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INTRODUCTION

Pharmaceutical drug delivery embraces a range of delivery carriers and constructs that have dimensions ranging from several nanometers (nanotechnology) to numerous millimeters (conventional dosage forms, i.e., pellets, tablets, and capsules). Such delivery systems spawn a whole array of assemblies for delivery of highly potent active drugs through different routes of administrations to numerous sites and targets in the human or animal body to treat disease conditions. Such delivery types and carrier systems, with their relative sizes together with some molecules and bacterial cells, are shown in Figure 12.1.
Typical pharmaceutical carriers, nanosized active agents, and delivery systems include dendrimers and nanoparticles with functionalized surface, antibody–drug conjugates, nanocrystals, nanoparticle albumin bound (nab) systems, lipid–polymer hybrid nanoparticles, liposomes, stealth liposomes, half-antibody functionalized ligand-targeted systems, micro-emulsions, nanosuspensions, emulsions, suspensions, oral-soluble strips, microcapsules, pellets, tablets, osmotic pumps, and encapsulated drug delivery systems in a capsule carrier. The latter seven delivery systems constitute greater than 80% of routinely used pharmaceuticals in current therapy.

According to the US Food and Drug Administration (FDA) and the US Pharmacopeia (USP), modified-release solid oral dosage forms encompass delayed/enteric-coated and extended-release drug products. Besides the delayed- and/or extended-release features, other newer types of oral modified-release products may include pulsatile-release, combination drugs (e.g., single dosage form containing immediate-release, enteric-coated, and/or extended-release components), targeted delivery (e.g., oral-mucosa, stomach, proximal intestine, distal intestine, and/or colon), or delivery systems that are based on the chronopharmacokinetics and interactions of drugs in the milieu of biologic rhythms from a clinical perspective and chronotherapeutics. These dosage forms can be designed to deliver drugs in a controlled and predictable manner over a prolonged time period or at a target location within the gastrointestinal (GI) tract to elicit the desired therapeutic effect. Moreover, development of such delivery systems having complicated features involved in their design has presented numerous challenges to the industry and regulatory authorities in ensuring pharmaceutical equivalence, bioequivalence, and therapeutic equivalence. Commonly used oral modified-release systems can be formulated as single-unit (e.g., tablet matrices, composites of layered tablets and compressed pellets) or multiple-unit dosage forms (e.g., based on encapsulation of pellets, spheres, granules, or multiparticulates). The relative merits of multiple unit dosage forms in terms of “release flexibility, increased bioavailability, predictable gastrointestinal transit time, less localized GI disturbances, more consistent blood levels, less intra or inter subject variability due to the food effects and greater product safety” over single-unit products are well established. In modified-release systems, the design of the dosage form allows for a specific drug delivery pattern so that the release rate becomes the rate-limiting step. This should be viewed in the context of existing parameters within
Modified-Release Delivery Systems

the GI tract. For example, the two major rate-limiting factors to drug absorption are GI environment (e.g., pH, absorption site, and regional differences in drug permeability across GI mucosa, gut metabolism, and GI content) and transit rate of the dosage form. From a manufacturing point of view, irrespective of the type of the dosage form (single or multiple units), currently the utilization of hydrophilic matrices, mini-tablets, coated pellets or spheres, and osmotic systems is common and offers significant flexibility in pharmaceutical technology. In view of the many benefits offered by multiple-unit dosage forms, it is speculated that such systems are particularly useful in many chronic disease conditions and delivery of highly irritant and potent drugs for site-specific targeting within the GI tract and for delivery of non-steroidal anti-inflammatory drugs, colonic delivery of anticancer drugs, enzymes, peptides/proteins, and vaccines.

CAPSULES AS A CARRIER PLATFORM FOR ORAL EXTENDED-RELEASE DRUG DELIVERY

The purpose of this chapter is to highlight and describe potential uses of hard shell capsules as carriers for extended-release drug delivery systems that, by virtue of their design and popularity, satisfy features of an ideal technology platform for drug delivery and reliable pharmaceutical production. These features include the following:

a. Availability, types, and sizes of the capsule shells through different suppliers
b. Simplicity, flexibility and ease of production, low cost, and time efficient
c. Process familiarity and acquaintance with technology and equipment
d. Robust, manageable, quick changeover, transferability, suitable for worldwide manufacturing
e. Significant potential for innovation including multiple drug delivery options for modified release, targeted release, and delivery of drug combinations

The word *capsule* is derived from the Latin word *Capsula*, meaning “a small box or packet.” Therefore, hard shell capsules can be regarded as containers for delivery of formulated drug substances that are generally designed for oral administration, although non-oral products for rectal or vaginal administration are available. Capsules as a platform for delayed or controlled-release delivery offer numerous advantages and adaptabilities over tablets. They can readily accommodate a range of special excipients, formulations, and pre-fabricated systems to target specific regions of the GI tract including the following:

a. Powders, particulate systems, pellets, mini-tablets, coated particulates, or mixed coated beads with enteric coat or diffusion-controlled membrane
b. Multiple tablets, smaller hard or soft shell capsules, small drug wafers, or casted sheets containing drug
c. Enteric-coated systems with or without sustained release components
d. Various controlled-release forms
e. Drug combinations for targeting different regions of the GI tract for both local and systemic effects
f. Micronized or nanosized formulated drug(s) with pH-sensitive coatings for delivery to stomach, proximal intestine, distal intestine, or colon
g. Incompatible drugs where one drug in the form of a coated pellet, tablet, small soft shell capsule can be separated by placing it in a larger capsule before adding the second drug
h. Fixed-dose combinations

Hard shell capsule sizes range from number 5, the smallest, to number 000, which is the largest, except for veterinary sizes. However, size number 00 generally is the largest size acceptable to patients. Hard shell capsules consist of two parts, cap and body piece. Generally, there are unique
grooves or indentations molded into the cap and body portion to provide firm closure when fully engaged or fitted, which helps prevent the unintended separation of the filled capsules during shipping and handling. To assure strong closure, spot fusion “welding” of the cap and body piece together through direct thermal means, or application of ultrasonic energy, sealed banding, or liquid sealing can be applied. This further guarantees greater product stability by limiting oxygen and moisture penetration and also augments consumer safety by making the capsules tamper proof and difficult to open without producing noticeable damage to the dosage form and the shell’s integrity.

