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Compatibility study between folic acid, vitamin B6 and tablet excipients using differential scanning calorimetry

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Several studies encourage the view that intake of folate and vitamin B6 above the current recommended dietary allowance may be important in the primary prevention of coronary heart disease [1, 2]. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. Differential scanning calorimetry (DSC) can be used to investigate and predict any physicochemical interactions between components in a formulation and therefore can be applied to the selection of suitable chemically compatible excipients [3, 4]. Using DSC, incompatibilities may be deduced from the appearance, shift or disappearance of peaks and/or variations in the corresponding ΔH values. Although it cannot be conclusively stated that an interaction will occur during storage at room temperature, there are usually sufficient excipients available to choose those vehicles which will not cause any problems [5–8].

This study was undertaken to establish the compatibility of folic acid and vitamin B6 with a number of commonly applied direct compression excipients. This was achieved by comparing the DSC curves of folic acid and vitamin B6 and each of the investigated excipients with curves for 1 : 1 mixtures of folic acid and the excipients and those of vitamin B6.

Fig. 1 illustrates the thermograms of folic acid, excipients and their physical mixtures while Fig. 2 shows the thermograms of vitamin B6, excipients and their physical mixtures. When two substances are mixed, the purity of each could be reduced and generally slightly lower melting points appear in the DSC thermogram. Fig. 1 indicates this phenomenon, where the maximum of the first endotherm peak (139 °C) of the physical mixture of folic acid and excipients was shifted to a lower temperature than that of folic acid alone. Any large shift in melting point signifies that a strong solid-solid interaction occured, although it does not necessarily indicate an incompatibility. The combination of vitamin B6-lactose (Cellactose, Tablettose, Ludipress) shows an endothermic peak with a maximum at 145 °C, as well as a broad overlapping endotherm with a maximum at

