Metadata of the chapter that will be visualized online

Series Title	Advances in Delivery Science and Technology	
Chapter Title	Oral Controlled Delivery Mechanisms and Technologies	
Chapter SubTitle		
Copyright Year	2011	
Copyright Holder	Controlled Release Society	

Corresponding Author	Family Name	Omidian
	Particle	
	Given Name	**Hossein**
	Suffix	
	Division	College of Pharmacy
	Organization	Nova Southeastern University
	Address	Fort Lauderdale, FL, USA
	Email	omidian@nova.edu
Author	Family Name	Fesharaki
	Particle	
	Given Name	**Shahin**
	Suffix	
	Division	Research & Development
	Organization	Watson Pharmaceuticals
	Address	Fort Lauderdale, FL, USA
	Email	
Author	Family Name	Park
	Particle	
	Given Name	**Kinam**
	Suffix	
	Division	Departments of Biomedical Engineering and Pharmaceutics
	Organization	Purdue University
	Address	West Lafayette, IN, USA
	Email	

Abstract	This chapter reviews release mechanisms and corresponding technologies used to control drug release from oral dosage forms. Products utilizing such approaches range from simple matrix systems to those employing more complex osmotic delivery technologies. Technologies including Oros™, gastroretentive devices, TIMERx™, Contramid™, Geomatrix™, and SODAS™ are discussed. These approaches are generally utilized to provide once-daily administration but some can also be used for differential release of more than one drug from the same dosage form or timed release of drug to align with time of clinical need.

Author's Proof

Chapter 6
Oral Controlled Delivery Mechanisms and Technologies

Hossein Omidian, Shahin Fesharaki, and Kinam Park

Uncorrected Proof

Abstract This chapter reviews release mechanisms and corresponding technologies used to control drug release from oral dosage forms. Products utilizing such approaches range from simple matrix systems to those employing more complex osmotic delivery technologies. Technologies including Oros™, gastroretentive devices, TIMERx™, Contramid™, Geomatrix™, and SODAS™ are discussed. These approaches are generally utilized to provide once-daily administration but some can also be used for differential release of more than one drug from the same dosage form or timed release of drug to align with time of clinical need.

6.1 Introduction and General Principles

Interaction between a drug and a polymeric material generally forms the basis of controlled oral drug delivery. Drug in solution exhibits random Brownian motion to equilibrate concentration, where concentration gradients exist. A polymer at certain concentration in such a solution imposes mandatory pathways for drug diffusion. Thus, polymers that dissolve in or otherwise hydrate in aqueous media can alter the drug diffusion process in a time-dependent manner. For example, hydroxypropyl methylcellulose (HPMC or hypromellose), which is water soluble, behaves as a swellable absorptive polymer in the limited volumes of aqueous media in the gastrointestinal (GI) tract. Drug dispersed in this polymer, as in monolithic tablets, diffuses through the viscous hydrated polymer at a rate dependent on the movement kinetics of the polymer chains. The faster these relax, the faster the diffusion rate.

H. Omidian (✉)
College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL, USA
e-mail: omidian@nova.edu

C.G. Wilson and P.J. Crowley (eds.), *Controlled Release in Oral Drug Delivery*,
Advances in Delivery Science and Technology, DOI 10.1007/978-1-4614-1004-1_6,
© Controlled Release Society 2011

Author's Proof

Hydrophilic polymers like HPMC may also control drug release by erosion mechanisms. After consumption of the dosage form, the GI tract fluid encounters the dosage unit, causing the polymer to hydrate and swell. Weakened mechanical properties in the swollen state may cause the hydrated polymer to break away from the prime particle (compact or pellet). Drug release may therefore be controlled by a combination of diffusion and erosion. Such release mechanisms can apply to systems where drug is dispersed in or coated with polymer.

Delivery to specific regions of the GI tract may be achieved using polymers with pH-dependent solubilities. These include enteric polymers with carboxylic acid functional groups; their pH-dependent solubility determines location for release. Drug can be released at different segments in the GI tract by using enteric coating polymers that dissolve at different pHs, e.g., Eudragit L100-55 (soluble at pH > 5.5), Eudragit L100 (soluble at pH > 6.0), and Eudragit FS 30D (soluble at pH > 7.0) (http://eudragit.evonik.com/) or combinations of these. Water insoluble polymers can extend or prolong drug release. These include methacrylate- or acrylate-based polymers, with little or low permeability (e.g., Eudragits NE 30D, NM 30D, and NE 40D) (http://eudragit.evonik.com/). Addition of hydrophilic functional groups such as trimethylaminoethyl methacrylate can improve permeability and swellability in water (e.g., Eudragits RL and RS series) thereby altering release behaviors.

Technologies have been developed to exploit diffusion, erosion, and other physicochemical mechanisms and provide drug and disease-specific release profiles. Some are based on the nature of the release-modifying material(s), others on the design of the dosage form:

- TIMERx™ technology controls drug release, consequent to interaction between the two hydrocolloids, xanthan gum and locust bean gum.
- Release from a Contramid™ tablet is controlled by the degree of crosslinking of high amylase starch.
- Alza's Oros™ and Duros™ technologies are based on osmosis-driven release.
- Release from Jago Pharma's Geomatrix™ technology is based on the surface area available for drug release.

These mechanisms and technologies are discussed and exemplified in this chapter. Appendix 1 lists examples of commercial products where release has been modified to enhance performance, safety, or patient convenience.

Uncorrected Proof

6.2 Diffusion-Controlled Drug Release

When a matrix comprising drug and a hydrophilic polymer is exposed to GI fluids, it may, depending on composition, break up (disintegrate) or simply hydrate. Disintegration leads to dispersion and dissolution of drug. If the unit retains its structure (does not disintegrate), GI fluid permeates the core and the polymer is hydrated, becoming a viscous mass. Drug must then diffuse through this hydrated

