

Review Article

**DOSAGE FORMS OF HERBAL MEDICINAL PRODUCTS AND THEIR STABILITY
CONSIDERATIONS-AN OVERVIEW**

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ABSTRACT

There has been an upsurge in the use of herbal medicinal products across both developing and advanced countries. Finished herbal products are presented in various dosage forms such as decoctions, herbal powders, alcoholic beverages, capsules, tablets, ointments and creams. The growing demand for herbal medicinal products across the world has resulted in the large scale manufacture of these products. Large scale production leads to longer storage periods which could lead to deterioration of products, thereby compromise product quality with adverse consequences on patient safety. Stability studies on herbal products have become necessary to help determine the shelf-life and enhance product quality at all times during storage periods and usage. Appropriate guidelines for stability testing of finished herbal products provides manufacturers, regulatory authorities and research institutions with a harmonized system for stability testing. This paper presents an overview of the various herbal dosage forms commonly available and their stability considerations. This information will help in the production of safe, stable and efficacious herbal medicinal products for use.

Keywords: Herbal medicines, Herbal dosage forms, Finished herbal products, Stability testing, Shelf-life, Storage temperature

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INTRODUCTION

Over the last three decades, there has been a huge increase in use of herbal products across the world. About 80% of the world's population, especially those in developing countries, uses herbal medicines as part of their primary health care needs [1, 2]. In Ghana, it has been estimated that 70% of the population use herbal medicinal products either alone or in combination with allopathic medicines for their health needs [3]. Herbal products may be defined as plants, parts of plants or extracts from plants that are used in healthcare or in combating the disease. To avoid confusion with culinary herbs, herbs and plant extracts that have some association with medical uses (prevention and treatment of diseases) are referred to as 'herbal medicinal products' (HMPs) [4]. Many of the plant species currently being used have been used for centuries in a limited part of the world but the increase in global travel and communications has resulted in many of these now being used worldwide [5]. Herbs and plants can be processed and used in different ways and forms, and they include the whole herb, teas, syrups, essential oils, ointments, liniments, capsules, and tablets that contain a ground or powdered form of a raw herb or its dried extract.

Commonly-available herbal dosage forms include decoctions, herbal teas, tinctures, glycerites, oxymels, and herbal soaps, herbal tablets, herbal capsules, herbal creams and ointments. Plants and herb extracts vary in the solvent used for extraction, temperature, and extraction time, and include alcoholic extracts, vinegars, hot water extracts, long-term boiled extract of roots or bark (decoctions), and cold infusion of plants [6]. The growing demand for herbal medicinal products has made large scale manufacture of these products a routine. Large scale production may result in longer storage times and possible product deterioration. Stability studies are useful in the determination of product shelf-life and enhancement of product quality [4]. Stability studies may involve physical or sensory tests, microbiological tests and chemical or chromatographic/spectral tests. Determination of the chemical stability of a herbal preparation is very challenging due to the fact that a plant extract may contain many different compounds. Additionally, plant enzymes such as esterases, glycosidases or oxidases plays a prominent role in the decomposition of secondary plant metabolites [7]. This article provides an overview of the various herbal dosage forms currently available and their stability considerations.

Dosage forms of herbal medicinal products

Dosage forms are the means by which drug molecules or plant parts are delivered to sites of action within the body. The routes for which herbal dosage forms may be administered include oral, rectal, topical, parenteral, respiratory, nasal, ophthalmic and otic [8]. Categorization of finished herbal products into dosage forms will help to define specific protocols for quality control and stability testing. Herbal medicinal products may be defined as finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations [9, 10]. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant materials combined with chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines [9]. Finished herbal products or herbal drug preparations are varied and various solvents may be used for their extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates [11].

Decoctions

Decoctions are made by boiling the herb in water for a period of time to extract soluble constituents [12]. The water decoction of a mixture of 2-12 herbal materials is the commonest traditional herbal dosage form [13]. Decoctions are normally suitable for hard plant materials such as barks and roots and may also be prepared from herbs with sparingly soluble constituents [14]. Decoctions are normally intended for immediate use, ideally within a 24-hour period, with about a 72-hour maximum limit if stored in a very cool place [12]. Excipients such as preservatives may be used in decoctions to prevent spoilage if long term storage is desired [15]. In this case, the stability of the preparation should be conducted to determine the shelf-life of the product at a particular storage condition. Decoctions may be sweetened using a syrup or honey [16]. Sijunzi decoction, a Chinese herbal remedy consists of *Panax ginseng*, *Poria cocos*, *Attractylodes macrocephala* and *Glycyrrhiza uralensis*. A high-performance liquid

chromatography tandem mass spectrometry (LC/MSⁿ) analysis of three active compounds ginsenoside (from *P. ginseng*) and flavonoid and triterpenoid (from *G. uralensis*) in both Sijunzi decoction and the single herb extracts was conducted. The concentration ratios of major active components found in the individual herbs were different from those in the decoction indicating the influence of the decocting process in the difference in the amount of active components [17]. The decoction extract of *Cassia fistula* pod pulp was chemically stable (rhein content) after 6 mo of storage under accelerated (40 °C±2 °C/75% RH±5% RH and real time storage (30 °C±2 °C/75% RH±5% RH) conditions. However, the anti dermatophyte activity of the decoction extract was very low compared with the hydrolysed mixture [18].

Tinctures

Tinctures are normally alcohol and water extracts of plant materials. Many plant constituents dissolve more easily in a mixture of alcohol and water than in pure water [19]. The preparation of tinctures by maceration of herbal parts in water-ethanol solutions results in the extraction of many structurally diverse compounds with varying polarities. The wide chemical diversity of the chemical constituent's demands quality control analytical tools optimized for the detection of single chemical compounds or a specific group of compounds [20]. Both NMR and MS have been successfully used to obtain a metabolic fingerprint to distinguish between different commercial tinctures, assess batch to batch homogeneity and evaluate the product degradation after the expiry date of the batch. There is the added advantage of the alcohol in a tincture being a preservative, allowing the extract to be kept for several years. The alcohol content of the finished extract needs to be at least 20 %v/v to adequately preserve it. Most commercially produced tinctures have a minimum alcohol content of 25 % v/v.

