European Journal of Pharmaceutics and Biopharmaceutics 120 (2017) 116–125

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

# Investigation of a new pH-responsive nanoparticulate pore former for controlled release enteric coating with improved processability and stability

Kuan Chen[a], Hao Han R. Chang[a], Alireza Shalviri[a], Jason Li[a], Jamie Anne Lugtu-Pe[a], Anil Kane[b], Xiao Yu Wu[a,*]

[a] Advanced Pharmaceutics and Drug Delivery Laboratory, Leslie Dan Faculty of Pharmacy, University of Toronto, ON, Canada
[b] Patheon Inc., Toronto Region Operations (TRO), Mississauga, ON, Canada

ARTICLE INFO

*Keywords:*
Terpolymer
pH-responsive nanoparticles
Pore formers
Ethylcellulose
Enteric polymer
Coated dosage forms

ABSTRACT

Water-soluble polymers are often used as pore formers to tailor permeability of film-forming hydrophobic polymers on coated dosage forms. However, their addition to a coating formulation could significantly increase the viscosity thus making the coating process difficult. Moreover, the dissolution of pore formers after oral administration could compromise film integrity resulting in undesirable, inconsistent release profiles. Therefore, a non-leaching, pH-responsive nanoparticulate pore former is proposed herein to preserve film integrity and maintain pH-dependent permeability. Poly(methacrylic acid)-polysorbate 80-grafted-starch terpolymer nanoparticles (TPNs) were incorporated within an ethylcellulose (EC) film (TPN-EC) by casting or spray coating. TPNs at 10%wt (pore former level) only increased viscosity of EC coating suspension slightly while conventional pore formers increased the viscosity by 490–11,700%. Negligible leaching of TPNs led to superior mechanical properties of TPN-EC films compared to Eudragit® L-EC films. As pH increased from 1.2 to 6.8, TPN-EC films with 10% pore former level exhibited an 8-fold higher diltiazem permeability compared to Eudragit® L-EC films. The pH-dependent drug release kinetics of diltiazem HCl beads coated with TPN-EC films was tunable by adjusting the pore former level. These results suggest that the TPNs are promising pH-sensitive nanoparticulate pore formers in EC-coated dosage forms.

## 1. Introduction

Pore formers of various properties are widely used to modify the permeability of film coating of controlled release dosage forms for achieving desirable drug release profiles [1–10]. Among these materials, water-soluble polymers, such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG), and hydroxypropylcellulose (HPC) are prevalently used due to their compatibility with hydrophobic polymeric coating materials (e.g. ethylcellulose, EC) [5–10]. Polymers with pH-dependent solubility, such as methacrylic acid–ethyl acrylate copolymer (Eudragit® L) and hypromellose acetate succinate, are typically used as pore former materials for more specific pH-sensitive applications (e.g., protection of acid-labile drugs, delayed release, targeted delivery to given regions of the gastrointestinal (GI) tract) [11–21]. These polymers are water-insoluble at low pH in the stomach and remain within the coating thus hindering drug release. At higher pH in the small and large intestines, they become water-soluble and leach out from the coating, resulting in a more porous and permeable film [14,22–25]. This pH-dependent leaching could reduce the mechanical strength of the film and compromise coating integrity, which can increase the risks of premature drug release and dose dumping in the GI tract, leading to unwanted toxicity [25,26]. Furthermore, the films could lose the ability to continuously modulate drug permeability once the pore former has leached out. Another problem with use of water-soluble polymers as pore former is the significantly increased viscosity of the coating dispersion. High viscosity of the coating formulation can cause clogging of equipment parts (i.e. spray nozzle and tubing) and inconsistency in the coating [27,28]. Therefore, development of new pore formers that would not leach out of the coating films nor noticeably increase viscosity of coating suspensions is needed for easy coating process and better control of drug release kinetics throughout the GI tract.

Herein a non-leaching poly(methacrylic acid)-polysorbate 80-grafted-starch (PMAA-PS 80-g-St) terpolymer nanoparticle (TPN) [29–34] pore former is proposed for use within EC films, as shown in Fig. 1A, to mitigate the major drawbacks of existing water-soluble pore formers described above. EC is a commonly used polymer coating in

* Corresponding author.
*E-mail address:* xywu@phm.utoronto.ca (X.Y. Wu).

http://dx.doi.org/10.1016/j.ejpb.2017.08.014
Received 28 July 2017; Received in revised form 30 August 2017; Accepted 31 August 2017
Available online 05 September 2017
0939-6411/ 

