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CHEMICAL STABILITY OF POLYHERBAL FORMULATIONS

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Abstract
Polyherbal formulations, consisting of multiple plant extracts or herbal ingredients, have become increasingly popular in traditional and alternative medicine practices. However, ensuring their chemical stability is essential for maintaining therapeutic efficacy and safety. This chapter provides a systematic and comprehensive examination of the factors influencing the chemical stability of polyherbal formulations. It covers various aspects including degradation pathways, storage conditions, and formulation strategies that impact stability. Understanding the degradation pathways is crucial as it allows for the identification of potential chemical reactions that may occur within the formulation. Factors such as temperature, humidity, light exposure, and oxygen can significantly influence the stability of polyherbal formulations during storage. Additionally, the selection of excipients and formulation techniques play a vital role in maintaining stability. Analytical techniques such as chromatography and spectroscopy are widely employed for assessing the stability of polyherbal formulations. High-performance liquid chromatography (HPLC), gas chromatography (GC), and mass spectrometry (MS) are commonly used methods for analyzing the chemical composition and degradation products of these formulations. Spectroscopic techniques like UV-Vi spectroscopy and infrared (IR) spectroscopy are also valuable tools for monitoring chemical changes. By understanding the chemical stability of polyherbal formulations, manufacturers can ensure product quality and consistency. Furthermore, regulatory authorities can establish guidelines for stability testing and shelf-life determination of these formulations. This comprehensive overview aims to provide valuable insights for researchers, manufacturers, and regulatory agencies involved in the development, production, and regulation of polyherbal products. It emphasizes the importance of systematic studies on chemical stability to enhance the efficacy and safety of polyherbal formulations in healthcare practices.

Keywords
Polyherbal formulations, Chemical stability, Degradation pathways, Storage conditions, Formulation strategies, Analytical techniques, Therapeutic efficacy and Regulatory guidelines.

INTRODUCTION

Polyherbal formulations refer to medicinal products that are composed of a combination of multiple plant extracts or herbal ingredients. These formulations have been widely used in traditional medicine systems, such as Ayurveda, Traditional Chinese Medicine (TCM), and indigenous healing practices across various cultures (Aladejana and Aladejana 2020; Madhusudhan et al. 2021; Sahu et al. 2021). Polyherbal formulations are believed to harness the synergistic effects of multiple herbs, enhancing therapeutic efficacy and minimizing adverse effects. The popularity of polyherbal formulations stems from their holistic approach to healing, as they target multiple pathways and provide a broader spectrum of bioactive compounds compared to single-herb preparations'(Enioutina et al. 2017; Martin and Ernst 2003; Mukazayire et al. 2011; Zheng et al. 2023).

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Polyherbal formulations often consist of herbs with complementary therapeutic properties. The combination of different herbs can lead to synergistic effects, where the collective action of multiple constituents enhances the overall therapeutic efficacy. Synergy can result from various mechanisms, including enhanced bioavailability, modulation of multiple targets, and improved absorption or metabolism of active compounds. These synergistic effects can potentially increase the therapeutic benefits of the formulation. Many diseases and health conditions involve complex mechanisms and multiple targets. Polyherbal formulations offer a multi-targeted approach by providing a diverse array of bioactive compounds that can act on different pathways simultaneously. This approach may provide a more comprehensive and effective treatment compared to single-herb preparations that target only one aspect of the disease (Maurya and Kumar 2019). The combination of herbs in polyherbal formulations can help mitigate potential adverse effects associated with individual herbs. Certain herbs may contain constituents that counteract or buffer the side effects of others, resulting in a more balanced and harmonious therapeutic response. Additionally, by using lower doses of individual herbs in the formulation, the risk of toxicity or unwanted reactions may be minimized '(Carvalhana et al. 2016; Hammer et al. 2006; Hand Hygiene and Adverse Skin Reactions: COVID-19 Prospect 2020; Inoue 2014).

Polyherbal formulations often draw from traditional knowledge and historical use in various medicinal systems. These formulations have been developed and refined over centuries, based on empirical evidence and observations of their therapeutic effects. By incorporating traditional knowledge into modern healthcare practices, polyherbal formulations contribute to the preservation and utilization of cultural wisdom related to herbal medicine. The popularity of herbal and natural products has been steadily growing worldwide. Polyherbal formulations, with their traditional roots and potential health benefits, have gained significant attention in the global market. They present opportunities for herbal product manufacturers and pharmaceutical companies to develop and market products that cater to the increasing demand for natural and alternative therapies (Albahri et al. 2022).

Analytical techniques play a crucial role in assessing the stability of herbal products, ensuring their safety, efficacy, and quality over time. These techniques allow researchers and manufacturers to monitor changes in the chemical composition, physical properties, and overall stability of herbal products throughout their shelf life. Various analytical methods are employed to evaluate different aspects of stability, including chemical degradation, physical changes, and microbial contamination. Below, we discuss the role of different analytical techniques in the assessment of herbal product stability. HPLC is one of the most widely used analytical techniques for assessing the stability of herbal products. It allows for the separation, identification, and quantification of active compounds and degradation products present in herbal extracts. By monitoring changes in the chromatographic profiles over time, HPLC can detect degradation pathways, identify degradation products, and assess the overall chemical stability of herbal formulations. Gas Chromatography (GC) is employed to analyze volatile compounds and assess the volatile profile of herbal products (Basist et al. 2022; Gaurav et al. 2022; Gautam 2022; Khan et al. 2022, 2024). It is particularly useful for detecting changes in essential oils, terpenes, and other volatile constituents that may be susceptible to degradation or evaporation during storage. GC analysis provides valuable insights into the aroma, flavor, and overall quality of herbal extracts and formulations. Thin-Layer Chromatography (TLC) is a simple and cost-effective technique used for qualitative analysis and fingerprinting of herbal products. It allows for the separation and identification of various compounds present in herbal extracts based on their differential migration on a thin layer of stationary phase. TLC can be employed to monitor changes in the chemical composition and detect the presence of degradation products or adulterants in herbal formulations (Agarwal and Yeluri 2023; Kalyana Sundaram et al. 2018; Ojiako, Chikezie, and Ogbuji 2016a, 2016b).