An alcohol content of 25 %v/v is recommended for water-soluble constituents like tannins, mucilage and certain flavonoids and some saponins, while an alcohol concentration of 45-60 %v/v is required for alkaloids, essential oils, some glycosides and most saponins, and 90 % v/v alcohol for resins and oleoresins [21]. The use of the right ethanol concentration is important in maximizing the quality of the herbal preparations [22]. When kept properly, most tinctures have a shelf life of around five years [23]. However, the shelf-lives of Passionflower (60 % v/v) and milk-thistle (60 % v/v) tinctures used in phytotherapy was found to be 6 mo and 3 mo, respectively, at 25 °C, due to the low thermal stability of the constituents determined from accelerated and long term testing [24]. Improperly stored samples of Strong Iodine Tincture which had been subject to household use for long periods showed an iodine content much higher than that permitted by the official pharmacopoeia [25]. The principal change during storage of tinctures of *Cannabis sativa* L. is the decarboxylation of Δ^9 -tetrahydrocannabinolic acid A (THCA) to Δ^9 -tetrahydrocannabinol (THC). This occurred after 15 mo storage in the 'fridge' and was comparable to 3 mo storage on the 'shelf' [26].

Herbal glycerites

Glycerites are made like tinctures but in this instance, glycerine is used in the extraction process instead of a mixture of alcohol and water. A glycerite will keep well as long as the concentration of glycerine is at least 50 % to 60 % in the finished product. The shelf-life is only about six months to two years. Glycerine should not be the solvent of choice for herbs that contain resins and gums; alcohol is needed to properly extract the active constituents of these herbs. Glycerites should be refrigerated for best effects [19]. Glycerine is a good preservative for fresh plant juices, in which half fresh plant juice and half glycerine are mixed, as it keeps the juice green and in suspension better than alcohol. This sort of preparation is called a succus. Glycerine is particularly good in making medicines for children, and for soothing preparations intended for the throat and digestive tract, or coughs [23]. Glycerites are normally less potent than alcoholic extracts and have a shorter shelf life.

Herbal alcoholic beverages (bitters/wines)

Herbal alcoholic beverages are normally ethanolic or hydroethanolic extracts of herbal materials [27]. Herbal beverages in the form of spirits and liquors are widely used in Africa, as well as the Southeast

European and Mediterranean regions as part of the local gastronomy [28]. They are normally meant for oral use as a beverage. The herbal material present in the product confers a certain degree of medicinal effect depending on the type and quantity used in the preparation [12]. In addition, the presence of the alcohol in the preparation normally confers a preservative effect on the product thereby prolonging the shelf-life compared to decoctions and infusions [29]. The antioxidant, antibacterial and antifungal activity, as well as the total phenolic and flavonoid compounds present in an herbal liqueur, were established to be dependent on storage conditions and duration [30]. The titrable acidity, pH and percentage alcohol content of pasteurized, noncarbonated, alcoholic orange juice beverage remained constant during storage at 4, 25 and 40 ° C for 14 w. However, the accumulation of furfural and the darkening of the alcoholic beverage during storage was indicative of the degradation of ascorbic acid in the product [31].

Oxymels

An oxymel is a specialized sweet and sour herbal honey preparation, a sweet honey mixed with a little sour vinegar. This combination may be used as a carrier for herbal infusions, decoctions, concentrates, tinctures, and other herbal extracts. Oxymels are used as a gargle or as a vehicle for intense herbal aids such as Garlic, Cayenne, and Lobelia [12]. The stability of oxymels may depend on the content of honey, vinegar as well as the preparation for which it is being used as a carrier [19].

Herbal capsules

Capsules are solid dosage forms containing drug and usually, appropriate filler (s) enclosed in a gelatin container [32]. Capsules may be available in hard gelatin for dry powdered herbal ingredients or granules [33], or soft gelatin shells for herbal oils and for herbal ingredients that are dissolved or suspended in oil. The gelatin shell readily ruptures and dissolves following oral administration. Drugs are normally more readily released from capsules compared to tablets [16]. Capsules may help mask the unpleasant taste of its contents and uniformity of dosage can be relatively readily achieved [8]. Herbal capsules normally consist of hard shelled gelatin capsules with the plant material finely milled and sifted and filled into shell or extracts of the herbal material(s) with appropriate excipients such as fillers [34]. The stability of herbal capsule preparations is relatively better when compared to aqueous preparations such as decoctions and infusions. Stability and shelf life of capsule preparations should be determined to provide appropriate instructions for storage of the product [8]. An accelerated stability study of herbal capsules indicated for immunomodulation and stress in India found the change in quantifiable active components to be within 90% of the initial amount showing the stability of the product at room temperature for 2 y [35]. Herbal capsules filled with pellets showed a uniform and stable release of phenolic compounds in various long-term storage conditions, indicating that the method of preparation of dry herbal extracts affects the stability of the active ingredients [36]. The carotene content of most pilot batches of soft gelatin capsules containing thick extracts of pine needles during long-term (3-24 mo) and accelerated (3-12 mo) stability studies at 25 °C±2 °C/60%±5% RH and 30 °C±2 °C/65%±5% RH was found to be satisfactory (≥30 mg%) [37].

Herbal tablets

A tablet is a hard, compressed medication in round, oval or square shape [32]. The excipients or formulation additives may include: binders, glidants (flow aids) and lubricants to ensure efficient tableting; disintegrants to ensure that the tablet breaks up in the gastrointestinal tract; sweeteners or flavours to mask the taste of bad-tasting active ingredients; and pigments to make uncoated tablets visually attractive [8, 16]. A coating may be applied to a tablet to: hide or mask the taste of the tablet's components; make the tablet smoother and easier to swallow; protect drug from the acid secretions of the stomach; and make it more resistant to environmental factors for stability purposes and extend its shelf life [8, 32].

