Chemical Stability of Drugs

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Abstract

Drugs or medicinal organic molecules can change by hydrolyzed or elimination based on the reaction circumstances. In addition, they may disintegrate by polymerization, oxidizing, or isomerization. The purpose of this chapter is to highlight the chemical reactions behind medication stability. Techniques might be helpful in this situation to describe how compounds develop in a chemical change media. Drugs degrade in accordance with the atmosphere in which they are being reacted to. In order to find solutions to maintain therapeutic efficacy, it is important to comprehend the circumstances that affect drug security. In fact, chemical or physical breakdown can affect a drug's therapeutic efficiency and produce unwanted byproducts.

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

I. Introduction

Pharmaceuticals' chemical breakdown is frequently a major limitation of their shelf life. Degradation of other formulated elements, such as antioxidants or antimicrobial preservatives, is another essential consideration. The type of byproducts that occur in the dosage form can affect how long a medication will stay fresh on the market. This might be as a result of the hazardous byproducts of decomposition. For instance, the antifungal flucytosine degrades to the cytotoxic fluorouracil. Alternately, the product may have an unfavourable look due to breakdown products For instance, epinephrine's (adrenaline's) oxidation products are brightly coloured. In the pharmaceutical sector, the utilisation of risk-based predictive stability studies is rising. 16 organizations acknowledged employing predictive stability studies in medication and product development, according to a 2017 survey of International Consortium for Innovation and Quality in Drug Development members [1].

Application include categorizing prototype formulations, assigning a shelf life for the initial test, choosing a package, choosing an expression equivalent, comprehending intrinsic stability, choosing a salt/polyester selection figure, and establishing standards. Although proteins are big molecules, stability prediction studies have also been used on tiny compounds. Pharmaceutical items must have stability as a fundamental attribute. It is regarded as the most crucial drug-related element in the creation of therapeutically effective dose forms. Preclinical formulation, process development, and packaging studies all involve evaluating the product's chemical and physical stability. The stable qualities of the active components and excipients determine a product's efficacy and safety. Regulatory organizations must comply with this rule for chemicals and pharmaceuticals. A drug's degradation routes and potential stabilization strategies can be predicted using knowledge of the precise chemical functional groups that make up the drug molecule. To guarantee the product's physical and chemical stability throughout storage and usage, a suitable packaging strategy must be used. Regulatory bodies are required by law to demand stability assessments of pharmaceutical ingredients and medicines.

Drug compounds are often not subject to irreversible chemical deterioration. Another reactive component in the dosage form is typically the culprit. Although medications may also interact with other components of the formulation or molecules of the same drug, the presence of water or molecular oxygen is frequently to blame. One of the main objectives in the design of dosage forms is to protect

formulations against chemical deterioration. The common kinds of chemical degradation that impact "small molecule" medications are covered in this chapter.

II. Chemical Degradation Reactions

Drugs are chemical substances that have a variety of structural arrangements and chemical bonding. Depending on the conditions triggering the breakdown, they can go through various decomposition processes in aqueous and organic solvents through distinct paths. The principal techniques for drug degradation are:

A. Hydrolysis
B. Oxidization
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

One of the least frequent reactions that destabilizes medications containing ester, amide, imide, carbamate, lactone, nitrile, and carbohydrate groups occurs in aqueous and liquid dosage forms.

Aspirin, paracetamol, sulfacetamide, indomethacin, procaine, digoxin, riboflavin, lincomycin, chloramphenicol, penicillins, cephalosporins, and benzodiazepines are just a few of the medications that are sensitive to acid and/or alkaline hydrolysis.

The pH of the media is crucial for the hydrolysis of drugs.

- **Hydrolysis of esters**

By attacking the ester group with water or OH- ions, ester molecules undergo hydrolysis.

  - **Acetylsalicylic acid (Aspirin)**

The most well-known occurrence of the hydrolysis of ester compounds is aspirin. It hydrolyzes to salicylic acid and acetic acid in an aqueous environment. With temperature rise, this response quickens[2].

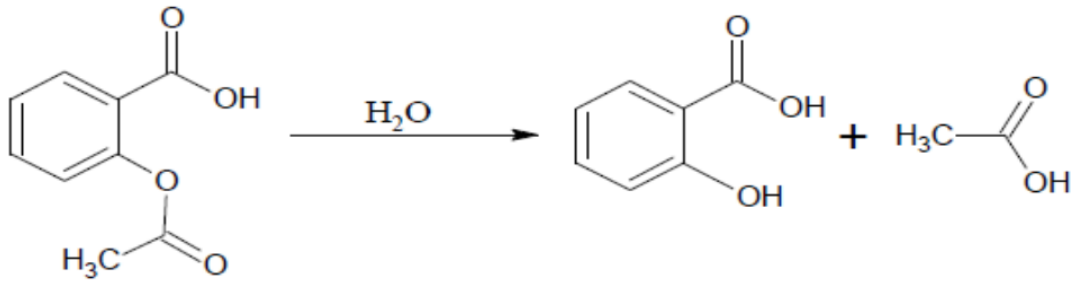


Figure:1 Hydrolysis of ester (Aspirin)

- Procaine

Hydrolysis is the most significant process in the breakdown of procaine. Diethylaminoethanol and -aminobenzoic acid are produced as a result. Ionization of the molecule has an impact on the reaction's speed (PKA 8.05)[3].

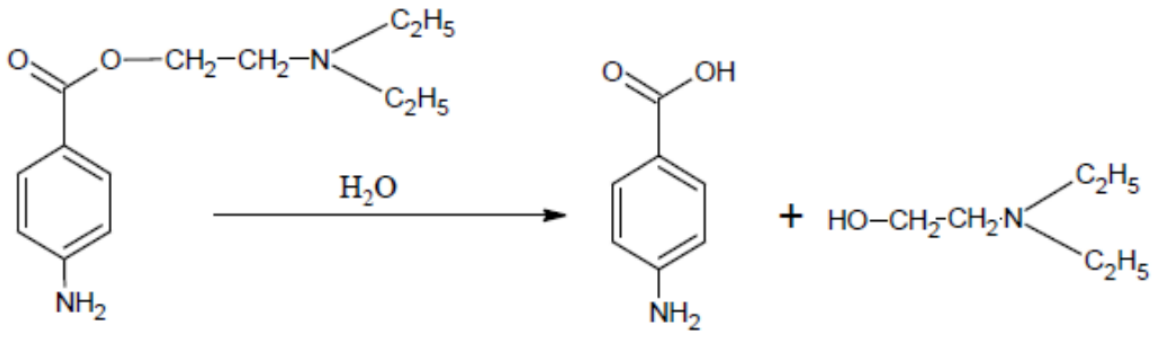


Figure: 2 Hydrolysis of ester (Procaine)

- Hydrolysis of amides

As opposed to compounds with ester bonds, those with amide bonds are less prone to hydrolysis. This is due to the reduced electrophilic nature of the carbonyl carbon in the amide bond.

