Review Article

Formulation and Stability of Ascorbic Acid in Topical Preparations

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ABSTRACT

Ascorbic acid (vitamin C) and its derivatives are known to perform various important physiological and metabolic functions in humans. In addition to dietary supplements, a number of topical formulations containing ascorbic acid and derivatives are now available that induce collagen synthesis, strengthening of skin tissues, reduction in pigmentation loss, and improved growth and health activities. It has also been used in a variety of cosmetic preparations as an antioxidant, pH adjuster, anti-aging and photoprotecting agent. Ascorbic acid is highly sensitive to air and light; and to achieve its stabilization in cosmetic preparations, it has been suggested to use ascorbic acid in microencapsulation form, in combination with other chemical moieties such as vitamin-E, by the control of pH and electrolyte concentration and use of stabilizing agents like citric, tartaric, or ferulic acids. A large number of cosmetic creams and lotions are available in the market containing the derivatives of ascorbic acid (e.g., sodium ascorbate, ascorbyl palmitate). Although these preparations are chemically stable, they lack the pharmacological activity of ascorbic acid. In the present review, it has been emphasized to consider the importance of various factors involved in the formulation of such preparations to achieve the stabilization of ascorbic acid as such, to maintain its pharmacological activity.

Introduction

Plants and most animals synthesize their own vitamin C (ascorbic acid), but humans lack this ability due to the deficiency in an enzyme, L-gulono-gamma-lactone oxidase that catalyzes the terminal step in ascorbic acid biosynthesis.[1] Therefore, humans obtain this vitamin from diet and/or vitamin supplements to avoid the development of scurvy and also for overall well being.[2-4] Ascorbic acid is vital for the growth and maintenance of healthy bones, teeth, gums, ligaments, and blood vessels and is involved in important metabolic functions.[4-6] It is required for the utilization of folic acid and for the absorption of iron. It is also necessary for normal immune responses to infection and for wound healing.[7] The minimal daily requirement for ascorbic acid in healthy adults is 40 to 60 mg.[8,9]

Ascorbic acid is a water-soluble vitamin and is extensively used as such or in the form of a derivative such as sodium ascorbate and ascorbyl palmitate as an ingredient of anti-aging cosmetic products.[10-28] It exerts several functions on the skin such as collagen synthesis, depigmentation and antioxidant activity.[15,29] As an antioxidant, it protects the skin by neutralizing reactive oxygen species (ROS) generated on exposure to sunlight.[30] In biological systems, it reduces both oxygen- and nitrogen-based free radicals[31] and thus delays the aging process. Ascorbic acid in skin care formulations is often used in combination with another redox partner such as vitamin E (alpha-tocopherol)[32,33] to retard its oxidative degradation. It is now medically recognized that sagging skin and other signs of degenerative skin conditions, such as wrinkles and age spots, are caused primarily by oxyradical damage.[13]

The aim of this review is to highlight the previous work in the field and to discuss the importance of various factors involved in the formulation and stabilization of topical ascorbic acid preparations. These would help the formulators and researchers to consider the problem and adopt an appropriate strategy for the development of a safe, stable, and effective formulation.

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Cosmetic formulations of ascorbic acid

Ascorbic acid is a very unstable vitamin and is easily oxidized in aqueous solutions and cosmetic formulations. It can also act as a coantioxidant with the tocopheroxyl radical to regenerate alpha-tocopherol.[34-36] In this reaction, the two vitamins act synergistically. Alpha-tocopherol first functions as the primary antioxidant that reacts with an organic free radical. In physiological systems, the ascorbyl radical formed by the regeneration of alpha-tocopherol is then converted back to ascorbate by the redox cycle.[3] The interaction of ascorbic acid with a redox partner such as alpha-tocopherol has been found useful to slow its oxidation and prolong its physiological action.[32]

Factors affecting formulations

Various physical and chemical factors are involved in the formulation of topical emulsion or cream preparations,[37-41] some of which are briefly described below:

Choice of emulsion type

Oil-in-water emulsions are used for the topical application of water-soluble drugs, mainly for local effect. They do not have the greasy texture associated with oily bases, and are therefore pleasant to use and easily washed from skin surfaces. Moisturizing creams, however, are designed to prevent moisture loss from the skin and thus inhibit drying of the stratum corneum. They are more efficient if formulated as o/w emulsions, which produce a coherent, water-repellent film.