Herbal tablets are normally designed for oral use with various herbal materials incorporated for a particular therapeutic effect

using excipients [38]. Like the herbal capsules, incorporation of the herbal material may be done with the finely powdered and sifted plant material or extracts from the plant materials using various solvents which are suitable for oral use [14, 16]. The stability of herbal tablets should be determined as the shelf life of the tablet is affected by storage conditions. Herbal tablets containing *Rhodiola rosea* L. extract were determined to be stable during six months storage at 25 °C/60% RH but the tablets failed the stability test at 40 °C/75% RH due to decreased hardness [39].

Herbal ointments

Ointments are semi-solid, greasy preparations for application to the skin, rectum or nasal mucosa. The base is usually anhydrous (hydrophobic) and immiscible with skin secretions [32]. Ointments may be used as emollients or to apply suspended or dissolved medicaments to the skin [8]. Herbal ointments normally have the plant material(s) either in finely sifted or extracted form incorporated into the base [40]. Herbal Ointments should not be used for deep wounds [19]. Ointments are relatively stable when compared with other liquid dosage forms [8]. However, the presence of herbal materials in an herbal ointment may lead to quick deterioration of the product. The stability of herbal ointments is necessary to provide appropriate labelling instructions for storage and shelf-life [41]. The chemical stability of an ointment containing herbal tinctures of calendula and arnica for the treatment of haemorrhoids was determined using a stability-indicating thin-layer chromatography technique. The shelf-life was determined to be one month and two months at 25 °C±2 °C/60% RH and 5 °C±3 °C, when protected from light, respectively [41].

Herbal balms

These may be classified as ointments meant for massage into the skin for relief of body aches and pains. They normally contain herbal materials which provide a rubefacient effect on the skin and by so doing cause relief of pain [42]. The stability of herbal balms may be compared to that of herbal ointments since the bases for preparation are similar. The difference arises in the type of herbal material being used to exert a particular effect [16].

Herbal creams

Creams are semi-solid emulsions that are mixtures of oil and water (hydrophilic) [32]. Herbal creams normally contain the herbal material in either finely sifted form or incorporated as an extract. Creams normally contain antimicrobial preservatives due to the presence of water in the base and may have a relatively shorter shelf life compared to ointments [40, 42]. Some herbalists tend to confuse creams and ointments. Herbal creams are those which have a hydrophilic base. If the base is purely hydrophobic, then the preparation must be qualified as an ointment [8].

Herbal oils

These are suspensions or solutions of herbal materials in an oily vehicle. Infused oils are often called macerated oils, and should not be confused with essential oils, which are aromatic oils isolated by distilling the plant material [23]. These preparations are normally meant for external or topical use as liniments [32]. In a few cases, however, some of these preparations may be meant for oral use [23]. Herbal materials such as leaves with essential oils may normally be found incorporated in these oils [43]. The stability and shelf life of a herbal oil depends largely on the type of oil being used in the extraction process since the stability of various essential oils differs [44].

Herbal soaps

A soap is a salt of a fatty acid usually made by saponification of a fatty acid with caustic soda or a suitable base [45]. Herbal soaps have the herbal materials incorporated in the detergent base. These herbal materials normally have an antifungal and antibacterial effect on the skin and helps in cleansing of the skin [46]. Herbal soaps are normally meant for microbial skin conditions such as dandruff, eczema, ringworm and boils [47]. Soaps have a relatively longer shelf-life when preservatives or antioxidants are added [46].

Herbal pastes

Pharmaceutically, topical pastes are ointments which may contain as much as 50 % powder dispersed in a fatty base [32]. These pastes normally localize the action of irritant or staining materials. They are normally less greasy than ointments [8]. Herbal pastes may contain the herbal ingredient dissolved or dispersed in a base (fatty base if it is meant for topical use or a more aqueous stiff base if it is meant for oral use as is done in herbal toothpaste) [40]. Herbal oral pastes should contain only herbal materials that are safe for oral use [48]. The stability of an herbal paste depends on the type of base used as well as the nature of the herbal material incorporated [40, 48].

Herbal teas

These are preparations meant for infusion or preparation to be taken as tea. Prepared infusions should be taken immediately after preparation since they do not store well due to the use of water in the extraction process [49]. They normally come as tea bags for hot infusion [23] or as powdered herbal materials (normally pulverized leaves) for boiling in hot water for a few minutes before straining and drinking as tea [50]. The stability of the powdered plant material used in the preparation depends on the type and nature of the herbal material as well the moisture content of the powder in the bags and packaging. The shelf life also depends on the extent the herbs have been crushed and storage conditions. Teas stored in airtight containers may last for up to a year whilst those stored in tea bags may last for a shorter period.

Herbal powders

These are preparations that come as powdered herbal materials meant for direct use or by incorporation into foods, beverages for drinking [23], insufflations [51], and wounds [52]. They may be finely sifted herbal materials from various parts of plants meant for a particular therapeutic effect [50]. Like the herbal teas, the stability of the powder depends on the type and nature of the herbal material as well as the moisture content of the powder in the bags and packaging. The dried herb and extract of the root of *Nauclea latifolia* S. M., an antimalarial plant found growing in Africa, was found to be stable under tropical room temperature conditions for over one year in sealed glass containers [53].

Herbal suppositories

Suppositories are solid dosage forms meant for insertion into the rectum. They are prepared by moulding with the incorporation of the medicinal agent into a suitable base which should melt or dissolve at body temperature to exert the therapeutic effect. Suppositories may be used for local or systemic effects [8, 32]. Herbal suppositories are normally prepared by mixing powdered and finely sited herbs or extracts with cocoa butter as the base [12]. They are normally used to soothe inflamed surfaces of the nasal mucosa and aid the healing process; reduce swollen membranes and overcome pus filled discharge or to act as a laxative to treat constipation [54]. The stability of suppositories, amongst other factors, depends on the temperature of storage and packaging. They are relatively stable at low temperatures of storage. Unless other information on stability is provided from a study, a shelf life of one month may be appropriate [32].

