Chemical Stability of Drugs

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Abstract

Depending on the reaction conditions, drugs or pharmaceutical organic compounds can be transformed through hydrolysis or elimination. They can also degrade by isomerization, oxidation or polymerization. This review aims to indicate the reaction mechanisms involved in drug stability. In this context, mechanisms are useful to explain the formation of products in a chemical reaction medium. When drugs are in an inappropriate reaction environment, they break down accordingly. Therefore, it is very important to understand the conditions that alter drug stability in order to identify ways to ensure drug stability. Indeed, chemical or physical degradation can alter the therapeutic efficacy of a drug and it can lead to the generation of undesirable products.

Keywords- Chemical, Stability, Hydrolysis, Oxydation, Beeakdown, Drugs

I. Introduction

Chemical degradation of pharmaceuticals is often a key factor limiting the shelf life of pharmaceuticals. Degradation of other ingredients in the formulation, like antimicrobial preservatives or antioxidants are also important factors. The nature of the degradation products formed in the dosage form can be a factor limiting the shelf life of the product. This may be because the decomposition products are toxic. For example, the antifungal drug flucytosine breaks down to fluorouracil, which is cytotoxic. Alternatively, decomposition products can give the product an unacceptable appearance. For example, the oxidation products of epinephrine (adrenaline) are highly colored. The use of risk-based predictive stability studies is increasing in the pharmaceutical industry. A survey of member companies of the International Consortium for Innovation and Quality in Drug Development published in 2017 found that 16 companies reported using predictive stability studies in drug and product development.[1]

Applications include classification of prototype formulations, initial test or shelf-life assignment, packaging selection, expression equivalence, understanding inherent stability, salt/polyester selection figure and set the specifications. Stability prediction studies are usually applied to small molecules1 but have also been applied to large molecules, such as peptides. Stability is an essential quality characteristic of pharmaceutical products. It is considered to be the most important drug-related factor for the development of therapeutically active dosage forms. Evaluation of the chemical and physical stability of the product is carried out in preclinical studies of formulation, process development, and packaging evaluation. The efficacy and safety of a product is based on the stable properties of the active ingredients and excipients. Knowledge of the specific chemical functional groups of a drug molecule can help predict its degradation pathways and possible approaches to stabilizing it. The selection of an appropriate packaging system is essential to ensure the physicochemical stability of the product during storage and use. Stability assessment of pharmaceutical substances and medicinal products is a mandatory requirement of regulatory agencies.

In general, drug molecules are not prone to spontaneous chemical degradation. The cause is usually another reactive molecule in the dosage form. This is often due to the presence of water or molecular oxygen, but drugs may also react with other formulation ingredients or other molecules of the same drug. Protecting formulations from chemical degradation is one of the primary goals in dosage form design. This chapter describes the general types of chemical degradation that affect 'small molecule' drugs.

II. Chemical Degradation Reactions

Drugs are chemical entities with different molecular structures and different functional groups. They can undergo decomposition reactions in aqueous and organic solvents through different pathways depending on the factors causing the decomposition. The main methods of drug degradation are:

A. Hydrolysis
B. Oxidation
C. Decarboxylation
D. Elimination
E. Isomerization
F. Dimerization
G. Epimerization
H. Dehydration
I. Dehydrogenation
J. Dehalogenation
K. Photodegradation

These reactions are described as follows:

A. Hydrolysis

Hydrolysis in aqueous and liquid dosage forms is one of the most common reactions that destabilize drugs containing ester, amide, imide, carbamate, and lactone, nitrile, and carbohydrate groups. Many drugs are susceptible to acid and/or alkaline hydrolysis, including aspirin, paracetamol, sulfacetamide, indomethacin, procaine, digoxin, riboflavin, lincomycin, chloramphenicol, penicillins, cephalosporins, and benzodiazepenes. Media pH plays an important role in drug hydrolysis.

- **Hydrolysis of esters**

Ester compounds hydrolyze by nucleophilic attack of water or OH- ions on the ester group.

- **Acetylsalicylic acid (aspirin)**

Aspirin is the best-known example of hydrolysis of ester compounds. In aqueous solution, it hydrolyzes to salicylic acid and acetic acid. This reaction accelerates with increasing temperature.[2]

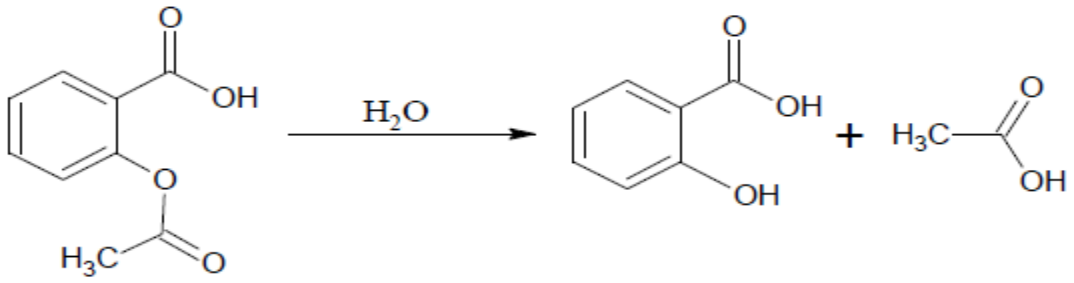

Figure:1 Hydrolysis of ester (Aspirin)

- **Procaine**

The most important reaction involved in the breakdown of procaine is hydrolysis. It leads to the formation of -aminobenzoic acid and diethylaminoethanol. The rate of the reaction is affected by the ionization of the molecule (PKA 8.05).[3]

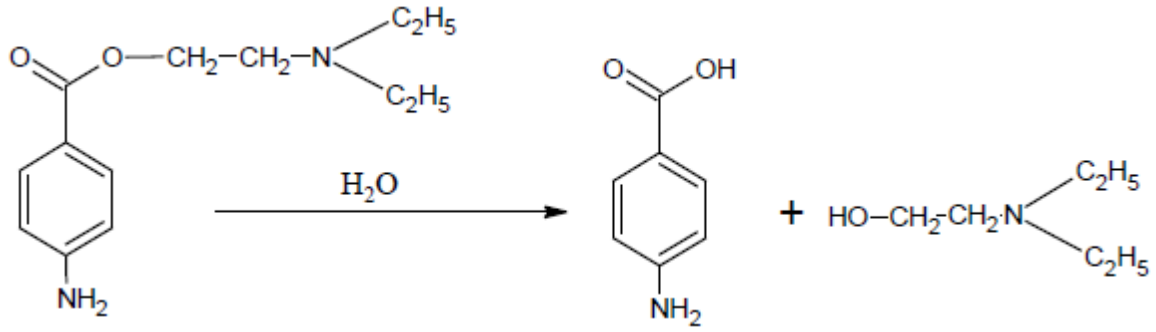

Figure:2 Hydrolysis of ester (Procaine)

- **Hydrolysis of amides**

Compounds containing an amide bond are less susceptible to hydrolysis compared with those containing an ester bond. This is because of the fact that the carbonyl carbon of the amide bond has a lower electrophilic character.

