HPMC Blends
Customizing HPMC to Minimize Drug Variability
Divya Tewari and Thomas Durig

Osmotic Systems
Controlling Drug Release Through Osmotic Systems
Adeline Siew, PhD

Patient Centricity
Drug Encapsulation for Patient-Centric Dosing
Joan FitzPatrick
The authors evaluated the performance and robustness of controlled-release tablets made with HPMC blends of unimodal and bimodal molecular weight distribution.

Hypromellose (HPMC) is a controlled-release polymer that has found widespread adoption in controlled-release dosage forms. Generally, higher molecular weight (MW) grades are preferred for highly soluble drugs, where drug release is predominantly controlled through diffusion through a swollen gel layer. Lower MW grades are preferred for low-solubility drugs where matrix erosion is required for effective release of the drug (see Table 1). As a result of the historically limited number of commercially available MW grades, formulators would blend various MW grades to tailor release profiles to meet specific therapeutic objectives and to accommodate the wide spectrum of drug solubilities encountered in daily practice.

Among the issues that arise when blending is used to achieve intermediate MW and release behaviors are the potential increase in release profile variability, reduced predictability, and lack of robustness. Dissolution variability due to blending is exacerbated in the presence of variations in gastrointestinal (GI) tract hydrodynamic conditions and GI fluid compositional factors such as fat, bile salt content, and ionic strength. It is difficult to develop good in vitro-in vivo correlations for controlled-release matrix systems due to variations in GI conditions.

Benecel K250 PH PRM HPMC, K750 PH PRM HPMC, and K1500 PH PRM HPMC (Ashland) grades were developed to obviate the need for blending (see Figure 1) and offer a potential solution to the problem of dissolution variability. These
custom Benecel HPMC grades are of intermediate viscosity and have tight, unimodal MW distribution.

In this study, the dissolution performance and robustness of matrix tablets developed with these custom Benecel HPMC grades under varying hydrodynamic stress conditions and in dissolution media of varying ionic strengths were investigated. Formulations containing blends of Benecel K4M and K100LV PHARM HPMC to achieve analogous viscosities were used as comparators (see Table II). Glipizide (GLIP; aqueous solubility ~ 37 mg/L) and carbamazepine (CBZ; aqueous solubility ~ 17.7 mg/L) were chosen as model low-solubility drugs.

**Methods**

**Wet granulation.** One kg batches comprising polymer (30%; blends of Benecel K4M and K100LV PHARM HPMC or the equivalent custom viscosity grade), drug (25% for GLIP and 67% for CBZ), and quantity sufficient microcrystalline cellulose were wet granulated in a high shear mixer. The granules were dried, milled, and lubricated with 0.5% magnesium stearate. Matrix tablets (400 mg for GLIP and 600 mg for CBZ) were compressed on a Manesty Beta Press equipped with an AIM-Metropolitan Computing Corporation data acquisition system.
Blend ratios were calculated according to the following formula:

\[ \eta = \eta_1 \frac{1}{8} c_1 + \eta_2 \frac{1}{8} c_2 \]

Where, \( \eta \) = viscosity of the polymer and \( c \) = weight fraction of the polymer.

**Drug-release profiles.** Dissolution was tested at 37 °C with 7.5 pH phosphate buffer with 0.1% polysorbate 80 for GLIP and 1% sodium lauryl sulfate in distilled water for CBZ. The hydrodynamic effects were simulated by running the dissolution with a United States Pharmacopeia (USP) Apparatus I at 100 and 150 revolutions per minute (rpm) or with USP Apparatus III (Bio Dis, Varian Inc.) at 5 and 25 dips per minute (dpm). The effect of fluid composition was determined by running the dissolution in media of varying pH (2 hr in 0.1 N HCl and then in corresponding buffer) and ionic strength (adjusted with NaCl).

**Erosion profiles.** Tablet erosion and uptake of the dissolution medium were determined gravimetrically under the same dissolution conditions as used for dissolution testing. Three tablets were used per time point. At predetermined times, the tablets were removed and patted to remove excess surface water. After determining the wet weight, the tablets were dried at 70 °C for 10 days, before reweighing to determine the dry weight (1).

Water uptake and mass loss were determined gravimetrically according to
Equation 1:

\[
\text{Dissolution medium uptake (\%) = } \frac{100 (\text{Wet weight} - \text{remaining dry weight})}{\text{Remaining dry weight}}
\]

\[
\text{Remaining mass (\%) = } \frac{100 (\text{remaining dry weight})}{\text{Original dry weight}}
\]

[Eq. 1]

Cloud point. The cloud point value was determined using a FP900 cloud point analyzer (Mettler Toledo) at 1.0% concentration in differing dissolution media, plotting the light transmission through the polymer solution as a function of the temperature.

