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Compatibility study between acetylcysteine and some commonly used tablet excipients

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Abstract—*Differential scanning calorimetry (DSC), Fourier transform infra-red spectroscopy (FT-IR), HPLC and TLC were used to investigate the interactions between the mucolytic drug acetylcysteine and a number of commonly used tablet and capsule excipients. Acetylcysteine was found to be compatible with microcrystalline cellulose (Avicel PH 101), sodium carboxymethylcellulose, amorphous silicon dioxide (Aerosil), PVP, cross-linked PVP (Polyplasdone XL), corn starch, saccharose and magnesium stearate. Acetylcysteine thermal stability (onset degradation temperature) was decreased in mixtures with corn starch, magnesium stearate, saccharose and lactose. Interactions of acetylcysteine with lactose, PEG 4000 and 6000, glycine, adipic acid and saccharin sodium were found using DSC and studied in detail with FT-IR, HPLC and TLC. The results suggest that acetylcysteine in mixtures with PEG 4000, glycine or saccharin sodium is degraded during storage at conditions of high temperature and humidity.*

Acetylcysteine is a widely used mucolytic drug. Originally, it was used as an aerosol, but currently it is mostly prescribed in tablet form.

The stability of a formulation depends, amongst other factors, on the compatibility of the active components with the excipients. It is of importance to detect any possible interactions, since it has been shown that certain interactions can change the bioavailability or stability of a product (Li Wan Po & Morso 1984).

A number of techniques can be used to indicate interactions in drug-excipient systems, including chromatography (HPLC and TLC), infrared spectrometry and differential scanning calorimetry (DSC). 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 (21°C), there are normally sufficient excipients available to choose only those unlikely to cause any problems. DSC has been recommended to be used in combination with short-term stress in order to evaluate DSC curves more easily (Van Dooren 1983). Additionally, Fourier transform infrared (FT-IR) spectra could give qualitative and quantitative data about interactions of drug with different excipients.

This study was undertaken to establish the compatibility of acetylcysteine with a number of commonly used tablet and capsule excipients. This was achieved by comparing the DSC curves of acetylcysteine and each of the investigated excipients with curves for 1 : 1 mixtures of acetylcysteine and the excipients. Interactions observed in DSC curves were studied and confirmed by FT-IR and HPLC and TLC studies.

The choice of binary concentration in equal parts of drug and excipient may not adequately reflect the final formulation. For magnesium stearate in particular, which is generally present at only 0·5–1% w/w, the many incompatibilities found by DSC are invariably irrelevant and not apparent in the stability of the formulation. Indeed, only isothermal stress in real time can satisfactorily predict, with confidence, the real situation. Most investigations therefore, supplement DSC in this way. Storage at 50°C for three weeks, equivalent to 12 weeks at ambient temperature, and evaluated by TLC is generally an acceptable compromise (Wells 1988).

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Materials and methods

Materials. The following materials were used: acetylcysteine (Diamalt, Germany); microcrystalline cellulose (Avicel PH 101, FMC, Switzerland); carboxymethylcellulose sodium (FMC, Switzerland); corn starch (Servo Mihajl, Yugoslavia); magne-

