

The Influence of Sodium Carboxymethylcellulose on Drug Release from Polyethylene Oxide and Hypromellose Extended Release Matrices

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Poster Reprint
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Purpose

Hydrophilic matrices represent a popular approach for oral extended release (ER) drug delivery.¹ The most commonly used ER polymers are cellulose derivatives, i.e. high viscosity grades of hypromellose [hydroxypropyl methylcellulose (HPMC)]. More recently, polyethylene oxide (PEO) has been explored as an alternative matrix former due to its wide regulatory acceptance, availability in a range of viscosity grades and good swelling and erosion characteristics, which can be used to modulate the release of various drugs.²⁻⁸

Production of ER profiles for freely water-soluble active substances is often a challenge due to a potential burst release during the first few hours of dissolution. In such a case, a combination of hydrophilic polymers with ionic ones can provide a significantly slower drug release compared to formulations where single polymers are used.^{1, 7-10}

The aim of this study was to investigate the influence of ionic polymer sodium carboxymethylcellulose (NaCMC) on the release of a freely water-soluble (572 mg/mL¹¹) model drug, venlafaxine hydrochloride, from ER formulations containing non-ionic polymers, PEO or HPMC, as matrix formers. The performance of PEO and HPMC was compared. Additionally, the effect of polymer concentration (30 or 50% w/w) on drug release was studied.

Methods

Materials	Concentration (% w/w)	
Venlafaxine HCl (Cadila, India)	49.50	49.50
PEO (POLYOX™ WSR Coagulant, IFF, USA), or HPMC (METHOCEL™ K100M CR, IFF, USA), or 1:1 mix with NaCMC (WALOCCEL™ CRT 60000 PPA 07, IFF, USA)	30.00	50.00
MCC (Microcel 102, Blanver, Brazil)	20.00	-
Fumed silica (Aerosil 200, Evonik, Germany)	0.25	0.25
Magnesium stearate (Peter Greven Ltd, Holland)	0.25	0.25

All ingredients, except magnesium stearate, were blended in a 1 L mixer (T2C, Turbula, Willi A. Bachofen) at 64 rpm for three minutes. Magnesium stearate (lubricant) was then added and blended for an additional minute. Tablets were manufactured by direct compression, with a target weight of 320 mg on a semi-automated hydraulic hand press (T8, Atlas, Specac), using round 10 mm diameter tooling; at 20 kN (255 MPa) compression force (compaction pressure).

The physical parameters of the tablets such as weight, diameter, thickness and mechanical strength were measured. In vitro drug release was obtained in a USP compliant dissolution bath (AT7 Smart, Sotax, Switzerland) using Apparatus II (paddles) with (15 x 31 mm) sinkers (Sotax) at 100 rpm. Dissolution media was purified water (900 mL) at $37.0 \pm 0.5^\circ\text{C}$. Absorbance was measured by a UV/Vis spectrophotometer (Lambda 25, PerkinElmer, USA) at 274 nm wavelength in 10 mm quartz cells. The produced profiles were compared using the f_2 factor. An f_2 value between 50 and 100 indicates that the two dissolution profiles are similar.^{12, 13}

Results

Robust matrix tablets with the breaking force values of 8-15 kp (2.3–4.4 MPa) were produced for all formulations studied here.

Reproducible extended drug release profiles were obtained for all studied formulations (**Figures 1, 2**). A combination of PEO or HPMC with NaCMC produced significantly slower venlafaxine HCl dissolution compared to the matrices where single polymers were used. This could be due to an interaction between the amine group of the drug and carboxyl group of NaCMC, resulting in the formation of a reversible drug-polymer complex with lower solubility in water. Similar results were previously reported for PEO or HPMC combinations with NaCMC when using propranolol HCl.⁷⁻¹⁰

For NaCMC only formulations, venlafaxine HCl release rate decreased when the concentration of the polymer was increased from 30% to 50%. **Figure 3** shows no effect of polymer concentration on drug release was found for formulations when either PEO or HPMC was included, without NaCMC. A significant influence of polymer concentration on venlafaxine HCl dissolution rate was found for matrices made of NaCMC combinations with either PEO or HPMC (**Figure 4**). This could be due to an increase in the amount of NaCMC (i.e. from 15% to 25% w/w) in the formulations and as a result, higher percentage of a bound drug, and possible formation of a stronger drug-polymer complex.⁷⁻¹⁰

