Application of a Binary Polymer System in Drug Release Rate Modulation. 1. Characterization of Release Mechanism

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Abstract □ A new binary polymer matrix tablet for oral administration was developed. The system will deliver drug at variable rates according to zero-order kinetics for total drug content and is manufactured by direct compression technology. Highly methoxylated pectin and hydroxypropyl methylcellulose (HPMC) at different ratios were used as major formulation components, and prednisolone was used as the drug model. The results indicate that by increasing pectin:HPMC ratios, release rates are increased, but zero-order kinetics prevail throughout the dissolution period (e.g., 3–22 h). Different pectin:HPMC ratios provide a range of viscosities that modulates drug release and results in rapid hydration/gelation in both axial and radial directions, as evidenced by photomicrographic pictures. This hydration-gelation contributes to the development of swelling/erosion boundaries and consequently to constant drug release. Combination of these particular polymers facilitates rapid formation of necessary boundaries (i.e., gel layer and solid core boundaries) to control overall mass transfer processes. The drug fraction released ($Mt/M\infty$), release kinetics, and mechanism of release were analyzed by applying the simple power law expression $Mt/M\infty = kt^n$, where $k$ is a kinetic constant and the exponent $n$ is indicative of the release mechanism. The calculated $n$ values for pectin:HPMC ratios of 4:5, 3:6, and 2:7 were >0.95, which is indicative of a Case II transport mechanism (polymer relaxation/dissolution). The achievement of total zero-order kinetics is due to the predictable swelling/erosion and final polymer chain degradation and dissolution that is regulated by the gelling characteristics of polymers in the formulation.

Introduction

Extended-release drug products are attractive because they provide greater selectivity of pharmacological activity by controlling the pharmacokinetics, pharmacodynamics, and input rate of drugs. These products also result in improved patient compliance by allowing therapeutically beneficial reduction in dosing frequency of a drug formulation from its regular release form. The appropriate characteristics of extended release drug products have come about by the simultaneous convergence of many factors, including discovery of novel polymers, expiration of existing patents, and modifications. Drug diffusion from the matrix is accomplished via swelling, dissolution, and/or erosion, thereby providing both Fickian and non-Fickian release kinetics, including Case II transport (polymer relaxation/dissolution). The major component of such systems is a hydrophilic polymer. The microstructure, chemical makeup, and porosity of the polymer determine its local stiffness, chain flexibility, and different morphologies. In general, diffusivity is high in amorphous polymers containing flexible chains and low in crystalline polymers. With changes in morphological characteristics, the mobility of the polymer segments will change and diffusivity can be controlled. Addition of components, such as a drug, another polymer, soluble or insoluble fillers, or solvent, can alter intermolecular forces, free volume, glass transition temperature, and, consequently, transport mechanisms.

For controlled-release delivery from hydrophilic matrices, hydroxypropyl methylcellulose, carboxymethylcellulose, polyvinyl alcohol, or polyethylene oxide, with dispersed drug in them are often tabletted to achieve simple matrix systems. Depending on the system modifications, various drug release rates and patterns can be accomplished. The swelling mechanisms and kinetics of drug release from these systems are highly complex and therefore difficult to understand, as evidenced in recent publications. In general, when such systems are exposed to dissolution media, drug delivery is governed by two distinctive processes; namely, matrix swelling and dissolution/erosion at the matrix periphery. The initial swelling (i.e., transition of glassy structure to rubbery state) occurs at a rate that is mainly a function of matrix composition and dissolution medium penetration into the matrix. At some point, front synchronization between the dissolution medium/swollen front and rubbery/glassy front may occur, after which the drug release could be linear. However, it is reported that linear drug release is also achievable in the absence of front synchronization. The final changes in release rates are associated with the degree of polymer disentanglement and/or dissolution/erosion. The release mechanism, therefore, operates via polymer relaxation (swelling) and drug diffusion/system erosion, and has been described by the following equations:

$$\frac{Mt}{M\infty} = \alpha t^{1/2} + \gamma t$$

where amount of drug released, $Mt/M\infty$, is the sum of a diffusional contribution (with $t^{1/2}$ dependence) and a relaxation contribution (with t dependence), and both $\alpha$ and $\gamma$ are constants describing the diffusion-controlled release mechanism and constant rate process (Case II transport), respectively. However, when gel layer thickness is constant (i.e., at front synchronization), the amount of drug released can be expressed as follows:

$$\frac{Mt}{M\infty} = \xi + \epsilon t$$

where the contribution of the $t^{1/2}$ term coefficient of eq 1 becomes negligible. More detailed mathematical treatment of drug/polymer matrix swelling and dissolution can be found in the literature. Under conditions where drug release and swelling is not limited to planar geometry, as usually is the case with simple hydrophilic matrix tablets, the exact analysis will be complicated, especially when more than one polymer is incorporated into the matrix. Nevertheless, release profiles and mechanisms can be interpreted and explained according to the principles upon which eqs 1 and 2 are based.

