Polymers for Solid Oral Dosage Forms

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INTRODUCTION

Polymers are used extensively in the development and manufacture of Solid Dosage Forms (SDFs) and serve many purposes. For Immediate Release (IR) SDFs, they are used as binders in order to increase the density, flowability, and compactibility of bulky Active Pharmaceutical Ingredients (APIs), which would otherwise not process acceptably on high-speed tablet presses and encapsulation machines. Polymers are used for non-functional (aesthetic) coatings to impart colors and favorable mouth feel to tablets without relying on the time-intensive and highly skill-based process of sugar coating, which was the only alternative prior to the advent of polymer-based coatings. Polymer-based functional coatings, such as those used for moisture or oxygen barriers, can nevertheless be formulated as IR dosage forms, still allowing quick release and absorption of the API. Cross-linked polymers that swell extensively in the presence of water and gastrointestinal fluids are used to promote disintegration of tablets and capsule plugs, and are available in commercially available powder forms designed to be readily compatible with tableting and encapsulation formulas and processes.

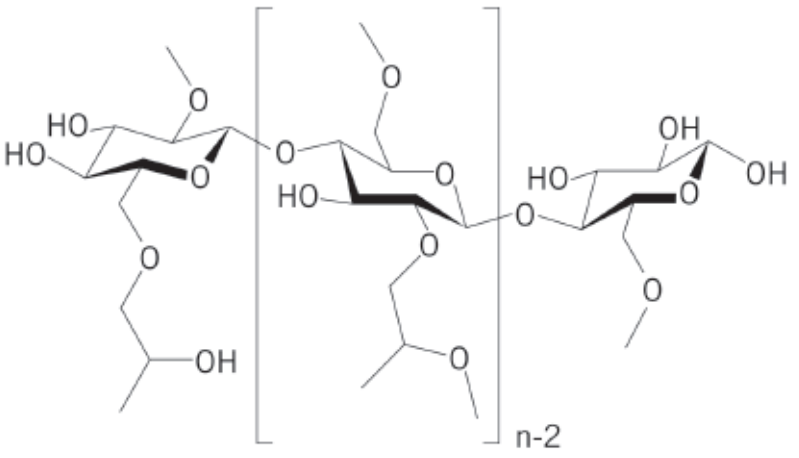
For Modified Release (MR) dosage forms, one use of polymers is for functional enteric coatings, which allow a dosage form to pass through the stomach without its internal contents being subjected to the harshly acidic and enzymatic conditions present there. This type of formulation is sometimes referred to as Delayed Release (DR). Other polymers are used for Controlled Release (CR) coatings or for CR diffusional matrices. Polymers can also be used to enhance the dissolution and bioavailability of the wide array of poorly soluble APIs that are the increasingly common products of current pharmaceutical discovery efforts. The following will present an overview of polymers used in the more exotic and technically challenging dosage forms involving MR (enteric and CR) as well as those used for enhancing the dissolution and bioavailability of poorly soluble APIs.

CONTROLLED RELEASE POLYMERS

One of the earliest distinct polymer systems for CR involved the use of hydroxypropyl methylcellulose (now officially called Hypromellose, Figure 1) for diffusional matrices. Earlier CR dosage forms were made using natural substances, such as shellac, waxes, or vegetable gums. The latter are technically polymeric in nature, but were, at least in earlier times, not well defined or well characterized. This presented challenges for reproducibility of release, although in that era, the standards for reproducibility were much less stringent than they are today. Hypromellose is available in a wide range of molecular weights (MWs) that can be

FIGURE 1

CHEMICAL STRUCTURE OF HYPROMELLOSE



used to modulate the rate of release. The higher MWs hydrate more slowly, and thus prolong release. Hypromellose is technically water soluble, but its rate of dissolving is highly dependent on MW. The lower MWs can be used for IR granulation binders and IR coatings, while the higher MWs gel before they dissolve, producing CR diffusional matrices that are also subject to some degree of erosion. Another technically water-soluble polymer with a similar mechanism of action is based on polyethylene oxide. This polymer has similar MW considerations as Hypromellose. Both of these substances, which are available as somewhat free-flowing powders, can sometimes be tableted using a simple Direct Compression (DC) process, although a wet granulation process may be necessary for high dosage strength products. When the percentage of API is high, and the API substance is not inherently flowable or compactable, wet granulation promotes acceptable tablet formation.

