

The Challenges of “Shelf Life Stability” in Vitamin C Cosmetics and Ph-Dependent stability strategies

Kehan Jiang

Jiangxi University of Science and
Technology Affiliated Middle
School, Nanchang, Jiangxi, China
Email: 13970989171@163.com

Abstract:

Vitamin C (L-ascorbic acid) is a cornerstone of topical skincare, renowned for its antioxidant efficacy and role in collagen synthesis. While extensive research and development, including water-powder separation technologies, have successfully mitigated the challenge of shelf-life stability, a critical bottleneck persists: in-use stability. This review synthesizes the current body of literature to address this emerging paradigm, focusing on the period after product opening or reconstitution where efficacy rapidly declines. Central to this discussion is the role of pH-dependent stabilization strategies. We critically evaluate and integrate evidence on how pH, concentration, and stabilizers interact dynamically to govern degradation kinetics, antioxidant performance, and cutaneous tolerability during the in-use phase. By mapping these complex interactions and highlighting the existing research gaps—particularly the lack of systematic studies on their synergistic effects—this review aims to consolidate current knowledge and propose a forward-looking framework for designing next-generation vitamin C formulations. The ultimate goal is to shift the industry focus towards ensuring sustained clinical performance throughout the entire product usage lifecycle, thereby guaranteeing that the initial promise of the formulation translates into consistent user benefit.

Keywords: ascorbic acid stability, topical vitamin C, pH stability, cosmetic formulation, dual-chamber system, antioxidant synergy

I. Introduction

Vitamin C (L-ascorbic acid, L-AA) holds a preeminent position in dermatology, primarily due to its

*multifaceted role as a potent antioxidant, an essential co-factor for collagen biosynthesis, and an effective inhibitor of melanogenesis .[1][2]
The quest to stabilize topical vitamin C has spawned*

extensive research and innovation, predominantly focused on extending shelf-life. This endeavor has yielded significant advances, including the development of stable derivatives (e.g., ascorbyl glucoside, magnesium ascorbyl phosphate), anhydrous vehicles, and sophisticated packaging solutions like water-powder separated (dual-chamber) systems. The latter, by physically isolating L-AA from an aqueous solvent until the point of use, represents a paradigm of success in solving the problem of storage instability, ensuring the ingredient's potency until the moment of reconstitution

Yet, this very success has unveiled the next, and perhaps more critical, frontier in vitamin C formulation science: in-use stability. The act of reconstitution, while delivering a fresh product, simultaneously creates a traditional aqueous solution whose chemical integrity is once again—and entirely—at the mercy of its microenvironment during the period of use. The degradation pathways that were paused during storage resume in earnest, leading to a rapid decline in efficacy that the consumer experiences directly. The stability of the product on the shelf and the stability of the product on the skin are, therefore, two distinct challenges. While the former has been extensively studied and mitigated, the latter remains comparatively overlooked, creating a critical gap between the promise of a fresh-mixed product and the reality of its in-use degradation.

The chemical stability of L-AA in this in-use phase is not governed by a single factor but by a complex, interdependent triad: pH, concentration, and the presence of stabilizers. Previous work established that skin penetration of L-AA is optimal at a pH below 3.5, where the molecule is predominantly in its unionized form [3]. Conversely, stability kinetics are highly pH-dependent, with degradation accelerating as pH rises. Furthermore, the efficacy of common stabilizers—such as metal chelators and synergistic antioxidants like vitamin E and ferulic acid—is intrinsically linked to the formulation's pH and the concentration of L-AA itself [4]. The current body of literature, however, often investigates these variables in isolation. A comprehensive synthesis that treats pH, concentration, and stabilizers as an interconnected system, specifically within the context of the in-use period of reconstituted formulations, is lacking.