- **Paracetamol**

In aqueous solution paracetamol is hydrolyzed to form 4-aminophenol and acetic acid.[4]

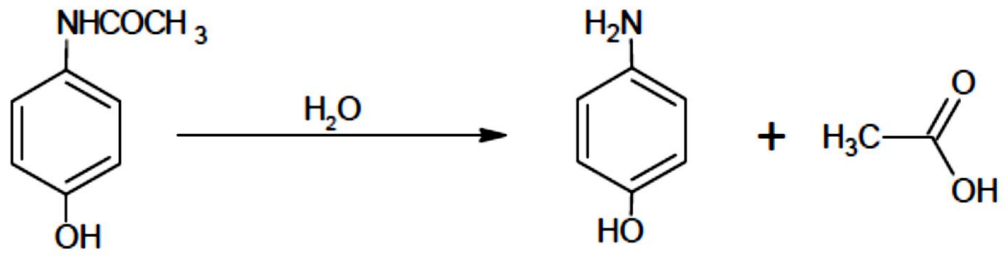

Figure:3 Hydrolysis of amides (Paracetamol)

- **Sulfacetamide**

Hydrolysis of Sulfacetamide in aqueous solution is to form sulfanilamide and acetic acid. Sulfanilamide undergoes oxidation to yield 4,4'- azobenzenedisulfonamid which is reoxidized to 4,4'-azoxybenzenedisulfonamide on exposure to light. These reactions are accompanied by the formation of a yellow to reddish brown color.[5,6,7]

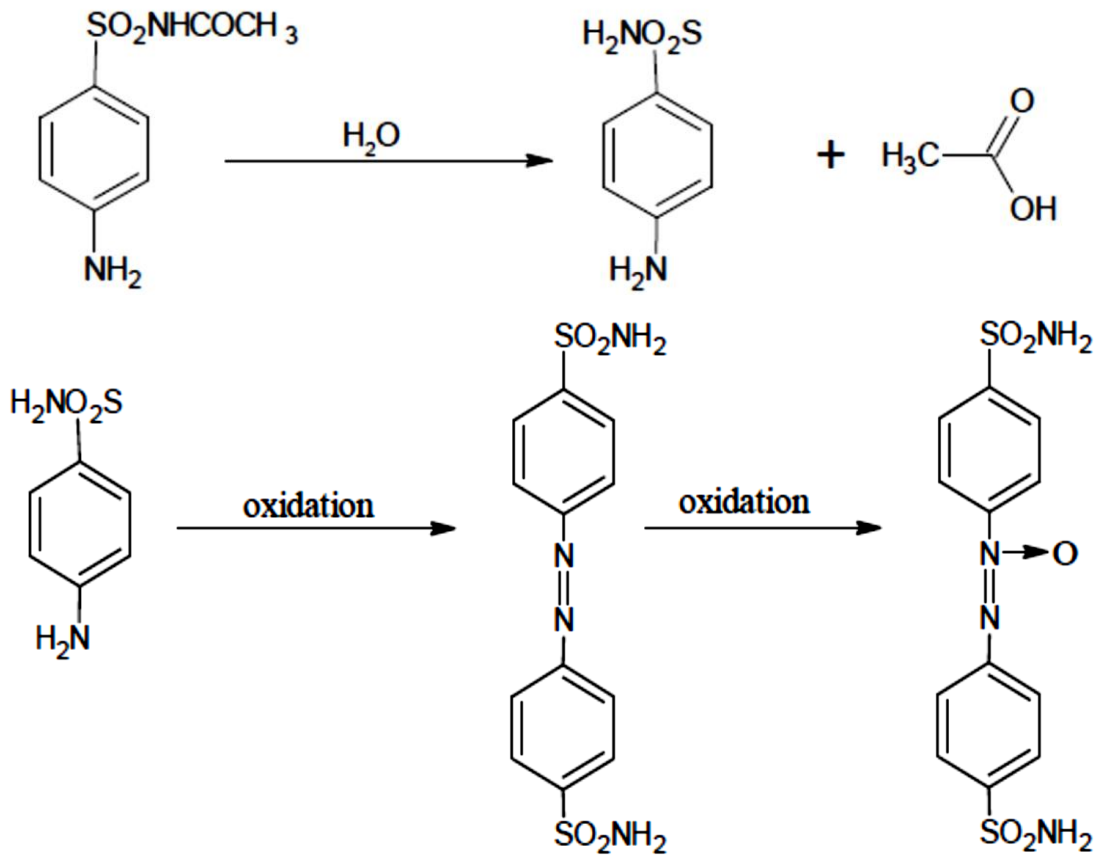

Figure:4 Hydrolysis of amides (Sulfacetamide)

- **Hydrolysis by ring opening**

The hydrolysis of a drug compound by ring opening could occur by the cleavage of the C–N bond.

- **Riboflavin**

Riboflavin (vitamin B2) goes through base-catalyzed hydrolysis by cleavage of the isoalloxazine ring to give 1,2-dihydro-6,7-dimethyl-2-keto-I-D-ribityl-quinoxaline-3-carboxylic corrosive (β-keto acid) and 6,7-dimethyl-4-D-ribityl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline (flavor-violet).

