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Identification of stabilizing and destabilizing effects of excipient-drug interactions in solid dosage form design

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Summary

The compatibility of pyridoxal hydrochloride with various tableting excipients has been investigated by isothermal stress testing of multicomponent mixtures and by differential scanning calorimetry (DSC) screening of binary drug excipient mixtures. A Plackett-Burman factorial design was used to conduct the isothermal stress testing experiment. Elevated moisture and temperature were found to be the dominant destabilizing factors. The factorial design experiment also revealed chemical incompatibilities with mannitol, lactose and corn starch. Simultaneously, the strong stabilizing influences of various cellulose derivatives and colloidal silicone dioxide were identified. It appears that these excipients function as moisture scavengers, thus decreasing the amount of free water available for interaction with pyridoxal hydrochloride. The major incompatibilities were also detected by DSC screening. The study demonstrates the value of employing a compatibility screening procedure capable of detecting both positive and negative drug-excipient interactions.

Introduction

The formulation of a stable and effective dosage form requires careful selection of excipients used to facilitate administration, promote consistent release and bioavailability of the drug and to protect the active moiety from the environment. Although often regarded as 'inert', excipients can in fact readily interact with drugs (Monkhouse, 1984; Fassihi and Persicaner, 1987).

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The evaluation of drug-excipient compatibility is therefore an essential aspect of any preformulation study. The two commonly employed compatibility screening techniques are isothermal stress testing of binary drug-excipient mixtures and thermal analysis using either DSC or differential thermal analysis (DTA).

In its simplest form isothermal stress testing involves the exposure of binary drug-excipient mixtures to elevated temperatures and moisture levels to accelerate drug ageing and drug-excipient interactions.After a specific storage time the samples can then be analysed by visual comparisons as well as by chromatography (Carstensen et al., 1964; Carstensen, 1974). On the other

hand, thermal analysis has significant advantages over the conventional technique of isothermal stress testing. No long-term storage of mixtures and subsequent chromatographic analysis is required and only a few milligrams of drug are needed per individual experiment. Thermal analysis can therefore be valuable during the early stages of a preformulation program where time is of the essence, only small amounts of drug are available and no chromatographic methods of analysis have been developed. However, several workers have found that the results obtained by DSC screening are often not conclusive (Smith, 1982; Van Dooren, 1983; Gordon et al., 1984; Chrzanowski et al., 1986) and frequently require further investigation. Reasons for this include the unrealistically high temperatures and heating rates used, the lack of moisture stress and difficulty in interpreting thermograms.

An alternative approach to excipient compatibility testing involves the application of factorial experimental designs to isothermal stress testing (Leuenberger and Becher, 1975). Plackett and Burman (1946) have developed saturated fractional factorial designs that allow the researcher to investigate accurately many factors simultaneously without having to investigate all the possible combinations of factors. Taken to the extreme, Placket-Burman designs can be employed to evaluate up to $N-1$ factors from only N experiments (e.g., 11 excipients from only 12 experimental runs). However, such designs do not incorporate any 'pseudo' variables and therefore the experimental error inherent in the design and the significance of the measured effects cannot be determined. The scientist therefore has to weigh up the need to obtain statistically sound and meaningful information against the additional work and material required if additional runs are added to the experiment. A further limitation is that only main effects can be detected. The interactions between two or more factors cannot be determined by this method. However, within the bounds of these limitations, the use of these screening procedures invariably results in a well designed, efficient experiment, the outcome of which can be supported with statistical significance. Thus, Plackett-Burman designs have been recommended for preformulation compatibility studies (Motola and Agharkar, 1984; Connors et al., 1986).

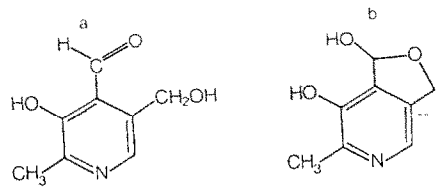

Fig. 1. Structure of (a) free aldehyde form of pyridoxal and (b) pyridoxal (hemiacetal) as found in the solid state.