This review, therefore, aims to map the transition of the field's focus from shelf-life to in-use stability. It will critically synthesize and evaluate the existing evidence on how the pH-dependent chemical behavior of L-AA dictates

its degradation kinetics, percutaneous absorption, and cutaneous tolerability after a product has been opened and mixed. By focusing on the synergies and antagonisms within the pH-concentration-stabilizer triad, this review will highlight the limitations of a univariate approach and identify key knowledge gaps. Ultimately, this work seeks to consolidate existing knowledge into a coherent framework to guide the future development of vitamin C formulations that are engineered not only to survive the shelf but to thrive throughout their entire usage lifecycle, ensuring that the efficacy promised at the time of mixing is delivered consistently until the last application.

2. KEY CEMICAL FACTORS AFFECTING THE STABILITY OF VC

2.1 The Core Role of PH

The chemical stability, percutaneous absorption efficiency, and cutaneous irritation potential of vitamin C (L-ascorbic acid, L-AA) are intrinsically governed by a complex, pH-dependent relationship. This interdependence originates from the fundamental ionization behavior of the L-AA molecule and its interaction with the physiological environment of the skin. of vitamin C (L-ascorbic acid, L-AA)

(A) Chemical Ionization Equilibrium and Species Distribution

The chemical structure of vitamin C (L-ascorbic acid) as shown in the figure 2.1 1 is centered on a 5-membered γ -lactone ring fused to a chain featuring a critical enediol group (at C2 and C3). This enediol structure is the molecular nexus of both its potent biological activity and its profound chemical instability. It functions as an excellent electron donor, conferring powerful antioxidant capacity, but also renders the molecule highly susceptible to oxidation, first to dehydroascorbic acid and then irreversibly to inactive degradation products[5]. Furthermore, the acidity of the enediol group ($pK_{a1} \approx 4.25$, $pK_{a2} \approx 11.79$) [6] results in a strong pH-dependence, where the distribution of its ionic species (neutral H_2A or anionic HA^-) directly governs its chemical stability, percutaneous absorption, and susceptibility to metal-ion catalysis. Consequently, the molecular architecture of vitamin C is the fundamental source of the intrinsic conflict between its efficacy and its instability.

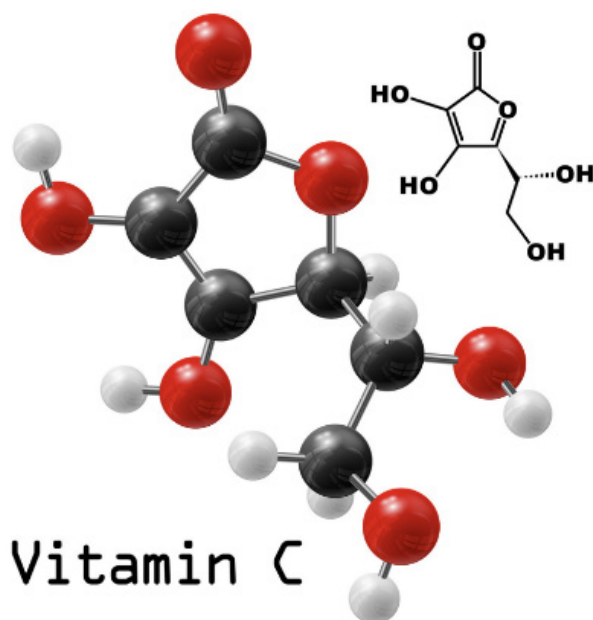


Figure 2.1.2 chemical structure of vitamin C (L-ascorbic acid)

(B) The Necessity and Enhancement Mechanism of low pH on Stability and Percutaneous Absorption

The charged ascorbate anion (Asc^-) has a higher highest occupied molecular orbital (HOMO) energy, facilitating electron loss. Its oxidation rate constant is orders of magnitude higher than that of the neutral HA molecule [7]. A low pH environment suppresses ionization, fundamentally reducing the thermodynamic driving force for spontaneous oxidation.

Attenuation of Metal Ion Catalysis: Trace transition metal ions (e.g., Fe^{3+} , Cu^{2+}) are potent catalysts of L-AA oxidation. They can form complexes with the Asc^- anion, dramatically accelerating oxidation via a single-electron transfer mechanism. The electroneutral HA form has a significantly weaker binding affinity for these metal ions, thereby slowing the catalytic reaction [8].