The debasement response is joined by the deficiency of assimilation of riboflavin at 445 nm and is advanced by an expansion in temperature.[9]

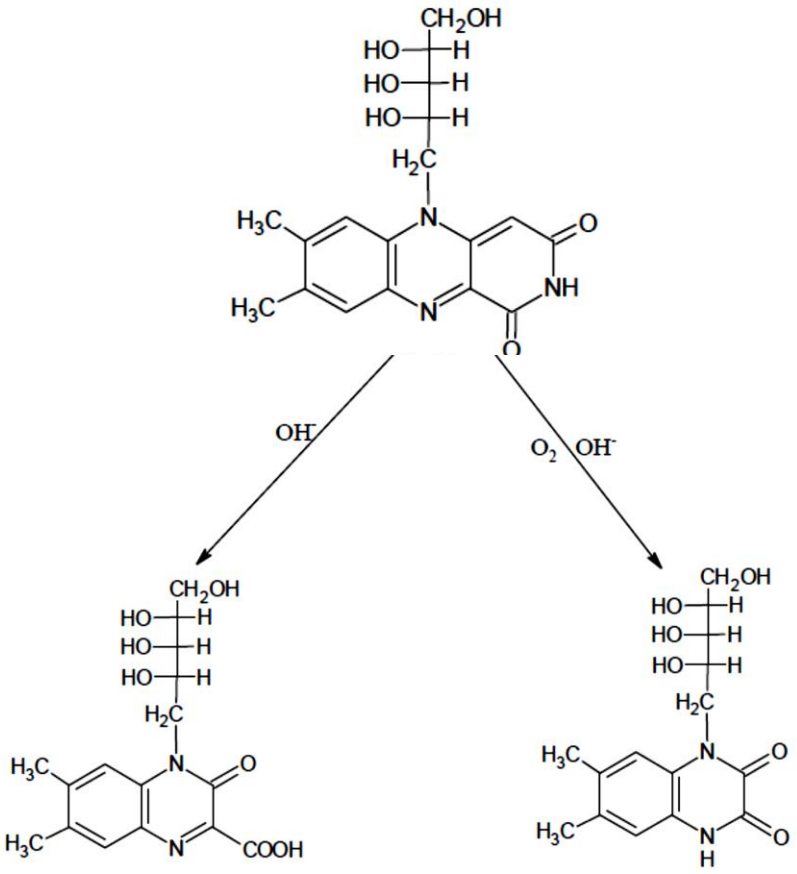

Figure:5 Hydrolysis by ring opening (Riboflavin)

B. Oxidation

Oxidative degradation of drugs is another common reaction in the presence of oxygen or oxidizing agents. Exposure of drugs to atmospheric oxygen during manufacturing, storage, or use can affect drug content through oxidation reactions. Many drugs are oxidized, including ascorbic acid, vitamin A, glucose, morphine, hydrocortisone, methyldopa, aldehydes, phenols, unsaturated compounds, thiols, phenothiazenes, and polyenes. The pH of the medium can influence the rate of oxidation reactions as a result of ionization of the species involved and changes in the redox potential.

- **Ascorbic acid**

Degradation of ascorbic acid (vitamin C) in aqueous solution under aerobic conditions leads to oxidation of the molecule to dehydroascorbic acid. Dehydroascorbic acid is hydrolyzed to diketogulonic acid in alkaline solutions. [10]

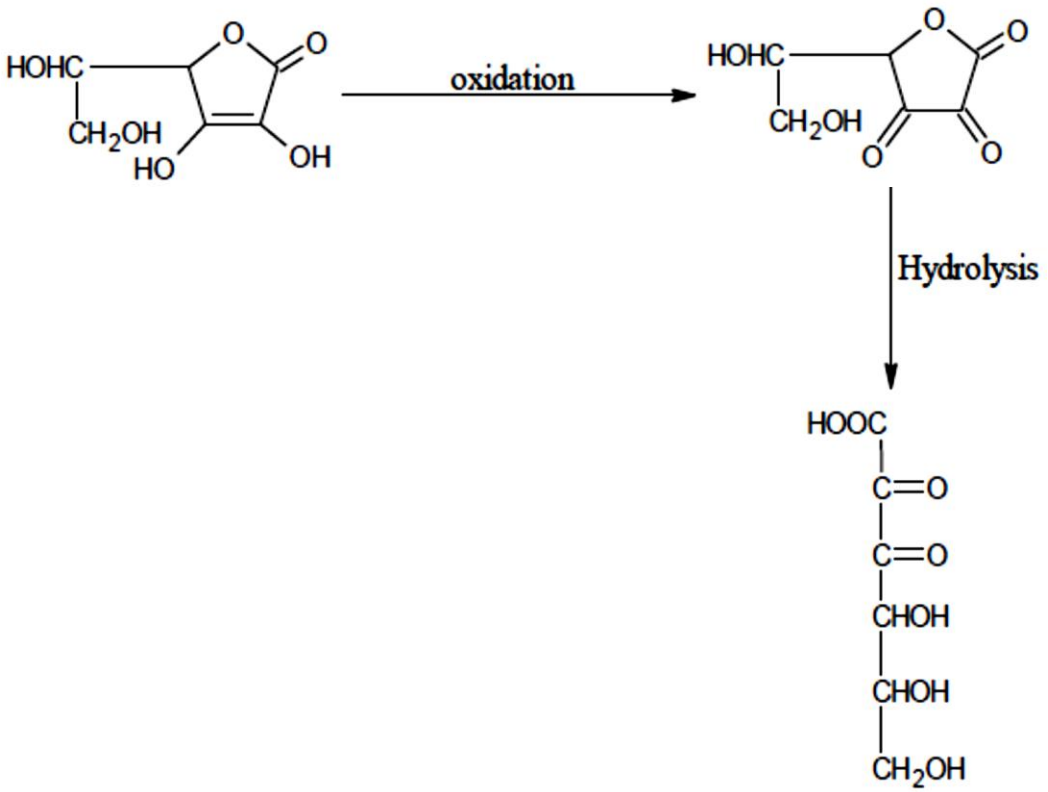

Figure:6 Oxidation of ascorbic acid.

- **Morphine**

The main decomposition reaction of morphine in aqueous solution is oxidation by air and light. Oxidation products of morphine include pseudomorphine (noxydimorphine) and morphine N-oxide. [11]

