ELSEVIER

Thermochimica Acta 380 (2001) 175–183

thermochimica acta

www.elsevier.com/locate/tca

Rapid, practical and predictive excipient compatibility screening using isothermal microcalorimetry

Eric A. Schmitt*, Kendall Peck[1], Yang Sun, Jean-Marie Geoffroy

Pharmaceutical Products Division, Department 4P3, Building AP9, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6122, USA

Abstract

Conditions for conducting excipient compatibility studies via isothermal microcalorimetry were explored using model reactions. The resulting recommended procedure for rapid and practical screening consisted of using binary mixtures (100 mg of each component), the addition of 20% (w/w) water, and monitoring the mixture at 50°C for 3 days using an isothermal microcalorimeter. The correlation between calorimetric excipient compatibility results and formulation stability was investigated for two developmental drugs. A comparison of calorimetric results to actual formulation stability suggested that it was possible to predict relative stability within functional classes. However, caution should be exercised in such predictions, because apparent reaction enthalpies were found to vary three-fold among excipients in the same functional class. Based on these observations, a two-step procedure is suggested for efficient development of stable formulations. First, excipient compatibility screening should be conducted using a rapid calorimetric technique. The calorimetric results are then used to evaluate relative risk of incompatibility for each excipient within a particular functional class. The calorimetric data and the functional requirements of the dosage form are then integrated in developing a limited number of model formulations that are likely to succeed from both a performance and a stability perspective. The second step of the process is to conduct traditional HPLC-based accelerated stability studies on the limited number of model formulations.

Keywords: Isothermal microcalorimetry; Drug–excipient compatibility

1. Introduction

All pharmaceutical products are required to show acceptable chemical stability during their distribution and storage. An expiration date of 2 years is generally desirable. Since real-time data are not available during the initial stages of development, formulation scientists must employ accelerated stability studies on model formulations to estimate long-term ambient stability. Such studies are costly, time consuming and labor intensive; therefore, it is desirable to minimize the number of model formulations evaluated. One way to achieve this reduction is through excipient compatibility testing. Over the years, various excipient compatibility methods have been developed to guide the selection of excipients. Excipient compatibility screening is generally recognized as an essential part of the development process [1,2], however it is not always successful and this has led some authors to question its utility [3]. Solid-state chemical reactions

* Corresponding author. Tel.: +1-847-938-4835; fax: +1-847-935-1889.
E-mail address: eric.a.schmitt@abbott.com (E.A. Schmitt).
[1] Present address: Department of Chemistry, Ricks College, Rexburg, ID 83460-0500, USA.

0040-6031/01/$ – see front matter
PII: S0040-6031(01)00668-2

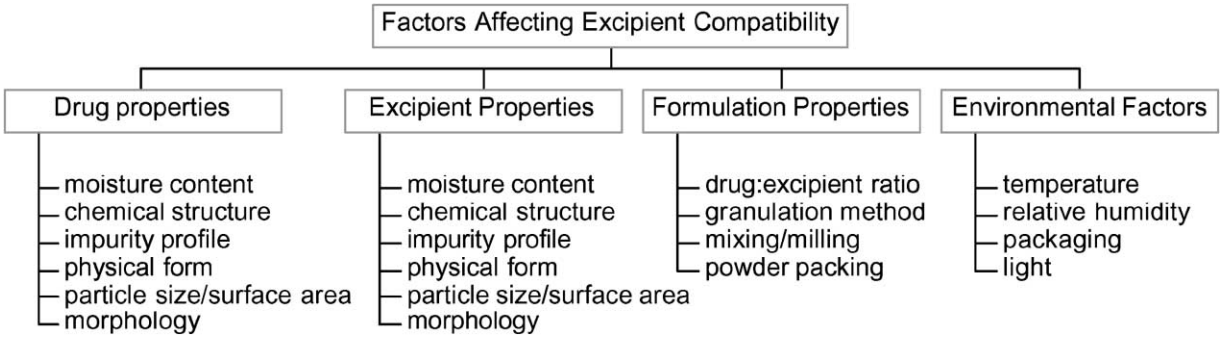

Fig. 1. Factors affecting solid formulation stability.

in general are extremely complex and not well understood [4]. This poor understanding exists even for simple one-component systems, so it is not surprising that the stability of complex heterogeneous mixtures such as tablets is nearly impossible to predict. The degradation kinetics and indeed the ability of two components to even react can depend on a number of factors, as shown in Fig. 1. Consequently, mechanism-based stability predictions for drug products are the exception rather than the rule. It is important to keep this fact in mind when setting expectations for excipient compatibility studies. The goal of compatibility screening in this report was to assign a relative risk level to each excipient. This information is integrated with the functional requirements of the dosage form to prepare a limited number of model formulations with a high probability of success for HLPC-based stability studies. The procedure described here is the first step in the process of developing a stable solid dosage form. Efficient excipient compatibility screening is vital for the timely and rational selection of excipients used in model formulations.