Optimization of Transdermal Absorption: The stratum corneum is a lipophilic barrier. The seminal work by Pinnell et al. (2001) demonstrated that effective transdermal delivery of L-AA occurs only at $\text{pH} < 3.5$, as the neutral HA species possesses higher lipophilicity, facilitating passive diffusion through the lipid-rich matrix of the stratum corneum [3].

(C) The Dilemma: Low pH Strategy vs. Cutaneous Irritation

The strategy of employing a low pH for maximum stability conflicts with the skin's physiological environment, introducing a significant risk of irritation:

Disruption of the "Acid Mantle" and Barrier Function: a healthy skin surface often maintains an "acid mantle" with a pH between 4.5 and 5.5. This slightly acidic microenvi-

ronment is crucial for maintaining stratum corneum lipid barrier integrity, the activity of key enzymes (e.g., serine proteases for desquamation), and a healthy microbiome balance [9]. Topical application of highly acidic formulations ($\text{pH} < 3.5$) can overshoot this optimal range, inhibiting enzymatic activity, compromising barrier function, increasing transepidermal water loss (TEWL), and inducing dryness and sensitivity [10].

Induction of Direct Neurosensory Irritation: The high proton (H^+) concentration in a low pH environment can directly activate acid-sensing ion channels (ASICs) and transient receptor potential vanilloid 1 (TRPV1) channels on cutaneous sensory neurons, provoking immediate stinging and burning sensations. Concurrent barrier impairment further increases nerve ending exposure, amplifying the inflammatory response [11].

Conclusion:

In summary, pH plays a paradoxical central role in L-AA formulation. It is both a "prerequisite" for maintaining chemical stability and promoting transdermal absorption and a "potential risk" for inducing skin irritation and barrier damage. Consequently, the primary challenge in formulation design is to identify a precise "optimal tolerance window" (typically near pH 3.0 - 3.5). This window aims to maximize the stability and bioavailability of L-AA within an acceptable range of cutaneous tolerability. The subsequent study of stabilizers (e.g., metal chelators) and buffering systems is fundamentally directed at widening this narrow pH window to achieve the optimal balance among efficacy, stability, and safety.

2.1.2 Concentration Effect

Normally, to pursue a highly effective effect on antioxidant, the formulation of Vitamin C tends to use high concentration (typically 15%-20%). However, concentration is not a case of "more is better"; it is a non-linear relationship with chemical stability.

The accelerated degradation of L-ascorbic acid (L-AA) at high concentrations represents a classic example of autocatalytic oxidation kinetics. This phenomenon is well-documented in pharmaceutical and cosmetic science literature [1, 2]. The oxidation mechanism involves free radical chain reactions where initial oxidation products act as catalysts for subsequent degradation reactions [12]. The reaction follows second-order kinetics relative to ascorbate concentration (figure 2.1.3): $-\text{d}[\text{AA}]/\text{dt} = k[\text{AA}]^2[\text{O}_2]$

