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Oral transmucosal delivery of naratriptan

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ABSTRACT

Naratriptan (NAR) is currently used as the hydrochloride salt (NAR.HCl) for the treatment of migraine and is available in tablet dosage forms for oral administration. Buccal drug delivery offers a number of advantages compared with conventional oral delivery including rapid absorption, avoidance of first pass metabolism and improved patient compliance. We have previously prepared and characterised the base form of NAR and shown that it has more favourable properties for buccal delivery compared with NAR. HCl. This study describes the design and evaluation of a range of formulations for oral transmucosal delivery of NAR base. Permeation studies were conducted using excised porcine buccal tissue mounted in Franz cells. Of the neat solvents examined, Transcutol® P (TC) showed the greatest enhancement effects and was the vehicle in which NAR was most soluble. The mechanisms by which TC might promote permeation were further probed using binary systems containing TC with either buffer or Miglyol 812® (MG). Mass balance studies were also conducted for these systems. The permeation of TC as well as NAR was also monitored for TC:MG formulations. Overall, TC appears to promote enhanced membrane permeation of NAR because of its rapid uptake into the buccal tissue. Synergistic enhancement of buccal permeation was observed when TC was combined with MG and this is attributed to the increased thermodynamic activity of NAR in these formulations. Significantly enhanced permeation of NAR was achieved for TC:MG and this was also associated with less TC remaining on the tissue or in the tissue at the end of the experiment. To our knowledge this is the first report where both enhancer and active have been monitored in buccal permeation studies. The findings underline the importance of understanding the fate of vehicle components for rational formulation design of buccal delivery systems.

1. Introduction

Migraine is a neurological syndrome of severe headache described as a throbbing pain in the front or one half of the head and may be associated with nausea and light sensitivity (Davidoff, 2002). It is a major public health problem and it affects over 20% of people at some stage in their lives; studies have shown that 4.5% of the population of Western Europe experiences headache a minimum of 15 days on average per month (Welch and Goadsby, 2002). Global studies indicate that up to 1% of the population worldwide may have chronic migraine (Natoli et al., 2010). The condition is accompanied by substantial personal suffering and disability and also has implications for economic output and productivity (Smitherman et al., 2013). There is currently no cure for migraine and the therapy is complicated by the different outcomes among, and within, individual patients and by the limited understanding of the pathophysiology of the syndrome (Brunton and Parker, 2008).

Triptans are indole derivatives that are used in the first-line management of migraines that do not respond to combination analgesics (Loder, 2010). Amotriptan, eletriptan, frovatriptan, naratriptan, and rizatriptan, are currently administered as oral tablet dosage forms. Sumatriptan is available as an oral tablet form and as an intra-nasal spray preparation. Zolmitriptan is formulated in three dosage forms: a conventional tablet, an oral disintegrating tablet and a nasal spray. These three zolmitriptan dosage forms were evaluated for patient preferences by Dowson et al. (2007). Initially the majority of patients preferred conventional oral tablets. After 4 months, 46.9% and 43.8% expressed preferences for the oral disintegrating tablet and the nasal spray respectively while only 6.3% preferred the ordinary tablet. The authors concluded that speed and efficacy of the migraine formulation were the key factors that influenced patient preferences.

Few publications have reported on the buccal or oral transmucosal route for delivery of triptans. This is surprising given that this mode of administration bypasses first pass metabolism and

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generally results in faster systemic delivery compared with conventional oral delivery (Sattar et al., 2014). Based on potency and physicochemical properties we have previously identified naratriptan (NAR) as a potential candidate for buccal delivery. We also reported the preparation and characterization of NAR base from NAR.HCl. Finally, we demonstrated that the base has more favourable properties than the salt for oral transmucosal delivery using *in vitro* studies in porcine buccal tissue (Sattar et al., 2015). The aims of the present work were to (i) evaluate a range of single and binary solvent vehicles for optimal buccal delivery of NAR and (ii) examine the mechanisms of action of vehicle components on NAR permeation. The solvents investigated in the present work were selected to span a range of NAR solubility values, based on data reported in our previous publication (Sattar et al., 2015).

2. Materials and methods

2.1. Materials

Naratriptan HCl (NAR.HCl) was obtained from Bioprogress (March, UK) and NAR base was prepared as described previously (Sattar et al., 2015). Ethanol (99.7–100% v/v, AnalaR® grade) was supplied by VWR (UK). Transcutol P® (TC) was a gift from Gattefossé (Saint Priest, France). Oleic acid (OA), Methocel® 60 HG (MC), and polyethylene glycol 400 (PEG 400) were purchased from Fluka (Germany). Dipropylene glycol (DPG) was purchased from Acros organics (USA). Miglyol® 812 N (MG) was obtained from Sasol GmbH (Germany). Polyethylene glycol (PEG) 200, propylene glycol (PG), phosphate buffer saline (PBS) tablets, HPLC grade solvents [acetonitrile (ACN), trifluoroacetic acid (TFA), triethanolamine, methanol and water] were also obtained from Fisher Scientific (UK).