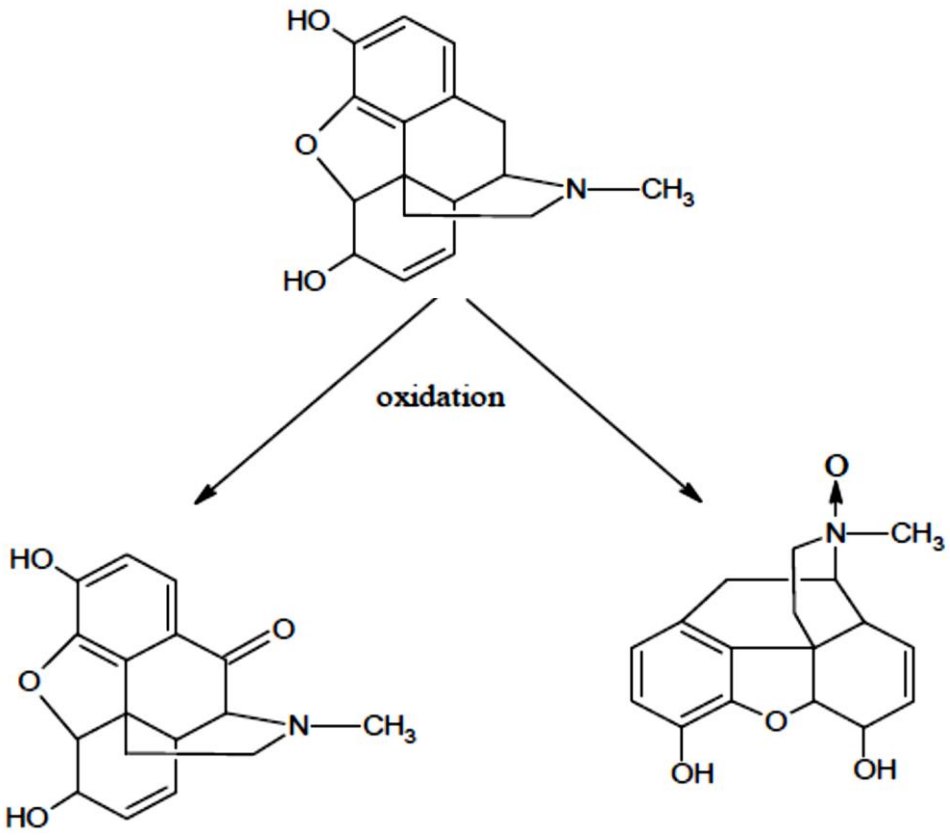

Figure:7 Oxidation of morphine.

- **Phenols**

Phenols go through facile oxidation reactions. The hydroxyl institution is strongly electron donating to the phenyl ring that's oxidizable. Abstraction of the proton offers a solid radical which then reacts with molecular oxygen. The deprotonation of phenol at better pH to the phenolate anion strongly catalyzes auto-oxidation reaction (base-catalyzed auto-oxidation). The phenolate anion is an powerful nucleophile that could react with electrophilic species at both the oxygen or the ortho or para positions. Phenolic compounds are oxidized withinside the presence of Fe3+ or Cu2+ ions.[12]

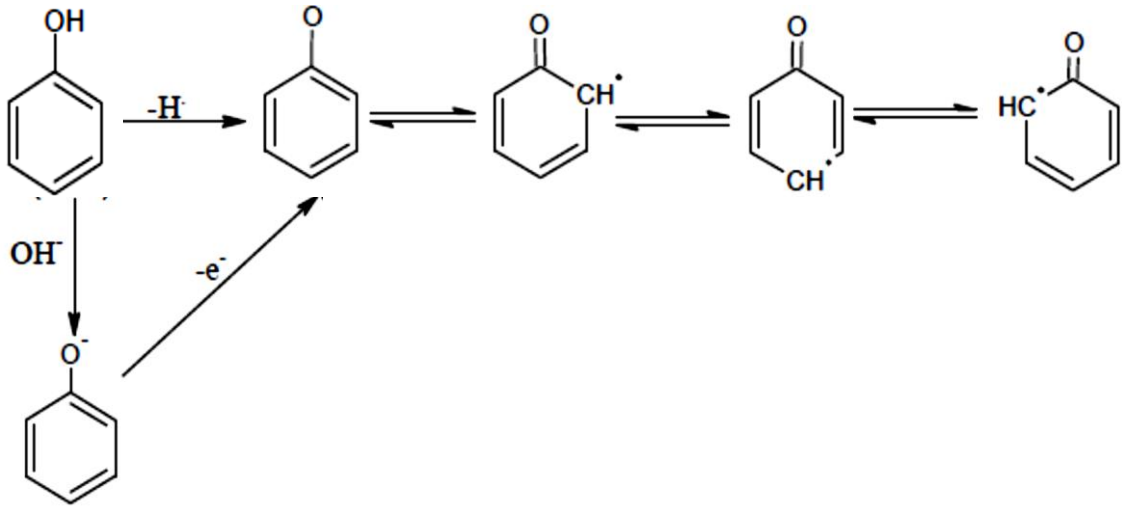

Figure:8 Oxidation of phenols.

C. Decarboxylation

Drugs with carboxyl groups can be degraded by decarboxylation under certain conditions.

- **4-aminosalicylic acid**

The main decomposition reaction of 4-aminosalicylic acid in aqueous solution is decarboxylation leading to the formation of 3-aminophenol. The reaction is faster in acidic media than in alkaline media, where the molecule is in ionized form.[13]

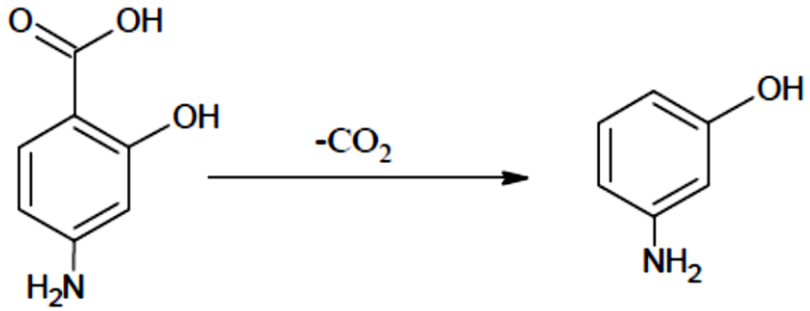

Figure:9 Decarboxylation of 4-aminosalicylic acid.

D. Elimination

Elimination reactions involve the removal of two or more substituents from a molecule in one or two steps. The one-step mechanism is known as the E2 reaction (bimolecular) and the two-step mechanism is known as the E1 reaction (unimolecular).