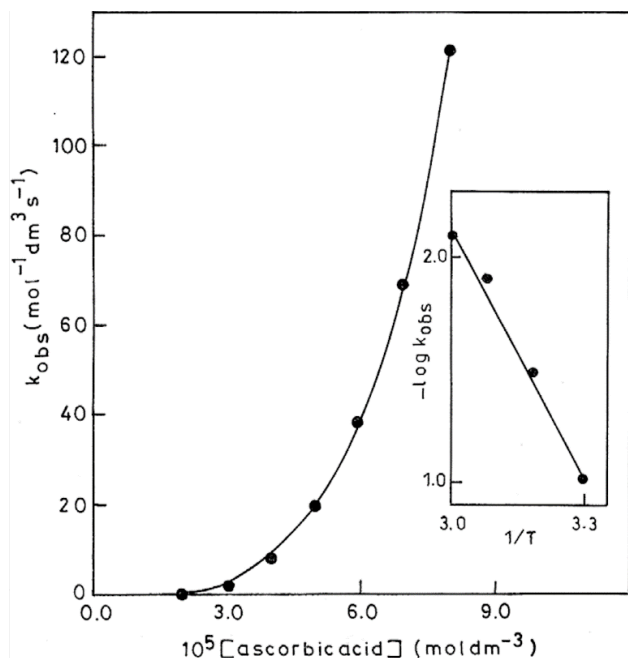


Figure 2.1.3 Dependence of second-order rate constant (k_{obs}) on [ascorbic acid].
Reaction conditions: $[n] = 8.0 \times 10^{-5} \text{ mol dm}^{-3}$; **temperature** = 40°C . **Inset-Arrhenius plot for the oxidation of ascorbic acid by MnO_2 .**
Reaction conditions: $[(\text{MnO}_2)_n] = 8.0 \times 10^{-5} \text{ mol dm}^{-3}$; **[ascorbic acid]** = $6.0 \times 10^{-5} \text{ mol dm}^{-3}$.

This mathematical relationship explains why doubling the ascorbic acid concentration can potentially quadruple the oxidation rate under certain conditions.

The autocatalytic nature of this process was further showed that the decomposition rate increases exponentially once the concentration exceeds a critical threshold of approximately 15-20% in aqueous solutions. This explains the paradoxical situation where higher concentrations, while offering potentially greater efficacy, also create an environment conducive to rapid oxidative degradation

(B) Metal Ion Catalysis and Concentration-Dependent Effects

The role of trace metal ions in catalyzing ascorbic acid oxidation becomes particularly significant at high concentrations. Buettner's seminal work [13] demonstrated that even sub-micromolar concentrations of transition metals (especially Cu^{2+} and Fe^{3+}) can dramatically accelerate oxidation rates.

At high L-AA concentrations (>15%), the probability of metal ion-ascorbate complex formation increases substantially. This effect is compounded by the fact that: [14]

Commercial L-AA raw materials typically contain 0.5-5 ppm metal ion impurities. Water used in formulations may contribute additional metal ions. [15]

Container materials can leach catalytic metals into the for-

mulation

The catalytic cycle involves redox cycling of metal ions, where each metal ion can catalyze the oxidation of thousands of ascorbate molecules through repetitive reduction and oxidation steps. [16]

(C) Interdependence of Concentration and pH Variables

The complex relationship between concentration and pH was systematically investigated by Smith et al. [8], who demonstrated that these two factors exhibit significant interaction effects on stability:

pH Influence on Concentration Effects: The detrimental effects of high concentration are markedly exacerbated at higher pH values. While 20% solutions may show acceptable stability at pH 3.0, the same concentration degrades rapidly at pH 4.0 [3].

Concentration-Dependent pH Effects: High L-AA concentrations (15-20%) naturally lower solution pH due to the compound's acidic nature ($\text{pK}_{\text{a}1} = 4.25$). This creates a self-buffering effect that must be considered in formulation optimization. [3]

Solubility Limitations: The practical upper limit for L-AA concentration is approximately 20-25% in aqueous solutions at room temperature, creating a natural ceiling for concentration-based efficacy enhancement. [18]

(D) Implications for Formulation Stability

The concentration-stability relationship has direct practical implications for cosmetic formulations:

Reaction Vessel Effects: High concentrations require careful selection of container materials to minimize metal ion leaching

Oxygen Exclusion Needs: Concentrated solutions demand more rigorous oxygen exclusion techniques during manufacturing and packaging

Stabilizer Requirements: The need for effective metal chelators and antioxidants increases disproportionately with concentration

Conclusion:

The relationship between vitamin C concentration and stability is characterized by complex autocatalytic kinetics and metal-ion-mediated degradation pathways. While increasing concentration enhances potential efficacy, it also exponentially increases oxidative instability beyond approximately 15-20% concentration. This relationship is further modulated by pH interactions and metal ion content. Successful formulation requires careful balancing of these factors, recognizing that simply increasing concentration without addressing the underlying stability mechanisms will compromise product performance. The optimal concentration range appears to be 15-20% when combined with appropriate pH control ($\text{pH} \approx 3.0$) and

comprehensive stabilization strategies.

