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Formulating Hydrophilic Matrix Systems

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EXCIPIENT UPDATE

Applications of Complementary Polymers in HPMC Hydrophilic Extended Release Matrices

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ABSTRACT

In the post Hatch-Waxman Act 1984 era, developing an extended release (ER) formulation of a new chemical entity with extended patent life has become very crucial to innovator companies. Patent, market share protection, and extension of a product's life cycle are of utmost importance. While multiple ER technology platforms are being developed, an important area that has not experienced significant change throughout the years is new pharmaceutical excipients for ER applications. This has been attributed mainly to the regulatory and safety framework, which hinders approval of new excipients outside the context of a new drug application (NDA) or abbreviated new drug application (ANDA). The net result is the very slow pace of global development and commercialization of ER excipients. Using blends of approved polymers may be a powerful strategy to overcome this regulatory barrier, but still brings resolution to current challenges (size limitations for high dose APIs, once-daily dose, burst effect with high solubility APIs, and potential food effect) in ER formulations. The following specifically examines the application of co-formulation of polymers in developing ER hydrophilic matrix systems to overcome these challenges and discusses its advantages in drug release modulation from matrices.

INTRODUCTION

For many drugs and therapeutic indications, conventional multiple dosing of immediate release formulations provides satisfactory therapeutic response with an appropriate balance of efficacy and safety. The rationale for development of an ER formulation of a drug is to enhance its therapeutic benefits and minimize its side effects, while improving the management of the disease condition. In addition to its clinical advantages, an innovative ER formulation provides an opportunity for a pharmaceutical company to manage product life cycles.

The prototypes of orally administered hydrophilic matrices were first described more than 4 decades ago, and since then, a number of ER technologies have been developed and registered.[1] From a commercial persepctive, hydrophilic matrices are economical to develop and manufacture due to the use of available equipment without further investment, stable formulations, and broad regulatory acceptance. In most instances, hydrophilic matrices use polymers with flexible chemistry that offer an opportunity to formulate an ER dosage form for a wide range of APIs with varying solubility and doses.

Various high molecular weight water-soluble or water-swellable polymers have been used in hydrophilic matrices, such as hypromellose [hydroxypropyl methylcellulose (Hypromelose, HPMC)], hydroxypropylcellulose, sodium carboxymethylcellulose, sodium alginate, carbomer, and polyethylene oxide. Table 1 shows FDA-registered oral ER formulations containing these commonly used hydrophilic or water-insoluble polymers along with their approved maximum potency levels.[2] HPMC, by far, is the most popular polymer in matrix applications because of its ability to obtain desired release profiles for a wide range of drugs, provide robust formulation, global availability, cost-effective manufacture, broad regulatory acceptance, and extensive history on its use.[3-7]

Although the use of HPMC as a rate-controlling hydrophilic polymer in ER formulations is well-documented, the following are still some unmet needs and challenges associated with ER hydrophilic matrices:

1. HPMC is a nonionic polymer and hence the matrices exhibit pH-independent drug release profiles when drug solubility is pH-independent. However, when drug solubility is pH-dependent, eg, for acidic or basic drugs, the release profile may be affected by the pH of the media.[8-11] In some cases, a pH-independent ER performance in the gastrointestinal tract may lead to consistent bioavailability of the drug.

2. HPMC matrices may exhibit an initial burst release for very soluble drugs.[6,12-14] This behavior has been attributed to the rapid dissolution of the drug from the surface and near the surface of the matrix, while the polymer undergoes hydration to form a protective gel layer.

3. Developing an ER hydrophilic matrix formulation of high dose APIs (eg 500 to 1000 mg) is challenging because of overall restrictions on size of the tablets for ease of swallowing.[5]

4. ER hydrophilic matrix formulations of very slightly soluble or practically insoluble drugs may exhibit food effects, ie, variable bioavailability, depending on administration during fasting or fed state.[15,16] This has been thought

to be attributed to the difference in the hydrodynamic activity of the gastrointestinal tract following postprandial dosing.

There has been a keen interest amongst formulation scientists to develop new polymeric excipients to overcome some or all of the aforementioned challenges. However, due to regulatory constraints, high costs, and time requirements for the development of a new polymeric substance, establishing its safety profile, and gaining market acceptance, there has been very few, if any, new polymeric excipients that have been introduced in the pharmaceutical market in recent years.[17-19] Therefore, efforts have been focused on combining approved polymers of different viscosities and/or chemistries to circumvent and resolve the aforementioned issues and achieve optimized drug release characteristics and product performance. HPMC is typically used as the primary polymer, and other approved polymer(s) have been added to enhance functionality and as a tool to modulate the drug release profile. Here, blends of HPMC with other polymers, including ionic, nonionic, and water-insoluble polymers, are discussed.

