compound must be able to move through both the barriers of the gastrointestinal tract and the hepatocyte cell membrane in order to induce a therapeutic response. Differences in permeability between various cell types can also be an issue, as differences in membrane composition, junction tightness (the space between cells), and transporter protein activity can all influence compound permeability. Compounds intended to modulate CNS functions, for example, must traverse the blood–brain barrier, which is far more restrictive in nature. Tight cellular junctions and higher levels of transport protein expression designed to protect the brain from xenobiotics must be overcome in order for CNS targeted compounds to elicit a response.

The observed permeability of any given compound across a biological barrier is the sum of five modes of transport: passive diffusion, active transport, endocytosis, paracellular transport, and efflux (Figure 6.10). In

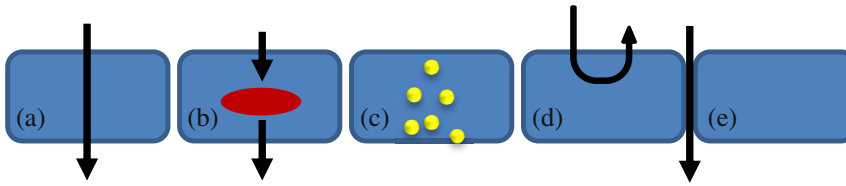

FIGURE 6.10 (a) Passive diffusion; (b) Active transport; (c) Endocytosis; (d) Efflux; (e) Paracellular transport.

considering the transfer of potential therapeutics across the GI tract, the most common mode of transport is passive diffusion. An estimated 95% of all marketed orally available drugs employ this method of transport.[11a,b] Simply put, compounds that are absorbed via passive diffusion move down a concentration gradient from areas of high concentration, such as the GI tract, to areas of low concentration, such as the systemic circulation. Compound polarity can play a major role in passive diffusion, as in order for passive diffusion to occur a compound must exit an aqueous environment, pass through the lipophilic environment of the cell membrane (which is composed of a phospholipid bilayer), and then reenter the aqueous environment on the other side of the biological membrane. It should be no surprise that neutral compounds undergo passive diffusion far more readily than charged species. Absorption in the GI track is further complicated by the requirement that compounds transit through two biological barriers, the apical and basolateral membranes of the GI tract.

Environmental pH also can influence rates of passive diffusion. In acidic regions such as the stomach, basic compounds are largely protonated, so the availability of neutral material capable of passing through a cellular barrier is low. In basic environments, on the other hand, basic compounds are largely neutral and therefore more available for passive diffusion. Compounds that are acidic in nature experience the opposite situations as those described for basic compounds.