Selection of Solid Dosage Form Composition through Drug–Excipient Compatibility Testing

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Abstract □ A drug–excipient compatibility screening model was developed by which potential stability problems due to interactions of drug substances with excipients in solid dosage forms can be predicted. The model involved storing drug–excipient blends with 20% added water in closed glass vials at 50 °C and analyzing them after 1 and 3 weeks for chemical and physical stability. The total weight of drug–excipient blend in a vial was usually kept at about 200 mg. The amount of drug substance in a blend was determined on the basis of the expected drug-to-excipient ratio in the final formulation. Potential roles of several key factors, such as the chemical nature of the excipient, drug-to-excipient ratio, moisture, microenvironmental pH of the drug–excipient mixture, temperature, and light, on dosage form stability could be identified by using the model. Certain physical changes, such as polymorphic conversion or change from crystalline to amorphous form, that could occur in drug–excipient mixtures were also studied. Selection of dosage form composition by using this model at the outset of a drug development program would lead to reduction of "surprise" problems during long-term stability testing of drug products.

Introduction

Excipients are integral components of almost all pharmaceutical dosage forms. What emerges from a drug discovery program is only a new chemical entity or drug substance. It becomes a drug product after formulation and processing with excipients. However, the general principles of selecting suitable excipients for dosage forms are not well-defined, and excipients are often selected without systematic drug−excipient compatibility testing.

Acceleration of drug development and optimization of dosage form stability are two major goals of any drug development program. Identification of dosage form composition at the outset of a drug developmental program, especially during the design of Phase I clinical formulations, based on thorough drug−excipient compatibility testing is a key step in accelerating drug development. This is because subsequent changes in formulation during Phases II and III as a result of unexpected stability problems usually lead to increases in time and cost of drug development. In addition, the stability of a formulation can be maximized and "surprise" problems during its formal stability testing for regulatory submissions can be minimized through drug−excipient compatibility testing.

Despite the importance of drug−excipient compatibility testing, no generally accepted method is available for this purpose. Most of the methods reported in the literature have poor predictive values.[1] They are labor-intensive and time-consuming, and the number of variables studied are limited. As a result of frustration over this situation, Monkhouse and Maderich[1,2] suggested that one should do away with drug−excipient compatibility testing and, instead, select excipients on the basis of physical and chemical characteristics of drug substances and literature data on excipients. They recommended that the final composition should be selected on the basis of accelerated stability testing of one or more target formulations at high temperature and high humidity. This latter approach may, however, have the disadvantage that it could prolong the time necessary for selecting dosage form compositions. Development of various target formulations for the purpose of screening different drug−excipient combinations is time-consuming and may require larger quantities of bulk drug substances than are generally available early in drug development. Additionally, meaningful differences in stability of different target formulations of a particular drug stored at high temperature and humidity (for example, 40 °C/75% RH) may not be observed within a short period of time, unless the compound degrades very rapidly in these formulations. Therefore, a rapid method for selection of excipients for dosage form design is essential for a practical drug−excipient compatibility screening method.

In this paper, we report a method that was used successfully to identify relative influences of different excipients on drug stability. The primary objective of developing this method was to identify in a short period of time excipients that would have low potential for adverse effects on chemical and physical stability of drug substances.

Materials and Methods

Materials—All drug substances used in this study were synthesized by Bristol-Myers Squibb, and their chemical structures are given in Table 1. The excipients, procured from commercial sources, were released by Bristol-Myers Squibb for use in drug manufacturing.

Preparation of Samples—The basic model used in the present study consists of multicomponent blends of drug substances with excipients, which were mixed with 20% added water and stored in closed vials at 50 °C for specific periods of time. Samples were analyzed for chemical and physical (appearance, color, etc.) stability after 1 and 3 weeks of storage.

Only a general method of preparation of samples is described here, because it evolved over the long time during which the studies reported in this paper were conducted. Accurately weighed amounts of drug substances were placed in 4-mL glass vials, each vial was labeled with the amount of drug to determine mass balance during chemical analysis, and weighed amounts of excipients were then added to the vials. The total weight of drug−excipient blend in a vial was usually kept at about 200 mg. The

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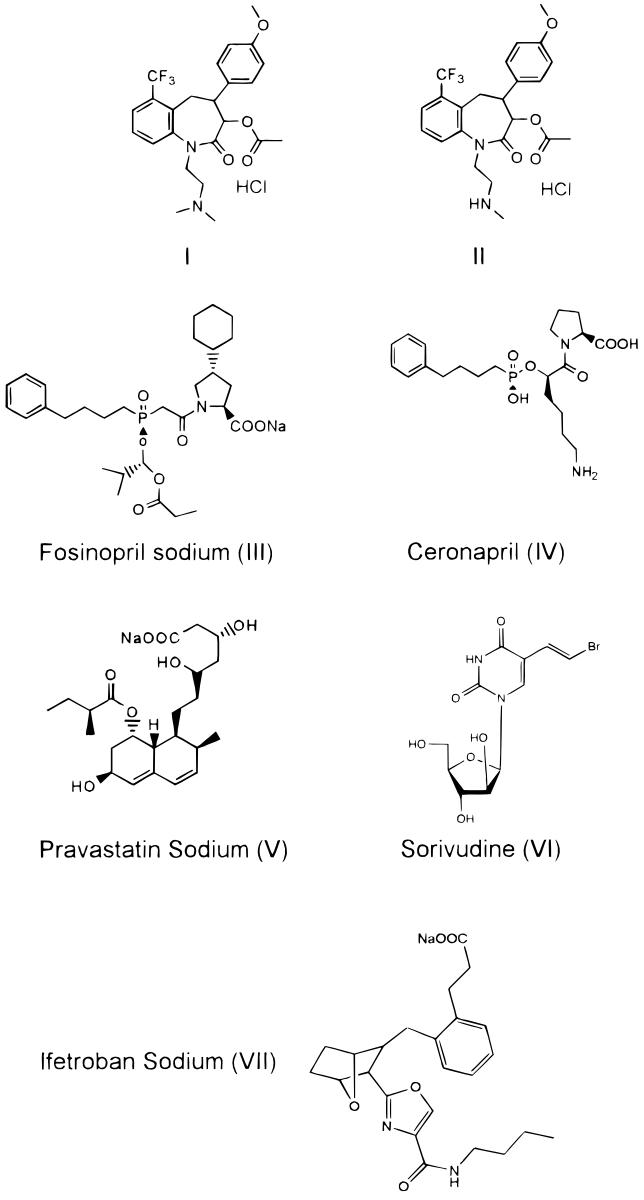
Table 1—Names and Chemical Structures of Drugs Used



