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STABILITY TESTING AND SHELF LIFE DETERMINATION OF AYURVEDA, SIDDHA AND UNANI MEDICINE

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ABSTRACT

There is an increasing concern for shelf life and stability of Ayurveda, Siddha and Unani system of medicine developed in Asia over the centuries. Stability is an important parameter for safety and efficacy of product. The concept of shelf life is found in classical texts as well as Drug and Cosmetic Acts (D & C act). According to Rule No. 161-B of D & C act 1940 and Rules 1945, a person applying for licence or renewal of licence for the manufacturing of patent & proprietary ASU medicines, has to submit scientific data based shelf life or date of expiry of the medicine based on the Real-time stability studies to the State Licensing Authority. The API (The Ayurvedic Pharmacopoeia of India) Part I, Vol. VIII prescribe guidelines for stability testing and shelf life determination for new and existing Ayurvedic drugs including Siddha and Unani medicine. The guideline covers scope and objective, general information, selection of batches, container and closure system, specification, testing frequency, storage condition and evaluation. The stability studies should be conducted on the dosage form packaged in the container and closure system proposed for marketing. Formal stability studies should be conducted on at least three primary batches. The recommended storage conditions for accelerated long term study are 40^0 C ± 2^0 C / 75 % RH ±5 % RH for minimum of 6 months and for long term study conditions are 30^0 ± 2^0 / 60 % RH ± 5 % RH for minimum of 12 months respectively. A product can be considered to be stable if "no significant change" occurs during at any time of testing.

Keywords: Shelf life, Stability, *Ayurveda, Unani, Siddha*

INTRODUCTION

Traditional or alternative medicine is widely used in the prevention, diagnosis and treatment of an extensive range of ailments[1]. Over the centuries many medical systems have emerged from Asia and today there is an increasing interest in Ayurveda, Siddha and Unani (ASU) systems of medicine. Ayurveda is the sacred system of health care, originated in India whereas Unani medicine originated in Greece and was introduced to India by the Arabs. Siddha system of medicine is practiced in Tamil speaking parts of India

and abroad[2]. The medicinal products of ASU system of medicine include single herb or polyherbal formulations with or without mineral drugs and/or drug substances of animal origin. Earlier the practicing physicians used to prepare medicine by themselves for his patients using simple instruments similar to mortar and pestle. Today drug products are usually manufactured on commercial scale and there is transition of "mortar-pestle pharmacy" to retail pharmacy or mail-order pharmacy. Typically a drug product is transported from manufacturer to distributor; from distributor to wholesaler; from wholesaler to hospital or pharmacy and finally to user. During transfer of product from manufacturer to user, the variations in external factors may create changes in stability. In order to obtain full therapeutic efficacy it is mandatory that the product should be stable at user end.

STABILITY AND SHELF LIFE IN CLASSICAL TEXT AND CURRENT SCENARIO

Stability is the capability of a specific formulation in a particular container/closure system to remain within its physical, chemical, microbiological, toxicological, therapeutic specifications at a defined storage condition. Stability is expressed in terms of shelf life. Shelf life is the time period during which a drug product is expected to remain within the approved specification for use, provided that it is stored under the conditions defined on the container label. Expiration date is the date placed on the container label of a drug product designating the time prior to which the product is expected to remain within the approved shelf-life specification if stored under defined conditions and after which it must not be used[3, 4, 5].

The concept of shelf life can be traced from classical texts (Table 1). Similarly the texts of Unani medicine provide the concept of shelf life. As per Jalinoos' book Kitabul Murakkabath the potency of Safoof (powder) is not more than 2 months and shelf life of Habub and Aqras (pills and tablets) is more than that of Safoof whereas shelf life of Sharbat (syrup) is about one year[10]. Arab physician Ali Ibne-Abbas Majoosi in his compilation Kitab-Al-Mulki, mentions shelf life of Aqraas Ashqueel, Aqraas Afaai, Tiryaaq Arba and Tiryaaq Shalisa from two months to two years and shelf life of Majoon Kibrit from 6 months to three years[12].

