The Relative Densities of Pharmaceutical Powders, Blends, Dry Granulations, and Immediate-Release Tablets

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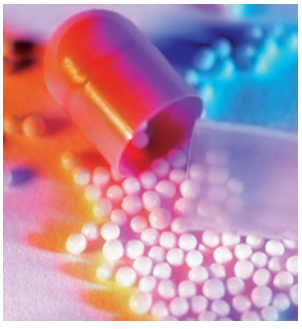
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The absolute and relative densities of pharmaceutical solids play an important role in determining their performance (e.g., flow and compaction properties) in both tablet and capsule dosage forms. In this article, the authors report the densities of a wide variety of solid pharmaceutical formulations and intermediates. The variance of density with chemical structure, processing history, and dosage-form type is significant. This study shows that density can be used as an equipment-independent scaling parameter for several common drug-product manufacturing operations.

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Many physical responses of powders, granules, and compacts such as powder flow and tensile strength are determined largely by their absolute and relative densities (1–8). Although measuring these properties is a simple task, a review of the literature reveals that a combined source of density data that formulation scientists can refer to does not exist. The purpose of this article is to provide such a reference source and to give insight about how these critical properties can be measured for common pharmaceutical solids and how they can be used for monitoring common drug-product manufacturing operations.

Density, solid fraction, and porosity relationships

The majority of pharmaceutical solids are initially presented in powder form. The relative densities of these powdered pharmaceutical materials generally increase as the materials are processed into solid dosage forms. This occurs irrespective of the processing pathway used or the type of manufacturing equipment chosen (see Figures 1 and 2). Densification is often necessary to enhance the handling properties of the solid materials (e.g., powder flow) and to permit more-efficient processing operations to be used (e.g., high-speed tablet compression). Densification also facilitates dosing the active ingredient to patients in acceptably sized dosage forms.

Several terms are commonly used to describe the apparent densities of solid pharmaceutical materials such as *specific volume*, *porosity*, and *solid fraction*. The following relationships between these parameters are:

$$\text{density} = \text{mass} \div \text{volume (units of g/mL or kg/m}^3\text{)} \quad [1a]$$

$$\text{specific volume} = \text{volume} \div \text{mass} = 1 \div \text{density (units of mL/g or m}^3\text{/kg)} \quad [1b]$$

$$\text{absolute density} = \text{true density} = \text{mass} \div \text{molecular volume} \quad [2a]$$

$$\text{apparent density} = \text{mass} \div \text{envelope volume} \quad [2b]$$

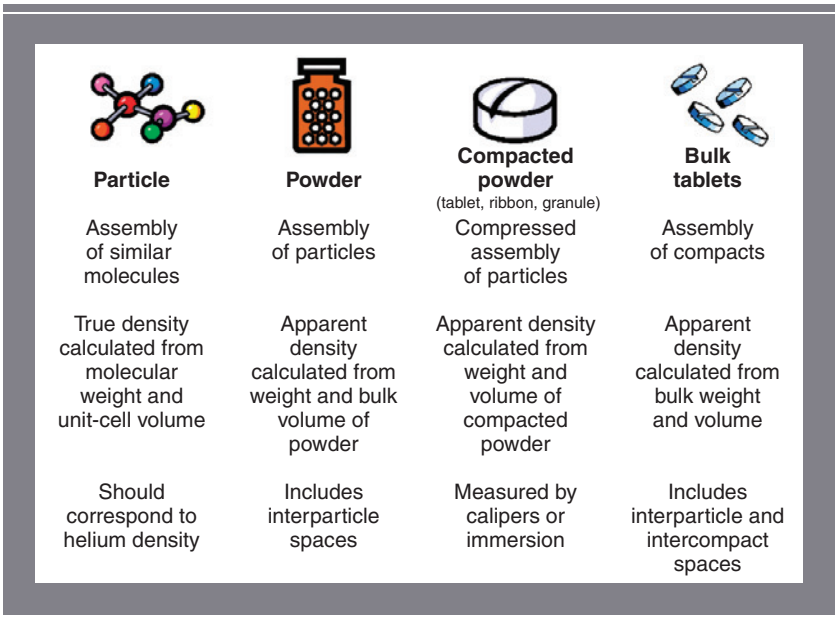

Figure 1: Schematic describing the densities of solid pharmaceutical samples.