Figure 1. Effect of NaCMC on Venlafaxine HCl Release from PEO ER Matrices

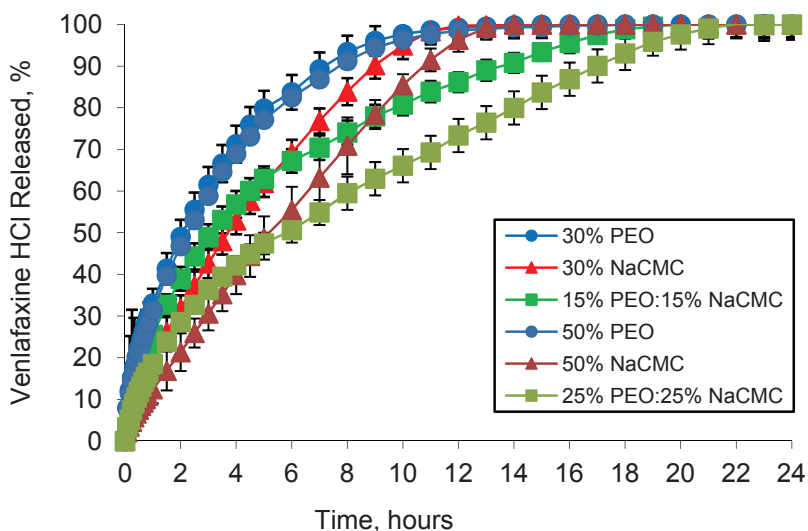


Figure 2. Effect of NaCMC on Venlafaxine HCl Release from HPMC ER Matrices

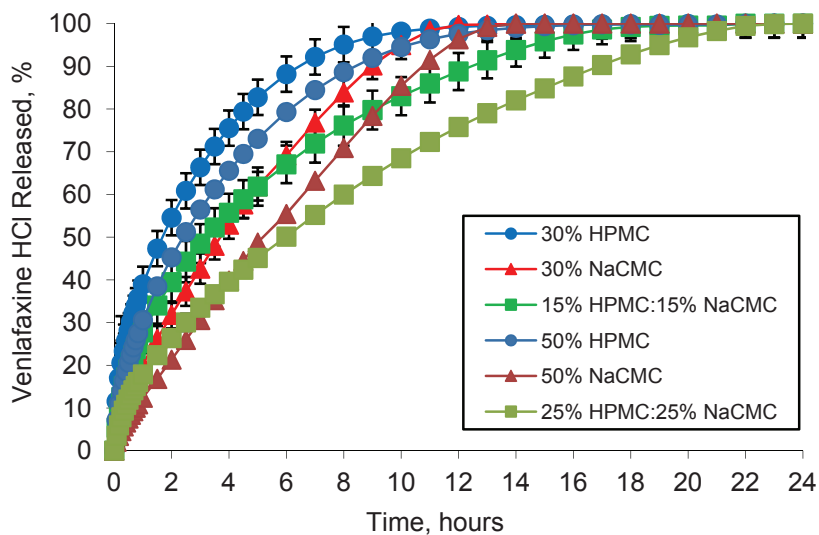


Figure 3. Venlafaxine HCl Release from PEO and HPMC Matrices

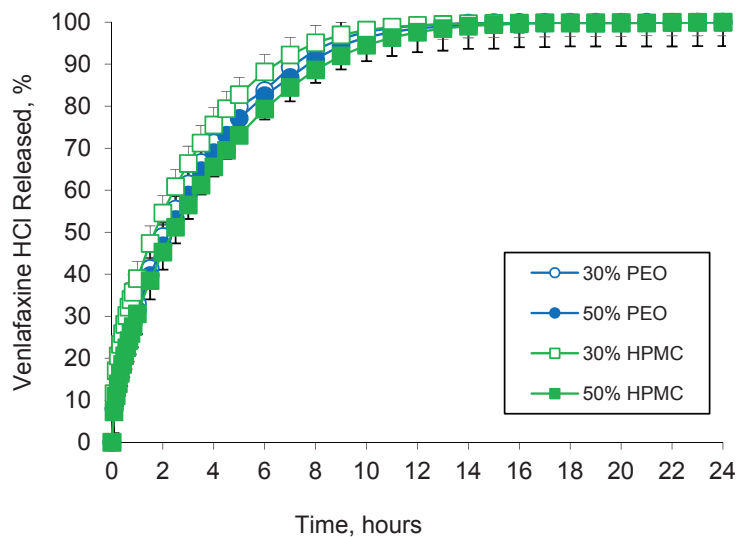
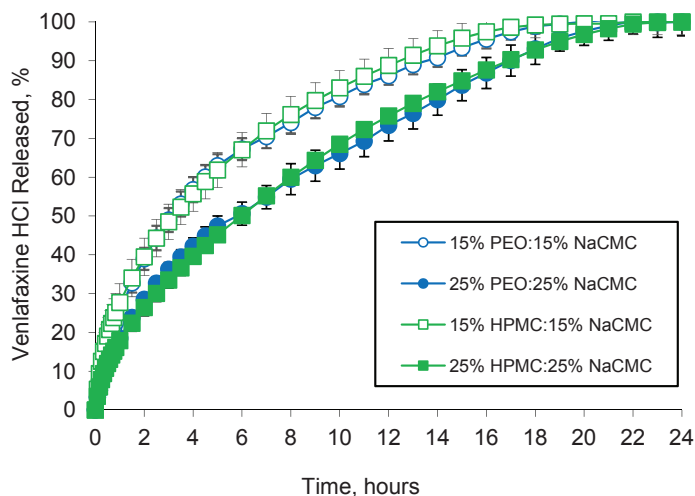


Figure 4. Venlafaxine HCl Release from PEO:NaCMC and HPMC:NaCMC Matrices



Conclusions

A combination of PEO and/or HPMC with NaCMC, produced significantly slower drug release compared to the matrices where single polymers were used. The mechanism of a potential drug-polymer and/or polymer-polymer interaction is currently under investigation and will be the subject of a future publication.

Performance of PEO and HPMC, either alone or in combination with NaCMC was similar, resulting in almost identical drug release profiles.

For NaCMC only formulations, an increase in the polymer concentration from 30% to 50% w/w, resulted in decrease in venlafaxine HCl release. For tablets where single PEO or HPMC polymers were used, an increase in the matrix former level had no effect on venlafaxine HCl release. However, for matrices made of NaCMC combinations with either PEO or HPMC, a significant influence of polymer concentration on drug dissolution rate was recorded.

