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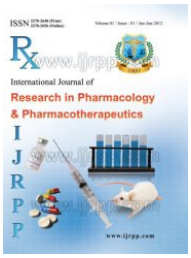

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Factors Affecting Drug Stability-A Major Concern to the Pharmaceutical Industry in the Drug Development and its Commercialization

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ABSTRACT

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. This includes the quality of starting materials, including active substances and excipients, for the production of medicinal products and here packaging materials are also covered. Any risks that may emanate from starting materials of inappropriate quality must be avoided for the benefit and safety of patients using medicinal products. Drug products are complex mixtures of drug and excipients, and as such, their chemical and physical stability kinetics are complex. A thorough knowledge of the chemical and physical stability of drugs and dosage forms is critical in the development and evaluation of pharmaceuticals. Each ingredient, whether therapeutically active or pharmaceutically necessary, can affect the stability of drug substances and dosage forms.It is most important to ensure that a particular formulation when packaged in a specific container will remain within its physical, chemical, microbiological, therapeutic and toxicological specifications on storage for a specified time period. In order to have such an assurance we need to conduct a rigorous stability testing program on the product in the form that is finally to be marketed. This paper presents a reasonably systematic and comprehensive approach to the subject of chemical and physical drug stability and the factors affecting drug stability.

Keywords: Shelf-Life of Drugs, Stability Studies, Drug Instability, Factors Affecting.

INTRODUCTION

Pharmaceutical products are prone to deteriorate on storage. The shelf-life of a pharmaceutical product is the period of time during which, if stored correctly, it is expected to retain acceptable Physical, Chemical, and Microbiological stability. The expiry date is the date given on the product packaging which represents the end of the shelf-life[1].In the drug development to the regulatory approval and marketing/commercialization of a pharmaceutical product, a shelf-life must be assigned and this assignment of shelf-life uses various factors to determine how long a product will be safe and effective for the patient under reasonable storage conditions. A shelf-life is assigned to materials used for clinical trials as well as to products distributed commercially[2].An acceptable stability report of the drug substance and drug product is one of the basic quality requirements. The overall stability of a drug product is related not only to the intrinsic chemical stability of the drug molecule, but also the physical form, manufacturing

processes, interactions among formulation components, package, and storage condition[3].

An Overview on Drug Stability

The term drug stability refers to, "the extent to which a drug substance or product retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture". The type of stability is generally divided into chemical, physical, microbiological, therapeutic, and toxicological.

Drug stability can be categorized as pre-market and commercial (marketed product) stability. Pre-market stability, which supports the clinical trial where drug products are stored under different conditions for safety and efficacy evaluation, is usually conducted throughout the clinical trial during the filing period. Commercial stability is continuous assurance on the post-approval batches for long-term stability monitoring on the drug product. Drug stability assessment generally involves the testing of the drug substance or drug product using a stability-indicating method in order to establish the retest period (for pre-market stability) and shelf life (for commercial stability).

Drug substance (also called the active pharmaceutical ingredient [API] as per USP-NF definition 1) is the material that is used to manufacture, usually with excipients, the drug product. Drug substances can be derived from chemical synthesis, plant or animal sources, or biological or recombinant technology. In addition to the API, the drug substance can contain product- and process-related substances or impurities. From the earliest stage of drug product development, information on drug substance stability has been an integral part of drug development. Data on the physical and chemical characteristics and other properties of the drug substance are helpful for designing methods that indicate the drug product's stability and are also helpful in designing formal stability studies.

Drug product (also called the dosage form or finished product per USP-NF definition 1) contains one or more drug substances, usually with excipients, in the final packaging intended for marketing. Stability studies on the drug product serve three purposes: (1) to support the stability of the drug product used in clinical/non-clinical studies, (2) to establish commercial expiry dating, and (3) to determine levels for certain specifications (API, preservatives, etc.) and set the control limits for lot release[4].

Factors Affecting Drug Substance and Product Stability

The understanding of the physicochemical characteristics of drug substance also known as active pharmaceutical ingredient or API is the prerequisite for formulation development and design of drug products with optimal stability. Drug substances can experience physical and /or chemical changes under the influences of external environmental factors such as temperature, humidity, lightand oxygen. Physical instability of drug substances can be generally classified into two categories based on the main cause. It is listed in detail in the figure-1below[3]

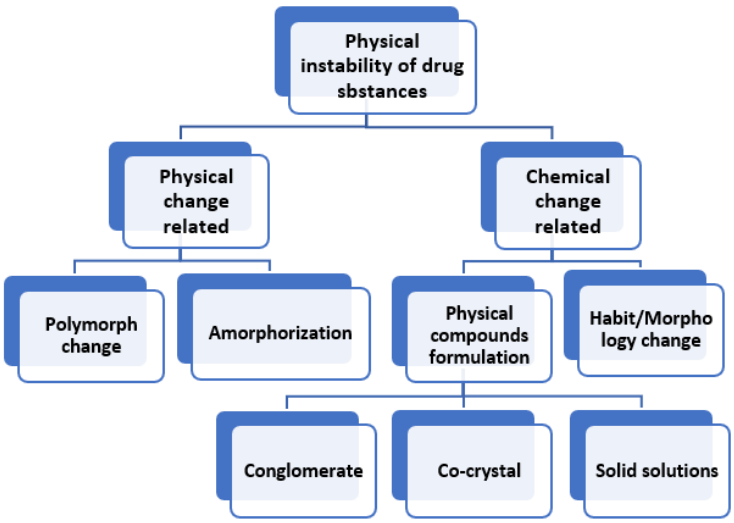

Figure-1: Physical Instability of Drug Substance

The stability of pharmaceutical products is a broad area encompassing many potential routes of degradation. Any change in the physical, chemical, micro biological and therapeutic properties in any component of the drug whether it is active or excipient will lead to the Instability. Apart from the stability of drug substances and products being influenced by the external environmental factors mentioned above, the major factors that influence drug stability in the solid dosage

or liquid form include particle size, pH, solvent system composition, solution ionic strength, cat ions and anions/excipients compatibility, chemical additives, and primary container and storage conditions. Information obtained from stability studies in different conditions will aid in establishing the retest period of the drug substance and shelf life of the drug product. Strict adherence to the storage requirements specified in the product labeling will help ensure product potency and stability through to the manufacturer's labeled expiration date. Several forms of instability can occur.

- First, there may be chemical degradation of the drug, leading to substantial lowering of the quantity of the therapeutic agent in the dosage form.
- Second, although the degradation of the active drug may not be that extensive, a toxic degradant may be formed in the decomposition process.
- Third, instability of a drug product can lead to a decrease in its bioavailability, and reduction in bioavailability can result in a substantial lowering in the therapeutic efficacy of the dosage form.
- Fourth, there may be substantial changes in the physical appearance of the dosage forms[5].
- Many factors affect the stability of a pharmaceutical product and include the stability of the active ingredients, the potential interaction between active and inactive ingredients, the manufacturing process, the dosage form, the container-linear closure system, and the environmental conditions encountered during shipment, storage and handling, and length of time between manufacture and usage. Classically, pharmaceutical product stability evaluations have been separated into studies of chemical (including biochemical) and physical stability of formulations[6].