Author's Proof

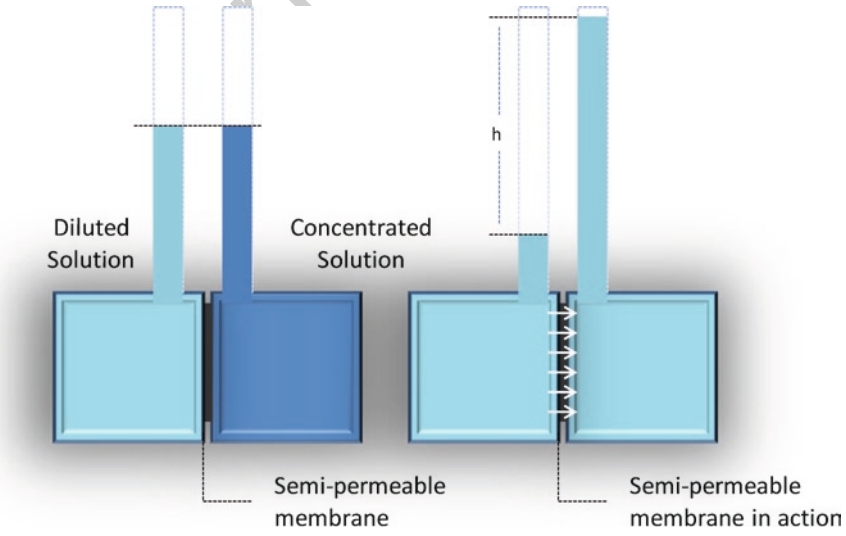
matrix at a rate depending on drug solubility and matrix permeability before release from the unit. Diffusion can also be influenced by membrane porosity if the unit is coated or by the presence of a pore-inducing filler in the coat. In such cases, the porosity of the coating membrane (pore size, shape, and distribution), and filler tortuosity can determine diffusion properties, and hence the drug release profile. Examples of matrix systems for water soluble and water insoluble drugs are given in Appendix 2. Biomedical materials may also exhibit matrix-type release profiles. Malcolm et al. developed a crosslinked silicone-based device to release metronidazole [1].

Matrix systems have also been utilized to provide pH-independent release of weakly basic drugs. In such a context, Streubel et al. showed that verapamil hydrochloride tablets exhibited pH-independent behavior when formulated in matrices containing ethylcellulose or HPMC with organic acids such as fumaric, succinic, or adipic acid [2].

Uncorrected Proof

6.3 Osmotic-Controlled Drug Release

The osmotic-controlled drug release (OROS™) concept for controlling delivery is based on dissolved drug being transported in a controlled manner from the dosage form to the external media under the influence of osmotic pressure. Figure 6.1 illustrates how a solution containing dissolved solute "attracts" water from an adjacent chamber, separated by a semipermeable membrane. Permeation rate depends on



this figure will be printed in b/w

Fig. 6.1 The concept of osmosis

Author's Proof

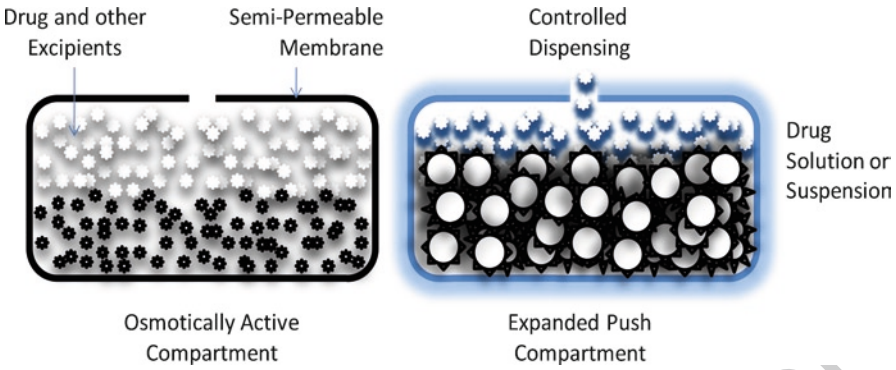


Fig. 6.2 OROS system

Table 6.1 Selected OROS products

Brand	Ditropan XL™	DynaCirc CR™	Covera HS™
Drug	Oxybutynin	Isradipine	Verapamil
Manufacturer	Alza	Novartis	G.D.Searle
Function	Antispasmodic	Calcium antagonist	Calcium antagonist
Solubility in water	Readily soluble	Insoluble	Soluble
Semipermeable membrane	Cellulose acetate	Cellulose acetate	Cellulose acetate
Water-soluble excipients	Hypromellose, poly(ethylene oxide), sodium chloride, poly(ethylene glycol) (http://www.rxlist.com/ditropan-xl-drug.htm)	Hydroxypropyl methylcellulose, poly(ethylene oxide), sodium chloride, poly(ethylene glycol) (http://www.rxlist.com/dynacirc-cr-drug.htm)	Poly(ethylene oxide), sodium chloride, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, poly(ethylene glycol), povidone (http://www.rxlist.com/covera-hs-drug.htm)

Uncorrected Proof

solute concentration ("number of molecules") in the receptor solution. Hence, materials that are ionizable and/or very soluble, and of low molecular mass are the most effective osmotic agents.

If the receptor chamber contains drug and excipients that are osmotically active the hydrostatic or hydraulic pressure exerted by the increased volume of fluid drives ("pushes") drug through one or more orifices in the dosage unit at a relatively constant rate (Fig. 6.2). Such delivery is believed to function independently of environmental conditions in the GI tract (pH, regional location, etc). The technology can be applied to compressed units (tablets) or capsules. The OROS™ concept or variations thereof has been applied to many medicinal agents for delivery in a controlled manner over an extended period of time (Tables 6.1 and 6.2).

Author's Proof

Table 6.2 Examples of OROS products with two release ports

Brand	Fortamet ER™	Altocor™
Drug	Metformin	Lovastatin
Manufacturer	Andrx/Watson	Andrx/Watson
Function	Antihyperglycemic	Cholesterol-lowering agent
Solubility in water	Freely soluble	Insoluble
Semipermeable membrane	Cellulose acetate	Cellulose acetate
Excipients	Hypromellose, PEG 400, PEG 8000, Povidone (http://www.rxlist.com/fortamet-drug.htm)	Hydroxypropyl methylcellulose, hypromellose phthalate, methacrylic acid copolymer, PEG 400, PEG 8000, poly(ethylene oxide), propylene glycol, sodium chloride (http://www.rxlist.com/altocor-drug.htm)

6.3.1 *Conventional OROS™*

Glucotrol XL™ (Novartis) delivers 2.5, 5, or 10 mg of the sulphonylurea, glipizide in a sustained manner to enable once-daily dosage. Release modifying components are poly(ethylene oxide), HPMC, cellulose acetate, with sodium chloride as the prime osmotic pressure inducer (http://www.rxlist.com/glucotrol-xl-drug.htm). The bilayer tablet core, containing drug and the osmotically active agents (in separate layers) is coated with cellulose acetate, which is permeable to water but not to the drug or the osmotic agent (Fig. 6.2). On ingestion, GI fluid diffuses through the semipermeable membrane into the tablet core. Dissolved drug from the drug-containing layer is driven through a laser-drilled orifice due to the osmotic pressure buildup in the layer containing sodium chloride (so-called push layer). Delivery rate is independent of pH and gastric motility, thereby extending drug release throughout the GI tract. Neither do other variables, such as posture or diet state have an effect. Since delivery is driven by osmotic pressure, drug is released at a constant rate so long as the osmotic gradient between the drug layer and the GI tract fluid is maintained. The osmotic gradient eventually decreases due to release of osmotic agent and drug, with delivery eventually tailing off (http://www.rxlist.com/glucotrol-xl-drug.htm). Water soluble as well as insoluble drugs have been formulated in such a system as given in Table 6.1.

