

# Acronyms Abound: DMPK and ADME in Drug Development

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## Overview

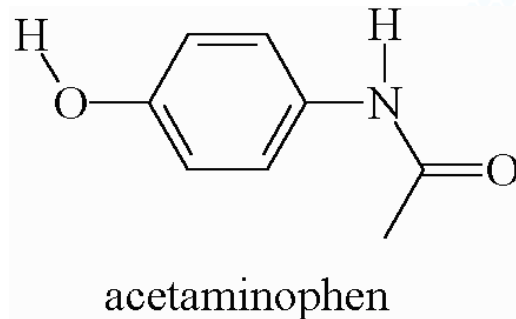
- Overarching aim of therapeutic drug development
- DMPK – Drug metabolism and pharmacokinetics
  - Based on ADME properties
  - Relates to DDI
- ADME properties
- A hint of DDI



# Chemical Compound to Therapeutic Drug

- Aim: get a compound with therapeutic benefit into the form of a practical medicine that can be dosed to patients, considering
  - Safety
  - Efficacy

Chemical compound



Synthetic powder



Therapeutic drug



# Developing Potential Therapies

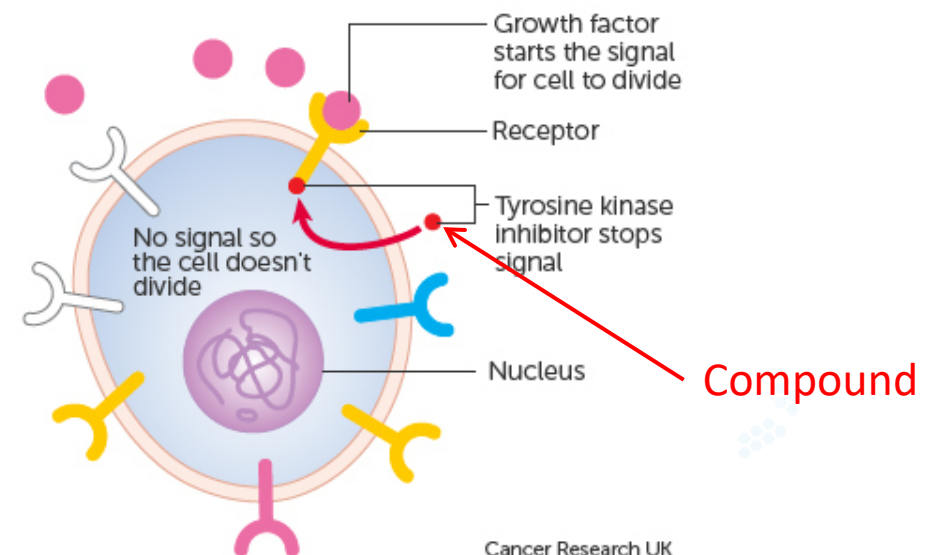
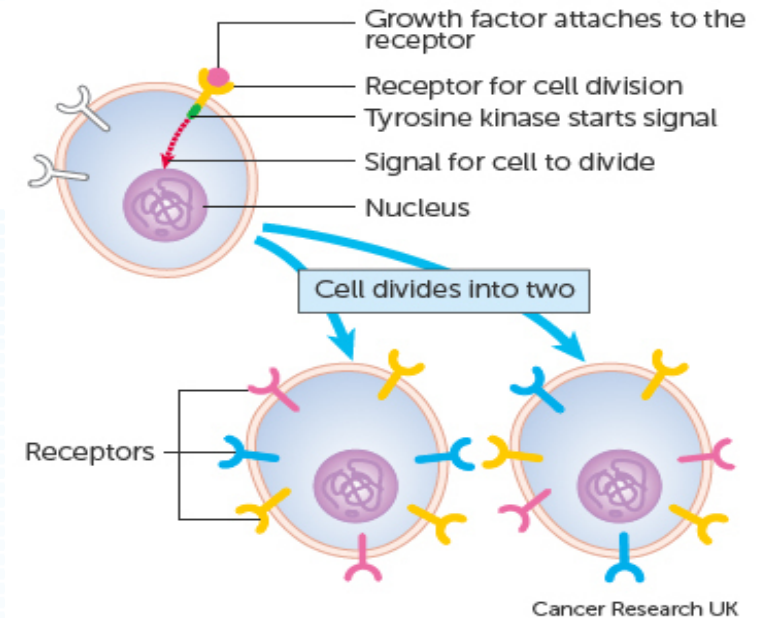
- Biological targets related to a disease state are selected
- Target: existing cellular structure or molecule related to disease state
- Initial objective: find chemical compounds that will interact with the target, with the idea they will impact the disease state
  