To date, many studies have investigated drug release from hydrophilic matrix tablets containing a single polymer, a mixture of synthetic polymers, synthetic and gelling agents with an optional cationic cross-linking agent, and polysaccharides and gums capable of cross-linking. In our laboratories, we evaluated a large number of both natural and synthetic polymers for their interactive behavior on controlling drug release and developed new methods for optimization of controlled-release formulations. In the present work, for the first time, we report the development of a novel formulation of a simple hydrophilic matrix consisting of two polymers (pectin and HPMC) manufactured by direct compression technology. Single and polymeric mixtures with different viscosities, swelling rates, and solubility properties were evaluated, and ratios were optimized to provide zero-order drug delivery with variable rates for prolonged time periods, using prednisolone as a drug model.

Experimental Part

Materials and Methods—Prednisolone was obtained from Sigma Chemicals (St. Louis, MO). Pectin type 621 (designated as high methyl pectin citrus with a degree of methylation of 67–70%) was obtained from Pectagel Company, Great Neck, NY. HPMC 2208 was supplied by Dow Chemicals as METHOCEL K4M with a nominal viscosity of 4000 cP in water at 2% (w/v) level. Magnesium stearate (AMEND Drug and Chemical Company, Irvington, NJ) was used as received.

Viscosity Measurements—Measurements of viscosity were carried out on various solutions (0.1, 0.2, 0.3, 0.4, or 0.5% w/v) of pectin, HPMC, and pectin:HPMC mixtures (3:6 ratio) in deionized water, dilute HCl (pH 1.2), and phosphate buffer (pH 7.4). All solutions were dispersed by vigorous stirring. Tests were performed at 37 °C in the Brookfield digital viscometer LVTD (Brookfield Engineering Laboratory Inc., Stoughton, MA) at 60 rpm. The viscometer was calibrated with distilled water at 20 °C, which gave a value of 1.002 cP.

Tablet Preparation—Tablets containing 10% (w/w) drug loading with different ratios of pectin to HPMC (w/w in all cases) were prepared by direct compression with a compactor press (model C, Fred S. Carver Inc., Wabash, IN) with a 7-mm flat-faced punch and die. All powders were passed through a standard US sieve number 22 and mixed in a cube mixer for 15 min. Then, 1% (w/w) magnesium stearate was added to all formulations, and the formulations were mixed for an additional 5 min prior to compression. Tablets were produced by accurately weighing 150 mg of the powder mixture, filling the die, and compressing at specific applied pressure to give a hardness of ~10 kPa, as determined with a laboratory hardness tester (Erweka hardness tester, model 2E, Schleuniger, Zurich, Switzerland). The total weight of each tablet was 150 mg, and the thickness was ~3.2 ± 0.05 mm. Six tablets were produced from each formulation.

Dissolution Studies—Tablet batches were subjected to dissolution study at 37 °C and 50 rpm with the USP XXIII dissolution apparatus II (paddle method) in 900 mL of deionized water (pH 7.0 ± 0.4 throughout the dissolution study). Samples (5 mL) were withdrawn at predetermined time intervals, filtered, and analyzed at 248 nm (HP diode array spectrophotometer, 8452A). Controlled-dissolution experiments showed that there was no interference in the UV absorption due to the dissolved pectin, HPMC, or their combinations. Fresh dissolution medium (5 mL), heated to 37 °C, was added to the vessel to maintain constant volume. Each experimental run (n = 3) was done in duplicate, unless stated otherwise.

Figure 1—Prednisolone release in water from tablets (n = 4) made under identical conditions, with different pectin:HPMC ratios but a constant drug loading dose (10%w/w). Key: (●) pectin only (n = 1.15); (X) 6:3 (n = 1.34); (○) 5:4 (n = 1.35); (□) 4.5: (n = 0.95); (●) 3:6 (n = 0.98); (□) 2:7 (n = 1.11); (●) HPMC only (n = 1.01). The standard errors of the means are not shown because they are smaller than symbols. The n values were calculated with eq 3 for all profiles except those for drug:HPMC tablets, where $n$ was calculated by incorporating a lag time ($t_0$) into the equation; that is, $Mt/M_{in} = kt - t_0^2$.