2.1.3 Stabilization Mechanisms

The inherent instability of L-ascorbic acid (L-AA) necessitates the incorporation of a sophisticated stabilization system beyond mere pH and concentration optimization. Effective stabilizers function through three primary mechanisms: chelation of catalytic metal ions, synergistic antioxidant regeneration, and physical protection.

(A) Metal Ion Chelation

Trace transition metal ions (e.g., $\text{Fe}^{2+/3+}$, Cu^{2+}) are potent catalysts for L-AA oxidation, initiating free radical chain reactions via single-electron transfer. Chelating agents mitigate this by forming stable, inert complexes with these pro-oxidant metals, effectively sequestering them and preventing their participation in the catalytic cycle.[19]

Ethylenediaminetetraacetic acid (EDTA): A highly efficient, broad-spectrum chelator. It forms exceptionally stable hexadentate complexes with a wide range of metal cations, making it a benchmark stabilizer in cosmetic science. However, concerns regarding its environmental persistence and biocompatibility have spurred the search for alternatives [20]

Phytic Acid: A natural, plant-derived chelator. Its six phosphate groups confer a high affinity for metal ions, particularly iron. It is increasingly employed as a biodegradable and “green” alternative to synthetic chelators[21]

(B) Synergistic Antioxidant Systems

The oxidation of L-AA generates reactive radical intermediates. Synergistic antioxidants intercept these radicals, regenerating active L-AA and prolonging the formulation’s overall antioxidant capacity through a redox cycling mechanism.

Ferulic Acid: The combination of L-AA, vitamin E, and ferulic acid constitutes a quintessential synergistic system. Ferulic acid not only donates electrons to regenerate the semidehydroascorbate radical but also stabilizes both L-AA and vitamin E, and significantly enhances the system’s ultraviolet (UV) photoprotection efficacy [22].

Vitamin E (α -Tocopherol): As a lipid-soluble antioxidant, vitamin E primarily functions at the oil-water interface. It acts as a primary scavenger of lipid peroxyl radicals. The resulting vitamin E radical (tocopheroxyl) is then efficiently reduced back to its active form by L-AA, completing a critical regenerative cycle that bridges aqueous and lipid-soluble antioxidant domains.

(C) Physical Stabilization Strategies

Physical methods focus on isolating L-AA from its destabilizing environmental factors (oxygen, light, water) prior to application.

Encapsulation (e.g., Silica Microencapsulation): This technology involves physically entrapping L-AA within

an inert matrix, such as porous silica microspheres. This creates a protective barrier that shields the payload from oxygen, light, and moisture during storage. The active ingredient is released upon contact with the skin or a solvent, ensuring maximum potency at the time of use. This is the foundational principle behind many anhydrous, water-powder separated formulations.

Anhydrous and Polyol Solvent Systems: Formulating in anhydrous vehicles (e.g., oils) or using polyols (e.g., propylene glycol, glycerin) can enhance stability. Polyols reduce water activity, impede oxygen diffusion due to increased viscosity, and may stabilize L-AA through hydrogen bonding interactions, thereby slowing hydrolytic and oxidative degradation pathways.[25]

Table 2.1. Summary of Key Stabilization Mechanisms for Topical Vitamin C

systems; polyols are common in liquid serums. |

Conclusion:

The stabilization of topical L-ascorbic acid is not achievable through a singular approach. A successful strategy mandates an integrated, multi-mechanism system that combines:

1. Preventative chelation to remove catalytic impurities.
2. Regenerative synergy to recycle oxidized L-AA and maintain redox homeostasis.
3. Physical barrier protection to minimize environmental exposure.

The efficacy of this combined system is intrinsically linked to the foundational pH and concentration parameters, underscoring the critical need for a holistic formulation design that optimizes all interacting variables concurrently.

