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Compatibility of chewing gum excipients with the amino acid L-cysteine and stability of the active substance in directly compressed chewing gum formulation

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Abstract

Using L-cysteine chewing gum to eliminate carcinogenic acetaldehyde in the mouth during smoking has recently been introduced. Besides its efficacy, optimal properties of the gum include stability of the formulation. However, only a limited number of studies exist on the compatibility of chewing gum excipients and stability of gum formulations. In this study we used the solid-state stability method, Fourier transform infrared spectroscopy and isothermal microcalorimetry to investigate the interactions between L-cysteine (as a free base or as a salt) and excipients commonly used in gum. These excipients include xylitol, sorbitol, magnesium stearate, Pharmagum S, Every T Toco and Smily 2 Toco. The influence of temperature and relative humidity during a three-month storage period on gum formulation was also studied. Cysteine alone was stable at 25°C/60% RH and 45°C/75% RH whether stored in open or closed glass ambers. As a component of binary mixtures, cysteine base remained stable at lower temperature and humidity but the salt form was incompatible with all the studied excipients. The results obtained with the different methods corresponded with each other. At high temperature and humidity, excipient incompatibility with both forms of cysteine was obvious. Such sensitivity to heat and humidity during storage was also seen in studies on gum formulations. It was also found that cysteine is sensitive to high pressure and increase in temperature induced by compression. The results suggest that the final product should be well protected from temperature and humidity and, for example, cooling process before compression should be considered.

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Introduction

Chewing gum plays an important role in dental and oral health. Medicated chewing gum is generally used as a drug delivery system for local treatment of diseases in the oral cavity and in the throat (Rassing 1996). Chewing gum offers a potential for systemic drug delivery as some active substances can be absorbed through the buccal mucosa into the systemic circulation or through the gastrointestinal tract when saliva is swallowed. There are many advantages of using chewing gum as a delivery agent, including its suitability for children, no water being required, rapid release of active substance and avoiding first-pass metabolism. As a result interest in chewing gum as a drug delivery system has risen over recent years. Apart from nicotine gum used as an aid in smoking cessation and xylitol and fluoride gums used in caries prevention, there are also other indications, such as allergy, diabetes and cold, for which chewing gum as a drug delivery system is successfully used.

It is well known that tobacco smoking may increase the risk of cancer to the upper gastrointestinal tract in man. The causal factor might be the high levels of carcinogenic acetaldehyde dissolved into the saliva during tobacco smoking (Salaspuro et al 2006; Kartal et al 2007). There is also evidence that acetaldehyde may also increase the addictive potential of tobacco (Talhout et al 2007). Many studies have reported that L-cysteine, a nonessential sulfur-containing amino acid, reacts covalently with acetaldehyde to form a non-toxic compound (2-methyl-thiolidine-4-carboxylic acid). Thus formulations with L-cysteine might

reduce the risk of upper gastrointestinal tract cancer induced by smoking (Sprince et al 1975; Salaspuro et al 2006; Kartal et al 2007). One alternative and successful approach to eliminating carcinogenic acetaldehyde is the use of chewing gum containing L-cysteine, which has been presented in our previous study (Kartal et al 2007).

There is a lot of evidence showing that there is a correlation between smoking and oral cavity diseases (Nguyen et al 2007; Muwonge et al 2008). Cysteine gum has a local effect on acetaldehyde in the mouth. Thus, in the future there may be some other potential drug molecules incorporated into chewing gum formulations, which can be used to minimize smoking disadvantages caused by other substances in tobacco smoke.

Chewing gum has attracted the interest of many researchers since in 1998 The European Pharmacopoeia accepted medical chewing gum as a drug delivery system. Much of the research has been focused on the manufacturing process, including traditional and directly compressed processes. Incompatibility between drug and excipients can have an effect on the stability and bioavailability of drugs and their therapeutic efficacy and safety. Consequently, information about the stability of an active drug in the final product is important in predicting the shelf-life of the final product (Ceschel et al 2003; Mora et al 2006). However, even if excipient compatibility screening is recognized as an essential part of the drug development process, limited information exists on compatibility studies on chewing gum excipients and the stability of gum formulations. Thus, a study of drug–excipient compatibility is an important process in the development of a stable gum form.

