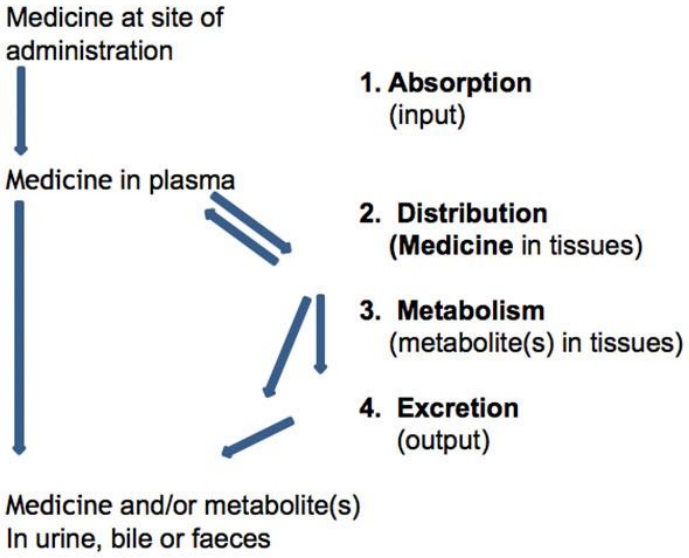
Pharmacokinetics and Pharmacodynamics



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Learning Outcomes

At the end of this lesson students will be able to

- Outline the relationship between pharmacokinetics and pharmacodynamics.
- Describe about oral availability.
- Describe about oral stability.
- Explain about oral activity.
- Explain about tissue availability.

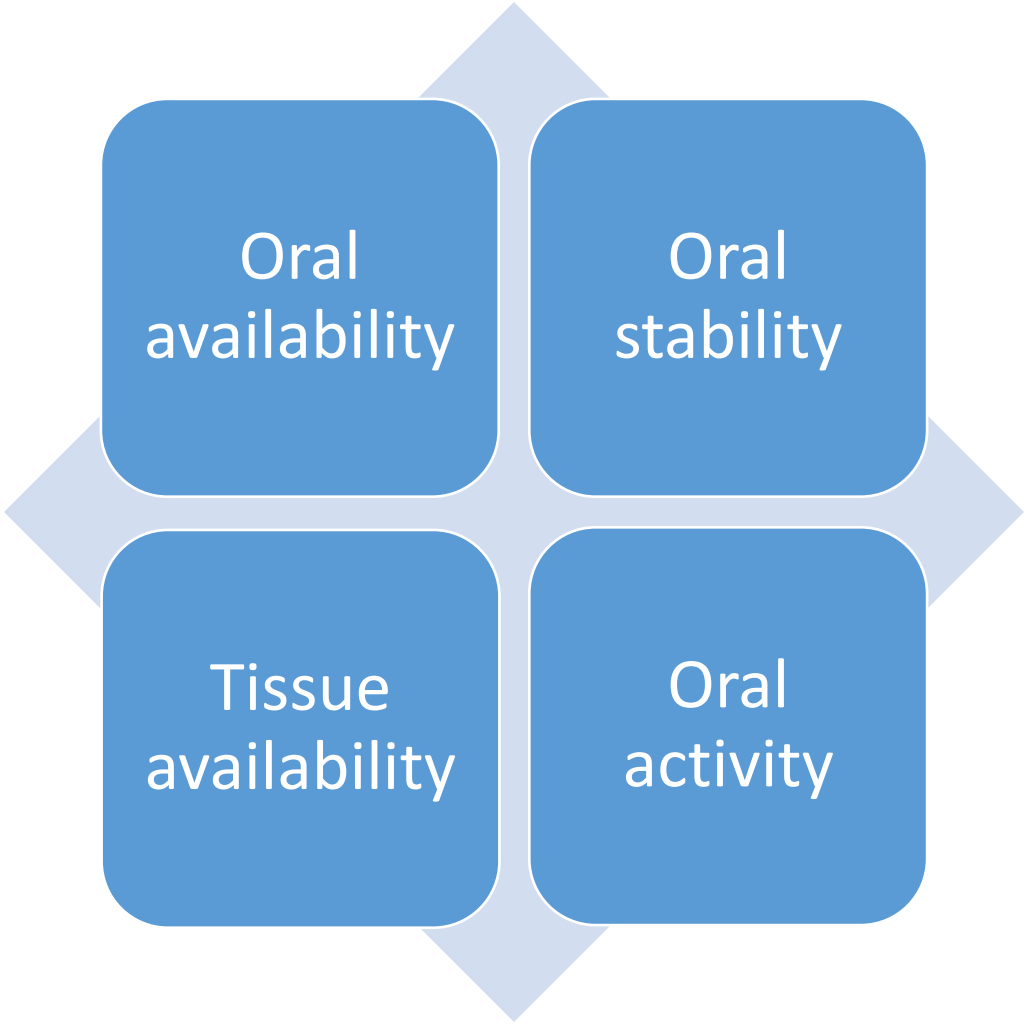
Pharmacokinetics and Pharmacodynamics: are they inter-related?