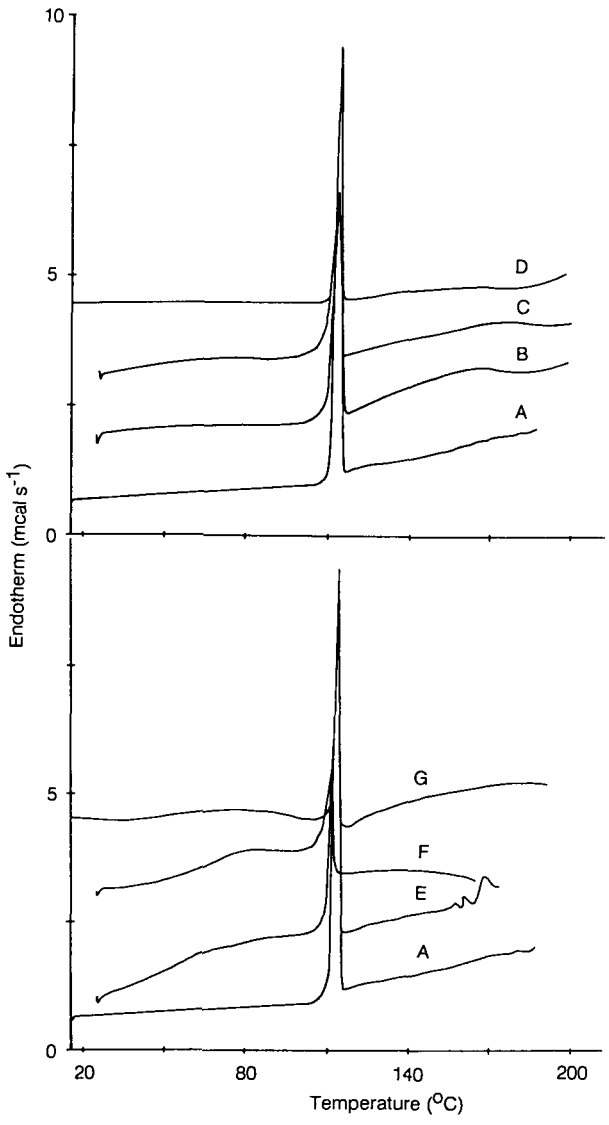

FIG. 1. DSC thermograms of acetylcysteine (A) and physical mixtures of acetylcysteine with Avicel PH 101 (B), carboxymethylcellulose sodium (C), Aerosil (D), starch (E), PVP (F) and cross-linked PVP (G).