Herbal pessaries

Pessaries are similar to suppositories but are meant for insertion into the vagina for local or systemic effects [8, 32]. Herbal pessaries may also be made using a glycerated-gelatin base which dissolves at body temperature to release herbal ingredients for the desired local or systemic effects [55]. The stability of pessaries may be compared to that of suppositories [32].

Herbal poultices and plasters

Poultices are made by mashing fresh herbs, wrapping in a gauze and applied to an affected area of the skin after the temperature is suitable for application [19, 54]. Poultices may be used externally to relax muscles or to ease minor skin eruptions, poison ivy, insect bites, superficial wounds, and inflammation. Since they are normally made from fresh herbs, they should be used immediately and cannot be stored [16].

Herbal compresses and fomentations

Compresses are normally prepared from an infusion or tincture in hot or cold water by soaking a cotton cloth or gauze. Compresses may be used externally and can be either warm or cold. Cold compresses reduce inflammation and help to relieve pain [12]. They are usually used in the treatment of sprains, contusions, strains, inflammation, headaches, and insect bites. Warm compresses are used to increase circulation to an area and to allow muscles, tendons, and ligaments to stretch [19].

Herbal liniments

Liniments are for external use for aches and pains. Herbal liniments are normally used as warming massage mediums to relieve soreness in muscles and ligaments [16]. Heat-inducing herbs such as cayenne are normally used in the preparation of liniments together with alcohol for extraction or a mixture of alcohol and/or oil. Liniments should not be used on cuts or broken skin [54]. The stability of liniments is similar to that of herbal oils (if oil was used as a vehicle in the preparation process).

Herbal baths

These are normally prepared by the addition of fresh or dried herbs to bath water. An infusion or tincture of an herbal material may also be added to bath water. Herbs normally used are aromatic in nature and may contain essential oils that may help in relaxation or stress relieve [19].

Herbal lozenges

A number of formulations have been developed to pleasantly and slowly release medicinal properties in the mouth [54]. Lozenges may be prepared by the use of the powdered herbs together with excipients such as sugar and honey to provide the sweet taste, gums (Acacia and tragacanth) and the white of an egg in some instances [16]. The lozenges normally may be used to soothe soreness in the throat as well as help in the treatment of throat infections. Lozenges normally do not contain disintegrating agents. The shelf life of lozenges may be compared to that of tablets but should be determined using an appropriate stability protocol [8].

Stability studies of finished herbal products

The World Health Organization (WHO) recommends that stability data be provided to support the shelf-life proposed for finished herbal products under the specified conditions of storage [9]. The shelf-life of a product is the period during which it remains within acceptable chemical, physical and microbiological stability if stored correctly [55]. The expiry date is represented on the product to indicate the end of the shelf life [57]. Finished herbal products are unique compared to synthetic products due to the varied nature of constituents that may be present even in an herbal product with only one herbal ingredient [35]. It is often not feasible to determine the stability of each active ingredient [58]. The herbal material, in its entirety, is normally regarded as the active ingredient and a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient [59]. Constituents (markers) for stability determination in herbal products may be categorized as; chemical, analytical and active markers [9, 10]. Chemical markers may be defined as chemically defined constituents or groups of constituents of an herbal medicinal product which are of interest for quality control purposes regardless of whether they possess any therapeutic activity [10]. The quantity of a chemical marker can be an indicator of the quality of an herbal medicine. Chemical markers may be used to evaluate product quality and stability over time and determine the recommended shelf life [60]. Analytical markers are the constituents or groups of constituents that serve solely for analytical purposes [57]. Active markers are the constituents or groups of constituents that contribute to therapeutic activities [9, 10, 38].

Stability determination of herbal medicinal products

The principle of a stability study is to provide evidence that an active substance or finished product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The importance of stability testing is to; evaluate the

efficacy of a drug; provide background information during the development phase of the product or drug discovery; develop suitable packaging information for quality, strength, purity and integrity of a product during its shelf-life [9, 38, 61].

Mechanisms that may indicate a change in stability include; loss of activity; change in concentration of active component; alteration in bioavailability of product; loss of content uniformity; loss of elegance; formation of toxic degradation products and loss of packaging integrity. It is difficult to develop analytical methods for herbal medicines due to the presence of phytochemical constituents which may be susceptible to enzymatic breakdown of these plant metabolites. Predictable chemical changes in herbal products includes; hydrolysis; oxidation (especially in fixed, volatile and essential oils); racemization; geometric isomerization and poly-merization [61].

General methods for stability testing

The stability of herbal medicinal products may be determined based on physical and sensory tests, microbial tests and chromatographic/spectral tests.

Physical and sensory methods

Herbal products, like pharmaceutical products, usually undergo physical changes during storage. These changes though not usually quantitative in nature may be used as a guide to check if the products are deteriorating. These include evaluation of changes in parameters such as colour, taste, odour, clarity, specific gravity, total solid residue, viscosity, the moisture content of powders, dissolution and disintegration tests for capsules and tablets. It must be noted that some of these methods of assessment such as taste and odour should be carried out only if they do not affect the safety of the personnel involved [8, 9, 10, 38].

