Pairwise Polymer Blends for Oral Drug Delivery

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ABSTRACT: Blends of polymers with complementary properties hold promise for addressing the diverse, demanding polymer performance requirements in amorphous solid dispersions (ASDs), but we lack comprehensive property understanding for blends of important ASD polymers. Herein, we prepare pairwise blends of commercially available polymers polyvinylpyrrolidone (PVP), the cationic acrylate copolymer Eudragit 100 (E100), hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethyl cellulose acetate butyrate (CMCAB), hydroxypropyl methylcellulose (HPMC), and the new derivative cellulose acetate adipate propionate (CAAdP). This study identifies miscible binary blends that may find use, for example, in ASDs for solubility and bioavailability enhancement of poorly water-soluble drugs. Differential scanning calorimetry, FTIR spectroscopy, and film clarity were used to determine blend miscibility. Several polymer combinations including HPMCAS/PVP, HPMC/CMCAB, and PVP/HPMC appear to be miscible in all proportions. In contrast, blends of E100/PVP and E100/HPMC showed a miscibility gap. Combinations of water-soluble and hydrophobic polymers like these may permit effective balancing of ASD performance criteria such as release rate and polymer–drug interaction to prevent nucleation and crystal growth of poorly soluble drugs. Miscible polymer combinations described herein will enable further study of their drug delivery capabilities, and provide a potentially valuable set of ASD formulation tools. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2871–2883, 2014

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INTRODUCTION

Polymers have been extraordinarily important to the development of drug delivery systems and effective pharmaceutical formulations. Polymer functions range from the simple, for example, enabling compression of the active and inert ingredients into a tablet with the needed physical properties (e.g. microcrystalline cellulose),[1,2] to the more demanding, such as enabling pH-controlled release of a medication in order to minimize drug-stomach exposure (e.g., cellulose acetate phthalate),[1,3–5] to highly demanding roles such as enabling zero-order drug release (e.g., cellulose acetate).[6–8] Polysaccharide derivatives including cellulose esters[3] are useful polymers for drug delivery; they are generally nontoxic, are not absorbed from the gastrointestinal (GI) tract, and can be readily modified to enhance properties critical for drug delivery. In recent times, the demands on drug delivery polymers have become greater, including expectations such as more precise timing, greater targeting selectivity, and delivery of compounds with poor solubility and/or permeability. It is often challenging for a single polymer to meet all of the demands for delivery of a particular drug with a diverse set of therapeutic requirements.

Oral drug delivery is a focal point of research on polymeric biomaterials as it is preferred by patients and is one of the most economical means of drug delivery. Recently, there has been strong interest in amorphous solid dispersion (ASD) formulations that suppress crystallization of poorly water-soluble drugs, enhance aqueous solubility, stabilize the drug against recrystallization in both solid and solution phases, and in some cases provide controlled release.[9] These characteristics are especially relevant when delivering insoluble and poorly bioavailable drugs; poor solubility is a substantial impediment to modern drug development.[10] ASD is a promising technology for enhancing solution concentration of these drugs, and indeed is in clinical use, for example in oral formulations of the HIV drug combination, Kaletra (lopinavir and ritonavir).[11–13] Molecular dispersion of the drug in the polymer matrix eliminates drug crystallinity and drives the formation of a supersaturated solution upon release.[14] The polymer must help stabilize the amorphous drug in the blend as well as in the supersaturated solution after release; typically, this requires polymer hydrophobicity to enhance interaction with hydrophobic drugs.[15,16] At the same time, the formulation must release the drug at an adequate rate; water-soluble polymers like polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) have received substantial attention for ASD formulations in part for this reason.[17] A number of studies reveal that HPMC is frequently effective at retarding drug crystal growth when combined in miscible blends with poorly soluble drugs such as felodipine and ritonavir.[16,18,19] PVP has also demonstrated significant utility when used alone or blended with cellulosics for amorphous dispersions with ritonavir, acetaminophen, and others.[14,15,20,21] Water-soluble polymers like PVP help to stabilize the drug after it has dissolved but before it has been absorbed; this is a two-edged sword as high polymer aqueous solution concentration can also change drug

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thermodynamic solubility, reducing the extent of supersaturation and thereby reducing the chemical potential gradient of the drug across the GI epithelium. PVP will also dissolve readily in the acidic milieu of the stomach, which may not be desirable for some drugs (e.g., those that degrade or may tend to recrystallize at low pH). In part for this reason, recently some investigators have focused on carboxyl-containing cellulose derivatives like cellulose acetate adipate propionate (CAAdP)[22,23] and hydroxypropyl methylcellulose acetate succinate (HPMCAS)[24,25] that are poorly soluble in acidic media but swell or dissolve at neutral pH.[26,27] Specific interactions between polymer carboxyl groups and drug functional groups [e.g., hydrogen bonding (H-bonding) with amines or amides] can also help to stabilize the drug against crystallization. The high glass transition temperatures (T_gs) of these cellulose derivatives are also useful for ASDs as they prevent drug mobility and crystallization even when humidity and ambient temperature are high. On the other hand, some of these polymers [e.g., CAAdP or carboxymethyl cellulose acetate butyrate (CMCAB)] are quite hydrophobic, and so may not release the drug at an adequate rate, or may not dissolve sufficiently at pH 6.8 to stabilize the drug after release. Studies in our laboratories of the drug clarithromycin, which is subject to acid catalyzed degradation, have shown enhanced chemical stability of the drug in ASDs containing CAAdP. They also demonstrate the difficulty in providing enhanced bioavailability of a target drug using just a single polymer system with hydrophobicity/hydrophilicity, polymer/drug interactions, and polymer aqueous solubility playing key roles in manipulating the behavior of the drug-containing ASDs.[28]