In this study, the possible interactions between two chemical forms of cysteine (L-cysteine free base or L-cysteine hydrochloride) and commonly used chewing gum excipients have been evaluated using Fourier transform infrared spectroscopy and isothermal microcalorimetry. The effect of temperature and humidity on solid-state stability was studied both in binary mixtures (cysteine and excipient) and in directly compressed gum formulations.

Materials and Methods

Materials

Active compounds: L-cysteine (Fluka BioChemika, Buchs, Switzerland) and L-cysteine hydrochloride (Gonmisol, Spain). Excipients: Pharmagum S (SPI Pharma, New Castle, USA), magnesium stearate (Ph. Eur.), Every T Toco (Gum Base Company S.p.A., Italy), Smily 2 Toco (Gum Base Company S.p.A., Italy), xylitol (Roquette, France) and sorbitol (Roquette, France). Reagents: ferric sulfate (J. T. Baker, Netherlands), ferrozine (Sigma-Aldrich ChemieGmbH, USA) and sodium perchlorate (Sigma-Aldrich ChemieGmbH, USA).

Preparation of chewing gum

Chewing gums were prepared with an instrumented eccentric tablet machine (Korsch EK-0; Erweka Apparatebau, Germany) using flat-faced punches with a diameter of 13 mm. The compression force applied was 7–8 kN. Chewing gum contained 7.7 mg of L-cysteine free base (formulation F_{base}) or 10 mg L-cysteine hydrochloride, corresponding to 7.7 mg L-cysteine (formulation F_{HCl}). Pharmagum S (95% of total weight) was used as a gum base and lemon flavour (1.85% of total weight) was used as a flavouring agent to disguise the unpleasant taste of L-cysteine. The components of each formulation, except for magnesium stearate, were mixed for 20 min in a Turbula shaker mixer (T2C; Willy A. Bachofen A6 Maschinenfabrik, Switzerland). Magnesium stearate (2% of total weight) was then added and the formulation mixed for a further 2 min. The total weight of chewing gum was 1080 mg.

Solid-state stability

Active compounds, in addition to a 1:1 (w/w) physical mixture of active compound and excipients (n = 6), were prepared by gently mixing the components with a spatula, and stored in stability test chambers (KBF 115, Binder GmbH, Germany) as follows:

In tightly closed and open amber glass vials at 25°C/60% RH (relative humidity).
In tightly closed and open amber glass vials at 45°C/75% RH.

The 1:1 (w/w) ratio was chosen so as to maximize the likelihood of observing any interaction (Mora et al 2006). Apart from the excipients used in formulations F_{base} and F_{HCl}, we also studied the compatibility of cysteine with xylitol, sorbitol and two gum bases, Every T Toco and Smily 2 Toco. Xylitol and sorbitol, non-cariogenic sugar alcohols, were chosen because of their wide use in chewing gum products. The remaining amounts of cysteine were analysed spectrophotometrically immediately after mixing and then at regular intervals (1, 2 and 3 weeks and 1, 2 and 3 months). The excipient mixture was shaken out in 20 mL distilled water for 3 min and 1.5 mL of sample was transferred to a 10-mL volumetric flask to which was added 0.1 mL 0.01 M ferric sulfate, 0.3 μL 0.01 M ferrozine and 4 mL 0.25 M sodium perchlorate. The mixture was diluted to the mark with distilled water. After 15 min at room temperature, the absorbance for each sample was measured spectrophotometrically at a wavelength of 562 nm (Ultrospec II; Pharmacia LKB Nephew, Falmouth, UK).

Fourier transform infrared spectroscopy (FT-IR)

The cysteine and 1:1 (w/w) physical mixture of active compound and excipients was prepared by gently mixing the components with a spatula, and was stored in stability test chambers at 25°C/60% RH for over 10 days. Samples were prepared in KBr pellets and FT-IR spectra of pure components and mixtures were carried out with a Vertex 70 FT-IR (Bruker Optics GmbH, Ettlingen, Germany). Pellets of samples were scanned over a wavenumber range of 4000 cm^{-1} to 550 cm^{-1}. Differential spectra were evaluated and interactions were determined by comparing differential spectra with that of pure cysteine as either a free base or a salt.

