DETERMINATION OF THE PERMEATION AND PENETRATION OF FLURBIPROFEN FROM A LOCALLY ACTING SORE THROAT LOZENGE AND SPRAY INTO HUMAN PHARYNX TISSUE USING A NOVEL *EX VIVO* MODEL AND A VALIDATED ANALYTICAL METHOD

TURNER R,[1] WEVRETT S,[1] EDMUNDS S,[1] BROWN MB,[1,2] ATKINSON R,[3*] SHEA T[4]

[1]MedPharm Ltd, Guildford, UK; [2]TDDT University of Hertfordshire, College Lane Campus, Hertfordshire, UK; [3]Medical Science, Reckitt Benckiser, Hull, UK; [4]Medical Science, Reckitt Benckiser, New Jersey, USA
[*]Presenting author

INTRODUCTION

- Inflammation occurring in the tissues of the pharynx, as a result of infectious or non-infectious causes,[1,2] leads to the pain and discomfort of sore throat commonly experienced by patients[3,4]
  - A survey in Europe and Asia found that each year 54% of people report experiencing sore throat,[5] which can last 3 to 7 days[6]
- Targeting the area of pain and inflammation within the throat tissues with an active pharmaceutical ingredient is an objective of sore throat treatment[7]
- Direct local delivery of an active ingredient with a throat spray would be expected to produce a higher concentration over a smaller focused area, compared with a lozenge which would achieve a lower concentration across a larger area
- Non-steroidal anti-inflammatory drugs (NSAIDs),[8,9] which are able to exert an analgesic and anti-inflammatory effect, have been shown to relieve the symptoms of sore throat when delivered locally[10–12]
- The aim of this study was to evaluate the permeation and penetration of flurbiprofen from locally delivered spray and lozenge formulations into human pharyngeal tissue

METHODS

STUDY DESIGN

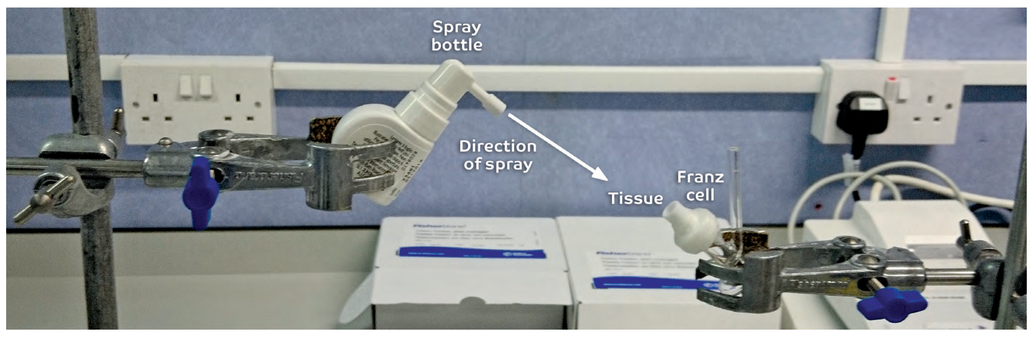
- The permeation and penetration of flurbiprofen (from flurbiprofen 8.75 mg spray and flurbiprofen 8.75 mg lozenge formulations) into human pharynx tissue was tested in a micro Franz cell model[13] and quantitated by a validated high-performance liquid chromatography (HPLC) method
  - Human pharynx tissue ethically sourced from cadavers was used for these experiments (Research Ethics Committee reference 220367)

FRANZ CELL MODEL

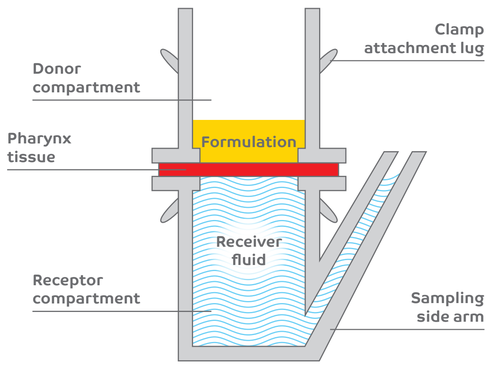
- Figure 1 shows the micro Franz cell used to mimic the physiological and anatomical conditions of the human pharynx tissue *in situ*
- Extraction (90:10 v/v ethanol:water) and receiver (phosphate-buffered saline [PBS]) fluids were selected and confirmed as compatible for the recovery of flurbiprofen
- Flurbiprofen equivalent to one dose of spray or lozenge was applied to the donor compartment
  - For the 8.75 mg spray formulation, three spray actuations (which is equivalent to one dose[14]) were used
  - For the 8.75 mg lozenge formulation, one lozenge was dissolved in 7.5 mL of receiver fluid, and a 15 µL aliquot of this solution was used. This dose was calculated to mimic *in vivo* conditions including the average size of human pharynx tissue and saliva production
  - This equated to doses of 187.73 (standard deviation [SD] ± 171.22) µg and 15.11 (SD ± 0.09) µg flurbiprofen applied to the pharynx tissue from the spray and lozenge formulations, respectively, as confirmed by HPLC
- Samples of receiver fluid were removed at 10-minute intervals from 0 to 60 minutes
- Flurbiprofen in both the receiver fluid and extraction solution were tested using the validated HPLC analytical method
  - Where recovered levels of flurbiprofen were consistently below the limit of quantitation (BLOQ) in the receiver fluid, the samples were concentrated approximately 10-fold (by pooling, evaporation and reconstitution in a smaller volume)

