Understanding Design and Development of Modified Release Solid Oral Dosage Forms

Yihong Qiu and Deliang Zhou

“Product and Process Design” discusses scientific and technical principles associated with pharmaceutical product development useful to practitioners in validation and compliance. We intend this column to be a useful resource for daily work applications.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator Yihong Qiu at qiu.yihong@abbott.com or to managing editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS
The following key points are discussed:
• Oral modified release (MR) dosage forms are developed by altering the drug release to achieve predetermined clinical objectives.
• MR solid oral dosage forms include extended release (ER) and delayed release (DR).
• Matrix, reservoir, and osmotic pumps are the most common ER delivery systems. Other MR systems include enteric, colonic, pulsatile, and bimodal release systems.
• Rational design of oral MR systems starts with identifying clinical need, defining the target product profile, performing the feasibility studies, selecting, formulating, and testing the appropriate MR system.
• Integrated understanding of drug characteristics, release control mechanism, and the key properties of rate-controlling materials is necessary to design a robust MR drug product during formulation and process development.
• Validation and compliance personnel should have a general understanding of the principles and design process of MR solid oral dosage forms, and be vigilant of raw material and manufacturing changes that may impact product quality and manufacturability.

INTRODUCTION
Modified release (MR) dosage forms are developed by altering drug absorption or the site of drug release in order to achieve predetermined clinical objectives. Possible therapeutic benefits of an MR product include improved efficacy and reduced adverse events, increased convenience and patient compliance, optimized performance, a greater selectivity of activity, or new indications (1). According to the US Food and Drug Administration (2), MR solid oral dosage forms include extended-release (ER) and delayed-release (DR) products. A DR dosage form releases a drug (or drugs) at a time other than immediately following administration. An ER dosage form is formulated to make the drug available over an extended period after ingestion, thus allowing a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g., a solution or an immediate release [IR] dosage form). For oral applications, the term “extended release” is usually interchangeable with “sustained release,” “prolonged release,” or “controlled release.”

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The objective of modifying oral drug release is to modulate the rate of drug input (i.e., dissolution or absorption) in the intestinal tract to achieve a predefined plasma profile. Common modes of drug release include delayed release (e.g., using an enteric coating), site-specific or timed release (e.g., for colonic delivery), extended release (e.g., zero-order, first order, etc.), or programmed release (e.g., pulsatile, etc.).

Figure 1 illustrates several examples of MR dissolution profiles. The delivery pattern required for a specific therapeutic agent depends on the understanding of its clinical pharmacology. For example, many body functions and diseases follow circadian rhythm (e.g., daily fluctuations of hormones and heightened tendency for asthmatic episodes). By timing drug release, therapeutic plasma concentration can be obtained at an optimal time to counter the diurnal nature of certain diseases such as angina, hypertension, asthma, early morning arthritis, and heart attacks at night. Classic examples of utilizing MR delivery that have achieved significant clinical and commercial successes include modified release products of nifedipine, methylphenidate, mesalamine, verapamil, and diltiazem.

Figure 1: Examples of oral modified release profiles (illustration).

Common Modified-Release Systems
Oral MR drug delivery technology has been used to develop new products for many years. Over the past three decades, significant progresses have been made in the development of theory, modeling, rate-controlling materials, technology platforms, and processing technologies. In addition, the emergence and maturation of new materials and aqueous-based polymeric dispersions have made MR dosage forms more amenable to conventional processing technology.

Extended-Release Systems
Various physical and chemical approaches can be used to design oral ER dosage forms that extend drug input in the gastrointestinal (GI) tract. The majority of modern proprietary and nonproprietary ER technologies are based on polymeric systems. Most ER products on the market fall into one of three categories: matrix, reservoir (or membrane controlled), and osmotic systems (see Table I). Drug release from these ER delivery systems generally involves one or more of the following mechanisms: drug diffusion, system swelling or erosion and dissolution, or osmotic pressure-induced release. Each type of system has its advantages and shortcomings with respect to the performance, applicability, manufacturing, control, development time and cost, and other considerations.

