dose aerosols containing the drug in liquefied inert propellant (e.g. salbutamol sulphate inhaler). Importantly, this delivery route is being increasingly recognized as a useful means of administering the therapeutic agents emerging from biotechnology requiring systemic distribution and targeted delivery, such as peptides and proteins.

Drug factors in dosage form design

Each type of dosage form requires careful study of the physical and chemical properties of drug substances to achieve a stable, efficacious product. These properties, such as dissolution, crystal size and polymorphic form, solid-state stability and drug-additive interaction, can have profound effects on the physiological availability and physical and chemical stability of the drug. By combining such information and knowledge with those from pharmacological and biochemical studies, the most suitable drug form and additives can be selected for the formulation of chosen dosage forms.

Whilst comprehensive property evaluation will not be required for all types of formulations, those properties which are recognized as important in dosage form design and processing are listed in Table 1.3. Also listed in Table 1.3 are the stresses to which the formulation might be exposed during processing and manipulation into dosage forms, as well as the procedures involved. Variations in physicochemical properties, occurring for example between batches of the same material or resulting from alternative treatment procedures, can modify formulation requirements as well as processing and dosage form performance. For instance, the fine milling of poorly aqueous soluble drug substances can modify their wetting and dissolution characteristics, important properties during granulation and product performance respectively. Careful evaluation of these properties and understanding of the effects of these stresses upon these parameters are therefore important in dosage form design and processing as well as product performance.

Table 1.3 Properties of drug substances important in dosage form design and potential stresses occurring during processes, with range of manufacturing procedures

Properties	Processing stresses	Manufacturing procedures
Particle size, surface area	Pressure	Precipitation
Particle surface chemistry	Mechanical	Filtration
Solubility	Radiation	Emulsification
Dissolution	Exposure to liquids	Milling
Partition coefficient	Exposure to gases and liquid vapours	Mixing
Ionization constant	Temperature	Drying
Crystal properties, polymorphism		Granulation
Stability		Compaction
Organoleptic		Autoclaving
Molecular weight		Crystallization
		Handling
		Storage
		Transport

Particle size and surface area

Particle size reduction results in an increase in the specific surface (i.e. surface area per unit weight) of powders. Drug dissolution rate, absorption rate, dosage form content uniformity and stability are all dependent to varying degrees on particle size, size distribution and interactions of solid surfaces. In many cases, for both drugs and additives, particle size reduction is required to achieve the desired physicochemical characteristics.

It is now generally recognized that poorly aqueous soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided form with a larger surface than as a coarse material. Examples include griseofulvin, tolbutamide, indomethacin and nifedipine. The fine material, often of micrometre or submicrometre (nanometre) size, with large specific surface, dissolves at faster rates which can lead to improved drug absorption by passive diffusion. With many of the new drugs being introduced exhibiting extremely low aqueous solubility, alternative formulation strategies to enhance drug dissolution are being used, such as co-precipitates of drug and adjuvant particles, complexation with hydrophilic polymers or oligosaccharides, or the formation of co-crystals with hydrophilic templating compounds.