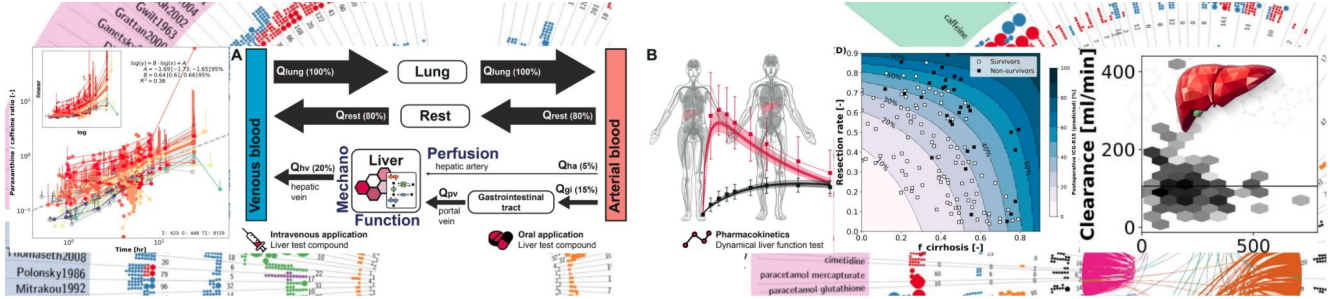

Pharmacokinetics Modeling Course

Absorption and Dosing

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Systems Medicine of the Liver
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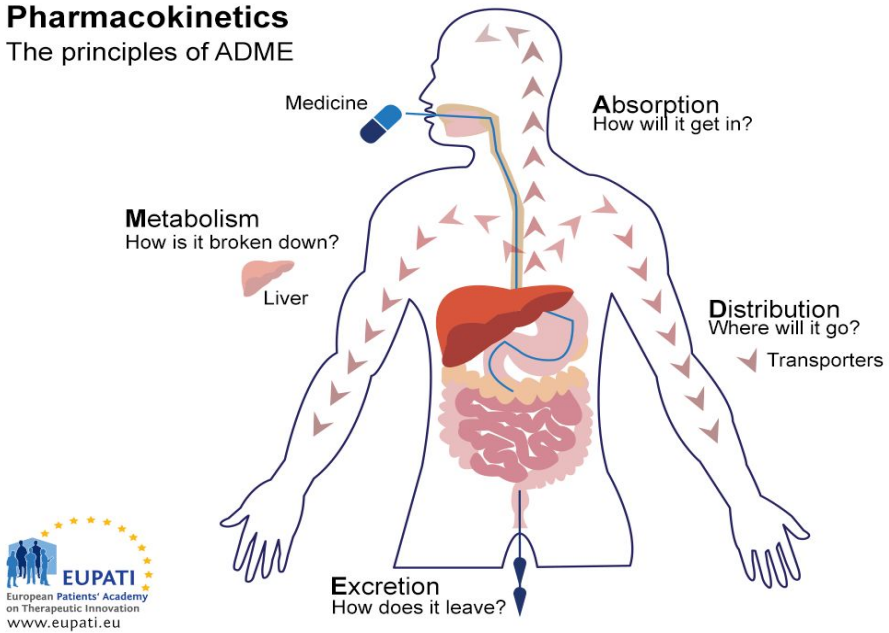
https://livermetabolism.com

🎯 Teaching Goals

By the end of this section, you should be able to:

1. Understand the principles of **drug absorption** and factors that influence it.
2. Describe common **routes of administration** and their impact on absorption.
3. Explain the concept of **bioavailability** and **first-pass metabolism**.
4. Explore models of **oral absorption** (e.g., **first-order**, **zero-order**, **lag time**).
5. Understand the relationship between **dosing**, **absorption rate**, and **plasma concentration**.
6. Compare **single vs. multiple dosing** and their effects on drug levels.
7. Apply absorption and dosing concepts to **optimize drug therapy**.

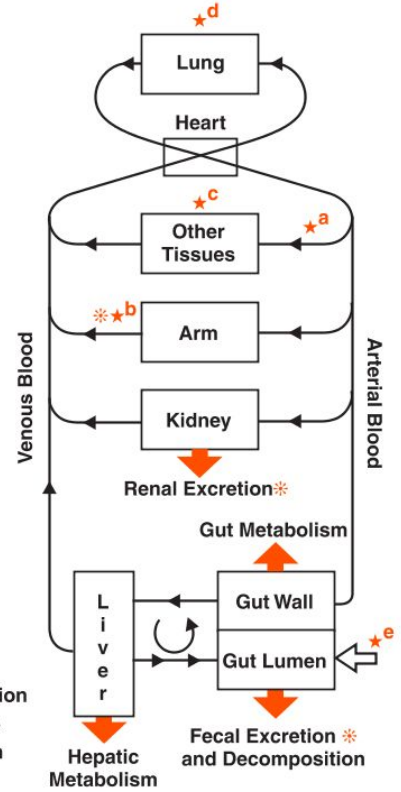
ADME



ADME processes determine pharmacokinetics

- **A**bsorption
- **D**istribution
- **M**etabolization
- **E**limination

Administration Sites



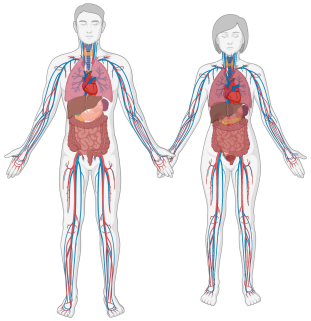


FIGURE 2-2 Once absorbed from any of the many sites of administration, drug is conveyed by blood to all sites within the body, including the eliminating organs. Sites of administration include: *a,* artery; *b,* peripheral vein; *c,* muscle and subcutaneous tissue; *d,* lung; and *e,* gastrointestinal tract, the most common route (denoted by *open arrow*). When given intravenously into an arm vein, the opposite arm should then be used for blood sampling. The movement of virtually any drug can be followed from site of administration to site of elimination.

many sites of administration

- a) artery
- b) peripheral vein (iv)
- c) muscle & subcutaneous tissue
- d) lung
- e) gastrointestinal tract (oral)

Tozer TN, Rowland M. **Essentials of pharmacokinetics and pharmacodynamics.** Second edition

