www.jahm.in
(ISSN-2321-1563)

REVIEW ARTICLE

A CONCEPTUAL REVIEW OF GRANULATION TECHNOLOGY IN AYURVEDIC PHARMACEUTICS

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ABSTRACT

In today's era of globalisation and large scale production of Ayurvedic formulations, there is an increasing need to enhance the shelf life of certain dosage forms. Shelf life can be enhanced by modifying the dosage forms by adopting modern technologies. Granulation is one such modern technology through which many dosage forms like *swarasa*, *kwatha*, *churna*, *avaleha* etc can be modified. Apart from increasing the shelf life, granule form of the medicament is having added benefits like rendering palatability to the drug, improving product appearance, convenience in handling, dispensing, and storage. It even improves dissolution of the drug, thus assuring maximum absorption and bio-availability. But while adopting these modern technologies utmost concern should be taken so that desired therapeutic efficacy of the drug is not compromised. This paper will shed light upon the details of various granulation techniques, their merits and de-merits when adopted to Ayurvedic formulations.

Keywords: Granulation, shelf life, modification, modern technology.

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INTRODUCTION

Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. Last decade has witnessed a sudden increase in the awareness of herbal formulations and globalization of Ayurveda has gained momentum. Hence there is a need for large scale production and marketing of Ayurvedic drugs. But there are many obstacles to meet these increasing demands like shelf life, palatability, presentation etc. Major issue of concern in the marketing of Ayurvedic drugs is the short shelf life of certain dosage forms like *Swarasa*, *Kashaya*, *Churnas* etc. Even in preparations like *Avaleha* which have longer shelf life, there are other problems like maintaining the stability, batch to batch consistency etc.

Considering this scenario, quest for certain modifications are a must to suit present day needs of palatability & enhanced storage. A number of such modifications have been emphasized in Ayurvedic classics, which have provided scientific basis in the development of newer dosage forms. Granules are one such modification which is based on *Khanda Kalpana* mentioned in the classics. Granules can be prepared through various recent advanced granulation techniques used in the modern pharmaceutical industry to make the drugs more suitable to the body elements and thus bring desired therapeutic effects.

Classical references of *Khanda paka*

The *Khanda Kalpana* mentioned in classics is nothing but the Granules. In *Khanda Kalpana* after *Paaka*, the final product attains granular consistency. *Haridra Khanda* (Bhai.Ra) [1], *Narikela Khanda* (Bhai.Ra) [2], *Vasa Khanda* (C.D) [3] and *Vasa Khanda Kushmanda* (C.D) [4] are best examples for *Khanda Kalpana.*

General method of preparation of *Khanda paka*

To the mentioned *Drava Dravya* (*swarasa, kashaya* etc), equal or double the quantity of *Khanda Sharkara* (Sugar candy) is added and *Paaka* is done. Then either *Churna* (powder) or *Kalka* of *Oushada Dravyas* (ingredient drugs) is added and heated till it attains *Paaka Siddhi Lakshanas* .Then heating is stopped and *Prakshepa Dravyas* are added followed by thorough mixing.

Use of modern technology in the preparation of granules

What are Granules?

Granules are the multi particle entities in which primary powder particles are made to adhere to form larger particle. Granule size ranges - between 0.2 to 4 mm, depending upon their subsequent use. Granules are the intermediate product

during the preparation of tablets & capsules[5].

Granulation

Granulation may be defined as a process of particle size enlargement, which converts fine or coarse particles into physically stronger and larger agglomerates. These agglomerates will be having good uniformity, flow property, wet ability, bulk density and good product appearance. The art and science for process and production of granules is known as Granulation Technology.

Manufacturing of granules

Manufacturing of granules involves incorporation of certain inactive ingredients to make up the bulk of the drug and also to meet and prevent certain pharmaceutical needs and problems. These active ingredients are called Additives/ Excipients and they are classified depending upon their functions as Diluents, Binders, Granulating agents, Disintegrants etc [6].

Types of Granulation

Granulation Technology can be broadly classified into 2 types based upon the type of processing involved:

1. Wet granulation
2. Dry granulation

Wet Granulation

Wet granulation is the most widely used and oldest process of granulation in the pharmaceutical industry. It involves addition of a liquid solution (with or without binder) to powders, to form a wet mass. This wet mass is dried and then screened to obtained granules.