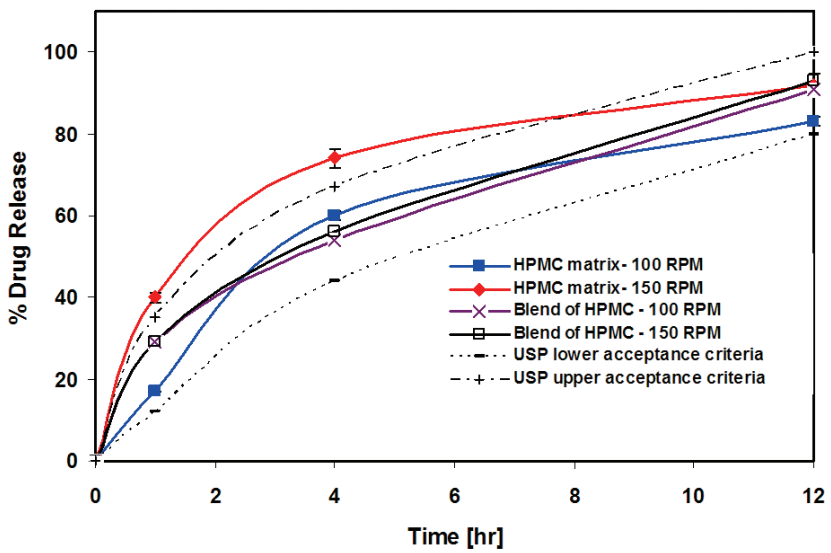
COMBINATIONS OF DIFFERENT HPMC POLYMERS

HPMC is mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropoxyl as substituent groups on the cellulose backbone. HPMC is a nonionic water-soluble polymer, and hence, the possibility of chemical interaction or complexation with other formulation components is greatly reduced, and the hydration and gel formation of its matrices are pH-independent. HPMC is available commercially from International Flavors and Fragrances Inc. under the trade name METHOCEL™, premium cellulose ethers.[3-5] High molecular weight METHOCEL Premium K (hypromellose 2208, USP) and E (hypromellose 2910 USP) chemistries are the most widely used in ER matrix formulations and are represented worldwide by Colorcon, Inc.

Drug solubility and dose are the most important factors to consider in the design of HPMC ER matrices. In general, ER formulation of extreme drug solubilities coupled with a high dose is challenging. Drug solubility is an important factor determining the mechanism of drug release from HPMC hydrophilic matrices, influencing the choice of polymer viscosity, chemistry, and other excipients.[20-23] Use of an appropriate viscosity grade will enable a formulation scientist to design matrices based on diffusion, diffusion and erosion, or via erosion mechanisms. Practically insoluble drugs (eg, solubility < 0.01 mg/mL) may dissolve slowly and have slow diffusion through the gel layer of a hydrophilic matrix.[5] Therefore, the main mechanism of release would be through surface erosion of the hydrated matrix. In these cases, the control over matrix erosion to achieve consistent ER throughout the GI tract is critical, hence, low viscosity grades of HPMC (eg, METHOCEL Premium K100LV or E50LV) that provide adequate erosion are recommended. For drugs with very high water solubility, the drug dissolves within the gel layer (even with small amounts of free water) and diffuses out into the media. Therefore, it is important to ensure integrity of the gel layer after the drug has been dissolved and released from the gel layer. In this case, it is critical to have a strong gel layer through which diffusion can occur and hence, high viscosity grades of HPMC (METHOCEL Premium K4M, K15M, or K100M) are recommended in their formulations.[24] For successful ER of drugs, either soluble or insoluble, it is essential that polymer hydration and surface gel layer formation is quick and consistent in order to prevent immediate tablet disintegration and premature drug release. For this reason, polymers for hydrophilic matrices can be supplied with a small particle size range (eg, METHOCEL CR or Controlled Release grades) for rapid polymer hydration and consistent formation of the gel layer on the surface of the tablet.[5,25]