- But the compounds must be appropriate for human consumption, reach the site of action, exert therapeutic effects, and then be eliminated from the body
- DMPK science explores how that can happen....



## Receptor-Based Cancer Therapy

- Tyrosine kinases – enzymes involved in signaling to stimulate cell replication
- Cancer therapy
  - Tumor growth is impacted by cell proliferation
- Tyrosine kinase inhibitor therapies enter the cells and inhibit the kinases

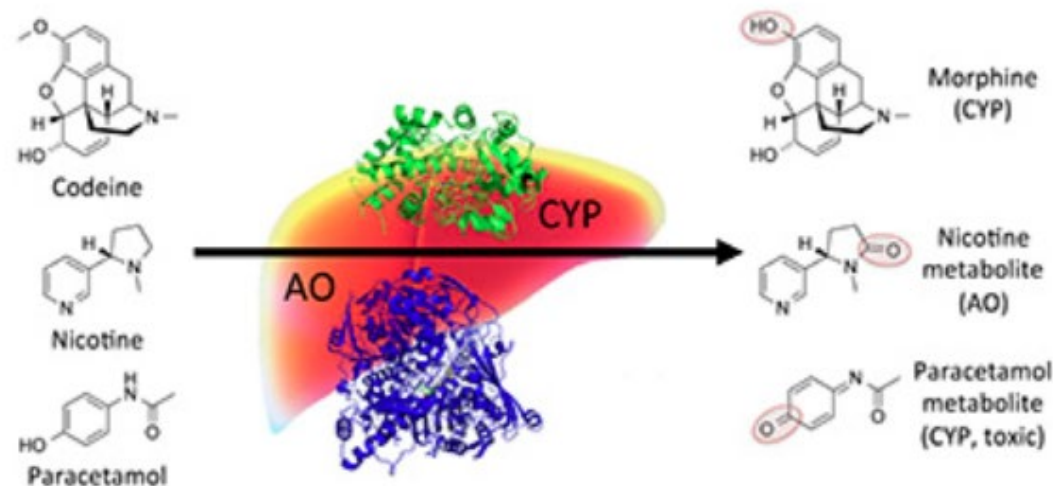
But the inhibitor compounds have to get to the receptors