Isothermal microcalorimetry (IMC)

A 2277 Thermal Activity Monitor (TAM) (ThermoMetric AB, Sweden) microcalorimeter was used. The measurements were carried out at 25°C and 45°C. At both temperatures, measurements were carried out without an extra moisture source and with a controlled relative humidity atmosphere. The relative humidity inside the sample ampoule was controlled with a saturated salt solution in a miniaturized ampoule. At 25°C, a saturated salt solution of NaBr was used to maintain about 60% RH, and at 45°C, NaCl was used to maintain about 75% RH. Before measuring started under the regulated humidity atmospheres (25°C/60% RH and 45°C/75% RH), pure components were stored under measuring conditions for at least 10 days. In each case, the samples of pure cysteine (as a free base or salt) and excipients, in addition to the binary mixtures, were prepared and measured in duplicate. Samples were weighed into glass ampoules sealed with teflon-coated discs of rubber and aluminium caps. An empty sealed glass ampoule was used as a reference. The ampoules were inserted into the pre-equilibrium state of the calorimeter (referred as t = 0 s) for 20 min, after which they were lowered into the final measurement position. The electrical calibration was performed each time after the temperature was changed. Data were collected using the dedicated Digitam (ThermoMetric AB, Sweden) software.

Chewing gum stability

Chewing gums were stored in stability test chambers (KBF 115; Binder GmbH, Germany) over a period of three months in the same conditions as mentioned above (n = 6). The remaining amount of cysteine was analysed spectrophotometrically as described above immediately after chewing gum preparation and then at regular intervals (1, 2 and 3 weeks and 1, 2 and 3 months).

Drug compressed on a hydraulic press

Flat-faced tablets (n = 4) were compressed at 185 MPa to study the influence of compaction on the pure cysteine stability. A 250-mg quantity of cysteine was weighed and compressed on a hydraulic press (Carver model C laboratory press; Menomonee, WI) to prepare the tablets. Uncompressed powder was used as a control. The remaining amounts of cysteine were immediately analysed spectrophotometrically as mentioned above.

Statistical method

Results are expressed as mean ± s.d, n = 6. The remaining amounts of cysteine in solid-state stability tests and in chewing gum stability tests were analysed using one-way analysis of variance, performed using Microsoft Excel.

Results and Discussion

Solid-state stability

From the results shown in Table 1, it can be concluded that pure cysteine, as a free base or as a salt, was stable after three month of storage period under various storage conditions and there were no significant differences in the amount of cysteine remaining ($P > 0.05$). At 25°C within tightly closed and in open vials (60% RH), cysteine in binary mixtures with several excipients remained at the same initial percentage ($P > 0.05$), showing that no interaction occurred between cysteine and excipients. However, it was obvious that higher temperature and higher relative humidity affected the remaining amount of cysteine ($P < 0.01$ and $P < 0.001$). Compared with the cysteine base, the salt was not so stable in a mixture with the excipients under the same conditions. After three months in closed vials at 25°C/60% RH, incompatibility was found with all excipients ($P < 0.001$), except with Every T Toco and Smily 2 Toco. In mixtures stored in open vials at 25°C/60% RH and 45°C/75% RH it was obvious that relative humidity decreased the remaining amount of cysteine. The reason for this might be found in hygroscopic excipients (Airaksinen et al 2005). When they were exposed to humidity, the absorbed moisture was a source of water solvent for cysteine. Subsequently, L-cysteine was dissolved and further degraded.

FT-IR

Figure 1 shows differences between the FT-IR spectra of pure cysteine and the spectra of the binary mixture of cysteine and several excipients. The characteristic peaks in FT-IR spectra of pure cysteine were observed at about 1585 cm^{-1} (COO-), 2552 cm^{-1} (-S-H) and 3175 cm^{-1} (NH_2-). Disappeared COO- and NH_2- bonds in cysteine free base binary systems with sorbitol and magnesium stearate indicated interactions. For the binary mixture with xylitol, the band corresponding to the NH_2- stretching mode, expected to be about 3175 cm^{-1}, was not clearly seen. The characteristic bands of cysteine were evident in the mixture with Pharmagum S, Every T Toco and Smily 2 Toco, indicating no interaction. According to compatibility studies, magnesium stearate is incompatible with several active substances in 1:1 blends (Kerc et al 1992; Mora et al 2006). However, those interactions are not too relevant as magnesium stearate was generally present in low amounts, typically within 0.5–2% (w/w) range. As a result, the formulation F_{base} is compatible at 25°C/60% RH with the excipients (Pharmagum S and magnesium stearate) used in the formulations and results were consistent with the results from solid-state stability. In mixtures, cysteine as a salt was not so stable and it could be concluded that possible interactions occurred with all excipients at 25°C/60% RH (not shown).

