6.2.4. Stabilisation of Medicinal Agents Against Common Reactions

Loss of drug through a chemical reaction resulting in reduction of potency is the most studied and most effortlessly understood form of drug instability. Poor product quality is the result of loss of potency. But, the potency of drug may lose through many pathways; it is one of the many possible reasons for calculating the loss of drug.

Quantitation of drug loss is also done due to the following reasons:

1) Drug degradation may result in toxic substances. Therefore, along with the determination of drug quantity lost with time, the degradants formed should also be evaluated which in few cases may cause toxicity. **For example**, pralidoxime degrades via two parallel pH-sensitive pathways forming cyanide (a toxic product) under basic pH conditions (**figure 6.4**). While, the toxicity of degradants of other drugs is not known, **e.g.,** a degradant of tetracycline is epianhydrotetracycline which causes Fanconi syndrome (**figure 6.5**).

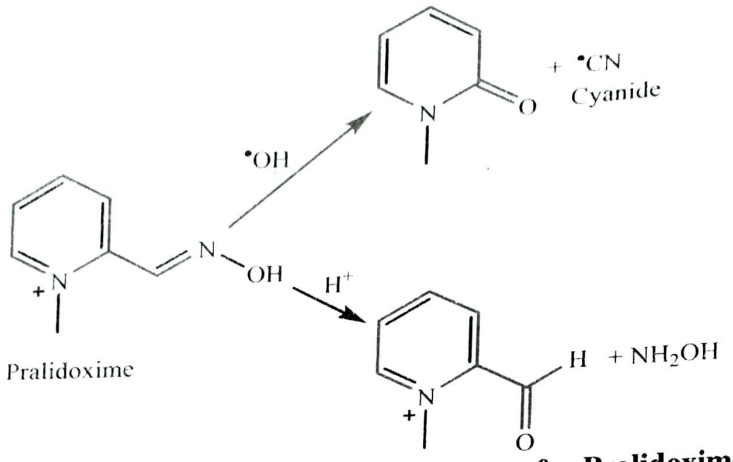


Figure 6.4: Parallel Degradation Pathways for Pralidoxime Leading to Cyanide Formation Under Basic pH Conditions

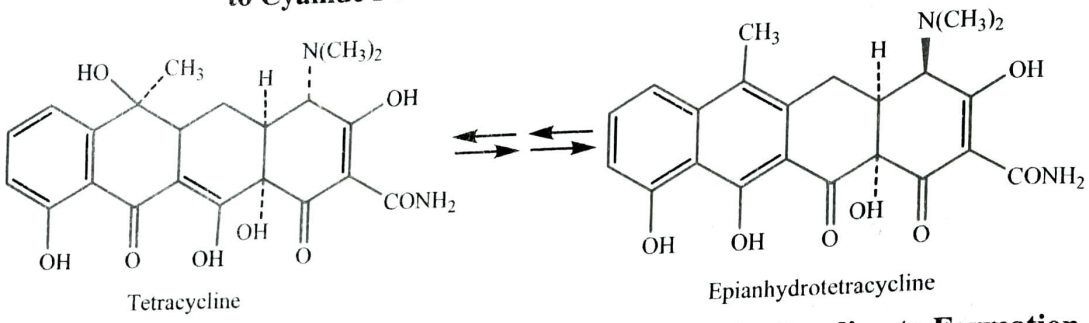


Figure 6.5: Dehydration and Epimerisation of Tetracycline Leading to Formation of Epianhydrotetracycline

In some cases, formation of reactive intermediates occur which may be toxic. **For example**, under acidic pH, penicillin undergoes rearrangement to form penicillanic which is the reason for allergy of penicillins (**figure 6.6**).

