**PHARMACOKINETICS OF DRUG INTERACTIONS**

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**Pharmacokinetic interactions** occur when the absorption, distribution, metabolism or elimination process of the object **drug** is altered by the precipitant **drug** and hence such **interactions** are also called as ADME **interactions**. The resultant effect is altered plasma concentration of the object **drug**

A Drug interaction is an interaction between a drug and some other substance, such as another drug or a certain type of food, which leads to interaction that could manifest as an increase or decrease in the effectiveness or an adverse reaction or a totally new side effect that is not seen with either drug alone that can be severe enough to alter the clinical outcome. Drug interactions are thus:

* Mostly undesirable
* Rarely desirable(beneficial)
* Eg: Enhancement of activity of Penicillin’s when administered

 with Probenecid.

* The drug whose activity is effected by such an interaction is called

 as a “Object drug”.

* The agent which precipitates such an interaction is referred to as

 the “Precipitant”.

**Classification**

Absorption interactions

Distribution interactions

Metabolism interactions

Elimination interactions

**PHARMACOKINETIC DRUG INTERACTIONS**:

Altered concentration, pharmacokinetic drug interactions occur when one drug changes the systemic concentration of another drug, altering ‘how much’ and for ‘how long’ it is present at the site of action.ss

**PHARMACODYNAMIC DRUG INTERACTIONS**:

Altered effect, pharmacodynamics drug interactions occur when interacting drugs have either additive effects, in which case the overall effect is increased, or opposing effects, in which case the overall effect is decreased or even ‘cancelled out’.

**DRUG ABSORPTION INTERACTIONS**

Absorption interactions are those where the absorption of the object drug is altered.

• Since the oral route is the one, most frequently used to administer drugs, interactions influencing absorption are more likely to occur within the gastrointestinal tract.

•The net effect of such an interaction is:

•Faster or slower drug absorption.

•More or, less drug absorption.

Most clinically significant interactions occur due to the following factors:

a) Changes in gastrointestinal pH

b) Changes induced by chelation

c) Changes in gastrointestinal motility

**CHANGES IN GASTROINTESTINAL pH**

•Absorption in the gut is governed by the gut pH, lipid solubility and pka of the drug.

•While changes in gastric pH induced by H2 and proton pump blockers and antacids containing Al/Mg formulations have been shown to significantly reduce drug bioavailability.

•However the alteration in pH has certain clinical implications as it can result in a significant reduction in

the absorption of Ketoconazole and Iitraconazole which are insoluble in water and are only ionized at low pH, hence gastric acidity plays an important part in this interaction.

Drugs can be present in either ionised or non-ionised form, depending on their [pKa](https://en.wikipedia.org/wiki/PKa%22%20%5Co%20%22PKa) (pH at which the drug reaches equilibrium between its ionised and non-ionised form).The non-ionized forms of drugs are usually easier to absorb, because they will not be repelled by the lipidic bylayer of the cell, most of them can be absorbed by passive diffusion, unless they are too big or too polarized (like glucose or vancomycin), in which case they may have or not have specific and non specific transporters distributed on the entire intestine internal surface, that carries drugs inside the body. Obviously increasing the absorption of a drug will increase its bioavailability, so, changing the drug's state between ionized or not, can be useful or not for certain drugs.

Certain drugs require an [acid](https://en.wikipedia.org/wiki/Acid) [stomach](https://en.wikipedia.org/wiki/Stomach) [pH](https://en.wikipedia.org/wiki/PH) for absorption. Others require the basic pH of the intestines. Any modification in the pH could change this absorption. In the case of the [antacids](https://en.wikipedia.org/wiki/Antacid), an increase in pH can inhibit the absorption of other drugs such as [zalcitabine](https://en.wikipedia.org/wiki/Zalcitabine%22%20%5Co%20%22Zalcitabine) (absorption can be decreased by 25%), [tipranavir](https://en.wikipedia.org/wiki/Tipranavir%22%20%5Co%20%22Tipranavir) (25%) and [amprenavir](https://en.wikipedia.org/wiki/Amprenavir%22%20%5Co%20%22Amprenavir) (up to 35%). However, this occurs less often than an increase in pH causes an increase in absorption. Such as occurs when [cimetidine](https://en.wikipedia.org/wiki/Cimetidine) is taken with [didanosine](https://en.wikipedia.org/wiki/Didanosine%22%20%5Co%20%22Didanosine). In this case a gap of two to four hours between taking the two drugs is usually sufficient to avoid the interaction.

