There are a few products, such as some of the antihistamine tablets, in which the drug substance is applied during the coating process. Other products require the active drug substance to be applied as a dust on tacky tablets as part of the coating process. For these products, it is particularly important to apply the drug in the coating solution in many controlled applications.

Again, it is important as part of the validation of these processes to demonstrate dose uniformity and dissolution and control the parameters of the coating process.

XVIII. EXCIPIENTS

Excipients are well defined in the official pharmacopoeia. No specific pharmaceutical grades are specified in this book, except where there is a specific reason to do so. However, it is known that different pharmacopoeia may have different specifications, such as particle size, impurities, moisture, etc. The harmonization of excipients, a global effort that is underway, would go a long way in making the choice of excipients. The manufacturer is referred to http://www.ipecamericas.org/index.html and the *Handbook of Pharmaceutical Excipients* for further advice. A large number of proprietary excipients are widely used, such as Ac-Di-Sol®, Explotab®, Aerosil®, Ludipress®, Avicel®, etc., and many of these are now part of pharmacopoeias. There is a significant advantage, though the cost is high, in using these ingredients because they offer additional benefits, often reducing processing time. Additionally, the suppliers of these ingredients are always willing to provide formulation support and have large databases, particularly pertaining to stability of drugs, that may be of great value to manufacturers. The following sections (A–F) list the most commonly used excipients in compressed solids.

A. Coating Agent

Carboxymethylcellulose, sodium cellacefate (formerly cellulose acetate phthalate), cellulose acetate, cellulose acetate phthalate (see cellacefate), ethylcellulose, ethylcellulose aqueous dispersion gelatin glaze, pharmaceutical hydroxypropyl, cellulose hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate (see hypromellose phthalate), hypromellose phthalate (formerly hydroxypropyl methylcellulose phthalate), methacrylic acid copolymer, methacrylic acid copolymer dispersion, methylcellulose PEG, polyvinyl acetate, phthalate shellac sucrose, titanium dioxide wax, carnauba wax, microcrystalline zein.

B. Glidant

Calcium silicate, magnesium silicate, silicon dioxide, colloidal talc.

C. Tablet Binder

Acacia alginic acid carboxymethylcellulose, sodium cellulose, microcrystalline dextrin ethylcellulose gelatin glucose, liquid guar gum hydroxypropyl methylcellulose, methylcellulose polyethylene oxide povidone starch, pregelatinized syrup.

D. Diluent

Calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate cellulose, microcrystalline cellulose, powdered dextrates, dextrin, dextrose, excipient, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, pregelatinized sucrose, sugar, compressible sugar, confectioner's sugar.

E. Disintegrant

Alginic acid cellulose, microcrystalline croscarmellose sodium, crospovidone polacrilin, potassium, sodium starch, glycolate starch, starch, pregelatinized.

F. Lubricant

Calcium stearate, glyceryl behenate, magnesium stearate, mineral oil, light PEG, sodium stearyl fumarate stearic acid, stearic acid, purified talc, vegetable oil, hydrogenated type I zinc stearate.

The choice of excipients is made based on three distinct considerations:

- Compatability with the active drug—Many excipients have active functional groups that can interact with the active drug and enhance its degradation. Even the water of hydration or moisture in the excipients can create difficulties in solid-state degradation of the active drug; so, it is not only the selection of the ingredient but also the grade (such as anhydrous or hydrous) that is important.
- Effect on efficacy—Excipients are known to alter the release patterns (e.g., a strong binder would delay break up of the tablet) and often bind the drug molecules in the gastrointestinal tract. The evaluation should be made in the full composition of ingredients because the presence of two ingredients may change their individual characteristics.
- Cost of formulation—Even though excipients contribute a small cost of the total formulation, the declining cost of APIs makes the selection of excipients based on cost an important consideration. This is particularly true when generic manufacturers are filing ANDAs knowing well that they will compete on a price basis. However, the total cost of formulation should not only be calculated on the basis of excipients. Often, the use of expensive excipients reduces process time, eliminates certain process steps, and even allows for the use of a cheaper packaging material. The manufacturer must, therefore, calculate the overall manufacturing cost. This aspect of formulation creates unique considerations by the multinational companies doing business worldwide; they are often forced to develop alternate formulations depending on the availability of excipients, manpower cost, and local environmental considerations.

The rule of thumb in the selection of excipients remains—keep it simple and at the bare minimum. The goal of excipients selection should be clearly defined—the dosage form yielding to a solution form at a predetermined rate (not necessarily the fastest in all instances).

The formulations described in this volume provide a quantitative listing of excipients recommended. An astute formulator would know the need to alter their quantity based on the type of equipment used to process them, the size of the batch processed at one time, and the quality of compressed product obtained. Therefore, all quantitative listings of excipients must be considered the best starting point, which can be adjusted and optimized, if necessary. In many instances, a range of excipients is allowed, such as in the case of a binder solution, to yield a suitable mass (as it is often described in the formulation of wet massing).

Where exact quantities of excipients are not available, but the excipients are identified for an innovator's product, this is still a better starting point than establishing the choice of excipients. Knowledge of the physicochemical