Organic Pharmaceutical Chemistry IV
1st Semester, Year 5 (2017-2018)
Lecture 1

Organic Pharmaceutical Chemistry: Prodrugs

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This lecture is mainly based on:
http://shodhganga.inflibnet.ac.in/bitstream/10603/3457/10/10_chapter%201.pdf

History & Basic Concept

The prodrug concept was first proposed by Albert in 1958.

Albert and his co-workers described prodrugs as pharmacologically inactive chemical derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness and/or to decrease associated toxicity.

This included both compounds that are **designed** to undergo a transformation to yield an active substance and those that were **discovered by serendipity** to do so.

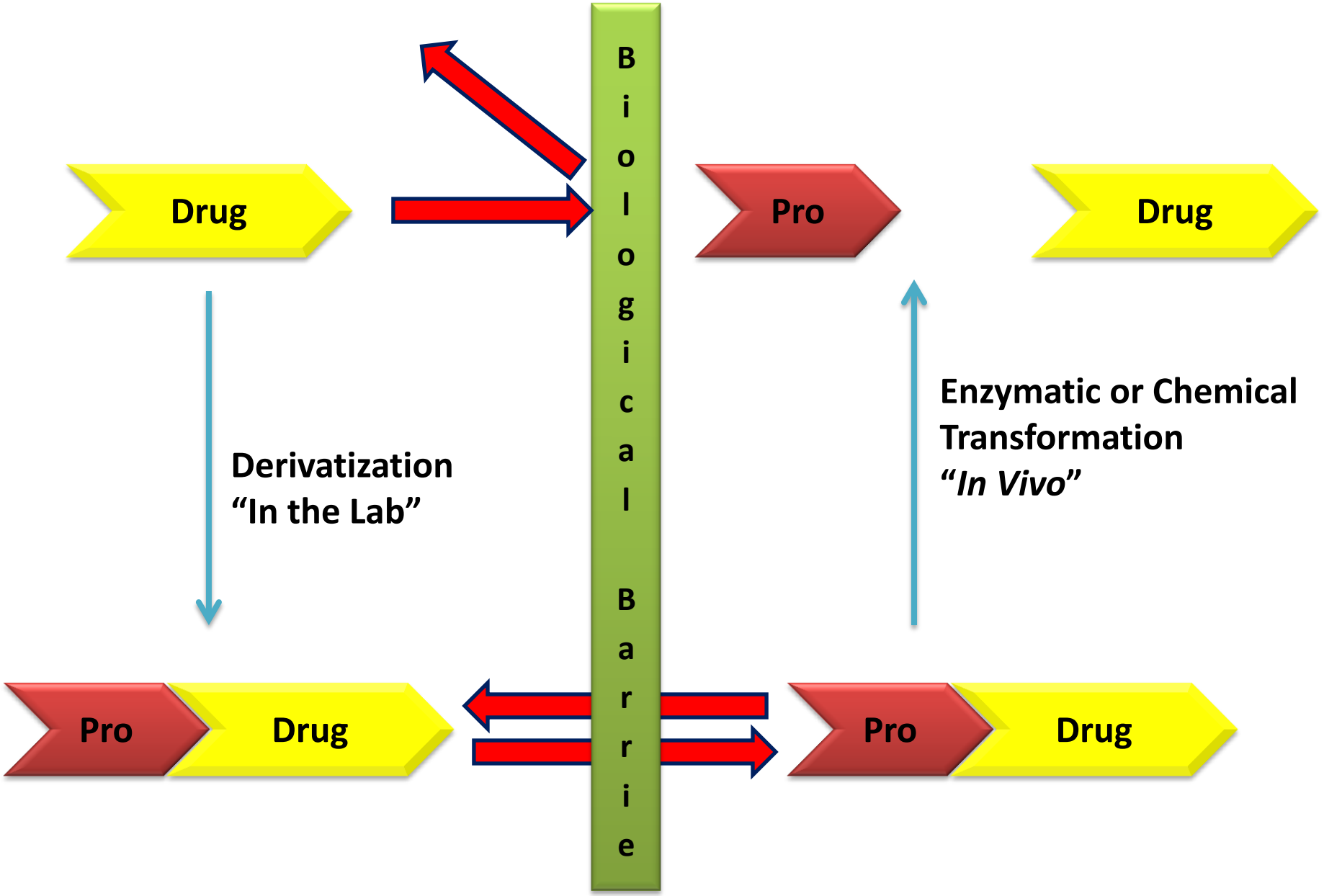
These two situations were distinguished by Harper, who in 1959 introduced the term drug **latentiation** to refer to drugs that were specifically designed to require bioactivation.