Physical stability

The physical dimensions are also equally important, hence the knowledge of the physical stability of a formulation is very important for three primary reasons: Firstly, a pharmaceutical product may appear fresh, elegant, and professional, for as long as it remains on the shelf. Any changes in physical appearance such as color fading or haziness can cause the patient or consumer to lose confidence in the product. Secondly, since some products are dispensed in multiple-dose containers, uniformity of dose content of the active ingredient over time must be ensured. A cloudy solution or a broken emulsion can lead to a non-uniform dosage pattern. Thirdly, the active ingredient must be available to the patient throughout the expected shelf-life of the preparation. A breakdown in the physical system can lead to non-availability or “dose dumping” of the medication to the patient. In the case of metered dose inhaler pulmonary aerosols, particle aggregation may result in inadequate lung deposition of the medication[6].

Physical factors, such as heat, light, and moisture, may initiate or accelerate chemical reactions, while every time a measurement is made on a chemical compound[6]. The primary environmental factors that can reduce stability include exposure to adverse temperatures, light, humidity, oxygen, and carbon dioxide. The major dosage form factors that influence drug stability include particle size (especially in emulsions and Suspensions), pH, solvent system composition (i.e., percentage of “free” water and overall polarity), compatibility of anions and cations, solution ionic strength, primary container, specific chemical additives, and molecular binding and diffusion of drugs and excipients. In dosage forms, the following reactions usually cause loss of active drug content, and they usually do not provide obvious visual or olfactory evidence of their occurrence[7].

In some cases, the shelf-life can be limited by the physical stability of a drug product rather than by its chemical stability. Physical stability is most important when it induces change in the performance of a dosage form after storage, particularly any factor that could alter the bioavailability of the active pharmaceutical ingredient (API). Like in solid dosage form, a change in dissolution performance (Disintegration and subsequent solubilization). Dissolution changes on storage of tablets and capsules can occur due to a number of factors. With tablets, the majority of issues are associated with picking up moisture from the environment, which can result in a change in the effectiveness of a disintegrant. With gelatin capsules (both normal and soft-gel capsules), the capsules themselves are subject to physical changes upon long-term storage. Sometimes, gelatin will undergo a cross-linking reaction due to low levels of impurities in the formulation or packaging. This cross-linking can make the gelatin slow to dissolve in standard dissolution media. Another potential physical change in solid dosage forms involves a change in the form of API itself. Most pharmaceutical dosage forms employ a crystalline form of the API with a particular packing morphology. In most cases the API is capable of assuming polymorphic forms having different energetics. If the polymorph used in a drug product turns out to be a high energy form, the potential exists for the polymorphic form of change during storage, which rarely could result in change in bioavailability. Desolvation results when a solvent molecule is lost from the crystal lattice. The result of such loss of crystallinity is generally an increase in drug solubility (dissolution rate), but a decrease in drug stability. For liquid dosage forms, altered bioavailability, upon storage generally manifest in precipitation of API or other formulation components. Precipitation can result from shifts in the pH of the solution (suspension), due to increase in the API Particle size[2].

The Common physical causes of instability are listed in the Table-1 below. Most of these are due to the changes in the physical properties of the dosage form, either spoiling the products appearance or reducing its effectiveness. The other potential problems are loss of drug due to sorption or communication of the product by extractives. Molecules of the drug or other drug product may be lost from a formulation by adsorption onto the surface of the container or closure or by absorption of molecules into plastic, or rubber container or closures. For example, diazepam is lost from solutions in contact with plastic packaging. In injection dosage form, there is loss of antimicrobial preservative to rubber closures. The

extent of sorption (adsorption and absorption operating together is collectively called as sorption) depends on the pHof the solution[1].

Table-1 Physical Stability of Pharmaceutical Products[1]

Serial No.	Formulation Type	Physical instability	Effect on dosage form
1	All Liquid Products	Sorption of drug to container or closure	Loss of drug
		Extraction of materials into liquid from container or closure	Possible toxicity of extractives, Change of pH solutions
		Shedding of particles from glass containers.	Poor appearance, Potential harm to patient with injection products
		Evaporation of chloroform (used as antimicrobial preservative)	Microbial contamination.
2	Solutions	Precipitation of drugs or degradation products	Poor appearance, Loss of efficacy
3	Suspensions	Caking of sediment	Inaccurate dose of drug taken by user
		Particle growth	Poor appearance, Grittiness
4	Emulsions	Creaming and cracking,	Poor appearance, Non-homogenous product,
		Reduction in viscosity	Increased risk of creaming and cracking, Poor application characteristics for tropical products.
5	Ointments	Separation of liquid onto surface(bleeding)	Poor Appearance
6	Solid dosage forms	Polymorphic change,	Reduced drug dissolution rate
		Change in disintegration time of dosage form	May affect drug dissolution
		Change in crushing strength	May cause change in disintegration time of tablets
		Cracking of coated tablets	Poor appearance
			Loss of protection of enteric- coated products from gastric acid
		Evaporation of glyceryl trinitrate (Nitro-glycerine)	Loss of drug
7	Transdermal patches	Change in drug release rate	Changed therapeutic effect
		Change in patch adhesive characteristics	Patch may not remain adhered to the skin.
8	Inhalation and nasal aerosols	Change in particle size distribution of emitted dose	Reduced therapeutic effect.

Chemical Stability

The loss of drug through a chemical reaction resulting in a reduction of potency is the most easily understood and most studied form of drug instability. Loss of potency is a well-recognized cause of poor product quality. Loss of drug potency by various pathways is only one of many possible reasons for quantitating drug loss. Identification of the products formed provides a better understanding of the mechanisms of these chemical reactions as well as other valuable information. The drug may degrade to a toxic substance. Therefore, it is important to determine not only how much drug is lost with time but also what are its degradants. In some cases, the degradants may be of known toxicity. Sometimes, reactive intermediates are formed that are known or suspected to be toxic for example, Penicillins rearrange under acidic pH conditions to penicillanic acids which are suspected to contribute to the allergenicity of penicillins[8].

Pharmaceutical active ingredients (APIs), whether biological or small molecules are susceptible to organic chemical

degradation processes[2].Degradation of the drug may make the product esthetically unacceptable. Products are presumed to be adulterated if significant changes in, for instance, color or odor have occurred with time. any epinephrine-containing product that develops a significant pink tinge is usually considered adulterated[8].Chemical degradation of the drug is often the critical 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[1].

