explained

How Does the Body Process Oral Medications?

It is almost second nature to reach for painkillers when a headache sets in or turn to antihistamines for relief from sneezing. But what exactly happens inside the body after ingesting these medications?

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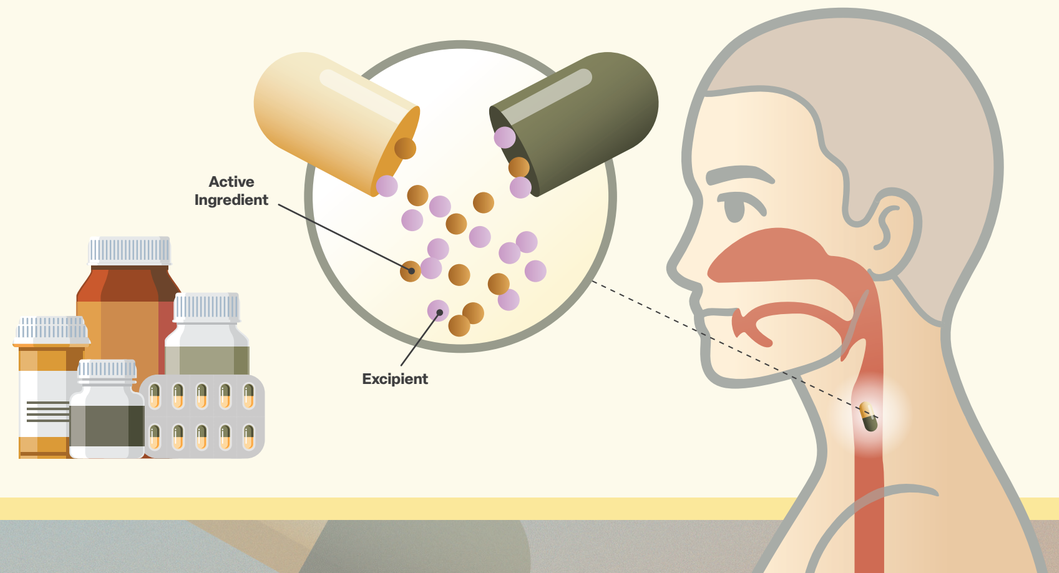
Once a pill enters the mouth, it embarks on an intricate journey through the body. From traversing multiple biological barriers to reaching its intended destination, and from delivering its therapeutic effects to safely leaving the body, the drug interacts with various organs, tissues, and biological systems, triggering a series of physiological events. Understanding this process is vital to developing effective oral medications and optimizing their behaviors within the body.

What does oral medication contain?

Often found in tablets, capsules, liquids, powders, or lozenges, oral formulations are the most common and convenient methods for administrating drugs. Inside each oral drug, there is a complex mixture of components that make up a specific pharmaceutical formulation.

The most important part of an oral medication is its active ingredients, which provide therapeutic effects (1). These substances interact with their biological targets in the body to treat the symptoms or conditions for which the medication is prescribed. For example, in many allergy medicines, the active ingredients are antihistamines such as diphenhydramine, which block the effects of histamine in the body to reduce or prevent allergic reactions (2).

The bulk of an oral drug does not produce pharmaceutical effects. These nonactive components, known as excipients, enhance the drug's physical properties, such as stability, appearance, and taste (1). For example, cellulose and its derivatives are common excipients that holds a drug together in a tablet and also sustain the release of active ingredients (3). During drug development, pharmacologists carefully select and combine excipients with active ingredients by considering various factors, such as particle size, crystal structures, pH, and solubility to create the final medicinal product (4).

