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A review on stability testing for herbal drugs

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Abstract
The quality consistency of pharmaceutical products is essential to ensure the expected therapeutic effects. Due to the physical and chemical complexity and inherent variability of herbal products, achieving consistent quality is challenging. Regulatory agencies around the world have issued regulations or guidelines for the stability test parameters and test procedures of herbal products stored under recommended conditions. The test parameters and methods of these herbal products are contained in the guidelines and regulations of 5 global authorities and 15 countries/regions, ie. H. Association of Southeast Asian Nations (ASEAN), Eurasian Economic Commission (EEC), European Medicines Agency (EMA), International Coordinating Committee for Technical Requirements for Human Medicines (ICH), World Health Organization (WHO), Australia, Brazil, Canada, China, Egypt, Hong Kong, India, Japan, Kenya, South Korea, the Philippines, Qatar, Switzerland, the United States and Zambia. The physical, chemical and biological stability tests between different dosage forms are compared, and the test conditions (temperature and relative humidity) for long-term, accelerated or intermediate tests have been included in the guidelines and regulations. Compare PMC Labs and tell us what you think. This review helps to understand the global status of herbal product quality testing related to storage.

Keywords: region of organistion and countries, stability testing parameters, factors

Introduction

Maintaining the quality of herbal products during storage is very important to ensure therapeutic activity. Stability testsare used to assess how herbal products retain their properties under specific storage conditions affected by heat, humidity, light, oxygen, other physical conditions, etc. physical and chemical differences (eg vibration or freezing) and container factors. Herbal products are manufactured in various dosage forms (eg, tablets, powders, or liquids for oral administration or topical creams), and therefore dosage form stability testing is required. Different mechanisms require appropriate methods. The stability of herbal products can be determined by testing properties that are sensitive to storage conditions and include physical (sensory characteristics, physical state, particle size, etc.), chemical (active ingredient test, pH) Properties., identification, etc.), microbiological, and toxicological properties. All of these properties can affect the quality, safety, or efficacy of herbal products, and therefore the shelf life of herbal products should be determined by stability testing. Global harmonization of stability testing has recently been emphasized in the context of herbal medicine development, but the adoption of international standards can only be achieved by sharing international information and experience. Family. Therefore, in this study, we detail the parameters and stability testing methods used for herbal products in different dosage forms, which are detailed in the guidelines. Guidelines and regulations are issued by competent authorities around the world including the Association of Southeast Asian Nations (ASEAN), the Eurasian Economic Commission (EEC), The European Medicines Agency (EMA).), the International Council on the Harmonization of Technical Requirements for Medicines for Human Use (ICH) and the World Organization (WHO), and those enacted by individual countries such as Australia, Brazil, Canada, China (and Hong Kong), Egypt, India, Japan, Kenya, Korea, Philippines, Qatar, Switzerland, USA, and Zambia.

Purpose and Objective [5]

Consistency in the quality of medicinal products is essential to ensure the expected therapeutic activity, and to achieve uniform drug quality. Herbal products are challenging due to their physicochemical complexity and inherent Variability. Regulatory authorities worldwide have issued regulations or guidelines on stability test parameters and test procedures for herbal products stored under suggested conditions. The parameters and methods of testing these herbal products are detailed in the guidelines and regulations issued by 5 global and 15 national authorities, namely the Association of Eastern Nations. South Asia (ASEAN), Eurasian Economic Commission (EEC), European Medicines Agency. (EMA), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), World Organization (WHO), Australia, Brazil, Canada, China, Egypt, Hong Kong, India, Japan, Kenya, Korea, Philippines, Qatar, Switzerland, USA, and Zambia. Physical, chemical, and biological stability tests are compared between different dosage forms and test conditions (temperature and relative humidity) used for accelerated long term or intermediate tests already included in guidelines and regulations.

Compare Try PMC Labs and let us know what you think. This review supports an understanding of the world situation regarding the quality control of herbal products as it relates to storage.

Overview of Stability Testing of Herbal Dosage Forms [6]

We sought guidelines and regulations from global authorities and countries where stability testing was required to maintain the quality of herbal products (or final herbal preparations). The test parameters (or quality control indicators) maintain the quality of herbal products (or final herbal preparations). The test parameters (or quality control indicators) provided are important depending on the different dosage forms of herbal products. storage temperature, relative humidity, time, etc.) are compared between countries and global authorities. Directives and regulations requiring only the quality of chemical drugs were excluded.

Stability Testing Parameters

1. ASEAN [7]

ASEAN publishes stability testing guidelines to ensure maintenance of the quality of final herbal products (traditional medicines) in their designated packaging apply to conditions and durations of recommended storage. The parameters of the dosage forms are as follows: oral powder (sensory, laboratory characteristics, strength and microbial content); Capsules (sensory, laboratory characteristics, solubility, disintegration, content and microbial content); Soft capsules (sensory, laboratory characteristics, solubility, disintegration, and microbial content); Tablets (coated and uncoated; organoleptic, laboratory characteristics, hardness, friability, solubility, disintegration, content and microbial content); Tablets and tablets (coated and uncoated; organoleptic, laboratory characteristics, solubility, disintegration, content and microbial content); Suspension (sensory, laboratory characteristics, viscosity, pH, microbial content, variation in particle or particle size, and dependence on again); Solution (sensory, laboratory characteristics, viscosity, pH and microbial content); Emulsion (sensory, laboratory characteristics, viscosity, pH and microbial content); Semisolid preparations (ointments, creams, gels, lotions, and pastes; organoleptic, laboratory characteristics, viscosity, pH and microbial content); Plaster (sensory, laboratory characteristics, microbial content, and adhesion); Particles (sensory, laboratory characteristics, content, microbial and particulate content or variation in particle size); Herbal infusion sachets and herbal sachets (sensory, laboratory characteristics, content and microbial content); and lozenges (sensory, laboratory, and microbial content).