# Drug Metabolism (DM) Vocabulary

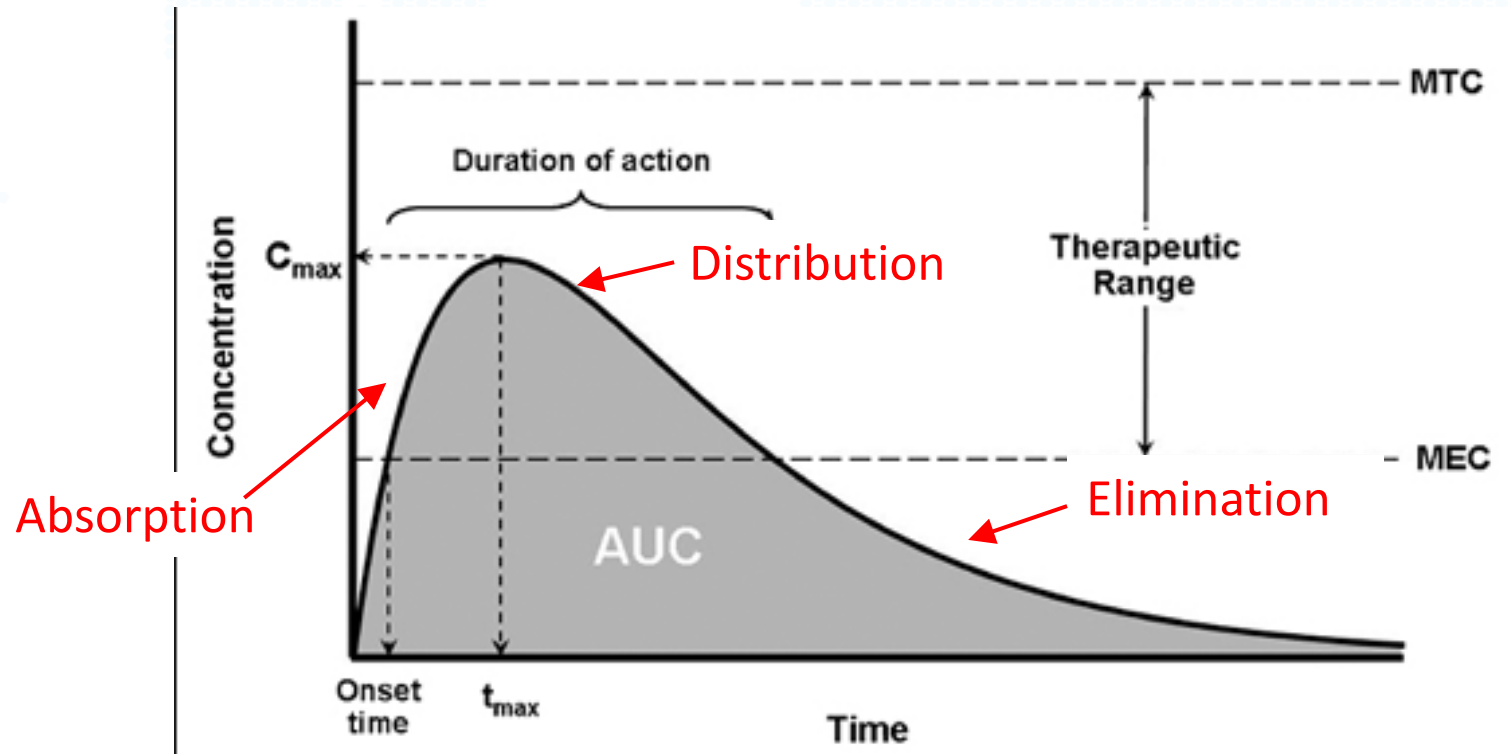
- Conversion of the drug compound into other related compounds
- Result of interaction with Drug Metabolizing Enzymes (DMEs)
- The new compounds are Metabolites



Retrieved from: [https://drug.ku.dk/disciplines/peptides-and-proteins/cytochrome\\_p450\\_and\\_drug\\_metabolism/](https://drug.ku.dk/disciplines/peptides-and-proteins/cytochrome_p450_and_drug_metabolism/)

# Pharmacokinetics (PK)

- Sometimes defined as what the body does to the drug
- Commonly associated with the plasma concentration-time curve



# ADME Properties

- Potential drugs need certain characteristics to become future therapies
- Compounds are evaluated for ADME/toxicology properties
  - Liberation
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**xcretion
  - Toxicology

Compounds with 'druggable' characteristics have ADME properties appropriate to move into development