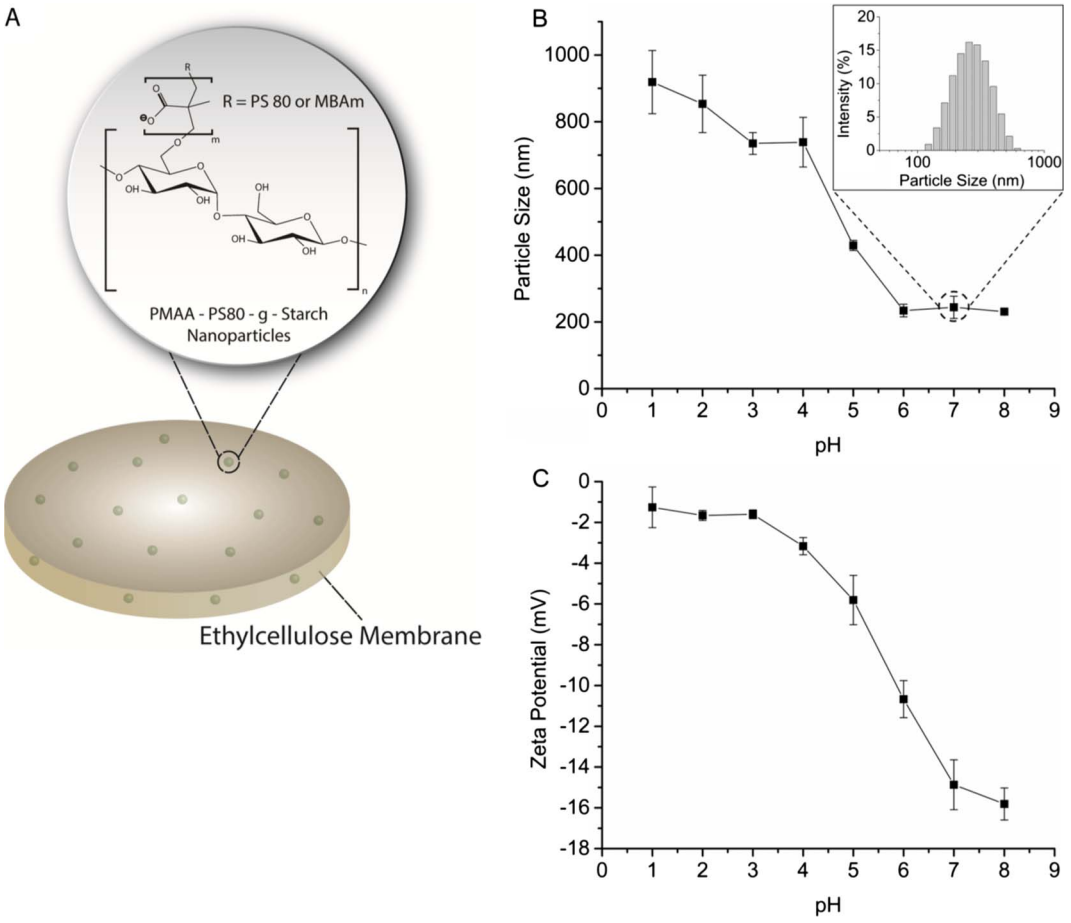


**Fig. 1.** (A) The chemical structure of TPN and the schematic diagram of TPN-EC film. (B) Z-average diameter and (C) zeta potential of TPNs in various pH. Insert in (B) is the representative particle size distribution of TPNs at pH 7. Aggregation of TPNs occurred below pH 6 as shown by the increase in Z-average diameter and more neutral zeta potential.

controlled release dosage forms. EC films are hydrophobic with very low permeability to drugs. Hence water soluble pore formers, such as HPMC or Eudragit® L (for enteric coating), are often incorporated in EC coating of oral dosage forms. We hypothesize that crosslinked TPNs, with good colloidal stability and compact chain structure [31], can be dispersed readily and uniformly in a commercial EC suspension for coating without significant increase in the viscosity. Furthermore, due to similar backbone structure of the polysaccharides (i.e., glucose units with $\beta(1 \rightarrow 4)$ linkages in EC and $\alpha(1 \rightarrow 4)$ linkages in starch) and hydrophobic domains in PMAA and PS 80, TPN is anticipated to be highly compatible with EC, which can facilitate uniform distribution of TPNs throughout the EC film and prevent leaching of TPNs during the drug release process.

The PMAA-PS 80-g-St TPNs were synthesized by grafting polymerization of PMAA and PS 80 onto starch, in which all components have been used in pharmaceuticals and are regarded as safe (GRAS). The PMAA component imparts pH-responsiveness to TPNs. It becomes unionized at low pH and ionized at high pH rendering pH-dependent hydration and permeability of the TPN-EC film [35], which is useful for pH-responsive drug release in the GI tract. PS 80, a non-ionic surfactant, can improve stability of TPNs in dispersion as well as the uniformity of the TPN-EC film.

In this work, TPNs with a composition suitable for the use in enteric coating were synthesized using a previously reported method [31]. The pH-dependence of the particle size and zeta potential of the TPNs were characterized. The effect of TPNs on the viscosity of EC coating dispersion was evaluated using mixtures of TPNs in a commercial EC dispersion product for coating (Surelease® EC) at various levels and compared with conventional pore formers HPMC and Eudragit® L (an acrylic polymer widely used as an enteric pore former). To investigate the potential of TPNs as a pore former of pH-responsive coating, the mechanical strength, weight loss and morphology of free EC films with no pore former (blank) or with 10% pore former level of TPNs or Eudragit® L were examined in dry state or after soaking in aqueous media. The pH-dependence of water uptake and permeability of the films to a model drug diltiazem HCl was determined. Finally, to demonstrate the application of the new pH-responsive pore former TPNs in enteric coated controlled release dosage forms, TPN-EC coated diltiazem HCl-layered beads were prepared using a fluid bed coater and their drug release profiles in media at simulated gastric and intestinal pH were determined.

## 2. Materials and methods

### 2.1. Materials

Soluble corn starch, methacrylic acid (MAA), N,N′-methylenebisacrylamide (MBAm), sodium thiosulfate (STS), potassium persulfate (KPS), and sodium dodecyl sulfate (SDS) were purchased from Sigma Aldrich (Oakville, ON, Canada). Diltiazem HCl was purchased from AK Scientific, Inc. (Union City, CA, USA). Sodium hydroxide (NaOH) and hydrochloric acid (HCl) were purchased from Caledon (Georgetown, ON, Canada). Sodium dibasic, potassium monobasic, and sodium chloride (NaCl) were purchased from BioShop (Burlington, ON, Canada). Microcrystalline cellulose (MCC) beads (VIVAPUR® MCC Spheres 700) were purchased from JRS Pharma (Weissenborn, Germany). HPMC (Methocel™ E5) was kindly donated by DOW (Midland, MI, USA). PVP (Kollidon®/PVPK30) was kindly donated by