# Lesson_5

# Preformulation II

# Hydrolysis, oxidation, reduction

-Dr Ajay Semalty
Department of Pharmaceutical Sciences,
H.N.B Garhwal University (A Central University)
Srinagar Garhwal-246174

**Learning outcomes**

After learning this module you will be able to understand

- Major chemical reactions
- Effect of chemical reactions in preformulation

**Lesson Plan**

- Types of major chemical reactions
- Hydrolysis
- Oxidation
- Reduction
- Effect of temperature
- Effect of humidity
- Photolysis

**Preformulation and Chemical Reactions**

In preformulation the stability is one of the three most important issues. Remember three key words.

"Safety, efficacy, stability."

Any API is likely to undergo changes due to many chemical reactions with the passage of time during storage, processing and its shelf life. The

degradation through various chemical reactions is triggered by the factors like temperature, pH, Humidity, light etc.

The preformulation aims to ensure the stability of API during storage, processing and throughout its shelf life. Let's see the major chemical reactions one by one.

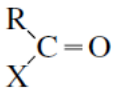
**Hydrolysis**

It is the most common degradation reaction of any API. As water is a universal solvent, the hydrolysis is almost always associated with any formulation development directly or indirectly. Basically, for a drug in a solution, it is a nucleophilic attack of labile bonds by water.

"Hydrolysis is a two-stage process, where a nucleophile, such as water or the hydroxyl ion adds to, for example, an acyl carbon, to form an intermediate from which the leaving group breaks away in the second stage."

The structure of the compound affects the hydrolysis rate; the stronger the conjugate acid that leaves, the faster the reaction.

Some functional groups are more vulnerable to hydrolysis.



Where in Type I hydrolysis X may be ester or amide

While in type II hydrolysis X may be a halogen or any other good leaving group



Type I hydrolysis reactions are catalyzed by acid or bases and hence they can be well controlled by pH modulation.

Can you remember some examples for acid or base catalyzed reactions? Get back to us with chemical reactions in discussion forum with examples…

These example of hydrolytic prone compounds are

ester example aspirin

thiol ester example spirolactone

amide example chloramphenicol

sulfonamide example sulfapyrazine

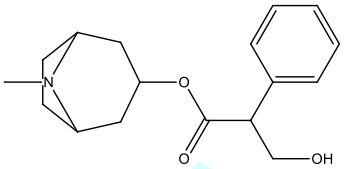
imide example phenobarbital

lactam example methicillin

lactone example spironolactone

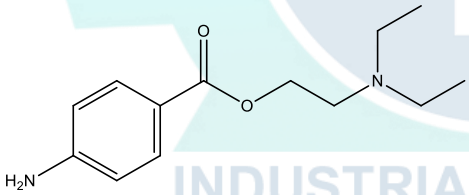
halogenated aliphatic example chlorambucil

**The classic example of hydrolysis of atropine**




**Atropine**

- Undergoes hydrolysis at pH values higher than four;
- Higher the pH, lower the stability;
- Soda lime glass avoided as container;
- aqueous atropine solutions buffered at around pH 3.5–4






**Procaine (anesthetic agent)**

- Undergoes acid-catalyzed hydrolysis < pH 2.5;
- Base-catalyzed hydrolysis > pH 5.5
- Maximum stability at pH 3.5;
- Hydrolysis protection is done by increasing solubility in a nonaqueous solvent and;
- By micellization of the drug using surfactant for shielding the drug hydrolysis

**Factors affecting hydrolysis:**

- **Solution pH,**
- **buffer salts,**
- **ionic strength**
- **Use of nonaquoeus solvents**
- **presence of co-solvents,**
- **presence of complexing agent**
- **presence of surfactant**
- **temperature**
- **humidity**

**pH, Buffer, ionic strength:** We have studied the relation of pH, ionic strength, solubility already in the earlier modules.

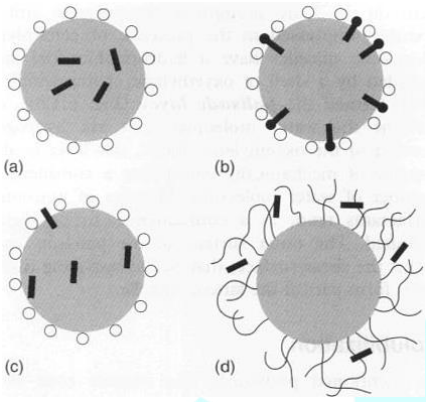
**Solvents:** For the intramuscular and subcutaneous routes, the use of nonaqueous vehicles may be considered as a method of avoiding hydrolysis. Same we studied for procaine. On the other hand the use of a cosolvent (a water-miscible solvent) in the formulation may increase stability by

- suppressing ionization
- reducing the extreme of pH required to achieve solubility
- reducing water activity by reducing the polarity of the solvent, e.g. 20% propylene glycol in chlordiazepoxide HCl injection.