The answer is definitely **Yes**

- If the drug not reaches the target, no pharmacological effect will be observed even if the drug is known to effectively bind to the target active-site.

- If the drug has desired pharmacokinetic properties and deposited in enough concentration around the site of action, then it can effectively bind to the target to exert its pharmacological actions.

What do we mean by:



Oral availability

- Oral availability or bioavailability measures the fraction of the drug being absorbed into the blood circulation.
- Factors affecting oral availability:-
  - Chemical nature of drug (lipophilicity and ionization state).
  - Water solubility.
  - Oral stability.
  - Physiological factors.

Oral stability

- Oral stable drugs must be:-
  - Chemically stable toward the GIT conditions; acidic (stomach) and basic (intestine) pH.
  - Enzymatically stable (first-pass metabolism): stable towards the digestive and metabolizing enzymes such as esterase, amidase and oxidase.
- If the drug is orally unstable, it will not be available to be absorbed…..low oral availability.
- First pass metabolism does not mean only **liver metabolism** of orally administered drugs before the drug being deposited in blood but also covers all metabolic transformation.

Oral stability

- First pass metabolism involves the following:-

  - All Oral cavity enzymes such as amylase and lingual lipase.
  - Stomach pepsinogen.
  - All GIT proteolytic enzymes.
  - All Intestinal hydrolase enzymes such as esterase and amidase.
  - All intestinal lipases and reductases.

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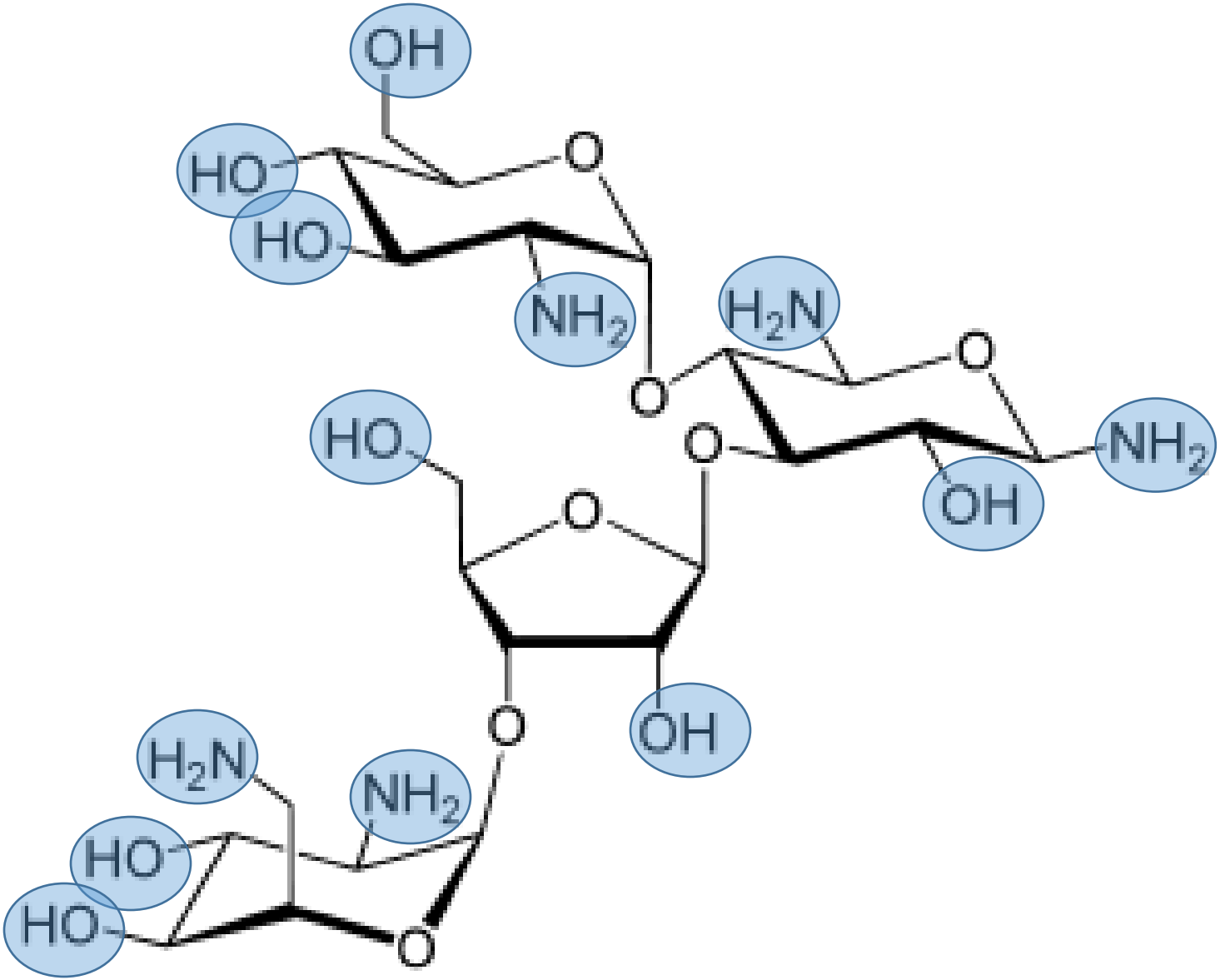
Orally activity