$$\text{Disposition} = A + D + M + E$$

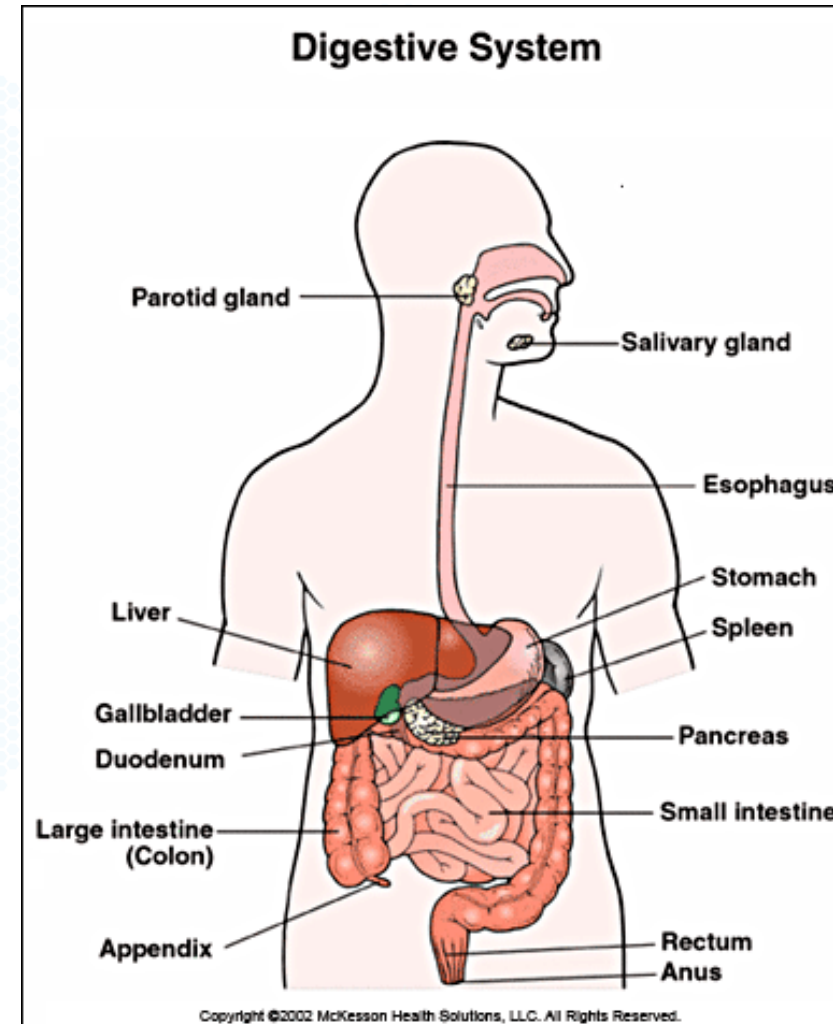
$$\text{Elimination} = M + E$$





## Absorption (Oral Drugs)

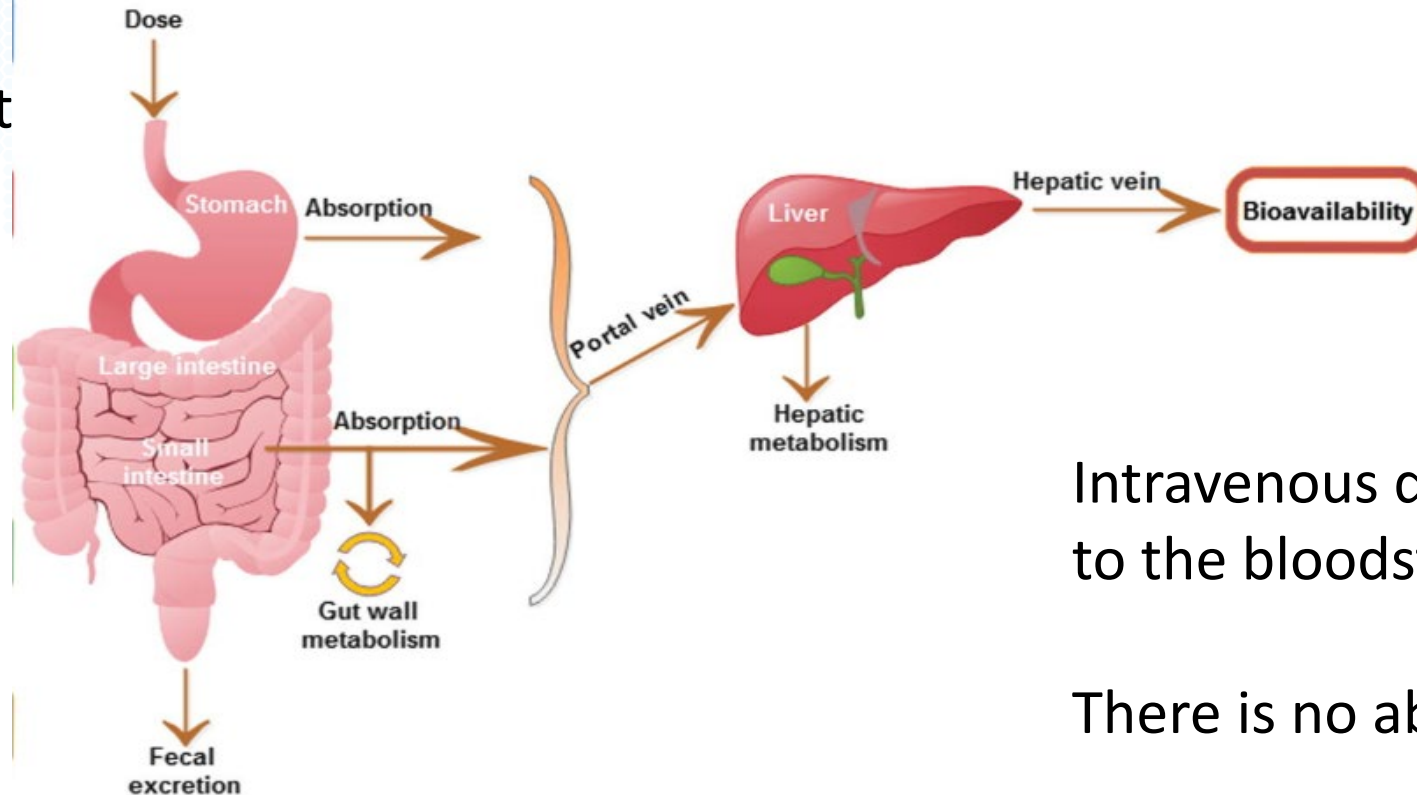
- Orally administered drugs are delivered to the gastrointestinal (GI) tract
- Compound has to be able to get into the bloodstream
- Biological barriers keep foreign substances out of cells
  - E.g., skin, cell membranes
- Affected by numerous characteristics