Another two terms ***hard drugs*** and ***soft drugs*** were also introduced

Hard drugs are compounds that are designed to contain the structural characteristics necessary for pharmacological activity but in a form that is not susceptible to metabolic or chemical transformation. In this way, the production of any toxic metabolite is avoided, and there is increased efficiency of action. Since the drug is not inactivated by metabolism, it may be less readily eliminated.

Soft drugs are active compounds that after exerting their desired pharmacological effect are designed to undergo metabolic inactivation to give a nontoxic product. Thus soft drugs are considered to be the **opposite** of prodrugs.

Ideally, the prodrug is converted to the original drug as soon as the derivative reaches the site of action, followed by rapid elimination of the released derivatizing group without causing side effects in the process.



Schematic Representation of Prodrug Concept

The Applications of Prodrugs:

The various applications of prodrug approach are:

1. Improved physicochemical properties (e.g., better solubility in the intended formulation).
2. Enhanced delivery characteristics and/or therapeutic value of the drug.
3. To improve drug penetration through biological membranes.
4. To increase site specificity of the drug.
5. To improve the drug's stability and solubility.
6. To increase duration of pharmacological activity.
7. To decrease the drug's toxicity and adverse effects.
8. To improve patient acceptance.

Ideal Requirements of Prodrugs

An ideal prodrug must meet the following requirements:

1. The prodrug is inactive or less active than the parent compound.
2. The linkage between the drug and the carrier must be cleaved *in vivo.*
3. The carrier molecule released *in vivo* must be non-toxic.
4. The metabolic fragments of carrier molecule, apart from the drug should be non toxic.

Barriers to Drug Action

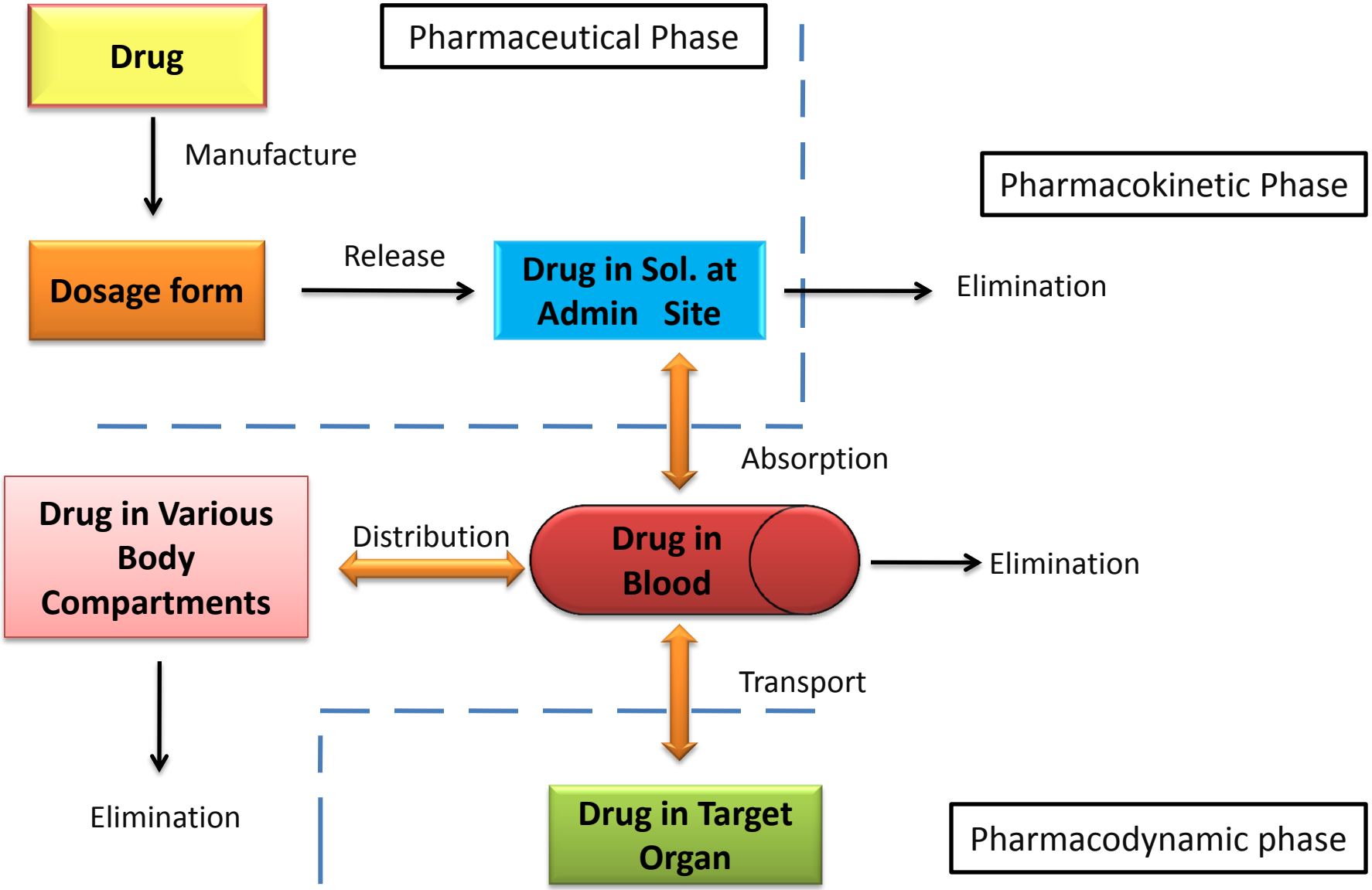
Administration of a prodrug is one of the avenues when attempting to control drug delivery and generate predictable drug concentration *vs*. time profiles at specific drug receptors.

