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Drug-excipient compatibility assessment of solid formulations containing meloxicam

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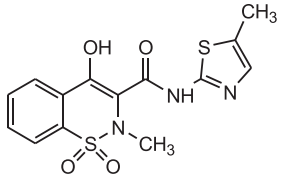
ABSTRACT

Meloxicam (MLX) is a non-steroidal anti-inflammatory cyclooxygenase (COX) inhibitor that is used to relieve inflammation and pain. MLX has a preferential affinity for COX-2, which is associated with a lower incidence of gastrointestinal side effects. The drug belongs to Class II of the Biopharmaceutical Classification System (BCS) in which dissolution is the limiting step of its bioavailability. In view of this classification, carrying out further studies regarding the compatibility of MLX with excipients and the mechanisms and kinetics of its degradation reactions is fundamental because any changes would directly influence the quality of the product. The aim of the present work is to evaluate solid pharmaceutical formulations containing MLX found on the market to define the more suitable excipients to improve the stability of the pharmaceutical formulations. Thermal analysis techniques were used to characterize and evaluate the compatibility between the drug and the excipients present in the market formulations. In the evaluation of its solid-state kinetics, MLX raw material under inert conditions had a shelf life of approximately 6 years. In the study of compatibility between the drug and excipients, MLX was found to be incompatible with magnesium stearate after DSC analysis under binary mixtures, which was confirmed by stress studies and chromatographic analyzes.

1. Introduction

Meloxicam (MLX) is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits prostaglandin synthesis by inhibiting cyclooxygenase (COX) activity and is used to combat inflammation and its symptoms. Low doses of MLX are considered preferentially selective due to its 10-fold greater affinity for the COX-2 subtype. This characteristic is generally associated with a lower incidence of gastrointestinal side effects (Engelhardt et al., 1996; Katzung, 2014).

The molecular formula of MLX is $C_{14}H_{13}O_4N_3S_2$, and its molecular structure is shown in (A). MLX has a molar mass of 351.38 g mol^{-1}, a melting point of 254 °C, and an octanol/water partition-coefficient (Log P) of 3.43. MLX exhibits low solubility in aqueous media as well as high permeability and is thus classified as a class II drug under the Biopharmaceutical Classification System (BCS) (Yazdanian et al., 2004). Dissolution is the rate-limiting step of absorption for drugs with low solubility and high permeability (class II). Therefore, it is important to evaluate the factors that influence absorption and, thus, bioavailability through studies during the development stages of pharmaceutical products.



(A)

Solid-state kinetic studies are performed to evaluate drug stability and to provide insights into possible reaction mechanisms. These studies are typically performed using thermogravimetry (TG), with either isothermal or non-isothermal methods, which include adjusted mathematical models that consider degradation rates and the reaction order. Using the Arrhenius equation, the thermodynamic parameters can be calculated, including the rate constant, pre-exponential factor and activation energy (Khawam and Flanagan, 2006; Zhou et al., 2003).

Solid-state kinetic models are classified as accelerating, decelerating, linear or sigmoidal based on the shape of conversion-versus-time curves. Therefore, equations that describe thermal decomposition are

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Table 1
Identification and classification of the products evaluated in this study and their respective listed excipients.

Product identification		Excipients	Classification
Tablets	Lab 1	Sodium citrate dihydrate, lactose monohydrate, microcrystalline cellulose, povidone, silicon dioxide, magnesium stearate, crospovidone	Reference drug
	Lab 2	Copovidone, lactose, sodium citrate anhydrous, magnesium stearate, colloidal silicon dioxide, microcrystalline cellulose and Sicovit Indigotine lake	Generic drug
	Lab 3	Microcrystalline cellulose, sodium citrate dihydrate, copovidone, crospovidone, silicon dioxide, magnesium stearate, lactose monohydrate	Generic drug
	Lab 4	Microcrystalline cellulose, sodium citrate, croscarmellose sodium, lactose, silicon dioxide, magnesium stearate	Generic drug
	Lab 5	Sodium citrate, lactose, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate	Generic drug
	Lab 6	Monohydrate lactose, microcrystalline cellulose, sodium citrate, crospovidone, povidone, magnesium stearate, colloidal silicon dioxide	Generic drug
	Lab 7	Sodium citrate dihydrate, dibasic calcium phosphate, lactose, sodium, croscarmellose, colloidal silicon dioxide, magnesium stearate	Biosimilar drug
	Lab 8	Copovidone, lactose, sodium citrate anhydrous, magnesium stearate, colloidal silicon dioxide, microcrystalline cellulose, Sicovit Indigotine lake	Biosimilar drug
	Lab 9	Microcrystalline cellulose, lactose monohydrate, povidone, ethyl alcohol, silicon dioxide, magnesium stearate, crospovidone	Biosimilar drug
Capsules	Lab 10	Not listed	Manipulated formulation
	Lab 11	Not listed	Manipulated formulation

classified based on distinct processes. These processes are controlled by nucleation and diffusion mechanisms as well as by reactions in the limiting phase, and they include geometric and physicochemical aspects, depending on the rate-limiting step of the reaction (Khawam and Flanagan, 2006).