Types of Chemical Degradation Reactions/Pathways

The chemical causes of drug deterioration have been classified as Hydrolysis, Dehydration, Isomerization and Racemization, Elimination, Epimerization, Polymerization, Decarboxylation, Oxidation Reduction, Interionic Compatibility, and Incompatibilities. The most frequently encountered chemical reactions, which may occur within a pharmaceutical product, are described below:

Hydrolytic Degradation/ Hydrolysis

Hydrolysis is one of the most common reactions seen with pharmaceuticals**.** Many researchers have reported extensively on the hydrolysis of drug substances. In the 1950s, elegant studies, especially considering the lack of high-throughput analytical techniques concerning the hydrolysis of procaine, aspirin, chloramphenicol, atropine, and methyl-phenidate were reported[8].Drug degradation that involves reaction with water is called hydrolysis. Hydrolysis and oxidation are the two most common mechanisms of drug degradation reported[9].

In this type of reaction, the active drug undergoes decomposition following reaction with the solvent present. Usually, the solvent is water, but sometimes the reaction may involve pharmaceutical cosolvents, such as ethyl alcohol or polyethylene glycol. These solvents act as nucleophiles, attacking the electropositive centers in drug molecules. The most common hydrolysis reactions encountered in pharmaceuticals are those involving "labile" carbonyl compounds, such as esters, lactones and lactams. Some functional groups subject to hydrolysis are shown in the Table-2.[8]As water is common in pharmaceutical products, either as an ingredient or as a contaminant, and hydrolysis reactions are the most common cause of chemical degradation[1].

Table-2: Some functional groups subject to hydrolysis[8]

Drug Type	Examples	References
Esters	Aspirin	4,6,10
	Alkaloids	10
	Cocaine	6
	Physostigmine	6
	Tetracaine	6
	Procaine	6,4
	Methyldopa	6
	Dexamethasone Sodium Phosphate	10
	Estrone Sulphate	10
	Nitro-glycerine	10
Lactones	Pilocarpine	10
	Spironolactone	10
Lactams	Penicillins	6,10
	Cephalosporin	6,10
Amides	Thiacinamide	10
	Chloramphenicol	10
	Dibucaine	6
Oximes	Steroid Oximes	10
Imides	Glutethimide	10
	Ethosuximide	10
	Amobarbital	6
Imines (Azomethine)	Diazepam	6,4
Malonic Urease	Barbiturates	10
Nitrogen Mustards	Melphalan	10

Hydrolysis reactions are typically acid or base catalyzed. Acidic, neutral and basic conditions should therefore be employed in order to induce potential hydrolytic reactions. This is especially important when the compound being tested has an ionizable functional groups and can exist in different ionization states under relevant aqueous conditions[9]. Estersand β-lactams are the chemical bonds that are most likely to hydrolyze in the presence of water. For e.g., the acetyl ester in aspirin is hydrolyzed to acetic acid and salicylic acid in the presence of moisture, but in a dry environment the hydrolysis of aspirin is negligible. The aspirin hydrolysis rate increases in direct proportion to the water vapor pressure in an environment. The lactam and azomethine (or amine) bonds in benzodiazepines are also labile to hydrolysis[10]. The amide group is frequently found in drug molecules. It degrades to a carboxylic acid and an amine. Amides tend to be more stable to hydrolysis than the corresponding esters. The antimicrobial drug chloramphenicol is an amide containing drugthat is relatively susceptible to hydrolysis compared to many amides. Eye drop preparations of chloramphenicol therefore require storage in refrigerator. The lactam group, which is a cyclic amide is important because it is present in penicillin and cephalosporin antibiotics and this group is very susceptible to hydrolysis[1].The major chemical accelerators or catalysts of hydrolysis are adverse pH and specific chemicals (e.g., dextrose and copper in the case of ampicillin hydrolysis. The amide bond hydrolyzes, though generally at a slower rate than comparable esters. For e.g., procaine (an ester) will hydrolyze upon autoclaving, but procainamide will not. The amide or peptide bond in peptides and proteins varies in the lability to hydrolysis[6,7].

Hydrolysis reactions are often pH dependent and are catalyzed by either hydronium ion or hydroxide ions (specific-acid or specific-base catalysis, respectively). Hydrolysis reactions can also be catalyzed by either a Bronsted acid or a Bronsted base (general-acid or general-base catalysis, respectively). Sources of Bronsted acid or base include buffers and some excipients. Sometimes it is necessary to compromise between the optimum pH for stability and that for pharmacological activity. For example, several local anesthetics are more stable at a distinctly acid pH, whereas for maximum activity they should be neutral or slightly alkaline. Small amounts of acids, alkalines, or buffers are used to adjust the pH of a formulation. Buffers are used when small changes in pH are likely to cause major degradation of the active ingredient[6].Since hydrolysis is frequently catalyzed by hydrogen ions (specific acid catalysis) or hydroxyl ions (specific base catalysis), the most usual method of controlling drug decomposition is to determine the pH of maximum stability from kinetic experiments at a range of pH values and to formulate the product at this pH[10].

Obviously, the amount of water present can have a profound effect on the rate of a hydrolysis reaction. When the reaction takes place fairly rapidly in water, other solvents sometimes canbe substituted. For example, barbiturates are much more stable at room temperature in propylene glycol-water than in water alone. Modification of chemical structure may be used to retard hydrolysis. In general, as it is only the fraction of the drug in solution that hydrolyzes, a compound may be stabilized by reducing its solubility. This can be done by adding various substituents to the alkyl or acyl chain of aliphatic or aromatic esters or to the ring of an aromatic ester. In some cases, less-soluble salts or esters of the parent compound have been found to aid product stability. Steric and polar complexation have also been employed to alter the rate of hydrolysis. Caffeine reduces the rate of hydrolysis and thus promotes stability by complexation with local anesthetics such as benzocaine, procaine, or tetracaine[6].

Alteration of the dielectric constant by the addition of nonaqueous solvents such as alcohol, glycerin, or propylene glycol may in many cases reduce hydrolysis. Since only that portion of the drug which is in solution will be hydrolyzed, it is possible to suppress degradation by making the drug less soluble. For example, reduced solubility of penicillin in procaine penicillin suspensions by using additives such as citrates, dextrose, sorbitol, and gluconate and, in so doing, significantly increased the stability.Higuchi and Lachman suggested adding a compound that forms a complex with the drug as a means of increasing stability. The addition of caffeine to aqueous solutions of benzocaine, procaine, and amethocaine was shown to decrease the base catalyzed hydrolysis of these local anesthetics in this way. Modification of chemical structure using appropriate substituents is a possible method for reducing chemical degradation[10].

The rate of hydrolysis depends on the temperature and the pH of the solution. A much-quoted estimation is that for each 10°C rise in storage temperature, the rate of reaction doubles or triples[6].When hydrolysis occurs, the concentration of the active ingredient decreases while the concentration of the decomposition products increases. The effect of this change on the rate of reaction depends on the order of the reaction. With zero-order reactions the rate of decomposition is independent of concentration of the ingredient. Although dilute solutions decompose at the same absolute rate as more concentrated solutions, the more dilute the solution, the greater the proportion of active ingredient destroyed in a given time. i.e., the percentage of decomposition is greater in more dilute solutions. Increasing the concentrationof an active ingredient that is hydrolyzing by zero-order kinetics will slow the percentagedecomposition[6].