Rheology (gel strength). The GLIP tablets were placed in pH 7.5 phosphate buffer with 0.1% polysorbate 80 for 2 hr at 37 °C. The deformation of the gel layer on the tablet was analyzed using a rheometer (Model #AR-G2, TA Instruments) in compression mode and an aluminum probe with a diameter of 6.4 mm. The compression stress (resistance of the gel layer) applied to the tablet was plotted against the true compression strain (the degree of gel layer deformation).

Results and discussion

Effect on dissolution profiles. Release profiles for repeat lots of Benecel K750 HPMC were superimposable with a t50 % of 12 hr and standard deviations at individual time points of less than 5%. It can be seen that tablets made of equivalent viscosity blends of Benecel K4M HPMC and K100 LV HPMC had slower and more variable drug release with t50 % of 15–18 hr and standard deviations at individual time points of up to 15% (see Figure 2). Table II details substitution and viscosities of the lots that were compared in the study.

For hydrophilic matrix polymers, erosion rate is known to vary with MW in a nonlinear inverse manner (Equation 2):

\[
\text{Erosion rate} = KM_n^{-a}
\]

[Eq. 2]

where K is a constant that is polymer-, solvent-, and temperature-dependent, \(M_n\) is number average molecular weight, and a is calculated from the slope of the erosion curve. In addition, the opposite relationship applies to matrix swelling (i.e., polymer solubility increases with MW up to a limiting MW threshold) (2). However, Figure 2 shows that in addition to average MW, the MW distribution also plays a key role in matrix erosion and swelling. In the case of the bimodally distributed HPMC blends, variability is greater than that of unimodally distributed custom grades, irrespective of the viscosity. Furthermore, slower release kinetics are obtained for bimodal blends where the higher MW fraction (Benecel K4M HPMC) dominates. This observation was seen for 750 cps and 1500 cps blends.
in comparison with custom made K750 and K1500. In contrast, for blends where the lower MW fraction (Benecel K100LV HPMC) dominates, comparatively faster release kinetics are obtained, as observed for the 250 cps blend in comparison with custom made K250 (data not shown).

Carbamazepine tablets made with repeat lots of custom Benecel K750 HPMC also exhibited consistent release profiles with a t50% of 7 hr and standard deviations at individual time points of less than 5% (see Figure 3). However, it can be seen that tablets made of equivalent viscosity blends of Benecel K4M HPMC and Benecel K100LV HPMC had much more variable drug release with t50% of 8–12 hr and standard deviations at individual time points of up to 7%.

Effect of hydrodynamic stress conditions. Table III shows the impact of increasing hydrodynamic stress on the variability of glipizide and carbamazepine tablets made with Benecel K750 HPMC and the equivalent 750 cps viscosity Benecel K4M/K100LV HPMC blend, at the 8-hr time point. Increasing the basket stirring rate from 100 to 150 rpm in the USP Apparatus I had only a marginal effect on Benecel K750 HPMC. However, variability increased greatly
for formulations containing the blend of HPMC grades with standard deviation of individual time points exceeding 15%. Extreme variability, including controlled-release failure, was seen when formulations containing a blend of Benecel K4M/K100LV HPMC were subjected to testing in USP apparatus III (reciprocating cylinder) at 5 and 25 dpm. By contrast, the custom Benecel K750 HPMC with tight, unimodal distribution showed extremely robust dissolution behavior with a small increase in rate when agitation was increased from 5 to 25 dpm. These results may be of particular significance when considering the in vivo behavior of HPMC matrix tablets dosed under fed and fasted conditions, when significant mechanical attrition and hydrodynamic stress is expected in fed conditions (3).

Effect of pH and ionic strength. When subjected to pH change from acidic simulated gastric fluid (SGF) to pH 7.5 simulated intestinal fluid (SIF), no significant differences were seen between formulations made with Benecel K750 HPMC or the equivalent viscosity K4M/K100LV HPMC blend. However, when subjected to increasing levels of ionic strength, the tablets made with Benecel K750 HPMC and glipizide and with carbamazepine continued to release drug in a robust and predictable manner, while tablets made with the equivalent viscosity Benecel K4M/K100LV HPMC blend resulted in increased variability and showed evidence of polymer salting out and dose dumping.