Two-piece hard shell capsules are commercially available and are manufactured from gelatin (animal derived) or hypromellose (hydroxypropylmethylcellulose [HPMC], plant derived) via the thermal gelation process. The HPMC capsules referred to as Vcaps Plus capsules or second-generation capsules are based on pure HPMC and generally dissolve similarly in different pH’s or ionic strengths and have a lower moisture content (4% to 9% w/w) relative to gelatin capsules (13% to 16% w/w). Unlike gelatin shells, which can undergo cross-linking in the presence of aldehyde groups and cause dissolution problems, the HPMC shells are stable and are not affected by the presence of aldehyde groups.

**MODIFIED-RELEASE DOSAGE FORMS**

Modified-release drug delivery technologies, which include both enteric-coated systems and a variety of controlled-release solid dosage forms, including capsules, have evolved as a multidisciplinary science. For example, the extended-release Spansule capsule, containing a large number of coated and uncoated drug beads (i.e., coated spheres) to modify drug dissolution by controlling access of GI fluids to the drug through a coating barrier, was first introduced and patented in 1952, as shown in Figure 12.2.

A similar approach has been practiced since the 1950s, and today, there are dozens of modified-release capsule dosage forms using the same or similar principle that are commercially available. Some examples of modified-release hard shell capsules that have been FDA approved and

![Spansule delivery system](image)

**FIGURE 12.2** An issued patent in 1952 describing the spansule capsule showing the hard shell gelatin capsule containing hundreds of coated and uncoated drug beads for extended release of an antihistamine.
Modified-Release Delivery Systems

are currently available in the marketplace are presented in Table 12.1. The list is not an exhaustive list of the available extended-release capsule products but rather an exemplary sample list that also includes fixed-dose combination products. Many of these products are marketed in different dose strengths for ease of clinical management of the disease conditions. For example, extended-release morphine sulfate (Kadian), listed in Table 12.1, has many different strengths with diversity in color(s), capsule size, and imprints in order to safely adjust the required dose for management of pain in patients having different pain thresholds and pain severity.

A brief but comprehensive history of modified-release delivery systems and significance of their performance through either manipulation of the drug molecule itself or delivery types with specific release configurations is presented elsewhere.4 The groundbreaking theoretical developments of various scientists5–9 and others whose contributions allowed for a more rational understanding and application of basic principles to the design and development of an array of more sophisticated and multifaceted controlled-release systems should not be overlooked. Extended-release capsules are produced in such a way as to deliver their content upon oral administration either in the stomach or different regions of the GI tract for absorption over a few hours to about 12 to 24 h. Figure 12.3

TABLE 12.1
Some Examples of FDA-Approved and Currently Marketed Modified-Release Capsule Dosage Forms

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Therapeutic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effexor-XR</td>
<td>Venlafaxine HCl</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Cardizem CD</td>
<td>Diltiazem HCl</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Dilacor XR</td>
<td>Diltiazem HCl</td>
<td>Antihypertension</td>
</tr>
<tr>
<td>Pancrecarb</td>
<td>Pancrelipase</td>
<td>Pancreatic enzyme insufficiency</td>
</tr>
<tr>
<td>Dilantin Kapseals</td>
<td>ER phenytoin sodium</td>
<td>Prevention and treatment of seizures</td>
</tr>
<tr>
<td>Bontril SR</td>
<td>Phendimetrazine tartrate</td>
<td>Management of exogenous obesity</td>
</tr>
<tr>
<td>Oruvail</td>
<td>Ketoprofen</td>
<td>Nonsteroidal anti-inflammatory</td>
</tr>
<tr>
<td>Cartia XT</td>
<td>Diltiazem HCl</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>Methylphenidate HCl</td>
<td>Attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>Carbatrol</td>
<td>Carbamazepine</td>
<td>Anticonvulsant drug</td>
</tr>
<tr>
<td>Kadian</td>
<td>Morphine sulfate</td>
<td>Management of pain</td>
</tr>
<tr>
<td>Cardene SR</td>
<td>Nicardipine HCl</td>
<td>Treatment of hypertension</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>Amphetamine, dextroamphetamine mixed salts</td>
<td>Attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>Verelan PM</td>
<td>Verapamil HCl</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Prozac Weekly</td>
<td>Fluoxetine HCl</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Nexium</td>
<td>Esomeprazole magnesium</td>
<td>Treatment of erosive esophagitis</td>
</tr>
<tr>
<td>Prilosec</td>
<td>Omeprazole</td>
<td>Treatment of duodenal ulcer</td>
</tr>
<tr>
<td>Delzicol</td>
<td>Mesalamine</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Linzess</td>
<td>Linaclotide</td>
<td>Irritable bowel syndrome with constipation</td>
</tr>
</tbody>
</table>

Fixed-dose combinations

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Therapeutic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggrenox</td>
<td>Aspirin/ER dipyridamole amldipine</td>
<td>Reduce the risk of stroke</td>
</tr>
<tr>
<td>Lotrel</td>
<td>besylate and benazepril HCl</td>
<td>Treatment of hypertension</td>
</tr>
</tbody>
</table>

Modified-release capsules encompass both enteric and extended-release products.

Note: Four selected modified-release capsule delivery systems representing different release mechanisms will be discussed in more detail in this text: Dilacor XR (multiple tablet matrices in capsule); Carbatrol extended release (diverse coated and uncoated multiparticulates in capsule); Prilosec delayed-release/enteric-coated pellets in capsule; and Linzess capsule containing drug-coated beads of a polypeptide for delivery to the distal intestine for topical effect via receptor binding in the intestine and colon.
Pharmaceutical Dosage Forms shows various physiological constraints and GI environments that a modified-release capsule dosage form encounters upon oral administration.

The GI constraints should be considered in conjunction with characteristics and limitations described by way of the Biopharmaceutics Classification System (BCS), implemented in 1995 as a new approach to better predict oral drug absorption and adopted by the FDA. According to the BCS, drug substances are classified as follows:

- **Class I**—High Permeability, High Solubility
- **Class II**—High Permeability, Low Solubility
- **Class III**—Low Permeability, High Solubility
- **Class IV**—Low Permeability, Low Solubility

Furthermore, the class boundaries described above is based on the following premise:

1. A drug substance is considered highly soluble when the highest dose strength is soluble in <250 mL of water over a pH range of 1 to 7.5.
2. A drug substance is considered highly permeable when the extent of absorption in humans is determined to be >90% of an administered dose, based on mass balance or in comparison to an intravenous reference dose.
3. A drug product is considered to be rapidly dissolving when >85% of the labeled amount of drug substance dissolves within 30 min using USP apparatus I at 100 rpm or II at 50 rpm in a volume of ≤900 mL of buffer solutions.

