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, as will be seen in later sections, for example with osmotic systems.

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 and (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'.

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).

There are various strategies which have been adopted in an attempt to control and manipulate drug release patterns. These are summarized in Table 31.2 and are discussed in more detail below.

Extended release

Before an extended-release dosage form is developed, the suitability of the drug in question should be considered. 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. 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.

Drugs are categorized according to steps 2 and 3. The Biopharmaceutics Classification System of drugs (see Chapter 21 for details) 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.

High solubility and high permeability drugs (Class I) are most suitable for extended-release delivery (ideally by passive diffusion). These properties mean that 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. 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, and dissolution of drug particles in the gut can be the rate-limiting step. After drug release and dissolution have occurred, absorption must then occur. Drugs with low permeability ($<0.5 \times 10^{-6}$ mm s^{-1} through CaCo-2 tissue culture [see Chapter 21]) 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.

Other considerations as to the suitability of a drug for extended release include 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 is another factor to consider. 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 (especially paediatric or geriatric patients, Chapter 43).

Hydrophilic matrix systems

Hydrophilic matrix systems can also be referred to as swellable soluble matrices. They are used for extended (sustained) release. Drug is mixed with a water-swellable, hydrophilic polymer (usually along