There are numerous ways to conduct excipient compatibility screening. In all cases, however, the basic method is the same — *mix two or more materials together and monitor any interactions*. In one type of study, drug–excipient mixtures are stored under accelerated stability conditions as binary blends [5], mini-formulations or statistically designed mixtures [6,7] and then assayed over time using TLC, HPLC, or spectrophotometry. A disadvantage of this type of study is that reactions must be monitored for several weeks. Also, since the quality of the results depends on the precision of the assays, well-developed and sufficiently validated methods are required. As the number of blends evaluated increases, method development and validation activities rapidly become overly time consuming and resource intensive, especially for the very early stages of development. Thermal analytical techniques such as DTA and DSC have been used to detect drug–excipient incompatibilities for over 30 years [8]. The advantages of DSC or DTA include minimal compound requirements, rapid measurements, and relative experimental simplicity. However, interpretation of the results is often difficult [5], and it has been shown that the relatively poor specific sensitivity of traditional DSC instrumentation requires high temperatures for chemical reactions to proceed at observable rates [9]. Often the reaction mechanisms at elevated temperatures are not relevant at room temperature and extrapolations to normal storage conditions are not valid.

Isothermal microcalorimetry offers a specific sensitivity on the order of 10,000-fold greater than traditional DSC [9]. This greater sensitivity allows the detection of reactions at more relevant temperatures, thereby improving the likelihood of valid extrapolations.

When using calorimetry for compatibility testing, it is imperative to recognize the nonspecific nature of the technique. The relationship between the processes taking place and the calorimetric response is

$$\frac{\mathrm{d}q}{\mathrm{d}t} = -\sum_{i=1}^{n} \Delta H_i \frac{\mathrm{d}n_i}{\mathrm{d}t}, \tag{1}$$

where $\mathrm{d}q/\mathrm{d}t$ is the measured power signal (typically in μW), $\mathrm{d}n_i/\mathrm{d}t$ the rate of the process i, and ΔH_i the

enthalpy change for the process. Several physicochemical processes can give rise to a calorimetric response, including dissolution, adsorption/desorption, evaporation, other phase transitions, crystallization, and chemical reactions. The primary focus of the present study was upon the chemical reactivity of a drug with excipients, therefore the compatibility experiments were designed to allow reasonable confidence that observed heat flow signals were the result of chemical interactions.

Isothermal microcalorimetry has been employed to study the degradation kinetics of drugs in solution [10,11] and in the solid state [12]. These reports have applied microcalorimetry to determine kinetic and thermodynamic parameters of model reactions with well-documented kinetics. Recently, reports on more complicated and unknown systems such as those encountered in excipient compatibility screening have also appeared in the literature [13,14]. This report will describe the selection of experimental conditions for conducting practical calorimetric compatibility screening, apply the technique to two drugs in clinical development, and investigate the correlation between compatibility results and formulation stability.

2. Experimental

2.1. Materials and equipment

Initially, the reaction between ε-amino-*n*-caproic acid, a primary amine, and lactose monohydrate was used to select experimental conditions that gave reasonable power outputs for a well-known incompatibility. After selecting the experimental conditions, excipient compatibility studies were conducted with ABT-627 (2*R*-(2α,3β,4α)-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoyphenyl)-3-pyrrolidinecarboxylic acid, monohydrochloride) an endothelin antagonist, and ABT-229 (*N*-demethyl-*N*-ethyl-9-deoxo-4″-deoxy-8,9-didehydro-6,9-epoxy-erythromycin B) an acid labile macrolide (Fig. 2).

All studies employed a thermal activity monitor (TAM) model 2277 (Thermometric AB, Sweden) consisting of four calorimetric units (part # 2277-201) and standard amplifiers. Data collection and analysis was performed using DIGITAM for Windows version 4.1 (Thermometric AB, Sweden).