IMC

The heat flow curves of the binary mixture containing cysteine, as a free base or as a salt, and Pharmagum S, the mean excipient used in formulation F_{base} and F_{HCl}, are shown in Figure 2. To investigate the incompatibility between the components quantitatively, the heat flow curves of the pure ingredients were obtained and are shown in the same figures. In general, when the compatibility of substances are studied, the heat flow curve measured from the mixture is compared with the theoretical curve obtained by summarizing the heat flow curves of the pure components.

Table 1 Effect of different storage conditions on the remaining amounts (%) of pure L-cysteine (as a free base or as a salt), and remaining amounts of cysteine in its 1:1 (w/w) mixtures with different excipients

Mixture components	Initial (%)	1 month at 25°C/60% RH closed/open vials 40°C/75% RH closed/open vials	2 months at 25°C/60% RH closed/open vials 40°C/75% RH closed/open vials	3 months at 25°C/60% RH closed/open vials 40°C/75% RH closed/open vials
L-Cysteine	100	ns	ns	ns
L-Cysteine + xylitol	100	ns	ns	ns
		ns	73.96 ± 2.18**/59.33 ± 1.49**	66.05 ± 7.98**/45.85 ± 3.24**
L-Cysteine + sorbitol	100	ns	ns	ns
		ns/70.83 ± 11.22*	62.00 ± 14.70**	44.95 ± 2.71**/21.03 ± 3.41**
L-Cysteine + Pharmagum S	100	ns	ns	ns
		ns/80.15 ± 5.45**	ns/34.32 ± 3.27**	ns/38.40 ± 5.34**
L-Cysteine + Smily 2 Toco	100	ns	ns	ns
				ns/91.10 ± 10.52*
L-Cysteine + Every T Toco	100	ns	ns	ns
				ns/88.84 ± 4.37*
L-Cysteine + magnesium stearate	100	ns	ns	ns
				71.66 ± 12.60*/92.53 ± 24.93*
L-Cysteine HCl	100	ns	ns	ns
L-Cysteine HCl + xylitol	100	ns	ns/75.40 ± 6.20**	86.44 ± 4.74**/63.00 ± 19.36**
		ns/53.08 ± 10.56**	ns/27.45 ± 12.97**	ns/8.50 ± 0.97**
L-Cysteine HCl + sorbitol	100	ns	ns/75.54 ± 0.00**	81.63 ± 4.16**/63.36 ± 1.44**
		ns/55.60 ± 5.09**	78.58 ± 1.75**/27.45 ± 13.16**	81.75 ± 0.29**/6.78 ± 7.51**
L-Cysteine HCl + Pharmagum S	100	ns	ns/81.81 ± 2.20**	76.53 ± 3.30**/88.39 ± 2.84**
		ns/76.17 ± 2.45**	75.02 ± 2.27**/36.53 ± 9.12**	76.53 ± 3.31**/41.46 ± 3.00**
L-Cysteine HCl + Smily 2 Toco	100	ns	ns	ns
		ns/67.75 ± 16.00**	ns/73.98 ± 1.41**	89.15 ± 0.64*/7.85 ± 9.36**
L-Cysteine HCl + Every T Toco	100	ns	ns	ns
		ns/50.24 ± 16.32**	ns/38.61 ± 1.05**	ns/8.60 ± 9.50**
L-Cysteine HCl + magnesium stearate	100	ns	ns	86.40 ± 3.20**/70.59 ± 14.37**
			ns/39.43 ± 13.28**	60.89 ± 6.60**/35.85 ± 3.00**

Results are expressed as mean ± s.d., n = 6. $^{**}P < 0.001$, $^{*}P < 0.01$, remaining amount of pure cysteine compared with cysteine amount at initial moment. ns, non-significant compared with cysteine amount at initial moment.

If the difference between these curves is obvious, then an interaction exists.