DELAYED RELEASE (DR) & SUSTAINED RELEASE (SR)

Acrylic-based polymers can achieve both DR and SR. Enteric (DR) polymers are usually protonated. These can be acrylic based (Figure 2), or based on a different class of chemistry, such as cellulose acetate phthalate. These can be purchased in powder form, but are commercially available as aqueous dispersions, which eliminates the need for extensive preparation steps. They may require the addition of some plasticizers and detackifying agents to render the polymers flexible and to prevent agglomeration during processing. The mechanism of action of enteric coatings is due to the property that they are not soluble in an acidic environment because an excess of hydronium ions renders them non-ionic. However, when they encounter the neutral pH of the intestinal tract, they deprotonate, becoming anionic, and readily dissolve. Various grades of enteric polymers have been designed to dissolve at different pH ranges, usually from 5.5 to 7.5. Stomach fluids range from pH 1.5 to 4.5, depending on the amount of food substances present.[1] When these exit from the stomach and mix with the neutral contents of the small intestine, the overall pH rises somewhat gradually. If a particular API needs to bypass the stomach to be protected against the acidic environment, but the formulator's goal is for it to be released quickly in the proximal portion of the small intestine, a polymer that dissolves at pH 5.5 might be chosen. Polymers that dissolve at higher pHs can be used to deliver the API to a certain section of the gastrointestinal tract, to take advantage of an "absorption window" or to inhibit degradation. It is desirable for some APIs to reach the more distal large intestine before they are released, either to avoid degradation or because they are intended to act locally (non-systemically) at that site. In this case, a polymer that dissolves only when the colonic pH of 7.5 is reached would be used.

Acrylic-based so-called reverse enteric polymers are non-ionic and somewhat hydrophobic and do not dissolve at neutral pH (for example in the mouth). These polymers are therefore used to mask the taste of bitter or foul-tasting APIs. Suspensions of particles coated with these polymers can be rendered organoleptically acceptable, but in the stomach

TABLE 1

SOLUMER FINGERPRINTS

Formulating lipophilic crystalline drugs results in a self-assembled drug-polymer complex. This provides two features that are required for improved bioavailability:

- Depression of melting temperature and energy
- Formation of colloidal dispersions upon contact with aqueous media

			Formulation		
	T_{melt} (°C)	ΔH_{melt} (J/g)	T_{melt} (°C)	ΔH_{melt} (J/g_{drug})	Particle size nm
Reservatrol	267.4	253.6	199.1	14.0	1224
Hesperetin	231.0	166.2	No peak of melting		1310
Nifedipine	172.4	113.4	140.9	8.4	749
Fenofibrate	81.5	74.3	64.4	9.3	669
Tacrolimus	135.0	60.5	118.0	52.0	836
Clarithromycin	227.6	70.2	207.9	40.1	1190
Albendazole	215.2	209.7	161.4	31.2	555
Fenbendazole	239.2	166.3	203.7	8.9	892
Itraconazole	169.7	84.4	155.6	21.9	910

FIGURE 2

CHEMICAL STRUCTURE OF ACRYLIC-BASED ENTERIC POLYMER

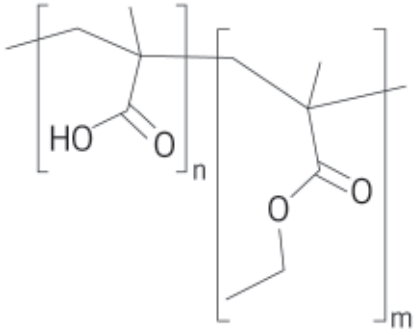
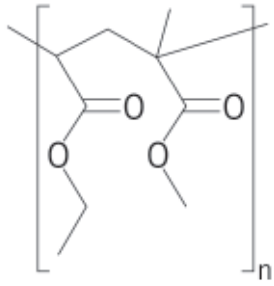


FIGURE 3

CHEMICAL STRUCTURE OF ACRYLIC-BASED CONTROLLED RELEASE POLYMER



where the pH level is lower, the polymer becomes ionic, and the drug is readily released.

Non-ionic acrylic-based polymers (Figure 3) can be formed into diffusion coatings. These coatings can be deposited onto whole tablets or onto beads that can then be filled into hard gelatin capsules or compressed into tablets. The latter can be accomplished by using a suitable "cushioning agent," such as microcrystalline cellulose, which prevents damage to the functional coating during the relatively high stress forces generated during the tableting process.

Ethyl cellulose is a water-insoluble, but organically soluble, hydrophobic polymer. It can be sprayed onto whole tablets or beads from an organic solution or from commercially available aqueous dispersions. The former process creates a molecularly coherent film; the latter process creates a coalesced latex film, similar to that produced by water-based latex paints. The advantage of a solvent-based process is the lack of dependence on a "curing" step; the disadvantage is the need to deal with organic solvents.

The latex-based process obviates the need for organic solvents, but is highly dependent on the precision of the coating process as the batch-to-batch consistency of the release profile requires predictable latex coalescence, which is a function of the curing temperature and time. While it appears this should be straight-forward, in practice, reproducibility is sometimes an issue.

Ethyl cellulose and other polymer films can be impregnated with so-called "pore formers." These are often water-soluble small molecules, such as lactose, which are added in small amounts to the spray solution or suspension. Once incorporated into the polymer film, these will dissolve and leach out, creating pores. This technique can be used to modulate the diffusional release. In this example, the release would be increased somewhat.

