REVIEW ARTICLE

STABILIZATION OF DRUGS IN PHARMACEUTICAL PREPARATIONS

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ABSTRACT
Drug substances may undergo chemical degradation which may result in the loss of potency and therapeutic activity. Drugs are often sensitive to environmental and chemical factors such as oxygen, temperature, humidity, light, pH, ionic strength, solvent, buffers and excipients. The degraded products may produce undesirable effects as well as toxic effects on the body. The delivery of stabilized formulated products is a necessary requirement for the optimum efficacy of the active drug. The drugs are usually stabilized by chelating agents, complexing agents, bio-polymers, naturally occurring protectors, encapsulation of drugs and use of antioxidants. It has been found that hydrolytic and oxidative degradation are the main routes of loss of active ingredients. Solid preparations are usually stabilized by complex formation while in some liquid and semi-solid preparations there is a need to consider other factors such as pH, solvents for the stabilization of the drugs.

Keywords: Stability, stabilization, antioxidant, pharmaceutical applications, complex formation.

1. INTRODUCTION
Pharmaceutical products are presumed to be contaminated if significant changes in color or odour have occurred with time. The drug substances present undergo chemical degradation. This is caused by several factors including temperature, light, pH, buffers, ionic strength, solvent and excipients. The freely mobile water in excipients can affect the solid dosage formulations and the degraded products may have undesirable as well as toxic effects on the body. The delivery of stabilized products plays an important role in the manufacturing in some pharmaceutical industry. It has been found that most of the drugs are degraded by hydrolytic and oxidative reactions. Solid preparations are usually stabilized by protecting against temperature, light, oxygen and humidity. In the case of liquid and semi-solid preparation, in addition to these factors there is need to take care of the effects of solvents, pH, salts, etc. To achieve the stabilization of drugs. Photo-sensitive products are usually stabilized by suitable excipients or photoprotectors. Chelating agents form complexes with heavy metal ions that could otherwise initiate an oxidation reaction. The pharmaceutical compounds are usually stabilized by the addition of chelating agents, complexing agents, bio-polymers, naturally occurring protectors, encapsulation of drugs and use of antioxidants. It has been taken into consideration that the use of these stabilizers should be in appropriate concentration for a particular dosage. The use of different stabilizers is observed in the following section:

1.1. Chelating Agents
Chelating agents are added to pharmaceutical preparations to protect the active ingredients against autooxidation. The most commonly used chelating agents are ethylenediamine tetraacetic acid (EDTA) derivatives and salts, citric acid and tartaric acid. Increasing the salt concentration, particularly from polyelectrolytes such as citrate and phosphate, can substantially affect the magnitude of the pK_a of ionizable drugs, causing a change in the rate constant for degradation or stabilization. Photostabilisation of ascorbic acid in aqueous solution have been achieved by using hydroxyl propyl-α-cyclodextrin and trimethanol amine as photostabilizer since matrix composition of
ascorbic acid\textsuperscript{4,5} mixture induced solid phase degradation of ascorbic acid\textsuperscript{6} and stability of plasma ascorbic acid\textsuperscript{7,8}.

1.2. Complex Formation
Complex formation between drugs and excipients may lead to stabilization of drugs. Complex formation may involve forces such as Vander Waals forces, dipole–dipole interactions, hydrogen bonding, Coulomb forces, and hydrophobic interactions\textsuperscript{9,10}. Caffeine and polyvinyl pyrrolidone are the most commonly used complexing agents in the stabilization of pharmaceuticals such as aromatic esters (benzocaine, procaine, tetracaine)\textsuperscript{2,11,12}. Stabilization of drugs by the formation of inclusion complexes with cyclodextrins have been reported. Cyclodextrins are non-reducing cycl oligosaccharides, consisting of six (\(\alpha\)-CD), seven (\(\beta\)-CD), or eight (\(\gamma\)-CD) dextrose units. Stabilisation of prostacycline and prostaglandin has been achieved by dextrin complexation. Complexation may affect the dissolution and/or permeability characteristics of the drug adversely. This could possibly cause a decrease in drug bioavailability\textsuperscript{9,11,13}.

1.3. Photostabilization
A large number of pharmaceutical compounds are sensitive to light. Photostabilization of these compounds is mainly carried out by spectral overlay, encapsulation in liposomes and bio-polymer complexation.