**Complexation/micellization/ solubilization:**

The effect of complexation and micellization is also well practiced for protection of drugs from hydrolysis. Complexation with various agents like EDTA, lipids etc. may shield the prone groups of the drug and can protect it from hydrolysis. The micellization with surfactants and other molecules also shield the molecule from hydrolytic attack. Solubilization (either by cosolvent, complexation or micellization) shows a modifying effect on the

rate of hydrolysis of drugs. The location of nonpolar and polar compound in the micelles governs their level of protection from hydrolysis.




***Location of drug in solubilization***

The non-polar compounds which are solubilized deep in the hydrocarbon core of a micelle are generally better protected than that of polar compounds located closer to the micellar surface.

**Temperature and humidity**

The higher temperatures may reduce the moisture content of the product, thus slowing hydrolysis. High humidity may trigger hydrolytic degradation.

TRY TO LEARN MORE EXAMPLES…



**Oxidation**

After hydrolysis the oxidation is the most common chemical reaction pathway of degradation. Oxygen being the most common element present in the molecules, the **sensitivity to oxidation is also common for many molecules.**

**The oxidation is**

- Removal of hydrogen atoms from a carbon atom or addition of an oxygen atom to a carbon atom.

- The most difficult reactions to understand,
- Difficult to prevent.
- Accelerated by the presence of trace metals
- Should be understood for the molecule under study and the formulation should contain suitable and compatible antioxidant or blend of antioxidants to prevent the same.
- Prevented by using antioxidants
    - **Type 1: water-soluble**: sodium bisulfate/ sulfite/ metabisulfite/ thiosulfate, sodium formaldehyde sulfoxylate, L- and D-ascorbic acid, cysteine, acetylcysteine, thiolactic acid, thioglycollic acid, thioglycerol, thiourea, dithithreitol;
    - **Type 2: Oil-soluble:** propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, ascorbyl palmitate, nordihydroguaiaretic acid, and a-tocopherol.

The oxidation problem is very common with vitamins and iron supplements. In that case, a little amount (as allowed by regulatory bodies like FIP) is added extra into the formulation to achieve the desired shelf life. This is called overages.

*Always use suitable antioxidants. Also see the effect of antioxidant on other reactions. E.g. the most common antioxidant- metabisulfite catalyze hydrolysis reactions.*

**Reduction**

Reduction is the third most important chemical reaction after hydrolysis and oxidation.

Basically, reduction is indispensible with oxidation reaction. If one thing is oxidized the other reactant is reduced.

- Removal of an oxygen atom from a carbon atom or addition of hydrogen atoms to a carbon atom is called reduction.
- Unlike oxidation which involves an increase in the oxidation number of an atom, the reduction involves decrease in oxidation number.
- An alkene upon reduction forms the corresponding alkane. (by reacting with hydrogen).
- All the factors, which affect oxidation, also affect reduction.
- If oxidation is being prevented the same time we are preventing the reduction.

Dear learners can we have some **classic examples of reduction**? I will wait in discussion forum. Pease do share the examples. You can use free software like "chemdoodle" and "xdrawchem" for drawing structures. If you are uncomfortable in using chemical structure drawing software, please do write the equations from your hand, put your name and the enrollment number on the sheet, scan it and post it onto the discussion forum.



**Effect of temperature**

Process of degradation generally increases with the increase in temperature. As per a well experienced fact, the rate of a chemical reaction increases by a factor of between to three fold for every 10 °C rise in temperature. This may be understood by that fact that the reaction rates are proportional to the

number of collisions per unit time. And the frequency of collisions increases with the increase of temperature.

Arrhenius studied the effect of temperature on the reaction rate constant (k) and expressed their relationship by the following equation (Arrhenius equation).

$$K = A\, e^{-Ea/RT}$$

Where A = a constant which is termed as the frequency factor

or $$\log K = \log A - \left(\frac{Ea}{2.303RT}\right)$$

Integrating the above equation between limits $k_1$ and $k_2$; and $T_1$ and $T_2$ the following equation is obtained.

$$\log \frac{K_2}{K_1} = -E_a / 2.303R.\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

or $$\log \frac{K_2}{K_1} = \frac{-E_a\left(T_2 - T_1\right)}{2.303R.T_1T_2}$$

Where $k_1$ and $k_2$ are the reaction rate constant at temperature $T_1$ and $T_2$.; Ea is the energy of activation (cal/mole): representing the minimum energy required by reacting molecule to undergo reaction; R is gas constant 1.987 (cal/mole. degree); T is absolute temperature (t °C + 273).

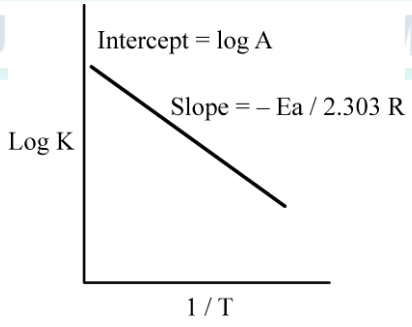



**Fig.** Arrhenius plot.

Therefore, the common logarithms of the reaction rate constant at the various temperatures, plotted against the reciprocals of the absolute temperatures (1/T) will yield a straight line whose slope (negative) will be Ea/2.303R (Fig. ).

