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COMPATIBILITY AND STABILITY STUDIES OF PROPRANOLOL HYDROCHLORIDE BINARY MIXTURES AND TABLETS FOR TG AND DSC-PHOTOVISUAL

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Abstract

This study demonstrates the thermal analysis applications in compatibility and stability studies of the propranolol binary mixtures and tablets A and B. The propranolol binary mixtures were prepared in the laboratory and compared to the fully formulated tablets using the thermogravimetric (TG) and calorimetric (DSC) methods. DSC of binary mixtures showed similar phase transition to propranolol drug. The tablets phase transition decreased and there was no detectable significant interaction in propranolol–lactose mixture and tablets. The DSC-photovisual test revealed an interaction similar to the Maillard reaction. The TG isothermal study showed a difference in the profile between the drug and tablets due excipients quality and problems in manufacture process. The kinetic parameters indicated a lower stability for the tablets than propranolol drug. The thermal techniques thermally differentiated the propranolol preparations demonstrating the importance in the design development of pharmaceuticals solid-dosage form.

Keywords: binary mixtures, propranolol, tablets, TG and DSC-photovisual

Introduction

In the recent years thermal analysis has been used – to a great extent – in the development and improvement of pharmaceutical formulations. Literature [1–5] shows its use in drug purity determinations, quantitative and qualitative analysis of the formulations, stability test, characterization of polymorphic mixtures and in compatibility studies with drug-excipients.

The photovisual system is a technique that combines DSC heat flow measure and visual monitoring of physical and chemical events occurring in the sample during temperature programming, which is accomplished through image capture. Decomposition processes involving gas evolution, and, loss of crystallization water can be observed by monitoring crystals in hot stage microscopy [6].

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The present work applies TG and DSC coupled to the photovisual system for obtaining useful properties in the development of the propranolol tablet.

Experimental

Sample preparation

Propranolol tablets A and B were acquired at local pharmacy. The binary mixtures were produced in laboratory based on the below composition: propranolol hydrochloride – 18.60%, microcel MC(101) – 32.56%, lactose – 13.95%, starch – 27.91%, PVP – 3.26%, talc – 2.32% and magnesium stearate – 1.40%. The binary mixtures were shifted in a 100 mesh fine-sieve, homogenized in porcelain grail for 10 min and conditioned in an amber flask. The medium and standard deviation (*sd*) values were determined from triplicates of DSC and TG curves.

Calorimetric studies

The DSC apparatus was calibrated with indium (156.6±0.2°C) and zinc (419.5±0.3°C) standards melting point. The heat flow and enthalpy were calibrated by indium heat of fusion (28.58±0.3 J g^{-1}) using the same conditions of the drug samples. DSC curves were obtained in Shimadzu differential scanning calorimeter, model DSC-50, with nitrogen flow of 50.0 mL min^{-1} and heating rate of 10.0°C min^{-1}, up to the temperature of 500.0°C. Samples (2.00 mg) were packed in a hermetically sealed aluminum cell; it was also used as a reference. The DSC-photovisual system is constituted with an Olympus microscope connected to the Sanyo camera, model VCC-D520, with Intel image capture software, and model Intel Smart Video Record III.

Thermogravimetric studies

The TG apparatus was calibrated with calcium oxalate monohydrate examined with the same conditions as the samples. TG dynamical and isothermal curves of the drug, binary mixtures and tablets A and B were obtained in Shimadzu thermobalance, model TGA-50H, in air atmosphere with flow of 20.0 mL min^{-1}, heating rate of 10.0°C min^{-1} in temperature interval of 25.0–900.0°C. The samples were packed in alumina cell with mass of 5.00–5.50 mg.

TG isothermal curves were obtained by plateau of the TG curve before the initial temperature of decomposition of the drug and tablets A and B [7]. The samples were heated with a heating rate of 20.0°C min^{-1} up to the isothermal temperature, where the isothermal temperature was held for 4 h. The isothermal temperatures were 140–200°C [8].