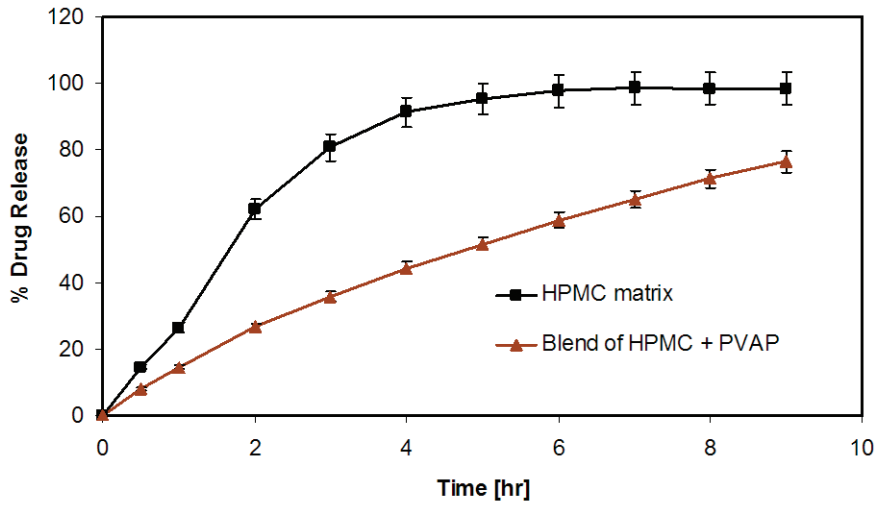
Depending on drug solubility, it may be necessary to blend different viscosity polymers to obtain intermediate viscosity grades of HPMC and achieve desired release kinetics. METHOCEL Premium products of the same substitution type, but of different viscosity grades, can be blended to obtain an intermediate viscosity grade. The following mathematical relationship (Equation 1), which is based on the Phillipof equation, can be used

FIGURE 1



Drug release profile of nifedipine from matrices containing 10% drug, 30% METHOCEL™ K100 LV CR, or combination of METHOCEL™ K15M CR + E15LV, 59% (Fast-flo lactose or Starch 1500®, partially pregelantinized maize starch) and 0.5% w/w of Cab-O-Sil and magnesium stearate. Dissolution study was performed using USP apparatus II at 100 (or 150) rpm and 900 ml of simulated gastric fluid without enzymes containing 0.5% w/v sodium lauryl sulfate.

FIGURE 2



Verapamil hydrochloride release from matrices containing 48% drug, 20% METHOCEL™ K100 LV CR, or combination of 20% K100 LV CR + 8% PVAP, qs% Fast-flo lactose and 0.5% w/w each of Cab-O-Sil and magnesium stearate. Dissolution study was performed using USP apparatus II at 50 RPM, 900 ml of simulated gastric fluid (0 to 1 hrs) and intestinal fluid (2 to 8 hrs) without enzymes.

for calculating the viscosity of the blend product.[25]

Equation 1.

$$\eta_B^{\frac{1}{8}} = X_1 \cdot \eta_1^{\frac{1}{8}} + X_2 \cdot \eta_2^{\frac{1}{8}}$$

Where η_B, η_1, and η_2 are the solution viscosity in mPas for polymer blend, polymer one, and polymer two respectively, and X_1 and X_2 are the weight fractions of polymer one and two, respectively. The influence of blending different polymer viscosity grades on an eroding HPMC matrix of a practically insoluble drug, nifedipine is shown in Figure 1.[26] Erosion is the principal mechanism of drug release for this formulation, containing a very slightly soluble drug and therefore, a low viscosity grade of polymer (ie, METHOCEL K100 Premium LV CR) was used. It was observed that although the dissolution profile of the formulation was within the USP requirement, it showed dependency on hydrodynamic conditions, ie, a faster dissolution rate resulted when the paddle speed was increased from 100 to 150 rpm (Figure 1). Such in vitro behavior may indicate a variable in vivo release rate and possibly food effect.[16,27,28] The study showed that a blend of high-viscosity grade HPMC (METHOCEL K15M Premium CR) to increase the gel strength, and a low-viscosity grade HPMC (METHOCEL E15 Premium LV) to allow for consistent erosion can be used to achieve the desired release profile and meet the USP requirements. Blending of these two viscosity-grade polymers produced matrices with improved release characteristics that exhibited similar dissolution profiles at agitation speeds of 100 and 150 rpm, respectively.