Matrix Erosion/Weight Loss Determination—Individual tablets were removed at different time intervals during dissolution studies and carefully placed on pieces of aluminum foil and dried under reduced pressure to a constant weight as determined by an analytical balance. The amount of drug released and total matrix weight loss were calculated for each time interval.

Drug Release Kinetics from Pectin:HPMC Tablets—In the experimental formulations used in this particular study, linear release kinetics and variable release rates were easily achieved for certain formulations, as illustrated in Figure 1. Release profiles show that by increasing the ratios of pectin to HPMC and keeping the drug loading constant, release rates are systematically increased and, in some cases, zero-order kinetics prevailed throughout the dissolution time. Similar release profiles were observed in phosphate buffers at pH 6.5, 7.0, and 7.4, with ionic strengths ($\mu$) of 0.17, 0.14, and 0.11, respectively.

Results and Discussion

Ideally, controlled-release products should provide slow continuous delivery of drug over the entire dosing interval. The ability of hydrophilic tablet matrices to hydrate and form a gel around the periphery of the tablet matrix is essential to prolong and control drug release. In such systems, tablet size increases manifold once the matrix is exposed to the dissolution medium or gastrointestinal (GI) environment. The rate and duration of drug release is therefore regulated by the swelling and the volume dimension of the core. Several studies have shown that the aforementioned parameters significantly influence drug release kinetics. There are also reports indicating that polymer properties (e.g., the degree of substitution of HPMC) have resulted in differential swelling characteristics with matrix expansion predominantly in the axial direction, at least in the initial phase of hydration, and that water mobility gradients are different in the axial and radial directions.

In the present study, we report the development of a new controlled-release formulation of a simple hydrophilic matrix consisting of two polymers (pectin and HPMC) manufactured by direct compression technology. Single and polymeric mixtures with different viscosities, swelling rates, and solubility properties were evaluated, and ratios were optimized to provide zero-order drug delivery with variable rates for prolonged time periods, using prednisolone as a drug model.
Typical profiles comparing kinetics of release in both deionized water and phosphate buffer (pH 7.4) for the 3:6 pectin:HPMC tablets are shown in Figure 2. Studies at low pH (i.e., <6) were not performed because of the degradation and instability of prednisolone in acidic medium. It is obvious that some of the formulations exhibit linear release with no burst effect or lag time. On the other hand, in some cases, an increase in release rates at a late time period (i.e., at higher release fraction) is evident. This late increase in release rate may be attributed to the heterogeneous nature of the gel structure, rapid matrix disentanglement, and drug dissolution at the dissolution front as the gel microstructure weakens, the polymer concentration decreases to a threshold disentanglement value, and the polymer completely dissolves. Under different experimental conditions, similar release profiles for highly loaded (i.e., 65%), highly soluble drugs in swellable HPMC matrix tablets have been observed by others. The cause of these release profiles has been related to quicker water penetration due to larger voids in the matrix. This particular phenomena will be discussed further in later sections.

The kinetics of release profiles can be analyzed by the following commonly used exponential equation extended with the constant b to identify the release mechanism:

$$\frac{M_t}{M_\infty} = k t^n + b$$

where $M_t$ and $M_\infty$ are the amounts of drug released at time $t$ and the overall released amount, respectively, $k$ is a release constant, $n$ is a release exponent indicative of the release mechanism, and $b$ is the y-axis intercept and represents the initial burst effect for the correct calculation of $n$ value. For a slab, $n = 0.5$, $0.5 < n < 1$, or $n = 1$ indicate Fickian release, anomalous transport, or Case II transport kinetics, respectively. In the case of a cylinder, $n = 0.45$ and 0.89 instead of 0.5 and 1. Equation 3 generally holds for the early portion of the release profile ($M_t/M_\infty \leq 60\%$). The calculated $n$ values
for profiles shown in Figure 2 were 1.01 and 0.98 for release in phosphate buffer and deionized water, respectively. The drug release rate profiles, calculated from the slopes of the curves (see Figure 3), indicate that the drug release rates are relatively smooth over the entire release period. A slight increase in release rates corresponding to an accelerated release fraction at the late time period (see Figure 1) is also evident. These data indicate that the drug release mechanism may be attributed to the influence of release-controlling parameters, like polymer swelling, erosion, and dissolution, as was noted by visual inspection during dissolution studies and is schematically shown in Figure 4. Confirmation of the latter observation is further illustrated in later sections (see Figures 7 and 8).

