Module 02

Hydrolysis

Hydrolysis is the breaking of a molecular bond by reaction with water. In liquid preparations, water can frequently be replaced or reduced in the formulation through the use of substitute liquid such as glycerin, propylene glycol, and alcohol. In injectable products; anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.

Decomposition by hydrolysis may be prevented by using dry form for reconstitution. When reconstituted, it remains stable for the period over which the preparation is normally consumed.

Molecules containing the ester group hydrolyse to produce a carboxylic acid and an alcohol. examples include aspirin and procaine.

The amide group is also frequently found in drug molecules; it degrades to a carboxylic acid and an amine. E.g. lidocaine and paracetamol. Refrigeration is advisable for most preparations considered subject to hydrolysis. Eye drop preparations of chloramphenicol therefore require storage in a refrigerator.

Oxidation

Oxidation reactions involve an increase in the number of carbon-to-oxygen bond in a molecule or a reduction in the number of carbon-to-hydrogen bonds. These reactions are a common cause of chemical instability of drugs. They are also responsible for deterioration of vegetable oils, which may be used in pharmaceutical products as a solvent or an emollient in emulsion and creams. Oxidation reactions tend to be complex, giving a variety of degradation products.

The oxidative process is diverted and the stability of the drug is preserved by agents called antioxidants, which react with one or progress of the chain reaction. E.g. sodium sulfite, sodium bisulfite, sodium metabisulfite and ascorbic acid. In oleaginous (oily) preparations, alpha-tocopherol, butyl hydroxyl anisole, and ascorbyl palmitate are used.

Oxidative reaction increased by the presence of ferric, ferrous, cupric, and chromic ions. These can be eliminated by chemically complexing or binding the metal through the use of chelating agents e.g. ethylenediamine tetra-acetic acid (EDTA). Light can also act as a catalyst to

oxidation reactions, As a precaution against acceleration of oxidation, sensitive preparations are packaged in light-resistant or opaque containers.

Drug stability

Chemical degradation of the drug is the factor which limits the shelf life of a formulation. A reduction of drug content down to 90% of the theoretical value is generally regarded as the maximum reduction acceptable.

A simple means of increasing the shelf life of a product can sometimes by adding more drug than is given on the label. This is known as an overage. If 110% of the theoretical amount of drug is added to the product when it is manufactured, twice as much degradation will be possible before the product reaches the end of its shelf life. This strategy is only possible for products where the dose is not critical and where the degradation products are not toxic, such as many vitamin products.

Polymerization

Reaction of a drug molecule with another molecule of the same drug may result in the formation of a dimer or polymer. Formaldehyde is the example of a drug capable of polymerization. It may polymerize to paraformaldehyde $(CH_2O)_n$.

Polymerization is a major mechanism of degradation of the disinfectant glutaraldehyde. Its disinfectant activity is optimal at a slightly alkaline pH but at this pH it is subject to polymerization. In order to avoid polymerization on storage, glutaraldehyde solution needs to be formulated at an acidic pH, where polymerization does not occur. It is then activated immediately before use by adding an alkaline buffer.

Isomerization

There are two main types of isomerism.

(i) Structural Isomerism and (ii) Stereoisomerism

Structural isomers are compounds that have the same molecular formula but different structural formula. Structural isomerization is sometimes a mechanism of drug degradation. E.g. betamethasone-17-valerate, a potent corticosteroid.

When isomerism is caused by the different arrangements of atoms or groups in space, the phenomenon is called stereoisomerism. Geometrical or Cis-trans isomerism is a type of stereoisomerism.

Optical isomerism is another type of stereoisomerism. An optical active compound can exist in two isomeric forms which rotates the plane-polarized light in opposite directions. These are called optical isomers and phenomenon is known as optical isomerism.

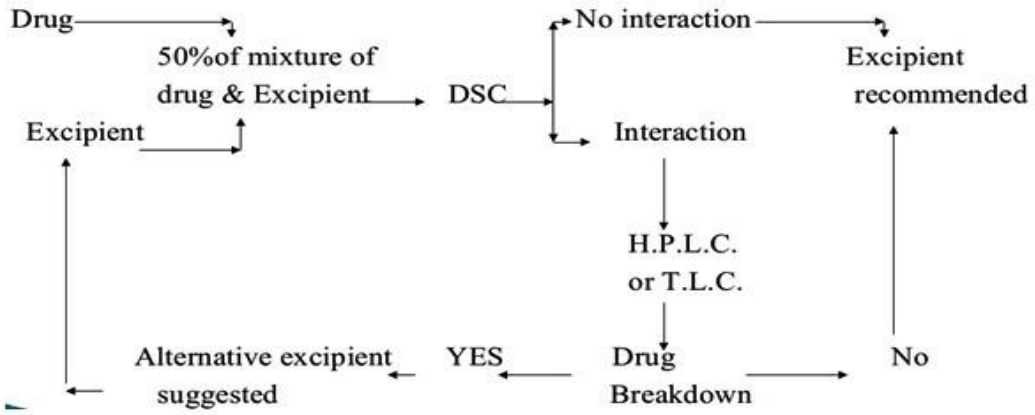
Racemization

The conversion of an optically active compound into a racemic mixture is called racemization. Racemic mixture is a mixture containing equal amounts of (+) and (-) isomers, as it does not rotate the plane of polarized light and it is optically inactive. Racemization reduce the potency of the drug. Epinephrine may undergo racemization in aqueous solution.