In this study a Plackett-Burman experimental design is used to investigate the compatibility of the B_6 vitamin, pyridoxal hydrochloride (PL HCl), with various tableting excipients. In addition, the results are then compared with those obtained by the DSC screening technique. The molecular structure of PL HCl in the solid state is shown in Fig. 1. Although often depicted as a free aldehyde, X-ray crystallography and infrared spectrophotometry of pyridoxal base and the hydrochloride salt have shown that in the solid state the molecule exists exclusively in the hemiacetal conformation (Rao et al., 1982; Kortnyk, 1986). The internal hemiacetal also exists in neutral and acidic solution (Metzler and Snell, 1955; Kortnyk and Singh, 1963).

Experimental

Materials

Analytical grade PL HCl (Fluka, Buchs) was used throughout. The following USP or BP grade excipients were used. Stearic acid, magnesium stearate, colloidal silicone dioxide (Aerosil 380), anhydrous lactose, corn starch, microcrystalline cellulose (Avicel pH101), methylcellulose, ethylcellulose and mannitol. In addition, polymethacrylate derivatives (Eudragit RSPM, Rohm Pharma, Weiterstadt) and a modified lactose (Ludipress, BASF, Ludwigshafen) were also used. HPLC grade 2-propanol (Merck, Darmstadt), double distilled water, analytical grade acetic acid and triethylamine (Merck, Darmstadt) and solutions of heptane and octane sulphonate (PIC B7,

PIC B8, Waters Associates, Milford, MA) were used to prepare the mobile phase for HPLC.

Equipment

All samples were stored in thermostatically controlled ovens (Memmert, Schwabach). HPLC analyses were carried out on a System Gold (Beckman, San Ramon, CA) liquid chromatograph equipped with a diode array detector and a Hypersil ODS (5 μm, 4.6 mm i.d. $\times$ 15 cm) analytical column. A thermal analysis system (TA 3000, Mettler, Greifensee) equipped with a DSC 20 cell was used for DSC screening.

Isothermal stress study based on Plackett-Burman design

13 variables (11 excipients and environmental temperature and humidity) were investigated at two levels of magnitude (high '+' and low '−', Table 1). For this purpose an experiment involving 24 different PL HCl-excipient combinations yielding results with 10 degrees of freedom was designed according to the method of Plackett and Burman (1946) (Table 2). The respective PL-excipient mixtures were prepared by blending the powders in a glass vial with the aid of a vortexing device (approx. 20 mg of accurately weighed PL HCl was used in each case). The mixtures were then placed in hygrostats containing saturated solutions of sodium chloride (75% relative humidity) or lithium chloride (11% relative humidity) (Nyqvist, 1983). The hygrostats were then stored in ovens at either 25 or 55°C.

After 14 days storage the amount of PL HCl remaining in each powder mixture was determined by HPLC. The entire powder sample was used in each case. The mobile phase consisted of 10% 2-propanol and an aqueous buffer of 0.1% acetic acid, 0.1% triethylamine and a mixture of sodium heptane- and sodium octanesulphonate (0.004 M). A solvent flow of 1 ml/min was maintained and the eluent was monitored at 288 nm. In addition, the diode array detector was programmed to analyze all peaks in the purity scan mode.

DSC screening

PL HCl-excipient mixtures containing lubricants and glidants were prepared in a 5:1 ratio. All other PL HCl-excipient mixtures were prepared in a 1:5 ratio. Each powder mixture (approx. 60 mg) was prepared by blending the powders in a glass vial with the aid of a vortexing device. Samples of the binary mixtures and of the individual components (3–8 mg) were weighed into standard aluminium pans with pierced lids and heated at 7°C/min over a range of 30–220°C in an atmosphere of flowing nitrogen. The thermograms were interpreted according to the guidelines of Van Dooren (1983) and Smith (1982). A classification of no incompatibility, possible incompatibility and probable incompatibility as proposed by Smith (1982) was used.