The strategy of blending high- and low-viscosity grades of HPMC has also been reported for achieving the zero-order release profile from matrix formulations and for reducing the drug release variability (low % Relative Standard Deviation, % RSD), thereby providing more uniform clinical levels of the drug.[29,30]

HPMC & IONIC HYDROPHILIC POLYMERS

Combination of HPMC and polymethacrylates, most notably anionic polymers (Eudragit L100 55) in hydrophilic matrices, has been reported for developing pH-independent release profiles for weakly basic drugs.[9,10] The incorporation of anionic polymers in the matrix can influence drug release in basic media by lowering the micro-environmental pH and also retard the drug release in acidic media by forming an insoluble mass, which acts as a barrier to drug diffusion. Moreover, because these enteric polymers have comparatively high molecular weights, they show longer residence time within the matrix gel layer, possibly facilitating their pH modulation effect to last longer compared to "smaller molecular weight" acids, such as citric acid.[9,31] In addition to the control of micro-environmental pH, anionic polymers may also alter the gel strength and erosion rate of the matrix and therefore, release rate of the drug. Similar to the development of pH-independent matrices for basic drugs, incorporation of cationic polymethycrylate polymers in HPMC matrices has been reported for developing pH-independent ER matrices for weakly acidic drugs. Combining of Eudragit E 100 with HPMC matrices has been shown to result in pH-independent release for acidic drugs, such as divalproex sodium.[31] This effect has been attributed to the enhanced solubility and hence, release of the drug in acidic media and retardation of the drug release in basic media.

Polyvinyl acetate phthalate (Phthalavin®, Colorcon) is another enteric polymer used in combination with HPMC to control the micro-enviornmental pH and enhance matrix properties, such as gel strength and erosion. Combining PVAP with HPMC to formulate matrices containing verapamil hydrochloride (HCl) has been reported.[32] When the formulation was subjected to dissolution according to USP 28 (Method 1) in simulated gastric fluid (0 to 1 hours) followed by intestinal fluid (2 to 8 hours), slower drug release was observed for blends of HPMC and PVAP compositions as compared to the single HPMC polymer matrix (Figure 2). Similar to polymethacrylates, PVAP is soluble in

simulated intestinal fluid as it is expected to behave like a soluble filler and result in a faster drug release rate. It has been proposed that the retardation of drug release is attributable to the synergistic interaction between PVAP and HPMC, resulting in the formation of a stronger gel layer and consequent slower diffusion and erosion rates.

Sodium alginate has also been used within HPMC matrices to obtain a pH-independent release profile for basic drugs.[33,34] It has been reported that at low pH (in gastric environment), sodium alginate precipitates in the hydrated gel layer as alginic acid. This alginic acid then provides a firm structure to the gel and retards rate of erosion. Solubility of basic drugs at this pH is high, hence diffusion through the matrix gel layer predominates as a mechanism of drug release. At higher pH values, the alginate remains as the soluble salt, thus providing less resistance to erosion. Erosion of the matrix facilitates release of the drug substance at these pH values, where drug solubility is reduced due to higher environmental pH. The balance of erosive and diffusive mechanisms at the pH extremes may explain the pH-independent drug release. This balance is required to be optimized for each new drug candidate to be incorporated, principally ensuring an adequate erosion rate at higher pH values compensate for the fall-off in driving force for diffusion/dissolution-mediated release as drug solubility decreases. There are commercially available ER matrices using the combination of HPMC and sodium alginate.[35]

Sodium carboxymethylcellulose (Na CMC) has been reported to have synergistic hydrogen-bonding interactions with HPMC.[36-38] Baveja et al reported combining HPMC with Na CMC may result into zero-order release profiles for the drugs propranolol hydrochloride, metoprolol tartrate, oxprenolol hydrochloride, and alprenolol hydrochloride.[39] The authors postulated that the polymers showed a synergistic increase in viscosity, which allowed erosion to occur at a rate equating to the movement of the front between the glassy and the rubbery polymer. However, it was later confirmed that enhancement in viscosity was not solely responsible for modulating the drug release profile, but that the complex formation between the anionic polymer and cationic drug also played an important role.[40] Freely soluble cationic drugs have been reported to be released slower from combinations of HPMC and Na CMC matrices than when formulated with HPMC alone, an effect attributed to drug/polymer interaction. However, for less-soluble drugs, which are released principally by erosion, this effect has been reported to be reversed. There are commercially available ER matrices using combinations of HPMC and Na CMC.[41]

