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Effect of solubility enhancement on nasal absorption of meloxicam

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ABSTRACT

Besides the opioids the standard management of the World Health Organization suggests NSAIDs (non-steroidal anti-inflammatory drugs) alone or in combination to enhance analgesia in malignant and non-malignant pain therapy. The applicability of NSAIDs in a nasal formulation is a new approach in pharmaceutical technology.
In order to enhance the nasal absorption of meloxicam (MX) as an NSAID, its salt form, meloxicam potassium monohydrate (MXP), registered by Egis Plc., was investigated in comparison with MX. The physico-chemical properties of the drugs (structural analysis, solubility and dissolution rate) and the mucoadhesivity of nasal formulations were controlled. *In vitro* and *in vivo* studies were carried out to determine the nasal applicability of MXP as a drug candidate in pain therapy.
It can be concluded that MX and MXP demonstrated the same equilibrium solubility at the pH 5.60 of the nasal mucosa (0.017 mg/ml); nonetheless, MXP indicated faster dissolution and a higher permeability through the synthetic membrane. The animal studies justified the short T_{max} value (15 min) and the high AUC of MXP, which is important in acute pain therapy. It can be assumed that the low mucoadhesivity of MXP spray did not increase the residence time in the nasal cavity, and the elimination from the nasal mucosa was therefore faster than in the case of MX. Further experiments are necessary to prove the therapeutic relevance of this MXP-containing innovative intranasal formulation.

1. Introduction

Intranasal and pulmonary administration are an effective way to deliver drugs into the systemic circulation as an alternative to the oral and parenteral routes for some therapeutic agents (Pacławski et al., 2015). Nasal dosage forms of drugs (spray, gel or powder) have gained importance in recent years because of the rapid onset of action, the circumvention of the first-pass elimination by the liver and the gastrointestinal (GI) tract, the non-invasiveness and the simple daily administration. Nasal transmucosal absorption is affected by the physicochemical properties of the drugs (such as charge, molecular weight, solubility, pKa, logP and permeability, *etc.*) and formulation factors like dosage form, excipients, pH, viscosity, volume or osmolality (Arora et al., 2002; Illum, 2002).

Intranasal formulations are well known in pain therapy, in particular in the case of chronic malignant pain (Striebel et al., 1993). The opioids (*e.g.* morphine, butorphanol, fentanyl, *etc.*) have been formulated as intranasal sprays, reaching T_{max} within 25 min, and in the bloodstream their bioavailability is high (in general, ~50%) as compared with opioids administered intravenously with 100% bioavailability (Veldhorst-Janssen et al., 2009).

The World Health Organization (WHO) has developed a protocol to guide the treatment of different forms of malignant and non-malignant pain therapy (WHO, 2007). Fig. 1 summarizes the ladders for pain management. In this standard management, besides the opioids, non-steroidal anti-inflammatory drugs (NSAIDs) are suggested for acute pain therapy or co-administered to enhance analgesia.

NSAIDs, which belong in BCS Class 2 with poor solubility and high permeability (Tsume et al., 2012), are really important drugs in pain therapy. Their solubility is pH-dependent (low solubility in acidic medium) and their permeability is influenced by various sections of the GI tract. An increase of the solubility of the NSAID can therefore result in faster absorption, *e.g.* from the gastric region, to reach an analgesic

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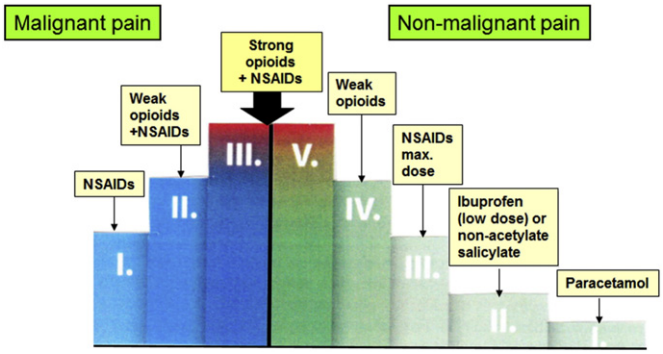

Fig. 1. Management for malignant and non-malignant pain therapy (WHO, 2007).

effect. On this basis, primarily solid and semi-solid dosage forms (tablets, capsules and suppositories) are on the market.

The intranasal application of NSAIDs may be an alternative route for acute pain therapy, with quick transcellular transport, a high plasma concentration and co-administration with other pain killer to enhance analgesia. Nonetheless, NSAID-containing nasal products as pain killers are not available in therapy. One reason may be a low pH value of the nasal liquid (pH: 5.60) and consequently a low solubility of the NSAID in this medium, as well as the dose amount, irritation, efflux mechanism, *etc.* The applicability of a NSAID in a nasal formulation is therefore a new approach in pharmaceutical technology. A dissolved MX-containing nasal formulation was patented by Castile et al. (2005). The aqueous compositions used co-solvents and contained the dissolved MX in high concentration, which was well tolerated when administered intranasally and provided rapid and effective systemic drug absorption in an animal study. Unfortunately, the composition was found to be unstable in long-term stability tests (precipitation was observed). Another analgesic NSAID agent (a ketorolac tromethamine-containing solution) was successfully administered intranasally to elicit a systemic effect (Li et al., 2015).