The rationale behind the prodrug approach is that the prodrug is capable of overcoming one or more of the barriers to drug delivery more efficiently than the parent drug. Some of the potential barriers related to the **pharmaceutical** and **pharmacokinetic** phase, respectively.

The pharmaceutical phase comprises:

I. Incorporation of a potential drug entity into a convenient drug delivery system or a dosage form.
II. Release of the active drug from the formulation.

Whereas the pharmacokinetic phase embraces the absorption, distribution, metabolism, and excretion of the drug.


Drug
Pharmaceutical Phase
Manufacture
Pharmacokinetic Phase
Dosage form
Release
Drug in Sol. at Admin Site
Elimination
Absorption
Drug in Various Body Compartments
Distribution
Drug in Blood
Elimination
Transport
Elimination
Drug in Target Organ
Pharmacodynamic phase

THE PHARMACEUTICAL PHASE

There are two **barriers** identified in the development phase of commercially usable drug products are:

A. **Aesthetic properties** such as odour, taste (in case of paediatric use or when intended for oral administration), pain upon injection, gastrointestinal (GI) irritability of the new molecule

B. **Drug formulation problems** such as stability profile, undesirable physicochemical properties like solubility, polarity, partition coefficient and p*Ka* values due to which precludes its incorporation into a specific drug delivery system.

THE PHARMACOKINETIC PHASE

This phase can be considered as the phase involving absorption, distribution, metabolism and excretion of the drug.

The pharmacokinetic studies provide valuable information regarding the *in vivo* properties of a drug's limitation such as poor absorption, too rapid elimination and pre systemic metabolism.

If these properties can be related back to the physicochemical and dosage form properties of the system, then corrections will require **prodrug** interventions.

What are the principal barriers which identified in the pharmacokinetic?!

1. Incomplete absorption of the drug from the delivery system or across biological barriers such as the gastrointestinal mucosal cells and the blood brain barrier.

2. Incomplete systemic delivery of an agent due to pre-systemic metabolism in the gastrointestinal lumen mucosal cells and liver.

3. Toxicity problems associated with local irritation or distribution into tissue other than the desired target organ.

4. Poor site specificity of the drug.

HOW CAN WE USE PRODRUGS TO OVERCOME THE PHARMACEUTICAL BARRIERS ?!

1- Masking Taste or Odour

The undesirable taste arises due to adequate solubility and interaction of drug with taste receptors.

So, what we have to do?!!

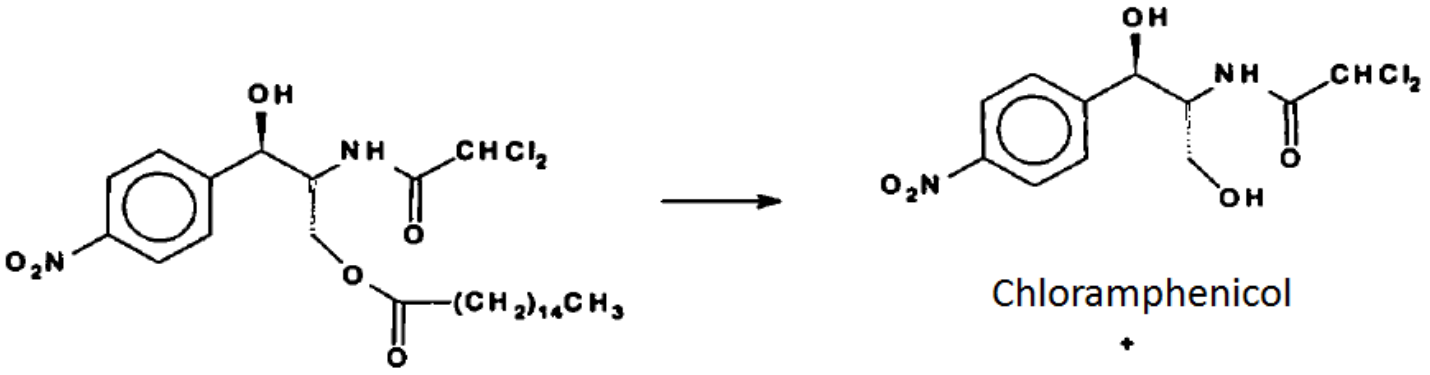
The answer is:

