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STABILITY ASPECTS OF HERBAL FORMULATION

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ABSTRACT

From the last decades the use of the herbal drug products is increased across both developing and advanced countries. Herbal medicinal products are accessible in different dosages form according to their use. Increase in the demand of herbal medicinal product around the world results in large scale production of these products. Longer storage of these products may cause the deterioration and degradation of the product and loss of the active metabolite which ultimately results in product that contain no therapeutic action or some time there is the formation of toxic metabolite and adverse effect. This may cause the hazardous affect in the patient health. Stability studies on herbal products must be carried out as it helps in identify the various physical, chemical and environmental factors that affect the stability of the products and also to determine product shelf-life or enhance product quality at all times during storage periods and usage. Number of stability testing methods are available to check various quality changes that may occur during the storage period of the product. This article gives an overview of the different herbal dosage forms that is generally available in market and various problems that comes during their stability consideration or the different chemical factors that affect the stability of the product. These all facts will help in manufacturing of safe, stable and effective product that is free from hazardous substances.

KEYWORDS: Herbal products, dosage form, instability, degradation, Stability testing.

INTRODUCTION

From the last three decades, there is increase in use of herbal product in world's different countries. About 80% of world population use herbal products according to the primary health care needs.[1,2] Herbal drugs are consider to be the safe since they are derived from the natural sources.[3] Various parts of plant or the whole plant are introduced to several treatment like extraction, distillation, purification, concentration or fermentation to get the herbal preparations.[4] It was estimated that people from the different countries are rely on the herbal products. They use herbal product alone or in combination with the allopathic medicine for their health needs.[5] Also it is believed that the herbal medicine are free from the side effect and adverse effect instead of allopathic medicine.[6] Therapeutic herbs are used to prevent and treat disease and ailment or to support health and healing.[7] Herbal drugs are used from ancient time for the health care treatment.[8] In many developed countries, people uses the herbal preparations as they have belief that it will promote the healthier living. And these preparation have the balanced and moderate approach of healing and individual can also use these preparations as home remedies and over the counter drugs.[9] As the global use of the herbal medicine are increased and these products are not only available in the drug store but also are present in the food store and the super market.[10]

It is the perception that herbal products are very safe, free from the adverse effects. It is not only false but also ambiguous. Herbal medicine are capable of producing large number of undesirable or adverse effects some of which causes the serious injury.[11,12,13] The toxicity evaluation of the poly-herbal formulation of the Yoyo "Cleanser" Bitters conducted recently.[14] was prompted by an unpublished case report of young male adult who had been taken the self medication of this polyherbal formulation and was later admitted to the hospitals on account of liver failure.[15]

There are number of causes of the adverse effect of the herbal medicines. These are divided into the two reasons "direct" and "indirect" reason.

1. **Intrinsic toxicity:** This type of the toxicity occurs by the over dose and normal therapeutic dosage of some drugs. Adverse effects caused by Ephedra, aconitum shows that herbs are also responsible to produce the toxicity in the human.

2. **External Toxicity:** Adverse effects caused by the herbal medicine is due to the contamination of the products with toxic substances.[16] and during manufacturing and extraction process of natural product , active molecules are expose to oxidation hydrolysis and the microbial attack and environmental degradation which causes the stability problems for the product.[17]

It is necessary to study the stability aspects of the herbal formulation to prevent the adverse effects of the drug and to maintain its therapeutic activity during its shelf life and storage conditions.[18]

There are some advantages and disadvantages of the herbal medicines:

Advantages

- Available at low price
- Increased the tolerance of patient
- More safe to use for long time
- Have less side effects as compare to pharmaceutical medicine
- Potency and efficiency of these products is very high.

Disadvantages

- These drugs are not able to produce the quick response in severe illness conditions.
- Standardizations of the herbal products is complex.
- There is the potential risk of self-medication.[19]

Dosages form of herbal product

Dosages form defined as the drug molecules or parts of plants that are delivered to different site of actions inside the body. There are different routes from which herbal dosage forms might be given. Those include- oral, rectal, topical, parentral, respiratory, nasal, ophthalmic and otic.[20] Assortment of finished herbal products into dosage forms will help to explain specific protocols for stability testing and quality control. These are the finished and labelled products and contain the active constituents from the aerial or subterranean and some other parts of the plant whether it is present in the crude form or formulation.[21,22]