amount of drug substance in a blend was determined on the basis of the expected drug-to-excipient ratio in the final formulation. The highest expected drug-to-excipient ratio was usually used. Both the highest and the lowest drug-to-excipient ratios were occasionally used to bracket drug concentrations in a formulation. The amount of the drug–excipient blend per vial sometimes differed as a result of practical reasons; a smaller amount was used when the drug supply was limited. The powder in each vial was mixed with the tip of a disposable Pasteur pipet or a thin glass rod and 20% water (40 μL per 200 mg blend) was then added using a microsyringe. The blend was further mixed, and to prevent any loss of material, the tip of the stirrer (Pasteur pipet) was usually broken and left inside the vial. Each vial was sealed tightly using a Teflon-lined screw cap.

The total number of drug–excipient blends for each study may be selected by statistical design. However, because it might be necessary to screen many diluents, lubricants, binders, disintegrants, coloring agents, coating agents, and so forth for a particular formulation, the number of blends selected this way becomes very high. To limit the number of samples, the drug–excipient compatibility testing may be conducted in two phases. In the first phase, the compatibility of drug with diluents and lubricants is tested, and on the basis of the results, one primary diluent and one primary lubricant are selected. Table 2 provides the design of such a study for one of the compounds (**I**) tested in the present investigation. Using one drug–diluent–lubricant mixture selected in the first phase, the compatibility of other excipients, such as binders and disintegrants, may then be tested in the second phase. Because capsule formulations, which do not require coating agents and coloring agents, are generally used during initial clinical studies, compatibility testing of such agents may be conducted later with the drug–excipient blend used in capsules.

Storage and Analysis of Samples—Closed vials containing drug–excipient blends with added water were stored in ovens at 50 °C. In some cases, samples were also stored as unwetted powders in closed vials at 50 °C or in open vials at 50 °C/75% RH for comparison with those stored in closed vials with added water. Drug–excipient blends without added water stored in a refrigerator or at room temperature served as controls for samples stored at 50 °C with added water or at 50 °C/75% RH. When the drug was photodegradable, clear glass vials containing certain drug–excipient–water mixtures, especially those with coloring agents, were also exposed to light (room light or high-intensity fluorescent light). In this case, identical vials wrapped in aluminum foil and stored side by side with exposed vials served as controls for light stability.

Duplicate samples of drug–excipient blends were analyzed after 1 and 3 weeks by using HPLC methods. Because the drug–excipient compatibility testing was conducted at an early drug developmental stage when fully validated HPLC methods were generally not available, it was not uncommon to use more than one isocratic HPLC method or a gradient HPLC method to distinguish as many degradation products as possible. The HPLC conditions used are recorded under tables and figures in the Results and Discussions section. Whenever feasible, the degradation products were identified by mass spectral, NMR, and other relevant analytical techniques.

To investigate physical changes in drug substances, for example, polymorphic transition or formation of an amorphous phase due to dissolution of the drug in granulating fluids and subsequent drying, drug–excipient–water mixtures stored in closed vials at 50 °C for a suitable period of time were dried overnight at 40 °C and then analyzed by powder X-ray diffraction, solid-state NMR, FTIR, and other appropriate methods. The techniques were described earlier.[3] To maximize the detection of possible physical changes in drug substances during analyses by these techniques, drug concentrations in the mixtures were usually kept at 25% or higher. It was also advantageous to limit the excipient to one that would have the least interference with the analysis of drug substances. Identical blends stored refrigerated or at room temperature without the addition of water served as controls.

Estimation of Microenvironmental pH—The microenvironmental pH of a drug–excipient blend was estimated by adding 1 mL of water to 200 mg of blend in a vial, mixing the suspension with a vortex mixer, and then recording the pH with a pH meter. It was necessary that the solid remained in equilibrium with the liquid phase; variation in pH was observed if filtered solutions were used.

Results and Discussion

Model—Some factors which may have critical influences on the stability of drug substances in the presence of excipients are the chemical nature of the excipient, drug-to-excipient ratio, moisture, microenvironmental pH of the drug–excipient mixture, temperature, and light. The model allowed identification of the potential roles of all of these factors on dosage form stability. Additionally, certain physical changes, for example, polymorphic conversion and the change from crystalline to amorphous form due to dissolution of drug by the sorption of water or during wet granulation and subsequent drying, that could occur in drug–excipient mixtures were also studied.

One important feature of the model is the incorporation of water in the drug–excipient mixture. Although purely solid-state degradation of drug substances is feasible, such instances are rare, and most drug degradation reactions in solid dosage forms involve moisture.[4,5] The presence of moisture is, therefore, essential in establishing the compat-

Table 2—Compositions of Drug–Excipient Blends Used for I and Assay Results after 3 Weeks of Storage at 50 °C in Closed Vials with 20% Added Water; Weights of All Ingredients Are in Milligrams

	experiment																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
drug substance (**I**)	200	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
lactose		175				170				170				170			
mannitol			175				170				170				170		
microcrystalline cellulose				175				170				170				170	
dibasic calcium phosphate dihydrate					175				170				170				170
magnesium stearate						5	5	5	5								
sodium stearyl fumarate										5	5	5	5				
stearic acid														5	5	5	5
potency remaining[a] (% initial)	96.4	95.7	95.8	93.9	85.0	64.3	65.4	65.3	68.1	77.9	81.9	77.6	81.8	90.0	92.9	88.1	78.3
hydrolysis product formed[b]	3.3	4.1	4.0	5.8	16.7	37.0	36.7	36.3	33.7	21.8	15.4	20.1	15.3	9.7	6.9	11.7	21.6

[a] Average of two samples. [b] Expressed as percentage of parent drug (**I**). Because in a separate study the molar extinction coefficients of the parent compound and the hydrolysis product were earlier determined to be the same, the hydrolysis product was quantitated directly from its AUC values in the chromatograms.