**CHANGES INDUCED BY CHELATION**

The various possible drug interactions that occur due to alterations in drug absorption the most clinically significant interactions occur due to chelation or formation of insoluble complexes.

•Clinically important interactions relate to use of Tetracyclines as well as ciprofloxacin that can form

insoluble chelates with Ca, Al, and iron, resulting in its reduced antibacterial effects.

•This interaction can however be avoided if the interval between the medications is at least 2-3 hours.

•Chelation also seems to play an important part in reducing the bioavailability of Penicillamine caused by some antacids.

The presence of di- or trivalent [cations](https://en.wikipedia.org/wiki/Ion%22%20%5Co%20%22Ion) can cause the [chelation](https://en.wikipedia.org/wiki/Chelation) of certain drugs, making them harder to absorb. This interaction frequently occurs between drugs such as [tetracycline](https://en.wikipedia.org/wiki/Tetracycline) or the [fluoroquinolones](https://en.wikipedia.org/wiki/Quinolone_antibiotic%22%20%5Co%20%22Quinolone%20antibiotic) and dairy products (due to the presence of Ca++)

**Formation of non-absorbable complexes:**

* Binding with proteins. Some drugs such as [sucralfate](https://en.wikipedia.org/wiki/Sucralfate%22%20%5Co%20%22Sucralfate) binds to proteins, especially if they have a high [bioavailability](https://en.wikipedia.org/wiki/Bioavailability). For this reason its administration is [contraindicated](https://en.wikipedia.org/wiki/Contraindicated) in [enteral feeding](https://en.wikipedia.org/wiki/Feeding_tube).[[12]](https://en.wikipedia.org/wiki/Drug_interaction#cite_note-Marduga-12)
* Finally, another possibility is that the drug is retained in the intestinal [lumen](https://en.wikipedia.org/wiki/Lumen_%28anatomy%29) forming large complexes that impede its absorption. This can occur with [cholestyramine](https://en.wikipedia.org/wiki/Cholestyramine%22%20%5Co%20%22Cholestyramine) if it is associated with [sulfamethoxazol](https://en.wikipedia.org/wiki/Sulfamethoxazol%22%20%5Co%20%22Sulfamethoxazol), [thyroxine](https://en.wikipedia.org/wiki/Thyroxine%22%20%5Co%20%22Thyroxine), [warfarin](https://en.wikipedia.org/wiki/Warfarin) or [digoxin](https://en.wikipedia.org/wiki/Digoxin).

**CHANGES IN GASTROINTESTINALMOTILITY**

Some drugs, such as the prokinetic agents increase the speed with which a substance passes through the intestines. If a drug is present in the digestive tract's absorption zone for less time its blood concentration will decrease. The opposite will occur with drugs that decrease intestinal [motility](https://en.wikipedia.org/wiki/Motility).

**Drugs that alter the stomach-emptying** rate can affect the rate of absorption of drugs as most of them are absorbed in the small intestine**.**

•Drugs with anticholinergic properties like Propantheline or those altering bowel motility like Diphenoxylate may affect the absorption of other drugs.

•Eg: Propantheline increases the absorption of slow dissolving Digoxin by 30% as the reduced gut motility allows a slow dissolving Digoxin formulation more time to pass into solution making a greater amount available for absorption but this effect is not seen with fast dissolving tablets.

•Metoclopramide on the other hand produces the opposite effects on motility and digoxin absorption.

**DRUG DISTRIBUTION INTERACTION**

Drug distribution interactions are those where the distribution pattern of the object drug is altered.

The main interaction mechanism is competition for plasma protein transport. In these cases the drug that arrives first binds with the plasma protein, leaving the other drug dissolved in the plasma, which modifies its concentration. The organism has mechanisms to counteract these situations (by, for example, increasing [plasma clearance](https://en.wikipedia.org/wiki/Clearance_%28medicine%29)), which means that they are not usually clinically relevant. However, these situations should be taken into account if other associated problems are present such as when the method of excretion is affected

•The major mechanism for distribution interaction is alteration in protein-drug binding.