- **Trimeramol**

Trimeramol (N2,N4,N6-trimethylol-N2,N4,N6-trimethylmelamine), a synthetic carbinolamine-containing antineoplastic drug, is degraded by two major pathways. One degradation pathway involves the loss of a hydroxymethylene group through elimination of formylaldehyde to form the parent trimethylmelamine.[14]

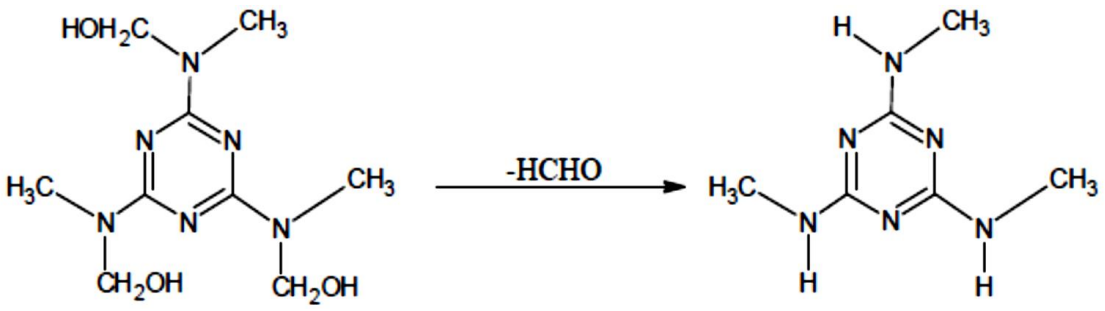

Figure:10 Elimination of trimeramol.

E. Isomerization

Isomerization reactions involve the conversion of one molecule into another having exactly the same atoms but with a different arrangement.

- **Cephalosporins**

Cephalosporins are known to undergo isomerization of the double bond involving the Δ^3 position to the Δ^2 position.

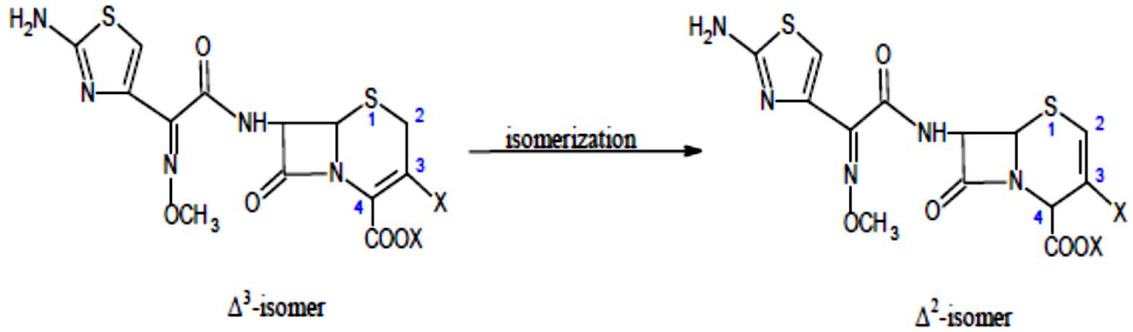

Figure:11 Isomeriztion of cephalosporins.

F. Dimerization

In this chemical reaction two molecular subunits are joined and formed dimer.

- **Nalidixic Acid**

Nalidixic acid undergoes dimerization on thermolysis by decarboxylation to form a dimer.

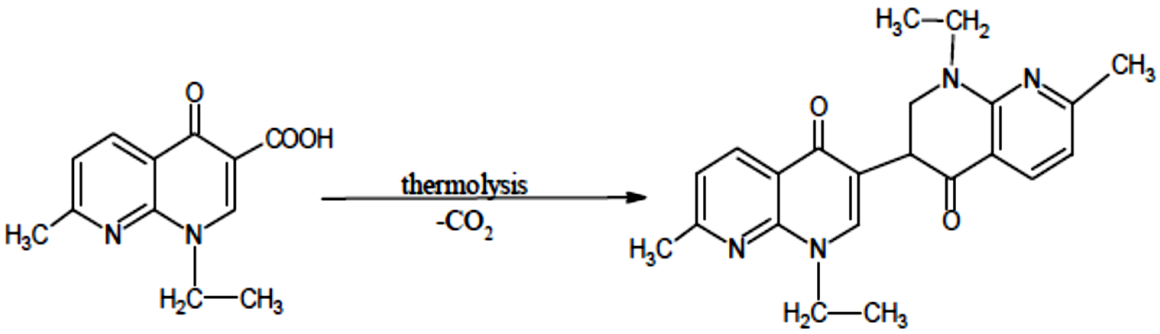

Figure:12 Dimerization of nalidixic acid.

G. Epimerization

The epimerization process modifies one of the chiral centers in a molecule to form another molecule called an epimer. Epimeric molecules differ from other molecules (its diastereomers) only in their chiral centers. Epimers are not mirror images of each other and have multiple stereocenters.

- **Ergotamine**

Ergotamine undergoes an acid-catalyzed reversible epimerization at the C-8 and C-2' positions of the molecule in the absence of air and light. Epimerization at C-8 occurs at the lysergic acid portion of the molecule in the temperature range 30-60°C and pH 3.8. Reaction at C-2' occurs at the cyclic tripeptide portion of the molecule at pH 3.6 and in the temperature range 50-80°C. Both isomers are detectable in parenteral solutions of ergotamine tartrate.[15]

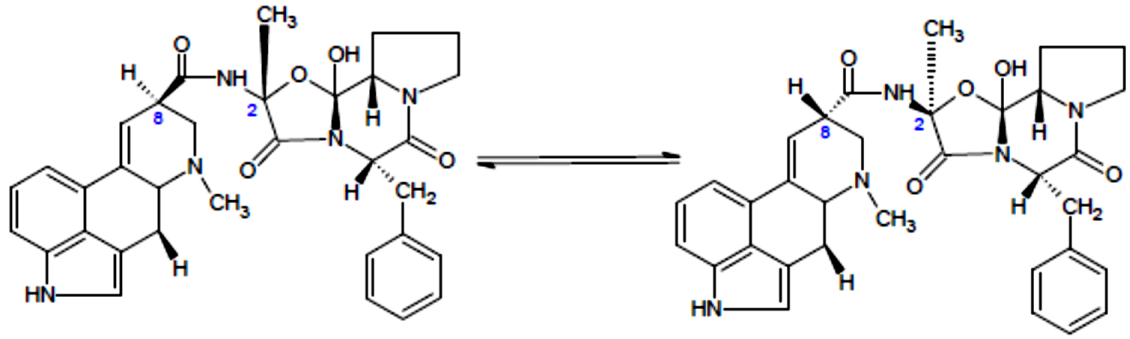

Figure:13 Epimerization of Ergotamine.

H. Dehydration

It is a chemical reaction that involves the loss of a water molecule from the reacting compound.