Role of drug-excipients interactions in preformulation studies.

Many excipients are used to prepare the desired dosage form of a drug substance. Drug excipients interactions can lead to degradation of the active ingredient, thereby reducing the amount available for therapeutic effect. For example Colloidal silica was shown to catalyze nitrazepam degradation in tablet dosage form.

Phenobarbital formed an insoluble complex with PEG-400, which resulted in slower dissolution and decreased absorption.



Methyl paraben undergoes reaction with sorbitol to produce a variety of sorbitol hydroxybenzoate esters by reaction with sorbitol's various hydroxyl groups.

The Maillard reaction involves a reaction between amine-containing drugs and lactose or other sugars when employed as diluents in tablet or capsule formulations. This reaction results in yellowing of white tablets on storage. The mechanism is reaction of the amine with sugar to a form a glycosyl amine, which rearranges to from a colored 1-amino-2-keto sugar. The incompatibility can be avoided by replacing the sugar with alternative diluents. If a sweetening agent is required in a solid dosage form of an amine drug, for example in a dispersible tablet, sucrose and glucose would undergo the Maillard reaction; however, mannitol can be used, as it does not undergo the reaction.

Dextrose is widely used as tonicity modifier in the parenteral dosage form and it is used as nutrition solution. Sterilizations by autoclaving of such parenteral preparations containing dextrose can cause isomerization of dextrose in fructose and formation of aldehyde (5-hydroxymethyl furfuraldehyde), which can react with primary amino group to form shiff base and colour development.

So Knowledge of drug–excipients interactions is a necessary prerequisite to the development of dosage forms that are stable and of good quality.

TGA

Thermal gravimetric analysis (TGA) is a method of thermal analysis in which changes in physical and chemical properties of materials are measured as a function of increasing temperature (with constant heating rate), or as a function of time (with constant temperature and/or constant mass loss).

TGA is commonly used to determine selected characteristics of materials that exhibit either mass loss or gain due to decomposition, oxidation, or loss of volatiles (such as moisture).

Concept of Prodrug- Almost all drugs possess some undesirable physiochemical and biological properties. Their therapeutic efficacy can be improved by minimizing or eliminating the undesirable properties while retaining the desirable ones. This can be achieved through biological, physical or chemical means.

- The biological approach is to alter the route of administration, which may or may not be acceptable to the patient.
- The physical approach is to modify the design of the dosage form such as controlled delivery of drugs.
- The chemical approach is the best approach in enhancing drug selectivity and minimizing the toxicity.

The three chemicals means for improving the drug efficacy are-

1. Design and development of new drugs- However it requires screening of thousand of chemical compounds for biological activity of which only one may become a clinically useful drug.
2. Design of hard drug and soft drug
3. Design of prodrug

Hard drug and soft drug

Hard drug- A hard drug is one which is resistant to biotransformation and therefore has a long biological half life. Design of hard drug involve metabolic stabilization of the existing drug molecules by replacing functional group that are susceptible to biotransformation with the stable ones.

An example of this approach is chlorpropamide, an analogue of tolbutamide with p-methyl replaced with a chloro group.

Tolbutamide ($t_{1/2}$ = 6h) $\longrightarrow$ Chlorpropamide ($t_{1/2}$ = 33h)

Soft drug- A soft drug is a biologically active compound that is biotransformed in vivo in a rapid and predictable manner into nontoxic moieties. Such an agent has a very short duration of action. e.g. insulin and adrenaline. Design of synthetic soft drugs involve introduction of a group or bond susceptible to rapid metabolic action, for example replacement of a part of alkyl side chain of the drug with an ester group that can be readily hydrolyzed in vivo.

Prodrug- A prodrug is a pharmacological substance (drug) that is administered in an inactive (or significantly less active) form. Once administered, the prodrug is metabolised *in vivo* into an

active metabolite. A prodrug is also called as pro-agent bioreversible derivative or latentiated drug. The design approach is also referred to as drug latentiation.

Ideal properties of prodrug

It should not have intrinsic pharmacological activity.

It should rapidly transfer chemically or enzymatically in to the active form where desire.

The metabolic fragment apart from the active drug should be non-toxic.