Choice of oil phase

Many emulsions for external use contain oils that are present as carriers for the active ingredient. It must be realized that the type of oil used may also have an effect both on the viscosity of the product and on the transport of the drug into the skin.[38] One of the most widely used oils for this type of preparation is liquid paraffin. This is one of a series of hydrocarbons, which also includes hard paraffin, soft paraffin, and light liquid paraffin. They can be used individually or in combination with each other to control emulsion consistency. This will ensure that the product can be spread easily but will be sufficiently viscous to form a coherent film over the skin. The film-forming capabilities of the emulsion can be further modified by the inclusion of various waxes, such as bees wax, carnauba wax, or higher fatty alcohols.

Emulsion consistency

A consideration of the texture or feel of a product intended for external use is important. A w/o preparation will have a greasy texture and often exhibits a higher apparent viscosity than the o/w emulsions. This fact imparts a feeling of richness to many cosmetic formulations. Oil-in-water emulsions will, however, feel less greasy or sticky on application to the skin, will be absorbed more readily because of their lower oil content, and can be more easily washed from the skin surface. Ideally, emulsions should exhibit the rheological properties of plasticity/pseudoplasticity and thixotropy. Emulsions of high apparent viscosity for external use (cream) are of a semisolid consistency. There are several methods by which the rheological properties of an emulsion can be controlled.[42]

Choice of emulsifying agent

The choice of emulgent to be used would depend on factors such as its emulsifying ability, route of administration, and toxicity. Most of the nonionic emulgents are less irritant and less toxic than their anionic and cationic counter parts. Some emulgents, such as the ionic alkali soaps, often have a high pH and are thus unsuitable for application to broken skin. Even in the normal intact skin with a pH of 5.5, the application of such alkaline materials can cause irritation. Some emulsifiers, in particular, wool fat can cause sensitizing reactions in susceptible individuals. The details of various types of emulsifying agents are available in the literature.[39,42,43]

Formulation by the HLB method

The physically stable emulsions are best achieved by the presence of a condensed layer of emulgent at the oil/water interface, and the complex interfacial films formed by a blend of an oil-soluble emulsifying agent with a water-soluble one produces the most satisfactory emulsions. The relative quantities of the emulgents necessary to produce the most physically stable emulsion for a particular formulation with water combination can be calculated by the hydrophilic-lipophilic balance (HLB) method. Each type of oil requires an emulgent of a particular HLB number in order to ensure a stable product. For an o/w emulsion, the more polar the oil phase, the more polar must be the emulgent system.[42-44]

Concept of relative polarity index

Apart from other formulation factors, the concept of relative polarity index should also be considered during the preparation of either o/w or w/o creams, so that the effective penetration of the active ingredient from the formulation to the desired delivery site can be achieved. The polarity of stratum corneum is 6.3, as expressed by its octanol/water partition coefficient and is reported to be more polar in nature than butanol.[45] This may also be compared with the active as well as the other oil phase ingredients present in the formulation to ascertain its ability to solubilize the desired component.[46,47]

Stability of ascorbic acid in topical preparations

Ultraviolet radiation generates ROS which produce some harmful effects on the skin including photocarcinoma and photoaging. In order to combat these problems, topical ascorbic acid formulations have been used in the concentration range of 1 to 20%.[10,11,13,16-18,20,25,27] Ascorbic acid has good photoprotective ability against ultraviolet A (UVA)-mediated phototoxicity.[10] Effective delivery of ascorbic acid through topical preparations is a major factor that should be critically evaluated, as it may be dependent upon the nature or type of the formulation.[11,16] The pH of the formulation should be on the acidic side (~pH 3.5) for effective penetration of the vitamin in the skin.[16]

Physical stability

The control of instability of ascorbic acid poses a significant challenge in the development of cosmetic formulations, and thus a variety of preparations containing ascorbic acid or its derivatives have been studied to evaluate their stability and delivery through the skin.[11,13,14,16-18,25] The major phenomena associated with the physical instability of emulsions are flocculation, creaming, coalescence, breaking and maintenance of elegance with respect to appearance, odor, color, and other physical properties. An emulsion is a dynamic system; however, any flocculation and resultant creaming represent

potential steps towards complete coalescence of the internal phase. In pharmaceutical emulsions, creaming results as a lack of uniformity of drug distribution. These factors have been discussed by Garti and Aserin,[48] Im-Emsap *et al*.,[44] and Sinko.[49] The stability of ascorbic acid in thixogel formulations may be improved by its use in the form of a fatty acid ester such as ascorbyl palmitate. Preliminary experiments have shown that ascorbic acid could be slowly released from the starch-oil emulsion matrix and act as an antioxidant.[32]