- Paracetamol

Paracetamol hydrolyzes in aqueous solutions to produce 4-aminophenol and acetic acid[4].

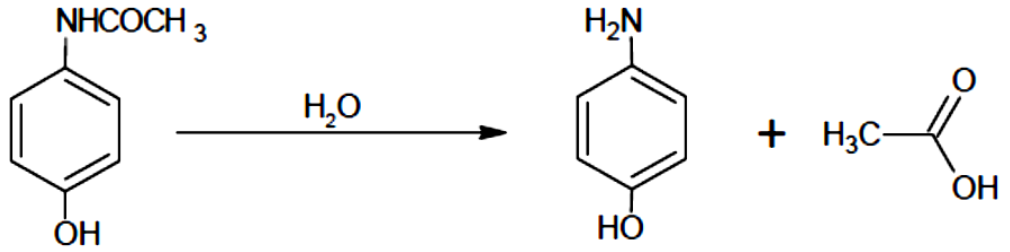


Figure:3 Hydrolysis of amides (Paracetamol)

- Sulfacetamide

Sulfacetamide is hydrolyzed in aqueous solution to produce sulfanilamide and acetic acid. Sulfanilamide is oxidized to create 4,4'-azobenzenedisulfonamid, which, on exposed of light, is re-oxidized to 4,4'-azoxybenzenedisulfonamide. A yellow to reddish brown tint is created as a result of these processes [5,6,7].

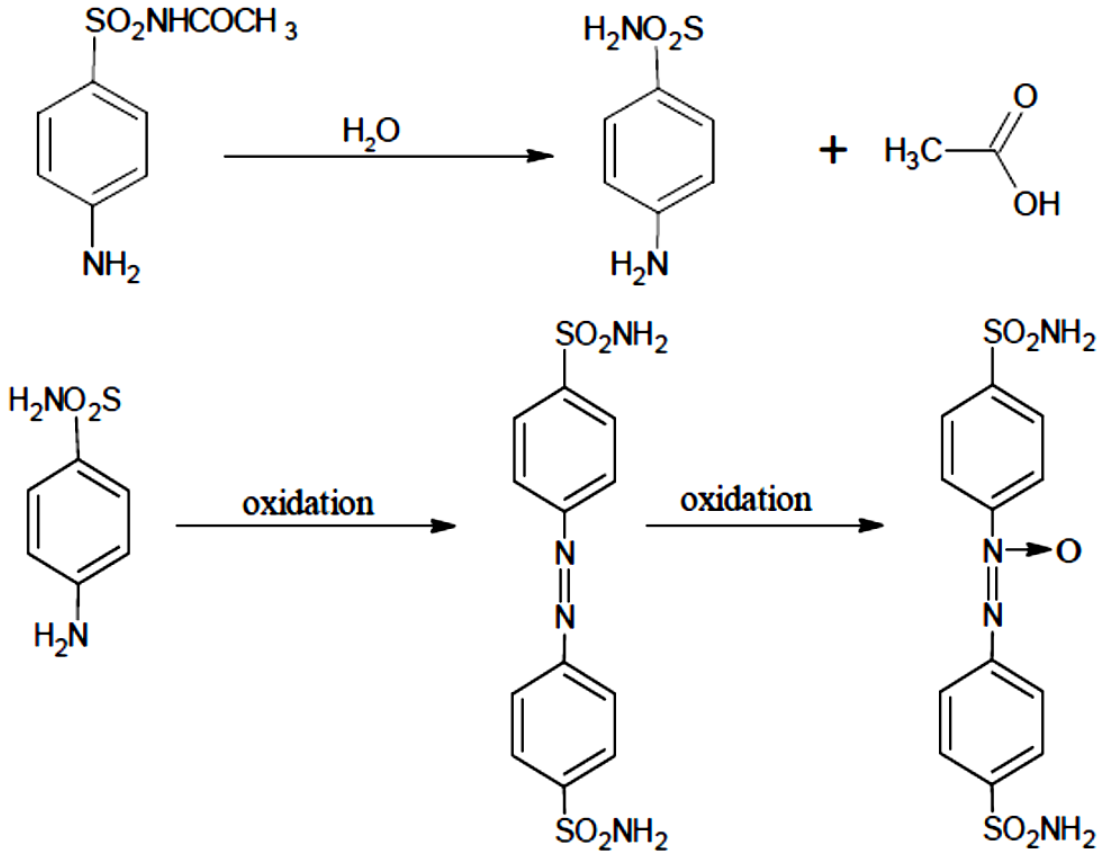


Figure:4 Hydrolysis of amides (Sulfacetamide)

- Hydrolysis by ring opening

The breakage of the C-N bond may result in the ring opening hydrolyzed of a medicinal molecule..

- Riboflavin

By cleaving the isoalloxazine ring, riboflavin (vitamin B2) undergoes base-catalyzed hydrolysis to produce 1,2-dihydro-6,7-dimethyl-2-keto-l-D-ribityl-quinoxaline-3-carboxylic corrosive (-keto acid) and 6,7-dimethyl-4-D-ribityl-2,3-dioxo-1,2 (flavor-violet).

A temperature increase and a lack of riboflavin absorption at 445 nm both contribute to the debasement response[9].