- Orally active agents are drugs either active locally in the GIT lumen (gastroenteritis) or must be absorbed into the blood circulation.

- Factors affecting oral activity:-
  - Chemical and enzymatic stability of drugs.
  - The physiological nature of the GIT lumen.

- The locally acting agents will act locally and must be stable in the GIT.
  - Given in active form or as a prodrug activated in GIT by special enzymatic reactions.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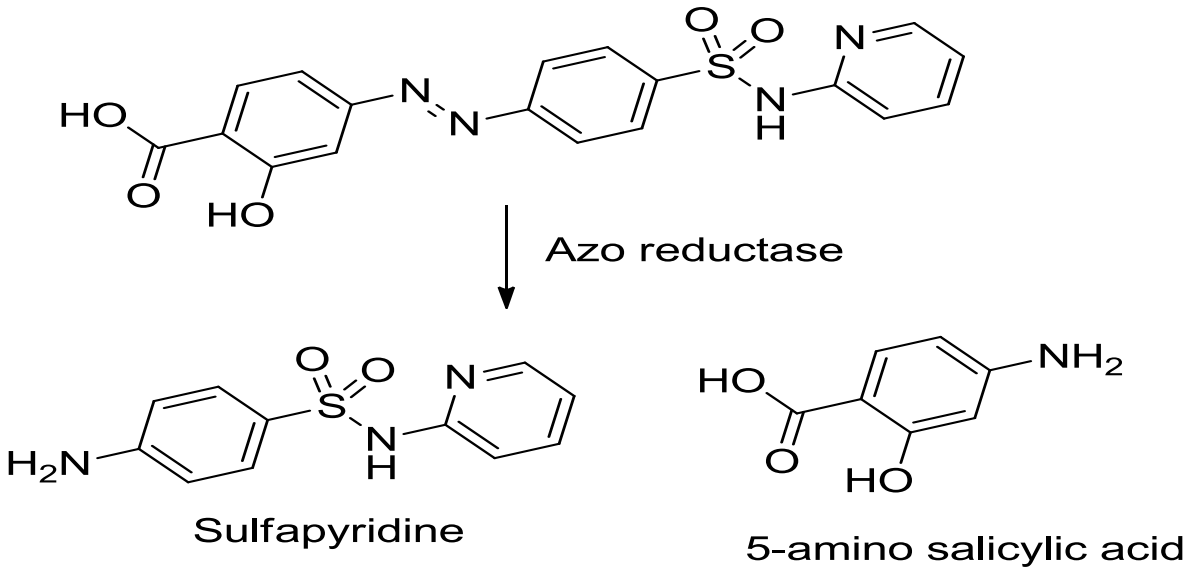
Orally activity

- Example:
  - Sulfasalazine; a commonly used drug in ulcerative colitis, although it will be given orally, small quantity will be absorbed.
  - It will be reduced by colorectal azoreductase to give the active sulfapyridine and *P*-aminosalicylic acid…both are actives.