Microbial tests

Microbial contamination or load tests and preservative efficacy or challenge tests (where preservatives are used) of finished herbal products are essential in the determination of stability and shelf life of the product [62]. Key factors affecting the efficacy of the antimicrobial preservative added are the active ingredient, excipients, storage conditions, the container and its closure. The British Pharmacopoeia states that for a product "it shall be demonstrated that the antimicrobial activity of the preparation as such or if necessary, with the addition of a suitable preservative or preservatives provides adequate protection from adverse effects that may arise from microbial contamination or proliferation during storage and use of the preparation" [63]. Analyses of such parameters with time allows the tracing of stability of the product and subsequent prediction or estimation of shelf-life. These tests should be done according to Pharmacopoeia methods (British Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia), WHO methods, or any other internationally recognized methods [64]. The microbial tests should involve: Total viable aerobic plate count; contaminating fungus (yeast and mould); Salmonella spp.; Escherichia coli and Staphylococcus aureus. Table 1 shows the British Pharmacopoeia acceptance criteria for microbiological testing of herbal products.

Criteria 'A' represents herbal medicinal products containing herbal drugs, with or without excipients, intended for the preparation of infusions and decoctions using boiling water (for example herbal teas, with or without added flavourings).

'B' represents herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where the method of processing (for example, extraction) or, where appropriate, in the case of herbal drugs, of pre-treatment reduces the levels of organisms to below those stated for this category).

'C' represents herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where it can be demonstrated that the method of processing (for example, extraction with low strength ethanol or water that is not boiling or low-temperature concentration) or, in the case of herbal drugs, of pre-treatment, would not reduce the level of organisms sufficiently to reach the criteria required under B.

Table 1: Acceptance criteria for microbiological tests

Microbiological quality	Acceptance criteria*		
	A	B	C
Total aerobic microbial count	Not more than 5x10 ⁷ CFU per g or per ml	Not more than 5 x10 ⁴ CFU per g or per ml	Not more than 5 x 10 ⁵ CFU per g or per ml
Total yeast and mould count	Not more than 5x10 ⁵ CFU per g or per ml	Not more than 5 x10 ² CFU per g or per ml	Not more than 5 x 10 ⁴ CFU per g or per ml
Bile-tolerant Gram negative bacteria	Not more than 10 ² CFU per g or per ml	Not more than 10 ² CFU per g or per ml	Not more than 5 x 10 ⁴ CFU per g or per ml
<i>Salmonella</i> spp.	Absent in 10 g or 10 ml	Absent in 25g or 25 ml	Absent in 25 g or 25 ml
<i>Escherichia coli</i>	Absent in 1 g or 1 ml	Absent in 1 g or 1 ml	Absent in 1 g or 1 ml

*British Pharmacopoeia [65]

Chromatography and spectral methods

Chromatographic methods used to assess the chemical stability of herbal products include thin layer chromatography (TLC), high (ultra) performance liquid chromatography (HPLC, UPLC), high performance-thin layer chromatography (HP-TLC), gas liquid chromatography (GLC), etc., while spectral methods used include ultraviolet-visible (UV-VIS) spectroscopy, infrared (IR) spectroscopy, nuclear magnetic resonance (NMR) and mass spectroscopy (MS). These techniques allow tracing of changes which may occur during storage of a complex mixture of biologically active substances contained in herbal materials. Comparisons of appropriate characteristic/fingerprint chromatograms allow the determination of the stability of identified active ingredients (if any) and other substances present in the finished herbal product (which may appear as markers) [10, 38, 66].

Assessment of safety parameters

The acute toxicity of the herbal medicinal product may be assessed at the beginning and end of the stability study for products used in

the treatment of acute conditions. Subchronic and chronic toxicity studies may also be done for products meant for the treatment of chronic conditions [27, 67]. However, due to the time is taken in doing such studies, they should be determined on a case by case basis depending on the nature of the herbal medicinal product involved with consideration to other already determined parameters. These tests if not possible for inclusion in a stability study should be used as quality control measures or tests [64, 68].

Conditions for stability testing of products

The shelf-life of a product depends on its storage temperature and also on humidity. These conditions may vary from country to country. Four climatic zones have been defined in order to enhance determination of stability testing conditions for products (table 2). The definition is based on observed temperatures and relative humidity, both inside and outside rooms, from which mean temperatures and average humidity values are calculated [8]. The general conditions for testing products in various containers and storage temperatures are shown in tables 3-6.

Table 2: Temperature and humidity distribution in climatic zones

Climatic zone	Climate	Mean temperature	Average humidity
I	Temperate	21	60
II	Subtropical	26	65
III	Tropical (dry)	31	60
IV	Tropical (wet)	31	70

Aulton [8], I-Temperate climate includes Canada, New Zealand, Northern Europe, United Kingdom and Russia, II-Mediterranean and subtropical climate includes Japan, Southern Europe and the USA, III-Hot and dry climate includes Argentina, Australia, Botswana and the Middle East, IV-Hot and Humid Brazil, Ghana, Indonesia, Nicaragua, Nigeria and the Philippines

Table 3: General conditions for testing of products (impermeable containers)

Study	Storage conditions	Time points for testing	Minimum data covered at submission
Long term	25 °C±2 °C/60% RH±5% RH or 30 °C±2 °C/65% RH±5% RH	0, 3, 6, 12, 18, 24, 36, 48, 60	12 mo
Intermediate	30 °C±2 °C/65% RH±5% RH	0, 1, 3, 6	6 mo
Accelerated	40 °C±2 °C/65% RH±5% RH	0, 1, 3, 6	6 mo

Table 4: Conditions for testing of products in semipermeable containers*

Study	Storage conditions	Time points for testing	Minimum data covered at submission
Long term	25 °C±2 °C/40% RH±5% RH or 30 °C±2 °C/35% RH±5% RH	0, 3, 6, 12, 18, 24, 36, 48, 60	12 mo
Intermediate	30 °C±2 °C/35% RH±5% RH	0, 1, 3, 6	6 mo
Accelerated	40 °C±2 °C/not more than 25% RH±5% RH	0, 1, 3, 6	6 mo
Accelerated	40 °C±2 °C/75% RH±5% RH	0, 1, 3, 6	6 mo

*Alternatively for products in semipermeable containers, samples may be stored under general conditions like that of impermeable containers and water loss calculated by determining permeation coefficient or using calculated ratio of water loss

Table 5: Conditions for testing of products intended for storage in a refrigerator