Table 1: AYURVEDIC DOSAGE FORM SHELF LIFE (SAVIRYTA AVADHI) AS PER CLASSICS [6, 7, 8, 9, 18, 19]

Dosage form	***Vangasen***	***Sharangdhara Samhita***	***Yogaratnakar***
Kvaath (decoction)			03 hours
Kalka (paste)			03 hours
Swarasa (expressed juice)			03 hours
Anjana (collyrium)			3 months
Churna (powder)		2 months	3 months
Vati (tablets/pills)		12 months	
Avaleha (semisolid oral dosage)	12 months	12 months	6 months
Ghrita (medicated ghee) and Taila (medicated oil)	6 months	16 months	12 months
Asav-Arista (tincture/ fermented oral liquid)		Long term stability	

The classical texts as well as the modern analytical tests conclude that the potency of ASU preparations is lost/ reduced after a certain period of time. The concept of expiry date or shelf life was introduced to ASU medicines in the year 2005. The notification GSR 764(E) dated October 15, 2009 incorporated the Rule no. 161- B referring shelf life of ASU medicine. It was modified in 2016 by the Gazette notification GSR 789 dated August 12, 2016 [12, 13, 14]. The Rule says to conspicuously display the date of expiry of Ayurvedic, Siddha or Unani medicines on their container or package and after the date of expiry no medicine shall be marketed, sold, distributed or consumable. Unless otherwise determined on the basis of scientific data, the shelf life or date of expiry of an Ayurveda, Siddha or Unani medicine defined under clause (a) of section 3 of the Act shall be as described under the Rule[14]. As per clause (a) of section 3 of the

Drug and Cosmetic Act Ayurvedic, Siddha or Unani drug includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in, the authoritative books of Ayurvedic, Siddha and Unani Tibb systems of medicine, specified in the First Schedule[15]. Table: 2 show Ayurvedic, Siddha or Unani medicine respectively in increasing period of their shelf life or date of expiry as given in the Rule 161-B [14]. Simply saying the Rules gives shelf life or expiry date of formulations of textual reference (classical medicine). The rule doesn't provide the shelf life or expiry date of patent and proprietary medicine but says after three years from the date of notification of the rules every person applying for licence or renewal of licence for the manufacturing of Ayurveda, Siddha or Unani medicines defined under clause (h) of section 3 of the Act shall submit to the State Licensing Authority scientific data based shelf life or date of expiry of the medicine based on the Real time stability studies of medicines[14]. Clause (h) of section 3 of the Act defines patent or proprietary medicine which is in relation to Ayurvedic, Siddha or Unani Tibb systems of medicine all formulations containing only such ingredients mentioned in the formulae described in the authoritative books of Ayurveda, Siddha or Unani Tibb systems of medicine specified in the First Schedule, but does not include a medicine which is administered by parenteral route and also a formulation included in the authoritative books as specified in clause *(a)* [15]. In the view of Rule 161-B, stability study has become a legal requirement for manufacturing licence of patent and proprietary ASU medicines.

Table 2: Shelf Life of ASU Medicine

Shelf life or date of expiry 1 year **Ayurvedic Formulation**: Anjana made from Kasthaushadhi, Arka, Netrabindu **Siddha Formulation**: Kallikkam/Mai/Kalimbu/Neer/Venney, Kattu (Medicated bandage cloth)/Seelai/Varthy/Thiri, Nasiyathuli/Kanthuli/Sevithuli, Oothal/ Nasigaparanam/ Thoopasarakku, Pakkuvam, Thennoral, Tinir **Unani Formulation**: Arq (except Arq-e-Ajeeb), Murabba, Burood, Qutoor, Sufoof (Containing salt)
Shelf life or date of expiry 2 years **Ayurvedic Formulation**: Anjana made from kasthaushadi along with Rasa/Uprasa/Bhasma, Churna, Kwatha Churna, Lepta Churna, Danta Manjan (Churna), Dhoopan, Ghrita, Karna/Nasabindu, Sattva (derived from medicinal plant), Shveta parpati, Varti **Siddha Formulation**: Araippu Karpam (e.g. Irunelli Karpam), Karam (Karanool), Karuppu containing only Mooligai ingredients (e.g. Vasambu Sutta Kari), Kutinir Curanam/Adai Curanam/Kanchi Curanma/Utkali Curanam/Pittu Curanam/ Podithimirthal Curanam/ Podi/ Pattru Curanam/Pottanam or Kizhi Curanam/Ottratam Curanam/ Vethu Curanam/Pugai Curanam/Kali Curanam/ Thuvalai Curanam, Mattirai/Vatakam containing only Mooligai ingredients (including Kudineer Curanam Mattirai) (e.g. Nilavembu kutinir Mattirai), Mooligai Karpam (e.g. Karisalai Karpam, Thiripala Karpam), Ney/Ghiruthan/Kadugu, Parpam/Centuram containing only Mooligai ingredients (e.g. Kungiliya Parpam), Peechu, Rasa-Paadana Marunthugal (All Mercurial Preparation) containing Mooligai ingredients along with Thathu, Porutkal/Parpam/Centuram/Cunnam/Kattu/Kalanku, Satthu derived from Mooligai (e.g. Seenthi Satthu), Sutigai, Tiravakam (derived from ThathuPorutkal) **Unani Formulation**: Ayarij/Sunoon/Zuroor/Ghazah, Marham/Zimad/Qairooti, Shiyaf, Sufoof (Without Salt)
Shelf life or date of expiry 3 years **Ayurvedic Formulation:** Anjana made only from Rasa/Uprasa/Bhasma, Avaleha, Khanda, Paka, Guda, Gutika or Vati containing only Kasthaushadhi (including Lepa Gutika and Ghan Vati), Malahar, Pravahi Kwatha, Sharkar/Panak/Sharbat, Taila **Siddha Formulation**: Idippu Meluku (e.g. Rasa Gandhi Meluku/Idi Vallthi Meluku), Ilakam/Lagiyam/Iracayanaam, Kutinir/Kiyazham (with preservatives), Manappaku/Panagam, Mooligai Meluku (e.g. Malaikudara Meluku), Tailam/Ennai/Poochu **Unani Formulation**: Habb, Halwa, Itrifal, Khamira, Laboob, Laooq, Majoon/Dawa, Mufarreh, Qurs, Raughaniyat/Tila,