The bilayer Oros™ oxybutynin tablet also provides extended release over 24 h based on essentially the same release mechanism as Glucotrol XL™. Following administration oxybutinin plasma concentration rises slowly over 4–6 h, followed by a relatively constant plasma level for up to 24 h. A study by Goldenberg showed that such dosage was well tolerated, and as clinically effective as its 5 mg "immediate release counterpart" [3].

Duan et al. prepared an osmotic tablet containing isosorbide-5-mononitrate (5-ISMN). Tablet composition, size, and location of the orifice, and membrane properties were affected by drug release. Based on pharmacokinetics and bioavailability

Uncorrected Proof

Author's Proof

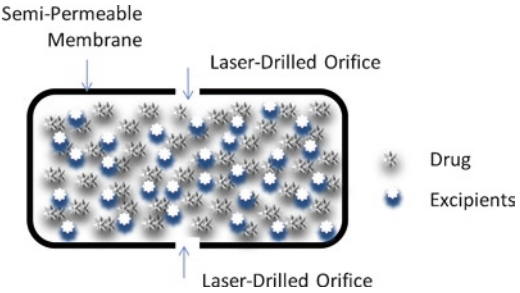


Fig. 6.3 SCOT system

data in Beagle dogs, the osmotic tablet was considered to be a more suitable long-acting preparation than a 5-ISMN SR matrix tablet for once-daily dosage [4].

Liu et al. studied factors affecting in vitro and in vivo behavior of an osmotic tablet containing nifedipine. Membrane and orifice size significantly affected release but release per se was independent of dissolution medium variables. The pharmacokinetic data suggested that the formulation was capable of sustaining plasma levels to enable once-daily dosing [5].

Swellable core technology (SCT) partners the drug with a water-swellable excipient. Thombre et al. studied in vitro and in vivo release of tenidap and sildenafil from SCT formulations with different core configurations (single layer, bilayer, and trilayer). Release rates were independent of core configuration, and the in vivo pharmacokinetic parameters in beagle dogs were consistent with in vitro performance [6]. Wagstaff et al. studied drug release from an extended release osmotic tablet containing the biguanide, metformin hydrochloride in patients with type 2 diabetes. The extended release formulation exhibited prolonged T_{max} but overall bioavailability (area under curve) was comparable for both presentations, as were GI adverse effects [7]. Waterman et al. developed an extrudable system for osmotic delivery of poorly soluble drugs. The dosage form comprises a monolith core coated with a semipermeable membrane. The core contains hydroxyethyl cellulose along with sugar as the osmotic agent [8].

6.3.2 *OROS™ with Twin Orifices*

The *SCOT*™ (Single Composition Osmotic Tablet) system shown in Fig. 6.3 has the osmotic agent and drug in a single layer, contrasting with systems comprising two layers. This single layer technology utilizes various osmotic modulating agents and polymeric coating to provide zero-order drug release. The system claims to effect substantially complete release of drug possibly due to twin exit ports on either side of the tablet.

The core comprises primarily drug with low levels of excipient. The coat is permeable to water, but not to higher molecular weight components in biological fluids. Table 6.2 lists examples of drugs utilizing this technology.

Uncorrected Proof

Author's Proof

Table 6.3 Examples of trilayer OROS™ products

Brand	Concerta™	Invega™
Drug	Methylphenidate	Paliperidone
Manufacturer	Johnson & Johnson	Johnson & Johnson
Function	CNS stimulant	psychotropic agent
Solubility in water	Freely soluble	Insoluble
Semipermeable membrane	Cellulose acetate	Cellulose acetate
Water-soluble excipients	Hypromellose, phosphoric acid, poloxamer, poly(ethylene glycol), poly(ethylene oxide), povidone, propylene glycol, sodium chloride (http://www.rxlist.com/concerta-drug.htm)	Hypromellose, hydroxyethyl cellulose, poly(ethylene glycol), poly(ethylene oxide), povidone, propylene glycol, sodium chloride (http://www.rxlist.com/invega-drug.htm)

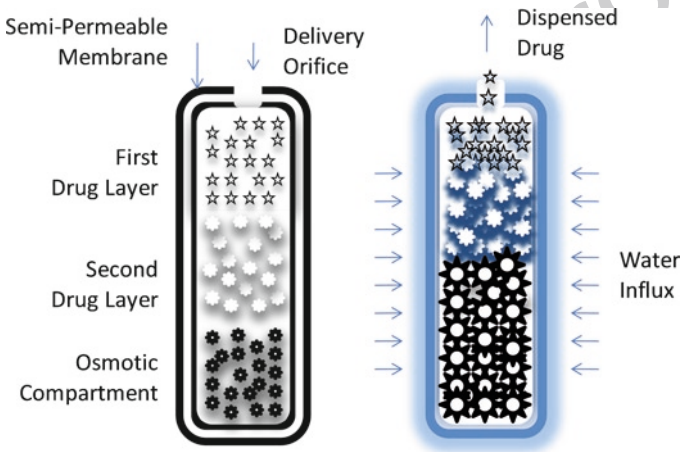


Fig. 6.4 Trilayer OROS system

Uncorrected

6.3.3 Trilayer OROS™

Trilayer OROS™ further advances the osmotic concept, being applied to brands such as Concerta™ and Invega™ (Table 6.3). Tablets comprise a core and a semipermeable membrane. The core is composed of three layers, i.e., two drug layers and one osmotically active compartment (Fig. 6.4). The drug layers may contain two drugs or the same drug at two concentrations. The Concerta™ presentation has an "immediate-release" overcoat to deliver a rapid initial dose fraction. An orifice in the first layer along with the semipermeable membrane controls subsequent drug release.

Author's Proof

The Invega™ tablet technology, while similar to that for Concerta™ is equipped with laser-drilled orifices on the dome of the drug layer. Tablets are coated with a water-dispersible polymer, which is quickly eroded on exposure to GI Tract media (http://www.rxlist.com/concerta-drug.htm). It is claimed that Invega 12 mg once-daily OROS™ tablet provides steady-state plasma concentrations over 6 days (http://www.janssencns.com/invega/schizoaffective-disorder/dosing-and-administration/oros-technology).

6.3.4 *Osmodex™*

Laser-drill technology is used in the Osmodex™ family of "platform" technologies in combination with a variety of single and multiple drug delivery approaches. The technologies are classified as (http://www.osmoticausa.com/):

- Osmodex SD™ for soluble drugs.
- Osmodex™ IR/CR (combined instant and controlled release of one or two drugs).
- Duodex Double CR™ (delivery of two drugs with different release patterns).
- Osmodex Triplet™ (to provide three different release rates).

