**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.

**Key words:** Naratriptan, base, migraine, *in vitro* permeation, porcine tissue

## 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 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® 812N (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 ± 0.5ºC. 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 $n \geq 3$. 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 37ºC 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 0.1-14.7 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.

## 3. Results and Discussion

### 3.1 Permeation from single solvents

The steady state flux ($J_{ss}$), lag time ($t_{lag}$), permeability coefficient ($k_p$) and amount of NAR permeated after 6 h ($Q_{6h}$) for all single solvents studied are shown in Table 1. NAR permeated to the highest extent from TC followed by DPG, PG, PEG 200 and PEG 400, respectively. When formulated in OA only 0.1% of the applied dose of the drug had permeated by the end of the experiment.

**Table 1. NAR permeation parameters for single solvents (n ≥ 3, mean ± SD)**

| Permeation parameter | $J_{ss}$ (µg/cm$^2$/min) | $t_{lag}$ (min) | $k_p$ (*$10^{-6}$cm/min) | $Q_{6h}$ (µg/cm$^2$) |
|---|---|---|---|---|
| *TC** | 2.35 ± 0.87 | 184.6 ± 12.3 | 94.3 ± 34.7 | 421 ± 175 |
| *DPG** | 0.68 ± 0.42 | 211.9 ± 2.3 | 27.34 ± 17.1 | 105 ± 61 |
| *PEG 200* | 0.10 ± 0.02 | 180.1 ± 43.2 | 4.19 ± 0.99 | 18.6 ± 3.1 |
| *PG* | 0.11 ± 0.04 | 216.1 ± 18.8 | 4.6 ± 1.6 | 16.9 ± 5.9 |
| *PEG 400* | 0.04 ± 0.02 | 133.3 ± 5.9 | 1.8 ± 1.1 | 9.8 ± 6.3 |
| *OA* | 0.014 ± 0.004 | - | 0.56 ± 0.16 | 3.4 ± 0.8 |

* Significantly higher than all other formulations; ANOVA, $p < 0.05$

When NAR was prepared as a solution in Transcutol P® the maximum buccal flux was observed (~2.4 µg/min/cm$^2$). As noted in our previous study (Sattar et al., 2015), the solubility of NAR in the neat solvents may be ranked as follows: TC>DPG>PEG

200>PG=PEG 400> OA. This reflects the rank order for the flux values in Table 1. The solubility of NAR in TC was determined to be 106 mg/mL at 37°C which was significantly higher than all other solvents studied ($p<0.05$).. TC is a common co-solvent which is used in oral, dermal, and parenteral pharmaceutical formulations (Strickley, 2004). Previously, TC:water (50:50) was reported to enhance the buccal permeation of lidocaine hydrochloride by a factor of 2.3 compared with water alone (Ganem-Quintanar et al., 1998). The enhancement observed was attributed to the ability of TC to promote the partitioning of lidocaine hydrochloride into buccal tissue. Additionally, Ceschel and co-workers (2000) reported that the permeation of an essential oil through excised porcine buccal mucosa was significantly increased by incorporation of TC at 10 or 20% in a microemulsion-gel formulation. The enhancement was directly proportional to the TC concentration in the formulation. Although the exact mechanism by which TC promotes permeation is still unclear, some authors have suggested that it enhances drug solubility in epithelial membranes. Puglia and Bonina (2008) studied the enhancement effect of TC on the dermal absorption of atenolol *in vitro*, using human skin. These workers suggested that TC increases the apparent membrane-solvent partition coefficient of the molecule rather than the diffusion coefficient.

Glycols have been widely used in the enhancement of topical drug permeation but as for TC their enhancement mechanisms have not been elucidated fully. It has been suggested that increased drug solubility in skin results from the interaction of glycols with the polar head groups of lipid bilayers and their occupation of hydrogen binding sites (Lane, 2013). NAR is more soluble in DPG (64 mg/mL) than PG (46 mg/mL) at 37°C (Sattar et al., 2015), suggesting that as for TC, favourable solubility in this solvent is related to uptake and/or permeation into buccal tissue. Aqueous buffer solutions of PG (40% v/v) have been shown to promote effective buccal permeation of buspirone

(Birudaraj et al., 2005). PG is currently also included in a number of commercial buccal film formulations. As DPG has not been studied to the same extent as PG for buccal delivery the results here suggest that it should be investigated further for this application.