The reaction order (*n*) was determined by graphical analysis and rate constants (*k*) were calculated using the Arrhenius' equations. The kinetic parameters (*n*) and (*k*) of the propranolol drug, binary mixtures and tablets A and B were chosen from statistic data: correlation coefficient (*r*) and standard deviation (*sd*).

Results and discussion

Calorimetric studies

The propranolol hydrochloride presented its melting point at (165.6±0.2°C) and heat of fusion of (137.42±0.30 J g^{-1}). The lactose showed three peaks, phase transition, with a melting point at (218.9±0.4°C). DSC curves of the propranolol–lactose showed a similar phase transition for propranolol hydrochloride melting point and did not present any incompatibility among propranolol drug and excipients. Tablets A and B had a reduction in the melting point and heat of fusion (161.9±0.4°C; 3.48±0.40 J g^{-1} and 161.4±0.3°C; 13.10±0.30 J g^{-1}) similarly to the propranolol–lactose profile (Fig. 1).

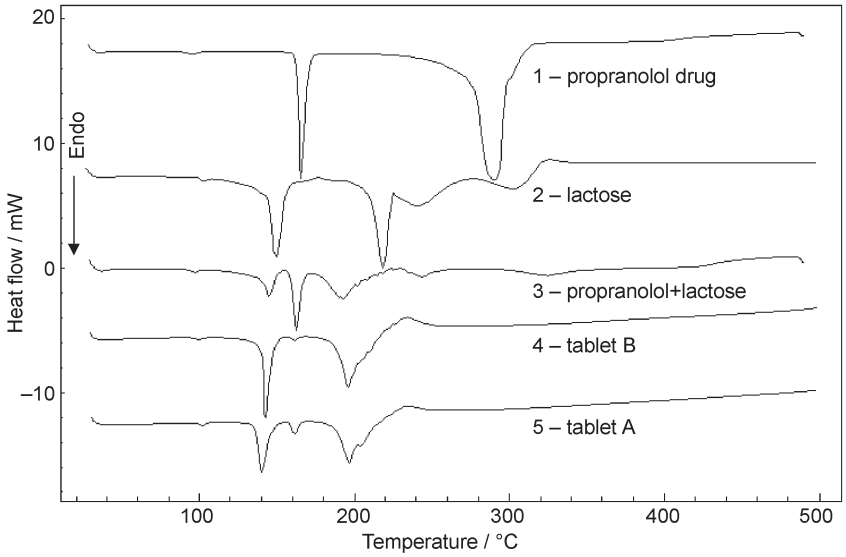

Fig. 1 DSC curves of the propranolol drug (1), lactose (2), propranolol+lactose (3), tablet A (4) and tablet B (5)

The analysis of DSC curves revealed that tablets A and B had similar formulations and contain lactose in the formulation based on melting peak at (218.4±0.5°C) corresponding to lactose. The melting peak appeared in DSC curves of the propranolol tablets A and B. The similar characteristics among DSC curves of the commercial tablets and propranolol–lactose mixture was the evidence for the presence of lactose in tablets.

The DSC-photovisual images showed a melting point at 164°C for propranolol drug (Fig. 2 – Picture B), followed by a volatilization process at 169°C (Fig. 2 – Picture C). The lactose melting peak (218°C) was characteristic of a monohydrate α-lactose form (Picture E), with a decreased melting point from 223°C due to grinding and compression during the sample preparation according to literature [6, 9 and 10]. Its

decomposition occurred at 236°C (Picture F). The propranolol–lactose mixture began melting at 162°C (Fig. 2 – Picture H) and an intense brown coloration was observed at 188°C (Picture I) prior to the lactose melting. Tablets A and B exhibited melting points simultaneously with the chemical interaction (Fig. 2 – Pictures K and N), resulting in brown coloration. The change of coloration was very intense at temperatures of 180 and 191°C (Fig. 2 – Pictures L and O), respectively. The conventional DSC did not show significant interaction between propranolol and lactose. However, DSC-photovisual images suggest a typical Maillard reaction in propranolol–lactose and tablets A and B as suggested by [11].