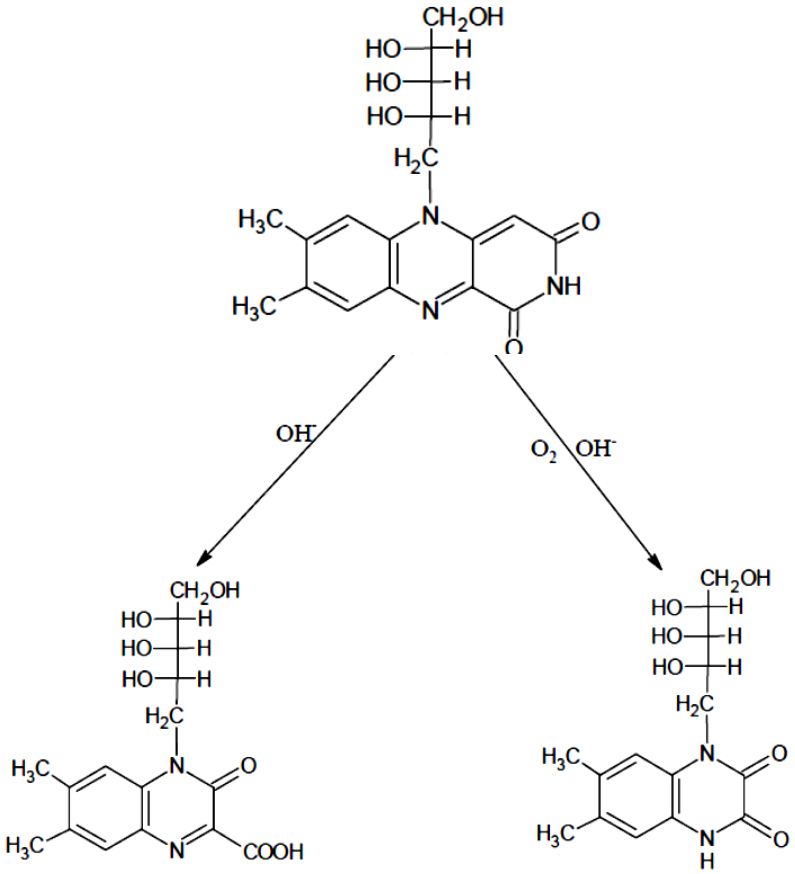


Figure:5 Hydrolysis by ring opening (Riboflavin)

B. Oxidation

Another frequent response that occurs when oxygen or other oxidizing chemicals are present is the oxidative destruction of medicines.

When medications are exposed to ambient oxygen during production, storage, or usage, oxidation processes may change the drug's composition.

Ascorbic acid, vitamin A, glucose, morphine, hydrocortisone, methyldopa, aldehydes, phenols, unsaturated chemicals, thiols, phenothiazenes, and polyenes are just a few of the medications that are oxidized.

Due to ionization of the species involved and changes in the redox potential, the pH of the medium

can have an impact on the pace of oxidation processes.

- Ascorbic acid

Ascorbic acid (vitamin C) is oxidized to dehydroascorbic acid when it is broken down in an aqueous medium under aerobic environment.

In alkali solution, dehydroascorbic acid hydrolyzes to diketogulonic acid. [10]

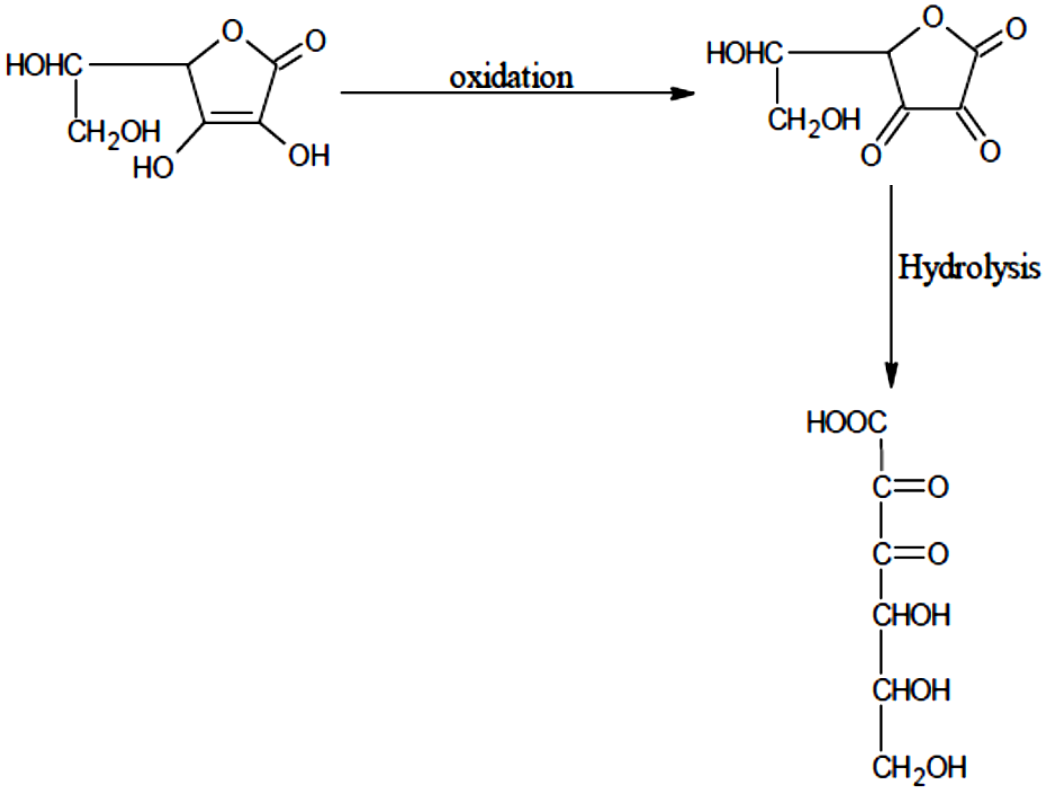
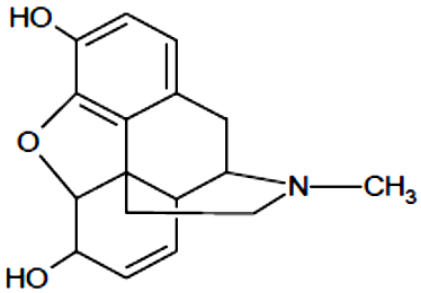


Figure:6 Oxidation of ascorbic acid.

- Morphine

Oxidation by light and air is the primary process by which morphine in aqueous medium breaks down. Pseudomorphine (noxydimorphine) and morphine N-oxide are examples of morphine's oxidation byproducts [11].