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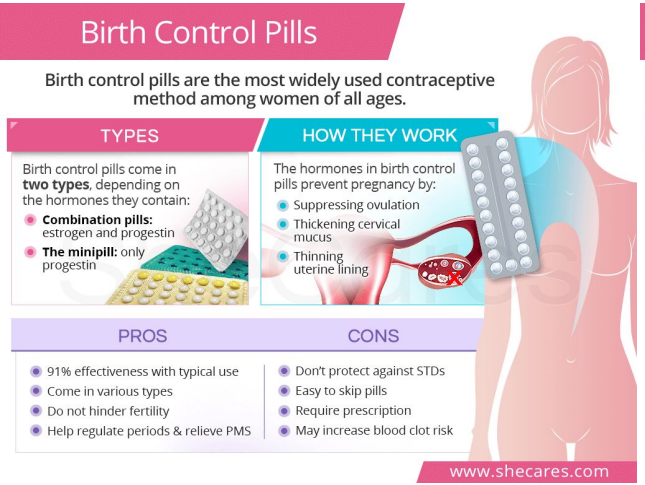
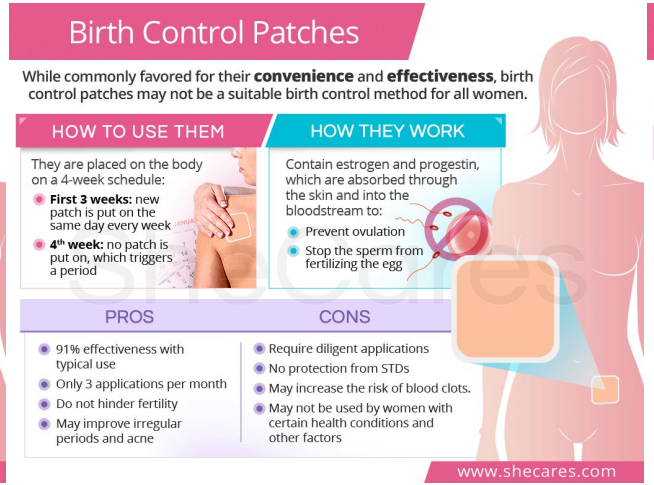
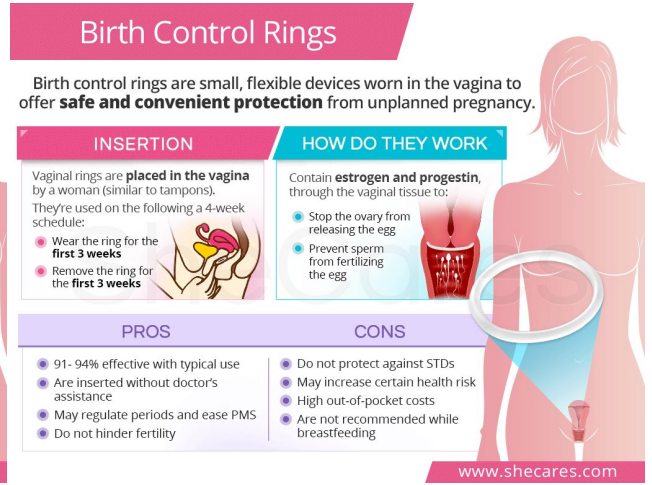
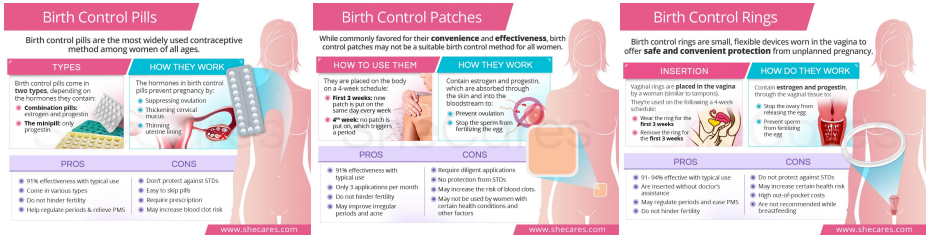
Application Forms: Contraceptives







Application Forms: Contraceptives



Ethinylestradiol: synthetic estrogen used in combination contraceptives

Mechanism of Action: inhibits ovulation by suppressing the hypothalamic-pituitary-ovarian axis.

Various routes of administration

- **Oral**: most common route, typically in combination with a progestin in oral contraceptive pills.
- **Transdermal**: patches that release ethinylestradiol and a progestin through the skin.
- **Vaginal**: vaginal rings that release ethinylestradiol and a progestin directly into the vaginal tissues and bloodstream.
- **Injectable**: Occasionally used in combination with a progestin in long-acting injectable contraceptives

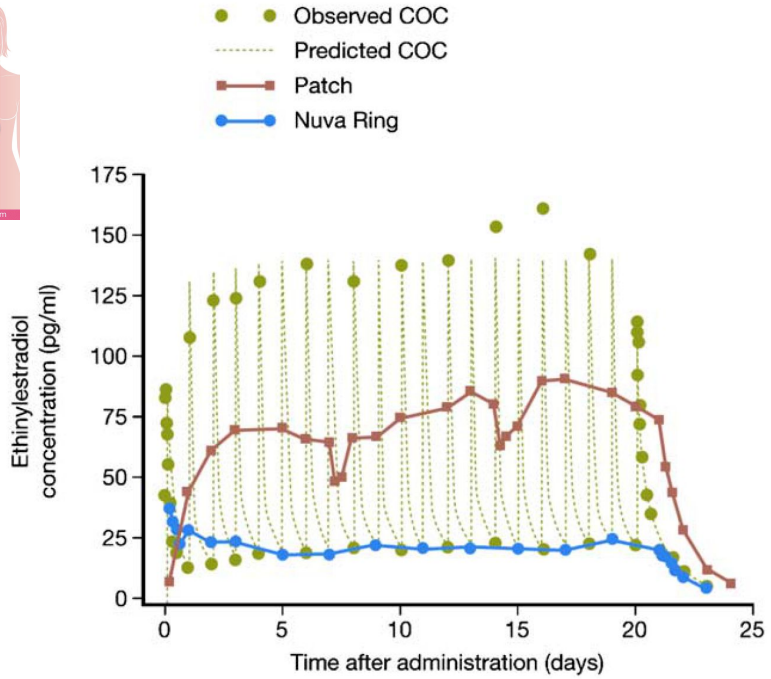


Fig. 2. Mean EE C-t curves for subjects (ASPE group) treated with NuvaRing ($n = 8$), the transdermal contraceptive patch ($n = 6$) and the COC ($n = 8$).

van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC. **Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive.** Contraception. 2005 Sep;72(3):168-74. doi: 10.1016/j.contraception.2005.03.005. PMID: 16102549.

Absorption

Various factors can influence drug absorption, including:

1. Route of Administration: The route of administration significantly impacts how a drug is absorbed. For instance, drugs administered intravenously bypass the absorption process as they are introduced directly into the bloodstream. However, orally administered drugs must pass through the stomach and intestines, where they are absorbed into the bloodstream. This can be influenced by factors such as pH levels, presence of food, and gastrointestinal motility.

2. Drug Formulation: The physical and chemical properties of the drug can influence how well it is absorbed. For example, drugs formulated in a liquid solution are often absorbed more rapidly than those in a tablet or capsule.

3. Physiological Factors: Individual characteristics like age, sex, genetic factors, and health status can also influence drug absorption. For example, certain conditions like malabsorption syndromes or diseases affecting the liver or kidney can alter the absorption of drugs.

4. Drug Interactions: Certain drugs can interact in the body and affect absorption. For instance, some medications can increase stomach acidity, which can affect the absorption of other drugs.