Another class of polymers that can be used for CR matrices or coatings is based on polyvinyl acetate. This is also commercially available as a dispersion that requires a plasticizer and a detackifying agent.

HOT MELT EXTRUSION

Hot Melt Extrusion (HME) has been used for decades to compound different materials into thermoplastic polymer melts, and is used in the pharmaceutical industry as a method to increase bioavailability of poorly water-soluble compounds when the API is compounded into an erodible polymer and in drug-eluting devices when the API is compounded into a non-erodible polymer (such as ethylene vinyl acetate or polyurethanes). The process of compounding allows both particle size reduction and mixing so that APIs can be incorporated into the polymer in dispersed form or, if the API solubility in the molten polymer is high enough, as a molecular solution. Because the extrudate cools rapidly upon exiting the extruder, any API that is dissolved in the polymer at the mixing temperature may quickly recrystallize into nanoparticulates or may be unable to recrystallize upon cooling, leading to supersaturated solid solutions. In the latter cases, stability of the product must be closely followed as recrystallization of the API over time is possible, especially at elevated storage temperatures and high API loadings. This may adversely impact the bioavailability due to formation of larger crystalline particulates of the API, and thus shorten the shelf-life of the final product. As with any dosage form, material selection is critical in the development of a successful product. For most applications, the polymer should be thermoplastic, stable at the temperatures used in the processing, and chemically compatible with the API during extrusion. For solid oral dosage forms, water-soluble polymers are usually chosen from among polymers already used in pharmaceutical products, such as polyethylene glycol and polyvinylpyrrolidinone. With the increased interest in using HME for pharmaceutical products, major polymer suppliers are beginning to offer polymers specifically designed for pharmaceutical applications. HME allows the API to be mixed with the polymer under the minimum of shear and thermal stresses, potentially minimizing the formation of process-related API degradants. Antioxidants are often included within the formulation, and the short residence time in the barrel (typically on the order of minutes) also helps to minimize thermal degradation compared to batch mixing and other compounding processes. For standard solid oral dosage forms, the compounded polymer and API may be extruded and cut directly into a slug, which can be encapsulated

into a hard or soft gelatin capsule, or can be extruded into spaghetti-like rods, cut into small cylinders, and spheronized while still warm and pliable using suitable equipment, such as a spheronizer. Another technique involves cryo-grinding the mixture to a powder followed by processing into a more conventional solid dosage form. Often the powder requires a densification step, such as roller compaction, and the addition of other excipients to enhance flow, compactibility, processability, and disintegration properties.

SPRAY-DRYING

Another technique to produce nanoparticulates of API dispersed in polymeric matrices is spray-drying a solution of the API and polymer. Though this may appear to be straightforward, to achieve the optimum dispersion and smallest particle size, careful consideration must be given to the composition of the polymeric matrix and feed solution. Key parameters include the API's solubility in various organic solvents, the API's molecular weight, the solubilities of the polymeric excipients, and the compatibility of the API and polymeric excipients in the spray-drying solution. Combinations of different polymer types, if properly formulated, can provide improved performance as compared to a single polymer type. A recent example of spray-drying technology is the Solumer technology, which employs a combination of a hydrophilic and amphiphilic polymer[2,3] The drug product exhibits modified thermal behavior, including depressed melting temperature and enthalpy of melting of the drug (Table 1), spontaneous formation of nanocolloidal dispersions upon contact with aqueous media, and enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and GI site-targeted release of the drug. The resulting free-flowing powder that typically results from spray-drying processes can contain high levels of API of 25% or more and are amenable to processing by various techniques into solid oral dosage forms.

SUMMARY

Having an understanding of polymer chemistry, including mechanisms of action, is critical for the solid dosage formulator. Knowledge of what specific polymers and polymer-based excipient products are available in the market, from both functional and regulatory perspectives, provide the formulator with a broad base of options and strategies for achieving virtually any type of release profile. ◆

REFERENCES

1. Eudragit® Applications Guidelines, 10th Edition. June 2008:43.
2. Lee R, Zalcenstein A, Mitchnick M. Solumer technology: a viable oral dosage form option for BCS class II molecules. ONdrugDelivery. May 2011:26.
3. Shi D, Loxley A, Lee RW, Fairhurst D. A novel spray-drying technology to improve the bioavailability of biopharmaceutical classification system class II molecules. Drug Development & Delivery. 2012;12(1):26.

BIOGRAPHY

Robert Gwozdz is responsible for solid dosage form development at Particle Sciences Inc. Before joining Particle Sciences, he held formulation positions at Teva Pharmaceuticals and American Home Products, developing both NCEs and generic products. He earned his BS in Biology from Penn State University and a Masters in Pharmaceutics from Temple University. Mr. Gwozdz has more than 30 years of experience in Pharmaceutical Research and Development and Process Engineering, specializing in modified release and enhancement of bioavailability.