Product-Centered Processing: Pharmaceutical Tablets and Capsules

Ka Y. Fung and Ka M. Ng
Dept. of Chemical Engineering, Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, People's Republic of China

A systematic procedure is presented for synthesizing and developing a manufacturing process for pharmaceutical tablets and capsules. The product quality factors — functional, physical and sensorial — are first identified. The dosage form and excipients are then selected, and the process flowsheet is synthesized along with the suitable equipment and operating conditions. Finally, the product and process are evaluated to ensure that the product possesses the desired quality factors. Design heuristics and physical models are provided to assist decision-making. Examples involving Vitamin C, antacid, and ginseng are provided to illustrate the procedure.

Introduction

Pharmaceuticals with global sales expected to reach $406 billion in 2002 constitute a significant fraction of the chemical processing industries (Bailey, 2000). They are delivered in different dosage forms—solids, liquids, creams, pastes, and aerosols. Since active pharmaceutical ingredients (API) are normally in the solid state, most common are solid dosage forms, particularly tablets and capsules (Zanowiak, 1988a), which are convenient to use and provide precise dosage.

There are a wide variety of tablets and capsules. While the majority are designed to be absorbed in the gastrointestinal tract, lozenges are expected to act on the mouth and throat. Most tablets are directly swallowed, but some are supposed to be chewed by children or elderly with swallowing difficulty. Effervescent tablets are dissolved either directly in the mouth or in water before ingestion. Prolonged release tablets and capsules provide an extended therapeutic effect.

Despite the economic significance of solid dosage forms, relatively little has been done from the process systems engineering perspective. This is a serious omission because an effective workflow is expected to reduce the time and effort required for launching a product. Indeed, it is generally accepted that product engineering and solids processing deserves much more attention (Tanguy and Marchal, 1996; Villadsen, 1997; Kind, 1999; Wintermantel, 1999; Cussler and Moggridge, 2001). Recently, Wibowo and Ng (2001b) considered the integration of product design and process design for creams and pastes; customer preferences lead to desirable quality factors that are then achieved by properly designing the process. This article presents such a product-centered systematic procedure for the synthesis and development of tablet and capsule manufacturing processes.

Correspondence concerning this article should be addressed to Ka M. Ng.

Systematic Procedure

There are 4 steps: (1) Identification of product quality factors, (2) Product formulation, (3) Design of manufacturing process, and (4) Product and process evaluation. Design heuristics and physical models are presented to assist decision-making in each step.

Step 1: identification of product quality factors

Product quality factors other than therapeutic effects can be divided into functional, physical, and sensorial. For pharmaceuticals, the primary concerns are the functional quality factors, most of which are defined in the preformulation study, which investigates the physical and chemical properties of the API with and without excipients (Wadke et al., 1989). Table 1 shows examples of various functional factors, as well as typical results from a preformulation study.

As indicated, the disintegration of the tablet should be sufficiently fast to release the API constituent particles. These particles should dissolve easily or be sufficiently small,

Table 1. Quality Factors in Tablets, Capsules and Powders and Typical Preformulation Results

Functional Quality Factors
Disintegrates to desired size quickly
The constituent particle size of the dosage form should dissolve and be absorbed in gastrointestinal tract at a pre-determined rate
Releases API in a pre-determined way
Physical Quality Factors
Must not break up on processing, packaging, transportation, dispensing and handling
Surface of tablet or capsule must be free of defects
Must be stable under anticipated environmental conditions
Have the same weight and composition for each tablet or capsule
Uniform distribution of ingredients in each tablet or capsule
Amount of API must be as close to the labeled amount as possible
Sensorial Quality Factors
Easy and pleasant to swallow
Preformulation Study
Physicochemical properties
Anticipated dose
Purity of API
Drug solubility and pH profile in solution
Drug dissolution and absorption rate
Drug solid state stability
Drug solution phase stability
Drug-excipient stability
Deformation characteristics of API and excipients
Crystal shape and polymorphism of API

preferably less than 5 μm for easy absorption. However, the cohesion and adhesion forces for such particles can be excessive, causing problems in solids processing (Zanowiak, 1988b). If the constituent particles are too large, size reduction operations need to be performed. Sometimes, prolonged release is preferred to immediate release in order to provide an extended therapeutic effect to the patient. However, the release of prolonged release drugs cannot be controlled exactly with current techniques; therefore, it is not suitable for drugs with a narrow therapeutic range because the fluctuation of the drug concentration may readily exceed the safety margin. Table 2 lists some situations in which prolonged release is not suitable (Lordi, 1986; Ansel and Popovich, 1990).

Physical quality factors refer to those attributes related to the state of the product. For example, it should be intact during routine handling and must be stable under anticipated environmental conditions. Crystal shape and structure (polymorphism) of the API have profound influence on the mechanical and physical properties of the tablet (Sun and Grant, 2001a,b). Deformation characteristics of the API and excipients are also very important since they affect tablet tensile strength and, hence, the chance of breaking up under anticipated environmental conditions. The weight, composition, and distribution of each ingredient should be uniform in each tablet or capsule. Whether these can be achieved depends on particle density and flowability, as well as the process flowsheet and operating conditions. Panels of human subjects can be used to judge whether the dosage is pleasant to administer; if not, coatings can be used to mask the unpleasant odor and taste.

Table 2. Situations in Which Prolonged Release Dosage are Not Suitable

- Drugs that absorb and excrete out of the body slowly or rapidly (that is, with short biological half-lives (< 2 h) or long biological half-lives (> 12 h)).
- Drugs that are not absorbed in the gastrointestinal tract uniformly and drugs that are not effectively absorbed in the lower intestines.
- Drugs with large doses (> 1 g).
- Drugs that possess a narrow therapeutic range.
- Drugs that are used in acute treatment rather than chronic conditions.
- Drugs for which precise dosage to patients is required.

Step 2: product formulation

Dosage form, product structure, and excipients are determined in this step.

Selection of Dosage Form: Tablets, Capsules and Powders. Tablets and capsules are the most widely used, although powder can also be administered as the simplest dosage form. Table 3 presents the heuristics for selecting among tablets, capsules and powders (Lachman et al., 1986; Lieberman et al., 1989).

The compression of a powder into tablets, and the subsequent disintegration, dissolution, and absorption of the drug in the gastrointestinal tract are important issues. For amorphous, flocculent, low density, and compressibility drugs, tablets cannot be produced. Tablets are not the suitable dosage form if the wetting and disintegration time is long. One should avoid using tablets for drugs with melting point below 100°C (Anderson, 2000), because compression usually produces 3–30°C localized temperature rise. In addition, a low melting point mixture may stick to the punches and is better to formulate as capsules. For drugs with bitter taste, unpleasant odor, sensitivity to oxygen or atmospheric moisture, capsule is the preferred dosage form. If tablets are really the only choice, coating can be applied.

The manufacturing process of hard and soft gelatin capsules has been discussed by Lachman et al. (1986) and Ansel and Popovich (1990). The moisture content of hard gelatin capsules should be kept between 13 and 16% (Ansel and Popovich, 1990). Therefore, efflorescent or deliquescent drugs are not suitable for capsules.

Soft gelatin capsules can be used when a liquid, a combination of miscible liquids, or a solution or suspension of solids in a liquid(s) is filled inside a capsule (Stanley, 1986). However, they are not suitable for volatile components (such as alcohols), plasticizers that soften the gelatin shell, and tacky liquids (such as glycerin) that may cause binding of slide valves and pumps in the capsule filling machine. For effective processing, liquids, solutions, or suspensions should flow by gravity at room temperature. In general, liquids with a wide range of viscosity from 0.2 cp to >3,000 cp at 25°C can be encapsulated. Also, capsulated liquids need to have a pH range between 2.5 and 7.5, beyond which the gelatin shell would deteriorate.

It is sometimes preferable to administer the powder directly. Powder dosage form is especially suited for children, elderly, or patients who cannot swallow tablets or capsules. It is preferred for very soluble drugs because, if they are made

Table 3. Heuristics for Dosage Form Selection

Heuristics for Selecting Tablet as Dosage Form
• Choose tablet dosage form if the drug exerts a local effect in the gastrointestinal tract (such as antacids).
• Do not choose tablet if the drug is amorphous, flocculent, with low density or low compressibility.
• Do not choose tablet if the drug has poor wettability, slow dissolution properties or optimum absorption in the early parts of the gastrointestinal tract.
• Do not choose tablet if the melting point of the drug is below 100°C.
Heuristics for Selecting Capsule as Dosage Form
General Considerations (apply for both hard gelatin and soft gelatin capsule)
• Choose capsule if the drugs have unpleasant taste or odor.
• Choose capsule if the drugs are sensitive to oxygen or atmospheric moisture.
• Do not choose capsule if the drugs or excipients will react with the gelatin capsule shell.
For hard gelatin capsules
• Choose hard gelatin capsule if physical and chemical interactions occur when the drugs are under intimate contact or compressed into a tablet, while no interactions occur when powders are mixed together.
• Do not choose hard gelatin capsule if the drugs are highly efflorescent or deliquescent.
• Do not choose hard gelatin capsule if the particle sizes or densities of the drugs and excipients are very different.
For soft gelatin capsules
• Choose soft gelatin capsule if a liquid, a combination of miscible liquids, or a solution or suspension of solids in a liquid(s) needs to be encapsulated.
• Do not choose soft gelatin capsule if the major constituents are volatile liquids (such as ethyl alcohol), gelatin plasticizers (such as glycerin, polyethylene glycol), or tacky liquids (such as glycerin).
• Soft gelatin capsule can be used for liquids with viscosity ranging from ethyl ether (0.222 cp at 25°C) to adhesive mixtures (> 3,000 cp at 25°C) and for liquids with pH between 2.5 and 7.5 (Stanley, 1986).
• If solids are present, it is better to dissolve them in a solution rather than encapsulated as a suspension.
• Do not choose soft gelatin capsule if the major constituents are water soluble solids or any substance that is unstable in the presence of moisture.
Heuristics for Selecting Powder as Dosage Form
• Choose powder if the drug is mainly administered to children, elderly, or patients with swallowing problem.
• Choose powder if the drugs are extremely soluble or for a very large bulky dose.
• Do not choose powder if the drug is sensitive to oxygen or moisture or has an unpleasant taste or odor.
• Do not choose powder if prolonged release is required.

in tablet or capsule dosage form, the sudden release of a high localized concentration of drug in a small portion of gastric fluids can cause nausea or stomach irritation. However, powder dosage form is not suitable for drugs which degrade under atmospheric conditions or have unpleasant taste or odor.

Determination of the Product Structure. Product structure includes characteristics such as the tablet or capsule size, particle-size distribution of the API and other ingredients, tablet porosity and coatings. A typical compressed tablet has a diameter range between 6 mm and 11 mm and a height range between 2 mm and 4 mm (Bandelin, 1989), since, if it is too small (large), it may be hard to handle (swallow). When the required dose exceeds 500 mg, the dose is often equally divided into two tablets (Parrott, 1970). Similarly, typical capsule size ranges from 0.15 mL to 0.75 mL (referred to as size 0). The amount of powder that can be filled inside the capsule depends on the bulk density of powder and the pressure used in the filling machine (van Hostetler, 1986). The constituent particle size should correspond to the rate of absorption, as determined in Step 1.

Coating is applied for a variety of reasons. It masks the taste and odor of the drug or the uneven color in tablets. It offers protection from exposure to the environment and assists the therapeutic action of the tablet such as controlling the rate and site of release of the API. For example, enteric coating is particularly suitable for drugs which cause irritation to the stomach, degrade rapidly in acidic solution, and deliver an API which is optimally absorbed or aims at providing therapeutic action in intestines. For coating to be applied successfully, a convex tablet surface is necessary since flat surfaces cause tablets to stick together through capillary action of the wet coating material. It is difficult to apply coating on hydrophobic surface, because the aqueous based coatings cannot wet the surface easily. However, a surfactant can be added to reduce the surface tension of the coating material, if necessary. Since a lot of tumbling action is encountered in coating operations, tablets need to have a high resistance to abrasion and chipping.

Selection of Excipients. Excipients including diluents, binders, disintegrants, lubricants, glidants, colorings and flavors are used to enhance the quality factors of the drug. Typical excipients and their concentration ranges are presented in Table 4 (Zanowiak, 1988b; Lieberman et al., 1989; Kibbe, 2000). Heuristics for selection of excipients are presented in Table 5.

Diluents, water soluble or water insoluble, can be used to modify bioavailability. They can be classified into two general categories: carbohydrate (cellulose, starch, sugar) and inorganic diluents (magnesium carbonate, calcium phosphate). The carbohydrate diluents are usually cohesive and can serve as binder as well.

For powders of small average particle size and large bulk density, the potential of surface bonding, cohesion and adhesion is high and may require lubricant, anti-adherent, and glidant for processing. Water insoluble lubricants, such as magnesium stearate, are the most common (Zanowiak, 1988b). An excessive amount of lubricant may reduce the bioavailability, disintegration, and dissolution rates of the formulation because the hydrophobic lubricant forms a film over the particles and retards the penetration of water. Some lubricants also serve the purpose of anti-adherent and glidant.

Flavoring in liquid emulsion or solid state is usually added to cover the unpleasant taste or odor of the drug. For example, common salt alone, or in combination with a sweetener, can tone down bitter taste, sugar or sweetener can tone down sour taste, and a neutral tasting and smelling thickening agent can tone down any unpleasant odor by binding to the volatile odor chemicals (Matheis, 1999).

Binders are added in granulation to increase the cohesiveness of the powder and hold the particles together to form granules. Van der Waals force is the major interparticle force for small and uncharged particles. In cases where granulation is not required, binders can help prevent de-mixing of a pow-

der mixture. The function of a binder in a granulation process and its effect on the granule properties have been discussed by Ennis et al. (1991), Tardos et al. (1997), Parikh (1997), and Pietsch (1997a).

There are three ways to incorporate a binder into granulation. A binder can be added as a binder solution (wet addition), added dry along with a solvent (dry mixing), or simply added dry without using solvent (dry addition). Granules produced by wet addition and dry mixing tend to possess both an internal binder matrix and outer binder shell (Krycer et al., 1983).