The degradation of many drugs in solution accelerates or decelerates exponentially as the pH is decreased or increased over a specific range of pH values. Improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug, resulting from hydrolysis and oxidation reactions. A drug solution or suspension, for example, may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it degrades in minutes or days. It is possible that a pH change of only one unit (e.g., from 4 to 3 or 8 to 9) could decrease drug stability by a factor of ten or greater. A pH- buffer system, which is usually a weak acid or base and its salt, is a common excipient used in liquid preparations to maintain the pH in a range that minimizes the drug degradation rate. The pH of drug solutions may also be buffered or adjusted to achieve drug solubility. For example, pH in relation to pKa controls the fractions of the usually more soluble ionized and less soluble nonionized species of weak organic electrolytes[6].Hydrolysis is important in the

degradation of the proteins and polypeptides. Breakdown of the amide bonds which link the aminoacids together in the protein or polypeptide chain is known as proteolysis[1].

Dehydration

There are two types of Dehydration processes like:

1. Covalent dehydration and
2. Physical dehydration.

Sugars such as glucose and lactose are known to undergo dehydration to form 5- (hydroxymethyl)furural. Erythromycin is susceptible to acid-catalyzed dehydration. Batanopride undergoes an intramolecular ring-closure reaction in the acidic Ph range due to dehydration, whereas Streptovitacin A exhibits two successive acid-catalyzed dehydration reactions[8].

Racemization and Isomerization

Racemization

The conversion of an optically active molecule with one chiral center into its mirror-image is known as racemization[1].The action or process of changing from an optically active compound into a racemic compound or an optically inactive mixture of corresponding R (Rectus) and S (Sinister) forms, which is known as racemization is a major consideration in pharmaceutical stability. Optical activity of a compound may be monitored by polarimetry and reported in terms of specific rotation. Chiral HPLC has been used in addition to polarimetry to confirm the enantiomer purity of a sample. In general racemization follows first-order kinetics and depends on temperature, solvent, catalyst, and the presence or absence of light. Racemization appears to depend on the functional group bound to the asymmetric carbon atom, with aromatic groups tending to accelerate the process[6].

The racemization of pharmacologically active agents is of interest because enantiomers often have significantly different absorption, distribution, metabolism, and excretion, in addition to differing pharmacological actions. Most racemization reactions are catalyzed by an acid or Base. For example, the isomerization of cephalosporin esters, which are widely used as intermediates in cephalosporin synthesis and as prodrugs for oral administration of parenteral cephalosporins, is base-catalyzed.The best-known racemization reactions of drugs are those that involve epinephrine, pilocarpine, ergotamine, and tetracycline. In these drugs, the reaction mechanism appears to involve an intermediate carbonium ion or carbanion that is stabilized electronically by the neighboring substituent group. For example, the racemization of pilocarpine, a carbanion is produced and stabilized by delocalization to the enolate. In addition to the racemization reaction, pilocarpine is also degraded through hydrolysis of the lactone ring[10,11].

Isomerization

Conversion of an active drug into an inactive or a less active drug is known as isomerization. Different isomers of a drug often have differing pharmacological activity or toxicity. so, any change in the proportion of isomers on storage of a pharmaceutical product is of importance. Structural isomerization is sometimes a mechanism of drug degradation.

The best-known example of this is with betamethasone-17-valerate, a potent corticosteroid. The best substances include trans-cis isomerization of amphotericin B[1]. Cephalosporin antibiotics will undergo isomerization of the double bond. The isomerization reaction is subject to general and specific base catalysis in both directions. The reaction also occurs at a much slower rate during either solution or solid-state degradation of non-esterified cephalosporins as in the case of cefaclor[12].

Epimerization

In drug molecules with more than one chiral Centre, racemization at one of the chiral centersis known as Epimerization[1].Members of the tetracycline family are most likely to incur epimerization. This reaction occurs rapidly when the dissolved drug is exposed to a pH of an intermediate range (higher than 3), and it results in the steric rearrangement of the dimethylamine group. The epimer of tetracycline, epitetracycline, has little or no antibacterial activity[6].

The Antibiotic tetracycline, forms the 4-epitetracycline epimer, which is not active against microbes and is more toxic than tetracycline[1]. Epimerization of the API reserpine to 3-isoreserpine occurs readily in strong acid solution but has also been observed in solution using heat and light conditions. Racemization of brinzolamide to the S isomer occurs under heat and light (pH independent) conditions. Epimerization also occurs under basic conditions for the lactone containing API pilocarpine[12].

Dimerization and Polymerization

Reaction of a drug molecule with another molecule of the same drug may result in the formation of a dimer or polymer[1].

Dimerization

Many compounds will undergo dimerization reactions: those containing thiols e.g., disulphide formation, olefins, alcohols, and carboxylic acids. Indoles have been shown to dimerize under acidic conditions. The phenols have been shown to dimerize under free radical initiated oxidative conditions, usually to ortho phenols. Nalidixic acid APIundergoes dimerization under thermolysis conditions to decarboxylate and produce a dimeric structure[12]. Amoxicillin, besides undergoing hydrolysis of the β-lactam ring, also undergoes dimerization by nucleophilic attack on the β-lactamring by the amino group. Especially in more concentrated solutions. The reaction can continue to produce a trimer and tetramer[1].

Polymerization

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 alkaloid buffer[1].

A few examples have been cited of drugs that undergo polymerization during storage in solution. For example, Bundgaard has shown that a polymerization process occurs during the storage of concentrated aqueous solutions of amino-Penicillins, such as ampicillin sodium. The reactive β-lactam bond of the ampicillin molecule is opened by reaction with the side chain of a second ampicillin molecule, and a dimer is formed. The process can continue to form higher polymers. Such polymeric substances have been shown to be highly antigenic in animals, and they are considered to play a part in eliciting penicilloyl-specific allergic reactions to ampicillin in man. The dimerizing tendency of the amino-Penicillins increases with the increase in the basicity of the side-chain group, the order, in terms of increasing rates being cyclacillin<< ampicillin <epicillin< amoxicillin[10].

Decarboxylation and Elimination

Decarboxylation

Drug substances having a carboxylic acid group are sometimes susceptible to decarboxylation. 4-Aminosalicylic acid is a good example[8]. Pyrolytic solid-state degradation through carboxylation usually is not encountered in pharmacy, as relatively high heats of activation (25 to 30 k Cal) are required for the reaction. However, solid p-amino salicylic acid undergoes pyrolytic degradation to m-aminophenol and carbon dioxide. The reaction, which follows first-order kinetics, is highly pH-dependent and is catalyzed by hydronium ions. The decarboxylation of p-aminobenzoic acid occurs only at extremely low pH values and at high temperatures. Some dissolved carboxylic acids, such as p-amino salicylic acid, lose carbon dioxide from the carboxyl group when heated. The resulting product has reduced pharmacological potency. β-keto decarboxylation can occur in some solid antibiotics that have a carbonyl group on the β-carbon of a carboxylic acid or a carboxylate anion. Such decarboxylations will occur in the following antibiotics: carbenicillin sodium, carbenicillin free acid, ticarcillin sodium, and ticarcillin free acid[6].