Figure 2A, B shows that pure cysteine and pure Pharmagum S are stable in studied conditions by giving hardly any heat flow signal during the measurement. It was also found that no interaction took place between cysteine and Pharmagum S at 25°C or at 25°C/60% RH. This conclusion was made by summarizing the individual heat flow curves of the pure ingredients mathematically. At 45°C, Pharmagum S seemed slightly unstable, as indicated by a weak endothermic heat flow signal. However, signs of interactions could not be observed (Figure 2C). When the sample was exposed to 75% RH, the instability of Pharmagum S was obvious (Figure 2D). An interaction between Pharmagum S and cysteine was improbable. These measurements indicate that the combination of cysteine with Pharmagum S or any mixtures containing Pharmagum S should not be exposed to high temperature and humidity.

Pure cysteine hydrochloride alone was stable when there was no extra moisture source present. However, it was obvious that there was an interaction between cysteine hydrochloride and Pharmagum S in a binary mixture at 25°C and 45°C without humidity (Figure 2E, F). This finding is a good reason to avoid the combination of cysteine as a salt with Pharmagum S, even at low temperatures.

The cysteine mixture with magnesium stearate was found to be stable at 25°C and at 25°C/60% RH (not shown). There was also a possible exothermic interaction at the temperature of 45°C, which was manifest when the mixture was exposed at 45°C/75% RH. This data suggest that incompatibility is not probable between cysteine and magnesium stearate at 25°C, whereas at 45°C an exothermic interaction is possible. On the other hand, there was a clear interaction between cysteine as a salt and magnesium stearate at 25°C and also at 45°C. In these measurements, at the beginning the heat flow signal was negative and rapidly changed from endothermic into exothermic. Consequently, an interaction between cysteine hydrochloride and magnesium stearate was probable, as could be observed when they were mixed together. Table 2 summarizes the possible occurrence of interactions for the rest of the mixtures studied.