Figure 1: The dosing apparatus (A), schematic representation of a Franz cell (B) and the pharynx tissue recovered from the Franz cell following the permeation and penetration experiment (C)

(A)



(B)

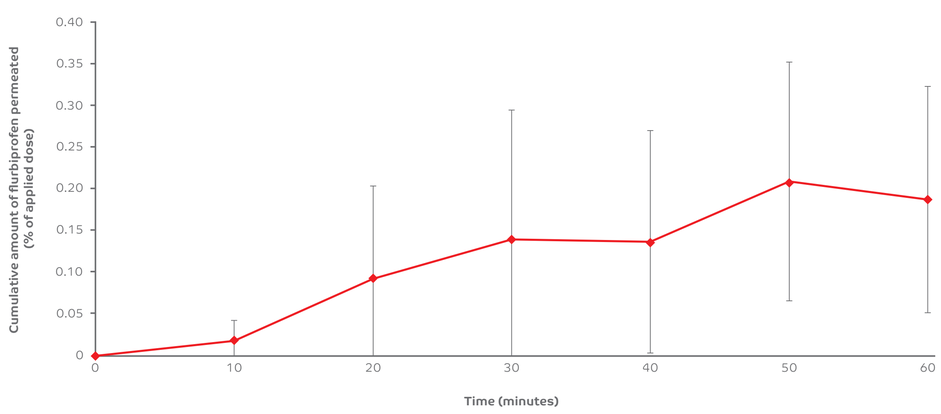


(C)

RESULTS

- The results are presented in Table 1 (permeation and penetration data), and Figures 2 and 3 (cumulative amount of flurbiprofen [% of applied dose] permeated through the pharynx tissue and total amount of flurbiprofen recovered from the human pharynx tissue and receiver fluid, respectively)
- Following spray application, flurbiprofen was present in receiver fluid from 20 minutes, although its presence was detected (BLOQ) from 10 minutes onwards. The total amount of flurbiprofen present in the receiver fluid at 60 minutes was 0.35 (± 0.25) µg
- Following lozenge application, flurbiprofen was consistently at levels BLOQ in receiver fluid (due to the dilution effect of mimicking *in vivo* conditions). After concentration, flurbiprofen was detected from 10 minutes onwards and was above the limit of quantitation in the receiver fluid from 40 minutes, confirming the flurbiprofen did penetrate through the pharynx tissue
- The flurbiprofen recovered from the surface of the pharynx tissue was 45.91 µg for spray (24.45% of applied dose) and 1.28 µg for lozenge (8.48% of applied dose)
- The amount of flurbiprofen recovered from within the pharynx tissue was 87.30 µg for spray (46.50% of applied dose) and 8.26 µg for lozenge (54.65% of applied dose)
- Significantly more flurbiprofen from the lozenge was recovered from within the pharynx tissue compared with the surface of the tissue ($p<0.05$)
- Less of the applied flurbiprofen remained on the surface of the tissue when administered via lozenge compared with spray (8.48% vs 24.45%, respectively)

Figure 2: Cumulative amount of flurbiprofen (% of applied dose) permeated through human pharynx tissue and recovered from receiver fluid over time for flurbiprofen 8.75 mg spray



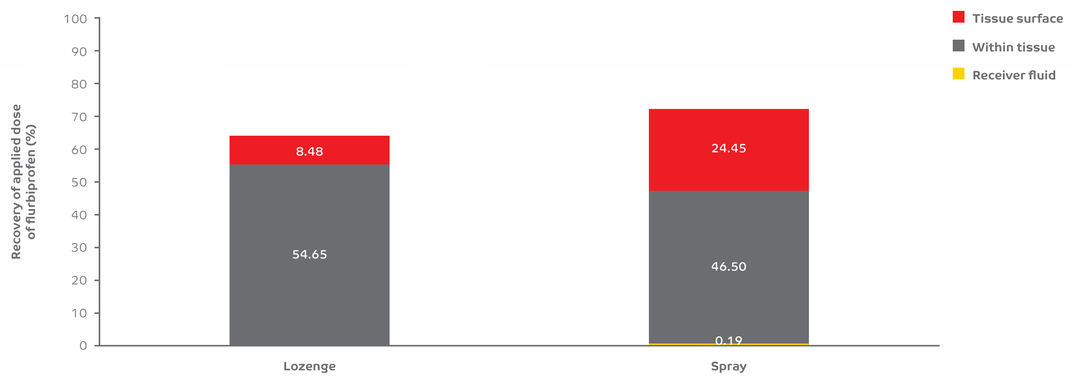
Values for flurbiprofen in the receiver fluid for the lozenge formulation were below the level of quantitation and the data are therefore not shown

