

REVIEW

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# Applications of polymer blends in drug delivery

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## Abstract

**Background:** Polymers are essential components of many drug delivery systems and biomedical products. Despite the utility of many currently available polymers, there exists a demand for materials with improved characteristics and functionality. Due to the extensive safety testing required for new excipient approval, the introduction and use of new polymers is considerably limited. The blending of currently approved polymers provides a valuable solution by which the limitations of individual polymers can be addressed.

**Main body:** Polymer blends combine two or more polymers resulting in improved, augmented, or customized properties and functionality which can result in significant advantages in drug delivery applications. This review discusses the rationale for the use of polymer blends and blend polymer-polymer interactions. It provides examples of their use in commercially marketed products and drug delivery systems. Examples of polymer blends in amorphous solid dispersions and biodegradable systems are also discussed. A classification scheme for polymer blends based on the level of material processing and interaction is presented.

**Conclusion:** The use of polymer blends represents a valuable and under-utilized resource in addressing a diverse range of drug delivery challenges. It is anticipated that new drug molecule development challenges such as bioavailability enhancement and the demand for enabling excipients will lead to increased applications of polymer blends in pharmaceutical products.

**Keywords:** Polymer blends, Drug delivery, Dosage forms, Solid dispersions, Bioavailability enhancement

## Background

Polymers are widely used in the formulation of pharmaceutical and healthcare products. Applications include controlling drug release, providing site specific delivery of active pharmaceutical ingredients (APIs) and improving drug stability. Polymers are commonly used in almost all major dosage forms including tablets, films, capsules, semi-solids, suspensions, gels, and transdermal patches as well as in specialized delivery systems such as long-acting injections and biodegradable implants.

There are a variety of polymers currently available with unique properties which have been used in marketed drug and healthcare products. Due to this precedent of use, these polymers may be used in the development of new pharmaceutical products, provided

that the amounts used are within the limits for which safety has been established. Despite the availability of these polymers, there is a demand for new and improved materials. While synthesis of new polymers to obtain desired functionalities is possible, the extensive safety testing requirements for new materials are often a limiting barrier to their use in new drug products. Considering the time and resources required to obtain regulatory approval when a new excipient is to be utilized, polymer blends present an attractive alternative means by which to address various formulation and drug delivery challenges.

The goal of blending polymers from a functionality standpoint is to improve, customize, or maximize material performance [1]. Table 1 lists applications of polymer blends in pharmaceutical dosage forms. Various mechanisms of drug release from polymer-based dosage forms

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**Table 1** Pharmaceutical applications of polymer blends

Dosage forms*	Applications
Tablets	Modulation of drug release profiles
Hard and soft capsules	Capsule shell formation, enteric protection
Film coatings	Plasticization, modulation of mechanical properties, adhesion, vapor permeability and drug release rates
Oral films	Plasticization, modulation of mechanical properties. Preventing settling of dispersed phases; modulating tear resistance
Liquids, emulsions, and suspensions	Rheological adjustment, suspension stabilization
Gels	Rheological modification, modulation of diffusion, swelling, dissolution/erosion and drug release rates
Topical semi-solids and transdermal patches	Rheological/mechanical properties modification, modulation of bioadhesion and drug release rates
Long-acting injectables, implants, ophthalmic inserts	Modulation of degradation, drug release rate and mechanical properties
Solid dispersions	Drug solubilization, dissolution enhancement, stabilization of solid state forms, crystallization inhibition, modulation of super-saturation and precipitation inhibition

\*Specific examples for various dosage forms are listed in Tables 2, 3, 4, and 5

are possible depending on the type of delivery system (Fig. 1). The scientific literature on the application of polymer blends in pharmaceutical products, excipients, and drug delivery systems has mostly focused on specific properties or applications of polymer blends such as miscibility [35, 36], film coating [37, 38], orally disintegrating films [39], matrix tablets [40–42], solid dispersions [43–45], biodegradable systems [46, 47], transdermal drug delivery [48], environmentally responsive systems [49, 50], and modifying or improving the performance of natural polymers [51–55]. Polymer blends have been used in recently emerging pharmaceutical processing techniques such as 3D printing [56–58] and electrospinning [59–61]. These techniques have also been used to prepare polymer blends for use in tissue engineering and wound dressings [62, 63]. Although most studies reported in the literature have focused on binary polymer blends, there has been some work performed on blends with more than two polymers such as ternary polyvinyl alcohol/poly(vinylpyrrolidone)/chitosan blends [64].

Despite the potential advantages of polymer blends, there is an absence of comprehensive reviews on their use and application in marketed products. Furthermore, the currently available literature on polymer blends in pharmaceuticals is very product specific and is highly fractured across many scientific journals, publications and patents. This paper therefore reviews the applications of polymer blends in excipients and drug delivery systems across a broad range of different dosage forms with an emphasis on commercialized products and technologies. Applications of polymer blends in drug solubility enhancement are also addressed.