The binder chosen should provide the tablet with sufficient strength that can withstand compaction stress. The breakage number N_{Br} defined below can be useful (Wibowo and Ng,

Table 4. Typical Excipients Used in Tablets, Capsules and Powders

Excipient*	Desired Function	Typical Examples	Typical Amount
Diluent/Filler (T, H, P)	Make up tablet size, capsule size or the required powder dosage	Microcrystalline cellulose	20–90%
		Calcium sulfate dihydrate	—
		Sucrose	—
		Lactose	65–85%
		Starch	5–75%
Binder (T, H, P)	Increase cohesiveness of powder and hold them together to form granules	Sucrose (Solvent: Water)	2–25%
		Microcrystalline cellulose	5–20%
		Pregelatinized starch	
		(Solvent: water)	2–5%
		(Dry addition)	5–10%
		Povidone (Solvent: Water or Water-alcohol solution)	2–5% (5–10%)†
		Alginic acid (Solvent: Water)	(1–5%)
Filler-Binder (T)	Use in direct compression	Spray-dried Lactose	> 80%
		Starch 1500	—
		Microcrystalline cellulose	10–25%
Disintegrant (T, H, P)	To facilitate the breakup of tablet or granule	Starch	5–20%
		Microcrystalline cellulose	5–15%
		Cross-linked povidone	0.5–5%
		Alginic acid	5–10%
Lubricant (T, H, P)	Reduce friction during tablet ejection or facilitate drug transport to filling machine	Magnesium stearate (I)‡	0.25–2%
		Talc (I)	5–10%
		Starch (I)	5–10%
		Magnesium lauryl sulfate (S)	1–3%
		Polyethylene glycol (S)	2–10%
Anti-adherent (T)	Reduce sticking of tablets to the punches or die wall	Talc	1–5%
		Magnesium stearate	0.25–1%
		Microcrystalline cellulose	5–10%
Glidant (T, H, P)	Promote flow of granules or powders by reducing friction between them	Calcium silicate	0.5–2%
		Silicon dioxide	0.1–0.5%
		Magnesium stearate	0.2–2%
		Starch	1–10%
Pigment (T, P)	Add color to tablet or powder	Titanium oxide	q.s.
Flavoring (T, P)	Add taste to tablet or powder	Flavor oils	q.s.
		Sweeteners	
		Salt	
Surfactant (T, H, P)	Wetting agent	Sodium lauryl sulfate	q.s.
Plasticizer (T, H, P)	Add to binder solution to increase binder efficiency	Glycerol	q.s.
		Propylene glycol	
Salt (T, H, P)	Modify aqueous solubility of API	Hydrochloride	q.s.
		Citrate	
		Tartrate	
Cosolvent (S)	To aid in the preparation of solutions incorporated in soft gelatin capsules	Water and alcohol	Up to 5%
		Glycerin and polyethylene glycol	Up to 10%
Suspending agent (S)	To prevent the settling of solids and to maintain homogeneity	Paraffin wax	5%
		Polyethylene glycol	1–15%
		Acetylated monoglycerides	5%

*T = tablet, H = hard gelatin capsule, S = soft gelatin capsule, P = powder.
†Concentration in parentheses represents dry mixing of binder (that is, mix with powder in blender and solvent is added in granulator).
‡I = water insoluble, S = water soluble.

Table 5. Heuristics for Excipient Selection

General Considerations
• Excipients must be physiologically inert, physically, and chemically stable alone and when combined with drugs.
• Hygroscopic excipients cannot be used for drugs that are moisture sensitive.
Selection of Diluents
• Diluents are needed if API alone does not make the desired tablet size, capsule size, or the required powder dosage.
• If it is desirable to enhance disintegration, use water soluble diluents with relatively water insoluble drugs and vice versa (tablet only).
• Diluents that exist as hydrates can still be used for water sensitive drugs provided that the water remains bounded in processing and storage.
Selection of Binder
• If carbohydrate or modified carbohydrate materials are used as diluents, it also functions as a binder. Generally, this is not true for inorganic diluents.
• Binder can be added to a powder mixture if de-mixing is a potential problem.
• If only a small amount of solvent is allowed, dry mixing is the preferred method of binder addition. If a large amount is required, binder solution is a better method.
• Surfactant and plasticizer can be added to the binder solution to improve the binder efficiency.
Selection of Disintegrant
• Disintegrant should have a high water affinity.
Selection of Lubricant, Anti-adherent and Glidant
• Powders of minimum porosity, small average particle size, tight packing, and large bulk density are likely to require lubricant, anti-adherent and glidant.
• Water insoluble lubricants (metallic stearates, talc, starch) are the most effective and are preferred.
• Water insoluble lubricants are also good anti-adherents (tablet only).
• Glidants need to be added for mixtures with angle of repose larger than 30° (Wells, 1988).
• Hydrophilic glidants are more effective on hydrophilic powders, while hydrophobic glidants are more effective on hydrophobic powders.
Selection of Flavoring
• Common salt alone or in combination with sweetener can be added to tone down the inherent bitter taste (tablet and powder only).
• Sugar or sweetener can be added to tone down the inherent sour taste (tablet and powder only).
• Dry flavorings are used extensively in solid dosage forms (tablet and powder only).

2001a)

$$N_{Br} = \frac{\sigma_c}{\sigma_T} \tag{1}$$

The critical number N_{Br}^* above which breakage occurs is

$$N_{Br}^* = \frac{1}{2} - \frac{1}{2}\sqrt{1 - 4(N_{BI})^{-0.5}} \tag{2}$$

where $N_{BI} = (3\sigma_T^2 D)/(2E\gamma_f)$, σ_c is the applied stress, σ_T is the tablet tensile strength, N_{BI} is the brittleness index, D is the tablet diameter, E is the tablet Young's modulus, and γ_f is the tablet surface fracture energy. Since the relationships of these material properties to the Hamaker constant may not be readily available, an alternative, simpler way can be developed as follows.

The compaction stress under normal handling situations can be expressed as (Stuart-Dick and Royal, 1992)

$$\sigma_c = \rho_t v_t^2 \sin^2\theta \tag{3}$$

where ρ_t is the tablet density, v_t is impact velocity, and θ is the angle of impact of the tablet onto a surface. Tensile strength can be related to binder Hamaker constant as (Pietsch, 1997a)

$$\sigma_T = \frac{9}{8} \cdot \frac{1-\epsilon}{\epsilon} \cdot \frac{F_{adh}}{d_p^2} \tag{4}$$

where ϵ is tablet porosity, d_p is the constituent particle size, and F_{adh} is the adhesion force due to van der Waals force which can be expressed as (Visser, 1989)

$$F_{adh} = F_{vdw} = \frac{Ad_p}{12z^2} \tag{5}$$

Here, z is the separation distance between particles and A is the Hamaker constant. z can be taken as 4 Å when particles are in close contact (Dahneke, 1971).

Combining Eqs. 3 and 4 leads to a calculated Hamaker constant. If it is larger than the Hamaker constant of the API, then a binder is needed. The Hamaker constant of a tablet with both binder and diluent can be estimated as (Visser, 1972)

$$A \approx \left(\sqrt{A_{\text{API}}} - \sqrt{A_{\text{binder}}}\right)\left(\sqrt{A_{\text{diluent}}} - \sqrt{A_{\text{binder}}}\right) \tag{6}$$

If the diluent also serves as a binder, it can be estimated as

$$A \approx \left(\sqrt{A_{\text{API}}} - \sqrt{A_{\text{diluent}}}\right)^2 \tag{7}$$

Note that these two approximate equations are not related.

Another function of a binder is to wet the powder particles effectively for granulation to take place. Spreading coefficients could be used to assess the quality of the granules. Strong and dense granules are produced if the spreading coefficient of the binder on the particles is positive (Rowe, 1989; Zajic and Buckton, 1990; Zhang et al., 2002).

There are two mechanisms of tablet disintegration: swelling (such as for starch) or dissolution (such as for povidone and amylopectine), both of which require a high tablet water affinity (De Jong, 1991). If most ingredients are water insolu-

Table 6. Dependence of Performance Indices on Material Properties, Structural Attributes and Operating Variables

Performance Index	Material Properties	Structural Attributes	Relationship between Structural Attributes and Operating Variables
Tensile strength, σ_T	Hamaker constant, A	Grain particle size, d_p Porosity, ϵ	Grain particle size d_p depends on air velocity (Fluid jet mill) Relationship: $v = \sqrt{\frac{N_{Br}^{*}\sigma_T}{\rho_b \sin^2\theta}}$ (11)
	Relationship: Order of magnitude model assuming equal-size particles. $\sigma_T = \frac{3}{32}\cdot\frac{1-\epsilon}{\epsilon}\cdot\frac{A}{z^2 d_p}$ (10)		Porosity ϵ depends on applied pressure (Rotary tablet press) Relationship: $\ln\frac{1}{\epsilon} = k'P + A'$ (12) where k' and A' are constants reflecting material properties and deformation.
Disintegration time, t_d	Diffusivity, D_i	Tablet height, H Grain particle size, d_p Porosity, ϵ	
	Relationship: Order of magnitude model derived from Fick's Law as shown in Eq. 8.		

ble, then a water soluble disintegrant should be considered. Disintegrants can be added both before granulation (intragranular disintegrants) and in tablet compression (extragranular disintegrants). When tablets are administered, extragranular disintegrants provide immediate disruption of tablet to granules and intragranular disintegrants provide further disruption of granules to powders. This is an effective way for rapidly increasing the surface area for drug release.

If the tablet mostly consists of soluble components, then the disintegration time, t_d, which depends on the rate of dissolution of these components, can be estimated as (De Jong, 1991)

$$t_d = \frac{2m^2}{\rho_t^2 \pi^2 D^4 D_i \epsilon (1-\epsilon)^2} \tag{8}$$

where m is tablet mass, and D_i is the diffusivity of the water soluble components. However, if most ingredients are insoluble, the disintegration time is approximately equal to the time for the body fluid to imbibe into the tablet. Using Darcy's law (Washburn, 1921) and the Blake-Kozeny equation for permeability (MacDonald et al., 1991), the time can be estimated as

$$t_d = 15\frac{1-\epsilon}{\epsilon}\frac{H^2\mu}{d_p\sigma} \tag{9}$$

where H is the tablet height, μ is the body fluid viscosity, and σ is the interfacial tension.

Step 3: design of manufacturing process

A summary of how performance indices depend on material properties and structural attributes, and how the structural attributes relate to the equipment and operating conditions are presented in the second and last column of Table 6, respectively. In this step, the manufacturing process is designed to yield such attributes. It involves three parts: flowsheet synthesis, selection of equipment, and choice of operating conditions.

Flowsheet Synthesis. The generic flowsheet with four blocks—milling, granulation, compression/filling, and coating—for producing tablets and capsules is shown in Figure 1. Milling and grinding of the API, as well as other ingredients,

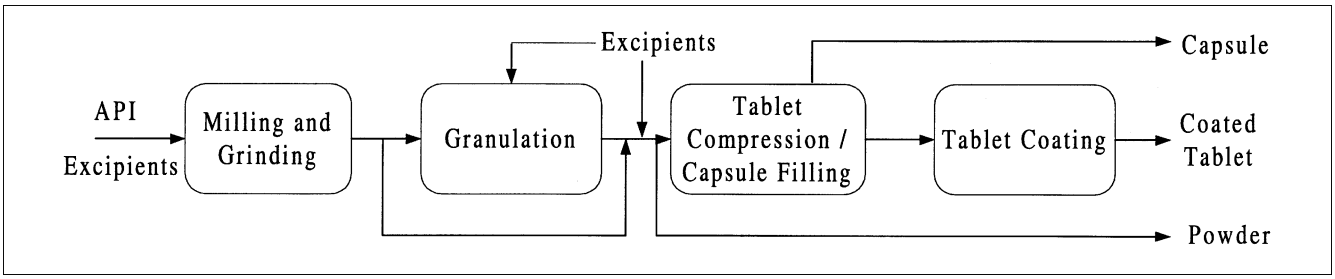

Figure 1. Generic structure for tablet, capsule and powder manufacture.

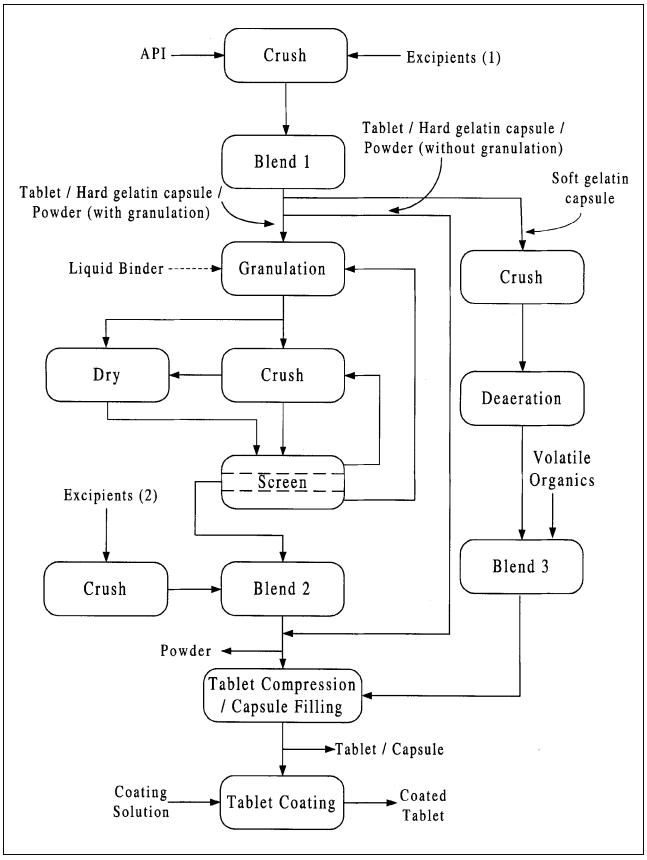

Figure 2. General flowsheet for tablet, capsule and powder manufacture.

is usually the first step. In some situations, granulation is used subsequently to further adjust the particle-size distribution (PSD). Then, the powder can either be the final product, or be compressed into tablets or filled into capsules.