The hard shell capsule itself, once in the desired GI environment/region, would dissolve fairly rapidly (10–30 min) and releases its content immediately (i.e., in the case of immediate release) for rapid absorption as opposed to modified-release systems such as controlled release or sustained release as shown in Figure 12.4.

When capsule dosage forms are designed for providing a particular release profile or sustained drug delivery, upon oral administration, it would deliver its content for further disintegration, dissolution, and release followed by absorption in various regions of the GI tract as shown in Figure 12.5.
Modified-Release Delivery Systems

TERMINOLOGY AND DEFINITION OF MODIFIED-RELEASE DOSAGE FORMS

FDA defines modified-release dosage forms as “dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms, such as a solution or an immediate-release dosage form. Modified-release solid oral dosage forms include both delayed- and extended-release drug products.”

The USP recognizes several types of modified-release systems including extended release, delayed release, or targeted release. However, expressions such as “prolonged-action,” “repeat-action,” “controlled-release,” “pulse-release,” “modified-release,” “ascending-release”, and “sustained-release”
have also been used to describe such dosage forms. Although many of these terms have been used interchangeably, the terms “extended-release” and “modified-release” are used for Pharmacopeial purposes, and requirements for drug release typically are specified in the individual monographs [see general release standard USP (724) and (1088)].

The platform is highly flexible and lends itself to a variety of delivery system designs that could be complementary with different biopharmaceutical properties of the drug in relation to physiological constraints imposed by the GI tract. Ideally, the extended-release delivery system should provide release rate and duration of release that would match the necessary amount of drug in the blood for a specific duration of therapy. The modified-release capsule delivery platform permits for constant release (zero-order), variable release (pulsatile), delayed release, or extended drug release and absorption over a prolonged period after ingestion. Capsules can be enteric coated, or coated pellets/granules that resist releasing in the acidic environment of the stomach can be encapsulated. Enteric coating delays release of medicament until the capsule or its contents have passed through the stomach. Potential modified-release capsule delivery systems and sophisticated release rates and patterns that can be realized from manufacturing of different controlled-release capsule delivery designs are shown in Figures 12.6 and 12.7a and b.

**FIGURE 12.6** (See color insert.) Controlled-release capsule drug delivery systems with different types of dosages or encapsulated formulations (transparent shell is chosen to show the content). Some of these are commercially available; others are possible examples that can be for investigation. EC, enteric coated; CR, controlled release; IR, immediate release.
FIGURE 12.7  (See color insert.) (a) Typical modified-release capsule delivery system and potential drug release rates and duration of release during dissolution studies. Drug may be released in a pulsatile manner, one portion may provide for a bolus dose while another portion provides for delayed release, or maintenance dose either at constant rate, ascending rate, repeat action, or sustained release. System may allow for delivery of either one drug or drug combinations (i.e., fixed-dose combination). (b) Types of drug release from different modified-release capsule dosage forms containing multiple tablets, enteric or controlled-release coated pellets and tablets, coated mini-tablets, and enteric-coated small capsule placed in a larger capsule with different tablet combinations. Various release profiles from different combinations are possible for different time periods (i.e., 1- to 24-h duration). Systems may allow for either one drug or drug combinations. Type of release: immediate release (IR); prolonged release (PR, with or without a bolus dose); delayed release (DR); release after lapse of certain time in a desired pH environment; controlled release (CR) with zero-order kinetics.
DISSOLUTION RATE OF DRUG FROM DRUG PARTICLES, PELLETS, OR FROM VARIOUS MODIFIED-RELEASE FORMULATIONS AND DELIVERY SYSTEMS ENCAPSULATED IN A CAPSULE SHELL AS A DELIVERY CARRIER

There are two major classes of dosage forms or drug delivery systems for oral administration:

1. Immediate-release solid dosage forms (orally disintegrating and immediate-release tablets and capsules)
2. Modified-/controlled-/sustained-release dosage forms

Drug release in vitro or in vivo from a conventional capsule is very similar to an immediate-release tablet dosage form except for a small lag time of less than 30 min for the capsule shell to dissolve. Release and subsequent bio-absorption are controlled by the physicochemical properties of the drug, its formulation, and the physiological conditions and constraints imposed by the GI tract. The release of a drug from these delivery systems is rapid and involves factors of dissolution and diffusion. The earliest work describing diffusion was by Fick in 1855. Fick’s first law of diffusion considers diffusion only under steady-state conditions.

\[ J = -D \frac{dc}{dx}, \]  

(12.1)

where \( J \) is the diffusion current, \( D \) is the diffusion coefficient, and \( dc/dx \) is the concentration gradient assumed to be constant at steady state. However, as the concentration of drug changes with time, Fick’s second law of diffusion is used; hence, it considers non–steady-state conditions.

\[ \frac{dc}{dt} = D \left( \frac{d^2c}{dx^2} \right) \]  

(12.2)

where \( dc/dt \) is the dissolution rate of the drug. Based on Fick’s second law of diffusion, Noyes and Whitney established a fundamental equation for dissolution. In its simplest form, the in vitro rate of solubility or dissolution rate of a drug substance is described by the Noyes–Whitney equation:

\[ \frac{dC}{dt} = \left( \frac{D}{h} \times S \right) \times (C_s - C_t) \]  

(12.3)

Under sink conditions, \( C_s \gg C_t \), and Equation 12.3 becomes

\[ \frac{dC}{dt} = \frac{(D \times S \times C_s)}{h}, \]  

(12.4)

where \( dC/dt \) is the dissolution rate at time \( t \), \( D \) is the diffusion rate constant, \( h \) is the thickness of the stagnant layer, \( S \) is the surface area of the dissolving solid, \( C_s \) is the concentration of the drug in the stagnant layer, and \( C_t \) is the concentration of the drug at time \( t \) in the bulk solution. Note that if the concentration in bulk solution is ≤15% of saturation solubility, “sink condition” prevails.

In an in vivo situation after dissolution, drug molecules move across a distance into a membrane and its membrane permeability depends on the velocity with which it moves. Apart from the role of transporters, channels, and carriers, a simplified absorption is described by Fick’s law of diffusion, which involves movement of the drug molecule from a region of high concentration to low...
Thus, the drug tends to move toward a region that we may regard as sink, which is passage through the epithelial membrane into blood circulation in accordance with the following equation:

\[
\frac{dC}{dt} = \frac{P_e \times A \times D \times (C_{GI} - C_{Blood})}{h},
\]

where \( \frac{dC}{dt} \) is the rate of absorption, \( P_e \) is effective permeability, \( A \) is the surface area of the membrane, \( D \) is the diffusion coefficient of the drug molecule in water, \( C_{GI} - C_{Blood} \) is concentration gradient across the GI membrane, and \( h \) is membrane thickness. In Equation 12.5, it is assumed that the unstirred aqueous boundary layer next to the membrane does not significantly affect the total transport process. Therefore, it is important to note that many factors influence the dissolution rate of a drug both in vivo and in vitro, including physicochemical (i.e., particle size, molecular size, hydrophilicity/hydrophobicity, and crystallinity), physiological (i.e., presence of surfactants, GI motility, viscosity and volume of GI fluid, and pH), and in vitro factors (i.e., surfactants, stirring rate and hydrodynamics, viscosity, pH, and volume of medium).

