Modified-release oral drug delivery

Introduction

- Oral route is the most commonly used route (>70% of all medicines).
- Oral medicines are easy to administer, improve patient compliance and are cheaper than some of the alternatives (e.g. injections).
- Most medicines administered by the oral route provide what is known as ‘immediate-release’ drug delivery.
- For example: the use of paracetamol for a headache; the tablet or capsule disintegrates quickly in the stomach fluids releasing the drug to provide rapid onset of effect.

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- Sometimes, rapid onset is not desirable and a modification of the drug release pattern (or profile) is necessary to slow it down or make the drug's effects last longer (e.g. for 24 hours).
- **Modified-release drug delivery (MR)** refers to the manipulation or modification of drug release from a dosage form (e.g. tablet, pellet, capsule) with the specific aim of delivering active pharmaceutical ingredients (API) at:

1. Desired rates
2. Pre-defined time points, or
3. Specific sites in the gastrointestinal tract.

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- The different types of modified release include:

➢ **Delayed-release dosage forms**: drug released at a time later than immediately after administration (i.e. there is a lag time between a patient taking a medicine, and drug being detected in the blood). Site-specific targeting is a type of delayed release which aims to target specific regions of the gastrointestinal tract, e.g. the small intestine or colon.

➢ **Gastro-resistant dosage forms**: the drug is released when a certain environmental pH is met. A common example of this type of dosage form ensures that the drug is not released in the acid of the stomach but in the higher pH of the small intestine. Such products may also be known as **enteric dosage forms**.

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- **Extended-release dosage forms:** these allow a reduction in dosing frequency compared to when the drug is present in an immediate-release dosage form (i.e. the drug plasma levels are sustained for longer periods). These are also known as **prolonged-release/sustained-release/controlled-release** dosage forms. Extended-release systems which are retained in the stomach are known as gastroretentive systems.

- The site of action of each of these systems is shown in Figure 31.1.

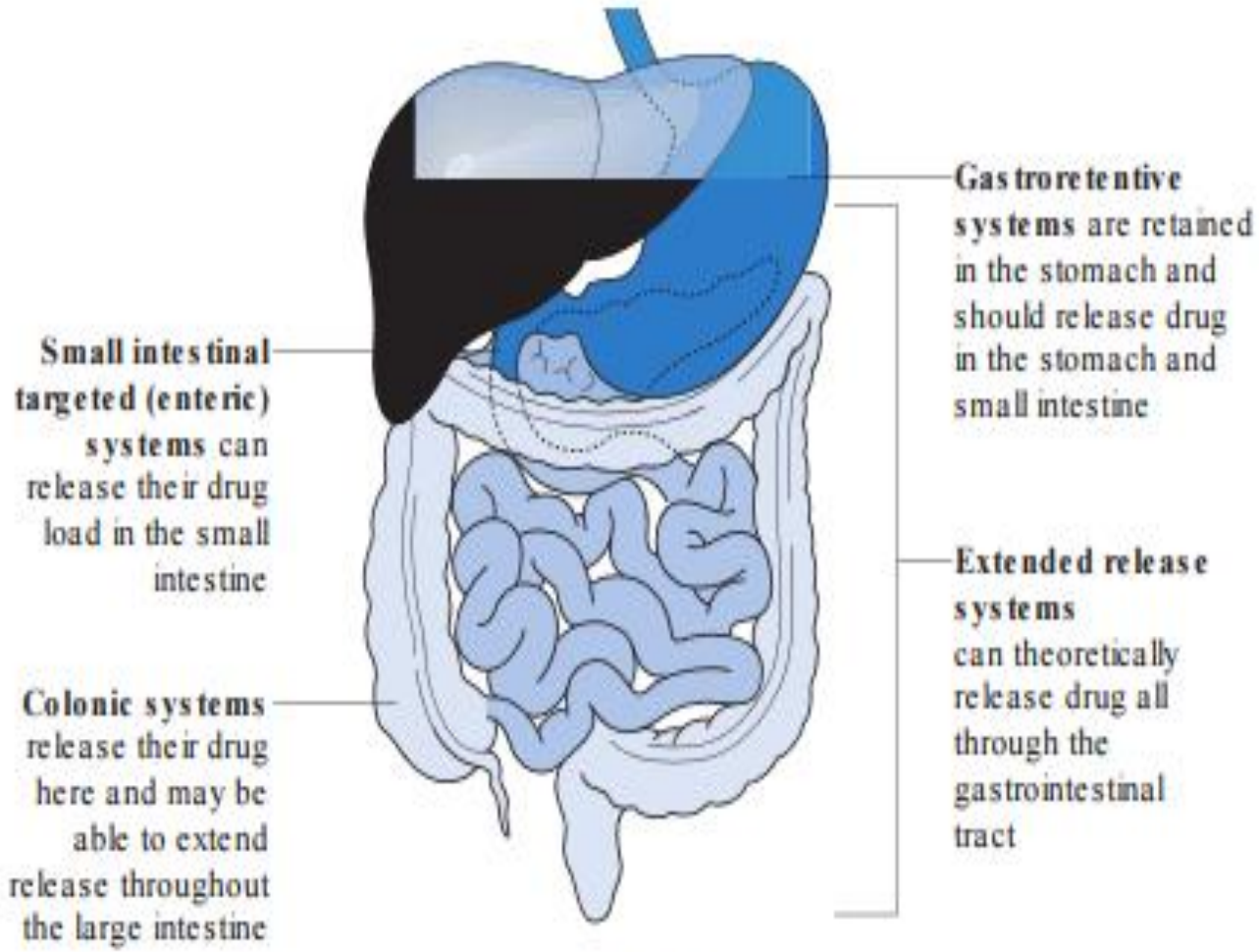

Fig. 31.1 • The site of action for various oral modifed drug delivery systems.

Introduction

- Modified-release delivery benefits to patients:

1. Maintaining drug levels overnight.
2. Reducing side effects. Immediate-release formulations can often have a high maximum concentration in the blood (C max). modified-release formulations to reduce C max can reduce the incidence and severity of the side effects of some drugs.
3. Improving compliance. A significant driver to developing a modified-release dosage form comes from trying to achieve once-daily dosing.

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4. Treatment of local areas in the gastrointestinal tract. Some conditions such as inflammatory bowel disease require topical treatment (e.g. with steroids) at the inflamed intestinal surface. Site-specific drug targeting (e.g. to the colon) can deliver the drug directly to its site of action.

- An extended-release formulation can keep the drug at therapeutic levels for longer (Fig. 31.3).

