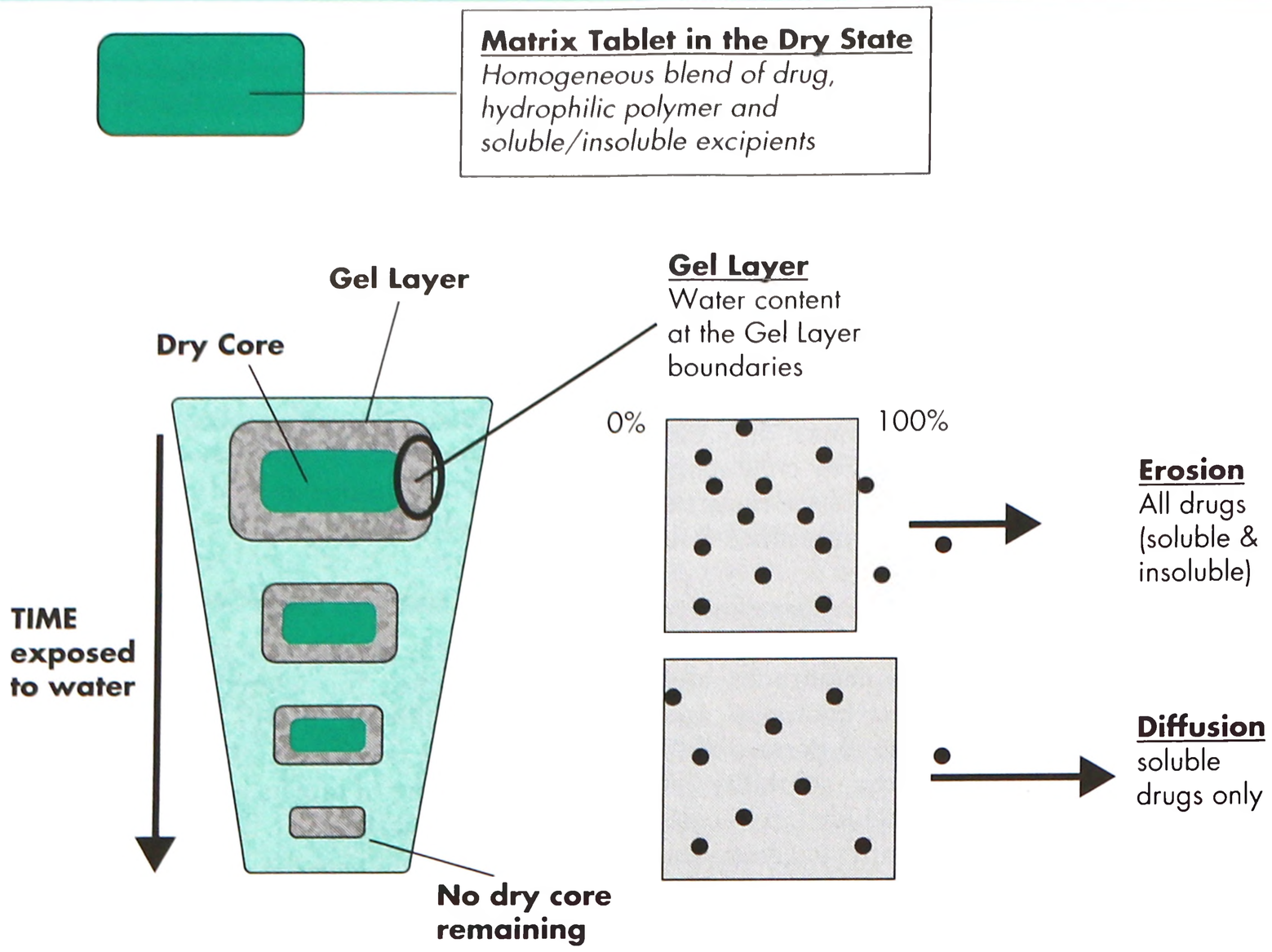

Figure 2: Hydration and drug release from a controlled release matrix tablet.

interval and may also potentially reduce the number of adverse events compared to an immediate release formulation.[10] Oral modified-release delivery systems that modify the rate of drug release can be broadly divided into 4 categories based on their mechanism of drug release:[45]

a(i) Dissolution-controlled release

Dissolution-controlled release of an API depends on modifying the rate at which either a polymer membrane or a polymer matrix dissolves in the dissolution fluid. A rate-controlling membrane is achieved by coating particles (often beads or pellets) with a relatively insoluble polymer, for example ethylcellulose or cellulose acetate using pan coating or, more commonly, an air suspension coating technique. API release is modified by the type of polymer and the thickness of the applied coat. Coated pellets are frequently tableted or filled into capsule shells. Ethylcellulose is available as a water-based coating system (e.g. *Surelease*, Colorcon, or *Aquacoat*, FMC Biopolymer) to reduce safety or environmental concerns around processing.

Dissolution-controlled release using a matrix involves the incorporation of the API into either a hydrophobic matrix or hydrophilic matrix. API release is controlled by the rate of penetration of the dissolution fluid into the matrix which is affected by the matrix composition and porosity. Excipients used to form a hydrophobic matrix include, for example, polyethylene, polypropylene, carnauba wax or ethylcellulose; examples for a hydrophilic matrix include hypromellose, methylcellulose, hydroxypropyl cellulose or sodium carboxymethylcellulose.

a(ii) Diffusion-controlled release

Diffusion-controlled release depends on controlling the partitioning of solubilised API molecules through a polymer; this polymer can either be applied as a coating around powder particles or, more frequently, it is dry blended with the powder and compressed using a conventional tablet press to form a continuous matrix tablet. As matrix tablets are relatively easy to develop and manufacture they are widely employed to modify the drug release rate from dosage forms, and are well understood as a result of several decades of research. On contact with the dissolution medium, the exterior surface of a matrix tablet forms a swollen gel layer which advances towards the interior of the tablet as hydration proceeds as shown in Figure 2. Whilst the release of soluble APIs is via diffusion through the polymer matrix, some release of both soluble and insoluble APIs can occur through erosion as the polymer chains in the outer surface begin to disentangle and the gel layer is slowly worn away. The importance of erosion can be determined comparing the dissolution profile of the API with the dissolution profile of the polymer alone.

Cellulose ethers are the most popular excipients used to formulate matrix tablets as they display good compactibility and swell rapidly on contact with aqueous media. In addition, they are available in a wide range of grades depending on their degree of substitution and viscosity, both of which have an effect on drug release.[45] Hypromellose (HPMC) is the most frequently encountered polymer used to formulate matrix tablets[46] but other materials include:

- Methylcellulose (MC)
- Ethylcellulose (EC)
- Hydroxyethyl cellulose (HEC)
- Hydroxypropyl cellulose (HPC)
- Carboxymethyl hydoxyethyl cellulose
- Hydoxyethylmethyl cellulose (HEMC)
- Cellulose acetate phthalate enteric coating

The characteristics of HPMC encourage the formation of a tight, strong gel compared to other cellulosics; as a result API release is slowed to a greater extent when using HPMC compared to using similar levels of methylcellulose, hydroxyethyl cellulose or carboxymethyl cellulose.[47]

The two grades of HPMC most frequently used for matrix tablets are HPMC 2208 (USP) & HPMC 2910 (USP). HPMC 2208 has a higher ratio of hydoxypropoxyl to methoxyl substitution, rendering it more hydrophilic and thus faster to establish the release-limiting gel barrier on the tablet surface. Rapid gel formation has a large effect on initial drug release i.e. the lag time during which release is uncontrolled and is of particular importance when formulating APIs of higher water solubility.[45]