Foscarnet also undergoes decarboxylation under strongly acidic conditions. Whereas etodolac is susceptible to decarboxylation by acid catalysis[8]. This action is minimized by passing CO_2 into the solution for one minute and sealing the container so as to make it gas-tight prior to autoclaving[8].

Elimination

Elimination reactions have been reported for various drug substances for e.g., Trometamol eliminates its hydroxymethyl groups and forms formaldehyde. Levothyroxine eliminates iodine. ADD-17014, a derivative of triazoline eliminates nitrogen and forms a derivative of aziridine. Ditiocarb eliminates carbon disulphide[8].

Ring transformations

Ring transformations are common in pharmaceuticals. The API lorazepam containing a seven membered non-aromatic ring can lose a molecule of water and rearrange with the driving force being formation of a six-membered aromatic pyrimidine ring. Imidazole and thiazole rings have demonstrated instability under photolysis conditions. For example, the API thiabendazole undergoes cleavage of the thiazole ring to form benzimidazole-2-carboxamide and benzimidazole as well as cleavage of the imidazole ring to form thiazol-4-(N-carbomethoxy)-carboxamide. The API Norfloxacin contains a piperazine ring. This undergoes degradation under light conditions in the solution and solid state to form the ring-opened ethyl diamine derivative and amino derivative. Additional degradants observed in the solid state include the amino and formyl derivatives. The API dipivefrin and epinephrine undergo ring formation when subjected to basic conditions to form adrenochrome[12].

Oxidative Degradation/Oxidation

Oxidative reactions are one of the two most common mechanisms of drug degradation[1]. It is a well-known chemical degradation pathway for pharmaceuticals[8].Oxidation is a prime cause of product instability, and often, but not always, the addition of oxygen or the removal of hydrogen is involved. When molecular oxygen is involved, the reaction is known as auto-oxidation because it occurs spontaneously, though slowly, at room temperature[6].As mentioned above, the oxidative drug degradation reactions are typically autoxidative. i.e., the reaction is radical initiated[9].

Oxidation reaction involve an increase in the number of carbon-to-oxygen bonds 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 the deterioration of the vegetable oils which may be used in the pharmaceutical products as a solvent or an emollient in emulsions and creams. Oxidation reactions tend to be complex, giving a variety of degradation products[1].

Oxidation involves removal of an electropositive atom, radical, or electron, or the addition of an electronegative atom or radical. Oxidative degradation can occur by autoxidation, in which reaction is uncatalyzed and proceeds quite slowly under the influence of molecular oxygen, or may involve chain processes consisting of three concurrent reactions: - Initiation, Propagation and Termination. The mechanisms are however, generally complex and involve multiple pathways for these three stages. Initiation can be via free radicals formed from organic compounds by the action of light, heat or transition metals such as copper and iron, which arepresent in trace amounts in almost every buffer[10].

The initiation phase results in the formation of a low concentration of free radicals. Initiation is promoted by the light and the presence of heavy metals which are inevitably found as trace contaminants of pharmaceutical products. During the propagation stage, the concentration of free radicals increases greatly. Oxygen is involved in the propagation stage by forming hydroperoxides which react further to produce stable oxidation products. In this phase degradation accelerates, with potentially disastrous results for the products. In the termination phase, the availability of oxygen or drug diminishes, the rate of reaction slows and free radicals combine to produce unreactive end products. Oxidation of some drugs occurs rapidly in solution at room temperature. Ascorbic acid (Vitamin C) undergoes a rapid oxidation in solution to dehydroascorbic acid. Some amino

acids such as cysteine and methionine possess side chains which contain a thiol group. Oxidation of these groups can be an important factor in the degradation of proteins and polypeptides[1].

Oxidation or the loss of electrons from an atom, frequently involves free radicals and subsequent chain reactions. Only a very small amount of oxygen is required to initiate a chain reaction. In practice it is easy to remove most of the oxygen from a container, but very difficult to remove it all. Hence, nitrogen and carbon dioxide frequently are used to displace the dead space air in pharmaceutical containers to help minimize deterioration by oxidation[7].

As an oxidation reaction is complicated, it is difficult to perform a kinetic study on oxidative processes within a general stability program. The redox potential which is constant and relatively easy to determine, can, however provide valuable predictive information. In many oxidative reactions, the rate is proportional to the concentration of the oxidizing species but may be independent of the concentration of the oxygen present. The rate is influenced by the temperature, radiation, and the presence of a catalyst. An increase in temperature leads to an acceleration in the rate of oxidation. If the storage temperature of the preparation can be reduced to 0 to 5° C, usually it can be assumed that the rate of oxidation will be at least halved[6].

The molecular structures most likely to oxidize are those with hydroxyl group directly bonded to an aromatic ring (e.g., phenol derivatives such as catecholamines and morphine), conjugated dienes (e.g., Vit A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives, and aldehydes (e.g., Flavorings). Products of oxidation usually lack therapeutic activity. Visual identification of oxidation, for example, the change from colorless epinephrine to its amber colored products, may not be visible in some dilutions or to some eyes.Some functional groups subject to autoxidation are listed inTable-3 for a quickglance[6,7].

Table-3: Some Functional Groups Subject to Autoxidation[6,7]

Functional Group	Examples
Catechol's	Catecholamines (Dopamine)
Ethers	Diethyl ether
Thiols	Dimercaprol (BAL)
Thioethers	Chlorpromazine
Carboxylic Acids	FattyAcids

Oxidation is catalyzed by pH values that are higher than optimum, polyvalent heavy metal ions (Example, copper and iron and exposure to oxygen and UV illumination. The latter two causes of oxidation justify the use of antioxidant chemicals, nitrogen atmospheres during ampule and vial filling, opaque external packaging, and transparent amber glass or plastic containers[7].

Oxygen, which participates in most oxidation reactions, is abundant in the environment to which pharmaceuticals are exposed, during either processing or long-term storage. oxidation mechanisms for drug substances depend on the chemical structures of the drug and the presence of reactive oxygen species or other oxidants. Catechols such as methyldopa and epinephrine are readily oxidized to quinones. Amino salicylic acid undergoes oxidation and forms quinone amine, which is further degraded to polymeric compounds. Ethanol amines such as procaterol are degraded to polymeric compounds, thiols such as 6-mercaptopurine, captopril are oxidized to disulfides. Phenothiazines such as promethazine are oxidized via complex pathways and yield various products. Polyunsaturated molecules suchas Vitamin A, polyenes such as ergocalciferol, cholecalciferol, fumagillin and filipin are susceptible to oxidation. Phenylbutazone, morphine, hydrocortisone and prednisolone are oxidized to various products. Spiradoline is susceptible to oxidative degradation, resulting in the formation of an imidazolidine ring in addition to hydrolysis of the amide bond. Sulphur atoms are becoming more common in new drug candidates and present a particular challenge owing to their propensity to oxidize to the corresponding sulfoxides and ultimatelysulfones[8].

