HPMC 2208 and HPMC 2910 are available in a range of molecular weight grades (classified by their viscosity in aqueous solution) and those of higher viscosity will retard drug release to a greater extent. These materials are also both produced in small particle size grades recommended for the formulation of matrix tablets with modified drug release. Polymer particle size appears to have a greater effect on the release of water soluble drugs; smaller particles ensure a more rapid gel layer formation, which is crucial where the release of soluble API is of interest.[47]

Drug release from HPMC-based matrix tablets is controlled by:

- Drug solubility in water
- Drug concentration in the tablet
- Hydoxypropoxyl : methoxyl substitution ratio
- Polymer viscosity grade
- Polymer concentration
- Polymer particle size

Products of different viscosity can be blended to obtain an intermediate viscosity where fine tuning of drug release rate is required. In addition, other excipients may be added to the formulation to aid the compactibility and other physical properties as outlined previously in this chapter. Where granulation is required (e.g. to improve flow), roller compaction is generally the preferred process as the addition of any aqueous binder solution to a blend containing these polymers will initiate irreversible gel formation and processing may be more difficult.

a(iii) Ion Exchange Resins

Ion exchange resins are water insoluble materials containing either:

- Anionic groups such as amino or quaternary ammonium groups.
- Cationic groups such as carboxylic acids or sulfonic groups in repeating positions on the resin chain.

An API–resin complex is formed by prolonged exposure of an API to the resin, and exchange of the ionic form of the API with the resins ionic functional group. This complex can be made into a range of dosage forms including tablets or capsules.[48] Exchange with ions in the gastrointestinal fluid releases the API, and is dependent on the concentration and affinity of the gastrointestinal ions to exchange.[49,50] The API is bound at both internal and external exchange sites, therefore release rate is influenced by diffusion to and from the internally bound exchange sites.[49,50] The release of the API from weak anionic or cationic resins is also influenced by the pKa of the resin and pH at the site of action, as the API release will only occur when the API–resin complex is in its ionized state.[49,50] The release of API can be further modified by coating the API–resin complex with a semipermeable membrane providing a barrier to diffusion.[49,50]

a(iv) Osmotically controlled systems

Osmotically controlled systems consist of a semipermeable membrane surrounding an osmotic tablet core containing the API. At a rate depending on the surface area, thickness and composition of the membrane, fluid is drawn into the tablet core causing an increase in pressure which forces the API, as either a solution or a suspension, out of the dosage form via a delivery port drilled through the membrane layer. Some systems use a bilayer tablet core where a sweller layer is used beneath the API layer to ensure constant and complete release of the drug content as shown in Figure 3. The increase in volume of the sweller layer pushes the API layer through the delivery port.

The semipermeable membrane comprises a mixture of a water insoluble material with a water soluble polymer, for example, cellulose acetate with polyethylene glycol, typically applied to achieve a coat thickness up to 250 µm. A low molecular weight grade of polyethylene oxide (e.g. *Polyox N80*, Dow Chemical Company; molecular weight approximately 200 000) is blended with the API to form the API layer; the sweller layer uses a higher molecular weight grade of polyethylene oxide (e.g. *Polyox coagulant*, Dow Chemical Company; molecular weight approximately 5 000 000) combined with an osmogen, such as sodium chloride. API release rates from these systems generally show a good correlation between *in vitro* and *in vivo* profiles as it is relatively immune to gastrointestinal pH and motility and the fed/fasted state of the patient.

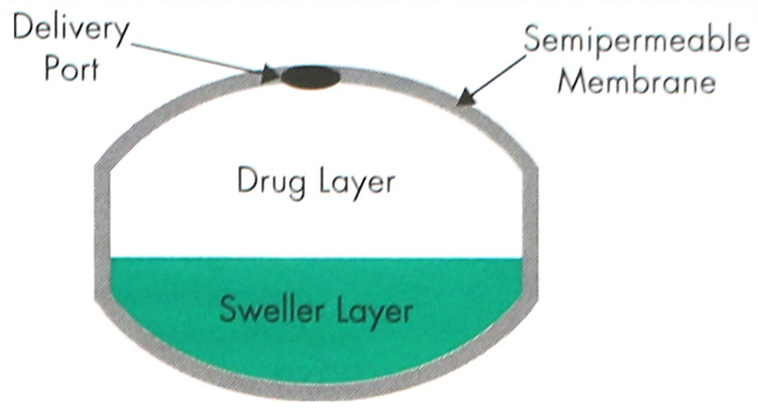

Figure 3: Schematic diagram of a bilayer osmotically controlled modified release dosage form.

b) Modifying the site of drug release

b(i) Gastroretentive systems

Variability in GI transit time can adversely affect the release profile of orally administered modified-release drug substances, particularly if the API has a narrow absorption window. A dosage form retained in the stomach whilst the API is released will ensure that a solution of the API regularly exits the stomach along with the gastric fluids and thus has the whole surface area of the small intestine for adsorption. In addition, it can offer enhanced drug therapy for local conditions affecting the stomach. Retention in the stomach can be achieved by formulating a low density or floating dosage form, based on a gel forming polymer (e.g hydroxypropylcellulose) or using a hydrophobic fatty material (e.g. stearates).

b(ii) Enteric coatings

Entero-soluble cationic polymers do not dissolve in the saliva of the patient but do dissolve in the acid media of the stomach, providing effective taste-masking but still ensuring rapid release of the API from the dosage form. Anionic polymers do not dissolve in either the saliva or the acid conditions of the stomach but do dissolve slowly in gastrointestinal (GI) fluid. This is known as enteric coating and may be used for modified-release formulations together with various insoluble polymers as described in Excipients for Capsule Formulation. *See also* Table V.

c) Modifying the time of drug release

c(i) Pulsatile Drug Delivery Systems

Some conditions require a dosage form which delivers its drug only after an initial delay or lag time has elapsed. This delay can be used to protect the drug from the acidic conditions of the stomach or to maximize drug delivery to the lower regions of the GI tract.[51] The onset of drug release can be time-controlled (i.e. as a result of changes in the delivery device itself) or site-controlled as a result of the biological environment within the GI tract (e.g. pH or enzymes).[52]

Delayed onset or pulsatile drug delivery is generally achieved using a drug reservoir based on a capsule or tablet which is coated with a polymeric barrier, which gradually dissolves or erodes or is ruptured as a result of swelling of the core. Core swelling is achieved through the use of effervescent excipients, for example, citric acid and sodium bicarbonate, or swellable materials such as cellulose ethers. In some devices water is drawn into the core through a semipermeable membrane via the action of an osmotically active material added to the formulation.[51]

The water-insoluble polymers used to form the barrier coat include cellulose acetate, ethyl cellulose, cellulose acetate phthalate or various types of methacrylic acid copolymers (e.g. *Eudragit RS* or *Eudragit RL*).[2] The pH-solubility of the methacrylic acid copolymers depends on their structure and composition – thus by careful choice, drug release can be targeted to specific regions of the