Study	Storage conditions	Time points for testing	Minimum data covered at submission
Long term	5 °C±3 °C	0, 3, 6, 12, 18, 24, 36, 48, 60	12 mo
Accelerated	25 °C±2 °C/60% RH±5% RH	0, 1, 3, 6	6 mo

If significant change occurs between 3 and 6 mo at accelerated storage conditions then shelf life based on real time data should be conducted in the long term

Table 6: Conditions for testing of products intended for storage in a freezer

Study	Storage conditions	Time points for testing	Minimum data covered at submission
Long term	-20 °C±5 °C	0, 3, 6, 12, 18, 24, 36, 48, 60	12 mo

The stability study should be conducted in the container closure system in which it will be marketed [8, 10, 64, 69]. In general, "significant change" for a finished herbal product may be defined as a 10 % change in assay from its initial value with respect to the marker being used; or failure to meet the acceptance criteria for potency when using biological or immunological procedures; any degradation product exceeding its acceptance criterion; failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e. g, colour, phase separation, re-suspendibility, caking, hardness, dose delivery per actuation, pH). It should be noted that accelerated stability tests may cause some dosage forms such as ointments and creams to change form due to the relatively high temperatures to be employed. This should not be mistaken for the failure of the product to meet acceptance criteria since such changes should be expected [8, 10, 38, 70].

Evaluation of stability data

A systematic approach should be adopted in the presentation and evaluation of the stability information. This should include results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms), where appropriate [69]. The stability study should help establish the shelf life of future batches of an herbal medicine based on testing a minimum

of two or three batches. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life. Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis. The overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria. The evaluation should consider not only the assay but also the degradation products and other appropriate attributes [9, 10, 69, 70, 71, 72].

The level of selected markers and possible degradation products should also be ascertained with time in order to help determine the shelf-life of the products. Depending on the availability of equipment, selected tests such as TLC, HPLC, HPTLC, UV-Visible spectrophotometry may be used to quantify selected markers as well as determine the levels of degradation products. It is not expected that every listed test be performed at each time point. The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every listed test be included in the design of a stability protocol for a particular finished herbal product [8, 9, 10, 72]. Table 7 presents some recommended stability tests for various herbal dosage forms.

Table 7: Recommended stability tests for different herbal dosage forms

Type of dosage form	Recommended stability tests
Decoctions (oral), Glycerites, Aceterites, oxymels Tablets	Change in colour, odour, taste, formation of a precipitate, clarity, specific gravity, total solid residue, pH, viscosity, extractable, phytochemical constituents, microbial contamination, preservative efficacy/challenge tests, and toxicity/safety [14].
Capsules	Change in colour, pH, total water or solvent extractive, phytochemical constituent, dissolution (or disintegration, if justified), water content, hardness, friability, swelling, crakes and clumping (coated tablets), microbial contamination, preservative efficacy/challenge tests, toxicity/safety [14].
Alcoholic beverages, Tinctures Teas and powders	Change in colour, pH, total extractive, phytochemical constituent, brittleness, hardening or softening of shell, dissolution (or disintegration, if justified), water content, microbial contamination, preservative efficacy/challenge tests, toxicity. Clarity, pH, specific gravity, alcohol content, extractable, change in colour, odour, taste, the formation of a precipitate, total solid residue, extractable, phytochemical constituents, microbial contamination, toxicity.
Ointment, balms	Change in odour, moisture content, pH, total water extractive, formation of hard mass, caking, Phytochemical constituents, microbial contamination, and toxicity.
Oils Pastes and creams	Change in colour, odour, homogeneity, pH, consistency, grittiness, excessive bleeding, phytochemical constituents, microbial contamination, and toxicity. Rancidity, change in colour, odour, pH, phytochemical constituents, microbial contamination, toxicity
Soaps	Change in colour, odour, homogeneity, pH, consistency, grittiness, cracking, shrinking due to evaporation of water, phytochemical constituents, microbial contamination, preservative challenge tests (where preservative are used), toxicity
Suppositories and Pessaries	Change in colour, odour, homogeneity, pH, phytochemical constituents, microbial contamination, preservative challenge tests (where preservative are used), toxicity/skin sensitivity tests
	Softening, hardening or drying, dissolution

CONCLUSION

Herbal products have gained wide acceptance in both developing and advanced countries and are being produced in commercial quantities. The stability of these herbal products is of paramount importance to assure product quality, safety and efficacy. It is expected that herbal product manufacturers will apply the necessary protocols and techniques to achieve and maintain the stability of their products during manufacture, storage, transportation and usage. This will contribute to patient safety, product efficacy and enhance patient confidence in herbal products and improve compliance.

CONFLICT OF INTERESTS

The authors declare no conflict of interest regarding the publication of this paper.

REFERENCES

1. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* 2014;4:177.
2. Thakur L, Ghodasra U, Patel N, Dabhi M. Novel approaches for stability improvement in natural medicines. *Pharmacogn Rev* 2011;5:48-54.
3. Doodoo ANO, Appiah-Dankwah A, Gyansa-Lutterodt M, Duwiejua M. Safety monitoring of herbal medicines in Ghana: challenges and opportunities. *Drug Safety* 2006;29:352.
4. Mukherjee PK, Houghton PJ. Evaluation of Herbal Medicinal Products-Perspectives on quality, safety and efficacy. London, UK, Pharmaceutical Press; 2009.
5. Mukherjee PK. Evidence-Based Validation of Herbal Medicine. 1st ed. Netherlands: Elsevier; 2015.