The tablet, capsule, and powder manufacture is shown in Figure 2. A crusher can be placed in the API and excipient streams to reduce particle size if the particle size of the raw material is larger than the desired size determined in Step 1. The same crusher can be used for both streams if the breakage characteristics and the outlet PSDs are similar. It can also be placed after the granulation subsystem to further manipulate the PSD. For particles with nonspherical shapes such as needles, flowability is poor and can be improved by grinding. Controlling API particle size is particularly important for drugs sparingly soluble in water, because this increases the dissolution rate, absorption rate, and bioavailability of the drug (Wadke et al., 1989). Charoenchaitrakool et al. (2000) showed that the dissolution rate was increased 5 times by reducing the particle size from 250 μm to a few microns.

Micron-sized particles can also be produced through supercritical fluid processes: the rapid expansion of supercritical solution (RESS), the supercritical antisolvent process (SAS), and the particles from gas saturated solutions (PGSS). They are particularly suitable for shock sensitive materials and materials that will thermally or chemically degrade in a crusher. Alessi et al. (1996) showed that a supercritical fluid process could produce 4.5 μm particles. Supercritical fluid processes can also be used to improve particle morphology and surface properties, and produce particles with a narrow PSD. RESS is more suitable for drugs with a solubility higher than several mg per gram of solvent; otherwise, SAS is preferred. For low melting point and thermally unstable materials, PGSS is more suitable (Alessi et al., 1996).

Table 7. Heuristics for Deciding Whether Granulation is Required

- Perform granulation when the particle sizes and densities are very different.
- Perform granulation for drugs with irregular shapes (such as long needle particles).
- Perform granulation when bulk density needs to be increased.
- Perform granulation if dusting occurs during processing.
- Perform granulation if metering of particles is a problem.

In some situations, granulation should be performed after milling and crushing (Table 7). Granulation is needed for streams with different densities to prevent segregation in subsequent processing steps or for materials with irregular shapes since mechanical interlocking will form during compaction. This results in tablets with lower tensile strength and longer disintegration time. On the other hand, granulation is not required for rounded crystalline materials since orientations are not required when forming van der Waals force under compression (Parrott, 1970).

Granulation can improve powder and granule flowability thereby avoiding flow problems that often occur in tableting machines or capsule filling hoppers. Adhesive powders tend to cause solid bridging in hopper outlets, which results in flow stoppage. The Flow number N_{Fw} which is defined as

$$N_{Fw} = \frac{\rho_s g D_0 d_p^2 \epsilon}{F_{adh}} \tag{13}$$

predicts whether the above situation is likely to occur. Here, ρ_s is the density of solid in the hopper, g is the gravitational constant, D_0 is the hopper outlet diameter, and ϵ_s is the porosity of solids in the hopper. The porosity of solids with a wide PSD, narrow PSD, and fine particles is estimated to be 0.5, 0.6, and 0.8, respectively (Pietsch, 1997a).

Flow stoppage is not a problem and granulation is not required if N_{Fw} is larger than the critical flow number N_{Fw}^*

$$N_{Fw} \geq N_{Fw}^*(\phi, \phi_w, \beta) \tag{14}$$

where ϕ is the angle of internal friction, ϕ_w is the angle of wall friction, and β is the half cone angle of the hopper. The critical number can be obtained from charts in various hopper design literature (Woodcock and Mason, 1987; Williams, 1990; Rhodes, 1998). After deciding that granulation is necessary, the heuristics in Table 8 (Pietsch, 1996, 1997a,b; Wibowo and Ng, 1999) can be used to select between wet and dry granulation.

To predict whether dry granulation (usually in a roller compactor) can provide the agglomerate with the desired strength, we can use the compaction number N_{Co}, defined as

$$N_{Co} = \frac{\sigma_c}{\sigma_y} \tag{15}$$

Table 8. Heuristics for Granulation Method Selection

- Use wet granulation (WG) if the powder is incompressible and use dry granulation (DG) if the powder is compressible.
- Use WG if API and excipients are wettable, physically, and chemically stable when exposed to moisture or heat.
- Use WG for pressure sensitive materials.
- Use WG if the material is too abrasive, brittle, or elastic.
- Use WG for an easily dissolved product with high porosity (> 40%).
- Use DG if the key properties of powder particles need to be retained.
- Use DG for feeds with high bulk density as a result of wide particle-size distribution.
- Do not use DG for particle size below 150 μm if air entrapment is a problem.

The critical compaction number N_{Co}^*, above which the agglomerates have sufficient strength is

$$N_{Co}^* = \frac{1}{k\sigma_y(1-\epsilon_a)} \ln \left(\frac{\frac{\sigma_{t,\max}}{\sigma_y} - N_{SI}}{\frac{\sigma_{t,\max}}{\sigma_y} - N_{SI,0}} \right) \qquad (16)$$

where N_{SI} is the strength index, which equals $(1 - \epsilon_a/\epsilon_a)(F_{adh}/\sigma_y d_p^2)$, $N_{SI,0}$ is its initial value, ϵ_a is the agglomerate porosity, σ_y is the material yield strength, $\sigma_{t,\max}$ is the maximum tensile strength of the compact in a fully compressed condition ($\epsilon = 0$), and k is a constant. After granulation, a crusher can be used to fine-tune the PSD if necessary (Figure 2). Drying is needed if a liquid binder is used for granulation.

After compression, coating can be performed as determined in Step 1. Sugar and film coating are the two most common coating processes. Extensive discussions can be found in Lachman et al. (1986), Porter and Bruno (1989), Cole et al. (1995), and Avis et al. (1999). The selection and operation of the coating process are still based on experience. However, heuristics can be used to assist decision-making. Sugar coating is more suitable for tablets that become brittle or soften in the presence of heat, since preheating needs to be performed in film coating before coating solution can be applied. It is also more suitable for tablets with minor surface imperfections, since it dries more slowly and fills up the nooks and crannies. However, sugar coating increases tablet weight by 50% to 100% (Lachman et al., 1986). Therefore, it is unsuitable for large tablets because the coated tablet may be too large to swallow. Selection of major ingredients is more flexible in film coating, which allows coating solutions to be tailor-made for the specific application such as sustained release. The major ingredients used in coating solutions are summarized in Table 9.

The manufacturing process for soft gelatin capsules follows a slightly different route in Figure 2. Crushing is not required if liquid API and excipients are encapsulated. If suspensions are encapsulated, crushing is required if the particle size is larger than the desired size determined in Step 1. The crusher following blender 1 breaks up any agglomerates formed during blending. Deaeration is performed in the next step to achieve a uniform fill weight and to protect the drug from oxidation during encapsulation (Stanley, 1986). Volatile organics, if needed, are usually added in the last step to prevent any loss of substances.

Selection of Equipment Units. After synthesizing the flowsheet, equipment needs to be selected to ensure that quality factors stated in Step 1 can be satisfied. Most of the equip-

Table 9. Coating Solution Materials

Ingredient	Desired Function	Coating Method	Addition Step	Examples
Sugar	Main component in sugar coating	Sugar	Subcoating, Grossing, Smooth, Color and Finish Coating	Sucrose, sorbitol
Filler	Fill up the tablet to provide a rounded tablet core	Sugar	Subcoating	Calcium carbonate, talc, titanium dioxide
Film Formers	Improve the structural integrity of coating	Sugar	Subcoating	Acacia, cellulose derivatives
Surfactants	As a wetting agent and facilitate faster dissolution of the coating	Sugar Film		Polysorbates, sorbitan esters
Colorants	Add color to coating	Sugar Film	Grossing and Color Coating Film and Gloss Coating	Dyes, iron oxides, titanium dioxide
Flavors	Mask the objectionable odor or provide a desired taste	Film	Film and Gloss Coating	Sweeteners
Antiadhesives	Prevent sticking of tablets	Sugar		Talc
Polymers	Provide sealing in sugar coating and main component in film coating	Sugar Film	Sealing Sealing, Film and Gloss Coating	Shellac, zein, hydroxypropyl methylcellulose
Plasticizers	Modify properties of polymer	Film	Film and Gloss Coating	Castor oil, propylene glycol
Solvent	Dissolve or disperse the polymer and convey them to the substrate surface	Film	Film and Gloss Coating	Water, ethanol, isopropanol, acetone, methylene chloride
Opaquant	Produce opaque films with good hiding power	Sugar Film	Grossing and Color Coating Film and Gloss Coating	Titanium oxide, aluminum silicate, talc
Wax	Give the tablet a gloss surface	Sugar Film	Polishing Polishing	Beeswax, Carnauba wax

ment involved is solid processing equipment such as a crusher, blender, granulator, and screen (Walas, 1988; Fayed and Otten, 1997; Perry et al., 1997; Wibowo and Ng, 1999).

Product size is the major criterion in crusher selection, and different equipment is available for different feed and product sizes. A fluid jet mill or pin disc mill can be used as the API or excipient crusher for product particles in the submicron and micron size range. A hammer mill can be used for the crusher after granulation to produce particles in the millimeter range.

Material cohesiveness is the primary criterion for blender selection. Shear or convective mixers (Ribbon blender and Nauta mixer) are suitable for cohesive materials with poor flowability. For materials with sufficient flowability, a tumbling mixer (V-blender) can be used if materials do not possess a large density difference. If the materials segregate easily, a blender with internal parts such as stirrers and pedals (Ribbon blender and Nauta mixer) is more suitable. Particles smaller than 300 μm or larger than 1,000 μm do not possess adequate flowability (Pietsch, 1997b). Such undersized and oversized particles can be separated using vibrating screens and recycled back to the granulator and crusher upstream, respectively (Figure 2).

Typical granulators include pan granulators, high shear mixer granulators, fluidized-bed granulators and roller compactors (Figure 3). The first three can be used for wet granulation, while the last one is used for dry granulation. Detailed description of granulators can be found in Snow et al. (1997) and Parikh (1997). Figure 4 presents a chart for granulator selection based on feed and product particle size. Product density is another important selection criterion. A high shear mixer granulator is preferred for producing granules with high density. The inlet blender in Figure 2 can be omitted, since the high shear mixer granulator also blends (Holm, 1997). Since a fluidized-bed granulator provides drying as well, a dryer is not required in the subsequent step. Heuristics for granulator selection are summarized in Table 10.

Tableting, capsule filling, and tablet coating machines are also required. The most common tableting machine is the rotary tablet press. A number of capsule filling machines are available, and a brief description is given by van Hostetler (1986). Tablet coating machines can be classified based on

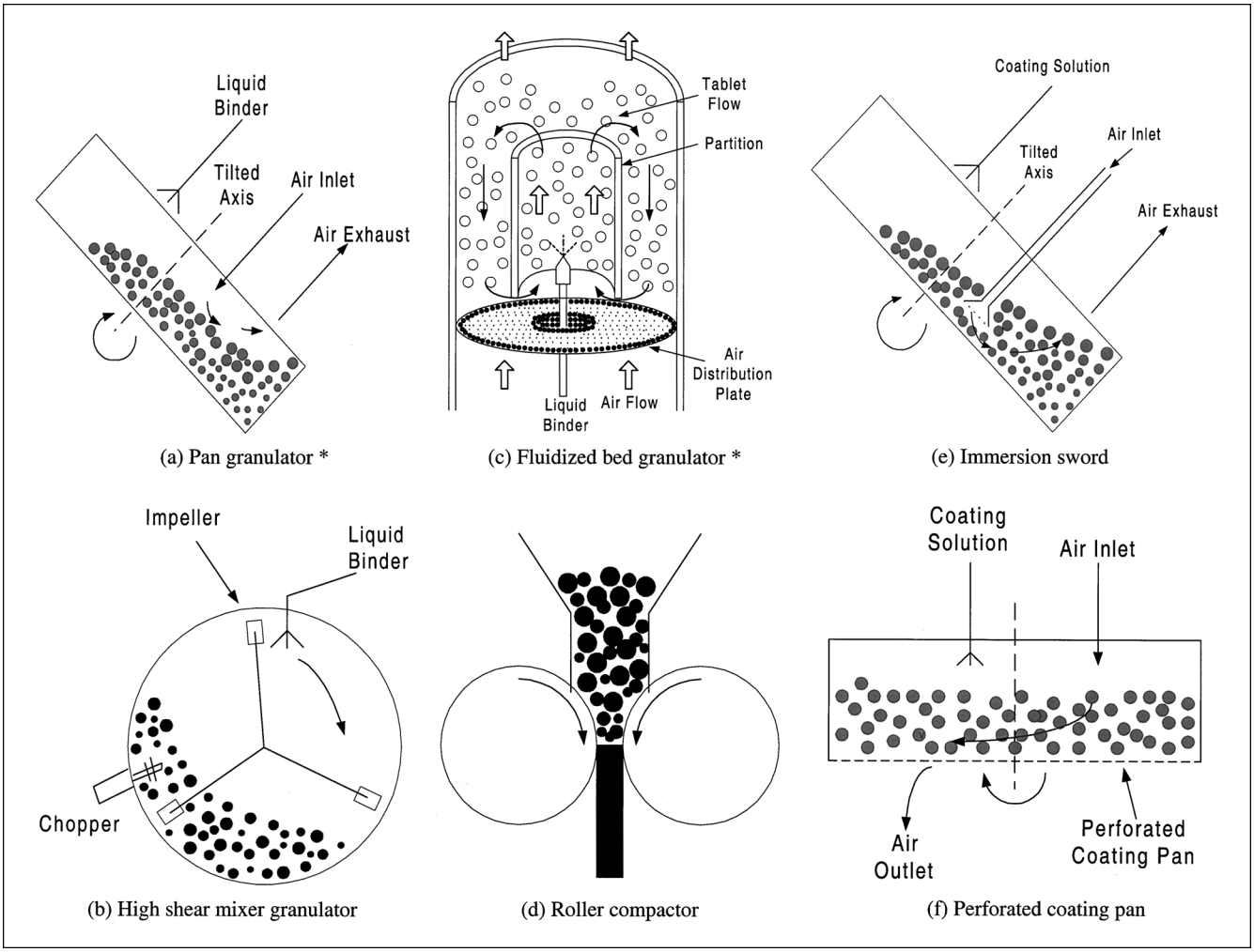

Figure 3. Granulation (a–d), and coating (e,f) equipment.

Pan granulator and fluidized-bed granulator can be used for coating with the liquid binder replaced by coating solution.

