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Gamma scintigraphy in the analysis of ketoprofen behaviour from matrix tablets

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ABSTRACT

The aim of this work was to study *in vitro* and *in vivo* the behaviour of matrix tablets (quick and extended release) containing ketoprofen (KTP) as a model drug and cellulose ether polymers, using gamma scintigraphy. The matrix tablets were prepared by the direct compression method and labelled by incorporating a drop of technetium (^{99m}Tc). It was spectrophotometricaly confirmed that the radioisotope inclusion did not modify the kinetics of KTP release. *In vitro* studies were carried out for the tablets using the paddle method of the USP 35/NF30. The images were processed by defining regions of interest over the tablet ^{99m}Tc and the percentage of remaining activity/time curves were generated for both formulations. *In vitro* gamma scintigraphy studies showed significant differences ($p < 0.05$) between both formulations. Identical results were obtained from the *in vivo* studies. *In vivo* tests were performed on five healthy volunteers. The scintigraphy images were acquired during 2.5 and 7.5 h for quick and extended release formulations, respectively. The position of the extended release formulation tablet along the gastrointestinal tract (GIT) was assessed. The described results demonstrate the *in vitro/in vivo* correlation for the drug release profile and exhibit the importance of gamma scintigraphy for the drug location through the GIT.

1. Introduction

In pharmaceutical terms, gamma scintigraphy assays (pharmacoscintigraphy) consist in administering a pharmaceutical formulation containing a small amount of a γ-emitting substance (radioisotope), followed by its subsequent detection (Martin et al., 2003). The radioisotope incorporated into the formulation allows to assess the drug's pharmacokinetics and biodistribution, quantifying the *in vivo* dissolution and disintegration parameters, as well as to determine the drug release sites (Wilson and Washington, 2000; Wilding et al., 2001). Several applications to oral, parenteral, nasal, and especially ophthalmic forms (where dosimetry to the lens is a concern), were recently reported (Wilson and Washington, 2000; Al-Ghananeem et al., 2008; McConville et al., 2009; Ghimire et al., 2010; Goodman et al., 2010; Tadros, 2010; Wilson et al., 2011; Depreter et al., 2012). This is a non-invasive technique which provides reliable information on the drug transit time in different regions of the gastrointestinal tract (GIT), as well as in various other body organs and is ideal for specialized dosage forms being applied particularly in modified-release ones (Terán et al., 2004; McDowell et al., 2005). Another benefits of this technique are directly associated by avoiding the need for volunteers to be subjected to the unpleasant and invasive procedure of oral intubation, facilitating early evaluation of performance release modifiers in its mixture with drugs and providing a rapid and cost-effective method for assessing the absorption/biovailability of drugs in specific regions of the GIT (Wilding et al., 1992; Martin et al., 2003).

The pharmacoscintigraphic study of such pharmaceutical forms allows to gain an insight into the drug release dependence regarding both the physiological and morphological characteristics of different regions of GIT (*e.g.* such gastric emptying and small intestinal transit), that can affect the absorption and pharmacokinetic profile of any drug (Marathe et al., 2000). The observed transit of the dosage form is correlated to the rate and extent of drug absorption, either in human volunteers or in appropriate animal models (*e.g.* dogs, cats or pigs) (Davis et al., 1992; McConville et al., 2009; Ghimire et al., 2011). Information such as the *in vivo* site of disintegration/dispersion or the physiological function under

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suspected pathological conditions can also be obtained (Wilson and Washington, 1988). Therefore, the behaviour of oral dosage forms, such as release and subsequent drug bioavailability, depends on these factors (Säkkinen et al., 2004, 2006; Ahmed and Ayres, 2011).

The amount and activity of the γ-emitting administered substance is usually so low that there is no risk of interfering significantly with the normal physiological processes. The most serious cases, although rare, are associated to hypersensitivity (allergy) through anaphylactic shock of the patient upon reaction to the unusually chemical agent (Al-Ghananeem et al., 2008). Moreover, comparative with *in vitro* release assays using both conventional and modified dissolution methods can provide an insight into the performance of drug-delivery systems, and radionuclides incorporated into the dosage form can yield evidence on the in *vivo* behaviour of these formulations (Terán et al., 2004).

Reported studies using X-ray methods give useful information on the gastric emptying of dosage forms, as well as on their passage through the intestine (McDowell et al., 2005), but the gastric emptying of dosage forms is highly variable and generally delayed in the presence of food (Ghimire et al., 2011). On the other hand, in many studies intended to determine the *in vivo* transit of dosage forms, as well as the absorption site and have been already undertaken; but, in general within these studies the authors obtained different conclusions, in accordance with the respective purposes (Borin et al., 1990; Hardy et al., 1993; Olsson et al., 1995; Marathe et al., 2000; Martin et al., 2003). For instance, Borin et al. (1990) mostly focused on the effect of food on sustained release of ibuprofen tablets transit through the GIT, by gamma scintigraphy and had observed little differences on drug bioavailability between fed and fasted volunteers. In its turn, Hardy et al. (1993) investigated the drug release sites from an oral sustained-release formulation of 5-ASA Pentasa® (designed as a tablet preparation consisting of a myriad of sustained-release ethylcellulose microgranules) in the GIT, also through gamma scintigraphy, confirming that drug release was hardly affected by food consumption. Hence, it is fair to ensure that although there are some published studies using gamma scintigraphy, there are many parameters to take into account that may influence the drug transit through the GIT, such as the type of drug and the physical–chemical characteristics of the polymer (bioadhesive properties, solubility in water, *etc.*) or the type of formulation (tablets, capsules, *etc.*).