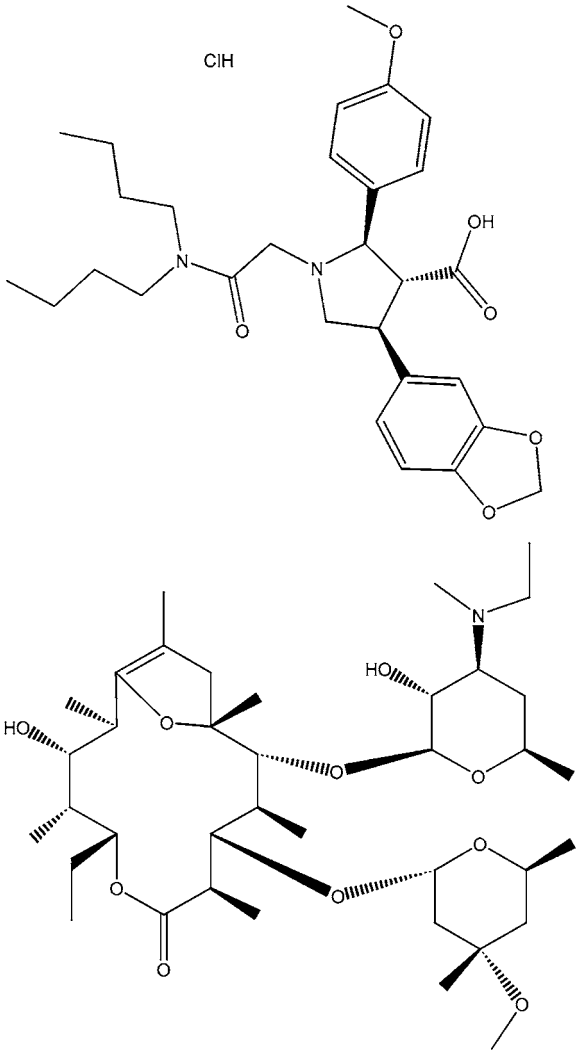

Fig. 2. Chemical structures of ABT-627 (top) and ABT-229 (bottom).

2.2. Procedures

2.2.1. General

Samples were placed in 3 ml glass crimp-top ampoules. The reference cells were loaded with identical ampoules containing 200 mg of dry talc to balance the heat capacities. Before starting a series of experiments, all four calorimetric cells were calibrated using a two-point static electrical calibration at 0 and 299.6 μW. The sample and reference ampoules were sealed with fresh Teflon-lined closures just prior to

starting the experiment [15], and data were collected as follows: day 1, every 10 s; day 2, every 30 s; after day 2, every 300 s. In each case, the data point was the mean value over 10 s.

2.2.2. Selection of experimental conditions

Experimental conditions for monitoring compatibility were evaluated using ε-amino-*n*-caproic acid and lactose monohydrate. These reactants were used to model the notorious drug–excipient incompatibility known as the Maillard reaction, which occurs between reducing sugars and drugs containing primary or secondary amines [16,17]. The selection of experimental conditions was based on two main criteria: (1) the Maillard reaction should give a signal > 10 μW, and (2) the method should be practical for routine screening studies. In our environment, a practical method required minimal sample preparation, a total evaluation time of <2 weeks for 10 excipients, and no more than 100 mg per excipient. With these constraints in mind, the effects of temperature, water, particle size, and mixing method were explored using binary mixtures containing 100 mg of each reactant.

The effect of temperature was investigated at 30, 40, and 50°C. Particle size effects were qualitatively investigated by either mixing the materials as received or grinding them with a mortar and pestle before mixing. Three different mixing methods were considered: (1) mixing together with a spatula as received, (2) grinding separately followed by mixing with a spatula, and (3) grinding the materials together using a mortar and pestle. In addition, the effect of moisture was evaluated by adding 10–100 μl of water or including a 75% RH hygrostat in the ampoule. When liquid water was added, it was mixed into the powder with a Pasteur pipette and the tip was broken off in the ampoule to insure none of the contents were lost. The hygrostats were constructed by adding a saturated aqueous solution of NaCl (containing sufficient excess solid) to 100 μl limited volume inserts for HPLC vials (Alltech Association, Deerfield, IL). Finally, since ε-amino-*n*-caproic acid is much more soluble than most drugs, the effect of water addition was also explored using a known incompatibility between the practically water-insoluble materials ABT-229 and hydroxypropyl methylcellulose phthalate (HP-55).

2.2.3. Excipient compatibility screening of ABT-627

After justifying the experimental conditions, an excipient compatibility screening study was conducted on ABT-627 at 50°C using binary blends containing 20% (w/w) water. Sixteen excipients from various functional classes were evaluated (see Table 1). Power–time curves were collected for drug + water, excipient + water, and drug + excipient + water. The separate drug and excipient curves were used to construct a theoretical noninteraction curve, which was then subtracted from the actual mixture curves to give an interaction curve. The results were expressed in terms of a time-averaged power, $\langle P \rangle$, value [15]. Time-averaged power values were calculated over an 8 h period after the signal had reached an approximately zero-order output, which was typically 2–3 days.

Experimental variability was evaluated using selected lubricants, which represented mixtures having high, medium, and low $\langle P \rangle$ values. An estimate of the pooled standard error was calculated by analysis of variance from eight separate measurements.

