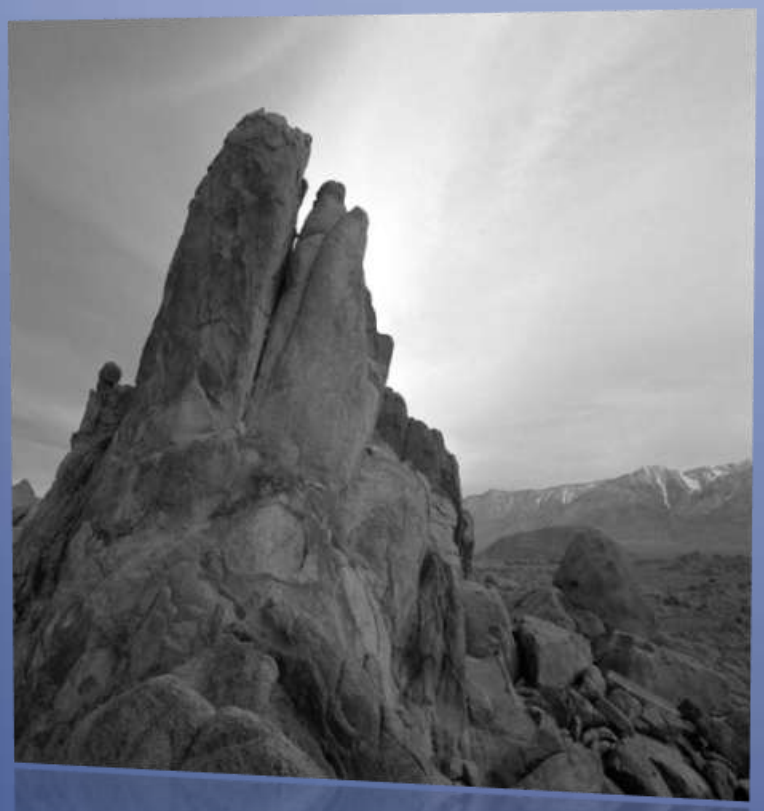

International Journal of Ayurveda and Pharmaceutical Chemistry

Volume 7 Issue 2 2017

www.ijapc.com

Int J Ayu Pharm Chem

REVIEW ARTICLE

www.ijapc.com

e-ISSN 2350-0204

In-process Standardization of Ayurvedic Drugs - Needs and Challenges

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ABSTRACT

Standardization of Ayurvedic drugs is an important and essential measurement for the quality control of drugs. It is necessary to provide drugs having good quality. While preparation of drug, standardization of raw material, standardization of the process i.e., in-process standardization and that of the final drug is necessary. Among these, in-process standardization carries more importance. It includes selection of the reference of the formulation, selection of the instrument to be used, development of Standard Operating Procedure (SOP) of the manufacturing of the drug, various tests to be carried out during the procedure, etc. A critical review has been done in present study regarding the needs and challenges in the in-process standardization.

KEYWORDS

Standardization, Quality Control, SOP, In-Process Standardization

Greentree Group

Received 30/06/17 Accepted 24/07/17 Published 10/09/17

INTRODUCTION

Standardization is an essential measurement for ensuring the quality control. It describes all the measures, which are taken during the manufacturing process and quality control leading to a reproducible quality.

Standardization of any drug includes following three steps-

1. **Raw Material Standardization:**

It includes the standardization of the raw material to be used for the preparation of the medicine.

2. **In-Process Standardization:**

It includes standardization of the procedure as well as that of the medicine during its preparation.

3. **Finished Goods Standardization*:***

It includes standardization of the final product i. e. the prepared medicine.