Decoctions

These are prepared by boiling the herb in a water for a duration of time to extract soluble constituents.[23] Water decoction is combination of 2-12 herbal substances is the commonest conventional herbal dosage form.[24] Decoctions are generally appropriate for hard plant materials such as barks and roots and may also be made from herbs with sparingly soluble constituents.[25] These are normally given for the instant use, consume within a 24-hour period and about a 72hour maximum limit if stored in a very cool place.[23] To prevent the spoilage if wants long term storage is then preservatives and excipients are added in the decoctions.[26] If so, the stability of the formulation should be taken to identify the shelf-life of the commodity at a specific storage condition. Decoctions can be sweeten by using a syrup or honey.[27]

Tincture

In tincture preparations, alcohol and water are used for the extraction of the plants active chemical constituents which are not much soluble in the water or when wants to store the products for the longer period. If the plant tincture is prepared in proper manner it can last for the many years and without changing its therapeutic potency. Percentage of the alcohol play important role to identifying the half -life of the tincture. More the alcohol used, longer is the shelf life of the tincture .Some herbs active constituents are soluble in water and some are soluble in alcohol . So the amount of the alcohol and water used in preparation of the plant tincture play the special role. A "standard 4:1 tincture" means 1 part of the herb and 4 part of liquid used in the preparation.[28]

Herbal glycerite

Glycerites are prepared same as tinctures but in this case, glycerine is used in the extraction process in place of a mixture of alcohol and water. If in the finished product, concentration of the glycerine is 50% to 60% then glycerite will store for long period of time. The shelf-life is only about six months to two years. For correct extraction of the active constituents of herbs, alcohol is require. For best effect, glycerite should be refrigerated.[29] For fresh plant juices glycerine is a good preservative, in which half fresh plant juice and half glycerine are mixed, as it preserve the juice green. This kind of preparation is called a succus. Formulating medicines for children, glycerine is good and also better for soothing preparations for the throat and digestive tract, or cough.[30]

Medicated wines

These herbal products are also called tonic wines. These are used in the pleasurable way to get strengthening and tonic herbs to increase liveness and enhance digestion. Wine is less stimulating for the body than high proof spirit and can be used for sipping in small quantities. These wines can be used for digestive related issues.[31] Herbal drinks are commonly ethanolic or hydroethanolic extracts of herbal materials.[32] In Africa and southeast Europe, these herbal drinks in form of liquor and spirits are largely used.[33]

Herbal capsule

These are solid dosage forms containing drug and commonly, proper filler closed in a gelatin container.[34] These may be available in hard gelatin shell for dry powdered herbal ingredients or granules,[35] or soft gelatin shells for herbal oils and for herbal ingredients that are dissolved or suspended in oil. The gelatin shell easily breaks, dissolves and follow oral administration. As compare to tablets, drug are more easily released from capsules.[27] Capsules mask the unpleasant taste of its contents.[20] Herbal capsules, mostly hard gelatin

capsules, contain the plant material finely grounded and filled into shell or also contain the herbal material extract with adequate excipients such as fillers.[36]

Herbal tablets

These herbal dosages form are hard, compressed and in round, oval or square shape.[34,20] The formulation contain the additives that may include: binders, glidants (flow aids) and also contain lubricant and disintegrants.[20] These are generally designed for the oral administration and containing the herbal constituents for specific therapeutic effects.[37] 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 increase in humidity and decreased hardness.[38]

Herbal ointment

These herbal preparations commonly contain the plant material(s) either in finely sieved or extracted form introduced in the base.[39] These are not used in case of deep wounds.[29] When compared with other liquid dosage forms, these formulations are quietly stable.[20] But the presence of herbal materials in an herbal ointment may lead to fast deterioration of the product. The stability of herbal ointments is important to ensure accurate labelling instructions for storage and shelf-life of the product.[40]

Herbal syrup

These are the preparations which are administered by oral route. Syrups are best of all liquid oral formulation. Because they are sweet in taste, people who don't like bitter taste, syrup offer a good introduction to the world.[41,42] These are prepared by addition of sugar with infusions, decoctions, expressed juices, fermented liquors or simple water solutions. These are also prepared with tinctures rather than infusions or decoctions. Instances of some syrup which can be prepared include simple syrup, orange syrup, tolu syrup, raspberry syrup, wild cherry syrup etc.[31]

Herbal creams

These are the semi-solid oil in water and water in oil type preparations and available in the different types [31]. Various types of herbal creams are-