An HPLC-based excipient compatibility study was also conducted on binary drug–excipient mixtures. Samples were assayed initially and after 3 and 5.2 weeks at 50°C. The total area percent of impurities was calculated from the chromatograms and compared to the calorimetric results. Tablets were prepared

Table 1
Summary of interaction powers between ABT-627 and various excipients

Functional class	Excipient	Interaction power (μW)
Diluents	Dibasic calcium phosphate	5.23
	Microcrystalline cellulose	2.92
	Lactose monohydrate	−0.345
	Pregelatinized starch	−1.31
Lubricants	Calcium stearate	12.15
	Sodium stearyl fumarate	10.66
	Magnesium stearate	6.51
	Zinc stearate	2.08
	Hydrogenated cottonseed oil	0.516
	Stearic acid	0.512
	Colloidal silicon dioxide	0.32
Binders and disintegrants	Sodium starch glycolate	7.12
	Povidone K30	2.59
	Crospovidone	2.37
	Hydroxypropyl methylcellulose	1.78
	Hydroxypropyl cellulose	1.66

containing three different lubricants and stability studies conducted to determine the relationship between calorimetric results and actual formulation stability. The tablets were assayed by HPLC using a validated impurity method and the results expressed in terms of chromatographic area percent.

2.2.4. Selection of an enteric coating polymer for ABT-229

Stability studies of early trial formulations suggested an incompatibility between ABT-229 and the enteric coating polymer HP-55. The suspected incompatibility and three potential substitutes were investigated by isothermal microcalorimetry at 50°C as 1:1 mixtures containing 20% added water. The potential substitutes included cellulose acetate trimellitate (CAT), cellulose acetate phthalate (CAP), and Eudragit® L100-55 (EL-55). The power–time curves were collected for 15 days and the degraded samples assayed for ABT-229 content at the end of the study. The integrated power–time curves and HPLC-determined amount degraded allowed calculation of an apparent reaction enthalpy for the four different enteric coatings.

Formulations were then prepared using the two most compatible coatings and the stability monitored at 40°C, 75% RH in closed and open vials. The HPLC analysis employed a validated impurity method with the results reported in terms of chromatographic area percent.

3. Results and discussion

3.1. Selection of experimental conditions

The effects of temperature, water addition, particle size, and mixing method on the reaction between ε-amino-*n*-caproic acid and lactose monohydrate were investigated. Fig. 3 shows the effect of temperature on the reaction with 20% (w/w) added water. The plateaus in the power–time curves indicate the reaction enters a pseudo-zero-order region where the power output is directly related to the product of the pseudo-zero-order rate constant, the apparent enthalpy, and the solubility of the reactants. The plateau power values were 0.23, 4.24, and 38.55 μW for mixtures

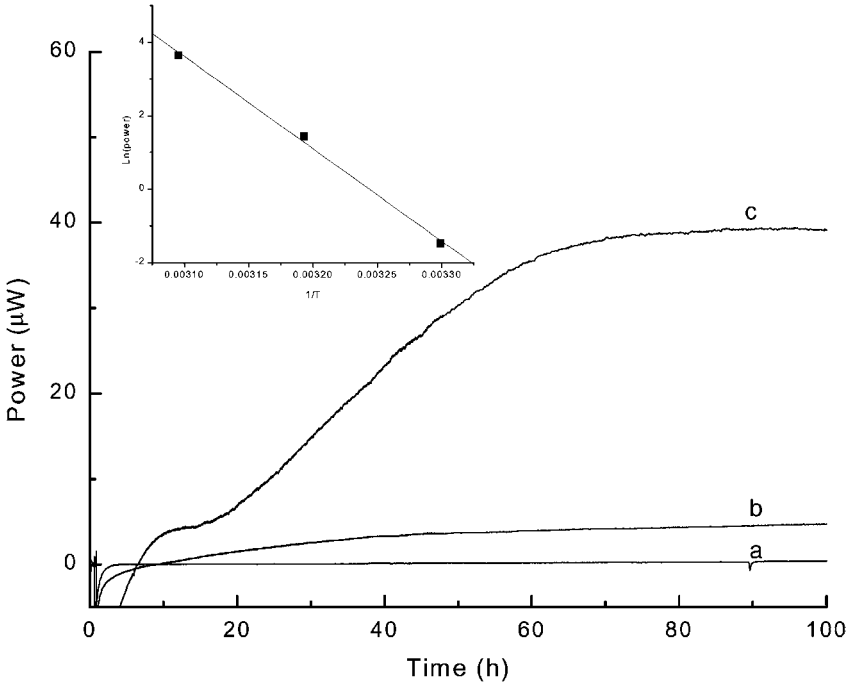

Fig. 3. Power–time curves of amine–lactose mixtures containing 20% (w/w) water at: (a) 30°C; (b) 40°C; (c) 50°C. The inset shows an Arrhenius plot of the plateau power values at each temperature.