1.4. Use of Spectral Overlay with Suitable Excipients
The rate of degradation of photolabile drug depends on both the intensity and spectral distribution of the light source used. For example, nifedipine (absorption maxima 238, 338 nm),\textsuperscript{14} absorbs in the wavelength region between about 350 and 450 nm. It is completely degraded by light in this region within 10 minutes. Addition of curcumin (absorption maxima 425 nm,\textsuperscript{15} leads to good photostabilization of the drug by covering the wavelength region between 300 and 450 nm. Other yellow food colourants and riboflavin have also been used to produce similar stabilization effect\textsuperscript{15}. Food dyes have been used for the stabilization of ascorbic acid in aqueous solution\textsuperscript{16}.

1.5. Use of Cyclodextrin Compounds
Cyclodextrin (CD) can modify the physical and chemical properties of drug substances by inclusion complexation. For example, the extent of photodegradation of benzaldehyde (BA) has significantly been reduced by inclusion complexation with molar ratio BA/\(\alpha\)-CD 1:1, BA/\(\beta\)-CD 3:2 and BA/\(\gamma\)-CD 2:1 in water\textsuperscript{17}. The photostability of emetine and cephaline in aqueous solution has been improved by complexation with \(\gamma\)- and 2, 6-dimethyl-\(\beta\)-cyclodextrins\textsuperscript{18}. The photodegradation of nifedipine, hydrochlorothiazide, pyridoxine HCl and retinol acetate in aqueous solution and in the solid state is decreased by the addition of \(\beta\)-cyclodextrin and its derivatives\textsuperscript{19}. The antioxidants act as reducing agent and are easily oxidized consuming oxygen and thus protect the drug from degradation.

1.6. Use of Liposomes
Liposomes have been used to stabilize photolabile drugs\textsuperscript{9}. In this manner liposomes can be used to transport certain drug to a definite area of the body\textsuperscript{20}. Drugs of different polarity and concentration can be encapsulated by phospholipids and then transported to the active sites\textsuperscript{21}. Water-soluble drugs can be entrapped in the liposomes by intercalation in the aqueous layer, whereas oil-soluble drugs can be solubilized with in the hydrocarbons interiors of the lipid bilayers\textsuperscript{10}. Various photolabile drugs including riboflavin\textsuperscript{22,23} and floroquinolones\textsuperscript{24-26} have been stabilized by liposomal encapsulation. This field may further be explored to improve the liposome formation and drug encapsulation to cover other substances.
1.7. Use of Naturally Occurring Photoprotective Agents

Ultraviolet (UV) radiation from the sun has been divided into UVC (270-290 nm), UVB (290-320 nm) UVA (UVA₂ 320-340 nm, UVA₁ 340-400 nm). UVC from the sun is filtered by ozone and does not reach the surface of the earth. On the earth surface the ratio of UVA and UVB is 20:1. UV radiation from sun is strongest between 10 am to 4 pm. UVA as compared to UVB, can penetrate deeper into the skin and is not filtered through the window glass. It has been estimated that about 50% of exposure to UVA occurs in the shade. Acute exposure to UVB irradiation results in erythema, edema and pigment darkening. The chronic UVB effects are photoaging, immunosuppressant and photocarcinogenesis.

Many agents affect the transmission of UV light to skin. These include photoprotective agents (zone, pollutants, clouds and fog), naturally occurring biological agents (epidermal chromophores), physical photoprotective agents (clothing, hats, make-ups, sun glasses and window glass), and UV light filters (sun screen ingredients e.g. para aminobenzoic acid (PABA), and sunless tanning agent e.g. dihydroxy acetone, dehydroascorbic acid). In addition to these, many agents can alter the effect of UV on skin (e.g. antioxidants).

1.8. Use of Antioxidants

Antioxidant compounds are added to pharmaceutical preparations as redox systems that possess higher oxidative potential than the drug to be protected. In addition to the control of pH for the stabilization of a drug, the oxidation of a substance can be controlled by adding certain compounds that are more easily oxidized than the drug in solution. In some cases, combinations of antioxidants are employed to increase their effectiveness in the medium.