Matrix systems.
The drug substance is homogeneously mixed with the rate-controlling material(s) and other inactive ingredients in a matrix system. Drug release occurs either by drug diffusion from or erosion of the system. Based on the characteristics of the rate-controlling material, the matrix systems can be divided into hydrophilic and hydrophobic systems. Matrix systems are cost-effective and generally easier to scale-up and manufacture compared with reservoir and osmotic systems. In addition, these types of systems are usually manufactured using conventional processes and equipment.

Hydrophilic matrix systems. Hydrophilic matrix systems are polymer-based drug delivery systems involving two mechanisms of drug release: Fickian diffusional and relaxational release. The primary rate-controlling materials are polymers that hydrate and swell rapidly in water and form a gel layer on the surface of the system. Diffusion across the viscous gel layer is not the only drug release pathway as ero-
Coordinated by Yihong Qiu.

Table I: Common oral-extended release system.

<table>
<thead>
<tr>
<th>ER system</th>
<th>Sub-category</th>
<th>General features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix</td>
<td>Hydrophilic</td>
<td>Drug dispersed in a hydrophilic matrix. Drug release by diffusion and/or erosion.</td>
</tr>
<tr>
<td>Reservoir</td>
<td>Single or multiple unit</td>
<td>Soluble drug enclosed by an insoluble membrane. Drug release by diffusion across the membrane. Multiple-unit system preferred for minimized risk of dose-dumping.</td>
</tr>
<tr>
<td>Osmotic</td>
<td>One-chamber</td>
<td>Drug and osmotic agents reside in the same compartment. Drug release by osmotic pressure. Limited to more soluble drugs.</td>
</tr>
<tr>
<td></td>
<td>Two-chamber</td>
<td>Drug and osmotic agents reside in separate compartments. Drug release by osmotic pressure developed in the osmotic compartment. Suitable for drugs with low and high solubility.</td>
</tr>
</tbody>
</table>

sion of the matrix following polymer relaxation or dissolution also contributes to the overall release. In addition, diffusional release is influenced by changes in the diffusion path length due to polymer erosion. The relative contribution of each component to total release is primarily determined by the properties of a given drug and matrix composition.

Hydrophobic matrix systems. Hydrophobic matrix systems were the earliest oral ER platform for medicinal use. A well-known example is Premarin tablets, which have been commercially available since 1942. In a hydrophobic inert matrix system, the drug is dispersed throughout the matrix that involves an essentially negligible increase of the device surface or change in dimension during drug release. In most cases, drug release involves ingestion of water followed by dissolution and diffusion of the drug through the matrix.

In a diffusion-controlled matrix system, the pathway for drug diffusion increases and releasing surface decreases with time as the diffusion front moves inward, resulting in decreasing release rate over time (i.e., drug release is nonlinear). In addition, release rate of a drug with pH-dependent solubility typically varies with pH of the release medium. To overcome these shortcomings, various designs have been reported that effectively alter the drug release behavior from the matrix systems (1). For example, non-uniform drug loading was used to offset the decrease in release rate by increasing the diffusional driving force over time. Geometry factors including cone shape, biconcave, hemisphere with cavity, etc. were utilized to compensate the decreasing release rate by increasing drug release surface over time. pH-independent drug release has been obtained by incorporating pH modifiers (e.g., salts and ionic polymers).

Reservoir systems. A reservoir system is normally utilized to control the release rate of water-soluble active agents. A typical reservoir system consists of a core containing solid drug surrounded by an insoluble film or membrane. A porous membrane is created by incorporating soluble or leachable additives (e.g., a water-soluble polymer, plasticizer, etc.), offering a predetermined resistance to drug diffusion upon contact with aqueous medium. The drug release rate is a function of drug's solubility, film thickness, and characteristics of both the film and the additives (pore formers). For a specific drug and formulation, the release rate remains unchanged (i.e., zero-order) before solid drug is completely dissolved in the core.