at 30, 40, and 50°C, respectively. The inset of Fig. 3 shows an Arrhenius-type relationship between the plateau power values and temperature giving an apparent activation energy of 209 kJ/mol. In comparison, Vickery and Maurin recently reported an apparent activation energy of 109 kJ/mol for a similar reaction between an HIV protease inhibitor and lactose [18]. One reason for this discrepancy may lie in the fact that Vickery and Maurin did not observe a zero-order power output, and therefore used peak power values to construct an Arrhenius-type plot. Also, the apparent activation energy reported here is a composite of the reaction activation energy and the enthalpies of solution and ionization. Fig. 4 shows the effect of added moisture. It is clear that over the time frame studied, a 75% RH hygrostat had a minimal effect compared to directly adding as little as 10 μl water. As expected, if mixtures containing hygrostats were monitored for longer times, an incompatibility was detected and smaller particles gave an earlier "take off" (Fig. 5). In addition to the longer time required for the hygrostat-containing samples, these samples also demonstrated very complicated power–time curves because of changes in hygroscopicity as the reaction proceeded. Meaningful analysis of these complicated thermograms was not possible. If liquid water was added, no dependence on particle size was observed, the power reached a level > 10 μW within 24 h and analysis was much simpler. When liquid water was added to the system, no significant differences were noted with any of the three mixing methods, suggesting the reaction occurs in the solution phase.

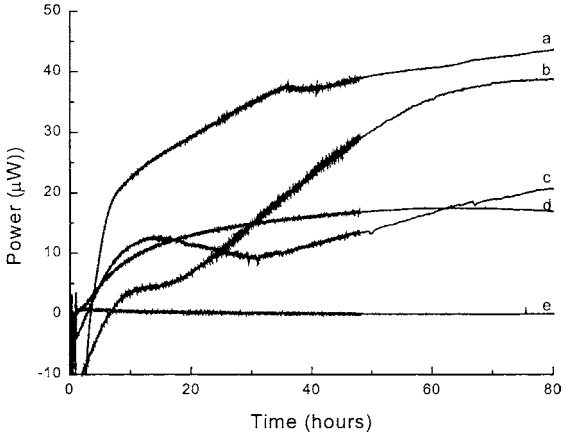

Fig. 4. Power–time curves of amine–lactose mixtures showing the effect of water addition at 50°C: (a) 100 μl; (b) 50 μl; (c) 25 μl; (d) 10 μl; (e) 75% RH hygrostat.

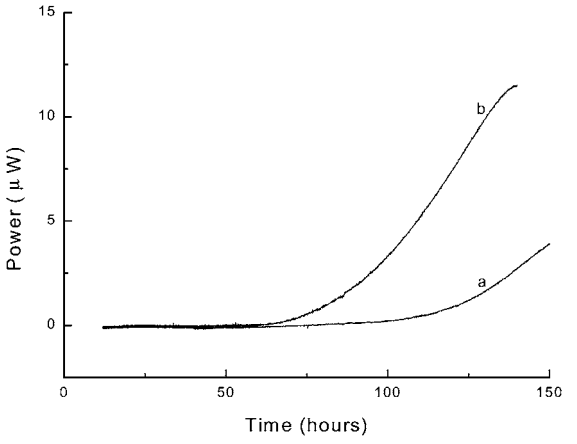

Fig. 5. Power–time curves of amine–lactose mixture showing the effect of particle size at 50°C and 75% RH: (a) mixture as received; (b) mixture after grinding the individual components.

Up to this point, all experiments conducted to select the experimental conditions had employed two water-soluble reactants. Since most drugs are far less soluble that our model, ε-amino-*n*-caproic acid, it was possible that the importance of added moisture was biased. Therefore, a known incompatibility between ABT-229 and HP-55 was investigated. In this case, both the drug and the excipient have water solubility values in the μg/ml range. Fig. 6 shows the power–time curves

