with good success (i.e., the formula developed based on the findings from the compatibility program is stable).

It should be noted that liquefaction at times occurs because of eutectic formation (e.g., often with caffeine combinations) and that this may not necessarily be associated with decomposition. On the other hand, discoloration (e.g., amines and sugars) usually is.

Finally, the reason for not forcing dicalcium phosphate (a very valuable formulation aid in direct compression) beyond 50°C is that at higher temperatures it converts to the anhydrate, a conversion that is, curiously enough, catalyzed by water. In other words, the dihydrate will be autocatalytic in this respect at elevated temperatures, and it should not be ruled out based on high-temperature findings.

Aside from magnesium stearate, dicalcium phosphate and lactose are the excipients that are the most often found incompatible with drugs. In the former case it is usually the pH effect, in the latter it is the formation of Schiff's bases with amines (and many drugs are amines), i.e.,

$$R_1CHO + H_2NR_2 \rightarrow R_1CH = NR_2 + H_2O$$

For instance, Eyjolfsson (1998) reported on the incompatibility of lisinopril with lactose.

Aso et al. (1997) have determined the decomposition rates of cephalotin in mixtures with pharmaceutical excipients and the effect of moisture. They found a linear relation between mobile water percentage and decomposition rate constants.

Several examples of this type of screening exist. Malan et al. (1997) have studied the compatibility of tablet excipients with albendazole and closantel. They prepared drug–excipient mixtures in a mixture and in 1 : 1 mixtures that were granulated with water and dried at 50°C. DSC and HPLC were used to evaluate the compatibilities. The excipients tested were colloidal silicon dioxide, microcrystalline cellulose, dibasic calcium phosphate monohydrate, starch, sodium starch glycolate, and magnesium stearate.

9.4. Compatibility with Containers

Compatibility studies may also include compatibility with container materials. Hourcade et al. (1997), for instance, reported that granisetron in concentrations of 1 mg/mL, when kept in polypropylene syringes, were quite stable, whereas dilutions with 0.9% NaCl or with 5% glucose resulted in unsatisfactory storage stability.

10. KINETIC pH PROFILES

pH profiles have been discussed in Chapter 3. Frequently, a broad screen of stability is performed on the initial small sample used for initial preformulation; this is frequently referred to as "forced decomposed studies" (Bodnar et al., 1983). In this the drug is exposed to "acid degradation," "base degradation," "aqueous degradation," "drug powder degradation," and "light degradation." More refined studies are eventually needed.