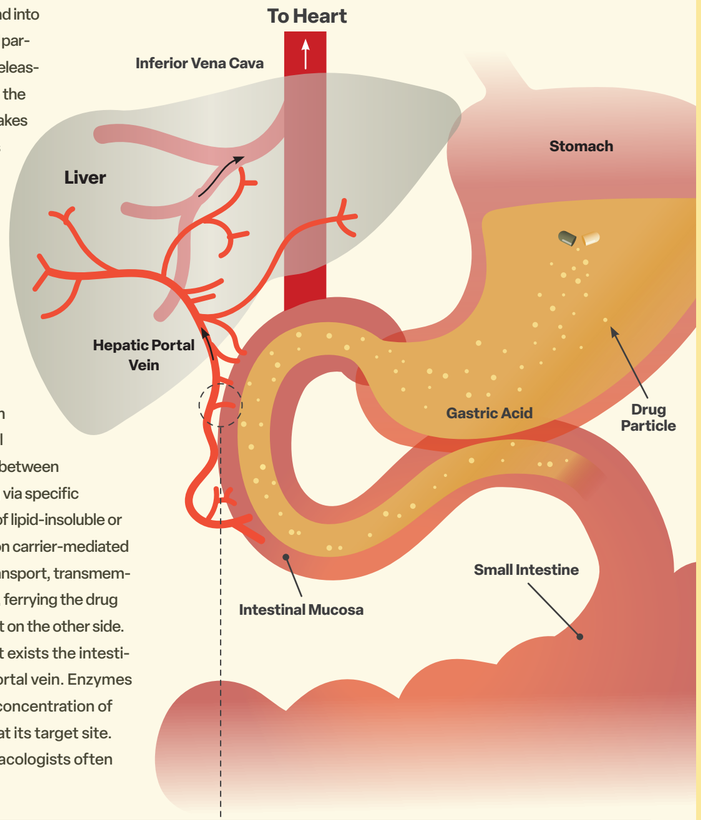


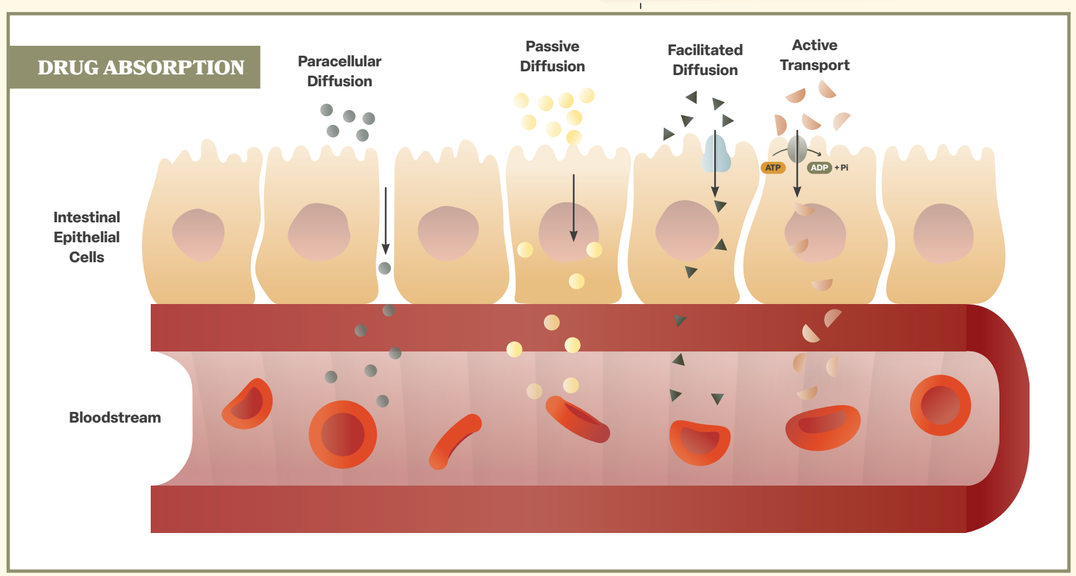
How do drugs enter the bloodstream?