Many autoxidation reactions are initiated by trace amounts of impurities, such as metal ions or hydroperoxides[10].Trace amounts of heavy metals such as cupric, chromic, ferrous, or ferric ions may catalyze oxidation reactions[6].Ferric ion catalyzes the degradation reaction and decreases the induction period for the oxidation of the compound procaterol.as little as 0.0002 M copper ion will increase the rate of Vit C oxidation by a factor of 10^5. Hydroperoxides contained in polyethylene glycol suppository bases have been implicated in the oxidation of codeine to codeine-n-oxide. Peroxides apparently are responsible for the accelerated degradation of benzocaine hydrochloride in aqueous cetomacrogol solution and of a corticosteroid in polyethylene glycol 300. Many oxidation reactions are catalyzed by acids and bases. Polyunsaturated fatty acids, commonly used in drug formulations, are particularly susceptible to oxidation, and care must be exercised to minimize degradation in formulations containing high concentrations of, for example, vegetable oils[10].

As little as 0. 2 mg of copper ion per liter considerably reduces the stability of penicillin. Similar examples include the deterioration of epinephrine, phenyl epinephrine, lincomycin, isoprenaline, and protaine hydrochloride. Adding chelating agents to water to sequester heavy metals and working in special manufacturing equipment (e.g., Glass) are some means used to reduce the influence of heavy metals on a formulation. Parenteral formulations should not come in contact with heavy metal ions during their manufacture, packaging, or storage[6].

The oxidation of phenothiazines to the sulfoxide involves two single-electron transfer reactions involving a radical cation intermediate, the sulfoxide is subsequently formed by reaction of the cation with water. The ether group in drugs such as econazole nitrate and miconazole nitrate is susceptible to oxidation. The process involves removal of hydrogen from the C-H bonds in the α-position to the oxygen to produce a radical, which further degrades to α-hydroperoxides and eventually to aldehydes, ketones, alcohols, and carboxylic acids[10].

Hydronium and hydroxyl ions catalyze oxidative reactions. The rate of decomposition for epinephrine, for example, is more rapid in a neutral or alkaline solution with maximum stability minimum oxidative decomposition at pH 3.4. There is a pH range for maximum stability for any antibiotic and vitamin separation, which usually can be achieved by adding an acid, alkali, or buffer[6].An obvious precaution to minimize oxidation is to avoid contact of the drug with ions such as iron, cobalt, or nickel that are initiators of the oxidation process. Similarly, the oxygen above the formulation should be replaced with nitrogen or carbon dioxide. Even traces of oxygen are, however, sufficient to initiate oxidation, and because it is difficult to remove all of the oxygen from a container, it is common practice to add low concentrations of antioxidants and chelating agents to protect drugs against autoxidation[10].

Oxidation may be initiated by the use of antioxidants, called negative catalysts. They are very effective in stabilizing pharmaceutical products undergoing a free-radical-mediated chain reaction. These substances, which are easily oxidizable, act by possessing lower oxidation potentials than the active ingredient. Thus, they undergo preferential degradation or act as chain inhibitors of free radicals by providing an electron and receiving the excess energy possessed by the activated molecule. The ideal antioxidant should be stable and effective over a wide pH range, soluble in its oxidized form, colorless, nontoxic, nonvolatile, nonirritating, and effective in low concentrations, the most able, and compatible with the container closure system and formulation ingredients[6].

Mechanistically, some antioxidants such as ascorbic acid, ascorbyl palmitate, sodium bisulfite, sodium metabisulfite, sodium sulfite, acetone sodium bisulfite, sodium formaldehyde sulfoxylate, thioglycerol, and thioglycolic acid, act as reducing agents. They are easily oxidized, preferentially undergo autoxidation, thereby consuming oxygen and protecting the drug or excipient. They are often called oxygen scavengers because their oxidation reaction consumes oxygen. They are particularly useful in closed systems in which the oxygen cannot be replaced once it is consumed. Primary or true antioxidants act by providing electrons or labile H, which will be accepted by any free radical to terminate the chain reaction. In pharmaceuticals, the most commonly used primary antioxidants are butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA), the tocopherols (Vitamin E), and propyl gallate. Chelating agents act by forming complexes with the heavy metal ions that are often required to initiate oxidation reactions. The chelating agents used most often are ethylene diaminetetraacetic acid (EDTA) derivatives and salts, citric acid, and tartaric acid[10].

The commonly used antioxidants for aqueous system include sodium sulfite, sodium metabisulfite, sodium bisulfite, sodium thiosulfate, and ascorbic acid. For oil systems, ascorbyl Palmitate, hydroquinone, propyl gallate, nordihydroguaiaretic acid, butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA) and alpha-tocopherol are employed.Synergists, which increase the activity of antioxidants are generally organic compounds that complex small amounts of heavy metal ions. These include the ethylenediamine tetra acetic acid (EDTA) derivatives, dihydroethyl glycine and citric, tartaric, gluconic, and saccharic acids. EDTA has been used to stabilize ascorbic acid, oxytetracycline, penicillin, epinephrine, and prednisolone.

Reduction reactions are much less common than oxidative processes in pharmaceutical practice. Examples include the introduction of gold, silver, or mercury salts by light to form the responding free metal[6].

Photolytic Degradation / Photolysis

Photolytic degradation can be an important limiting factor in the stability of pharmaceuticals[6].

Light sensitivity of a pharmaceutical product can limit shelf-life, or in many cases determine the packaging requirements for the product. In some cases, light exposure can induce chemical degradation in an API when the light is absorbed and then initiates a chemical reaction. Photochemical reactions commonly include oxidations and free radical rearrangements[12].

Photolytic degradation is the degradation that results from exposure to ultraviolet light in the wavelength range of approximately 300-800 nm. Exposure to radiation at wavelengths<300nm is not needed because a pharmaceutical compound would not experience such exposure during its life cycle.According to the first law of photochemistry, "only radiation that is absorbed by a molecule can be effective in producing chemical changes in the molecule". Thus, in order for photolytic degradation to occur, radiation must be absorbed- either by the drug substance or by the formulation. Photodegradation rates are therefore directly dependent on the amount of incident radiation and on the amount of radiation that is absorbed by the compound or the formulation. It is important to remember that a compound may undergo photolytic degradation even if it does not itself absorb radiation in the UVA or visible region. This can happen only if there is some additional agent in the formulation, intentionally or adventitiously present, that felicitates absorption[9].