  - e.g., Solubility, dissolution, ionization, particle size, molecular size etc.



Retrieved from <http://cephalicvein.com/2016/05/gi-tract/>

# Oral vs. Intravenous Administration

Oral drugs traverse the gut and liver to get into the bloodstream



Intravenous drugs go directly to the bloodstream

There is no absorption phase

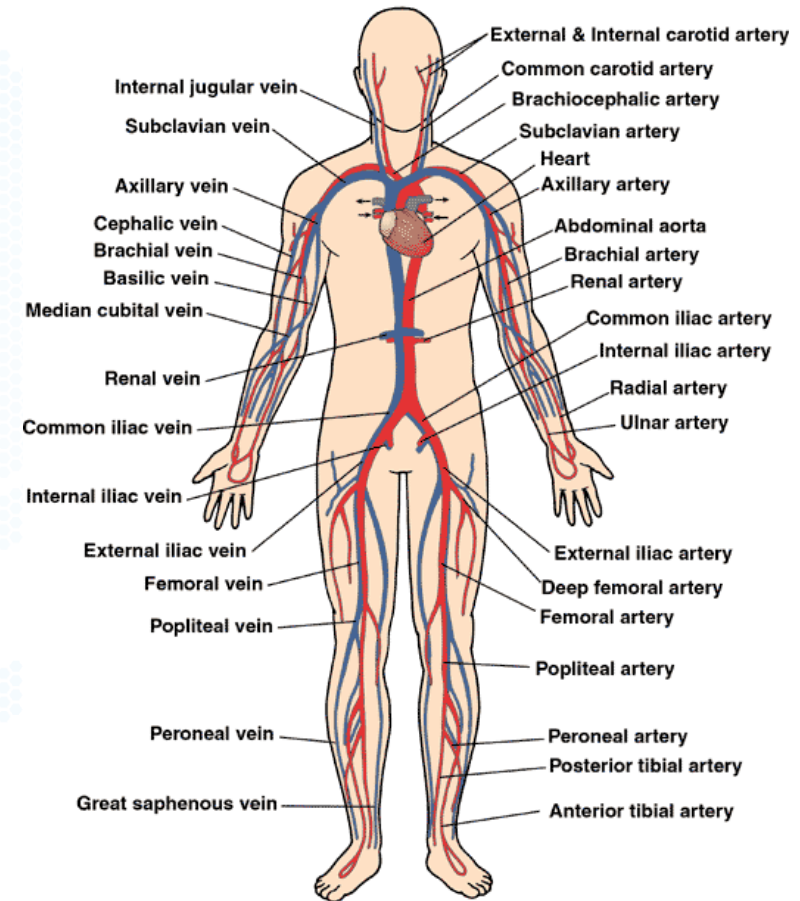
Ahmad et al., *Eur. J. Pharmaceut. And Biopharmaceut.* 2017, 112: 234-248.