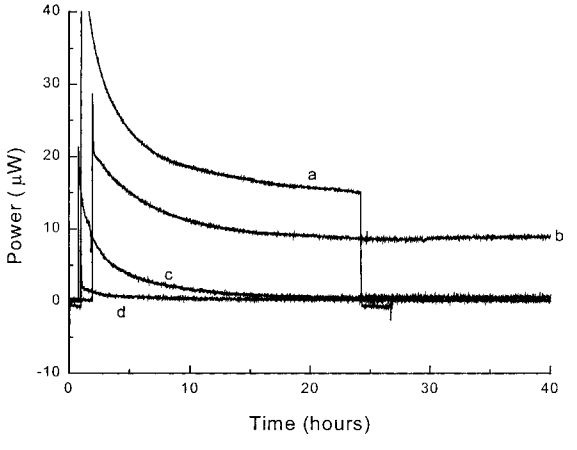

Fig. 6. Power–time curves showing the effect of temperature and water addition on a reaction between the practically insoluble reactants, ABT-229 and HP-55: (a) 50°C, 100 μl H_2O; (b) 50°C, 50 μl H_2O; (c) 30°C, 50 μl H_2O; (d) 50°C, dry.

obtained under dry conditions, 75% RH, and with added water. The mixtures without added water do not show an incompatibility over the time studied, while those containing 50–100 μl of added water show power outputs $\geq$ 10 μW at 50°C. If the mixtures were monitored at 30°C with 50 μl added water, the power outputs were insignificant. These results along with those obtained using water-soluble reactants clearly indicated that water addition and a temperature of 50°C were necessary for rapid and practical excipient compatibility screening. Conducting excipient compatibility studies in suspensions may seem somewhat unrealistic, however the use of suspensions to understand pharmaceutically important solid-state reactions dates back to at least 1967 [19]. More recently, Ahlneck and Lundgren have also advocated the use of suspensions as a quick screening method for assessing the risks of incompatibility between drugs and excipients [20]. Based on the results obtained with ε-amino-*n*-cuproic acid–lactose and ABT-229–HP-55, the procedure used for subsequent studies was as follows: (1) mix 100 mg of drug and excipient together as received and transfer to ampoule, (2) add 50 μl of water, mix with Pasteur pipette breaking the tip off in the ampoule, and (3) collect power–time curves at 50°C.

3.1.1. Excipient compatibility screening of ABT-627

The compatibility of ABT-627 with a number of excipients was examined. Power–time curves for the mixture of ABT-627 with calcium phosphate are shown in Fig. 7, which illustrates typical results.

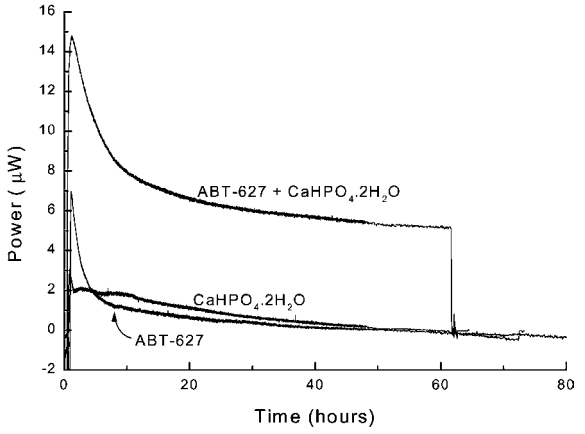

Fig. 7. Typical raw power–time curves used for an excipient compatibility study.

The three curves are used to calculate the time averaged interaction power, $\langle P \rangle$, as described earlier. Under cases where the power values reach a zero-order or nearly zero-order output, $\langle P \rangle$ values can be used for semi-quantitative comparisons among excipients. Table 1 gives the $\langle P \rangle$ values for the 16 excipients tested. Since the proportion of an excipient in a formulation depends on its functional class and the drug–excipient ratio is expected to impact stability, it is important to divide them according to their functional classes when making comparisons. Obviously, a 10 μW power output for a diluent and a lubricant, where the drug–excipient ratio could differ by orders of magnitude, are not equivalent. Grouping the results according to functional classes minimizes systematic errors due to differences in drug–excipient ratios between the test mixture and the actual formulation.

Experimental variability in the $\langle P \rangle$ values was estimated from replicate runs of mixtures with three different lubricants: calcium stearate ($n = 2$), magnesium stearate ($n = 3$), and zinc stearate ($n = 3$). Average $\langle P \rangle$ values for the three different excipient mixtures ranged from approximately 2 to 12 μW. The pooled estimate of the standard error from ANOVA in Microsoft Excel version 5.0 was 0.48 μW.

