Table 19.2 Examples of transport mechanisms of commonly used drugs across the gastrointestinal absorptive epithelia

Route	Examples	Therapeutic class
Transcellular passive diffusion	Propranalol	β-blocker
	Testosterone	Steroid
	Ketoprofen	Non-steroidal anti-inflammatory
	Oestradiol	Sex hormone
	Naproxen	Non-steroidal anti-inflammatory
Paracellular	Cimetidine	H_2 antagonist
	Loperamide	Antidiarrhoeal
	Atenolol	β-blocker
	Mannitol	Sugar used as paracellular marker
	Tiludronate	Bisphosphonate
Carrier mediated	Cefalexin	Antibacterial
	Captopril	ACE inhibitor
	Levodopa	Dopaminergic
	Foscarnet	Antiviral
Transcellular diffusion subject to P-glycoprotein efflux	Ciclosporin	Immunosuppressant
	Nifedipine	Calcium channel blocker
	Verapamil	Calcium channel blocker
	Paclitaxel	Anticancer
	Digoxin	Cardiac glycoside

structural diversity (Table 19.2) are susceptible to efflux from the intestine via P-glycoprotein. Such efflux may have a detrimental effect on drug bioavailability. These countertransport efflux proteins pump drugs out of cells in a similar way to which nutrients, and drugs are actively absorbed across the gastrointestinal membrane. This process therefore requires energy, can work against a concentration gradient, can be competitively inhibited by structural analogues or by inhibitors of cell metabolism, and is a saturable process.

Transporters in the gastrointestinal tract

As discussed earlier in this chapter there are a number of transporters in the gastro-intestinal tract. These can be classified as either efflux or uptake (or influx) transporters depending on the direction of the transport. Both these transporters can be also classified as unitransporters, symporters and antiporters. Uniporters bind and transport only one type of substrate at a time. There are both passive and active uniporters for example the glucose and nucleoside transporters which are driven by an electrochemical gradient and P-glycoproteins, the breast cancer resistance protein (BRRP), the multidrug resistance protein proteins (MRPs) and sodium, potassium and ATPase which are driven by ATP. In contrast, symporters and antiporters are active transporters which can move more than one type of substrate at once, usually a drug molecule and a metal ion. Symporters (or cotransporters) transport ions and substrates simultaneously in the same direction while antiporters (or counter transporters) simultaneously transport ions in one direction and substrates in the opposite direction. As the driving force for symporters and antitransporters are voltage or ion gradients (usually sodium), they are also called ion-couple solute transporters, however as the driving force for these transporters is voltage (H^+) or sodium they can also be known as secondary active transporters. A number of substrates can usually bind to a transporter and thus different drugs can compete for the same transporter. Thus, the transporter can be inhibited; competitively, non-competitively or uncompetitively. Competitive inhibition occurs when both the substrate and inhibitor compete for the same binding site. Non-competitive inhibition occurs when the inhibitor does not bind to the transporter active site but an allosteric site which lowers the affinity of the transporter for the substrate due to changing the conformation of the transporter. Uncompetitive binding occurs when the inhibitor binds to the intermediate of the substrate-transporter complex to terminate the translocation step.

In summary, drugs can be absorbed via passive diffusion and carrier mediated pathways. A drug can cross the intestinal epithelium via one pathway or a combination of pathways. The relative contribution of these pathways depends on the drug's location within the gastrointestinal tract, the formulation and the physicochemical properties of the drug which are discussed in Chapter 20. Table 19.2 summarizes the main mechanisms of drug transport across the gastrointestinal epithelia for a number of commonly used drugs.

Presystemic metabolism

As well as having the ability to cross the gastrointestinal membrane by one of the routes described,