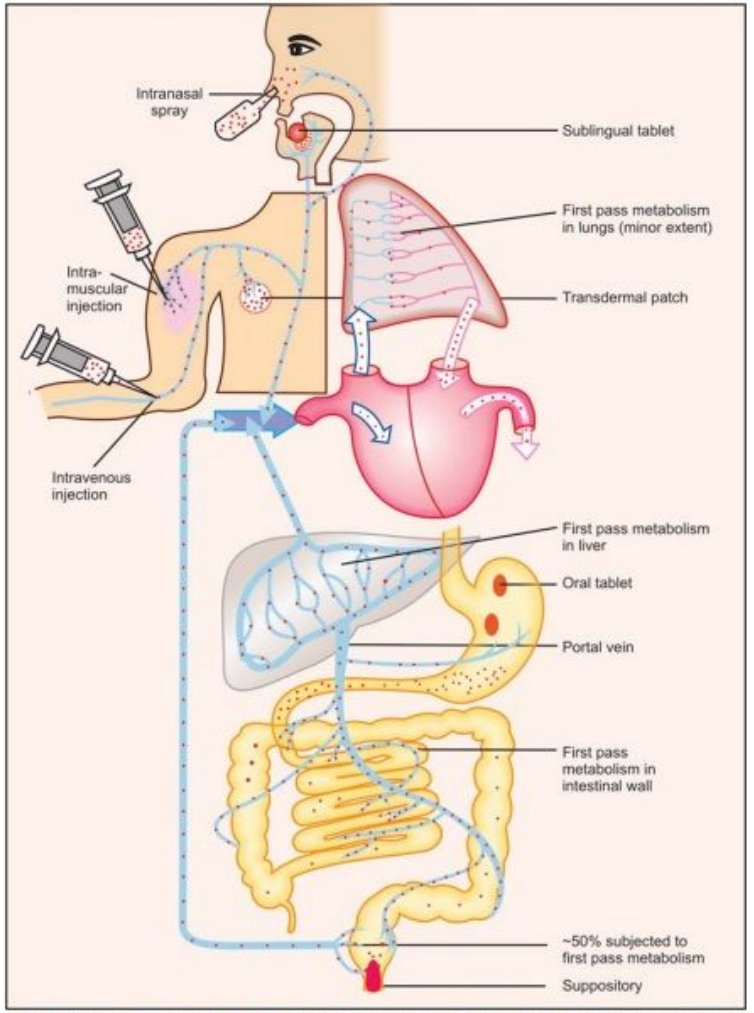


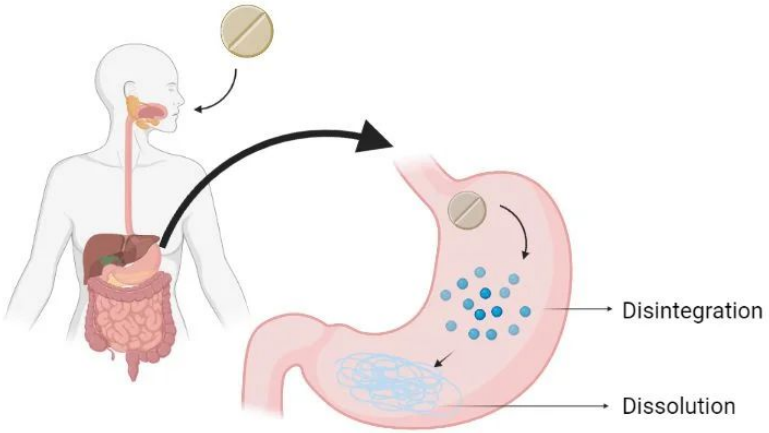
Fig. 1.1: Vascular pathway of drugs absorbed from various systemic routes of administration and sites of first pass metabolism

Dissolution of Oral Medication

Dissolution: process by which a solid drug disintegrates and dissolves in a solvent (like gastrointestinal fluids) to form a solution that can be absorbed into the body.

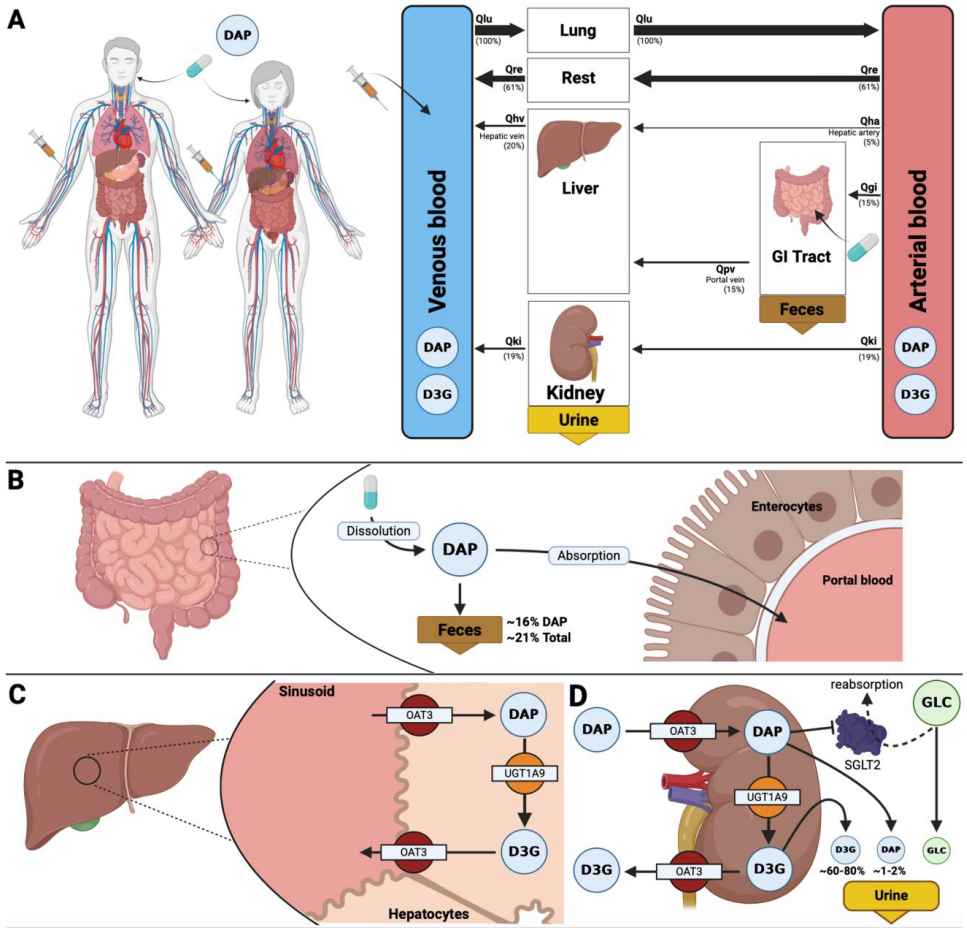
- Dissolution is crucial for drug absorption in solid dosage forms.
- The dissolution rate depends on the drug's solubility.
- Drug **formulation** can significantly impact dissolution rate.
- The rate of dissolution can influence **drug bioavailability**.
- In vitro dissolution testing is used to estimate how a drug will dissolve and be absorbed in the body.
- Physiological conditions like pH, motility, and the presence of food can affect drug dissolution.

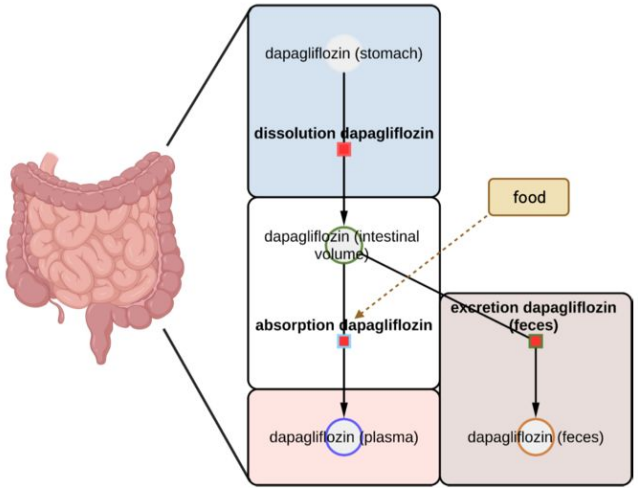
In essence, dissolution is vital in pharmaceutical science to ensure the drug dissolves properly for effective absorption and therapeutic effect.

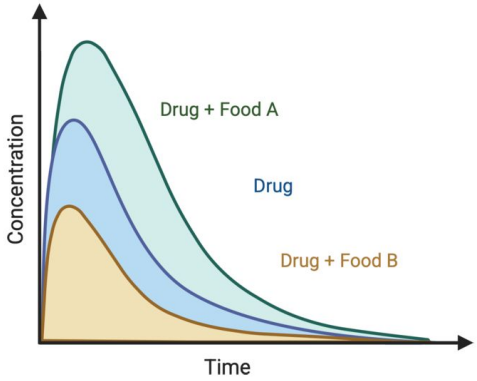


https://www.pharmacistopinions.com/adme-in-pharmacokinetics/
https://www.britannica.com/science/small-intestine

Example: Food Effect Dapagliflozin







Example: Food Effect Dapagliflozin

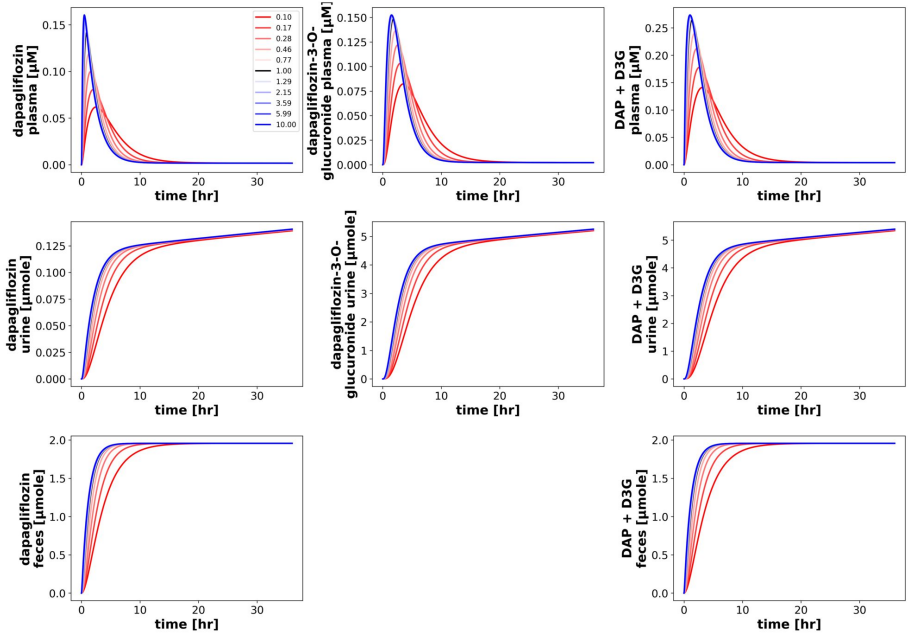


Figure 25: **Pharmacokinetic simulations of dapagliflozin under food-effect conditions.** Simulated concentrations of dapagliflozin (DAP), dapagliflozin-3-O-glucuronide (D3G) and dapagliflozin total (DAP+D3G) in plasma, urine and feces over time.