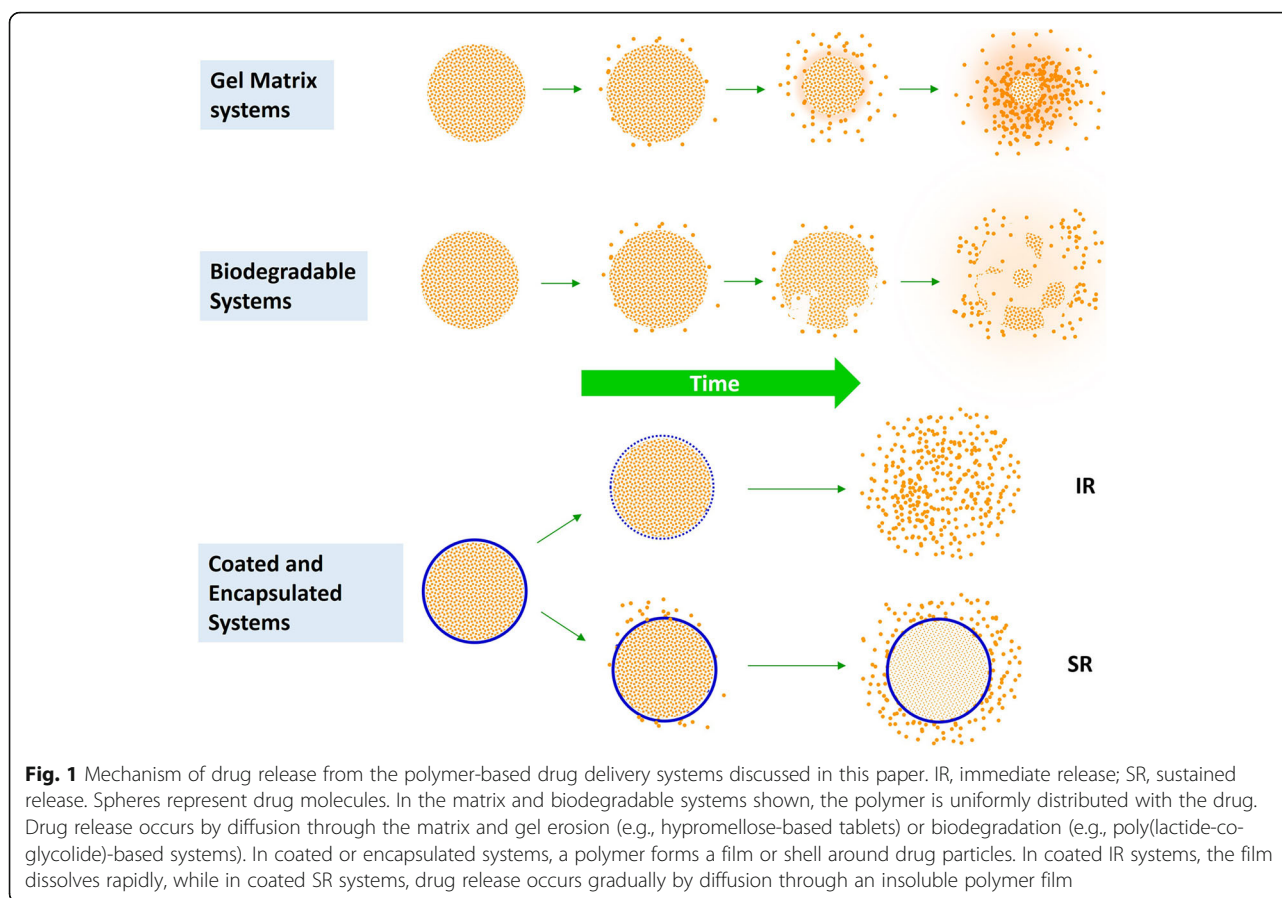
## Main text

### Polymer blend interactions

Noncovalent polymer-polymer interactions may range from van der Waals forces in physical mixtures to stronger intermolecular interactions such as hydrogen bonding, ionic interactions, and hydrophobic interactions that may occur during processing. Many experimental techniques are available for the characterization of polymer blends depending on the state of the material being studied [65]. Widely used methods include molecular weight characterization, spectroscopy, light and x-ray scattering, diffraction, microscopy, imaging techniques, thermal analysis, rheology, and mechanical testing in conjunction with evaluation of long term product stability.

Key factors influencing polymer-polymer interactions are shown in Fig. 2. These factors include the characteristics of the polymers, blend composition (i.e., polymer ratio), the type of manufacturing process, processing conditions, solvent, and other ingredients in the formulation. For example, varying the polymer chemistry (poly(lactide-co-glycolide) with various lactide and glycolide ratios), anti-solvent and process temperature was observed to influence the degree of interaction and phase separation in blends of these biodegradable polymers with chitin [66].

Polymer blend interactions can also be influenced by the addition of other components. For example, the addition of sodium carboxymethyl cellulose (NaCMC) was found to facilitate miscibility in polyvinyl alcohol (PVA) and polyethylene oxide (PEO) solutions which exhibited phase separation in the absence of the ionic polymer [67]. The authors ascribed the miscibility



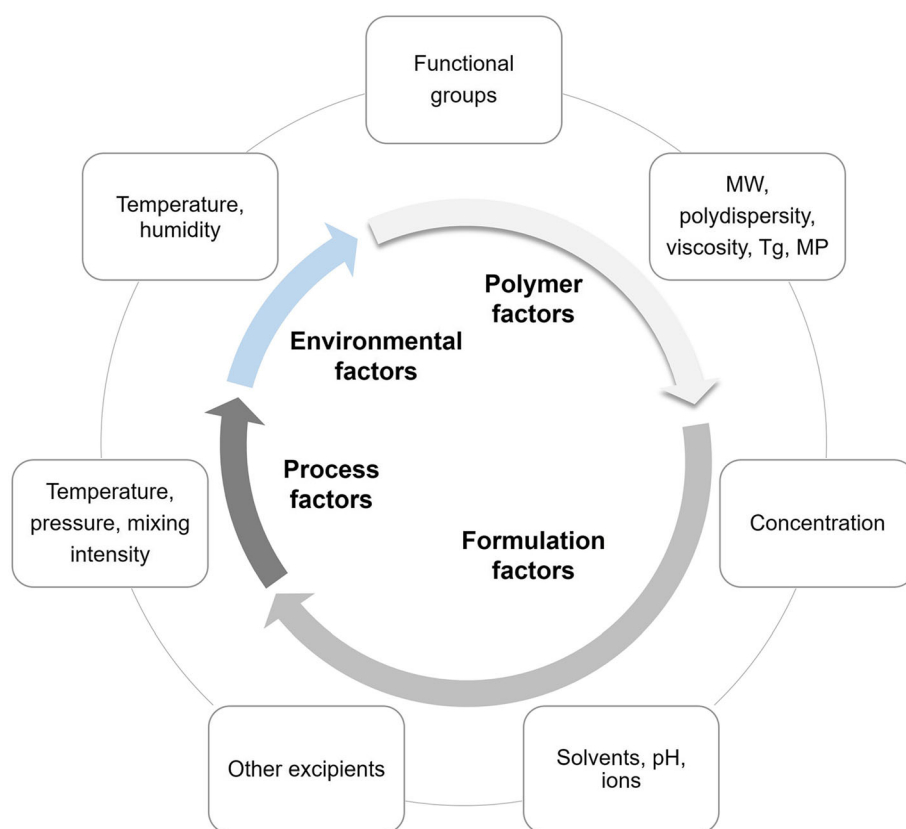
enhancement to the ability of NaCMC to form hydrogen bonds with both PVA and PEO.

Environmental factors such as temperature and humidity are an important consideration during long-term storage since they may influence drug product stability. Yang et al. reported that a ternary system of amorphous felodipine hot melt extruded with an immiscible Eudragit® EPO/poly(vinylpyrrolidone-co-vinyl acetate) polymer blend exhibited better stability of the amorphous drug to stress temperature and humidity compared to binary drug-polymer blends [68].