•Many drugs interact by displacement of each other’s binding to plasma proteins.

•Acidic drugs are known to have an affinity to bind to plasma proteins, hence when two or more are given concomitantly, competitive binding for the same site or receptor may

displace one drug from the protein binding site increasing the amount of the displaced free drug in plasma and various tissues setting up an interaction leading to an enhanced potential for toxicity.

Eg:Concomitant administration of warfarin with Phenylbutazone or other highly protein bound drugs leads to increased levels of warfarin.

•The drugs most likely to lead to clinically significant interactions are those that are: 90% or more protein bound, those bound to tissues or having a small volume of distribution, having a low therapeutic index, low hepatic extraction ratios, or those that are administered I.V.

•Drugs that are more likely to displace other drugs from protein binding sites include NSAID’s, Phenylbutazone, salicylic acid, and sulfonamides.

**METABOLISM INTERACTIONS**

Many drug interactions are due to alterations in [drug metabolism](https://en.wikipedia.org/wiki/Drug_metabolism).[[15]](https://en.wikipedia.org/wiki/Drug_interaction#cite_note-GENENG15June2008-15) Further, human drug-metabolizing enzymes are typically activated through the engagement of [nuclear receptors](https://en.wikipedia.org/wiki/Nuclear_receptor).[[15]](https://en.wikipedia.org/wiki/Drug_interaction#cite_note-GENENG15June2008-15) One notable system involved in metabolic drug interactions is the enzyme system comprising the [cytochrome P450 oxidases](https://en.wikipedia.org/wiki/Cytochrome_P450_oxidase).

**CYP450**

[Cytochrome P450](https://en.wikipedia.org/wiki/Cytochrome_P450) is a very large family of [haemoproteins](https://en.wikipedia.org/wiki/Hemeprotein%22%20%5Co%20%22Hemeprotein) (hemoproteins) that are characterized by their [enzymatic](https://en.wikipedia.org/wiki/Enzyme) activity and their role in the metabolism of a large number of drugs.[[16]](https://en.wikipedia.org/wiki/Drug_interaction#cite_note-16) Of the various families that are present in human beings the most interesting in this respect are the 1, 2 and 3, and the most important enzymes are [CYP1A2](https://en.wikipedia.org/wiki/CYP1A2), [CYP2C9](https://en.wikipedia.org/wiki/CYP2C9), [CYP2C19](https://en.wikipedia.org/wiki/CYP2C19), [CYP2D6](https://en.wikipedia.org/wiki/CYP2D6), [CYP2E1](https://en.wikipedia.org/wiki/CYP2E1) and [CYP3A4](https://en.wikipedia.org/wiki/CYP3A4).[[17]](https://en.wikipedia.org/wiki/Drug_interaction#cite_note-Nelson-17) The majority of the enzymes are also involved in the metabolism of [endogenous](https://en.wikipedia.org/wiki/Endogenous) substances, such as [steroids](https://en.wikipedia.org/wiki/Steroid) or [sex hormones](https://en.wikipedia.org/wiki/Sex_hormones), which is also important should there be interference with these substances. As a result of these interactions the function of the enzymes can either be stimulated ([enzyme induction](https://en.wikipedia.org/wiki/Enzyme_induction)) or inhibited ([enzyme inhibition](https://en.wikipedia.org/wiki/Enzyme_inhibition)).

**Stimulation of metabolism**

If drug A is metabolized by a cytochrome P450 enzyme and drug B induces or increases the enzyme's activity, then blood plasma concentrations of drug A will quickly fall as its inactivation will take place more rapidly. As a result, enzymatic induction will cause a decrease in the drug's effect.

As in the previous case, it is possible to find paradoxical situations where an active metabolite causes the drug's effect. In this case the increase in active metabolite A2 (following the previous example) produces an increase in the drug's effect.

It can often occur that a patient is taking two drugs that are enzymatic inductors, one inductor and the other inhibitor or both inhibitors, which greatly complicates the control of an individual's medication and the avoidance of possible adverse reactions.