**Limitations of Arrhenius Equation**

- Arrhenius equation was based on the assumption that the reaction mechanism does not change as a function of temperature, i.e., *E*a is independent of *T*, but this is not true practically for every case. Therefore, it may not be valid for some reactions, especially the complex reactions.
- Higher temperature may evaporate solvents thus producing unequal moisture content at different temperatures.
- At elevated temperatures, there is less relative humidity and oxygen solubility, which makes it difficult to predict the stability of drugs (which are sensitive to the presence of moisture and oxygen) at room temperature.
- The viscosity of disperse systems is decreased at high temperatures, and thereby altering the physical characteristics.

**Relative Humidity (RH)**

Have you experienced to visit coastal area or if you live in the area like Mumbai, Goa Vishakhapattnam, you better know what the humidity is exactly.

You might have seen that the biscuits, snacks, chips and sugar crystals absorb moisture in rainy season, if remained open at room temperature.

**"Water vapor carrying capacity of air is called humidity."**

The water vapor present in the air should be controlled in the pharma plant and storage. The vapor present in the air (moisture) when adsorbed onto the drug or excipients may trigger the degradation reaction like hydrolysis, oxidation, reduction and microbial degradation. These adsorbed films of moisture are saturated with drug compared to the dilute solutions as in injectables.

When a piece of air of certain temperature and pressure is saturated with water vapors, then the humidity of that air is called saturation humidity or 100

% RH. In comparison to this the humidity is expressed in % RH. Actually at a particular temperature and pressure air can carry a certain amount of water vapor only. After that the vapor gets condensed and this is called dew point. This thing you might have experienced when you add chilled water in a glass. The outer surface show the dew formation.

This is the difference of partial vapor pressure of the surface and the free vapor pressure of environment which leads either to evaporation or condensation. Higher the RH higher will be the water absorption onto the drugs or the excipients. And other associated degradation reactions.

The drug in crystal form may be damp if exposed to higher RH environment.

So to ensure the stability, a critical humidity must be maintained so as to make the drugs or excipients dry.

ICH guidelines on stability gives the specific range of RH along with temperature for performing the stability studies.

**Photolysis**

Various drugs are sensitive to sunlight and upon exposure to the light these are degraded. For example indomethacin, amphotericin B, riboflavin, tetracycline etc.

The energy associated with the light radiation increases from UV light to IR but it is independent of temperature. Out of the natural sunlight EMR range 280-790 nm, the UV range of 280-320 nm is the one which causes the photodegradataion. The photons are absorbed at a particular wavelength by molecules. And then depending on the nature of drug it may cause degradation, energy or heat emission, or emission of light at a new wavelength (phosphorescence, fluorescence).

**Avoiding Photolysis**

Work in dark/ cover the apparatus by dark paper/film using

- amber glass bottles,
- cardboard outers
- aluminium foil overwraps

- blisters

**Take Away Message**

- Hydrolysis, oxidation and reduction are the major chemical degradation reactions.
- In preformulation the sensitivity of the drug and excipient must be studied and the protection of drug and excipients against these reactions must be ensured.
- Effect of temperature, relative humidity and Photolysis should also be studied thoroughly and vulnerability against these must be minimized
- Now, I suggest you as always to refer further readings, see the weblinks given, read the e content carefully, learn more examples and free feel to ask any question regarding the topic covered in discussion forum. We will surely get back to you with solution.
- If you have forgot to attempt your weekly quiz do it without failure.
- Stay tuned guys… we will be coming back with racemization and polymerization.

Happy learning….

**Further Readings**

- Introduction to Oxidation Reduction (Redox) Reactions https://www.youtube.com/watch?v=5rtJdjas-mY
- Gibson M. (Ed), Pharmaceutical preformulation and formulation: a practical guide from candidate drug selection to commercial dosage form, II edn, Informa Healthcare.
- Qiu Y, Chang Y and Zhang GZ (Exe. Eds), Developing solid oral dosage forms: Pharmaceutical theory and practice, Elsevier, 2009.

**References**


- Niazi SK, Handbook of Preformulation, Informa health care, 2007.
- Gibson M. (Ed), Pharmaceutical preformulation and formulation: a practical guide from candidate drug selection to commercial dosage form, II edn, Informa Healthcare, 60- 75.

- Qiu Y, Chang Y and Zhang GZ (Exe. Eds), Developing solid oral dosage forms: Pharmaceutical theory and practice, Elsevier, 2009, pp 25-35.
- Aulton ME (Ed), Pharmaceutics, The science of dosage form design, II edn, Churchill Livingston, London, 2006, pp- 113-122.
- Semalty A, Semalty M, Rawat MSM, Essentials of Pharmaceutical Technology II edn, Pharma Med press, Hyderabad India.