Bimodally distributed blends result in greater variability.

These differences in release profile for unimodal custom Benecel K750 HPMC and the equivalent viscosity K4M/K100LV HPMC blend were further studied by examining cloud points (see Figure 4) of the respective polymer solutions at different ionic strengths and by measuring the gel strengths (see Figure 5) of hydrated matrix tablets. The bimodal K4M/K100LV HPMC blend showed greater susceptibility to cloud point depression in the presence of media of different ionic strengths as opposed to the unimodal Benecel K750 HPMC. Additionally, gel strength was found to be significantly higher for the custom Benecel K750 HPMC.

While the cloud point effects in Figure 4 appear modest, these effects need to be understood in the context of the dilute polymer solvent system, which is far removed from the physical reality of hydrating gel matrices where free water is limited. Mechanistically, hydrating gel matrix tablets can be understood as a solvent-lean environment, in which
HPMC is only marginally soluble. For such systems, the net free energy of solution increases as molecular weight increases. This molecular weight dependent solubility of HPMC under marginal solvent conditions would be further exacerbated with an increase in ionic strength. It is, therefore, expected that the HPMC blends, having a larger component of higher MW HPMC and displaying earlier onset of clouding, as seen in Figure 4, will show dramatically different gel properties.

In essence, salting out of the higher MW polymer species results in insoluble gel domains, leading to disruption in gel network integrity and faster, highly variable erosion, which is also reflected in lower gel strength (see Figure 5).

Conclusion
The custom Benecel (K250, K750, and K1500) HPMC grades have fundamentally different behaviors when compared with equivalent viscosity bimodal blends. Matrix tablets comprising equivalent viscosity HPMC blends showed significantly higher variability and the release profiles were dependent on the MW of the higher percentage component of the blend. In addition, custom Benecel HPMC grades were more robust in the simulated gastrointestinal environment in comparison with blends of similar viscosities. For erosion dependent dosage forms, both average MW and
the MW distribution are important for matrix erosion and swelling. Bimodally distributed blends result in greater variability and, in some cases, failure to control release as compared with HPMC grades with unimodal MW distribution.

References

Who sees opportunity at a molecular level?

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Osmotic systems are versatile for delivering drugs with varied properties and dosage requirements.

The design and development of controlled-release drug-delivery systems have been traditionally used to extend a product’s lifecycle, for example, by modifying an existing drug product that requires multiple dosing a day to a once-daily formulation to maintain dominance over generic competition (1, 2). While this rationale still holds true today, the number of compounds formulated into controlled-release systems are increasing because of their added value and well-recognized advantages such as improved systemic bioavailability, more favorable pharmacokinetic profiles (e.g., the maintenance of drug levels within a desired range without exposing patients to potentially toxic or subtherapeutic levels), reduced side effects, and better patient compliance among others (3–5). From a strategic perspective, commercial and industrial advantages of controlled-release drug delivery, apart from prolonging product lifecycle, include patent extension, market expansion, and product differentiation (6, 7).

Controlled-release technologies play a vital role in today’s current healthcare market, given the strong emphasis placed on product value and cost effectiveness. Treatment of many diseases requires a dosage regimen that delivers acceptable therapeutic concentrations of the drug at the site of action, which can be attained immediately and then constantly maintained over the desired duration of treatment (8). Controlled-release drug delivery offers solutions to conventional problems of drug administration by regulating the patterns of drug release and absorption as well as the localization of therapeutic agents. The maintenance
of stable drug levels in the plasma over a defined and extended period, achieved with controlled-release systems, minimizes peak-to-trough variations of drug concentration in the systemic circulation and allows dosing frequency to be reduced, thereby improving patient compliance and overall clinical utility (1, 6). There are, however, potential disadvantages of controlled-release systems that should not be overlooked, such as dose dumping, possible toxicity or nonbiocompatibility of the materials used, undesirable by-products of degradation, higher manufacturing costs, and for implants, the requirement of surgical procedures to insert or remove these systems as well as possible patient discomfort from the delivery device (4, 5).

**Osmotically controlled oral drug-delivery systems**

One way to control drug release is by using osmotic systems, which operate on the principles of osmosis (i.e., the movement of solvent through a semipermeable membrane into a region of higher solute concentration until the solute concentrations are equal on both sides of the membrane). Osmotic systems consist of a drug core contained within a semipermeable polymer membrane that is permeable to water molecules but not to the drug, with an orifice for drug delivery.