These three steps cannot be described independently as these are interlinked with each other. However throwing light on the In-process Standardization as follows-

In-Process standardization:

In-Process standardization includes –

1. Selection of the reference of the specific formulation

2. Development of Standard Operating Procedure (SOP) of Manufacturing Process of drug

3. Various Parikshas (tests) of the drug to be carried out during its preparation.

4. Atmospheric conditions during the preparation of the drug

1. Selection of the Reference-

The first and foremost important step for the standardization of any drug is selection of the reference of that specific formulation. Some formulations having similar name are found in the same or various *Granthas* but, they vary in the ingredients, proportion, manufacturing process and *Rogadhika*r, etc. e. g. in Bhaishajya Ratnavali, various formulations having the same name Agnikumar Rasa are found which are having different ingredients and are indicated in different diseases i. e. *Jwar Chikitsa, Grahani Chikitsa and Agnimandya Chikitsa*.

Development of SOP of Manufacturing Process of drug-

During the preparation of any drug, standardization of the procedure is necessary. For this purpose, development of SOP is necessary. It includes mainly selection of the instrument for the preparation of the drug as it plays an important role. As per the *kalpana* (Dosage form), instrument to be used are different. Also use of traditional or advanced instruments differ the quality of the final medicine.

3. Various *Parikshas* (tests) of the drug to be carried out during its preparation-

In Rasagrantha, various tests have been described for different types of medicines. These have to be carried out during their preparation to ensure quality of respective drug. The tests are described as follows-

***Bhasma*:** *Rekhapurna, Niswadu, Varitar, Unam, Apunarbhav, Niruttha, Awami, Amla,* etc.

***Churna*:** *Sookshma tantava pata chyutam i.e.* the powder should pass through the fine fibrils of cloth.

SnehaKalpana*[1]*:

Formation of *Varti* (wick) of the *kalka*

No sound when *kalka* sprinkled over fire

Observation of foam on completion of *Taila paka*

Subsidence of foam on completion of *Ghrita paka*

Specific colour, odour and taste of the ingredients

Avaleha Kalpana*[2]*:

Tantumatvam- It should have a thread like consistency,when pressed between two fingers.

Apsumajjati- In water, it should sink in it.

Kharatva- Solid/Rough to touch

Pidite Mudra- Should give finger prints, when pressed between fingers

GandhavarnaRasodbhva- It should possess *Gandha* (smell), *Varna* (colour) and *Rasa* (taste) as that of its ingredients

***Sandhan Kalpana*[3]:**

On the onset of fermentation following signs are seen-

Floating of *prakshep dravyas*, effervescence, hissing sound, and extinguishing of burning candle

On the completion of fermentation following signs are seen-

Sunken *Prakshep dravyas*, absence of effervescence (froth), no sound, appreciation of alcoholic odor, continuation of burning of a lighted candle

Along with these, modern analytical tests can also be applied for In-process standardization of ASU drugs. Common analytical parameters for in-process standardization of different categories of ASU Formulations are displayed in **Table 1** and **Table 2**. These tests could be helpful in the in-process standardization.

Table 1 Analytical parameters for metallic Preparations

Dosage Form	Parameters
Bhasma, Sindhura, Mandura, Rasayoga and Lauha	Organoleptic characters like Roopa, Rasa, Gandha, etc. Loss on drying at 105^0C Particle size Total ash, Acid insoluble ash and Water soluble ash

Table 2 Analytical parameters for herbal Formulations

Dosage Form	Parameters
Arka, Asava / Arista, Avaleha, Churna, Lepa, Malahara, Netrabindu,Karnabindu, Anjana, Varti, Pishti, Ghana, Sneha, Guggulu, Vati / Gutika / Modaka, Shaarkara	Applicable organoleptic characters like Color, Odor, Taste etc. pH Total ash, Acid insoluble ash, Water soluble ash Alcohol, Water soluble extractive Loss on drying at 105^0C Identification (TLC, HPTLC, HPLC, etc.) Specific Gravity at 25^0C

2. Atmospheric conditions during the preparation of the drug-

Atmospheric Conditions affect the In-process standardization of the drug as below-

1. Powdering - Hygroscopic material cannot be powdered easily in humid conditions.

2. Triturating - Required quantity of *bhavana dravya* varies according to season.

3. Fermentation - Time period for fermentation process varies according to season.

Also the layout plan of manufacturing unit must be taken into consideration for In-process standardization.