Prodrug in improvement of elegancy

Improvements of taste- By reducing the solubility of the bitter drug in saliva make the bitterness unnoticeable. Examples of drugs are chloramphenicol and clindamycin and formation of their prodrug as chloramphenicol palmitate and clindamycin palmitate respectively.

Improvement of odour- ethylmercaptan (ethanethiol) is one of the liquid drug (B.P. 35^{o}C) having unpleasant smell is useful in treatment of leprosy. It is converted into its phthalate ester, Diethyldithio-isophthalate which has higher B.P. & is odourless. The prodrug is administered by rubbing on skin. After absorption the esters is metabolized to parent drug by thioesterases.

Enhancement of solubility& dissolution rate (hydrophilicity) of drug- Drug with hydroxyl function can be converted in to their hydrophilic form by use of half-esters such as hemisuccinates, hemiglutarates or hemiphthalates. The other half of these acidic carriers can forms sodium, potassium or amine salts & make the moiety water soluble in the case of steroidal drug such as cortisol, prednisolone, betamethasone & dexamethasone.

Enhancement of bio-availability (lipophilicity)- A big advantage of increased bioavailability through increased lipophilicity is the reduction in drug dose. For example: bacampicillin (Prodrug of ampicillin) is as effective as ampicillin in just one-third of the dose.

Prevention of presystemic metabolism- Several corticosteroids undergo extensive first-pass hepatic metabolism which can be prevent by use of their esters or ether prodrugs. For example, Propranolol is one of drug with high first pass metabolism. Its hemisuccinate prodrug is resistant to esterases of liver.

Enhancement of chemical stability- The prodrug design is also a good alterative to improve stability. An example of anti-neoplastic drug azacytidine. The aqueous solution of this drug is

readily hydrolyzed but the bisulfite prodrug is stable to such a degradation at acidic pH & is more water soluble than the parent drug. The prodrug converts to the active drug at the physiological PH of 7.4.

Carbenicillin, a broad spectrum penicillin is susceptible to hydrolysis and destabilization in gastric acid. Its ester prodrug- Carindacillin (α-indanol ester) and Carfecillin (α-phenyl ester) are stable at gastric pH. In the intestine, hydrolysis of these agents release Carbenicillin at pH above 7.0.

Erythromycin also has a similar acid instability problem. Its sterate, ethyl succinate prodrugs are stable to hydrolysis in stomach.

Reduction of GIT irritation- Several drug cause irritation & damage to the gastric mucosa through direct contact by increased stimulation of acid secretion or through interference with protective mucosal layer. The NSAID's especially salicylates have such a tendency. They lower the gastric PH & induce ulceration.

e.g. Aspirin is a prodrug of salicylic acid.

Reduction of pain on injection- Intramuscular injections are particularly painful when the drugs precipitate in to the surrounding cell or when the solution is strongly acidic, alkaline or alcoholic. For example: the low aqueous solubility of clindamycin. This can be overcome by use of more water soluble prodrug of such agent like the 2-phosphate ester of clindamycin.

Reduction of toxicity- Intraocular instillation of timolol and epinephrine cause irritation to eyes and systemic absorption cause undesirable cardiovascular effects due to poor intraocular penetration. Lipophilic ester prodrug of such type of drugs have better intraocular penetration which result in reduction of the instilled dose and adverse effect are limited.

Ibuterol, the diisobutyrate ester of terbutaline, a selective β2-agonist is 100 times more potent, has longer duration of action and is free of both local and systemic toxicity.

Site-specific drug delivery- The prodrug is converted into its active form only in target organ/tissues by utilizing either specific enzyme or a pH value different from the normal pH for activation. Mesalamine **(**5-aminosalicylic acid) is an effective drug useful in treatment of inflammatory bowel disease (ulcerative colitis) but drug is inactivated before reaching of the site

of action. Covalent binding of this drug to sulfapyridine yields the prodrug sulfasalazine, an azo compound. This prodrug reaches the colon intact where cleavage by the bacterial enzyme azo reductase releases the active Mesalamine for local action.

Another example of site specific delivery is Acyclovir, anti viral drug useful in Herpes infections. After entry into infected cell, the drug is acted upon by the viral enzyme thymidine kinase to form acyclovir monophosphate that is further converted to the active triphosphate form by cellular enzymes. The triphosphate form destroys the viral DNA. So activation of acyclovir occurs only in cells infected by virus.

To treat poisoning of organophosphorus compound which are cholinesterase inhibitor, antidote N- methyl pyridinium- 2- carbaldoxime (2-PAM or pralidoxime) is used that is a potent reactivator of cholinesterase, penetrates the BBB poorly due to its quarternary nitrogen. However reduced dihydropyridine form of 2-PAM, called as pro-2-PAM, readily enters the CNS. Inside the brain, it is oxidized to polar 2-PAM.