TABLE 1

High (+) and low (−) levels for the variables used in the experiment

Variable	(+)	(−)
(A) Stearic acid	2 mg	0 mg
(B) Magnesium stearate	2 mg	0 mg
(C) Aerosil 380	2 mg	0 mg
(D) Lactose	50 mg	0 mg
(E) Ludipress	50 mg	0 mg
(F) Corn starch	50 mg	0 mg
(G) Avicel pH101	50 mg	0 mg
(H) Methylcellulose	50 mg	0 mg
(I) Ethylcellulose	50 mg	0 mg
(J) Eudragit RSPM	50 mg	0 mg
(K) Mannitol	50 mg	0 mg
(L) Relative humidity	75%	11%
(M) Temperature	55°C	25°C

Results and Discussion

Isothermal stress testing using the Plackett-Burman experimental design

The full design showing the percentage of PL HCl recovered from each excipient combination is shown in Table 2. From the percentage recoveries the average effect was determined for each variable and pseudo variable (Plackett and Burman, 1946). Using the average effects of the pseudo variables, the standard deviation of the variable effect (s_{VE}) was calculated (Motola and Agharkar, 1984). From this the minimum signifi-

TABLE 2

Plackett-Burman design showing % PL HCl recovered per trial (excipient combination)

Trial	Variable													Pseudo variable									% REC
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	
1	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	95.15
2	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	94.50
3	−	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	97.14
4	−	−	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	80.00
5	−	−	−	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	92.33
6	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	97.14
7	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	93.60
8	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	97.17
9	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	78.43
10	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	76.14
11	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	+	+	+	67.96
12	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	−	−	86.33
13	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	−	100.0
14	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	+	99.50
15	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	+	98.10
16	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	−	88.67
17	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	+	96.30
18	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	−	96.33
19	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	100.0
20	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	95.44
21	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	+	96.15
22	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	+	95.10
23	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	+	87.18
24	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	98.40

A, stearic acid; B, magnesium stearate; C, Aerosil 380; D, lactose; E, Ludipress; F, corn starch; G, Avicel pH101; H, methylcellulose; I, ethylcellulose; J, Eudragit RSPM; K, mannitol; L, relative humidity; M, temperature; N–W, pseudo variables; % REC, percentage of PL HCl recovered.

TABLE 3

Summary of the compatibility test using a Plackett-Burman factorial design

Variable	Average effect	Significant $2P < 0.1$ [a] ($VE_{ms} = 1.782$)	Significant $2P < 0.4$ [b] ($VE_{ms} = 0.864$)
Stearic acid	−0.239	no	no
Magnesium stearate	0.661	no	no
Aerosil 380	2.205	yes	yes
Lactose	−1.086	no	yes
Ludipress	−0.381	no	no
Starch	−0.898	no	yes
Avicel pH101	1.790	yes	yes
Methylcellulose	2.322	yes	yes
Ethylcellulose	1.510	no	yes
Eudragit RSPM	−0.455	no	no
Mannitol	−2.496	yes	yes
Relative humidity	−3.725	yes	yes
Temperature	−4.550	yes	yes

[a] 90% level of confidence.
[b] 60% level of confidence.

cant variable effects ($VE_{ms} = t \times s_{VE}$) were calculated at the 90 and 60% levels of confidence. As compatibility studies are of a predictive and preventative nature, the 60% level of confidence was considered in addition to the 90% level of confidence. This enables the adoption of a conservative approach to excipient selection. Excipients deemed to have a significant destabilizing effect at the 60% level of confidence nevertheless constitute a risk to the stability of the final dosage form and can thus readily be identified and omitted. Table 3 compares the average effects (main effects) of the variables with the VE_{ms} at various levels of confidence.

It appears that relative humidity and temperature are the dominant destabilizing factors (Table 3). This supports earlier findings which had shown PL HCl to be a moisture-sensitive drug, undergoing physical changes at elevated moisture levels (Durig and Fassihi, 1991).