## Distribution

- Drug moves to site of action – via bloodstream
- Biological considerations
  - Vascularity – where the blood vessels go
  - Transport – passive or active
  - Blood/placental barriers
  - Plasma binding proteins

Circulatory System

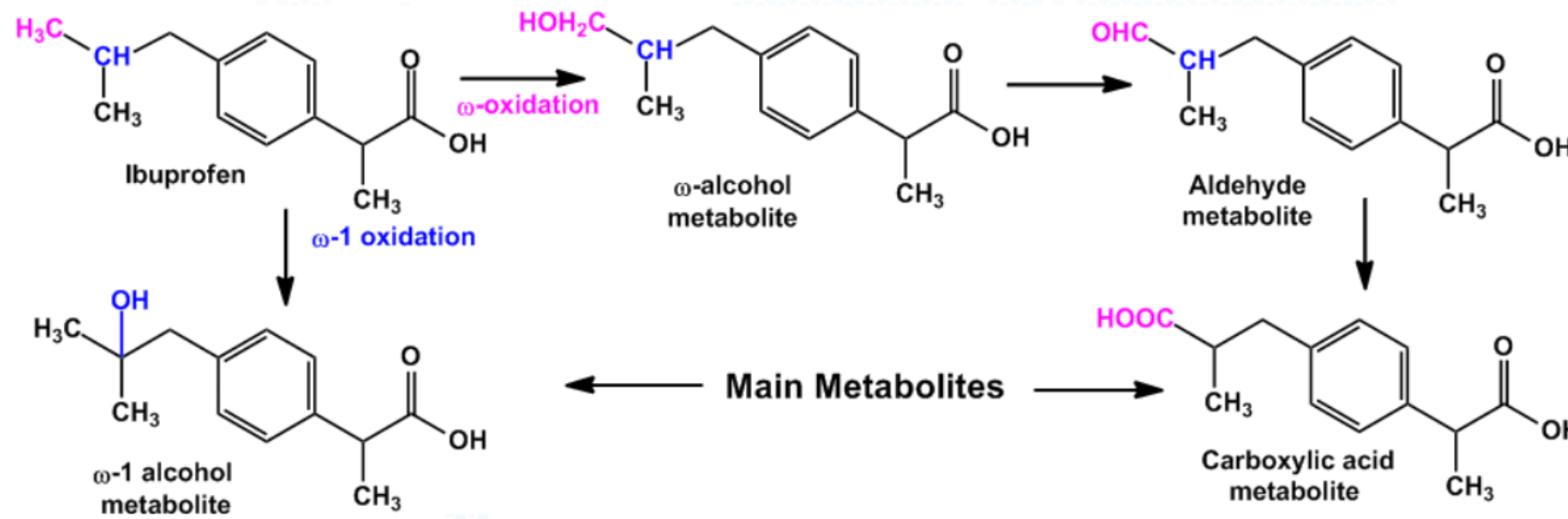


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Retrieved from <http://7mlkbodysystems.weebly.com/circulatory-system.html>

# Metabolism

- The biochemical structural modification of a drug
- Often changes the chemical structure of a lipophilic compound to make it more hydrophilic (water-soluble) for elimination
- Often by DMEs in the liver; sometimes intestines, kidney etc.