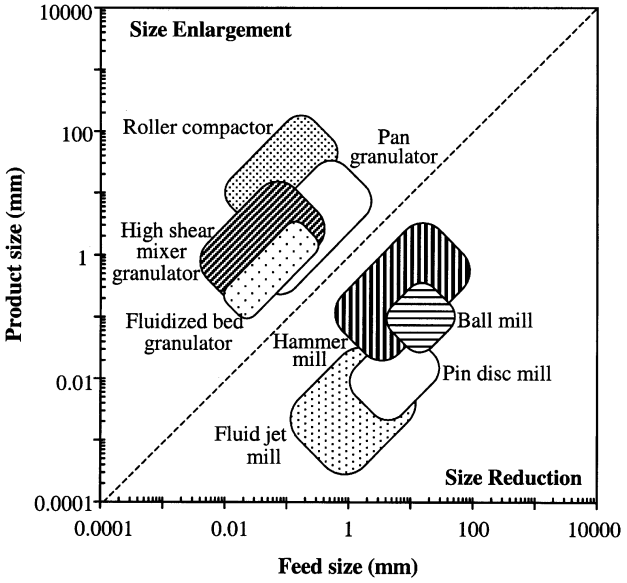

Figure 4. Equipment selection for crusher and granulator.

the passage of carrier gas (air) through the tablet bed (Figure 3). Extensive description of coating equipment can be found in Porter and Bruno (1989), Lachman et al. (1986), and Bauer et al. (1998). Table 11 is provided for coating equipment selection based on the level of control required and drying efficiency.

Drying in conventional coating pans takes place on the tablet bed surface which results in low drying efficiency. Sugar coating requires a long drying time for coating fluid to spread evenly on the tablets, and film coating requires rapid drying because the highly adhesive coating can otherwise lead to sticking. Therefore, only sugar coating and film coating using volatile organic solvents can be carried out in conventional coating pans. Immersion tube and sword, which can be used for film coating, are similar to conventional coating pans, but drying efficiency is improved by directing the drying air into the tablet bed. Coating of small particles is better done in fluidized beds. Fluidized-bed coating has the highest drying efficiency that is too high for sugar coating. Also, it is not suitable for tablets that are friable, or liable to chipping or edge abrasion because of the considerable degree of tablet-tablet contacting.

The equipment used in soft gelatin capsule production is not the same as those used in tablet and hard gelatin capsule production. A blender with internal parts such as a ribbon blender or an agitated vessel can be used. The high shear of the agitator mixes the viscous liquid or suspension. Deaeration is accomplished with simple equipment which exposes a thin layer of material to vacuum and transfers the material to the hopper of the capsule filling machine.

Selection of Equipment Operating Conditions. Operating conditions need to be identified to ensure that the equipment operates effectively to produce the desired results. Table 12 summarizes the relevant equations and typical values for selecting operating conditions.

In a fluid jet mill, particles traveling at high velocity break up upon hitting a target. The breakage number (Eq. 1) and the compaction stress (Eq. 3) can be used to estimate the necessary velocity for breakage by equating N_{Br} and N_{Br}^{*}. A fluid jet mill is usually connected to an air classifier, which recycles the oversized materials.

Table 10. Heuristics for Granulator Selection

- Use pan granulator, high shear mixer granulator, and fluidized-bed granulator for wet granulation and roller compactor for dry granulation.
- Use fluidized-bed granulator to obtain granules of low relative density (0.3–0.5), pan granulator for medium relative density (0.5–0.7), and high shear mixer granulator for high relative density (0.6–0.8).
- Use pan granulator only for producing granules larger than 1 mm.
- Use high shear mixer granulator for cohesive materials.
- Use high shear mixer granulator if viscous binder needs to be used.
- Use fluidized-bed granulator if simultaneous drying is desired.

The operating velocity of a pan granulator depends on the disc diameter and inclination. It is an important variable, because sliding will occur if it is too low or particles will be thrown out of the pan if it is too high. For a fluidized-bed granulator, air velocity that is sufficient to fluidize particles can be estimated (Fan, 1989). Throughput and compaction characteristics of the roller compactor are determined by the diameter, velocity, and gap of the roller. It is not very suitable for fine chemicals, which tend to have a high porosity, trapping air inside the compact. When pressure is released, expansion of trapped air may destroy the formed compact. However, a lower rotational speed would allow more time for deaeration to occur.

The output of the rotary tablet press is determined by the number of stations and rotation speed of the machine. The operating pressure can be determined using Eq. 11 in Table 6 (Heckel, 1961).

Step 4: product and process evaluation

The product should be evaluated to check for deviations from the quality factors stated in Step 1. Potential deviations and processing problems, along with the necessary modifications, are summarized in Table 13. Whether the process meets the PSD requirement is evaluated using discretized popula-

Table 11. Heuristics for Coating Equipment Selection

	Drying Efficiency	Low → High				
Level of Control	Coating Equipment	Sugar Coating	Film Coating (VOC Solvents)	Film Coating (high drying Efficiency Solvent)	Aqueous Film Coating	Film Coating of Powders
Low	Conventional coating pan	✓	✓			
	Immersion sword	✓	✓	✓		
	Perforated coating pan	✓	✓	✓	✓	
High	Fluidized-bed coating		✓	✓	✓	✓

Table 12. Equipment Operating Conditions

Equipment	Operating Conditions	Ref.
	Crusher	
Fluid jet mill	Minimum fluid velocity as shown in Eq. 11	Wibowo and Ng (2001a)
Pin disc mill	Disc peripheral rotational speed = 80 − 160 m/s	Kukla (1991)
Hammer mill	Hammer peripheral rotational speed = 20 − 60 m/s Discharge screen opening size = 2 − 10 mm	Hixon et al. (1990) Bernotat and Schönert (1988)
	Blender	
General considerations	Mixing time should be less than 10 min if lubricant is added to the blender before tableting.	Lieberman et al. (1989)
V-blender	Rotation speed ~ 14 rev/min Maximum filling level = 50%	Sastry et al. (1997) van den Bergh (1994)
Ribbon blender	Filling level ~ 50% Tip speed ~ 1.5 m/s	van den Bergh (1994) Sastry et al. (1997)
Nauta mixer	Screw revolutional speed ~ 65 rev/min Screw rotational speed ~ 2.5 rev/min	Sastry et al. (1997)
	Screen	
Vibrating screen	Inclined screen: 600−7,000 vibrations/min Horizontal screen: 300−3,000 vibrations/min	Walas (1988)
	Granulator	
Pan granulator	N_c = 50 to 75% of $N_{c,cr}$ (17) $N_{c,cr} = \sqrt{\frac{g\sin\phi_d}{2\pi^2 D_d}}$, $\phi_d = 45-55°$ (18)	Snow et al. (1997)
High shear mixer granulator (such as Plow-shaped mixer)	Typical speed of impeller = 60−800 rpm Typical speed of chopper = 500−3,500 rpm Residence time = 5−10 min	Snow et al. (1997)
Roller compactor	$C = 60\pi D_r l h_A n \gamma$ (19) $D_r = \frac{h_A}{1-\cos\alpha_E}\left(\frac{\gamma_0}{\gamma_t}(1-\epsilon)-1\right)$ (20) Typical roller speed = 0.7−1.5 m/s	Pietsch (1997a,b)
	Tableting Machine	
Rotary tablet press	Typical number of stations per press = 15−90 Typical rotational speed of press = 10−150 rpm	Lachman et al. (1986)
	Coating Machine	
Conventional coating pan	Typical rotation speed = 10−15 rpm Rotates at about 25° or horizontally (for diameter larger than 1.8 m) Air flow rate = 200−300 CFM	Bauer et al. (1998) Avis et al. (1999)
Immersion sword	Typical rotation speed = 10−15 rpm	
Perforated coating pan	Typical rotation speed = 12−15 rpm	

tion balance equations shown in Table 14 (Hill and Ng, 1995, 1996).

Manufacture of Tablets. United States Pharmacopeia (USP) has set standards on tablet quality. Each batch of tablets needs to pass tests on weight variation, content uniformity, disintegration, and dissolution. The API needs to be within a range of the labeled amount in the content uniformity test. The nonuniformity in the dosage form can be caused by segregation, which can be modified by using a binder or by adjusting the moisture content to affect particle cohesiveness.

If the disintegration time is too long, porosity can be increased by reducing compaction pressure. It can also be improved by using a higher concentration of disintegrant. In some cases, the limiting factor is low dissolution rate or low drug solubility. The dissolution time can be increased by reducing the constituent particle size. The solubility of a drug can be modified by adding salt to the formulation to modify its aqueous solubility (Bastin et al., 2000).

If the tablet strength is too weak, it will break up on handling. On the other hand, the disintegration time will be excessively long if tablet strength is too strong. For a weak tablet, bonding force among particles can be increased by reducing constituent particle size or by increasing the compaction pressure and vice versa. Binder concentration can also be increased (decreased) to increase (decrease) the binder effect.

Many problems may occur in tableting such as binding, sticking, picking, filming, capping, lamination, and chipping (Banker and Anderson, 1986; Bandelin, 1989). Binding to the die wall causes difficult ejection. This can be improved by increasing lubricant concentration or reducing the lubricant particle size. Sticking or picking is due to the improperly lu-

Table 13. Typical Deviations from Product Quality Factors and Necessary Modifications

Deviations/ Manufacturing Problems	Modifications
Tablet, Capsule and Powder	
Weight variation	• Avoid particle segregation • Add glidant to improve flowability and metering
Content nonuniformity	• Add binder to the granule mixture • Adjust moisture content of mixture
Disintegration time too long	• Increase porosity of tablet or granules • Reduce tablet size • Increase disintegrant concentration
Dissolution time too long	• Reduce constituent particle size
Drug dissolution too fast (tablet and capsule only)	• Increase constituent particle size • Consider using powder as the dosage form
Drug solubility too low in gastrointestinal tract	• Reduce constituent particle size • Add salts to the system to modify aqueous solubility
Tablet Only	
Tablet strength too weak	• Increase particle bonding force by reducing constituent particle size or by increasing compaction pressure • Increase binder concentration
Binding in the die or difficult ejection	• Increase amount of lubricant • Reduce lubricant particle size • Compress at lower temperature and humidity
Sticking, picking or filming	• Use a more effective lubricant • Increase the amount of anti-adherent • Decrease the moisture content of granulation • Polish punch faces
Capping and lamination	• Increase amount of binder • Add dry binder • Reduce the tableting rate (speed of rotary tableting press) • Reduce final compression pressure
Chipping	• Reduce fines and granule size • Polish punch faces
Bonding index too large	• Same as modifications for sticking and picking
Strain index too large	• Same as modifications for capping and lamination
Brittle fracture index too large	• Same as modifications for capping and lamination
Chipping of sugar coating	• Add small amounts of polymer to coating formulation • Reduce the use of insoluble fillers and pigments
Cracking of sugar coating	• Increase the time between compaction and sugar coating
Color variation in sugar and film coating	• Add sufficient coating solution to coat completely all tablets • Mix tablets thoroughly • Choose light color instead of dark color
Sticking and picking in film coating	• Reduce the coating solution application rate • Increase the drying air temperature and volume • Use a less tacky coating formulation
Roughness/Orange peel effects	• Reduce the degree of atomization of coating solution for air-spray systems • Increase spray rate and reduce processing temperature and airflows • Add a solvent to reduce the viscosity of the solution
Cracking of film coating	• Use a higher molecular weight polymers or polymer blends in the coating solution (Increase film tensile strength) • Adjust plasticizer, and pigment type and concentration (Reduce the internal stress in the film)
Bridging in film coating	• Increase plasticizer concentration • Use another plasticizer
Blistering in film coating	• Reduce the drying temperature

Table 14. Equipment Models Based on Discretized Population Balance Equations Using Geometric Size Intervals

Blender	$\omega_i = \dfrac{\sum_{k=1}^{m} W_{f,k}\,\omega_{fi,k}}{\sum_{k=1}^{n} W_{f,k}} \quad i = 1, ..., n$	(25)
Screen	$\omega_{i,1} = \dfrac{W_f \omega_{fi}(1-P_i)}{\sum_{i=1}^{n} W_f \omega_{fi}(1-P_i)} \quad i = 1, ..., n$	(26)
	$\omega_{i,2} = \dfrac{W_f \omega_{fi} P_i}{\sum_{i=1}^{n} W_f \omega_{fi} P_i} \quad i = 1, ..., n$	(27)
Crusher	$\omega_i = \dfrac{\omega_{f,i} + \tau \sum_{j=i+1}^{n} \beta_j b_{Mi,j} S_{Mj} \omega_j}{1 + \tau S_{Mi} \delta_i} \quad i = 1, ..., n$	(28)
	$\beta_j = \dfrac{1}{2 - \dfrac{1}{\bar{v}_j} \sum_{i=1}^{j-1} \bar{v}_i b_{i,j}}$	(29)
	$\delta_i = \dfrac{\dfrac{1}{\bar{v}_i} \sum_{j=1}^{i-1} \bar{v}_j b_{j,i}}{2 - \dfrac{1}{\bar{v}_i} \sum_{j=1}^{i-1} \bar{v}_j b_{j,i}}$	(30)
	(for binary breakage, $S_1 = 0$)	
Agglomerator	$N_i = \dfrac{N_{f,i} + \tau N_{i-1} \sum_{j=1}^{i-2} a_{i-1,j} N_j \left(\dfrac{\bar{v}_j}{\bar{v}_i - \bar{v}_{i-1}} \right) + \tau N_i \sum_{j=1}^{i-1} a_{i,j} N_j \left(\dfrac{\bar{v}_{i+1} - \bar{v}_i - \bar{v}_j}{\bar{v}_{i+1} - \bar{v}_i} \right) + \dfrac{\tau}{2} a_{i-1,i-1} N_{i-1}^2 \left(\dfrac{\bar{v}_{i-1}}{\bar{v}_i - \bar{v}_{i-1}} \right) + \dfrac{\tau}{2} a_{i,i} N_i^2 \left(\dfrac{\bar{v}_{i+1} - 2\bar{v}_i}{\bar{v}_{i+1} - \bar{v}_i} \right)}{1 + \tau \sum_{j=1}^{n} a_{i,j} N_j}$	(31)
	$i = 1, ..., n$	
	(for binary agglomeration)	

bricated or dried granules which cause tablets to stick to the punch surfaces. Capping and lamination is the breakup of the tablet horizontally and vertically, respectively. They are caused by the expansion of air entrapped in granulation, which cannot escape during compression. This can be improved by reducing tableting rate or compression pressure. Chipping occurs around the edge of a tablet. This is usually due to tooling problems and can be improved by polishing the punch faces.