UV-Visible spectroscopy is utilized to assess the stability of herbal products by monitoring changes in the absorbance of specific wavelengths of light. This technique is particularly useful for quantifying the concentration of active compounds, such as polyphenols, flavonoids, and alkaloids, in herbal extracts. By measuring changes in absorbance over time, UV-Visible spectroscopy can indicate degradation, oxidation, or photodegradation of key constituents in herbal formulations. Fourier Transform Infrared Spectroscopy (FTIR) spectroscopy is employed to analyze the chemical composition and detect structural changes in herbal products. It provides information about functional groups present in herbal extracts and can identify chemical bonds associated with degradation or oxidation processes. FTIR analysis is useful for assessing the stability of herbal formulations and detecting changes in their molecular structure over time. Differential Scanning Calorimetry (DSC) is a thermal analysis technique used to investigate changes in the physical properties of herbal products, such as melting point, crystallization, and phase transitions. It can detect alterations in the thermal behavior of herbal formulations due to chemical degradation, polymorphic transitions, or physical instability. DSC analysis provides valuable insights into the thermal stability and compatibility of herbal extracts with excipients and packaging materials. Microbiological analysis is essential for evaluating the microbial stability and safety of herbal products. It involves assessing the presence of bacteria, fungi, yeasts, and molds in herbal formulations using microbial enumeration and identification techniques. Microbiological analysis helps ensure that herbal products meet microbiological quality standards and are free from microbial contamination that could compromise their safety and efficacy' (Brown and Wright 2020; L. Hu et al. 2023; Huang et al. 2022; Mo et al. 2023).

However, accelerated stability testing involves subjecting herbal products to accelerated aging conditions, such as increased temperature, humidity, and light exposure, to predict their long-term stability. This approach allows researchers to assess the effects of environmental stressors on the stability of herbal formulations and identify potential degradation pathways. Accelerated stability testing is a valuable tool for estimating shelf life and determining appropriate storage conditions for herbal products. Hence, analytical techniques play a critical role in the assessment of stability for herbal products, providing valuable insights into their chemical composition, physical properties, and microbial safety. By employing a combination of chromatographic, spectroscopic, thermal, and microbiological methods, researchers and manufacturers can ensure the quality, safety, and efficacy of herbal formulations throughout their shelf life. These analytical techniques are essential tools for regulatory compliance, quality control, and product development in the herbal industry (Ahmad and Othman 2013; Farizah et al. 2015; Wang and Yang 2019; Zakaria et al. 2019).

REVIEW FINDINGS

Chemical stability of polyherbal formulations

Ensuring the chemical stability of polyherbal formulations poses several challenges due to the complex nature of phytoconstituents. Polyherbal formulations often consist of multiple herbal ingredients, each containing a diverse range of bioactive compounds. The variability in the composition and concentration of these compounds can influence the stability of the formulation. Different herbs may have different degradation pathways and susceptibility to degradation under specific conditions, making it challenging to predict the overall stability of the formulation (More et al. 2022). The combination of herbal ingredients in polyherbal formulations can lead to complex interactions that affect their stability. Some herbs may interact synergistically, enhancing stability, while others may exhibit antagonistic effects, leading to degradation or reduced stability. Incompatibilities among herbs can result in the formation of insoluble precipitates, chemical reactions, or alterations in the pH of the formulation, impacting its stability(Fakher et al. 2020; Frosio et al. 2023; Osorio et al. 2024; Ulvestad et al. 2018).

Polyherbal formulations are prone to various degradation pathways, including hydrolysis, oxidation, and photodegradation. Each herbal ingredient within the formulation may have different degradation mechanisms and rates, complicating the overall stability profile. Factors such as temperature, humidity, and light exposure can accelerate these degradation processes, necessitating careful control of storage conditions. The formulation process itself introduces challenges to maintaining stability. Factors such as the selection of excipients, solvents, and preservatives can impact the stability of polyherbal formulations. The pH of the formulation and the solubility of herbal constituents can influence stability, as some compounds may degrade under acidic or alkaline conditions. Additionally, the presence of certain excipients or preservatives may interact with herbal ingredients, affecting their stability (Enaru et al. 2021; Mohammadi et al. 2023; Nosirov 2023; X. Zhang et al. 2020). Assessing the stability of polyherbal formulations requires the development and validation of analytical methods capable of simultaneously quantifying multiple bioactive compounds. The complexity of polyherbal formulations makes it challenging to analyze individual compounds accurately, especially when they have similar chemical structures or co-elute during analysis. Analytical techniques must be sensitive, selective, and capable of detecting changes in the concentration of active compounds over time. Determining the shelf-life of polyherbal formulations presents a challenge due to the interplay of multiple factor s, including the stability of individual herbal ingredients, formulation complexity, and storage conditions. Conducting long-term stability studies to determine the expiration date of the formulation requires resources and time. Polyherbal formulations often fall under the regulatory purview of various agencies, and demonstrating their chemical stability is a crucial aspect of obtaining regulatory approvals. Compliance with regulatory guidelines and ensuring batch-to-batch consistency in stability is essential for quality control and commercialization(Bhope, Nagore, et al. 2011).