Tissue Availability

- Tissue availability means the amount of the drug that reached the site of action or the target tissue.

- In most cases, tissue availability is lower than the oral availability due to one of the following factors:-
  - Extensive drug metabolism.
  - Blood protein binding.
  - Rapid drug excretion.
  - Deposition of drug in fat.
  - Many barriers need to be penetrated to reach the site of action.

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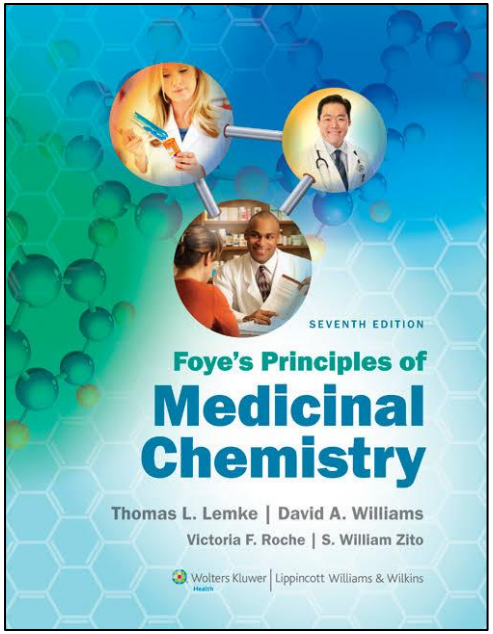

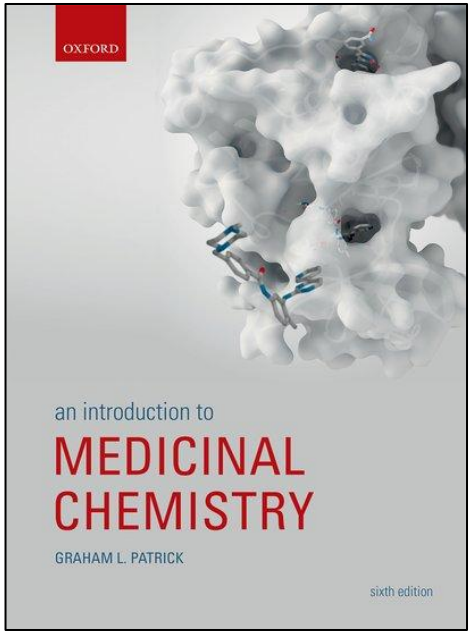

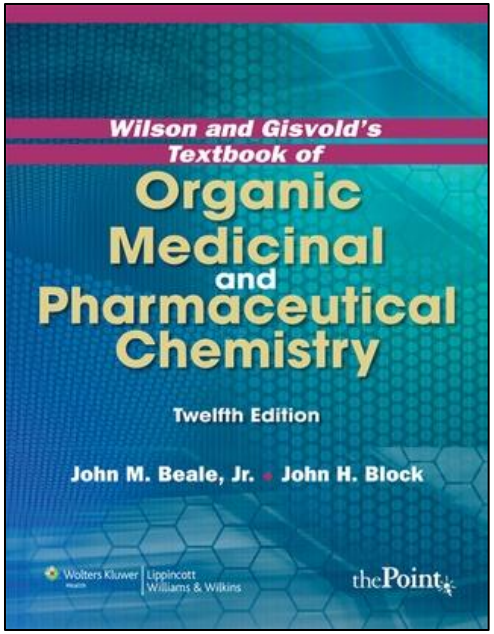

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3. Foyes principle of medicinal chemistry by David H. Williams, Thomas L. Leuke, Williams O. Foye. Lippincott William and Wilkins. 7th edition, 2013.


Thank
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