6. Benzie IFF, Wachtel-Galor S. Herbal Medicines, Biomolecular and Clinical Aspects. 2nd ed. New York: CRC Press; 2011.
7. Gafner S, Bergeron C. The challenges of chemical stability testing of herbal extracts in finished products using state-of-the-art analytical methodologies. *Curr Pharm Anal* 2005;1:203-15.
8. Aulton ME. Aulton's pharmaceuticals-the design and manufacture of medicines. 3rd ed. London: Churchill Livingstone; 2007.
9. World Health Organization (WHO). Stability Testing of Active Substances and Pharmaceutical Products. Restricted Working document QAS/06.179; 2006. p. 10-32.
10. European Medicines Agency (EMA). Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products. EMA/HMPC/3626/2009 Committee on Herbal Medicinal Products (HMPC); 2009.
11. European Pharmacopoeia. Vol. 1. Herbal drug preparations; 2005.
12. Green J. The Herbal medicine-makers Handbook: A Home Manual. USA: Crossing Press; 2002.
13. Yi YD, Chang LM. An overview of traditional Chinese herbal formulae and a proposal of a new code system for expressing the formulae titles. *J Evidence-Based Complementary Altern Med* 2004;1:125-32.
14. Ghiware Nitin B, Gattani Surendra G, Chalikwar Shailesh S. Design, development and evaluation of oral herbal formulations of *Piper nigrum* and *Nyctanthes arbortristis*. *Int J PharmTech Res* 2010;2:171-6.
15. Bone K, Mills S. Principles and practice of phytotherapy: modern herbal medicine. 2nd ed. Elsevier Health Sciences; 2013.
16. Hoffman D. Medical Herbalism: The Science and Practice of Herbal Medicine. Vermont: Healing Arts Press; 2003.
17. Liu Y, Yang J, Cai Z. Chemical investigation on Sijunzi decoction and its two major herbs *Panax ginseng* and *Glycyrrhiza uralensis* by LC/MS/MS. *J Pharm Biomed Anal* 2006;41:1642-7.
18. Chewchinda S, Wuthi-udomlert M, Gritsanapan W. HPLC quantitative analysis of rhein and anti dermatophytid activity of cassia fistula pod pulp extracts of various storage conditions. *BioMed Res Int* 2013. <http://dx.doi.org/10.1155/2013/821295>
19. Bascom A. Incorporating Herbal Medicine into Clinical Practice. Philadelphia: F. A. Davis Company; 2002.
20. Politi M, Zloh M, Pintado ME, Castro PML, Heinrich M, Prieto JM. Direct metabolic fingerprinting of commercial herbal tinctures by nuclear magnetic resonance spectroscopy and mass spectrometry. *Phytochem Anal* 2009;20:328-34.
21. Bone K. Dosage considerations in herbal medicine Part 3. *Mediherb Professional Review*; 1993. Available from: <http://www.mediherb.com/media/276930/prno33.pdf>. [Last accessed on 25th Aug 2016]
22. Morgan M. Ethanol in medicine—a phytotherapist's perspective; 2009, p. 1-4.
23. Bruton-Seal J, Seal M. Backyard medicine-harvest and make your own herbal remedies. New York: Skyhouse Publishing; 2009.
24. Bilia AR, Bergonzi MC, Gallori S, Mazzi G, Vincieri FF. Stability of the constituents of Calendula, Milk-thistle and Passionflower tinctures by LC-DAD and LC-MS. *J Pharm Biomed Anal* 2002;30:613-24.
25. Beal GD, Walters KL, Block Jr P. Stability of iodine solutions and tinctures. *J Pharm Sci* 1947;36:203-7.
26. Peschel W. Quality control of traditional cannabis tinctures: pattern, markers, and stability. *Sci Pharm* 2016;84:567-84.
27. Ogbonnia SO, Mbaka GO, Igbokwe NH, Anyika EN, Alli P, Nwakakwa N. Antimicrobial evaluation, acute and subchronic toxicity studies of *Leone Bitters*, a Nigerian polyherbal formulation, in rodents. *Agric Biol J North Am* 2010;1:366-76.
28. Komes D, Belscak-Cvitanovic A, Horzic D, Drmic H, Skrabal S, Milicevic B. Bioactive and sensory properties of herbal spirit enriched with cocoa (*Theobroma cacao* L.) polyphenolics. *Food Bioprocess Tech* 2012;5:2908-20.
29. Buglass AJ. Handbook of alcoholic beverages: technical, analytical and nutritional aspects. Vol. 1. Wiley Publications; 2011.
30. Karabegovic IT, Vukosavljevic PV, Novakovic MM, Gorjanovic SZ, Dzamic AM, Lazic ML. Influence of the storage on bioactive compounds and sensory attributes of herbal liqueur. *Digest J Nanomaterials Biostructures* 2012;7:1587-98.
31. Rodriguez M, Sadler GD, Sims CA, Braddock RJ. Chemical changes during storage of an alcoholic orange juice beverage. *J Food Sci* 1991;56:475-9.
32. Winfield AJ, Rees AJ, Smith I. Pharmaceutical practice. London: Churchill Livingstone; 2009.
33. Bayor MT, Johnson R, Gbedema SY. The oral capsule-the most appropriate dosage form for *Croton membranaceus*. *Int J Pharm Sci Res* 2011;2:55-62.
34. Johnson R, Bayor MT, Adotey J. Formulation and evaluation of *Bridelia ferruginea* and *Canthium glabriflorum* herbal capsules. *J Herbal Med Plants* 2010;1:18-22.
35. Bankoti K, Rana MS, Bharadwaj MK. Accelerated stability study of herbal capsules. *IOSR J Pharm* 2012;2:1-6.
36. Pranskuniene Z, Bernatoniene J, Kalveniene Z, Masteikova R, Mekas T, Velziene S, et al. New formula herbal pellets demonstrate a uniform and stable release of the active ingredients *in vitro*. *Acta Pol Pharm* 2013;70:727-36.
37. Daberte I, Barene I, Rubens J, Daugavietis M, Sazhenova N. Stability of soft gelatin capsules containing thick extract of pine needles. *Medicina (Kaunas)* 2011;47(Suppl 2):71-7.
38. Mishra US, Murthy PN, Sahoo SK, Sahu KC. Formulation and evaluation of herbal tablet containing methanolic extract of *Calophyllum inophyllum*. *Int J Pharm* 2012;2:181-6.
39. Kucinskaite A, Sawicki W, Briedis V, Sznitowska M. Fast disintegrating tablets containing *Rhodiola rosea* L. Extract *Acta Pol Pharm* 2007;64:63-7.
40. Al-Achi A. An introduction to botanical medicines: History, Science, Uses and Dangers. Connecticut: Praegers Publishers; 2008.
41. Zdoryk OA, Khokhlova KO, Georgiyants VA, Vyshnevskaya LI. Investigation of physical and chemical stability of ointment with herbals. *Int J Pharm Compd* 2014;18:248-52.
42. Vincent WM. The complete guide to growing healing and medicinal herbs: Everything you need to know simply explained. Atlantic publishing company; 2011.
43. Russell ND, LW Sneyd LW. Healthy solutions: a guide to simple healing and healthy wisdom. Basic Health Publications Inc. USA; 2006.
44. Turek C, Stintzing FC. Stability of essential oils: a review. *Compr Rev Food Sci Food Saf* 2013;12:40-53.
45. Jones M. The Complete Guide to Creating Oils, Soaps, Creams, and Herbal Gels for your Mind and Body. Atlantic Publishing Company; 2011.
46. Grosso A. The Everything Soapmaking Book: Learn How to Make Soap at Home with Recipes. Massachusetts: Adams Media; 2013.
47. Panda H. Herbal soaps and detergents handbook. Natl Institute Industrial Res 2000;1:194-6.
48. Van Loveren C. Toothpastes. Amsterdam: Karger Medical and Scientific Publishers; 2013.
49. Packer L, Ong CN, Halliwell B. Herbal and Traditional Medicine, Molecular Aspects of Health. New York: Marcel Dekker; 2004.
50. Bouwman Y, Fenton-May V, Le Brun P. Practical Pharmaceuticals, An International Guideline for the Preparation, Care and Use of Medicinal Products. Netherlands: Springer; 2015.
51. Tiwari M. Ayurveda: the secrets of healing. Delhi: Motilal Banarsidass Publishers, India; 1995.
52. Castleman M. The New Healing Herbs: The Classic Guide to Nature's Best Medicines. Rodale Inc., USA; 2001.
53. Ameh S, Obodozie O, Gamaniel S, Abubakar M, Garba M. Physicochemical variables and real time stability of the herbal substance of Niprd-AM1@-an antimalarial developed from the root of *Nauclea latifolia* S. M. (Rubiaceae). *Int J Phytomed* 2010;2:332-40.
54. Page L. Linda Page's Healthy Healing: a guide to self-healing for everyone. 12th ed. Healthy healing Inc; 2004.
55. Philips N, Philips M. The Herbalist's Way: The Art and Practice of Healing with Plant Medicine. Chelsea Green Publishing; 2005.
56. Shao L, Chow SC. Drug shelf-life estimation. *Stat Sin* 2001;11:737-45.
57. Kruse SO. Stability testing of herbal medicinal products; Bridging Science to Industry. *Planta Med*; 2013. p. 79-PK15.

