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ORIGINAL ARTICLE

Compatibility study of paracetamol, chlorpheniramine maleate and phenylephrine hydrochloride in physical mixtures

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Abstract Paracetamol (PAR), phenylephrine hydrochloride (PHE) and chlorpheniramine maleate (CPM) are commonly used in clinical practice as antipyretic and analgesic drugs to ameliorate pain and fever in cold and flu conditions. The present work describes the use of thermal analysis for the characterization of the physicochemical compatibility between drugs and excipients during the development of solid dosage forms. Thermogravimetric analysis (TGA) and Differential Scanning Calorimetry (DSC) were used to study the thermal stability of the drug and of the physical mixture (drug/excipients) in solid binary mixtures (1:1). DSC thermograms demonstrated reproducible melting event of the prepared physical mixture. Starch, mannitol, lactose and magnesium stearate influence thermal parameters. Information recorded from the derivative thermogravimetric (DTG) and TGA curves demonstrated the decomposition of drugs in well-defined thermal events, translating the suitability of these techniques for the characterization of the drug/excipients interactions.

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1. Introduction

The development of a new pharmaceutical dosage form involves preliminary pre-formulation studies for which information about the physical, chemical and mechanical properties of the formulation constituents is necessary. Mixture of drug/excipient can affect the long-term stability of the solid dosage form, as well as the drug bioavailability, therapeutic efficiency and safety profile (de Oliveira et al., 2013b; Tiţa et al., 2011). In addition, the interactions between drug and excipients can affect the quality of the mixture, including the polymorphic form and crystallization profile of the drug, but also the formulation properties such as the solubility of the mixture, color, odor, and taste (Wu et al., 2011).

Thermoanalytical techniques are useful for the analysis of drug/excipient interactions during the development of new formulations based on classical solid dosage forms (e.g. powders, tablets, capsules). The physical properties, stability, compatibility and interactions between drugs and drugs/excipients can be assessed by the study of the changes occurring in the onset and endset temperatures, melting point and enthalpy (Mazurek-Wadołkowska et al., 2012). The advantages of Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) rely on the fast sample processing, small amount of sample required, and easy detection of physical interactions (Chadha and Bhandari, 2014; Severino et al., 2011). The development of solid dosage forms (e.g. capsules and tablets) for oral administration of drugs for the treatment of flu is an usual practice in commercially available medicines (de Oliveira et al., 2013a, 2011). Examples of drugs are paracetamol (PAR), phenylephrine hydrochloride (PHE) and chlorpheniramine maleate (CPM) (Palabiyik and Onur, 2010; Samadi-Maybodi and Nejad-Darzi, 2010). These drugs are used in combination such as analgesic, decongestant and anti-histaminic (Samadi-Maybodi and Nejad-Darzi, 2010) to ameliorate cough, pain and fever.

It is important to evaluate the interaction of drugs with excipients. The presence of degradation products is not desired, as they may interfere with the formulation stability and cause toxicity. DSC and TGA are important tools in various stages of formulation development. Application in the study of compatibility between substances has gained great prominence because they allow predicting possible interactions and/or incompatibilities in the final product (Neto et al., 2009). These methods are described in the European Pharmacopoeia, United States Pharmacopoeia, Japanese Pharmacopoeia and the Brazilian Pharmacopoeia. The objective this work was the assessment by thermal analyses using TGA and DSC of free drugs (PAR, CPM and PHE) and their physical mixtures (drug/excipient).

2. Materials and methods

2.1. Materials

Paracetamol (PAR), phenylephrine hydrochloride (PHE), chlorpheniramine maleate (CPM), Plasdone®S-630, lactose, microcrystalline cellulose, croscarmellose, magnesium stearate, corn starch, Aerosil® (colloidal silica), and mannitol were purchased from Henrifarma (São Paulo, Brazil).

2.2. Methods

2.2.1. Binary mixtures

The binary mixtures were obtained by manual mixing of 1:1 ratios of drug/excipient using a pestle and mortar. For the preparation of the mixtures, selected excipients were Aerosil®, starch, lactose, Plasdone®S-630, microcrystalline cellulose, magnesium stearate, and mannitol.

2.2.2. Differential Scanning Calorimetry (DSC)

Thermal behavior of drugs and excipients was assessed by accurately weighting 3 mg of sample loaded into an aluminum pan and sealed hermetically, in inert atmosphere (N_2). The analysis was performed from 25 to 300 °C at a heating rate of 10 °C/min. The assessment of drug purity and other thermodynamic parameters was determined by the program (TA Instruments, USA) by cryoscopic depression using the Van't Hoff equation, as follows:

$$T_m = T_0 - \frac{RT_0^2X}{\Delta H_f} \times \frac{1}{F}$$

where T_m is the sample temperature (in K), T_0 is the melting point of pure sample (in K), R is the gas constant (8.314 J/mol K), X is the mole fraction of impurity, ΔH_f is the heat fusion (J/mol), and F is the fraction of total sample melted at T_m.

2.2.3. Thermogravimetric analysis (TGA)

The thermogravimetric curves were recorded employing a thermoanalytical balance (2950, TA Instruments, USA) in the temperature range 25–400 °C. The drugs were carefully weighted and transferred to a platinum crucible, sample mass of ~10.0 mg, heating rate 10 °C/min under a dynamic atmosphere of nitrogen at a flow rate of 100 mL/min. All data were processed by the program software (TA Universal Analysis, USA).

3. Results and discussion

Respiratory tract infections are common clinical situations diagnosed worldwide, usually requiring the treatment of the symptoms (e.g. cough, pain, fever) by the use of classical drugs such as PAR, CPM, and PHE, either isolated or in combination (Tiţa et al., 2011).

PAR is the agent of first choice in the treatment of acute and chronic pain, associated or not with peripheral inflammatory reaction, being effective and having better safety profile compared to other analgesic drugs (Corvis et al., 2015). It is presented in the form of white crystalline powder, odorless and slightly bitter, with melting point recorded between 168 °C and 172 °C, being soluble in water, ethanol and sodium hydroxide and chloroform and slightly soluble in ether. It belongs to the Biopharmaceutical Classification System (BCS) Class I, i.e. it has high permeability and high solubility in aqueous medium. It is, therefore, possible to obtain the PAR in 3 polymorphic forms, from which two polymorphic forms can be isolated, i.e. I (monoclinic) and II (orthorhombic). Form I is more stable compared to form II, being ideal for the formulation in medicinal products (Mazurek-Wadołkowska et al., 2012). CPM is the first generation drugs