ibility of drugs with excipients. Although the moisture may be incorporated in the system by exposing samples to high humidity, it has been our experience that the drug–excipient interaction at high humidity conditions always depends on the amount of free moisture present and on relative hygroscopicities of drug substances and/or excipients. Variability in degradation of drugs as a result of differences in the hygroscopicity of excipients has been reported in the literature.[6] Addition of a predetermined amount of water removes this unpredictability from the system. It facilitates intimate mixing of drug substances with excipients and establishes around undissolved drug particles aqueous layers saturated with drugs, excipients, and any impurities that may be present in the system. Such saturation layers also provide a microenvironmental pH to the system. The use of 20% water ensured that a sufficient amount of water would still remain in contact with the drug–excipient blend after evaporation of a certain fraction of added water to saturate the headspace inside the 4-cc vial. The model also works efficiently with lower or higher than 20% water; addition of water ranging from 5% to 20% was reported in the literature.[7–9]

Another important aspect of the model is that the dissolution of drugs and excipients in the added water facilitates the formation of their disordered or amorphous phases. Zografi and co-workers[10] demonstrated that water absorbed in such amorphous phases accelerates drug degradation. Any possible drug–excipient interaction would therefore be facilitated in the amorphous phase as a result of the presence of water and the intimate mixing of drug with excipients. However, it might be argued that the amount of water used in the protocol (20%) might be in excess of what is required to change the glass transition temperature of an amorphous phase and may indeed dissolve the drug in an aqueous solution, thereby increasing its degradation rate. Although this is a possibility for highly water-soluble drugs, most drugs are relatively water-insoluble and amounts dissolved in the added water are usually very small. Also, in the presence of certain excipients, such as cellulose- and starch-derived excipients[11] and poly(vinylpyrrolidone),[12] a large part of the water may be tightly or partially bound with excipients and thus unavailable to dissolve the drug. Even for highly water-soluble drugs, the model is capable of determining relative influences of different excipients of a particular class on the drug degradation. It has been our experience that the absence of a drug–excipient interaction in the present model leads to drug products with long shelf lives. However, if an interaction is observed and no suitable alternative excipient is available, additional studies are needed to determine the impact of such an interaction on the product shelf life and to ascertain whether any restrictive manufacturing and packaging conditions to increase the stability of the drug product would be necessary.

Case Histories—Case histories of the interaction of selected drug molecules with excipient and how such interactions influenced dosage form design decisions are given below.

*Calcium Channel Blockers (**I** and **II**)*—Compounds **I** and **II** are the hydrochloride salts of two calcium channel blockers of the benzazepine series discovered by Bristol-Myers Squibb.[13] They are structurally similar, except for the side chains with amine groups: **I** is a tertiary amine, whereas **II** is a secondary amine. Each compound contains an O-acetyl group that undergoes hydrolysis in aqueous media, forming one degradation product. No degradation product other than the hydrolysis product was observed in aqueous solutions. The formation of hydrolysis products was, therefore, studied during the drug–excipient compatibility testing. Additionally, possible interactions of the compounds with lactose were considered because it has been reported in the literature that amine drugs react with lactose.[14] However, most published reports were for compounds containing primary amines, and it was important to determine how tertiary and secondary amines would behave in the presence of lactose.

The 3-week results of the compatibility screening of **I** with the four diluents and the three lubricants used are shown in Table 2. Since the hydrolysis product **VIII** was the only degradation product formed and there was a good mass balance in all the samples, the results are expressed as the intact drug remaining and the amount of the hydrolysis product formed. As shown in Table 2 and also represented by the chromatograms in Figure 1, the degradation of **I** in the neat drug and in drug–lactose and drug–mannitol mixtures was low and practically similar, indicating that there was no significant interaction of **I** with lactose and mannitol. The degradation of **I**, however, increased in the presence of microcrystalline cellulose (Avicel, FMC) and dicalcium phosphate (DCP, DiTab, Rhone-Poulenc). Among the three lubricants used, stearic acid had the least influence on the degradation of **I**, followed by sodium stearyl fumarate and magnesium stearate in the increasing order of degradation. The HPLC chromatograms of drug–diluent–magnesium stearate mixtures are shown in Figure 2 to indicate that the hydrolysis product **VIII** was the only product formed even when the degradation was high. In a separate study, the compound was observed to have the maximum stability in solution at pH 4, and the stability decreased with an increase or decrease in pH. The maximum stability of **I** in the presence of stearic acid may, in part, be explained by the microenvironmental pH of the systems. The microenvironmental pH of drug–lactose and drug–mannitol mixtures in the

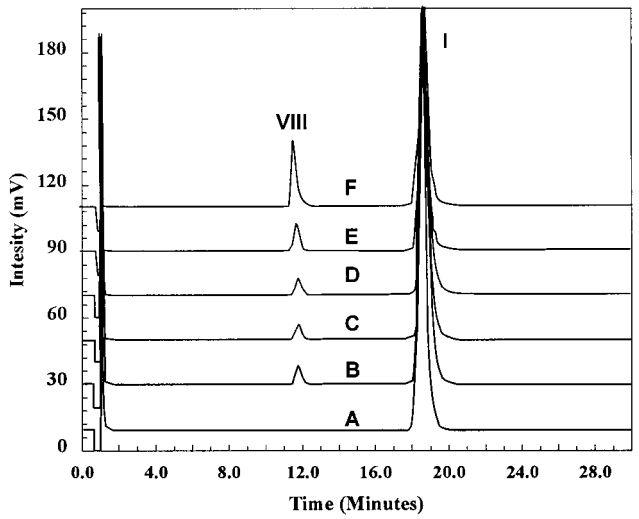


Figure 1—HPLC chromatograms of compound **I**–excipient mixtures (1:7) exposed to 50 °C for 3 weeks with 20% added water. Key: A, reference standard; B, neat drug without excipient; C, drug–lactose mixture; D, drug–mannitol mixture; E, drug–microcrystalline cellulose mixture; and F, drug–dicalcium phosphate dihydrate mixture. Chromatograms were recorded using a 15 cm Novapak C_{18} column and a mobile phase containing 55% aqueous solution (sodium acetate, 14 g/L, and sodium hexane sulfonate, 1.98 g/L) and 45% acetonitrile (flow rate, 1.0 mL/min; UV detection wavelength, 229 nm).