2.2 Current Research and Technological Landscape

Despite decades of research into the topical application of vitamin C, the understanding of its formulation stability remains fragmented. Current research and commercial practices primarily focus on optimizing single variables or developing specific complex formulations, lacking a systematic analysis of multivariate synergistic effects.

2.2.1 Depth and Limitations of Single-Variable Studies

Substantial foundational research has robustly confirmed the decisive influence of individual factors on VC stability, establishing a solid knowledge base for the field.

Central Role of pH: Classical studies have definitively demonstrated that reducing pH to 3.0-3.2 enables 15-20% L-AA to achieve the highest skin penetration rate, with stability at this pH being significantly superior to envi-

ronments with higher pH [3]. Subsequent multiple studies support this conclusion, indicating that the discoloration rate and activity decay rate of VC solutions at pH 3.0 are considerably lower than controls at pH 3.5 or 4.0 [3].

Validation of Stabilizer Efficacy:

Ferulic Acid: Research has shown that adding 0.5% ferulic acid to a solution of 15% L-AA and 1% vitamin E at pH 3.2 not only doubles the photoprotection efficacy but also significantly slows the discoloration rate of the formulation under light and elevated temperatures. The mechanism is attributed to ferulic acid's ability to both regenerate the vitamin E radical and form a resonance-stable phenoxyl radical itself, thereby interrupting free radical chain reactions.

Metal Chelators: Studies confirm that EDTA can reduce the autoxidation rate of VC by several orders of magnitude through potent chelation of trace Cu^{2+} and Fe^{3+} . Phytic acid, as a natural alternative, has also been proven effective in chelating iron ions and delaying VC degradation.

2.2.2 Technical Analysis of Prominent Commercial Products

Mechanism	Key Agents	Primary Function	Key Consideration
Metal Chelation	EDTA, Phytic Acid	Sequester catalytic metal ions (Fe, Cu)	DTA is highly effective but faces regulatory scrutiny; phytic acid is a natural alternative
Synergistic Regeneration	Ferulic Acid, Vitamin E	Regenerate L-AA from its radical intermediate; extend antioxidant network	Regenerate L-AA from its radical intermediate; extend antioxidant network. Requires optimal molar ratios for maximum efficacy (e.g., 1:1:1 or 2:1:1 for C+E+Ferulic).
Physical Protection	Silica Encapsulation, Polyols	Create a physical barrier against O_2 , light, and H_2O ; reduce water activity	Encapsulation is ideal for powder systems; polyols are common in liquid serums.

Other Product Strategies: Other brands utilize VC derivatives (e.g., Ascorbyl Glucoside, Magnesium Ascorbyl Phosphate) to enhance stability, although their conversion efficiency and bioavailability in the skin are often lower than pure L-AA [7]; or employ technologies like silica-encapsulated VC powder* to achieve physical isolation.

2.2.3 Research Gaps and the Value of This Review

In summary, the current research landscape exhibits a significant gap:

1. **Isolated Variables:** Extensive literature delves into the impact of single variables (e.g., pH, or a specific stabilizer) but fails to reveal the potential complex interactions between these key factors.
2. **Systemic Understanding Deficiency:** For the “water-powder separated” novel dosage form, research focus-

es on its “physical isolation” advantage for storage but generally overlooks the equally critical issue of “post-reconstitution stability,” which is highly dependent on the chemical system.

3. Unknown Synergies: Do minor pH variations affect the optimal concentration of ferulic acid? Does a high concentration of 20% VC require a corresponding increase in chelator concentration? These questions remain systematically uninvestigated.

Therefore, the core value of this review lies in: for the first time, treating pH, VC concentration, and stabilizer compatibility as an inseparable “ternary system,” systematically lease existing evidence to reveal their intrinsic relationships, and clearly pointing out that to truly optimize the final performance of water-powder separated VC products, future research must employ multivariate system

optimization methods (e.g., Response Surface Methodology) to study this complex system, thereby filling this critical knowledge gap.