The granulation liquid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol, either alone or in combination.

Steps in Wet Granulation

- Milling of drugs and excipients
- Mixing of milled products
- Preparation of binder solution
- Mixing of binder solution with powder mixture, to prepare wet mass
- Coarse screening of the wet mass using 6 – 12 mesh screen
- Drying the moist granules
- Screening of dry granules through 14-20 mesh screen

***Dry Granulation*:**

Dry granulation involves granule formation without using liquid solution by direct compression.

When To Choose DRY method?

- Direct compression not possible due to the properties and dose of the drug
- Drugs sensitive to heat and moisture

- For improved disintegration, as powder particles are not bonded together by a binder
  E.g.: Aspirin, Vitamins

Steps in Dry Granulation

- Milling of drugs and excipients
- Mixing of milled powders
- Pre-compression into slugs
- Mixing lubricants and disintegrants
- Direct compression into granules

Methods of Granulation

There are various methods adopted, which mainly include

- Single pot granulation
- Fluid bed top spray granulation
- High shear granulation/fluid bed drying combination
- Continuous fluid bed granulation
- Fluidized spray drying
- Pellet production line

Granulators

There are many varieties of granulators used in the pharmaceutical industry. The following three are the most commonly used,

1. Fluid bed spray granulator
2. Topo granulator
3. CF granulator

Advanced Granulation Techniques

Over a period of time, due to technological advancements and in an urge to improve commercial output,various newer granulation technologies have been evolved such as [7],

Steam granulation

It is modification of wet granulation. Here steam is used as a binder instead of water. Its several benefits include higher distribution uniformity, inhibits excessive wetting and lumping of the particles during their granulation and more favourable thermal balance during drying. Steam granules are more spherical; have large surface area thereby resulting in increased dissolution rate of the drug from granules. But the limitation is that it is unsuitable for thermo labile drugs. Moreover, special equipment's are required and are unsuitable for binders that cannot be later activated by contact with water vapour.

Melt/thermoplastic granulation

Here granulation is achieved by the addition of melt able binder. Binder is in solid state at room temperature but melts in the temperature range of 50 – 80˚C.There is no need of drying phase since dried granules are obtained by cooling it to room temperature. Moreover, amount of liquid binder can be controlled precisely and the production and equipment costs are reduced. It is useful for granulating water sensitive material. But this method is "not suitable for thermo labile substances". Hence drugs with

volatile components cannot be processed with this technique.

- **Moisture activated dry granulation (MADG**)

  It involves distribution of moisture to induce agglomeration. It utilizes very little granulating fluid and hence decreases drying time. Granules prepared using this method has better content uniformity and excellent flow ability.

  - **Moist granulation technique (MGT)**

    Here a small amount of granulating fluid is added to activate dry binder and to facilitate agglomeration. Then a moisture absorbing material like Microcrystalline Cellulose (MCC) is added to absorb any excess moisture, making drying step unnecessary. This is the current technique adopted for most of controlled release formulations.

- **Thermal adhesion granulation process (TAGP)**

TAGP is performed under low moisture content or low content of pharmaceutically acceptable solvent by subjecting a mixture containing excipients to heat. Heating is done in the temperature range of about 30ºC to 130ºC in a closed system, under mixing by tumble rotation until the formation of granules. This method utilizes less water or solvent than traditional wet granulation method. This is the best method to formulate granules having good flow properties.

Foam granulation

Here liquid binders are added as aqueous foam. It has several benefits over wet granulation such as it requires less binder and less water than wet granulation, rate of addition of foam is greater than rate of addition of sprayed liquids. It has no detrimental effects on granules, no over wetting, reduces drying time, uniform distribution of binder and also reduces manufacturing time. It is best for granulating water sensitive formulations.

Analytical tests for granules

Certain analytical tests are necessary when it comes to standardization and quality control aspects of granules.The granules must be evaluated for Carr's index, Hausner's ratio,angle of repose, bulk and tapped densities and percentage compressibility.

Adopting modern granulation techniques in *Bhaishajya kalpana*

Granules can be prepared very easily in small scale even without the use of any sophisticated machines or techniques as told in classics. Now a day, at the stage of *Khanda paaka* the preparation is sieved through different size meshes to obtain

granules. For instance, preparation of *Shatavari* granules from *Shatavari swarasa*, *Ashwagandha* granules from *Ashwagandha kashaya* etc.