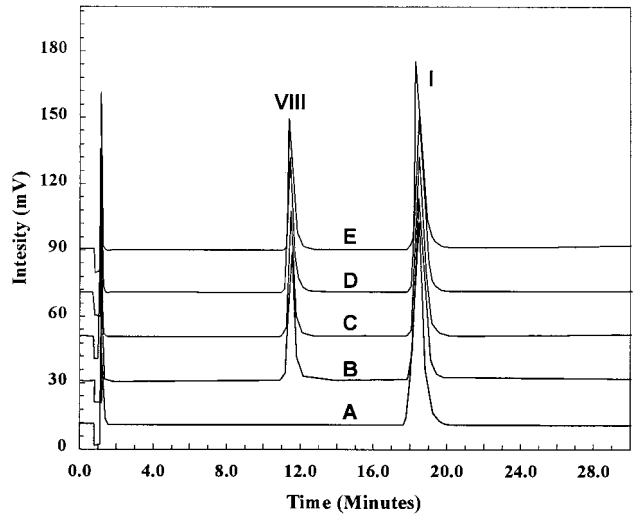
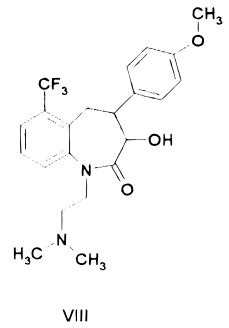
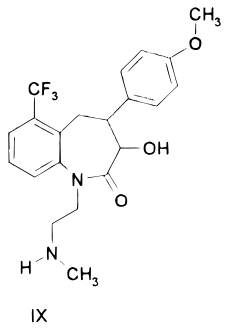


Figure 2—HPLC chromatograms of compound **I**–diluent–magnesium stearate mixtures (25:170:5) exposed to 50 °C for 3 weeks with 20% added water. Key: A, reference standard; B, neat drug without excipient; C, drug–lactose–magnesium stearate mixture; D, drug–mannitol–magnesium stearate mixture; and E, drug–microcrystalline cellulose–magnesium stearate mixture. Chromatographic conditions are the same as in Figure 1.

presence of stearic acid was 3.8, whereas sodium stearyl fumarate and magnesium stearate raised the microenvironmental pH to ~5.5. Mixtures of **I** with DCP gave an initial pH of 6.2−6.5. Additionally, its surface acidity[15] and propensity for forming H_3PO_4 upon its hydrolysis in the presence of water would contribute to the acid-catalyzed degradation of the ester bond in **I**. Thus, there appears to be a good agreement between the microenvironmental pH of the excipient blends and the hydrolysis of the drug. From this phase of the study, it was concluded that mixtures of **I** with either lactose or mannitol as the diluent and stearic acid as the lubricant would provide maximum stability of the drug. The microcrystalline cellulose was also considered to be an acceptable diluent because the extent of drug degradation in its presence was not much higher.



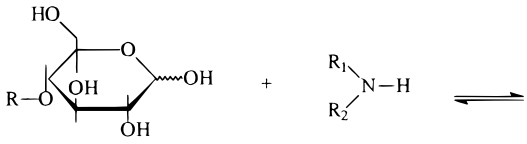
VIII



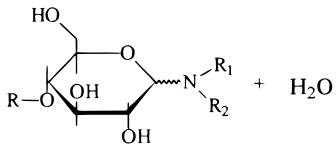
IX

During compatibility screening of the hydrochloride salt of the secondary amine, **II**, it was observed that the drug did not have any significant interaction with lactose and mannitol in binary mixtures (Figure 3). The only significant degradation product formed was the hydrolysis product **IX**. As in the case of **I**, the influence of stearic acid on the compatibility of **II** with lactose and mannitol was minimal; the chromatograms remained similar to those in Figure 3, with hydrolysis being the only drug degradation product. In contrast, both sodium stearyl fumarate and magnesium stearate adversely influenced the drug stability. Figure 4 shows that the hydrolysis product, **IX**, was the major degradation product in the presence of both sodium stearyl fumarate and magnesium stearate. As with **I**, the hydrolysis of **II** was higher with magnesium stearate. Additional peaks at the elution times of 2−3 min were obtained when lactose was present in the mixture, possibly a result of the interaction of lactose with the secondary amine groups of **II** and the hydrolysis product, **IX** (Figure 4, chromatograms B and C). Unidentified degradation products with the elution time of ~1 min were also observed in the presence of magnesium stearate (Figure 4, chromatograms B and D).

The tertiary amine is expected to be nonreactive toward lactose, because the product of such a reaction would lead to unstable ionic species that would revert back to reactants, and for this reason, compound **I** was compatible with lactose. In the case of a secondary amine, a glycosylamine would be formed:



Lactose



Glycosylamine

For the above reaction to occur in the solid state, optimal microenvironmental conditions of humidity and pH would be required. Under acidic conditions, the reactivity was reduced as a result of the protonation of the amine and the consequent decrease in its nucleophilicity. The observed lack of interaction of the hydrochloride salt of **II** and lactose could thus be rationalized. However, in the presence of magnesium stearate and sodium stearyl fumarate, the microenvironmental pH of the system was expected to rise because of the basicity of the excipients. This would liberate the nucleophilic free base of the drug from the salt to react

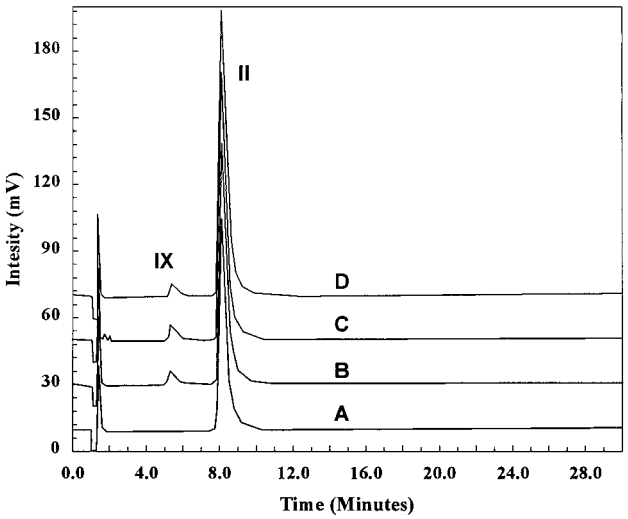


Figure 3—HPLC chromatograms of compound **II**–diluent–stearic acid mixtures (25:170:5) exposed to 50 °C for 3 weeks with 20% added water. Key: A, reference standard; B, neat drug without excipient; C, drug–lactose–stearic acid mixture; and D, drug–mannitol–stearic acid mixture. Chromatographic conditions are the same as in Figure 1.