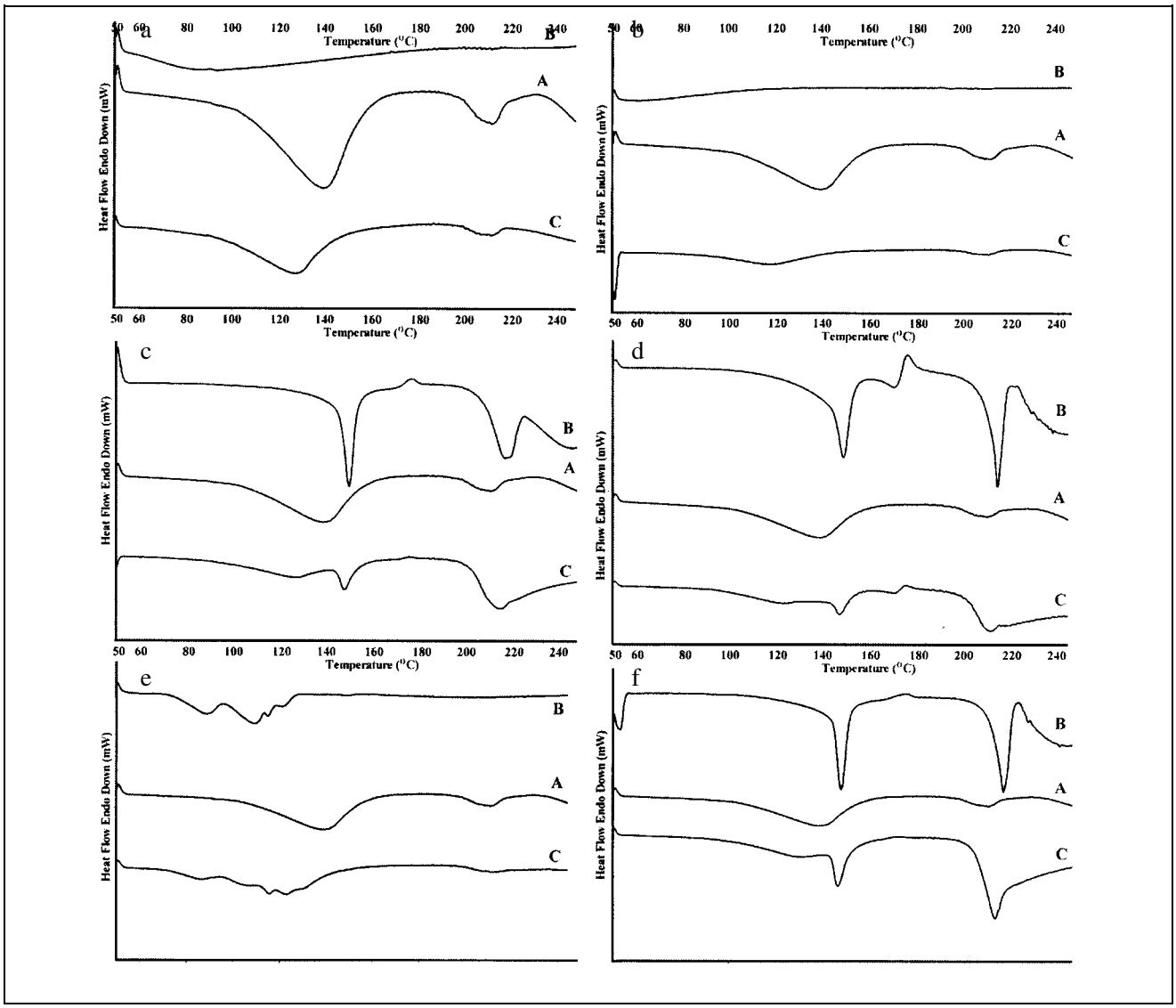

Fig. 1: DSC thermograms of folic acid (A), excipient (B) and physical mixture of folic acid/excipient (C)
Excipients as follows: a: Ac-Di-Sol; b: Avicel PH101; c: Cellactose; d: Ludipress; e: magnesium stearate; f: Tablettose.