We can overcome this problem by lowering the solubility of drug or prodrug in saliva.

Example 1 : “ The undesirable taste”

Chloramphenicol which produces a bitter taste when given as the parent drug.

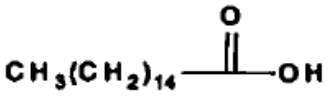
The hydrophobic palmitate ester does not dissolve to any appreciable extent in the mouth, so there is little chance for interaction with taste receptors.



Chloramphenicol Palmitate

Chloramphenicol

+



Palmitic Acid

The ester moiety is subsequently hydrolyzed in the GI tract, and the agent is absorbed as chloramphenicol.

Example 2 : “The malodour”

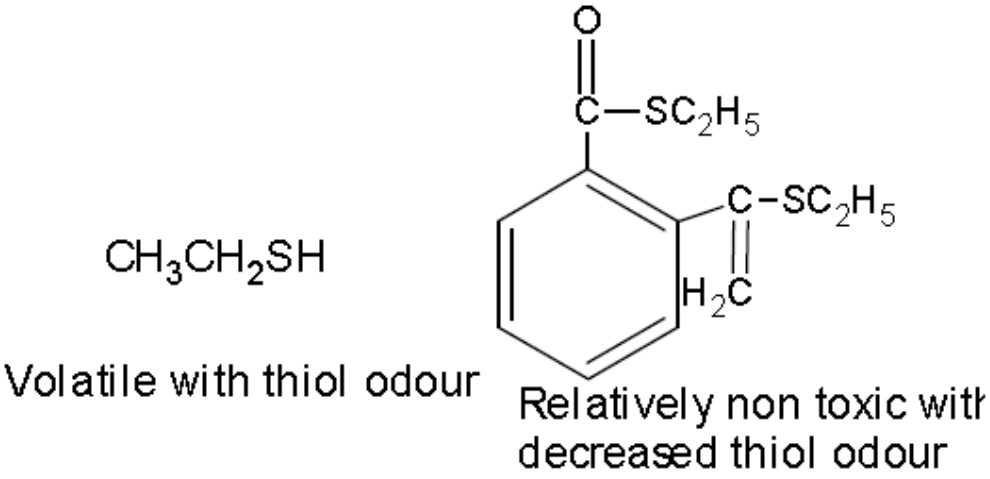
Odour is another aesthetic concern for some drugs, that are often volatile liquid or solids with significant vapour pressure that makes them difficult to formulate.

How can we use organic chemistry to sort out this problem?

A classic example is the volatile mercaptans used as tuberculostatic agents for the treatment of leprosy.

The ethyl mercaptan has a boiling point of 25ºC and a strong disagreeable odour.

On the other hand, diethyl dithio isophthalate, a prodrug of ethyl mercaptan has a higher boiling point and is relatively odourless.



