PHARM.D • YEAR 4

Biopharmaceutics & Pharmacokinetic

CHAPTER 6

Nonlinear Pharmacokinetics

PPT CHAPTER COVER



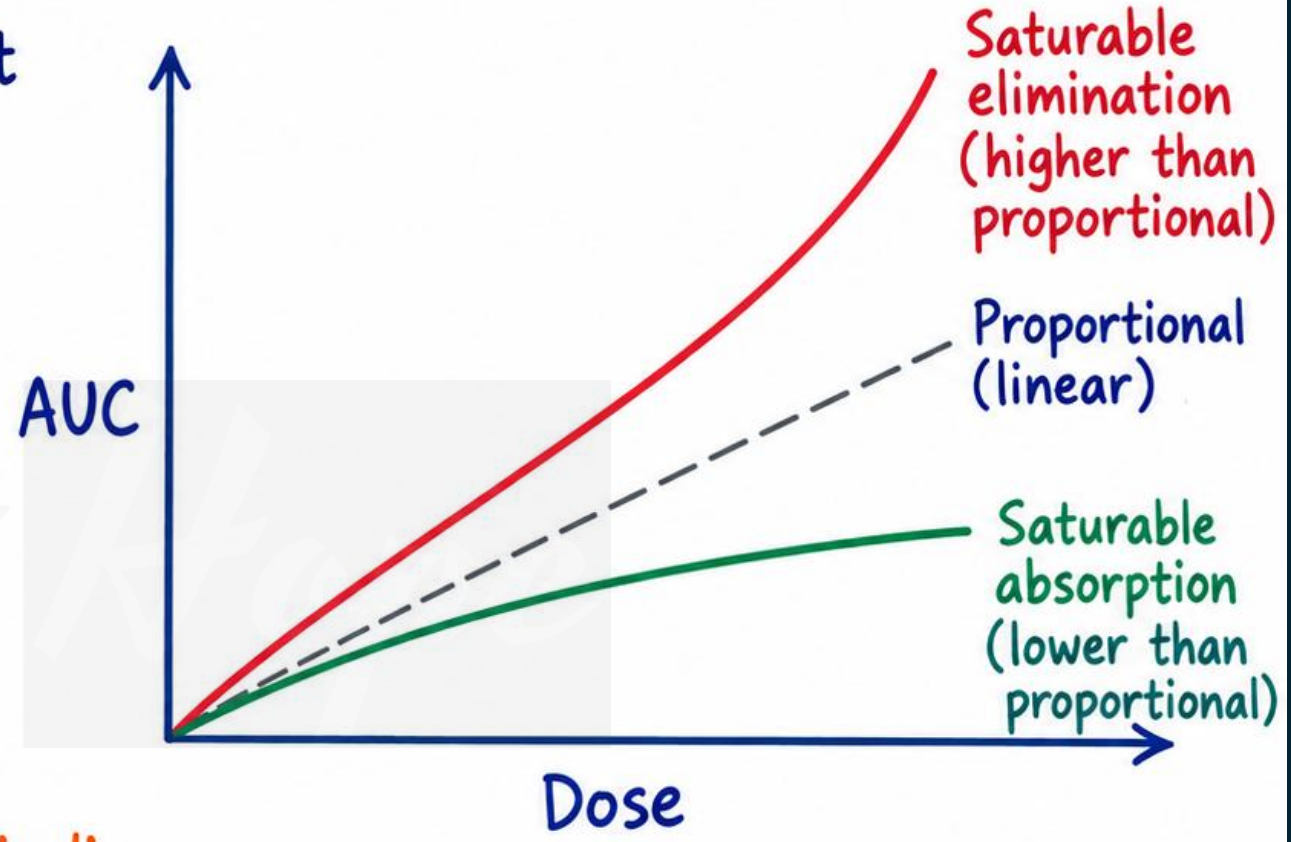
DOCTOR OF PHARMACY

Recognising nonlinear pharmacokinetics

Nonlinear pharmacokinetics means that exposure is not proportional to dose over the range studied.

Doubling a dose may produce more or less than twice the AUC.

Apparent clearance, half-life or bioavailability may change with concentration or dose.



Capacity limits can involve absorption, binding, metabolism or excretion.