2. EEC [8, 9]

EEC requires the recording of stability studies during the storage of herbal preparations in accordance with the regulations of drug substances and drugs. Stability testing involves determining the physical, chemical, biological, and microbiological values, and the content of preservatives (such as antioxidants and Antimicrobial preservatives), and the function of the delivery device (such as a dose delivery system). Regulations require evaluation of the appearance, active ingredients, decomposition products, preservatives, and antioxidant content of all drugs. In addition, EEC regulations require the following tests for dosage forms: Pills (pill dissolution, disintegration, content, and abrasion resistance); hard gelatin capsules (brittleness, solubility, disintegration, content, and microbial purity); Soft gelatin capsules (dissolution, disintegration, microbial purity, pH, tightness and adhesion); oral emulsions, suspensions and solutions (sludge formation, pH, viscosity, extractables, and microbial purity) and solutions (transparency), Suspension (dispersion, rheological properties, average particle size/distribution, polymorphic transformation, and polymorphic mutual transformation) required additional test parameters) and emulsion (phase separation and average size and distribution of dispersed spheres); Powders and granules for oral solutions or suspensions (content and recovery); metered-dose inhalers (dose uniformity, valve activation times, aerodynamic particle size distribution, microscopic evaluation, content, airtightness, microbial contamination, Valve delivery or injection weight, weight loss, pump management, foreign mechanical inclusions, and substances removal and discharge from the plastic and elastic parts of the container, cover, and pump); suspended aerosol (valve parts and container contents appearance, large Microscopic analysis of inclusions, drug particle morphology changes, agglomerates, crystals, foreign mechanical inclusions, and internal surface corrosion of containers and gasket wear); nasal sprays (solution transparency, microbial purity, pH value, mechanical inclusions, Uniformity of the content of the active ingredient in the injection, droplet or particle size distribution, weight loss, pumping, microscopic evaluation of the suspension, foreign mechanics of inclusions, and removal and discharge of materials from the plastic and elasticity of the container, closure, and pump Parts); dosage forms for topical (external use), eye and ear applications, including topical ointments, creams, pastes, gels, solutions, eye drops and sprays (transparency, uniformity, pH, wash Resuspension, thickness, viscosity, particle size distribution) suspension, microbial purity and weight loss), including additional parameters of ophthalmic and ear medicines, including creams, ointments, solutions and suspensions (sterile, mechanical inclusions and Extractable volume) and topical aerosols (pressure, weight reduction, total removable weight, delivery rate, microbial purity, spray performance, content and particle size distribution of the suspension); suppositories (soften and Degree of disintegration); parenteral drugs (color, solution transparency, mechanical inclusions, pH, sterility, pyrogenicity, endotoxin content, and volume); and transdermal patches (in vitro release rate, tightness, Microbial purity/sterility, tear-resistance, and shear adhesion). Asterisks indicate optional test parameters.

3. EMA[10, 11]

EMA requires specific storage stability tests for herbal products to ensure quality, as detailed in the "Guidelines for New Medicinal Substances and Product Stability Testing" (CPMP / ICH / 2736/99) and "Stability Guidelines". Testing of Veterinary Drugs and Substances (CVMP/VICH/899/99)" and "Guidelines for Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02 and EMEA/CVMP/846/99)". According to the EMA guidelines, all herbs must be tested to verify that they meet specifications, including instructions, identification, analysis, impurities, and microbial limits following test parameters are also specified: tablets (coated and uncoated) and hard capsules (dissolution,

disintegration, hardness, friability, uniformity of quality, content and microbial limit); oral suspension (Quality uniformity, pH, microbial limit, antibacterial preservative content, antioxidant preservative content, extractable, alcohol content, dissolution (for oral suspension) and resuspension (for dry powder products), particle size distribution, dispersibility, Relatively viscous rheological properties of the solution or suspension, viscosity, specific gravity (for oral suspension, relatively viscous or non-aqueous solution), reconstitution time and content); and herbal infusions (loss on drying, identification, purity, Quality uniformity or average quality of the coating, determination, particle size, and microbiological quality or microbial limit test).

4. ICH [12]

The ICH guidelines provide general requirements for the storage stability testing of new pharmaceutical products, covering the description, identification, analysis, and impurity content of chemicals [10]. However, we believe that the ICH guidelines are also applicable to herbal products because the global documents regulated by EMA, Australia, Japan or Switzerland are based on the ICH guidelines. The specific dosage form stability test parameters are as follows: tablets (coated and uncoated) and hard capsules (dissolution, disintegration, hardness, friability, uniformity of dosage unit, moisture content and microbial limit); oral liquid (Uniformity of dosage unit, pH value, microbial limit, content of antibacterial preservatives and antioxidants, extractables, alcohol content, dissolution, particle size distribution of oral suspension, redispersibility of oral suspension, relative viscosity Rheological properties, reconstitution time and content of thick solutions or suspensions); parenteral drugs (uniformity of dosage unit, pH value, sterility, endotoxin, pyrogen, particulate matter, content, antibacterial and antiseptic) The content of agents and antioxidants, extractables, functional testing of the drug delivery system, including pre-filled syringes, auto-injector barrels or their equivalents, osmotic pressure, particle size distribution of the injection suspension, redispersibility, and reconstitution time).