1.9. Selection of Antioxidants

The selection of an antioxidant can be achieved by a consideration of the difference in redox potential between the drug and the antioxidant. The effectiveness of an antioxidant is determined by studying the pharmaceutical system with the antioxidant under standard oxidation conditions and assaying the drug content periodically. Drug substances may significantly be affected by oxidation-reduction reactions, for example, ascorbic acid, riboflavin, cyanocobalamin, menadione, α-tocopherol, epinephrine, morphine, chlorpromazine. Aqueous solutions of ascorbic acid are oxidized in the presence of air by a reversible reaction (Fig. 1).

![Fig. 1. Oxidation of ascorbic acid to dehydroascorbic acid](image)

At pH values of 4.58 and 5.20 (30°C), the values of E⁰ for the ascorbic acid system are +0.136 and +0.115 V respectively, indicating a change in the standard reduction potential with pH. At pH 7.0, the value of E⁰ is + 0.058 V, indicating that a decrease in the value of E⁰ of ascorbic acid with an increase in pH results in a higher rate of oxidation. Antioxidants as redox systems in pharmaceutical preparations should possess higher oxidative potential than the drug to be protected or as chain inhibitors of radical induced degradation. In general, antioxidants act by breaking the chains formed during the propagation process by providing a H⁺ labile proton or an electron to the free radical to terminate the chain reaction and receiving the excess energy of the activated molecule.

Most of the antioxidants for e.g. butylated
hydroxylanisole (BHA), butylated hydroxyl toluene (BHT) propyl gallate, vitamin E, thioglycerol, thioglycolic acid, sodium bisulphate, sodium sulphite, sodium metabisulphite) are more easily oxidized than the drug and so protect it from oxidation\textsuperscript{10}. The efficiency of an antioxidant depends on its redox characteristics, concentration and pH of the medium. The more readily reduced form of the compound loses electron to produced oxidized form, the better a reducing agent (antioxidant) it is. An important consideration in the oxidation of drugs is the amount of available oxygen. The rate of oxidation of ascorbic acid depends on oxygen concentration\textsuperscript{34}. In its ground state, oxygen exists as a diradical (triplet oxygen), but it can be excited by light to singlet oxygen which is a highly oxidizing specie (Fig. 2).

\textbf{Fig. 2.} Activation of triplet oxygen to singlet oxygen by light.

1.10. Examples of Stabilization

Several examples of the use of sulphur compounds as antioxidants include the stabilization of morphine by sodium sulphite, sodium bisulphite and sodium metabisulphite,\textsuperscript{35} 4- aminosalicylic acid by sodium metabisulphite,\textsuperscript{36-38} ascorbic acid by sodium bisulphite and citric acid (0.1-0.2 % w/v),\textsuperscript{39} 5-azacytidine by sodium bisulphate,\textsuperscript{31} benzocaine by thiourea,\textsuperscript{40,41} cyanocobalamin by citric acid,\textsuperscript{42} epinephrine by sodium bisulphite and sodium metabisulphite,\textsuperscript{43,44} neomycin by sodium metabisulphite,\textsuperscript{45} nystatin by BHA, BHT, propyl gallate,\textsuperscript{31} promethazine by sodium metabisulphite (0.5 % w/v) and propyl gallate,\textsuperscript{46-48} sulphaetamide by sodium thiosulphate (1 % w/v) and sodium thiosulphate (0.1 % w/v),\textsuperscript{49} and sodium sulphite, sodium thiosulphate, sodium metabisulphite and thiourea (all 0.01 % w/v),\textsuperscript{50} vitamin A by propyl gallate (0.05 %), citric acid (0.02 % w/v) and BHA (0.04 % w/v) and α-methyl dopa by sodium bisulphate\textsuperscript{51}.

1.11. Reactions of Antioxidants

Sodium bisulphite, sodium metabisulphite, other bisulphite and sulphones are strong reducing agents. As in SO\textsubscript{2}, all these compounds contain sulphur in the +4 oxidation state. Sodium bisulphite or sodium metabisulphite are used as an antioxidant for drug substances. The use of these compounds requires an acidic pH to function. Bisulphite is used in ascorbic acid injections as reducing agent\textsuperscript{52}.

1.11.1. Sodium sulphite

Sodium sulphite can be employed as a useful antioxidant for those drugs that undergo oxidation-reduction reactions with smaller positive oxidation potential (e.g. epinephrine +0.380 V)\textsuperscript{13}.