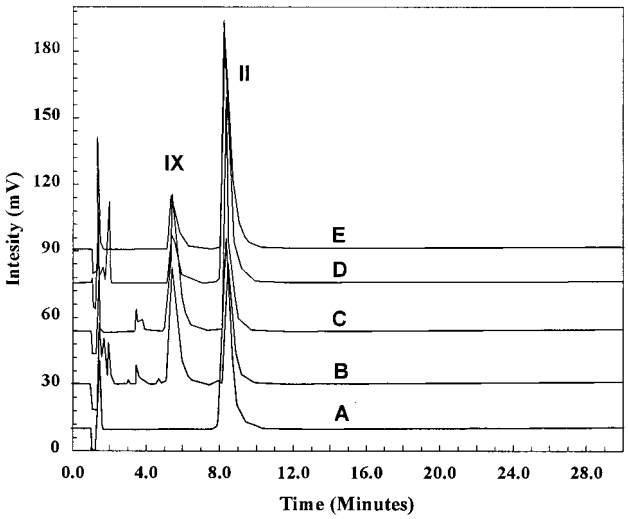


Figure 4—HPLC chromatograms of compound **II**–diluent–lubricant mixtures (25:170:5) exposed to 50 °C for 3 weeks with 20% added water. Key: A, reference standard; B, drug–lactose–magnesium stearate mixture; C, drug–lactose–sodium stearyl fumarate mixture; D, drug–mannitol–magnesium stearate mixture; and E, drug–mannitol–sodium stearyl fumarate mixture. Chromatographic conditions are the same as in Figure 1.

with lactose and form an adduct. A second adduct due to the interaction between the hydrolysis product, **IX**, and lactose could also be formed. A similar reaction between a secondary amine and lactose, which was catalyzed by magnesium stearate, was reported in the literature.[16] The lack of interaction with lactose in the presence of stearic acid is also consistent with this explanation. As shown in the scheme above, the equilibrium of the interaction will be dependent on the moisture content of the system. In the absence of moisture, very little glycosylamine formation would occur because the reaction is postulated to occur in the sorbed layer of water between excipient and drug. In an excess of water, however, the equilibrium will be shifted to the left. Thus, the proposed model attempts to optimize conditions for the observation of the potential interaction between lactose and amine drugs in a relatively short period of time.

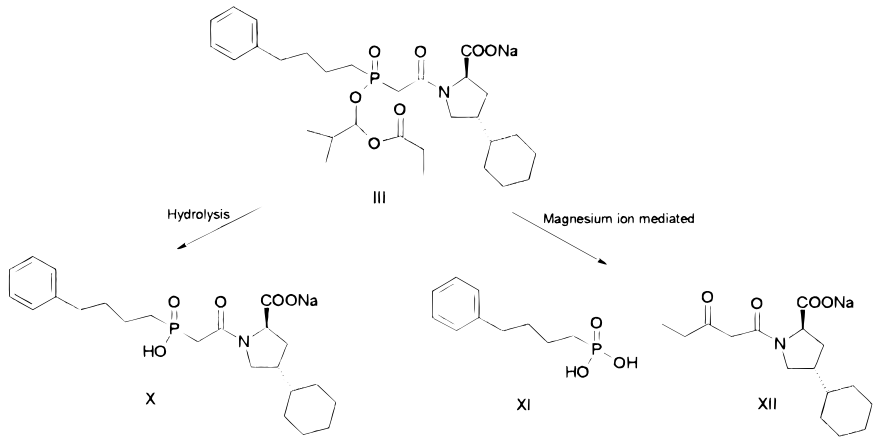
On the basis of the above studies, drug−lactose−stearic acid and drug−mannitol−stearic acid mixtures were selected for the solid dosage forms of **I** and **II**, respectively. The compatibility of these mixtures with various binders and disintegrants were studied in the second phase of the screening, in which the compatibility of povidone, crospovidone, and pregelatinized starch with the drugs was established. Because these studies also indicated that the stability of both drugs was susceptible to moisture, their exposure to moisture during processing and storage was minimized to ensure prolonged stability of the solid dosage forms.

*Fosinopril Sodium (**III**)*—Compound **III** is the prodrug form of an angiotensin-converting enzyme inhibitor which produces in vivo the active moiety fosinoprilat (**X**) by hydrolysis of the phosphinic acid ester side chain. Compound **X** was the only degradation product observed in aqueous media during preformulation testing, indicating that the compound would require protection from moisture during processing and storage. In drug−excipient compatibility testing using 20% added water, **X** was also the only degradation product observed, except in the case of interaction with magnesium stearate. Interaction with magnesium stearate not only accelerated the formation of **X**, it also produced two other major degradation products, **XI** and **XII** (Scheme 1). This is shown with the HPLC chromatograms in Figure 5, which indicate that ~90% of the drug degraded in 1 week when tested according to the model. Although the conditions of the model may appear to be very drastic with such a rapid degradation of **III**, it was by this model that the unexpected interaction with magnesium stearate could be discovered within such a short period of time. The mechanism of this magnesium-mediated reaction was later elucidated.[17]

In a separate study, when a 1:1 mixture of **III** and magnesium stearate was exposed to 75% RH at 50 °C, the degradation of **III** after 3 weeks was less than 1% (Figure 6). This is because both **III** and magnesium stearate were nonhygroscopic, although the interaction between them is mediated by water. This, however, would not be the case in capsules and tablets where other formulation components, such as microcrystalline cellulose, starch, gelatin shell, and so forth, would result in moisture sorption. Therefore, a model in which a limited amount of water is added to a system is often more predictive of drug−excipient compatibility because it does not depend on the hygroscopicity of individual components.

From the above study, it was concluded not only that **III** requires protection from moisture in dosage forms, but also that magnesium stearate should be excluded from formulations. This was later confirmed by accelerated stability testing of the tablet formulation of **III**, where **XI** and **XII** were detected only in a formulation lubricated with magnesium stearate.[17] Thus, the elimination of magnesium stearate from a formulation through drug−excipient compatibility screening maximized product stability and eliminated the necessity of monitoring the formation of two extra degradation products during stability testing.

