The Influence of Sodium Carboxymethyl Cellulose on Drug Release from Polyethylene Oxide Extended Release Matrices

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Abstract Summary

The aim of this study was to investigate the effect of sodium carboxymethyl cellulose (NaCMC) on the release of three model drugs from polyethylene oxide (PEO) extended release (ER) matrices.

Introduction

Hydrophilic matrices represent the most common approach used for oral ER drug delivery.[1]

Polyethylene oxide (POLYOX™) and sodium carboxymethyl cellulose are popular matrix forming polymers, with wide regulatory acceptance, availability in a range of viscosity grades and with good swelling and erosion characteristics, which can be used to modulate the release of various drugs.[1-4]

Due to the stringent regulatory requirements for the introduction of new excipients, recent efforts in industry have been directed towards investigation of blends of pharmaceutically approved polymers in development of drug delivery dosage forms.[5, 6] Polymer blends were reported to be used for prevention of burst release, to increase the resistance to agitation (food effect) and to lower microenvironmental pH within the matrix, which may be beneficial for improving solubility or stability of some APIs.[7]

In this study, the influence of NaCMC on the release of three model drugs with different ionic nature and aqueous solubility from POLYOX™ ER matrices was investigated.

Experimental Methods

Model formulations containing 49.75% w/w drug; 49.75% w/w matrix former and 0.5% w/w of magnesium stearate (Peter Greven, Germany) were prepared. PEO (POLYOX™ WSR 1105 or Coagulant, both from International Flavors and Fragrances Inc., USA) or NaCMC (CELLOGEN® HP-SH, 150,000 Da, Dai-Ichi Kogyo Seiyaku, Japan), or their 1:1 mixture were used as a matrix former.
The following drugs were used in the study:

- ibuprofen (IMCD, UK), practically water-insoluble (0.06 mg/mL)[8];
- theophylline (Sigma-Aldrich, UK), slightly water-soluble (8.6 mg/mL)[9] and
- propranolol HCl (S.I.M.S., Italy), freely water-soluble (360 mg/mL)[10].

All ingredients, with the exception of magnesium stearate, were blended in a 1 L mixer (T2C, Turbula, Willi A. Bachofen, Switzerland) at 64 rpm for three minutes. The lubricant was then added and blended for an additional one minute. Round, flat-faced 10 mm diameter tablets with a target weight of 320 mg were produced on a semi-automated tablet hand press (T8, Specac, UK) at 20 kN compression force.

The choice of polymer viscosity grade was based aqueous solubility of API. Lower molecular weight (MW) PEO (POLYOX™ WSR 1105; 900,000 Da) was used in the ibuprofen and theophylline formulations and high MW PEO (POLYOX™ WSR Coagulant; 5,000,000 Da) in the propranolol HCl formulations.

The physical parameters of the tablets such as weight, diameter, thickness and mechanical strength were measured.

In vitro drug release (n=3) was obtained in a USP compliant dissolution bath (AT7 Smart, Sotax, Switzerland) using Apparatus II (paddles) with 15 x 31 mm sinkers (Sotax); operated at 100 rpm in 900 mL medium at 37.0 ± 0.5°C. Theophylline and propranolol HCl tablets were tested in water. Sink conditions for ibuprofen were only achieved in pH 7.2 phosphate buffer. Absorbance was measured using a UV-Vis spectrophotometer (Lambda 25, PerkinElmer, US) at

222, 272 and 319 nm for ibuprofen, theophylline and propranolol HCl, respectively. The resulting profiles were compared using the f_2 factor. An f_2 value between 50 and 100 indicated that the two dissolution profiles were similar.[11, 12]

Results and Discussion

Robust matrix tablets with the breaking force values of 10-14 kp (1.8–2.7 MPa) were produced for all formulations studied here.