Three tablet indices can be used to evaluate tablet strength: Bonding Index (BI), Strain Index (SI), and Brittle Fracture Index (BFI) (Hiestand, 1996; Jain, 1999)

$$BI = \frac{\sigma_T}{P} \tag{21}$$

$$SI = \frac{P}{E'} \tag{22}$$

$$BFI = \frac{1}{2}\left(\frac{\sigma_T}{\sigma_{To}} - 1 \right) \tag{23}$$

where P is dynamic indentation hardness, σ_{To} is the tensile strength of tablet with a hole, and E' is the reduced Young's Modulus

$$E' = \frac{E}{1 - \upsilon_1^2} \tag{24}$$

where υ_1 is its Poisson's ratio.

Typical BI is between 0.005 and 0.04. If the BI is too large, sticking or picking problems result during tableting. If it is too low, the tablet may be friable. A typical SI value is less than 0.04. If it exceeds 0.04, potential structural failure such as capping and lamination may result. Capping or lamination also occur if the BFI is larger than 0.2.

Problems may occur in sugar and film coating (Seitz et al., 1986; Porter and Bruno, 1989). Chipping of sugar coating can be improved by adding small amounts of polymer to increase the plasticity or by reducing the amount of insoluble filler and pigments to decrease the brittleness. The major cause of color variation in coating is due to the color migration of

water soluble dyes during drying. If this happens, using a light color instead of a dark color can improve the color distribution because light color usually shows little color distribution (Banker and Anderson, 1986).

Another common problem encountered in film coating is roughness or orange-peel effects. A gritty surface results if drying is so rapid that dry powders instead of small droplets of coating solution deposit on tablets. This can be improved by reducing the degree of atomization of coating solution, which results in larger droplets and, hence, longer drying time. Orange-peel surface can also be caused by inadequate spreading of the coating solution before drying. This can be improved by increasing spray rate to provide a sufficient amount of solution to coat tablets, and by reducing processing temperature and airflow to reduce the drying rate. A gritty surface caused by a viscous coating solution can be improved by adding a solvent.

Bridging occurs when the internal stress of the film is so high that partial or complete detachment of the coating occurs in the region of the logo. Increasing the plasticizer concentration or using another plasticizer can reduce the internal stress encountered in the film. Blistering may occur in the coating if the solvent evaporates too rapidly from tablets and can be avoided by reducing the drying temperature.

Manufacture of Capsules. Inside the gastrointestinal tract, gelatin capsules readily dissolve. However, long dissolution time and low solubility of API can be encountered. Modifications as mentioned in tablet manufacture can be applied to capsules as well. The disintegration time of the granules in the capsule can be shortened if granule porosity is increased.

Examples

Three examples are presented here to illustrate the use of this systematic procedure for process synthesis and development.

Example 1: development of Vitamin C tablet

A company wants to produce ascorbic acid (Vitamin C) tablet as a dietary supplement. The tablets should be absorbed into the body quickly and should not break up on routine handling. Also, they should release the designated amount of ascorbic acid to the body. The input information is shown in Table 15. Some of the parameters are not readily available and are estimated. The details of breakage and agglomeration parameters are not reported here. Production of 10,000 tablets per min is planned.

Step 1: The standard disintegration time of a vitamin tablet is 30 min (United States Pharmacopeia, 1990). Ascorbic acid is water soluble (30 g/100 mL) and, therefore, dissolution is fast. The constituent particle size is around 5 μm. The USP also sets standards on ascorbic acid tablets to contain not less than 90% and not more than 110% of the labeled amount.

Step 2: Since the melting point of ascorbic acid is well above 100°C and it has high solubility in water, a tablet is

Table 15. Input Table for Example 1 (Vitamin C Tablet)

Properties of Ascorbic Acid	
Mass	350 mg
Melting point	191°C
Water solubility	30 g/100 mL
Crystal form	Monoclinic platelets and needles
Taste	Sharp acidic taste
Hamaker constant, A	4.5×10^{-20} J
Bulk density	530 kg m^{-3}
Yield strength, σ_y	1 MPa
Mean particle size	150 μm
Angle of internal friction, ϕ	40°
Angle of wall friction, ϕ_w	23°
Properties of Microcrystalline Cellulose	
Mass	79 mg
Water solubility	Insoluble
Hamaker constant, A	1.85×10^{-19} J
Mean particle size	100 μm
Properties of Magnesium Stearate	
Mass	3.5 mg
Mean particle size	50 μm
Properties of Povidone	
Mass	17.5 mg
Mean particle size	100 μm
Properties of Tablet	
Mass, m	450 mg
Diameter, D	10 mm
Constituent particle size, d_p	5 μm
Agglomerator	
Roller diameter, D_r	0.2 m
Agglomerate porosity, ϵ_r	20%
Tableting Machine	
Hopper outlet diameter, D_o	5 cm

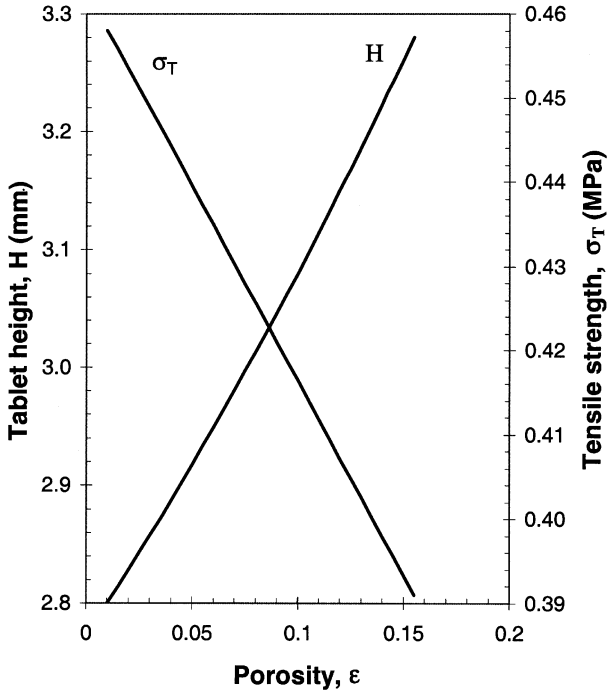

Figure 5a. Dependence of tablet height and tensile strength on table porosity (Vitamin C tablet).

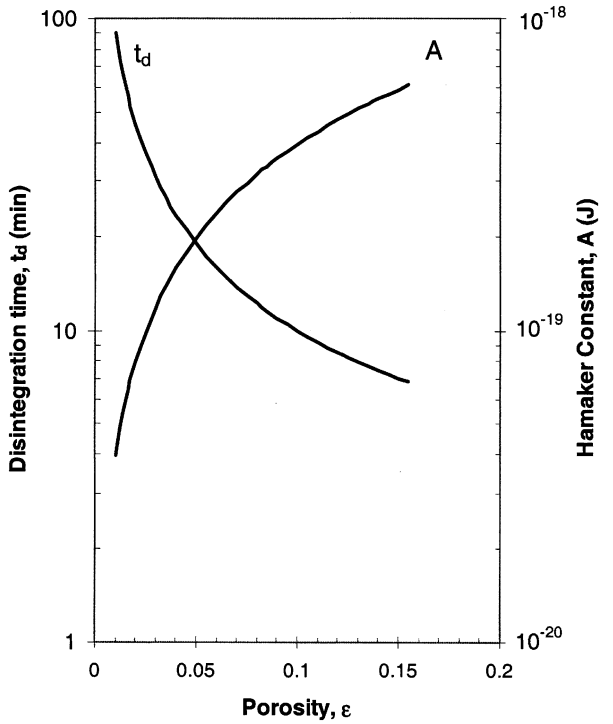

Figure 5b. Dependence of disintegration time, and required Hamaker constant on tablet porosity (Vitamin C tablet).

chosen to be the dosage form (Table 3). The nonhygroscopic tablet is stable at room conditions.

It is decided to manufacture 450 mg tablets containing 350 mg ascorbic acid and a diameter of 10 mm. Coating is needed for Vitamin C tablets to cover the unpleasant taste of ascorbic acid. Enteric coating is not necessary, because Vitamin C does not cause stomach irritation. Microcrystalline cellulose (79 mg), which is water insoluble, is added as a diluent. Magnesium stearate (3.5 mg), a common lubricant, is used in this system (Bhagavan and Wolkoff, 1993).

Figure 5a shows the dependence of tablet height and tensile strength on porosity. The tensile strength is calculated as $\sigma_T = 1.5\sigma_c$ where σ_c is in turn calculated using Eq. 3 for fixed values of v_t and θ. In other words, we have assumed a safety factor of 50% to ensure that the tablet does not break up for this impact velocity and angle of impact. An increase in tablet porosity causes tablet height to increase, and tensile strength to decrease. It is desired to determine the Hamaker constant required to yield such a tensile strength. Figure 5b shows the dependence of such a calculated Hamaker constant on porosity (Eq. 10).

Before deciding whether a binder is needed to provide the required Hamaker constant for the tablet, the porosity has to be selected first. Since microcrystalline cellulose is insoluble, a soluble disintegrant such as povidone (17.5 mg) is added before compression. The disintegration time can be calculated using Eq. 9 and Figure 5b also shows its dependence on porosity. With a disintegration time of 30 min or less, porosity should be larger than 3% and the Hamaker constant should be larger than 1.18×10^{-19} J. If a typical tablet porosity of around 10% is chosen, the tablet having a Hamaker constant of 4×10^{-19} J disintegrates in 10 min. Also, such a porosity gives a tablet height of 3.1 mm and a tensile strength of 0.416 MPa. The required Hamaker constant is larger than the Hamaker constant of the API and, therefore, a cohesive material needs to be added. Microcrystalline cellulose is cohesive and Eq. 7 can be used to check its applicability as binder. The required Hamaker constant of the binder is 1.77×10^{-19} J, which is similar to that of microcrystalline cellulose (Table 15) and, therefore, it can also serve as a binder.

Step 3: After choosing excipients and the tablet structure, a flowsheet needs to be synthesized and equipment needs to be selected. Figure 6 shows a possible flowsheet. A crusher is required since the ascorbic acid and microcrystalline cellulose particles in the feed are larger than 5 μm. It is also used to make the needle-shaped ascorbic acid more rounded. Since micron-sized particles are produced, a pin disc mill is used and the disc rotation speed is set at 120 m/s (Table 12).

After blending, a decision needs to be made on whether granulation or compaction should be performed. Flowability is an important criterion and the minimum outlet diameter for a particular particle size calculated using the flow number (Eqs. 13–14) is shown in Figure 7. For a hopper of 0.05 m outlet diameter, particles smaller than 0.6 mm might cause flow stoppage. Since our particle size is 5 μm, granulation is recommended. More importantly, metering of such small particles and dusting are potentially serious problems in processing. For both reasons, a granulation method will be chosen. Whether we can use dry granulation can be determined using Eq. 16 which is plotted in Figure 8a as the dependence of critical compaction number N_{co}^* on a strength index. With a desired agglomerate porosity of 20% and $F_{adh}/\sigma_y d_p^2 =$

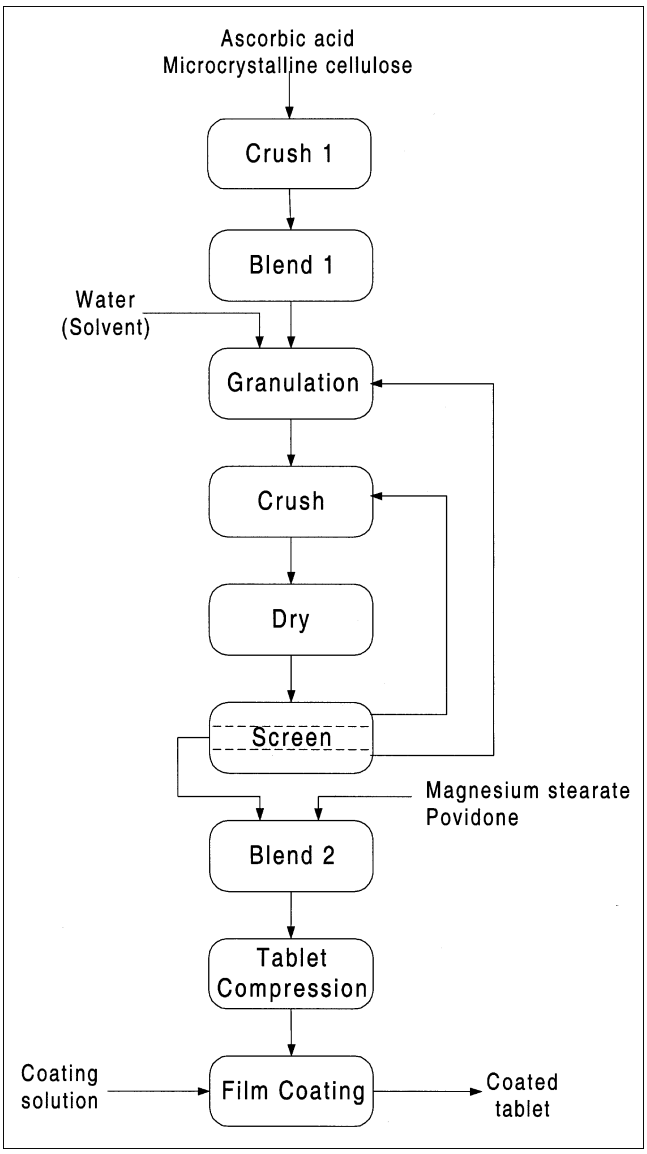

Figure 6. Flowsheet for Vitamin C tablet manufacture.

