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Compatibility study between chlorpropamide and excipients in their physical mixtures

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Abstract Chlorpropamide ((4-chloro-*N*-(propylamino)-carbonyl)-benzenesulfonamide) belongs to compounds having sulfonylurea group and is widely used as an oral antidiabetic agent. In this work differential scanning calorimetry (DSC) was used during pre-formulation of chlorpropamide tablets to determine the drug-excipients compatibility. The DSC curves of chlorpropamide and binary mixtures with excipients (sodium croscarmellose, sodium lauryl sulfate, microcrystalline cellulose, magnesium stearate and calcium carbonate) showed that chlorpropamide exhibited interaction with magnesium stearate and sodium lauryl sulfate. The binary mixtures of chlorpropamide–magnesium stearate presented a single endothermic process at 96–108 °C and chlorpropamide–sodium lauryl sulfate showed a wide endotherm at 99–120 °C.

Keywords Chlorpropamide · Pharmaceutical technology · Thermal analysis

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Introduction

Chlorpropamide is an oral hypoglycemic drug belonging with a sulfonylurea group and is used for the treatment of Type II diabetes mellitus in adults when not complicated, stable, mild or moderately severe that can not always be controlled with diet [1]. Chlorpropamide is a class II drug considering the Biopharmaceutic Classification System (BCS), where the rate and extent of dissolution is critical for optimum bioavailability [2].

Successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients. Interactions in the solid state between the active ingredient(s) and excipients in pharmaceutical dosage forms can give rise to changes in the stability, solubility, dissolution rate and bioavailability of drugs [3, 4]. When an excipient affects negatively some of the factors above we can assume it is incompatible with that drug.

Incompatibility study involves the evaluation of drug stability and the possible physical and chemical interaction with excipients used upon the preformulation.

In recent years, applications of thermal analytical techniques at the preformulation stage of development of solid dosage forms have increased immensely [4]. In particular differential scanning calorimetry (DSC) has been proposed as a rapid method to examine the possibility of physicochemical interactions between drug(s) and excipient(s). Additional advantage is that just a few milligrams of sample are needed for each run. In fact it provides fast and reliable information about potential physical or chemical incompatibilities between the components of formulation through the appearance, shift, or disappearance of endotherms or exotherms and/or variations in the relevant enthalpy values [5].

The present study was undertaken to establish the compatibility of chlorpropamide with a number of commonly

used excipients for tableting using differential scanning calorimetry

Experimental

Materials

Chlorpropamide drug (CP/EXP-396) and excipients (magnesium stearate, microcrystalline cellulose, sodium croscarmellose, calcium carbonate, lauryl sulfate sodium) used on this work were of pharmaceutical grade and were purchased by the Nucleos of Research on Food and Pharmaceuticals (NUPLAM, Natal, Brazil).

Binary mixtures

DSC curves of the drug and excipients alone were compared to those of each drug–excipient 1:1 (m/m) mixtures.

Differential scanning calorimetry (DSC)

DSC curves were obtained in a Shimadzu DSC-60 cell using aluminum crucibles with about 2 mg of samples under dynamic N_2 atmosphere (flow rate: 50 mL min^{-1}) and at a heating rate of 10 °C min^{-1} in the temperature range from 25 to 200 °C. DSC cell was calibrated with indium (*m.p.* 156.6 °C) and zinc (*m.p.* = 419.6 °C).

Results and discussion

The DSC curve of chlorpropamide presented three endothermic events (Fig. 1, curve 1). The first and second, at 122.7 °C ($\Delta H = -30.45$ J g^{-1}) and 127.7 °C ($\Delta H = -92.95$ J g^{-1}), respectively, are endothermics corresponding to the "double melting peak", which fits to form A as described in [6]. The third at 172.2 °C was the beginning of thermal decomposition of chlorpropamide. The phase transition above 200 °C in the DSC curve is not presented.

