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Improvement of the surface hydrophilic properties of naproxen particles with addition of hydroxypropylmethyl cellulose and sodium dodecyl sulphate: *In vitro* and *in vivo* studies

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ABSTRACT

In this study, a new surface-modified naproxen was developed to enhance brain concentration in acute migraine treatment. Fast-dissolving naproxen granules were made by mixing hydroxypropylmethylcellulose (HPMC) sodium dodecyl sulphate (SDS) and sodium croscarmellose with micronized naproxen particles. The aim of this study was to evaluate the effect of adding proportions of SDS to the HPMC film caused changes in the polymer chains of the HPMC, producing a new hydrophilic HPMC-SDS structure. These formulations with different HPMC/SDS ratios were characterised using electron microscopy (SEM), powder X-ray diffraction (PXRD), and differential scanning calorimetry (DSC). SDS 10% (w/w) produced a highly hydrophilic HPMC-SDS structure on the surface of the naproxen microparticles. The fast dissolution granules (SF-10%) showed a significant improvement in the dissolution rate of naproxen. Pharmacokinetic studies were conducted with mice, showing an improvement of Cmax (1.38 and 1.41-fold) and AUC0-2h (30% and 10% higher) for plasma and brain samples compared to the reference naproxen suspension. The faster Tmax ratio for SF-10% may be related to increased hydration in the gastrointestinal environment, enabling the drug to permeate the gastrointestinal hydration layer more easily due to the presence of the hydrophilic HPMC-SDS structure in the formulation.

1. Introduction

Migraine is a complex condition with a wide variety of symptoms. For many people, its main feature is a painful headache. Other symptoms include feeling sick, vomiting and sensitivity to light and sound. Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat migraine headaches (Sheshala et al., 2011).

A rapid onset of the therapeutic effect is required in acute migraine attacks (Girotra and Singh, 2016). Different drugs used for migraine attacks such as sumatriptan, rizatriptan and zolmitriptan, and analgesics such as ibuprofen and naproxen, have been investigated to develop rapid dissolution systems. There has been an increase in the development of new treatments for these acute conditions, including fast-disintegrating tablets (Sheftell et al., 2005; Sheshala et al., 2011; Stange et al., 2014).

Naproxen has been reported to have low permeability and prolonged absorption throughout the gastrointestinal tract (Figueroa and Bose, 2013). Its poor solubility and low partitioning decrease its ability to cross the blood-brain barrier (BBB) (Sheha, 2012). In the steady state, naproxen achieved a low brain/plasma ratio (approx. 0.03 B/P ratio), similar to that obtained with indomethacin (approx. 0.05 B/P ratio), but lower than with ibuprofen (approx. 0.11 B/P ratio) (Andersen et al., 2014). Naproxen is a poorly soluble drug that requires high plasma concentrations to achieve effective brain concentrations in migraine. Current oral naproxen formulations have several drawbacks, such as the slow onset of action, low bioavailability and large inter-subject variability in the absorption rate (T_{max}) (Choi et al., 2015). The plasma values of T_{max} for naproxen were between 2 and 4 h

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(Della Rocca et al., 2014; Sheha, 2012). Fast-dissolving formulations of naproxen that produce a rapid onset of action and improve pharmacokinetic parameters such as C_{max}, T_{max} and AUC_{0-t} values in plasma and brain for the first 2 or 4 h after dosing are particularly important in these formulations (Choi et al., 2015; Haberer et al., 2010). The improved B/P ratios for 2 h post oral administration have been used to evaluate the onset of action (Girotra and Singh, 2016).

Microparticles and nanoparticles were obtained by milling (wet and dry) in order to improve naproxen plasma and brain pharmacokinetic parameters. The last few years have seen the publication of different strategies for naproxen formulation, including the addition of a hydrophilic polymer such as HPMC (Ha et al., 2015; Kumar and Burgess, 2014; Mishra et al., 2015), or surfactants (Li et al., 2016; Mosquera-Giraldo et al., 2014; Stange et al., 2014) to avoid agglomeration problems and improve wettability. Some studies report that these formulations may have similar dissolution profiles to those obtained with naproxen sodium formulations.

Nonionic cellulose derivatives are a broad group of hydrophilic polymers which provide interesting properties in aqueous media. The use of hydrophilic polymers such as hydroxypropylmethylcellulose (HPMC) and hydroxypropyl cellulose have been shown to enhance the steric and electrostatic stabilisation of the crystal (Figueroa and Bose, 2013). In aqueous solution, they produced important results in the stabilisation of the formulation due to hydrogen bonding to the hydrophobic core of the drug (Douroumis et al., 2007; Mishra et al., 2015). Fast-dissolving granules using these hydrophilic polymers as a binding agent can reduce the hydrophobicity of drug crystals, for which the solution is rate-limiting.