Viscosity Measurements and Influence of Gelation on Drug Release—It is apparent that the matrix hydration rate is influenced by polymer–polymer interactions, solvent effect, drug solubility, and ionic strength. To evaluate the effect of parameters of interest on drug release, pectin:HPMC (3:6 ratio), 10% (w/w) drug loading, and deionized water as the dissolution medium were used for additional studies. Influences of pH and ionic strength on viscosity of the 3:6 pectin:HPMC mixture were determined. The viscosities of pectin, HPMC, and the 3:6 pectin:HPMC mixture when various concentrations (w/v) were dissolved in deionized water were measured at 37 °C and are shown in Figure 5. The viscosity of pectin at a concentration of 0.5% is approximately 4 cP, whereas that of HPMC at a similar concentration is ~16 cP. Pectin:HPMC at a 3:6 ratio at similar concentration (i.e., 0.5%) had a viscosity of ~11.5 cP. A similar trend prevailed at other concentrations and, as shown in Figure 6, variations in pH and ionic strength did not seem to significantly affect the viscosity of the polymeric mixture (pectin:HPMC). It should be pointed out that because pectin is an anionic polysaccharides composed of 1-4-linked α-D-galacturonic acid, its gelation is expected to be influenced by variation in pH and the ionic strength. However, in this study, highly methoxylated pectin (degree of methoxylatation, ~70%) was used and no significant changes in viscosity and gelation of the pectin:HPMC mixture was evident over a wide range of pH (i.e., 1–7.4); see Figure 6. Gelation of HPMC, because it is a nonionic polymer, is independent of the pH, and HPMC
constitutes a major proportion of the matrix formulation investigated in this study. Furthermore, the gel microstructure and its molecular organization is likely to be composed of domains of pectin and HPMC that will influence the viscoelastic behavior of the final gel and thus the diffusion/erosion process. The nature of the viscoelastic properties of the swollen gel in hydrophilic tablet matrices is naturally influenced by factors such as temperature and the presence of other formulation components (i.e., lubricant, drug-to-matrix ratio, and drug solubility). Full confirmation of the role of these factors on the gelation mechanism and a better understanding of their effect on actual drug release behavior requires further work.

Mechanics of the Erosion and Gelation Process—The kinetics of drug release in this study can be best interpreted by evaluation of drug release and erosion simultaneously. As shown in Figure 7, linear release kinetics were noted when matrix erosion was measured immediately after matrix exposure to dissolution medium. Apparently, drug release and matrix erosion operate simultaneously.

The formation and growth of the surface-hydrated gel layer was investigated for pure pectin, HPMC K4M, and a mixture of both at various ratios. Representative profiles for radial, axial, and aspect ratio (diameter divided by thickness) over a period of 20 h, where possible, are shown in Figure 8. This study was performed in deionized water at 37 °C. All tablets hydrated to different extents in both radial and axial directions. It is known that when drug and HPMC tablets are exposed to the dissolution medium, the polymer interacts slowly with water and does not gelify rapidly and often initial drug release is high (i.e., burst effect), whereas addition of pectin appears to modulate and promote gelation. The dynamics of hydration/gelation is rapid in all cases (i.e., axial, radial, and aspect ratio), as shown in Figure 8. It is interesting to note that the initial radial expansion (up to <5 h) is in the order pectin > pectin:HPMC (3:6) > HPMC, whereas similar expansion in the axial mode is in the order HPMC > pectin:HPMC (3:6) > pectin. It appears that the swelling of combined pectin:HPMC mixture falls between the two extremes of radial—axial expansion, which might provide a more symmetrical three-dimensional matrix expansion.

Influence of Compaction Pressure on Matrix Swelling—Compressibility and compactibility of polymeric materials vary significantly. For example, HPMC has good compressibility and produces coherent compacts, whereas pectin on its own produces poor compacts. Such differences
in compatibility may be attributed to inherent physicochemical properties and consolidation mechanisms, which could be by particle fragmentation, plastic deformation, or both. Depending on the nature of the material and the type of consolidation, hydration dynamics will vary. The greater axial expansion compared with radial expansion in the case of HPMC has been reported in the past,\(^5\), although no explanation has been provided for such phenomena. It is possible that as a result of compression of HPMC within the confines of the die, polymer particles align/deform in such a manner that upon exposure to dissolution medium they relax or swell in the direction opposite to the direction of compression (i.e., axial expansion). This type of behavior may not necessarily apply to all materials compressed because, as mentioned earlier, physicochemical, mechanical, and viscoelastic properties vary and force distribution within the compact is highly anisotropic.