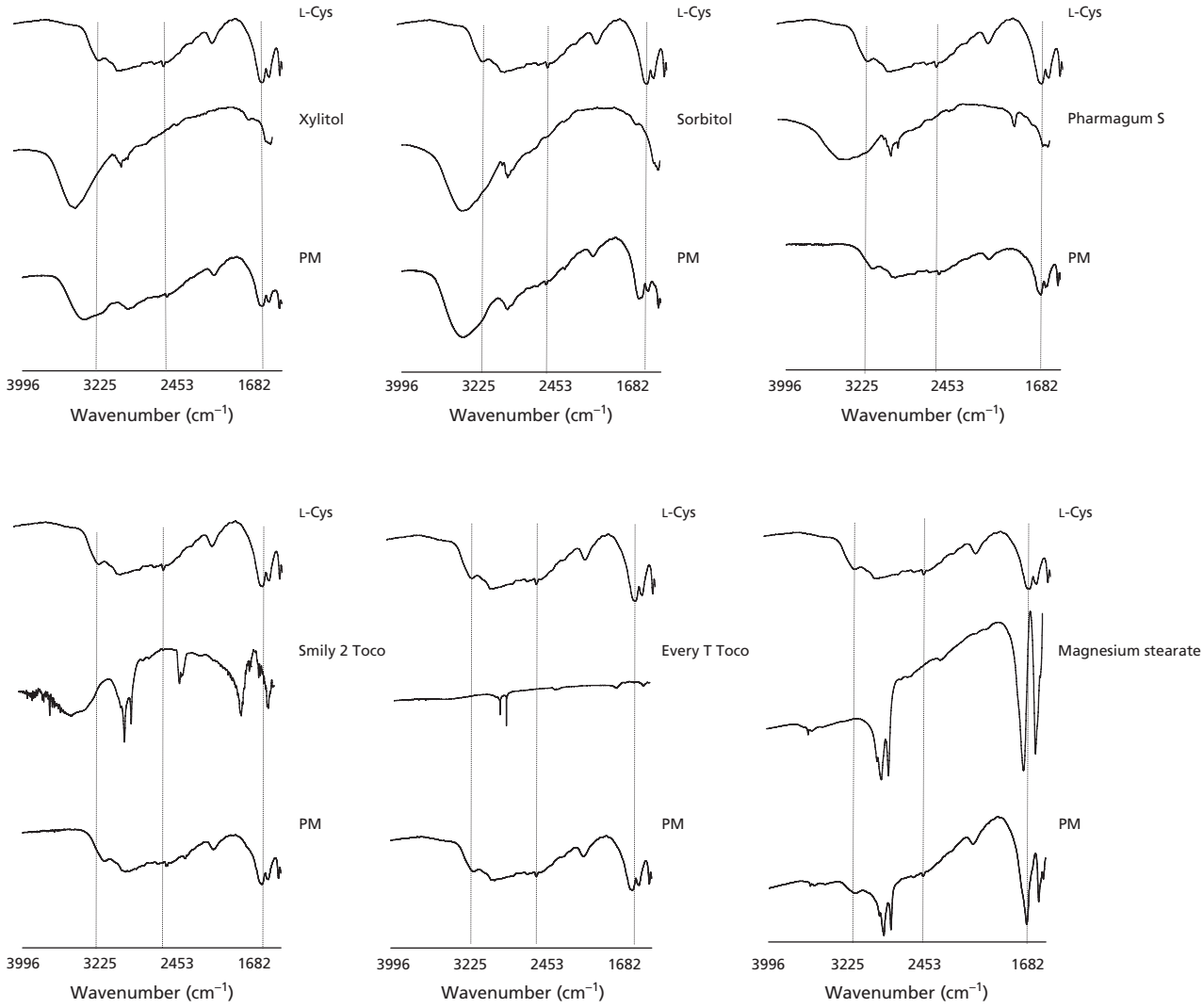

Figure 1 FT-IR spectra of pure L-cysteine free base (L-cys) and excipients, and their 1:1 (w/w) physical mixtures (PM). Excipients as follows: xylitol, sorbitol, Pharmagum S; Smily 2 Toco, Every T Toco, magnesium stearate. Samples were stored over 10 days at 25°C/60% RH.

Chewing gum stability

As shown in Figure 3, the remaining amounts of cysteine immediately after gum preparation were found in both formulations to be less than 90% ($80 \pm 1.25\%$ and $88 \pm 1.5\%$ for formulation F_{base} and F_{HCl}, respectively). Factors that can have critical influences on the stability of drug substances are moisture and temperature, in addition to the incompatibility between the active compound and excipients (Serajuddin et al 1999; Airaksinen et al 2005). Temperature can significantly increase during compression and therefore can have an effect on temperature-sensitive compounds (Picker-Freyer & Schmidt 2004; Turner et al 2006). Thus the increase in temperature due to tablet compression may result in decreased potency of the active ingredient.

Storage stability studies indicated that after three months the formulation F_{HCl} was less stable than formulation F_{base}, even when exposed to normal room temperature and humidity ($P < 0.001$) (Figure 3B). In open vials, both formulations were very sensitive to 75% RH at 40°C. In both cases, the remaining amount of cysteine after three months was 0. It was found that in comparison with the zero-level at the beginning, the remaining amount of cysteine from both formulations under other conditions at the end of the study was lower by about 10%.

Based on our results, it can be concluded that high temperature and humidity together are important factors for the stability of final cysteine-containing product. Therefore, to minimize the level of moisture and also protect the product from higher temperatures, the final product should be properly sealed during its shelf-life and stored under lower temperature and humidity conditions.

Drug compressed on a hydraulic press

This study was performed to obtain more information about the low remaining amount of cysteine found immediately after gum preparation. Compared with the remaining amounts

