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Research paper

Properties and mechanisms of drug release from matrix tablets containing poly(ethylene oxide) and poly(acrylic acid) as release retardants

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ABSTRACT

The interactions between poly(ethylene oxide) (PEO) and poly(acrylic acid) (PAA) in aqueous medium at pH 6.8 were investigated in the current study. We have also studied the effect of interpolymer interactions and various formulation variables, including the molecular weight of PEO, the ratio between PEO and PAA, the crystallinity of PEO, and the presence of an acidifying agent, on the release of theophylline from matrix tablets containing both PEO and PAA as release retardants.

At pH 6.8, the synergy in solution viscosity between PEO and PAA as the result of ion-dipole interaction was observed in this study. The release of theophylline from the matrix tablets containing physical mixtures of PEO and PAA was found to be a function of dissolution medium pH because of the pH-dependent interactions between these two polymers. Because of the formation of water insoluble interpolymer complex between PEO and PAA in aqueous medium at pH below 4.0, the release of theophylline was independent of PEO molecular weight and was controlled by Fickian diffusion mechanism in 0.01 N hydrochloric acid solution. In comparison, the drug release was a function of PEO molecular weight and followed the anomalous transport mechanism in phosphate buffer pH 6.8. The presence of PAA exerted opposite effects on the release of theophylline in phosphate buffer pH 6.8. In one aspect, theophylline release was accelerated because the erosion of PAA was much faster than that of PEO at pH 6.8. On the opposite aspect, theophylline release was slowed down because of the formation of insoluble complex inside the gel layer as the result of the acidic microenvironment induced by PAA, and the increase in the viscosity of the gel layer as the result of the synergy between PEO and PAA. These two opposite effects offset each other. As a result, the release of theophylline remained statistically the same even when 75% PEO in the formulation was replaced with PAA.

In phosphate buffer pH 6.8, the release of theophylline was independent of the crystalline form of PEO. The release profile remained identical whether PEO was present as a semicrystalline powder blend with PAA or an amorphous complex with PAA in the matrix tablets. It has also been observed that the presence of citric acid as an acidifying agent had negligible effect on the drug release rate.

1. Introduction

Various controlled release oral dosage forms based on the interactions between polymers have been developed. Interpolymer interactions could be classified into four categories: [a] electrostatic interaction between positively-charged and negatively-charged polymers [1]; [b] hydrogen-bond interaction between proton-donating and proton-accepting polymers [2]; [c] van der Waals interaction between polymers with different stereochemical structures such as enantiomer and diastereomer [3]; and [d] charge transfer interaction between electron-donating and accepting polymers [4]. Electrostatic and hydrogen-bond interactions are most commonly utilized in controlled release oral drug delivery.

Cationic polymers such as chitosan and Eudragit® E PO, and ionic polymers such as pectin and poly(acrylic acid) are used in electrostatic-interaction based matrices. Ionic interpolymer interaction has been used to develop drug delivery systems such as positively-charged nanoparticles for chronic wound healing and fast-swelling gastro-retentive tablets [5,6].

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Polysaccharides, starch derivatives and cellulose derivatives are commonly used in hydrogen-bond based matrices. Hydrogen bonding between xanthan gum and locust bean gum was applied to develop TIMERx™ controlled-release platform technology [7,8]. Synergistic enhancement in the viscoelastic properties of the hydrogel as the result of the hydrogen-bond interactions between Starch 1500 and Hypromellose was explored to control the drug release rate of the matrix tablets [9].

Drug release from matrix tablets containing both poly(ethylene oxide) (PEO) and poly(acrylic acid) (PAA) is the subject of this study. Both PEO and PAA are commonly-used hydrophilic retardants for preparation of controlled-release dosage forms. PEO is a neutral homopolymer synthesized from ethylene oxide via a radical polymerization process. It is available in a wide range of molecular weights (100,000–7,000,000 Da) under the trade name PolyOx® WSR from Dow Chemical. PEO has been used in monolithic matrix tablets and osmotic pump tablets for controlled release oral drug delivery [10,11]. PAA is an atactic weakly-acidic homopolymer synthesized from acrylic acid via a radical polymerization process. It is available in either linear or cross-linked grades under the trade name Carbopol® from Lubrizol Advanced Material. Carbopol has been used in matrix tablets and multiparticulates for controlled release oral delivery [12,13]. Interpolymer interaction between PEO and PAA in aqueous medium was first reported by Bailey in 1964 [14].