2. FACTORS AFFECTING CHEMICAL STABILITY

2.1. Degradation Pathways

Degradation pathways play a crucial role in the chemical stability of polyherbal formulations. Understanding these pathways is essential for identifying the potential degradation mechanisms and developing strategies to enhance stability. (Bhope, Nagore, et al. 2011) The following are common degradation pathways that can occur in polyherbal formulations. Hydrolysis is a common degradation pathway in which the chemical bonds within the herbal constituents are cleaved by water molecules. Hydrolysis can occur in polyherbal formulations when the formulation contains water or when the herbs themselves contain hydrolytically labile compounds. Factors such as pH, temperature, and the presence of catalysts can influence the rate of hydrolysis. Hydrolytic degradation can lead to the formation of degradation products, loss of potency, and changes in the therapeutic profile of the formulation.

Oxidation is a significant degradation pathway that occurs when herbal constituents are exposed to oxygen or other oxidizing agents. Oxidation can lead to the formation of reactive oxygen species, resulting in the degradation of bioactive compounds. Herbs containing phenolic compounds, terpenes, or other susceptible functional groups are particularly prone to oxidation. Factors such as temperature, light exposure, and the presence of transition metal ions can accelerate oxidation reactions. Antioxidants and packaging materials that minimize oxygen exposure can be employed to mitigate oxidation-related degradation.(Bakr et al. 2019; Sahu et al. 2021)

Photodegradation refers to the degradation of herbal

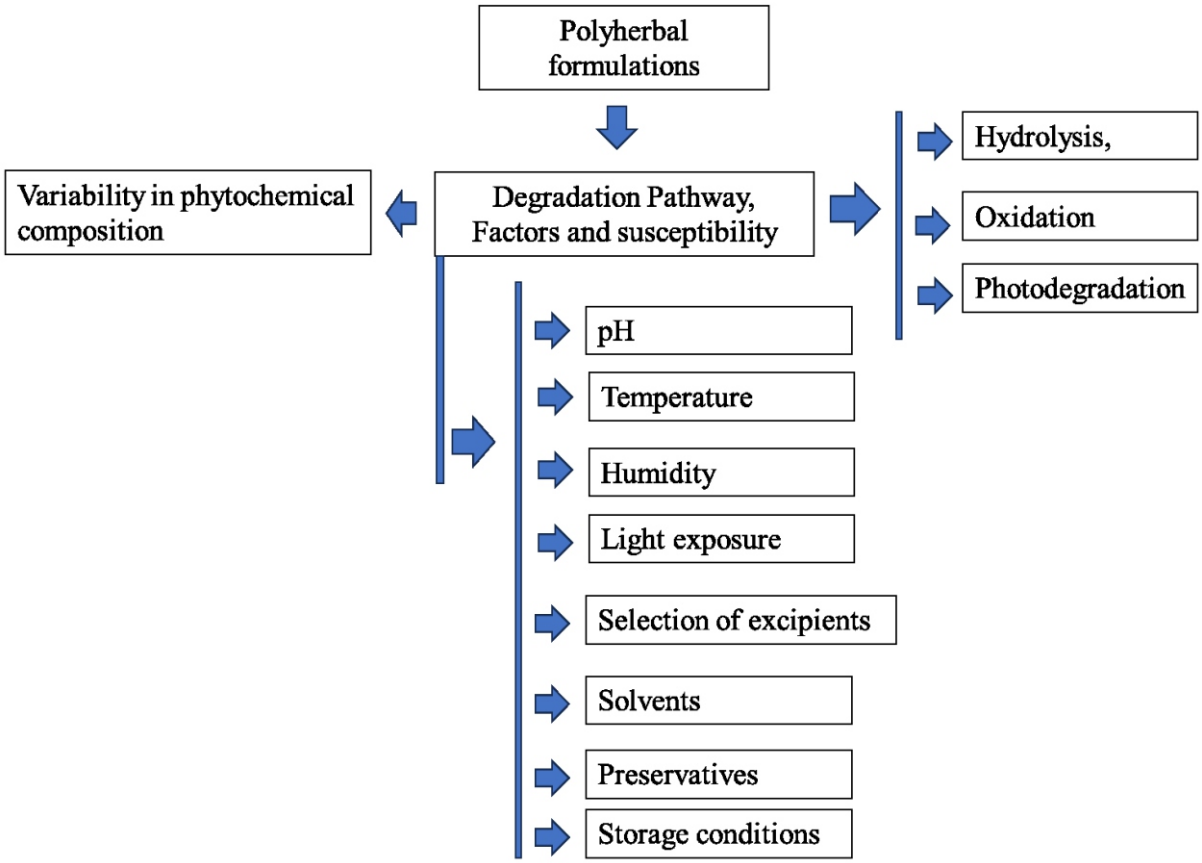

Fig. 1: Degradation pathway, factors affecting pf polyherbal formulation.

constituents induced by light exposure. UV and visible light can trigger photochemical reactions, leading to the formation of free radicals and subsequent degradation. Some herbal compounds, such as flavonoids and photosensitive pigments, are especially vulnerable to photodegradation. The intensity and duration of light exposure, as well as the formulation's packaging and storage conditions, can influence the extent of photodegradation. Light-protective packaging and storage in opaque containers can help reduce photodegradation. Thermal degradation occurs when polyherbal formulations are exposed to elevated temperatures. Heat can promote chemical reactions, including hydrolysis, oxidation, and other degradation pathways. The rate of thermal degradation is dependent on factors such as temperature, time, and the heat sensitivity of the herbal constituents. Storage at controlled temperatures and avoiding exposure to excessive heat during manufacturing, transportation, and storage are critical to minimizing thermal degradation.(Blais, Day, and Wiles 1973)