Sharbat/Sikajabeen, Surma/Kohal, Tiryaq
Shelf life or date of expiry 4 years **Unani Formulation**: Jawarish
Shelf life or date of expiry 5 years **Ayurvedic Formulation:** Dravaka, Lavana, Kshara, Guggulu, Gutika or Vati containing Kasthaushadi along with Rasa/Uprasa/Bhasma/Guggulu (including Lepa Gutika and Ghan Vati), Naga Bhasma, Vanga Bhasma and Tamra Bhasma, Rasayoga Containing Rasa/Uprasa/Bhasma along with Kasthaushadhi/Guggulu **Siddha Formulation**: Araippu Kulampu (e.g. Agathiya Kulampu), Araippu Meluku (e.g. Linga Meluku), Erippu Kulampu (e.g. Kumatti Kulampu), Karuppu containing Mooligai ingredients with Jeeva Porutkal (e.g. Kasthuri Karuppu, Pattu, Karuppu), Karuppu containing Mooligai ingredients with Thathu Porutkal (e.g. Sivanar Amirtham, Thalaga Karuppu), Mattirai/Vatakam containing Mooligai ingredients along with Thathu Porukal/Jeeva Porukal/Parpam/Centuram/Cunnam. (including Kutinir Curanam Mattirai), Mooligai based Patankam (e.g. Sambirani Patankam), Mooligai Thathu Karpam (e.g. Aya Bringaraja Karpam), Satthu derived from Jeeva Porutkal (e.g. Sembu Satthu derived from Poonagam, Mayiliragu) **Unani Formulation**: Arq-e-Ajeeb, Jauhar/Jawahir
Shelf life or date of expiry 10 years **Ayurvedic Formulation:** Asava/Arista, Gutika/Vati containing only Ras/Uprasa/Bhasma except Naga, Vanga and Tamra Bhasma, Kupipakva Rasayana, Madura-Lauha, Parpati, Pishti and Bhasma except Naga, Vanga and Tamra Bhasma, Rasayoga Containing only Rasa/Uprasa/Bhasma except Naga, Vanga and Tamra Bhasma **Siddha Formulation** : Kattu/Kalanku/Cunnam, Mattirai/Vatakam containing only Thathu Porutkal/ Parpam/ Centuram/ Cunnam/Kattu/Kalanku., Panda Vaippu, Parpam/Centuram containing Mooligai ingredients with Jeeva Porutkal (e.g. Sangu Parpam), Parpam/Centuram containing Mooligai ingredients with Thathu Porukal/ Parpam/Centuram/Cunnam/Kattu/Kalanku (e.g. Aya Centuram), Rasa based Patankam (e.g. Rasa Centuram), Rasa-Paadana Marunthugal (All Mercurial Preparation) containing only Thathu Porutkal/ Parpam/ Centuram/ Cunnam Kattu/ Kalanku, Satthu derived from Thathu Porutkal (e.g. Aya Satthu, Eya Satthu, Thurusu Satthu) **Unani Formulation** : Kushta, Nabeez

PROTOCOL FOR STABILITY STUDY

The stability depends on various factors like the nature of the product itself, the ingredients, the packaging material and the environmental condition. Stability testing is a complex set of procedures as variety of factors influence the stability of a product. The formulations itself are complex, the degradation reactions may be complicated by possible interactions of several components of the formulation. The study of degradation pattern of each ingredient individually would be difficult, time consuming and expensive. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of variety of environmental factors such as temperature, humidity, light, and also to establish a retest period for drug substance or a shelf life for drug products. It is not necessary to determine the mechanism of degradation. It is usually sufficient to follow the some property of degradation as a function of time at several elevated temperature using the kinetic expression presented and then to extrapolate the data to ambient condition to obtain an estimate of the shelf life of the product [3, 4, 5. 16, 17.].