PEG 200 and PEG 400 are stable, hydrophilic substances, and are widely used in oral, parenteral, ophthalmic, topical, and rectal formulations. These specific PEG grades were selected because NAR exhibited good solubility in both at 37°C, namely 55 mg/mL in PEG 200 and 34 mg/mL in PEG 400 (Sattar et al., 2015). Almost twice the amount of naratriptan permeated from PEG 200 compared with PEG 400 (*t*-test, $p < 0.05$). PEG 400 has also been shown to retard the buccal permeation of donazepil in a concentration-dependent manner (Caon et al., 2014). This was attributed to a direct interaction between the drug and PEG 400 and its effects on the thermodynamic activity of the molecule.

OA has been reported to enhance the buccal permeation of buspirone and propranol when combined with PG (Manganaro and Wertz, 1996; Birudaraj et al., 2005). Manganaro and Wertz (1996) proposed that the change in permeation may reflect the lipid fluidizing effects of OA, because of the presence of its cis-bond which disrupts lipid packing. However, the potential effects of PG in contributing to permeation via displacement of water molecules were also acknowledged by these authors. Birudaraj et al. (2005) postulated that OA enhances buccal permeation of buspirone via the transcellular pathway because of its ability to act as a penetration enhancer for transdermal delivery. The failure of OA to enhance NAR delivery compared with the other solvents studied (Table 1) might reflect ionic complexation between the ternary amine group of naratriptan and the carboxylic group of OA. The reduction in the permeation of the basic drug, donepezil, through porcine buccal tissue in the presence of OA has been attributed to a similar interaction with OA (Caon et al., 2014).

MG is a mixture of medium chain triglycerides of fractionated $C_8$ (caprylic), $C_{10}$ (capric) and $C_{12}$ (lauric) fatty acids derived from coconut oil (Pouton and Porter, 2008). Because of the low solubility of NAR in MG, a saturated solution was prepared for buccal permeation studies. MG delivered around 16% of the applied dose, with a calculated flux of 0.08 ± 0.01 µg//cm$^2$/min and a permeability coefficient of 95.4 ± 10.1 x10$^{-6}$ cm/min. Interestingly, the lag time (97±5 min) was the shortest of all solvents evaluated, and the permeability coefficient was similar to that observed for the TC vehicle. MG has typically been used as a component of emulsion vehicles for oral or dermal delivery of actives (Sahle et al., 2013; Le Bars et al., 2015). The use of MG as a potential excipient in buccal formulations does not appear to have been examined previously.

### 3.2. Permeation from binary systems of TC with PG, DPG or OA

Since NAR permeation was highest from TC, binary systems were prepared by combining this solvent with PG, DPG or OA in a 1:1 ratio. Binary systems of TC with PEG 200 or PEG 400 were not evaluated because of the low permeation obtained with PEG 400 and the comparable solubility values of NAR in PG and PEG 200. Permeation studies were subsequently conducted using the same dose and conditions as for the previous section. The permeability parameters and permeation profiles of NAR for these mixtures are shown in Table 2.

**Table 2. NAR permeation parameters from binary systems of TC with PG, DPG, OA (n ≥ 3, mean ± SD)**

| Permeation parameters | $J_{ss}$ (µg/min/cm$^2$) | $t_{lag}$ (min) | $k_p*10^{-5}$ (cm/min) | $Q_{6h}$ (µg/cm$^2$) |
|---|---|---|---|---|
| *TC* | 2.35 ± 0.87 | 184.6 ± 12.3 | 94.3 ± 34.7 | 421 ± 175 |
| *TC: PG* | 2.51 ± 0.13 | 136.1 ± 23.9 | 100.6 ± 5.3 | 566.5 ± 70.5 |
| *TC: DPG* | 1.82 ± 0.18 | 194.7 ± 11.6 | 73.0 ± 7.0 | 309.7 ± 46.8 |
| *TC:OA* | 0.66 ± 0.01 | 97.4 ± 25.1 | 26.3 ± 0.3 | 175.1 ± 13.4 |