2- Minimizing Pain at Site of Injection

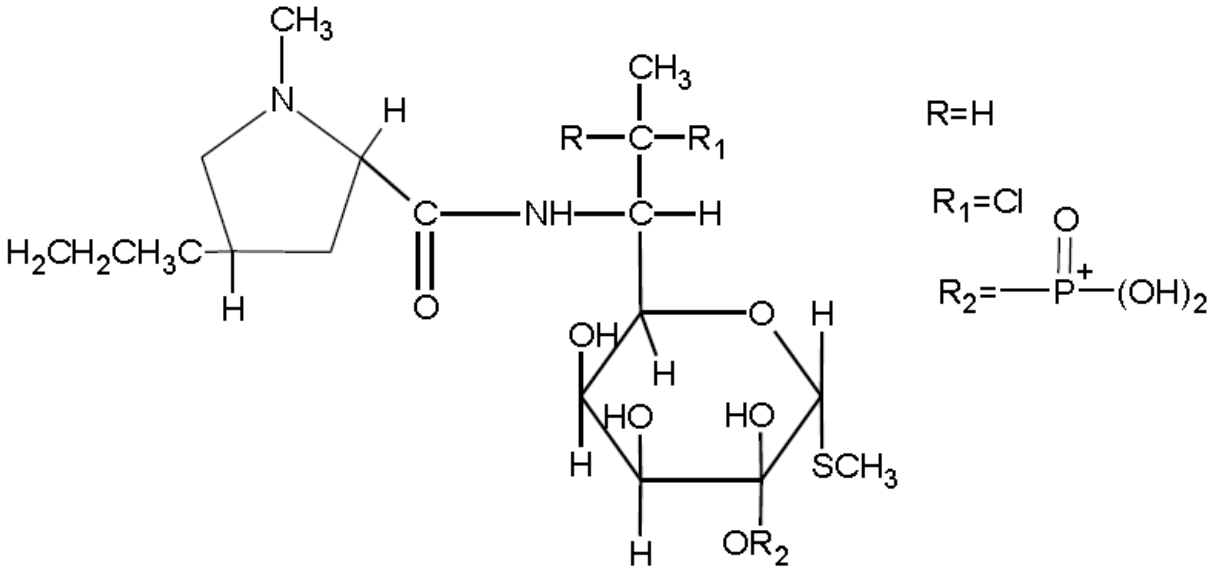
Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs.

So, it is the problem of **poor aqueous solubility** of drugs!!

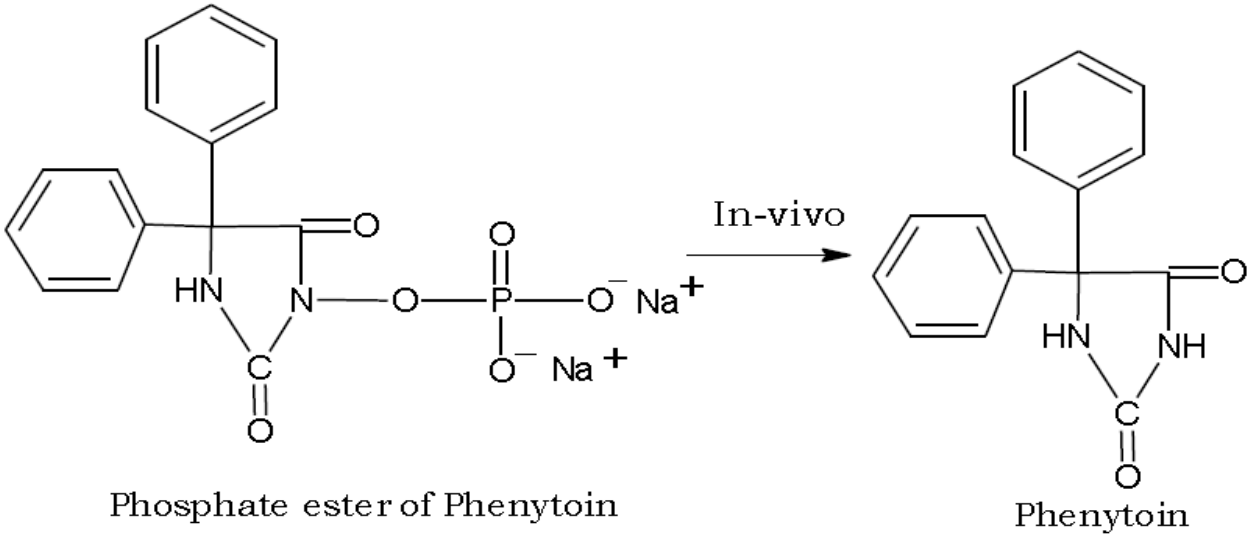
What we have to do?!

We can find the answer in the following examples:

Intramuscular injection of antibiotic like **clindamycin** and anticonvulsant drug like **phenytoin** was found painful due to poor aqueous solubility and could be overcome by making phosphate ester prodrugs respectively and maintaining the formulations at pH 12



Clindamycin–2 dihydrogen phosphate- prodrug of clindamycin



Phosphate ester of Phenytoin

Phenytoin

Phenytoin and its prodrug

3- Alteration of Drug Solubility

The prodrug approach can be used to **increase** or **decrease** the solubility of a drug, depending on its ultimate use.