Researchers have designed new cellulose derivatives in the hopes of achieving a balance in the properties needed for an effective single polymer ASD system.[23] However, criteria like hydrophilicity for enhanced drug release versus hydrophobicity for enhanced polymer–drug interactions may conflict with one another, challenging the polymer designer. Therefore, polymer blending may be an attractive alternative for dealing with deficiencies of existing or novel drug delivery polymers, including those for ASD. Miscible blends of polymer and drug are of great interest as reduction in the drug domain size to molecular scale decreases the likelihood that the drug will recrystallize from the formulations and revert to its more stable crystalline form.[13] A greater likelihood of producing stable homogenous amorphous systems results from strong H-bonding, dipole–dipole interactions, hydrophobic, acid–base ionic interactions, or a combination of interactions between the components.[20,29] We hypothesize that by identifying miscible combinations of somewhat hydrophobic polymers with somewhat hydrophilic polymers, the resulting pairwise blends may better address these complex, at times conflicting requirements for an effective ASD system. The hypothesis is supported by findings that demonstrate more effective crystal growth inhibition by hydrophobic/hydrophilic polymer combinations.[20,22] Polymer blends may in some cases provide synergistic benefits, giving properties that are not just the weighted average of those of component polymers, but that go beyond those of individual components; for example, by enhancing solution concentration of poorly soluble drugs beyond that available from dispersion in either individual polymer.[20] It must also be noted that such miscible blends may find use in drug delivery systems other than for those for ASD, and may be useful as well for a much wider variety of applications, for example, in coatings or in agricultural films.

There have been relatively few reports of the use of polymer blends in oral drug delivery. Researchers at Eastman Chemical investigated cellulose ester blends with PVP and with poly (2-ethyl-2-oxazoline) (PEOx). They illustrated that by incorporating just 20% of PVP or PEOx into miscible blends with cellulose diacetate (casting clear films with dextromethorphan incorporated into the blend), effective dextromethorphan release could be achieved in contrast to the impractically slow release rate from films of pure cellulose diacetate.[3] In 2005, Lyu et al.[30] demonstrated the ability to tune release behavior by blending polyvinyl acetate (PVA) and cellulose acetate butyrate (CAB). Although the release of dexamethasone from PVA alone was very fast and from CAB extremely slow, a predictable reduction in the release rate of the drug was achieved by adding increasing proportions of CAB to the PVA/drug mixture.[30] Researchers in Belgium have also demonstrated dissolution enhancement of the antifungal agent itraconazole and the anti-HIV drug UC 781 through various binary combinations of HPMC, polyvinylpyrrolidone/vinyl acetate copolymer (PVP-VA), polyethylene glycol, E100, and others.[31–34] Recent studies in our laboratories have highlighted the effectiveness of polymer blends composed of novel cellulosic polymers including suberate, adipate, and sebacate esters of cellulose acetate propionate mixed with commercial cellulose-based and synthetic polymers. Blending two moderately hydrophobic cellulosic polymers, or combining a hydrophobic cellulosic polymer with a more hydrophilic synthetic polymer, afforded synergistic crystal growth inhibition of the poorly soluble CYP-3A4 inhibitor ritonavir.[20,23]

Several methods exist for determining polymer blend miscibility. To achieve miscibility upon mixing pairs of polymers, a free energy of mixing lower than zero is needed. Based on the thermodynamics of mixing in binary polymer blends, there is predicted to be only a small combinatorial entropy contribution if only weak intermolecular forces exist between the pair. This may not be enough to ensure blend miscibility; however, miscibility is greatly improved when the paired polymers possess specific interactions including hydrogen bonding that contribute to a favorable free energy of mixing.[35–38] Several methods are available for assessing blend miscibility, which can be challenging to assess in some cases. Cast films of blends indicate, if they are clear, that there is no phase separation of the components on the micron scale,[39] providing initial evidence of miscibility. This evidence can then be used to rule out blends that exhibit very obvious phase separation before carrying out additional analyses. Differential scanning calorimetry (DSC) is one of the most widely used methods for investigating blend properties[40–42] and is useful for determining miscibility of polymers with other polymers and/or with drugs.[42–47] Phase separation in DSC can typically be detected for domain sizes greater than 20–30 nm.[12] DSC detects the change in heat capacity of the material and the resultant endothermic baseline shift that typically occurs as the system passes from the glassy to the rubbery state during heating; the glass transition. For blends that are completely mixed at the microscopic level a single glass transition is observed, and is characteristic of a miscible blend. In contrast, immiscible blends will generally show two T_gs, or a single T_g similar to that of one blend component. In cases where the T_gs of the individual components are broad and/or are close to each other (T_g difference $\leq 20^\circ$C), alternative methods such as modulated DSC (MDSC)[48] or solid-state nuclear magnetic resonance spectroscopy[49–51] may be necessary