The preferred reservoir system normally consists of many coated units such as beads, pellets, and mini-tablets. Unlike a single-unit tablet, the number of particulates of a reservoir system is often sufficient to minimize or eliminate the impact of any individual coating defect. An additional important feature of a multiunit system is that tailored drug release can be readily obtained by combining subunits with different release characteristics. The multiunit system is also adaptable to varying dose strengths without the need of changing the formulation. This feature is highly desirable during clinical trials of the new drug candidates where dose levels are frequently adjusted based on study outcome.

Similar to matrix systems, drug release from a reservoir system usually varies with pH unless the solubility of the active is pH-independent. To achieve pH-independent release, buffering agents are incorporated to control pH in order to maintain constant drug concentration in the core.

Osmotic pump systems. An osmotic pump is similar to a reservoir device in that it consists of a drug-containing core enclosed by an insoluble membrane. The difference is that the device has an orifice for drug release, and its core also contains an osmotic agent that acts to imbibe water from the surrounding medium via a semi-permeable membrane. Such a device, known as
the elementary osmotic pump (EOP), was first described by Theeuwes and Higuchi in 1975 (3). Drug release from the device is controlled by water influx across the semi-permeable membrane. The drug is forced out of the orifice by the osmotic pressure generated within the device. The size of the orifice is designed to minimize diffusion and prevent the build-up of a hydrostatic pressure head that can change the osmotic pressure and the volume of the device.

In developing oral products, two types of osmotic pump systems have been utilized. These are a one-chamber EOP system and a two-chamber system (e.g., Push-Pull). In general, an EOP system is only feasible for molecules with a narrow range of solubility (e.g., approximately 50-300 mg/mL) to achieve zero-order and complete release. The two-chamber device was designed mainly to accommodate less soluble drug or higher drug loading. It consists of a bilayer tablet with one push layer containing a highly swellable polymer and a drug-containing layer. In the GI tract, water is imbibed through the semi-permeable membrane into both layers by the osmotic excipients. As both the drug and push layers hydrate, a drug suspension or solution is formed in situ and the push layer begins to expand as a result of the hydration and swelling of the hydrophilic polymers. Drug release begins when the volumetric expansion of the push layer starts to “push” the active in the drug layer through the orifice on the drug layer side. Because rate-control resides within the rate-controlling membrane, drug release is essentially insensitive to environmental effects, such as pH, agitation, and type of apparatus.

In summary, classic osmotic pump systems offer zero-order release profiles that are independent of the drug properties and release environment in most cases. However, fabrication of this type of system often requires specialized equipment with complex processes. This is particularly true with the two-chamber systems, which often translates into higher cost, longer development time, and larger numbers of formulation and processing variables to define and control. Additional drawbacks include the solvent process required for semi-permeable membrane coating, sensitivity of the drug release to formulation and process variables, and delayed onset of drug release.

**Other Types of Oral Modified-Release Systems**

With the improved understanding of active substances and clinical pharmacology, various delivery profiles such as those illustrated in Figure 1 are often required for effective and improved clinical therapy. Common examples of the non-monotonic and multi-cargo delivery patterns include delayed drug delivery in different segments of intestines, pulsatile delivery, biphasic delivery, and associated combinations. These drug release profiles can generally be obtained through combining different immediate-release, delayed-release, and extended-release formulation approaches.

**Enteric-release systems.** Enteric release is intended to delay the release of an active drug until the dosage unit has passed through the stomach. The delayed liberation of oral drugs has been achieved through a range of formulation approaches, including single- or multiple-unit systems coated with pH-sensitive films. The earliest physicochemical approach to delaying drug release is by applying enteric coating to dosage forms as a barrier. Materials used for enteric coating prevent drug release in the stomach because they are typically acidic polymers that are insoluble and stable at acidic pH. The coatings dissolve rapidly when the dosage forms reach the small intestine. Drugs that are irritating to the stomach (e.g., aspirin) can be coated with an enteric film that will only dissolve in the small intestine. Enteric coating is also used to prevent certain acid-labile drugs (e.g., proton pump inhibitors) from degrading in the acidic environment. Common enteric dosage forms include coated tablets or capsules, and coated multi-particulates in a capsule or compressed into a disintegrating tablet.