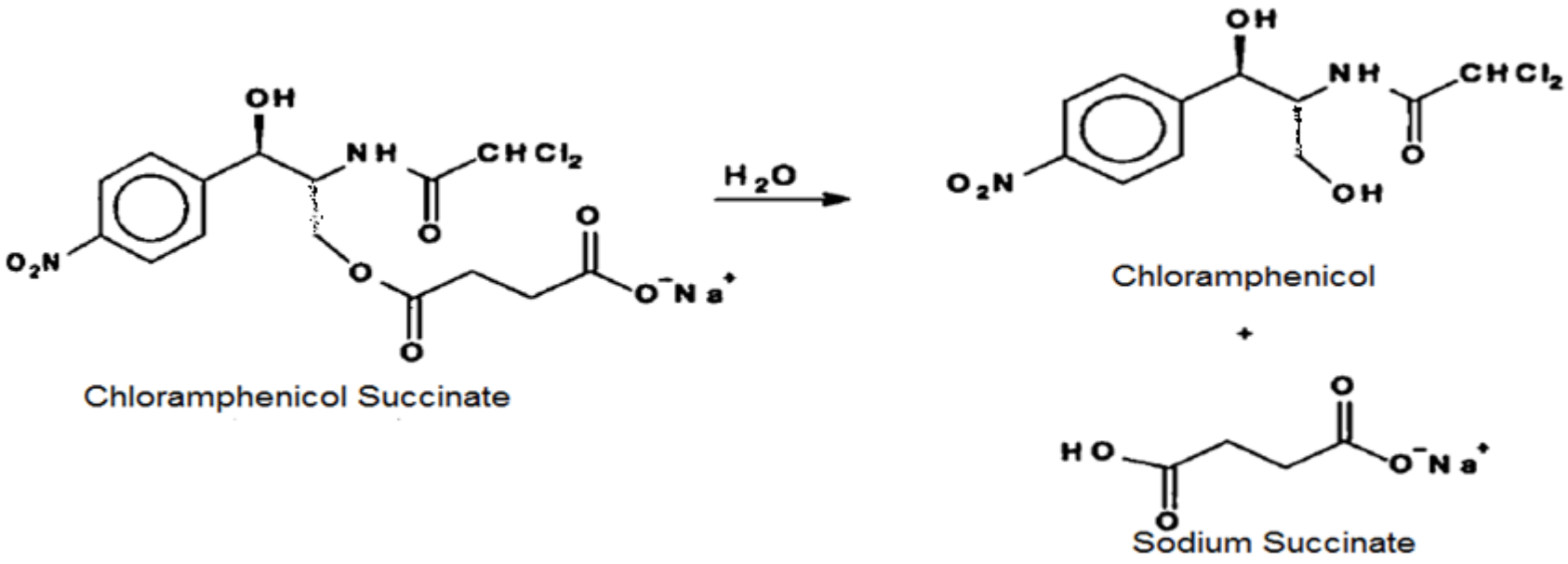
For example, chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively.

On the basis of altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration.

Administration of a drug parenterally may cause pain at the site of injection, especially if the drug begins to precipitate out of solution and damage the surrounding tissue.

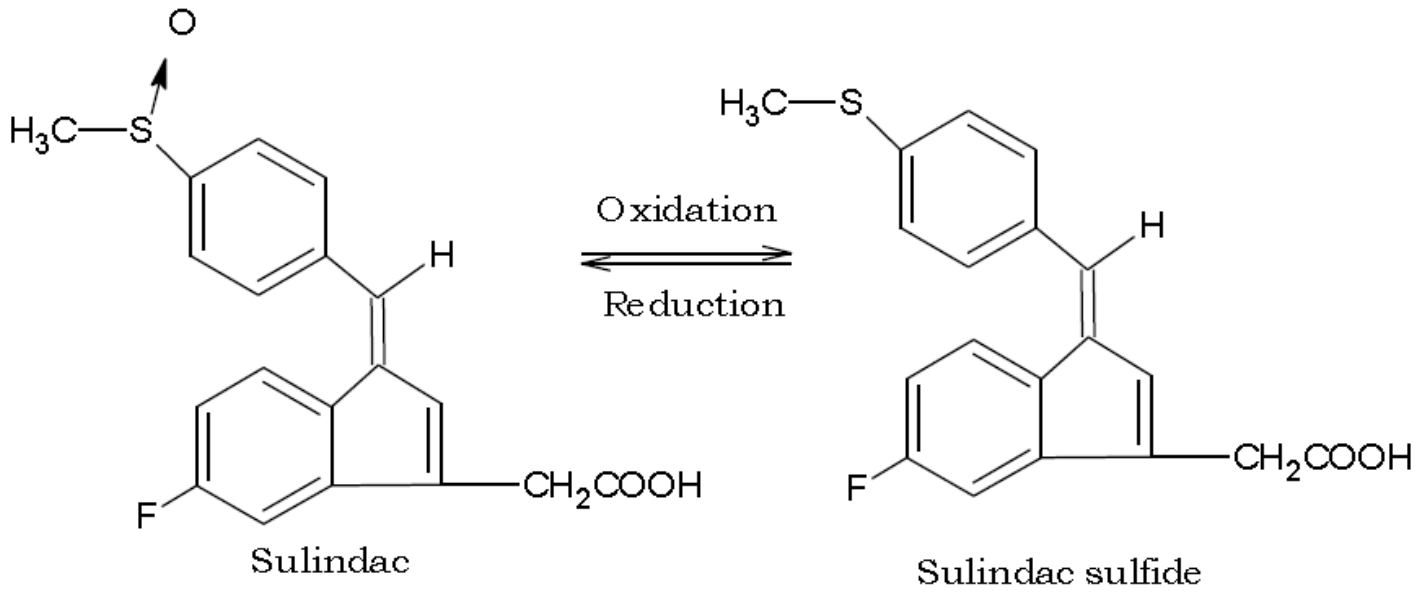
This situation can be remedied by preparing a drug with increased solubility in the administered solvent. Since chloramphenicol has low water solubility, the succinate ester was prepared to increase the water solubility of the agent and facilitate parenteral administration.