58. Gautam A, Kashyap SJ, Sharma PK, Garg VK, Visht S, Kumar N. Identification, evaluation and standardization of herbal drugs: a review. *Pharm Lett* 2010;2:302-15.
59. Awang DVC. Standardization of herbal medicinal products. *Acta Hort* 2004;629:112-4.
60. Bodhisattwa M, Nagori BP, Rambir S. Recent trends in herbal drugs: a review. *Int J Drug Res Tech* 2011;1:17-25.
61. Jain SK. Stability protocols for different dosage forms. Department of Pharmacy, Institute of Biomedical Education and Research, Magalayan University; 2011. Available from: <http://www.slideshare.net/sachin1409/stability-protocols-for-different-dosage-forms-by-sachin-jain>. [Last accessed on 18th Aug 2016]
62. Joshi DD. Herbal drugs and fingerprints: evidence based herbal drugs. Springer Sciences and Media; 2012.
63. Ngoc ATP. The microbiological requirements of a stability study. AMS Laboratories Pty Ltd; 2012. p. 6-15. Available from: <http://www.amslabs.com.au/WS/files/54/546be2aa-bdbe-43e3-84af-d44f9114a599.pdf> [Last accessed on 18th Aug 2016]
64. Food and Drugs Authority (FDA), Ghana. Guidelines for Registration of Herbal Medicinal Products in Ghana. FDA/HMD/GL-HB/2012/01 2013;1:5-7.
65. British Pharmacopoeia. Vol. IV. Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal products. British Pharmacopoeia Commission, MHRA, London; 2013.
66. Chhetri HP, Yogol NS, Sherchan J, Anupa KC, Mansoor S, Thapa P. Formulation and evaluation of antimicrobial herbal ointment. *Kathmandu University J Sci Eng Technol* 2010;6:102-7.
67. Lam YWF, Huang SM, Hall SD. Herbal supplements–drug interactions: scientific and regulatory perspectives. New York: CRC Press, USA; 2006.
68. Leung PC. A comprehensive guide to Chinese medicine. 2nd ed. World Scientific; 2015.
69. ICH Q1 AR2, Stability testing guidelines: stability testing of new drug substances and products. Available from: <http://www.ikev.org/haber/stabilite/kitap/29%201.1%20Stability%20Workshop%20ICH%20Q1AR2%20C.pdf>. Last accessed on 18th Aug 2016].
70. Guidelines on specifications, test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2820/00, EMEA/CVMP/815/00, current version). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003393.pdf. [Last accessed on 23rd Aug 2016].
71. Ahuja S, Scypinski S. Handbook of modern pharmaceutical analysis. 2nd ed. Academic Press; 2011.
72. Zahn M, Källberg PW, Slappendel GM, Smeenge HM. A risk-based approach to establish stability testing conditions for tropical countries. *J Pharm Sci* 2006;95:946-65.

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