Typically when immediate-release capsule dosage forms are administered orally, the capsule shell disintegrates within a few minutes (i.e., <15 min) and its content dissolves, and the dissolved drug is absorbed as shown in Figure 12.8.

**OPERATING RELEASE MECHANISMS ASSOCIATED WITH DIFFERENT ENCAPSULATED MODIFIED-RELEASE DOSAGE FORMS**

Modified-release delivery from hard shell capsules may contain a variety of fabricated delivery systems. These include granules, powders, systems with different functional coatings such as enteric-coated, extended-, sustained-, controlled- (such as osmotic pump), and/or programmed-release systems including pulsatile or targeted-delivery systems and drug combinations, all of which can be placed in a capsule shell as a carrier for administration. It is also customary to coat hard shell capsules with polymers that prevent dissolution at low pH and can avert gastric degradation or release. Formulation methods vary and usually when needed allow for rapid release followed by slow release of the maintenance dose. All modified-release formulations employ a chemical, physical,
or electrical constraint to deliver sustained release of the drug dose. In general, they can be divided into two major groups:

1. Matrix based systems—pellets, mini-matrices, or small tablets
2. Membrane diffusion-controlled systems—coated pellets, tablets, and osmotic pumps

Production of modified-release delivery systems is based on numerous formulation approaches, methodologies, and innovative methods, and they each have their own specific operating release-controlling mechanisms as shown in Figure 12.9.

**MATHMATICAl MODELS TO DESCRIBE RELEASE KINETICS FROM EXTENDED-RELEASE CAPSULES CONTAINING FORMULATED DELIVERY SYSTEMS**

Various mathematical models have been used to describe the rate of drug release from different types of encapsulated dosage forms and modified-release systems. For example, an analysis of drug diffusion from simple monolithic devices (i.e., cylinders or spheres representing small tablet matrix or an extruded and spheroidized pellet type) designed for controlled release of drug has been described using exact solutions or reasonably accurate approximations.\(^1\) From experimental work, it is evident that, from such monolithic systems, initial amount of drug released (i.e., early time) is in accordance with the square root of time while release in a later stage follows an exponential decay with time (i.e., late time). Equations shown in Table 12.2 predict such drug release from an infinite system, assuming that the edge or end effects are inconsequential.\(^1\)

\[ \frac{M_t}{M_\infty} = k\sqrt{t}, \]

\(M_t\) is the amount released at time \(t\), \(M_\infty\) is the total amount of drug, and \(D\) is the diffusion coefficient of the solute.

Besides, a more practical approach in evaluating drug release from matrix systems designed for controlled release using “insoluble waxes or hydrophilic and soluble/erodible polymers such as polyethylene oxide or hydroxypropylmethyl cellulose or hydroxypropyl cellulose” is described by the Higuchi approach:\(^5\)
where \( \frac{M_t}{M_\infty} \) indicates that the fraction of drug released is proportional to the square root of time. \( K \) is a constant reflecting formulation characteristics, which may include drug diffusion coefficient in matrix \( D \), the solubility of drug in polymer/wax matrix \( C_s \), the porosity \( \varepsilon \), tortuosity of the capillary systems created within the matrix, and property of the matrix (i.e., homogeneous, granular, hydrophilic, erodible, or insoluble). The model assumes that in these matrices, drug dissolves from the exposed surface regions, and as it becomes exhausted of dissolved drug, a more gradual drug depletion of the deeper regions to the core is followed, as shown in Figures 12.10 and 12.11.

It is an important fact to note from Equation 12.6 that, in general, the relationship between \( \frac{M_t}{M_\infty} \) and square root of time is linear for both simple insoluble and hydrophilic granules, pellets, mini-tablets or matrices. A more general equation that can be applied to most types of drug delivery systems (excluding osmotic pump systems) to describe drug release rate is a modification of the above equation:

\[
\frac{M_t}{M_\infty} = K t^n,
\]

where exponent \( n \) has values between 0.45 and ≤0.85. The values around 0.5 or square root are generally associated with a burst effect (rapid initial drug release) followed by a tailing of release profiles beyond at least 60% drug release.\(^{18,19}\)

**TABLE 12.2**

Approximate Solutions for Diffusional Release from Cylinder and Spheres

<table>
<thead>
<tr>
<th>Geometry</th>
<th>Early Time</th>
<th>Late Time</th>
</tr>
</thead>
</table>
| Cylinder | \[
\frac{M_t}{M_\infty} = 4 \left( \frac{Dt}{\pi r^2} \right)^{1/2} - \frac{4}{(2.405)^2} \exp \left( -\frac{(2.405)^2 Dt}{r^2} \right)
\]
| Sphere   | \[
\frac{M_t}{M_\infty} = 6 \left( \frac{Dt}{\pi r^2} \right)^{1/2} - 3 \frac{Dt}{r^2}
\] |

where \( M_t/M_\infty \) indicates that the fraction of drug released is proportional to the square root of time. \( K \) is a constant reflecting formulation characteristics, which may include drug diffusion coefficient in matrix \( D \), the solubility of drug in polymer/wax matrix \( C_s \), the porosity \( \varepsilon \), tortuosity of the capillary systems created within the matrix, and property of the matrix (i.e., homogeneous, granular, hydrophilic, erodible, or insoluble). The model assumes that in these matrices, drug dissolves from the exposed surface regions, and as it becomes exhausted of dissolved drug, a more gradual drug depletion of the deeper regions to the core is followed, as shown in Figures 12.10 and 12.11.