The 300-400 nm wavelength tend to be most damaging but are not of practical concern because they are not found in sunlight or artificial room light. Many photolysis reactions involve oxidation mechanisms, although other mechanisms may occur. photodegradation of retinol, as well as promoting oxidative reactions also results in the formation of a cis-isomer of the molecule[1]. Normal sun light or room light may cause substantial degradation of drug molecules. The energy from light radiation may be absorbed by the molecules to cause a

photolytic reaction, and if that energy is sufficient to achieve activation, degradation of the molecule is possible. Saturated molecules do not interact with visible or near-ultraviolet light, but molecules that contain π-electrons usually do absorb light throughout this wavelength range[11].

Ultraviolet radiation, which has a high energy level, is the cause of many degradation reactions. Exposure to, primarily, UV illumination may cause oxidation (photo-oxidation) and scission(photolysis) of covalent bonds. Nifedipine, nitroprusside, riboflavin, and phenothiazines are very labile to photo-oxidation. In susceptible compounds, photochemical energy creates free radical intermediates, which can perpetuate chain reactions. If the absorbing molecule reacts, the reaction is said to be photochemical in nature. When the absorbing molecule do not participate directly in the reaction, but pass their energy to other reacting molecules, the absorbing substance is said to be a photosensitizer. As many variables may be involved in a photochemical reaction, the kinetics can be quite complex. The intensity and wave length of the light and the size, shape, composition, and color of the container may affect the velocity of the reaction. The photodegradation of chlorpromazine through a semiquinone free-radical intermediate follows zero order kinetics. On the other hand, alcoholic solutions of hydrocortisone, prednisolone, and methylprednisolone degrade by reactions following first-order kinetics[6].

Photodegradation has been reported for a large number of drug substances. The mechanisms for these reactions are generally very complex. For e.g., as in Chloroquine and Primaquine. Photodegradation generally yields numerous products through complex pathways and it is often accompanied by Oxidation in the presence of oxygen. Thus, drug substances such as fumagillin, phenothiazines and cholecalciferol are degraded to different products in the presence and absence of light. Representative photodegradation routes for drug substances include dehydrogenation of nifedipine, reserpine, and nicardipine. Dehydrogenation accompanied by transmutation of a Nitro group is nimodipine. Oxidation of a reactive methylene group to a carbonyl in 4-methoxy-2-(3-phenyl-2-propynyl) phenol(CO/1828), tiaprofenic acid and KBT3022, a derivative of diphenyl thiazole and rearrangement of chlordiazeperoxide.In addition, hydrolysis of mefloquine, furosemide and LY277359, a derivative of benzofuran carboxamide, elimination of hydrogen halide from meclofenamic acid, oxidation of a hydroxyl group of 21-cortisol tert-butyl acetate and α-[dibutylamino)methyl]-6,8-dichloro-2-(3',4'-dichlorophenyl)-4-quinoline methanol, and rearrangement of benzylamine. Oxidation of menadione is enhanced by light[8].

Colored-glass containers most commonly are used to protect light-sensitive formulations. Yellow-green glass gives the best protection in the ultraviolet region, while amber confers considerable protection from ultraviolet radiation but little from infrared. Riboflavin is best protected by a stabilizer that has a hydroxyl group attached to or near the aromatic ring. The photodegradation of sulfacetamide solutions may be inhibited by an antioxidant such as sodium thiosulfate or metabisulfite[6].Coating with a polymer film containing ultraviolet absorbers has been suggested as an additional method for protection from light[1o]. Tonnesen has reviewed the mechanisms of photodecomposition of drugs[13].

Evaluation of the propensity of a drug substance or drug product to undergo photodegradation should be guided by the ICHQ1B guidance document on photostability testing[9].

A systematic approach to photostability testing is recommended covering, studies such as tests on the drug substance, tests on the exposed drug product outside of the immediate pack, and if necessary, tests on the drug product in the immediate pack. The ICH guideline Q1B discusses the minimum requirements for assessing photostability. Drug substance is first assessed by exposing sample powder having a depth of not more than3mm to an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than200 watt hours/square meter. If the drug substance shows sensitivity to photodegradations, then the drug product will need to be tested as well. The testing of drug product uses the same light exposure that was used to test drug substance. The drug product should be tested directly exposed to light and in its container closure system[6].

Thus, the knowledge of the photodegradation paths can be critical to the devising of a suitable protection of the drug dosage form, in principle, this can be obtained either by blocking the access of light to the drug with external protection or by the use of an additive that competitively absorbs or reflects the light reaching the sample. In the case of tablets or capsules, external protection from package is generally suitable, and can be obtained by using an opaque blister or an opaque gelatin for capsules, or covering tablets with an opaque film. The opaqueness can be obtained by adding a pharmaceutically acceptable dye, the absorption spectrum of which is the same as that of the drug principle or by adding a reflecting pigment such as titanium dioxide. Alternately, absorbing excipients or opacizers can beaded to the drug preparation, thus protecting the drug outside the package. this is the only choice with creams, ointments, and liquid preparations. Several other additives have been proved effective. Other techniques, such as minimization of solubilization of the drug in the vehicle, microencapsulation, or inclusion into cyclodextrins is not applicable since cyclodextrins are good hydrogen donors, and in some cases may increase the decomposition of the drug[14].

Table-4: Showing the Antioxidants Commonly Used for Stabilization of Drugs Against Hydrolysis, Oxidation and Photolysis

Aqueous systems	Oil systems
Sodium Metabisulfite	Ascorbyl palmitate

Sodium Thiosulfate	Butylated hydroxy toluene
Ascorbic acid	Butylated hydroxy anisole

Confirmation of proteins

The therapeutic effect of protein-based drugs depends on the three-dimensional structure of the molecule. Changes to this on storage or if a protein solution is accidentally frozen lead to a reduction of the protein's efficacy[1].

Interionic (Ion N+ Ion N-) Compatibility

The compatibility or solubility of oppositely charged ions depends mainly on the number of charges per ion and the molecular size of the ions, i.e., the ionic strength of a medium is related to the concentration of ionic species in it. Changing the ionic strength by adding electrolyte to a solution has some influence on the rate of many degradation reactions. This effect is not high enough to be of importance in the formulation of drug solutions. However, it can be important in laboratory experiments to investigate the influence of pH on degradation rate. In this case care should be taken to ensure the ionic strength of the various buffer solutions used is kept the same to avoid interference with the results[1]. In general, polyvalent ions of opposite charge are more likely to be incompatible. Thus, an incompatibility is likely to occur upon the addition of a large ion with a charge opposite to that of the drug. As many hydrolytic reactions are catalyzed by both hydronium and hydroxyl ions, pH is an important factor in determining the rate of a reaction. The pH range of minimum decomposition (or maximum stability) depends on the ion having the greatest effect on the reaction. If the minimum occurs at about pH 7, the two ions are of equal effect. A shift of the minimum toward the acid side indicates that the hydroxyl ion has the stronger catalytic effect and vice-versa in the case of a shift toward the alkaline side. In general, hydroxyl ions have the stronger effect. Thus, the minimum is often found between pH 3 and 4. The influence of pH on the physical stability of two-phase systems, especially emulsions, is also important. For example, intravenous fat emulsion is destabilized by acidic pH[6].