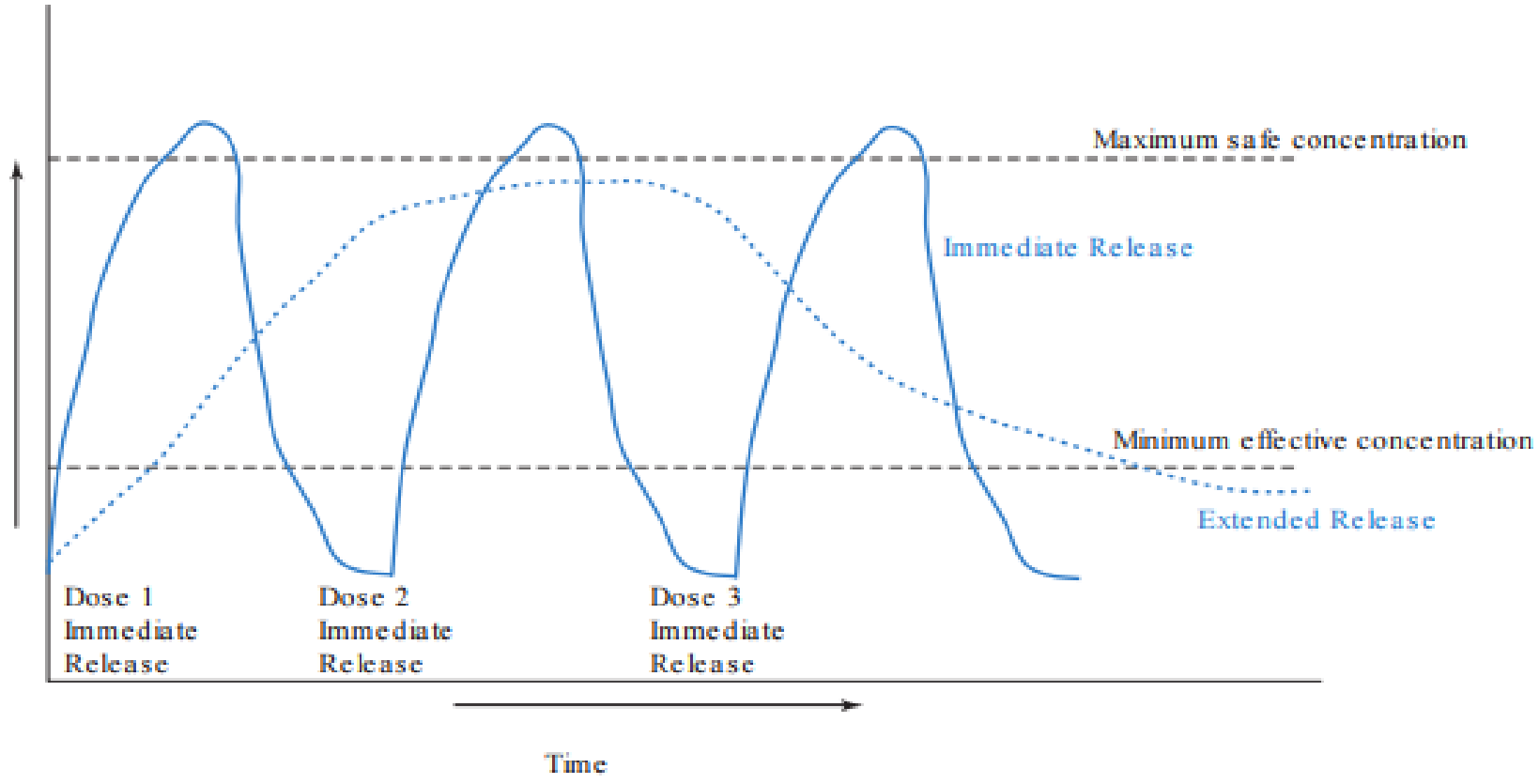


Fig. 31.3 • Figure showing theoretical plasma (blood) profles of immediate and extended release. The immediate release dosage form requires three doses to keep the drug levels effective over the time period shown and the maximum concentration (C_{max}) exceeds the upper safety limit in this example. The extended release profle (dotted line) represents one dose of a sustained release dosage form over the same time period. The latter reduces C_{max} and extends the release.

Biopharmaceutical considerations (pH, Transit time, Fluids)

- Biopharmaceutical factors (i.e. the effect of the gastrointestinal physiology and environment on drugs and dosages forms) influence the in vivo behaviour of modified release dosage forms.
- The most common possible rate-limiting steps for bioavailability following oral administration of a solid dosage form are:

(1) drug release from the dosage form.

(2) dissolution of the drug.

(3) absorption of drug molecules.

Biopharmaceutical considerations

- **pH**:

The stomach generally has a low pH and is therefore acidic. Gastro-resistant coated dosage forms are designed to be acid resistant.

Gastrointestinal pH generally increases in the small intestine. The pH gradually increases to a maximum of about pH 7 at the ileocaecal junction. In the colon, the pH drops slightly due to the production of short chain fatty acids by bacteria here, but gradually rises again distally.

- **Transit time:**

The time that a dosage form spends in the stomach, small intestine and colon can be critical for some modified-release systems.

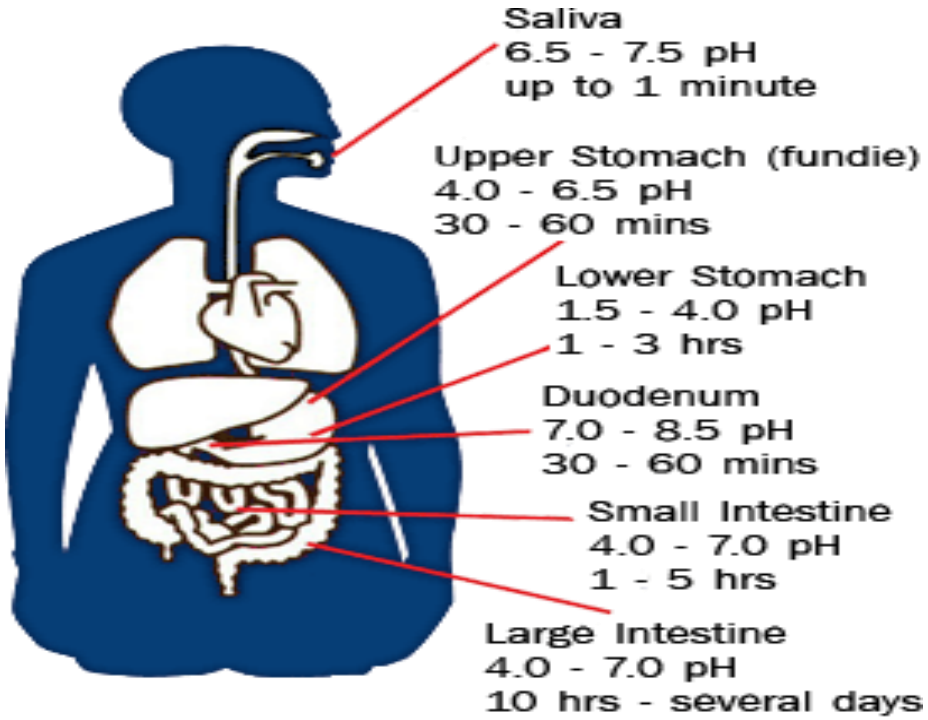
Biopharmaceutical considerations

- Stomach: fasted (1-2 hrs),fed state (>2hrs)
- Small intestine: is the site of absorption for most drugs, normally 3-4 hrs but can be highly variable (0.5-9 hrs).
- Colon: highly variable (1-72 hrs)

➢**Fluid**:

- Fluid levels can be highly variable in the stomach, small intestine and colon.
- Stomach 100 mL, small intestine 50–100 mL, colon 10 mL of free fluid available for disintegrating dosage form (not bound up with digested material)
- Fluid composition (beyond pH) is also important. The presence of ions, fats, enzymes and salts can all affect drug release

S. No.	Main part	Sub part	pH [18 – 20]
1.0	Stomach		1 to 2
2.0	Small intestine		
2.1		Proximal small intestine	6.5
2.2		Distal small intestine	7.5
3.0	Large intestine		
3.1		Ascending (proximal) colon	5.7
3.2		Transverse colon	6.6
3.3		Descending colon	7.0



This diagram illustrates the average time food spends in each part of the digestive system along with the average pH.

Designing a modified-release formulation: factors to consider

- Single-unit dosage form or multiple-unit dosage form?
- Matrix formulation or coated formulation?
- Type of release rate?

Single-unit dosage form or multiple-unit dosage form?

- A modified-release formulation can be designed as a single-entity (usually a tablet) or referred as **monolithic dosage forms**.
- A single-unit dosage form is advantageous from a manufacturing standpoint, as it can often be manufactured using conventional techniques, such as compaction and film coating.
- There may be some biopharmaceutical disadvantages to tablet formulations however. For example, as they do not disintegrate in the stomach, the dosage form could become trapped in the stomach for a long time (with food). For drugs targeted to the small or large intestine, this could prevent them reaching their site of action