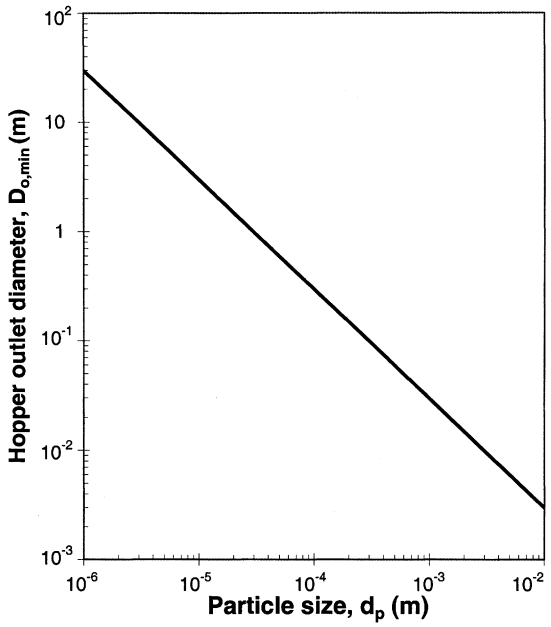

Figure 7. Relationship between minimum hopper outlet diameter and particle size.

0.0034, a strength index of 1.36×10^{-2} is obtained for this system which in turn leads to a critical compaction number of 32. For a roller compactor, its maximum compaction pressure can be related to roller diameter, roller speed, gap width, precompaction pressure and material characteristics (Pietsch, 1991). The dependence of the compaction pressure on roller diameter for this system is shown in Figure 8b. The roller diameter available is 0.2 m, which gives a maximum compaction pressure σ_c of 18 MPa. Substituting into Eq. 15 yields a compaction number of 18, which is smaller than the critical compaction number. Therefore, wet granulation has to be used as the granulation method. This decision is also supported by the heuristic in Table 8, which suggests that wet granulation is preferred for particles smaller than 150 μm if air entrapment is a potential problem. This is because dry granulation needs to be carried out at low roller speed for such small particles. The relative density of the granules is 0.8 for a porosity of 20%, and a high shear mixer granulator is used (Table 10). The impeller and chopper speed is set at 300 rpm and 1,000 rpm, respectively (Table 12). The diluent, microcrystalline cellulose, is mixed with ascorbic acid first and water is added in the granulation step as solvent.

Film coating is chosen for its ease of control. Anyway, sugar coating produces unacceptably large tablets. A perforated coating pan is selected because it offers a high drying efficiency (Table 11). The pan rotation speed is set at about 15 rpm (Table 12).

Step 4: Vitamin C tablets are then produced according to the flowsheet shown in Figure 6 and the operating conditions suggested in Step 3. The product is examined to see whether deviations from the desired quality factors have occurred. For illustrative purposes, three possible scenarios are discussed and possible modifications are suggested to fix the problem.

Scenario 1: The disintegration test shows that the time for Vitamin C tablets to disintegrate is longer than the standard set by USP (30 min). A possible modification is to increase the porosity of tablets to allow more body fluid to imbibe into the tablet. This can be achieved by reducing the compaction pressure. Increasing the disintegrant concentration or using a more effective disintegrant (such as starch) can also reduce the disintegration time. This should be balanced with tablet strength since tablets may be too weak if too much disintegrant is added.

Scenario 2: Capping results in some of the tablets produced. It is mainly caused by the expansion of air which cannot escape during compaction. As suggested by Table 13, reducing the speed of the rotary press and the final compression pressure would allow more air to escape. However, this would lead to reduced output due to the reduction of the tableting rate. Another remedy is to increase the binder concentration to bind particles together to prevent capping. However, this might increase the disintegration time due to the larger adhesion force among particles. Experiments are

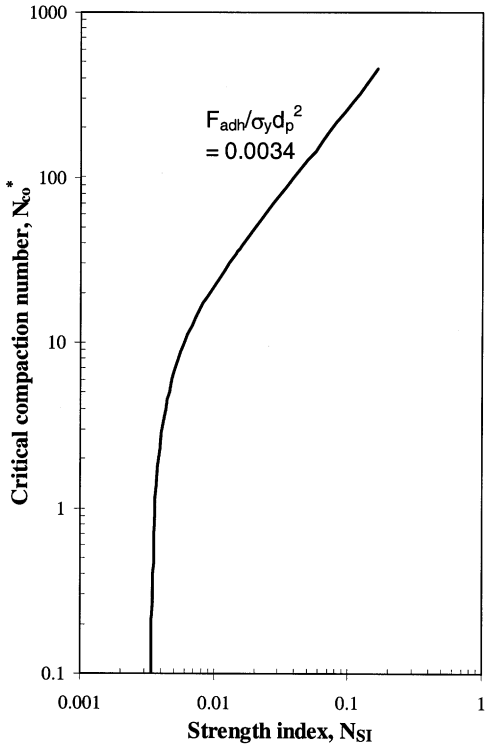

Figure 8a. Dependence of critical compaction number on strength index.

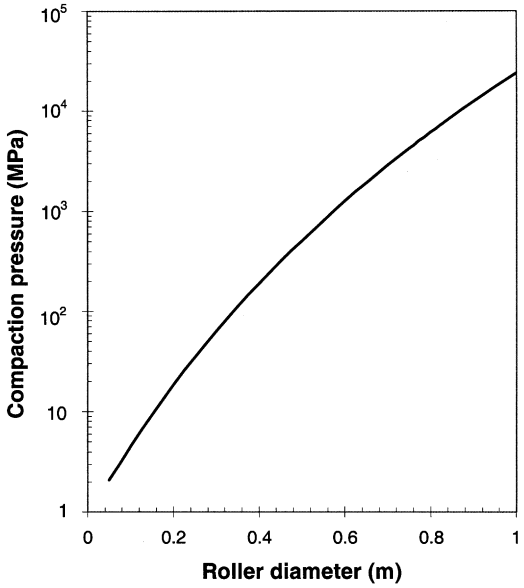

Figure 8b. Relationship between compaction pressure and roller diameter.

required in such a case in order to compare the two remedies and suggest the best suitable solution.

Scenario 3: The tablet coating appears gritty. According to Table 13, the degree of atomization can be reduced to prevent the deposition of dry powders on tablets. The surface can also be improved by reducing the processing temperature and airflows to allow a longer time for spreading. Adding a solvent such as ethanol provides easier spreading of coating solution on tablets.

The process of producing Vitamin C is simulated based on the flowsheet shown in Figure 6. Figure 9 shows the PSDs for each stream calculated by using the population balance equations in Table 14. Liquid binder is ignored in the simulation, because most of the binder solvent will be removed in a subsequent drying step. Also, drying is not included in the simulation because tray drying is not expected to change the PSD.

Example 2: development of antacid effervescent tablets

This example illustrates the use of the systematic procedure to produce effervescent tablets which are supposed to dissolve in water before ingestion. Effervescent tablets contain three main ingredients: API, a soluble acid source, and an alkali metal carbonate. The acid source and metal carbonate react to release carbon dioxide gas on contact with water. The acid source and the metal carbonate used in this example are citric acid and sodium bicarbonate, respectively. No API is used in this example. Citric acid (1206.6 mg) and sodium bicarbonate (1583.4 mg) are available in granular form of particle size about 10 μm. The input information is given in Table 16. Only Steps 1 to 3 are illustrated.

Step 1: Effervescent tablets are disintegrated and dissolved in water prior to ingestion. A properly effervescent tablet should disintegrate and dissolve within 2 min (Mohrle, 1989). The constituent particle size should be small (about 15 μm) to allow fast dissolution. As for conventional tablets, they should contain less than 10% variation of the labeled amount. They should not break up on routine handling. Weight and composition need to be uniform for each tablet. They should be properly packaged to keep moisture away, because water will initiate the effervescent reaction, degrading the product.

Step 2: First, we select the dosage form. The melting point of citric acid and sodium bicarbonate are above 100°C; therefore, tableting of these ingredients should pose no problem (Table 3). Citric acid is deliquescent and, therefore, it cannot be encapsulated (Verhoff, 1988). Both ingredients are very soluble in water and powder might appear to be the preferred dosage form. However, the ingredients are dissolved in water before ingestion and, therefore, stomach irritation will not be a problem. Also, since the ingredients are very reactive with water, a powder dosage form is more likely to degrade than tablets.

Since effervescent tablets are not directly swallowed, a large tablet size is acceptable. It is decided to produce 3,100 mg tablets with a diameter of 25 mm. Coating is not needed; however, packaging needs to be carefully designed to prevent exposure to the environment.

Diluents are not required to make up tablet size. Although water insoluble lubricant provides better lubricating power, all excipients need to be water soluble in effervescent tablets. A water soluble lubricant such as polyethylene glycol (155 mg) is used. Metal carbonate acts as a disintegrant so that no disintegrant is needed. Figure 10a is a plot of tablet height and tensile strength against porosity, and Figure 10b plots the Hamaker constant and disintegration time against porosity. Equation 8 is used to calculate the disintegration time since all components are water soluble. For tablets to disinte-

grate within 2 min, a porosity of 16% and a Hamaker constant of 3.3×10^{-19} J is required (Figure 10b). Since citric acid and sodium bicarbonate are not cohesive, a soluble binder sucrose (155 mg) with the required Hamaker constant is selected. This gives a tablet height and tensile strength of 5.3 mm and 0.1 MPa, respectively (Figure 10a).

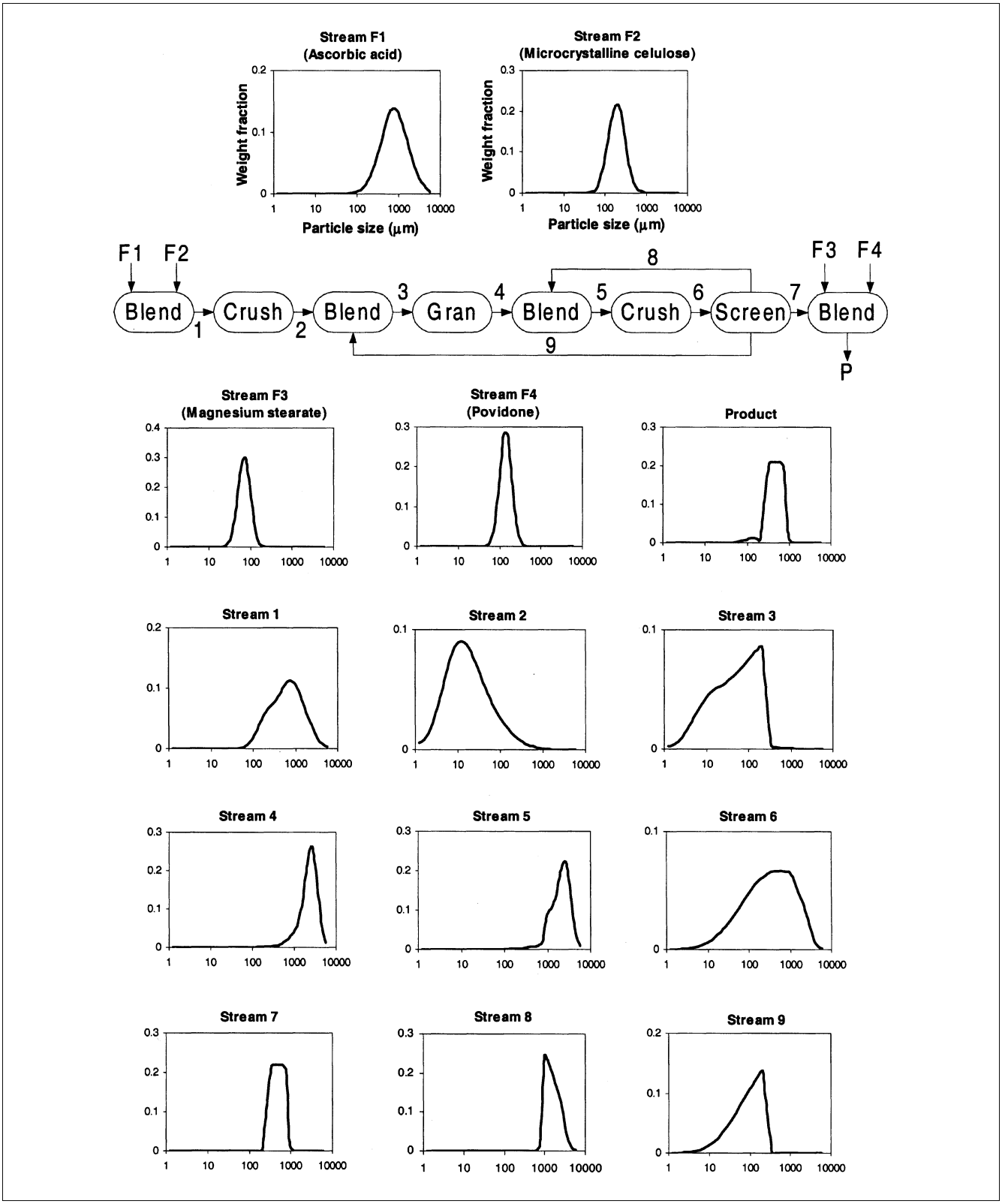

Figure 9. Particle-size distribution in each stream of the Vitamin C process.

Table 16. Input Table for Example 2 (Antacid Effervescent Tablet)

Properties of Citric Acid	
Mass	1,395 mg
Melting point	153°C
Water solubility	200 g/100 mL
Crystal form	Monoclinic holohedra
Taste	Odorless
Hamaker constant, A	3×10^{-20} J
Bulk density	1,665 kg m^{-3}
Mean particle size	10 μm
Properties of Sodium Bicarbonate	
Mass	1,395 mg
Melting point	270°C
Water solubility	8.3 g/100 mL
Crystal form	Monoclinic prisms
Taste	Odorless
Hamaker constant, A	6.5×10^{-20} J
Bulk density	869 kg m^{-3}
Mean particle size	10 μm
Properties of Citric Acid and Sodium Bicarbonate Mixture	
Yield strength, σ_y	0.8 MPa
Angle of internal friction, ϕ	30°
Angle of wall friction, ϕ_w	20°
Properties of Sucrose	
Mass	155 mg
Hamaker constant, A	4×10^{-19} J
Properties of Polyethylene Glycol	
Mass	155 mg
Water solubility	miscible
Properties of Tablet	
Mass, m	3,100 mg
Diameter, D	25 mm
Constituent particle size, d_p	15 μm
Diffusivity of water soluble components in tablet, D_i	2.6×10^{-7} m^2/s
Agglomerator	
Roller diameter, D_r	0.2 m
Agglomerate porosity, ϵ_r	25%
$F_{adh}/\sigma_y d_p^2$	0.00213
Tableting Machine	
Hopper outlet diameter, D_o	5 cm

Step 3: Figure 11 shows the flowsheet for effervescent tablet production. A crusher is not required since the feed citric acid and sodium bicarbonate particles are sufficiently small. An analysis of whether granulation is necessary shows that for a hopper outlet diameter of 0.05 m, the minimum particle size that does not cause flow stoppage is 0.35 mm. Therefore, granulation needs to be performed. Dry granulation is selected because wet granulation with water would start the effervescent reaction. For a desired agglomerate porosity of 25%, the strength index is 6.38×10^{-3} and the corresponding critical compaction number is 20.5. A roller compactor with a roller diameter of 20 cm gives a maximum compaction pressure 18 MPa and compaction number 22.5. This implies that dry granulation can be used.