#### Polymer blend classification

In polymer chemistry literature, polymer blends are usually described as being miscible (i.e., homogeneous at the molecular level), partially miscible or immiscible [65]. From a pharmaceutical product viewpoint, this review proposes a further classification based on the dimensional scale in which the bulk of the polymer molecules in the blend are processed and interact (Fig. 3). The term “bulk” in this context refers to the majority of molecules. For example, in powders, the bulk of the polymer molecules are in the interior of the constituent particles as opposed the surface. The scheme classifies polymer blends as occurring on three levels—particulate,

colloidal, and molecular. These levels correspond to the size range of the polymer particles that are used to prepare the blend. Particle size is an important material parameter for pharmaceutical products as it influences several key manufacturing and product performance attributes. These include powder mixing, blend uniformity and solvent interaction rates. Consequently, given the wide variety of polymer blends that have been used in a range of different applications and dosage forms, classification systems which distinguish between blends based on key physical properties are useful in further understanding their characteristics. An additional consideration is whether a polymer blend exhibits long term stability in the sense that it does not undergo physical changes or phase separation during storage. This is especially a concern for (initially miscible) molecular level blends which in the absence of specific intermolecular interactions and a sufficient enthalpy of mixing may undergo phase separation leading to changes in the properties of the blend. Consequently, molecular level blends may require a more detailed investigation of their physical characteristics and microstructure compared to particulate or colloidal level blends. For explanatory purposes, the following discussion will focus on binary



**Fig. 2** Factors influencing polymer-polymer interactions. Tg, glass transition temperature (amorphous polymers); MP, melting point (crystalline polymers); MW, molecular weight

blends although the concepts are also applicable to blends of more than two polymers.

#### **Particulate level blends**

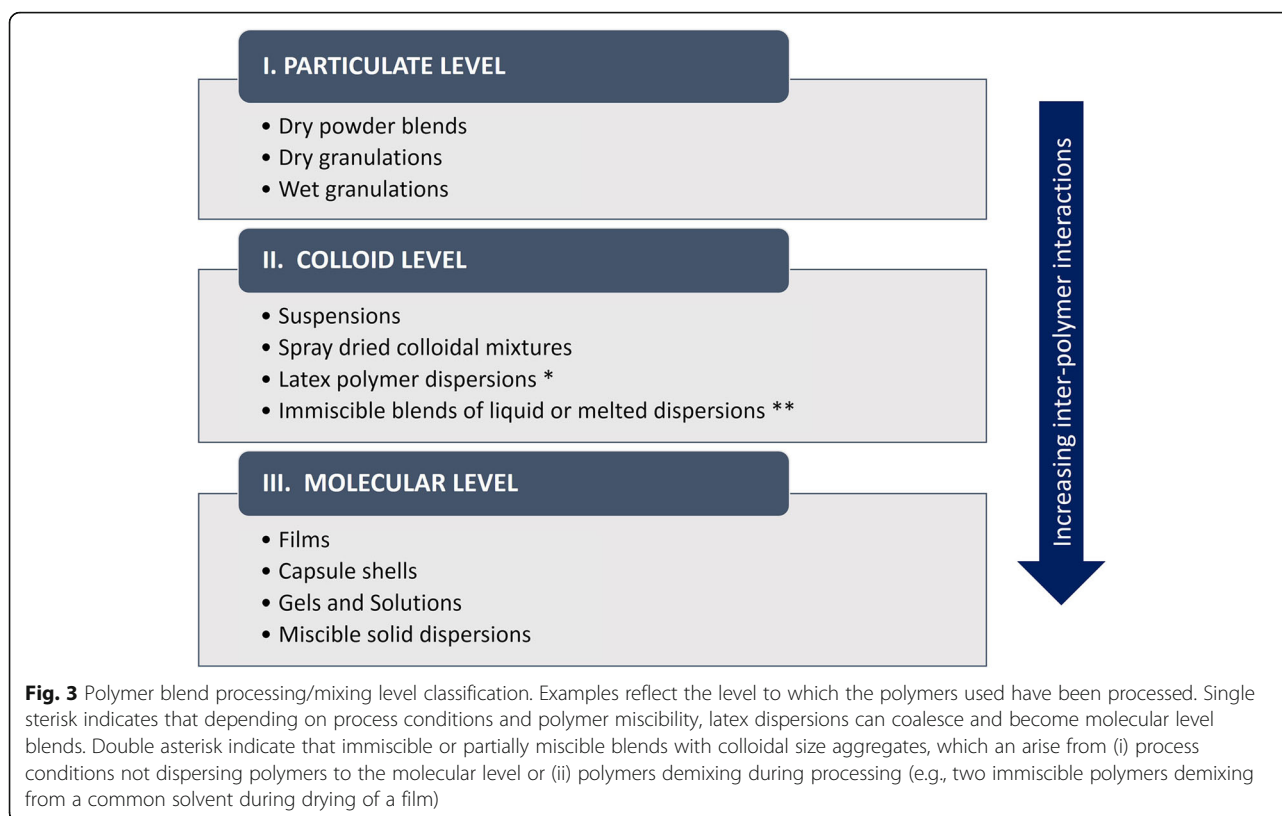
Particulate level blends are formed by the mixing of polymers as powders which do not undergo further processing to reduce their initial particle size substantially. Pharmaceutical manufacturing processes such as direct compression, roller compaction, and wet granulation use powders which are generally in the size range of tens to hundreds of microns. The level of interactions between materials processed by these techniques is generally confined to powder surfaces. Therefore, polymer blends used in most conventional tableting operations can be considered to have inter-polymer interactions occurring at a particle level. Additionally, the uniformity of mixing in such polymer blends does not extend beyond individual particles. The addition of water or organic solvents during wet granulation processes may promote a certain degree of localized mixing at particle surfaces or interfaces.

Examples of particulate level blends from commercial products are not readily available as specific particle size information for individual blend excipients that are used

is not commonly published. Therefore, the distinction between particulate level and some colloidal level blends may not always be readily determinable. However, in general, most direct compression and granulation processes would be considered to be particulate level blends given the size of their constituent particles. A relevant example from the recent literature describes the use of 90–250  $\mu\text{m}$  particle size range chitosan and xanthan gum blends for use as a direct compression matrix [69]. In this case, the polymer blend is clearly at the particulate level given its particle size range and the use of a direct compression process which does not involve size reduction of the powders.