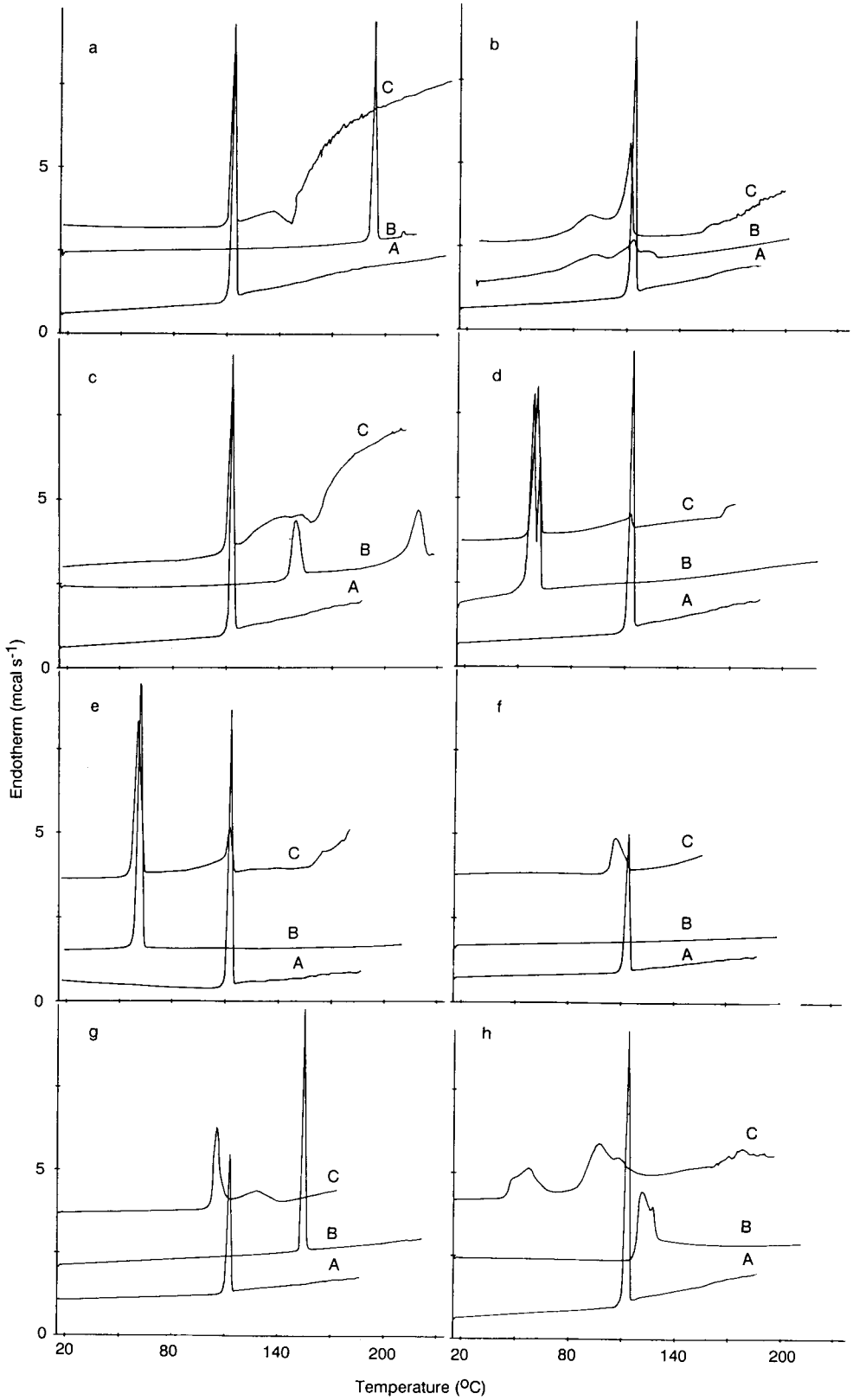

FIG. 2. DSC thermograms of acetylcysteine (A), excipient (B) and a physical mixture of acetylcysteine/excipient (C). Excipients as follows: a, saccharose; b, magnesium stearate; c, lactose; d, PEG 4000; e, PEG 6000; f, glycine; g, adipic acid; h, saccharin sodium.

sium stearate (Lek, Yugoslavia); polyvinylpyrrolidone (PVP, BASF, Germany); cross-linked polivinylpyrrolidone (Poliplasdone XL, GAF, Germany); glycine (Merck, Germany); lactose (DMV, Holland); saccharose (Tovarna Sladkorja, Ormož, Yugoslavia); saccharin sodium (Jeil Moolsan Co, South Korea); adipic acid (Merck, Germany); PEG 4000 and PEG 6000 (Hoechst, Germany); amorphous silicon dioxide (Aerosil 200, Degussa, Germany).

Differential scanning calorimetry. Samples (2–5 mg) were weighed and hermetically sealed in flat-bottomed aluminium pans. Samples of individual substances as well as 1:1 physical mixtures of acetylcysteine and excipients, prepared by grinding in a mortar with a pestle, were analysed. DSC analyses were carried out with a Perkin Elmer DSC 4 Thermal Analyser. The instrument was calibrated with an indium standard. Thermograms were obtained by heating over the temperature range 25–200°C in a dynamic nitrogen atmosphere (40 mL min^{-1}) at a constant heating rate of 10 K min^{-1}.

Fourier transform infrared spectroscopy. Samples were prepared in KBr tablets and FT-IR spectra of pure components and mixtures were carried out with a Perkin Elmer FT-IR 1600 spectrometer.

Differential spectra were evaluated and interactions were established by comparing differential spectra to that of pure acetylcysteine.

HPLC and TLC. Analyses were performed after 2 months storage of the mixtures at four different conditions: 25°C/r.h. <60% (room conditions); 45°C/r.h. <25%; 25°C/80% r.h.; 45°C/70% r.h.

The appearance of the mixtures (organoleptic properties) was determined visually according to Ph. Jug. IV, 3-010. Assay was by HPLC according to USP XXII without internal standard solution. Degradation products were determined by TLC (chromatoplate: cellulose; mobile phase: n-butanol:acetic acid:water (40:10:10 v/v/v%); detection reagent: 0·5% ninhydrin in butan-1-ol.

Results and discussion

The DSC and FT-IR results are displayed in Figs 1–3.

If no interaction occurred, DSC curves of mixtures of excipients with acetylcysteine would reflect the characteristic curve of acetylcysteine. No interactions were observed in physical mixtures of acetylcysteine with Avicel PH101, carboxymethyl cellulose, Aerosil 200, corn starch, PVP, or cross-linked PVP (Fig. 1). The thermogram of acetylcysteine-PVP mixture (trace C, Fig. 1) showed a small downward shift of the acetylcysteine melting endotherm. When two substances are mixed, the purity of each may be reduced and generally slightly lower melting points appear in the DSC thermogram. If the solid-solid interaction is weak or non-existent, the reduction of the melting point is usually inconsequential. On the other hand, any large shift in melting point signifies that a strong solid-solid interaction has occurred, although it does not necessarily indicate an incompatibility. In the physical mixture of acetylcysteine with corn starch, no changes in acetylcysteine melting endotherm can be seen, but degradation of acetylcysteine at the temperature of 155°C is observed.