5. WHO[3]

The WHO Expert Committee publishes a technical report on pharmaceutical preparations and guidelines on good herbal processing practices (Annex 1) and guidelines on active pharmaceutical ingredients and stability testing of finished drugs (Annex 10). General requirements for the stability of finished drugs include appearance, determination and degradation products, and content of preservatives and antioxidants. Specific parameters are also provided according to the dosage form of the product (ie, liquid, solid, or other forms). Liquid herbal dosage forms include liquid extracts, decoctions, infusions, tinctures, syrups, and oral solutions, all of which have been tested for precipitation levels, clarity, pH, viscosity, extractables, and microbial contamination. Test the oral suspension for precipitation formation, clarity, pH, viscosity, extractables, level of microbial contamination, dispersibility, rheological properties, average particle size or distribution, and polymorphic transformation. Test the oral emulsion for precipitation formation, transparency, pH, viscosity, extractables, microbial contamination level, phase separation, and average bead size or distribution. For fragrances and powders or granules used in oral solutions or suspensions, the content and reconstitution time need to be analyzedn. Solid herbal dosage forms include herbal bags, plant powders, dry extract powders, granules, pills, hard gelatin capsules, soft gelatin capsules, tablets, and lozenges. Hard gelatin capsules have been tested for friability, dissolution, disintegration, content, and microbial contamination levels. Softgel capsules have been tested for dissolution, disintegration, microbial contamination level, pH, leakage, and film build. Test the dissolution, disintegration, content, hardness, and friability of tablets. Other dosage forms include ointments, creams, and ointments. The transparency, uniformity, pH, suspending ability (for emulsions), consistency, viscosity, particle size distribution (for suspensions), microbial contamination levels, sterility, and weight loss of these ointments taking the test. Ophthalmic and otological products (for example, creams, ointments, solutions, and suspensions) have been tested for sterility, particulate matter, and extractives. The uniformity of the dose content of the inhaler, the number of labeled drug applications per container that meets the established dose delivery, streamlined particle size distribution, microscopic evaluation, content, leakage rate, microbial contamination level, valve delivery or injection weight, extractable or available Leaching tests for plastic and elastic parts, weight loss, pump delivery, extractable or leachable plastic foreign particles, and elastic parts of containers, closures, and pumps. The dressings and patches were tested for in vitro release rate, leakage, microbial contamination level, sterility, peel strength, and adhesion. Medicinal oil is also included in other dosage forms, but no test parameters are provided.

Country level regulatory organization:

1. Australia[13, 14]

The Australian government provides mandatory guidelines for the stability test of auxiliary drugs in different dosage forms as follows: solutions, suspensions, creams, ointments, tablets (direct compression production), tablets (granulation production), Capsules (two tablets, produced by dry blending), capsules (two tablets, produced by granulation), soft capsules containing solutions (soft gels), soft capsules containing suspensions and powder mixtures (soft gels). According to the EMA guideline "Guidelines for Stability Testing of Stability Testing of Existing Active Substances and Related Finished Products (CPMP / QWP / 122/02 rev 1 corr.)".

2. Brazil [15, 16]

Brazil The Brazilian Regulatory Agency (ANVISA) takes the position that the stability of herbal products depends on environmental factors (temperature, humidity, and light) and product-related parameters (physical and chemical properties of active substances and excipients, The form, product composition, manufacturing, and performance of pharmaceutical packaging materials). Stability studies must be accelerated in nature and conducted for a long period of time to establish shelf life and appropriate storage conditions ANVISA provides the following parameters for the stability test of phytotherapy drug forms: pills and tablets (description, disintegration, dissolution, hardness, content, friability, the dosage unit, the average weight, and the uniformity of the active ingredient content); Capsules (description, disintegration, dissolution, content, uniformity

of dosage units, average weight and content of active ingredients); granules (description, particle size, content, friability, fluidity, bulk density, uniformity of dosage units) Properties, average weight, and content of active ingredients); tinctures and syrups (description, pH, viscosity, relative density, sucrose content, uniformity of dosage units and content of active ingredients); semi-solid (introduction, pH, the Dosage unit, average weight, phase separation, and uniformity of active ingredient content); transdermal adhesive (description, uniformity of dosage unit, adhesion, tensile strength, and active ingredient content); intravaginal suppository (description, Disintegration, dissolution, pH, softening temperature, uniformity of dosage units, average weight, and content of active ingredients); and medicinal soaps (description, pH value, uniformity of dosage units, average weight and content of active ingredients). In addition, all dosage forms require microbiological testing.

3. Canada [17, 18]

The Canadian government requires shelf-life testing of natural and non-prescription medical devices to determine the shelf life after packaging and storage conditions. These tests involve purity, physical properties, levels of medicinal ingredients, amount per dosage unit, and potency. The Canadian government provides guidelines for providing physical test parameters for different dosage forms, as follows: immediate-release tablets, lozenges, and capsules (description, disintegration, and weight change or average weight); fast-dissolving tablets (description, dissolution, and weight or average weight) Changes); tablets and capsules for extended-release, combined release or timed release (changes in dosage unit description, dissolution, weight or average weight, and uniformity); sustained-release tablets and capsules, including enteric-coated tablets and capsules (Description, disintegration, and weight or average weight change); oral solutions and suspensions (description and preservative effect); topical preparations (description and preservative effect); transdermal patches (description, uniformity, and adhesion of the dosage unit or Peel force); and metered dosage form (the number of discharges per container and the uniformity of the administered dose).