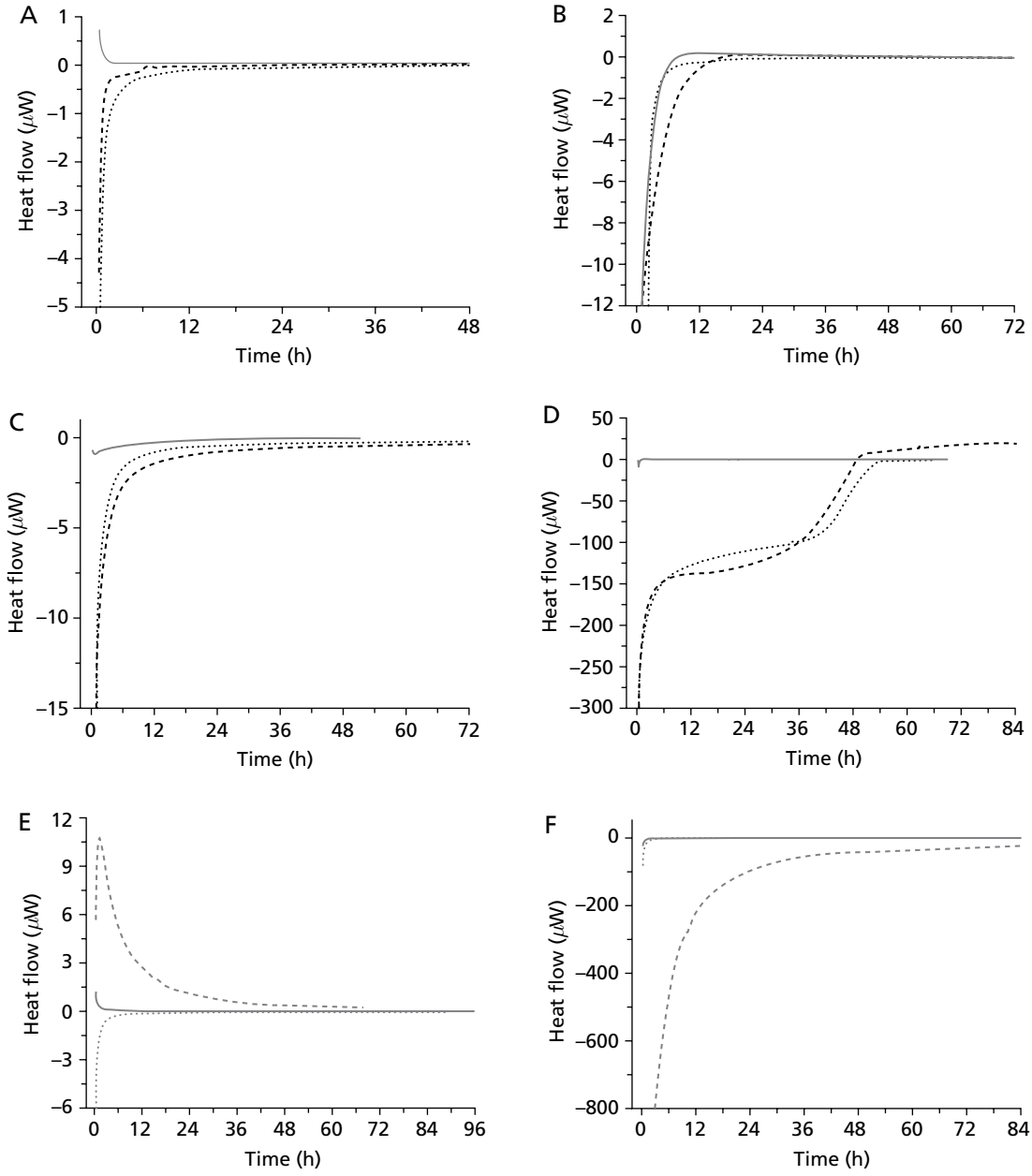

Figure 2 Heat flow measured by IMC (n = 2): cysteine alone (black line), Pharmagum S alone (black dotted line) and their binary mixture (black dashed line) at 25°C (A), 25°C/60% RH (B), 45°C (C) and 45°C/75% RH (D); cysteine hydrochloride alone (dark grey line), Pharmagum S alone (dark grey dotted line) and their binary mixture (dark grey dashed line) at 25°C (E) and at 45°C (F).

of cysteine for the uncompressed powder (100 ± 0.64% and 100 ± 1.2% for free base and hydrochloride form, respectively), those for the compacts formed with hydraulic press were lower (88.52 ± 3.81% and 89.81 ± 4.7% for free base and hydrochloride form, respectively). Results indicated that compaction affected the remaining amount of cysteine. The reason for this could be high pressure and increase in temperature induced by compression and, thus, tableting has an effect on this temperature-sensitive compound.

This finding may explain why cysteine drug substance alone or as a constituent of mixtures with different excipients was more stable than the cysteine in gums immediately after preparation. The increase in temperature due to tablet compression may result in low amounts of cysteine found immediately after gum preparation. As a thiol, cysteine is prone to be oxidized to cystine at elevated temperatures (Tan et al 2003). To minimize unwanted degradation of temperature-sensitive cysteine other manufacturing options should be considered (e.g. cooling process before compaction) (Athanikar & Gubler 1999). Traditional chewing-gum preparation should be avoided because during the manufacturing process, the gum base, together with all ingredients, is

Table 2 Interaction occurrence in binary mixture 1:1 (w/w) measured by IMC of cysteine with different excipients at different temperature and relative humidity (RH) conditions (at 25°C/60% RH and 45°C/75% RH in closed/open vials) (n = 2)