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\[
\frac{M_t}{M_\infty} = K t^n,
\]

where exponent \( n \) has values between 0.45 and ≤0.85. The values around 0.5 or square root are generally associated with a burst effect (rapid initial drug release) followed by a tailing of release profiles beyond at least 60% drug release.\(^{18,19}\)

**FIGURE 12.10** Release of drug from a granular insoluble matrix dosage form. Schematic shows the receding boundary as drug diffuses from the dosage form.
On the other hand, reservoir systems for extended release are characterized by a drug core surrounded by a particular polymeric membrane that determines rate of release from the system. The process of drug release is described by Fick’s law of diffusion and, in its simplest form, it can be written as

\[ J = \frac{M_t}{M_\infty} = \frac{DAK\Delta c}{L}, \]  

(12.8)

where \( J \) or \( M_t/M_\infty \) indicates that the fraction of drug released with time is proportional to the surface area \( A \), the diffusion coefficient \( D \), the distribution coefficient \( K \) of the permeant toward the polymer, and \( \Delta c \) is the concentration difference across the membrane having thickness \( L \). Therefore, alteration of polymer in terms of type, molecular weight, and degree of crystallinity coupled with membrane thickness and drug properties can give rise to the desired drug release. Equations of similar form can be written for other geometries such as spheres, cylinders, or multi-laminates. Graphic representations for pellets or matrices with different properties that are routinely encapsulated in hard shell capsules for extended release are shown in Figure 12.12.

In systems where the value of \( n \) is in excess of 0.5, release rates tend to approach linearity as \( n \) increases and mechanisms of drug release depend on both diffusional and erosional properties of the system (i.e., hydrophilic matrix). This situation is more applicable when a polymer matrix is swellable and erodible at the same time. A well-known empirical model that describes these phenomena is given by

\[ \frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}, \]  

(12.9)

where \( M_t/M_\infty \) represents the drug fraction released in time \( t \) (\( M_t/M_\infty \leq 60\% \)); \( k_1 \) and \( k_2 \) represent kinetic constants associated with diffusional and relaxational release, respectively; and \( m \) is the purely Fickian diffusion exponent. For example, when small matrix tablets with potential for encapsulation were formulated using guar, a natural polymer, as its rate-controlling excipient, verapamil hydrochloride as a model drug, and glycine as a soluble release aid excipient, zero-order release of drug in pH 1–6 was achieved (see Figure 12.13). When such a matrix formulation is placed in a
FIGURE 12.12  An illustration of cross section of pellets, matrix systems, or coated spheres and their corresponding drug release rate by diffusion through channels from an insoluble matrix (a), swelling and eroding matrix (b), and diffusion from the reservoir system (c).

FIGURE 12.13  Verapamil release from guar matrix using USP apparatus-II, 1000 mL, buffer pH 1.5 at 50 rpm. Upper schematics show dynamics of changes in matrix dimensions in terms of swelling/erosion over time during dissolution. The sum of calculated curves using Equation 12.9 showing drug release based on the principle of diffusion and/or erosion results in an experimentally determined linear release rate shown with open triangles. Calculated diffusion and erosion contributions as part of release mechanisms associated with this hydrophilic matrix are also shown.22,23
capsule shell, it is assumed that the capsule shell will dissolve within 15–30 min, and drug release would follow and release mechanism can be best described by Equation 12.9.

Accordingly, the degree and exactness of control over the rate of drug release from modified-release delivery systems differ according to the system design and associated mechanism(s) by which drug release is accomplished. Thus, the rate of drug release from the designed delivery systems may result in an input rate for absorption, which would match the desired concentration in the blood to elicit the preferred clinical outcome and potentially allow for establishment of level A in vitro–in vivo correlation (IVIVC).19

For example, control over the rate of drug release from matrix-type systems that are based on hydrophilic/swelling and eroding polymers is exemplified for drugs of different solubility by analyzing dynamics of changes that occur during dissolution testing, leading to desired release as shown in Figures 12.14 and 12.15.

Multiple small matrices using swelling and eroding principles or different populations of multiparticulates, such as coated and uncoated pellets or multiple small coated pellets that release the drug by generation of osmotic pressure within the core, can be placed in a single hard shell capsule to provide for different release patterns, including zero order, delayed release, delayed and extended release, ascending, and/or pulse drug release, which are commercially available.

**TYPES OF BLOOD LEVELS FOR DIFFERENT THERAPEUTIC EFFECTS**

Typically, zero-order release or bolus and zero-order release may include profiles in which rapid attainment of a therapeutic level followed by either a constant maintenance level or prolonged duration of blood levels is the objective (Figure 12.16). Other delivery alternatives include repeat-action, delayed-release, extended-release, and ascending-release delivery systems, as shown in Figures 12.17 and 12.18.

**EXAMPLES OF COMMERCIALLY AVAILABLE HARD SHELL EXTENDED-RELEASE CAPSULE DELIVERY SYSTEMS**

**Encapsulated Matrix Tablets for Extended Drug Release**

Representative and commercially available modified-release capsule dosage forms containing four individual tablet matrices each containing 60 mg diltiazem hydrochloride designed for 24-h zero-order release is shown in Figure 12.19. In this delivery system, each tablet has three layers. Two external layers act as a barrier to release from the middle layer, which contains a highly soluble drug. The system is hydrophilic and will hydrate and swell, allowing drug diffusion. Diffusion of drug occurs laterally as barrier layers remain on both side of the middle matrix layer. The delivery
FIGURE 12.15 (See color insert.) Graphic representation of a matrix undergoing hydration and swelling. Depending on the properties of polymer(s), drug, and excipients. Exact release is influenced by synchronization of various fronts as shown. Left panel illustrates hydration of matrix from periphery to the center of the matrix showing different fronts and dynamics of changes in matrix from tablet center to the erosion front. Middle panel shows synchronization of drug diffusion front within a hydrating matrix dominated by either swelling aspect or erosion aspect contingent upon drug solubility. The right panel shows achievement of zero-order drug release owing to front synchronization.25,26

FIGURE 12.16 A graphical representation of the plasma concentration against time following the oral administration of controlled (A) and sustained (B) release products. MTC, minimum toxic concentration; MEC, minimum effective concentration. A maintains constant therapeutic plasma concentration of drug; B ensures prolonged duration of plasma levels of drug.
FIGURE 12.17 A graphical representation of the plasma concentration against time following the oral administration of a repeat action dosage form or a delayed release product. MTC, minimum toxic concentration; MEC, minimum effective concentration.

FIGURE 12.18 A graphical representation of the plasma concentration against time profiles following the oral administration of an ascending-release product and an extended-release dosage form. MTC, minimum toxic concentration; MEC, minimum effective concentration. Ascending-release dosage form provides for disease conditions in which chronopharmacological interactions prevail. An extended-release dosage form ensures prolonged duration of plasma levels of drug and more desirable therapeutic effect.