(1) Cold creams – these are water in oil type emulsion and provides the cooling effects when applied on the skin. Cooling effects occurs due to the evaporation of the water from the skin.
(2) Vanishing creams – these are oil in water emulsion based preparation. These disappear when rubbed into the skin and for this phenomena, they are also called foundation creams.
(3) Cleaning creams – these are water in oil type emulsion. They melt at the body temperature. When applied on the skin they spread quickly on the applied area,[43]

Aromatherapy

Aromatherapy is the different form of medicine in which essential oils and other volatile oil are used for the purpose of changing the person mood or health. Some essential oils are not effective against the infection caused by the virus, bacteria and fungi but they shows the antimicrobial properties example tea tree oil. Still there is no specific evidence that aromatherapy is effective in treatment of the medical conditions.[31,44] But some evidences are present that shows that essential oil contain some therapeutic actions[45] that is beneficial for the treatment of medical conditions. In therapeutic, cosmetic, spiritual, fragrant, aromatic uses essential oil obtained there values.[46,47] In this therapy, highly concentrated constituents which having the main therapeutic agents are extracted from the different parts of the plant like, flower, fruit, leaves, stalks and roots or from the distilled resins.[48] Essential oils are the mixture of the saturated and unsaturated hydrocarbons, ketone, aldehyde alcohol, esters, ethers, phenol, oxides and terpenes which produces the characteristics odour.[49,50] These oils does not contain any color and available in concentrated form or works effectively on the vital points and rejuvenates.[51] They are administered by the various method in small amount e.g. inhalational route, by body massage, or some are taken internally by oral route. For the massage, they are simply apply on the skin surfaces.[47,52] Aromatherapy is famous to reduce the stress, rejuvenate and refresh the person mind. These oils shows their action via olfactory nerves. Now a days this therapy trend is increased. People are using it in cancer and sleep disorder.[55,56] Because of organic nature of these oils, these acts in the supportive way with the body and produces the feeling of the well beingness.[57] In a study when the mice is treated with the rosemarry essential oil, it is observed that the locomotor activity of the mice increased greatly by the rosemarry oil which is used as the refreshing and activating medicine for the exhaustion.[58] In holistic medicine, the use of the aromatherapy has taken long time in past years.[59]

Stability aspects of herbal formulation

Stability study of herbal formulation is essential not only during the production of product but also to assess the storage conditions and shelf life of the existing preparations over a period of time.[60] Stability is defined as the maintenance of quality until the end of the stated shelf –life.[61] Stability is aimed at assuring that the drug and drug product remains within the specification established to ensure its identity, strength, purity and quality. It can be explained as the length of time under specific condition and storage that a product remain within the pre-defined limits for all important characteristics. Every constituent whether it is therapeutically active or inactive in product can affect the stability.[18] because of different factors like physical and chemical properties of the substances and environmental factors like light, temperature and humidity. Pharmaceutical product may experience changes like change in consistency, moisture content, pH

etc. Stability of the product can also affected by microbiological changes.[62] Similarly, factors such as particle size, pH, the properties of water and other solvents employed, the container nature and the presence of the other chemicals as a result from contamination or from the deliberate mixing of various products can affect the stability[Figure 1].[18] Stability study ensure product quality and safety, and the degradation of the active ingredient may form toxic compounds. Aside from this, real time stability study data also gives information like shelf life of newly prepared drug and its storage conditions.[63] Stability testing of typical natural extract of the plant like flavonoid containing herbal drugs has reported by the researchers. It helps to understand the stability measure of the natural products [64]. A report on stability testing of herbal medicinal product and the problematic cases from practice with discussion of possible resolution approaches has been determined.[65]

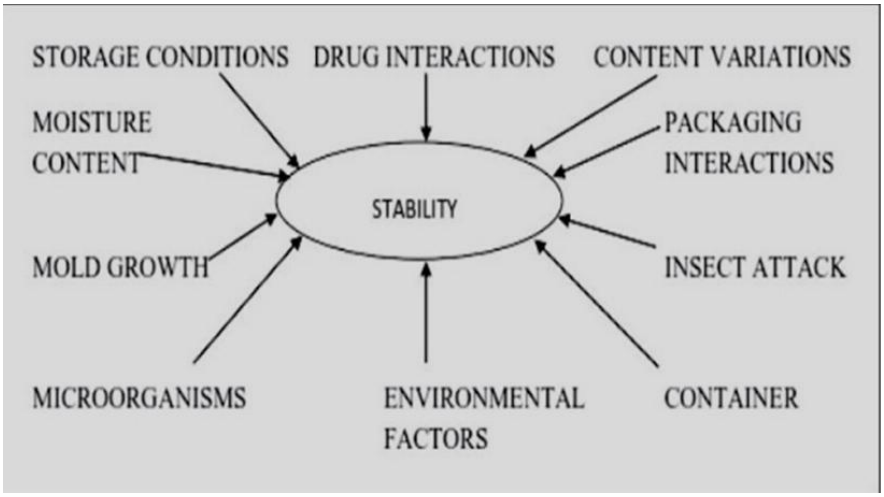

Figure 1: Stability Problems in herbal product.