The same effect of acetylcysteine decreased thermal stability (onset degradation temperature) was seen in the mixtures with saccharose (Fig. 2a), magnesium stearate (Fig. 2b) and lactose (Fig. 2c). No other interaction was found in the mixture with saccharose. In the case of magnesium sterate mixture (trace C, Fig. 2b) a small downward shift of the acetylcysteine melting endotherm is observed.

The combination of acetylcysteine-lactose (trace C, Fig. 2c) shows an endotherm with onset temperature of 109°C, as well as a broad overlapping endotherm with a maximum at 139°C which is followed by an endothermic degradation. The trace of lactose (trace B, Fig. 2c) shows transitions at 145 and 210°C. Thus the endotherm of acetylcysteine can be recognized, with the feature of an additional peak at 115–157°C and the loss of the characteristic lactose endotherm. The reaction between lactose and primary amines is well-documented (Blaug & Huang 1972; Duvall et al 1965) and although acetylcysteine is an amide, this result might be indicative of such interaction.

In the thermogram of acetylcysteine mixtures with PEG 4000 (trace C, Fig. 2d) and PEG 6000 (trace C, Fig. 2e) the size of the acetylcysteine melting peak is appreciably smaller than expected, indicating a possible interaction of acetylcysteine with PEG.

HPLC and TLC studies of the acetylcysteine/PEG 4000 mixture were also carried out. At 45°C/70% r.h. the mixture was organoleptically completely changed: crystals were found on the bottom of a transparent liquid. The amount of acetylcysteine in the sample determined by HPLC decreased to 21·8%.

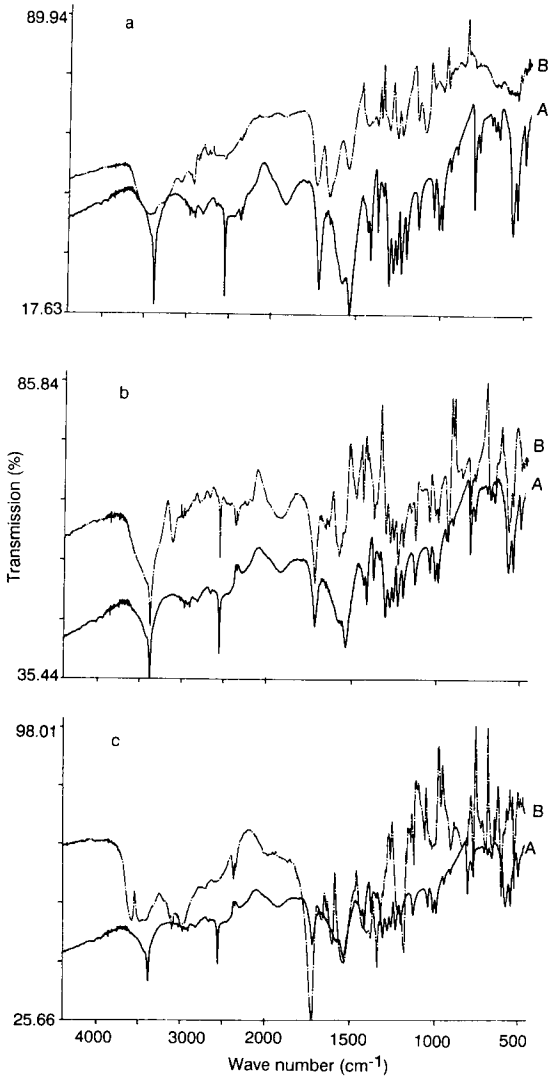

FIG. 3. FT-IR spectrum of acetylcysteine (A) and differential spectrum of a physical mixture of acetylcysteine/excipient (B). Excipients as follows: a, PEG 4000; b, glycine; c, saccharin sodium.

Fig. 3a shows differences between differential FT-IR spectrum of the mixture of acetylcysteine and PEG 4000 and the spectrum of pure acetylcysteine.