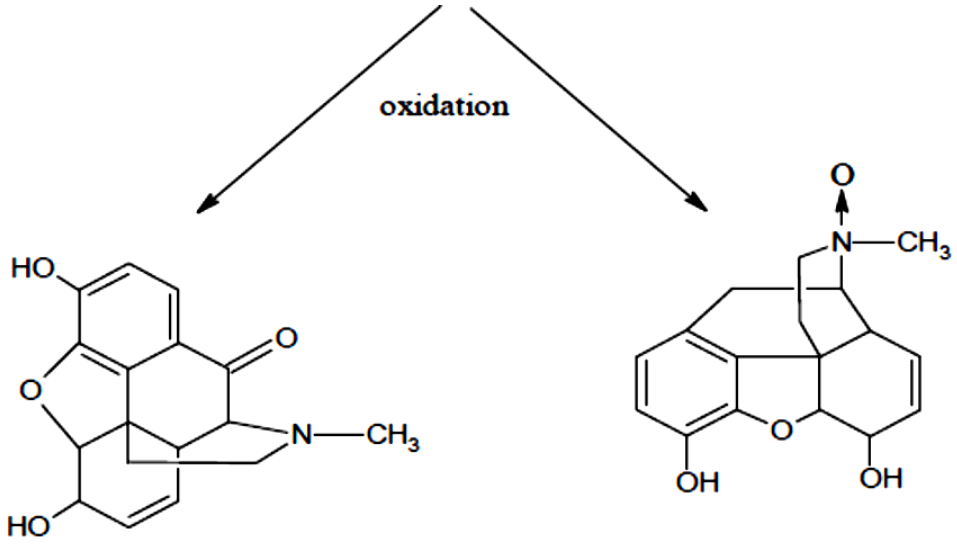


Figure:7 Oxidation of morphine.

- Phenols

it is simple for phenols to undergo oxidation processes. The phenyl ring that is oxidizable receives a substantial electron donation from the hydroxyl group. The proton may be extracted to generate a solid radical, which then interacts with molecule of oxygen.

Strongly catalyzing the auto-oxidation reaction is the deprotonation of phenol to the phenolate anion at a higher pH. (base-catalyzed auto-oxidation). The phenolate anion is a potent nucleophile that may interact with electrophilic molecules in the ortho- or para-positions as well as with oxygen. When Fe3+ or Cu2+ ions are present, phenolics oxidize. [12]

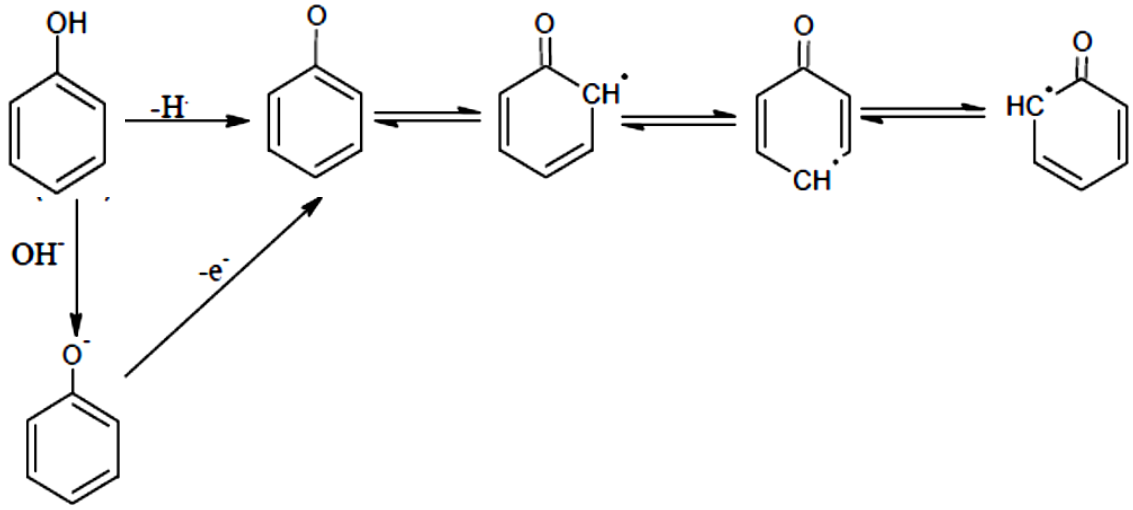


Figure:8 Oxidation of phenols.

C. Decarboxylation

Under some circumstances, decarboxylation can be used to break down drugs that contain

carboxyl groups.

- 4- aminosalicylic acid

The primary process by which 4-aminosalicylic acid breaks down in aqueous solution is decarboxylation, which produces 3-aminophenol.

In alkaline medium, when the atom is in ionized state, the reaction goes more quickly than in acidic environment[13].

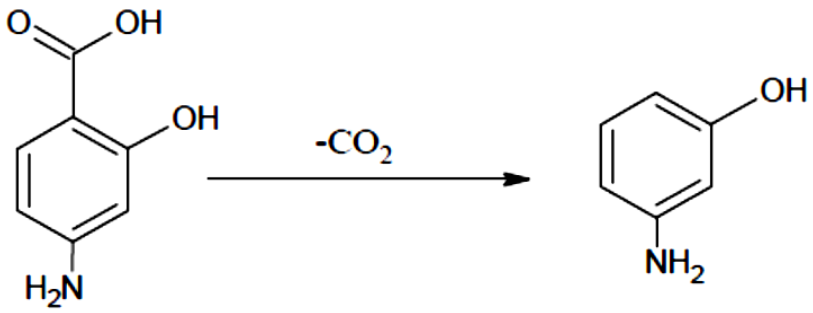


Figure:9 Decarboxylation of 4-aminosalicylic acid.

D. Elimination

In elimination processes, two or more groups are taken out of a compound in one or more stages.

The E2 reaction (bimolecular) is the name of the one-step process, whereas the E1 reaction is the name of the two-step mechanism (unimolecular).

- Trimeramol

Two main mechanisms are involved in the breakdown of the synthetic carbinolamine-containing antineoplastic medication trimeramol (N2,N4,N6-trimethylol-N2,N4,N6-trimethylmelamine).

One method of degradation entails the removal of formylaldehyde to create the parent trimethylmelamine while losing a hydroxymethylene group[14].

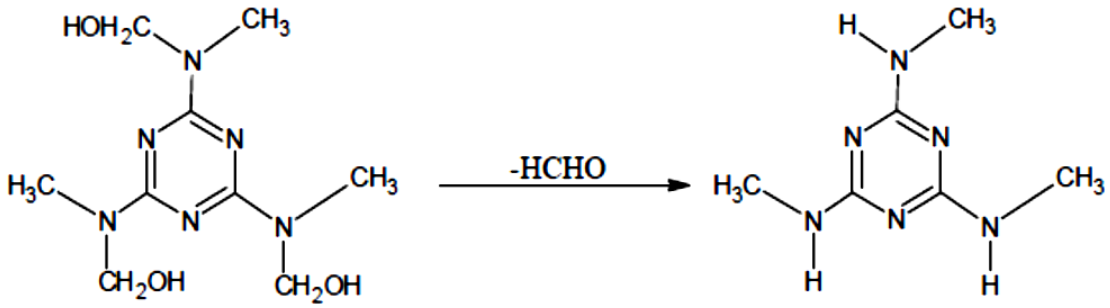


Figure:10 Elimination of trimeramol.