4. China[19, 20]

The Chinese government requires accelerated and long-term stability testing to ensure the shelf life and proper storage conditions of herbal products. The Anhui Food and Drug Administration (China) stipulates the stability test parameters of different dosage forms of Chinese herbal medicine products specified in the Chinese Pharmacopoeia as follows: pills (description, identification, disintegration, content, microbiological determination and limit); powder (Description, identification, uniformity of appearance, content, particle size, measurement, and sterile powder for topical treatment of wounds or burns or external use and microbial limits); particles (description includes moisture softening, identification, content, solubility, particle size, Test and microbial limit); tablets (description, identification, hardness, disintegration, foamability, testing and microbial limit); concentrated decoction (description includes sucrose crystallization and phase separation, identification, relative density, insoluble content, Testing and microbial limit); colloid (description, identification, content, test and microbial limit); syrup (description, identification, relative density, pH, test and microbial limit); transdermal (description, identification, gypsum quality extraction, Heat resistance, excipient properties, adhesion and microbial limit); liquid mixture (description including transparency, identification, relative density, pH, content and microbial limit); drop pill (description, identification, disintegration, test and microbial limit) Limit); soft capsule (description, identification, disintegration, content, test and microbial limit); medicinal liquor (description, identification, ethanol content, methanol content, total solids, test and microbial limit); tincture (description, identification, ethanol Content, test and microbial limit); liquid extract (description, identification, ethanol content, test and microbial limit); extract (description, identification, test and microbial limit); plaster (description, identification, softening point and test); Gel (description, identification, pH, viscosity, test and microbial limit); ointment (description including rancidity, odor, color, phase separation, identification, particle size, sterility used to treat burns or wounds, and microbial limit); fragrance Family solution (description, identification, pH, test and microbial limit); bag (description, identification, content, solubility, test and microbial limit); liniment, lotion and smear (description, identification, relative density, pH, Ethanol content, refractive index and microbial limit); suppositories (description, identification, disintegration, testing and microbial limit); nasal preparations (description, identification, pH, determination, sterility and microbial limit); ophthalmic preparations (description, Identification, pH, visible foreign matter, particle size, foreign metal content, sterility and microbial limit); aerosol (description, identification, transfer rate, total spray volume, total number of transfers per container, emissions per transfer, Active ingredient content per transfer, particle size, sterility and microbial limit); and spray (description including precipitation and phase separation trend, identification, particle size, spray test, determination, sterility and microbial limit).

Egypt [21]

The Egyptian Medicines Agency requires that finished products meet minimum registration specifications,

- Common quality parameters: physical appearance (color, smell, shape, shape, size, and texture), content, identification test or qualitative determination of related plant substances (such as fingerprint chromatogram), quantification of active ingredients, test use Due to residual solvents, other toxins, and microbial contamination.
- Specific quality parameters of the drug form; tablets (weight uniformity, disintegration time, hardness/friability and dissolution of uncoated tablets); single-dose powder (weight uniformity); suppositories (weight and disintegration) Uniformity of disintegration time); sachet of herbal (uniform weight); capsules (uniformity of weight, disintegration and dissolution time); tablets (disintegration time); internal and external fluids (viscosity); and semi-solid formulations (consistency).

5. Hong Kong [22, 23]

The Hong Kong Legislative Council stipulates that, as stated in the "Technical Guidelines for Product Quality Documents", the stability evaluation of proprietary Chinese medicines is necessary to determine the shelf life of retail

packaging at room temperature or recommended storage conditions. The Hong Kong government provides the stability test parameters of several common Chinese medicines, as follows: Injection (test transparency, pH, sterility, pyrogen, hemolysis and irritation); Mixture (clarity, relative density and pH value); Syrup (relative density and pH); medicinal liquor (ethanol content and total solid content); tablets (disintegration and content test); powder (powder uniformity, content and applicability); concentrated decoction (description includes Crystallization and cambium tendency, relative density, solubility and pH value); instillation of capsules and pills (content and disintegration); tablets (hardness and disintegration); liquid extracts (pH, ethanol content and total Solid); granules (content and size of the particles); ointment (skin irritation); plasters (softening point and skin irritation); tape (tension, skin irritation and resistance to cold and heat); glue (content); suppositories and pills (Disintegration and pH); aerosols (spray effect, odor and irritation); medicinal films (dissolution, irritation and pH); extracts and suspensions. All dosage forms usually require description, identification (except for medicinal films), determination, and microbial limits (excluding injection drugs, dressings, and viscous dressings).

6. India[24]

The Government of India stipulates the quality inspection requirements of herbal products used in Ayurveda, Siddha, and Unani systems based on dosage forms, as follows: Tablets (description, labeling, weight uniformity, uniformity diameter, disintegration tests, and tests); capsules * (description, identification, weight uniformity, diameter uniformity, disintegration test, and determination); and parental preparations (clarity, pH, identification, container volume, sterility, pyrogen test, toxicity test, and determination). Asterisks indicate optional test parameters.

7. Japan [25, 26]

The japan of Pharmaceutical Safety and Environmental (Ministry of, Labor and Welfare) provides the quality parameters of Kampo formulations as follows: granules (content, description, identification, loss on drying, uniformity, disintegration, and content); uncoated and film-coated tablets (content, description, identification, loss on drying, uniformity, disintegration, and content); sugar-coated tablets (content, description, identification, loss on drying, uniformity, and content); and hard and soft capsules (content, description, identification, loss on drying, uniformity, disintegration, and determination) [23]. It should be noted that the stability test procedure should be carried out according to the ICH guidelines.

8. Kenya[27]

According to the registration guidelines for herbal and supplement products, the Kenyan government requires that finished products meet the minimum specification range. General specifications include toxin and microbial contamination testing, physical appearance (color, smell, shape, shape, size, and texture), content, characteristic testing, qualitative determination, quantification of related active ingredients, and residual solvent testing. The specific specifications of different dosage forms are as follows: tablets (weight uniformity, disintegration time, hardness/friability, and dissolution of uncoated tablets), single-dose powder (weight uniformity), suppositories (weight uniformity and dissolution) Herbal in medicine packets (weight uniformity), capsules (weight uniformity, disintegration and dissolution time), pills (disintegration time), internal and external fluids (viscosity) and semi-solid formulations (consistency). The guidelines stipulate that the physical and chemical stability after long-term storage must comply with the ICH guidelines.