FIGURE 12.19 Near-zero-order delivery of highly soluble drug diltiazem hydrochloride (240 mg) from hard shell capsule containing 4 three-layer tablets each with 60 mg diltiazem sandwiched between two barrier layers. Dissolution was performed using USP-26, apparatus-II, in 900 mL of phosphate buffer (pH 6.8) at 37°C, with a paddle rotation of 100 rpm.
system provides 240 mg of diltiazem release in a near–zero-order manner. The principle mechanism of drug release is based on surface restriction, matrix swelling, drug diffusion, and system erosion as illustrated in the earlier discussion (see Figures 12.14 and 12.15).

**Encapsulated Coated and Uncoated Pellets for Extended Drug Release**

Many marketed extended-release capsule dosage forms containing different populations of pellets, mini-tablets, granules, or multiparticulates with varying polymer types and functionality to sequentially release their drug content in different pH's and regions of GI tract for prolonged absorption are commercially available. For example, in one US patent, specific formulation strategies to provide rapid, delayed, and extended release with enhanced solubility features for extended release of carbamazepine base especially in a more alkaline portion of the distal intestine are shown in Figure 12.20. In pellet C, one of the excipients used in the core is citric or tartaric acid. Since carbamazepine base has low solubility and limited dissolution in the more alkaline pH environment of distal intestine, the addition of acidic excipient in the pellet core once dissolved will create a low-pH microenvironment with increased osmotic pressure, thus enhancing diffusion and dissolution rate of carbamazepine. A similar approach has also been adopted in matrix systems to control dynamics of hydrations and dissolution rates of highly soluble compounds.27

The main mechanism of drug release from these three pellet types is based on immediate release and dissolution of pellet A, followed by delayed release from pellet B, and a more extended release that is based on enhanced solubility of the drug within the coated pellet C followed by diffusion from inside to outside of the permeable membrane as a result of both osmotic pressure and concentration gradient across the coating barrier. These release principles are discussed under the section “Dissolution Rate of Drug from Drug Particles, Pellets, or from Various Modified-Release Formulations and Delivery Systems Encapsulated in a Capsule Shell as a Delivery Carrier.”

**FIGURE 12.20** Extended-release carbamazepine capsule (200 mg) containing three different bead types, each with their own formulation and rate controlling membrane, combined in exact proportions to provide sustained release of drug in different pH environment within the GI tract. Each pellet type is designed to release drug in different pH’s at different rates. Summation of all release portions from each pellet type after dissolution testing is also shown. (For more details, see US patent 5326570.)
ENCAPSULATED ENTERIC-COATED PELLETS AND ENTERIC-COATED MINI-TABLETS FOR DELAYED RELEASE AND/OR DELAYED EXTENDED RELEASE

The coating of solid substrates in the form of pellets or tablets is one of the most commonly used operation in the pharmaceutical industry for purposes of taste masking, esthetic and trade marking matters, stability improvement, or generating functionalyzed coatings such as enteric or controlled-release coatings. The functional coating option allows formulators to develop pH-dependent dosage forms of the drug that can resist gastric dissolution or to induce delayed release kinetics as part of modified-release drug delivery systems. A variety of dissolution kinetics can be addressed in this way, together with GI targeting of drug via pulsatile release or slow release through permeable or semipermeable coating having one or more orifices. Coating is accomplished by applying a uniform coat on a substrate in a drum/pan coater or fluidized bed system by means of liquid spraying, immersion into a liquid, or powder deposition by electrostatic forces.28,29

Enteric coating is typically and successfully employed when

1. Drug substance is destroyed by gastric acid or enzymes and should be protected.
2. Drug causes irritation to the gastric mucosa and thus improving tolerability is achieved by release in the small intestine.
3. Absorption and bioavailability is substantially enhanced in the intestine via temporal and pH-dependent dissolution and release.
4. It is desirable to deliver the drug after a time delay (i.e., controlled onset delivery) particularly as part of controlled-release drug delivery.
5. Targeting in the GI tract is desirable, especially in delivery to the colon, for topical effect or systemic absorption. For example, delayed release in pH ≥7.0 (ileum and colon) for distal GI delivery is particularly advantageous in the treatment of ulcerative colitis and Crohn’s disease (i.e., dosage forms containing mesalamine or budesonide).30

Frequently used materials for enteric coating are polymeric acids with free carboxyl groups that confer gastric resistance. They include anionic polymethacrylates (copolymerisate of methacrylic acid: methylmethacrylate or ethyl acrylate, Eudragit L 30 D-55, Eudragit FS 30 D, or Eudragit-L100, with a pH value of aqueous dispersion of ~3.05) and cellulose-based polymers (i.e., hypromellose acetate succinate [HPMCAS], with pH about 3.85) or hypromellose phthalate (HPMCP), aqueous cellulose acetate phthalate (Aquateric), or polyvinyl derivatives such as polyvinyl acetate phthalate (Coateric). Since aqueous dispersions of Eudragit L 100 have high film-forming temperatures of about 85°C, mixing with the softer Eudragit L 30 D 55 makes it possible to reduce the film-forming temperature to about 40°C, which is a more acceptable range especially when hard gelatin capsules and HPMC capsules are coated. For modulation of drug release in pH 5.5 to 7.0, further mixing with Eudragit NE 30 D and FS 30 D is an acceptable option. Explicitly aqueous dispersions for enteric coating (Eudragit L 30 D-55) and colonic coating (Eudragit FS 30 D) of HPMC and hard shell gelatin capsules have been investigated.31,32 Apart from enteric film formers, other enteric film coating components include plasticizers (i.e., diethyl phthalate, triacetin), anti-adhesion agents, colorants, pigments, solubilizers, and dispersing agents. To these may be added viscosity-enhancing suspension stabilizers designed to retard the sedimentation of undissolved excipients or dispersed film formers.

Mention must be made that the acid-labile drugs can also be degraded as a consequence of contact with the acidic nature of enteric coating polymers during formulation development and manufacturing. Thus, it is essential to not only protect the drug against acid exposure in the acidic environment of the stomach and prevent its degradation but also have protective measures during formulation development to prevent degradation and also enhance drug storage stability for predictive bioavailability and therapeutic efficacy after oral administration.33,34 Figure 12.21 shows a typical pellet with an acid-labile drug omeprazole that is layered onto a sugar sphere and protected with a layer of neutral barrier before the application of acidic enteric coating solution.
Two frequently used techniques to produce pellets that contain drugs include drug layering onto spherical substrates or direct pelletization via wet extrusion of drug and excipient mixture followed by spherization and drying. Pellets can be directly enteric coated with pH-sensitive polymers or coated for the controlled-release delivery of drug over a prolonged period. The coating process can be accomplished by using an air suspension coating approach where the solution of the polymers or suspension of drug in polymer solution is sprayed via nozzle(s) atomization onto the pellets in a fluid bed apparatus under the controlled conditions of air pressure and temperature to achieve percent target weight gain (i.e., desired coat thickness) for specific delivery rate or release location in the GI tract. The core materials could also be a formulated mini-tablet or a filled capsule, where both fluidization or the pan coating approach are used. Typical examples of encapsulated enteric-coated pellets of omeprazole, a proton pump inhibitor, and delayed extended-release coated mini-tablets of 5-amino salicylic acid, an anti-inflammatory drug, for delivery to the proximal and distal intestine (i.e., ileum and colon) with their respective dissolution profiles are shown in Figure 12.22.