Figures 1-3 show the influence of NaCMC on ibuprofen, theophylline and propranolol HCl release from PEO ER matrices, respectively. For ibuprofen, drug release was not dependent on the choice of the polymer (**Figure 1**), which may be due to high pH of the dissolution medium. A relatively fast theophylline release (100% in 4 hours) was obtained from matrices containing NaCMC (**Figure 2**).

The rapid drug dissolution and relatively fast erosion of those matrices may be explained by the high aqueous solubility and hydrophilic nature of NaCMC due to the presence of ionized carboxylic acid groups within the polymer structure.[13, 14] The slowest theophylline release was recorded from PEO tablets. A combination of PEO and NaCMC resulted in theophylline dissolution profile similar to the one obtained from the matrices based on NaCMC.

Figure 3 shows that the slowest propranolol HCl release was produced when both PEO and NaCMC were used in the formulation. As a result, 100% of the drug dissolution occurred after 22 hours. This indicates a potential synergistic interaction (chemical and/or physical) between polymer to polymer and/or drug to polymer, the mechanism of which is currently under investigation. For example, one explanation may be that NaCMC reacts with the drug to form NaCl and propranolol $H^+(CMC^-)$, i.e. the drug forms a new salt form with the polymer that may then retard drug release. Similar results were previously reported for NaCMC and HPMC combinations.[10, 13, 14] The authors claimed an ionic interaction (i.e. hydrogen bonding) between the amine group of propranolol HCl and carboxyl group of NaCMC resulting in a formation of a propranolol-NaCMC reversible complex leading to a retardation of the drug releaserate.

Figure 1. Effect of NaCMC on Ibuprofen Release from PEO ER Matrices (in pH 7.2 phosphate buffer)