The highest and lowest values for NAR flux and permeation were observed for the TC:PG and TC:OA combinations respectively. Interestingly, the lowest lag time for NAR was also evident for the TC:OA, suggesting a faster interaction between this vehicle and the buccal membrane. OA has previously been suggested to fluidise intercellular lipids in skin (Francoeur et al., 1990), but this has not been reported for buccal tissue The permeation parameters of NAR for the TC:PG system, namely; $J_{ss}$, $k_p$, and $Q_{6h}$ are significantly higher than the corresponding parameters for the TC:DPG and TC:OA systems (ANOVA, $p < 0.05$). These results may reflect the lower thermodynamic activity of NAR in the TC:DPG system compared with TC:PG, based on solubility in the neat solvents (Sattar et al., 2015), and with reference to the TC:OA system, an interaction between OA and NAR, as discussed in Section 3.1.

### 3.3 NAR permeation from TC:PBS (pH 6.8) systems

To gain further insight into the buccal permeation enhancement properties of TC, binary mixtures of TC and PBS (pH 6.8) in different proportions were prepared (NAR 2.5 mg/100 µL) and permeation was evaluated. This pH was selected to simulate that of the oral cavity as saliva has a normal pH range of 6.2 - 7.6 (Newman et al., 2014). Mass

balance studies were also conducted at the end of this set of experiments. As the minimum ratio of TC required to dissolve this amount of NAR was 50%, the binary systems tested contained TC at 50, 75, and 90%. Figures 1a and 1b show the corresponding permeation profiles and mass balance data for these vehicles.