E. Isomerization

The transformation of one compound into another, which has the same identical elements but a different configuration, is known as isomerization.

- Cephalosporins

A double bond coupling the Δ^3 place to the Δ^2 place in cephalosporins is known to undergo isomerization.

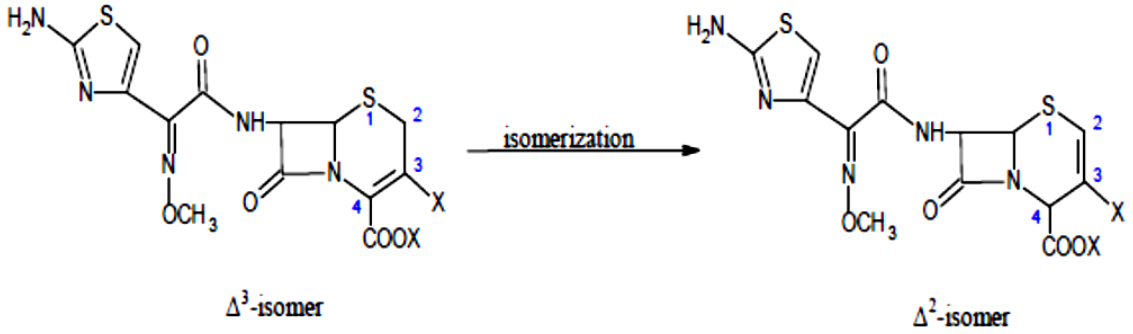


Figure:11 Isomeriztion of cephalosporins.

F. Dimerization

This chemical process results in the joining of two molecular subunits to create a dimer..

- **Nalidixic acid**

On thermal decomposition, nalidixic acid induces dimerization by decarboxylation to create a dimer.

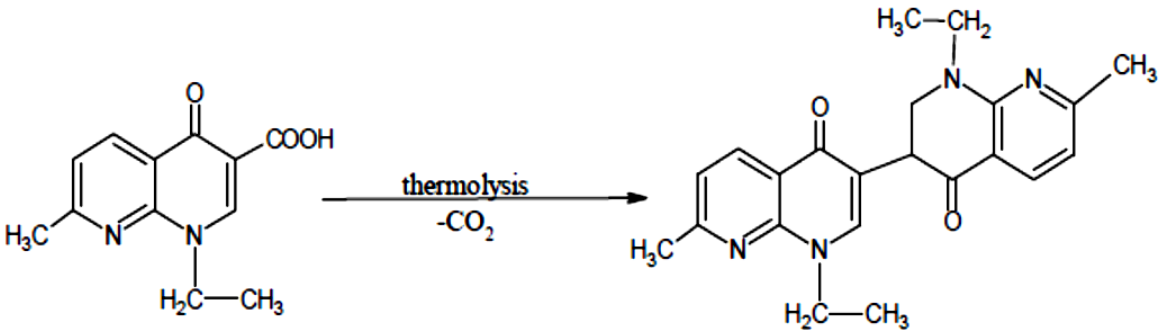


Figure:12 Dimerization of nalidixic acid.

G. Epimerization

One of a molecule's chiral centers is altered during the epimerization process to create an epimer, which is a different kind of molecule. Only their chiral centers set epimeric compounds apart from their diastereomeric counterparts.

Epimers have several stereocenters and are not mirror reflections of one another.

- **Ergotamine**

In the elimination of air and light, ergotamine conducts an acid-catalyzed reversible epimerization at the C -8 and C-2' locations of the structure. When the pH is 3.8 and the heat is between 30 and 60 °C, epimerization at C-8 takes place at the lysergic acid section of the molecule.

At pH 3.6 and temperatures between 50 and 80 °C, the cyclic tripeptide component of the molecule undergoes reaction at C-2'. In injectable ergotamine tartrate solutions, dual isoforms are discernible[15].

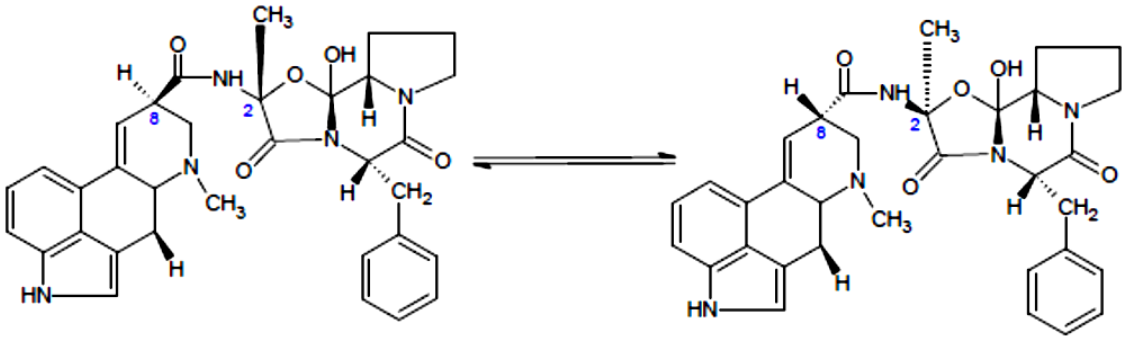


Figure:13 Epimerization of Ergotamine.

H. Dehydration

It is a chemical process in which the reactive substance loses a molecule of water.

- **Glucose**

When heated with hydrochloric acid, glucose passes through a dehydration process to produce 5-(hydroxymethyl)-2-furaldehyde[16].

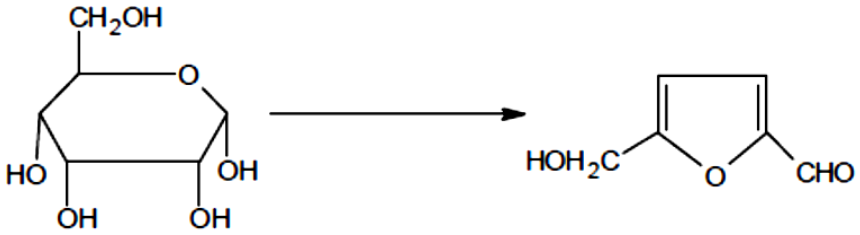


Figure:14 Dehydration of glucose.