#### **Colloidal level blends**

In colloidal level blends, at least one of the polymers predominantly exists as aggregates that are near or within the submicron size range. Such systems can be obtained by methods such as comminution, mixing of colloids (e.g., latex polymer dispersions), or phase separation (e.g., from solution, dispersions or melt processed polymer blends). Polymeric mixed micelles, which are formed by the assembly of two or more amphiphilic block copolymers [55, 70], may also be included in this



class of polymer blends. The increase in unit surface area relative to that of particulate level blends results in the interfacial region having a greater influence on inter-polymer interactions. Surface charge therefore plays an important role in these polymer blends.

For colloidal polymer particles dispersed in liquids, flocculation may occur if the two species have opposite surface charges. In aqueous latex dispersions that are used for film coating, flocculation may also occur upon the addition of water soluble polymers which are sometimes used as pore forming agents [71]. Nonionic water soluble polymers may cause flocculation of polymeric dispersions by bridging flocculation (adsorbed polymers) or depletion flocculation (non-adsorbed polymers) [72, 73].

An example of a commercial product that is a colloidal level blend is Avicel® RC 591 (a co-processed microcrystalline cellulose (MCC) and sodium carboxymethyl cellulose (NaCMC) powder) which is discussed further in the section on excipients of this review. The product is manufactured by spray drying an aqueous dispersion of colloidal MCC (water insoluble) and NaCMC (water soluble) [74]. NaCMC, an anionic polymer, adsorbs onto the surface of the colloidal MCC particles [75]. The particle size of this product after dispersion in water is around 90–200 nm [76], which reflects the starting size of the MCC used to manufacture it. The interaction

between the two polymers has been attributed to electrostatic forces and hydrogen bonding [76].

#### **Molecular level blends**

Molecular level blends are formed by processing two polymers in or to a state where they can interact at a molecular level. Processing methods generally involve the use of a common solvent or thermally co-processing the polymers together in molten or above the glass transition temperature ( $T_g$ ) states. Depending on their thermodynamic compatibility, polymer ratio, and the temperature, the resulting mixture may have one or more detectable phases. Examples of systems containing blends in which polymers can be homogenous at the molecular level include clear films, capsule shells, gels, and solutions. Polymer-polymer miscibility in all proportions has been observed for hypromellose (HPMC) and methylcellulose blend films, with mixing following ideal behavior [36]. In films and capsule shells, polymer miscibility is desirable as it generally results in clear, transparent films (if there are no insoluble or highly crystalline additives). Molecular scale interactions are also important in amorphous solid dispersions so that the drug does not crystallize during the shelf life of the drug product. In solutions, polymer-polymer miscibility reduces the potential for phase separation.



### Excipients

Polymer blends have been used as excipients for suspending and stabilizing disperse systems. An example is the previously mentioned MCC and NaCMC blend. Co-processed MCC/NaCMC is available as a powder and has monographs in the USA and European pharmacopoeias. Several types are available from different manufacturers with the NaCMC level ranging from 5 to 22% [77]. The co-processed product is used to create thixotropic gels that are used to stabilize suspensions, emulsions, and gels. For this reason, MCC/NaCMC is used in several marketed nasal spray products including Avamys [78], Beconase [79], and Nasacort Allergy [80].

The viscosity of MCC/NaCMC systems is less affected by temperature changes than that of NaCMC solutions. The NaCMC component serves as a protective colloid reducing inter-particle interactions that may lead to the aggregation of the MCC particles. NaCMC also facilitates dispersion of the MCC/NaCMC powder when it is dispersed in water [81]. The stabilizing properties of MCC/NaCMC have been attributed to it forming aqueous dispersions having a three-dimensional network structure [76].

Another excipient based on a polymer blend is Avicel® CE 15, a co-processed MCC and guar gum (85:15) powder that is used to provide improved mouth feel in chewable tablets. MCC and guar gum combinations have been studied as fat substitutes due to their favorable sensory characteristics [82]. The product is also claimed to add a creamy mouthfeel while reducing tooth packing and grittiness thereby improving the overall sensory characteristics of chewable tablets [83, 84]. Avicel® CE 15 is manufactured by co-processing MCC and guar gum into rounded aggregates by spray drying an aqueous mixture of the two components [4]. As in the production process used for MCC/NaCMC, the manufacturing method for Avicel® CE 15 uses colloidal size MCC as a starting material, which would make it a colloidal level blend. The beneficial organoleptic properties of the Avicel® CE 15 product are attributed to the intimate association of the polymers achieved during co-processing as well as the rounded shape of the aggregates [4].

### Tablets

While tablets are complex mixtures in which non-polymeric excipients such as sugars and polyols may be more prevalent (on an overall tablet weight basis), there are a number of cases where polymer blends provide unique functionality (Table 2). As for most direct compression and wet granulated based powder mixtures, these products would be classified as particulate level blends with the exception of the previously discussed co-processed Avicel® CE 15 excipient.

Polymers have been used extensively in the formulation of sustained (SR) release tablets. SR products are advantageous as they provide a reduction in dosing frequency and better control of the therapeutic window. Matrix tablets based on hydrogel forming polymers are commonly used in this regard. Gel formation creates a diffusion barrier to water and soluble drug substances. Gel erosion also contributes to drug release, especially for poorly soluble actives. HPMC, the most widely used polymer in this field, is available in a range of chemical substitution types and molecular weight grades [85]. Different HPMC molecular weight grades can be blended, thereby providing a convenient approach by which to adjust drug release profiles. Furthermore, it has been observed that such blends can increase the robustness of matrix tablets to hydrodynamic conditions during dissolution [86]. This finding has been attributed to the contribution of the higher molecular weight HPMC grades to forming stronger gels that are more resistant to changes in media agitation speeds.

In addition to viscosity and gel strength, other polymers blended with HPMC may influence matrix hydration, swelling, and erosion rates [86]. An interesting concept has been the addition of other polymers to HPMC matrices to control pH-dependent dissolution profiles of ionizable APIs [87, 88]. In some cases, the use of ionic polymers with HPMC has resulted in pH-independent drug release for weak bases [89] and weak acids [90]. In the latter study, this effect was attributed to the control of microenvironmental pH by the basic polymer, Eudragit® E 100.