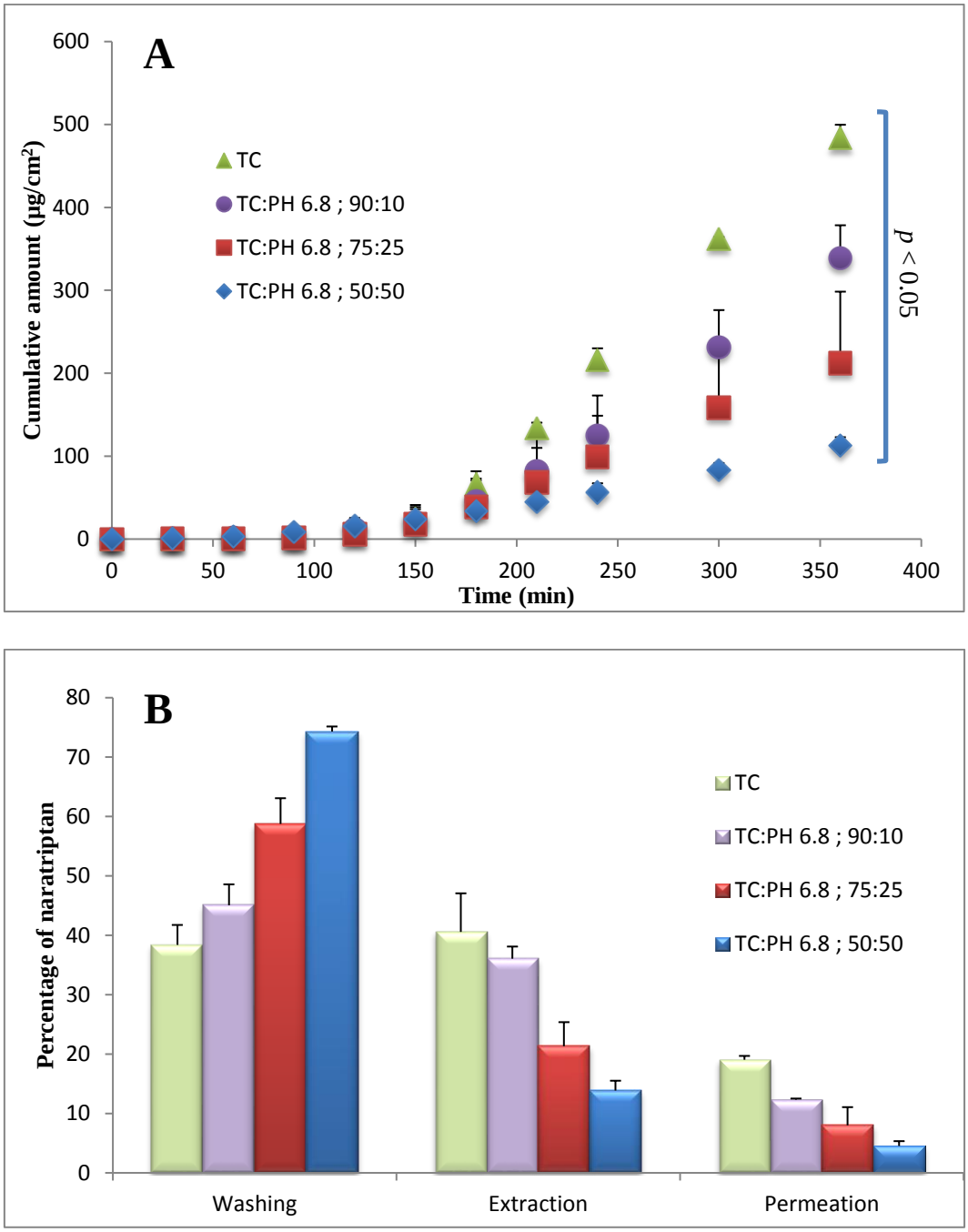


**Figure 1. (A) NAR permeation and (B) NAR mass balance data for binary systems of TC:PBS (pH 6.8) in porcine buccal tissue (n ≥ 3, mean ± SD)**

**Table 3. NAR permeation parameters from TC-PBS systems (n ≥ 3, mean ± SD)**

| Permeation parameters | $J_{ss}$ (µg/min/cm$^2$) | $t_{lag}$ (min) | $k_p*10^{-5}$(cm/min) | $Q_{6h}$ (µg/cm$^2$) |
|---|---|---|---|---|
| *TC* | 2.34 ± 0.11 | 150.3 ± 6.3 | 9.4 ± 0.47 | 476 ± 16 |
| *TC:pH 6.8; 90:10* | 1.73 ± 0.04 | 165.9 ± 28.4 | 6.9 ± 0.2 | 308 ± 4 |
| *TC:pH 6.8; 75:25* | 0.97 ± 0.36 | 139.9 ± 31.5 | 3.9 ± 1.5 | 200 ± 76 |
| *TC:pH 6.8; 50:50* | 0.44 ± 0.09 | 100.9 ± 50.2 | 1.8 ± 0.4 | 114 ± 20 |

As shown in Figure 1 and Table 3, for TC:PBS (50:50), values for $J_{ss}$, $Q_{6h}$, and amounts of NAR extracted from buccal membrane were decreased by 5, 4, and 2 fold, respectively, compared with values for neat TC (ANOVA, $p < 0.05$). NAR permeation from the TC:PBS binary systems increased with an increase in the TC proportion. At the same time, the percentage of NAR extracted from the buccal membrane at the end of the permeation experiment was also dependent on TC content. Accordingly, it is reasonable to hypothesise that TC may enhance the permeation of naratriptan through the porcine buccal mucosa by increasing drug uptake into tissue. This finding is also consistent with other studies whereby TC is proposed to act as a permeation enhancer by improving drug partitioning with biological membranes (Ganem-Quintanar et al., 1998; Ceschel et al., 2000; Puglia and Bonina, 2008).

### 3.4 NAR and TC permeation from TC:MG vehicles

Formulations with TC with MG were also tested to examine how a binary mixture of solvents with variable solubility parameters might influence buccal permeation. Binary mixtures of TC and MG were prepared in the following proportions: 50:50, 75:25, 90:10. The concentration of NAR and dose applied was the same as for the previous sections.

Cumulative amounts of NAR permeated per $cm^2$ of porcine buccal mucosa as well as mass balance results are shown in Figures 2a and 2b.