Chemical stability

The application of well-established kinetic principles may throw light on the kinetics of degradation of a drug and provide valuable insight into the mechanism of degradation.[50-52] The chemical stability of individual components within an emulsion system may be very different from their stability after incorporation into other formulation types. For example, many unsaturated oils are prone to oxidation and their degree of exposure to oxygen may be influenced by factors that affect the extent of molecular dispersion (e.g., droplet size). This could be particularly troublesome in emulsions, because emulsification may introduce air into the product and also due to the high interfacial contact area between the phases.[38] The use of antioxidants retards oxidation of unsaturated oils used in the formulations, which in turn can retard the degradation of certain active ingredients.[53] The stability problems of dispersed systems and the factors leading to these stability problems have been discussed by Weiner[54] and Lu and Flynn.[55]

Microbial stability

Topical bases often contain aqueous and oily phases, together with carbohydrates and proteins, and are susceptible to bacterial and fungal attack. Microbial growth spoils the formulation and is a potential toxic hazard. Therefore, topical formulations need appropriate preservatives to prevent microbial growth and to maintain their quality and shelf-life.[38,56] These aspects in relation to dermatological formulations have been discussed by Barry[38,57] and Vimaladevi.[53]

Stabilization of ascorbic acid

Attempts have been made to achieve the stabilization of ascorbic acid in multiple emulsions by controlling the pH and electrolyte concentration.[17] Formulations containing derivatives of ascorbic acid have been found to be more stable, but they do not produce the same effect as that of the parent compound.[26] The stability problems of dispersed systems have been discussed by Weiner[54] and Lu and Flynn[55] and could be helpful in stabilizing ascorbic acid formulations.

Utilization of an effective antioxidant system is required to maintain the stability of ascorbic acid in cream preparations.[13,16,27] Ferulic acid and sodium metabisulphite have been used as antioxidants for the stabilization of ascorbic acid in topical formulations.[10,22,27,28] The antioxidants have been reported to retard the degradation of certain active ingredients such as ascorbic acid.[53] Effect of some physical properties such as viscosity and dielectric constant on the stability of ascorbic acid in emulsions has also been investigated.[47,58] Viscosity of the medium is an important factor that should be considered for the purpose of ascorbic acid stability, as higher viscosity formulations have shown some degree of protection.[14,59] Along with other factors, formulation type also plays an important role in the stability of ascorbic acid. It is reported that ascorbic acid is more stable in emulsified system as compared with aqueous solutions.[11,17] In multiemulsions, ascorbic acid is reported to be more stable as compared with simple emulsions.[11,14,17,25]

It has been reported that certain metal ions or enzyme systems effectively convert ascorbic acid's antioxidant action to pro-oxidant activity.[20] Although the chemical stability of ascorbic acid has been studied in emulsions and creams by several workers,[10,11,17,18,20,25] there is a lack of information on the photostability of ascorbic acid in cream formulations. A recent study has shown the effect of emulsifying agents and humectants on the photostability of ascorbic acid in cream formulations. Ascorbic acid is most stable in the presence of palmitic acid and glycerin.[60]

Formulation and stabilization strategy of creams

As a rule, the formulation and stabilization strategy for a drug would largely depend upon its chemical characteristics and reactivity in a particular preparation. The formulator has to adopt appropriate measures to achieve the stabilization of the drug during its storage period and use. For the formulation of oxidizable and ionizable substances such as ascorbic acid or derivatives in an emulsion or cream preparation, factors such as solubility, pH, viscosity, polarity of the medium, choice of emulsion type and emulsifying agent, HLB value of the system, compatibility of the active with formulation ingredients, use of appropriate antioxidant/preservative, etc. should be considered. In addition to this, it is important to consider packaging factors to achieve maximum stability during storage and use. This may involve the choice of container, filling of the material, exclusion of air and temperature, light, and humidity control.

The selection of oil phase ingredients in the cream is an important factor to achieve an increased rate of drug transport through the skin, enhance product viscosity, improved consistency and spreadabilty. Most of the nonionic emulgents are less irritant and less toxic than their anionic and cationic counter parts, and are frequently used for preparing an appropriate formulation to be safely applied on the skin without causing irritation or sensitizing reactions.

Conclusion

A large number of topical preparations are available in the market, containing ascorbic acid and its derivatives such as sodium ascorbate and ascorbyl palmitate. These preparations have problems regarding the stability and activity of ascorbic acid. Several physical and chemical factors are involved in the development of topical preparations which should be considered to achieve the stabilization of the active ingredient. All these factors have been highlighted, and the roles of various formulation variables in imparting stability to the active ingredient have been discussed. It is also important to consider the packaging aspects and storage conditions to prolong the shelf-life of the product.

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