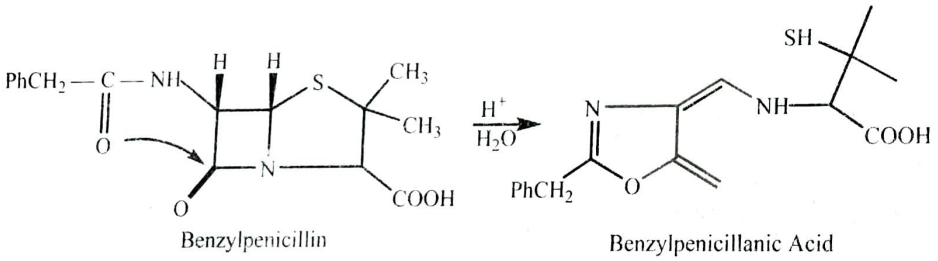


Figure 6.6: An Example of the Rearrangement of Penicillins to their Penicillanic Acids under Acidic pH Conditions

2) Degraded products are considered as adulterated due to significant changes in colour or odour, and dispensing of such products are aesthetically unaccepted. **For example**, on oxidative degradation of epinephrine, a red coloured adrenochrome is formed (**figure 6.7**). Any epinephrine-containing product developing a pink colour is considered to be adulterated.

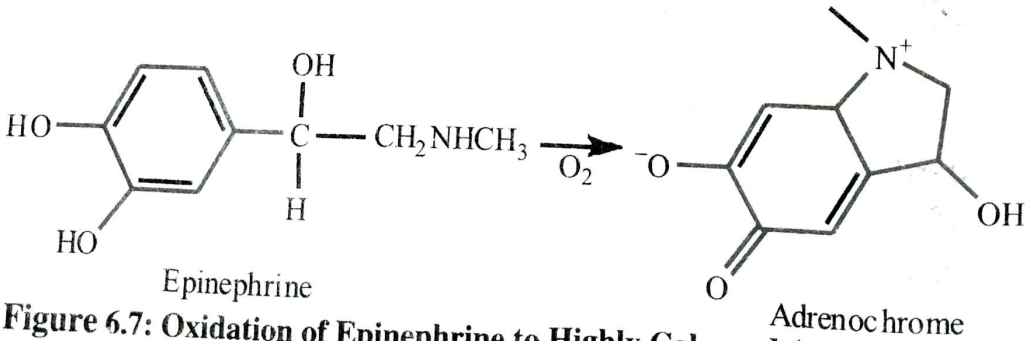


Figure 6.7: Oxidation of Epinephrine to Highly Coloured Adrenochrome

3) The drug formulator should make sure that a drug stabilised in its formulation, should also be stable in acidic pH conditions of GIT (if the drug is administered orally). Mostly the drugs remain stable at neutral pH values of small intestine (disregarding enzymatic degradation) but lose their stability at acidic pH values of the stomach.

Examples of very acid-labile drugs are various penicillins, erythromycin and some of its analogues and the 2′,3′-didoxypurine nucleoside anti-HIV drugs. Knowledge of the stability of a drug in the pH range of 1-2 at 37°C is important in designing potentially acid-labile drugs and their dosage forms.

6.2.4.1. Hydrolysis

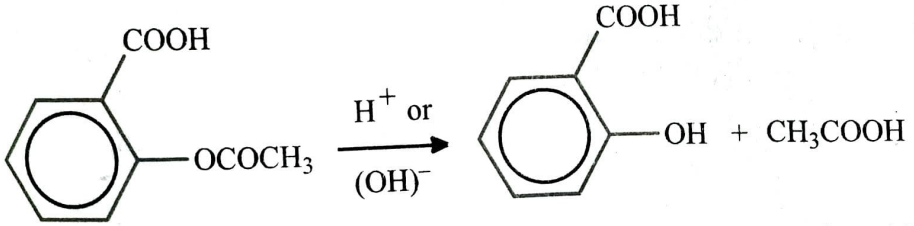
Hydrolysis involves chemical breakdown of a compound due to reaction with water. Hydrolysis reactions are governed by the following **principles**:

1) Drugs having amide and ester group hydrolyse by reacting with a water molecule. Amide group have a slow decomposition rate than ester groups.
2) Drug molecules are available in ionic form or as neutral molecules because they are either weak bases or acids. Hydrolysis of neutral molecules is slower than that of ionic species because hydrolysis is a solubility related phenomenon.
3) Reactions of hydrolysis are catalysed by H^+ and OH^- ions; however, hydroxyl ions (OH^-) catalyse hydrolysis reaction 100-1000 times more actively than the hydrogen ions (H^+).