Drug release is driven by the osmotic pressure generated within the drug core upon exposure to water and is, to a large extent, independent of physiological factors (9, 10). Release characteristics can be modulated by optimizing the properties of both the drug and system (4).

Osmotically controlled oral drug-delivery systems have gained popularity because of the following advantages over other controlled-release strategies (9, 11, 12):

- Zero-order kinetic release is achievable.
- The drug is delivered at a constant rate that is independent of time and drug concentration.
- The release rate is highly predictable.
- Higher release rates are possible compared with conventional drug-delivery systems.
- Drug release is independent of physiological factors of the gastrointestinal tract, including gastric pH and hydrodynamic conditions.
- Drug release is generally not affected by the presence of food.
- The release rate can be programmed by modulating release-control parameters.
- Delivery may be delayed or pulsed if desired.
There is a high degree of *in vivo-in vitro* correlation.

Soluble and insoluble compounds can be delivered.

Production scale-up is easy.

**Basic components**

Osmotic systems essentially contain a drug and a semipermeable membrane. Ideal candidates for these systems are drugs with short biological half-life, which require prolonged treatment, such as drugs for hypertension (e.g., nifedipine) or diabetes (e.g., glipizide) (12).

Drugs with good water solubility may act as an osmotic agent or osmogen that draws water into the osmotic core. However, if the drug does not possess osmogenic properties, osmogenic salts (e.g., sodium chloride and potassium chloride) and sugars can be incorporated into the formulation (11). When selecting an osmogen, the two most important properties to consider are water solubility and osmotic activity.

The semipermeable membrane is an important component because it controls the rate of water influx into the drug core as well as retains water-soluble components within the core to create the osmotic pressure gradient that drives the osmotic system (9). The semipermeable membrane must possess certain performance criteria, such as sufficient wet strength and water permeability, and should be selectively permeable to water and biocompatible (13). Cellulose acetate, a water-insoluble film-forming polymer, is commonly used in osmotic systems. Release rate is affected by the molecular weight and acetyl content of the various grades of cellulose acetate. The semipermeable membrane usually contains a plasticizer, which moderates the permeability of the membrane, and in some cases, surfactants, flux regulators and pore-forming agents (11).

**Formulation factors affecting drug release**

Key parameters (i.e., drug solubility, osmotic pressure, the size of the delivery orifice and semipermeable membrane) that influence the design of osmotically controlled drug-delivery systems are briefly summarized.

*Ideal candidates for osmotic systems are drugs with short biological half-life, which require prolonged treatment, such as drugs for hypertension.*

*Drug solubility:* To achieve optimized drug release, the API for osmotic delivery should have sufficient water solubility, given that the release rate is directly proportional to the solubility of the API within the core. Drugs with extremes of
solubility are generally poor candidates for osmotic delivery. There are, however, approaches to modify the solubility of such drugs within the core so that the desired release patterns can be attained.

The effect of membrane thickness on dissolution fluid entering the asymmetric membrane capsule showed that as the membrane thickness increased, the volume of dissolution fluid entering into the system decreased.

For compounds with low solubility, solubilizing strategies can be employed; for example, by using alternative salt forms or cyclodextrins. Swellable polymers (e.g., vinyl acetate copolymer and polyethylene oxide) can also be added; the uniform swelling of these polymers facilitates drug release at a constant rate. Wicking agents help to increase the contact surface area of the drug with incoming fluids. The use of wicking agents can help enhance the rate of drug release from the orifice of the osmotic system.

Osmotic pressure: The osmotic pressure gradient between the drug core of the osmotic system and the external environment is another important factor that controls drug release, with release rate being directly proportional to the osmotic pressure of the core. The simplest and most predictive way to achieve constant osmotic pressure would be to maintain a saturated solution of osmotic agent in the drug-core compartment.

Size of the delivery orifice: The size of the orifice must be within a certain range for controlled release. The typical range is 0.5 mm to 1.0 mm in diameter. For an optimal zero-order delivery profile, the cross-sectional area of the orifice must be small enough to minimize drug passage through the orifice but large enough to minimize the build-up of hydrostatic pressure within the osmotic system. The orifice can be created by using a mechanical drill or by laser drilling, which is now a well-established technology that offers reliability at low costs. Other methods to create an orifice are by indentation with modified punches that have a needle on the upper punch or by using leachable substances in the semipermeable coating.