Table 3 Various interpretations of the classical reference of Arogyavardhani Vati

Sr. No.	Name of the ingredients	Quantity	Interpretations			
			I	II	III	IV
1.	ShudhhaParad	Samansha	1	1	1	1
2.	ShuddhaGandhak	Samansha	1	1	1	1
3.	LohaBhasma	Samansha	1	1	1	1
4.	AbhrakBhasma	Samansha	1	1	1	1
5.	TamraBhasma	Samansha	1	1	1	1
6.	Triphala	Dviguna	2	6	10	30
7.	ShuddhaShilajit	Triguna	3	3	15	15
8.	ShuddhaGuggulu	Chaturguna	4	4	20	20
9.	***Chitrakmoola / Erandamoola(AFI)***	Chaturguna	4	4	20	20
10.	Kutki	Sarvasama	18	22	70	90
		Total Parts	**36**	**44**	**140**	**180**

DISCUSSION

In-process standardization carries somewhat more importance as it includes the standardization of the processing of the drug. It affects the quality of the final drug prepared. It can be discussed step-wise as follows.

1. Selection of the reference-

In classical *granthas*, various references of the same drug are found. These are having variation in the ingredients, procedure of its

preparation and its indication**.** In some cases, variation in the interpretation of the *Shloka* (Verse) is also seen regarding the same reference e.g. Aarogyavardhani Vati[4]. Variation is seen in the interpretation of the *Shloka* as shown in the **Table 3**. As shown in this Table, due to variations in the interpretation of the *Shloka*, various compositions of ingredients are found, though the reference is same. Eventually it differ the quality of the drug. So firstly, selection of a specific reference, clarification of the interpretation and following it thoroughly is necessary for the standardization. **2. Development of SOP of Manufacturing Process of drug-**

Several procedures performed during the preparation of medicines are triturating, sieving, boiling, heating, fermentation, filtration, etc. During preparation of any drug, the instrument used plays an important role. The quality of the medicine differs as per the instrument used for its preparation. In the modern era, various instruments have been developed and used in the manufacturing process. It has been found that similar drug prepared using traditional method and that using modern instrument differs in its quality.

In the production of any medicine, if standard operating procedure of the respective medicine is strictly followed, the batch to batch variation could be minimized to a large extent. SOP includes use of similar equipment/instruments while preparing the medicine. For this purpose, it is the need of hour to develop the SOP of the medicines. It requires pharmaceutical and analytical study of the medicine in various batches, which can conclude with an accurate result.

It can be discussed well Kalpana-wise (according to dosage forms) as below.

***Churna* (Powder):**

For the preparation of Churna, it is found that use of Khalva Yantra (Mortar and Pestle) takes more time than the modern instruments like Grinder, Pulveriser, etc**.(Figure 1 and Figure 2).** Therefore, for developing SOP of Churna, the instrument to be used must be specified, it may be traditional or modern. It will be helpful in the in-process standardization of Churna.

***Kwath* (Decoction):**

In the preparation of *Kwath*, following factors may affect the quality and quantity of final product.

1. Mesh size of *Kwath Dravya* - Coarse/ Fine
2. Nature of *Kwath Dravya* - *Mrudu, Madhyam, Kathin* (Dry/Wet)
3. Time/ stage of Filtration - Immediately after preparation/ after self cooling

Figure 1 Traditional Khalva yantra

Chakki **Pata varvanta** **Khalva yantra**

Figure 2 Modern khalva yantra

Multi mill **Pulverizer**

4. Method of Filtration - Manual/Instrumental

5. Method of Presentation - Fresh / Only Preservative / Syrup Base / Fermentation

6. Container used for Storage - PET/Glass

Vati - Guti (Tablets):

For the preparation of *Guti-vati, bhavana* (levigating) is the first step to be carried out.