Retrieved from <https://pharmaxchange.info/2014/09/phase-i-metabolism-oxidative-reactions-oxidation-of-aliphatic-and-alicyclic-compounds/ibuprofen/>





## Excretion

- Irreversible loss of drug from system
- Drug-related material (drug and metabolites) has to be cleared from the organism
- Commonly occurs through
  - Kidneys (renal) - urine
  - Liver (biliary) - bile/feces
  - Lungs (respiratory) - breath
  - Other – sweat, tears, saliva







## Other Considerations

- Sometimes **liberation** and **toxicity** included in this (LADME/tox)
- Liberation is the release of the active substance from the delivery system, e.g., dissolution, disaggregation etc.
- Toxicity of a drug comprises drug-related side effects and adverse reactions/events caused by administration of a drug
- Toxicity is an important safety consideration for a potential new drugs in development



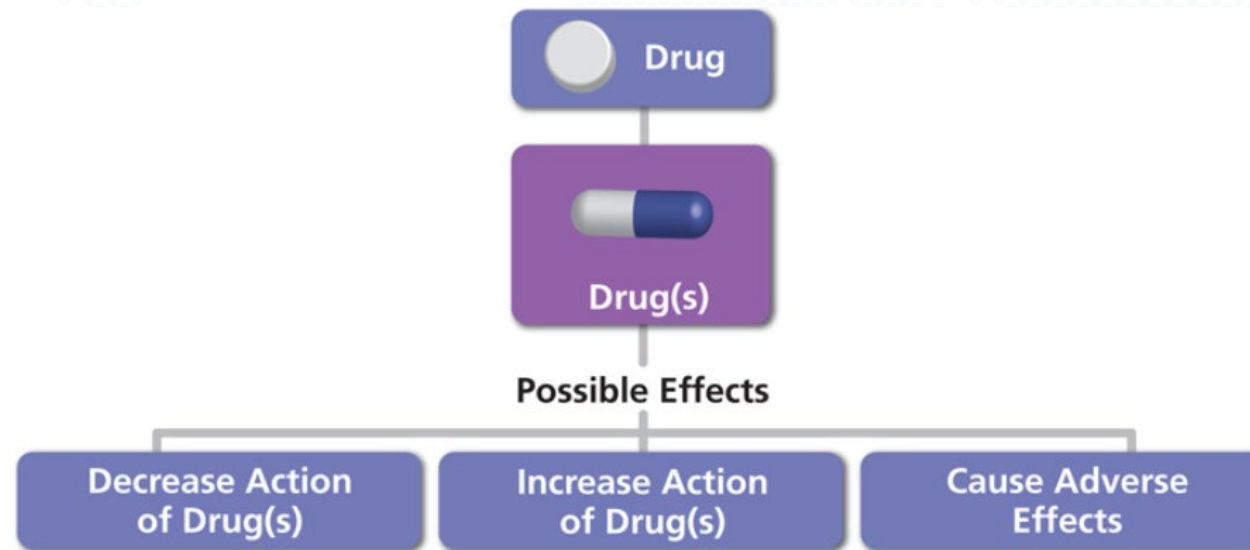
# Compounds with desirable ADME properties

- Get into the bloodstream (L+A)
- Move from the bloodstream to the site of action (D)
- Remain unchanged long enough to be active and are converted to safe metabolites (M)
- Completely excreted in urine/feces/breath (E)
- Do not cause harm to the organ or system (Tox)



## A Hint of Drug-Drug Interactions

- Drug-drug interactions – when a drug cause changes in the PK/ADME behaviors of a second coadministered drug
- Usually caused by a drug changing the available levels or activity of a DME or a drug transporter



Retrieved from <https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/213/drug-drug-interaction>



## Conclusions

- Drug development aims to turn compounds with impact on disease into viable therapies
- DMPK / ADME properties determine how that happens
- They also help predict DDI potential