- **Glucose**

Glucose undergoes dehydration reaction to form 5-(hydroxymethyl)-2-furaldehyde, on heating with hydrochloric acid.[16]

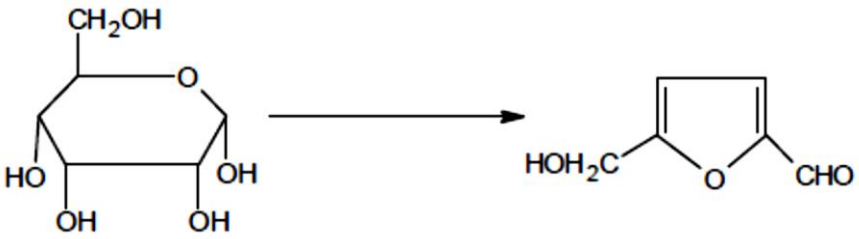

Figure:14 Dehydration of glucose.

- **Batanopride Hydrochloride**

In acidic media (pH 2–6) batanopride hydrochloride, an antiemetic drug, is degraded by intramolecular cyclization followed by dehydration to form 2,3-dimethylbenzofuran.[17]

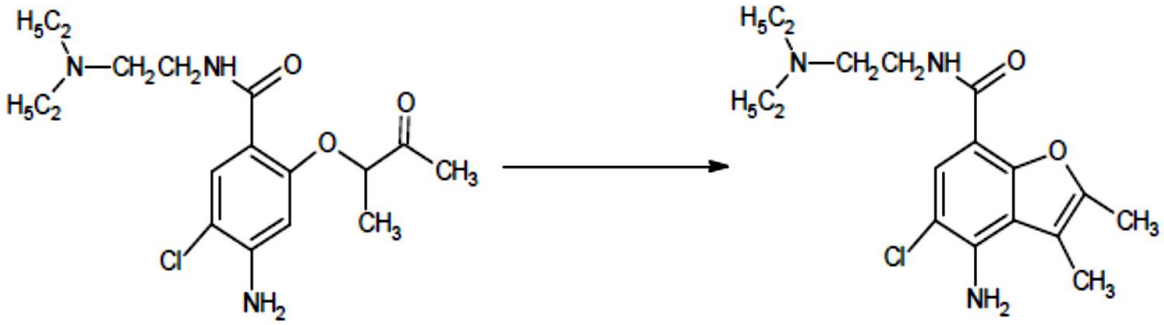

Figure:15 Dehydration of batanopride hydrochloride.

I. Dehydrogenation

It is a chemical reaction that involves the removal of hydrogen from a reacting compound.

- **2- Aminofluorene**

2-Aminofluorene undergoes oxidative dehydrogenation to 2-nitro-9-fluorenone in acetonitrile using potassium iodide-tert-butyl hydroperoxide (KI–TBHP) as catalytic system at 80 ^{0}C.[18]

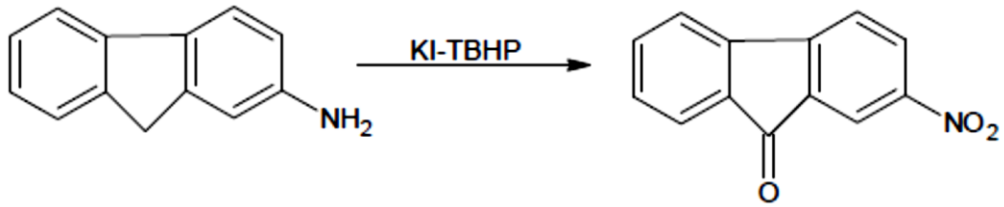

Figure:16 Dehydrogenation of 2- aminofluorene.

J. Dehalogenation

A reaction involving the removal of a halogen atom from a molecule.

- **Norfloxacin**

Norfloxacin undergoes defluorination in neutral aqueous solution to form the product.[19]

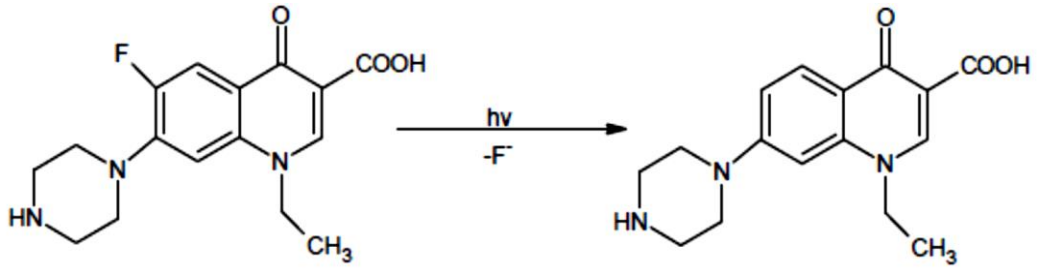

Figure:17 Dehalogenation of norfloxcin.

K. Photodegradation

Molecules that absorb wavelengths of light associated with sunlight or artificial light can be susceptible to photodegradation (photolysis). Wavelengths between 300 and 400 nm are usually the most harmful. Shorter wavelengths are also harmful, but are of practical importance because they are not present in sunlight or artificial light. Carbonyls, nitros, alkenes, aryl chlorides, and phenolic compounds are the most susceptible to photodegradation. Although many photodegradation reactions involve oxidative mechanisms, other mechanisms may also occur.

- **Retinol**

Photolysis of retinol results in the formation of cis isomers around the double bond at position 9 of the molecule, in addition to promoting oxidation reactions. In contrast, degradation that occurs in the absence of light causes isomerization at the 13-position. Both isomers are detectable in parenteral solutions of ergotamine tartrate.

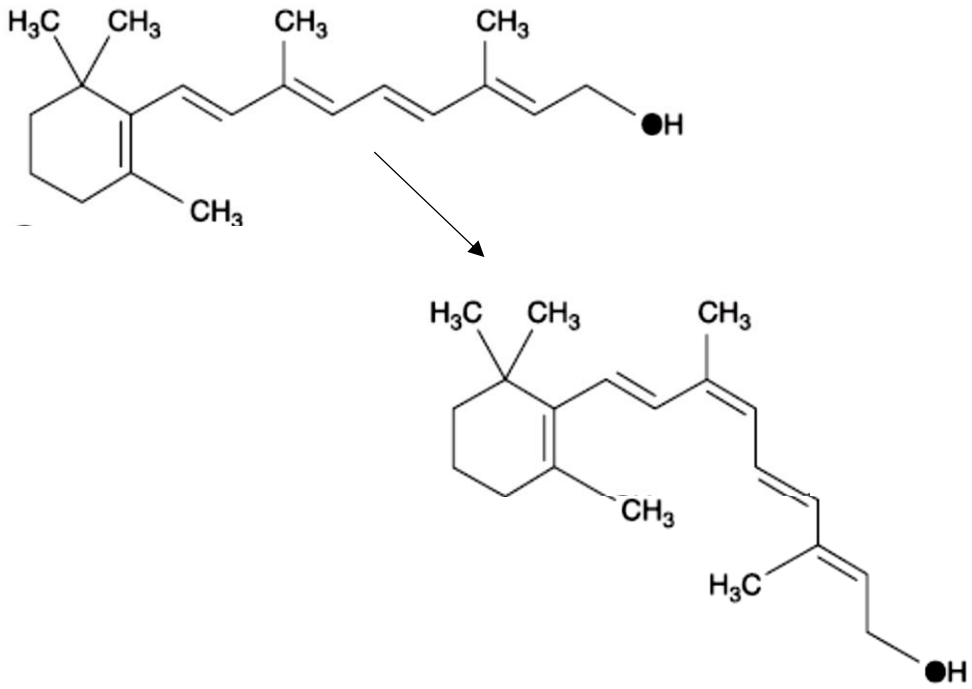

Figure:18 Photodegradation of retinol.