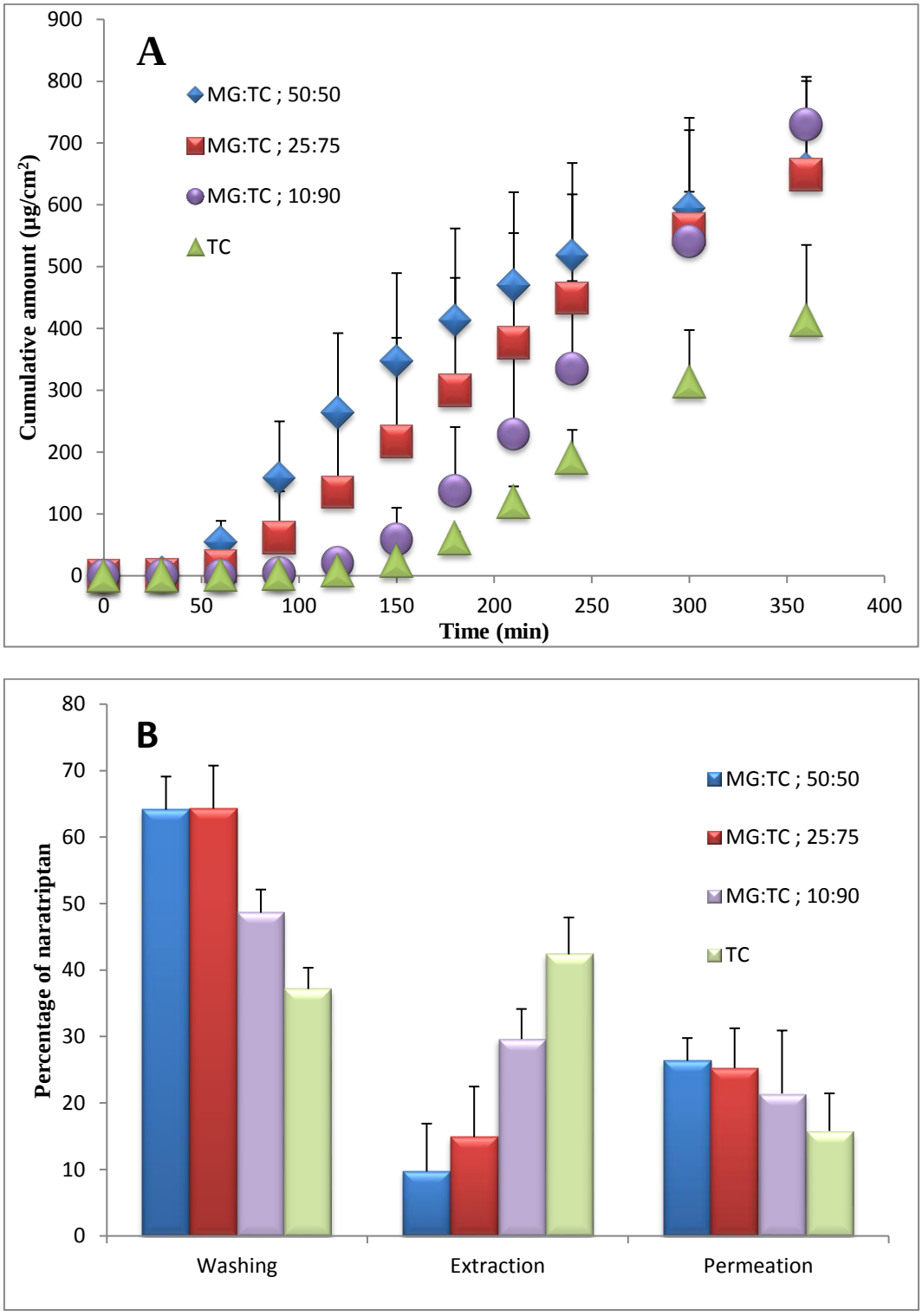


**Figure 2. (A) NAR permeation and (B) NAR mass balance data for binary systems of MG:TC in porcine buccal tissue (n ≥ 3, mean ± SD)**

Data for the first 4 h of the permeation profiles were used for comparative analysis of the different formulations as profiles started to plateau after this time point. Clearly, the presence of MG enhanced the rate and the extent of NAR permeation compared with neat TC. The cumulative amount of NAR permeated at 6 h for MG:TC (50:50, v/v) was almost double that for TC (ANOVA, $p<0.05$). Interestingly, the presence of MG did not affect the percentage of NAR extracted from the buccal tissue at the end of the permeation experiment. A comparison of the mass balance results indicated that the major determinant of the buccal tissue uptake of NAR appears to be the proportion of TC in the different formulations. Thus the synergistic enhancement obtained by inclusion of MG appears to reflect a different mechanism to that of TC, which promotes increased NAR uptake into the tissue. A fixed dose was used in all formulations, and thus it is possible that the enhancement observed for MG:TC systems compared with TC may reflect the higher thermodynamic activity of NAR in the former vehicle based on the solubility data reported previously (Sattar et al., 2015).