We can even find several formulations in the market which are in the form of granules. To quote a few – *Kutajastakadi* granules(Pentacare), Allergin granules(Nagarjuna), *Madhumehari* granules(Baidyanath),Galakol granules(Charak) and so on. But by making use of above said recent advanced granulation techniques of modern pharmaceutical industry, classical dosage forms of Ayurveda can be modified for better storage and presentation.

Many research works have also been carried out in this regard.

A study was done by Paneliya *et al* [8] ; on the Pharmaceutical Development of Granules of *Vasa Avaleha*. It concluded that, by changing the proportion of *Sharkara, Go-ghrita,* and *Madhu, Vasavaleha* can be successfully modified into granules which are more palatable and also had better shelf life.

A study done by Basawaraj S.Patil *et al* [9]; on *Triphala* granules revealed that granules possessed better flow properties than *Triphala churna* and were more stable. Another study carried out by Vibhushree Kumar *et al* [10] ; reported that *Triphala churna* as such was not acceptable & pungent in taste. But the developed *Triphala churna* granules was acceptable with suitable taste. Additionally the conversion of granules reduced the effective surface area of the churna having pungent taste that come in contact with the tongue upon oral intake. All the volunteers concurrently accepted the taste of developed *Triphala churna* granules.

In a study by Ghosh Kuntal *et al* [11]; *Vasa Khanda Kushmanda Avaleha* was converted into *Vasakhanda Kushmandaka* granules. It improved its palatability & was convenient in storage & dispensing. Another study done by same authors [12]; concluded that *Shunti Khanda* when converted into granules was economical in terms of time & machinery usage.

Study carried out on *Kooshmanda beeja churna* & its granules Mishra Shiromani *et al* [13] ; concluded that for therapeutic use of *Kushmanda beeja* and for long shelf life, granules can be prepared as major components are not changed during preparation process.

In a study done by Nidhi Khemuka R Galib *et al* [14] ; Kamsa Hareetaki avaleha was converted into granules. It showed that granules help in fixing the dose, easy to administer & also increase the shelf life.

DISCUSSION

Primarily granules are prepared to improve flow and compression characteristics of the blend but there are many other benefits of granulation such as-

- Enhanced shelf life and excellent stability
- Increasing palatability of the drug
- Storage of rare and seasonal drugs
- Improving flow properties of the mix and hence the uniformity of the dose;
- Increasing the bulk density of a product;
- Facilitating metering or volumetric dispensing;
- Controlling the rate of drug release;
- Decrease dust generation and reduce employee exposure to drug product;
- Improving product appearance

Apart from enhancing shelf life, with all the added benefits, modification of certain dosage forms into granules can bring about a positive development in Ayurvedic pharmaceutics. Modern technology comes as a boon in this regard. Various recent advanced granulation technologies can very well be adopted in *Bhaishajya Kalpana*. In depth knowledge of the processing techniques and their merits and demerits is required to efficiently adopt each stage during the development of the product. A systematic approach should be followed for selecting the suitable granulation process.

Even though these techniques can modify the formulations very well pharmaceutically, due consideration has to be taken in retaining the potency and desired therapeutic effects of the drug. The hazards or interaction of the excipients added with the drugs should also be studied well before incorporating these techniques. The modified products should be evaluated in comparison with their original forms to know whether the effectiveness in the treatment remains the same. Long term effects of these modified forms should also be properly researched before finally brought in for therapeutic use.

CONCLUSION

Shelf life and such others problems are a major threat for Ayurveda in the pharmaceutical industry. Logical modifications of the classical dosage forms may be a solution for this problem. Granules are one such modification, which can be effectively done utilizing varied granulation techniques. A judicial selection of appropriate technology for carrying out the granulation process is the key to achieve a targeted granulation and final product parameters. In this way, by combining the contemporary technology with the classical knowledge we can bring

about a new hope in increasing the glory of Ayurveda.

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Cite this article as: Shilpa S N, Dayanand R D, Prasanna Venkatesh T S. A conceptual review of granulation technology in Ayurvedic pharmaceutics, *J of Ayurveda and Hol Med (JAHM)*.2018;6(5):31-38

Source of support: Nil

Conflict of interest: None Declared