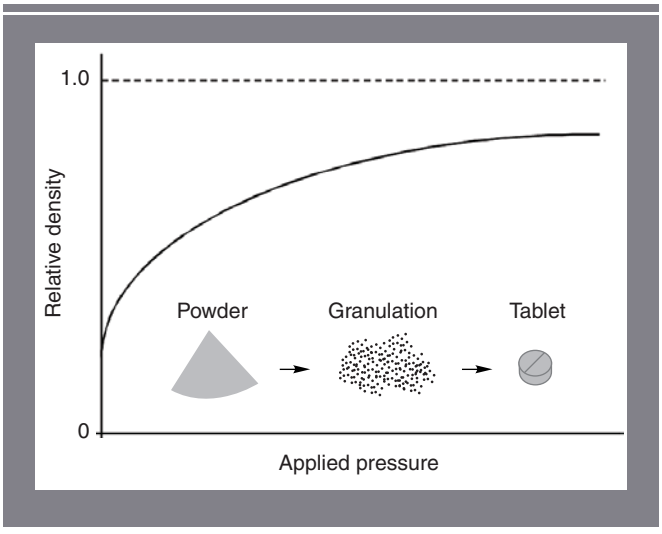

Figure 2: Relative density changes expected during the manufacture of a solid dosage form.

in which the apparent density is usually bulk or tapped, and the envelope volume is the space bounded by the exterior surface of the sample.

$$\text{relative density} = \text{apparent density} \div \text{absolute density} \quad [3a]$$

$$\text{solid fraction} = \text{relative density} \quad [3b]$$

$$\text{percent porosity} = 100\,(1 - \text{relative density}) \quad [3c]$$

Pharmaceutical scientists almost always refer to the mean density of a sample; however, evidence for density gradients in solid pharmaceutical samples does exist (9), and under some circumstances it may be more appropriate to describe a sample in terms of its minimum or maximum density or even its density heterogeneity.

Methods

True (absolute) density measurement. The true or absolute densities of finely divided solids is most often measured by pycnometry. Such measurements work by using a displacement fluid such as helium, air, mercury, or oil to penetrate the voids between neighboring particles, thereby providing an estimate of the volume of the solid part of a sample. The principles of such measurements are described in Chapter ⟨699⟩ "Density of Solids" in the current United States Pharmacopeia (10). In this work, the true densities of powder samples (~1 g) were determined using a helium pycnometer (Quantachrome Inc., Boynton Beach, FL) that was operated according to the manufacturer's recommended procedures. Calibration was performed using standard stainless steel spheres of known mass and volume. The mean value of triplicate determinations is reported. This property of the roller-compacted ribbons and granulations was measured in exactly the same way as it was for the powders, whereas tablets were lightly crushed using a mortar and pestle before testing. All samples were equilibrated at controlled ambient conditions (22 ± 2 °C, 40 ± 5% RH) before testing to ensure reproducible results.

Bulk (envelope) density measurement for powders and granules. The bulk and tapped densities of powdered excipients, drugs, blends, and granulations are commonly determined using the methods described by the American Society for Testing and Materials (ASTM) (11,12) and in the United States Pharmacopeia Chapter ⟨616⟩ "Bulk Density and Tapped Density" (10). The results of these measurements can be easily affected by the choice of equipment, operator technique, or measurement conditions; therefore, one of these standardized procedures (10–12) should be closely followed (13–15). All measurements for this study were conducted at controlled ambient conditions (22 ± 2 °C, 40 ± 5% RH) using a tapped density instrument (VanKel, Cary, NC) fitted with 100-mL glass volumetric cylinders. All samples were tapped (14.25-mm height; 300 taps/min) until they reached a terminal density (typically after 2000 taps).

Bulk (envelope) density measurement for compacted samples. The envelope volume of roller-compacted ribbons and immediate-release tablets can be determined by direct measurement with calipers or by using standard fluid-displacement techniques. Both methods were used in this study. The direct measurement of ribbon and tablet dimensions was achieved with a standard digital micrometer calibrated using National Institute of Standards and Technology traceable gauge blocks. The instrument used for fluid displacement measurements was a Geopyc 1360 instrument (Micromeritics Instrument Corp., Norcross, GA), and the displacement fluid comprised graphite lubricated glass spheres of a small size (mean volume diameter ~132 μm). Cylindrical sample chambers with diameters between 12.7 and

Table I: Densities, solid fractions, and porosities of various powdered and granular pharmaceutical solids.