Amongst the excipients mannitol clearly had the greatest destabilizing effect (average effect −2.406, Table 3). Mannitol was selected for testing as it is known to be non-hygroscopic and had shown excellent compatibility with vitamins A, B and C (Wai et al., 1962). The hemiacetal ring in PL HCl is known to react readily with aliphatic alcohols (Nuernberg, 1961). Mannitol is a hexahydric alcohol molecule and the destabilizing effect could therefore be due to a strong interaction between the hemiacetal and one or more of the hydroxyl groups of mannitol.

Corn starch, lactose and Ludipress (a granulate consisting of lactose, povidone and crospovidone) also appear to be of limited value for any formulation containing PL HCl (see average effect, Table 3). Lactose is known to undergo a non-enzymatic browning reaction (generally known as the Maillard reaction) with amines. Although the reaction is believed to occur mainly in primary amines (Duvall et al., 1965), the possibility of an interaction between the protonated pyridine nitrogen of PL HCl and free lactose carbonyl groups should therefore be considered. The lower average effect of Ludipress (Table 3) may be due to the protective effects of povidone and crospovidone. Crospovidone in particular is able to sorb large quantities of moisture (Handbook of Pharmaceutical Excipients, 1986) this may create less favourable reaction conditions and reduce molecular mobility in the system.

A relatively very low destabilizing effect was also observed for Eudragit RSPM. The effect may largely be due to the alkalinity of the excipient (Handbook of Pharmaceutical Excipients, 1986). Alkaline conditions are known to be detrimental to the stability of PL HCl (Cunningham and Snell, 1945; Ang, 1979). Eudragit RSPM is unlikely to be used in the large proportions that were used in this study (Eudragit:PL HCl, 5:1) as it is used mainly for film coating and in small quantities for inclusion in delayed release matrices. Therefore, it is unlikely that Eudragit RSPM will cause serious stability problems.

A very small destabilizing effect was also observed with stearic acid. It is possible that the melting of stearic acid under experimental conditions had an effect on the interaction with PL HCl. Various melting points reported for stearic acid include 59–64, 51–62.5 and 63–69.2°C (Handbook of Pharmaceutical Excipients, 1986). Therefore, a certain amount of melting can be expected at 55°C. As the interaction does not exclusively occur in the solid state, no conclusions can be made.

A common trend in this study is the relatively large positive effect observed for the cellulose derivatives, i.e., Avicel, methylcellulose and ethylcellulose. The effects of methylcellulose and Avicel are significant at the 90% level of confidence. These excipients are relatively hygroscopic and would be used with caution in conjunction with moisture-sensitive drugs. However, it is known that ethylcellulose stabilizes ascorbic acid (Schmidt, 1982). Furthermore, in stability studies on acetylsalicylic acid in various cellulose mixtures, it was shown that water is not readily available to cause degradation (Ahlneck and Alderborn, 1988). It appears that water becomes strongly bound to the free hydroxy groups in the amorphous regions of the cellulose. As moisture is a major destabilizing factor for PL HCl, it is possible that the celluloses tested in this experiment exercise a protective effect on PL HCl in a similar way. A considerable proportion of the moisture may therefore be strongly bound (low

water activity, a_w) and unavailible for degradation reactions. The existence of various thermodynamic states of water in biopolymers such as cellulose has been extensively documented (Zografi et al., 1984; Zografi and Kontny, 1986; Zografi, 1988), although the rigidity of this concept has recently been challenged (Ahlneck and Zografi, 1990). In addition, the lower stabilizing effect of ethylcellulose may be due to the lower hygroscopicity of this polymer which leads to greater water activity and chemical instability.

The strong stabilizing effect observed for Aerosil 380 (colloidal silicon dioxide) may also be attributed to its moisture scavenging role. Colloidal silicone dioxide can sorb large quantities of water (up to 18% at 78% RH) and can be used as a drying agent for hygroscopic materials (Handbook of Pharmaceutical Excipients, 1986). Furthermore, Aerosil is acidic and may also exert a stabilizing effect by maintaining an acidic microenvironment. Pyridoxal solutions are most stable in the acidic range (Cunningham and Snell, 1945; Ang, 1979).