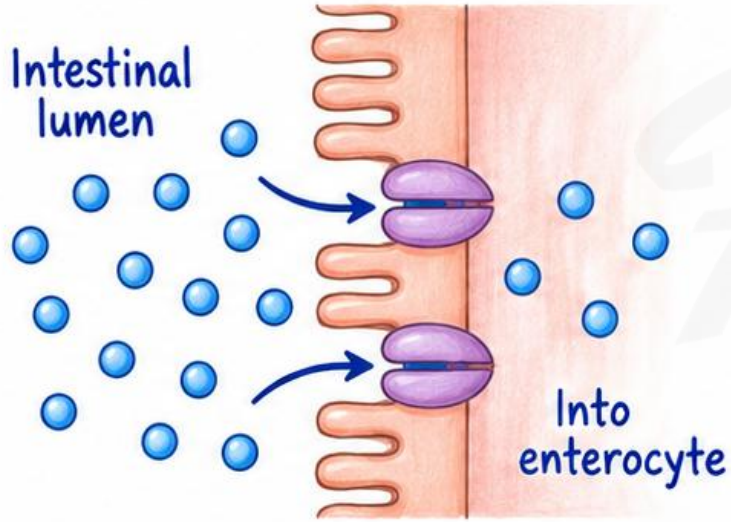
The direction of the change depends on the mechanism.

Nonlinearity is a property of a dose range and system, not a label that applies identically at every dose.

Nonlinear absorption and binding

Absorption

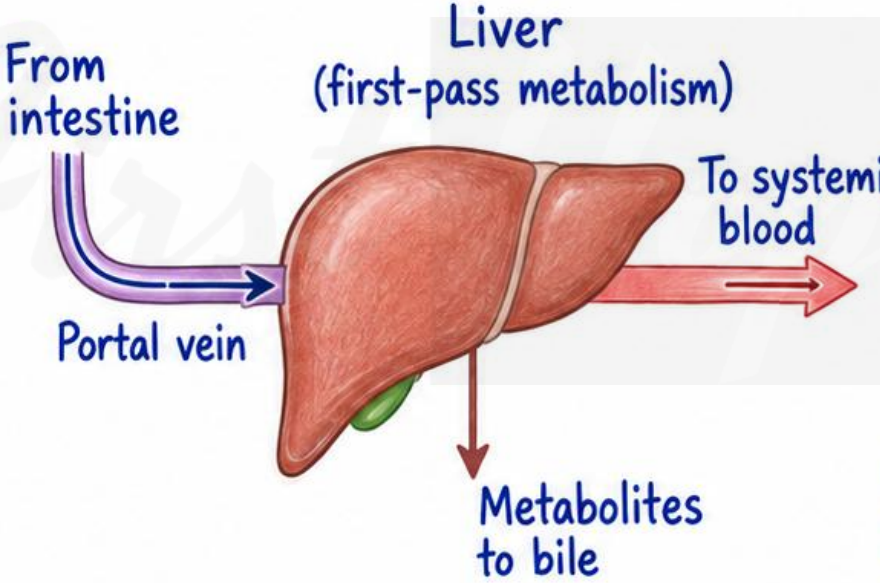
Limited solubility or saturable uptake can reduce the absorbed fraction as dose increases.



Gabapentin is an example of capacity-limited intestinal uptake.

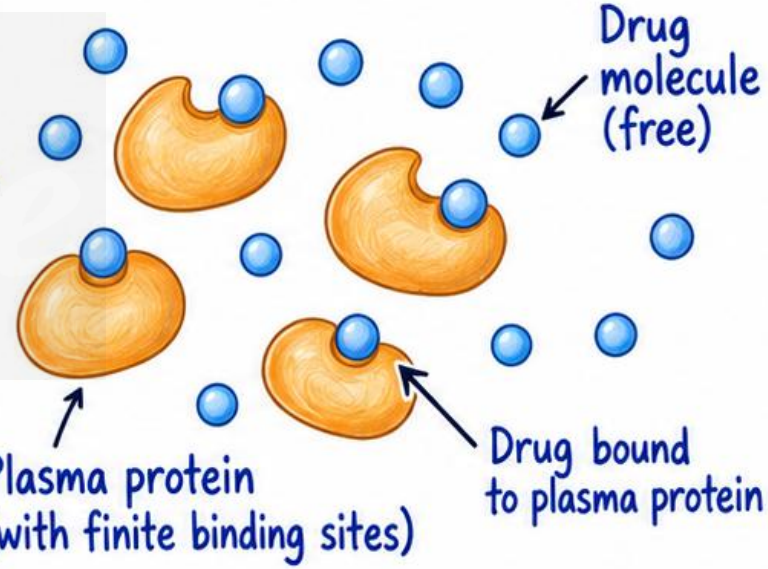
First-pass metabolism

Saturation can increase the fraction reaching systemic blood.