FIGURE 12.21 Fluorescence image of a fractured omeprazole pellet, where a spherical nonpareil seed was coated with the omeprazole drug layer followed by application of an inert barrier layer and further coating with an acidic polymer enteric layer on top of the subcoat for the enhancement of drug stability during manufacturing and shelf life storage stability.

FIGURE 12.22 Dissolution profiles for encapsulated enteric-coated omeprazole pellets and delayed extended-release 5-amino salicylic acid mini-tablets, using USP 26, apparatus-II at 100 rpm, 900 mL of buffers with different pHs.
Encapsulated Beads of a Polypeptide Linaclootide for Once-a-Day Oral Administration

Linaclootide is a 14-amino acid peptide agonist of guanylate cyclase-C (GCC). Both linaclootide and its active metabolite bind to GCC and act locally on the luminal surface of the intestinal epithelium that is intended for the treatment of chronic idiopathic constipation and irritable bowel syndrome constipation in adults. It reduces activation of colonic sensory neurons, which reduces pain, and activates colonic motor neurons, which increases smooth muscle contraction and thus promotes bowel movements. The product is a hard gelatin capsule (145 and 290 μg strengths) containing linaclootide drug substance coated onto microcrystalline cellulose beads along with HPMC and stabilizing agents such as calcium chloride dihydrate and L-lucine for once-a-day administration. The molecular formula of linaclootide is C_{59}H_{79}N_{15}O_{21}S_{6}, and its molecular weight is 1526.8. It is a 14-amino acid synthetic peptide with three disulfide bridges. All amino acids are of L-configuration with the following sequence: L-tyrosine, L-cysteinyl–L-cysteinyl–L alpha-glutamyl–L-tyrosyl–L-cysteinyl–L-cysteinyl–L-asparaginyl–L-prolyl–L-alanyl–L-cysteinyl–L-threonylglycyl–L-cysteinyl–cyclic (1→6),(2→10),(5→13)-tris(disulfide).

![Disulfide bridges in linaclootide](image)

It is an amorphous, white powder with no x-ray powder diffraction patterns, soluble in water; pH (2.4 mg/mL) = 3.4; isoelectric point (IP) = 4.0; specific optical rotation = −235° to −261° (589 nm, c = 0.1 in 1% acetic acid). Linaclootide is minimally absorbed with low systemic availability following oral administration (i.e., plasma levels are below the limit of quantitation after oral doses of 145 μg or 290 μg). Its solubility in aqueous solution over a pH range 1.0 to 7.5 is >100 μg/mL. Therefore, it is considered to be a BCS Class 3 (high solubility, low permeability) compound. The hard shell capsule appears to be an ideal carrier for this compound. Being a polypeptide, if subjected to compression forces used in tableting, it is likely to lose its structural features owing to mechanical shearing followed by loss of its therapeutic value. It is known that mechanical perturbation and shearing forces of impaction and compression during tableting consolidation are high enough to kill bacterial cells and mold spores. Consequently, if proteins and polypeptides are subjected to similar conditions, they may not maintain their molecular stability and folded state and result in conformational changes with loss of biological function.

Encapsulated Drug Formulation for Time-Delayed and Targeted Delivery During Drug Development Phases and Research to Assess Drug Absorption

Multiple delivery systems with potential use in chronotherapeutics in concord with the circadian rhythms of the disease have been developed with specific time-dependent “trigger” mechanisms for delivery of drug at a particular rate to a specific region of the GI tract. One such delivery system is Pulsincap, which consists of an insoluble and impermeable capsule body and a water-soluble cap with possibility for pH-sensitive coating as graphically shown in Figure 12.23. The capsule cap is soluble in water or a desired pH environment while the capsule body is impermeable to water. Drug and swelling polymer can be used as part of drug formulation together or independent of each other and filled into the body of the capsule. A swelling and eroding hydrogel plug or an eroding compressed tablet is used to seal the content. Upon oral administration, the cap will dissolve in the specific pH environment followed by gradual but controlled hydration, swelling, and erosion of the plug. Compositionally, the plug is made of a swellable, erodible (e.g., HPMC, soluble
Modified-Release Delivery Systems

as a time trigger inciting drug release.

polymethacrylate, polyvinyl alcohol), or congealed melted excipient (e.g., glyceryl monooleate), or an enzymatically degradable polysaccharide like pectin. Once the plug is dissolved, fluid gradually enters the capsule body from the open end. For rapid release of insoluble drugs, a disintegrant or an effervescent agent may be added to the formulation. The expulsion agent also swells and expands and the drug formulation is expelled for complete dissolution. The second-generation Pulsincap has been further optimized for a more predictable and accurate plug ejection and composition of the expulsion agent to rapidly and completely expel the contents. The system has been used in several human studies demonstrating that the system was well tolerated in the volunteers as well as in the clinic, and its performance and location within the GI tract are monitored using scintigraphy studies.

PORT SYSTEM

Another system that has been investigated in research include the Port System, which is a compartmentalized semipermeable gelatin or HPMC capsule body divided into multiple compartments and is capable of drug delivery in accordance with zero order, pulse release, or their combinations especially for release in the lower ileum or colon. The mechanism of drug release is based on water diffusion into the capsule body. Dissolved drug and excipients will generate an osmotic pressure gradient across the slidable separator and between the inside and outside of the capsule body pushing the separator and the dissolved drug into the GI tract.

EGALET

This particular system, which is also based on delayed release to achieve temporal or spatial targeted delivery of actives to the distal intestine, involves Egalet technology. The system consists of an impermeable shell with two eroding lag plugs enclosing a formulation plug in the middle of the unit. Release mechanism is mainly based on swelling and erosion of the plugs and formulation. Other variants of the Egalet system allowing for burst release followed by extended or pulsatile release have also been investigated.