Allegra-D 24HOUR™ utilizes the Osmodex™ IR/CR technology. It is designed to provide an immediate release of the antihistamine, fexofenadine (180 mg) combined with extended release (240 mg) of the decongestant, pseudoephedrine hydrochloride for 24-h cover of nasal allergy. Excipients facilitating such prolonged delivery are sodium chloride (osmotic agent), poly(ethylene glycol), povidone, hypromellose, croscarmellose sodium, and copovidone (release modifiers). The tablet has cellulose acetate-based coat as a semipermeable membrane, and the coated tablet is then covered with an immediate release drug layer (http://www.rxlist.com/allegra-d-24-hour-drug.htm). Figure 6.5 shows an Osmodex™ system with an immediate release coating and an extended release core.

6.3.5 *OROS™ Safety and Clinical Aspects*

Benefits of osmosis-driven technology relate to its capability to:

- Release drug at a constant (zero order) rate.
- Provide consistent release regardless of drug or environment, i.e., independent of drug, patient physiology, or food effect [9].
- Sustain delivery over a significant time period.
- Pulse and/or delay delivery to align with patient needs or mode of drug action.

Treatment tolerability and patient compliance may improve with some medications as a consequence of such delivery. OROS™ technology, with its capability to provide lower peak plasma levels and "smoother" plasma profiles

Uncorrected Proof

Author's Proof

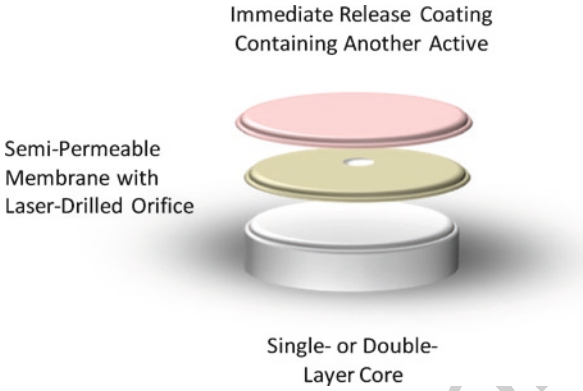


Fig. 6.5 OSMODEX system

may also result in reduced plasma level-related side effects [10]. Wonnemann et al. compared the bioavailability of nifedipine from two commercial modified release nifedipine products, viz., Adalat OROS 30™ and Nifedipine Retard 30™. A significant food interaction effect was noted with Nifedipine Retard 30™. In contrast, food intake did not have a significant effect on release from the OROS™ dosage form, based on pharmacokinetic parameters. Variable and unpredictable plasma levels, suggestive of inconsistent delivery were also noted with the Nifedipine Retard 30™ formulation. Such findings illustrate the hazard of switching medications that might ostensibly seem to have comparable efficacy and safety [11].

Sathyan et al. reported that side effects associated with immediate-release oxybutinin can be alleviated using an extended release OROS™ presentation of the drug [12]. Paliperidone is an oral psychotropic agent for treating schizophrenia. It undergoes limited hepatic metabolism if formulated utilizing OROS technology. Davidson et al. studied safety and efficacy of once-daily paliperidone in acute schizophrenia. All doses of extended-release paliperidone were well tolerated and shown to improve personal and social functioning [13]. In another clinical study in acute schizophrenia, symptoms were improved significantly in patients who used paliperidone ER [14].

Potential drawbacks associated with the OROS™ platforms include the high costs of manufacture (laser drilling is required). Dose dumping is also a potential issue if the semipermeable coat is compromised and the entire daily dose being contained in a single unit. Bass et al. comprehensively reviewed safety aspects of tablets based on OROS™ technology. Long-term safety data indicated a low incidence of clinically significant GI tract side effects including intestinal, gastric, and esophageal irritation, injury, and obstruction. The general experience indicates that for some drugs OROS™-based products can provide substantial therapeutic and convenience benefits without delivery-related risks [15].

Uncorrected Proof

Author's Proof

6.4 Geomatrix™ Technology

Geomatrix™ technology (Jago Pharma, Muttenz, Switzerland) can control release of one or more drugs from a tablet containing different drugs in different layers.

Different layers in the tablet with different swelling, gelling, and erosion behaviors can provide separate drug release modes (http://www.skyepharma.com/Technology/Oral_Technology/Geomatrix/Default.aspx?id=62). In general, hydrophilic polymers progressively swell on encountering aqueous media thereby increasing gastric residence time, core surface area, and diffusivity for release. Thus, as amount of drug in the core is depleted the rate of release is increased due to the greater surface area, consequent to swelling. Appropriate matching of drug and polymer(s) provides the desired balance between drug depletion and increased diffusion through the matrix to deliver a steady flux.

Various release mechanisms can be achieved using the Geomatrix™ technique. These include:

- Zero order (constant rate over time).
- Binary (release of two drugs at different rates and times).
- Biphasic release (combination of slow and fast release for a same drug).

Biphasic delivery can be further subgrouped as "quick–slow" release and "slow–quick release." With the former, a burst release of a drug is followed by extended release over time (e.g., Zyflo CR™) (http://www.skyepharma.com/Technology/Oral_Technology/Geomatrix/Default.aspx?id=62). Zyflo CR™ (Cornerstone Therapeutics) is an extended release tablet containing the antiasthmatic, zileuton. The triple layer provides an immediate release dose fraction, and a middle layer to regulate drug release from an extended release layer to prolong drug release and effect.

HPMC is one of the most common release modifiers in matrix tablets. Maggi et al. studied poly(ethylene oxide) as an alternative for Geomatrix-based products. HPMC provided more controllable and slower release rates in multiple layer Geomatrix™ systems [16].

Conte et al. reviewed Geomatrix™ technology in terms of efficacy, reproducibility, and technological characteristics [17].

Geomatrix™ technology is primarily intended for water soluble drugs and the release rate is significantly reduced if drug has poor aqueous solubility [18]. It has been successfully applied to drugs for a wide spectrum of clinical conditions. Examples include:

- Dilacor XR™ (Watson Labs) is an extended release capsule providing 24 h release of Diltiazem HCl and prolonged control of hypertension. Ethylcellulose and hypromellose act as release modifiers for this water-soluble drug.
- The antidepressant Paroxetine (Paxil CR™ GSK) is an enteric-coated tablet, controlling drug dissolution over 5 h for gradual release in the small intestine. The enteric coat delays release until tablet leaves the stomach (http://us.gsk.com/products/assets/us_paxilcr.pdf). Drug solubility is about 5 mg/ml and the release modifiers comprise hypromellose, poly(vinyl pyrrolidone), glyceryl behenate,

Uncorrected Proof

Author's Proof

and methacrylic acid copolymer type C. One tablet layer comprises a degradable barrier, and the other layer contains the active in a hydrophilic matrix.