*Ceronapril (**IV**)*—Compound **IV** is an ACE inhibitor with a primary amine group in its structure. Its interaction with lactose was, therefore, expected. What was unexpected was an interaction with DCP. Figure 7 shows representative HPLC chromatograms of the mixtures of **IV** with three diluents, lactose, DCP, and mannitol. In 3 weeks, **IV** degraded 8.4% and 2.5% in the presence of lactose and DCP, respectively, whereas no degradation was observed in the presence of mannitol or any other excipient. By LC-MS and LC-MS-MS studies, the degradation products formed in the presence of lactose and DCP were identified to be **XIII** and **XIV**, respectively. The formation of **XIV** was oxidative in nature, which could not be predicted on the basis of initial preformulation testing. The model served



Scheme 1

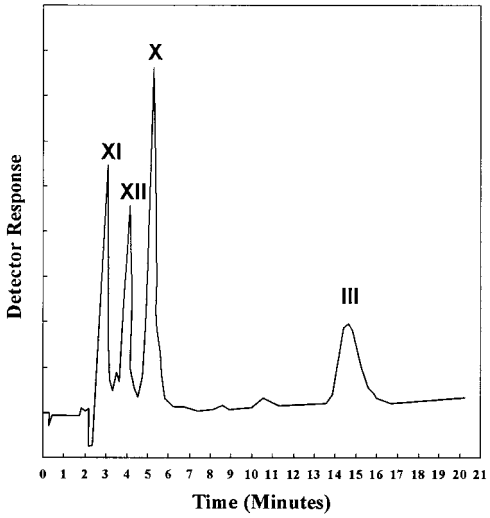


Figure 5—HPLC chromatogram of a fosinopril sodium **(III)**–lactose–magnesium stearate mixture (40:150:10) containing 20% added water stored at 50 °C for 1 week. Compounds **X**, **XI**, and **XII** were the major degradation products formed. A phenyl column (Type C-402, 4.6 mm × 30 cm, 10 μm packing, Column Resolution, Inc., San Jose, CA) using a mixture of methanol and aqueous 0.2% phosphoric acid (72:28) as the mobile phase was utilized (flow rate, 1.5 mL/min; UV detection wavelength, 220 nm).

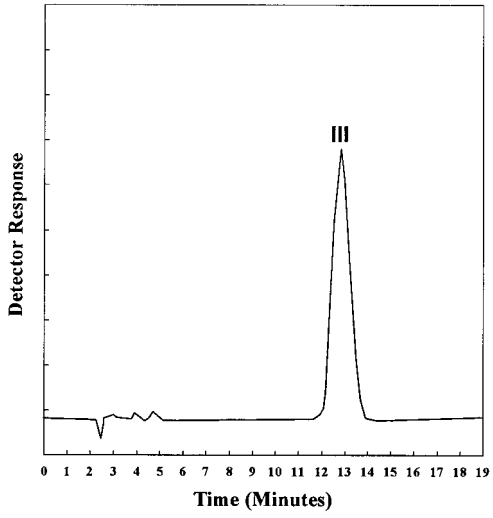
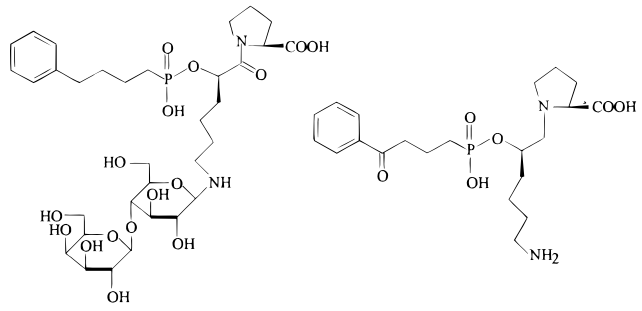


Figure 6—HPLC chromatogram of fosinopril sodium **(III)**–magnesium stearate (1:1) mixture stored at 50 °C under 75% RH for 3 weeks. Chromatographic conditions are the same as in Figure 5.

as a powerful tool in identifying this interaction between **IV** and DCP.



On the basis of the above results, lactose and DCP were excluded from the primary tablet formulation of **IV**. However, because DCP is a commonly used excipient for the direct compression of tablets and the degradation of **IV** in its presence was relatively low, a back-up formulation containing this excipient was also prepared and subjected to accelerated stability testing. For a 20-mg potency tablet with the total weight of 200 mg, the extent of degradation of **IV** upon exposure to 40 °C and 75% RH in an open container for 1, 4 and, 6 months was <1%, 2%, and 5%, respectively. The compound **XIV** was the principal degradation product. These findings indicate that an interaction between **IV** and DCP would possibly have been overlooked if, instead of using the model described in this paper, the drug–excipient blends or miniformulations were exposed to high temperature and humidity for up to 1 month. In closed vials stored at 25 °C, it took about 6 months for the concentration of **XIV** in DCP-based tablets to reach the threshold level of 0.1%. Although such a low concentration of a degradation product may be acceptable in a formulation, it is important that all potential degradation products are detected by drug–excipient compatibility testing prior to dosage form design instead of "discovering" them during formal long-term stability testing. Decisions regarding the potential liability of the presence of any degradation product in a formulation must be made during the dosage form design.

*Pravastatin Sodium (**V**)*—The model described in this paper was also used to study the effects of different excipients on the degradation pattern of **V** in solid dosage forms. An optimal degradation product profile was then selected on the basis of such studies. Figure 8 shows the relative amounts of degradation products formed in two blends of pravastatin sodium containing microcrystalline cellulose, lactose, and magnesium stearate; compositions