The excipients and additives used in polyherbal formulations can interact with herbal ingredients, leading to chemical changes and degradation. For example, certain excipients may cause pH shifts, alter solubility, or introduce reactive impurities that can degrade the herbal constituents over time. Incompatibilities between herbal ingredients and excipients can result in precipitation, chemical reactions, or destabilization of the formulation. Careful selection of compatible excipients and additives is necessary to maintain chemical stability. Temperature, humidity, and light exposure are important environmental factors that can significantly affect the chemical stability of polyherbal formulations. These factors can accelerate degradation pathways and lead to changes in the composition and potency of the formulation''(Burton et al. 2017; Lee et al. 2023; Merish and Walter 2019; Widyani 2019).

Higher temperatures can accelerate degradation reactions, such as hydrolysis, oxidation, and thermal degradation, in polyherbal formulations. The rate of chemical reactions typically doubles with every 10°C increase in temperature due to the increased kinetic energy of the molecules. It is crucial to store polyherbal formulations at appropriate temperatures to minimize degradation and maintain their stability, while cold temperatures can slow down degradation reactions, extreme cold conditions can affect the stability of polyherbal formulations. Freezing temperatures can cause physical changes, such as the formation of ice crystals, which can damage the formulation's structure and compromise its stability. Freeze-thaw cycles should be avoided, as they can cause further damage. Polyherbal formulations, particularly those in liquid or semi-solid forms, can absorb moisture from the surrounding environment. Moisture uptake can lead to hydrolysis reactions, especially if the formulation contains hydrolytically labile compounds. Additionally, moisture can

promote microbial growth, which can further degrade the formulation. Proper packaging, storage in dry conditions, and the use of desiccants can help prevent moisture-related degradation.

Light exposure, especially in the UV and visible light spectrum, can initiate photochemical reactions that contribute to photodegradation of polyherbal formulations. UV light can generate reactive oxygen species, leading to oxidative degradation. Certain herbal constituents, such as photosensitive pigments and flavonoids, are particularly vulnerable to photodegradation. Transparent or translucent packaging materials allow light penetration, and prolonged exposure to light should be minimized by storing formulations in opaque containers or utilizing light-protective packaging. Temperature, humidity, and light exposure can act synergistically to accelerate degradation processes. For example, elevated temperatures can promote moisture uptake, thereby increasing the likelihood of hydrolysis reactions. Similarly, light exposure can cause temperature elevation within a formulation, amplifying degradation kinetics. Understanding the interplay between these factors is crucial for designing appropriate storage conditions and ensuring chemical stability. (Deepaka, Bhatnagar, and Kumar 2010) To maintain the chemical stability of polyherbal formulations, it is recommended to store them in a cool, dry place, away from direct light exposure. Controlling storage conditions within appropriate ranges (e.g., room temperature, low humidity) helps to minimize the potential for degradation and preserve the formulation's integrity. Stability testing under different temperature and humidity conditions can provide insights into the formulation's stability profile and inform appropriate storage recommendation ' '(Alkhalidi et al. 2022; Mondal, Mukhopadhyay, and Chattopadhyay 2022; Prange and Wright 2023; Vlieland et al. 2018).

2.2. Interactions among Herbal Ingredients:

Interactions among herbal ingredients in polyherbal formulations can significantly impact their chemical stability. The combination of different herbs can lead to complex chemical reactions and interactions, which can influence the stability and potency of the formulation. Various types of interactions that can occur among herbal ingredients and their implications for chemical stability are Chemical reactions can occur between the bioactive compounds present in different herbal ingredients. These reactions can result in the formation of new compounds or degradation products, altering the overall composition and stability of the polyherbal formulation. For example, alkaloids from one herb may react with polyphenols from another herb, leading to the formation of new chemical entities. The pH of the formulation can also influence chemical reactions. Certain herbal constituents may be sensitive to pH changes, leading to chemical transformations or hydrolysis reactions. Incompatibilities between acidic and alkaline compounds can result in pH shifts that impact the stability of the formulation. Synergistic interactions occur when the combined action of multiple herbal ingredients produces a greater therapeutic effect than the sum of their individual effects. While synergistic interactions are desirable for therapeutic efficacy, they can also influence the chemical stability of the formulation. Synergistic interactions can enhance stability by protecting certain herbal constituents from degradation or improving their bioavailability (Di Lorenzo et al. 2021; Manach et al. 2004; Thilakarathna and Vasantha Rupasinghe 2013).

For example, one herb may contain compounds that act as antioxidants, preventing the oxidation of susceptible constituents from other herbs in the formulation. Conversely, synergistic interactions can also lead to chemical reactions that degrade or modify the herbal constituents. For instance, the presence of specific compounds from one herb may catalyze the degradation of sensitive compounds from another herb, affecting the stability of the formulation. Antagonistic interactions occur when the combined action of herbal ingredients inhibits or reduces the individual effects of certain constituents. These interactions can impact the chemical stability of the formulation by altering the activity or availability of specific compounds. Antagonistic interactions may lead to decreased stability by reducing the efficacy of certain compounds that contribute to the stability or shelf-life of the formulation. For example, the presence of one herb may inhibit the antioxidant activity of another herb, leaving susceptible constituents vulnerable to oxidation and degradation.(Delgoda and Westlake 2004).