- **Betanopride hydrochloride**

An anti - emetic medication called batanopride hydrochloride is broken down in acidic environment (pH 2-6) via intra - molecular cyclization and dehydration to create 2,3-dimethylbenzofuran[17].

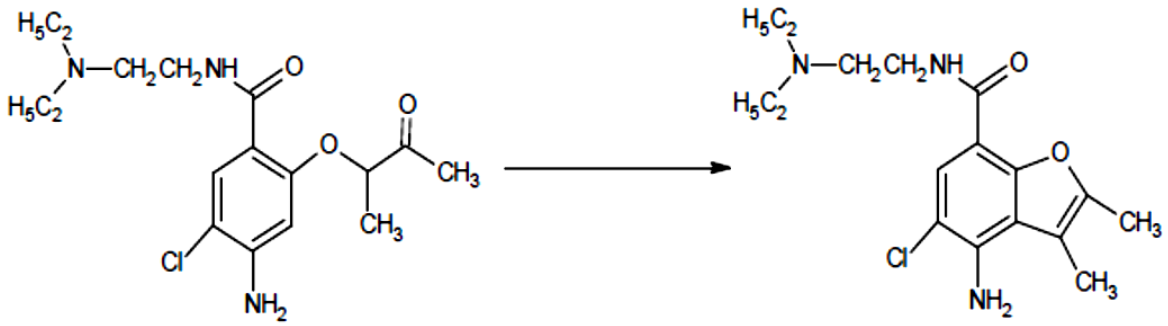


Figure:15 Dehydration of batanopride hydrochloride.

I. Dehydrogenation

This is a chemical change in which hydrogen is taken out of the component that is participating.

- **2- Aminofluorene**

At 80 ℃, 2-aminofluorene is converted into 2-nitro-9-fluorenone by oxidative dehydrogenation with potassium iodide-tert-butyl hydroperoxide (KI-TBHP) as the catalyst18].

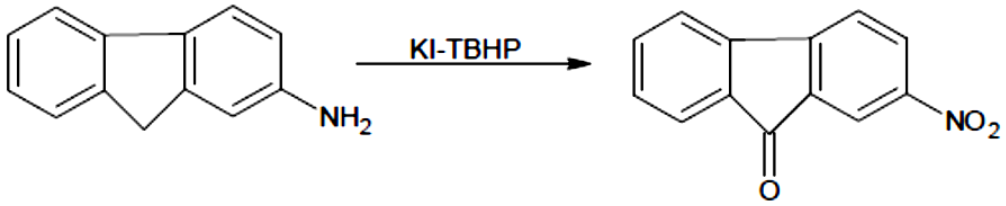


Figure:16 Dehydrogenation of 2- aminofluorene.

J. Dehalogenation

a process where a halogen atom is removed from a compound.

- Norfloxacin Norfloxacin

To generate the product, norfloxacin is defluorinated in neutral aqueous medium[19].

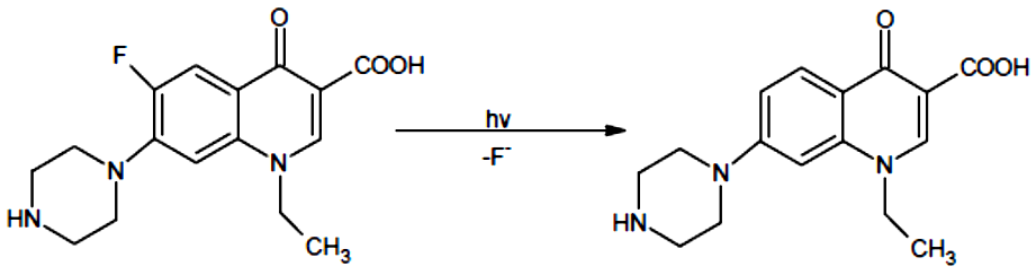


Figure:17 Dehalogenation of norfloxcin.

K. Photodegradation

Photolysis may occur in compounds that absorbs sunlight- or artificial-light-related spectrum (photolysis). The most dangerous spectra are often of between 300 and 400 nm. Although shorter wavelengths are likewise damaging, they are important practically since neither daylight nor artificial light contains them.

The substances that are most vulnerable to photo - degradation include carbonyls, nitros, alkenes, aryl chlorides, and phenolic compounds. Even while oxidative pathways are common in photo - degradation events, other processes can also operate.

- Retinol

In addition to accelerating oxidation processes, photolysis of retinol causes the production of cis isomers across its double bond at position 9 of the structure. On the other hand, when light isn't present, degrading takes place, which leads to isomerization at the 13-position. In injectable ergotamine tartrate preparations, dual isomers are discernible.

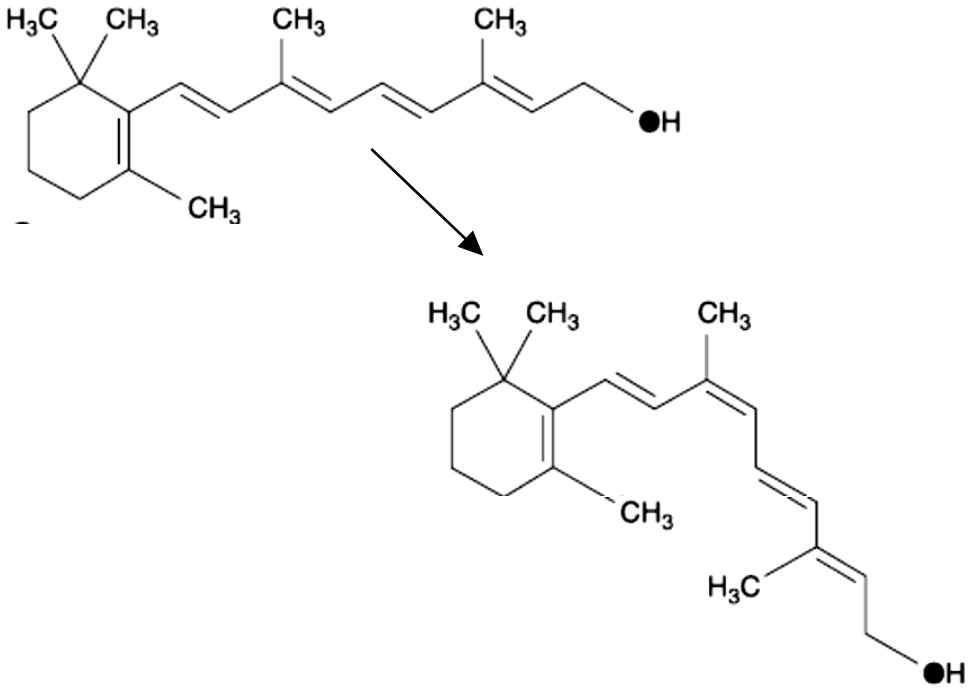


Figure:18 Photodegradation of retinol.