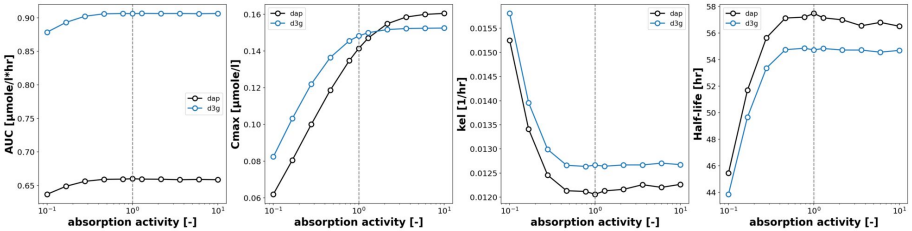
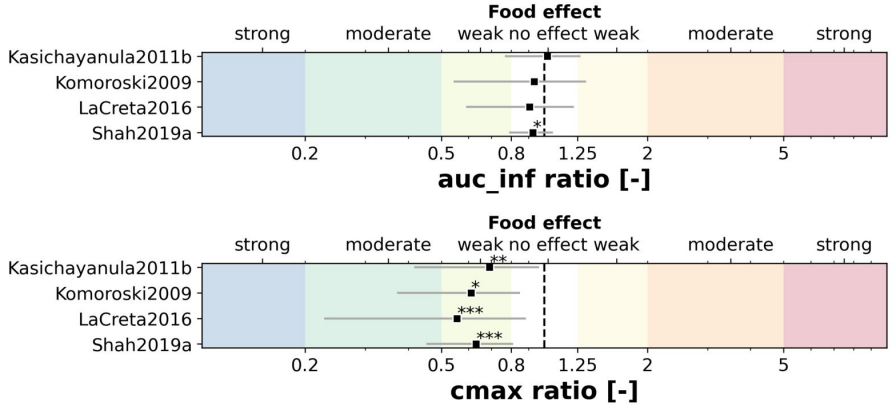
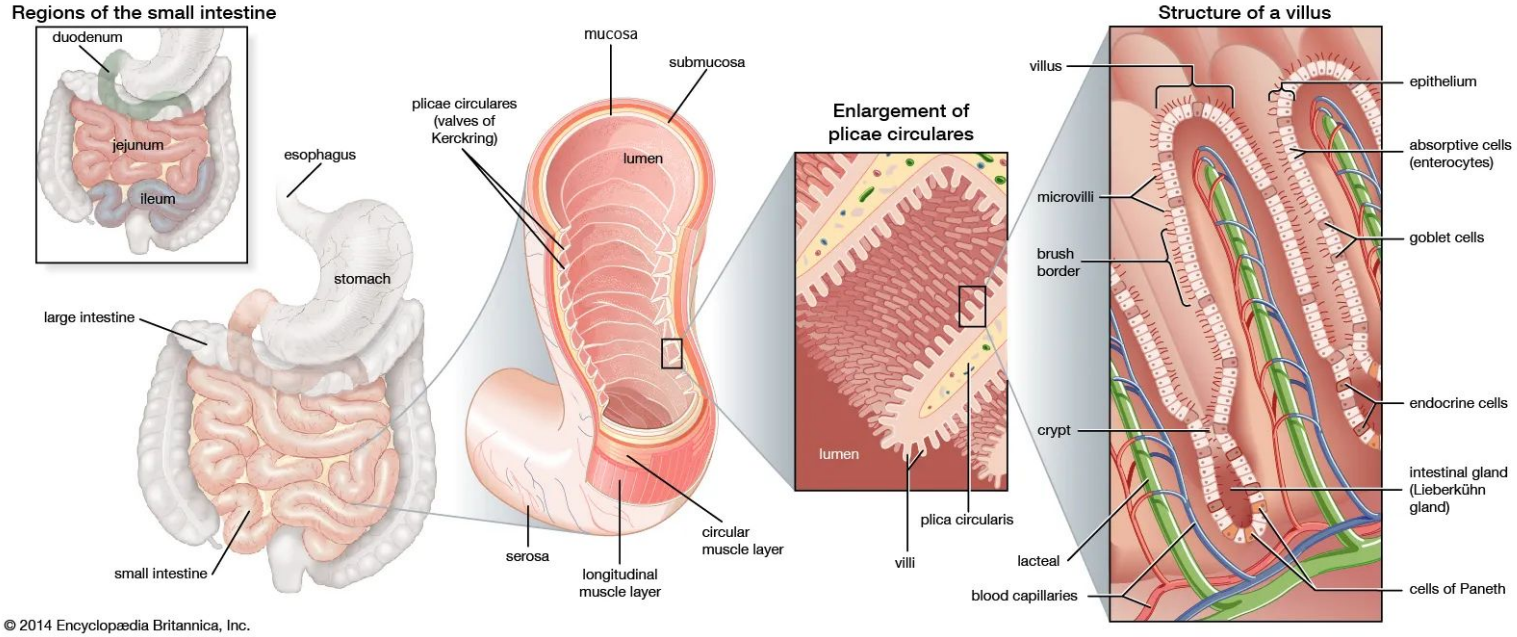


Figure 27: **Pharmacokinetic parameters of dapagliflozin and dapagliflozin-3-O-glucuronide for absorption activity scan.** AUC, C_{max}, kel and half-life for absorption activity of dapagliflozin (black) and dapagliflozin-3-O-glucuronide (blue).



Absorption of Oral Medication in the Intestine



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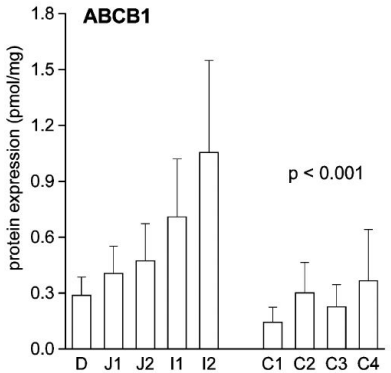
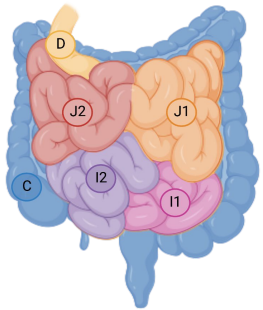
https://www.britannica.com/science/small-intestine