Sample type	Description	True density (g/mL)	Apparent density (g/mL)	Relative density (solid fraction)	Porosity (%)
Powders	*Excipients*				
	Sorbitol (bulk)	1.48	0.59	0.40	60
	Sorbitol (tapped)	1.48	0.73	0.49	51
	Lactose spray-dried (bulk)	1.55	0.53	0.34	76
	Lactose spray-dried (tapped)	1.55	0.67	0.43	67
	Microcrystalline cellulose (PH101) (bulk) (17)	1.56	0.33	0.21	79
	Microcrystalline cellulose (PH105) (bulk)	1.57	0.25	0.16	84
	Microcrystalline cellulose (PH105) (tapped)	1.57	0.46	0.29	71
	Dibasic calcium phosphate anhydrous (bulk)	2.80	0.70	0.25	75
	Dibasic calcium phosphate anhydrous (tapped)	2.80	1.43	0.51	49
	Cross-linked poly(vinylpyrrolidone) (bulk)	1.21	0.29	0.24	76
	Stearic acid (bulk)	0.99	0.59	0.60	40
	Glyceryl behenate (bulk)	1.00	0.57	0.57	43
	Drug substances				
	Bulk drug P (bulk)	1.29	0.14	0.28	72
	Bulk drug P (tapped)	1.29	0.36	0.38	62
	Bulk drug Q (bulk)	1.31	0.43	0.33	67
	Bulk drug Q (tapped)	1.31	0.69	0.53	47
	Bulk drug R (bulk)	1.42	0.25	0.18	82
	Bulk drug R (tapped)	1.42	0.44	0.31	69
Blends	*Direct compression*				
	Formulation A (bulk)	1.52	0.57	0.38	62
	Formulation A (tapped)	1.52	0.64	0.42	58
	Formulation B (bulk)	1.93	0.60	0.31	69
	Formulation B (tapped)	1.93	0.72	0.37	63
	Formulation C (bulk)	1.91	0.73	0.38	62
	Formulation C (tapped)	1.91	0.84	0.44	56
	Formulation D (bulk)	1.56	0.59	0.38	62
	Formulation D (tapped)	1.56	0.70	0.45	55
	Formulation E (bulk)	1.76	0.43	0.24	76
	Formulation E (tapped)	1.76	0.58	0.33	67
Granulations	Formulation E (bulk) (made from 0.60 solid-fraction ribbons)	1.76	0.48	0.27	73
	Formulation E (tapped) (made from 0.60 solid-fraction ribbons)	1.76	0.69	0.39	61
	Formulation E (bulk) (made from 0.80 solid-fraction ribbons)	1.76	0.58	0.33	67
	Formulation E (tapped) (made from 0.80 solid-fraction ribbons)	1.76	0.90	0.51	49
	Microcrystalline cellulose (PH101) (bulk)				
	(13 roller compacted) (17)	1.56	0.44	0.28	72
	(2× roller compacted) (17)	1.56	0.51	0.32	68
	(3× roller compacted) (17)	1.56	0.53	0.34	66
	(5× roller compacted) (17)	1.56	0.56	0.36	64
	(10× roller compacted) (17)	1.56	0.59	0.38	62

50.8 mm were used so that a variety of sample types and sizes could be analyzed, and fluid pressures from 0.07 to 0.22 MPa were used depending upon the size of the sample chamber. To permit the calculation of the bulk density of each sample using equation 2b, the samples were weighed using standard analytical techniques.

Materials

The densities of a wide range of pharmaceutical actives, excipients, and formulations (placebo and active) were measured during this study (see Tables I–IV and Figure 3). Powdered excipients and active pharmaceutical ingredients (APIs) were evaluated for their true, bulk, and tapped densities to determine the normal range of powder densities that might be encountered during the development of solid dosage forms. These materi-

Table II: Densities, solid fractions, and porosities of various roller-compacted and tableted pharmaceutical samples.

