The Influence of Polymer Concentration on Release of Poorly Soluble Drugs from Polyethylene Oxide Extended Release Matrices

Dasha Palmer, Marina Levina, Thomas P. Farrell and Ali Rajabi-Siahboomi

Colorcon Inc., Global Headquarters, 275 Ruth Road, Harleysville, PA 19438 USA; www.colorcon.com/about/contact

Purpose

Hydrophilic matrices are popular and widely used formulation options for oral extended release (ER) drug delivery. Polyethylene oxide (PEO) is gaining popularity as a matrix-forming polymer, mainly attributed to its FDA acceptance, availability in a range of viscosity grades and unique swelling/erosion characteristics, which can be utilized for modulating drug release.[1,2] The aim of this study was to investigate the influence of PEO concentration on the release of poorly water soluble APIs from ER matrices.

Methods

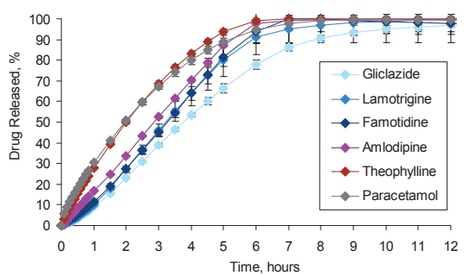
Model formulations containing 15% w/w APIs with various aqueous solubility (gliclazide, < 0.055 mg/mL; lamotrigine, 0.17 mg/mL; famotidine, 1 mg/mL; amlodipine besylate, 3.16 mg/mL; theophylline, 8 mg/mL; or paracetamol, 20 mg/mL) 0-84% w/w PEO (POLYOX™, water soluble resins, WSR-1105, MW 900,000 Da; International Flavors and Fragrances Inc.), 0-84% w/w microcrystalline cellulose (MCC, Microcel 102, Blanver), 0.5% w/w fumed silica (Aerosil 200, Degussa) and 0.5% w/w magnesium stearate (Peter Greven) were prepared. MCC and fumed silica were screened through a 500 µm sieve. Then, all ingredients except for the lubricant were blended in a 1L tumbler mixer (T2C, Turbula) at 64 rpm for 10 minutes. Magnesium stearate was added last, and the formulation was blended for an additional one minute. Tablets with a target weight of 200 mg were manufactured on an instrumented 10-station rotary press (Piccola, Riva) using 7 mm standard concave tooling at a compression force of 20 kN.

Dissolution tests were conducted in a USP compliant A7 Sotax bath using Apparatus II with 8-mesh (2.38 mm) quadrangular baskets (Quality Lab Accessories) positioned within the vessel perpendicular to and 3 cm above the paddle operated at 100 rpm.[3] Purified water (1000 mL, at 37.0 ± 0.5°C) was used as a dissolution medium for all of the formulations. Absorbance was measured using a dual-beam UV/Vis spectrophotometer (PerkinElmer) for drug detection at wavelengths of 306, 228, 282, 240, 272 and 243 nm, for lamotrigine, gliclazide, famotidine, amlodipine, theophylline and paracetamol, respectively.

Results

All formulations produced low ejection forces (<450 N) and robust tablets with excellent mechanical strength (2-7 MPa). Aqueous solubility of the APIs had an effect on their release from the PEO ER matrices (**Figure 1**). Drugs with lower solubility produced slower release profiles.

Figure 1. Effect of Aqueous Solubility of API on its Release from Matrices Containing 35% w/w PEO



Results (cont'd)

Most formulations with different drugs and polymer concentrations resulted in reproducible zero- and first-order release profiles (**Figures 2-7**). For all tested APIs, an increase in PEO concentration resulted in faster drug release. This effect was most pronounced with drugs having aqueous solubility of 1 mg/mL or below, ie, gliclazide, lamotrigine and famoditine (**Figures 2-4**). This phenomenon may be related to a possible enhancement of API solubility by PEO, or some other physicochemical interaction rendering faster drug release from the matrices.

Tablets containing 0-15% w/w PEO and drugs with solubility of less than 1 mg/ml did not erode even after 24 hours of dissolution testing, possibly due to the insoluble nature of MCC and low water solubility of the active leading to the entrapment of the drug within the tablet and an incomplete release. For APIs with higher than 1 mg/mL solubility, the release rate appeared not to be significantly affected by polymer concentrations above 15% w/w POLYOX in the formulation.

The relationship between polymer concentration and drug release rates from PEO hydrophilic matrices is under further investigation.