Surfactants can prevent the aggregation of microparticles and nanoparticles by improving the stability of nanocrystalline suspensions (Kumar and Burgess, 2014). Surfactants such as sodium dodecyl sulphate (SDS) also improve the dissolution rate of poorly soluble drugs (Mosquera-Giraldo et al., 2014). However, large amounts of surfactants are required to achieve a high naproxen solution (Tiong and Elkordy, 2009). The addition of SDS with hydrophilic polymers such as HPMC produces a synergistic effect between HPMC and SDS, and facilitates interaction with the crystal surface. These hydrophilic HPMC-SDS systems require smaller amounts of surfactant agent to obtain a rapid dissolution rate with hydrophobic drugs (Li et al., 2016). Hydrophilic excipients such as Pharmacoat (Li et al., 2016), Avicel pH 102, Cab-o-sil (Tiong and Elkordy, 2009), and mannitol (Figueroa and Bose, 2013) have been used as adsorption carriers in various drugs and surfactants. These surfactants in adsorption carriers help disperse the drug in the gastrointestinal environment. An interesting alternative is to use a hydrophilic disintegrant such as croscarmellose sodium or sodium starch glycolate, which may improve drug-water interaction by increasing dispersibility with a lower amount of excipient (Maghsoodi et al., 2008; Maggi et al., 2013; Matji et al., 2017).

The aim of this study was to develop fast-dissolving granules with a hydrophilic structure of HPMC-SDS for application with different drugs used in migraine treatment. In this work, naproxen was used as a model drug, and *in vitro* and *in vivo* improvements produced in these immediate release formulations were studied. The influence of SDS and HPMC polymer on the surface of poorly water-soluble drugs such as naproxen was investigated with different techniques such as scanning electron microscopy (SEM), powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC). The improvement in the dissolution profiles allows the most effective polymer and surfactant ratios to be selected for *in vivo* studies. The differences in pharmacokinetic parameters for SF-10% in C_{max}, AUC_{0-2h}, B/P ratios, and T_{max} (plasma and brain) may be considered critical to prevent or treat the first symptoms of a migraine attack.

2. Materials and methods

2.1. Materials

Naproxen and naproxen sodium were obtained from Zhejiang Charioteer Pharmaceutical Co., Ltd. (Zhejiang, China). Croscarmellose sodium was procured from FMC (Philadelphia, USA). Hydroxypropylmethylcellulose (Methocel E15LV) (Dow Chemical), sodium dodecyl sulphate and carboxymethylcellulose sodium salt (CMC 1000) were obtained from Sigma (Copenhagen, Denmark). Water was obtained from the Milli-Q water purification system (Billerica, USA). All reagents and chemicals used were of analytical grade.

2.2. Methods

2.2.1. Preparation of formulations

Naproxen raw material (NAP) and anhydrous naproxen (A-NAP) were used for the characterization (SEM, XPRD, and DSC) and dissolution studies. A-NAP was obtained by drying in an oven at 60 °C for 48 h. Sodium naproxen raw material (NAP Na) was used as a reference in the dissolution studies.

2.2.1.1. Polymeric formulation (PF). Naproxen granules containing 1.5% HPMC (w/w) were obtained by wet granulation (PF). 750 mg of naproxen was mixed with 560 μL of the binder solution (2% HPMC w/v). The wet mass was passed through a 0.840 mm sieve and the granules were dried in an oven at 60 °C for 48 h. The final product was sieved to isolate the 0.297-0.840 mm fraction, see Table 1.

Table 1
Composition of the different formulations.

Formulation Code	Naproxen (mg)	Binder HPMC (%)	Disintegrant Croscarmellose (%)	Surfactant SDS (%)
NAP Na[a]	100	–	–	–
NAP	100	–	–	–
A-NAP	100	–	–	–
PF	100	1.5	–	–
DF-5%	100	1.5	5	–
DF-10%	100	1.5	10	–
DF-15%	100	1.5	15	–
SF-3%	100	1.5	10	3
SF-6%	100	1.5	10	6
SF-10%	100	1.5	10	10
SF-12%	100	1.5	10	12
PM	100	1.5	10	10

[a] NAP Na: Sodium naproxen.