The moderate stabilizing effect of magnesium stearate was unexpected. A possible explanation could be that magnesium stearate provides a hydrophobic coat on the PL HCl particles, thus reducing drug-water interactions. Water soluble vitamins stabilized by coating with hydrophobic fatty acids and mono- and diglycerides are commercially available (Schmidt, 1982).

Based on this study it can be recommended that mannitol, lactose, Ludipress and starch should not be combined with PL HCl. The destabilizing effect of Ludipress appears to be relatively low. However, Ludipress is best avoided as

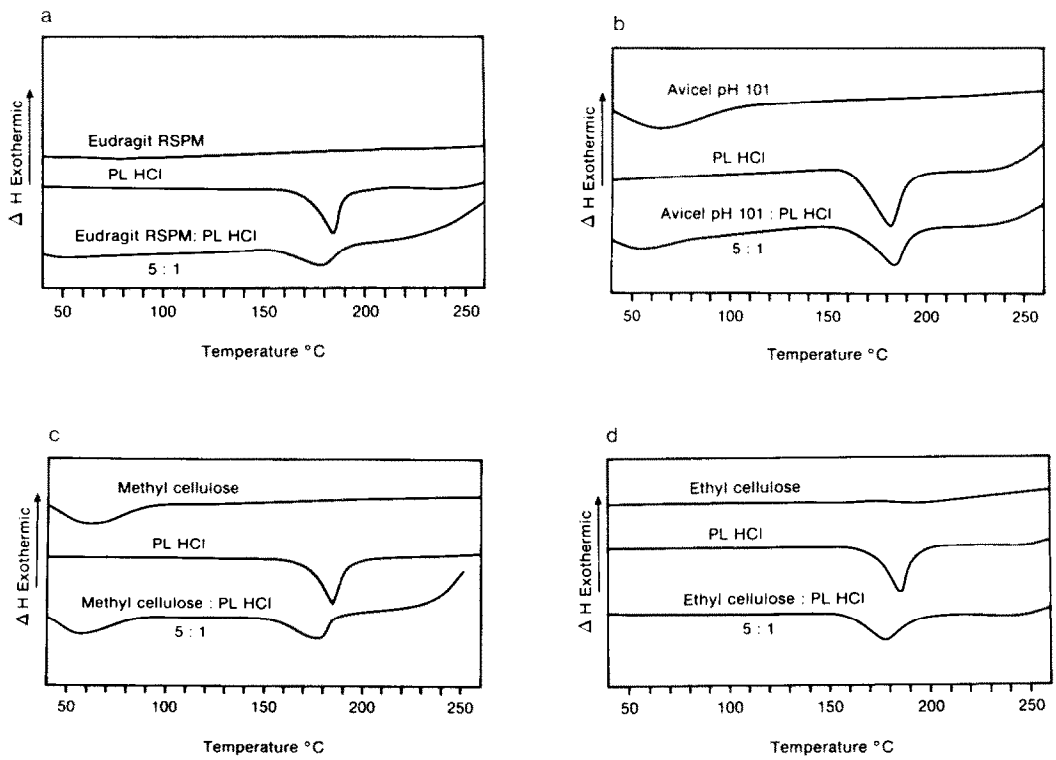

Fig. 2. DSC thermograms of (a) Eudragit RSPM, PL HCl and a PL HCl: Eudragit RSPM (1 : 5) mixture; (b) Avicel pH101, PL HCl and a PL HCl: Avicel pH101 (1 : 5) mixture; (c) methylcellulose, PL HCl and a PL HCl: methylcellulose (1 : 5) mixture; (d) ethylcellulose, PL HCl and a PL HCl: ethylcellulose (1 : 5) mixture.

it is used in relatively large quantities as a filler/diluent and its main component, lactose, has a substantial destabilizing effect on PL HCl.

Stearic acid and Eudragit RSPM have relatively small negative effects and are unlikely to be used in large quantities in solid dosage forms. They could therefore be used if no alternatives were available. On the other hand, magnesium stearate, which has superior lubricity, appears to be compatible with PL HCl.