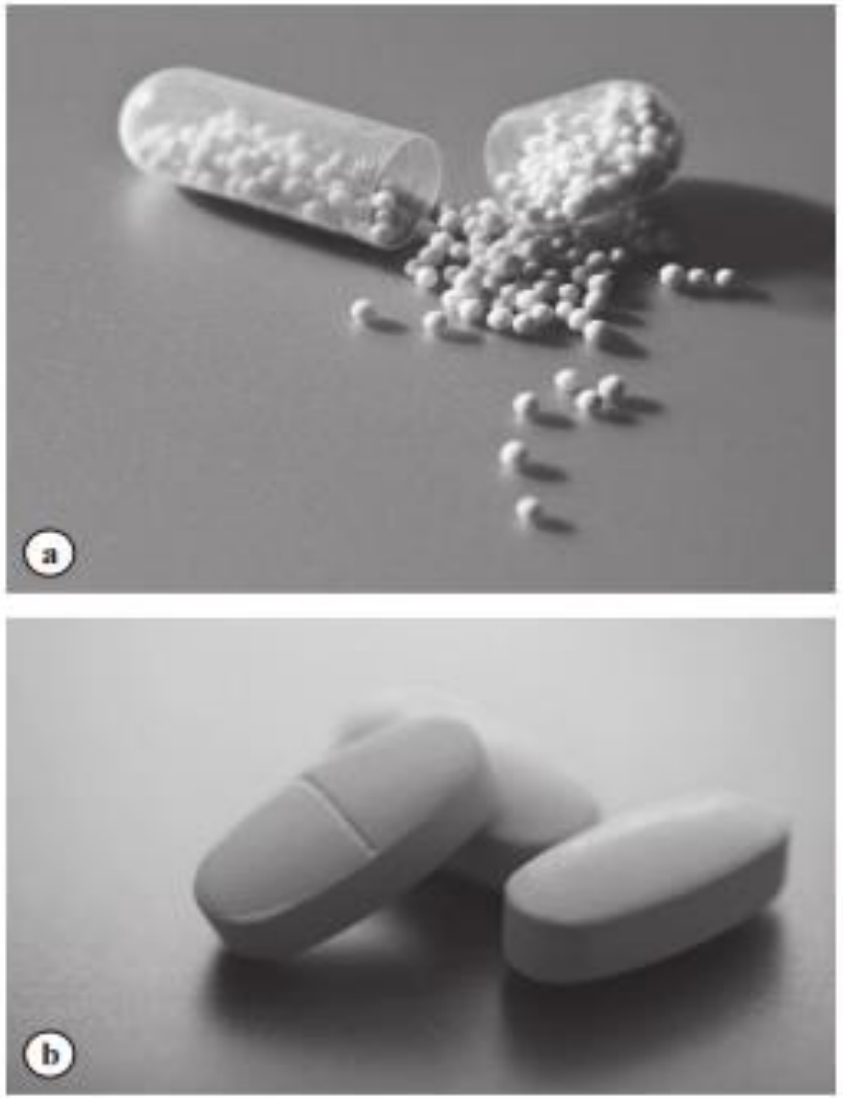


Fig. 31.5 • The use of multi-unit pellets in a capsule **(a)** or a single-unit tablet **(b)** for modified-release drug delivery.

Single-unit dosage form or multiple-unit dosage form?

- Multiple-unit systems (e.g. pellets or granules filled into a hard capsule shell, Fig. 31.5a) may have more reproducible gastric emptying and have a reduced risk of dose dumping. However these can be more difficult to manufacture (requiring extrusion spheronization for drug loading onto seed cores) and to scale-up.

Matrix formulation or coated formulation?

- The release of an active pharmaceutical ingredient can be modified by two main methods:
- Firstly, the release modifying ingredients can be incorporated throughout the matrix of the dosage form wherein the whole dosage form encompasses the modified-release element.
- The second option is the application of a modified-release coating to a dosage form, wherein the drug is usually contained in the core and is released through, or via the dissolution of, the MR coat.
- There are slight deviations from these two techniques however for example with osmotic systems.

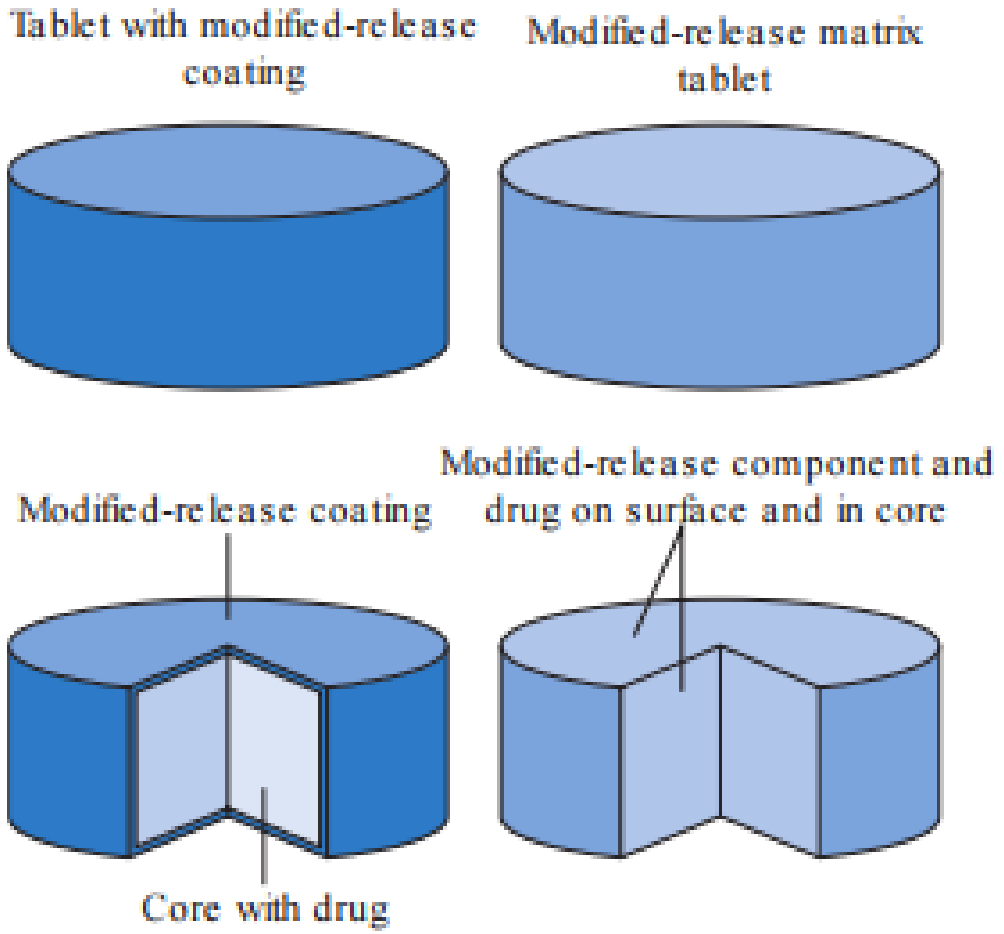


Fig. 31.6 • Coated and matrix tablets for modifed release.

Type of release rate?

Two basic mechanisms can control the rate and extent of drug release. These are:

(1) dissolution of the active drug component
(2) diffusion of dissolved species.

There are four processes operating in a modified-release dosage form to facilitate this:

1. hydration of the device (either swelling or dissolution of some component of the modified release dosage form)
2. diffusion of water into the device
3. dissolution of drug
4. diffusion of the dissolved drug out of the device. However, drug that is in contact with the surface of the dosage form does not need to diffuse and is often quickly dissolved in a 'burst release'.

Type of release rate?

- Given the multi-step process of drug release from modified-release dosage forms, and the complex gastrointestinal environment, it is understandable that precisely controlling drug release is difficult. However, there are various release patterns that are desirable (Table 31.1).

Table 31.1 Release patterns for modified release

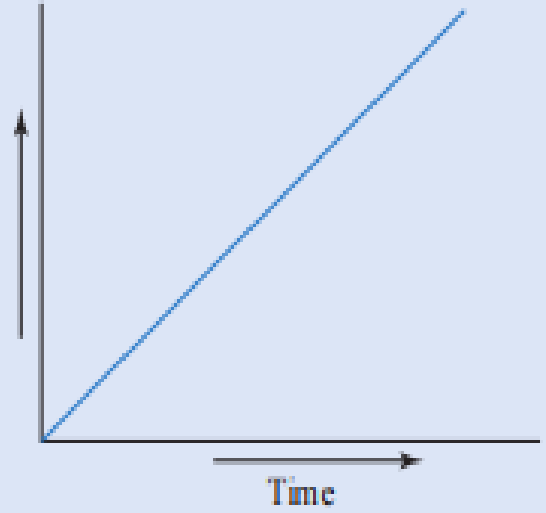
Release patterns for modified release include:

(a) constant release rates
(b) declining drug release profile
(c) delayed release and
(d) bimodal release.

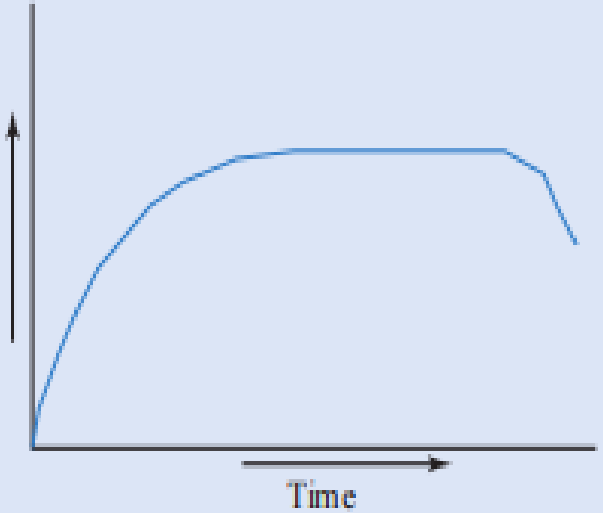
Note that drug release profiles show how the drug is released in a simple system e.g. into dissolution media and the figures (left graphs) show a cumulative release over time (ideally 100% of drug should be released) and are only influenced by drug release from the dosage form. Drug in blood profiles (right graphs) are influenced by drug release, but also by absorption, distribution, metabolism and elimination (ADME) and so drug levels in the blood rise and fall according to all these parameters combined. Thus, drugs with the same release profile may have different blood drug profiles. An example blood drug profile for each is shown here.