Sample type	Description	True density (g/mL)	Apparent density (g/mL)	Relative density (solid fraction)	Porosity (%)
Roller-compacted ribbons	Microcrystalline cellulose (PH105) (140 psi roll pressure)	1.57	0.77	0.49	51
	Microcrystalline cellulose (PH105) (355 psi roll pressure)	1.57	0.94	0.60	40
	Microcrystalline cellulose (PH105) (640 psi roll pressure)	1.57	1.13	0.72	28
	Formulation E (~0.1-kg scale production)	1.76	1.06	0.60	40
	Formulation E (~1-kg scale production)	1.76	1.14	0.65	35
	Formulation F (~0.1-kg scale production)	1.50	1.11	0.74	26
	Formulation F (~1-kg scale production)	1.50	1.09	0.73	27
	Formulation F (>10-kg scale production)	1.50	1.09	0.73	27
	Placebo tablet formulation X (calipers)	1.55	1.11	0.72	28
	Placebo tablet formulation X (Geopyc)	1.55	1.11	0.72	28
	Placebo tablet formulation Y (calipers)	1.55	1.22	0.79	21
	Placebo tablet formulation Y (Geopyc)	1.55	1.16	0.75	25
	Placebo tablet formulation Z (calipers)	2.03	1.37	0.68	32
	Placebo tablet formulation Z (Geopyc)	2.03	1.38	0.68	32
Tablets	*Direct compression*				
	Formulation A				
	(5 kP; 100-mg weight tablet; eccentric press)	1.52	1.23	0.81	19
	(15 kP; 800-mg weight tablet; eccentric press)	1.52	1.28	0.84	16
	(6 kP; 100-mg tablet weight; rotary press)	1.52	1.35	0.89	11
	(20 kP; 800-mg tablet weight; rotary press)	1.52	1.37	0.88	12
	Formulation B				
	(6 kP; 100-mg tablet weight; rotary press)	1.93	1.49	0.77	23
	(20 kP; 800-mg tablet weight; rotary press)	1.93	1.51	0.78	22
	Formulation C				
	(6 kP; 100-mg tablet weight; rotary press)	1.91	1.53	0.80	20
	(20 kP; 800-mg tablet weight; rotary press)	1.91	1.57	0.82	18
	Formulation D				
	(5 kP; 100-mg tablet weight; rotary press)	1.56	1.39	0.89	11
	(15 kP; 800-mg tablet weight; rotary press)	1.56	1.40	0.90	10
	(20 kP; 800-mg tablet weight; rotary press)	1.56	1.42	0.91	9
	Dry-granulated (roller-compacted)				
	Formulation E				
	(7 kP; 100-mg tablet weight; rotary press)	1.76	1.50	0.85	15
	(12 kP; 100-mg tablet weight; rotary press)	1.76	1.55	0.88	12
	(17 kP; 800-mg tablet weight; rotary press)	1.76	1.37	0.78	22
	Formulation F				
	(12 kP; 160-mg tablet weight; rotary press)	1.50	1.37	0.91	9
	(18 kP; 640-mg tablet weight; rotary press)	1.50	1.29	0.86	14
	(23 kP; 640-mg tablet weight; rotary press)	1.50	1.37	0.91	9
	Commercial tablets				
	Tums (10 kP, 1319-mg tablet weight)	1.84	1.55	0.84	16
	Alka-Seltzer (9 kP, 325-mg tablet weight)	1.90	1.59	0.84	16
	Motrin (5 kP, 390-mg tablet weight)	1.42	1.21	0.85	15
	Generic aspirin (8 kP, 377-mg tablet weight)	1.42	1.31	0.93	7
	Generic acetominophen (20 kP, 555-mg weight)	1.29	1.16	0.90	10
	Dimetapp tablet(16 kP, 470-mg tablet weight)	1.34	1.04	0.78	22

Table III: Direct-compression placebo tablet formulations (values in %).

Material	Formulation A	Formulation B	Formulation C	Formulation D
Microcrystalline cellulose, NF[a]	48.25	48.25	0.00	47.5
Lactose spray-dried, NF[b]	48.25	0.00	48.25	47.5
Dibasic calcium phosphate anhydrous, USP[c]	0.00	48.25	48.25	0.00
Croscarmellose sodium, NF[d]	3.00	3.00	3.00	3.00
Magnesium stearate, NF[e]	0.50	0.50	0.50	2.00

[a]Avicel PH200, FMC Corporation (Newark, DE)
[b]Fast-Flo, Foremost Farms (Rothschild, WI)
[c]A-Tab, Rhodia Inc. (Chicago, IL)
[d]Ac-Di-Sol, FMC Corporation
[e]Vegetable-derived, Malinkrodt (St. Louis, MO)

Table IV: Roller-compacted formulations (values in %).

Material	Formulation E	Formulation F
Drug substance	2.9	7.3
Microcrystalline cellulose, NF[a]	62.4	59.5[b]
Dibasic calcium phosphate anhydrous, USP[c]	31.2	0.0
Mannitol, NF[d]	0.0	29.7
Croscarmellose sodium, NF[e]	3.0	3.0
Magnesium stearate, NF[f]	0.5	0.5

[a]Avicel PH200, FMC Corporation
[b]Added half as intragranular and half as extragranular
[c]A-Tab, Rhodia Inc.
[d]2080 Granular, SPI Pharma (Newcastle, DE)
[e]Ac-Di-Sol, FMC Corporation
[f]Vegetable-derived, Malinkrodt

als were stored at controlled ambient conditions (22 ± 2 °C, 40 ± 5% RH) and used as they were received from their suppliers. Active and placebo blends were made from the powdered materials using either a low-shear V-blender (Blendmaster, Patterson-Kelley, East Stroudsburg, PA) or a high-shear mixer (Turbula, Glen Mills Inc., Clifton, NJ), and their true, bulk, and tapped densities were determined. Several of the excipients and formulations (active and placebo) were roller compacted with TF-mini or TF-156 roller compactors (Vector Corp., Marion, IA). Roll speeds, pressures, and ribbon thicknesses were 2–4 rpm, 100–700 psi, and 1–3 mm, respectively. Both smooth and serrated rollers were used, and ribbon samples were taken once steady-state operating conditions had been reached. Lastly, placebo and active tablets of a variety of sizes were manufactured from the blends and granulations at the laboratory scale using either a single-station tablet press (F-press, Manesty, Knowsley, Merseyside, UK) or a nine-station rotary tablet press (T-100 model, Kilian & Co. Inc., Horsham, PA). Operating conditions included the use of gravity or force-feeding systems and production rates of 5000–60,000 tablets/h. The formulations were lubricated by low-shear blending with 0.5 or 1.0% magnesium stearate.