Methylcellulose, ethylcellulose, Avicel pH101 (microcrystalline cellulose), Aerosil 380 (colloidal silicone dioxide) and magnesium stearate are the excipients of first choice as they tend to stabilize PL HCl in these powder systems.

The finding that the celluloses and colloidal silicone dioxide exert a significant stabilizing effect on PL HCl deserves further investigation. This may provide new insights on simple ways to stabilize moisture sensitive drugs.

DSC screening

The DSC traces of PL HCl, the excipients and their corresponding mixtures are shown in Figs 2–4. The thermograms of the PL HCl mixtures containing Eudragit RSPM, Avicel pH101, methylcellulose, ethylcellulose, Aerosil 380 and stearic acid (Figs 2 and 3a, b) exhibit all the thermal features of the individual components. In general, the broad melting endotherm of PL HCl (approx. 178°C) appears even broader and shallower and occurs at a slightly lower temperature. However, this may be attributed to the mixing process, which lowers the purity of each component in the mixture, thus resulting in slightly broader and lower melting points (Smith, 1982). Slight varia-

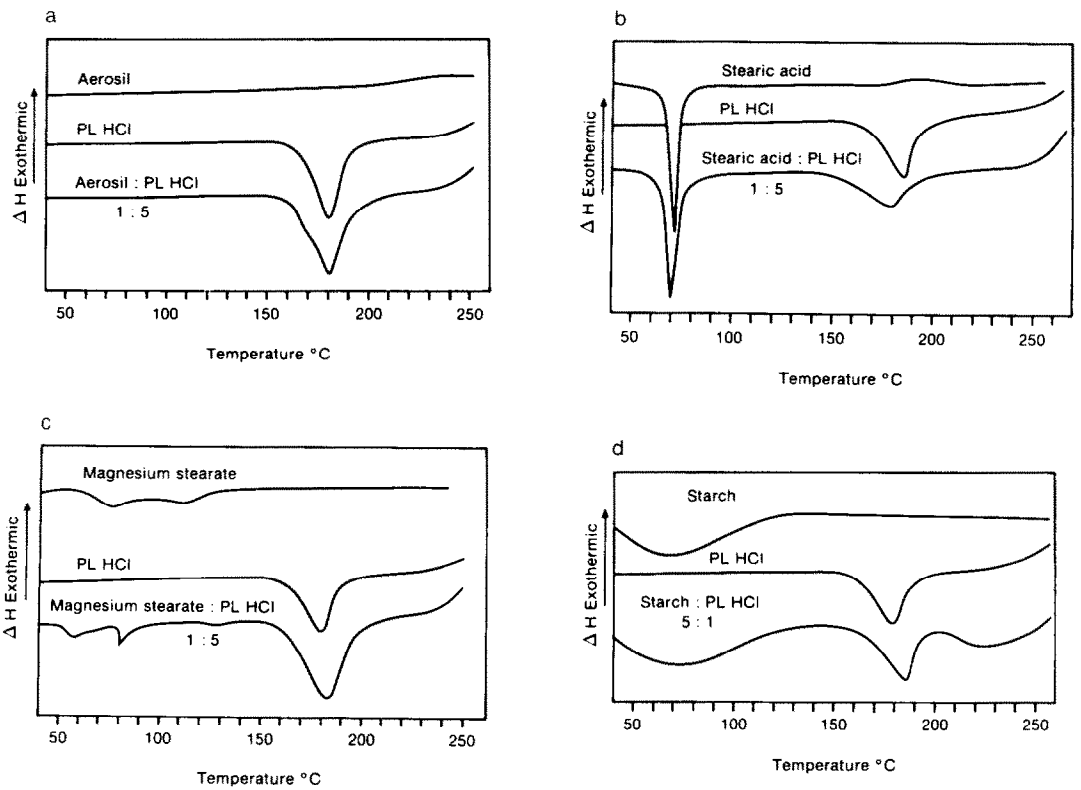

Fig. 3. DSC thermograms of (a) Aerosil 380, PL HCl and a PL HCl : Aerosil 380 (5 : 1) mixture; (b) stearic acid, PL HCl and a PL HCl : stearic acid (5 : 1) mixture; (c) magnesium stearate, PL HCl and a PL HCl : magnesium stearate mixture; (d) starch, PL HCl and a PL HCl : starch mixture.

tions in peak shape and melting point may also be caused by varying sample geometries (Giron-Forest, 1984). The characteristic broad endotherms between 40 and 140°C observed for the celluloses can be attributed to the loss of residual water from these polymers (Botha and Loetter, 1990). No incompatibility could therfore be detected for Eudragit RSPM, Avicel, methylcellulose, ethylcellulose, Aerosil, and stearic acid.