(a) Constant release

Drug release profile



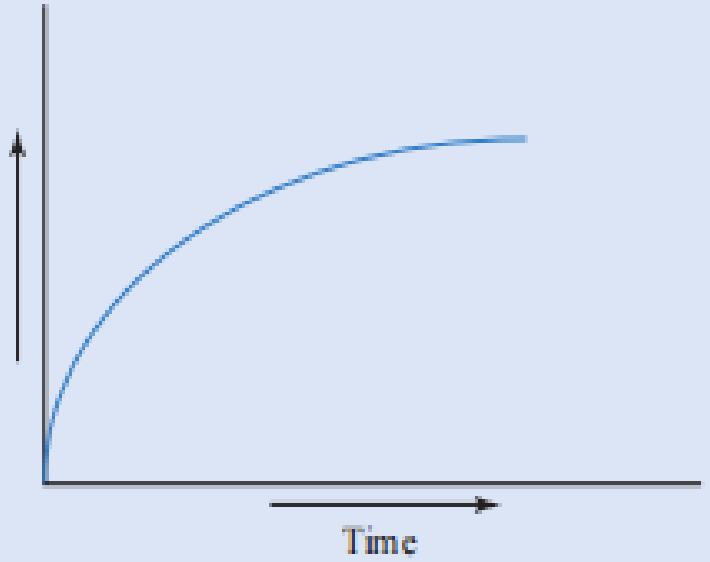
Drug in blood profile



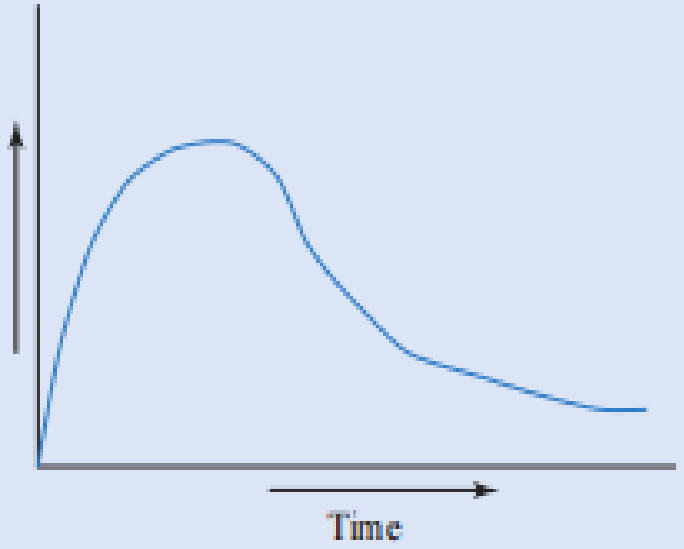
To maintain constant drug blood concentrations a constant release rate is preferred. These follow zero-order kinetics. In the human body, these drug levels take time to build up in the blood to a stable level.

(b) Declining release

Drug release profile



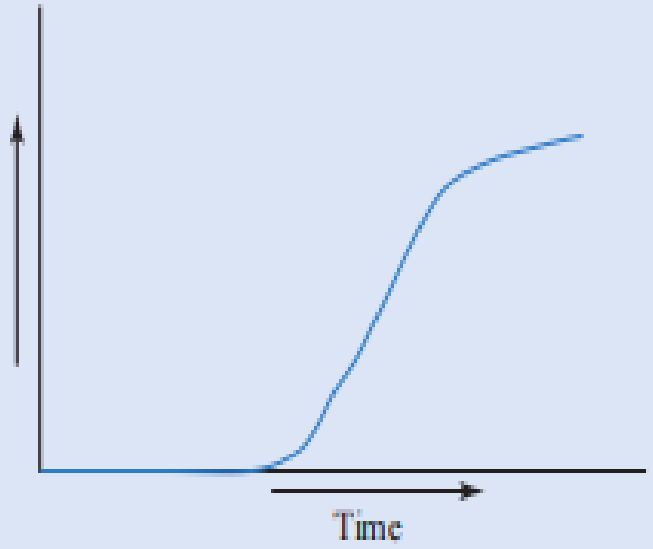
Drug in blood profile



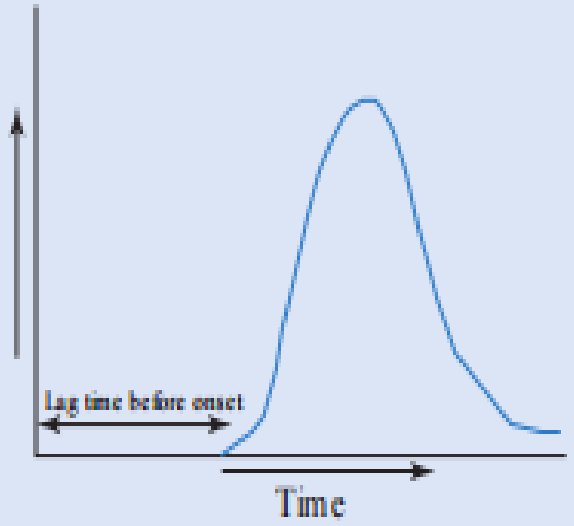
Drug release from these types of systems is often a function of the square root of time or follows first-order kinetics. They do not maintain a constant blood drug concentration but can provide a sustained release.

(c) Delayed release

Drug release profile

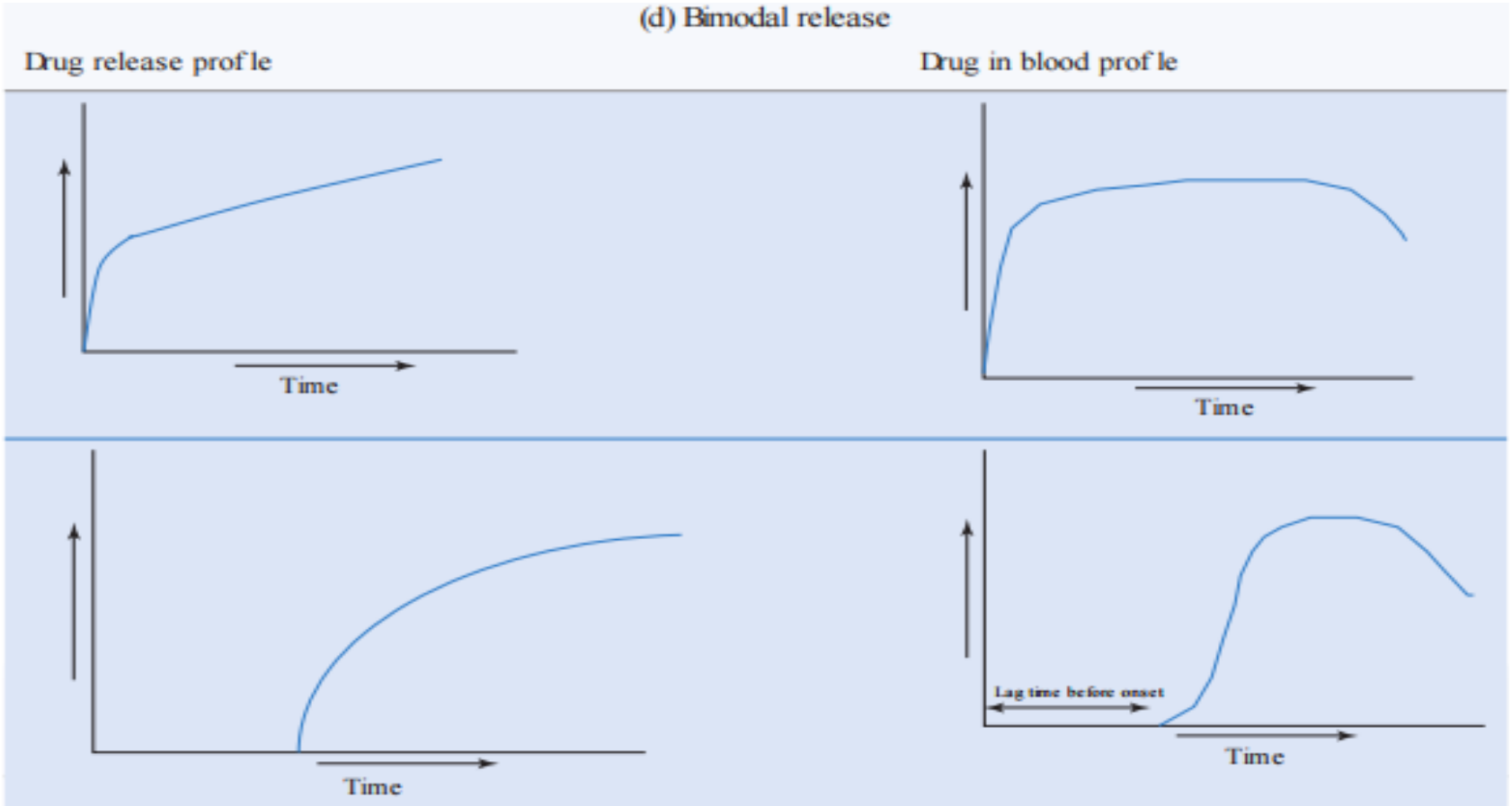


Drug in blood profile



This could be considered a type of bimodal release in which zero or negligible drug is released until a desired time or site in the gastrointestinal tract.