Site-dependent Absorption

- transporters/processes specific to certain intestinal segments
- E.g. ABCB1





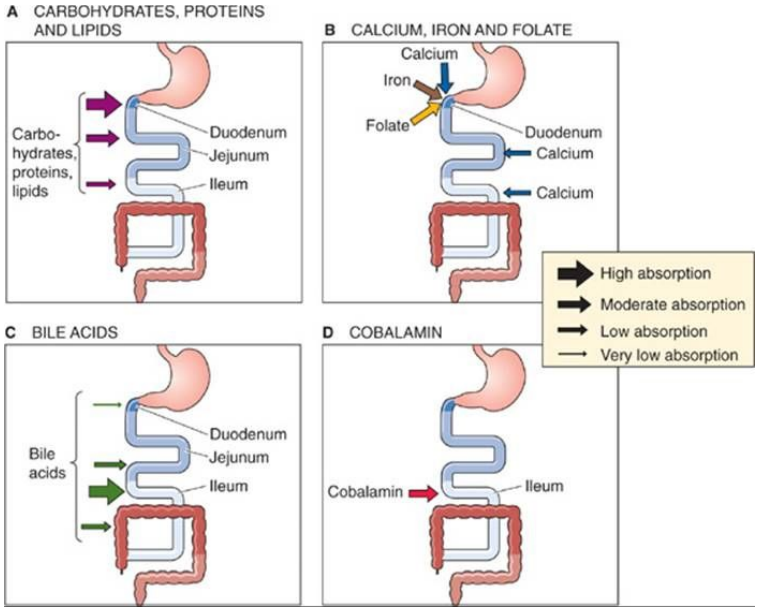


Figure 45-2 Sites of nutrient absorption. **A**, The entire small intestine absorbs carbohydrates, proteins, and lipids. However, the absorption is greatest in the duodenum, somewhat less in the jejunum, and much less in the ileum. The thickness of the *arrows in the inset* indicates the relative magnitude of total absorption at the indicated site in vivo. The maximal absorptive capacity of a specific segment under *optimized* experimental conditions (e.g., substrate concentrations) may be greater. **B**, Some substances are actively absorbed only in the duodenum. **C**, Bile acids are absorbed along the entire small intestine, but active absorption occurs only in the ileum. **D**, The vitamin cobalamin is absorbed only in the ileum.

https://www.britannica.com/science/small-intestine

Bioavailability

Bioavailability

Due to losses during absorption, intestinal metabolism, efflux and hepatic extraction only a fraction of the drug appears in the systemic circulation.

Clinical implications

- **Delays or loss of drug during absorption** can introduce a large variability in drug response.
- **Disease conditions** and **co-medications** may profoundly affect the absorption of certain drugs.

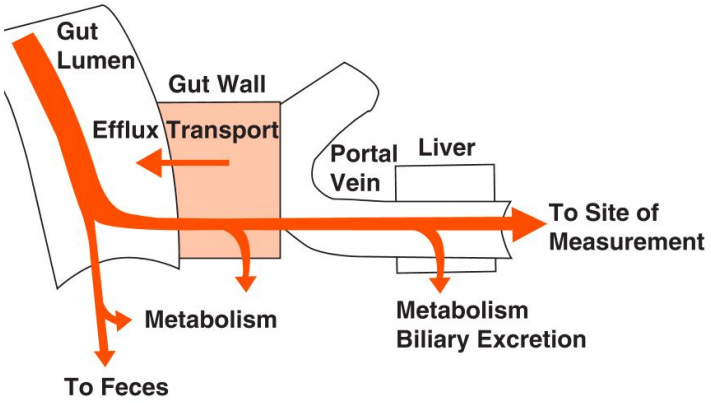


FIGURE 2-3 A drug, given as a solid, encounters several barriers and sites of loss in its sequential movement (colored arrows) through the gastrointestinal tissues and the liver. Incomplete dissolution, degradation in the gut lumen, metabolism by enzymes, and efflux by transporters, in the gut wall are causes of incomplete input into the systemic circulation. Removal of drug as it first passes through the liver may further reduce systemic input.

Table 1. Some Common Drugs with Low Oral Bioavailability and Susceptibility to First-Pass Drug Interactions.

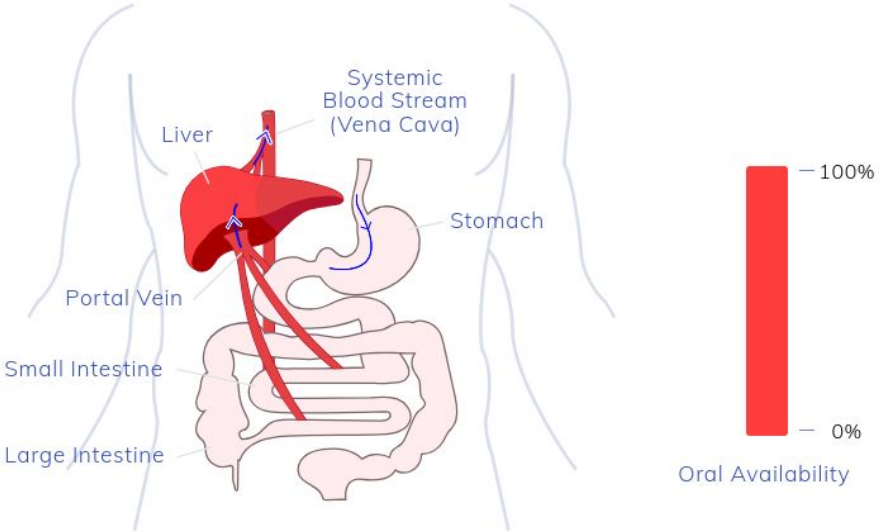
Drug	Metabolizing Enzyme	Bioavailability*
		percent
Amiodarone	CYP3A	46±22
Amitriptyline	CYP2D6, CYP3A	48±11
Aspirin	Esterases	68±3
Bromocriptine	CYP3A	3–6
Captopril	S-methyltransferase	~75
Codeine	Glucuronosyltransferase	50±7
Cyclosporine	CYP2C9, CYP3A	28±18
Desipramine	CYP2D6	38±13
Diclofenac	CYP2C9	54±2
Diltiazem	CYP3A	38±11
Erythromycin	CYP3A	35±25
Felodipine	CYP3A	15±8
Imipramine	CYP1A2, CYP2D6, CYP3A	42±3
Labetalol	Glucuronosyltransferase	18±5
Losartan	CYP2C9, CYP3A	36±15
Lovastatin	CYP3A	<5
6-Mercaptopurine	TPMT	12±7
Metoprolol	CYP2D6	38±14
Midazolam	CYP3A	44±17
Morphine	Glucuronosyltransferase	24±12
Naloxone	Glucuronosyltransferase	~2
Nefazodone	CYP2C9, CYP3A	15–23
Nicardipine	CYP3A	18±11
Nimodipine	CYP3A	10±4
Omeprazole	CYP2C19, CYP3A	53±29
Propafenone	CYP2D6	5–10
Propranolol	CYP2D6, CYP1A2	26±10
Saquinavir	CYP3A	4–13
Spironolactone	Thioesterase	25±9
Tacrine	CYP1A2	17±3
Tacrolimus	CYP3A	25±10
Terbutaline	Sulfotransferase	14±2
Triazolam	CYP3A	44
Venlafaxine	CYP2D6, CYP3A	10–45
Verapamil	CYP3A	22±8

* Plus–minus values are means ±SD.

Tozer TN, Rowland M. **Essentials of pharmacokinetics and pharmacodynamics.** Second edition
Wilkinson GR. **Drug metabolism and variability among patients in drug response.** N Engl J Med. 2005 May 26;352(21):2211-21. doi: 10.1056/NEJMra032424. PMID: 15917386.

🏃 Bioavailability 🏃

https://www.icp.org.nz/oral-availability/oral-availability



Drug Absorption	Poor	Good
First Pass Metabolism	Low	High

Example: oral semaglutide

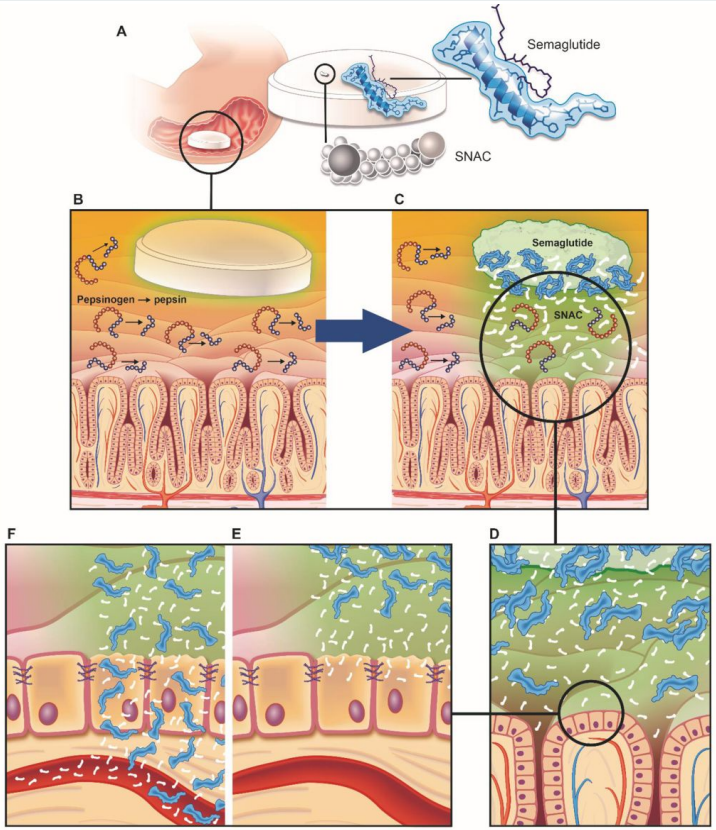
- first available oral GLP-1 agonist
- mimic the action of GLP-1, a hormone that enhances glucose-dependent insulin secretion, inhibits glucagon release, and slows gastric emptying