In order to investigate further the influence of MG:TC binary systems, analysis of the permeation and mass balance samples for TC content was conducted using GC (Figure 3). Permeation results are expressed as percentage values because different ratios of TC were employed in the formulations.

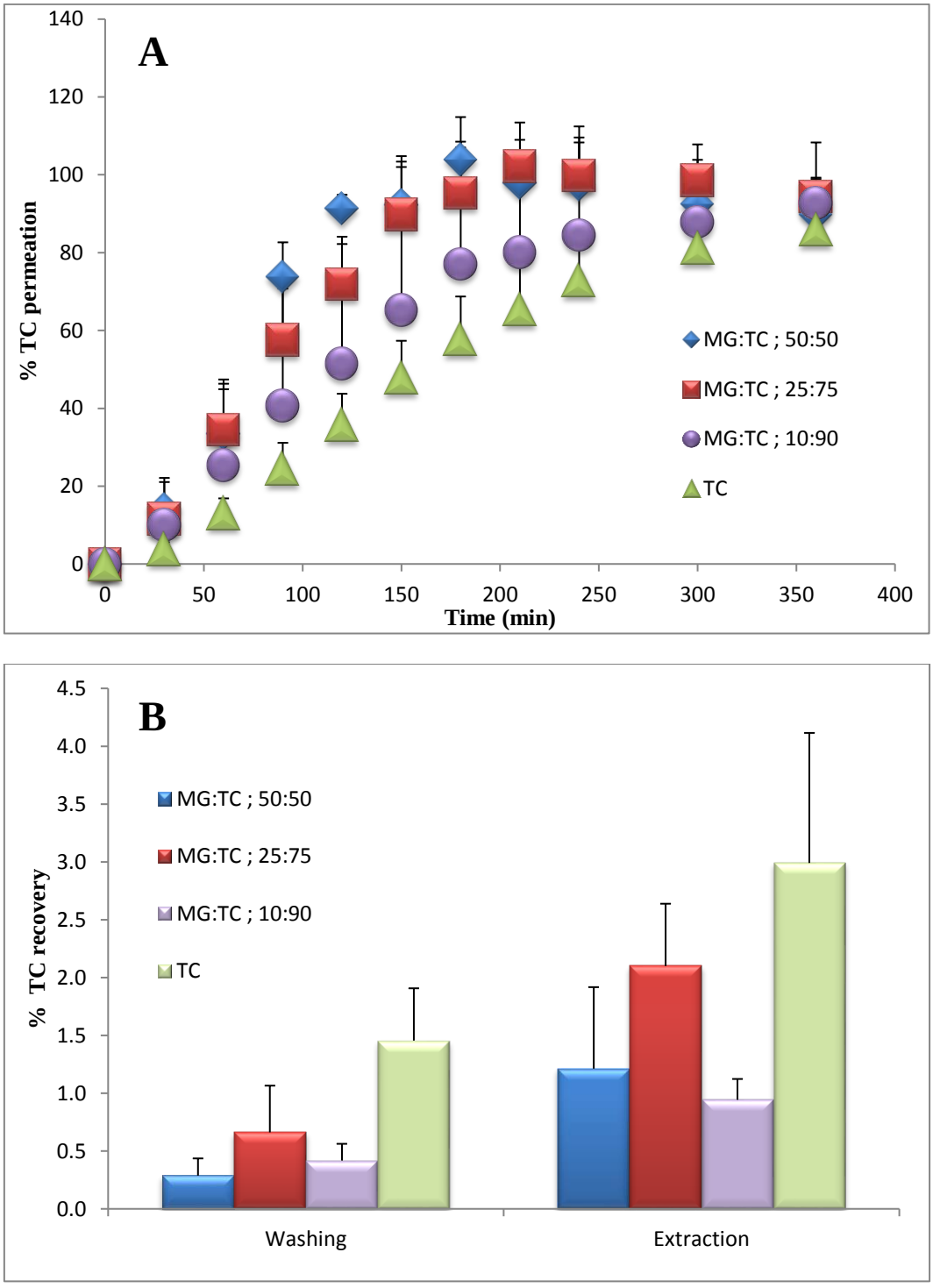


**Figure 3. TC (A) TC permeation and (B) TC mass balance data for binary systems of MG:TC in porcine buccal tissue (n ≥ 3, mean ± SD)**