1.11.2. Sodium bisulphite

Sodium bisulphite is a mixture of sodium bisulphite (NaHSO\textsubscript{3}) and sodium metabisulphite (Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5}) in varying proportions. It should contain not less than 58.5% and not more than 67.4% SO\textsubscript{2}. The solid is unstable in the presence of air and produces SO\textsubscript{2}. It is used as an antioxidant along with other bisulphite according to the reaction given under metabisulphite\textsuperscript{52}. In the stabilization of epinephrine, a catecholamine, bisulphite displaces the hydroxyl group and prevents oxidation\textsuperscript{53}.

1.11.3 Sodium thiosulphate

Sodium thiosulphate possess sulphur in two different oxidation states. The oxidized sulphur atom is in a +6 state with no further oxidation, and the other sulphur atom is in a +2 oxidation state. On the basis of this property, it acts as a reducing agent or as an oxidant. Sodium thiosulphate is used as an antioxidant in iodide containing solution in a concentration of 0.05%. In aqueous medium sodium
thiosulphate (0.04% w/v) was used to stabilize ascorbic acid. It is found that it is a soluble antioxidant for ascorbic acid as UV method of assay of ascorbic acid is very accurate, precise and simple\textsuperscript{54}.

**1.11.4. Sodium metabisulphite**

The pure compound should contain an amount of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} equivalent to not less than 66.0% and not more than 67.4% of SO\textsubscript{2}. Most of the commercial sodium bisulphate is sodium metabisulphite. It can be used in place of sodium bisulphate. On dissolving in water, it immediately converts to bisulphite.

\[
\text{Na}_2\text{S}_2\text{O}_3 + \text{H}_2\text{O} \rightarrow 2\text{NaHSO}_3
\]

**1.11.5. Thiourea**

Thiourea is soluble in water (1gm/1ml) and in alcohol. It is sparingly soluble in ether. It forms addition compounds with metallic salts. Urea has been used as an antioxidant in pharmaceutical preparation. It may act as reducing agent by donating the lone pair of electron in sulphur atom. The electrooxidation of thiourea and its voltametric determination by graphite pencil electrode and the electrochemical analysis of thiourea on platinum on non-aqueous electrolyte\textsuperscript{55,56}.

**1.11.6. Citric acid**

Citric acid (monohydrate and anhydrous) is used in pharmaceutical formulations and food products primarily to adjust the pH of solutions. It is used in the preparation of effervescent granules and tablets. It is used as flavor enhancer in food products. It is also used as sequestering agent and antioxidant synergists. It is a component of anticoagulant citrate solution\textsuperscript{57}.

**1.11.7. Tartaric acid**

Tartaric acid is used in beverages, confectionary food products and pharmaceutical formulations as an acidulant. It may also be used as an acidifying agent, a sequestering agent and antioxidant synergists. In pharmaceutical formulations it is widely used in combination with bicarbonate as the acid component of effervescent granules, powders and tablets\textsuperscript{57}.

**2. CONCLUSION**

Stabilization of drug substances and their pharmaceutical preparations is the most important part in drug delivery systems. It is well known that the chemically degraded products did not produce any therapeutic effect in the patients but may produce undesired effects and even toxicity. The drugs can be destabilized by oxygen, temperature, humidity, and light and may also be sensitive to pH, ionic strength, solvent, dielectric constant, buffers, and excipients. Pharmaceutical industries overcome these problems by improving the formulation and/or by the use of suitable stabilizers like chelating agents, complexing agents, bio-polymers, naturally occurring protectors, encapsulation of drugs and use of antioxidants. The use of these agents depends on the chemical nature of the drug and the composition of the formulation ingredients.

**REFERENCE**

3. Gaenero C, Longhi M. Development of HPLC and UV spectrophotometric method for the determination of ascorbic acid using hydroxypropyl-β-cyclodextrin and
24. Kaszas N, Budai M, Budai L, Grof P, Zimmer M, Klebovich I. Method to increase the encapsulation efficiency for liposomal drugs.
39. Birch TW, Harris LJ. The titration curve and dissociation constants of vitamin C. Biochem J. 1933; 27: 595-599.