Semipermeable membrane: Drug release rate is affected by the type and nature of the membrane-forming polymer used, membrane thickness, and the presence of other additives (e.g., type and nature of plasticizers used). Membrane permeability can be increased or decreased by the proper choice of membrane-forming polymers and other additives.
Evolution of osmotically controlled-release systems

Osmotically controlled oral drug-delivery systems have come a long way. The first elementary osmotic pump, invented by Theeuwes, consists of a single compartment containing the drug and an osmotic agent surrounded by a semipermeable membrane (15, 16). Upon ingestion, water is drawn into the core through the semipermeable membrane to saturate the drug, which is then released in liquid form at a controlled rate through the orifice(s) (see Figure 1a).

The limitation of the elementary osmotic pump, however, is that it can only deliver water-soluble drugs. The design was further improved by Cortese and Theeuwes, resulting in the development of the push-pull osmotic pump, which is a bilayer tablet capable of delivering both highly and poorly soluble drugs (17). The upper layer (i.e., the drug layer, also known as the pull layer) consists of the drug and an osmotic agent while the lower layer (i.e., the push layer) consists of water-swellable polymers and osmotic agents (see Figure 1b). Both layers are coated with a semipermeable membrane that regulates water influx into the system. As water enters the tablet, pressure increases and the polymer swells to push against the drug layer, thereby releasing the drug solution or suspension through the laser-drilled orifice(s).

Zentner et al. reported on the development of the controlled-porosity osmotic pump in the mid-1980s. The controlled-porosity osmotic pump does not require a delivery orifice for drug release, hence eliminating the need for complicated laser-drilling procedures (18, 19). It consists of the drug and an osmotic agent in a tablet core surrounded.
by a semipermeable coating membrane containing leachable pore-forming agents, which dissolves upon contact with water, forming pores through which the drug solution is pumped out. The rate of drug release is dependent on the thickness of the coating membrane, levels of leachable pore-forming agents, the amount of soluble components incorporated in the coating, drug solubility within the tablet core and the osmotic pressure differences across the membrane, but unaffected by pH and gastrointestinal motility (20–22).

In the mid-1990s, Herbig et al. described a new type of membrane coating for osmotic drug delivery. The new coating has an asymmetric structure, similar to asymmetric membranes made for reverse osmosis or ultrafiltration, in that the coating consists of a porous substrate with a thin outer skin (23). Asymmetric membranes are made from water-insoluble polymers (usually cellulose derivatives, such as cellulose acetate, ethyl cellulose and cellulose acetate butyrate) and pore-forming agents (e.g., glycerol, sorbitol, polyethylene glycol, polyglycolic acid and polylactic acid) using a phase-inversion process.

The use of asymmetric membrane coatings in osmotically controlled oral drug-delivery systems has increased in the past decade because of the advantages it offers. These benefits include: a higher rate of water influx, which facilitates osmotic delivery of poorly soluble drugs and enables higher release rates of such drugs; more controlled-release of freely soluble drugs; pH-independent release and minimized exposure to the gastrointestinal tract, which results in reduced gastric irritation and degradation of drugs (23–25).

Water permeability of the coating can be adjusted by controlling the membrane structure, thereby allowing control of release kinetics without altering the coating materials used or significantly varying the coating thickness. The porosity of the membrane can also be controlled to minimize the lag time that occurs before drug delivery begins (23). Asymmetric membrane coatings can be applied on pharmaceutical tablets and capsules (23, 26, 27). The basic design of an asymmetric membrane capsule is similar to a hard-gelatin capsule, except that the shell contains pore-forming water-soluble additives, which dissolve after coming in contact with water, resulting in an in situ formation of a microporous structure (28, 29). A delivery orifice is, therefore, not required due to the in situ pore formation of the asymmetric membrane.

**Asymmetric membrane capsules in application**
An asymmetric membrane capsule for controlled release of terbutaline sulfate
was recently described by Gobade et al. (29). The drug is a beta agonist used in the treatment of asthma. The oral dosage regimen of terbutaline sulfate is 5 mg twice or three times daily. The plasma half-life is approximately 3–4 hours. The asymmetric membrane was prepared using ethyl cellulose as the polymer and sorbitol as the pore-forming agent. Dissolution studies showed that the formulation provided zero-order drug release over a 12-hour period.

