characteristics of the API takes a more pivotal role when the information available is limited. Obviously, one can readily identify the role of the identified, but not quantified, excipients. Some experimentation is required. However, as provided throughout this volume, significant knowledge can be gained by benchmarking the formulation. Other similar drugs or excipients should provide a good clue of the starting quantities. It is noteworthy that in obtaining the copies of competitor NDAs, through the Freedom of Information Act, some quantities are often redacted, leaving the formulator to guess. However, this should not be a difficult step, as long as the quantities of excipients chosen provide a similar weight, thickness, and disintegration and dissolution characteristics.

A common practice by innovator companies, as the NCE gets closer to the patent term expiry, is to patent a variety of formulations; for example, in the case of Aug-mentin®, the innovator chose to patent a different combination of amoxicillin and clavulanic acid and developed a composition for pediatric therapy. The purpose of this exercise is to keep generic competition out; the generic product in some cases may be the same, but not exact. The patent-end changes may also include changes in specification, choice of solvent systems used, or other cosmetic changes. However, a generic manufacturer would do well by just following the original formulation (for obvious reasons of regulatory compliance) because this has withstood the test of time. The author recommends that no changes should be made to an otherwise working formula, albeit this may improve processing, until such a time that the generic manufacturer has sufficient experience with the product. Most unusual things can happen when unsuspecting changes, appearing benign at the surface, are made to proven formulas. Given the cost of bioequivalence study requirements for compressed solids, changes in formulation should not be made unless essential and, even then, only for compliance purposes.

XIX. DIRECT COMPRESSION

The technology involved in direct compression assumes great importance in the tablet formulations, because it is often the cheapest means, particularly in the production of generics, that the active substance permits. The limiting factors are the physical properties of the active substance and its concentration in the tablets. Even substances such as ascorbic acid that are hardly suitable for direct compression, owing to the friability of their crystals, can normally be directly pressed into tablets at concentrations of 30% to 40%. However, this technique is not as suitable if the content of ascorbic acid is higher. This limit may be shifted upward by special direct compression auxiliaries, for example Ludipress. Two important alternatives, viz. Ludipress grades and Kollidon VA 64, can be found in the BASF line of pharmaceutical excipients for direct compression.

Ludipress is a speciality derived from lactose, Kollidon 30, and Kollidon CL. It thus combines the properties of a filler, binder, disintegrant, and flow agent and also often acts as a release accelerator. By virtue of its versatility, formulations containing it are usually very simple. It can also be combined with almost all active substances with the exception of those that enter into a chemical interaction with lactose (Maillard reaction).

Active substances, for example many analgetics, behave very differently with Ludipress when the dosage is extremely high. Acetylsalicylic acid and metamizole can be pressed when little Ludipress has been added; ibuprofen requires a larger amount; and the fraction of Ludipress required in the tablets is too large for paracetamol (= acetaminophen).

An alternative to the Ludipress grades is the outstanding dry binder Kollidon VA 64 together with excipients, for example calcium phosphate, microcrystalline cellulose, lactose, or starch, and a disintegrant, for example Kollidon CL. This combination even allows 500 mg of paracetamol to be pressed into good tablets with a weight of 700 mg.

No other dry binder has a binding power and plasticity comparable to those of Kollidon VA 64. Plasticity, in particular, is an important parameter in direct compression. This property of Kollidon VA 64 is not adversely effected by increasing the pressure. The beneficial properties of Kollidon VA 64 can also be exploited for the production of concentrated active substance that is subsequently used for direct tabletting. Kollidon VA 64 and Ludipress can also be combined with one another.

XX. FILL WEIGHTS

Fill weights are provided in all formulations. These may not coincide with scale for many reasons, as described elsewhere: differences in the salt forms, hydrates, or overages added in manufacturing and also to provide the extra margin of variation in filling during fast compression operations.

XXI. FINAL PACKAGING

A formulation design does not end with assuring that good tablets are formed; it must allow for handling during packaging, such as sliding into blister sheets or dropping into bottles. Actual fill runs must be conducted, and then the finished product must be subjected to simulated, and finally, the actual rigors of shipping before finalizing a formulation. Know that during shipping, the product may be exposed to diverse and often harsh weather conditions. Silica gel is often placed in the finished packs, or cotton is inserted, mainly to provide moisture or absorb odor (in the case of cotton).

XXII. FINAL TESTING

Finished product testing, particularly assay, content uniformity, and dissolution, is required. In the review of dissolution test results, it is important to eventually see results close to 100% dissolution. In some cases, manufacturers profile the dissolution results only to the specification. However, if lower but still acceptable results are obtained (such as 85%), it is important to continue the test. This can be performed by increasing the speed of the apparatus. If a product completely dissolves, yet only results in a value of 85%, it may indicate some problem with the test. Likewise, high dissolution results (115%) also indicate some problem with the test. Obviously, unusual or atypical results should be explained in the validation report.

XXIII. FINES

Solids, when grinded to small particle sizes (as when passing through sieves or crushing granules), yield a distribution of various particle sizes. A certain amount of very fine particles,