(d) Bimodal release



Extended release dosage forms often aim to achieve an initial primer dose of drug to achieve prompt therapeutic response. This primer dose could be an immediate-release layer or coating.

This can then be followed by a slow release of the remaining drug (the maintenance dose) which should sustain the blood levels in the therapeutic range. First-order release kinetics can be used to achieve the primer dose in a rapid fashion. Dose maintenance will follow zero-order kinetics.

Another example of bimodal release is delayed release followed by extended release.

Extended release

- The solubility of a drug in aqueous media and the intestinal permeability of the drug are key considerations when assessing whether a drug may be suitable for modified release.
- The Biopharmaceutics Classification System of drugs classifies drugs into four categories:

✓Type I: high solubility, high permeability

✓Type II: high solubility, low permeability

✓Type III: low solubility, high permeability

✓Type IV: low solubility, low permeability

Extended release

- There are three potential rate-limiting steps in the bioavailability of drug from a dosage form:

1. release from the dosage form.
2. dissolution of drug.
3. absorption through the gastrointestinal mucosa.

- High solubility and high permeability drugs (Class I) are most suitable for extended-release delivery (ideally by passive diffusion). Drug release from dosage forms can be the rate-limiting step in the process and this can then be tailored by the dosage form design.

Extended release

- For drugs with low solubility (<1 mg/ ml), the low rate of dissolution can already give some inherent sustained-release behaviour of the pure drug molecule.
- Drugs with low permeability (<0.5 × 10−6 mm s−1 through CaCo-2 tissue culture) are unlikely to be suitable for extended-release preparations. This is because they are already rate-limited in their absorption.
- Class IV drugs have low solubility and low permeability and these are the most challenging to formulate as modified-release products.

Extended release

- Other considerations as to the suitability of a drug for extended release include:

✓**Plasma half life**: How quickly a drug is eliminated once in the blood stream. The most suitable drugs may have relatively short half lives (t 1/2 = 4–6 hours). Drugs with long half-lives may achieve pseudo-sustained release blood levels despite being formulated as immediate release, whereas shorter half-lives may need very high doses to maintain blood levels.

✓**Dose**. To limit the size of the dosage form, the potency of the drug in the modified-release form can be critical. Up to 1000 mg potency tablets are available in extended-release formulations, but this is only achieved by using very large tablets, which may not always be acceptable for some patient populations.

Extended release

- Types of extended release systems:

- Hydrophilic matrix systems
- Insoluble polymer matrix
- Membrane-controlled systems
- Osmotic systems
- Gastroretention

Hydrophilic matrix systems

- Also referred to as **swellable soluble matrices**. Drug is mixed with a water-swellable, hydrophilic polymer (usually along with some other excipient materials) and compressed into a tablet.
- The resulting tablet has drug material interspersed between polymer particles. On exposure to fluid, the polymer material in the tablet starts to swell, producing a gel matrix.
- The gel can then allow drug release by dissolution of the gel and the drug trapped within it or erosion of the gel and release and dissolution of drug particles trapped within it.

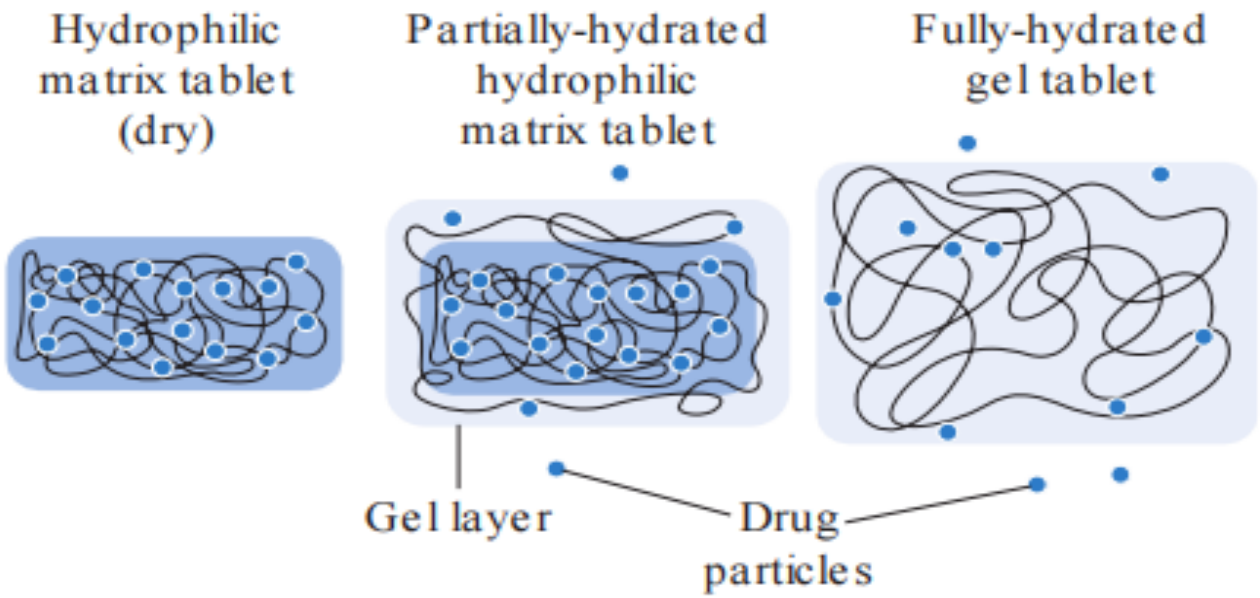


Fig. 31.7 • Process of drug release from a hydrophilic matrix. Water has to penetrate the dry matrix tablet, as the tablet becomes hydrated, drug can diffuse out.

Hydrophilic matrix systems

- The rate at which water can diffuse through the tablet is affected by the structure of the polymer (tortuosity or pathways, Mwt, crosslinking) and the polymer concentration. Water diffusion affects gel hydration and drug release.
- The mechanism of drug release seen in (Figure 31.7). Diffusion-based release mechanisms usually follow zero-order or first-order kinetics (assuming sink conditions in the GIT and sufficient fluid) but additional erosion of the matrix due to gastrointestinal motility and hydrodynamics can complicate the true in vivo release rate.
- Often polymer type and concentration are used to control drug release, which can be tailored (faster and slower) as required (Fig. 31.8).