The succinate ester itself is inactive as an antibacterial agent, so it must be converted to chloramphenicol for this agent to be effective. This occurs in the plasma to give the active drug and succinate. The ester hydrolysis reaction can be catalysed by esterases present in large amounts in the plasma.



The prodrug approach is also made useful for better gastrointestinal absorption.

It was observed that sulindac, a prodrug of sulindac sulfide being **more water soluble with sufficient lipophilicity**, makes this drug suitable for oral administration.



Sulindac

Sulindac sulfide

4- Enhancement of Chemical Stability

Chemical stability is a most extreme necessary parameter for every therapeutic agent to bring out its pharmacological activity for a longer duration.

A shelf life of at least 2 years is desirable except for vaccines, cytotoxic agents and other life saving drugs.

Although chemical unstability can be solved to a greater extent by appropriate formulations, its failure necessitates the use of prodrug approach.

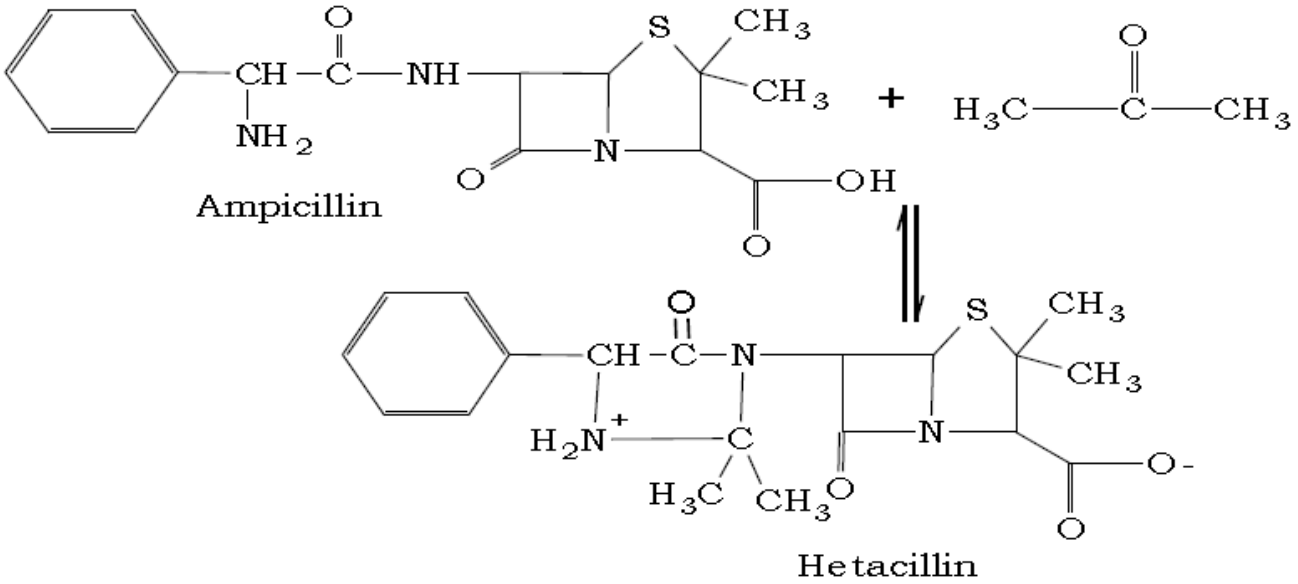
How this work?!