The DSC trace of magnesium stearate (Fig. 3c) shows two shallow, broad endotherms in the region of 50–110°C corresponding to different hydrated states or pseudo-polymorphs. The DSC trace of the PL HCl : magnesium stearate (5 : 1) mixture also shows several small endothermic peaks in this region. The peaks could not be directly correlated with those of pure magnesium stearate. However, the PL HCl peak remains largely unchanged. Incompatibilities involving magnesium stearate are frequently observed by DSC. However, these are often of a physical nature. Due to the low concentrations of magnesium stearate in the final dosage form such interactions are often irrelevant (Gordon et al., 1984; Wells, 1988). Magnesium stearate is widely regarded as the lubricant of first choice and any improvement in the stability of the formulation must be weighed up against the difficulties of finding a suitable substitute. Judging from the appearance of the DSC trace a significant solid-solid interaction is unlikely, but nonetheless possible.

Similar to the celluloses, starch exhibits a broad and shallow endotherm between 40 and 120°C (Fig. 3d). This may again be attributed to the loss of bound water. The DSC trace of the PL HCl : starch (1 : 5) mixture shows several interesting features. The PL HCl endotherm is broad-

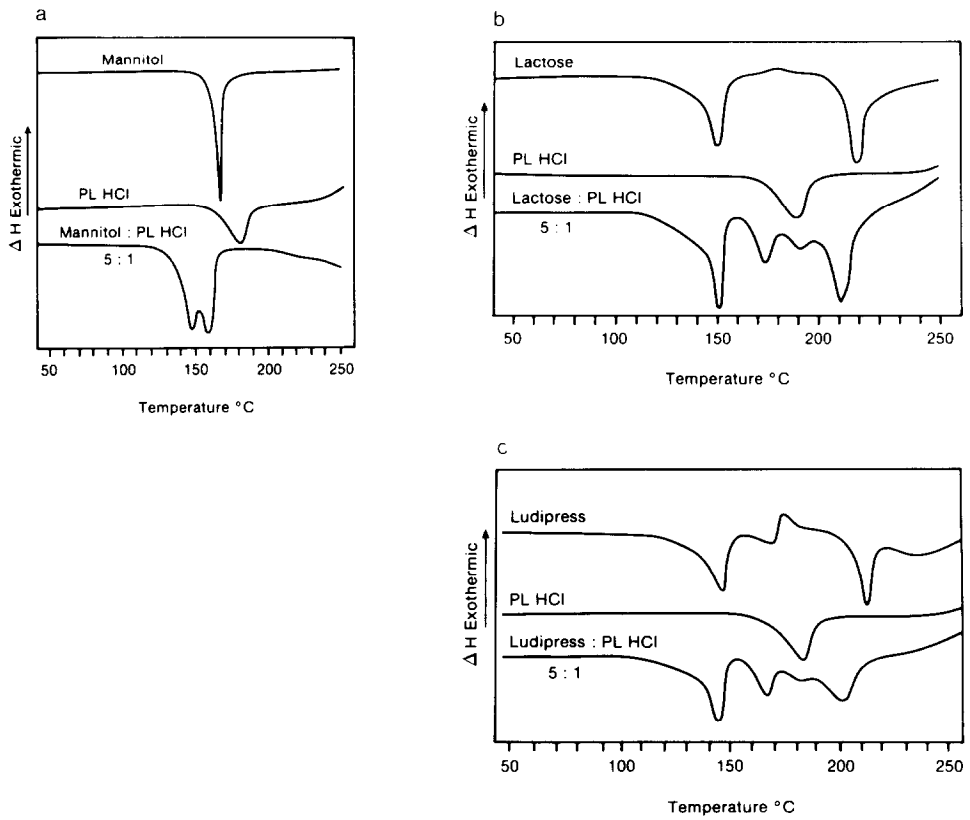

Fig. 4. DSC thermograms of (a) mannitol, PL HCl and a PL HCl : mannitol mixture (1 : 5); (b) lactose, PL HCl and a PL HCl : lactose mixture; (c) Ludipress, PL HCl and a mixture of PL HCl : Ludipress (1 : 5).

ened and peak temperature has been shifted upwards (approx. 185°C). An additional broad and shallow endotherm occurs at 220°C, close to the pyrrolytic temperature for PL HCl. The observed interaction therefore involves a liquid phase and may also involve pyrrolytic degradation products. The evidence for a solid-solid incompatibility is therefore not conclusive. Nonetheless, starch should be used cautiously until more information on its possible interaction with PL HCl can be obtained.

Mannitol exhibits a prominent sharp melting endotherm with a peak temperature of 168°C. This coincides with the onset of the PL HCl melting endotherm (Fig. 4a). The DSC trace of the PL HCl : mannitol mixture shows two large partially overlapping endothermic peaks. The peak temperatures occur at 145 and 158°C, respectively. Such large shifts in peak temperature are most probably indicative of a strong physicochemical interaction between the two components. PL HCl and mannitol are likely to be incompatible.

An examination of Fig. 4b and c supports the earlier finding that lactose and Ludipress may be incompatible with PL HCl. The thermograms of the PL HCl : lactose and PL HCl : Ludipress (1 : 5) mixtures show an additional prominent endotherm in the region of 160–170°C. In both cases, the small exothermic peak occurring between the characteristic exotherms is obliterated. However, unlike in the isothermal stress study it is not possible to discern any difference between the destabilizing effects of these two excipients. This may partially be due to the lack of moisture stress.