- Ropinirole HCl is formulated with sodium carboxymethylcellulose, glyceryl behenate, hypromellose, and povidone as a controlled release tablet for Parkinsonism (Requip XL™) (http://www.rxlist.com/requip-xl-drug.htm). It is a triple layer tablet, with the active in the center layer, laminated between two placebo layers, which control the surface area available for the drug release. The relatively low dosage of this drug facilitates the rather complex dosage form design.
- El-Nabarawi utilized Geomatrix technology to prolong duration of action of the anti-inflammatory, tenoxicam from a bilayer unit. The drug-containing layer (drug and HPMC) is welded to a drug-free layer containing HPMC and ethyl cellulose (EC) using a casting/solvent evaporation technique. Study showed that the addition of the drug-free layer, its composition and thickness could change the release profile [19].
- Wilding et al. used gamma scintigraphy and pharmaco-scintigraphy to evaluate the effect of fed/fasting state on GI transit and drug release behavior of a Diltiazem Geomatrix™ tablet formulation. Pharmacokinetic data showed ready absorption in the colon in the fasted state, the tablet remaining intact for almost 17 h. Food slightly increased the overall extent of absorption without changing the release characteristics [20].
- Goutte et al. proposed an experimental design for developing and preparing a Geomatrix™ system for cost effectiveness and time saving (a typical Geomatrix™ system requires one compression and three granulation processes) [21].

6.5 TIMERx™

The TIMERx™ technology developed by Pennwest offers the following modes of release:

- First order, i.e., the release rate decreases over time.
- Zero order release (constant rate over time).
- Combinations of immediate release and controlled release.

The technology is based on a customized, agglomerated hydrophilic complex that forms a matrix on compression. The matrix comprises two polysaccharides, viz., xanthan gum and locust bean gum. Interactions between these in an aqueous environment result in formation of a viscous gel with a slowly eroding core. Such synergy between xanthan and galactomannans was first reported in 1971, when researchers observed formation of a thermoreversible gel in xanthan gum: locust bean gum mixtures. Further studies showed that total polysaccharide concentration, not gum ratio, influenced the setting and melting temperatures of the gel [22].

Uncorrected Proof

Author's Proof

Tobyn et al. found that interactions between these gums were synergistic in aqueous media when a third component such as dextrose is present [23]. Staniforth et al. reviewed the physicochemical interactions between the two gums, and how they could influence release [24]. Dosage forms utilizing TIMERx™ technology can prolong release over 4 h [25], either as zero-order or chronotherapeutic release modes by manipulating the gum interactions [24]. Tobyn et al. showed that electron spin resonance (ESR) was a useful indicator of interactions between hydrocolloids and drugs, intended for presentation in TIMERx™ systems [26].

The analgesic, *oxymorphone* hydrochloride, has been formulated as an extended release tablet using TIMERx™ technology (Opana ER™; Endo Pharma).

Variants of the TIMERx™ platform comprise:

- Geminex™ technology enabling release of different actives independent of each other.
- SyncroDose™ is designed to deliver the drug at a desired site and time in the body.

6.6 Gastroretention

Retention of a dosage form in the stomach is an attractive concept for prolonging release and absorption from controlled release dosage forms containing the following categories of drug:

- Drugs with narrow absorption windows.
- Drugs locally active in the stomach.
- Drugs unstable in the colon or distal small intestine.
- Drugs with low solubility at high pH.

Discussion in this chapter is limited to the mechanisms that may be considered to provide gastroretention. A separate chapter provides more detailed discussion.

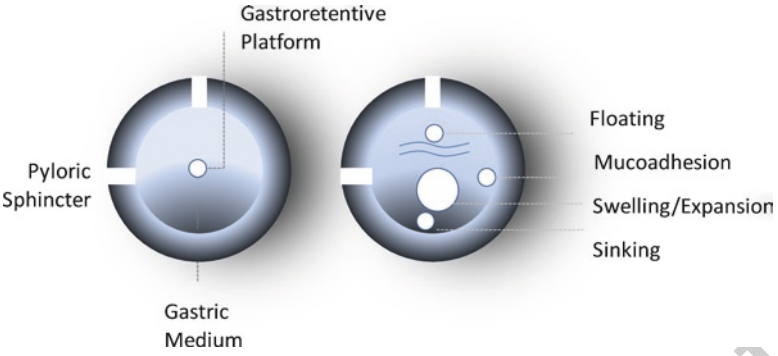
Gastroretention can conceptually be achieved through floating, size expansion (swelling or unfolding), mucoadhesion, sinking, and magnetic attraction as outlined in Fig. 6.6 [27]. The extent of gastric retention, however, depends on various factors, and clinically effective gastric retentive devices are yet to be developed.

6.6.1 Floating Systems

A dosage unit with lower relative density than gastric contents is less disposed to be propelled towards the pyloric sphincter but to reside in the fundus or body of the stomach [27–29]. Units can be either monoliths or multiparticulate. Such buoyancy might be affected by a number of techniques, viz.

Uncorrected Proof

Author's Proof



this figure will be printed in b/w

Fig. 6.6 Gastro-retentive systems

Uncorrected Proof

- Gel formation: Hydrocolloids (xanthan gum), polysaccharides (HPMC), synthetic polymers (poly(ethylene oxide), carbopol), and natural gums (alginates, guar gum) have been used to prepare flotation platforms [30–34].
- Effervescent systems: Inclusion of an effervescent couple, e.g., sodium bicarbonate, citric acid in the unit leads to interaction and evolution of carbon dioxide in the gastric medium. Gas entrapment by the hydrophilic polymers reduces density, enhances buoyancy, flotation, and gastroretention [31].

6.6.2 Size Expansion

Size expansion strategies comprise enlargement of the dosage unit on exposure to the gastric environment such that passage through the pyloric sphincter is constrained. Swelling systems incorporate polymer capable of absorbing gastric fluid while folding systems are designed to unravel on hydration. Unit size must be sufficiently small to afford oral administration but expansion must be sufficient for gastric retention. Collagen sponge has been utilized to confer unfolding properties [35, 36].

Gastric retention may also be induced by changing the unit rigidity by judicious choice of materials. Drug depletion and physical breakdown can combine to reduce unit size and allow passage to the duodenum [37].

6.6.3 Mucoadhesion

Gastric residency can conceptually be prolonged, by incorporating in the dosage form synthetic or natural polymers with an affinity for gastric mucosa. Drug is then released in a controlled manner for prolonged absorption in the intestine.

Author's Proof

Mucoadhesive polymers that have been evaluated include chitosan and its thiolated derivative, carbopol and methylcellulose [38].

Information on the effectiveness and consistency of gastroretentive technologies in humans is rather sparse at this time. The factors that affect gastric residence are manifold and complex and present formidable barriers to consistent, controlled drug delivery. Hence, it remains in the realms of "promise" than delivery.

6.7 Contramid™

Contramid™ technology (Labopharm) utilizes crosslinked, high-amylase starch to control drug release. Release is essentially dependent on unit swelling, with degree of starch crosslinking being the rate controlling factor. When a unit is placed in an aqueous medium, the starch forms a hard gel and displays sponge-like viscoelastic behaviors. X-ray tomography reveals a uniform membrane at the gel surface that controls drug release [39].