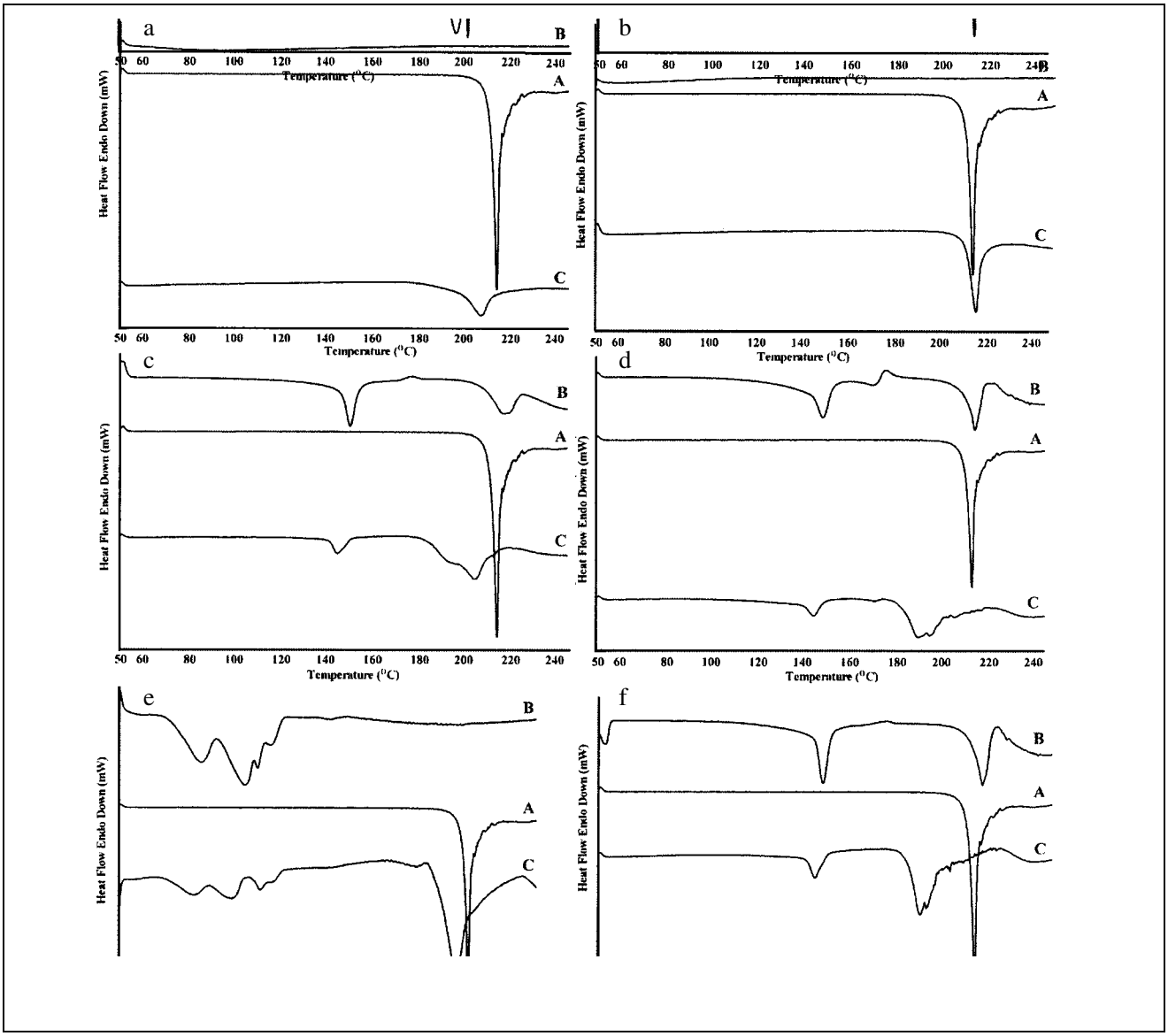

Fig. 2: DSC thermograms of vitamin B6 (A), excipient (B) and physical mixture of vitamin B6/excipient (C)
Excipients as follows: a: Ac-Di-Sol; b: Avicel PH101; c: Cellactose; d: Ludipress; e: magnesium stearate; f: Tablettose

195 °C, while the trace of lactose transitions at 148 °C and 215 °C and the vitamin B6 has an endothermic melting point with onset temperature of 210 °C (Fig. 2). The reaction between lactose and primary amines is well documented [9, 10] and although vitamin B6 is a pyridine derivate, this result might be indicate of such an interaction. The obtained results demonstrate that the selected excipients are likely to be suitable to a tablet formulation. The thermograms of vitamin B6-lactose containing excipients could indicate interaction, but no attempt was made during this study to determine the nature of the interaction.

Experimental

1. Materials

Folic acid (Ph.Hg.VII), vitamin B6 (Ph.Hg.VII), Ac-Di-Sol (FMC Europe NV, Belgium), Avicel PH101 (FMC Europe NV, Belgium), Cellactose (Meggle GmbH, Germany), Ludipress (BASF, Germany), Magnesium stearate (Ph.Hg.VII.), Tablettose (Meggle GmbH, Germany).

2. Differential scanning calorimetry

Samples (2–4 mg) were weighed and hermetically sealed in flat-bottomed aluminium pans. Samples of individual substances as well as 1 : 1 physical mixtures of drugs (folic acid, vitamin B6) and excipients, prepared by grinding in a mortar with a pestle, were analysed. DSC analysis were carried out with a Perkin Elmer DSC 7 Thermal Analyser. The instrument was calibrated with an indium standard. Thermograms were obtained by heating over the temperature range 50–250 °C in a dynamic nitrogen atmosphere at a constant heating rate of 10 K $min^{-1.}$

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