**Colonic-release systems.** Targeted drug release in the colon is known to offer therapeutic advantages for certain drugs, such as more effective treatment for local disorders of the colon (e.g., ulcerative colitis and Crohn’s disease) with reduced incidence of systemic side effects. Colonic delivery systems are delayed release dosage forms that are designed to provide either an immediate or sustained drug release in the large intestine. One of the examples is colonic delivery of mesalazine for the treatment of inflammatory bowel disease. For drugs that are well absorbed throughout GI tract, sustained delivery in the colon has also been utilized in the treatment of nocturnal asthma or angina (e.g., cardiovascular chronotherapeutics products Adalat CC and Verelan PM).

For optimal colonic delivery, the active needs to be protected from the environment of the upper GI tract before it reaches the large intestine. Based on the considerations of the unique colonic environment (e.g., pH, pressure, or microflora), various strategies and approaches have been investigated for colon-specific drug delivery. These include coated delivery systems using pH-sensitive or slow-erosing polymers, swelling or osmotic controlled system for timed release, and carriers degraded specifically by colonic bacteria. Among these approaches, coated
systems that utilize the transit time and pH differential in the GI tract have been utilized in commercial products.

**Pulsatile-release systems.** Pulsatile delivery usually refers to immediate release of the entire dose in two or more portions separated by predetermined lag times. In particular, oral pulsatile drug release pertains to the burst delivery of drugs following a programmed pattern from the time of oral administration. For example, Ritalin LA capsule is a pulsatile delivery product that provides immediate release of 50% of the total dose upon oral ingestion followed by a burst release of the remaining drug after four hours. In the field of modified release, these types of non-monotonic and multi-cargo release profiles have been proven to offer clinical benefits in optimizing chronotherapy, mimicking natural patterns of endogenous secretion or multiple dosing regimens, and providing optimal therapy for tolerance-inducing drugs where constant levels lead to receptor down-regulation (i.e., acute tolerance). Pulsatile-release systems have received increasing interest in new product development.

A variety of pulsatile release systems have been investigated and successfully applied in commercial products. The fundamental system design is based on the combination of single or multiple immediate-release units with delayed release systems. The delayed release component in pulsatile delivery systems includes site-specific systems in which the drug is released at the desired site within the intestinal tract, or time-controlled devices in which the drug is released after a predefined time lag. Recent literature reviews have provided detailed information on design rationale, strategies and various single- and multiple-unit oral pulsatile delivery systems, including Pulsincap, Pulsys, and PORT technologies (4,5).

**Bimodal-release systems.** Bimodal or biphasic delivery profiles have also been frequently used among non-monotonic extended release patterns. The usual rationale for such designs includes providing rapid onset of action by adding an immediate release component to an extended release dosage form, optimizing dosing schedules for chronotherapeutic drugs by incorporating a delayed-release component in an extended-release dosage form, generating fluctuations of plasma levels to avoid or attenuate the development of acute tolerance, and overcoming the problems associated with non-linear pharmacokinetics and extensive first-pass metabolism, resulting in reduced bioavailability or altered drug or metabolite ratios (6-9). Since the 1980s, many marketed products with biphasic drug release have been developed for various drugs, including verapamil, diltiazem, nifedipine, and methylphenidate.