- Ryzolt™ (Purdue Pharma) is an extended release tablet containing the antiarthritic, tramadol. It comprises a dual matrix with immediate and extended release components. Release modifying ingredients include pregelatinized modified starch, poly(vinyl acetate), povidone, and xanthan gum.
- Oleptro™ (Labopharm) is an extended release tablet containing the antidepressant, trazodone, which releases drug over a 24-h period. From an absorption perspective, Oleptro™ 300 mg tablets exhibit a T_{max} of about 9 h, postdose under fasting condition. The tablet contains hydroxypropyl distarch phosphate and polymeric ingredients such as hypromellose, poly(ethylene glycol) 3350, and poly(vinyl alcohol) (http://www.rxlist.com/oleptro-drug.htm).
- The in vitro release of sodium diclofenac from a Contramid™ system was studied by Rahmouni et al. Factors such as pH, ionic strength of the medium, and enzyme concentration were studied, which could affect the enzymatic hydrolysis of the crosslinked high amylase starch, and hence the drug release. Excipients such as HPMC and PEO also influenced tablet erosion. In vitro studies to determine the effect of low and high amylase concentrations revealed that the release mechanism is changed from diffusion to a combined diffusion and erosion mechanisms [40].
- Rioux et al. studied the effect of crosslink density of high amylase starch on various mechanical properties of Contramid™ films. Young's modulus, elongation at break, tensile strength, permeability to water and oxygen were all affected by level of crosslinking and environmental humidity [41].

Contramid™-based products have been shown to be safe and effective in clinical studies in patients:

- Once-daily tramadol (Contramid OAD™) was safe and effective for pain management [42]. Contramid OAD™ has also been compared with BID tramadol.

Uncorrected Proof

Author's Proof

The Contramid presentation provided sustained analgesia throughout the dosing interval [43].

- Sheehan et al. evaluated once-daily trazodone (Contramid™) in major depressive disorder. The extended release formula was well tolerated and more effective than placebo [44].

6.8 Multiparticualte Systems

Multiple Unit Pellet Systems are discussed in a separate chapter in this book. Mechanism-related facets are considered here.

6.8.1 Micropump™ Technology

Flamel's Micropump™ technology has been designed to extend small intestine residence time of appropriately sized small particles that become "lodged" in intestinal villi, thereby prolonging small intestinal retention. Controlling drug release from such particles may sustain absorption. The concept is illustrated in Fig. 6.7.

The approach has been used to provide a prolonged release formulation of the antiviral, acyclovir, for twice daily administration [45]. It may be appropriate for drugs with short half-lives that are absorbed primarily in the small intestine. Coreg CR™ (GSK) also utilizes Micropump technology and comprises three kinds of microparticles, viz.

- Uncoated microparticles that release a fraction of the dose rapidly providing early onset of action.
- Coated microparticles that delay release of another drug fraction.
- A second population of coated microparticles that release drug even later in the small intestine, thereby sustaining absorption and duration of action.

The product provides once-daily therapy for congestive heart failure.

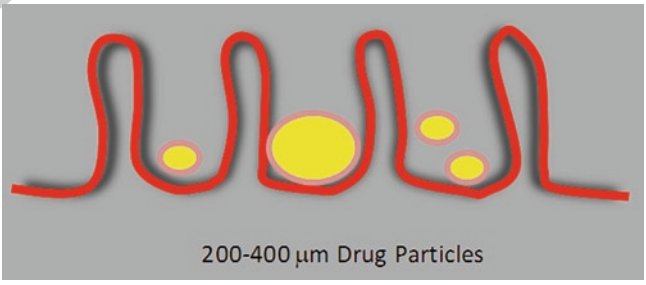


Fig. 6.7 Micropump delivery system

Uncorrected Proof

Author's Proof

6.8.2 *Spheroidal Oral Drug Absorption System*

Capsules utilizing Elan's Spheroidal Oral Drug Absorption System (SODAS™) technology contain spherical beads, 1–2 mm in diameter. The beads contain a drug core plus excipient as well as a coating of controlled release polymer. Once ingested, the water-soluble polymers of the coating layer are dissolved, which leaves a porous layer through which the active can diffuse out at a controlled rate. Depending on the drug's physicochemical properties, the polymer composition of the membrane can be different.

- SODAS™ technology is employed to provide once-daily dosage of methylphenidate hydrochloride for treating Attention Deficit Hyperactivity Disorder (ADHD). Bimodal plasma profiles comparable to those obtained after twice daily dosage of immediate release units are obtained with both products (Ritalin LA™ and Focalin XR™).
- Kowalik et al. and McGough et al. reviewed a SODAS™ dosage form containing dexmethylphenidate. The dosage form provided immediate release followed by delayed release after 4 h. The product was shown to be clinically effective over a 12-h period [46, 47].
- Aragon et al. studied the pharmacokinetics of an oral morphine formulation containing both immediate and extended release components. The SODAS™ technology sustained plasma concentrations over 24 h. However, clinical benefit was considered to be limited due to low drug plasma concentration and high variability [48].

Avinza™ (morphine sulfate extended release capsules) has also been formulated utilizing SODAS™ technology, and offers a bimodal release of morphine sulfate. It provides an instant release fraction and an additional fraction to give a sustained pain management over 24 h [49]. Hilleman and Banakar showed that SODAS™ formulations were less vulnerable to food and pH effects than wax-matrix systems as the latter systems may display dose dumping at low pH [50].

6.9 Conclusions

Many concepts and technologies are available for delaying, prolonging, or otherwise modifying drug release. While a relatively limited number of excipients (mainly polymeric materials) are available it is possible, by judicious combinations of these, to design a release profile, suited to specific therapeutic agents. It is important that such design reflects the physicochemical, absorption characteristics, pharmacokinetic behaviors, and dose of drug. Knowledge of the relationship between plasma presence (and plasma concentration) and drug action (duration, onset dose response, viz., a clear target plasma profile) is also a prerequisite for success. Consequently, focusing on a single "platform technology" is undesirable. The variability of the GI tract, with respect to local environment and transit rates also needs to be considered when deciding on a strategy for dosage form design.