A) semaglutide is co-formulated with absorption enhancer SNAC

B-C) highly localized release of SNAC which neutralizes pH and prevents conversion of pesinogen → pepsin

D) SNAC weakens semaglutide self-interactions

E-F) SNAC inserts in the mucosa membrane



Kim HS, Jung CH. **Oral Semaglutide, the First Ingestible Glucagon-Like Peptide-1 Receptor Agonist: Could It Be a Magic Bullet for Type 2 Diabetes?** Int J Mol Sci. 2021 Sep 14;22(18):9936. doi: 10.3390/ijms22189936.

Unerwartete Schwangerschaften unter Abnehmspritze

Montag, 3. Juni 2024

Newsletter abonnieren | Zur Startseite

/AntonioDiaz, stock.adobe.com

Berlin – Derzeit erregen national wie international Meldungen in den sozialen Medien Aufmerksamkeit, wonach Frauen unter dem Abnehm- und Diabetesmedikament Semaglutid unerwartet und ungeplant schwanger geworden seien. Das könne selbst unter Kontrazeptionsschutz geschehen, heißt es in Artikeln mit Schlagzeilen wie „Warum ‚Ozempic-Babies' kein Grund zur Freude sind" oder „Ozempic-Babies".

Ozempic ist der Handelsname für den GLP-1-Rezeptoragonisten Semaglutid als Diabetespräparat, die höher dosierte Variante zur Gewichtsabnahme mit demselben Wirkstoff heißt Wegovy – beides vom Hersteller Novo Nordisk.

Im Wesentlichen werden für die erhöhte Wahrscheinlichkeit, schwanger werden zu können, 2 Gründe diskutiert: Zum einen könnte die Gewichtsabnahme als solche dafür verantwortlich sein, zum anderen eine Veränderung der Magen-Darm-Passage und konsekutiv einer Veränderung der Resorption von Hormonpillen, die zur Verhütung eingenommen werden.

- Ozempic-Babies (Wegovy)
- possible explanations
  - weight loss and normalization of hormonal balance
  - altered stomach passage

Example absorption models

A. first-order absorption with different rate of absorption
B. first-order absorption with different lag-times
C. Transit chain (n=3, different rates)
D. Transit chain (different n)

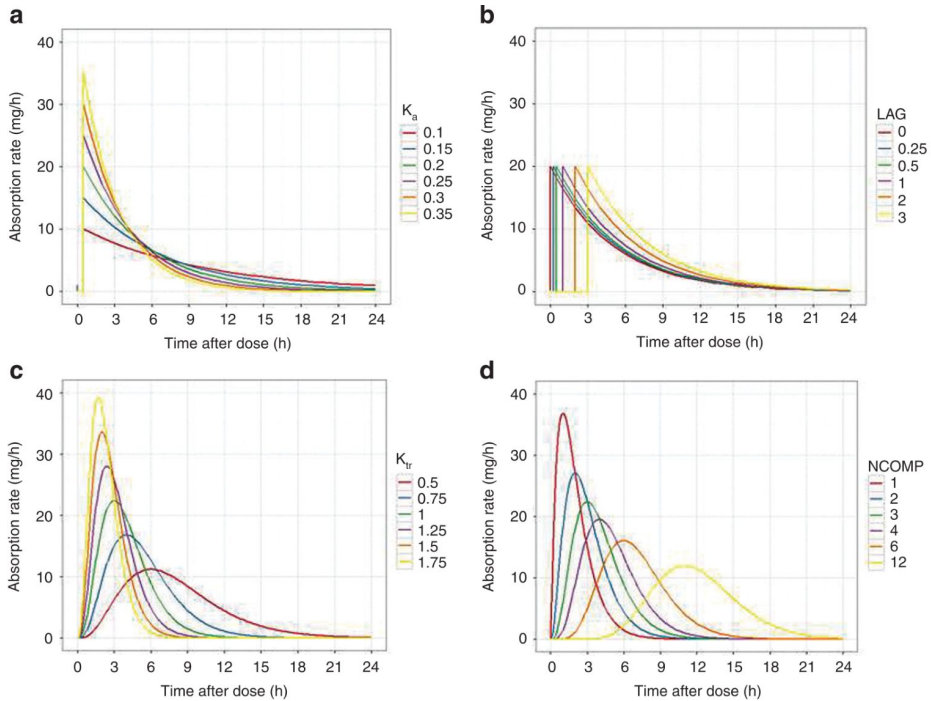


Figure 1 Models of extravascular absorption. The time profile of absorption rate for selected absorption models. (**a**) A first-order absorption model with different values of the absorption rate constant (k_a). Absorption lag was 0.5 h in all cases. (**b**) A first-order absorption model with different values of the absorption lag (LAG). Absorption rate constant was 0.5/h in all cases. (**c**) A three-compartment transit chain model with different values of the transit chain rate constant (k_{tr}). Note that decreasing the rate constant lowers the overall absorption rate and delays the time of its maximum value. (**d**) Transit chain models with different numbers of transit chain compartments (NCOMP). The transit chain rate constant was 1/h in all cases. Note that increasing the number of compartments introduces a delay before absorption, and functionally acts as a lag. The dose was 100 mg in all cases (hence the area under the curve should be 100 mg for all models).

Mould DR, Upton RN. **Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods.** CPT Pharmacometrics Syst Pharmacol. 2013 Apr 17;2(4):e38. doi: 10.1038/psp.2013.14. PMID: 23887688; PMCID: PMC3636497.

Drug formulation

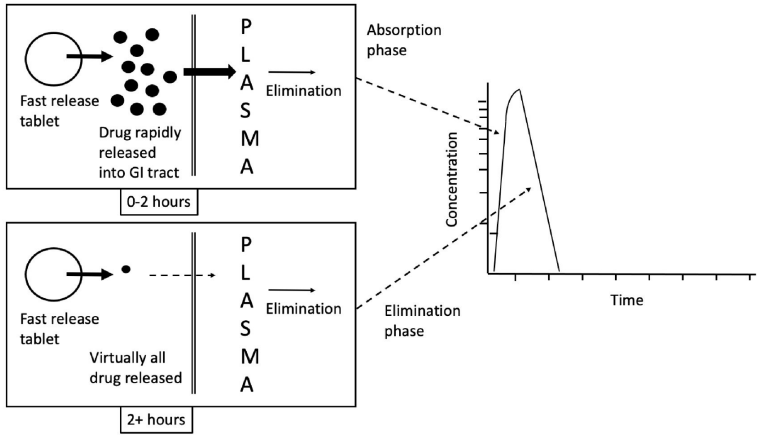


Figure 8: illustration of how the absorption and elimination phases are affected by rapid release of drug into the gastrointestinal tract (GI Tract).