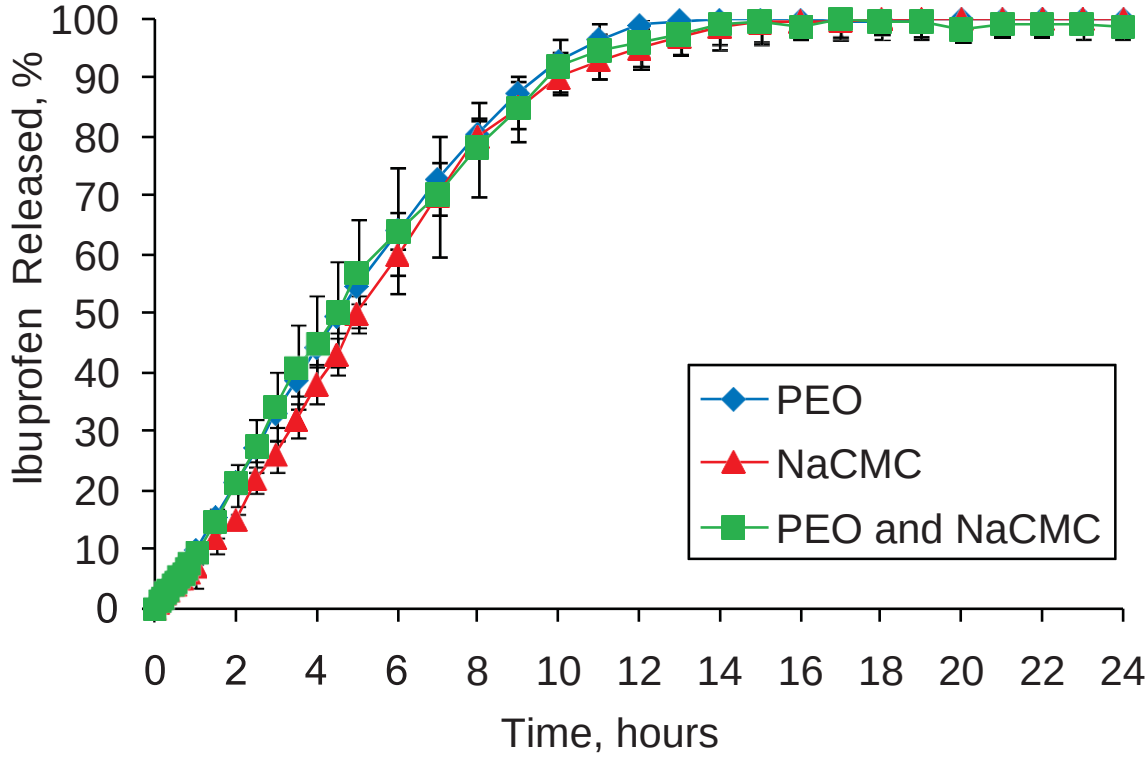


Figure 2. Effect of NaCMC on Theophylline Release from PEO ER Matrices (in water)

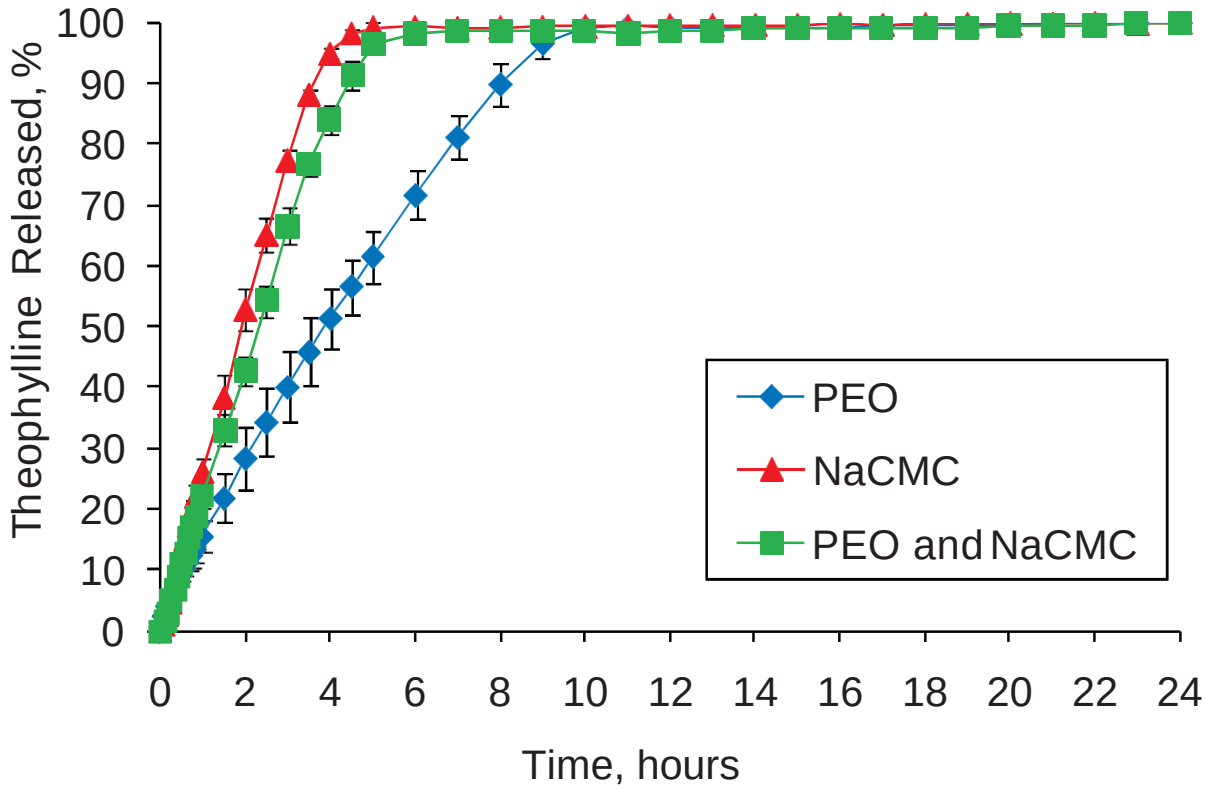
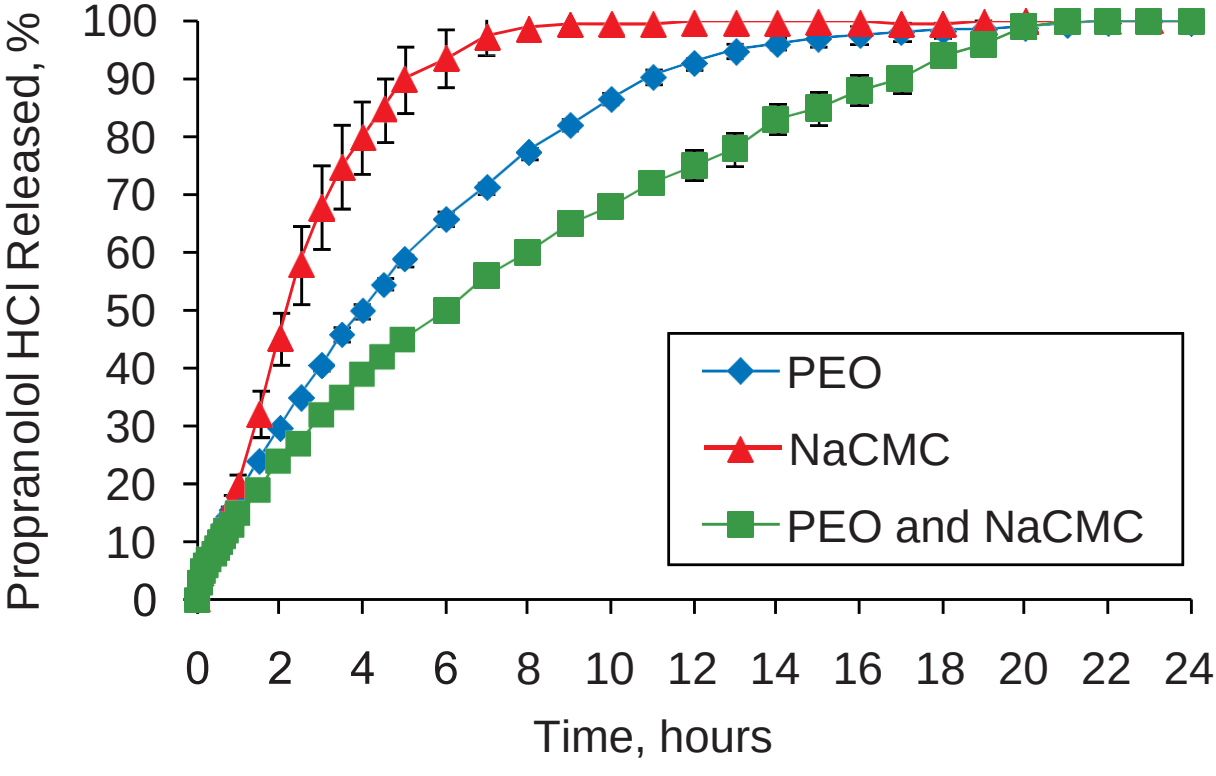


Figure 3. Effect of NaCMC on Propranolol HCl Release from PEO ER Matrices (in water)



Conclusions

Robust POLYOX™ ER matrices were produced for all the formulations. For ibuprofen and theophylline, no unusual or unexpected release profiles were obtained from matrices containing a mixture of the two polymers. However, for propranolol HCl, a combination of PEO with NaCMC produced a significantly slower drug dissolution compared to the matrices where single polymers were used. Based on the results of this study, the observed phenomenon has been related to the ionic nature of the APIs, where possible drug to polymer and/or polymer to polymer interaction has been postulated.

This potential synergistic interaction can be used to design new oral ER pharmaceutical dosage forms with more prolonged release using lower polymer amounts, which could be particularly beneficial for freely or very water-soluble drugs, where accommodation of high doses is required and once daily administration is preferred.

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