INDUSTRIAL PHARMACY-I

UNIT I-PREFORMULATION

CLASS:5

TOPIC:Chemical Properties: Hydrolysis, oxidation, reduction, racemisation,

OXIDATION

It is a very common pathway for drug degradation in both liquid & solid formulation .

Oxidation occurs in two ways:-

Auto oxidation.

Free radical chain process .

OXIDATION SELECTED FUNCTIONAL GROUPS

Alkenes. Substituted aromatic groups. (Toluene, phenols, anisole). Ethers. Thioethers . Amines .

FACTORS AFFECTING OXIDATION PROCESS

1) Oxygen concentration
2) Light.
3) Heavy metals particularly those having two or more valence state.(e.g. copper, iron, nickel, cobalt .)
4) Hydrogen & Hydroxyl ion.
5) Temperature .

The oxidation process involves several steps viz.: initiation, propagation, and termination, and can be catalysed by heat, light, metals or free radicals.

Typically the reaction is as follows

Initiation:

$X^* + RH \rightarrow R^* + XH$

Propagation: $R^* + O2 \rightarrow ROO^*ROO^* + RH \rightarrow ROOH + R^*$

Termination: $ROO^* + ROO^* \rightarrow$ stable product

$ROO^* + R^* \rightarrow$ stable product

$R^* + R^* \rightarrow$ stable product

PREVENTION OF OXIDATION .

1. Reducing oxygen content.-Boiling water & purged with nitrogen gas.
2. Storage in a dark & cool condition.
3. Addition of chelating agent. [Eg . EDTA, Citric acid, Tartaric acid].
4. Form complexes with trace amt of heavy metal ions and inactivating their catalyzing activity . Adjustment of pH.
5. Changing solvent. [Eg . Aldehydes, ethers, ketones may influence free radical reaction].
6. Addition of antioxidant.-Reducing agent or Chain inhibitors of radical induced decomposition

HYDROLYSIS.

it mainly involves nucleophilic attack of labile group.
eg.. Lactam > Ester > Amide > Imide.
If attack is by water- hydrolysis.
If attack is by solvent -solvolysis .
Generally follows 2 nd order kinetics as there are 2 reacting species, water and API.
In aqueous solution, water is in excess, the reaction is 1 st order.
Effectiveness of molecule therefore depends on hydrolytic stability of molecule.
For example, lidocaine is amide derivative of procaine, which is ester derivative used as local anesthetic. As ester derivative is more readily hydrolyzed; its duration of action is short while amide derivative is more stable and hence used as long-acting local anesthetic.
Beta-lactam antibiotics are susceptible to hydrolysis and hence they are supplied as dry powder injection where they are reconstituted before intravenous administration

Conditions that catalyze the breakdown:-
1. Presence of hydroxyl ion.
2. Presence of hydride ion.
3. Presence of divalent ion.
4. Heat .
5. Light.

6. Ionic hydrolysis.
7. Solution polarity & ionic strength.
8. High drug concentration .

Prevention of hydrolysis :-

pH adjustment.

Formulate the drug solution close to its pH of optimum stability.

Addition of water miscible solvent in formulation.

Optimum buffer concentration to suppress ionization .

Addition of surfactant:

Nonionic, cationic & anionic surfactant stabilizes the drug against base catalysis .

Salts & esters: E.g.. Phosphate ester of Clindamycin.

The solubility of pharmaceuticals undergoing ester hydrolysis can be reduced by forming less soluble salts.

Store with dessicants .

By use of complexing agent

RACEMIZATION

The inter conversion from one isomer to another can lead to different Pharmacokinetic properties (ADME) as well as different Pharmacological & toxicological effect.

eg.. l -epinephrine is 15 to 20 times more active than d -form, while activity of racemic mixture is just one half of the l - form. It follows first order kinetics. It depends on temperature, solvent, catalyst & presence or absence of light .

Racemization is mostly affected by the conditions like pH, type of solvents, presence of light, and temperature. So main goal in this study is to design optimum condition in which molecule can remain stable

Photostability

Photolysis refers to decomposition of a molecule by absorption of energy when exposed to light. Exposure to light not only brings photodegradation but may trigger oxidation. It is absorption of shorter wavelength components that may bring oxidation than longer wavelength components.

Prior knowledge of photochemical behavior can provide guidance regarding storage condition, packaging, and handling condition. In most of the cases, the photochemical behavior of molecule is studied in the range of different spectral regions that are 200–290, 290–320, 320–400, and 400–700 nm.

For example, riboflavin and vitamin B12 are susceptible to photodegradation directly and oxidation induced by light. So to avoid the decomposition, the formulation containing vitamin B12 and riboflavin is stored in amber color vials. Amber color bottles do not allow the ultraviolet radiation to pass through, which is the main factor for photodegradation

For those substances that may degrade when exposed to light, a number of opportunities exist to prevent or minimise instability through the choice of specialised coatings or packaging.

Solid-state photostability can be evaluated by exposing thin layers of samples to high-intensity light (HIL)/UV conditions initially at 25 °C (but subsequently at more elevated temperatures) in a photostability chamber.

The ICH guidelines recommend exposure at 1.2 million lux hours to visible light and 200 W hours m−2 to UV to represent the frequencies of light radiation in various geographical locations.

Since the drug may be required to be formulated as a solution (e.g. oral, parenteral or topical), photostability should also be evaluated in aqueous and, where appropriate, non-aqueous solution.

For both solid and solution photostability studies, samples protected from light are stored under the same conditions and used as controls.

PHOTODECOMPOSITION PATHWAYS

N-Dealkylation : E.g. Diphenhydramine, Chloroquine , Methotrexate .

Dehalogenation : E.g. Chlorpropamide , Furosemide . Dehydrogenation of Ca ++ channel blocker. E.g. Solution of Nifedipine → Nitrosophenylpyridine (with loss of water). Rapidly yellow color Brown

drug excipient Compatibility

Although early preclinical studies—and some animal studies on a lead candidate drug—may use simple solutions derived from preformulation studies on solubility and stability, as the candidate progresses to clinical trials, especially confirmatory large-scale trails, it will be required to be formulated with excipients.

Thus drug–excipient compatibility studies are required to determine the flexibility of choice available for various types of oral, parenteral, topical etc. formulation.

Based on a knowledge of the stability characterises of the drug substance, stability tests can be conducted on the drug in the presence of various excipients.

Clearly the range of excipients that might be eventually be chosen for the final, marketed, product can be extensive and, hence, a considerable number of possible combinations for evaluation can be identified. This is not usually justified at the early stages of development. Such initial studies should therefore be restricted to a few major potential excipients,

e.g. lactose, sucrose, dextrose, magnesium stearate etc., as a prelude to more extensive evaluation later in formulation design and development.

An incompatibility may result in

change in physical,chemical ,microbiological and therapeutic properties of dosage form,

change in dissolution performance

decrease in potency

increase in degradation

Method:

Sample A: ACTIVE DRUG SUBSTANCE

Sample B: Active drug substance+ 5% distilled water

Sample C: Drug in suspension with excipients

All are taken into clear neutral glass ampoules separately and sealed.The ampoules are then stored at suitable temperature and analysed at various time points

Method of analysis

Thermal techniques-DSC

Chromatographic techniques-HPLC,TLC

Mass spectroscopy and NMR