Philip and Pathak developed a nondisintegrating, controlled-release, asymmetric membrane capsule of ketoprofen and evaluated the in vitro and in vivo correlation of the formulation (30). Ketoprofen is a nonsteroidal anti-inflammatory drug, used in treatment of rheumatoid arthritis, osteoarthritis, and musculoskeletal disorders. Multiple dosing is required to achieve and maintain therapeutic concentration because of its short half-life (4.2 h) and poor solubility. The asymmetric membrane capsule was made of ethyl cellulose and glycerol. Sodium chloride was used as an osmotic agent and citric acid as a solubilizer. The formulation provided controlled release of ketoprofen and the half-life of the drug was prolonged for more than 16 hours. In vivo pharmacokinetic studies showed excellent level A correlation (r² > 0.99), demonstrating that the in vitro drug-release profile of ketoprofen from the asymmetric membrane capsule could be used to accurately predict the in vivo performance.

A double-membrane system of cefadroxil using ethyl cellulose as the inner membrane and cellulose acetate phthalate as the outer membrane has been developed by Philip et al. (31). The asymmetric membrane in a membrane capsule was prepared on glass pins using a two-step phase-inversion process. The first step was to form a nondisintegrating, asymmetric membrane capsule and the second step involved formation of a pH-sensitive, disintegrating, asymmetric membrane formed over the nondisintegrating membrane. This double-membrane formulation was able to delay the release of cefadroxil for the first two hours in the gastric medium and provide controlled release in the intestinal medium for an extended 12-hour period. Drug release was independent of pH and agitation intensity and followed zero-order release kinetics.

More recently, Garg et al. reported on the development of asymmetric membrane capsules with two compartments for simultaneous delivery of two poorly soluble antihypertensive drugs, atenolol and amlodipine (32). Scanning electron microscopy showed a dense outer region and a porous inner region of the asymmetric membrane.
before dissolution. Pore size of the outer and inner layers increased after dissolution. Buffering agents were used to increase the solubility of atenolol and amlodipine. The formulation followed zero-order release kinetics, which was not affected by the agitation intensity of the dissolution fluid. Drug release was dependent on the diffusion rate of the drug across the membrane and the osmotic pressure. The effect of membrane thickness on dissolution fluid entering the asymmetric membrane capsule showed that as the membrane thickness increased, the volume of dissolution fluid entering into the system decreased.

A gastroretentive asymmetric membrane capsule of famotidine was recently developed by Guan et al. (33). The drug is used for the treatment of duodenal, gastric and peptic ulcers. It has a relatively short half-life (3 h) and a low bioavailability (45–50%). Increasing gastric residence time would allow the drug to penetrate through the gastric mucus layer and produce a more pronounced effect. Polyethylene oxide was used as floating agent in the formulation. Pharmacokinetic studies in beagle dogs showed that the gastroretentive asymmetric membrane capsule displayed complete drug delivery with zero-order release kinetics and a 12-hour floating time. The system had the ability to prolong drug action, minimize dosing frequency, and reduce the average peak plasma concentration.

Chauhan et al. also reported on the design of a floating asymmetric membrane capsule for site-specific delivery of ranitidine in a controlled manner (34). Ranitidine was given 150 mg twice daily or 300 mg once daily as an oral dosage form. Dosing has to be increased to 150 mg 4–5 times a day for the treatment of endoscopically diagnosed erosive esophagitis. The conventional formulations could only inhibit acid secretion for up to 5 hours, hence, requiring frequent dosing, which would cause fluctuations of drug levels in the plasma. The aim was to develop a buoyant asymmetric capsule with density less than the gastric fluid for controlled release of ranitidine in the gastric cavity. The capsule shell was prepared by the phase-inversion process wherein the polymeric membrane was precipitated on glass pins by dipping them in a solution of cellulose acetate followed by quenching. The solubility of ranitidine was suppressed by the ion effect, using optimized coated sodium chloride crystals as a formulation component. Drug release with zero-order kinetics was achieved and the asymmetric membrane capsule demonstrated floating ability for up to 12 hours.
Conclusion

Osmotic systems will continue to play an important role in controlled-release drug delivery for decades to come. Today, there is available a wide range of osmotic drug-delivery systems that can be adapted to various drug properties and dosage requirements. The area of controlled-release remains a challenge, but advances in technology promise bright prospects for the future of healthcare.

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Adeline Siew, PhD, is the editor of Pharmaceutical Technology Europe.
Drug Encapsulation for Patient-Centric Dosing

Joan FitzPatrick

A review of encapsulation technologies for solubility/bioavailability enhancement, controlled release, and formulation of drug combinations and patient-friendly dosage forms.