Figure 2. Effect of PEO Concentration in ER Matrices on Gliclazide Release

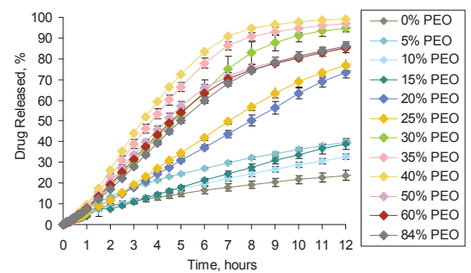


Figure 3. Effect of PEO Concentration in ER Matrices on Lamotrigine Release

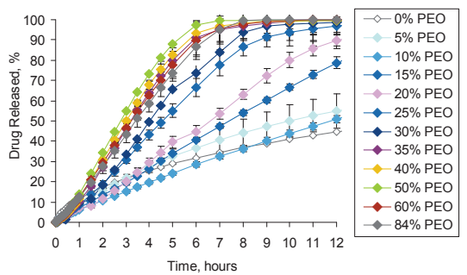


Figure 4. Effect of PEO Concentration in ER Matrices on Famotidine Release

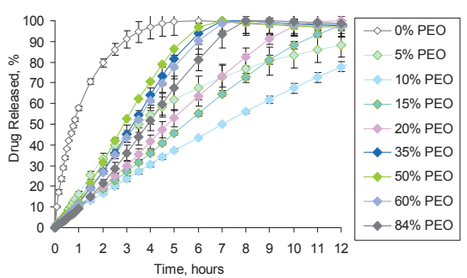


Figure 5. Effect of PEO Concentration in ER Matrices on Amlodipine Besylate Release

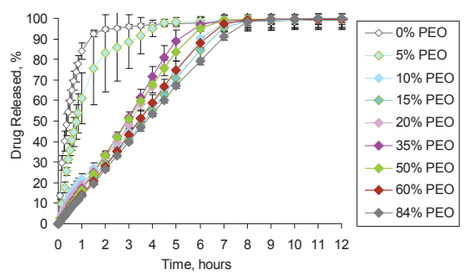


Figure 6. Effect of PEO Concentration in ER Matrices on Theophylline Anhydrous Release

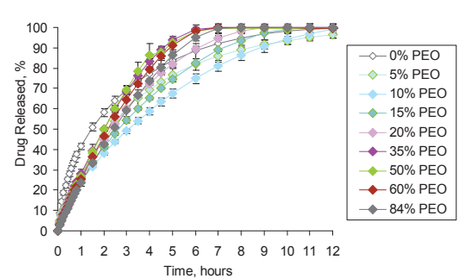
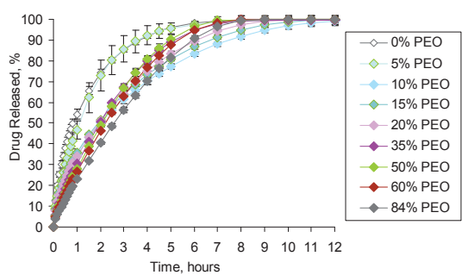


Figure 7. Effect of PEO Concentration in ER Matrices on Paracetamol Release



Conclusions

- Mechanically strong ER PEO matrix tablets were produced for all formulations in this study.
- For different APIs, use of a sufficient quantity (at least 20% w/w) of POLYOX 1105 as a matrix former resulted in reproducible zero- and first-order drug release profiles.
- Solubility of the API and PEO concentration had a significant effect on drug release. An unexpected trend of increased release rate with an increase in the PEO concentration was observed. This phenomenon may be related to a possible enhancement of the drug solubility by the PEO, or some physicochemical interactions (further investigation is underway). Therefore, PEO may be used as a solubility enhancer for poorly soluble active substances when utilized in ER matrix systems.

References

1. Choi S.U., Lee J., Choi Y.W. Development of a directly compressible PEO matrix for the sustained-release of dihydrocodeine bitartrate. *Drug Dev. Ind. Pharm.*, 29 (2003) 1045-1052.
2. Li H., Hardy R.J., Gu X. Effect of drug solubility on polymer hydration and drug dissolution from PEO matrix tablets. *AAPS PharmSciTech*, 9(2) (2008) 437-443.
3. Levina M., Palmer D., Rajabi-Siahboomi A.R., 2010. Evaluation of In Vitro Dissolution Methods for the Assessment of Drug Release from Hydrophilic Extended-Release Matrices Based on Polyethylene Oxide, *Drug Del. Tech.*, June 2010, Vol. 10 No 5.