Protein binding

Finite binding sites can make the unbound fraction concentration-dependent.

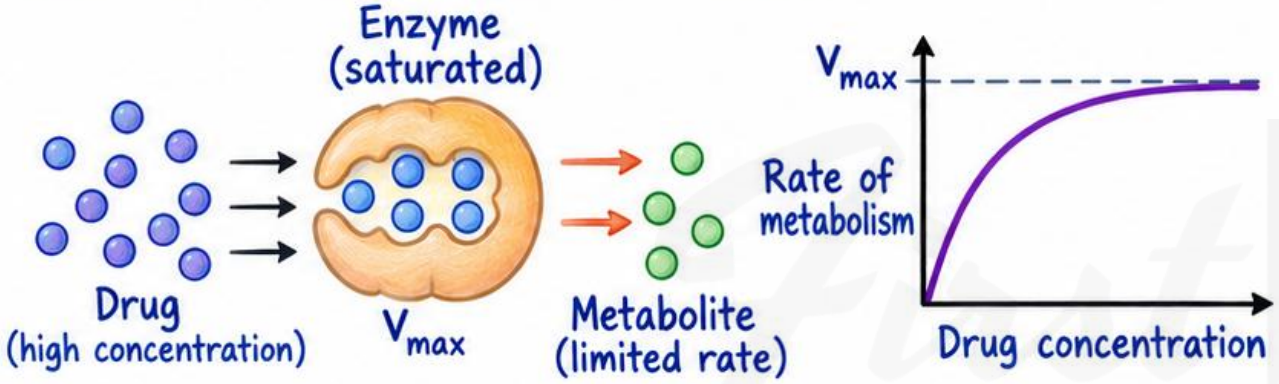


Changes in total concentration do not necessarily match changes in active unbound concentration.
Interpret binding, distribution and clearance together.

Nonlinear metabolism and excretion

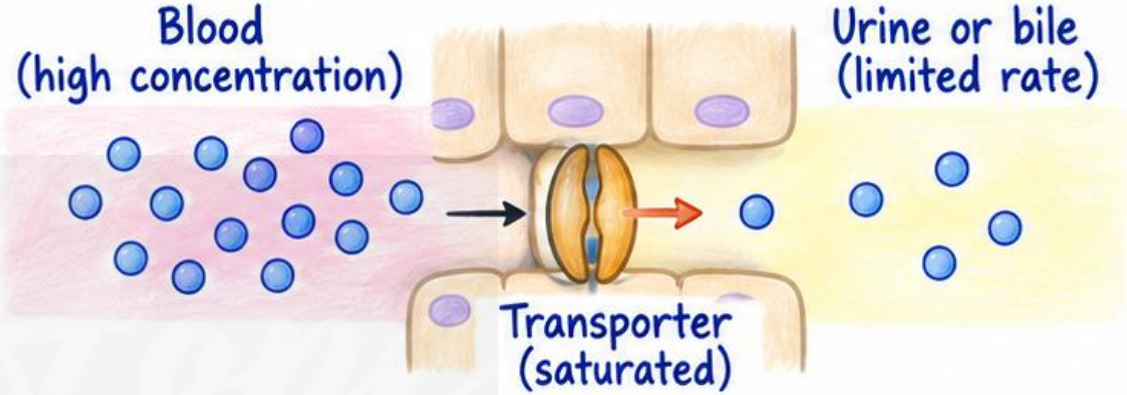
Enzymatic capacity can be saturated

Metabolism can approach a finite enzymatic capacity, reducing clearance as concentration rises.



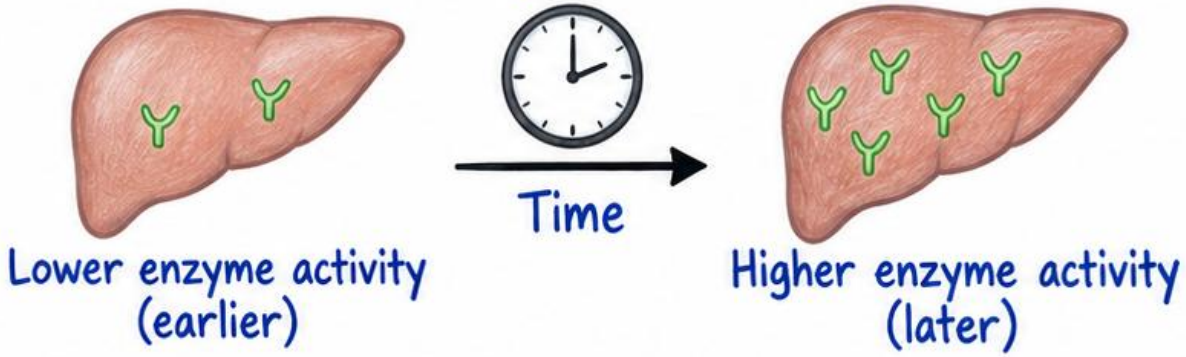
Transporter capacity can be saturated

Renal secretion or biliary transport may also become capacity-limited.



