Stability and Stabilization of Ascorbic Acid: A Review

KEYWORDS: Ascorbic acid; stability; stabilization, cosmetic and pharmaceutical preparations.

Abstract
Ascorbic acid (vitamin C) is extensively used in a variety of formulations including creams. It is an ingredient of anti-aging cosmetic products alone or along with alpha-tocopherol (vitamin E). In solutions and creams, ascorbic acid is susceptible to air and light and undergoes oxidative degradation to dehydroascorbic acid and further to inactive products. The degradation is influenced by oxygen, temperature, viscosity and pH of the medium and is also catalyzed by metal ions, particularly Cu²⁺, Fe²⁺, and Zn²⁺. This review highlights the stability and modes of stabilization of ascorbic acid in both the cosmetic and pharmaceutical preparations. A number of approaches involved in the stabilization of the vitamin such as the use of antioxidants, stabilizers, synergists, other vitamins, and formulation of multiple emulsions, nanosuspensions, microencapsulation, etc. have been discussed.

INTRODUCTION
Ascorbic acid (AA) is known to play an important role as an antioxidant due to its presence in the body fluids (1). It causes an increase in the rate of absorption of iron, calcium and folic acid and hence reduces allergic reactions, boosts the immune system, stimulates the formation of bile in the gallbladder and facilitates the excretion of various steroids (2). In the body AA plays an essential role in the production of collagen tissue around bones, teeth, cartilage, skin and damaged tissue (3). It has shown a prominent pharmacological effect in a number of disease conditions such as scurvy, common cold, osteoarthritis, hypertension, heart diseases, cancer, diabetes mellitus, asthma, wound healing, pregnancy, gout and eye diseases (4). Because of all these favourable effects, AA has been used in a variety of cosmetic and pharmaceutical formulations (5). It is highly soluble in water and alcohol, and is easily oxidised to dehydroascorbic acid in its solubilised form (1). The rapid degradation of AA in aqueous media is still a major factor in the formulation of its products. It is also reported that AA oxidation occurs rapidly in an alkaline environment especially at higher temperatures (>50°C) (6) and its reaction with oxygen is strongly catalysed by metal ions, particularly cupric and ferric ions (7, 8). The degradation of AA proceeds both by aerobic and anaerobic pathways and depends upon many factors such as oxygen, temperature, light, pH and storage conditions (1, 3, 9–12).

STABILITY OF AA
The stability of a pharmaceutical formulation, particularly, the semisolid dosage form depends on its formulation characteristics and the nature of the active ingredients. These characteristics are influenced by the nature and amount of the excipients to be added and their sensitivity to the environmental factors to which these dosage forms are exposed. In the semisolid dosage forms a careful selection of bases including oil-in-water (o/w) and water-in-oil (w/o) emulsifying agents, humectants, emollients, etc. would provide physical stability to the formulation and enhance the shelf-life of the product. In the selection of these ingredients the formulator has to take into consideration the nature of the active ingredient and the possible effect of formulation ingredients on its stability profile. The stability of AA and various modes of its stabilization are discussed in the following sections:

Vegetables and Fruits
AA is a white crystalline organic compound and can be synthesized from glucose or extracted from certain natural sources such as fruits and vegetables to meet the nutrient requirements of a healthy diet. Plants and most animals synthesize their own AA but humans lack this ability due to the deficiency of an enzyme known as L-gulono-gamma-lactone oxidase (13).

AA along with its derivatives is added to foods and fruit
the studies related to the stabilization of AA.

STABILIZATION OF AA
In order to achieve maximum stability of AA in various foods, cosmetics and pharmaceutical formulations, different strategies have been employed, some of which are briefly described below:

Use of Other Vitamins in Combination with AA
AA is known to be one of the important members of the water-soluble vitamin group. It has been reported that AA acts synergistically with other water- and fat-soluble vitamins including alpha-tocopherol (vitamin E) (TP) (31). In recent years, AA has been successfully used in a number of cosmetic and dermatological formulations along with TP. They are specifically indicated for topical applications such as skin depigmentation and ability to take part in proline and lysine hydroxylation in collagen biosynthesis (3). The stabilizing effect of TP on the photodegradation of AA has been studied using UV spectrometry. Similarly, the stability of AA in o/w creams in the presence of vitamins including riboflavin (RF), nicotinamide (NA) and TP has been investigated by Ahmed et al. (31), Jung et al. (37), Kim et al. (38) and the results showed the highest stability of AA with TP.