Chemical Incompatibilities/(Drug-Drug and Drug-Excipient Interactions)

Drugs are rarely formulated as just the drug substance itself. Often, additives or excipients are present in the formulation. Quite often, reactions can occur between the drug and one or more additives. Similarly, two drugs might be formulated in the same product and react with each other[8]. Degradation of a drug may be caused by reaction with another drug present in the formulation or with a formulation excipient[1]. Hence, not only it is important to be aware of chemical instability of the drug itself, but it is also necessary to consider possible instability of the product caused by chemical interactions between two or more drug components in the same dosage form, or between an active ingredient and a pharmaceutical adjuvant**.** An example of drug-drug incompatibility is the inactivation of cationic aminoglycoside antibiotics, such as kanamycin and gentamicin, by anionic Penicillins in IV admixtures. The formation of an inactive complex between these two classes of antibiotics occurs not only in vitro, but apparently also in vivo in patients with severe renal failure[10,15]**.**Hydroxybenzoate ester (paraben) antimicrobial preservatives undergo transesterification reactions with sugars and sugar alcohols, which may be present in a formulation as sweetening agents. For e.g., methyl hydroxy benzoate undergoes reaction with sorbitol to produce a variety of sorbitol hydroxybenzoate esters by reaction with sorbitol's various hydroxyl groups. A related reaction involves the interaction of aminophylline with suppository bases. Aminophylline is a complex of theophylline and ethylenediamine, which is used to increase the aqueous solubility of theophylline. On storage of aminophylline suppositories, the melting point of the base increases to above physiological temperature, preventing release of drug. This is due to formation of amide bonds between ethylenediamine and the carboxyl groups of fatty acids present in the suppository base. The reaction is the reverse of the amide hydrolysis reaction[1].

Trans acetylation reactions have been reported for some drugs. for instance, in tablet formulations containing both aspirin and phenylephrine hydrochloride (a drug used as a nasal decongestant), the acetyl group is transferred to phenylephrine. A similar reaction occurs between aspirin and paracetamol (acetaminophen). Aspirin also reacts with the polyethylene glycol base of suppository formulations, transferring the group to the polyethylene glycol.

The milliard reaction involves a reaction between an amine and a reducing sugar. The reaction is responsible for the browning of the cooked foods, where the amino group is provided by the amino acids present in the food. It may also occur between amine-containing drugs and lactose or other sugars when employed as a diluent in tablet or capsule formulations. This reaction results in the yellowing of white tablets on storage. the mechanism is reaction of the amine with the sugar to form a glycosyl amine, which rearranges to form a colored1-amino-2 keto sugar. The incompatibility can be avoided by replacing the sugar with an alternative diluent. If a sweetening agent is required in a solid dosage form of an amine drug, for instance in a dispersible tablet, sucrose, and glucose would tend to undergo the milliard reaction. However, mannitol can be used, as it does not undergo the reaction[1]**.**

Summary-Factors Determining the Chemical Stability of Drug Substances

This includes the intrinsic factors such as the molecular structure of the drug itself and the environmental factors such as temperature, pH, buffer species, ionic strength, light, oxygen, moisture, additives, and excipients. In the case of solid-state degradation, the solid-state properties of the drug such as melting point, crystallinity, and hygroscopicity are very important. In addition, mechanical forces, such as pressure and grinding applied to drug substances may affect

their chemical as well as physical stability. By approving well established kinetic concepts, it is possible not only to summarize, numerically, the role that each variable might play in altering the kinetics of degradation but also to provide valuable insight into the mechanisms of degradation[8].

Chemical stability is important for selecting storage conditions (temperature, light, humidity),selecting the proper container for dispensing (glass versus plastic, clear versusamber or opaque, cap liners), and anticipating interactions when mixing drugs and dosage forms. Stability and expiration datingare based on reaction kinetics, that is, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical species and by factors such as solvent, pressure and temperature. In considering chemical stability of a pharmaceutical, one must know the reaction order and reaction rate. The reaction order may be the overall order (the sum of the exponents of the concentration terms of the rate expression) or the order with respect toeach reactant (the exponent of the individual concentration term in the rate expression[15].

Microbiological stability

Microbiological deterioration is a critical factor in the stability of sterile products once the container is opened. Deterioration due to microorganism can either render the product harmful to the patient or have an adverse effect on the product's properties. Injection products generally need to be used immediately the container is opened and products for use in the eye have a short in-use life once opened[1].

CONCLUSION

In the development and commercialization of a pharmaceutical product, a shelf-life must be assigned. This assignment uses various factors to determine how long a product will be safe and effective for the patient under reasonable storage conditions. This is particularly important for pharmaceutical products that are prepared before dispensing to the patient and hence carrying out stability studies is of prime importance.Stability program also helps guarantee that the patient receives the correct medicine. Designing the stability program to learn how those factors impact the product and how to best protect the product from those factors is the best way to achieve the goal[2].

The main purpose for running stability studies is to determine the expiration period and recommended storage conditions for the product. Stability data are also used to build a knowledge base describing the chemical and physical attributes of the product and what environmental factors (such as heat, water, oxygen, and light) can be harmful. The goal of a pharmaceutical product development program is to successfully register and launch a drug product in global markets. A robust and well-thought-out stability–testing program can help deliver that milestone[8].

Pharmaceutical products tend to deteriorate due to many causes and five types of stability concern pharmacists, like, Chemical stability whereeach active ingredient retains its chemical integrity and labeled potencywithin the specified limits. Physical Stability, where, the original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability,are retained. Microbiologic Stability, where, Sterility or resistance to microbial growth is retained according tothe specified requirements. Therapeutic Stability, in which the therapeutic effect remainsun changed, and Toxicologic Stability, in which no significant increase in toxicityoccur[16].

Chemical degradation of the drug in a product is influenced by factors such as the presence of water, oxygen, light or incompatible ingredients in the product. Careful formulation of the product is necessary to ensure adequate stability. This may be through attention to general factors such as appropriate selection of the solvent or pH or by including specific stabilizing additives such asan antioxidant or antimicrobial preservative. Packaging plays an important role in the prevention of product deterioration. Storage conditions of the manufactured product like temperature, humidity and light exposure need to be appropriate. Adequate stability of the product needs to be demonstrated during its development before it can be assigned shelf life. Stress testing is valuable in predicting the likely stability of a product but long-term testing is needed before it is marketed. In conclusion, the stability is an important factor which affects the quality and efficacy of a pharmaceutical product[1].

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CONFLICT OF INTEREST

The authors declare noconflict of interest.

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