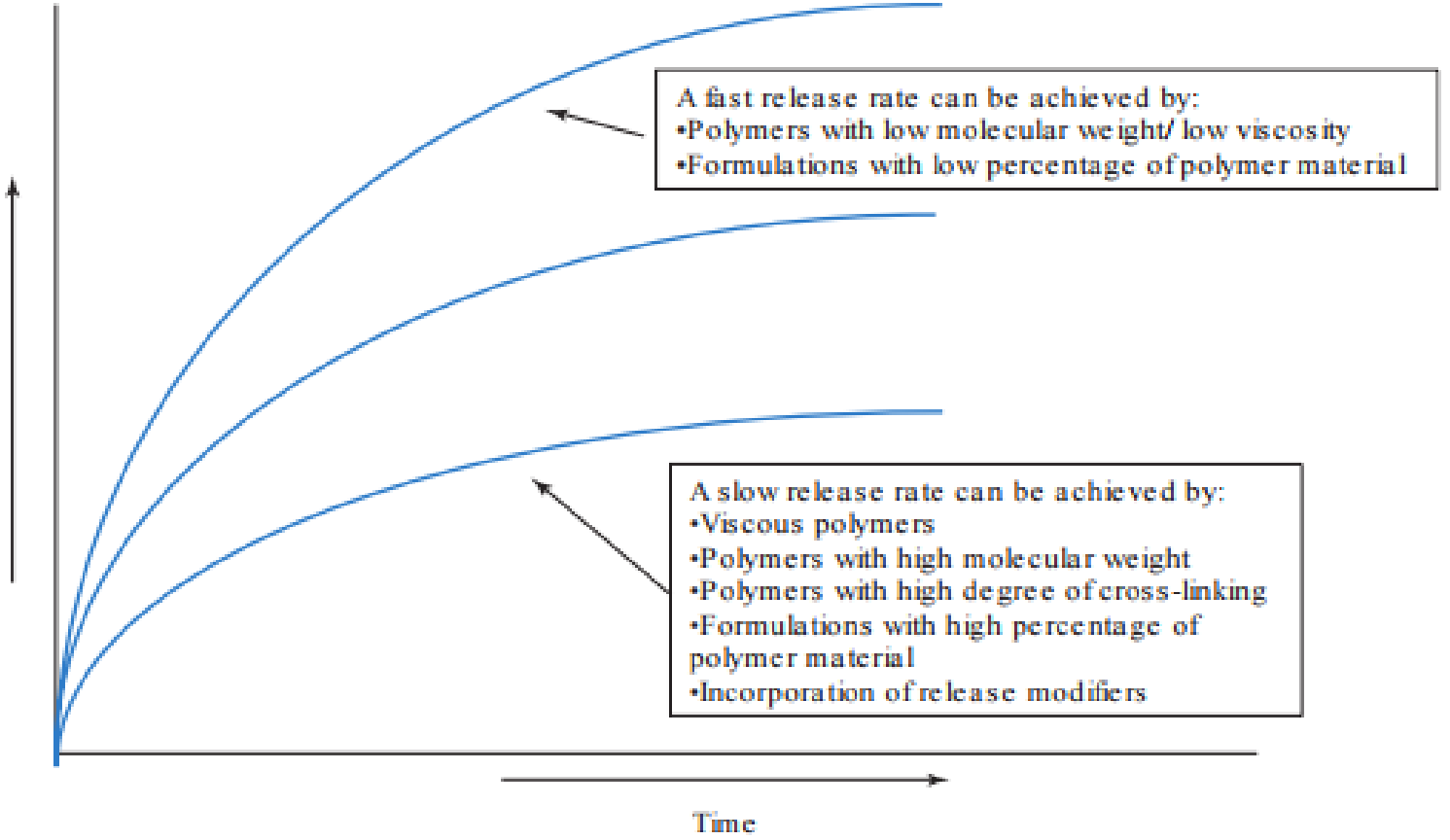


Fig. 31.8 • Theoretical release profles for hydrophilic matrix tablets for extended release (fast, medium and slow profles).

Insoluble polymer matrix

- They consist of an inert matrix system in which drug is embedded in an inert polymer. Their structure is similar to a sponge. If drug molecules were interspersed throughout a sponge and water was applied, drug could leach out via the water filled channels (Fig. 31.9).
- In contrast to hydrophilic matrices, these systems stay intact throughout the gastrointestinal tract.

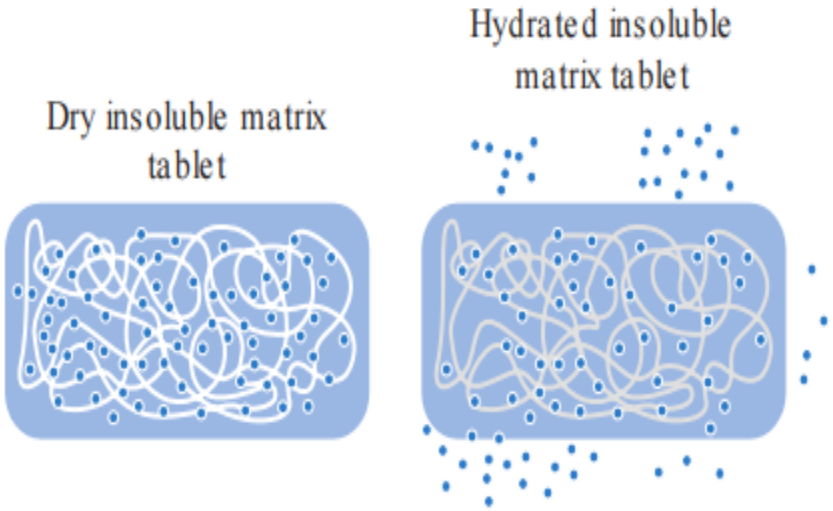


Fig. 31.9 • Dry insoluble matrix tablet has channels (white) interspersed within the polymer. These channels hydrate and drug can diffuse out.

Insoluble polymer matrix

- Drug release rate from insoluble polymer matrices is controlled by the pore size and number of pores, and tortuosity of the matrix.
- Pore-forming agents can be added to increase tortuosity and facilitate drug release. The release mechanism will also depend greatly on how the drug is dispersed within the system (dissolved, molecularly dissolved, or dispersed).
- The drug release does not follow zero-order kinetics; drug release decreases with time due to the increasing distance drug molecules have to travel to reach the surface of the device.

Membrane-controlled systems

- The rate-controlling part of the system is a membrane through which the drug must diffuse, rather than diffusing through the whole matrix. Generally, drug is concentrated in the core, and must traverse a polymeric membrane or film which slows down the release rate.
- The drug should not diffuse in the solid state. Upon exposure to an aqueous environment, water should be able to diffuse into the system and form a continuous phase through which drug diffusion and release can occur (Fig. 31.10).
- Drug release through a membrane is controlled by the thickness and the porosity of the membrane, as well as the solubility of the drug in the gastrointestinal fluids.

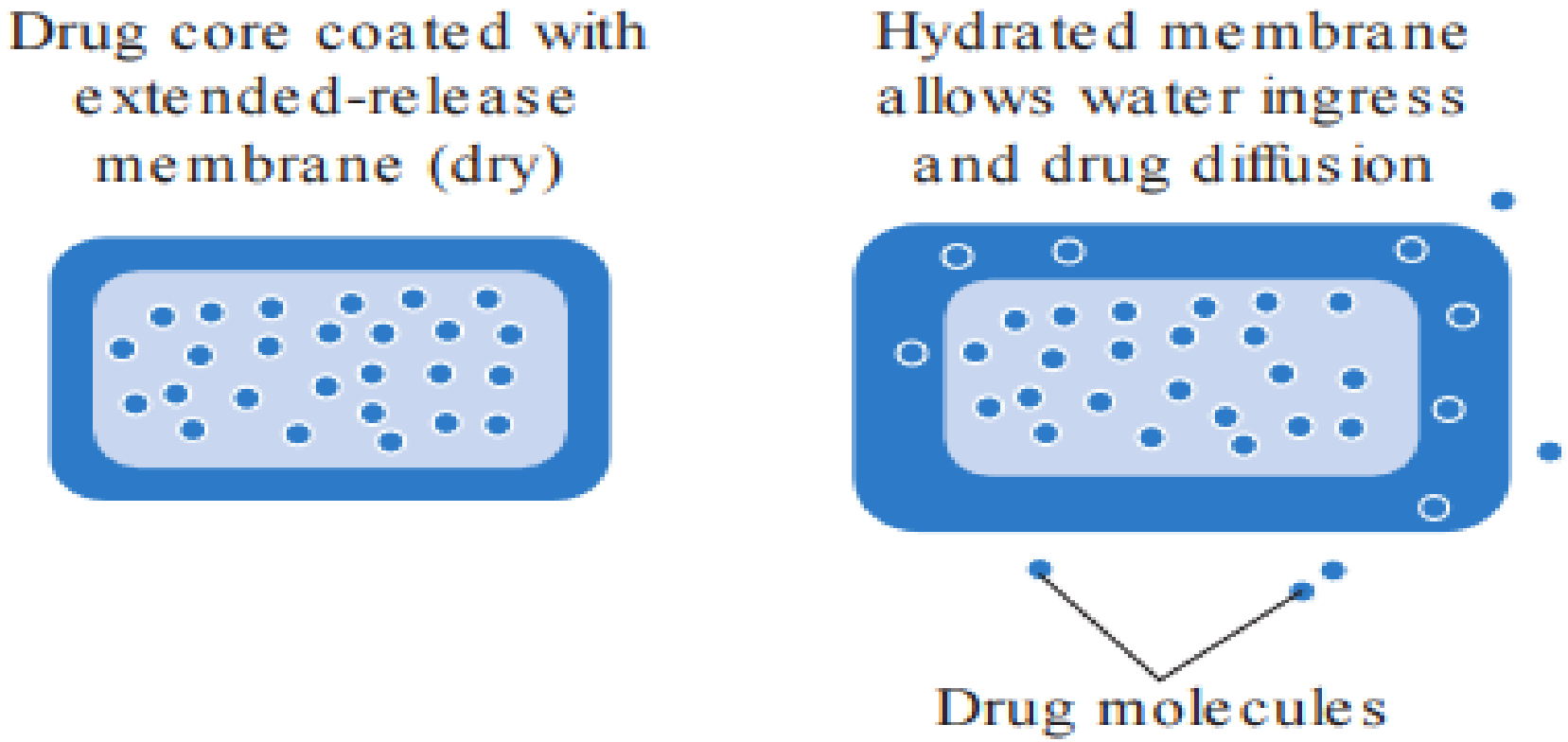


Fig. 31.10 • Drug release mechanism from a dosage form coated with a modifed-release membrane.