Certain polymer blends can produce synergistic effects in which a combination of two polymers results in a change in a measured property that is greater than

**Table 2** Polymer blends in tablet technology platforms and excipients

Polymers	Advantage(s)	Commercial Product	Reference
Polyethylene oxide, hypromellose	Gastric retention and controlled drug release facilitating upper GI tract delivery by controlled swelling and erosion	Acuform® Technology	[2]
Xanthan gum, locust bean gum	Sustained release from synergistic polymer interaction	TIMERx Technology	[3]
Microcrystalline cellulose, guar gum	Improved sensory characteristics of chewable tablets	Avicel® CE 15	[4]

would be expected from the sum of the individual components. Synergistic rheological effects have been observed for combinations of NaCMC (anionic) and HPMC (non-ionic) with the increases in viscosity being attributed to hydrogen bond mediated cross-linking between the carboxylic acid and hydroxyl groups of the polymers [91]. An advantage of such synergistic combinations is that they allow for a reduction in the overall concentrations of the polymers required in the formulation, which is useful when the drug product size or excipient levels must be minimized [2, 91]. Polymer blends have also been used in matrix tablets for the design of specific drug release profiles. Mixing nonionic (HPC or methylcellulose) and anionic (NaCMC) polymers in optimum amounts has been used to obtain zero-order release profiles for two highly soluble drugs (metoprolol tartrate and alprenolol hydrochloride) [40]. This was in contrast to the individual polymers which yielded first-order or sigmoidal dissolution profiles. The reasons for the observed zero order release profiles of the polymer combinations have not been fully elucidated, but it has been proposed that an interaction between the cationic forms of these APIs and NaCMC may lead to the formation of a complex which is released at a slower rate permitting a modulation of drug release to a constant rate when the appropriate levels of nonionic and anionic polymer are used [92, 93].

TIMERx is a matrix tablet drug delivery technology that was developed based on synergistic interactions between xanthan gum and locust bean gum. When used together, the association between the polymer secondary structures formed in solution enhances gelation and viscosity resulting in a much stronger gel than that of the individual polymers [3]. Modulation

of drug release profiles from these matrix tablets can be accomplished by varying factors such as the ratio and concentration of the polymers, as well as the addition of ions and saccharides. Acuform® is a gastro-retentive drug delivery technology based on the use of PEO and HPMC [94]. In this regard, the aim of gastric retention is to maintain the drug product in the stomach for an extended duration so as to prolong the time during which APIs with a narrow absorption window can be absorbed. Rapidly swelling systems are one means by which to improve gastric retention as larger dosage forms are emptied from the stomach more slowly. In the Acuform® system, PEO is used as a rapidly swelling and SR matrix former. HPMC is described as modulating the rate of PEO swelling and erosion so that a more even and reproducible drug release profile is obtained [2]. The use of HPMC also permits lower levels of PEO to be used, which is important due to the lower daily intake limits for PEO [95].

#### Film coatings and oral films

Polymer blends have been used extensively in the film coating of tablets, pellets, and capsules. A second polymer may be used with a primary film former to improve adhesion to the substrate, modify the mechanical properties of the coating, improve moisture protection, or to modulate drug release. Cost reduction may be another reason for combining polymers. A number of commercially marketed film coating systems are based on polymer blends. These include products for both non-functional (immediate release) and functional (controlled release) coatings (Table 3).

**Table 3** Polymer blends used in film coatings

Polymers	Advantage(s)	Commercial product/application	Ref.
Polyvinyl alcohol, polyethylene glycol (PEG) 3350	PEG 3350 can be used as a dry powder plasticizer for fully formulated coating systems	Opadry II 85F	[5]
Hypromellose, hydroxypropyl cellulose	Improved adhesion, increased film elasticity	SheffCoat™ HS	[6]
Hypromellose, polyvinyl alcohol	Improved moisture protection, increased film elasticity	SheffCoat™ MP	[6]
Hypromellose, polydextrose or starch	Cost reduction; shorter coating times due to higher spray solids contents due lower viscosity	SheffCoat™ D (HPMC/polydextrose) SheffCoat™ S (HPMC/starch)	[6]
P-MAA-EA, P-EA-MMA	Increased film flexibility, eliminates plasticizer requirements and facilitates the compression of enteric coated particles	Eudragit® FL 30 D-55	[7]
P-EA-MMA-TMAEMA (1:2:0.2), P-EA-MMA-TMAEMA (1:2:0.1)	Modulation of drug release rates	Eudragit® RL and RS combinations for sustained release	[8]
Ethylcellulose, sodium alginate	Alginate serves as a pH-dependent pore former and provides enteric functionality, GRAS excipient-based enteric film coating for nutraceuticals	Nutrateric®	[9]

**Abbreviations:** P-MAA-EA poly(methacrylic acid-co-ethyl acrylate) (1:1), P-EA-MMA poly(ethyl acrylate-co-methyl methacrylate) (2:1), P-EA-MMA poly(ethyl acrylate-co-methyl methacrylate), P-EA-MMA-TMAEMA poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride), GRAS generally regarded as safe

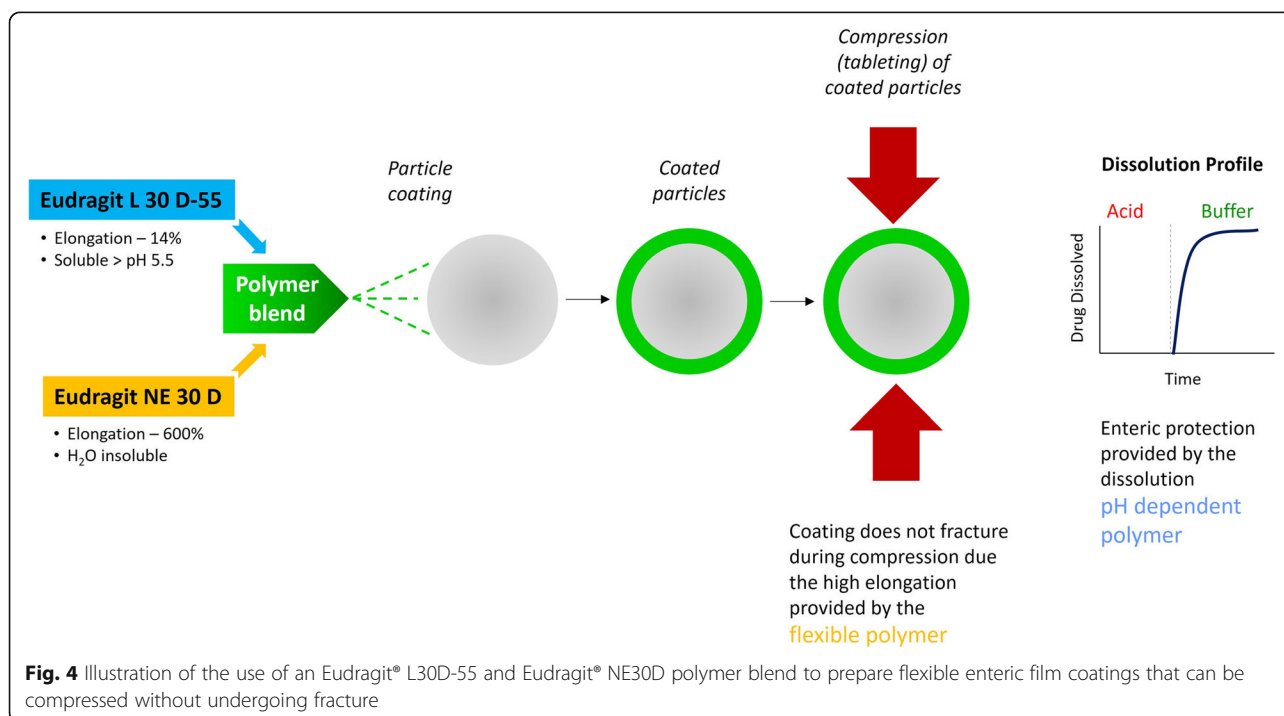
Non-functional coatings are applied for the purpose of esthetic appearance, product identification, improving stability (to moisture and light) and taste-masking. The most commonly used polymers for non-functional coating are low-viscosity HPMCs. When HPMC is used for tablet coating, the addition of plasticizers is required to improve film flexibility. Polyethylene glycol (PEG) is commonly used as a plasticizer for HPMC films. Another mechanical property that can be modified by blending additional polymers with HPMC is film-substrate adhesion. Hydroxypropyl cellulose (HPC) is an example of a polymer which has been blended with HPMC to improve film adhesion. HPC has also been reported to reduce logo bridging and film cracking at the edges when used with HPMC [96]. Additional reasons for using polymeric blends in non-functional film coatings are to improve drug stability by reducing water vapor permeability, to reduce the duration of the coating process, and to prepare dry, fully formulating coating systems.