***Bhavana Sanskar* (levigating):**

In this concern, again the example of Aarogyavardhani Vati can be discussed. In the classical reference, it has been mentioned to give *bhavana* of *Nimba Patra Swaras* to the mixture of the ingredients for the time period of two days. Here, controversy regarding time period is seen. Various opinions regarding the time period of one day are found as 6, 8, 12 and 24 hrs.. Therefore, it is necessary to determine the exact time period of one day. In addition, use of the instrument for *bhavana* process also affects the quality of product. While triturating the mixture for this time period in Khalva Yantra, it has been found that less amount of *Nimba Patra Swaras* is required for the *bhavana* as compared to that using the modern instruments like end runner, edge runner, etc.

Thus, the quantity of *Bhavana dravya* absorbed differs, which ultimately is seen in the composition of the medicine. The maintenance of a desired level of quality in a product, especially by means of attention to every stage of the process of production i.e., quality assurance is very important. In this concern, determination of *Kaal* (time period) and instrument used for the preparation plays an important role.

Preparing *Vati-Guti* manually and that using modern instrument like tablet making machine also differs in the uniformity, consistency, etc. of *Vati-Guti*. In addition, type of excipient and its proportion used varies according to various drug manufacturing units. Therefore, it is the need to specify the method of preparation for in-process standardization.

***Sneha Kalpana* (Medicated Oil and Medicated Ghrita):**

Temperature plays an important role while preparing *Sneha Kalpa*. Ignorance for a little time can also result in spoiling of the *Sneha kalpa*. It needs to develop standard temperature required for the preparation of Sneha Kalpa. In addition, the tests mentioned should be carried out while preparing *Sneha Kalpa*.

Use of Jacketed Vessel (Oil/ Steam/ Electric) can be helpful for the preparation of Sneha kalpa. There is no need of a continuous attendant, as the temperature is preset. Also, there is no risk of spoiling the *Sneha* due to maintained temperature. Using this method, the in-process standardization of *Sneha Kalpana* can be done easily[5] .**(Figure 3)**

***Sandhan Kalpana* (Fermented products):**

Sandhan Kalpana includes fermented products like *Asava, Arishta, Kanji*, etc. For the fermentation, various types of containers are used i.e. Wooden, Plastic, Stainless Steel, Earthen, etc. **(Figure 4).** These may also affect the quality of the final product.

***Bhasma Nirman*: (Figure 5)**

Bhasma is the speciality of *Rasashastra*. A variety of opinion is seen in the context of preparation of bhasma. Preparation of *bhasma* is really a tedious procedure. While preparing *bhasma* using traditional *Puta* (Heating) method, many difficulties are found regarding-

1. Size, shape and number of cow dung cakes to be used
2. Size, shape and number of *Sharava Samputa* (earthen pots)to be used
3. Quantity and quality of the drug placed in *Sharava Samputa*
4. Pit and its surrounding
5. Number of Cow dung cakes placed above and below the *Sharava Samputa*

After giving *Puta*, the obtained material has to be observed and then only number of cow dung cakes for next *Puta* can be decided. *Bhasma Parikshas* of the product should be carried out in between the *Putas*. Therefore, it signifies the need of developing S.O.P. of *bhasma*, which could be helpful in the in-process standardization of *bhasma*. Use of a modern instrument named electric furnace is also found to be done for the preparation of *bhasma*. It needs to follow the temperature pattern from traditional *Puta* method and apply it to furnace. However, challenge remains there regarding the therapeutic efficacy of the *Bhasma* prepared by these two methods. It can be compared to the *Roti* prepared using traditional *Chullha* and that prepared using Gas stove. Use of modern instruments is beneficial but the therapeutic efficacy should be checked by comparing with that of the traditional method.

***Kupipakwa Rasayan Nirman* :(Figure 6)**

In the preparation of *Kupipakwa Rasayan*, following factors may affect the quality and quantity of final product.