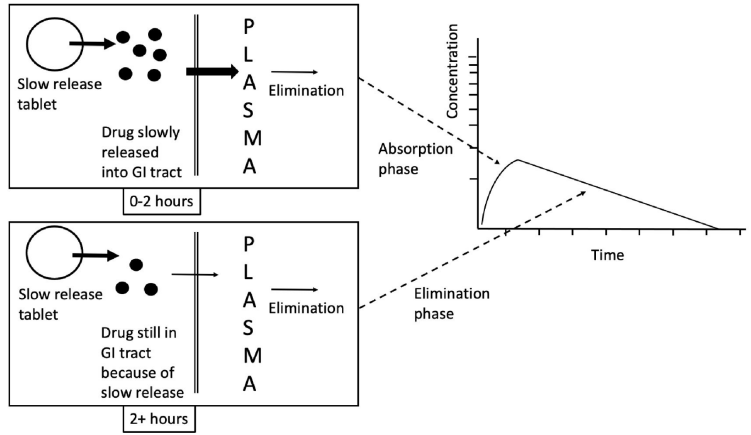
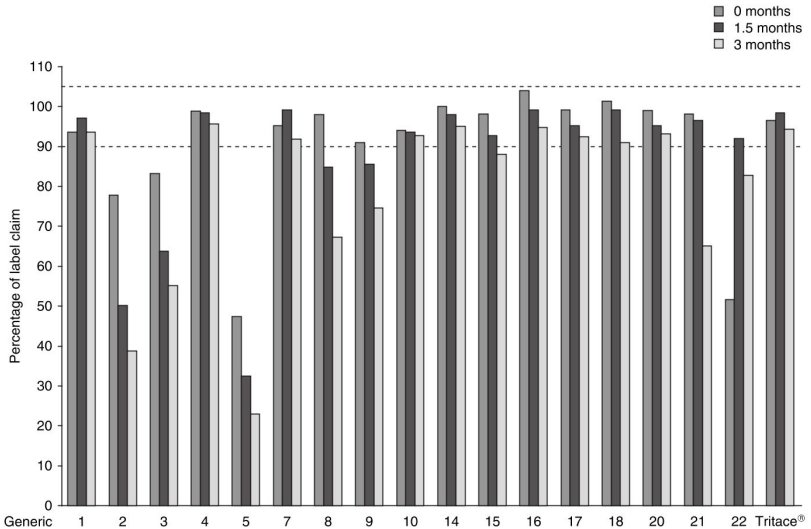


Figure 9: illustration of flip-flop kinetics caused by slow release of drug into the gastrointestinal tract (GI Tract).

Lappin & Seymour 2022. **Clinical Pharmacokinetics From The Beginning: A Practical Approach.**

Variability in Dose & Dissolution



Generic	1	2	3	4	5	7	8	9	10	14	15	16	17	18	20	21	22	Tritace®
0 months	93.6 (1.7)	77.6 (4.2)	83.2 (27.0)	98.8 (1.4)	47.2 (2.2)	95.2 (1.4)	98 (2.2)	90.8 (6.3)	94 (1.6)	100 (1.8)	98 (4.0)	104 (7.3)	99.2 (5.9)	101.2 (5.3)	98.8 (2.1)	98 (2.2)	51.6 (52.9)	96.4 (2.6)
1.5 months	97.2 (2.2)	50 (9.1)	63.6 (31.0)	98.4 (0.9)	32.4 (3.5)	99.2 (4.4)	84.8 (2.3)	85.6 (9.7)	93.6 (1.0)	98.0 (1.5)	92.8 (2.7)	99.2 (8.0)	95.2 (2.2)	99.2 (5.8)	95.2 (3.1)	96.4 (1.1)	92 (3.0)	98.4 (1.7)
3 months	93.6 (2.3)	38.8 (5.1)	55.2 (38.9)	95.6 (1.2)	22.8 (5.8)	91.6 (3.1)	67.2 (5.8)	74.4 (4.1)	92.8 (2.3)	95.2 (2.5)	88.8 (3.4)	94.8 (5.0)	92.4 (5.0)	90.8 (4.3)	93.2 (1.3)	65.2 (2.6)	82.8 (2.8)	94.4 (3.3)

Fig. 2. Assay of ramipril levels vs label claim. Percentage of ramipril in 17 ramipril generics/copies vs the reference ramipril product (Tritace®) before and after 1.5 and 3 months of temperature-stressed storage, as determined using a validated high-performance liquid chromatography system (see Materials and Methods section for details of the assay).[16] Results represent the mean (relative standard deviation) of the average values for ten individual tablets. No data are reported for Generics 6, 11, 12, 13 and 19 as the assays for these were not completed because of a shortage of tablets. Sanofi-Aventis specification limits (within 90–105% of label claim) are illustrated by the dotted lines.

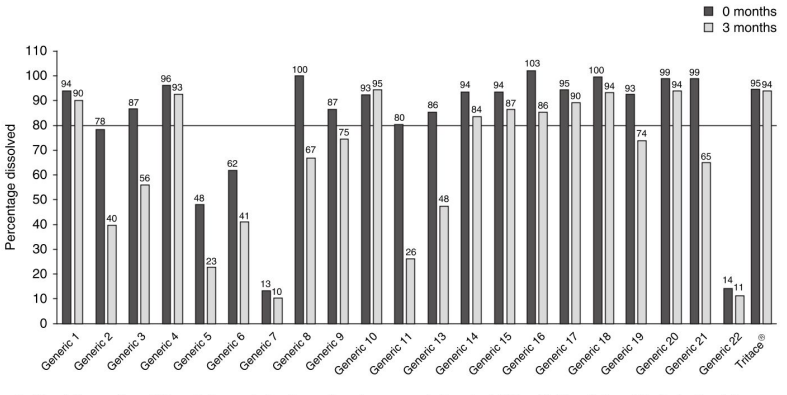


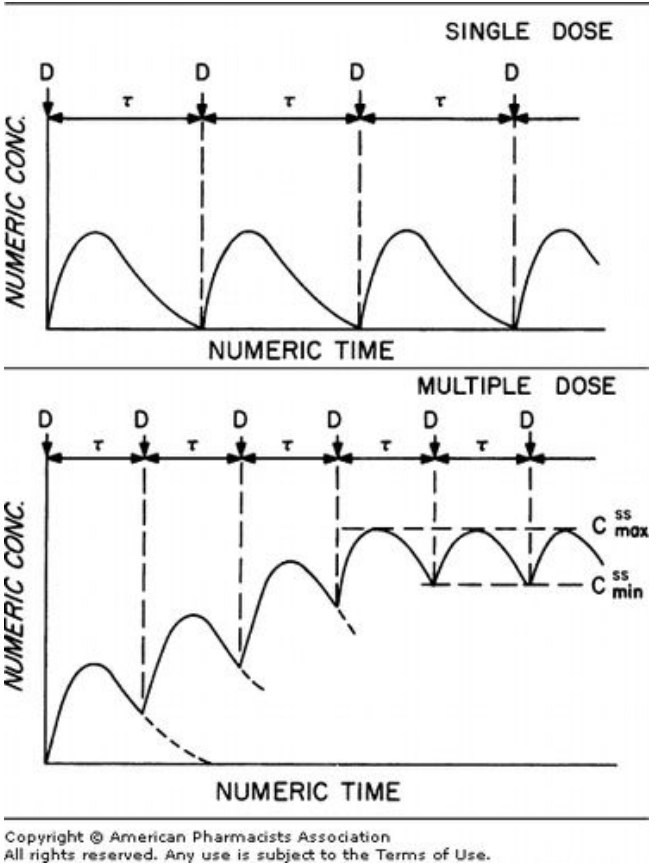
Fig. 4. Dissolution profiles of 21 ramipril generics/copies vs the reference ramipril product (Tritace®). Results from 30-minute dissolution assays conducted at baseline (day 0) and after 3 months' temperature-stressed storage; results are the mean of the average values from six individual tablets. The Sanofi-Aventis specification limit (≥80% dissolution in 30 minutes) is illustrated by the black line. No data are reported for Generic 12 as the dissolution assay was not completed because of a shortage of tablets. Dissolution assays were conducted according to validated dissolution tests for solid dosage forms using a paddle system (Apparatus 2 as described in the European Pharmacopoeia 6.0[17]); dissolved contents were assayed using a validated high-performance liquid chromatography system (see Materials and Methods section for details of the assay).[16]

Angeli DG, Trezza C. **Quality and stability of ramipril generics/copies versus reference ramipril (Tritace): a 3-month stability comparative study.** Clin Drug Investig. 2009;29(10):667-76. doi: 10.2165/11315270-000000000-00000. PMID: 19715383.