An example of this is shown in the following table for the [CYP1A2](https://en.wikipedia.org/wiki/CYP1A2) enzyme, which is the most common enzyme found in the human liver. The table shows the substrates (drugs metabolized by this enzyme) and the inductors and inhibitors of its activity.

|  |
| --- |
| Drugs related to CYP1A2 |
| **Substrates** | **Inhibitors** | **Inductors** |
| * [Caffeine](https://en.wikipedia.org/wiki/Caffeine)
* [Theophylline](https://en.wikipedia.org/wiki/Theophylline)
* [Phenacetin](https://en.wikipedia.org/wiki/Phenacetin)
* [Clomipramine](https://en.wikipedia.org/wiki/Clomipramine)
* [Clozapine](https://en.wikipedia.org/wiki/Clozapine)
* [Thioridazine](https://en.wikipedia.org/wiki/Thioridazine)
 | * [Omeprazole](https://en.wikipedia.org/wiki/Omeprazole)
* [Nicotine](https://en.wikipedia.org/wiki/Nicotine)
* [Cimetidine](https://en.wikipedia.org/wiki/Cimetidine)
* [Ciprofloxacin](https://en.wikipedia.org/wiki/Ciprofloxacin)
 | * [Phenobarbital](https://en.wikipedia.org/wiki/Phenobarbital)
* [Fluvoxamine](https://en.wikipedia.org/wiki/Fluvoxamine)
* [Venlafaxine](https://en.wikipedia.org/wiki/Venlafaxine)
* [Ticlopidine](https://en.wikipedia.org/wiki/Ticlopidine)
 |

Enzyme [CYP3A4](https://en.wikipedia.org/wiki/CYP3A4) is the enzyme that the greatest number of drugs use as a substrate. Over 100 drugs depend on its metabolism for their activity and many others act on the enzyme as inductors or inhibitors.

Some foods also act as inductors or inhibitors of enzymatic activity.

|  |
| --- |
|  Foods and their influence on drug metabolism |
| **Food** | **Mechanism** | **Drugs affected** |
| [Grapefruit](https://en.wikipedia.org/wiki/Grapefruit) juice | Enzymatic inhibition | * [Calcium channel blockers](https://en.wikipedia.org/wiki/Calcium_channel_blocker): [nifedipine](https://en.wikipedia.org/wiki/Nifedipine%22%20%5Co%20%22Nifedipine), [felodipine](https://en.wikipedia.org/wiki/Felodipine%22%20%5Co%20%22Felodipine), [nimodipine](https://en.wikipedia.org/wiki/Nimodipine%22%20%5Co%20%22Nimodipine), [amlodipine](https://en.wikipedia.org/wiki/Amlodipine)
* [Cyclosporine](https://en.wikipedia.org/wiki/Cyclosporine), [tacrolimus](https://en.wikipedia.org/wiki/Tacrolimus%22%20%5Co%20%22Tacrolimus)
* [Terfenadine](https://en.wikipedia.org/wiki/Terfenadine), [astemizole](https://en.wikipedia.org/wiki/Astemizole%22%20%5Co%20%22Astemizole)
* [Cisapride](https://en.wikipedia.org/wiki/Cisapride), [pimozide](https://en.wikipedia.org/wiki/Pimozide%22%20%5Co%20%22Pimozide)
* [Carbamazepine](https://en.wikipedia.org/wiki/Carbamazepine), [saquinavir](https://en.wikipedia.org/wiki/Saquinavir%22%20%5Co%20%22Saquinavir), [midazolam](https://en.wikipedia.org/wiki/Midazolam), [alprazolam](https://en.wikipedia.org/wiki/Alprazolam), [triazolam](https://en.wikipedia.org/wiki/Triazolam%22%20%5Co%20%22Triazolam)
 |
| [Soya](https://en.wikipedia.org/wiki/Soybean) | Enzymatic inhibition | [Clozapine](https://en.wikipedia.org/wiki/Clozapine), [haloperidol](https://en.wikipedia.org/wiki/Haloperidol), [olanzapine](https://en.wikipedia.org/wiki/Olanzapine), [caffeine](https://en.wikipedia.org/wiki/Caffeine), [NSAIDs](https://en.wikipedia.org/wiki/Non-steroidal_anti-inflammatory_drug), [phenytoin](https://en.wikipedia.org/wiki/Phenytoin), [zafirlukast](https://en.wikipedia.org/wiki/Zafirlukast), [warfarin](https://en.wikipedia.org/wiki/Warfarin) |
| [Garlic](https://en.wikipedia.org/wiki/Garlic) | Increases antiplatelet activity | * [Anticoagulants](https://en.wikipedia.org/wiki/Anticoagulant)
* [NSAIDs](https://en.wikipedia.org/wiki/Non-steroidal_anti-inflammatory_drug), [acetylsalicylic acid](https://en.wikipedia.org/wiki/Acetylsalicylic_acid)
 |
| [Ginseng](https://en.wikipedia.org/wiki/Ginseng) | To be determined | [Warfarin](https://en.wikipedia.org/wiki/Warfarin), [heparin](https://en.wikipedia.org/wiki/Heparin), [aspirin](https://en.wikipedia.org/wiki/Aspirin) and [NSAIDs](https://en.wikipedia.org/wiki/Non-steroidal_anti-inflammatory_drug) |
| [*Ginkgo biloba*](https://en.wikipedia.org/wiki/Ginkgo_biloba) | Strong inhibitor of platelet aggregation factor | [Warfarin](https://en.wikipedia.org/wiki/Warfarin), [aspirin](https://en.wikipedia.org/wiki/Aspirin) and [NSAIDs](https://en.wikipedia.org/wiki/Non-steroidal_anti-inflammatory_drug) |
| [*Hypericum perforatum*](https://en.wikipedia.org/wiki/Hypericum_perforatum) (St John's wort) | Enzymatic inductor (CYP450) | Warfarin, [digoxin](https://en.wikipedia.org/wiki/Digoxin), [theophylline](https://en.wikipedia.org/wiki/Theophylline), cyclosporine, [phenytoin](https://en.wikipedia.org/wiki/Phenytoin) and antiretrovirals |
| [Ephedra](https://en.wikipedia.org/wiki/Ephedra) | Receptor level agonist | [MAOI](https://en.wikipedia.org/wiki/MAOI), central nervous system stimulants, alkaloids [ergotamines](https://en.wikipedia.org/wiki/Ergotamine%22%20%5Co%20%22Ergotamine) and [xanthines](https://en.wikipedia.org/wiki/Xanthine%22%20%5Co%20%22Xanthine) |
| Kava (*Piper methysticum*) | Unknown | [Levodopa](https://en.wikipedia.org/wiki/Levodopa) |
| [Ginger](https://en.wikipedia.org/wiki/Ginger) | Inhibits thromboxane synthetase (*in vitro*) | Anticoagulants |