2.3 The Art of Balancing Efficacy and Safety

The design of water-powder separated vitamin C products centers on achieving a precise equilibrium among storage stability, usage efficacy, and dermal safety. This balancing art presents greater challenges than conventional formulations, as it must simultaneously ensure absolute stability during storage while maintaining effectiveness and safety during use.

For efficacy maintenance, water-powder separation technology employs a unique dual-phase strategy. The liquid phase requires a pre-designed precise buffering system that rapidly establishes and maintains the optimal pH range of 3.0-3.5 upon mixing with vitamin C powder, ensuring both vitamin C activity and transdermal absorption. Product design must incorporate clear concentration guidance to help users achieve the ideal 15-20% concentration, avoiding reduced absorption efficiency due to improper concentration. More importantly, an innovative phased stabilization strategy is adopted: quick-acting stabilizers such as ferulic acid are added to the liquid phase, while long-acting stabilizing components are included in the powder phase, collectively ensuring activity maintenance throughout the entire process from mixing to complete usage.

Safety considerations require special attention to the unique challenges posed by water-powder separation technology. Mixing uniformity directly affects safety, as incompletely dissolved vitamin C powder may create localized high-concentration areas, increasing the risk of skin irritation. Usage timeliness is another critical factor: the product's labeled usage period represents not only an activity requirement but also a safety guarantee, since using expired mixtures may expose skin to higher concentrations of degradation products. Additionally, potential operational errors during user preparation must be addressed, as deviations in pH or concentration may increase irritation risks.

Achieving optimal balance requires multidimensional innovative solutions. Intelligent packaging design is recommended, incorporating tools such as quantitative spoons and graduated bottles to physically limit the mixing concentration range and reduce user operational errors. The development of indicator-based formulations also holds value; by adding pH-sensitive natural pigments to the liquid phase, visual cues can indicate whether the product is within the optimal pH range. Establishing dual time-effectiveness standards is essential: not only specifying the

unopened shelf life, but also determining the safe usage duration after mixing through scientific research, and establishing personalized usage guidelines for different skin types.

This balancing art demands that product developers combine chemical expertise with user experience design. Through the integration of technological innovation and human-centered design, users can ultimately achieve safe and effective skincare experiences through simple operations, truly realizing the advantages of water-powder separation technology.

iii.Future Perspectives

Based on the current research status and identified gaps, several promising research directions emerge:

1. Multivariate System Optimization: Future studies should employ advanced multivariate optimization methods, particularly Response Surface Methodology (RSM), to systematically investigate the interaction effects between pH, concentration, and stabilizers. This approach will enable researchers to identify optimal parameter combinations and build predictive models for formulation stability and efficacy.

2. Development of Novel Natural Stabilizers: There is an urgent need to develop milder yet effective natural stabilizers to replace synthetic alternatives like EDTA. Promising candidates include optimized phytate formulations and novel amino acid-based chelators that offer both excellent stabilization properties and improved safety profiles. Research should focus on understanding their stabilization mechanisms and synergistic effects with other formulation components.

3. Standardized Testing Protocols for Post-Mixing Stability: The field requires establishment of standardized testing methods specifically designed for water-powder separated products. This should include accelerated oxidation tests with defined VC residue rate criteria, real-time stability monitoring protocols, and performance evaluation standards that simulate actual usage conditions. These standards will provide crucial guidance for product development and quality control.

4. Intelligent Formulation Systems: Future research should explore smart formulation technologies that can automatically adjust to environmental changes, such as pH-responsive release systems and self-regulating antioxidant networks. These advanced systems could maintain optimal stability during storage while ensuring rapid activation upon application.

5. Personalized Formulation Approaches: Developing personalized formulation strategies based on different skin types and usage scenarios represents another important direction. This includes creating concentration-adjustable systems and skin-adaptive formulations that can automat-

ically modify their properties based on individual user characteristics.

By addressing these research priorities, the scientific community can overcome current limitations in vitamin C formulation technology and develop next-generation products that offer superior stability, enhanced efficacy, and improved safety for consumers.

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