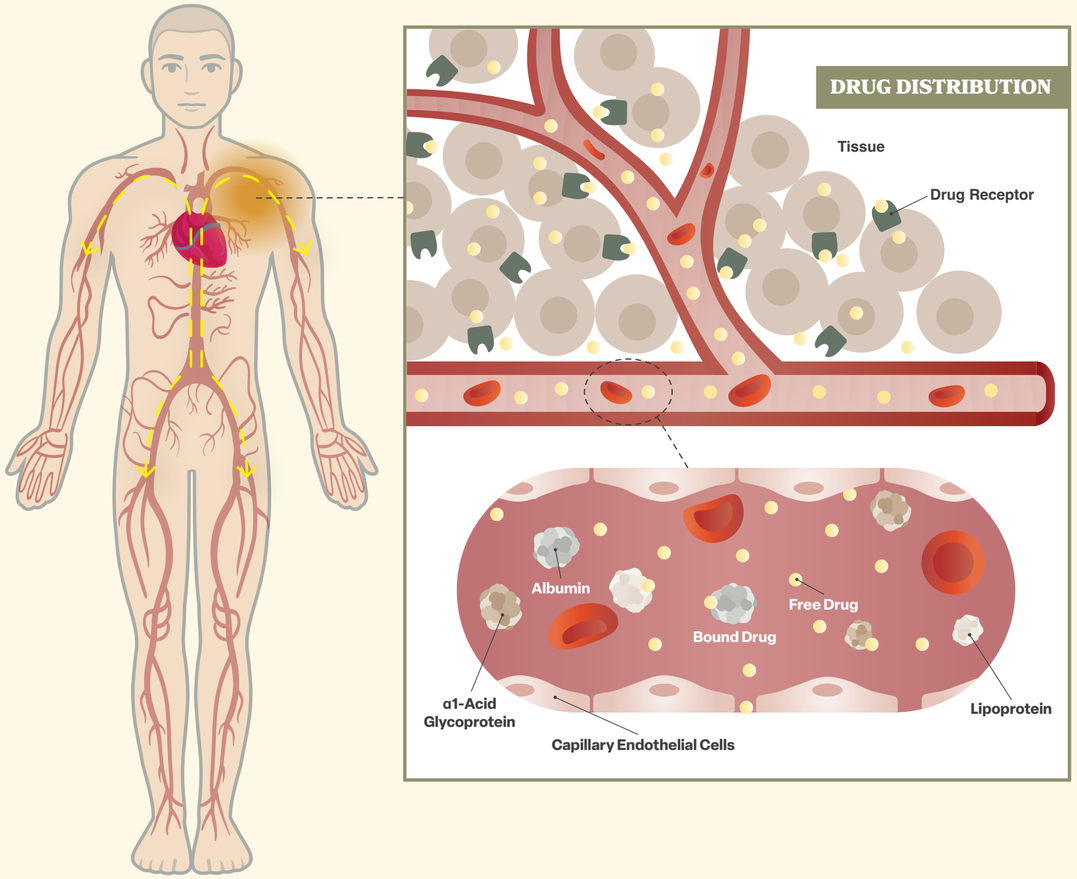
Once a drug is ingested, it travels through the esophagus and into the stomach. In the stomach, the drug breaks down into small particles (if in solid form) and dissolves in the acidic gastric fluid, releasing its active ingredients. The dissolved drug then moves from the stomach to the small intestine, where most of its absorption takes place. The intestinal mucosa lining the small intestine contains numerous finger-like projections called villi, which are covered by a layer of epithelial cells that create an absorptive surface (5). Blood vessels lie beneath the epithelial cells. For drug molecules to enter the bloodstream, they must cross the intestinal mucosa.

Drug absorption typically involves passive diffusion or active transport, depending on the drug's physicochemical properties. Most lipid-soluble small-molecule drugs, such as acetaminophen, move from a higher concentration in the intestinal mucosa to a lower concentration in the bloodstream by diffusion (6,7). These molecules can travel across epithelial cells in different ways, including by slipping through the gaps between cells, passing directly through the cell membrane, or crossing via specific transmembrane carrier proteins. In contrast, the absorption of lipid-insoluble or larger-molecule drugs, such as calcium and levodopa, relies on carrier-mediated transport to actively move drug molecules (7). With active transport, transmembrane transporters or carriers recognize and bind to the drug, ferrying the drug molecule across the cell membrane and disassociating from it on the other side.