The solubility of herbal constituents and their interactions can influence the chemical stability of polyherbal formulations. Incompatibilities between herbal ingredients can lead to the formation of insoluble precipitates or complexation, altering the physical and chemical properties of the formulation. Precipitation can result in the loss of active compounds, reduced bioavailability, and changes in the formulation's appearance, texture, and consistency. In some cases, precipitates can also catalyze chemical reactions or act as sites for oxidation, impacting the stability of the formulation (Guo, Shalaev, and Smith 2013; Musakhanian, Rodier, and Dave 2022; Pinto et al. 2021).

2.3. Incompatibilities and complex formation

Interactions among herbal ingredients in polyherbal formulations can give rise to incompatibilities and complex formation, which can impact the chemical stability of the formulation. These interactions can lead to changes in the physical and chemical properties of the formulation, affecting its stability and overall quality. Incompatibilities occur when two or more herbal ingredients in a polyherbal formulation react with each other or with other components, resulting in undesirable effects on stability. Incompatibilities can manifest as changes in color, odor, pH, precipitation, or the formation of insoluble complexes. Incompatibilities can arise due to differences in pH, solubility, or reactivity between herbal ingredients. For example, acidic and alkaline compounds may react with each other, leading to pH shifts

that can impact stability. Additionally, certain herbal constituents may be incompatible with specific excipients or preservatives commonly used in formulations. Incompatibilities can result in the degradation of active compounds, loss of therapeutic potency, reduced bioavailability, and compromised stability of the formulation. They can also lead to physical changes, such as changes in appearance, texture, or precipitation, which can affect the overall quality of the product'—(Chaerudin and Syafarudin 2021; Ghodsi and Stehrer 2022; Namjoshi et al. 2020; Suttikun and Meeprom 2021).

Complex formation occurs when two or more herbal ingredients interact and form stable complexes or associations. These complexes can alter the physicochemical properties of the formulation and influence its stability. Complex formation can lead to changes in solubility, bioavailability, or stability of the herbal constituents. The formation of complexes may result in increased or decreased solubility, affecting the dissolution rate and absorption of the bioactive compounds. Complexes can also shield or protect certain constituents from degradation or oxidation, thereby enhancing stability. On the other hand, complex formation may also result in reduced bioavailability or interaction with other formulation components, leading to altered pharmacokinetics or reduced therapeutic efficacy –(García-Bernal et al. 2021; Gubae et al. 2023; Taha et al. 2022).

3. Evaluation of Stability:

Evaluating the stability of a polyherbal formulation involves assessing its physical, chemical, and microbiological properties over time to ensure that it maintains its quality, safety, and efficacy throughout its shelf life. Stability studies are critical for determining the shelf life of the product and guiding proper storage and packaging requirements. The first step is to design a comprehensive stability study protocol. The study should consider factors such as the intended storage conditions (temperature, humidity, light exposure), the proposed shelf life of the product, and the frequency of testing at various time points. Physical stability assessment involves monitoring changes in the appearance, color, odor, and texture of the polyherbal formulation over time. Any signs of physical degradation or alteration may indicate a decrease in product quality. Chemical stability involves analyzing the active compounds and key chemical constituents present in the polyherbal formulation. Techniques like high-performance liquid chromatography (HPLC) or gas chromatography (GC) can help determine the degradation of active ingredients——(Figueiredo et al. 2023; Jin et al. 2022; Piñón-Balderrama et al. 2020; Rajendiran et al. 2021).

The pH of the polyherbal formulation should be monitored as fluctuations may affect the stability of the product. Microbiological stability is essential to ensure that the formulation remains free from microbial contamination throughout its shelf life. Microbiological testing includes evaluating the presence of microorganisms like bacteria, yeast, and mold. These studies expose the polyherbal formulation to elevated temperature and humidity conditions to assess its stability over a shorter period, simulating what would happen over a more extended period under normal storage conditions. These studies involve storing the formulation under recommended storage conditions for the proposed shelf life to observe its stability under actual storage conditions. (Madhusudhan et al. 2021; Maurya and Kumar 2019; More et al. 2022; SHARMA et al. 2022)

It is essential to evaluate whether the polyherbal formulation interacts with its packaging material, potentially affecting its stability. Compatibility studies involve storing the formulation in different packaging materials and analyzing any changes. Analyze the data obtained from stability studies using appropriate statistical methods to determine if the product meets the predefined stability criteria. Based on the stability data, the shelf life of the polyherbal formulation can be determined, which indicates the period during which the product is expected to remain stable under recommended storage conditions– – – (Barajas-Álvarez, González-Ávila, and Espinosa-Andrews 2022; Ge et al. 2014; Zhai et al. 2023).

3.1. Accelerated Stability Studies:

Accelerated stability studies are conducted to predict the stability of a polyherbal formulation over an extended period by subjecting it to elevated temperature and humidity conditions. These studies provide valuable information about the product's stability in a relatively short time, allowing manufacturers to estimate its shelf life more quickly than real-time stability studies. Determine the appropriate elevated temperature and humidity conditions for the accelerated stability study. These conditions should be chosen based on previous experience or knowledge of the product's behavior and its expected storage conditions. For example, higher temperatures (e.g., 40-50°C) and humidity levels (e.g., 75-85% relative humidity) are commonly used for accelerated stability studies. Prepare multiple batches of the polyherbal formulation following the standard manufacturing procedure. Ensure that the samples are representative of the actual product intended for commercialization. Place the samples in appropriate containers (e.g., sealed bottles, blister packs) to prevent any contamination or moisture ingress. Label and store the samples under the predetermined accelerated temperature and humidity conditions' – – ——(W. Chen et al. 2022; Manso, Marcelino, and Caldeira 2021; Rybakov et al. 2022).