Use of Stabilizers / Preservatives / Synergists
The photosensitivity of AA makes it highly unstable for use in cosmetic (9) and pharmaceutical preparations (26) and hence it requires the use of appropriate stabilizing agents. As mentioned above, TP acts as a synergist with AA, by acting as an electron donor to restore the tocopheroxyl radical (7, 39). TP first functions as the primary antioxidant that reacts with an organic free ascorbyl radical in the physiological system and is then converted back to ascorbate through the redox cycle (40). The interaction of AA with a redox partner such as TP has been found to be useful to slow down its oxidation and prolong its physiological action (3, 41, 42).

Similarly, chemical oxidation has also been found as a major cause of AA degradation in the dark (9, 20, 21, 31) thus making it difficult to be used in cosmetics and pharmaceutical formulations. The contact of AA with metals in solution form has been reported to form free radicals which are then converted to molecular oxygen that oxidizes AA in solution. The rate of oxidation has been found to increase with pH, oxygen content and concentration of metal ions in the solution (32, 33). In an attempt to study the stability of AA in pure water solutions (without buffers), it has been observed that the rate of oxidation is pH dependent, showing a minimum at pH 2.5 to 3.0 and a maximum at pH 4.0. The pH adjustment is necessary to preserve the physical, chemical and therapeutic properties of AA because fruit juices containing this vitamin have pH values ranging from 2.5 to 5.0 (34).

A number of derivatives of AA such as sodium ascorbate and ascorbyl palmitate are used as antioxidants in cosmetics and pharmaceutical preparations (29, 35). However, they lack the biological activity similar to that of AA (5, 36); therefore, this review particularly emphasizes the studies related to the stabilization of AA.
and enhances its level in plasma (53). Stabilization of AA is also achieved by using other antioxidants such as DL-methionine, mannitol, sorbitol, succrose, dextrose, sodium thiouosphate, halide salts, triplet quenchers, metal-complexing agents and various viscosity enhancing agents (54, 55). For the maximum stability of AA in solutions the use of metaphosphoric acid is also reported (56, 57) with greater efficacy than that of CT, perchloric, acetic, and orthophosphoric acids (57, 58). In another study palmitic acid (PA), an emulsifier, has been observed to exert a greater stabilizing effect against the degradation of AA in creams than the myristic and stearic acid (9). The drugs prepared in the form of extruded granules with low substituted hydroxyl propyl cellulose (L-HPC) and water have been investigated using AA and thiamine nitrate (TN) as model drugs. D-Mannitol is used as the control additive for a comparison with L-HPC. The percentage of AA remaining after a storage period of 14 days at 60°C in a closed glass bottle was 57% in D-mannitol granules and 89% in L-HPC granules, showing higher stability of AA in L-HPC granules (33).

**Formulation of Multiple Emulsions**

Multiple w/o/w emulsions are vesicular systems in which small water droplets are entrapped within oil drops, and then dispersed in the aqueous phase (59). They may be used as a potent drug and cosmetic vehicles to prolong the action after administration (60–63). The w/o emulsions containing AA complexed with surfactants have been reported (64–66). In a separate formulation, AA is added into the inner aqueous phase of the w/o/w emulsion using paraffin oil at a concentration of 1% and a two step method for the preparation of the emulsion. Stability studies on AA have been performed at different temperatures, such as 8°C (refrigerator), 25°C (oven) and 40°C (oven) at 75% RH (stability cabin) for a period of 28 days to foresee the changes in these formulations. Different parameters, such as pH, globule size, electrical conductivity and effect of centrifugation (simulating gravity) have been evaluated during the stability studies. Multiple emulsion formulations have been found to be stable at lower temperatures (i.e. 8° and 25°C) during the study period with no phase separation in all the samples (67). Another study has been conducted using a high concentration of AA up to 30% in the dispersed phase of w/o emulsions, with their continuous phase containing refined soybean oil or Moringa oleifera oil and a food-grade hydrophobic emulsifier. All the w/o emulsions appeared stable for more than 30 days at 4°C or 25°C with slight increase in the average droplet diameter and without any phase separation. AA retention ratio of these emulsions followed first-order kinetics showing good stability (68). In order to study the effect of composition on AA formulations such as surfactant/co-surfactant associations and the use of different oils on the physicochemical characteristics of the system, a polyglycoside microemulsion has been developed which showed good stability. It can protect AA from degradation with enhanced penetration ability into the skin for topical application. The study also revealed that the control of pH and electrolyte concentration is necessary for the stabilization of AA in the formulations (69, 70).