Example 3: development of ginseng extract capsule

A common traditional Chinese medicine ginseng is considered in this example. Each dosage provides 250 mg ginseng extract. For these types of health products and dietary supplements, only limited information on their physical and chemical properties is available. Steps 1 to 3 are discussed here.

Step 1: Dissolution and absorption needs to be fast for the therapeutic effect. Ginseng extract is water soluble and the constituent particle size should be sufficiently small for easy dissolution or absorption.

Step 2: Since most herbal powders lack compressibility, it is decided to encapsulate ginseng in hard gelatin capsules (Cunningham, 2001). Also, since ginseng has a special odor, it is better to be encapsulated anyway. In order to encapsulate 250 mg ginseng, a capsule of size 0 is selected, which holds up to 0.75 mL powder. Therefore, this allows the inclusion of microcrystalline cellulose which serves both as a diluent and a dry binder for enhanced processing. Water insoluble lubricant, magnesium stearate, is selected.

Step 3: For most traditional Chinese medicine, after extracting the key ingredients, they are sent to a spray dryer to produce powder. The typical product size of a spray dryer is 150 μm. Since metering and flowability are usually problems for small particles, granulation is recommended. A study on whether granulation is necessary shows that for a hopper outlet diameter of 0.05 m, the minimum particle size that does not cause flow stoppage is 0.25 mm. Therefore, particles are granulated to a size of 500 μm to allow easier processing.

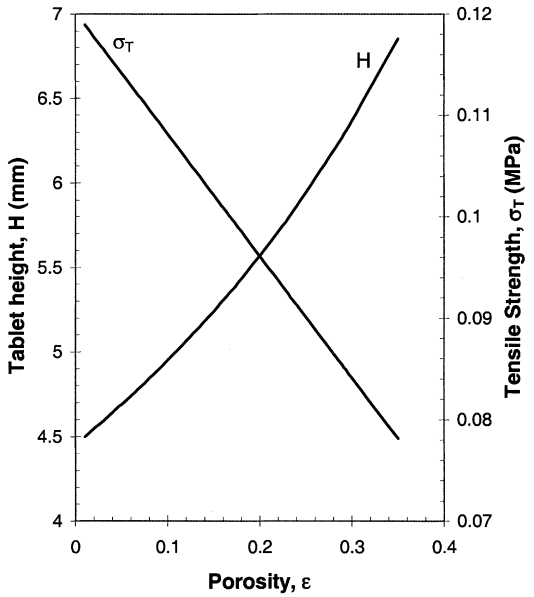

Figure 10a. Dependence of tablet height and tensile strength on tablet porosity (antacid effervescent tablet).

Conclusions

High-value-added products have gained increasing attention in the chemical processing industries (Kind, 1999; Cussler and Moggridge, 2001; Wibowo and Ng, 2001b, 2002). For these products, product quality and reduced time to market are the primary concerns. To design such products and the manufacturing process, the combination of process systems engineering and basic engineering sciences is crucial. Based on a multiscale approach which considers plant, equipment, and particle scale issues (Ng, 2001), a systematic product-centered process synthesis and development procedure for tablets and capsules is formulated (Figure 12). The desired product quality factors are identified based on the therapeutic and physical requirements. Supporting ingredients and product structure are selected. A process flowsheet is then synthesized to produce products with the desired qualities. Finally, product and process are evaluated and the necessary modifications are identified. Heuristics and mathematical models are developed for each step to assist decision-making. The procedure is expected to provide a more efficient development workflow and thus a lower development cost and reduced time to market.

The present study can be extended in many ways. Multifunctional equipment such as a one-pot processor can be used to perform several unit operations and its applicability to tablet and capsule processing needs to be studied. Ultrafine particles allow effective absorption of insoluble drugs. A systematic design procedure for ultrafine solids processing is not

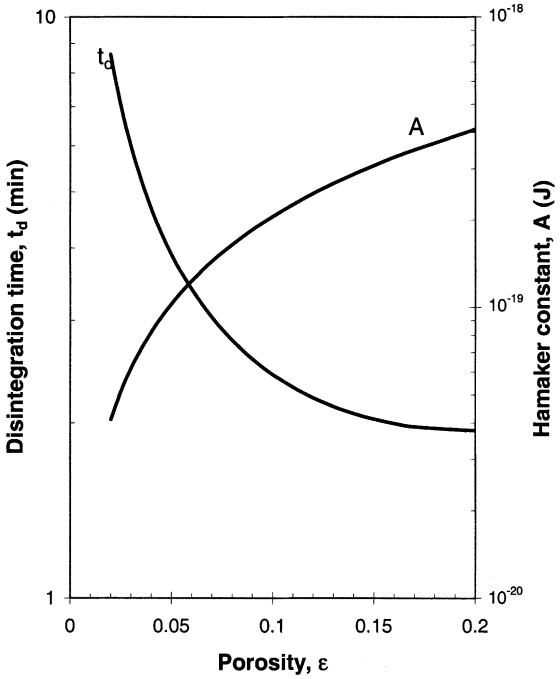

Figure 10b. Dependence of disintegration time, and required Hamaker constant on tablet porosity (antacid effervescent tablet).

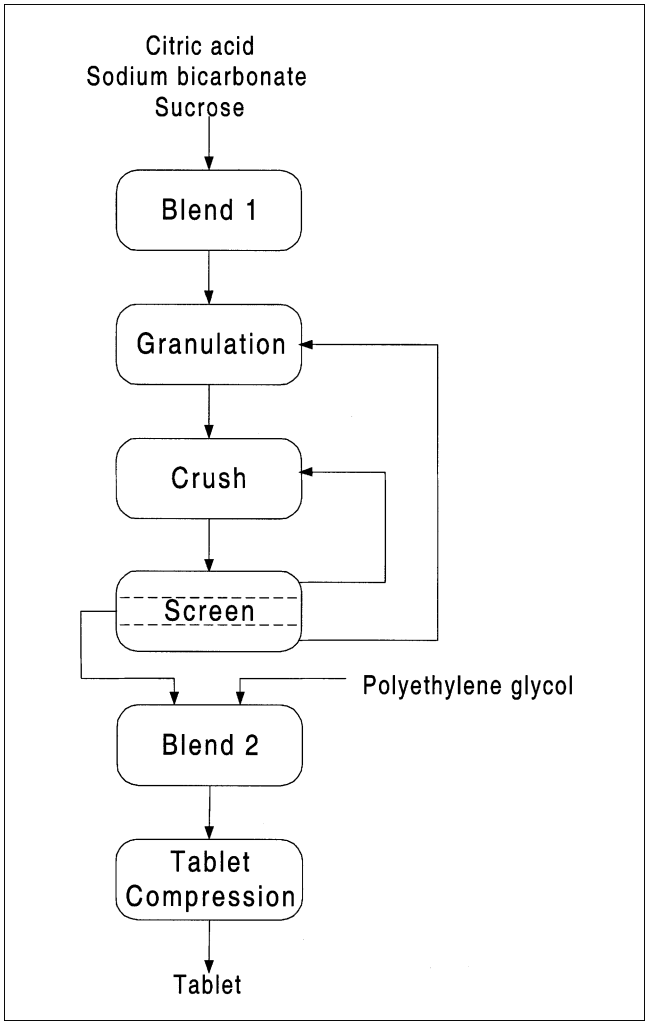

Figure 11. Flowsheet for antacid effervescent tablet manufacture.

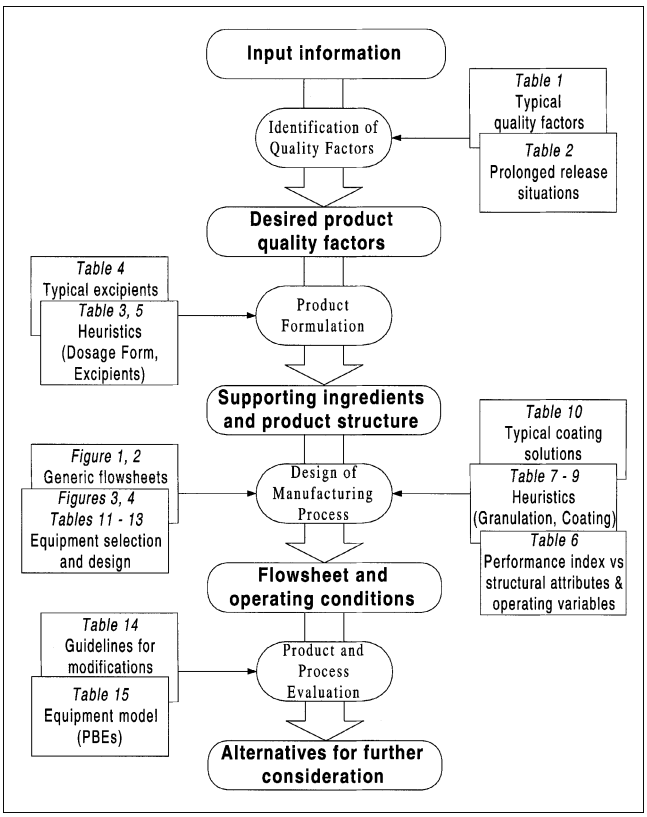

Figure 12. Systematic procedure for synthesis and development of tablet, capsule and powder manufacturing process.

yet available. The heuristics and mathematical models developed here are only applicable to tablets and capsules. The procedure can be extended to general solid dosage forms including prolonged release. Efforts in these directions are now underway.

Acknowledgments

Financial support from the Research Grant Council DAG00/01 is gratefully acknowledged. We also thank Christianto Wibowo for his comments and assistance on solids processing problems in this study.

Notation

$a_{i,j}$ = specific rate of agglomeration between a particle in size interval i and a particle in size interval j, $kg^{-1} \cdot min^{-1}$
A = Hamaker constant, J
A' = constant reflecting material deformation in Eq. 12
$b_{Mi,j}$ = mass fraction of material broken from size interval j which appears in size interval i
BI = bonding index, dimensionless
BFI = brittle fracture index, dimensionless
C = throughput of roller compactor, kg/h
d_p = constituent particle size, μm
D = tablet diameter, mm
D_d = disc diameter, m
D_i = diffusivity of water soluble components, m^2/s
D_o = hopper outlet diameter, cm
D_r = roller diameter, cm
E = tablet Young's modulus, N/m^2
E' = reduced Young's modulus, N/m^2
F_{adh} = adhesion force among particles, N
F_{vdw} = van der Waals force among particles, N
g = gravitational constant, m/s^2
h_A = gap width between rollers, cm
H = tablet height, mm
k = constant in Eq. 16
k' = constant reflecting material properties in Eq. 12
l = roller length, working width, cm
m = tablet mass, kg
m = total number of input streams in Table 14
n = roller speed, rev/min
n = total number of geometric size intervals in Table 14
N_{BI} = brittleness index, dimensionless
N_{Br} = breakage number, dimensionless
N_c = operating speed of disc, m/s
$N_{c,cr}$ = critical speed of disc, m/s
N_{Co} = compaction number, dimensionless
N_{fi} = number of particles in size interval i in feedstream
N_{Fw} = flow number, dimensionless
N_i = number of particles in size interval i in product stream
N_{SI} = strength index, dimensionless
P = dynamic indentation hardness, N/m^2
P_i = probability that a particle in size interval i ends up in the underflow
SI = strain index, dimensionless
$S_{M,j}$ = specific rate of breakage of particles in size interval i, min^{-1}
t_d = disintegration time, s
v = minimum fluid velocity, m/s
v_I = Poisson's ratio
$\bar{v}_i$ = dimensionless volume in size interval i, $\mu m^3/\mu m^3$
v_t = tablet impact velocity, m/s
W_f = feed flow rate, kg/min
z = separation distance, m

Greek letters

α_E = gripping angle, deg
β = half cone angle of a hopper, deg
β_j = probability function in the breakage equation
γ = apparent sheet density, kg/m^3
γ_0 = tap density at the gap of the roller compactor, kg/m^3
γ_f = tablet surface fracture energy, J/m^2
γ_t = tap density at the gripping angle, kg/m^3
θ = angle of impact of tablet onto surface, deg
δ_i = probability function in the breakage equation
ϵ = tablet porosity
ϵ_r = agglomerate porosity at the gap of the roller compactor
ϵ_s = porosity of solid in hopper
ϕ = angle of internal friction, deg
ϕ_d = angle of the disc to the horizontal, deg
ϕ_w = angle of wall friction, deg
μ = viscosity, $kg/m \cdot s$
ρ_s = density of solid in hopper, kg/m^3
ρ_t = tablet density, kg/m^3
σ = interfacial tension, N/m
σ_c = applied stress, N/m^2
σ_T = tensile strength of tablet, N/m^2
σ_{To} = tensile strength of tablet with a hole, N/m^2
σ_y = material yield strength, N/m^2
τ = residence time, s
ω_{fi} = weight fraction of particles in size interval i in feed stream
ω_i = weight fraction of particles in size interval i in product stream

Superscripts

i, j, k = indices
max = maximum value
0 = initial value
$*$ = critical number

Literature Cited

Alessi, P., A. Cortesi, I. Kikic, N. R. Foster, S. J. Macnaughton, and I. Colombo, "Particle Production of Steroid Drugs Using Supercritical Fluid Processing," *Ind. Eng. Chem. Res.*, **35**, 4718 (1996).
Anderson, N. G., "Final Product Form and Impurity Considerations,"