The global pharmaceutical industry loses an estimated $564 billion annually due to medication non-adherence (1). The development of innovative products, custom-made for specific patient populations and indications, is the first step towards increasing patient compliance and improving treatment outcomes. In general, such dosage forms incorporate user-friendly elements to support product marketing and differentiation. Much development effort in the industry is currently being applied to patient-centric drug delivery, including bioavailability enhancement to provide equivalent therapeutic action at lower doses (and to reduce adverse events); customized drug release to influence efficacy and safety and lower dosing frequencies; drug combinations to reduce the number of medications taken; and patient-friendly dosage forms to enhance patient acceptability of the medicines and to customize dosage forms for specific patient populations and/or indications. These objectives can be achieved by the use of drug-encapsulation techniques. This article reviews the key attributes of patient-centric dosage forms in relation to drug-encapsulation technologies.

Multiparticulate systems

The pharmaceutical industry has long recognized the advantages of multiparticulate systems for improving pharmacokinetic behavior and enhancing bioavailability of formulations. Compared to monolithic devices, multiparticulates have less variable gastric emptying, show lower inter- and intra-subject variability,
minimize the risk of dose dumping, and better facilitate customized drug release.

Microencapsulation can be defined as a process by which particles of solid or liquid material (the core) are enveloped with a continuous film of polymeric material (the shell) to produce capsules in the micrometer or millimeter range. Microencapsulation can be achieved using a number of chemical or physical techniques, including interfacial polymerization, extrusion spheronization, spray drying, and solvent evaporation to name a few.

Interfacial polymerization involves the polymerization of a monomer at the surface of two immiscible liquids (water and an organic solvent). Monomers are dissolved in the two separate phases, which are emulsified to reach the desired particle size. The monomers polymerize at the interface of the emulsion droplets, thereby encapsulating the drug.

Extrusion spheronization is a two-step process in which the drug and excipients are combined and then extruded, followed by spheronization of the extrudate to round out the particles. Hot melt extrusion (HME) is now being used to disperse APIs in a matrix at the molecular level, thus forming solid solutions/dispersions to enhance drug dissolution. Spray drying is a low-cost microencapsulation process and is widely used for fragrances and flavors. Drug particles are dispersed in a polymer solution and sprayed into a hot chamber, and the polymer solidifies onto the core particles as the solvent evaporates. Solvent evaporation is a common technique in which the drug is either dissolved or dispersed in an aqueous phase combined with a polymer in an organic solvent to create an emulsion, and the solvent is subsequently evaporated to yield the microspheres.

Another method is coextrusion (Ethicap gel technology, Freund Pharmatec), which can be achieved by the use of vibrational force to drive materials through concentric nozzles to create droplets that subsequently form seamless minicapsules by surface tension in a collection medium. Drug encapsulation allows for the conversion of liquids to solids to support downstream processing, accommodates solubility-enhancing formulations and controlled drug release, and can improve drug stability.

Solubility and bioavailability enhancement
More than 40% of oral drug products contain poorly soluble drugs (2). It is estimated that up to 90% of new molecular entities fall under the BCS class II or IV category, showing poor and variable oral bioavailability in vivo (3). BCS Class II compounds have poor aqueous solubility but reasonable
permeability, so the rate limiting step for absorption is drug dissolution. Numerous techniques have been developed to address the issue of poor solubility and bioavailability with varying degrees of success. The main technologies to target oral bioavailability for poorly soluble drugs include the use of micronization, nanosizing, crystal engineering, solid dispersions, cyclodextrins, solid lipid nanoparticles, and other colloidal drug delivery systems, such as microemulsions, self-emulsifying drug delivery systems, self micro-emulsifying drug delivery systems, and liposomes (4). In recent years, the development of amorphous solid dispersions by HME has yielded one of the most effective technologies for oral bioavailability enhancement (5).

Improvements in drug solubility in microencapsulated systems are attained firstly by the multiparticulate nature and corresponding increased surface area, which can increase drug release and subsequent dissolution. Secondly, some microencapsulation techniques allow for the incorporation of solubility enhancers in the formulation or may use process temperatures above the melting point of the drug to create an amorphous form. A combination of formulation additives and temperatures above the melting point can be applied in some cases when using HME or coextrusion techniques. This combined approach can result in improvements in solubility even greater than the nanocrystalline form of certain BCS Class II compounds. Using the coextrusion method, a three-fold increase in aqueous solubility in vitro was observed for a selected compound as compared to the nanocrystalline form (see Figure 1).