Polymer blends have been used extensively as functional film coatings for controlled release applications [97]. Although functional film coatings may be applied using organic solvent-based solutions, there is a preference for aqueous systems which are latex dispersions [98, 99]. These systems are colloidal dispersions of water insoluble polymers such as polymethacrylates, ethylcellulose, or poly(vinyl acetate). In addition to drug release rate and mechanical properties modulation, polymeric additives may be used to improve the long term dissolution

profile stability of controlled release film coatings [100].

An example of the use of a polymer blend to obtain optimized mechanical properties is illustrated in the tableting of enteric coated particles (Fig. 4). In tableting of coated particles, films of the enteric polymer Eudragit® L 30D-55 tend to be brittle and fracture during compression. The polymer Eudragit® NE 30D however, while not possessing enteric functionality, is extremely flexible and its films when coated onto particles retain integrity during compression. Mechanically, the percent elongation at break values of Eudragit® L 30D-55 and Eudragit® NE 30D films are 14% and 600%, respectively [8]. A blend of the two polymers can therefore be used to prepare coatings that are flexible enough to withstand compression while maintaining enteric functionality.

Film coatings based on natural or generally regarded as safe (GRAS) materials appeal to nutraceutical and dietary supplement markets. This is because the typical enteric polymers used for pharmaceutical products have daily intake limits. One approach to developing enteric film coatings for nutritional products has been to use GRAS polysaccharides with anionic functional groups. Nutratric® a coating system based on the use of a combination of sodium alginate and ethylcellulose has been developed on this principle [9, 101]. In this blend, ethylcellulose serves as the primary film former. The alginate polymer provides enteric protection due to pH-dependent ionization of its carboxylic acid groups. At low pH it is insoluble, while at higher pH, it dissolves





forming pores in the ethylcellulose coating which promote disintegration and drug release. An enteric coating based on an alginate and pectin blend has also been reported [102].

Oral thin films are used in lingual (for enteral), sublingual, and buccal drug delivery. Orodispersible films (ODFs) are a convenient dosage form for pediatrics and persons with dysphagia [103, 104]. Oral films are matrix systems with the polymers determining key factors such as drug loading, mechanical characteristics, handling, mucoadhesion, and disintegration times [103]. In a patented system which combines PEO and cellulosic polymers, controlling the polymer ratio is used as a means to modulate resistance to tearing, film flexibility, mucoadhesion, and drug release rates [23]. Furthermore, because of their inherent flexibility, polymers such as PEO and HPC can be used instead of low molecular weight plasticizers in oral films made by wet casting [24].

### Capsules

For many years, gelatin was the sole option as the shell forming material for both hard and soft capsules. However, its animal origin, bovine spongiform encephalopathy/transmissible spongiform encephalopathy concerns, and its cross-linking potential have been major concerns which have led to the development of non-animal origin capsules. Many of these plant-based capsules use more than one polymer to form the capsule shell (Table 4).

First-generation hard (two-piece) HPMC capsules incorporate an additional polymer such as carrageenan or gellan gum [10, 105]. This additional polymer facilitates setting of the polymer solution and gelling, which is required for capsule manufacturing by a dip molding process. Interestingly, the amounts of the additional polymer required to facilitate gelling are very low, being in the range of 1% (w/w) or less (based on the HPMC level) [106]. Second-generation HPMC capsules have

now been developed which do not require a gelling agent instead inducing gelation by the use of heated molding pins (thermogelling process). Non-gelatin capsules are currently more expensive than gelatin capsules due to higher raw material and manufacturing costs; however, their lower sensitivity to environmental temperature and moisture should also be considered in an overall cost analysis [107, 108].

Another application of polymer blends has been in the development of non-coated enteric hard capsules. While capsules can be film coated with enteric polymers, this process adds an additional unit operation and level of complexity in drug product manufacturing. The development of capsules with an enteric functionality incorporated within the shell has therefore been a significant advancement in capsule technology. Another advantage of enteric capsules is that they can be used for very small batches that are prepared by filling individual capsules manually or with small scale capsule filling equipment which is extremely useful in early drug development and preclinical studies where there is a limited supply of the drug substance.