In the case of acetylcysteine-glycine mixture (trace C, Fig. 2f) an endothermic peak at a temperature of 100–115°C can be seen which is probably the melting endotherm of acetylcysteine. A large shift in melting point signifies that a strong solid-solid interaction has occurred.

At 45°C/70% r.h. the mixture was found to become intensively yellow and hardened. The increase of degradation products was evident by TLC and the amount of acetylcysteine decreased to 32·2%. Fig. 3b shows changes in the FT-IR spectrum of acetylcysteine in the mixture with glycine in comparison with the spectrum of the pure drug. The FT-IR spectrum showed changes over the whole range.

The thermogram of acetylcysteine-adipic acid (trace C, Fig. 2g) shows a downward shift of the acetylcysteine endotherm to a temperature of 100–114°C, which is followed by a broad endotherm (114–140°C), but the adipic acid melting endotherm is absent which can be indicative of an interaction. If characteristic new peaks can be seen in the thermograms of drug-excipient mixtures, it can be inferred that an interaction is occurring between the compounds and is likely to result in a chemical incompatibility (Monkhouse & Van Campen 1984).

No evident interaction in acetylcysteine-adipic acid mixture was indicated by HPLC, TLC or FT-IR spectroscopy after 2 months' storage at 45°C/70% r.h.

Two broad endothermic peaks are found in the case of the acetylcysteine-saccharin sodium mixture (trace C, Fig. 2h) with onsets of transitions at 45 and 85°C. The trace of saccharin sodium (trace B, Fig. 2h) shows two broad overlapping endothermic peaks at 119–130°C, which are absent in the trace of the mixture. The acetylcysteine melting endotherm is also absent. Extra thermal effects in a thermogram before the peak of the lower melting component might be indicative of an incompatibility (Van Dooren 1983).

At 45°C/70% r.h. the mixture became a hard, sticky yellow mass and an increased amount of degradation products was shown by TLC. The amount of acetylcysteine determined by HPLC decreased to 13·7%. From the differential FT-IR spectra it can be concluded that a strong chemical interaction has occurred in this mixture. The differential spectrum shows completely changed signals in the whole spectrum region as shown in Fig. 3c.

No attempt was made during this study to determine the nature of the interactions, be it chemical or physical interaction, eutectic, solid solution or complex formation. The results suggest that acetylcysteine in mixtures with PEG 4000, glycine and saccharin sodium is degraded during storage at humid and elevated temperature conditions. In the case of non-aged mixtures, no changes were observed by FT-IR spectroscopy.

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Polyethylene glycol: its adverse gastric effects in rats

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Abstract—The effects of polyethylene glycol (PEG) on gastric function and on lesion formation, evoked by topical applications of absolute ethanol to an ex-vivo stomach chamber preparation have been examined. Parenteral injection (i.p. or s.c.) of PEG with different molecular weights (PEG 300, 400 or 4000), dose-dependently reduced the gastric mucosal blood flow and volume of gastric secretion; these effects were greater in rats given PEG by the i.p. route, which also lowered acid output. Topical application of 1·5 mL absolute ethanol produced severe gastric mucosal injury, which was exacerbated by PEG; this lesion-aggravating effect was higher in the i.p.-injected groups. These findings indicate that when PEG is given by injection, it can adversely affect gastric function and increase the damaging action of alcohol. It is suggested that the use of PEG as a vehicle for injection should be re-assessed.

Polyethylene glycol (PEG) is used as a pharmaceutical aid (ointment and suppository base) and it also can be employed as a solvent for some pharmaceutical preparations (Merck Index 1989) because the compound has relatively low toxicity (Smyth et al 1950). However, a preliminary study has shown that PEG of various molecular weights (mol. wt) has a profound adverse effect on the stomach when it is given parenterally (Wong et al 1987). The present study investigates the effects of PEG 300, 400 and 4000 on gastric secretory function and gastric mucosal blood flow (GMBF), using an ex-vivo stomach chamber. The interactions between PEG and ethanol on the stomach are also examined since it is likely that the two compounds would be used in the same preparation; ethanol produces significant gastric damage and has been widely used as an experimental ulcerogen in rodents (Szabo & Cho 1988).

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Materials and methods

Female Sprague-Dawley rats, 220 ± 10 g, were fed a normal