Figure 3 shows that the presence of MG enhanced TC movement through the buccal mucosa. Approximately 90% of TC permeated within 2 h from MG:TC (50:50)

compared with only 35% from neat TC. The more rapid depletion of TC from the binary systems with high MG content may explain the plateau in the NAR permeation profiles observed in Figure 2. The impact of enhancer depletion on drug permeation in skin has previously been studied by Trottet et al. (2004) and Santos et al. (2010). These authors found that the drug permeation ceased once the enhancer had been exhausted from the vehicle. Since most of the TC permeated with a minimal amount (~3%) remaining on the surface, MG did not influence. the amount of TC inside the buccal membrane nor the residual amount on the surface

A comparison of TC and NAR permeation profiles (Figures 2, 3) strongly suggests that (i) TC permeation drives NAR movement through the buccal membrane, and (ii) MG may enhance NAR permeation in a synergistic manner increasing the rate of TC absorption. The higher thermodynamic activity of NAR in the binary mixture should promote enhanced drug permeation and simultaneously, the faster TC flux contributes further to the increase in NAR penetration.

## 4. Conclusions

The present study builds on our previous work which characterised NAR base and investigated its permeation in excised porcine buccal tissue. Initially, *in vitro* permeation of NAR was investigated in the same model from a range of simple solvents; the highest permeation was observed for TC which was the vehicle in which NAR was most soluble. For binary systems, the combination of DPG, PG or TC did not result in significant enhancement of NAR permeation. A range of TC:PBS systems were subsequently evaluated for NAR delivery, where the pH of PBS was 6.8. As TC content increased so did NAR permeation; higher amounts of NAR were also extracted from tissue for systems with high TC content. The combination of TC with MG did result in significantly

enhanced permeation of NAR compared with TC alone. The enhanced permeation of NAR was shown to be associated with greater uptake of TC into the tissue as well as a faster initial rate of permeation of TC into the membrane**.** The maximum cumulative amount of NAR (~730 μg/cm$^2$) which permeated at 6 h was for MG:TC (10:90, v/v) formulation. The mean plasma concentration and clearance values of NAR following oral administration are reported as 8 μg/L (ranging from 5.9-10.7 μg/L) and 6.6 mL/min/kg (Moffat, 2014). Assuming a 70 kg patient and calculating NAR input from the flux of 3.25 μg/min/cm$^2$, a plasma level of 7 μg/L of NAR is possible from an area of application of 1 cm$^2$. Therefore an application area of 1.1 cm$^2$ should theoretically result in a plasma concentration of 8 μg/L. To our knowledge this is the first investigation of MG as a vehicle for buccal delivery. It is also the first investigation of the fate of the excipient as well as the active in buccal delivery. These findings underline the importance of monitoring vehicle components in the development of optimal formulations for oral transmucosal delivery.

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**References**


Birudaraj, R., Berner, B., Shen, S., Li, X. 2005. Buccal permeation of buspirone: mechanistic studies on transport pathways. J. Pharm. Sci. 94(1):70-8.

Brunton, L.L., Parker, K.L. 2008. 5-Hydroxytryptamine (Serotonin). *Goodman & Gilman's: Manual of Pharmacology and Therapeutics.* USA: McGraw-Hill Companies, 188-202.

Caon, T., Pan, Y., Simões, C.M., Nicolazzo, J.A. 2014. Exploiting the buccal mucosa as an alternative route for the delivery of donepezil hydrochloride. J. Pharm. Sci. 103(6):1643-51.

Ceschel, G.C., Maffei, P., Moretti, M.D., Demontis, S., Peana, A.T. 2000. In vitro permeation through porcine buccal mucosa of Salvia desoleana Atzei & Picci essential oil from topical formulations. Int. J. Pharm. 195**,** 171-7.

Davidoff, R.A. 2002. Migraine. manifestations, pathogenesis and management. 2002 2nd Edition. Oxford: Oxford University Press. 375 pages. .

Dowson, A., Bundy, M., Salt, R., Kilminster, S. 2007. Patient preference for triptan formulations: a prospective study with zolmitriptan. Headache, 47**,** 1144-51.