Examples of drugs decomposing by hydrolytic pathways are:

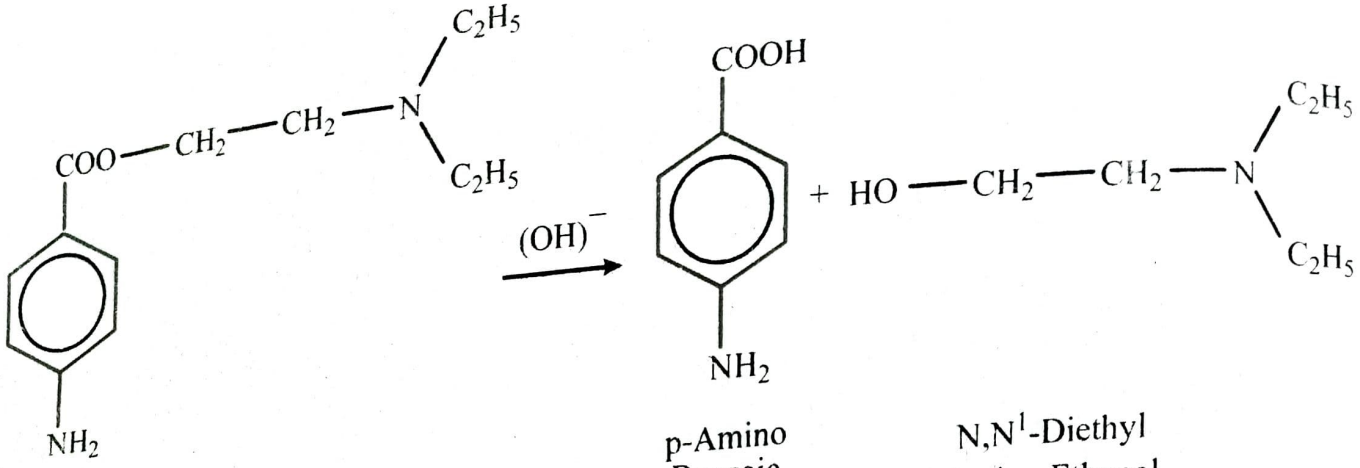
Esters	Amides
Aspirin	Chloramphenicol
Procaine	Ampicillin
Atropine	1) Cephalosporins
	2) Barbituric acids

Ester group containing drugs (**e.g.,** aspirin, atropine, procaine, etc.) hydrolyse to give alcohols and acids.



Aspirin — Salicylic Acid — Acetic Acid

Generally, sterilisation is performed either with high temperature and short time period (HTSP) or low temperature and long time period (LTLP). Conditions of sterilisation should be selected carefully because drugs like procaine hydrolyse easily. For sterilising procaine solutions, autoclaving at 120°C for a short period of time is preferred instead of prolonged heating at 100°C.



Procaine
Neutral or Singly Charged

p-Amino Benzoic Acid

N,N[1]-Diethyl Amino Ethanol

Preventive Measures

Hydrolysis reactions mainly occur in the presence of moisture, and catalyt species H^+ and $(OH)^-$. To eliminate the influence of these factors, the preventi measures to be taken are:

1) **Buffers:** Buffers are used for the stabilisation of drugs. By adjusting the pH a solution, stability and therapeutic activity of the drugs are maintained. Thu the buffer type and optimum pH for a drug should be established through practical approach. In most of the cases, optimal pH remains 3.5-5 because this range hydrolysis catalysed by H^+ and OH^- ions are almost equal.

2) **Complexation:** Caffeine inhibits the hydrolysis of benzocaine in aqueou solution by forming a complex which decreases the attack of catalytic specie on benzocaine, as well as the ion-dipole interactions between $[OH]^-$ or [H ions and drug molecules. Thus, the hydrolysis rate is influenced by th amount of free un-complexed benzocaine in solution.

3) **Suppression of Solubility:** Drug concentration in the solution phase linearly proportional to drug solubility in the solution. Therefore, o decreasing the solubility of a drug in the solution, its concentration in th solution also decreases. This results in reduced rate of hydrolysis. But mostl drugs are insoluble or a small fraction is present in the solution for depending on the saturation solubility.

4) **Removal of Water:** Water content should be completely removed from th formulation because it causes hydrolysis. Removal of water content can b done by:
   i) Storing the drug in dry form and reconstituting the product when needed **e.g.,** streptomycin dry powder for injection.
   ii) Using water-immiscible vehicle for the dispersion of drug, **e.g.,** silicon fluid for aspirin.