Before the absorbed drug reaches the rest of the body, it exists the intestinal mucosa and first enters the liver through the hepatic portal vein. Enzymes in the liver break down a portion of the drug, reducing the concentration of its active ingredients and limiting the drug's bioavailability at its target site. To counteract this and maintain the drug's efficacy, pharmacologists often add excess active ingredients to the oral formulation (8).







How do drugs reach their target tissues and cells?

The circulatory system carries active drug molecules that emerge from the liver to different parts of the body. In the blood, many drugs interact reversibly with various proteins depending on their chemical properties. Acidic drugs such as aspirin and nitrofurantoin, an antibacterial agent, bind predominantly to albumin, the most abundant protein in plasma. Basic drugs such as propranolol, a drug used for controlling blood pressure and heart rate, preferentially bind to α1-acid glycoprotein, a common protein found in the blood (7). Additionally, lipoproteins in the bloodstream can bind to certain hydrophobic drugs (9).

Drugs in the blood exist in two forms: bound and unbound, which are in dynamic equilibrium with each other. To act on their target sites, drugs must traverse the blood-tissue barrier formed by capillary endothelial cells and exit the bloodstream. Free drugs can readily cross the barrier through passive diffusion or carrier-mediated transport, whereas large protein-bound drugs are usually unable to permeate cell membranes. Instead, protein-bound drugs act as a reservoir, steadily releasing drug molecules in the unbound state for prolonged pharmacological effects.

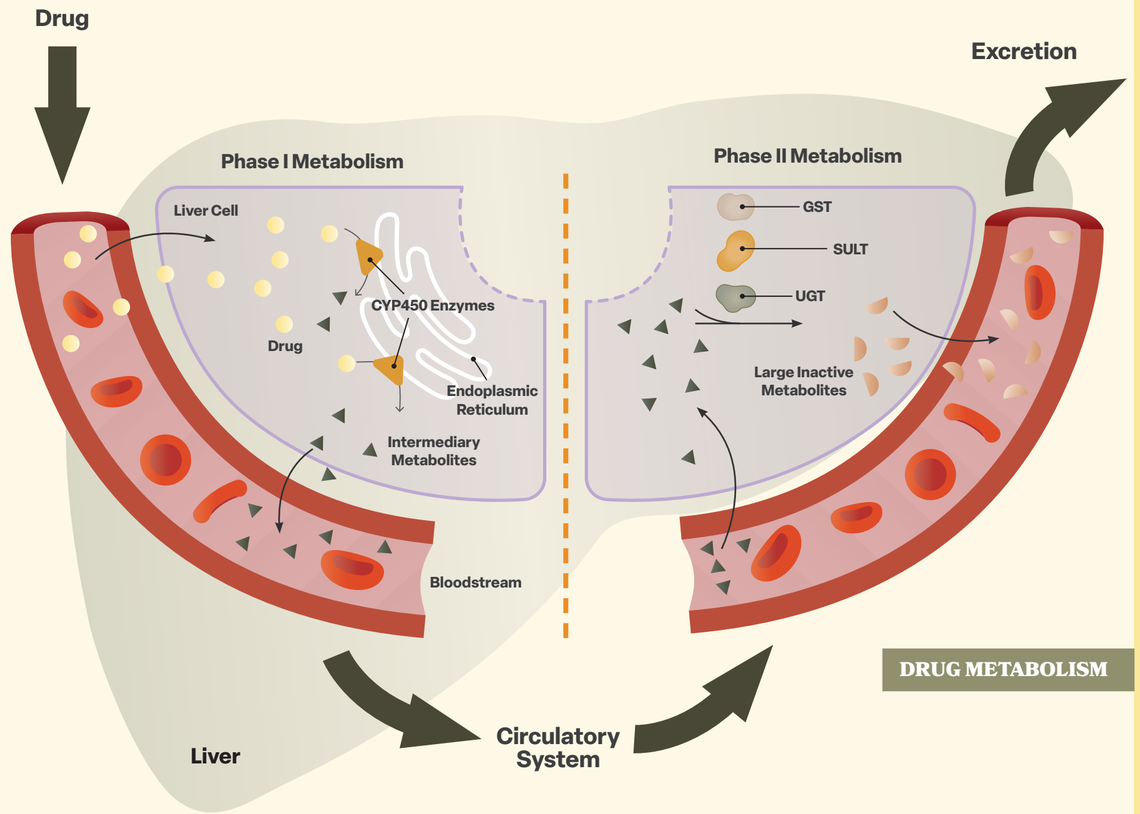
While traveling across the body, drugs find their way to their intended destination by identifying their biological targets, including receptors, ions, ion channels, enzymes, and carrier molecules. As drugs bind to their targets, they accumulate within specific cells, tissues, or body compartments to produce the desired therapeutic effects. For example, the active ingredient in aspirin, acetylsalicylic acid, specifically binds and acetylates cyclooxygenase, an enzyme that catalyzes an initial step in inflammation across various tissues. Once aspirin arrives at the site of inflammation, it enters cells and blocks the function of cyclooxygenase, relieving pain, swelling, or fever (10).