The DSC curve of sodium lauryl sulphate (Fig. 1, curve 2) presented two endothermic effects, between 95.1–102.8 °C ($\Delta H = -17.44$ J g^{-1}) and 182.5–188.3 °C ($\Delta H = -17{,}11$ J g^{-1}), respectively, while in the DSC curve of calcium carbonate (Fig. 1, curve 3) no any transition in the studied temperature range.

The DSC curve of magnesium stearate (Fig. 1, curve 4) has three endothermic events: the first at 84.3–97.4 °C ($\Delta H = -5.78$ J g^{-1}) corresponds to dehydration [7]; second at 112.6–121.9 °C ($\Delta H = -58.07$ J g^{-1}) and a third at 150.6–158.7 °C ($\Delta H = -26.98$ J g^{-1}) indicates the melting of palmitic- and stearic-acid compounds.

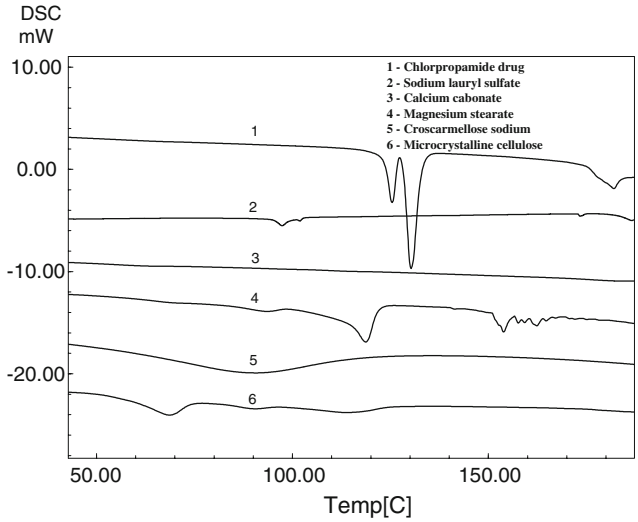

Fig. 1 DSC curves of (1) chlorpropamide drug and excipients: (2) Sodium lauryl sulfate, (3) calcium carbonate, (4) magnesium stearate, (5) croscamellose sodium, (6) microcrystalline cellulose

The DSC curve of croscamellose sodium (Fig. 1, curve 5) shows one phase transitions: a broad endothermic peak due to water loss between 56.5 and 117.4 °C ($\Delta H = -214.95$ J g^{-1}) [8], while the DSC curve of microcrystalline cellulose (Fig. 1, curve 6) indicates three consecutive endothermic events: at 57.5–74.1 °C ($\Delta H = -32.76$ J g^{-1}) corresponding to loss of humidity and two others at 83.9–95.6 °C ($\Delta H = -4.33$ J g^{-1}) [9], 100.4–124.7 °C ($\Delta H = -17.75$ J g^{-1}).

All these temperatures are in the good agreement with the literature values.

DSC curves of the drug and the corresponding excipients were compared their 1:1 (m/m) mixture as it is used to done (see e.g. [10]) and has the advantage of maximize the likelihood of an interaction.

The DSC curves of the binary mixture of chlorpropamide:microcrystalline cellulose, chlorpropamide:croscamellose sodium and chlorpropamide:calcium carbonate (Fig. 2, curves 2, 3 and 4, respectively) show the double melting peak of chlorpropamide with more than 2 °C compared to that of chlorpropamide alone.

The DSC curve of chlorpropamide/sodium lauryl sulfate (Fig. 2, curve 5) shows some sort of interaction with this excipient evidenced by the disappearance of the double melting peak of the drug.

The same was observed in the DSC curve of chlorpropamide/magnesium stearate (Fig. 2, curve 6) that presented only one endothermic event at 96.3–108.6 °C ($\Delta H = -106.63$ J g^{-1}) suggesting a drug–excipient interaction upon heating.