•Certain drugs stimulate the activity of hepatic microsomal enzymes. This effect is referred as enzyme induction.

•The increased activity is due to enhanced enzyme synthesis results in increased amounts of drug metabolizing enzyme.

•Enzyme induction will result in increased metabolism and excretion and reduced effect of agent which is metabolized by the hepatic enzymes.

•Eg :Warfarin and phenobarbital

•Phenobarbital increases the rate of metabolism of warfarin resulting in decrease anticoagulant activity.

**Inhibition of metabolism**

•If one drug inhibits metabolism of another drug it result in prolonged action or intensified activity.

•Alcohol-disulfiram inhibit the activity of alcoholdehydrogenase, thus inhibiting oxidation of acetaldehyde , an oxidation product of alcohol. This result in accumulation of acetaldehyde and development of the characteristic unpleasant effect of disulfiram.

**Drug Elimination Reactions**

Drug elimination reactions are those where the excretion pattern of the object drug is altered.

•The major routes for elimination of drugs remain the kidney and bile, but there are no significant drug - drug interactions through bile elimination, but only drug-disease ones.

•Some drugs are excreted from the body unchanged in the active form, usually in the urine or via the biliary tract in the faeces.

•Drugs that are chiefly excreted by the kidneys can get involved in drug interactions by different mechanisms such as competition at active transport sites, or alterations in glomerular Filtration, passive renal tubular reabsorption or active secretion and urinary pH.

Changes in renal drug clearance may occur due to effects on renal tubular function or urine pH.

•For example, probenecid reduces the renal clearance of anionic drugs such as methotrexate and penicillin.

•Major mechanisms of excretion interactions are:

.Alteration in renal blood flow

.Alteration of urine pH

Competition for active secretions

Forced diuresis

Alteration in renal blood flow- eg: NSAIDs (reduce renal blood

flow) with Lithium.