Autoinduction increases enzyme activity over time

Autoinduction changes enzyme activity over time; carbamazepine is an example.



Inhibition can alter exposure

Enzyme inhibition can alter exposure and apparent kinetics.

Different mechanisms

Dose-dependent saturation and time-dependent changes are different mechanisms.

Consider other factors

Kidney function, interactions and sampling conditions must be considered before attributing unusual exposure to saturation.

Michaelis–Menten elimination

Elimination rate:

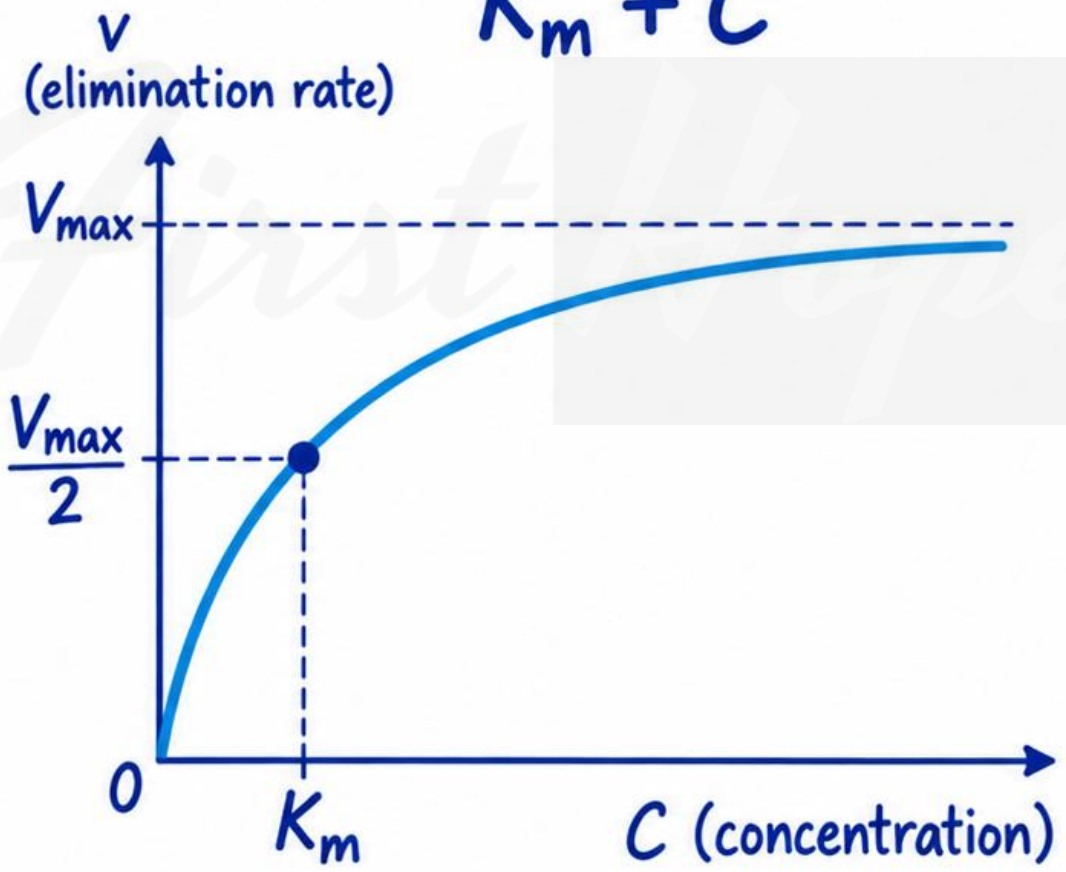
$$v = \frac{V_{max}\, C}{K_m + C}$$

V_{max}

V_{max} is the maximum elimination rate, with units of amount/time.

K_m

K_m is the concentration at which $v = \frac{V_{max}}{2}$.



C and K_m

C and K_m must use the same concentration units.

Curve

The curve rises with concentration and approaches V_{max}.

Interpretation

K_m describes the model's concentration dependence; it is not a therapeutic concentration range.

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