Table 2 gives results from the HPLC-based compatibility study. Variation in ABT-627 recovery with different excipients required the chromatograms to be analyzed in terms of peak area percent. This

Table 2
Results of HPLC analysis on binary mixtures of ABT-627 and various excipients[a]

Excipient	Area percent impurities		
	Initial	After 3 weeks	After 5.2 weeks
Dibasic calcium phosphate	0	0.06	0.22
Microcrystalline cellulose	0	0.056	0.108
Pregelatinized starch	0.05	0.048	0.102
Lactose monohydrate	0	0.051	0.076
Magnesium stearate	0.546	1.25	2.04
Stearic acid	0	0.05	0.03
Povidone K30	0.059	0.10	0.54
Sodium starch glycolate	0	0.21	0.51
Crospovidone	0.052	0.25	0.39
Drug only (control)	0	0.07	0.05

[a] Each mixture contained 20% (w/w) water.

analysis assumes the drug and its degradation products are recovered to the same extent. Comparing the results of Tables 1 and 2 shows that the conclusions from the two methods are qualitatively in good agreement. But the HPLC-based method required significantly more resources for method development, sample preparation, and data analysis. Moreover, the HPLC method required nearly 6 weeks to complete as compared to 3 days for the calorimetric method.

Various workers have concluded that binary drug–excipient mixtures cannot model the conditions present in a dosage form, and therefore results from binary mixtures can be misleading. These conclusions are not questioned, however we were interested in investigating the predictive power of the compatibility results within a functional class. For this study, tablets were prepared containing ABT-627, microcrystalline cellulose, and either stearic acid, zinc stearate or magnesium stearate as the lubricant. These three lubricants gave interaction powers of 0.5, 2.1, and 6.5 μW, respectively. The formulation components were mixed in a ratio of 96:3:1 (diluent:drug:lubricant) and directly compressed into tablets. Tablets were then stored at 40°C, 75% RH, and assayed after 5 months or stored at room temperature and assayed after 3 years. All three formulations appeared stable after 5 months at 40°C, 75% RH. A second analysis of the tablets conducted after 3 years at room temperature gave 87.1 ± 0.3, 91 ± 1, and 81 ± 2 area percent ABT-627 for tablets prepared with stearic acid, Zn stearate and Mg stearate, respectively. Although, the rank-order in formulation stability was not identical to the calorimetric outputs (Table 1), the 3-year room temperature results show that the worst lubricant was correctly identified. Lubricants typically represent less than 1% to perhaps a few percent of the formulation. This means excipient compatibility studies on binary mixtures with lubricants are probably the least predictive of any functional class. Thus, the fact that the worst lubricant was correctly identified by a rapid and relatively simple compatibility method is a significant achievement.

3.1.2. Selection of an enteric coating polymer for ABT-229

Rapid excipient compatibility testing is also important when troubleshooting formulation stability problems. The macrolide, ABT-229, was not stable in acidic pH and therefore required an enteric coated dosage form for oral administration. During development, HP-55 was suspected to be the root of a stability problem. Therefore, the compatibility of ABT-229 with HP-55, CAP, CAT, and EL-55 was investigated. Fig. 8 shows the power–time curves for each of the coatings. The experiments were allowed to run for approximately 15 days and the amount of ABT-229 remaining after this time was determined by HPLC. Combining the integrated power–time curves with the amount degraded from HPLC analysis allowed calculation of an apparent enthalpy of degradation (Table 3). The apparent enthalpies for degradation varied by nearly three-fold among the coatings. Eq. (1) shows that the calorimetric power depends on both the rate and the enthalpy of the processes occurring. In compatibility testing, we are most interested in rates of degradation. Therefore, it is important to remember that enthalpy variation such as this can be misleading in terms of rank-order compatibilities. In the present

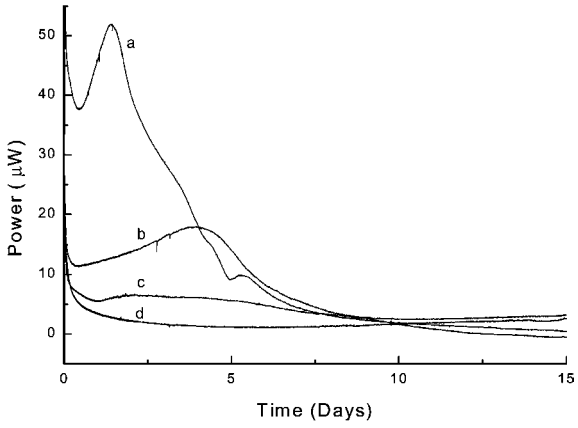

Fig. 8. Power–time curves of ABT-229 with: (a) CAT; (b) CAP; (c) HP-55; (d) EL-55.