Results and discussion

To draw applicable conclusions, several data sources are considered in the remainder of this article. First, a search of a proprietary database of development tablet formulations was used to provide comparative data for various material types, which were broadly classified as drug substances, excipients, blends, roller-compacted ribbons, granulations (wet and dry), and tablets. The mean and ranges of these data are summarized in Figure 3. Second, specific examples of each of these types of materials were selected for more-detailed consideration, and their properties are presented in Table I and II. Finally, some commercial tablet samples were characterized, and their properties are presented in Table II. Following is a sequential discussion of these data, from raw materials through in-process samples to final tableted products.

Drug substance and excipient powders. The true densities of solid pharmaceutical samples should directly reflect the fundamental chemical properties (e.g., molecular weight, molecular formula, and unit-cell dimensions) of the materials concerned. Because drug substances and excipients are primarily organic materials, their true densities did not vary greatly for the most part, with most materials exhibiting values that fell within the range of 1.2–1.6 g/mL (see Table I) (16). Notable exceptions to this behavior were observed for materials with very different chemical structures such as inorganic excipients (e.g., dibasic calcium phosphate) (2.8 g/mL) and waxy materials (e.g., glyceryl behenate, stearic acid; 1.0 g/mL and 0.99 g/mL, respectively).

In general, the powdered APIs had the lowest relative densities. All samples had bulk relative densities <0.4, and some samples had bulk relative densities <0.2. This finding suggests that the majority of APIs must be densified before manufacturing the final dosage form so that sufficiently high doses can be administered in a reasonably sized dosage form. Most of the excipients that were evaluated had densities that were more suited to processing directly into solid oral dosage forms, and the range of bulk relative densities for 48 excipients was between 0.5 and 0.2 (see Table I and Figures 3 and 4). Several excipients such as sorbitol and dibasic calcium phosphate anhydrous exhibited tapped relative densities >0.4; therefore, they can be considered well suited for use in direct-compression tablet formulations in which no additional densification step is performed.

Blends. Combinations of materials should have true densities that are intermediate to their component materials, which was the case for all formulations (blends, granulations, tablets) considered in this work (see Tables I and II). The formulations, including blends, with true densities >1.6 g/mL almost always contained some significant amount of a dense inorganic excipient such as calcium phosphate.

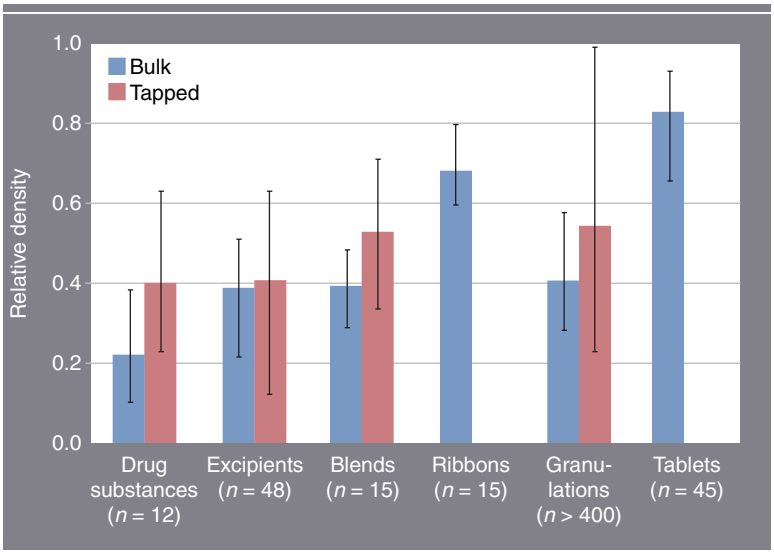

Figure 3: Relative density averages and ranges for solid pharmaceutical development samples.