Francoeur, M.L., Golden, G.M., Potts, R.O. 1990. Oleic acid: its effects on stratum corneum in relation to (trans)dermal drug delivery. Pharm Res. 7(6):621-7.

Ganem-Quintanar, A., Quintanar-Guerrero, D., Falson-Rieg, F., Buri, P. 1998. Ex vivo oral mucosal permeation of lidocaine hydrochloride with sucrose fatty acid esters as absorption enhancers. Int. J. Pharm. 173**,** 203-210.

ICH 2005. International conference on harmonization, Validation of analytical procedures: text and methodology Q2(R1) USA: ICH Harmonised Tripartite Guideline. 1-13.

Joint Formulary Committee. British National Formulary. 68th edition. Ed. London: BMJ Group and Pharmaceutical Press.

Lane, M.E. 2013. Skin penetration enhancers. Int. J. Pharm. 447(1-2):12-21.

Le Bars, G., Dion, S., Gauthier, B., Mhedhbi, S., Pohlmeyer-Esch, G., Comby, P., Vivan, N., Ruty, B. 2015. Oral toxicity of Miglyol 812(®) in the Göttingen(®) minipig. Regul. Toxicol. Pharmacol. 73(3):930-7.

Loder, E. 2010. Triptan therapy in migraine. N. Engl. J. Med. 363:63-70

Manganaro, A.M., Wertz, P.W. 1996. The effects of permeabilizers on the in vitro penetration of propranolol through porcine buccal epithelium. Mil. Med. 161**,** 669-72.

Natoli, J.L., Manack, A., Dean, B., Butler, Q., Turkel, C.C., Stovner, L., Lipton, R.B. 2010. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 30(5):599-609.

Newman, M.G., Takei, H.H., Klokkevold, P.R., Carranza, F.A. Eds. Carranza's Clinical Periodontology. 2014. Elsevier Health Sciences. Pp. 904.

Oliveira, G., Hadgraft, J. and Lane, M.E., 2012. The influence of volatile solvents on transport across model membranes and human skin. Int. J. Pharm. 435(1)**:**38-49.

Pouton, C.W., Porter, C.J. 2008. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Adv. Drug. Deliv. Rev. 60**,** 625-37.

Puglia, C., Bonina, F. 2008. Effect of polyunsaturated fatty acids and some conventional penetration enhancers on transdermal delivery of atenolol. Drug Deliv. 15**,** 107-1

Santos, P., Watkinson, A.C., Hadgraft, J., Lane, M.E. 2010. Oxybutynin permeation in skin: the influence of drug and solvent activity. Int. J. Pharm. 384(1-2):67-72.

Sattar, M., Sayed, O.M., Lane, M.E. 2014. Oral transmucosal drug delivery--current status and future prospects. Int J Pharm. 471(1-2):498-506.

Sattar, M., Hadgraft, J., Lane, M.E. 2015. Preparation, characterization and buccal permeation of naratriptan. Int. J. Pharm. 493(1-2):146-51.

Sahle, F.F., Metz, H., Wohlrab, J., Neubert, R.H. 2013. Lecithin-based microemulsions for targeted delivery of ceramide AP into the stratum corneum: formulation, characterizations, and in vitro release and penetration studies. Pharm. Res. 30(2):538-51.

Smitherman, T.A., Burch, R., Sheikh, H., Loder, E. 2013. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 53**,** 427-36.

Strickley, R.G. 2004. Solubilizing excipients in oral and injectable formulations. Pharm. Res. 21**,** 201-30.

Trottet, L., Merly, C., Mirza, M., Hadgraft, J., Davis, A. F. 2004. Effect of finite doses of propylene glycol on enhancement of in vitro percutaneous permeation of loperamide hydrochloride. Int. J. Pharm. 274**,** 213-9.

Watkinson, R.M., Guy, R.H., Oliveira, G., Hadgraft, J., Lane, M. E. 2010. Optimisation of cosolvent concentration for topical drug delivery III - Influence of lipophilic vehicles on ibuprofen permeation. Skin Pharmacol. Physiol. 24**,** 22-26.

Welch, K.M., Goadsby, P.J.2002. Chronic daily headache: nosology and pathophysiology. Curr. Opin. Neurol. 15(3):287-95.