Table 3
Apparent degradation enthalpies obtained for the reaction between ABT-229 and four different enteric coating polymers

Polymer	Drug remaining (%)	Integral heat (J)	Apparent degradation enthalpy (kJ/mol)
EL-55	79.6	2.0	70
HP-55	31.5	4.3	44
CAP	0	9.1	64
CAT	0	16.6	116

Table 4
Summary of HPLC stability study on ABT-229 formulation

Polymer	Impurity increase after 8 weeks, 40°C, 75% RH (%)		Power after 24 h (μW)
	Closed	Open	
EL-55	0.29	1.18	3.5
HP-55	3.31	7.87	5.5

case, the two coating polymers that gave the lowest power outputs, HP-55 and EL-55, were chosen for preparing model formulations. A particulate formulation was coated with either HP-55 or EL-55 using conditions recommended by the polymer manufacturers. The formulations were then stored at 40°C and 75% RH in both closed and open vials. After 8 weeks, the formulations were assayed by HPLC and compared to the initial assay values. The results of the HPLC and calorimetric analyses are summarized in Table 4. Water exposure accelerated the degradation and the most compatible coating also had the lowest power output after 24 h. Although, the percent degradation over time could not be predicted, a simple 1-day experiment in the calorimeter did correctly identify the most compatible coating.

4. Conclusions

Solid-state stability is extremely complicated and depends on many factors. Therefore, it is unreasonable to expect any excipient compatibility screening method to quantitatively predict the reactivity of a drug and an excipient in a formulation. With realistic expectations rapid, practical, and predictive excipient compatibility screening is possible using isothermal microcalorimetry. The basic conditions suggested for compatibility testing included monitoring binary mixtures containing 100 mg of each component at 50°C and adding 20% (w/w) water. These conditions gave acceptable power outputs from incompatible mixtures with aqueous solubility values ranging from freely soluble to practically insoluble. While the suggested conditions may seem rather stressful for accurate predictions at room temperature, they are not unprecedented [2,19,20].

The ability to predict reactions in dosage forms depends on the similarity of the binary mixture to the formulation. Reactions with lubricants and in low-dose formulations are notoriously difficult to predict; however, a simple comparison of interaction powers within the functional class gave reasonable predictability for the ABT-627–lubricant interaction and the ABT-229–coating interaction. Calorimetric excipient compatibility data can be collected in a few days and together with functional excipient requirements provide a rational basis for designing model formulations stability studies.

Acknowledgements

The authors thank Dr. Ninus Simonzadeh, Dawn Raymond, and Colleen Flood for analytical assistance.

References

[1] J.I. Wells, Pharmaceutical Preformulation — The Physicochemical Properties of Drug Substances, Ellis Horwood, Chichester, UK, 1988.
[2] A.T. Serajuddin, A.B. Thakur, R.N. Ghoshal, et al., J. Pharm. Sci. 88 (1999) 696.
[3] D.C. Monkhouse, A. Maderich, Drug Dev. Ind. Pharm. 15 (1989) 2115.
[4] S.R. Byrn, R.R. Pfeiffer, J.G. Stowell, Solid-State Chemistry of Drugs, 2nd Edition, SSCI, West LaFayette, IN, 1999.
[5] A.A. van Dooren, Drug Dev. Ind. Pharm. 9 (1983) 43.
[6] J.O. Waltersson, Acta Pharm. Suec. 23 (1986) 129.
[7] T. Durig, A.R. Fassihi, Int. J. Pharm. 97 (1993) 161.
[8] H. Jacobson, G. Reier, J. Pharm. Sci. 58 (1969) 631.
[9] A.E. Beezer, S. Gaisford, A.K. Hills, et al., Int. J. Pharm. 179 (1999) 159.
[10] R. Oliyai, S. Lindenbaum, Int. J. Pharm. 73 (1991) 33.
[11] S. Gaisford, A.K. Hills, A.E. Beezer, J.C. Mitchell, Thermochim. Acta 328 (1999) 39.
[12] X. Tan, N. Meltzer, S. Lindenbaum, Pharm. Res. 9 (1992) 1203.
[13] M.A. Phipps, R.A. Winnike, Use of isothermal microcalorimetry in the early detection of potential drug formulation incompatibilities, Proc. Workshop Microcalorim. Energ. Mater. (1997) M1–M14, CODEN: 66QLAR CAN 129:321053 AN 1998:576053 CAPLUS.
[14] T. Selzer, M. Radau, J. Kreuter, Int. J. Pharm. 171 (2) (1998) 227.
[15] M.J. Pikal, K.M. Dellerman, Int. J. Pharm. 50 (1989) 233.
[16] D.D. Wirth, S.W. Baertschi, R.A. Johnson, et al., J. Pharm. Sci. 87 (1998) 31.
[17] R.N. Duvall, K.T. Koshy, J.W. Pyles, J. Pharm. Sci. 54 (1965) 607.
[18] R.D. Vickery, M.B. Maurin, J. Pharm. Biomed. Anal. 20 (1999) 385.
[19] S.S. Kornblum, M.A. Zoglio, J. Pharm. Sci. 56 (1967) 1569.
[20] C. Ahlneck, P. Lundgren, Acta Pharm. Suec. 22 (1985) 305.