Table 1: Permeation and penetration results (n≥3), mean (standard deviation)

	Formulation	
	Lozenge	Spray
Amount of flurbiprofen applied (µg)	15.11 (0.09)	187.73 (171.22)
Flurbiprofen recovered from the surface of the pharynx tissue		
Amount (µg)	1.28 (0.40)	45.91 (56.96)
Proportion of applied dose (%)	8.48 (2.66)	24.45 (30.34)
Flurbiprofen recovered from within the pharynx tissue		
Amount (µg)	8.26 (0.81)	87.30 (58.65)
Proportion of applied dose (%)	54.65 (5.35)	46.50 (31.24)
Flurbiprofen present in the receiver fluid		
Amount (µg)	BLOQ	0.35 (0.25)
Proportion of applied dose (%)	N/A	0.19 (0.14)

BLOQ, below the level of quantitation (<0.045 µg/mL); N/A, not applicable

Figure 3: Total amount of flurbiprofen recovered from the human pharynx tissue and receiver fluid (% of applied dose) for flurbiprofen 8.75 mg spray and lozenge formulations

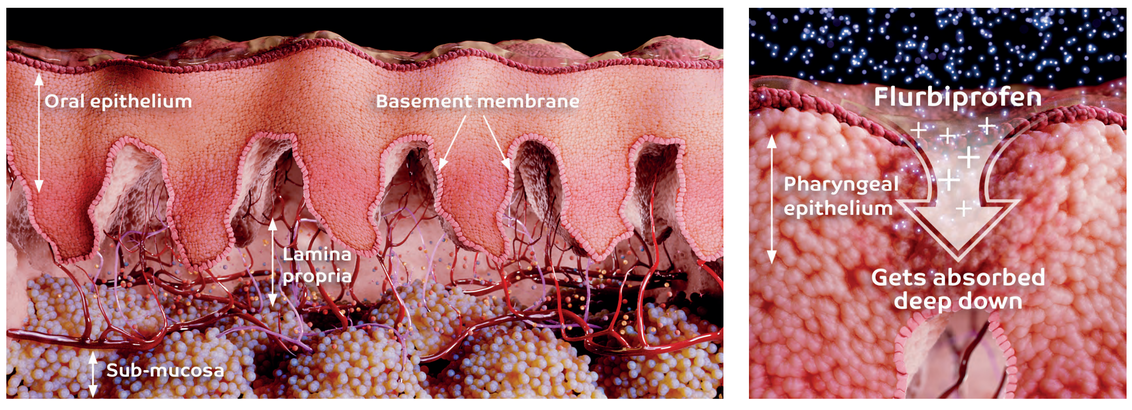


Values for flurbiprofen in the receiver fluid for the lozenge formulation (% of applied dose) were below the level of quantitation
Full mass balance was not performed, therefore the residual flurbiprofen present on the Franz cell apparatus was not quantified

DISCUSSION

- The results show that the 8.75 mg spray and lozenge formulations deliver flurbiprofen to the human pharynx tissue and that the method of application/format and formulation is likely to affect the rate of permeation and penetration
- The proportions of the applied dose of flurbiprofen recovered from within the pharynx tissue were similar for both the spray and lozenge formulations (46.50% and 54.65%, respectively), demonstrating that both formulations effectively penetrate into pharynx tissue, specific to the formulation tested
- Whilst significantly more flurbiprofen from the lozenge was recovered from within the pharynx tissue compared with the surface of the tissue, this was not the case for spray
  - The numerically higher recovery of flurbiprofen from the surface of the pharynx tissue after application of the spray may be due to the larger amount of flurbiprofen applied to the same surface area of tissue from the spray formulation compared with the lozenge
- The low recovery of flurbiprofen from the lozenge formulation in receiver fluid was likely a consequence of the efforts to replicate the *in vivo* scenario (a dilution effect)
- A treatment that relieves the pain and discomfort of sore throat, and which can be applied locally to provide delivery of the active ingredient deep into the throat tissue, could provide multiple benefits including a lower dose than systemic drugs, thus reducing the potential for adverse effects[15]
- The lozenge formulation allows prolonged delivery of flurbiprofen to the throat whilst it dissolves,[16] whereas the spray formulation delivers a highly targeted dose of flurbiprofen directly to the throat,[17] providing relief of sore throat pain and discomfort for up to 4 to 6 hours[11,12,18]

Figure 4. Flurbiprofen from 8.75 mg spray and lozenge formulations penetrates into human pharynx tissue



CONCLUSION

- The results show that flurbiprofen from 8.75 mg spray and lozenge formulations penetrates into human pharynx tissue (Figure 4). These data help to confirm that flurbiprofen can reach the site of pharyngeal inflammation in the deeper layers of the tissue after local application

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CONFLICTS OF INTEREST

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