Osmotic systems

- A drug is included in a tablet core which is water soluble, and which will dissolve (or suspend) the drug in the presence of water.
- The tablet core is coated with a semi-permeable membrane which will allow water to pass into the core. As the core components dissolve, a hydrostatic pressure builds up and forces (pumps) drug solution (or suspension) through a hole drilled in the coating (Fig. 31.11).

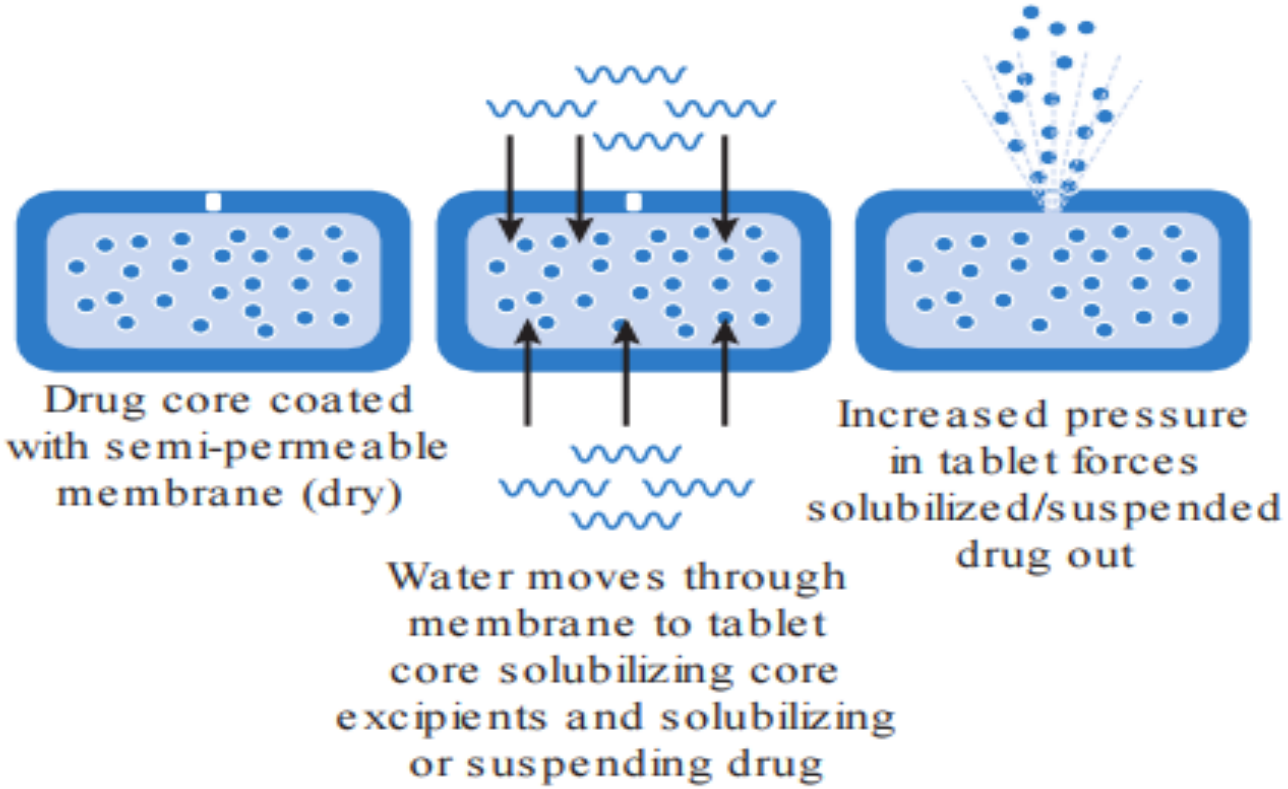


Fig. 31.11 • Release mechanisms from an osmotic pump delivery system.

Osmotic systems

- The rate of drug release is governed by:

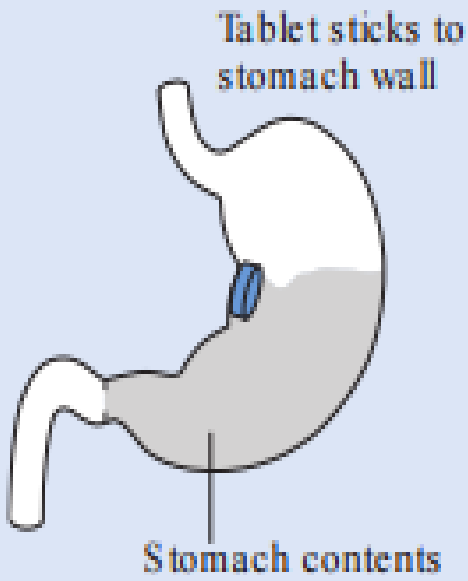
1. The rate at which water is able to pass through the membrane
2. how quickly the drug solution (or suspension)

The orifice needs to be small enough to prevent diffusion, but large enough to minimize hydrostatic pressure (600 µm to 1 mm diameter is normal). The orifice can be made by laser drilling, indentations in tablet (not fully covered by coating) or the use of leachable substances (pore formers).

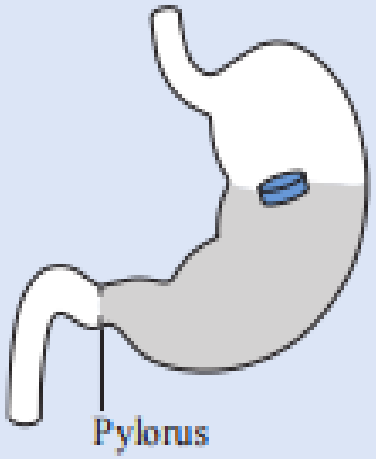
Gastroretention

- Gastroretention is the mechanism by which a dosage form is retained in the stomach, generally for the purposes of improving drug delivery.
- It has been proposed as a mechanism by which drug absorption in the upper gastrointestinal tract can be maximized.
- Gastroretentive approaches to drug delivery aim to overcome the physiological mechanisms in the stomach which would normally enable gastric emptying, so that a modified-release dosage form is retained for longer in the stomach.
- Drugs which may benefit from gastroretention include: **those for local action in the stomach (e.g. to treat H. pylori), drugs which have a narrow absorption window in the small intestine** and **drugs which are degraded in the colon.**

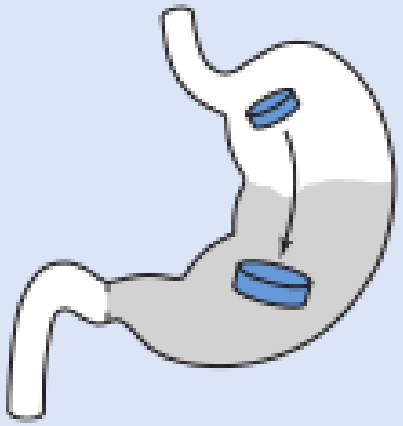
Gastroretention approaches (Mucoadhesion)

Approach to achieve gastroretention	Concept	Formulation considerations	Biopharmaceutical comments
Mucoadhesion 	Mucoadhesive polymers could theoretically adhere a dosage form to the stomach mucosa to retain it in the stomach.	Chitosan, Carbopol, polycarbophil are mucoadhesive polymers which have been researched (with limited success)	Although animal studies suggest this to be a sound concept, it has not been realized in man, probably due to the fast mucus turnover and high motility of the stomach.