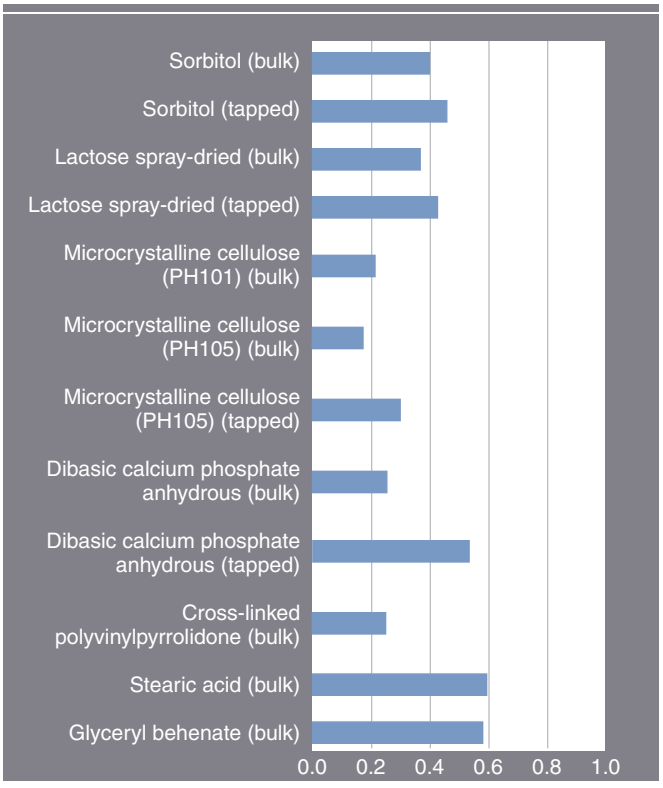

Figure 4: Mean relative densities of some pharmaceutical excipient powders.

The relative densities of the blends were very similar to those of the single excipient samples, which is not surprising because these materials were used in the majority of the blends. The range of relative densities for blends was narrower than that of both the drug substance and excipient powders, which suggests that simply blending these powdered raw materials in a formulation may lead to a more consistent range of densities.

Roller-compacted ribbons. The relative densities of the roller-compacted ribbons from typical development formulations ranged from ~0.6 to 0.8 and were markedly higher than those of the powdered-drug, excipient, and blended formulation samples (see Tables I and II and Figure 3). For one model excipient (microcrystalline cellulose, Avicel PH105, FMC BioPolymer, Philadelphia, PA) the relative density of the roller-compacted ribbons was between 0.49 and 0.72 (depending upon the compaction conditions used), compared with a value between 0.16 and 0.29 for the powdered material (see Tables I and II). This amounts to a two- or threefold increase in the material's density upon roller compaction and clearly illustrates the significant effect that this processing operation can have upon the bulk properties of common pharmaceutical raw materials. For active Formulation E, the relative density of the roller-compacted samples also was increased by two- to threefold more than that of the blended formulation, thereby indicating that this finding is not unique to single excipient samples. Notably, the range of ribbon relative densities that was recorded for 15 roller-compacted excipient and formulation samples was narrower than that of the powdered drug substances, excipients, and blends, which suggests that processing these materials by roller compaction causes them to have more-consistent relative densities (see Figure 3).

The relative densities of the roller-compacted microcrystalline cellulose samples varied measurably with changes in the roller compaction conditions such as roll pressure (see Table II). Because relative density is an intrinsic sample property, it may be a very useful parameter to track during scale-up and process optimization experiments. Relative density would be expected to reflect the overall mechanical performance of roller-compacted ribbons and to be sensitive to changes in raw material properties, major process modifications, and even batch-to-batch processing variations. Measuring this property using calipers and a fluid-displacement method resulted in similar results and identical relative rankings of the three placebo formulations (see Table II and Figure 5). The data show that either method could be used as an in-process test to track changes in ribbon properties or in process performance once the appropriate calibration and methods validation experiments have been performed.

Screened bulk granulations. The relative densities of more than 400 wet and dry development granulations fell within a very wide range. On average, the densities were not significantly different from those of a similar set of powder blends (see Figure 3). Although granulating usually increases the apparent densities of many materials, a significant number of occasions exist in which the granulation process has no effect or even the opposite effect. One can speculate that this finding is due to the use of noncompressive granulation operations such as fluid-bed granulation or that it is the result of suboptimal granulation, milling, and screening operations being used. Another possible explanation is that the density of some individual agglomerates is increased by the granulation process, but the overall bulk density of these granulations is not increased because of changes in the particle packing efficiency induced by shifts in the particle-size distribution (e.g., altered fines content).

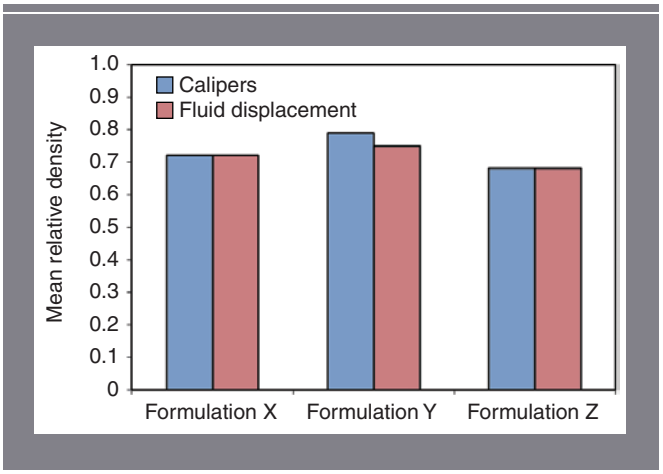

Figure 5: Comparison of the relative densities for roller-compacted ribbons of Formulations X, Y, and Z determined using the caliper and fluid-displacement methods (standard deviation <0.01 in all cases).