Combination of HPMC with xanthan gum has been reported to result in greater retardation in drug release profile compared to single polymer systems.[12,42] Rapid hydration of xanthan gum combined with firm gel strength of HPMC have been attributed to slower drug release of high-solubility APIs. In this system, the initial burst release, which is typical of highly soluble drugs, was controlled by rapid hydration of xanthan gum, whereas subsequent drug release and matrix integrity were maintained by the firm gel of HPMC.[12] The rapid gel formation property of xanthan gum has also been exploited in gas-generating gastro-retentive matrices of ciprofloxacin formulated with HPMC.[43]

Combination of HPMC with carbomers has been studied for achieving ER characteristics for various drugs.[44,45] The reported advantages with the use of this blend composition were the use of low levels of the total polymer in the matrix, flexibility in drug release modulation, and ability to extend the release of some cationic drugs.

Recently, the work of our research group has shown that combining HPMC with carbomer and polyvinyl acetate phthalate (PVAP) in a matrix system resulted in slower drug release as compared to matrices comprising single or binary polymer systems.[46] This has been related to a synergistic increase in the viscosity, and therefore gel strength, of the matrix, possibly due to stronger hydrogen bonding between -OH groups of HPMC and the carboxylic groups of the carbomer or PVAP. This stronger hydrogen-bonding between the polymers resulted in a more rigid structure through which drug diffusion can occur. The influence of combination of carbomer, PVAP, and HPMC blend in a matrix formulation of a

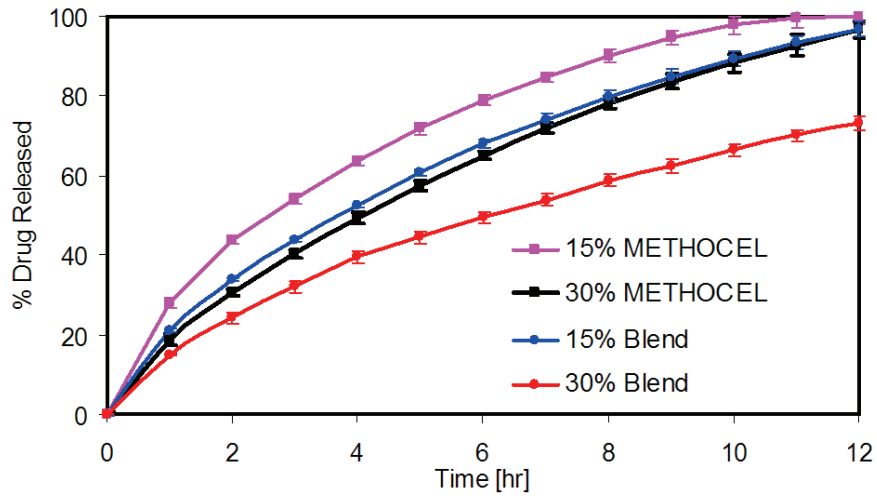
TABLE 1

FDA Registered Oral ER Formulations Containing Commonly Used Hydrophilic or Water-Insoluble Polymers[#]

Polymer/ Material	No of Hits on FDA Web Page[*]	Maximum Potency Listed for Oral ER Formulations (mg)[**]
Hydrophilic polymers		
Methylcellulose	15	96[§]
Hypromellose (Hydroxypropylmethylcellulose, HPMC)	91	670.04[#]
Hydroxypropylcellulose (HPC)	34	240
Sodium carboxymethylcellulose (Na-CMC)	21	155
Sodium alginate	09	350
Xanthan gum	21	109.52
Polyethylene oxide	07	543.90
Carbomers	14	195[§]
Water-insoluble and hydrophobic polymers		
Ethylcellulose	20	308.80
Polymethacrylates (Methycrylic acid copolymers)	54	70.90[@]
Polyvinyl acetate phthalate	02	NA
Fatty acids/alcohols/waxes		
Carnauba wax	21	300
Cetyl alcohol	05	59
Stearyl alcohol	04	244
Glyceryl behenate	09	50.60
Glyceryl monosterate	12	264.30
Hydrogenated cottonseed oil	08	402
Hydrogenated castor oil	11	410.82
Hydrogenated vegetable oil	11	228.5[b]