Uncorrected Proof

Author's Proof

Appendix 1. Commercial Products and Their Corresponding Release Mechanisms

Brand name	Active ingredient	Release mechanism	Company
Nexium[a]	Esomeprazole magnesium	Multiparticulate	AstraZeneca
Effexor XR[b]	Venlafaxine HCl	Multiparticulate	Wyeth
Cymbalta[c]	Duloxetine HCl	Multiparticulate	Lilly
Adderall XR[d]	Dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate H_2O, and amphetamine sulfate	Multiparticulate	Shire
Flomax[e]	Tamsulosin HCl	Multiparticulate	Boehringer Ingelheim
Detrol LA[f]	Tolterodine tartarate	Multiparticulate	Pfizer
Focalin XR[g]	Dexmethylphenidate HCl	Multiparticulate bimodal release (rapid and delayed)	Novartis
Coreg CR[h]	Carvedilol phosphate	Multiparticulate Micro Pump	GSK
Kadian[i]	Morphine sulfate	Multiparticulate	Actavis
Avinza[j]	Morphine sulfate	Multiparticulate	King
Ultram ER[k]	Tramadol HCl	Diffusion Controlled Tablet	Ortho-McNeil-Janssen
Wellbutrin XL[l]	Bupropion HCl	Diffusion Controlled Tablet	GSK
Ambien CR[m]	Zolpidem tartrate	Matrix Tablet	Sanofi-Aventis
Depakote ER[n]	Divalproex sodium	Matrix Tablet	Abbott
Budeprion XL[o]	Bupropion HCl	Matrix Tablet	Teva
Asacol[p]	Mesalamine	Colonic Delivery Tablet	Proctor & Gamble
Solodyn[q]	Minocycline HCl	Matrix Tablet	Medicis
Allegra-D 12 Hour[r]	Fexofenadine HCl/ pseudoephedrine HCl	Matrix Tablet	Sanofi-Aventis
Enablex[s]	Darifenacin	Matrix Tablet	Novartis
Opana ER[t]	Oxymorphone HCl	Matrix Tablet TIMERx	Endo
Allegra-D 24 Hour[u]	Fexofenadine HCl/ pseudoephedrine HCl	Osmotic	Sanofi-Aventis
Concerta[v]	Methylphenidate HCl	Advanced Osmotic	Ortho-McNeil-Janssen

[a] http://www.nexiumtouchpoints.com/nexium-information/dosing/#Delayed-Release
[b] http://www.effexorxr.com/
[c] http://www.cymbalta.com/
[d] http://www.adderallxr.com/
[e] http://www.4flomax.com/

(continued)

Uncorrected Proof

Author's Proof

Appendix 1 (continued)

[f] http://www.detrolla.com/
[g] http://www.focalinxr.com/
[h] http://www.coregcr.com/
[i] http://www.kadian.com/
[j] http://www.avinza.com/
[k] http://www.ultram-er.com/
[l] http://www.wellbutrin.com/
[m] http://www.ambiencr.com/
[n] http://www.depakoteer.com/
[o] http://www.rxlist.com/budeprion-xl-drug.htm
[p] http://www.asacol.com/
[q] http://www.solodyn.com/
[r] http://www.allegra.com/allegra-D/allegra-D_12hour.aspx
[s] http://www.enablex.com/
[t] http://www.opana.com/
[u] http://www.allegra.com/allegra-D/allegra-D_24hour.aspx
[v] http://www.concerta.net/

Appendix 2. Conventional Matrix System for Selected Soluble/Insoluble Drug Products and Their Corresponding Release Modifier(s)

Drugs that are sparingly soluble or insoluble in water		
Lovastatin (antihyperlipidemic)	Advicor™ – a niacin combination (Abbott)	Hypromellose, povidone[a]
Simvastatin (antihyperlipidemic)	Simcor™ – a niacin combination (Abbott)	Hypromellose, povidone[b]
Clarithromycin (antibiotic)	Biaxin XL™ (Abbott)	Cellulosic polymers[c]
Carbamazepine (anticonvulsant)	Tegretol XR™ (Novartis)	Cellulose compounds[d]
Zolpidem tartartae (Insomnia)	Ambien CR™ (Sanofi)	Hypromellose, PEG, sodium starch glycolate[e]
Alprazolam (Panic disorder)	Xanax XR™ (Pharmacia)	Hypromellose[f]
Fluvoxamine (Anxiety disorder)	Luvox CR™ (Elan)	Ammonio methacrylate copolymer[g]
Guanfacine (ADHD)	Intuniv™ (Shire)	Hypromellose, methacrylic acid copolymer, povidone, crospovidone, glyceryl behenate[h]

(continued)

Uncorrected Proof

Author's Proof

Appendix 2 (continued)

Drugs that are freely soluble, very soluble, or highly soluble in water		
Niacin (antihyperlipidemic)	Niaspan™ (Abbott)	Hypromellose, povidone[i]
Metformin (antihyperglycemic for type 2 diabetes)	Glucophage XR™ (Bristol Myer Squibb)	Sodium carboxymethyl cellulose, hypromellose[j]
Bupropion HCl (Major depressive disorder)	Wellbutrin SR™ (GSK)	Hypromellose[k]
Levetiracetam (Seizure)	Keppra XR™ (UCB)	Hypromellose, PEG6000, partially hydrolyzed polyvinyl alcohol[l]

[a] http://www.rxlist.com/advicor-drug.htm
[b] http://www.rxlist.com/simcor-drug.htm
[c] http://www.rxlist.com/biaxin-drug.htm
[d] http://www.rxlist.com/tegretol-drug.htm
[e] http://www.rxlist.com/ambien-cr-drug.htm
[f] http://www.rxlist.com/xanax-xr-drug.htm
[g] http://www.rxlist.com/luvox-cr-drug.htm
[h] http://www.rxlist.com/intuniv-drug.htm
[i] http://www.rxlist.com/niaspan-drug.htm
[j] http://www.rxlist.com/glucophage-drug.htm
[k] http://www.rxlist.com/wellbutrin-sr-drug.htm
[l] http://www.rxlist.com/keppra-xr-drug.htm

[AU1]

References

1. Malcolm RK et al (2004) Controlled release of a model antibacterial drug from a novel self-lubricating silicone biomaterial. J Control Release 97(2):313–320
2. Streubel A et al (2000) pH-independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets. J Control Release 67(1):101–110
3. Goldenberg MM (1999) An extended-release formulation of oxybutynin chloride for the treatment of overactive urinary bladder. Clin Ther 21(4):634–642
4. Duan XY et al (2009) Development of monolithic osmotic pump tablet system for isosorbide-5-mononitrate delivery and evaluation of it in vitro and in vivo. Drug Dev Ind Pharm 35(4):499–507
5. Liu X, Chen DW, Zhang RH (2003) Evaluation of monolithic osmotic tablet system for nifedipine delivery in vitro and in vivo. Drug Dev Ind Pharm 29(7):813–819
6. Thombre AG et al (2004) Osmotic drug delivery using swellable-core technology. J Control Release 94(1):75–89
7. Wagstaff AJ, Figgitt DP (2004) Extended-release metformin hydrochloride. Single-composition osmotic tablet formulation. Treat Endocrinol 3(5):327–332
8. Waterman KC, MacDonald BC, Roy MC (2009) Extrudable core system: development of a single-layer osmotic controlled-release tablet. J Control Release 134(3):201–206
9. Malaterre V et al (2009) Oral osmotically driven systems: 30 years of development and clinical use. Eur J Pharm Biopharm 73(3):311–323
10. Lautenschlager M, Heinz A (2008) Paliperidone-ER: first atypical antipsychotic with oral extended release formulation. Expert Rev Neurother 8(2):193–200