In our previous work, MX was chosen as NSAID for intranasal administration in order to attain an analgesic effect. MX has poor aqueous solubility (4.4 μg/ml at 25 °C) (Ambrus et al., 2009), and we therefore used a "top-down" method with the aim of reducing the particle size into the micro or the nano-range and hence improving its bioavailability, such as dry ball-milling (Kürti et al., 2011), high-pressure homogenization (Pomázi et al., 2013) and combined wet milling technology (Bartos et al., 2015). Nanosuspensions, as potential drug formulations, can be achieved by combined wet milling technology (Liua et al., 2011). The results indicated that the reduction of the MX particle size into the nano-range led to increased saturation solubility and dissolution rate, and an increased adhesiveness to surfaces as compared with micronized MX particles. In our earlier studies, MX proved not to be toxic in a cell culture model of the nasal epithelium and did not influence the paracellular pathway (Kürti et al., 2013).

In order to enhance the bioavailability of MX, salt formation may be a new approach to increase its solubility and dissolution rate and to attain fast absorption through the nasal membrane to reach the blood stream. One-salt form of MX is meloxicam potassium monohydrate (MXP), which is a new agent registered by Egis Plc. (Budapest, Hungary) - patent number: US8097616 B2 (Mezei et al., 2012).

The novel meloxicam potassium salt monohydrate is a valuable intermediate in the synthesis of high-purity MX drug substance. The key intermediate of this protocol is the new potassium salt monohydrate of meloxicam, which makes possible the efficient removal of impurities, resulting in an environmentally friendly manufacturing process of the high-purity (>99.90%) drug substance (Mezei et al., 2009).

MXP-containing dosage forms have not been described to date. Our aim was therefore to investigate the physicochemical properties of MXP in comparison with those of MX and to prepare intranasal liquid formulations with both agents. *In vitro* and *in vivo* studies were carried out to determine the nasal applicability of MXP as a drug candidate in pain therapy.

2. Materials and methods

2.1. Materials

MX (4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2H-benzothiazine-3-carboxamide-1,1-dioxide) and MXP (4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2H-benzothiazine-3-carboxamide-1,1-dioxide potassium monohydrate) were obtained from Egis Plc. (Budapest, Hungary) (Fig. 2). Both of the raw materials are yellow. The melting point of MX is 267 °C and that of MXP is 253 °C (Hughey et al., 2011). Sodium hyaluronate (HA) (M_w = 1400 kDa) as viscosity enhancer and mucoadhesive agent was obtained as a gift from Gedeon Richter Plc. (Budapest, Hungary). For the rheological measurements, mucin (porcine gastric mucin type II) and reagents were purchased from Sigma Aldrich (Sigma Aldrich Co. LLC, St. Louis, MO, USA).

2.2. Investigation of raw materials

Measurement of micrometric properties (SEM, particle size analysis) and equilibrium solubility were carried out to compare MX and MXP before the preparation of the nasal formulations.

2.2.1. Scanning electronmicroscopy (SEM)

SEM (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan) was used to visualize the shape and surface characteristics of the samples. The samples were sputter-coated with gold–palladium under an argon atmosphere, using a gold sputter module in a high-vacuum evaporator, and the samples were examined at 10 kV and 10 μA; the air pressure was 1.3–13 MPa.

2.2.2. Particle size analysis

The particles of MX and MXP were measured with the Leica Image Processing and Analysis System (Leica Q500MC, LEICA Cambridge Ltd., Cambridge, UK). The particles were described in terms of their length, breadth, perimeter, roundness and surface area. The roundness was calculated from the ratio of the perimeter squared to the area (1). An adjustment factor of 1.064 corrected the perimeter for the effect of the corners produced by the digitization of the image. The mean values were determined by the examination of 500 particles from each sample.

$$Roundness = \frac{Perimeter^2}{4 \cdot \pi \cdot Area \cdot 1.064} \quad (1)$$

2.2.3. Equilibrium solubility of raw materials

The equilibrium solubilities of MX and MXP were determined by a standardized saturation shake-flask (SSF) method. The specifications of the method were published earlier (Baka et al., 2008).

First, 3–15 ml of different media (phosphate buffers (PBs) with a pH of 5.60 or 7.40 and water with a pH of 5.50) and 5–80 mg of MX or MXP were measured in a glass container to ensure an excess of the solid material. After waiting for 1 h, the pH values of the samples were adjusted with 1 M NaOH or 1 M HCl, depending whether there was a slight shift

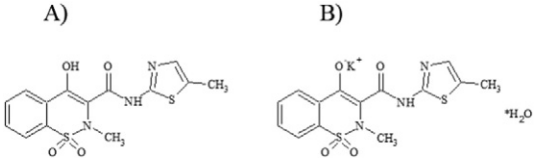

Fig. 2. Chemical structures of MX (A) and MXP (B).