As with pulsatile-delivery systems, biphasic-release profiles are often achieved by combining different formulation approaches, such as single- or multiple-unit immediate release, delayed-release, and extended-release systems based on coating, matrix, and osmotic pump technologies. Among common designs that have been applied are mixing dosage units with varying release rates, using layered tablets or multi-walled coatings, compression-coated tablets with a slow eroding outer layer, and combinations of delayed-release coatings with osmotic pumps. For example, Cardizem CD consists of a rapid-release bead and an extended-release bead producing a unique stair-step release profile. Adalat CC is a compression-coated matrix tablet that provides zero-order sustained release followed by a delayed burst release. Lodotra also uses press-coated tablets (GeoClock) that provide rapid release of prednisone about four hours after administration at bedtime for a more effective treatment of the morning symptoms of rheumatoid arthritis (10).

**COMMON RATE-CONTROLLING MATERIALS**

Polymers are most widely employed in various MR systems to provide modulation of drug release. Many choices of polymers are available for hydrophilic matrix systems. Among them are cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), synthetic polymer such as poly(ethylene oxide) and poly(methacrylic acid) of varying degree of cross-linking, and natural polymers such as xanthan gum and alginate. Some of these polymers such as alginate and poly(methacrylic acid) are polyelectrolytes in nature, thus exhibiting certain unique release-modifying properties.

Materials for hydrophobic matrix systems are more limited. Fatty acids and their various glycerol esters or other wax-like materials have been used previously. Insoluble polymers such as Eudragit RL, RS, ethyl cellulose, cellulose acetate, and other cellulose esters may be also used.

Water-insoluble polymers with or without pore formers are often used in the membrane coating of reservoir systems. Ethylcellulose, polyvinylacetate, and acrylic copolymers (i.e., Eudragit RL 30D, RS 30D, NE 30D) have been used in these applications.

Cellulose acetate is the most commonly used in semi-permeable membrane coating of an osmotic pump. Other cellulose derivatives such as ethyl cellulose and cellulose butyrate have also been used. Sodium chloride, highly swellable poly(ethylene oxide), and other polymers (e.g. poloxamer) are often used as the osmotic, agent, swelling, and flux enhancer, respectively.
Materials used in delayed release are enteric polymers that dissolve at higher pHs. Depending on drug properties and design objectives (e.g., the extent of release delay), different polymers or different polymer concentrations may be used. For example, Eudragit L 55 consisting of random copolymer of ethyl methacrylate and methacrylic acid at ~ 1:1 ratio is soluble at pH > 5.5. Eudragit L 100, a copolymer of methyl methacrylate and methacrylic acid at ~1:1 ratio, is soluble at pH > 6. Eudragit S (100) made of the same monomers but with more insoluble component (2:1) is soluble at pH > 7. These polymers may be used alone or in combination to achieve a predetermined release delay.

RATIONAL DESIGN OF ORAL-MODIFIED RELEASE SYSTEMS

The ability to achieve desired in vitro and in vivo performance for a given drug substance is highly dependent upon several important factors. These include dose, physicochemical, biopharmaceutical, pharmacokinetic, and pharmacodynamic properties of the drug, drug delivery technology, and dosage form design. Each drug substance possesses inherent properties that require specific considerations to both the drug and the delivery system.

In designing a MR delivery system, a defined clinical rationale with the characteristics of the drug for feasibility evaluation must be integrated. An appropriate MR technology and design formulation, based on an understanding of the drug characteristics, dosage form attributes, and manufacturing considerations, is then selected. In vitro and in vivo evaluations follow.

Identifying Clinical Need and Defining the in vivo Target Product Profile

The basic clinical objective for an MR product is to achieve optimal drug treatment via programming drug input to provide advantages in efficacy, safety, and patient compliance. According to the regulatory directive issued by the European Agency for the Evaluation of Medicinal Products (EMEA) (11), development of MR products should be based on a relationship between the pharmacological and toxicological response and the systemic exposure to the drug or metabolite(s) forms.