Uncorrected Proof

Author's Proof

11. Wonnemann M et al (2006) Significant food interactions observed with a nifedipine modified-release formulation marketed in the European Union. Int J Clin Pharmacol Ther 44(1):38–48
12. Sathyan G, Chancellor MB, Gupta SK (2001) Effect of OROS (R) controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. Br J Clin Pharmacol 52(4):409–417
13. Davidson M et al (2007) Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. Schizophr Res 93(1–3):117–130
14. Kane J et al (2007) Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. Schizophr Res 90(1–3):147–161
15. Bass DM, Prevo M, Waxman DS (2002) Gastrointestinal safety of an extended-release, nondeformable, oral dosage form (OROS (R))(1) – a retrospective study. Drug Saf 25(14):1021–1033
16. Maggi L, Bruni R, Conte U (2000) High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms. Int J Pharm 195(1–2):229–238
17. Conte U et al (1993) Multilayered hydrophilic matrices as constant release devices (Geonatrix systems). J Control Release 26(1):39–47
18. Conte U, Maggi L (1996) Modulation of the dissolution profiles from Geomatrix(R) multilayer matrix tablets containing drugs of different solubility. Biomaterials 17(9):889–896
19. El-Nabarawi MA (2005) Modulation of tenoxicam release from hydrophilic matrix: modulator membrane versus rate-controlling membrane. Chem Pharm Bull 53(9):1083–1087
20. Wilding IR et al (1995) Pharmacoscintigraphic evaluation of a modified release (Geomatrix) diltiazem formulation. J Control Release 33(1):89–97
21. Goutte F et al (2002) Power of experimental design studies for the validation of pharmaceutical processes: case study of a multilayer tablet manufacturing process. Drug Dev Ind Pharm 28(7):841–848
22. Stephen AM (1995) Food polysaccharides and their applications. Marcel Dekker, New York, p 478
23. Tobyn MJ et al (1996) Prediction of physical properties of a novel polysaccharide controlled release system. Int J Pharm 128(1–2):113–122
24. Staniforth JN, Baichwal AR (2005) TIMERx: novel polysaccharide composites for controlled/programmed release of drugs in the gastrointestinal tract. Expert Opin Drug Deliv 2(3):587–595
25. Endo/Penwest (2003) Oxymorphone--Endo/Penwest EN 3202, EN 3203. Drugs R D, 4(3):204–206
26. Tobyn MJ et al (1996) Investigations of the interactions between a novel polysaccharide controlled release matrix and model compounds using ESR. J Control Release 40(3):147–155
27. Streubel A, Siepmann J, Bodmeier R (2006) Drug delivery to the upper small intestine window using gastroretentive technologies. Curr Opin Pharmacol 6(5):501–508
28. Murphy CS et al (2009) Gastroretentive drug delivery systems: current developments in novel system design and evaluation. Curr Drug Deliv 6(5):451–460
29. Arza RAK, Gonugunta CSR, Veerareddy PR (2009) Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. AAPS PharmSciTech 10(1):220–226
30. Badhan AC et al (2009) Development and evaluation of sustained release gastroretentive mini-matrices for effective treatment of *H. pylori* infection. AAPS PharmSciTech 10(2):459–467
31. Basak SC, Rahman J, Ramalingam M (2007) Design and in vitro testing of a floatable gastroretentive tablet of metformin hydrochloride. Pharmazie 62(2):145–148
32. Boldhane SP, Kuchekar BS (2009) Gastroretentive drug delivery of metformin hydrochloride: formulation and in vitro evaluation using 3(2) full factorial design. Curr Drug Deliv 6(5):477–485
33. Bomma R et al (2009) Development and evaluation of gastroretentive norfloxacin floating tablets. Acta Pharm 59(2):211–221
34. Singh S et al (2007) Gastroretentive drug delivery system of metoclopramide hydrochloride: formulation and in vitro evaluation. Curr Drug Deliv 4(4):269–275

Uncorrected Proof

Author's Proof

35. Groning R et al (2007) Compressed collagen sponges as gastroretentive dosage forms: in vitro and in vivo studies. Eur J Pharm Sci 30(1):1–6
36. Groning R, Cloer C, Muller RS (2006) Development and in vitro evaluation of expandable gastroretentive dosage forms based on compressed collagen sponges. Pharmazie 61(7):608–612
37. Klausner EA et al (2003) Expandable gastroretentive dosage forms. J Control Release 90(2):143–162
38. Dhaliwal S et al (2008) Mucoadhesive microspheres for gastroretentive delivery of acyclovir: in vitro and in vivo evaluation. AAPS J 10(2):322–330
39. Ravenelle F, Rahmouni M (2006) Contramid (R): High-amylose starch for controlled drug delivery. Polysaccharides Drug Deliv Pharm Appl 934:79–104
40. Rahmouni M et al (2001) Enzymatic degradation of cross-linked high amylose starch tablets and its effect on in vitro release of sodium diclofenac. Eur J Pharm Biopharm 51(3):191–198
41. Rioux B et al (2002) Structure-properties relationship in cross-linked high amylose starch cast films. Carbohydr Polym 50(4):371–378
42. Burch F et al (2007) A comparison of the analgesic efficacy of tramadol contramid OAD versus placebo in patients with pain due to osteoarthritis. J Pain Symptom Manag 34:328–338
43. Mongin G et al (2004) Efficacy and safety assessment of a novel once-daily tablet formulation of tramadol – a randomised, controlled study versus twice-daily tramadol in patients with osteoarthritis of the knee. Clin Drug Invest 24(9):545–558
44. Sheehan DV et al (2009) Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study. Psychiatry (Edgmont) 6(5):20–33
45. Barnard DL (2001) Genvir (Flamel Technologies). Curr Opin Investig Drugs 2(5):622–623
46. Kowalik S, Minami H, Silva R (2006) Dexmethylphenidate extended-release capsules for the treatment of attention deficit hyperactivity disorder. Expert Opin Pharmacother 7(18):2547–2557
47. McGough JJ, Pataki CS, Suddath R (2005) Dexmethylphenidate extended-release capsules for attention deficit hyperactivity disorder. Expert Rev Neurother 5(4):437–441
48. Aragon CL et al (2009) Pharmacokinetics of an immediate and extended release oral morphine formulation utilizing the spheroidal oral drug absorption system in dogs. J Vet Pharmacol Ther 32(2):129–136
49. Semenchuk MR (2002) Avinza Elan. Curr Opin Investig Drugs 3(9):1369–1372
50. Hilleman DE, Banakar UV (1992) Issues in contemporary drug delivery. Part VI: Advanced cardiac drug formulations. J Pharm Technol 8(5):203–211

Uncorrected Proof

Author's Proof

Author Query

Chapter No.: 6

Query	Details Required	Author's Response
AU1	Website references have been moved appropriately into the text as per the style and renumbered accordingly. Please check.	

Uncorrected Proof