Two hard capsule products with pH-dependent dissolution are currently marketed—DRcaps® (for nutritional products and dietary supplements) and Vcaps® enteric capsules. DRcaps® are made of HPMC and gellan gum. Delayed release is obtained by the use of higher levels of gellan gum compared to those used in immediate release HPMC/gellan gum-based capsules [109]. Gellan gum is a heteropolysaccharide comprised of glucose, rhamnose and glucuronic acid units. Zeta potential measurements have shown that the ionization of gums which contain acidic groups decreases with pH [110], which explains the basis for the pH-dependent dissolution of capsules made with higher levels of gellan gum. Vcaps® enteric capsules, which are based on HPMC and hydroxypropyl methylcellulose acetate succinate (HPMC-AS), are an enteric product for pharmaceuticals, with the enteric

**Table 4** Polymer blends used in capsules

Polymers	Advantage(s)	Commercial product	Ref.
HPMC, carrageenan	Plant based (gelatin free)	Quali-V® hard capsules (Shionogi Qualicaps)	[10]
HPMC, gellan gum	Plant based (gelatin free)	Vcaps® hard capsules (Capsugel)	[10]
HPMC, gellan gum	<ul style="list-style-type: none"> <li>• Enteric functionality (without the need for enteric coating)</li> <li>• GRAS excipients</li> <li>• Plant based (gelatin free)</li> </ul>	DRcaps® hard capsules (Capsugel)	[10]
HPMC, HPMC-AS	<ul style="list-style-type: none"> <li>• Enteric functionality (without the need for enteric coating)</li> <li>• Plant based (gelatin free)</li> </ul>	Vcaps® enteric hard capsules (Capsugel)	[10]
Carrageenan, starch/modified starch	Plant-based (gelatin free) soft capsules	<ul style="list-style-type: none"> <li>• Vegesoft vegetarian softgels (Eurocaps)</li> <li>• Versagel™ (Procaps)</li> </ul>	[11, 12]
Gelatin, methacrylic acid copolymer type A	Gelatin-based softgels with enteric functionality (avoids the need for enteric coating)	Entericare™ softgels (Patheon)	[13]

**Abbreviations:** GRAS generally regarded as safe, HPMC hypromellose, HPMC-AS hydroxypropyl methylcellulose acetate succinate

function coming from the HPMC-AS polymeric component.

Soft capsules, which are more amenable to liquid, paste, and oil fills than hard capsules, have also become available in plant-based versions. Immediate release non-gelatin soft capsules made of modified starch and carrageen are commercially available [111].

Polymer blends have been used to develop inherently enteric soft shell capsules in which pH-dependent dissolution is obtained by combining enteric polymers with gelatin [13, 112–114]. Enteric soft shell capsules using natural anionic GRAS polysaccharides, such as pectin, to provide enteric function have also been patented [115].

#### Bioavailability enhancement and melt extrusion

Polymer blends have been used to improve drug dissolution especially by techniques, such as hot melt extrusion (HME), which can be used to manufacture solid dispersions. The HME process provides thermal energy that melts or softens materials along with intense mixing, facilitating the dissolution or fine dispersion of drug substances in polymeric matrices. Under certain conditions, it is possible to produce amorphous or microcrystalline dispersions which exhibit improved drug dissolution. A balance of hydrophobicity and hydrophilicity in solid dispersions may be required to prevent crystallization and control drug dissolution and supersaturation [116]. These requirements may necessitate the use of more than one polymer. Synergistic effects on crystal growth inhibition of ritonavir have been reported for binary polymer blends [117]. Interestingly, combinations of a hydrophobic polymer (zein) and a hydrophilic polymer (HPMC) in spray dried isradipine solid dispersions were observed to reduce drug crystallinity and enhance drug dissolution more effectively than the individual polymers [118].

The Noxafil® and Nucynta® ER products listed in Table 5 are manufactured by melt extrusion [119, 120]. HME is listed as alternative manufacturing method for sublingual films which are commonly manufactured by wet casting techniques [23, 24].

Mixtures of low molecular weight polymers such as polyethylene glycols and poloxamers have been utilized in a marketed solid dispersion. In the patented Melt-dose® technology, a combination of PEG 6000 and poloxamer 188 is used to dissolve tacrolimus and create a solid dispersion which is then sprayed onto a lactose carrier [21].

HME is also used to produce delivery devices such as implants and inserts. Lacrisert®, an ophthalmic insert made solely of hydroxypropyl cellulose and used to treat dry eye syndrome, was the first pharmaceutical melt extruded product [121]. An example of an implant which combines several polymers is Durysta™ (bimatoprost),

a recently approved (2020) ophthalmic sustained release implant that is administered by intercameral injection. The product is used to reduce intraocular pressure in patients with open angle glaucoma or ocular hypertension. The implant is made from the biodegradable polymers poly(D,L-lactide) (PLA), poly(D,L-lactide-co-glycolide) (PLGA), and poly (D,L-lactide) with an acid end group [30]. The Durysta™ implant is designed to release bimatoprost for 3–4 months, which is a significant advantage in reduction of dosing frequency compared to the daily use of eye drops [122]. The implant is manufactured by extruding a blend of the polymers and the active into filaments which are then cut to the dimensions of the implant [123]. In contrast to the previously mentioned HPMC-type polymers which are biologically inert in vivo, these polymers hydrolyze in vivo yielding natural carboxylic acids. The different biodegradable polymer chemistries are used to tailor the duration of drug release and the mechanical properties of the implant. PLA degrades more slowly as it is more hydrophobic than PLGA, while (carboxylic) acid end-capped polymers are more hydrophilic than their ester end-capped counterparts. The acid end groups also increase the rate of degradation by autocatalyzing hydrolysis of ester linkages in the polymer backbone [124].

#### Commercial products and technology platforms

Polymer blends have been used in several commercially marketed products, a number of which are listed in Table 5. For ease of reference, the polymeric blend components used in these products are listed separately from other excipients in the formulation. In general, the techniques in which the polymer blends are formed can be divided into three types: (1) powder-based blending, (2) melt/thermal blending, and (3) solvent-based liquid blending. In the case of solvent-based blending, the product may be further processed by drying to obtain a final product (e.g., oral films, capsule shells).

Several of the products listed in Table 5 have patented compositions and methods of manufacturing. A number of these patents are also part of proprietary technology platforms. For example, Acuform® [125] BEMA® (abbreviation for BioErodible MucoAdhesive) [126], NOVA-DUR [127], and Pharmfilm® [25] are technology platforms used for the products Glumetza®, Belbuca®, Durysta™, and Sympazan®, respectively.