Alteration of urine pH- eg: Antacids with Amphetamine

Competition for active secretion

Filtration depends on a number of factors including the [pH](https://en.wikipedia.org/wiki/PH) of the urine, it having been shown that the drugs that act as [weak bases](https://en.wikipedia.org/wiki/Base_%28chemistry%29) are increasingly excreted as the pH of the urine becomes more acidic, and the inverse is true for [weak acids](https://en.wikipedia.org/wiki/Weak_acid)

|  |
| --- |
| Drugs that act as weak acids or bases |
| **Weak acids** | **Weak bases** |
| * [Acetylsalicylic acid](https://en.wikipedia.org/wiki/Acetylsalicylic_acid)
* [Furosemide](https://en.wikipedia.org/wiki/Furosemide)
* [Ibuprofen](https://en.wikipedia.org/wiki/Ibuprofen)
* [Levodopa](https://en.wikipedia.org/wiki/Levodopa)
* [Acetazolamide](https://en.wikipedia.org/wiki/Acetazolamide)
* [Sulfadiazine](https://en.wikipedia.org/wiki/Sulfadiazine)
* [Ampicillin](https://en.wikipedia.org/wiki/Ampicillin)
* [Chlorothiazide](https://en.wikipedia.org/wiki/Chlorothiazide)
* [Paracetamol](https://en.wikipedia.org/wiki/Paracetamol)
* [Chloropropamide](https://en.wikipedia.org/wiki/Chloropropamide)
* [Cromoglicic acid](https://en.wikipedia.org/wiki/Cromoglicic_acid)
* [Ethacrynic acid](https://en.wikipedia.org/wiki/Ethacrynic_acid)
* [alpha-Methyldopamine](https://en.wikipedia.org/wiki/Alpha-Methyldopamine)
* [Phenobarbital](https://en.wikipedia.org/wiki/Phenobarbital)
* [Warfarin](https://en.wikipedia.org/wiki/Warfarin)
* [Theophylline](https://en.wikipedia.org/wiki/Theophylline)
* [Phenytoin](https://en.wikipedia.org/wiki/Phenytoin)
 | * [Reserpine](https://en.wikipedia.org/wiki/Reserpine)
* [Amphetamine](https://en.wikipedia.org/wiki/Amphetamine)
* [Procaine](https://en.wikipedia.org/wiki/Procaine)
* [Ephedrine](https://en.wikipedia.org/wiki/Ephedrine)
* [Atropine](https://en.wikipedia.org/wiki/Atropine)
* [Diazepam](https://en.wikipedia.org/wiki/Diazepam)
* [Hydralazine](https://en.wikipedia.org/wiki/Hydralazine)
* [Pindolol](https://en.wikipedia.org/wiki/Pindolol)
* [Propranolol](https://en.wikipedia.org/wiki/Propranolol)
* [Salbutamol](https://en.wikipedia.org/wiki/Salbutamol)
* [Alprenolol](https://en.wikipedia.org/wiki/Alprenolol)
* [Terbutaline](https://en.wikipedia.org/wiki/Terbutaline)
* [Amiloride](https://en.wikipedia.org/wiki/Amiloride)
* [Chlorpheniramin](https://en.wikipedia.org/wiki/Chlorpheniramine)e
 |

#### Bile excretion

[Bile](https://en.wikipedia.org/wiki/Bile) excretion is different from kidney excretion as it always involves energy expenditure in active transport across the epithelium of the bile duct against a concentration [gradient](https://en.wikipedia.org/wiki/Gradient). This transport system can also be saturated if the plasma concentrations of the drug are high. Bile excretion of drugs mainly takes place where their [molecular weight](https://en.wikipedia.org/wiki/Molecular_weight) is greater than 300 and they contain both polar and lipophilic groups. The [glucuronidation](https://en.wikipedia.org/wiki/Glucuronic_acid%22%20%5Co%20%22Glucuronic%20acid) of the drug in the kidney also facilitates bile excretion. Substances with similar physicochemical properties can block the receptor, which is important in assessing interactions. A drug excreted in the bile duct can occasionally be reabsorbed by the intestines (in the enterohepatic circuit), which can also lead to interactions with other drugs.