III. CHEMICAL STABILITY/DEGRADATION STUDIES

Several studies have been conducted to assess the chemical stability and degradation of drug substances and drug products. Some of these studies are listed below.

A. Aqueous Solution

A kinetic study of the alkaline hydrolysis of 7,8-dimethyl-10-(formylmethyl) isoalloxazine (FMF), an intermediate in the photolysis of riboflavin, was performed in the pH range 9-12. FMF forms lumicrom (LC) and lumiflavin (LF) in alkaline solutions with second-order rate constants of 0.348 and 0.063 M-1 s-1 at pH 9 and 0.068 and 0.132 M-1 s-1 at pH 12 To do. FMF and hydrolysis products LC and LF were identified by chromatography and determined by multicomponent spectroscopy. LC and LF were extracted from pH 2.0 chloroform-digested solutions and measured at 356 nm and 445 nm by a two-component method. FMF was measured directly in the aqueous phase at 385 nm. Molar concentrations of these compounds were used to assess reaction kinetics.[20]

High performance liquid chromatography (HPLC) was used to investigate the chemical stability of 5-aza-2'-deoxycytidine over a pH range. It undergoes rapid reversible degradation to N-(formylamidino)-N'β-D-2-deoxyribofuranosyl urea, which in alkaline solution further yields 1-β-D-2'-deoxyribofuranosyl- It is degraded to 3-guanyl urea. The kinetics of decomposition reaction was studied. The degradation of 5-aza-2'-deoxycytidine in alkaline solutions is similar to that of 5-aza-cytidine. Reaction intermediates are most stable in neutral solutions stored at low temperatures.[21]

Cefoxitin sodium undergoes specific acid-base catalyzed hydrolysis of the ester group and β-lactam ring in aqueous solution. Apparent first-order rate constants for hydrolysis reactions at pH 3-9 were determined. Under these pH conditions, cefoxitin sodium shows a loss of approximately 10% over 2 days at 25°C. Amorphous forms of drugs are less stable than crystalline forms.[22] The chemical stability of ranitidine hydrochloride in aqueous solution at different pH values and temperatures was investigated using an HPLC method. The rate of drug degradation increases as the medium pH decreases and temperature increases. This result indicates that the degradation of ranitidine is a specific acid-catalyzed reaction.[23]

B. Pharmaceutical Preparations

Insulin preparations stored at different temperatures have been shown to be susceptible to hydrolysis. Degradation is rapid in acidic media by deamidation at the AsnA21 residue and slowed in neutral media by deamidation at the AsnB3 residue. The rate of insulin degradation at residue B3 varies with temperature and preparation. A reduction in B3 conversion was observed with crystalline insulin compared to the amorphous form. A8–A9 peptide bond cleavage occurs in certain crystal suspensions. The hydrolysis of insulin involves an imide intermediate in the reaction. Preparations containing rhombohedral crystals with free zinc ions only undergo hydrolysis of the peptide chain.[24]

Storage of insulin formulations at 4-45°C results in the formation of covalently bound high molecular weight products that are predominantly covalent insulin dimers. In protamine-containing preparations, a covalent insulin-protamine product is formed. Formation of oligo-compounds and polymers also takes place by parallel or subsequent reactions at temperatures above 25°C. Temperature has a marked effect on the formation of various products in insulin formulations. Dimerization occurs between molecules within the hexameric unit present in all types of insulin formulations, with dimerization being more pronounced in formulations containing glycerol.[25]

Lyophilized proteins and peptides contain sugars and polyols as bulking agents and cryoprotectants, but reducing sugars have been found to react with proteins. Recombinant human relaxin in a lyophilized preparation undergoes rapid covalent modification in reaction with glucose used as an excipient. LC/MS and tryptic mapping of the protein indicated that one degradation pathway involved covalent adduct formation of glucose with amino groups (ie, Lys and Arg) of the side chains of the protein via the Maillard reaction. Another pathway leads to Ser cleavage from the C-terminus of the β-strand of the protein. The latter reaction occurs predominantly in the solid state and involves reaction of glucose with the Ser hydroxyl group and hydrolysis of the Trp-Ser amide bond via a cyclic intermediate. Mannitol (a polyhydric alcohol) and trehalose (a non-reducing sugar) do not react in this way with relaxin.[26]

Studies have been performed to determine 1) the relationship between chemical stability, aging state, and global molecular motion, and 2) molecular mobility in multicomponent systems. We also investigated whether tempering the glass below its transition temperature (Tg) affects its chemical stability, the overall relaxation time and/or T1 and T1rho where the decomposition rate is determined by calorimetry. It was also intended to determine whether it was related to Relaxation times were determined by solid-state NMR spectroscopy. This study investigated the chemical degradation of lyophilized aspartame/sucrose and aspartame/trehalose (1:10, w/w) preparations and evaluated the effect of annealing on chemical stability by applying long-term kinetics. Did. The results supported the hypothesis that molecular mobility for structural relaxation is affected by thermal transitions. Such effects are important for chemical stability, and annealing leads to stabilization of the preparation.[27]

Biodegradable polyester pseudolatexes, poly (D,L-lactide) and poly(ε-caprolactone), are used as aqueous coating materials for sustained release dosage forms. A study was conducted to determine the effects of surfactant, temperature, pH, and particle size on the hydrolysis of these polymers in the form of colloidal dispersions. Nonionic surfactants do not affect dispersion stability. A small change in the molecular weight of the polymer was observed when the dispersion was stored in unbuffered solution at 5 °C for 1 year. At 37°C, rapid hydrolysis of the dispersion was observed. Polymer stored at 37°C, pH 1.65 showed accelerated degradation, while polymer stored at 5°C, pH 1.65 was stable for 4 months.[28]