A combination of a hydrophilic nonionic and an ionic polymer can be used to design new oral ER pharmaceutical dosage forms with more prolonged drug release at lower polymer levels, which could be beneficial for freely or very water-soluble APIs, particularly where accommodation of high doses is required and once daily administration is preferred.

References

- Tiwari S.B., Rajabi-Siahboomi A.R., *Pharm. Tech. Eur.*, 2008.
- Tiwari S.B., Rajabi-Siahboomi A.R., in *Methods in Molecular Biology*, Kewal K.J. (Ed.), Humana Press, Totowa, NJ, 2008; 437: 217-243.
- Palmer D., Levina M., Farrell T., Rajabi-Siahboomi A.R., *AAPS*, Los Angeles, CA, USA, 2009.
- Li H., Hardy R.J., Gu X., *AAPS PharmSciTech*. 2008; 9: 437-443.
- Choi S.U., Lee J., Choi Y.W., *Drug. Dev. Ind. Pharm.* 2003; 29: 1045-1052.
- Conti S., Maggi L., Segale L., Ochoa Machiste E., Conte U., Grenier P., Vergnault G., *Int. J. Pharm.* 2007; 333: 136-142.
- Palmer D., Levina M., Nokhodchi A., Douroumis D., Farrell T., Rajabi-Siahboomi A.R., *AAPS PharmSciTech*. Published on line: 28 June 2011.
- Palmer D., Levina M., Nokhodchi A., Farrell T., Rajabi-Siahboomi A.R., 38th Annual Meeting & Exposition of the CRS, Maryland, USA, 2011.
- Takka S., Rajbhandari S., Sakr A., *Eur. J. Pharm. Biopharm.* 2001; 52: 75-82.
- Dabbagh M.A., Ford J.L., Rubinstein M.H., Hogan J.E., Rajabi-Siahboomi A.R., *Pharm. Dev. Technol.* 1999; 4: 313-324.
- Moffat A.C., Osselton M.D., Widdop B. *Clarke's Analysis of Drugs and Poisons*, Volume 2, Pharm. Press, London, 2004; 1694-1695.
- Moore J.W., Flanner H.H., *Pharm. Tech.* 1996; 20: 64-74.
- FDA, Federal Register. 1995; 60: 61642.

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