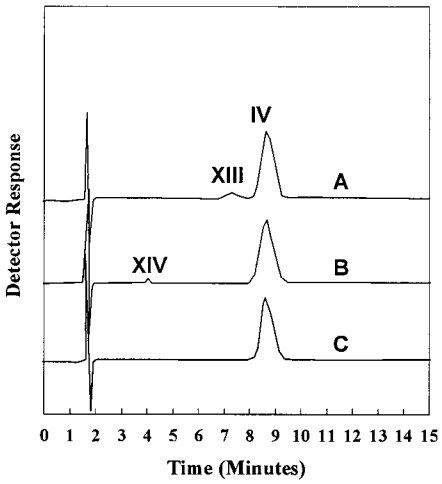
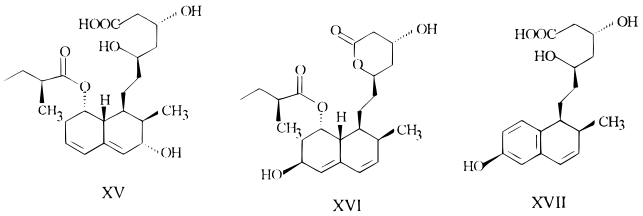
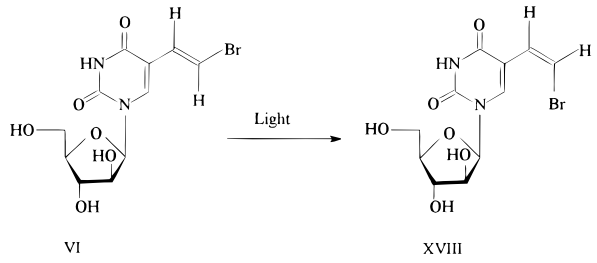


Figure 7—HPLC chromatograms of ceronapril (**IV**)–diluent–magnesium stearate mixtures (40:150:10) containing 20% added water stored at 50 °C for 3 weeks. Diluents used were (A) lactose, (B) dicalcium phosphate dihydrate, and (C) mannitol. Compounds **XIII** and **XIV** are the degradation products formed in mixtures with lactose and dicalcium phosphate dihydrate, respectively. Waters Novapak C_{18} column heated to 30 °C was used. A mixture of acetonitrile and aqueous 0.1% phosphoric acid (19:81) at a flow rate of 1.3 mL/min was used as the mobile phase (detection wavelength: 210 nm).

of the two blends were identical, except for the presence of 3.3% magnesium oxide in Blend 2. The difference in microenvironmental pH values of the two blends (6.5 for Blend 1 vs 9.9 for Blend 2) was responsible for the difference in degradation product profiles; the lower pH favored the formation of **XV** and **XVI**, whereas the higher pH favored the formation of **XVII**. Long-term stability testing of the dosage forms of **V** containing magnesium oxide was in agreement with these results. Thus, by selecting the excipient to adjust microenvironmental pH, the solid dosage form composition of pravastatin sodium was optimized.[18]



*Sorivudine (**VI**)*—Drug–excipient compatibility testing led to the stabilization of **VI**, an antiviral drug, against photodegradation. When exposed to light, the compound forms its Z-isomer (**XVIII**). The initial compatibility testing



with excipients was, therefore, conducted by protecting samples from exposure to light. This and other preformulation studies suggested that a tablet formulation of the compound would require opaque film coating to protect it from photodegradation. In a later drug–excipient screening study to select coloring agents for the tablet, it was noticed

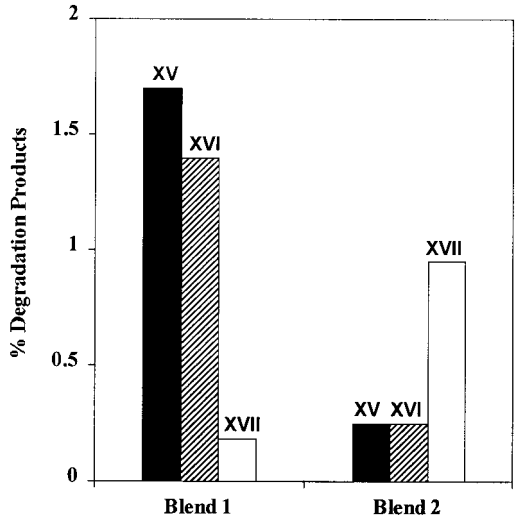


Figure 8—Amounts of degradation products **XV**, **XVI**, and **XVII** formed when pravastatin sodium formulations without magnesium oxide (Blend 1) and with 3.3% magnesium oxide (Blend 2) containing 20% added water were stored at 50 °C for 3 weeks. Products were extracted with a 1:1 mixture of methanol and pH 5.5 aqueous phosphate buffer and analyzed by HPLC using a Waters μ-Bondapak column. A 500:500:1:1 mixture of methanol, water, triethylamine, and acetic acid was used as the mobile phase (flow rate, 1.3 mL/min; UV detection wavelength, 238 nm).

Table 3—Conversion of Sorivudine (VI) to its Z-isomer (XVIII) upon Exposure of Dry and Wet Drug–Excipient Blends Containing Iron Oxides to 900 ft-c Light for 7 Days

	% Z-isomer (**XVIII**) formed[b]	
composition[a]	dry blend	wet blend
no coloring agent	21.1	9.0
red iron oxide	3.4	0.7
yellow iron oxide	2.6	0.7
black iron oxide	2.6	1.3

[a] A 100 mg portion of each blend containing 12.5 mg of drug, 5 mg of iron oxide, and 82.5 mg of other excipients (87.5 mg when no coloring agent was present) was sealed in a 4-mL clear borosilicate glass vial. Each wet blend contained 20 μL of water. The vials were exposed to light from the side by placing them flat. [b] Assayed by HPLC using a 5 μm Lichrosorb RP-18 column (250 mm × 4 mm) using a 15:5:80 mixture of acetonitrile, triethyl ammonium acetate aqueous solution (14% v/v, pH adjusted to 7.0 with acetic acid), and water as the mobile phase (flow rate, 1 mL/min; detection wavelength, 250 nm).

that the formation of **XVIII** was relatively low when drug–excipient blends containing iron oxide dyes were exposed to light. A systematic compatibility testing with iron oxides was therefore conducted by exposing the samples to light, and the results, as shown in Table 3, indicated that iron oxides can greatly reduce the formation of photodegradation product. On the basis of this study, a tablet formulation of **VI** was developed in which iron oxides were admixed with the drug and other excipients to provide color. The tablet did not require any film coating; its stability upon exposure to light was as good as a film-coated tablet which did not contain any iron oxide.[19]

Other Physicochemical Changes—The applications of the model described in this paper are not limited to the testing of the chemical interaction between drugs and excipient. We have used it for many other purposes, including the investigation of (a) dissolution instability of drugs in dosage forms due to conversion of salts to free acid or base forms, (b) changes in crystal forms, such as polymorphic conversion, the formation of an amorphous phase due to dissolution of the drug in granulating fluids and subsequent drying, and so forth, and (c) relative stability of various salt forms during the final form selec-