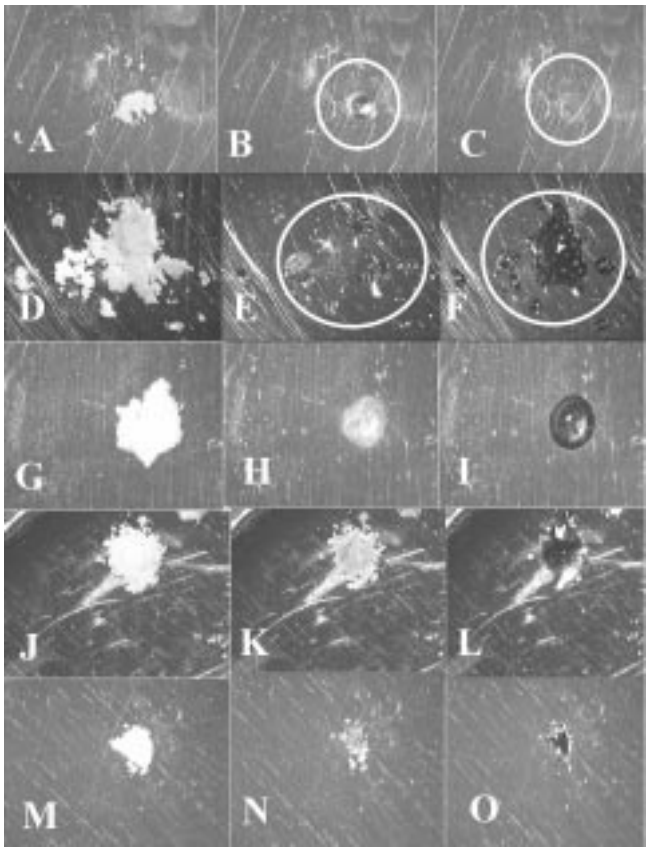

Fig. 2 Pictures A (room temperature), B (164°C) and C (169°C) of propranolol drug; D (room temperature), E (218°C) and F (236°C) of lactose; G (room temperature), H (162°C) and I (188°C) of propranolol+lactose; J (room temperature), K (164°C) and L (180°C) of the tablet A; M (room temperature), N (164°C) and O (191°C) of the tablet B

DSC-photovisual demonstrated the propranolol melting followed by the decomposition and volatilisation. This does not occur with tablets A and B. The usefulness of this thermal microscopy technique is seen in compatibility studies and verification

at the thermal stability of drug-excipients by the melting profile and decomposition of pharmaceutical solid dosage form.

Thermogravimetric studies

The thermogravimetric profile of propranolol drug presented two thermal decomposition stages and the initial temperature of decomposition was (252.5±0.3°C). The TG curves of binary mixtures revealed the same decomposition profile of the propranolol drug, only initial mass loss due to excipients humidity. The starch and lactose reduced the initial temperature of decomposition of the propranolol, respectively at (201.2±0.3 and 242.4±0.2°C). The TG curves of tablets A and B were similar to propranolol–lactose binary mixture revealing that this excipient changes the drug behaviour in mixture (Figs 3a and 3b).