The hydrogen-bond induced interaction between PolyOx N12K and Carbopol 907 has been thoroughly investigated in our previous study (unpublished results). As shown in Fig. 1, the ether oxygens in PEO function as hydrogen bond acceptors and carboxyl groups in PAA function as hydrogen bond donors. Formation of the interpolymer complex could only take place below certain pH value since carboxyl groups need to be protonated in order to function as hydrogen bond donors. The complexation was initiated between pH 5.0 and 6.0. With gradual decrease in pH, the interpolymer complex began to precipitate at pH 4.0. The precipitate was amorphous with a glass transition temperature of 3.97 °C. The milled precipitate was stored in a freezer (−20 °C) to prevent agglomeration at ambient conditions. The molar ratio between ethylene oxide and acrylic acid units in the complex was measured to be 1.3 using quantitative ^{13}C solution NMR. This molar ratio is equivalent to a weight ratio of 45–55 between PolyOx N12K and Carbopol 907.

The combination of PEO and PAA for controlled release drug delivery has been reported [15,16]. However, the interaction between PEO and PAA was neither discussed nor studied in those articles. Drug release testing was conducted in phosphate buffer pH 7.4, at which PAA was fully ionized and not able to complex with PEO via hydrogen bonds. Furthermore, cross-linked PAA was used in both articles and cross-linking is known to hinder the interactions between polymers.

The first objective of this study was to understand the impact of interpolymer interaction between PEO and PAA on drug release from the controlled-release tablets containing both polymers as release retardants. The second objective was to investigate various formulation variables on the drug release characteristics of the matrix tablets containing PEO and PAA. The formulation variables included PEO molecular weight, the ratio between PEO and PAA, the crystallinity of the release retardants (semicrystalline crystalline PEO in powder mixture vs. amorphous interpolymer complex), and the presence of an acidifying agent.

We hypothesized two advantages of a sustained release matrix containing both PolyOx and Carbopol 907 as release retardants. For the first advantage, drug release in acidic medium was anticipated to be less dependent on the molar mass of PolyOx, as a result of *in situ* complexation between these two polymers. The hydrogen bond-based interpolymer complexation functions as an agent physically crosslinking PolyOx and Carbopol. Release of theophylline from this insoluble matrix will be controlled by the particles size, rather than the molecular weight of PolyOx. This would eliminate the stability problems associated with matrix tablets containing PolyOx because of PolyOx's degradation during the storage and the resulting changes in drug release rate. For the second advantage, we anticipated that ion-dipole interaction at pH 6.8 would provide synergistic effect in controlling drug release at pH 6.8. This synergistic effect could potentially result in a drug release rate being less sensitive to PolyOx molar mass at pH 6.8 as well.

2. Materials and methods

2.1. Materials

Poly(ethylene oxide) of three different grades, PolyOx WSR 205, N12K and N60K with viscosity average molar mass of 500,000, 1,000,000, and 2,000,000 Da respectively, was received from Dow Chemical (Midland, MI, US) as samples. Carbopol® 907 (weight average molar mass of 600,000 Da) was supplied by Lubrizol Advanced Material (Louisville, KY, US). Theophylline anhydrous, USP, was purchased from Letco Chemical (Decatur, AL, US). Magnesium stearate (HYQUAL® 5712) was received as a sample

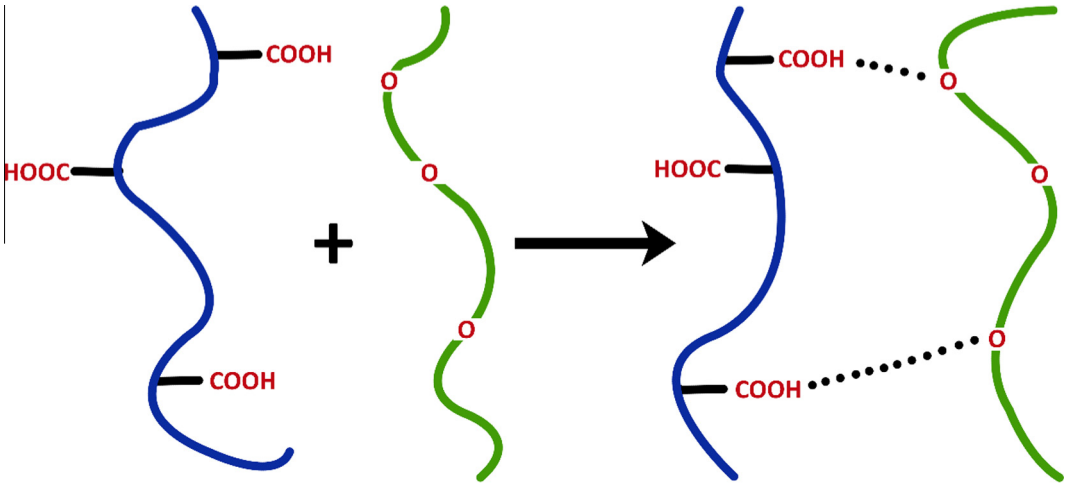

Fig. 1. Illustration of hydrogen-bond induced interpolymer complexation between poly(acrylic acid) and poly(ethylene oxide) in an acidic environment.