In most of the examples listed, the polymer blends are formed during the manufacture of the dosage form with the exception of the XHANCE® nasal spray product in which the polymer blend in the formulation derives from the use of a co-processed excipient (MCC/NaCMC). Various manufacturing techniques are used to incorporate the polymers including direct compression and HME for tablets. Casting from solution is used for

**Table 5** Polymer blends in selected marketed products

Commercial product/API/dosage form/ manufacturing process	Polymeric/non-polymeric excipients (manufacturing process)	Company	Ref.
Glumetza®/Metformin HCl 500-mg/tablets/not disclosed (patent examples list direct compression)	Hypromellose, microcrystalline cellulose, polyethylene oxide/coloring, magnesium stearate	Assertio Therapeutics	[2, 14]
Noxafil®/posaconazole 100 mg/gastro-resistant tablets/HME	<i>Tablet core:</i> hypromellose acetate succinate, cellulose microcrystalline, hydroxypropylcellulose, croscarmellose sodium/silica dental type, magnesium stearate <i>Film coating:</i> polyvinyl alcohol, macrogol 3350/titanium dioxide, talc, iron oxide yellow	Merck	[15, 16]
Isoptin® SR/verapamil HCl 120, 180, 240-mg/sustained-release tablets/not disclosed	<i>Tablet core:</i> alginate, microcrystalline cellulose, polyvinyl pyrrolidone/magnesium stearate <i>Film coating:</i> hypromellose, polyethylene glycol/talc, titanium dioxide, color additives	Ranbaxy	[17–19]
Nucynta® ER/tapentadol 50, 100, 150, 200, 250-mg/extended-release tablets/HME	<i>Tablet core:</i> hypromellose, polyethylene glycol, polyethylene oxide/alpha-tocopherol (vitamin E) <i>Film coating:</i> polyvinyl alcohol, polyethylene glycol/talc, titanium dioxide, coloring agents and printing inks	Collegium Pharmaceutical	[20]
Envarsus XR®/tacrolimus 0.75 mg, 1 mg, 4 mg/extended-release tablets/melt drug-polymer solution coated onto carrier	Polyethylene glycol, poloxamer, hypromellose/lactose monohydrate, magnesium stearate, tartaric acid, butylated hydroxytoluene, and dimethicone	Veloxis	[21, 22]
Sympazan® oral film/clobazam/5, 10, 20 mg/orally dissolving film strips/wet casting (HME listed as an alternative)	Hypromellose, polyethylene oxide/artificial cooling flavor, citric acid, glycerol monooleate, maltitol, natural and artificial bitter masker, natural raspberry type flavor, purified water, sodium phosphate dibasic, and sucralose	Aquestive Therapeutics	[23–25]
Belbuca®/buprenorphine 75, 150, 300, 450, 600, 750, 900 mcg/buccal film/wet casting	<i>Mucoadhesive layer:</i> carmellose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, polycarbophil/propylene glycol, sodium benzoate, methylparaben, propylparaben, iron oxide, anhydrous citric acid, vitamin E acetate, monobasic sodium phosphate (anhydrous), sodium hydroxide <i>Backing layer:</i> hydroxypropyl cellulose and hydroxyethyl cellulose and non-polymeric components	BioDelivery Sciences	[26, 27]
Cod liver oil high strength/omega 3 fish oils/capsules/liquid-gel mixing	<i>Capsule shell:</i> modified maize starch, carrageenan/glycerol, sodium carbonate	Seven Seas	[28]
Gentleal® tears severe lubricant eye gel/HPMC/gel/liquid mixing	Hypromellose, carbopol 980/phosphoric acid, purified water, sodium hydroxide, sodium perborate, and sorbitol	Alcon	[29]
Durysta™/bimatoprost 10 mcg/biodegradable implant/HME	Poly(D,L-lactide), poly (D,L-lactide-co-glycolide), poly (D,L-lactide) acid end, polyethylene glycol 3350	Allergan	[30]
Sinuva™/1350 mcg of mometasone furoate/sinus implant/drug-polymer coating of extrudate	Poly(D,L-lactide-co-glycolide), polyethylene glycol	Intersect ENT	[31]
XHANCE®/93 mcg of fluticasone propionate in each 106-mg spray/nasal spray/liquid mixing	Microcrystalline cellulose, carboxymethylcellulose sodium/dextrose, benzalkonium chloride, polysorbate 80, edetate disodium dihydrate, purified water	OptiNose	[32]
Neupro®/rotigotine 2 mg/transdermal patch/film casting	<i>Self adhesive matrix layer:</i> poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidone K90/sodium metabisulphite, ascorbyl palmitate, DL-α-tocopherol (NB: product also has a backing layer and release liner)	UCB Pharma Limited	[33, 34]

**Abbreviations:** API active pharmaceutical ingredient, HME hot melt extrusion, HPMC hypromellose

the oral film and transdermal patch products. It is also possible to manufacture such products by melt extrusion provided the components have adequate thermal stability. The solution and suspension type liquid dosage forms incorporating polymer blends include an ophthalmic gel and the previously mentioned nasal spray, respectively. The large number of products prepared by HME indicates that this technique is particularly suited to polymer processing, especially in cases where fine or molecular dispersion of the API and excipients is required.

Polymer blends are often used in lubricating ophthalmic drops as a combination of polymers helps optimize the product requirements for lubrication, viscosity and ocular retention time. Examples of these blends include HPMC/Carbopol (Gentleal® tears, Table 5) and polyvinyl alcohol/povidone [128, 129].

A number of products listed in Table 5 use more than two polymers. Noxafil® tablets and Belbuca® buccal films, for example, both use four polymers. The individual polymers provide various functionalities. In Noxafil® tablets, hypromellose acetate succinate, microcrystalline

cellulose, hydroxypropyl cellulose, and croscarmellose sodium provide bioavailability enhancement, diluent/dry binding, dry binding/disintegrant, and disintegrant functionality, respectively. The contributions of the individual polymers used in Belbuca® are not described in the relevant patent, but in general (with regard to oral films), carmellose sodium and polycarbophil have mucoadhesive properties while hydroxyethyl cellulose and hydroxypropyl cellulose are film formers.

## Conclusion

The blending of polymers is a valuable approach in addressing limitations of individual polymers. The key advantages of using blends of approved polymers in drug delivery are twofold: (1) complementary polymer functionality or benefits can be achieved and (2) the resource-intensive, lengthy regulatory and safety evaluation process for a novel excipient is not required. The large number of currently existing polymers with established safety profiles and a history of use in pharmaceutical and biomedical products means that there are numerous polymer blend combinations that are possible, with the potential to address many of the formulation challenges encountered in the development of new drug products. Of critical importance to the rational selection and use of these polymer blends is the characterization and understanding of the nature of polymer-polymer interactions in these systems. This enables the design of novel polymer blends that can be manufactured in a consistent manner and address unmet needs in polymer-based drug delivery.

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