How does the body metabolize drugs?

Metabolic or biotransformative processes help clear foreign substances like drugs by converting them into biologically inactive, easily eliminable metabolites. When the drug circulates across the body, it takes several passes through the liver, the key metabolic organ, and undergoes various phases of enzymatic breakdown.

The initial phase of drug metabolism involves oxidation, reduction, and hydrolysis reactions catalyzed by hepatic enzymes, primarily the cytochrome P450 (CYP450) superfamily located on the smooth endoplasmic reticulum of liver cells. CYP450 enzymes modify the drug's chemical structure by adding or exposing polar functional groups, yielding a water-soluble intermediate metabolite that is often still active (7). Understanding this pathway has allowed scientists to create prodrugs — inactive medications that become effective within the body once they interact with drug-metabolizing enzymes such as CYP450s — to improve drug solubility, bioavailability, and duration of action (11).

After being partially metabolized, the drug enters the second phase of metabolism. Several enzymes, including uridine 5'-diphospho (UDP)-glucuronosyltransferases (UGTs), glutathione S-transferases (GSTs), and sulfotransferases (SULTs), attach the drug to a hydrophilic endogenous substrate, such as glucuronic acid, sulfate, or glycine (12). This further increases the drug's polarity, resulting in large, inactive metabolites, which are subsequently transported out of the cells by the ATP-binding cassette (ABC) and solute carrier (SLC) transporters on the cell membrane, preparing the metabolites to be excreted from the body (12).