III. Chemical Stability/Degradation Studies

To evaluate the stabilities and breakdown of drug ingredients and drug derivatives, several research have been carried out. The collection below includes a number of these research.

A. Aqueous Solution

Inside the pH levels of 9 to 12, it was possible to analyze the kinetic of the hydrolysis process of 7,8-dimethyl-10-(formylmethyl) isoalloxazine (FMF), a step in the photodegradation of riboflavin. Having 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, FMF produces lumicrom (LC) and lumiflavin (LF) in alkaline solutions. FMF and byproducts of hydrolysis Chromatography was used to identify LC and LF, and multicomponent spectroscopy was used to determine them.

A two-component technique was used to extract LC and LF from pH 2.0 chloroform-digested solutions and measure them at 356 nm and 445 nm. At 385 nm, FMF was directly detected in the aqueous phase. The reaction kinetics of these substances were evaluated using molar concentrations [20].

The chemical stability of 5-aza-2'-deoxycytidine was examined using high performance liquid chromatography (HPLC) throughout a pH range. It quickly breaks down into N-(formylamidino)-N'-D-2-deoxyribofuranosyl urea, which breaks down further into 1-D-2'-deoxyribofuranosyl urea in alkaline solution.

The degradation reaction's kinetics was investigated. Similar to 5-aza-cytidine, 5-aza-2'-deoxycytidine also degrades in alkali solution. The most robust reaction intermediate are those that are kept in neutral solutions at low temperatures [21].

The ester group and -lactam ring of cefoxitin sodium are hydrolyzed specifically by an acid-base catalyst in aqueous medium. We found apparent first-order rate constants for hydrolysis processes ranging from pH 3 to 9. Cefoxitin sodium exhibits a loss of around 10% over 2 days at 25°C at these pH circumstances. Drugs in amorphous forms are less stable than those in crystalline forms[22].

Using an HPLC technique, the functional properties of ranitidine hydrochloride in aqueous medium at various pH values and altitudes was examined. As the medium's pH falls and its temperature rises, the rate of drug breakdown accelerates. This finding suggests that a particular acid-catalyzed process is responsible for the breakdown of ranitidine[23].

B. Pharmaceutical Preparations

It has been demonstrated that insulin formulations maintained at various temperatures are sensitive to hydrolysis. Deamidation at the AsnA21 residue speeds up degradation in acidic medium whereas deamidation at the AsnB3 residue slows it down in neutral media Temperature and preparation affect how quickly insulin breaks down at residue B3. When crystalline insulin was used instead of amorphous insulin, a decrease in B3 conversion was seen.

Cleavage of the A8-A9 peptide link happens in certain crystal suspensions. An imide intermediates is used in the hydrolysis of insulin. Only the peptide chain is hydrolyzed in preparations with rhombohedral crystals of free zinc ions[24]

Insulin preparations which are stored at 4–45 °C create covalently bonded, high-molecular weight products, the majority of which are covalent insulin dimers. A covalent insulin-protamine product is developed in formulations that include protamine. At heats over 25°C, oligo-compounds and polymers are also formed by parallel or subsequent processes.

The development of different products in insulin compositions is significantly influenced by temperature. All forms of insulin formulations contain a hexameric unit that undergoes dimerization; dimerization is more apparent in glycerol-containing formulations [25].

As bulking agents and cryoprotectants, sugars and polyols are added to lyophilized proteins and peptides, however it has been shown that reducing sugars interact with proteins. Rapid covalent alteration of recombinant human relaxin occurs in a lyophilized formulation when it reacts with the excipient glucose. According to LC/MS and tryptic mapping of the protein, one pathway for degradation involves the Maillard reaction to produce covalent adducts of glucose with the amino groups (Lys and Arg) of the protein's side chains.

Ser cleavage from the C-terminus of the protein's -strand occurs via a different mechanism. The latter process includes the hydrolysis of the Trp-Ser amide bond via a cyclic intermediate and the interaction of glucose with the Ser hydroxyl group, which mostly takes place in the solid state. Mannitol (a polyhydric alcohol) and trehalose (a non-reducing sugar) do not react in this way with relaxin[26].

The link between chemical stability, aging condition, and global molecular motion, as well as the mobility of molecules in multicomponent systems, have both been the subject of studies. Additionally, we looked at how tempering glass below its transition temperature (Tg) might alter its chemical stability, the total relaxation time, and/or T1 and T1rho, where the calorimetry-determined breakdown rate is concerned. Additionally, solid-state NMR spectroscopy was used to establish relaxation periods in order to ascertain whether they were connected.

In this investigation, aspartame/sucrose and aspartame/trehalose (1:10, w/w) preparations were lyophilized. Long-term kinetics were used to assess the impact of annealing on chemical stabilization done.

The findings confirmed the idea that heat transitions have an impact on molecule mobility for structural relaxation. Such effects are important for chemical stability, and annealing leads to stabilization of the preparation.[27]

IV. Chemical Incompatibilities

Drug breakdown may be brought on by interactions with other medications or formulation additives. The anti - microbial inhibitors hydroxybenzoic acid esters (parabens) transesterify with any sugars and sugar alcohols that could be included as sweeteners in the composition. By reacting with various hydroxyl groups in sorbitol, for instance, methyl hydroxybenzoate can yield a variety of sorbitol hydroxybenzoates. Aminophylline and suppository base interactions are among the relevant responses.

Theophylline and ethylenediamine combine to generate aminophylline, which is more water soluble than theophylline by itself. The melting point of the base is raised above specific temperature when aminophylline suppositories are stored, which stops the medication from dissolving.

The amide bonding that forms among ethylenediamine and the carboxyl groups of fatty acids found in the suppository base is the process. The amide hydrolysis process is the opposite of this reaction. For several medicines, transacetylation reactions have been documented.

For instance, the acetyl group from aspirin is moved to phenylephrine in a tablet dosage form comprising aspirin and phenylephrine hydrochloride (a medication used as a nasal decongestant). Aspirin and paracetamol respond in a manner that is comparable (acetaminophen). Aspirin also interacts with the polyethylene glycol base used in suppository preparations, giving it an acetyl group.