1. Size and Shape of *Kupi*(bottle)
2. *Matkapad/ Kapadmitti* - Number of layers, thickness of Cotton cloth and Clay
3. Nature and Dimensions of *Valuka Yantra* - Earthen/Metallic
4. Nature of *Valuka* (Sand) - Coarse/Fine
5. Number and arrangement of *Kupi* in *Valuka Yantra*
6. Source of Heat - Wooden/Gas/Electric
7. Temperature – *Mrudu*(low), *Madhya*(medium) and *Tivra* (high)Agni

3. Various *Parikshas* (tests) of the drug to be carried out during its preparation-

Significance and probable scientific reasons behind the tests described for the drugs during their preparation can be discussed as-

***Bhasma*-** For *bhasma* the tests which are described as *varitar*, *Rekhapurna* are indicative of its lightness and fineness. *Apunarbhav* and *Niruttha* are indicative of being free from the free metal and its complete conversion into *bhasma* i.e., ash form.

Specific colors are mentioned of specific metals/minerals. The color may be indicating the specific chemical configuration of the *bhasma*. Presence of free metal in the *bhasma* or intolerable taste of the *bhasma* can cause vomiting sensation when swollen. So the *bhasma* should be tasteless and it should not contain any free metal. If any free conjugated metal is persistent in the *bhasma* or the conversion process is not complete then such *bhasma* reacts with the *amla dravya* (e.g. curd, lemon juice, etc.) and some salt compounds are formed which may be changing the color

of the *amla dravya*. Thus this *pariksha* indicates presence/absence of free metal in the prepared bhasma[6].

Churna- Fineness of *churna* is expected; as more the fineness, more easily its assimilation and absorption takes place in the body.

***Sneha Kalpana* (Medicated Oil and Ghee)-**

Kalka remains soft in consistence and non-sticky due to complete evaporation of water content, so *kalka* can be made into *varti* form in between the fingers.

Kalka put on fire burns without any crackling sound. It is indicative of complete evaporation of water content in it. Any water content remaining in it may spoil the prepared *Sneha Klapa* earlier.

Goghruta (Cow ghee) contains saturated fatty acids. For the preparation of *sneha kalpana*, all the contents i.e. *kalka, ghrita,* and *drava dravya* are mixed together and heated continuously. At room temperature, *ghrita* which is in solid consistency, when heated with some liquids, due to liquefaction, it produces such a mixture, which resembles *phena* (foam).Because of the specific composition of *goghrita* and also its heat resisting capability, from the starting of preparation only the foam is generated and this produced foam will subside at one particular stage, when total water content is evaporated. Hence our *Acharya* has mentioned very scientifically disappearance of foam as a significant character among the *sneha siddhi lakshanas*. This character is quite opposite in case of medicated oil preparation, because the composition of taila differs from *ghrita*[7].

Specific color, odor and taste of the ingredients to the prepared *sneha kalpa* indicate its proper preparation with proper required heating.

***Avaleha Kalpana* (confection)-**

Tantumatvam indicates proper *paka* (digestion) of the *avaleha*. *Apsumajjan kharata* and *pidite mudra* also indicates its proper *paka* and consistency. These tests also indicate complete evaporation of its water content. Specific color, odor and taste of the ingredients to the prepared *avaleha* indicate its proper preparation with proper required heating.

***Sandhan kalpana* (fermented drugs)-**

When the process of *sandhan* i. e. fermentation is going on, froth is formed, which disappears after the completion of the process and no sound is heard.

On the onset of the fermentation, there is liberation of Carbon dioxide from the mixture which extinguishes the burning candle. But after the completion of the

process, obviously Co_2 is not liberated, so continuation of the burning candle is seen.

After the completion of fermentation, alcohol formation takes place so appreciation of alcoholic odor is seen.

CONCLUSION

While taking into consideration all the above points, it can be stated that even though the basic principles of drug manufacturing are followed, 100 percent standardization of any Ayurvedic medicine is quite difficult. Compared to the synthetic drugs, standardization and development of quality profiles for Ayurvedic drugs is much more complex, as they contain number of ingredients in a single drug. However, batch-to-batch variation can be minimized and quality of product can be maintained by developing own in-house quality control standards.

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