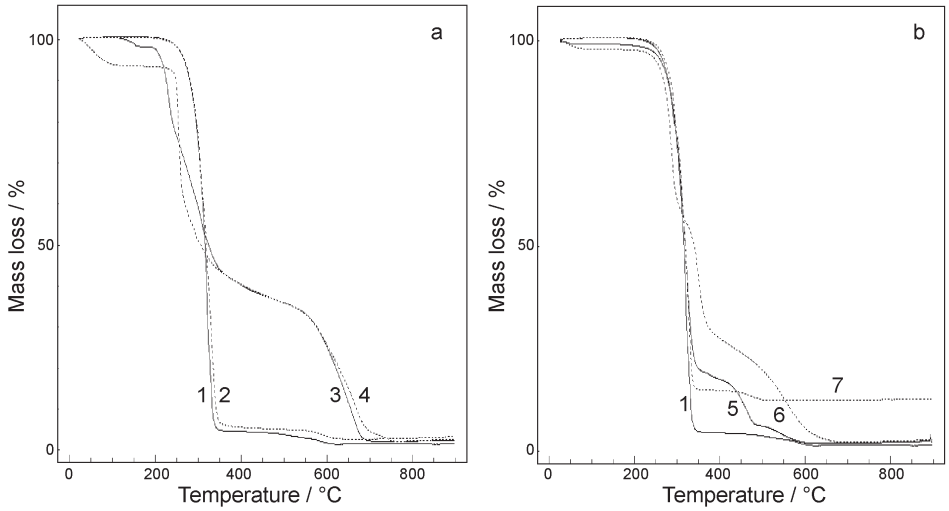

Fig. 3 TG curves of the propranolol drug (1), propranolol-stearate Mg (2), propranolol+lactose (3), propranolol+starch (4), propranolol+PVP (5), propranolol+microcel (6) and propranolol+talc (7)

The superficial humidity can alter the stability of solid pharmaceuticals, which may influence the flow and compression characteristics of powders during the manufacture process and hardness of final tablets [6].

TG isothermal curves of drugs presented a decomposition profile similar to that observed in DSC-photovisual images with decomposition by volatilisation. Tablets A and B showed decomposition in two stages that could be explained in two ways. The first is by excipients quality and its amount in relation to the drug in the tablets and the second is by the manufacturing process. The isothermal data were important to establish the relationship between the drug and tablets verifying the characteristics of

the product before and after the manufacturing process and to differentiate products on the market.

Kinetics studies

The graphical analysis showed that the propranolol drug had the best statistic parameters (r=0.9990 and sd=1·10^{-4}) for the mass *vs*. time fit. The data indicated zero order kinetics. Tablets A and B best fit (r=0.9985; sd=1.6·10^{-4}, r=0.9988; sd=2.4·10^{-4}) to the 1/mass *vs*. time revealed second order kinetics. The latter suggests interaction between the drug and some excipients.

Table 1 Rate constant of the propranolol drug and tablets A and B

Temperature/°C	Rate constants; k/s^{-1}		
	Drug	Tablet A	Tablet B
200	2.05·10^{-5}	3.06·10^{-4}	–
190	1.14·10$^{-5(a)}$	1.60·10$^{-4(c)}$	3.07·10$^{-4(e)}$
180	4.57·10^{-6}	9.03·10^{-5}	9.15·10^{-5}
170	2.78·10^{-6}	3.18·10^{-5}	3.20·10^{-5}
160	1.39·10^{-6}	7.85·10^{-6}	1.07·10^{-5}
150	6.27·10$^{-7(b)}$	2.36·10$^{-6(d)}$	5.50·10$^{-6(f)}$
140	–	9.45·10^{-7}	1.25·10^{-6}

(a–b) standard deviation of propranolol drug (±0.13 and ±0.16), (c–d) standard deviation of the tablet A (±0.12 and ±0.18), (e–f) standard deviation of the tablet B (±0.14 and ±0.18)

The rate constants are in agreement with the Arrhenius' classical kinetics and revealed that propranolol drug is more stable relatively to tablets A and B, which showed a similar kinetics of decomposition. The rate constant values confirmed small incompatibility promoted by some excipients in propranolol formulations; however it was not enough to decrease their stability (Table 1).

Conclusions

- DSC-photovisual demonstrated that the amount of lactose was enough to promote interaction in a propranolol mixture and suggests its substitution in propranolol tablets.
- TG, dynamical and isothermal, showed differences in stability of the propranolol tablets compared to the propranolol drug. The kinetic parameters confirmed incompatibility and a lower stability for propranolol tablets than propranolol hydrochloride.
- Thermal analysis (TA) demonstrated that different formulations showed different thermal profiles. TA can be adapted for compatibility and stability studies of

pharmaceuticals. DSC, DSC-photovisual and TG are important in design development of pharmaceutical solid form.

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