ELECTRONIC CAPSULE DEVICES FOR SITE-SPECIFIC DETERMINATION OF THE DRUG ABSORPTION

Over the last 30 years, a number of electronic capsule devices with sizes generally equivalent to standard capsule size of “0” or “00” have been developed and investigated in humans to determine the drug absorption in various regions of the GI tract in a noninvasive manner. The primary emphasis of these electronic capsule devices has focused on control of time and the location of drug release via external activation of the capsule device after oral administration. One of the more advanced capsule shape devices in this category is called the Enterion capsule.
The Enterion capsule shown in Figure 12.24 is designed and patented by Quotient Clinical to assess targeted delivery of a wide range of modified-release drug formulations. It is a remote-controlled device that is capable of precisely delivering drug formulations (both liquid and solid) to specific sites within the GI tract. It is a round-ended capsule with a drug chamber of about 1 mL in volume and can be loaded with either liquid dispersions, pellets, mini-tablets, or particulate matters, through an opening of 9 mm in diameter, which is then sealed by inserting a push-on cap fitted with a silicone O-ring. The base of the drug reservoir chamber is the piston face, which is held back against a compressed spring by a high–tensile strength polymer filament. The filament can be melted or ruptured wirelessly, pushing the drug formulation out of its chamber into the region of interest within the GI tract. The drug released may provide local and topical effect or it may be absorbed. A gamma-emitting marker may be placed inside a separate sealed tracer port to allow real-time visualization and transit location of the capsule in the GI tract after oral administration via scintigraphy.

The technology has potential for targeted delivery of highly potent drugs in specific regions of the GI tract especially when high localization of drug within a narrow segment of intestine for topical effect is needed. Such an application may include delivery of peptides, proteins, and anticancer drugs in colon cancer within any part of the colonic environment.49

**IntelliCap device**

Medimetrics’ IntelliCap is a wirelessly controlled, electronic capsule system that delivers drug to the region of interest in the GI tract for regional absorption studies. The 11 mm × 26 mm (approximately “000” size capsule) is composed of a microprocessor, battery, pH sensor, temperature sensor, wireless transceiver, fluid pump, and drug reservoir capable of storing up to 275 μL of test compound (see Figure 12.25). It communicates via its wireless transceiver to an external control unit worn by the subject.

Radiolabeling and scintigraphic monitoring of IntelliCap allow one to determine its position within the GI tract (Figure 12.26). This assures that the drug is released at the desired site, thus increasing its value in animal and clinical studies during product development phases.

The IntelliCap system allows for more predictable drug release within the target region. At the same time, transit time from stomach to colon can be easily monitored via a wireless pH sensor. Figure 12.27 shows representative data collected from an IntelliCap study in a dog. The capsule was programmed to release atenolol at a constant rate for 6 h starting at arrival in the duodenum. The zero-order release strategy allowed examining the entire intestinal tract with a single experiment. Regional transit and location are clearly described along with the pH data, drug release duration, and concurrent plasma concentration of the drug. An additional application of IntelliCap device for quantifying regional drug delivery and absorption in humans in bioequivalency studies using diltiazem as model drug is presented elsewhere.50
FIGURE 12.25  (See color insert.) “IntelliCap” system and its components. (Courtesy of Medimetrics.)

FIGURE 12.26  (See color insert.) A scintigraphic study showing the location of IntelliCap device after oral administration. (Courtesy of Medimetrics and Bio-Images Research partnership.)

FIGURE 12.27  Concurrent determination of drug release, transit time, pH values, and drug plasma concentration; data collected from an IntelliCap study in a dog. (Courtesy of Medimetrics.)
Wireless capsule endoscopy is a new and noninvasive tool to examine all or specifically parts of the GI tract (i.e., the middle portion of the small intestine) that cannot be seen with other types of endoscopy. The technique was invented in Japan and allows video recording and imaging of the digestive tract for use in medicine. The capsule dimensions and its features are generally equivalent to capsule size “00,” and its general components are shown in Figure 12.28. Common reasons for doing capsule endoscopy is to diagnose GI tract problems such as internal bleeding, abdominal pain, detection of polyps, ulcers, tumors, and inflammatory bowel disease such as Crohn’s disease. The capsule endoscope is a wireless and disposable device able to capture images and transmit these images to electrodes attached to the patient’s body, permitting data storage. The capsule is capable of transmitting at a rate of 2 images per second, about 50,000 images within 8 h. There are four different manufacturers of capsule endoscopes: Endo Capsule (Olympus America), PillCam SB2 (Given Imaging), MiroCam (IntroMedic), and OMOM (Jinshan Science and Technology).

**SUMMARY**

Because of the space restrictions for the chapter, complete coverage of all types of mechanisms and delivery innovations related to modified-release capsules as drug delivery was not probable. However, an attempt has been made to comprehensively elucidate and cover the major and more commonly used extended-release capsules that are FDA approved and currently marketed. The development of hard shell capsule products for modified-release drug delivery is focused on the choice and/or construction of the most desirable dosage form for a drug that will provide safe and effective drug delivery to treat patients. Other objectives of drug delivery are improvement in patient compliance, enhancement of bioavailability and drug efficacy, and reduction in dosing frequency with improved therapeutic performance. Capsules are the second most frequently used dosage forms for oral drug delivery (e.g., first being the tablets). The major advantage of capsules as delivery systems is that the shell can be used as a carrier for formulated drugs, coated pellets, mini-tablets, multiparticulates, fixed-dose combinations, as well as inclusion of smaller capsules or delivery systems. The capsule shell can be enteric coated for drug delivery to the proximal and/or distal intestine, especially for delivery of acid-labile drugs, peptides, proteins, biotechnology-derived drugs, and macromolecules that are destroyed by mechanical shearing or manufacturing processes. Additionally, controlled or extended release of drug from capsule delivery system with potential for pulsatile and targeted delivery within the GI tract is easily attainable. Drug targeting of the GI tract and specifically colon is advantageous in that many side effects are reduced, lower drug dose is used, and drug is released as close as possible to the target region. In some cases, the content of capsules can be easily dispersed onto semisolid food or liquids for patients who cannot swallow the dosage form. Furthermore, a variety of innovations in design of new capsule shells (i.e., microbiologically triggered systems, biodegradable, rupturable, or pressure-sensitive shells)
and delivery types for targeting various regions of the GI tract are under investigation and development. Extended-release capsule delivery systems offer many opportunities and challenges not only in delivering drug in a controlled manner to the target area within GI tract but also in developing bio-relevant and appropriate in vitro dissolution methods simulating the in vivo conditions. The future of modified-release and extended-release capsules as drug delivery systems is limited only by the inventiveness of research scientists involved in the field.

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