The results of the DSC compatibility screening can be summarized as follows:

No or unlikely incompatibility: Aerosil 380, Avicel pH101, methylcellulose, ethylcellulose, Eudragit RSPM, magnesium stearate and stearic acid.

Possible incompatibility: corn starch.

Probable incompatibility: anhydrous lactose, Ludipress and mannitol.

It should be emphasized that the observed aberrations in the thermograms may be caused by physical rather than chemical interaction.

Conclusion

The ability to assign a statistical significance to the observations made and to identify both destabilizing and stabilizing factors clearly distinguishes isothermal stress studies based on a suitable factorial experimental design from other excipient compatibility testing methods. DSC screening proved to be a reliable indicator of major incompatibilities. The shortcomings of this method are the inability to give good estimates of the extent and significance of the destabilizing effects and the inability to detect stabilizing effects. An additional disadvantage of DSC screening is the uncertainty as to whether or not the observed interaction is chemical in nature. Additional isothermal stress studies are usually required to confirm the results. This largely negates the advantages of DSC screening.

It appears that in excipient compatibility testing the emphasis is often mainly on the detection of incompatibilities. Yet, the benefits of simultaneously investigating the stabilizing effects of various excipients are obvious, especially when formulating inherently unstable drugs. This aspect may become increasingly important with the increasing use of drugs of biological origin such as peptide drugs developed by rDNA technology. From this point of view, isothermal stress testing based on a Plackett-Burman experimental design provides a superior method of excipient compatibility testing. DSC screening is suitable as a complementary method to isothermal stress studies and to gauge excipient compatibility during preliminary stages when no stability indicating method is available. In terms of excipient-drug interaction studies the most useful area of application for DSC would appear to be the study of pharmaceutically important physical interactions such as the formation of a solid dispersions of a poorly soluble drugs in water soluble carrier materials (Grant and Abougela, 1982; Ford and Francomb, 1985).

An 'ideal' preformulation excipient compatibility test which is rapid, consumes only small quantities of drug and provides accurate, reliable, quantitative data remains yet to be developed.

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