**Formulation of Nanosuspensions**

Since AA is not as stable as its derivatives such as tetrapeptamitoxyl ascorbic acid (IPAA), it is often, recommended to use the latter in dermocosmetic products (71). It has been stated that the stability of AA may be achieved by preparing a solid-in-oil-nanosuspension (SONS) having medium chain triglycerides such as sucrose erucate (i.e. lipophilic surfactant) and sucrose monolaurate (i.e. hydrophilic surfactant) stored at 25°C, protected from light. A lipase-based enzymatic technique has been used to degrade a formulation phase making it easier for AA to be extracted. The results showed that the entire encapsulated AA (95.3%) has been successfully extracted from the SONS with the addition of a medium-chain triglyceride. Hence the SONS showed increased stability of AA due to low moisture contents (65).

**Use of Solvents**

In aqueous solution AA undergoes rapid oxidation (1) but its stability is increased in acidic and weakly alkaline media upon the addition of acetonitrile. It has been observed that acetonitrile decreases the rate of AA degradation to four fold at a concentration of 0.2% while at a concentration of 2.0% the rate of reaction reaches to the least value and remains unchanged upon further addition of acetonitrile (58). This may be due to a change in the polarity of the medium to inhibit the rate of degradation of ionized AA. The effect of ethanol on the stabilization of AA was also studied and the results indicated a markedly lower effect of this solvent compared to acetonitrile (58).

**Effect of Viscosity, Dielectric Constant and pH**

The rate of a chemical reaction may be affected by a number of factors including the pH, viscosity and dielectric constant of the medium which can greatly influence the stability of oxidisable substances (72, 73). A study has been performed to determine the effect of different humectants such as ethylene glycol, propylene glycol and glycerine in cream formulations containing AA. The humectants showed stabilizing effect on the degradation of AA, depending upon their viscosity, in the order of ethylene glycol>propylene glycol>glycerine (9). A study of the rate of photolysis of AA in aqueous and organic solvents has been carried out using UV irradiation. It has been observed that there is a linear relation between the rate of photolysis and the solvent dielectric constant or the reciprocal of viscosity. Hence an increase in the solvent dielectric constant or a decrease in solvent viscosity leads to an increase in the rate of photolysis. This should be taken into consideration during the formulation of pharmaceutical preparations containing AA (50). As stated earlier the rate of photolysis of AA in cream formulations is also affected by pH and redox potential of AA (e.g. E° at pH 5.0 = +0.127 V and at pH 7.0 = –0.058 V) and is due to the change in the ionization of AA. An increase in the viscosity of creams is also known to affect the physical stability of AA in cream formulations. It has been reported that the higher the viscosity of the medium the lower will be the degradation of AA. Therefore, a careful selection of excipients including emollients and humectants is of utmost importance to improve the stability of AA (21).

**Microencapsulation**

Microencapsulation and emulsification are the widely used techniques for the stabilization of AA in formulations particularly at a concentration of 1–5% (18, 69, 74).
Both w/o and w/o/w emulsion methods have been used for encapsulation of AA [3, 67–69, 74–76]. In order to improve AA microencapsulation by complex coacervation, both gelatine and gum arabic have been used as encapsulating agents. In a w/o emulsion using corn oil, a 30% solution of AA and polyglycerol polyricinoleate (PGPR 90) as surfactant has been made for making coacervation of a hydrophilic core material. The encapsulation was carried out successfully in the double emulsion with the complex coacervation thus confining AA to a more stable microcapsule form rather than in solution. It suggests the option of controlled release under specific conditions and masking the acidic taste of AA [77]. Microencapsulated AA is also reported to be more stable to colour change [18]. Starch and betacyclodextrin encapsulated AA delays its degradation during storage at a temperature of 38°C and relative humidity of 84% [18].

**CONCLUSION**

The stability of air sensitive drugs such as AA has always been a problem for the formulator. Various approaches have been adopted to achieve stabilization of AA in cosmetic preparations. These include the use of stabilizers, antioxidants, preservatives, synergists, emulsifiers etc. The techniques of entrapment of AA in multiple emulsions and encapsulation in nanosuspensions have shown significant improvement in the stabilization of AA. The control of medium pH, polarity and viscosity also prolong the shelf-life of AA in cosmetic preparations.

**REFERENCES AND NOTES**