Excipient in binary mixture	25°C/60% RH		45°C/75% RH	
	Closed vials	Open vials	Closed vials	Open vials
L-Cysteine free base				
Magnesium stearate	No	No	Yes	Yes
Xylitol	No	No	Yes	Not measured
Sorbitol	No	No	No	Yes
Every T Toco	No	No	Yes	Not measured
Smily T Toco	No	No	No	No
L-Cysteine hydrochloride				
Magnesium stearate	Yes	Not measured	Yes	Not measured
Xylitol	No	No	Yes	Not measured
Sorbitol	Yes	Not measured	Yes	Not measured
Every T Toco	No	No	No	Not measured
Smily T Toco	Yes	Not measured	Yes	Not measured

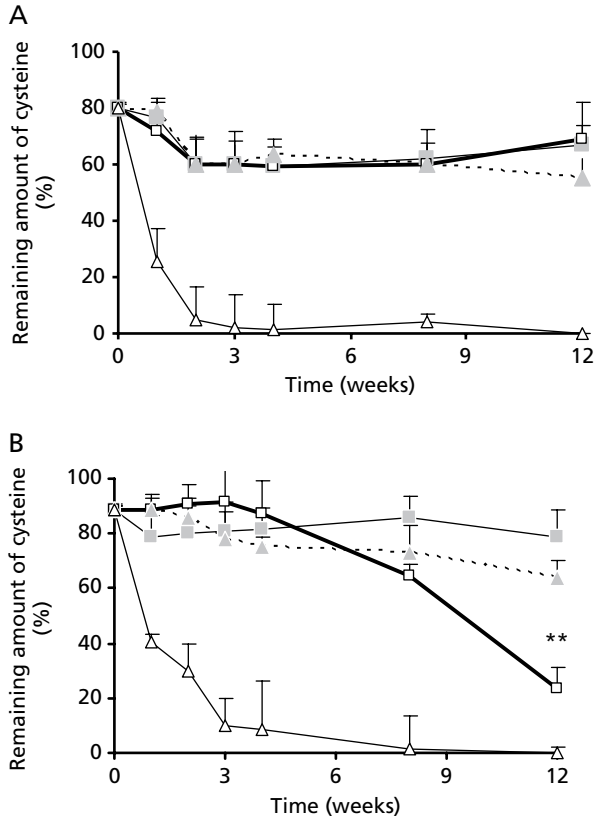

Figure 3 Effect of storage conditions on remaining amount of chewing gum L-cysteine (formulation F_{base} (A); formulation F_{HCl} (B)) in tightly closed vials at 25°C/60% RH (closed squares); open vials at 25°C/60% RH (open squares), in tightly closed vials at 45°C/75% RH (closed triangles); open glass vials at 45°C/75% RH (open triangles). Results are represented as mean ± s.d., n = 6. $^{**}P < 0.001$ compared with remaining amount of cysteine at same time in formulation F_{base}.

heated to a very high temperature. Moreover, stability studies for formulation development should not focus only on the stability of the drug in powder mixtures with excipients (Qiu et al 2005). Therefore, investigation of the effect of manufacturing process (e.g. compression) should be included in the stability studies.

Conclusions

Pure cysteine, as a free base or as a salt, was stable at 25°C/60% RH and 45°C/75% RH during the three-month storage period, regardless of being contained in open or closed glass ambers. Incompatibility studies, using either a solid-stage method, FT-IR or IMC, suggested that cysteine in free base form is more stable with different excipients than its salt form. All the used methods are powerful tools in chewing-gum preformulation studies. Cysteine in salt form was incompatible with all the used excipients and the results with all used methods corresponded to each other. Free base or salt form cysteine binary mixtures with excipient were sensitive to temperature and humidity. Therefore, according to our results, the final product must be well protected from temperature and humidity variations during its shelf-life. Sensitivity to heat and humidity during storage was also seen in stability studies on gum formulations.

This study has also shown that cysteine is very sensitive to high pressure and increases in temperature induced by compression. To minimize disadvantages of direct compression, some other manufacturing process should be considered. In addition, it is important to screen the possible interactions between an active drug and the excipients. This study has also shown that for a stable and effective medicated chewing gum, the preformulation studies should include analysis of the effect of the processing method.

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