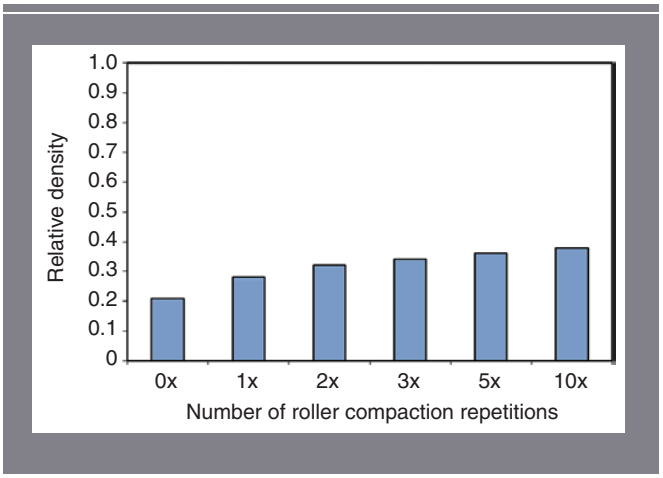

Figure 6: The influence of repeated roller compaction on the relative density of microcrystalline cellulose (Avicel PH101) (17).

To address this unanticipated result in more detail, granules of Formulation E were obtained by gently milling the roller-compacted ribbons using a cone mill (Mini or 193S model Co-mill, Quadro Engineering Inc., Waterloo, ON, Canada). Data for dry-granulated samples of microcrystalline cellulose were also obtained from a recent article (17). The bulk and tapped solid fractions of Formulation E granules varied according to the solid fractions of the ribbons from which they were produced, with the most-dense ribbon samples producing the most-dense granules (see Table I). A similar pattern of behavior was observed with the microcrystalline cellulose samples that were roller compacted on multiple occasions, with the material that had been compacted to the greatest extent producing the most-dense granule samples (see Table I and Figure 6) (17). For Formulation E, the granules had as much as a twofold lower density than the ribbons that they were produced from, but they still had a greater density than the uncompacted blend of the same formulation. Similarly, the roller-compacted microcrystalline cellulose granules were 30–80% more dense than the ungranulated excipient. These two data sets support the widely

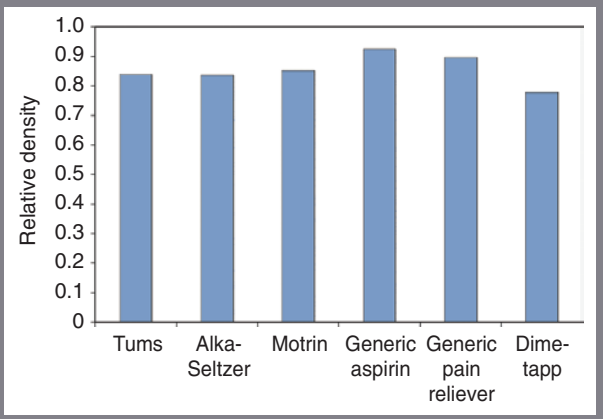

Figure 7: Mean relative densities of some commercial pharmaceutical tablets (standard deviation <0.02 in all cases).

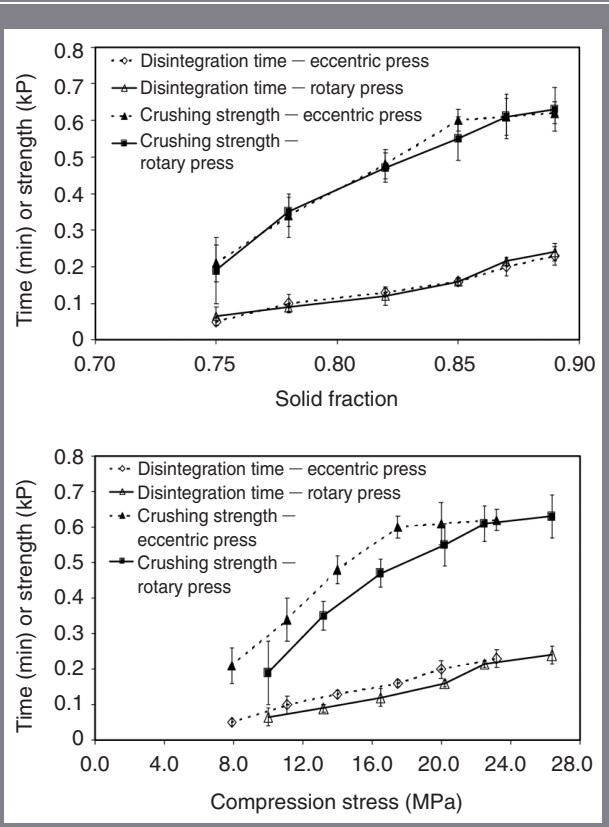

Figure 8: (a) Mean tablet-crushing strength and disintegration time as a function of solid fraction for Formulation A (error bars denote ± one standard deviation); (b) Mean tablet-crushing strength (kP) and disintegration time (min) as a function of compression stress for Formulation A (error bars denote ± one standard deviation).

held belief that granulation normally increases the density of pharmaceutical powders, at least when using a compressive granulation process such as roller compaction. Further research is required to determine the specific circumstances that could lead to a reverse trend and could result in no significant degree of bulk densification occurring upon granulation.