Stability testing is performed following well-designed regulatory guidelines representing a framework for the experimental design and data analysis as well as the type of documentation needed to meet regulatory requirements. ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), WHO (World Health Organization), ASEAN (Association of South East Asian Nations) and EMEA (European Agency for Evaluation of Medicinal and Health Products) guidelines have been followed for stability testing of pharmaceutical products. ICH guidelines are now common in the industry for assessing stability of a drug substance or drug product[3, 5, 20, 21. 22, 23, 24, 25].

The Ayurvedic Pharmacopoeia of India, Part-I, Volume-VIII under the appendices 3.9 prescribes guideline for stability testing and shelf life determination of all licensed ASU medicines[26].

GUIDELINE FOR STABILITY TESTING AND SHELF LIFE DETERMINATION OF ASU MEDICINE

Stability studies are carried out to demonstrate that the medicine will remain suitable for consumption during shelf period when stored under the condition(s) mentioned on the packaging. On the product label, if there is no mention about any specific storage condition, then it is assumed that the product can be stored at room temperature (below 30^0).[26]

Selection of Samples and batches

Two approaches can be followed to monitor the stability of the product. The first approach is to store the samples of same batch material at standard storage and accelerated storage conditions and test them periodically. Based on the evaluation of the results, the expiry date or shelf life may be determined. The second approach called "cross sectional approach" is applicable for existing products which do not have yet a declared shelf life. The approach is to select samples from batches manufactured over a period of last five years spanning six months and evaluate them simultaneously. Based on the result obtained the expiry date or shelf life may be determined.

At least three primary batches of the same formulation as proposed for marketing are required for formal stability studies. For cross sectional approach at least two batches per year to be selected. For new products, the batches should be manufactured to a minimum of pilot scale (at least 1/10 of the commercial batch size) by the same route and using a method of manufacture and procedure that simulates the final process to be used for production batches. The overall quality of the batches of drug placed in formal stability studies should be representative of the quality of the material made on production scale. Where possible, batches of drug product should be manufactured by using different batches of drug substance. Stability to be performed on each individual strength and container size of the product unless bracketing and matrixing is applied. For cross sectional approach at least two batches per year to be selected. For example if stability to be evaluated for four years eight batches should be selected[26].

Container and closure system

For the stability studies, the drug product should be packaged in the same container and closure system as proposed for marketing of dosage form with secondary packaging and container label as appropriate. Each individual strength and container size of the proposed packaging configuration should be placed on stability, unless bracketing and matrixing designs are used. For drug substances, if the container is too large the stability studies should be conducted in a container and closure system that is the same as or simulates the packaging proposed for storage and distribution[26].

Specification

Specification is the established quality criteria to which a product should conform to be considered acceptable for release or use. It is a list of tests, reference to testing procedures and proposed acceptance criteria. Stability study should include testing of those attributes of the drug that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies.

The physical parameters included in the specification need not be limited to colour, odour, appearance, shape and taste only. The chemical parameters should include colour reaction, *p*H value, weight variation, disintegration, bulk density, extractive values, estimation of active or marker or category compound by suitable methods and chromatographic profiling. A suitable bioassay may be employed wherever possible. The limits of acceptance for the products should be those specified in pharmacopoeia. If limits are not available these should be derived from release specification. Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. When an anti-microbial preservative is required in the formulation, its selec-

tion should be based on several considerations like pH of formulation, interaction with ingredients and container. Differences between the release and shelf life acceptance criteria for anti-microbial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during development of the product in its final formulation (except for preservative concentration) intended for marketing[26].

