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Dissolution of theophylline from extended-release tablets under cyclic retrograde peristaltic contractions in the Dynamic Colon Model

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SUMMARY

The dynamic colon model is a biorelevant in vitro model of the human proximal colon. In vivo, the large intestine mixes its contents using peristaltic waves that propagate both forwards (antegrade) and backwards (retrograde). This work studies the dissolution profile of theophylline from Uniphyllin Continus 200 mg prolonged release tablets and the distribution of dissolved theophylline in viscosity-enhanced media under the influence of a cyclic retrograde peristaltic contraction. At 16- and 24-hours, 80.73 ± 3.28 and 95.4 ± 4.73 % theophylline dissolved from the tablet and the fluid inside the mimic intestinal system approached homogeneity.

INTRODUCTION

The dynamic colon model (DCM) is a model of the human proximal colon that replicates segmental peristaltic motility (1). The DCM can be used for dissolution studies of colon-targeted formulations (2).

The DCM can be programmed to mimic different intestinal motility patterns observed in vivo. This permits in vitro analysis of different motility parameters such as occlusion degree and rate, isolated single contractions versus wave contractions and direction of propagation. The release rate and distribution of drug along the DCM lumen may depend on the pattern applied.

Previous experiments inside the DCM have used an antegrade (caecum to hepatic flexure) propagating contraction that travelled the length of the DCM (10 segments over a total length of 22 cm) (2,3). In vivo however, peristaltic contractions have also been observed to propagate in the retrograde direction (hepatic flexure to caecum).

This work reports the dissolution of theophylline from a prolonged-release formulation under the influence of a retrograde propagating contraction. The aim is to understand how effective this motility pattern is at releasing drug from an extended-release formulation and at distributing dissolved drug throughout the intestinal model.

MATERIALS AND METHODS

Sodium carboxymethyl cellulose (NaCMC) 700,000 MW and potassium phosphate mono- (KH_2PO_4) and dibasic (K_2HPO_4) were purchased from Merck. Uniphyllin Continus 200 mg prolonged release theophylline tablets were purchased from New Castle Healthcare NHS pharmacy.

The tablet was directly inserted into the ileocecal port of the DCM, pre-filled with 100 mL 0.25 % (w/w) NaCMC solutions adjusted to pH 7.4 using phosphate buffer. A retrograde propagating peristaltic contraction was applied to the DCM, with an occlusion rate of. 30.4 mm s^{-1}, occlusion degree of 40 % and a

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frequency of 120 s. The temperature of the fluid inside the lumen was maintained at 37 ± 0.3 °C.

Samples were taken at 5 different locations along the length of the DCM model and drug concentration was measured using UV-Visible spectrophotometry at 270 nm.

RESULTS AND DISCUSSION

Figure 1 presents the concentration of theophylline measured at segment 1 (S1) (close to the 'caecum', the point of tablet insertion) and segment 10 (adjacent to the 'hepatic flexure' at the opposite end of the tube). Initially, the concentration of theophylline increased in both S1 and S10, although at a higher rate, r, in S1. This is likely because S1 was the insertion point of the tablet so dissolved drug accumulated locally at a higher rate than it can be distributed along the length of the DCM lumen by the retrograde peristaltic waves. After 10 hours, $r_{S1} = r_{S10} = 0.09\, mg\, mL^{-1} hr^{-1}$ and from this point $r_{S1} \to 0$ as the measured concentration plateaued, with the final concentration measurements being 2.33 ± 0.20 and $2.05 \pm 0.25\, mg\, mL^{-1}$ respectively in S1 and S10. The similarity in the concentration at S1 and S10 suggests a homogenous system (the theoretical homogeneous concentration would be 2 mg mL^{-1} based on a 200mg tablet in a volume of 100 mL).

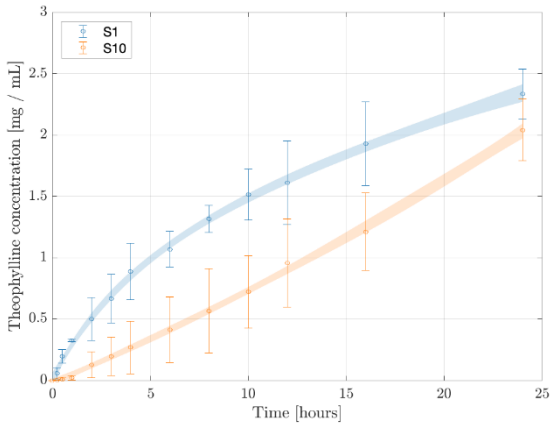

Fig. 1. *Measured theophylline concentration over 24 hours at S1 and S10.*

Figure 2 displays the dissolution profile of theophylline from Uniphyllin 200 mg tablets over 24 hours. Overall, 80.73 ± 3.28 % of theophylline was released after 16 hours and 95.4 ± 4.73 % after 24 hours.

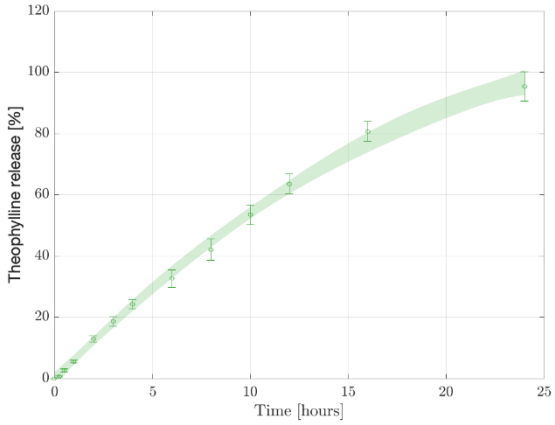

Fig. 2. *Dissolution profile of Uniphyllin 200 mg tablets in the DCM partially filled with 100 mL 0.25 % NaCMC solution buffered to pH 7.4.*

CONCLUSIONS

Over 24 hours, complete release of theophyllin from an extended-release dosage form was achieved in the DCM. Initially, dissolved drug accumulated locally to the point of administration. Over time, the contents were well mixed by cyclic retrograde peristaltic contractions.

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