The effects of spray drying and processing conditions on the residual water content and biochemical stability of inhalable protein powders were investigated. Mannitol-formulated humanized monoclonal antibody (anti-IgE) and recombinant human deoxyribonuclease (rhDNase) powders were prepared by spray drying and residual moisture and moisture absorption were determined by thermogravimetric analysis and gravimetric moisture sorption isotherm, respectively. Protein aggregates, the major protein degradation products observed during long-term storage, were determined by size-exclusion HPLC. The results showed that a spray-dried powder containing about 3% moisture, corresponding to a freeze-dried powder, was obtained by high-temperature spray-drying. The powder retains its aerosol performance (fine particle fraction) if the relative humidity is less than 50% during processing and storage. Powders improve the long-term biochemical stability of proteins when stored dry.[29]

We investigated the effect of surface charge on the degradation rate of methylparaben, which is used as a model solute in oil-in-water emulsions. The surface charge is altered by adding phosphatidylglycerol (an anionic surfactant) or stearylamine (a cationic surfactant) to intravenous lipid emulsions stabilized with egg phospholipids. The kinetics of hydrolysis (pH 8.0) in aqueous, oil, interfacial, and aqueous micellar phases were determined using a four-phase kinetic model. The degradation rate in the aqueous phase depends on the zeta potential due to the pH surface charge (surface activity) of the oil droplet microenvironment. The hydrolysis rate of methylparaben is dependent on microenvironment pH and bulk pH. The rate of hydrolysis is reversed. Proportional to the partition coefficient of methylparaben. Surface charge effects are greater for smaller partition coefficients and smaller for larger partition coefficients.[30]

A study was conducted to determine the effect of drying method on the stability of dried vaccine formulations. Sucrose-based preparations of live attenuated vaccines of the parainfluenza strain itself, containing surfactants, were dried by freeze-drying, spray-drying, and foam-drying methods. The dry powder was characterized using differential scanning calorimetry, specific surface area analysis and electron microscopy. The preparations were stored at 4, 25 and 37°C and the rate constants for degradation were determined. The spray-dried formulation exhibited the highest specific surface area (~2.82 m2g-1) in the absence of surfactant, while the foam-dried formulation exhibited the lowest specific surface area (~0.1 m2g-1) in the presence and absence of surfactant. m2g-1) was shown. Electron microscopy measurements showed the highest surface coverage for the spray-dried formulation and the lowest surface coverage for the surfactant-free foam-dried formulation. The vaccine showed the highest stability at 25 and 37 °C in the surfactant-containing foam-dried formulation and the lowest in the surfactant-free spray-dried formulation.[31]

Brij 58 (nonionic surfactant), Poloxamer 188 (nonionic copolymer), Cremophor RH40 (solubilizer), Gelucire 44/14 (nonionic surfactant) and PEG 6000 (37 and 60° C). The major degradation product, thioether, rabeprazole, was identified by LC/MS, and rabeprazole and its degradation products were determined by HPLC. Rabeprazole degrades according to first-order kinetics, with rate constants at 37 and 60 °C of 0.75 and 2.78 h-1, respectively, in the absence of excipients. The addition of excipients has been shown to improve the stability of rabeprazole. The greatest stabilizing effect was observed in the presence of Brij 58, which reduced the degradation rate constants to 0.22 and 0.53 h–1 at 37 and 60 °C, respectively. It was concluded that the presence of appropriate excipients in rabeprazole formulations enhances intestinal stability and maximizes bioavailability.[32]

The effects of pH, suspending agent, and temperature on suspensions of ibuprofen powder and microspheres were investigated by an accelerated stability protocol using an HPLC method. Suspensions in various suspension media were found to be stable when stored at 23, 37 and 45 °C for 3 months. The dissolution stability of microspheres prepared from the optimized formulation (17% drug loading) was determined by a suspension of ceresin wax microspheres stored at 37 °C and a suspension of ceresin wax microspheres stored at 23 °C. Shown to give faster drug release than Microsphere suspensions in syrup stored at 37°C exhibited faster dissolution rates than those suspended in methylcellulose. This is likely due to interactions between the microsphere components and the syrup. Microcrystalline wax microparticle suspensions exhibit better solution stability than ceresin wax microparticles. Higher pH results in faster drug release from suspended microspheres. The dissolution stability of microspheres is largely independent of particle size.[33]

IV. Chemical Incompatibilities

Drug degradation can be caused by reaction with another drug or formulation excipients present in the formulation. Hydroxybenzoic acid esters (parabens) antimicrobial preservatives undergo transesterification reactions with sugars and sugar alcohols that may be present in the formulation as sweeteners.

For example, methyl hydroxybenzoate reacts with sorbitol to produce various sorbitol hydroxybenzoates by reaction with different hydroxyl groups of sorbitol. Relevant reactions include interactions between aminophylline and suppository bases. Aminophylline is a complex formed from theophylline and ethylenediamine that has increased water solubility compared to theophylline alone. Storing aminophylline suppositories raises the melting point of the base above physiological temperature, preventing drug release.

The mechanism is the formation of an amide bond between ethylenediamine and the carboxyl groups of fatty acids present in the suppository base. This reaction is the reverse of the amide hydrolysis reaction. Transacetylation reactions have been reported for some drugs.

For example, in a tablet formulation containing aspirin and phenylephrine hydrochloride (a drug used as a nasal decongestant), the acetyl group is transferred from aspirin to phenylephrine. A similar reaction occurs between aspirin and paracetamol (acetaminophen). Aspirin also reacts with the polyethylene glycol base of suppository formulations, transferring an acetyl group to the polyethylene glycol.

A reducing sugar and an amine are involved in the Maillard reaction. Reducing sugars tautomerize to open ring forms containing reactive aldehyde or keto groups. This reaction causes cooked foods to brown with amino groups provided by proteins present in the food. Can also occur between sugars. This reaction causes the white tablets to turn yellow during storage. For example, lactose, tautomerizes to its aldehyde form and reacts with amines through several intermediate steps to form colored 1-amino-2-keto sugars.

Other reducing sugars are glucose and fructose. Non-reducing sugars that do not undergo this reaction include sucrose and mannitol. Sodium metabisulfite is commonly added to epinephrine (adrenaline) injections as an antioxidant. However, it reacts with drugs to form epinephrine sulfonic acid, which is the key pathway for epinephrine degradation.

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