Mechanisms of transport across the gastrointestinal membrane There are two main mechanisms of drug transport across the gastrointestinal epithelium: transcellular (i.e. Therefore the rate of appearance of drug in the blood at the absorption site is given by d d C t = − k where dC/dt is the rate of appearance of drug in the blood at the site of absorption, k is the proportionality constant, Cg is the concentration of drug in solution in the gastrointestinal fluid at the absorption site and Cb is the concentration of drug in the blood at the site of absorption.Hepatic metabolism The liver is the primary site of drug metabolism and thus acts as a final barrier for oral absorption.The bioavailability of sustained−release propranolol is even less as the drug is presented via the hepatic portal vein more slowly than from an immediate−release dosage form, and the liver is therefore capable of extracting and metabolizing a larger portion.The bioavailability of a susceptible drug may be reduced to such an extent as to render the gastro− intestinal route of administration ineffective, or to necessitate an oral dose which is many times larger than the intravenous dose (e.g. propranolol).The proportionality constant k incorporates the diffusion coefficient of the drug in the gastrointestinal membrane (D), and the thickness (h) and surface area of the membrane (A): k A h = D Thus the small intestine, primarily the duodenum, is the major site of drug absorption, owing principally to the presence of villi and microvilli, which provide such a large surface area for absorption (discussed earlier in this chapter).Specific membrane transport− ers are expressed in the luminal and/or basolateral membranes of enterocytes, hepatocytes, renal tubular epithelial cells and other important barrier tissues, including the blood−brain barrier, blood−testis barrier and the placental barrier.Transcytosis is also a means by which some viruses, bacteria and prion proteins can gain entry to the lymphatic system through absorption by enterocytes and specialized cells (M cells) in the gut−associated lymphoid tissue (GALT).In summary, drugs can be absorbed via passive diffusion, via membrane transporters or carrier− mediated pathways, paracellular transport or trans−cytosis.Noncompetitive inhibition occurs when the inhibitor binds not to the transporter active site but to an allosteric site, which lowers the affinity of the transporter for the substrate due to changing the conformation of the transporter.Many peptide−like drugs, such as the penicillins, cephalosporins, angiotensin−converting enzyme (ACE) inhibitors and renin inhibitors, rely on the peptide transporters for their efficient absorption.

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