The prodrug approach is based on the modification of the functional group responsible for the instability or by changing the physical properties of the drug resulting in the reduction of contact between the drug and the media in which it is unstable.

Example:

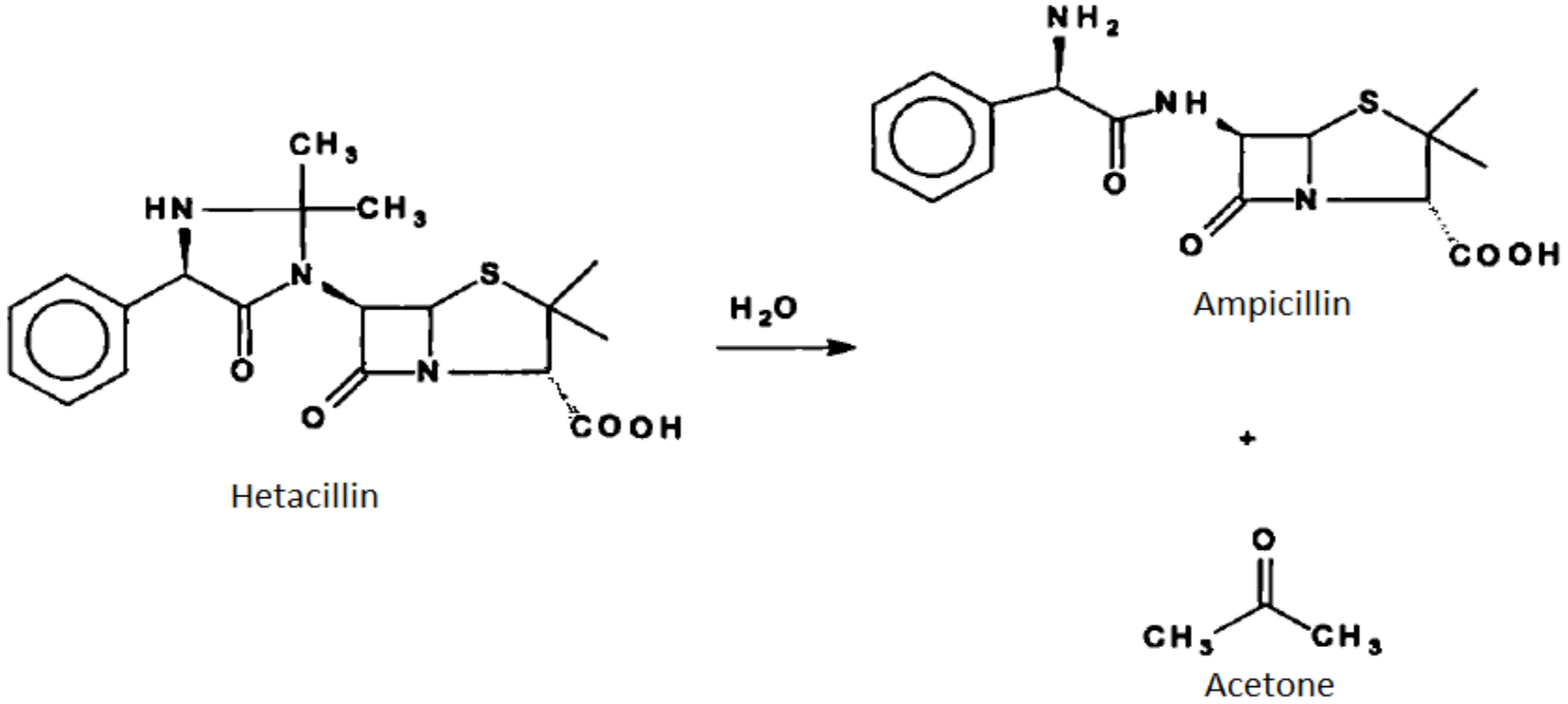
This approach was successfully used to inhibit the auto aminolysis, which occur due to capability of NH_2 group of side chain to attach β–lactam ring of other molecule, in ampicillin molecule in concentrated solution it generates polymeric species of ampicillin.

By making hetacillin, a prodrug of ampicillin formed by the reaction of acetone and ampicillin „ties up" the amine group and thus inhibits auto aminolysis.



The other advantage of this modification is it decreases the basicity of the α-amino group and reduces protonation in the small intestine so that the agent is **more lipophilic**.

In this manner, the absorption of the drug from the small intestine is increased after oral dosing, and chemical hydrolysis after absorption regenerates ampicillin.



Hetacillin

Ampicillin

Acetone

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