2.2. Methods

2.2.1. Preparation of liquid dosage forms and solubility determination

The preparation of liquid dosage forms was conducted by dissolving a known amount of NAR base in the required volume of solvent(s). A range of single and binary systems were prepared using TC, PG, DPG, OA, PEG 200, PEG 400, and MG. The recommended NAR dose is 2.5 mg per attack with a maximum daily dose of 5 mg (Joint Formulary Committee, 2014). The concentration of NAR was therefore selected to give a final dosage of 2.5 mg per 100 μL application, with the exception of MG. A saturated solution of NAR in MG was prepared because of the low solubility of the molecule in this solvent. Solubility data for all neat solvents are reported in our previous publication (Sattar et al., 2015).

2.2.2. Miscibility studies

To identify appropriate binary solvent systems miscibility studies were carried out at room temperature. Appropriate proportions of solvents were carefully mixed in a glass test tube to a final volume of 3 mL, left to stand and observed after 24 h. Mixtures were considered to be miscible only after a clear and transparent solution was visualized.

2.2.3. In vitro *permeation and mass balance studies*

Permeation experiments were conducted as reported previously (Sattar et al., 2015) with porcine buccal tissue obtained from a local abattoir. A dermatome (Padgett instruments®, USA) was used to ensure uniform membrane thickness (0.8 ± 0.1 mm). The tissue was cut to suitable dimensions and mounted in Franz diffusion cells with effective diffusional areas of ~1 cm^2 and the area for each cell was measured accurately as detailed previously (Oliveira et al., 2012). Permeation studies were conducted with caffeine to confirm the integrity of all tissues (data not shown) as reported in our previous publication (Sattar et al., 2015). The receptor phase was PBS (pH 7.4) and 1 mL of PBS was added to the donor chamber for 30 min to ensure tissue hydration. The solubility of NAR in PBS was 1.1 mg/mL and sink conditions were maintained during the experiment.

The temperature of the cells was measured at regular intervals with a thermometer (Corby, UK) until all cells were equilibrated at 37 ± 0.5 °C. Permeation experiments were conducted under occlusion by covering the donor compartments with Parafilm™. An aliquot of 200 μL was withdrawn from each receptor chamber at specific time intervals and replaced with an equal amount of warm fresh degassed PBS. Samples were analysed by HPLC (Sattar et al., 2015) and the number of assays conducted each sample was n ≥ 3. The cumulative amount of drug permeated per unit area of buccal mucosa (μg/cm^2) was plotted against the collection time (min) using Excel 2010 (Microsoft, USA) as reported previously. The slope of this graph at the steady state was considered as the flux (J_{ss}) and the extrapolated x-axis intercept as the lag time (t_{lag}) as reported by Watkinson et al. (2010). The cumulative amount/area (Q_n) at time (n) was determined and the permeability coefficient (k_p) was calculated from J_{ss} as reported in our previous publication (Sattar et al., 2015).

At the end of the permeation experiment the residual formulation in the donor chamber was removed, diluted and NAR was analysed by HPLC (Sattar et al., 2015). The surface of the membrane was washed three times with 1 mL of methanol:water (50:50, v/v). Finally, the cells were disassembled and the buccal membranes were cut into small pieces and incubated in 5 mL of methanol:water (50:50, v/v) at 37 °C with shaking to extract the drug inside the tissue. The buccal washes and extracts were centrifuged for 20 min at 13.2 (×1000) rpm (Eppendorf centrifuge, UK) and a sample of the supernatant was diluted and analysed by HPLC (Sattar et al., 2015). The final cumulative amount of drug permeated was used to calculate the recovery of the drug in the receptor phase. Method validation for the mass balance studies has also been reported in our previous publication.

2.2.4. Gas chromatography (GC) analysis

TC was analysed using a gas chromatography instrument (Agilent 7890A, USA) equipped with a flame ionisation detector and operated by ChemStation® for GC systems software. A stock solution of 100 μmol/mL of TC in water was used to prepare a series of concentrations ranging from 0.1 to 14.7 μmole/mL. Analyses were performed on a Zebron™ ZB-WAX column (30 m × 0.5 mm × 0.1 μm; Phenomenex, USA). The chromatographic conditions were as follows: Nitrogen was used as a carrier gas at a flow rate of 6.6 mL/min. The injection volume was 0.5 μL with a 1:1 split ratio with nitrogen and an inlet temperature of 225 °C. The column was operated under the following gradient mode: the oven starting temperature was set at 80 °C and this was increased to 215 °C at a rate of 15 °C/min with a total run time of 9 min. The detector temperature was set at 300 °C and the retention time of TC was ~5.48 min. The method was validated in terms of specificity, linearity, accuracy, precision, detection limit (LOD) and quantification limit (LOQ) according to the International Conference of Harmonization guidelines (ICH, 2005). The values for LOD and LOQ were 0.26 μmol/mL and 0.79 μmol/mL respectively.

2.2.5. Statistical analysis

All data were analysed using SPSS version 22 and Excel (Microsoft Office 2010). The results are presented as mean ± standard deviation (SD). The Student's *t*-test and one-way ANOVA with replication using the Post Hoc Tukey test were used to investigate statistical differences. A probability of $p < 0.05$ was considered statistically significant.