9. Republic of Korea (MFDS) [28, 29]

Ministry of Food and Drug Safety of the requires that the results of stability tests be carried out in accordance with existing regulations and that they provide long-term, accelerated, and intermediate tests during a specified time period under specified storage conditions for registration of herbal products. MFDS provides general specifications for all herbal dosage forms, including description, identification, analysis, and purity testing, as well as specific specifications for each dosage form:patch (disintegration, dissolution, alcohol content, adhesive strength, uniformity of dosage units and texture); particles (microbial limit, disintegration, dissolution, particle size distribution and uniformity of the dosage unit); dust (microbial limit, disintegration, dissolution, particle size distribution and uniformity of the dosage unit); optical ointment (foreign metal particles, sterility, disintegration, dissolution, particle size distribution and uniformity of dosage units); oral liquids, including lemonade, fragrances, syrups, solutions, extracts, elixirs, liquid extracts, emulsions, suspensions, decoctions, infusions, liqueurs, and tinctures (microbial limit, disintegration, dissolution, alcohol content, particle size distribution, and dosage uniformity); external liquids, including lotions, liniments, fragrances, solutions, emulsions, and suspensions (microorganism limit, disintegration, dissolution, alcohol content, particle size distribution, and dosage unit uniformity); Aerosol (microbial limit, alcohol content, particle size distribution and uniformity of the dosage unit); semi-solid for external use, including ointments, creams and pastes Agent (microbial limit, particle size distribution and uniformity of dosage unit); ophthalmic solution (sterile, insoluble particles, insoluble foreign matter, disintegration, dissolution, particle size distribution and uniformity of the dosage unit); spray (per supply container Total amount of spray, microbial limit, disintegration, dissolution, alcohol content, particle size distribution, and dosage unit uniformity); tablets and capsules (microbial limit, disintegration, dissolution and uniformity of the dosage unit); suppositories (microbial limit, disintegration, dissolution and uniformity of dosage units); injections (sterile, insoluble particles, insoluble foreign bodies, disintegration, dissolution, endotoxin, pyrogen, particle size distribution and uniformity of dosage units); plasters and pastes (dissolution by disintegration, dissolution, alcohol content, adhesive strength and texture); tablets (microbial limit, disintegration, dissolution and uniformity of dosage units); and pills (microbial limit, disintegration, dissolution and uniformity of dosage units). Asterisks indicate optional test parameters.

10. Philippines [30, 31]

The Philippine Food and Drug Administration requires stability studies under recommended conditions and must determine the most suitable conditions for storage and shelf

life. The government also requires physical description, testing, and quality standards for finished products (herbal medicines and traditional herbal products), including sensory and macro descriptions (appearance, texture, color, odor, and flavor), moisture content, pH value, alcohol content (if applicable)), microbial limits and identification. In addition, the Philippine government provides specific specifications for different dosage forms, such as tablets (weight change, content uniformity, disintegration, hardness test, friability, and microbiological tests); capsules (weight change, content uniformity, and microbiological tests)); syrups and liquids (viscosity, pH, and microbiological tests); suspensions (suspension, uniformity, viscosity, minimum fill, pH and microbiological tests); ointments, creams, and semisolid preparations (accessibility, homogeneity, pH, melting point, sensitization, and microbiological tests); suppositories and pessaries (allergic and microbiological tests); and decoctions, infusions, extracts (liquids, pills, and powders), tinctures, syrups, lotions, and emulsions (they must pass all the requirements stipulated in the pharmacopeias of other countries).

11. Qatar [30]

The Government of Qatar establishes general requirements for the quality specifications of registered herbal and dietary supplements. These include physical inspection, identification (chemical, spectral, or chromatographic tests), main ingredient levels, heavy metal concentrations, microbial limits, and other quality standards based on the dosage form, including disintegration, dissolution, friability, hardness., pH, The content, and residues in the combustion test. Applicable dosage forms are tablets, hard and soft gelatin capsules, semi-solid preparations (ointments, creams and gels), herbal sachets and sachets, syrups, oral suspensions, drops, or oral powders. General requirements for quality parameters of sterile products (eye drops, contact lenses, and dermal fillers) also include pH, osmotic pressure, viscosity, volume, and bacterial endotoxin testing (dermal fillers).

12. Switzerland [33]

Recommended by Swiss institutions: Bulk and finished drugs in capsule or tablet form containing herbal preparations or granules require specific test parameters for drug formulation (eg disintegration time and average weight). Stability tests should be carried out in accordance with ICH international guidelines, which include test parameters such as description, identity, loss on drying, determination, and microbial purity.

13. United States [34, 35]

The United States Food and Drug Administration (FDA) requires the use of analytical methods or bioassays related to stability to monitor the stability of botanical raw materials and pharmaceuticals and provide the properties quality testing requirements for botanical registry products to ensure that the clinical protocol is properly designed during phase 1, 2 and 3 clinical studies. General attributes include appearance, chemical identification, determination of active ingredients or characteristic markers, bioassay (optional), concentration by dry weight (API), and specific attributes of microbial limits and dosage forms (dissolution of solid oral products, non-bacterial, non-bacterial). Pyrogenic and animal safety tests for injection).

14. Zambia [36-39]

The Zambian government requires final product specifications and test methods for all dosage forms to comply with its herbal registration guidelines, including description, identification, analysis, and impurities (degradation products and microbial limits of active ingredients). The guide also provides other tests for specific dosage forms, as follows: coated and uncoated gelatin capsules and tablets (dissolution, disintegration, hardness, friability, uniformity of dosage units, and content); oral liquids (content uniformity, pH value, limit microbes, the content of antimicrobial preservatives and antioxidants, extractable from containers or closed systems, alcohol content, the solubility of suspensions and powders, dispersibility of suspensions, suspension Viscosity and specific gravity of the liquid or viscous solution. Taking into account global standards and guidelines, the test parameters for oral or topical dosage forms generally specified in more than two global guidelines are divided into three groups:

1. Physical parameters, e.g. description, purity, transparency, hardness, friability, content, unit dosage uniformity, weight change, particle size change, viscosity, relative density, and resuspension;
2. Chemical parameters, such as tests, identification (in most cases, by chromatographic fingerprinting), dissolution, disintegration, pH, and ethanol content; and
3. Biological parameters, such as microbial limit, sterility tests, and irritation.

Investigation and stability test parameters [40-47]

Enayatifard *et al* fh monitored the antioxidant activity of the decoctions and infusions of four medicinal materials in different storage periods (0, 30, 60, and 120 days), and confirmed that the storage time will affect the antioxidant activity and the content of different dosage forms. *Et al*. By studying the changes in pH, UV absorbance, viscosity, and color at different temperatures (4°C, 25°C, 37°C, and 45°C) and 12 weeks in the sun, the creams containing licorice extract were tested The stability of Pushpalatha *et al*. By using real-time and accelerated test conditions (0, 1, 2, 3, and 6 months) [41].