Practical Process Research & Development, Academic Press, San Diego, p. 251 (2000).
Ansel, H. C., and N. G. Popovich, "Peroral Solids, Capsules, Tablets, and Controlled-Release Dosage Forms," *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea & Febiger, Philadelphia (1990).
Avis, K. E., A. J. Shukla, and R. K. Chang, eds., *Pharmaceutical Unit Operations: Coating*, Interpharm Press, Buffalo Grove, IL (1999).
Bailey, E. J., ed., *Financial Times Pharmaceuticals Global Pharmaceutical Industry Facts & Figures Sourcebook 2000*, Financial Times Pharmaceuticals, London (2000).
Bandelin, F. J., "Compressed Tablets by Wet Granulation," *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, 2nd ed., H. A. Lieberman, L. Lachman, and J. B. Schwartz, eds., Marcel Dekker, New York (1989).
Banker, G. S., and N. R. Anderson, "Tablets," *The Theory and Practice of Industrial Pharmacy*, 3rd ed., L. Lachman, H. A. Lieberman, and J. L. Kanig, eds., Lea & Febiger, Philadelphia (1986).
Bastin, R. J., M. J. Bowker, and B. J. Slater, "Salt Selection and Optimization Procedures for Pharmaceutical New Chemical Entities," *Org. Process Res. Dev.*, **4**, 427 (2000).
Bauer, K. H., K. Lehmann, H. P. Osterwald, and G. Rothgang, *Coated Pharmaceutical Dosage Forms*, CRC Press, Boca Raton, FL (1998).
Bernotat, S., and K. Schönert, "Size Reduction," *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. B2, 5th ed., VCH, Weinheim, Germany (1988).
Bhagavan, H. N., and B. I. Wolkoff, "Correlation Between the Disintegration Time and the Bioavailability of Vitamin C Tablets," *Pharm. Res.*, **10**(2), 239 (1993).
Charoenchaitrakool, M., F. Dehghani, N. R. Foster, and H. K. Chan, "Micronization by Rapid Expansion of Supercritical Solutions to Enhance the Dissolution Rates of Poorly Water-Soluble Pharmaceuticals," *Ind. Eng. Chem. Res.*, **39**, 4794 (2000).
Cole, G., J. Hogan, and M. Aulton, *Pharmaceutical Coating Technology*, Taylor & Francis, London (1995).
Cunningham, C. R., "Method for Increasing the Compressibility of Herbal Powder Dosages," *Proc. of 5th ACPA Int. Conf.*, Singapore (2001).
Cussler, E. L., and J. D. Moggridge, *Chemical Product Design*, Cambridge University Press, Cambridge, U.K. (2001).
Dahneke, B., "The Capture of Aerosol Particles by Surfaces," *J. Colloid Interf. Sci.*, **37**, 342 (1971).
De Jong, J. A. H., "Tablet Properties as a Function of the Properties of Granules Made in a Fluidized Bed Process," *Powder Technol.*, **65**, 293 (1991).
Ennis, B. J., G. I. Tardos, and R. Pfeffer, "A Microlevel-based Characterization of Granulation Phenomena," *Powder Technol.*, **65**, 257 (1991).
Fayed, M. E., and L. Otten, eds., *Handbook of Powder Science and Technology*, 2nd ed., Chapman and Hall, New York (1997).
Fan, L. S., *Gas-Liquid-Solid Fluidization Engineering*, Butterworths, Boston (1989).
Heckel, R. W., "Density-Pressure Relationships in Powder Compaction," *Trans. Metal. Soc. AIME*, **221**, 671 (1961).
Hiestand, E. N., "Rationale for and the Measurement of Tableting Indices," *Pharmaceutical Powder Compaction Technology*, 1st ed., G. Alderborn and C. Nyström, eds., Marcel Dekker, New York (1996).
Hill, P. J., and K. M. Ng, "New Discretization Procedure for the Breakage Equation," *AIChE J.*, **41**, 1204 (1995).
Hill, P. J., and K. M. Ng, "New Discretization Procedure for the Agglomeration Equation," *AIChE J.*, **42**, 727 (1996).
Hixon, L., M. Prior, H. Prem, and J. van Cleef, "Sizing Materials by Crushing and Grinding," *Chem. Eng.*, **97**(11), 94 (1990).
Holm, P., "High Shear Mixer Granulators," *Handbook of Pharmaceutical Granulation Technology*, D. M. Parikh, ed., Marcel Dekker, New York (1997).
Jain, S., "Mechanical Properties of Powders for Compaction and Tableting: an Overview," *Pharmaceutical Sci. & Technol. Today*, **2**(1), 20 (1999).
Kibbe, A. H., ed., *Handbook of Pharmaceutical Excipients*, 3rd ed., American Pharmaceutical Association, Washington, DC (2000).
Kind, M., "Product Engineering," *Chem. Eng. Process*, **38**, 405 (1999).
Krycer, I., D. G. Pope, and J. A. Hersey, "An Evaluation of Tablet Binding Agents: I. Solution Binders," *Powder Technol.*, **34**, 39 (1983).
Kukla, R. J., "Understand Your Size-Reduction Options," *Chem. Eng. Prog.*, **87**(5), 23 (1991).
Lachman, L., H. A. Lieberman, and J. L. Kanig, eds., *The Theory and Practice of Industrial Pharmacy*, 3rd ed., Lea & Febiger, Philadelphia (1986).
Lieberman, H. A., L. Lachman, and J. B. Schwartz, eds., *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, 2nd ed., Marcel Dekker, New York (1989).
Lordi, N. G., "Sustained Release Dosage Forms," *The Theory and Practice of Industrial Pharmacy*, 3rd ed., L. Lachman, H. A. Lieberman, and J. L. Kanig, eds., Lea & Febiger, Philadelphia (1986).
MacDonald, M. J., C. F. Chu, P. P. Guilloit, and K. M. Ng, "A Generalized Blake-Kozeny Equation for Multisized Spherical Particles," *AIChE J.*, **37**, 1583 (1991).
Matheis, G., "Flavorings for Pharmaceutical Products," *Food Flavorings*, 3rd ed., P. R. Ashurst, ed., Aspen Publishers, Gaithersburg, MD (1999).
Mohrle, R., "Effervescent Tablets," *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, 2nd ed., H. A. Lieberman, L. Lachman, and J. B. Schwartz, eds., Marcel Dekker, New York (1989).
Ng, K. M., "A Multiscale-Multifaceted Approach to Process Synthesis and Development," *ESCAPE 11*, R. Gani and S. B. Jorgensen, eds., Elsevier Amsterdam (2001).
Parikh, D. M., ed., *Handbook of Pharmaceutical Granulation Technology*, Marcel Dekker, New York (1997).
Parrott, E. L., "Solid Pharmaceuticals," *Pharmaceutical Technology: Fundamental Pharmaceutics*, Burgess Publishing Company, Minneapolis (1970).
Perry, R. H., D. W. Green, and J. O. Maloney, eds., *Perry's Chemical Engineers' Handbook*, 7th ed., McGraw-Hill, New York (1997).
Pietsch, W., *Size Enlargement by Agglomeration*, Wiley, Chichester, U.K.; Otto Salle Verlag, Frankfurt/M, Germany; and Verlag Saureländer AG, Aarau, Salle Sauerlander, Germany (1991).
Pietsch, W., "Successfully Use Agglomeration for Size Enlargement," *Chem. Eng. Prog.*, **92**(4), 29 (1996).
Pietsch, W., "Granulate Dry Particulate Solids by Compaction and Retain Key Powder Particle Properties," *Chem. Eng. Prog.*, **93**(4), 24 (1997a).
Pietsch, W., "Size Enlargement by Agglomeration," *Handbook of Powder Science & Technology*, 2nd ed., M. E. Fayed and L. Otten, eds., Chapman and Hall, New York (1997b).
Porter, S. C., and C. H. Bruno, "Coating of Pharmaceutical Solid Dosage Forms," *Pharmaceutical Dosage Forms: Tablets*, Vol. 3, 2nd ed., H. A. Lieberman, L. Lachman, and J. B. Schwartz, eds., Marcel Dekker, New York (1989).
Rhodes, M., "Storage and Flow of Powders—Hopper Design," *Introduction to Particle Technology*, Wiley, Chichester (1998).
Rowe, R. C., "Binder-Substrate Interactions in Granulation: A Theoretical Approach Based on Surface Free Energy and Polarity," *Int. J. of Pharmaceutics*, **52**, 149 (1989).
Sastry, K. V. S., H. Cooper, R. Hogg, T. L. P. Jespen, F. Knoll, B. Parekh, R. K. Rajamani, T. Sorenson, I. Wechsler, C. McCleary, and D. B. Todd, "Solid-Solid Operations and Equipment," *Perry's Chemical Engineers' Handbook*, 7th ed., R. H. Perry, D. W. Green, and J. O. Maloney, eds., McGraw-Hill, New York (1997).
Seitz, J. A., S. P. Mehta, and J. L. Yeager, "Tablet Coating," *The Theory and Practice of Industrial Pharmacy*, 3rd ed., L. Lachman, H. A. Lieberman, and J. L. Kanig, eds., Lea & Febiger, Philadelphia (1986).
Snow, R. H., T. Allen, B. J. Ennis, and J. D. Litster, "Size Reduction and Size Enlargement," *Perry's Chemical Engineers' Handbook*, 7th ed., R. H. Perry, D. W. Green, and J. O. Maloney, eds., McGraw-Hill, New York (1997).
Stanley, J. P., "Capsules—Soft Gelatin Capsules," *The Theory and Practice of Industrial Pharmacy*, 3rd ed., L. Lachman, H. A. Lieberman, and J. L. Kanig, eds., Lea & Febiger, Philadelphia (1986).
Stuart-Dick, D., and T. A. Royal, "Design Principles for Chutes to Handle Bulk Solids," *Bulk Solids Handling*, **12**, 447 (1992).
Sun, C., and D. J. W. Grant, "Influence of Crystal Shape on the Tableting Performance of L-Lysine Monohydrochloride Dihydrate," *J. Pharm. Sci.*, **90**(5), 569 (2001a).
Sun, C., and D. J. W. Grant, "Influence of Crystal Structure on the

Tableting Properties of Sulfamerazine Polymorphs," *Pharm. Res.*, **18**(3), 274 (2001b).
Tanguy, D., and P. Marchal, "Relations between the Properties of Particles and Their Process of Manufacture," *Chem. Eng. Res. Des.*, **74**, 715 (1996).
Tardos, G. I., M. I. Khan, and P. R. Mort, "Critical Parameters and Limiting Conditions in Binder Granulation of Fine Powders," *Powder Technol.*, **94**, 245 (1997).
The United States Pharmacopeia, United States Pharmacopeial Convention, Inc., Rockville (1990).
van den Bergh, W., "Removing the Uncertainty in Solids Mixer Selection," *Chem. Eng.*, **101**(12), 70 (1994).
van Hostetler, "Capsules—Hard Gelatin Capsules," *The Theory and Practice of Industrial Pharmacy*, 3rd ed., L. Lachman, H. A. Lieberman, and J. L. Kanig, eds., Lea & Febiger, Philadelphia (1986).
Verhoff, F. H., "Citric Acid," *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A7, 5th ed., VCH, Weinheim, Germany (1988).
Villadsen, J., "Putting Structure into Chemical Engineering," *Chem. Eng. Sci.*, **52**, 2857 (1997).
Visser, J., "On Hamaker Constants: A Comparison between Hamaker Constants and Lifshitz-van der Waals Constants," *Adv. Colloid Interface Sci.*, **3**, 331 (1972).
Visser, J., "An Invited Review: Van der Waals and Other Cohesive Forces Affecting Powder Fluidization," *Powder Technol.*, **58**, 1 (1989).
Wadke, D. A., A. T. M. Serajuddin, and H. Jacobson, "Preformulation Testing," *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, 2nd ed., H. A. Lieberman, L. Lachman, and J. B. Schwartz, eds., Marcel Dekker, New York (1989).
Walas, S. M., *Chemical Process Equipment: Selection and Design*, Butterworths, Boston (1988).
Washburn, E., "The Dynamics of Capillary Flow," *Phys. Rev.*, **17**, 273 (1921).
Wells, J. I., "Powder Flow Properties," *Pharmaceutical Preformulation: the Physicochemical Properties of Drug Substances*, Ellis Horwood Limited, Chichester, U.K. (1988).
Wibowo, C., and K. M. Ng, "Synthesis of Bulk Solids Processing Systems," *AIChE J.*, **45**, 1629 (1999).
Wibowo, C., and K. M. Ng, "Operational Issues in Solids Processing Plants: Systems View" *AIChE J.*, **47**, 107 (2001a).
Wibowo, C., and K. M. Ng, "Product-Oriented Process Synthesis and Development: Creams and Pastes," *AIChE J.*, **47**, 2746 (2001b).
Wibowo, C., and K. M. Ng, "Product-Centered Processing: Chemical-Based Consumer Product Manufacture," *AIChE J.*, **48**, 1212 (2002).
Williams, J. C., "The Storage and Flow of Powders," *Principles of Powder Technology*, M. Rhodes, ed., Wiley, Chichester (1990).
Wintermantel, K., "Process and Product Engineering: Achievements, Present and Future Challenges," *Chem. Eng. Res. Des.*, **77**, 175 (1999).
Woodcock, C. R., and J. S. Mason, *Bulk Solids Handling*, Blackie Academic & Professional, London (1987).
Zajic, L., and G. Buckton, "The Use of Surface Energy Values to Predict Optimum Binder Selection for Granulations," *Int. J. of Pharmaceutics*, **59**, 155 (1990).
Zanowiak, P., "Dosage Forms: Nonparenteral," *Encyclopedia of Pharmaceutical Technology*, Vol. 4, J. Swarbrick and J. C. Boylan, eds., Marcel Dekker, New York (1988a).
Zanowiak, P., "Lubrication in Solid Dosage Form Design and Manufacture," *Encyclopedia of Pharmaceutical Technology*, Vol. 9, J. Swarbrick and J. C. Boylan, eds., Marcel Dekker, New York (1988b).
Zhang, D., J. H. Flory, S. Panmai, U. Batra, and M. J. Kaufman, "Wettability of Pharmaceutical Solids: Its Measurement and Influence on Wet Granulation," *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, **206**, 547 (2002).

Manuscript received Oct. 12, 2001, and revision received Nov. 27, 2002.