The Maillard reaction occurs an amine and a reducing sugar. Reactive aldehyde or keto groups are present in open ring forms of reducing sugars that tautomerize. Cooked meals begin to brown as a result of this process since the food's proteins contain amino groups. also possible between sugars. During storage, this reaction happens the white tablets to become yellow. For instance, lactose tautomerizes to an aldehyde form and then, after undergoing a number of intermediate reactions, combines with amines to produce colorful 1-amino-2-keto sugars.

Glucose and fructose are two more lowering sugars. Sucrose and mannitol are non-reducing sugars that do not experience this response. Injections of epinephrine (adrenaline) frequently include sodium metabisulfite as an antioxidant. But the primary mechanism is the reaction with medicines to produce epinephrine sulfonic acid.

[1] Williams H, Stephens D, McMahon M, Qui F, Wu Y, Hahn D, Orr R, webb D, Hyzer CH, Debie E, Sechler L, Risk-based predictive stability – an industry perspective. Pharm Tech 2017;41(3):52-57.
[2]Fersht AR, Kirby AJ. The hydrolysis of aspirin. Intramolecular general base catalysis of ester hydrolysis. J Am Chem Soc. 1967;89:4857–
4863.
[3]Higuchi T, Havinga A, Busse LW. The kinetics of the hydrolysis of procaine. J Am Pharm Assoc Sci Ed. 1950;39:405–410.
[4]Koshy KT, Lach JL. Stability of aqueous solutions of N-acetyl-p-aminophenol. J Pharm Sci. 1961;50:113–118.
[5]Ahmed S, Anwar N, Sheraz MA, Ahmad I. Stability of sulfacetamide in pharmaceutical preparations: a review. In: Berhardt LV, editor, Advances in Medicine and Biology, Nova Science Publishers, Inc., New York, USA, 2016, Chap. 8.
[6]Ahmad T, Ahmad I. Photo-oxidation of sulphanilamide to azo and azoxy compounds. Pak J Pharm Sci. 1989;2:1–5

[7]Ahmad T, Ahmad I. Degradation studies on sulphacetamide eye-drops. Part 1. Pharmazie. 1981;36:619–621.
[8]Ahmad I, Beg AE, Zoha SMS. Studies on degradation of riboflavin and related compounds II. Multicomponent spectrophotometric determination of thermal degradation products of riboflavin. J Sci Univ Kar. 1973;2:84–91.
[9]Surrey AR, Nachod FC. Alkaline hydrolysis of riboflavin. J Am Chem Soc. 1951;73:2336–2338.
[10]Blaug SM, Hajratwala B. Kinetics of aerobic oxidation of ascorbic acid. J Pharm Sci. 1972;61:556–562.
[11]Yeh SY, Lach JL. Stability of morphine in aqueous solution. III. Kinetics of morphine degradation in aqueous solution. J Pharm Sci. 1961;50:35–42.
[12]Baertschi SW, editor. Pharmaceutical Stress Testing Predicting Drug Degradation. Taylor & Francis, New York, USA, 2005, Chap. 3.
[13]Connors KA, Amidon GL, Stella VJ. Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists, 2nd ed., John Wiley, New York, USA, 1986.
[14]Jackson C, Crabb TA, Gibson M, Gibson R, Godgery R, Saunders R, Thurston DE. Studies on the stability of trimelamol, a carbinolamine-containing antitumor drug. J Pharm Sci. 1991;80:245–251.
[15]Ott H, Hofmann A, Frey AJ. Acid-catalyzed isomerization in the peptide part of ergot alkaloids. J Am Chem Soc. 1966;88:1251–1256.
[16]Wolfrom ML, Schuetz RD, Cavalieri LF. Chemical interaction of amino compounds and sugars. III. The conversion of D-glucose to 5-(hydroxymethyl)-2-furaldehyde. J Am Chem Soc. 1948;70:514–517.
[17]Nassar MN, House CA, Agharkar SN. Stability of batanopride hydrochloride in aqueous solutions. J Pharm Sci. 1992;81:1088–1091.
[18]Kumar RA, Maheswari CU, Ghantasala S, Jyothi C, Reddy KR. oxidative dehydrogenation of 3H-quinazolin-4-ones abd 4H-3,1-benzoxazin-4-ones via benzylic oxidation and oxidative dehydrogenation using potassium iodide-tert-butyl hydroperoxide. Adv Synth Catal. 2011;353:401–410
[19]Fasani E, Barberis Negra FF, Mella M, Monti S, Albini A. Photoinduced C–F Bond Cleavage in Some Fluorinated 7-Amino-4-quinolone-3-carboxylic Acids. J Org Chem. 1999;64:5388–5395.
[20]Ahmad I, Rapson HDC, Heelis PF, Phillipis GO. Alkaline hydrolysis of 7,8-dimethyl-10-(formylmethylflavin)isoalloxaine. A kinetic study. J Org Chem. 1980;45:731–733.
[21]Lin KT, Momparler RL, Rivard GE. High-performance liquid chromatographic analysis of chemical stability of 5-aza-2'-deoxycytidine. J Pharm Sci. 1981;70:1228–1232.
[22]Oberholtzer ER, Brenner GS. Cefoxitin sodium: solution and solid-state chemical stability studies. J Pharm Sci. 1979;68:863–866.
[23]Teraoka R, Otsuda M, Matsuda Y. Effect of temperature and humidity on the solid-state chemical stability of ranitidine hydrochloride. J Pharm Sci. 1993;82:601–604.
[24]Brange J, Langkjaer L, Havelund S, Vølund A. Chemical stability of insulin. 1. Hydrolytic degradation during storage of pharmaceutical preparations. Pharm Res. 1992a;9:715–726.
[25]Brange J, Havelund S, Hougaard P. Chemical stability of insulin. 2. Formation of higher molecular weight transformation products during storage of pharmaceutical preparations. Pharm Res. 1992b;9:727–734.
[26]Li S, Patapofi TW, Overcarhier D, Hsu C, Nguyen TH, Borchardt RT. Effect of reducing sugars on the chemical stability of human relaxin in the lyophilized state. J Pharm Sci. 1996;85:873–877.
[27]Luthra SA, Hodge IM, Utz M, Pikal MJ. Correlation of annealing with chemical stability in lyophilized pharmaceutical glasses. J Pharm Sci. 2008;97:5240–5251.