Consequently, the release rate should be dependent on the diffusion coefficient of the drug in the fluid, of the drug solubility (at the local pH), the drug concentration in the formulation, as also as the own structure of pharmaceutical dosage forms (Olsson et al., 1995).

Ketoprofen (KTP) is an effective anti-inflammatory and analgesic drug, used in the clinical practice, mainly for the treatment of rheumatoid arthritis and osteoarthritis. It is as effective in clinical trials as other non-steroidal anti-inflammatory drugs (NSAIDs) (namely naproxen), both regarding efficacy and side effects (Liversidge, 1981). Like most NSAIDs, KTP is advantageous since it lacks additive potential and does not result in sedation or respiratory depression. In addition, KTP displays analgesic and antipyretic pharmacological properties (Green, 2001). This drug is currently marketed worldwide in a variety of forms: capsules, tablets, injectable solutions, suppositories and gels (Kantor, 1986). The peak plasma concentrations (C_{max}) are reached within 1–2 h (T_{max}) after administration of a single dose, with almost the entire dose being absorbed (Shohin et al., 2012). KTP is metabolized in the liver, 60–75% of the administered dose appearing in the urine primarily as the glucuronide metabolite and less than 10% being excreted as unchanged drug (Shohin et al., 2011, 2012), and its elimination half-life is 2–4 h (Roda et al., 2002; Martindale, 2011). Thus, the use of cellulosic polymers for the preparation of KTP hydrophilic matrix tablets has lately become more and more important, as extended-release (either constant or pulsed) dosage forms of the drug may often be beneficial (Vueba et al., 2012).

The main objective of this work was to assess the significance of scintigraphy studies, by combining *in vitro* and *in vivo* evaluation in the progress stages of matrix tablets in healthy volunteers, attempting to better understand the performance of the drug through the GIT. For this purpose, Technetium 99 m (^{99m}Tc) was selected as a radiotracer, and it was embedded in two formulations during the manufacture process. ^{99m}Tc is the most commonly used radionuclide for this kind of studies, due to its optimal emission energy (within the 140 keV range), low radiation doses absorbed by the volunteer and short plasma half-life (6 h), which leads to a high efficiency in image acquisition of Wilson and Washington (2000). The two formulations used in this study, containing methylcellulose (MC) and a mixture of hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC) showed different dissolution rates in accordance with the composition of each formulation. Those polymers are bioadhesive and designed to increase the contact time in the various mucosal routes of drug administration (in the case of water-soluble polymers, the duration of residence time on tissue surfaces is based on dissolution rate of the polymer) and considered safe by the regulatory agencies (Lee et al., 2000).

2. Materials and methods

2.1. Materials

Ketoprofen batch no. 043K0684 was purchased from Sigma–Aldrich Chemie, Germany, and used as a model drug. Polymers: methylcellulose, Methocel® MC25, Fluka, Switzerland; hydroxypropylcellulose, Klucel, USA; hydroxypropylmethylcellulose, Methocel® K100M, Colorcon, England. Diluent: lactose monohydrate ((LAC) Median particle size 32.04 μm. Granulac® 200, Meggle, Wasserburg, Germany). Lubricants were talc and magnesium stearate (Mg S), of analytical grade. Technetium-99 (^{99m}Tc) was obtained from a Tc-99 M 21.50 Gbq generator (Mallinckrodt, Medical BV, Netherlands). The in *vitro* and in *vivo* analyses were performed using a gamma camera (CAMSTAR AC/T, General Electric). The activity was measured in a dose calibrator Capintec CRC® 15R, 1998, USA.

2.2. Preparation of the matrix tablets

The tablets were prepared by direct compression method previously described (Vueba et al., 2012), using a single punch press (Speca Press–Automatic Press Ltd., England) at a compaction pressure of 624 MPa with faced-punches of 10 mm diameter. Two formulations of KTP tablets containing cellulose ethers polymers as matrix former were used in the study (Table 1). In both cases, the drug content was kept at 200 mg, for a total tablet weight constant of 350 ± 1 mg. The following percentage composition was thus considered: KTP, 57.14%; polymer or polymer mixture, 20.00%; diluent, 20.29%; talc, 1.71% and magnesium stearate, 0.86%.

2.3. Radiolabelling

The radiolabelled process of tablets was made by incorporating into the compression camera a fraction of 50% of the total mass weight (350 mg); continuously a drop of ^{99m}Tc, using a needle of 21G (0.8 mm), was deposited; finally, the last part of the mass was included and directly compacted. The labelled tablets were left to dry 1 h before use weighed (target weight 350 mg) and activity measured in a dose calibrator.