The impact of input rate on the efficacy and safety ratio can be illustrated by methylphenidate. To meet the clinical need for a more convenient dosing regimen of this controlled drug, several new MR products with different release modes were designed and clinically proven to be effective since the mid-1990s. The product designs include pulsatile release and biphasic extended release, which provide fluctuations of plasma levels. These designs overcame the acutely acquired tolerance due to the constant level of drug exposure associated with Ritalin SR, the extended release version of Ritalin. This example and above discussed ER nifedipine show that a positive or negative clinical outcome may be rendered by constant exposure of a drug depending on the relationship between the kinetics of drug effects and the pattern and timing of drug input. The design of release characteristics for an MR product should be based on the optimal drug concentration-time profile defined by understanding of clinical pharmacology.

Feasibility Study

In developing MR dosage forms, feasibility assessment is essential to product design and development success. Once the delivery mode and in vivo target product profile are defined and pharmacokinetic disposition parameters are available, the corresponding drug input profile can be obtained by prospective pharmacokinetic simulation (e.g., via deconvolution of the target plasma profile). With a known therapeutic window, the required input duration and kinetics can be readily determined by ensuring the plasma levels are maintained above the effective concentration over a dosing interval. Feasibility of the simulated delivery in the GI tract is then evaluated. For example, if a predefined plasma profile of a drug corresponds to 16 hours of drug input, the majority of the given dose will need to be absorbed in the large intestine because of the limited residence time of solid dosage forms in the upper GI tract. Understanding absorption characteristics of the individual active drug in the lower GI tract is crucial.

The regional absorption characteristics of a compound in the GI tract and residence time of dosage forms are the most important parameters in assessing the suitability of oral MR delivery (1, 12). Because of significant regional differences in surface area, permeability, secretion, enzymes, transporters, water, and other factors, drug absorption often differs in different segments of the GI tract. In general, the transit time of most dosage forms prior to arrival at colon is approximately four to six hours depending on type of dosage forms and food intake. This may become a limiting factor for drugs requiring absorption beyond this time frame after dosing (13). For certain drugs, favorable absorption in the large intestine may allow continued drug delivery for up to a total of 20–24 hours (14). If drug release is not completed by the time the dosage form passes through the absorption region, a portion of the dose will not be delivered. Hence, it is important to define the absorption regions or window of a specific compound in the GI tract.
Techniques used to assess regional absorption characteristics of a compound include *in vitro* or *in-situ* models and site-specific delivery in animal models and human subjects. Permeation characteristics of drugs in different GI segments can be evaluated through *in vitro* permeability of excised tissues or *in-situ* perfusion studies using animal models. Site-specific delivery via indwelling access ports in conscious animals (e.g., dog and rat) offers direct comparison of drug absorption in jejunum, ileum, and colon through concurrent monitoring of plasma levels. These can serve as a predictive model for human exposure depending on the drug properties and absorption mechanism. Since the early 1990s, gamma scintigraphic studies have become one of the commonly used techniques in screening drug candidates for oral MR delivery (15). Regional differences in absorption can be determined by using non-invasive delivery devices, such as the Enterion capsule of Pharmaceutical Profiles (UK). The radiolabeled capsule loaded with a drug solution or powder can be tracked via gamma scintigraphy and externally activated to release the drug when it reaches a certain location in the GI tract.

In summary, it is essential to take into consideration the drug’s physicochemical and biopharmaceutical properties, the required dose, physiological and biological constraints, and disposition kinetics in assess technical feasibility.

**Designing and Testing MR Dosage Form**

Once feasibility is confirmed, an appropriate MR technology and *in vitro* test method to design and evaluate prototype formulations are selected. This decision should be primarily based on drug properties, dose, desired release or absorption kinetics, and clinical and commercial needs. Additional practical considerations include development time and cost and commercial production factors (e.g., process, equipment, facility, manufacturability, robustness, cost, capacity, and environment).

