be susceptible to metabolism and biliary clearance. Although there is no general rule that can be applied to *all* drug molecules, within a homologous series, such as the barbiturates or β-blockers, drug absorption usually increases as the lipophilicity rises.

Sometimes, if the structure of a compound cannot be modified to yield lipid solubility while maintaining pharmacological activity, medicinal chemists may investigate the possibility of making lipid soluble prodrugs to improve absorption. A prodrug is a chemical modification, frequently an ester of an existing drug, which converts back to the parent compound as a result of metabolism by the body. A prodrug itself has no pharmacological activity. Examples of prodrugs which have been successfully used to improve the lipid solubility and hence absorption of their parent drugs are shown in Table 20.3.

Molecular size and hydrogen bonding. Two other drug properties that are important in permeability are the number of hydrogen bonds within the molecule and the molecular size.

For paracellular absorption, the molecular weight should ideally be less than 200 Da; however, there are examples where larger molecules (up to molecular weights of 400 Da) have been absorbed via this route. Shape is also an important factor for paracellular absorption.

In general, for transcellular passive diffusion, a molecular weight of less than 500 Da is preferable. Drugs with molecular weights above this are absorbed less efficiently. There are few examples of drugs with molecular weights above 700 Da being well absorbed.

Too many hydrogen bonds within a molecule are detrimental to its absorption. In general, no more than five hydrogen bond donors and no more than 10 hydrogen bond acceptors (the sum of nitrogen and oxygen atoms in the molecule is often taken as a rough measure of hydrogen bond acceptors) should be present if the molecule is to be well absorbed. The large number of hydrogen bonds within peptides is one of the reasons why peptide drugs are poorly absorbed.

Table 20.3 Prodrugs with improved lipid solubility and oral absorption

Prodrug	Active drug	Ester
Pivampicillin	Ampicillin	Pivaloyloxymethyl
Bacampicillin	Ampicillin	Carbonate
Indanylcarbenicillin	Carbenicillin	Indanyl
Cefuroxime axetil	Cefuroxime	Acetylethyl
Enalapril	Enalaprilat	Ester of 1-carboxylic acid
Ibuterol	Terbutaline	Dibutyl
Valaciclovir	Aciclovir	L-valyl (amino acid)
Fosamprenavir	Amprenavir	Phosphate

Summary

There are many properties of the drug itself that will influence its passage into solution in the gastrointestinal tract and across the gastrointestinal membrane, and hence its overall rate and extent of absorption.

Dosage form factors influencing bioavailability

Introduction

The rate and/or extent of absorption of a drug from the gastrointestinal tract have been shown to be influenced by many physiological factors and by many physicochemical properties associated with the drug itself. The bioavailability of a drug can also be influenced by factors associated with the formulation and production of the dosage form. Increasingly, many dosage forms are being designed to affect the release and absorption of drugs, for example controlled-release systems (see Chapter 31) and delivery systems for poorly soluble drugs. This section summarizes how the type of dosage form and the excipients used in conventional oral dosage forms can affect the rate and extent of drug absorption.

Influence of the type of dosage form

The type of dosage form and its method of preparation or manufacture can influence bioavailability; that is whether a particular drug administered in the form of a solution, a suspension or solid dosage form can influence its rate and/or extent of absorption