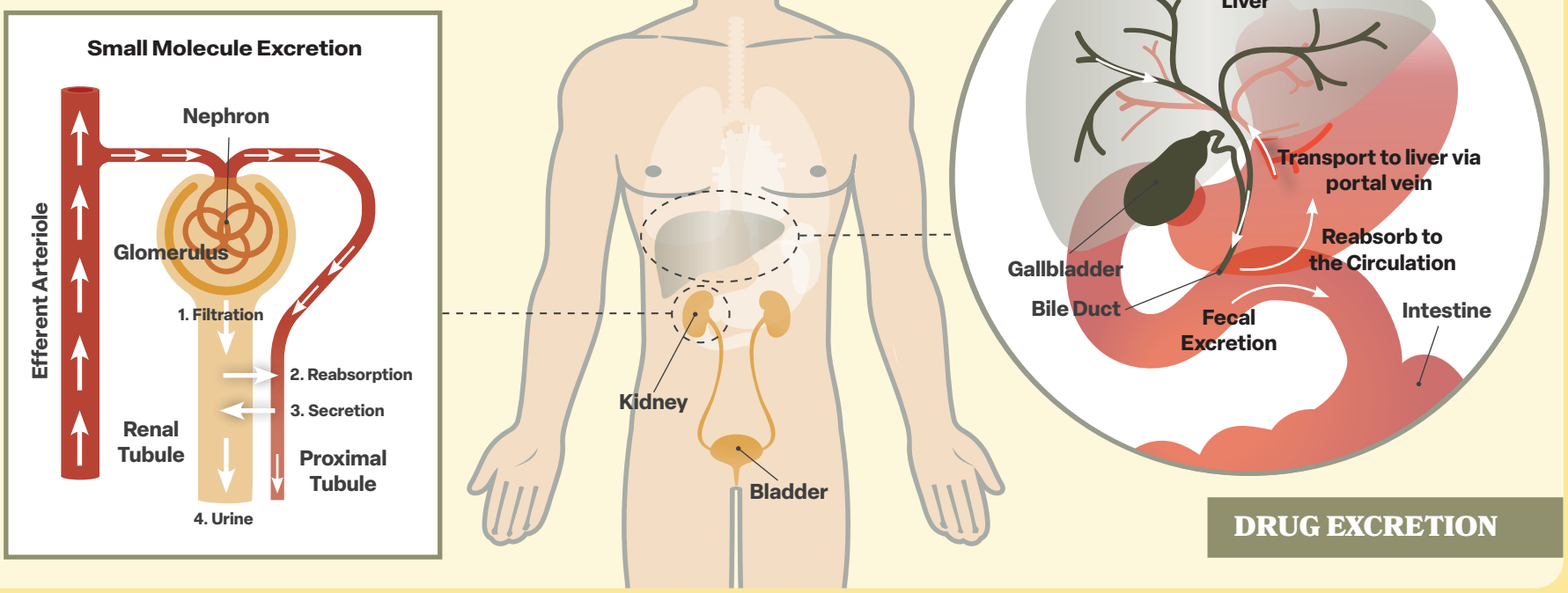
How does the body eliminate drug metabolites?

While the liver is the major organ for metabolizing drugs, it is the kidney that eliminates most small drugs and their metabolites from the body. The kidney contains about one million tiny structural units called nephrons. Each nephron is made up of a filter, called the glomerulus, which connects to the renal tubule for secretion (13). As drug-loaded blood passes through the nephron, the glomerulus filters the blood, letting small molecules, wastes, and fluid flow into the tubule. The tubule returns needed substances to the blood, while the remaining substances in the tubule become urine.

Most small drug metabolites can be readily filtered through the glomerulus. Meanwhile, acidic and basic small drug metabolites can be actively secreted into the renal tubule via carrier-mediated transport. Some drugs and their metabolites, particularly un-ionized ones, may be reabsorbed into the bloodstream after entering the renal tubule. Urinary pH can significantly affect drug reabsorption and excretion because it determines the ionization state of the drug (7).

To eliminate large drug metabolites, the body utilizes biliary excretion, which involves actively secreting large water-soluble drug metabolites from liver cells into bile. The bile, carrying these metabolites, travels through the bile ducts and reaches the gallbladder, where it is stored before being released into the gastrointestinal (GI) tract. In the GI tract, the metabolites undergo further breakdown by gut bacteria. Similar to renal tubular reabsorption, these drug metabolites can also be reabsorbed from the small intestine and carried back to the liver. This cycle, known as enterohepatic circulation, repeats until the drugs are ultimately removed from the body through feces (7).

Besides the kidney and bile, there are various other routes of drug excretion, including sweat, saliva, tears, breast milk, and exhalation from the lungs. These pathways are quantitatively less important for drug elimination, but scientists have identified their potential as noninvasive approaches for monitoring drug pharmacokinetics in patients (14,15).