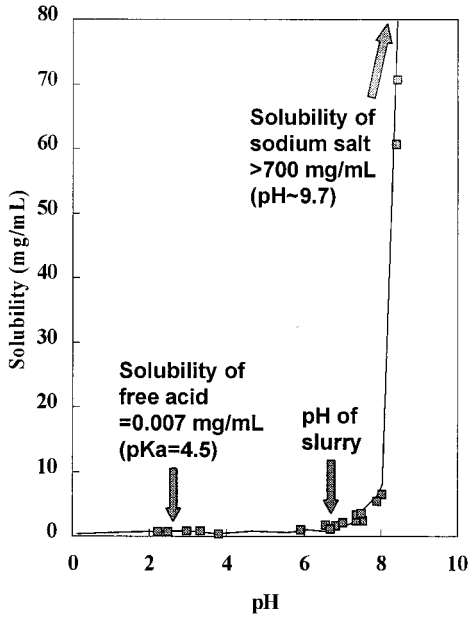


Figure 9—Partial pH-solubility profile of ifetroban sodium (**VII**) at 23 °C. Drug was analyzed by HPLC using a Zorbax Stablebond Cyano column heated to 40 °C. A 35:65 mixture of acetonitrile and 0.005 M KH_2PO_4 aqueous solution, pH adjusted to 3.0 with H_3PO_4, was used as the mobile phase (flow rate, 1.5 mL/min; UV detection wavelength, 215 nm).

$$CaHPO_4.2H_2O \rightarrow\rightarrow Ca_5(OH)(PO_4)_3 + H_3PO_4 + H_2O$$

(Dibasic calcium phosphate dihydrate) (Hydroxyapatite)

$$R\text{-}COO^-Na^+ + H_3PO_4 \rightarrow R\text{-}COOH + NaH_2PO_4$$

(Drug, sodium salt) Water-soluble (Drug, free acid) Water-insoluble

Scheme 2

tion of a drug. Brief descriptions of some of these studies are given below.

Dissolution Instability—During drug–excipient compatibility testing, ifetroban sodium **(VII)** showed excellent chemical stability in the presence of all excipients tested. However, its capsule formulations exhibited a decrease in dissolution rate during accelerated stability testing.[20] This was most pronounced in formulations containing DCP. When the drug–excipient compatibility testing was repeated, the microenvironmental pH values of various dosage form compositions were observed to be between 6.2 and 6.6, where the sodium salt form of the drug could convert to the insoluble free acid form. This is apparent from the pH-solubility profile of the compound as shown in Figure 9. When a mixture of **VII** and DCP containing 20% water was stored at 50 °C for 1 week, almost complete conversion of the sodium salt to free acid was observed.[21] Liberation of H_3PO_4 from DCP at high temperature[22,23] served as the source of hydrogen ions for the salt-to-acid conversion. Indeed, it was observed that the microenvironmental pH of the mixture decreased with time. The conversion of **VII** to the water-insoluble free acid form in a formulation containing DCP is described by Scheme 2.

It is now a common practice in our laboratory to measure the microenvironmental pH values of drug–excipient blends initially and after exposure to 50 °C, with 20% added water, for various intervals of time. If salt forms of drugs are used, any propensity for their conversion to free acid or base forms can be ascertained from such studies. Adjustment of microenvironmental pH with an appropriate excipient can eliminate any such conversion and the consequent drug dissolution problem. For **VII**, alkalizing agents were added to formulations to keep microenvironmental pH above 9, where the compound has high solubility and would not convert to the free acid form.[23]

Crystal Form Changes—Polymorphic and other crystal form changes may lead to dissolution instability of drugs, especially for compounds with low aqueous solubilities. They also cause various physical stability problems in solid dosage forms, including changes in appearance, hardness, disintegration time, and so forth.[24]

Any propensity for polymorphic change was investigated by recording powder X-ray diffraction patterns and solid-state ^{13}C NMR spectra of drug–excipient mixtures initially and after subjecting them to 50 °C with added water for up to 1 week. The wet samples were dried before analysis. If there is any potential for polymorphic conversion, it would be facilitated by the "pressure cooker" effect of the experimental condition and the presence of excipients that could serve as nuclei for recrystallization. In the absence of any chemical degradation, significant change in powder X-ray diffraction patterns or solid-state NMR spectra would indicate polymorphic transformation.

If the drug substance is water-soluble, instead of a polymorphic conversion the drug substance may convert partially or completely to an amorphous form due to wet granulation with the excipient and subsequent drying. This may affect dosage form stability because an amorphous form may be less stable than a crystalline one. The amorphous form thus produced may, in turn, recrystallize into the original or a different crystal form,[25] leading to dissolution or other physical instability problems if this occurs during stability testing of dosage forms. We have studied such changes by recording powder X-ray diffraction patterns of a drug–excipient blend initially and after mixing with water and drying.[3]

Salt Selection—The model was also applied to determine the relative stability of different salt forms of a compound.[26] Inorganic and organic acids and bases used to prepare salts may interact with drug molecules. The tromethamine salt of ketorolac was found to partially convert to the 1-keto analogue and an amide on exposure to high humidity and temperature.[27] Schildcrout et al.[28] reported 1,4-Michael adduct formation between seproxetine and maleic acid in a maleate salt, and Stahl[29] reported the covalent addition of a secondary amine to fumaric acid in a fumarate salt. Different counterions used in salt formation may also provide different microenvironmental pH values to a compound. When the stability of a compound is sensitive to a change in pH, the stability of salts may differ as a result of such a difference. The salt form of a compound with optimal chemical stability may be selected in less than 1 month by stress stability testing according to the model.

Conclusions

In the present health care economic climate, acceleration of the drug development process and optimization of dosage form stability are two major goals of any drug development program. One key step in achieving these goals is the identification of optimal dosage form compositions at the outset of a drug developmental program, which is generally during the design of Phase I clinical formulations. Subsequent changes in formulation during Phases II and III usually lead to increases in time and cost of drug development. In this paper, a practical drug–excipient compatibility screening model to identify potential chemical and physical stability problems with a drug substance in the presence of different excipients has been presented. Case histories described in the paper demonstrate that the

stability of drug products can be optimized by selecting the excipient according to this model. Selection of dosage form composition based on such drug−excipient compatibility testing reduces "surprise" problems during long-term stability testing of drug products.

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