[*] Listings on FDA web page for use in oral dosage forms.
[**] Listed potency is for generic material; refer to FDA web page for specific grade listing. Also the maximum potency number value may be higher if the current status of some listings is "pending" or not listed at the time of writing this article.
[§] A potency of 183.6 mg is also listed for oral tablets however the dosage form i.e. IR or ER is not listed. [$] Listing under carboxypolymethylene
[@] Listing for enteric product 430.8 mg. [a] This listing for oral capsule sustained action (Hypromellose 2208 listing is at 480 mg).
NA: not available. [b] Listing for oral capsule hard gelatin is at 261 mg
[#] Inactive ingredient search for approved drug products, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm [accessed May 31, 2009]

FIGURE 3



Drug-release profile of guaifenesin from matrices containing 69% drug, 15% or 30% METHOCEL™ K4M CR, or combination of METHOCEL™ K4M CR + carbomer and polyvinyl acetate phthalate, qs% Fast-flo lactose and 0.5% w/w Cab-O-Sil and magnesium stearate. Dissolution study was performed using USP apparatus II at 100 rpm and 900 ml of deionized water.

soluble drug, Guaifenesin, is shown in Figure 3.[47] It was observed that the dissolution profile of the matrix blend formulation was significantly slower than the HPMC formulation when a similar level of total polymer was used.

The results showed that 15% of the total polymer blend resulted in a drug release profile that was similar to 30% HPMC alone. This may indicate that one can achieve a drug release profile in vitro similar to HPMC matrices at overall lower polymer inclusion in the matrix. Such polymer or excipient-sparing phenomenon can improve processing, allow larger dose to be accommodated or lower tablet weights to be achieved, and can reduce the overall cost of the final dosage form. The use of this blend also resulted in lower micro-environmental pH (3.5 to 4.5) within the gel layer (micro-environmental pH of HPMC alone matrix: 7.4 to 8.2), which may be beneficial for improving the solubility or stability of some basic drugs. Moreover, as the matrices containing the blends (carbomer, PVAP, and HPMC) produced higher gel strength compared to HPMC matrices, they exhibited less sensitivity to hydrodynamic conditions.[48]

HPMC & FATTY ACIDS, ALCOHOLS, OR WAXES

Combinations of HPMC and fatty acids, alcohols, or waxes have been reported with varied degrees of success.[49,50] Low-melting lipophilic materials blended at low concentrations (≤ 7.5% w/w) with HPMC have shown potential in achieving the ER of metformin, a highly solubile active, suggesting the possibility of niche applications for such matrix blends.[49] However, combinations of HPMC with lipophilic materials at higher concentrations have produced mixed results. While one researcher suggested levels of 20% w/w or more to tailor the drug release profile, other sources have shown the failure of such systems to provide ER.[6,50] When used at high concentrations, because of their low melting points, fatty acids or waxes may enable processing of HPMC formulations by melt granulation.[51]

HPMC & NONIONIC HYDROPHILIC POLYMERS

HPMC and poly (ethylene oxide) [PEO] has been used for modulating drug release and to prevent the burst release of highly soluble APIs.[52,53] In addition, the high-swelling capacity of PEO has been used in HPMC matrices to achieve expanded swelling, resulting in enhanced gastro-retention of the dosage form.[53] There are commercially available products using the combination of HPMC and PEO to achieve enhanced gastro-retention and selective delivery of the drug to the upper part of gastrointestinal tract.[53,54]

Combination of HPMC and HPC in the matrix system has been reported to provide retardation in the drug release profiles compared to single polymer systems.[55-57] This retardation has been attributed to a stronger gel layer of the resultant matrix, reducing diffusion and erosion rate characteristics of the gel layer.

CONCLUSIONS

Hydrophilic matrix systems have been widely studied and accepted as an ER approach for oral drug delivery, with numerous products in the marketplace. However, there are still some challenges associated with hydrophilic matrix systems, such as potential burst release with high-solubility APIs, size limitations for high dose APIs, potential food effect, and obtaining pH-independent release profiles for drugs that show pH-dependent solubility. Developing new polymeric excipients to overcome these challenges remains limited due to the regulatory constraints, cost, and establishing safety and market acceptability. It was shown that blends of pharmaceutically approved polymeric excipients have been a powerful strategy to achieve and optimize desired drug release characteristics and product performance. Combinations of HPMC with ionic and nonionic polymers have been used in hydrophilic matrices to modulate the release profile and overcome some or all of the challenges observed with hydrophilic matrices. The addition of ionic polymers has

been shown to not only modify the drug release profile, but also allow micro-environmental pH control of the gel layer, which may enhance solubility or stability of drugs.

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