Pharmaceutical companies that produce reference, generic or biosimilar drugs provide a list of some of the excipients present in meloxicam tablets, such as microcrystalline cellulose, corn starch, magnesium stearate, disodium citrate dihydrate, lactose, povidone and colloidal silicon dioxide, among others. Assessing the compatibility between these excipients and the drug is important for evaluating the stability of the pharmaceutical formulations. Many drug-excipient compatibility studies are performed using differential scanning calorimetry (DSC), such as those for imatinib mesylate (Łaszcz et al., 2007) and trioxsalen (Lima et al., 2014).

In compatibility assessments performed with DSC, a given interaction can be identified as a shift in the melting point, changes in the peak shape or area, the development of a transition, and/or an increase or decrease in the number of peaks due to the mixture of components. However, after the binary mixing of 2 components, shifts in the transition temperature and peak shape and area invariably occur and do not necessarily represent a harmful interaction, so these changes need to be carefully evaluated (Oliveira et al., 2011).

DSC is the most common thermal analysis method, as it is fast and simple. DSC is used to measure differences in the heat flow between a sample and a reference material as a function of a heating and cooling cycle. In pharmaceutical sciences, DSC is used in the thermal characterization and assessment of drug purity, in the assessment of the stability and compatibility of formulation components and in the identification of polymorphisms by determining the enthalpy of crystalline formations (Balestrieri et al., 1996; Oliveira et al., 2011).

Compatibility studies using DSC are examined in conjunction with assessments of the intrinsic stability of a raw drug, where degradation by stress is evaluated. Taken together, these 2 types of analysis can reveal potentially incompatible excipients as well as unstable conditions, thus improving drug development.

The objective of the present study is to assess solid pharmaceutical formulations containing MLX that are available in Brazil and to define the excipients that improve drug stability.

2. Materials and methods

Analyses were performed with MLX tablets and capsules found on the Brazilian market, and the following excipients were present in the formulations: starch; microcrystalline cellulose (MC); copovidone (copov); magnesium stearate (MS); dibasic calcium phosphate anhydrous (CPA); calcium phosphate dihydrate (CPD); lactose (lacto); red iron oxide (IO); talc; mannitol; stearic acid (SA), trisodium citrate (SC); croscarmellose (CCS); sodium starch glycolate (SSG); sodium lauryl sulphate (SLS); colloidal silicon dioxide (CSD); povidone K-30 (PVP); and crospovidone (PVPP).

For solid-state kinetic analysis, 3 mg of MLX was weighed into tin cups and analysed using a DTG60 (Shimadzu). The temperatures used for the analysis were 228, 231, 234 and 237 °C with a heating rate of 10 °C min^{-1} under 50 mL min^{-1} nitrogen flow for 1 h. The temperature range was selected based on an assessment of the TG and DSC curves for MLX and thermal characterization.

For compatibility assessment, DSC curves were obtained using a DSC50 cell (Shimadzu) under 50 mL min^{-1} nitrogen flow with heating to 400 °C at 10 °C min^{-1}. Approximately 1 mg of sample was weighed into tin cups and partially sealed. The tests were performed with samples of a) MLX; b) excipients of formulations available on the market; c) binary mixtures of excipient and MLX at 1:1 to increase the probability of an interaction between the drug and the excipient; and d) multicomponent mixtures (formulations available on the market). The results were analysed by comparing the DSC curves and assessing changes in the melting range of the drug in the mixtures. HPLC analysis was also applied to the API/excipient mixtures to confirm the DSC results.

The market formulations listed in Table 1 were also subjected to quality control tests defined by the Brazilian Pharmacopoeia. However, due to the lack of a monograph on meloxicam in the Brazilian Pharmacopoeia, the British Pharmacopoeia was used to perform the dissolution tests (Brazil, 2010; British Pharmacopeia Commission, 2013).

For assessment of the intrinsic stability (forced degradation) of the drug, 20 mL aliquots of an MLX stock solution (0.5 mg mL^{-1} in acetonitrile) were pipetted into individual volumetric flasks each containing 20 mL of a previously prepared stress solution (0.1 M NaOH, 0.1 M HCl, 3% H_2O_2 or 0.05% $FeSO_4$) plus 40 mL of methanol. The forced degradation study was carried out by exposing MLX to the following stress conditions for 4 h: water (neutral hydrolysis); 0.1 M NaOH (basic hydrolysis); 0.1 M HCl (acid hydrolysis); 3% H_2O_2 (oxidation); 0.05% $FeSO_4$; dry heat at 60 °C; and UV radiation. After exposure, samples were diluted to 0.04 mg mL^{-1} in methanol, and aliquots were sampled for high-performance liquid chromatography (HPLC) analysis.

Chromatographic analyses were performed by HPLC coupled to an ultraviolet diode array detector (UV/DAD) (Waters e2695/2998 PAD) to assess the intrinsic stability of MLX. The method was optimized and validated to quantify the drug and possible degradation products using a C18 column (250 × 4.6 mm, 5 µm, Varian) at 25 °C with