Plan the sampling time points based on the intended duration of the accelerated study. Typically, samples are tested at various intervals (e.g., 1, 3, 6, and 12 months) to observe changes over time. At each time point, remove the samples from the accelerated storage conditions and conduct stability testing. This testing should include assessments of physical appearance, color, odor, pH, chemical composition (using analytical techniques like HPLC or GC), and microbiological properties. Compare the stability data obtained from

accelerated studies with the data from real-time stability studies (if available) and/or historical stability data. Analyze the results to identify any trends or indications of degradation or changes in the polyherbal formulation. Extrapolate the data obtained from accelerated studies to estimate the product's stability under real-time storage conditions. This estimation is usually done using mathematical models that consider the relationship between temperature and stability. Based on the results of the accelerated stability studies and the extrapolation to real-time conditions, determine the expected shelf life of the polyherbal formulation when stored under recommended storage conditions.'" (Rani, Rahman, and Younis 2015; To Evaluate Accelerated Stability Study of a Polyherbal Formulation-Turmocin Plus Tablet 2021; Wayal and Gurav 2020)

3.2. Analytical Techniques:

The evaluation of the chemical stability of a polyherbal formulation involves analyzing the composition of the formulation to determine the degradation or changes in its active compounds and key chemical constituents over time. Several analytical techniques are commonly used to assess the chemical stability of polyherbal formulations High-Performance Liquid Chromatography (HPLC): HPLC is one of the most widely used techniques for analyzing the chemical composition of polyherbal formulations. It allows for the separation, identification, and quantification of individual compounds present in the formulation. HPLC can detect and quantify active compounds, markers, and other chemical constituents, making it a valuable tool for stability studies——'(Capelli et al. 2022; Gomez-Rioja et al. 2023; González-González et al. 2022; Kosović, Sýkora, and Kuchař 2021).

Gas Chromatography (GC): GC is employed for the analysis of volatile and semi-volatile compounds in polyherbal formulations. It is particularly useful for determining the stability of essential oils and other volatile components. Thin-Layer Chromatography (TLC): TLC is a simple and cost-effective technique used to separate and identify different components in a polyherbal formulation. It can be employed as a rapid screening tool during stability studies. Spectroscopic Techniques: Techniques like UV-Visible Spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), and Nuclear Magnetic Resonance (NMR) can be utilized to identify and quantify specific compounds or functional groups in the polyherbal formulation. Mass Spectrometry (MS): MS is used in combination with chromatographic techniques to identify and characterize compounds based on their molecular weight and fragmentation patterns. Liquid Chromatography-Mass Spectrometry (LC-MS) and Gas Chromatography-Mass Spectrometry (GC-MS) are commonly used in stability evaluations– (Cho et al. 2018; Hao et al. 2023; Klassen, Tatusch, and Conrad 2023).

Elemental Analysis: Techniques such as Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Atomic Absorption Spectroscopy (AAS) are employed to determine the levels of trace elements in the polyherbal formulation. Nuclear Magnetic Resonance (NMR): NMR can provide detailed structural information about chemical compounds present in the formulation, aiding in their identification and quantification. Stability-Indicating Methods: These methods are specifically designed to separate and quantify degradation products or impurities that may aris e during the stability testing of the polyherbal formulation. They help distinguish the stability of the active compounds from potential degradation products.(Aslam et al. 2016; Deepaka, Bhatnagar, and Kumar 2010; SHARMA et al. 2022)(Bhope, Kuber, et al. 2011)

4. Stability-Enhancing Strategies:

Stability-enhancing techniques are used to improve the shelf life and preserve the quality of polyherbal formulations. These techniques help prevent degradation, maintain the potency of active compounds, and ensure the formulation remains safe and effective during storage. Careful selection of high-quality raw materials and herbs with well-established stability profiles is crucial. Ensuring the purity and potency of the ingredients can contribute to the overall stability of the formulation. Standardization involves establishing the minimum levels of active compounds or markers in the formulation. By maintaining consistent levels of these compounds, the stability of the formulation can be enhanced. (Manish Kumar Gupta et al. 2020; Pandey et al. 2023).

Incorporating antioxidants into the formulation can help protect sensitive compounds from oxidative degradation. Natural antioxidants like tocopherols (vitamin E), ascorbic acid (vitamin C), and polyphenols can be used to enhance stability. Excipients, such as stabilizers, surfactants, and emulsifiers, can be added to the formulation to improve stability. These excipients can help maintain the homogeneity of the formulation and prevent phase separation. Microencapsulation involves coating the active compounds with a protective layer, which can help protect them from degradation caused by factors like light, oxygen, and moisture. Freeze drying (lyophilization) is a technique that involves removing water from the formulation at low temperatures, preserving the active compounds and preventing microbial growth. Packaging the polyherbal formulation in an environment with controlled gas composition can help extend its shelf life by reducing oxidative degradation and microbial spoilage. Controlling the pH of the formulation within a specific range can enhance stability, as some active compounds may be sensitive to changes in pH. Regular testing and monitoring of the formulation during its shelf life can help identify any changes or degradation, allowing timely intervention if stability issues arise. Ensuring that the packaging material is compatible with the formulation is important. Some materials may interact with the formulation, leading to stability issues. Adhering to GMP guidelines throughout the manufacturing process can help maintain the quality and stability of the formulation. Storing the polyherbal formulation under

recommended temperature, humidity, and light conditions is essential for maintaining stability. Proper storage helps prevent degradation and ensures the formulation's longevity. (Calderón-Oliver and Ponce-Alquicira 2022; Choudhury, Meghwal, and Das 2021; Sousa et al. 2022)\