Sawan *et al*. An ointment containing neem (Azadirachta indica) and turmeric (Curcuma longa) extracts were formulated and evaluated at different temperatures (2 ° C, 25 ° C, and 37 ° C) for more than four weeks. Alexander *et al*. After 6 months of storage at 0 ° C and 25 ° C, the characteristics, color and sensory phenol quality, and the effect of steaming treatment on the shelf life of a flavonoid green herbal bag (Cyclopia maculata Andrews Kies) was measured. Huang *et al*. The physical and chemical stability of the Triphala solution was tested by measuring sediment formation and chromatograms for 5 consecutive days, Lee *et al*. The stability of the Mawang decoction was tested by evaluating the pH value, total soluble solids, marker compound levels, and in vitro anti-inflammatory and antioxidant activities after storage at 4 ° C or room temperature for 3 months.

Generally, a stability test is required. [44]

The drug cannot be used after a period of time. Some can only for a short time. In 1984, Rhodes listed 6 general reasons for limiting the storage time of medicines.

These are

- Drug loss (such as hydrolysis or oxidation)

- Carrier loss (such as evaporation of or other volatile components)
- Inhomogeneity (such as suspension agglomeration or emulsion)
- Biological Utilization changes (especially tablets, where aging reduces usability)
- Appearance changes (such as color changes)
- Appearance of toxic and irritating products (due to chemical changes)
- Microbiological activity
- En important Be aware of and be aware of the potential instability of manufactured an expired products. The storage conditions and shelf life of need to be specified to ensure effective inventory control and pay attention to the packaging used in the distribution of Although the reason for the stability test is
- Our concern for the well-being of the patient
- Protect the reputation of manufacturers
- Provide a database of formulations that may be valuable for other products

Factors that affect product stability Physical degradation [45, 46]

Drug components (raw materials and excipients) exist in different microscopic physical states with different degrees. The conversion rate will depend on the chemical potential corresponding to the difference in free energy between states and the energy barrier that must be overcome for conversion to occur (such as the energy barrier of a chemical reaction). It is obvious from the reported data that a higher temperature can have a destructive effect on the physical stability of the formulation.

1. Chemical stability[47, 48]

Chemical degradation of active ingredients in pharmaceuticals generally leads to loss of efficacy, eg hydrolysis of β-lactams Various chemical reactions can lead to degradation of APIs and excipients; The most common reaction is oxidation and hydrolysis. Sometimes more than one reaction can occur at the same time. The main environmental factors that can reduce stability include exposure to unfavorable temperatures, light, humidity, oxygen, and carbon dioxide. The main dosage form factors that affect drug stability include particle size (especially in emulsions and suspensions), pH, composition of the solvent system (ie, percent of "free", and general polarity), compatibility of anions and cations, and ionic solutions. Concentration, primary packaging, specific chemical additives and molecular binding and diffusion of drugs and excipients.

2. Hydrolysis [49, 50]

The ester and beta-lactam are the chemical bonds most likely to hydrolyze in the presence For example, the acetyl ester in aspirin hydrolyzes to acetic acid and salicylic acid in the presence of, but in a dry environment, the hydrolysis of aspirin is negligible. The rate of hydrolysis of aspirin is proportional to the pressure of the vapor in the environment.

3. Epimerization [49, 50]

When the dissolved drug is exposed to a midrange pH value (greater than 3), this reaction occurs rapidly and leads to an example of the spatial arrangement of the dimethylamino groups of the family of tetracyclines.

4. Decarboxylation [49, 50]

Some dissolved carboxylic acids, such as p-aminosalicylic acid, lose carbon dioxide from the carboxyl group when heated. The pharmacological effect of the resulting product is reduced.

5. Dehydration [49, 50]

Dehydration is formed by acid catalyzed dehydration, a product that lacks antibacterial activity and causes toxicity.

6. Oxidation [49, 50]

Oxidation The most likely molecular structure of to be oxidized is a hydroxyl group directly attached to aromatic rings, conjugated dienes, heterocyclic aromatic rings, derivatives of nitroso and nitrite, and aldehydes. The visual recognition of oxidation, for example, the change from colorless adrenaline to its amber product may not be visible in certain dilutions or in certain eyes.

7. Photochemical decomposition [49]

Mainly exposure to ultraviolet radiation will cause the oxidation (photo oxidation) and cleavage (photolysis) of covalent bonds. For example, nifedipine riboflavin is very prone to photooxidation.

8. Ionic strength[49, 50]

The influence of the total concentration of dissolved electrolyte on the rate of the hydrolysis reaction comes from the influence of ionic strength on the attraction between ions. The high ionic strength of inorganic salts can also reduce the solubility of some other drugs.

9. The effect of pH [49, 50]

The degradation of many drugs in solution accelerates or decelerates exponentially as the pH increases or decreases within a certain pH range. The drug solution or suspension may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes pH, it will degrade within minutes or days. A single unit change in pH from 4 to 3 or from 8 to 9 can reduce drug stability by a factor of 10 or more.

10. Inter ionic compatibility [49, 50]

Compatibility between ions the compatibility or solubility of oppositely charged ions depends mainly on the number of charges per ion and the molecular size of the ion.

11. Solid state stability [49, 50]

Solid state reaction is relatively slow, so solid state drug stability rarely attracts attention. The rate of degradation of dry solids is generally characterized by first- kinetics or S-shaped curves. Therefore, a solid drug with a lower melting point temperature should not be combined with other chemicals that will form a eutectic mixture.