Storage Condition

Real time (long-term) testing is normally performed for longer duration to allow significant degradation of the product under specified storage conditions. Accelerated testing is performed at high temperatures, humidity, light intensity etc. The accelerated testing should be then carried out at least 10^0 C more than the long term storage condition along with appropriate relative humidity condition for that temperature. The reference samples for the above study should be stored in a temperature less than 10^0 C. Table: 3 shows recommended storage conditions are for Real time and accelerated stability testing as per API. Uses of other storage conditions are not prohibited, if suitably justified. Intermediate testing are mainly conducted when the accelerated studies for general case failed to meet the acceptance criteria and are designed to moderately increase the rate of degradation for a drug intended to be stored long-term at 25°C. Stress testing includes the effect of temperature (above that used in accelerated study), humidity (e.g., ≥75% RH), oxidation, photolysis and hydrolysis. Forced degradation testing is performed with objective to provide intrinsic stability assessment of the drug, to elucidate the possible degradation pathways by identifying the likely degradation products and to have an idea of the stability of the analytical process applied for the drug.

For products which are temperature sensitive, to be stored in lower temperature which will then become the condition designated long term storage temperature[26].

Table 3: Recommended storage conditions for ASU medicines

S. No.	Study	Storage condition	Minimum time
1	Accelerated	40º C ± 2º C 75 % RH ± 5% RH	6 months
2	Long Term	30º C ± 2º C 60 % RH ± 5% RH	12 months

Testing frequency

For long term studies frequency of testing should be sufficient to establish the stability profile of the drug. For drug with proposed shelf life of at least 12 months, the frequency of testing at long term storage condition should normally be every six months over first year, and the second year and annually thereafter through the proposed re-test period or shelf life. At the accelerated storage condition, a minimum of three time points including the initial and final time points (*e.g*. 0, 3 and 6 months) from a 6 month study is recommended. Reduced designs *i.e*., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified[26].

REDUCED DESIGNS: Bracketing and Matrixing

The Ayurvedic Pharmacopoeia of India, Part-I, Volume-VIII allows applying reduced stability study designs like bracketing and matrixing. During the design of stability studies, bracketing and matrixing may be used to achieve reduced testing while at the same time generating enough stability data for evaluation of shelf life. Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all-time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering differ-

ent batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems[23].

Evaluation

The purpose of stability is to establish, based on testing a minimum of at least three batches of the drug, a retest period applicable to all future batches for the drug substance, or a shelf life and label storage instructions applicable for all future batches of the drug product manufactured and packed under similar circumstances.

An Ayurvedic drug (or Siddha drug or Unani drug) can be considered to be stable if "no significant change" occurs during at any time of testing at accelerated storage condition or at real time storage condition[26].

"Significant change" for a drug is defined as

1. A ± 20 % change from the initial assay value when the drug is analysed for its marker.
2. A ± 15 % change from the initial assay value when the drug is analysed for its active compound).
3. Completely disappearance of existing spot or appearance of new spots in identification by TLC (when compared with the sample stored in less than 10^0).
4. The physico-chemical parameters (moisture, ash, particle size) shall not vary beyond 25 % of the initial value.
5. Failure to meet the acceptance criteria as per individual monographs or specification.
6. Failure to meet acceptance criteria for appearance (Physical attributes, and functionality tests *e.g.*, Colour, phase separation, caking, hardness).

DISCUSSION

Over the centuries many medical systems have emerged from Asia. Today there is an increasing interest in Ayurveda, Siddha and Unani (ASU) systems of medicine for prevention, diagnosis and treatment of an extensive range of ailments. Interest in these Asian medicines is particularly by those who have not benefited from previous treatment of orthodox medicine, by those who benefit from the holistic approach and by those who have apprehensions concerning the toxicity and safety of drugs. To have the efficient efficacy and safety, it is required that the formulation should be stable. Stability means ability to remain unchanged, but it is common experience that all objects including formulations changes or deteriorates with time and get spoiled after a specified period. A formulation is considered stable when it full-fill its defined specification. Stability is expressed in term of shelf life. Ayurvedic Pharmacopoeia of India, part-I volume-VIII prescribes the guideline for stability testing of ASU medicine. Stability is confirmed when there is "no significant changes" in marker compound, active compound, TLC spot, physico-chemical parameters, acceptance criteria as per monographs or specification. The challenges in stability studies include complex chemical nature of formulation, absence of studies on interactions between the ingredients, unavailability of marker and validated analytical procedures.

CONCLUSION

It is known that potency of ASU preparations is reduced after a certain period of time. To have the efficient efficacy and safety it is mandatory that product should be stable physically, chemically, microbiologically and therapeutically as well as free from toxicity. Rule 161-B gives the shelf life of ASU medicine of textual references and specify the shelf life determination of patent and Proprietary medicines as the guidelines prescribed in The Ayurvedic Pharmacopoeia of India, part-I volume-VIII. Stability is confirmed when there is "no significant changes" in marker compound, active compound, TLC spot, physico-chemical parameters, acceptance criteria as per monographs or specification.

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