Numerous case studies have been reported in the literature on the use of HME to improve oral bioavailability of poorly soluble drugs. Fule and Amin developed immediate-release solid-
dispersion formulations of the anti-ulcer drug lafutidine using a HME technique (6). Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus, BASF) was used as the primary solubilizing agent, with different concentrations of selected surfactants, such as PEG 400, Lutrol F127, and Lutrol F68, to investigate the influence of these surfactants on formulations processed by HME. Dissolution rate and solubility of lafutidine was enhanced remarkably in the developed solid dispersion formulations. The ratio of polymer to surfactants played a crucial role in dissolution rate enhancement of lafutidine and overall, the application of HME proved successful in enhancing in-vitro dissolution.

Controlled release
For some microencapsulation techniques, controlled release of the drug can be accomplished through the encapsulation method itself or by subsequent coating onto the encapsulated drug particles. Multiparticulates typically provide a good substrate for the application of polymer coatings using conventional techniques such as fluid-bed coating. Major advances in polymeric coatings have allowed for customized drug release based on pH changes or timed-release functions, but coating efficiency and performance is dependent on a number of factors, including particle shape and size distribution. The different microencapsulation processes available show variable shape and size distribution properties, which can affect coating efficiency.

Gowda et al. used spray-drying to prepare controlled-release microparticles of indapamide and reported that this approach achieved a 24-hour profile comparable with the marketed product, Lorvas (Indian Market) (7). Selected polymers were used to provide the controlled-release functionality. The authors concluded that the application of spray-drying in combination with the selected excipients allowed for the development of a controlled-release formulation of a highly water-soluble drug.

For coextruded minicapsules, their spherical shape and narrow particle size distribution (within 3% by weight) can facilitate uniform application of polymeric coatings (see Figure 2). In this case, a methacrylate sustained-release coating was applied to a minicapsule containing a BCS Class II drug. High coating efficiency on multiparticulates can result in sustained-release action comparable to specifically designed sustained-release devices such as osmotic pump systems (see Figure 3).

Drug combinations
Treatment regimens that require multiple products are a significant burden on patients, and compliance decreases with
followed as treatments for a single condition or multiple conditions (e.g., Pfizer’s Caduet containing atorvastatin and amlodipine). A key advantage of FDCs is improved medication compliance by reducing the pill burden of patients. Pill burden refers not only to the number of pills to be taken by the patient, but also the burden of understanding the various instructions of several medications.

The main issue in the formulation of FDCs is the chemical incompatibilities between drugs. A commonly reported interaction is between rifampicin and isoniazid (drugs used in the treatment of tuberculosis) at stomach pH, leading to poor stability and bioavailability of rifampicin. Extrusion spheronization was used to formulate enteric-coated pellets of rifampicin and isoniazid. The formulation showed improved stability for rifampicin in in-vitro conditions (8).

Using the coextrusion encapsulation technique, the concentric nozzle design allows for up to three layers within
the minicapsule. A median layer can, therefore, act as a physical barrier between drug layers (see Figure 4). This technique can eliminate the issues associated with incompatibilities, thereby facilitating the development of stable FDC products.

**Patient-friendly dosage forms**

Patient-friendly dosage forms provide clear benefits for specific patient populations, including geriatric and pediatric groups, patients with dysphagia, or those with neurodegenerative diseases. One way to enhance patient compliance is to create dosage forms that are easy to take, and multiparticulate systems can enable various options for user-friendly presentations. Multiparticulates can be formulated as dry syrups or sprinkles that may be added to food, orally dispersible tablets or granules (ODT/ODG), and liquid formulations. Such dosage forms may require taste-masking and/or controlled drug release and should be easy to swallow. As an example, the spherical nature of coextruded seamless minicapsules eases swallowing. Taste-masking functionality can also be incorporated into the shell of the minicapsules, which can in some cases, eliminate the need for further coating.

Other proprietary technologies use microencapsulation methods to taste-mask bitter compounds, which is especially important for the pediatric population. For example, the Aptalis’ proprietary Microcaps coacervation process was used to create an oral taste-masked granulation formulation of tenofovir disoproxil fumarate (Viread), which can be administered by mixing with food for enhanced compliance in pediatric patients.

In the development of new products, line extensions, and differentiated generics, consideration of patient compliance is vital for improving clinical outcomes, reducing the cost burden of many diseases, and moderating the losses experienced by the industry due to non-adherence. Multiparticulate systems can solve formulation problems and allow the formulator to develop a convenient and user-appropriate dosage form.
References


**Joan FitzPatrick** is director of Business Development and Scientific Affairs at Freund Pharmatec, Unit 1, IDA Business & Technology Park, Srah, Tullamore, Co. Offaly, Ireland, email: joan.fitzpatrick@freundpharmatec.com.
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