12. Temperature [50]

Generally speaking, for every 100 ° C increase in temperature, the rate of the chemical reaction increases exponentially. This relationship has been observed in almost all drug hydrolysis reactions and in some drug oxidation reactions. The actual rate increase factor depends on the activation energy of the particular reaction. Activation energy is a function of the specific reaction bond and drug formulation (eg, solvent, pH, additives). At controlled room

temperature, the shelf life of the drug should be reduced to one quarter to one.

13. Microbiological stability [51]

In the past 15 years, it is relatively common to pay attention to the microbiological status of drugs only when they are used for parenteral or ophthalmic administration. Now the situation has changed.

Although we don't want all medical products to be sterile (that is, completely free of all life forms, including plants and spores), we are concerned about the microbiological status of any drug delivery system. First, the microorganisms present in the product can multiply during manufacturing, thereby increasing the number of living organisms. Second, if the integrity of the packaging is compromised during distribution or storage, the microbiological status of the product may be compromised due to the growth of microorganisms. In order to reduce or eliminate the first type of microbial problems, attention should be paid to the quality of raw materials and the nature of production facilities and their operations. Some raw materials that are usually microbial (pathogenic and non-pathogenic) sources are of natural origin. For example, the microbiological status of raw materials such as corn starch and lecithin should be carefully monitored to eliminate pollution during the production process. Factors such as positive airflow, equipment design, employee training, and clear SOPs all come into play.

Conclusion

The stability test for herbal products with a known chemical composition is the same as for chemically defined API, but the main herbal products are complex in nature. The main research on herbal and chemically determined products is the same. The specific characteristics of herbal medicines are as follows:

- Two batches of raw materials and three batches of drugs
- No three-month test points for drugs at 30 ° C / 65% RH
- Materials Herbal raw materials are only at 25 ° C / 60% RH, No need for intermediate/accelerated tests
- Selection of analytical methods, a combination of methods and fingerprints for labeling substances from extracts "quantitative" and "other" Instead of stated values, such as the percentage of standardized extracts and chemical APIs,
- Requirements for ongoing stability studies.

References

1. World Health Organization. Quality assurance of pharmaceuticals: a compendium of guidelines and related materials; World Health Organization, 1997, 1.
2. Silva J, Fernandes AR, Baptista PV. Application of nanotechnology in drug delivery. Application of nanotechnology in drug delivery,2014:25:128-54.
3. World Health Organization, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.
4. Fan TP, Deal G, Koo HL, Rees D, Sun H, Chen S, Dou JH, Makarov VG, Pozharitskaya ON, Shikov AN, Kim YS. Future development of global regulations of Chinese herbal products. Journal of ethnopharmacology,2012:140(3):568-86.
5. Chauhan SK, Tyagi A, Singh B, Agarwal S. Accelerated stability studies of a polyherbal preparation (eazmovr) capsule. Ancient science of life,1999:18(3-4):210. 49Kim JH, Lee K, Jerng UM, Choi G. Global comparison of stability testing parameters and testing methods for finished herbal products. Evidence-Based Complementary and Alternative Medicine, 2019, 20.
6. Kim JH, Lee K, Jerng UM, Choi G. Global comparison of stability testing parameters and testing methods for finished herbal products. Evidence-Based Complementary and Alternative Medicine,2019:20:2019.
7. Kim JH, Lee K, Jerng UM, Choi G. Global comparison of stability testing parameters and testing methods for finished herbal products. Evidence-Based Complementary and Alternative Medicine, 2019, 20.
8. Zakharochkina ER, Garankina RY, Bekhorashvili NU, Lisovskaya SB, Lavrenteva LI, Chukreeva NV. The common pharmaceutical market of the Eurasian economic union: regulatory analysis. Journal of Advanced Pharmacy Education & Research|,2020:10(2):189.
9. Vinokurov E. Common Markets within the Eurasian Economic Union: Movement of Goods, Services, Labour, and Capital. InIntroduction to the Eurasian Economic Union Palgrave Macmillan, Cham, 2018, 67-107.
10. Knoess W, Wiesner J. The globalization of traditional medicines: Perspectives related to the European Union regulatory environment. Engineering,2019:5(1):22-31.
11. Kumadoh DO, Ofori-Kwakye KW. Dosage forms of herbal medicinal products and their stability considerations-an overview. J Crit Rev,2017:4(4):1-8.
12. Rahman N, Azmi SN, Wu HF. The importance of impurity analysis in pharmaceutical products: an integrated approach. Accreditation and Quality Assurance,2006:11(1):69-74.
13. World Health Organization. Regulatory situation of herbal medicines: a worldwide review.
14. Kim JH, Lee K, Jerng UM, Choi G. Global comparison of stability testing parameters and testing methods for finished herbal products. Evidence-Based Complementary and Alternative Medicine,2019:20.
15. The Federative Republic of Brazil Agência Nacional de Vigilância Sanitária. Consolidado de normas da COFID (Versão IV) Brasilia, Brazil: The Federative Republic of Brazil Agência Nacional de Vigilância Sanitária, 2013.
16. Maciel A. Medicamentos líquidos orais pediátricos contendo etanol: bases para o registro no Brasil.
17. Bardala S. Natural Health Products: The Gap between Perceptions and Reality. UBCM. 2015:11.
18. Disch L, Drewe J, Fricker G. Dissolution testing of herbal medicines: challenges and regulatory standards in Europe, the United States, Canada, and Asia. Dissolut. Technol,2017:1(24):6-12.
19. Liao S, Zhang Z, Li G, Zhou L, Jiang J, Zhang N *et al*. Chinese Herbal Formula Xuefu Zhuyu for Stable Angina (CheruSA): Study Protocol for a Multicenter Randomized Controlled Trial. Evidence-Based Complementary and Alternative Medicine,2020:31:2020.