In selecting an MR system that matches development needs, dose and solubility of the active are often the most important factors to consider because both variables impact the release mechanism and processing behaviors. There is generally no technology that is one-size-fits-all. From an enablement point of view, different MR systems can be equally effective in achieving the delivery objective when drug properties and dose are desirable. For example, similar MR performance of verapamil, theophylline, and methylphenidate have been obtained using matrix, reservoir, or osmotic pump technologies. However, depending on dose and solubility, one type of delivery system may become more or less suitable for meeting a particular delivery need.

In developing an MR dosage form, *in vitro* assessment of its attributes is essential prior to testing in humans. For solid MR dosage forms, drug release testing is the most important among various physical and chemical characterization methods. The United States Pharmacopeia (USP) drug release test is commonly used for guiding formulation screening. Factors that often affect the system performance (e.g., drug loading, excipients, release control mechanism, etc.) need to be considered when choosing appropriate *in-vitro* test methods. Development of *in vitro* release tests and their relationship with *in vivo* performance has been discussed previously (16).

Following completion of the dosage form design and *in vitro* testing, *in vivo* bioavailability study of prototype formulations is required to identify a formulation with acceptable *in vivo* performance for further development. In certain cases, iteration of studies is necessary to define or refine a formulation. When designed properly, the study may also offer an opportunity to explore *in vitro-in vivo* relationship (IVIVR) or correlation (IVIVC) to aid product development.

**FORMULATION AND PROCESS DEVELOPMENT**

The usual options of MR solid dosage forms are single-unit tablets, multi-unit beads or mini-tablets in capsules, and multi-particulates for reconstitution or sprinkle administration. These are manufactured using essentially the same processes as used for the IR dosage forms. Table II lists common dosage forms for different types of MR systems.

The general aspects of these dosage forms, process development, and in-process controls have been discussed extensively in the literature. In general, processes for tablet manufacture include direct compression, wet granulation, dry granulation, and melt granulation or thermoplastic pelletizing (e.g., high shear, melt-extrusion, spray-congealing). Processes for producing spherical beads encompass extrusion-spheronization, drug layering of non-pareil seeds, spray-granulation or spray-drying, and spray-congealing. Conventional compression processes are also used to prepare mini-tablets using either small tooling or multi-head tooling depending on the tablet size and throughput considerations. MR coating of tablets or beads is most often carried out in pan coater or fluid-bed depending on the nature of the coating substrate (e.g., size, tensile strength, etc.). Compression coating (tablet-in-tablet) requires a special compression machine. In most cases, use of conventional manufacturing processes and equipment is highly preferred. When a more complex process is required (e.g., multi-layered tablets, compression coating, mixed beads, or mini-tablets), emphasis should be placed on increased process and product understanding throughout
the development lifecycle to ensure successful development from small to commercial scale. Compared to the IR counterpart, a higher standard is usually required to ensure rate-modifying function of the MR product. For example, tighter or additional control of rate-controlling materials, or uniformity of functional coat for the reservoir and osmotic pump systems, is often necessary to assure consistent batch-to-batch product performance.

In formulation and process development, an integrated understanding of the drug release mechanism and key properties of the rate-controlling materials is important. Release rate control of a MR system is achieved through the use of an appropriate functional polymer. Compared with small molecules, polymers have inherently higher variability in physicochemical properties. It is important to understand the structural diversity of these polymers and potential impact on product performance.

Polymers may differ in several chemical aspects. Individual polymer molecules have different molecular weight. Each batch usually has different average molecular weights and distribution, even within the same grade of a polymer. A conventional viscosity test only reflects the average molecular weight. Most rate-controlling polymers are either synthetic or natural copolymers. The exact composition (i.e., ratio between different repeating units) and their distributions are likely to vary, potentially affecting their rate-controlling properties. Further chemical modification of polymers leads to an added layer of potential differences in functionality (e.g., hydroxypropyl methylcellulose). Typically compendial monographs are very general in defining the chemical structures of polymers, allowing for a wide range of specification values. As a result, the same compendial grade of materials from different manufacturers can have different chemical properties that may influence its performance in a specific MR system. In many cases, significant variability also exists between different lots from the same vendor. Polymer variability and its potential impact on formulation and processing need to be understood during product and process development. In general, to better control material variability, it is usually preferred to select a synthetic or semi-synthetic polymer (e.g., HPMC) over a natural polymer (e.g., alginate) because the chemistry and properties of the natural polymers are often influenced by a number of factors that are difficult to control.

