case where the use of alkaline excipients (e.g. hydroxyapatite) can be deleterious at higher temperatures. In the absence of (or at low levels of) moisture the reaction may not proceed. It is also characteristic that often, higher temperatures are not indicative of what will happen at room temperature.

If it is desired to control the pH of the microenvironment then citric, tartaric, and fumaric acids are the acids of choice. They are, however, all corrosive, and their pharmaceutical handling is far from ideal. In the case of alkali, sodium bicarbonate, sodium carbonate, and magnesium and calcium oxides are common. They are not as corrosive as the acids mentioned, but they are abrasive, and they, too, are not the most ideal substances to handle in a tablet or a capsule.

For certain compounds it is necessary to control the microenvironment in even more drastic fashion. Gu et al. (1990) report on drug excipient incompatibility studies of moexipril hydrochloride and demonstrate that (even "wet") adjustment of the microenvironmental pH (i.e., adding small amounts of water to a mixture of the drug with sodium bicarbonate or sodium carbonate) did not sufficiently stabilize the mix. But when the mixture *was wet granulated*, and when *stoichiometric amounts of alkali were used*, then stabilization resulted. This essentially means that in the solid state *the sodium salt is stable* as opposed to the acid. It might be argued that in such a situation the sodium salt should be manufactured and used as such. It might be argued that it should be claimed as the active ingredient (equivalent to a certain amount of free acid, or in the case of amphoteric substances, the acid addition salt), but often the salt is very soluble and hygroscopic (e.g., potassium clavulanate) and hence difficult to produce. The situation is referred to in the Federal Register as a *derivative drug*.

11. INTERACTIONS INVOLVING A LIQUID PHASE

At times an active ingredient or a decomposition product in a solid dosage form is a liquid, and this may interact with other ingredients in the dosage form. A typical example is the work by Troup and Mitchner (1964) dealing with aspirin and phenylephrine. The authors showed that the decomposition of phenylephrine was linearly related to the formation of salicylic acid. They showed that the decomposition of phenylephrine was an acetylation. This can be thought of in many ways. There has to be some moisture present to allow for the hydrolysis of aspirin. If the salicylic acid is formed by interaction of aspirin with traces of water, then the acetic acid formed may react with the phenylephrine ($R(OH)_3$), again liberating water, so that the moisture does not play a part quantitatively in the overall reaction; in other words,

$$C_6H_4(OCOCH_3) + H_2O \rightarrow C_6H_4(OH)COOH + CH_3COOH \tag{6.68}$$

$$CH_3COOH + 1/3\,R(OH)_3 \rightarrow 1/3\,R(OCOCH_3)_3 + H_2O \tag{6.69}$$

$$C_6H_4(OCOCH_3) + 1/3\,R(OH)_3 \rightarrow 1/3\,R(OCOCH_3)_3 \tag{6.70}$$

An alternate explanation would be that phenylephrine interacted directly with aspirin in an anhydrous solid state to transacetylate, which is not probable. The