Description	Factors Affecting Magnitude
fc	Force per unit area	Unconfined yield strength, a measure of the cohesive forces between particles.	• Increases greatly with increased solids contact pressure. • Increases with reduced particle size. • Increases with increased moisture content. • Increases with time at rest.
γ	Weight per unit volume	Bulk-specific weight, a measure of the unit weight of a particle assemblage.	• Increases with increased solids contact pressure. • Decreases with reduced particle size. • Decreases in low pressure range with increased moisture. • Increases slightly with time at rest.
φ'	Degrees	Kinematic friction angle of a powder on a flat plate, or a powder's angle of slide on a surface.	• Usually decreases with increased solids contact pressure, but may increase when powder is abrasive. • Increases with reduced particle size. • Usually increases with increased moisture. • Increases with time at rest. • Usually increases with increased surface roughness, but materials with an orange peel-type roughness may decreases the angle.
φ	Degrees	Angle of internal friction, a mathematical concept that describes incipient failure stresses of a particle assemblage.	• Usually decreases slightly with increased unconfined yield strength. . Useful more as a mathematical concept tied to yield strength than as a direct correlation with physical occurences.
6	Degrees	Effective angle of internal friction, a mathematical concept that approximates steady flow stresses of a particle assemblage.	• Usually increases with increased unconfined yield strength. At low consolidation pressures it may reach 90 degrees as compared to 50 degrees at higher pressures. This variability with solids contact pressures suggests that conservative values of 6 should be used in any application.
a	Degrees	Angle of repose of a powder as it is deposited on a pile.	• Extremely dependent on the test technique and physical conditions such as impact velocity on the pile, entrained air, time the powder is at rest in the container or conveyor above the pile, flow rate into the pile, and cohesion or unconfined yield strength on the powder. This makes the angle of repose almost useless as a powder property except of very free-flowing, coarse particles such as sand. In this case a = 6 = φ where the angle of repose is determined with essentially no impact on the pile.
K	Velocity	Permeability factor, or the velocity of air passing through a bed of powder that causes a pressure gradient through the bed equal to the bulk-specific weight.	• Decreases by orders of magnitude with increased solids contact pressure, and the associated increases in density and voids between particles. * Increases significantly with even slight increases in moisture content in powders because of superfines agglomeration.
E	Percent	Elastic modulus or the percent springback exhibited by a uniaxially compressed sample of a particle assemblage when compressed under a give solids contact pressure.	• Increases with increased solids contact pressure at low values of contact pressure. At higher value of solids contact pressure, the springback may be over come with cohesive strength. • Particle shape greatly effects this property, E is usually higher with elongated, curly or stringy particles. • Particle elasticity is a factor.
a	Force per unit area	Adhesive strength or shear force per unit area required to initially dislodge a particle assemblage from a surface.	• Increases with solids contact pressure. • Usually increases with reduced particle size. • Usually increases with increased moisture content. • May increase with time at rest.

TABLE II
Johanson Indices

d = Hopper outlet diameter indices basis
D = Bin diameter indices basis

Symbol	Units	Name	Relation to Basis Bulk Properties
AI	Linear	Arching Index	AI = 2.2 fc / y where fc and y are measured at a solids contact pressure equal to y d/2.
RI	Linear	Raholing Index	RI = 2.5 fc / y where fc and y are measured at a solids contact pressure equal to y D/2.
FRI	Weight per unit time	Flow Rate Index	FRI = $60(\sqrt{B^2-4AC}-B)/(2A)$ where $A = 4 \tan\theta K / (g \pi d^3 \gamma / 4)$ $B = 1 - \gamma / BDI$ $C = - K \gamma d^2 \pi / 4$ where K and y are measured at a solids contact pressure of y d / 2, θ is the hopper angle measured from the vertical, and g is the gravitational constant dependent on units of y.
FDI	Weight per unit volume	Feed Density Index	FDI = y measured at a solids contact pressure equal to γd.
BDI	Weight per unit volume	Bin Density Index	BDI = y measured at a solids contact pressured equal to γD.
HI	Degrees	Hopper Index	HI = 42-φ' where φ' is measured at a solids contact pressure equal to yd, or if φ' is larger at a higher pressure, then use φ' at a pressure about γD.
CI	Degrees	Chute Index	CI = ASC + 10 where ASC is the angle of slide on a flat surface after the powder sample has been pressed against a surface at a solids contact pressure of 4700 N/m^2, then released before the surface is tilted to determine ASC.
SI	Percent	Springback Index	SI = the percent springback after a sample has been uniaxially compressed under a solids contact pressure equal to γD, and then reduced to zero.
COM	Dimensionless	Compressibility	COM = BDI/FDI - 1.
β	Dimensionless	Compressibility Coefficient	β = log (BDI/FDI) / log (2D/d)
TI	Dimensionless	Tableting Index	TI - (RI/3.5 - AI/2,2) / D
ADI	Degrees	Adhesion Index	ADI = (CI + HI - 52)

Table III
Indices for a Biomodal Sucrose Mixture
Coarse 400 micrometers particle size
Fines minus 10 micrometers particle size



Fines in Mixture	Arching Index AI	Rathling Index RI	Flow Rate Index FRI	Feed Density Index FDI	Bin Density Index BDI	Compressibility Index		Hopper* Index HI	Chute* Index CI	Adhesion * Index ADI	Tablet Strength Index TSI
Percent	mm	mm	Kg/min	Kg/m^3	Kg/m^3	COM Dimensionless	β	Degrees	Degrees	Degrees	Dimensionless
0	0	0	4560	849	867	.021	.0069	20	32	0	0
10	0	0	1436	862	899	.043	.0139	19	33	0	0
20	90	250	155	862	961	.115	.0351	20	32	0	.011
50	250	2740	14.5	729	972	.334	.0878	15	37	0	.227
70	320	2880	8.6	628	884	.408	.1025	16	42	6	.231
100	390	3290	7.0	506	766	.512	.1213	14	88	50	.260

* Values are for a 304-2B finish stainless steel plate.

Table IV
Repeat Tests with Diatomite Sample

Test	FRI lb/min	HI Degrees	CI Degrees	AI ft	RI ft
1	41.6	15	43	0.3	2.1
2	41.2	14	43	0.4	2.0
3	40.1	15	44	0.3	2.0
4	40.9	15	42	0.4	2.1
5	41.3	15	44	0.3	2.1
6	41.6	14	44	0.3	2.1
7	41.7	15	43	0.3	2.0
6	40.4	14	44	0.3	2.0
Mean	41.10	14.63	43.88	0.33	2.05
Standard Deivation	0.59	0.52	0.74	0.05	0.05
- Confidence Interval	40.69	14.27	42.86	0.29	2.01
+ Confidence Interval	41.51	14.98	43.89	0.36	2.09
Confidence Level	95%	95%	95%	95%	95%