**IMPLICATIONS OF UNDERSTANDING MODIFIED-RELEASE PRODUCTS IN VALIDATION AND COMPLIANCE**

Validation and compliance personnel should have a general understanding of the principles and design process of modified-release solid oral dosage forms. Specifically, they should be very aware of differences and similarities among different types of MR products. As with IR dosage forms, attention should be directed toward drugs and excipients that may interact with each other and with manufacturing processes, and processes that may potentially impact product quality and performance.

MR products are complex products. Validation and compliance personnel must be especially vigilant of raw material and manufacturing changes that may impact product quality and manufacturability. Special attention should be paid to the rate-controlling excipients of which the physicochemical and mechanical properties may vary depending on batch, grade and source, etc. Changes in material sources or vendors must be thoroughly evaluated. Consultation with development scientists is mandatory whenever any of the above situations are encountered. Validation protocols developed in response to such changes should require appropriate sampling and testing in support of the changes. Knowledge of the product and process characteristics must also be considered in determining appropriate validation testing.

**CASE STUDY: MR DOSAGE FORMS OF METHYLPHENIDATE**

Methylphenidate (MPH) is an amphetamine-like central nervous system stimulant commonly prescribed to treat attention-deficit/hyperactivity disorder (ADHD)
in children, adolescents, and adults, as well as narcolepsy. It is soluble, stable, and highly permeable in the intestinal tract with a short elimination half-life of three-four hours. These favorable properties combined with a low dose make MPH an ideal candidate for oral MR regardless of technologies applied.

The IR product (Ritalin) that has been on the market since the 1950s is taken two or three times per day. It is inconvenient for repeated administration while children are at school because MPH is a Schedule II controlled substance. To offer more convenient dosing and control of behavior during the entire school day, several modified-release formulations have been developed. An early ER product (e.g., Ritalin SR) is a matrix tablet designed to maintain relatively steady plasma drug levels after administration. However, the product was found to be less efficacious due to its drug release pattern that led to the development of acute tolerance (17). Further studies demonstrated that varying rate of drug input would overcome the tolerance observed with monotonic drug release. As a result, a new generation of once-daily MR products was developed that offers the equivalent efficacy of repeated administrations of IR MPH by altering the drug’s input profile. Successful commercial products (18) include ER products generating biphasic release profiles for a rapid onset of action and a prolonged duration of action (Metadate CD capsules consisting of 30% IR and 70% coated ER beads and Concerta tablets consisting of an ER osmotic pump coated with IR component [Figure 2a, 2b]) and Pulsatile release products that better mimic PK performance of standard schedules of IR product (Ritalin LA capsules consisting of 50% IR and 50% DR beads that provide IR release 4h later [Figure 2c]). This case study shows that understanding drug properties is critical to the design of clinically efficacious MR products, and all three types of technologies are equally effective in achieving a range of in vivo delivery performance when the molecule exhibits desirable characteristics suitable for development of MR dosage forms.

**SUMMARY**

The key elements of designing MR solid oral dosage forms include understanding the drug substance and defining the clinical rationale. The success of designing a commercially viable MR product depends on the basic properties of the drug candidate, rather than on a particular delivery technology. Most oral MR delivery needs can be met using three types of mature delivery technologies (i.e., matrix, reservoir, and osmotic pump systems). Design and development of the manufactur-
ing process for a majority of MR products are essentially the same as those for IR dosage forms. Therefore, selecting an MR technology for a particular drug should be based on considerations of technical feasibility, effectiveness, practicality, development, and manufacturing efficiency and cost.

REFERENCES