It is important to note that the majority of polymers used in the formulation of hydrophilic matrices are viscoelastic and would go through significant changes during the postcompression cycle (i.e., viscoelastic recovery, changes in crystallinity, stress relaxation, etc.). Such changes would affect the swelling properties of the matrices produced. One major flaw in the studies of front movements and swelling boundary determinations in the past is the fact that free-three-dimensional swelling of matrices has been totally ignored either by placing the cylindrical matrix between plexiglass disks,\(^8\) or coating portions of the tablet,\(^44\) and measuring the dynamics of events from the lateral side, or by investigating the compress disk within a die.\(^14\) There is no doubt that the existence of stress loci, strain, and uniaxial expansion will affect polymer relaxation, swelling, and especially kinetics of such processes; consequently, reported front boundaries may not reflect the real dimensional changes. Schematics and results of macroscopic examination of the actual gel layer boundaries and dimensional changes of the solid core (i.e., glassy core) of the matrix as a function of time during the 5-h period are shown in Figure 9. The initial matrix exposure to the dissolution medium corresponds to the zero position. It is evident that both the gel layer and solid core boundaries move together in opposite directions, but in a balanced proportion. The variations in gel microstructure within the thickness of the gel layer boundary were not determined, and no attempt was made to determine the drug diffusion boundary or diffusional front. In addition, further determination of boundary movements beyond 5 h was not feasible. The photomicrographs in Figure 10 further illustrate the dimensional changes associated with gel layer formation and the solid core during the hydration process. Normalized swelling thickness (i.e., swollen thickness divided by original thickness) in both radial and axial directions over a 20-h period is illustrated in Figure 11. Rapid hydration and swelling during the first hour is evident, after which radial expansion increases very slowly. In contrast, axial expansion is significantly higher and its attainment is much faster. The influence of a large axial/radial ratio on drug release behavior and erosion/dissolution is the subject of a future investigation.

**Conclusion**

In the present study differential swelling characteristics of pectin:HPMC, particularly in the initial hydration period, help to establish and modify the drug concentration gradient in the gel layer and the process of gelification. Furthermore, swelling/erosion boundaries operate as a function of the combined effects of polymer—polymer interactions (characteristics) and concentration, the relative contributions of gel layer boundary and core volume reduction to the overall dimensional changes associated with the gel network, and the microstructure. Finally, during the late time period (i.e., the last 20–30% of release profiles) when swelling/erosion boundaries are no longer in operation, rapid matrix deaggregation and dissolution result in a final release pattern.

As suggested in eq 1, the amount of drug released can be approximated by \(t^{0.25}\) (\(a\), zero-order (\(\gamma\)), or mixed kinetics (\(a\) and \(\gamma\)). In the latter case, diffusion, polymer swelling/dissolution, or structural changes induced in the polymer may be the rate-limiting step in the release process. In the present work, with \(n\) values in excess of 0.98 (as shown in Figure 2), a meaningful physical interpretation of constant \(\gamma\) in eq 1 can be attributed to polymer relaxation, erosion, and drug dissolution; that is, the so-called Case II transport.

An interesting observation in release profiles (as shown in Figure 1) is that the dissolution rate during the last 20 to 30% of the dissolution time for specific pectin:HPMC ratios is accelerated suddenly as a result of rapid polymer disentanglement and drug dissolution. This particular aspect would be applicable to those drugs that are absorbed throughout the GI tract. In the case of controlled-release systems, more rapid drug release in the distal GI tract, especially the...
colon, can compensate for the smaller surface area available for absorption, resulting in greater bioavailability.

Based on our observations and recently published work,15,38,45,46 the general dynamics of hydration, drug release and mechanisms, as well as final matrix disentanglement for the hydrophilic matrix systems can be best presented schematically in three phases, as shown in Figure 12. To achieve linear drug release, a very rapid hydration rate in phase I is essential to prevent a burst effect (i.e., minimize b value of eq 3), and swelling/erosion, drug dissolution, as well as gel layer thickness influence drug release kinetics from hydrophilic matrix systems. Finally, well-characterized polymeric combinations can provide gel structure that vary in thickness and viscoelastic behavior resulting in controlled rates of drug release. Such simple hydrophilic tablet matrix systems can be manufactured by direct compression. Optimization of formulation components for different drug loadings and drug solubilities, as well as the influence of hydrodynamic stress on release rate will be presented in part two of this communication.

References and Notes


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