4.1. Formulation Optimization:

Rational selection of ingredients and their proportions in a polyherbal formulation involves a systematic and evidence-based approach to choose the right herbs and determine their appropriate ratios to achieve the desired therapeutic effect. For this clearly define the specific health condition or symptom you intend to address with the polyherbal formulation. Understanding the therapeutic goals will guide the selection of herbs with relevant properties, conduct a thorough review of peer-reviewed scientific literature and clinical studies related to the potential herbs for your formulation. Look for evidence of their medicinal properties, active constituents, and relevant mechanisms of action. Traditional knowledge can offer valuable insights into the safety and efficacy of herbal combinations that have been used for generate Evaluate the individual herbs' efficacy and safety profiles for the targeted health condition. Pay attention to clinical trial results and any reported adverse effects. Synergy occurs when the combined effect of herbs is greater than the sum of their individual effects. Additionally, ensure that the selected herbs have complementary actions to address different aspects of the health condition. Be aware of potential interactions between the herbs and any medications the users might be taking. Avoid combinations that could lead to adverse effects or reduced efficacy of either the herbs or the medications. The dosage should be within safe and effective ranges while avoiding toxic levels. Ensure that the herbal ingredients used in the formulation are of high quality, purity, and authenticity. Work with reputable suppliers and conduct appropriate quality control tests. Consider the bioavailability of active compounds in the selected herbs. Some compounds may have low bioavailability, and strategies may be required to enhance their absorption. Experiment with different proportions of the selected herbs to find the optimal combination. Keep in mind their potency and potential synergistic effects when determining the ratios.(Chopra et al. 2007; Rahim et al. 2018; Tiwari et al. 2020)

Conduct preclinical studies on the formulation to assess its safety and efficacy in animal models. This step provides valuable insights before proceeding to human trials. If possible, conduct well-designed clinical trials to evaluate the safety and efficacy of the polyherbal formulation in humans. Use appropriate controls and endpoints to measure the outcomes accurately. Ensure that the polyherbal formulation complies with the regulations and guidelines for herbal supplements or medicines in the target market. Consider feedback from patients who have used the formulation during the optimization process. Their experiences and outcomes can provide valuable insights for further refinement'—(Loopstra and Rietveld 1969; Oliveira et al. 2022; Ren 2023).

4.2. Use of stabilizers and antioxidants:

Stabilizers and antioxidants play essential roles in maintaining the stability, shelf life, and quality of the product. These additives help prevent deterioration, degradation, and oxidation of the active compounds in the formulation. Stabilizers are added to polyherbal formulations to enhance their physical and chemical stability. They help prevent undesirable changes such as phase separation, precipitation, or degradation of active constituents over time. In polyherbal formulations where different herbs have varying solubilities, emulsifiers and surfactants can help create stable and uniform mixtures. Gelling agents are used to provide a consistent texture and prevent settling in liquid polyherbal formulations. They can help maintain homogeneity and improve ease of administration. In cases where the formulation contains water or is susceptible to microbial growth, preservatives may be added to prevent contamination and maintain the product's integrity. Stabilizing the pH within an optimal range can prevent chemical reactions or precipitation that could lead to reduced efficacy or altered therapeutic properties. In freeze-dried or frozen polyherbal formulations, cryoprotectants are used to safeguard the herbs from damage caused by freezing and thawing. Antioxidants are compounds that protect herbal ingredients from oxidation. Oxidation can lead to the degradation of active compounds and reduce the therapeutic efficacy of the polyherbal formulation. Antioxidants scavenge free radicals and prevent oxidative stress, preserving the integrity and bioactivity of the herbal constituents. By reducing oxidative reactions, antioxidants can extend the shelf life of the polyherbal formulation, ensuring its effectiveness over a more extended period. Antioxidants help maintain the formulation's stability, especially in formulations that are exposed to air, light, or heat. Common antioxidants used in polyherbal formulations include ascorbic acid (vitamin C), tocopherols (vitamin E), beta-carotene, and various plant-derived polyphenols like flavonoids and tannins.(Buacheen et al. 2023; Kirschweng et al. 2017; Shahidi and Zhong 2010).

It's important to note that while stabilizers and antioxidants can improve the formulation's stability and quality, excessive use of these additives might lead to adverse effects or interfere with the herbs' therapeutic actions. Therefore, it's essential to use these additives judiciously and in compliance with regulatory guidelines (Basudkar et al. 2022; Calixto 2000; A. Singh and Narsinghani 2023).

4.3. Packaging and Storage Conditions:

Packaging and storage conditions are critical factors that can significantly impact the stability, efficacy, and shelf life of polyherbal formulations. Proper packaging and storage practices are essential to preserve the integrity of the active constituents and maintain the quality of the product. Guidelines for packaging and storage of polyherbal formulations are: Choose packaging materials that are suitable for the specific formulation. For liquid formulations, dark-colored glass bottles are commonly used to protect the contents from light exposure. For solid formulations, such as

powders or capsules, use airtight and moisture-resistant containers. Ensure that the selected packaging materials are inert and do not react with the formulation's ingredients, which could lead to degradation or chemical changes. Polyherbal formulations, especially those containing light-sensitive compounds, should be stored in opaque or dark-colored containers to protect them from light exposure. Light can accelerate the degradation of certain active constituents. Proper moisture control is vital for preserving the stability of polyherbal formulations. Moisture can lead to microbial growth, spoilage, and degradation of the herbal ingredients. Choose moisture-resistant packaging and store the formulations in a cool and dry environment to prevent moisture absorption —(C. Chen et al. 2023; Gudayu et al. 2022; Guloglu and Altan 2020; Xia et al. 2023).