20. Jin LU, Fei YA, Fu-dong KE. Stability of salicylic acid collodiun. Anhui Medical and Pharmaceutical Journal, 2012, 10.
21. Alostad AH, Steinke DT, Schafheutle EI. Herbal medicine classification: policy recommendations. Frontiers in medicine,2020:11:7:31.
22. Fung VS. Integrating traditional Chinese (herbal) medicines into risk based regulation-With focus on non-clinical requirements to demonstrate safety. Journal of Traditional Chinese Medical Sciences,2020:7(2):88- 94.
23. World Health Organization. Experts' Consultation Meeting on Regional Strategy for Traditional Medicine in the Western Pacific Region, Hong Kong Special Administrative Region (China) 18-19 November 2010: report. Manila: WHO Regional Office for the Western Pacific, 2010.
24. Kim JH, Lee K, Jerng UM, Choi G. Global comparison of stability testing parameters and testing methods for finished herbal products. Evidence-Based Complementary and Alternative Medicine, 2019, 20.
25. Ministry of Health, Labour and Welfare. About partial revision of about the statement of application for prescription for over-the-counter products with approval criteria and the handling of attached materials. Drug Pharmacopoeia 0331, 2017, 19.
26. Ministry of Health, Labour and Welfare. About revision of stability test guidelines. Medical Review. 20030603001
27. Mokaya EG. A Retrospective Review of Pharmaceutical Product Dossiers Submitted at the Pharmacy and Poisons Board Between 2010 and, 2014. (Doctoral dissertation, University of Nairobi).
28. Code MF. Ministry of Food and Drug safety. Republic of Korea, 2010.
29. Republic of Korea Ministry of Food and Drug Safety. Stability Test Standards for Medicines, Republic of Korea Ministry of Food and Drug Safety, 2014, 59.
30. Zarsuelo MA, Zordilla ZD, Anacio DB. Review of regulatory policies on and benefits of herbal medicine in the Philippines. Acta Medica Philippina,2018:28:52(5).
31. Sharma S. Current status of herbal product: regulatory overview. Journal of pharmacy & bioallied sciences,2015:7(4):293.
32. Sarhan N. Cultural Sensitivity and Global Pharmacy Engagement in the Arab World. American Journal of Pharmaceutical Education,2019:20:83(4):619-36.
33. Bansal G, Kaur I, Kaur J. Herbal health products quality through stability studies: a global regulatory concern. Applied Clinical Research, Clinical Trials and Regulatory Affairs,2017:4(1):26-35.
34. Wu C, Lee SL, Taylor C, Li J, Chan YM, Agarwal R *et al*. Scientific and regulatory approach to botanical drug development: a US FDA Perspective. Journal of natural products,2020:24;83(2):552-62.
35. Food US. Drug Administration Centre for Drug Evaluation and Research (FDA) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products–General Considerations, Office of Training and Communications, Division of Communications Management. Drug Information Branch, HFD-210, Rockville MD. 2003 Mar;20857.
36. Authority PR. Guidelines on application for registration of herbal medicines, 2008.
37. Guideline E. Stability testing: of existing active substances and related finished products. issued as CPMP. QWP/122/02, 2003.
38. Diaz DA, Lynch M, McMahon M, Oblessuc R, Colgan ST. Science and Risked-Based Stability Testing Strategies—a Test Case on the Global Implementation and Regulatory Reception. The AAPS Journal,2020:22(6):1-1.
39. Kim JH, Lee K, Jerng UM, Choi G. Global comparison of stability testing parameters and testing methods for finished herbal products. Evidence-Based Complementary and Alternative Medicine, 2019, 20.
40. Enayatifard R, Asgarirad H, Kazemi Sani B. Microbial quality of some herbal solid dosage forms. African Journal of Biotechnology,2010:9(11):1701-1705. doi: 10.5897/ajb10.1673.
41. Guimarães R, Barreira JCM, Barros L, Carvalho AM, Ferreira ICFR. Effects of oral dosage form and storage period on the antioxidant properties of four species used in traditional herbal medicine. Phytotherapy Research,2011:25(4):484-492. doi: 10.1002/ptr.3284.
42. Kim HJ, Jang HN, Bae JY, Park SN. A study on the stability of the cream containing Glycyrrhiza uralensis extract. Journal of the Society of Cosmetic Scientists of Korea,2013:39(2):117-125. doi: 10.15230/scsk.2013.39.2.117.
43. Pushpalatha H, Shyam R, Sundaram R, Pramod K. Pasteurization as a tool to control the bio-burden in solid herbal dosage forms: a pilot study of formulating Ashoka tablets with an industrial perspective. Journal of Advanced Pharmaceutical Technology & Research,2014:5(4):191-195. doi: 10.4103/2231-4040.143039.
44. Winfield AJ, Richards RME. Pharmaceutical practice. 3rd ed., Elsevier health sciences, 2003, 113.
45. Yoshioka S and Stella VJ. Stability of drug and dosage forms. Kluwer Academic publishers. New York, 2002, 139-140
46. Pandey A, Rath B, Dwivedi AK. Pharmaceutical Preformulation Studies with special emphasis on Excipients compatibility. International Journal of Pharmacy and technology,2011:3(2):1029-1048. www.ijptonline.com
47. Christopher R. Physicochemical characterization and mechanism release of theophyllin from melt extruded dosage forms based on methacrylic acid polymer. International journal of pharmaceutics. Elsevier, 2005, 301(1). www.deepdyve.com
48. Beezer AE, Gaisford S. Pharmaceutical Micro calorimetry, Applicationsto Long Term Studies. IJPSR,1999:179(2):159-165.Discovery.ucl.ac.uk
49. Walter L. The Pharmaceutical Codex-Principles and Practice of Pharmaceutics. 12thed. Great Britain: The pharmaceutical Press, 1994, 277-288.
50. Chauhan SK, Tyagi A, Singh B, Agarwal S. Accelerated stability studies of a polyherbal preparation (eazmovr) capsule. Ancient science of life,1999:18(3-4):210.
51. Kim JH, Lee K, Jerng UM, Choi G. Global comparison of stability testing parameters and testing methods for

finished herbal products. Evidence-Based Complementary and Alternative Medicine,2019:20:2019.