Multiple Dosing

Multiple dosing in drug therapy refers to the practice of administering multiple doses of a drug or medication

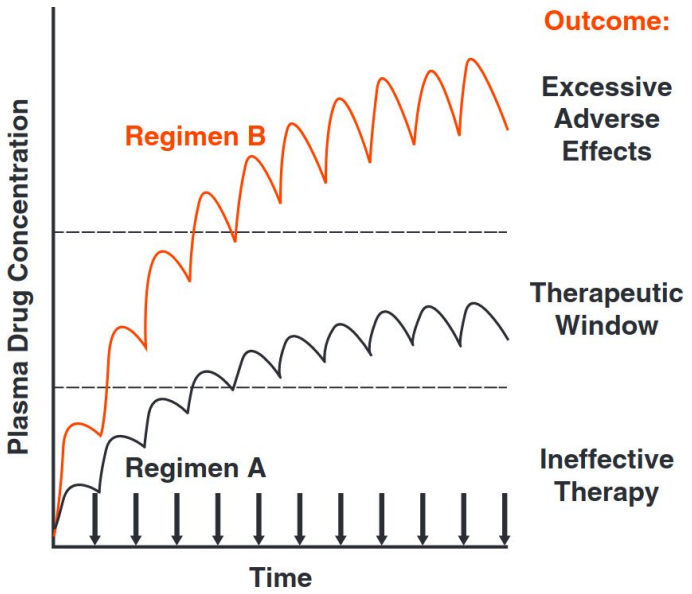
1. **Steady-state Concentration**: Over time, multiple doses of a drug lead to a steady-state concentration in the blood.
2. **Dosing Interval**: The dosing interval is the time between two consecutive doses.
3. **Therapeutic Window**: This is the range of drug concentrations in the blood that provide effective treatment without causing toxicity.
4. **Dose and Frequency**: The size of the dose and frequency of dosing are critical in multiple dosing strategies.
5. **Accumulation and Elimination**: When drugs are administered repeatedly, they can accumulate in the body, leading to higher concentrations than after the first dose.
6. **Interindividual Variability**: There can be a significant difference in how different individuals respond to the same drug and dosage due to genetic factors, age, gender, organ function, and the presence of other diseases or drugs.
7. **Compliance**: Compliance with the dosing regimen is essential for the success of the treatment.



Optimal Dosing Regime & Therapeutic Window

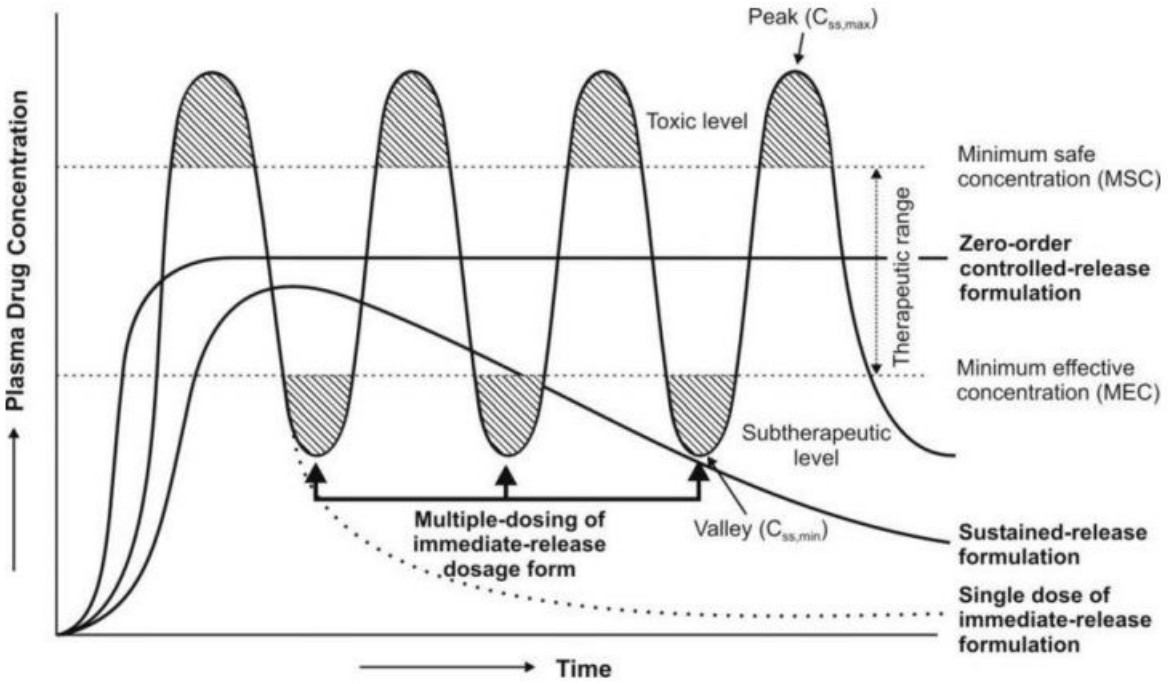
The therapeutic window is determined by two main factors: **the minimum effective concentration (MEC)** and the **maximum tolerable concentration (MTC)**.

- The **minimum effective concentration (MEC)** is the lowest concentration of a drug in the patient's bloodstream that still produces the desired therapeutic effect. If the concentration falls below this level, the drug may not be effective in treating the condition, leading to ineffective therapy.
- The **maximum tolerable concentration (MTC)** is the highest concentration of a drug that can be tolerated without causing significant toxic effects or side effects. If the drug concentration exceeds this level, the risk of side effects and toxicity increases.



Tozer TN, Rowland M. **Essentials of pharmacokinetics and pharmacodynamics.** Second edition

Controlled release medication



🏃 Dosing Variation 🏃

https://www.icp.org.nz/dosing-variations/dosing-by-injection

Compliance

- after the end of first year only ~50% continue to take the prescribed medication
- anti-hypertensive drugs

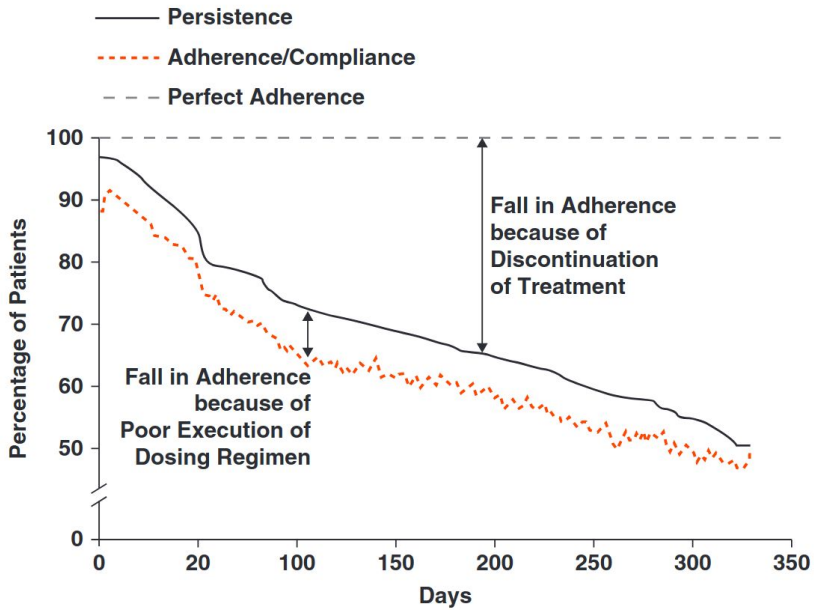


FIGURE 1-9 Nonadherence to prescribed medication is a major source of variability in drug therapy. Shown is the gradual but persistent decrease in adherence in the percentage of 4783 patients prescribed a variety of once-a-day antihypertensive therapies due to discontinuation of treatment, such that by the end of the first year only 50% of the patients prescribed the treatment for an indefinite duration continue to take the prescribed medication. The initial 3% drop in adherence is due to some patients never even starting the medication. The data were obtained using an electronic monitoring device that detects and logs each time the container with the medication is opened. (Taken from Vrijens B, Vincze G, Kistanto P, et al. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *Brit Med J* 2008;18:1–6.)