These findings may be confirmed by other analytical techniques able to elucidate the mature of drug–excipient interaction. Despite the interactions could be seen above

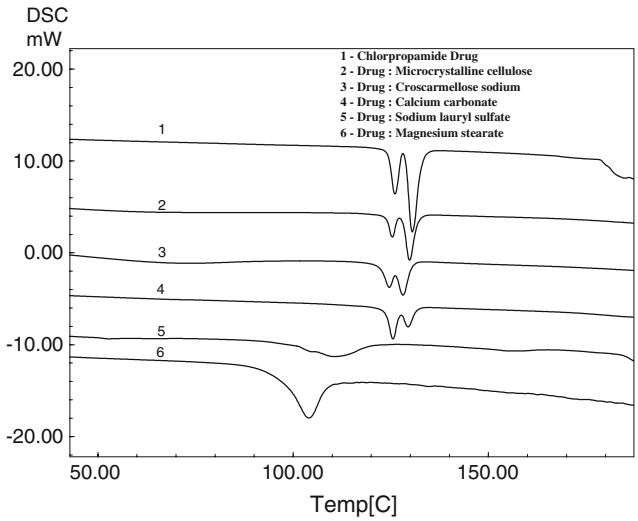

Fig. 2 DSC curves of chlorpropamide and chlorpropamide/excipient 1:1 (m/m) binary mixtures

120 °C and not at ambient temperature, an remarkable decrease was observed in the dissolution rate of chlorpropamide from tablets containing those excipients after 6 months under controlled conditions (40 °C and 75% RH), that is a strong evidence of drug–excipients incompatibility.

Conclusions

The results demonstrated the applicability of DSC as a fast screening tool for drug–excipient interaction in a preformulation process. The results confirmed the usefulness of DSC for for this purpose at the early stage of formulation studies. The presence of solid–solid interaction does not necessarily indicate pharmaceutical incompatibility, the use of other analytical techniques, such as FTIR and EGA can help in the interpretation of DSC results [11], in order to confirm the changes observed in chlorpropamide–magnesium stearate and sodium lauryl sulfate curves.

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References

1. Gilman AG, Hardman JG, Limbird LE, Molinoff PB, Ruddon RW. 9th ed. Rio de Janeiro: Goodman & Gilman.
2. Guo J, Elzing PA, Hangeman MJ, Herron JN. Rapid throughput solubility screening method for bcs class II drugs in animal Gl Fluids and simulated human Gl Fluids using a 96-well format. J Pharm Sci. 2008;97:1427.
3. Filho ROC, Franco PIBM, Conceição EC, Leles MIG. Stability studies on nifedipine tablets using thermogravimetry and differential scanning calorimetry. J Therm Anal Calorim. 2008;93:381–5.
4. Santos AFO, Basilio ID, de Souza FS, Medeiros AFD, Pinto MF, de Santana DP, et al. Application of thermal analysis in study of binary mixtures with metformin. J Therm Anal Calorim. 2008;93:361–4.
5. Filho MSSC, Pacheco RM, Landin M. Compatibility of the antitumoral β-lapachone with different solid dosage forms excipients. J Pharm Biomed Anal. 2007;45:590–8.
6. Drebushchak VA, Drebushchak TN, Chukanov NV, Boldyreva EV. Transitions among five polymorphs of chlorpropamide near the melting point. J Therm Anal Calorim. 2008;93:343–51.
7. Miller TA, York P. Physical and chemical characteristics of some high purity magnesium stearate and palmitate powders. Int J Pharm. 1985;23:55–67.
8. Thirbert R, Hancock BC. Direct visualization of superdisintegrant hydration using environmental scanning electron microscopy. J Pharm Sci. 1996;85:1255–8.
9. Pokharkar VB, Joshi BV, Patil VB. Compatibility studies between carbamazepine and tablet excipients using thermal and nonthermal methods. Drug Dev Ind Pharm. 2002;6:687–94.
10. Giron D. Applications of thermal analysis and coupled techniques in pharmaceutical industry. J Therm Anal Calorim. 2002;68:335–57.
11. Heidarian M, Mihranyan A, Stromme M. Influence of water-cellulose binding energy on stability of acetylsalicylic acid. Int J Pharm. 2006;323:139–45.