Store the polyherbal formulations at a controlled room temperature unless specified otherwise by the manufacturer or herbal expert. Avoid exposure to extreme heat or cold, as temperature fluctuations can affect the stability and efficacy of the product. Minimize the exposure of the formulation to air, as oxygen can lead to oxidation and degradation of active compounds. For liquid formulations, ensure that the container is tightly sealed after each use. Provide clear and comprehensive labeling on the packaging, including the formulation's name, ingredients, dosage instructions, batch number, expiration date, and any specific storage instructions. Conduct stability studies to determine the formulation's shelf life under various storage conditions. This will help establish an appropriate expiration date and storage recommendations for consumers. For liquid formulations, ensure that the cap or lid provides an airtight seal to prevent the entry of air and potential contamination. Store the polyherbal formulation in a safe place, out of reach of children and pets, to prevent accidental ingestion or tampering. Regularly monitor the quality of the polyherbal formulation during its shelf life to ensure it remains stable and effective.– (Othman et al. 2021; Sanmartin et al. 2018) Common container materials used for polyherbal formulations include: Amber or dark-colored glass: Offers excellent protection against light exposure. High-density polyethylene (HDPE): Provides good moisture barrier properties and is chemically inert. Aluminum foil pouches: Offers excellent moisture and light barrier, making it suitable for sensitive herbal formulations. Tin or steel containers: Durable and provides protection against light and gas exchange. PET (polyethylene terephthalate) plastic: Suitable for dry formulations and offers a moderate barrier to moisture and gas. Multilayer laminates: Combines different materials to create a package with optimal barrier properties(Boer et al. 2020; D. Hu et al. 2022; Ross et al. 2023).

4.4. Process Validation and Quality Control:

Process validation is the systematic and documented process of confirming that the manufacturing process consistently produces polyherbal formulations meeting predetermined quality standards. The goal is to establish evidence that the process is capable of consistently delivering a product that is safe, effective, and of high quality. The process validation typically involves three stages: Stage1-Process Design: In this stage, the formulation's process is designed and defined based on scientific knowledge and understanding of the herbs' characteristics, interactions, and requirements. Critical process parameters (CPPs) and critical quality attributes (CQAs) are identified. Stage2-Process Qualification: The process is then evaluated to ensure it consistently produces polyherbal formulations that meet the predetermined specifications. This involves performing process qualification batches and analyzing the results to verify process reproducibility— (Pineau et al. 2021; Said et al. 2024; Zhu et al. 2023).

Stage3-Continued Process Verification: After successful process qualification, the process enters routine production. Ongoing monitoring and verification are conducted to ensure that the process remains in a state of control throughout the product's lifecycle. Quality control (QC) involves the systematic and comprehensive testing and evaluation of the polyherbal formulation at various stages of production. The primary objective of QC is to ensure that the final product meets the defined quality standards and is safe for use. Key aspects of quality control for polyherbal formulations include: Raw Material Testing: All herbal ingredients used in the formulation are subjected to rigorous testing to verify their identity, purity, potency, and absence of contaminants or adulterants. In-process Testing: Testing and analysis are performed during the different stages of the manufacturing process to monitor and control critical parameters. This helps ensure that the formulation is being produced as intended''''' (Blay-Roger et al. 2024; COVID-19 (Coronavirus) 2020; Marková and Prajová 2021; Mele and Campana 2022).

Finished Product Testing: The final polyherbal formulation is extensively tested to assess its overall quality, potency, and safety. This includes testing for active compounds, physical characteristics, microbial load, heavy metals, and other relevant parameters. Stability Testing: Stability studies are conducted to determine the shelf life of the formulation under different storage conditions. This helps establish appropriate storage recommendations and expiration dates. Quality Documentation: All testing and quality control activities are documented thoroughly, including the specifications, test methods, results, and any corrective actions taken.– (Choudhary and Sehgal 2021; Husár, Pecha, and Šánek 2021; Karthick and Kathiresan 2022; K. Singh, Tamta, and Mukopadayay 2022)

Both process validation and quality control are crucial components of Good Manufacturing Practices (GMP) in the pharmaceutical and herbal industries. Implementing robust process validation and quality control measures ensures that the polyherbal formulation consistently meets the required quality standards, enhancing patient safety and confidence in the product(Hartini, Kurniawati, and Ihwanudin 2022; Rutz et al. 2019; Y. Zhang, Guan, and Jin 2022).

5. Conclusion

Polyherbal formulations offer a promising avenue for herbal medicine, combining multiple herbs to create synergistic and comprehensive therapeutic effects. As the interest in natural remedies grows, polyherbal formulations have gained significant attention from researchers, healthcare professionals, and consumers alike. The optimization of polyherbal formulations through rational selection of ingredients, appropriate proportions, stabilizers, and antioxidants, along with suitable packaging and storage, is critical for ensuring their efficacy, safety, and shelf life. In conclusion, polyherbal formulations hold significant promise as safe and effective therapeutic options. However, their development, optimization, and stability assessment require a multidisc ciplinary approach, integrating traditional knowledge with modern scientific methods. Addressing the challenges related to stability assessment will be pivotal in realizing the full potential of polyherbal formulations and ensuring their reliable use in healthcare.

Conflict of interest

The authors declare no conflict of interest.

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