Tablets. The tablet samples had the highest relative densities of all the material types considered (mean = 0.84) (see Figure 3 and Table II), and the range for typical development tablet formulations was between 0.66 and 0.93. For commercially available tablets the average relative density was practically identical to this, and the range of tablet relative densities was also very similar (see Table II and Figure 7). No obvious difference was noted between the relative densities of the direct-compression, dry-granulated, or commercial tablets evaluated in this study. One should note that the relative density of conventional pharmaceutical tablets is such that they have a significant porosity and thus they cannot be expected to behave as if they were solid bodies, which is an important consideration for those interested in studying the physical and mechanical properties of pharmaceutical tablets.

The tablets of the direct-compression placebo Formulations A, B, C, and D (see Table III) had relative densities that somewhat depended on the type of tablet press used and the tablet size, although the greatest differences were due to changes in the formulation composition (see Table II). The direct-compression formulations containing dibasic calcium phosphate formed tablets that were less dense at any given tablet-crushing strength, even though this particular excipient has a high true density. The effect of increasing the lubricant level from 0.5 to 2.0% in the direct-compression microcrystalline cellulose–lactose blends (Formulation A versus D) was to slightly increase the degree of densification required to achieve a given tablet-crushing strength. Tablets of the dry-granulated Formulation E had relative densities that were two- to fourfold greater than their starting blends, two to three times higher than their granulations, and ~10–20% greater than their roller-compacted ribbons (see Table II). When compared with the starting bulk drug substance, these tablets were more than four times more dense.

Scale-up. The choice of tablet press operating conditions and tablet characteristics such as size and shape clearly influences the relative density of the tablets that are produced (see Table II), and this parameter could thus be used as a parameter to discriminate between samples made using different conditions. Because the relative density can be determined for tablets of all shapes and sizes (and also for powders, blends, granulations, and roller-compacted ribbons), it is a very attractive parameter to use when comparing various solid pharmaceutical samples. Instead of using equipment-dependent variables such as compression pressure as a common condition for comparing samples, one can compare them at a common relative density. For fundamental mechanical property testing of pharmaceutical compacts, several authors have advocated collecting data from a range of relative densities and extrapolating to the theoretical zero-porosity point to permit such material comparisons (18,19). This approach requires more material and time than comparisons at a single experimentally accessible relative density and does not consider the properties of the materials in their normal operating state. Routinely comparing the properties of pharmaceutical compacts at a standardized relative density (i.e., 0.9 [10% porosity]) as advocated by several researchers (16,20) seems to be the most reasonable approach for formulation development and process scale-up experiments.

The data in Figures 8a and 8b provide an example of the usefulness of solid-fraction measurements during tablet formulation development and process scale-up studies. During the early stages of tablet development, the supply of the API for Formulation A was limited, thus prototype tablets required to evaluate the stability of the formulation were manufactured using an instrumented single-station eccentric tablet press. As the project progressed, more of the API was synthesized, and the manufacture of sufficient tablets for clinical studies required the use of a small rotary tablet press. Because the compression characteristics and instrumentation of eccentric and rotary tablet presses are quite different, the solid fraction of the tablets was used as the parameter to gauge the equivalence of tablets made using two types of tablet presses (see Figure 8a). From the data, one can observe that using this approach resulted in tablets with equivalent mechanical properties and in vitro disintegration performance, whereas comparisons made on the basis of the measured compression forces of the two types of presses, as is done in many cases, would not have resulted in equivalent tablets being manufactured for the stability evaluations and clinical studies (see Figure 8b).

Conclusions

The authors have reported the absolute and relative densities of a wide range of pharmaceutical solids and probed some of the influences of chemical structure, processing history, and dosage-form type on these properties. Monitoring the relative density of solid pharmaceutical materials (e.g., API, excipients, blends, ribbons, granules, tablets, etc.) can be useful during the design, optimization, and scale-up of manufacturing processes for solid pharmaceutical dosage forms and may help achieve robust drug-product manufacturing processes. For example, the bulk densities of excipient and API powders will clearly indicate whether a need exists for a densifying unit operation such as dry granulation before the manufacture of tablets. Similarly, when attempting to manufacture uniform tablet dosage forms using various tablet presses, monitoring the compact relative density instead of a remote instrument parameter should provide a more robust means of ensuring consistent product performance.

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