Physical instability

Herbal products have the problem of the physical instability. It occurs when product contain the impurities and various active components and they shows the reaction with the container during storage of the product. Growth of microorganism and insect feeding affect the secondary metabolite or the chemical composition of the plant. Herbal medicine that contain the volatile substances having the problem of volatility and their activity is decreased when stored for long period of time**.**

Environmental conditions

Environmental conditions namely rainfall, temperature, altitude , soil , storage conditions along with various harvesting procedure, time and method of collection, manufacturing processes such as selecting ,drying, purifying, extracting and genetic variation produce a long term variance in product quality, stability and concentration of plant chemicals in the various products.

Chemical instability

During the storage, the degradation of the herbal formulation occurs due to the oxidation, hydrolysis, crystallization, emulsions breakdown, enzymatic deterioration and reactions of the products constituent with the formulation ingredients like additive and excipient. Most of the time, quality and stability of the herbal product are affected by the two major factors like temperature and moisture. When moisture absorbed on to the surface of solid drug, it increases the rate of decomposition if it is susceptible to hydrolysis. If enzyme is present in the product, it also enhance the rate of chemical degradation during storage.

Complex mixtures, variance

Herbal products contain the complex mixture of the various components obtained during the extraction process. Every component have the different activity, concentration and shelf life. And it causes problems to determine the storage conditions for products due to the difference in the activity and stability profile of the every individual component.[66] Many time the *in vitro* and *in vivo* biopharmaceutical characteristics of the herbal products are complicated to understand due to the complex composition of the product and resulting to this, analysis of the products is become very tough to do.[67]

Moisture content

Interactions of the active constituents of the product with the packaging material occurs when the moisture content in the product is more than the critical value and presence of mould growth. Sometime during storage, the active constituent of the product show the interactions with the formulation ingredients and change the activity of the drug. Herbal formulation contain the different constituents like glycoside, alkaloids, tannins, flavanoids and further more and stability conditions for the each component is different. So that the real stability conditions for the herbal product is different as compare to its single constituent.[68]

Factor influencing stability of herbal products

There are many factor such as temperature, pH, light that can affect the reactivity of the components. Most of the time, hydrolysis and oxidation reactions occur. Factors that are responsible for hydrolysis and oxidation.[69]

pH: The effect of the pH on the stability of the product is determined for catechins,[70,71] gingerols.[72,59] isoflavones.[73] The effect of the pH on the stability is depends on the chemistry of the herbal extract. In various case of the phytochemicals, the molecules of the interest is more stable at acidic pH. It is due to the marker compound analysed by the researchers were phenolics. It is observed that in the basic pH oxidative degradation was increased of phenolic marker compound.[69]

Light: It is the other crucial factor that effects the stability of the plant metabolites. It is recognized that the redox reactions are produced by the ultra violet rays. Hperforin and hericine are the two important constituent of the *Hypericum perforatum*. One of the study described that there is reduction in the flavanoid content because of their exposure in light.[76]

Temperature: Kinetics of the redox reaction are enhanced by increasing the temperature. In vitamins, it is studied that if the temperature is increased more than 25^0C and 5^0C, it enhances the activity loss rate. Although the confined data is present that shows the effects of the dry heat on the composition of the herbal extract. It has been reported that there was the degradation of the guggulsterone in exudates of *Commiphora mukul*. There is a very rapid decrease of sennosides in senna leaf extract after keeping for 16 days at 70^0C in dry oven.[77] There is another study which showed the effect of the heat on the stability and reported that the decomposition of dihydroandroghrapholide occurs during the production of *Androghraphics paniculata* tablets.[78]

Enzymatic degradation: Enzymatic degradation can be seen in the herbal preparation containing pressed juice. Fresh as well as dried plant material are used for the preparation of the herbal product. Nusslein *et al*.[79] stated the enzymatic degradation in *Echlinacea purpurea* roots by adding 0.5% citric or malic acid, or 5-15% hibiscus extract. Enzymatic degradation moreover observed in garlic where enzyme allinases and oxidases lead to the formation of the sulphur-containing flavorants.[80]

Metal ions: Metal ion mostly iron, copper and other transition metal, are able to cause hydrolysis and oxidative reaction with the redox active molecules.[69,81] These effects was described by the S. Thorsen and Hildebrandt.[82] They assessed the stability of carnosic acid and diterpene from the rosemary leaves in various solvents. In their study, they founded that the carnosic acid degraded more quickly in amber vial as compare to clear vials. And founded the fact that the amber vials greatly have the more amount of the iron and titanium.