Advancing oral drug delivery

It is not surprising that oral medication is typically less effective than intravenously administered drugs, which directly deliver drugs into the bloodstream and bypass the GI system. The main challenge of oral drug delivery is that many drugs have poor water solubility and membrane permeability that limit their absorption in the body. To address this, scientists are exploring diverse strategies, including optimizing drugs' physicochemical properties by modifying their structures, sizes, and pHs to improve their solubility. Some researchers are developing novel drug delivery systems such as nanoparticles and micelles, tiny aggregates of molecules with a hydrophilic shell and a hydrophobic core. These carriers can help solubilize drugs and provide protective barriers around drugs, preventing their degradation and enhancing their absorption (16). As these drug delivery technologies advance, how oral drugs are made and how they behave in the body will continue to evolve.

References

1. Reker, D. *et al.* "Inactive" ingredients in oral medications. *Science Translational Medicine* **11**, eaau6753 (2019).
2. Church, M. K. & Church, D. S. Pharmacology of antihistamines. *Indian Journal of Dermatology* **58**, 219 (2013).
3. Marques-Marinho, F. D., Vianna-Soares, C. D., Marques-Marinho, F. D. & Vianna-Soares, C. D. *Cellulose and Its Derivatives Use in the Pharmaceutical Compounding Practice. Cellulose - Medical, Pharmaceutical and Electronic Applications* (IntechOpen, 2013). doi:10.5772/56637
4. Afrin, S. & Gupta, V. in *StatPearls* (StatPearls Publishing, 2023). at <http://www.ncbi.nlm.nih.gov/books/NBK562239/>
5. Helander, H. F. & Fändriks, L. Surface area of the digestive tract - revisited. *Scand J Gastroenterol* **49**, 681–689 (2014).
6. Raffa, R. B., Pergolizzi, J. V., Taylor, R., Decker, J. F. & Patrick, J. T. Acetaminophen (paracetamol) oral absorption and clinical influences. *Pain Pract* **14**, 668–677 (2014).
7. *Pharmacological Basis of Acute Care.* (Springer International Publishing, 2015). doi:10.1007/978-3-319-10386-0
8. Maheshwari, R. *et al.* in *Dosage Form Design Considerations* (ed. Tekade, R. K.) 701–729 (Academic Press, (2018). doi:10.1016/B978-0-12-814423-7.00020-4
9. Wasan, K. M. & Cassidy, S. M. Role of plasma lipoproteins in modifying the biological activity of hydrophobic drugs. *Journal of Pharmaceutical Sciences* **87**, 411–424 (1998).
10. Vane, J. R. & Botting, R. M. The mechanism of action of aspirin. *Thrombosis Research* **110**, 255–258 (2003).
11. Rautio, J. *et al.* Prodrugs: design and clinical applications. *Nat Rev Drug Discov* **7**, 255–270 (2008).
12. Jančová, P., Šiller, M., Jančová, P. & Šiller, M. *Phase II Drug Metabolism. Topics on Drug Metabolism* (IntechOpen, 2012). doi:10.5772/29996
13. Bertram, J. F., Douglas-Denton, R. N., Diouf, B., Hughson, M. D. & Hoy, W. E. Human nephron number: implications for health and disease. *Pediatr Nephrol* **26**, 1529–1533 (2011).
14. Hutchinson, L., Sinclair, M., Reid, B., Burnett, K. & Callan, B. A descriptive systematic review of salivary therapeutic drug monitoring in neonates and infants. *British Journal of Clinical Pharmacology* **84**, 1089–1108 (2018).
15. Tai, L.-C. *et al.* Methylxanthine Drug Monitoring with Wearable Sweat Sensors. *Advanced Materials* **30**, 1707442 (2018).
16. Alqahtani, M. S., Kazi, M., Alsenaidy, M. A. & Ahmad, M. Z. Advances in Oral Drug Delivery. *Frontiers in Pharmacology* **12**, (2021).