Gastroretention approaches (Floating)

Approach to achieve gastroretention	Concept	Formulation considerations	Biopharmaceutical comments
Floating Tablet floats on stomach contents  	Dosage form should float on the stomach contents, thus avoiding gastric emptying.	Gas generating agents like bicarbonate can be used, or lipids.	Requires food to be present in the stomach. Has not shown clinical success for drug delivery but agents like Gaviscon which form a raft on stomach contents have been used for heartburn and indigestion.

Gastroretention approaches (Size increasing systems)

Approach to achieve gastroretention	Concept	Formulation considerations	Biopharmaceutical comments
Size increasing systems Tablet expands making it difficult to pass through pylorus. 	A dosage form that swells and increase in size as soon as it reaches the stomach to avoid being able to pass through the pyloric sphincter.	Swellable polymers such as hydroxypropyl methyl cellulose, polyethylene oxide, and xanthan gum have all been investigated.	Some marketed products use this approach but need to be given in the fed state and gastric emptying is delayed primarily by the effect of food on the stomach. The resting size of the pylorus (open) is around 10–11 mm but it can stretch further than this.

Delayed release

- Gastro-resistant coatings
- Colonic drug delivery

Gastro-resistant coatings

- The concept here is similar to that of membrane controlled extended release, except that the membrane is designed to disintegrate or dissolve at pre-determined point.
- Gastro-resistant coatings are polymer coatings which are insoluble at low pH but are soluble at higher pH (5–7 depending on polymer used).

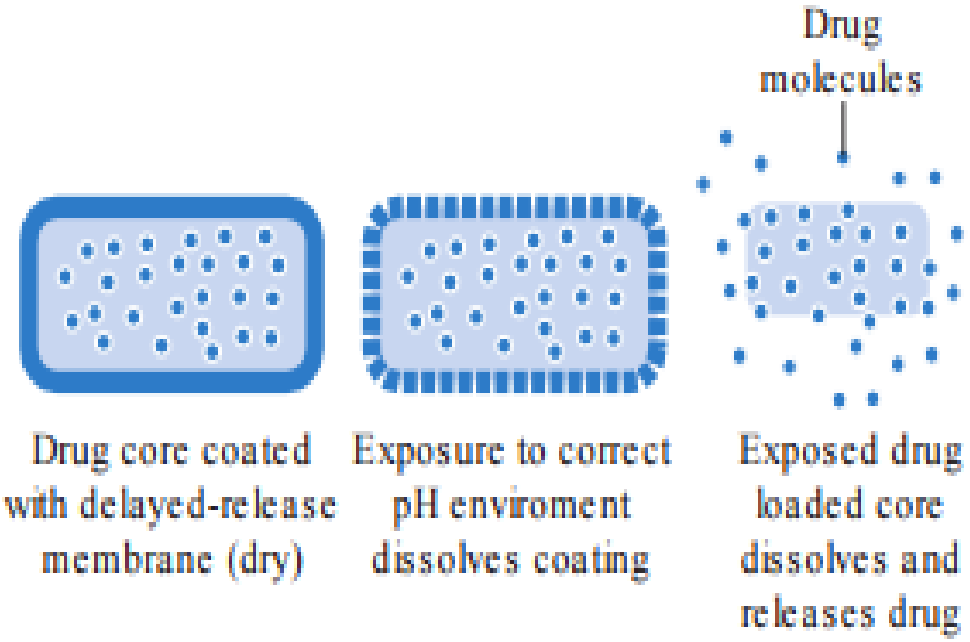


Fig. 31.12 • Drug release mechanism from a gastro-resistant-coated dosage form.

Gastro-resistant coatings

- This approach is most commonly used for releasing drug in the small intestine.
- The highest pH in the gastrointestinal tract is generally at the ileocaecal junction, just before the colon. Here the pH can be around pH 7. Using polymers which dissolve at pH 7 should theoretically dissolve a dosage form here and release.
- This approach has been used to deliver anti-inflammatory medications including budesonide, beclometasone and mesalazine to treat ulcerative colitis in the large intestine.

Gastro-resistant coatings

- Gastro-resistant coating of formulations has two functions:

i) to protect the stomach from the drug or

ii) to protect acid-sensitive drugs from the stomach environment.

Colonic drug delivery

- Colonic drug delivery can be achieved by the utilization of **pH responsive polymers** e.g. Eudragit S which dissolves at around pH 7 to target the colon.
- Targeting the colon is difficult as a tablet or pellet may only be in the region of highest pH (at the ileocaecal junction) for a short time, and the target pH (often pH 7) may not be reached. This can lead to dosage form failure (i.e. it does not disintegrate and is passed intact in the stools, consequently, not releasing the drug).
- An alternative approach to this is the use of the **gut bacteria as a trigger** for drug release.

Colonic drug delivery

- A coating is prepared from a material which is insoluble in the gastrointestinal fluids (e.g. ethylcellulose), but it will also contain a component that can be digested only by colonic bacteria (not by pancreatic enzymes).
- An example of a material that can be used is the polysaccharide known as ‘resistant starch’. This type of starch can only be broken down by bacterial enzymes in the colon. When the dosage form reaches the colon, the starch component of the coat is digested and dissolves, leaving pores through which drug can be released.

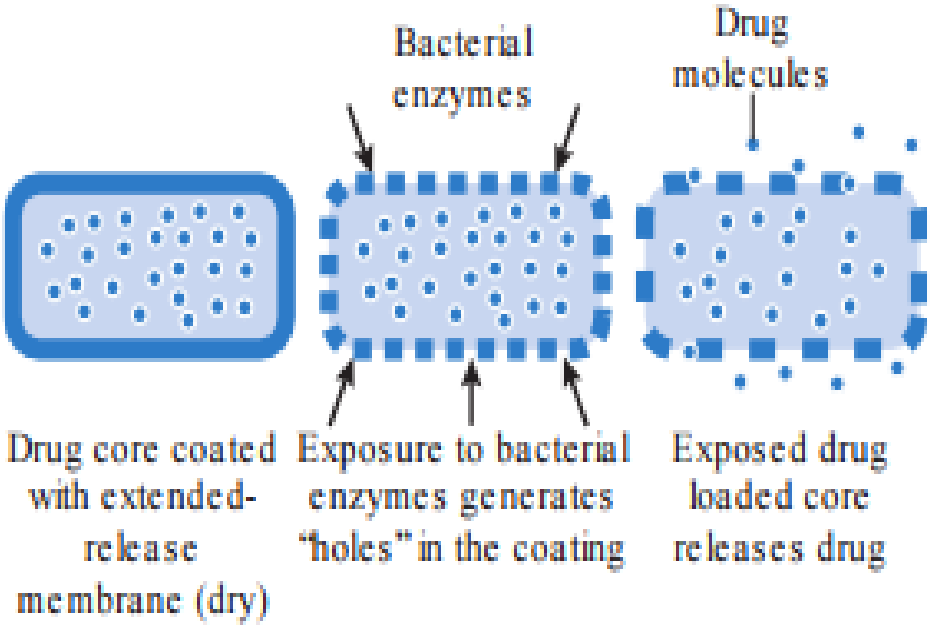


Fig. 31.13 • Release mechanisms for bacterially-triggered colonic targeting.

Colonic drug delivery

- Bacterially triggered systems tend to be more reproducible in terms of consistent drug release than pH responsive system. However, there may be some patient in which bacterial levels are affected by disease.
- Being a relatively recent development, this technology has also not advanced as far clinically as pH-responsive colonic drug delivery, and is still in the experimental and clinical testing stages.
- Other new systems have also been proposed which combine both Eudragit S as the polymer and resistant starch to give a dual release mechanism (i.e. release is triggered by both the pH change and the bacteria). This is said to ensure rapid and consistent drug release.

Key points

- Modified-release drug delivery aims to deliver drugs at specific rates, times or physiological sites.
- Modified release can refer to extended, sustained, controlled, delayed or gastroresistant release.
- Modified release can be employed to achieve once-daily dosing, to reduce side effects, to have long acting medicines or to target a site in the gastrointestinal tract, e.g the colon.
- Extended release can be achieved by using matrix polymer tablets, polymer coated pellets or osmotic-based systems.

Key points

- Gastroretention is a type o extended release which aims to keep the drug in the upper gastrointestinal tract (stomach and upper small intestine)

- Gastro-resistant coatings (pH-controlled) protect a drug rom the stomach and can be used or delivery to the small intestine or colon

- Drugs can be targeted to the colon by using bacterial enzymes to initiate drug release