Solvents: There is many evidence from many reports that the choice of the solvents have the big impact on the stability of the products. Mao *et al* stated the difference in stability of triptolide, a diterpenoid triepoxide obtained from *Trypterguim wilfordii*, in various solvents. The solvent in which stability is best comes are ethanol followed by the methanol and DMSO.[83] And interactions with the solvents also leads development of new chemical structure. Tava *et al* stated that in *Medico sativa*, there is the formation of the ester between ethanol and the glucuronic acid moiety of saponins.[84]

Air: The destructive effect of the air exposure of many plant extract occurs because it contain the oxygen. Fatty oils are mostly affected when they are exposed in the air.[85] The essential oils are also affected by the air when they are not properly stored in the container and to prevent the oxidation, they are filled equal to the rim. Orav *et al*, describes the effect of air on the essential oils of the *Piper nigrum* fruit. He observed that there is increase in the oxygenated terpenoids after one year of the storage.[86]

Importance of stability testing

Stability testing vital for the wellness of the patient who is suffering from the diseases for which the product is manufactured. When the product is degraded by the different factors like physical, chemical, environmental etc., it contain the toxic substances and loss its therapeutic activity and can cause the failure of the therapy and result in death of the patient. Due to this consideration it is important to gives the all data of the stability testing of various tests to the regulatory agencies before the approval of the new drug product.

In the development stages of the drug product, it is important to perform the stability studies. It will provide the database of the product that help to select excipient for the formulation and container and closure system for the packaging of the new products. And it also provides an idea to identify the storage and shelf life of the new product or verify that there is no changes occurs during the manufacturing of the product that may affect the stability of the herbal product.[87,88]

Method of testing of the stability

Stability testing of the drug products occurs in the routine bases and is performed at the various stages of the drug development. Depending on the aim and the steps followed, stability testing procedure are of different types.

Retained sample testing

This type of testing has been performed to collect the stability data of the marketed product. For sampling every year one batch is selected for retained storage. If the marketed batches number increase to 50 than it is

suggested that select the two batches for the sampling. During the first introduction of the product into the market the stability sample from the each batch is carried. On later stages it is decreased to 2 to 5% for the marketed batch. Stability sample those are tested at predefined interval that occur if the shelf life of the product is 5 year and the samples are tested at 3, 6, 9, 12, 18, 29, 36, 48, 60 months.[89,90]

Cyclic temperature stress testing

This method is not routinely practice on the marketed product. In this test the conditions for the storage of the product are created like cyclic temperature, stress conditions. These conditions are same as the marketed storage place of the product and the period of the cycle is 24 hour. The temperature for the testing the product during cyclic stress is selected on the basis of various form of the product and also examined the factor like suggested temperature for that product and the physical or chemical degradation of product. It is suggested that during test, 20 cycles are practiced usually.[89,80]

Real time stability testing

In this method, stability testing of the product performed for the longer period of time until the degradation of the product is occurs on the suggested conditions for the storage. When the test is performed the data should be collected in proper frequency so the trend analysis is capable to differentiate the instability from daily vagueness. The accuracy of the data interpretation can be enhanced by comparing the one batch with the reference whose properties for stability are already determined. Stability of the reference batch also contain the stability of the reagent along with the performance uniformity of the instruments those are used during the stability testing. Although system performance and control for drift and discontinuation results from changes in both reagents and instrumentation should be controlled.[90]

CONCLUSION

The use of the herbal product are increased all over the world. Herbal products are available in different dosages form. Stability study of the herbal product is crucial to ensure the quality, safety and efficacy of the product. By studying the various factor like temperature, pH, air, moisture, solvents, light and enzymatic degradation that effects the stability of the product or by performing the different stability test, things become easy for the herbal product manufacture that to consider the various stability facts and develop technique that is needed during the storage, transportation and usages of the herbal product. It is beneficial for the patient safety and increase the people belief toward the safe and effective use of herbal product.

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