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Hard gelatin capsules – A formulation design perspective and evaluation

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ABSTRACT

Process validation is collection of data to have reproducibility in quality within the product specifications. This principle of process validation invokes the understanding that the Quality, safety, and efficacy are designed to the product. This research describes practical steps that pharmaceutical manufacturers can take when applying the concept of process validation in hard gelatin capsules. End product analysis alone does not assure product quality, hence every processing steps need to be controlled and reproducible. Documentation of validation data is important for evaluation and to understand the process parameters. The process parameters that need to be monitored during process validation of a liquid fill solid oral dosage formulation depend on its method of manufacture. Process validation of a liquid fill solid oral dosage form has to be specific to its batch formula and the operating principles of equipment used for its manufacture. This liquid fill technology in hard gelatin capsules has captured the imagination of formulation and research scientists of many pharma giants. The process and validation of Vancomycin hydrochloride can be used as a guide for process validation of liquid fill capsules.

Keywords: Process validation, Hard gelatin capsules, Quality Assurance, Protocol, Dosage forms.

1. INTRODUCTION

Hard gelatin capsules are solid oral dosage form, in which the pharmaceutically active drug in powder form or pellet form or liquid form is filled. In 1982 only about 17.5 % of the newly licensed products were manufactured in capsules form, this rose to 34 % in the year 1986 and it is now a preferred dosage form for the researchers. The total manufacturing cost which include cost from machineries, The space required as per good manufacturing practice, the in process quality controls tests, analytical costs, cleaning and validation work are much cheaper than tablets and soft gelatin capsulation. The hard gelatin capsule can cover up the taste, odour and it is easy to swallow [1]. The empty gelatin capsule shells have two cylindrical portions. The bottom portion is the body and the top portion is the cap. The drug is filled in the body using appropriate filling machine and the caps is fitted above the body to keep the drug inside the capsules. The design of the empty shell has a self-locking arrangement to avoid spillage and opening of the filled capsules. There are various sizes of the empty hard gelatin capsule according to the dosage requirement of the drug [2].

1.1. Hard gelatin capsule (HGC)

They consist of a cylindrical body and cap, both with hemispherical end and are usually made from gelatin and water with added preservative. Although quite hard, they soften readily and dissolve after swallowing with water. The problems associated with SGC are overcome by HGC [3].

1.2. Vancomycin hydrochloride

Vancomycin hydrochloride Capsules USP, contains chromatographically purified Vancomycin hydrochloride, a tricyclic glycopeptides. It is derived from Amycolatopsis oriental is (formerly Nocardia orientalis), which has the chemical formula $C_{66}H_{75}Cl_2N_9O_{24}$•HCl. Vancomycin is used for full time treatment for the severe infection and susceptible strains due to methicillin resistant staphylococci (MRSA) virus, the increasing number of methicillin-resistant isolates of Staphylococcus aureus, Staphylococcus epidermidis and Staphylococcus pneumonia. Similar to problems of treating patients allergic to beta-lactum antibiotics, led to the rehabilitation of Vancomycin [4]. Vancomycin hydrochloride is the antibiotic indicated for treatment of Clostridium difficile-associated diarrhea. It is also used for the treatment of enter colitis caused by Staphylococcus aureus (including methicillin-

resistant strains). Parenteral administration of Vancomycin hydrochloride is not effective for the above infections; therefore, Vancomycin hydrochloride must be given orally for these infections. Orally administered Vancomycin hydrochloride is not effective for other types of infections. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancomycin hydrochloride and other antibacterial drugs, this drug should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Vancomycin hydrochloride is highly hygroscopic in nature and formulating them in hard gelatin capsule is very difficult as it absorb the available moisture from the hard gelatin capsule shell and makes the capsule shells brittle. Formulators use Macrogol 6000 as a hydrophilic matrix to reduce the hygroscopic character of Vancomycin hydrochloride. This formulation produced fecal, urine and plasma levels of the antibiotic similar to that of the market product of solution for reconstitution [5]. As it is a very new and expensive formulation to manufacture in hard gelatin capsules the product is usually exported to overseas market due to the cost factor. Due to high complication in the manufacture of this product the process validation assumes significance [6].

2. MATERIAL AND METHODS

2.1. Formulating hard gelatin capsules

Various factors are looked while designing the dosage form in hard gelatin capsules. A normal capsule formulation contains only about 1 to5 excipients. These factors make a formulation run effectively in a high speed capsule filling machine.

2.2. Diluents

Diluents are used to cover up the fill volume or weight of the capsules. Preferred diluents in a capsule formulation are Maize starch, Starch 1500, Lactose and Micro crystalline cellulose.

2.3. Lubricants

They help in smooth running of a high speed automatic capsule filling machine facilitating the powders do not stick to the tamping pins and dosing disc. Examples of lubricants are Magnesium stearate, Stearic acid.

2.4. Glidants

They help in the powder in granulation form or pellets form to flow from the hopper to the empty hard gelatin capsules. Talc and Aerosil (Colloidal silicon di oxide) are preferred as glidants

2.5. Disintegrating agents

These are agents which facilitate the disintegration of the slugs inside the capsule. Normally the diluents will perform this action, however in some instances Cross povidone, Sodium Starch glycolate and Croscarmellose sodium are used.

2.6. Wetting agents

These agents help the drug to get wetted with water there by facilitating the disintegration of the capsule contents. Examples of wetting agents are Sodium Laurylsulphate and Tween 80.

3. RESULTS AND DISCUSSION

3.1. Determination of capsule size

The bulk density of the ingredients along with the excipients helps in deciding the capsule size. The availability of capsule filling machine change parts and packaging change parts also play an important role on deciding the capsule size.

Table - 1: Determination tapped density

Capsule Size	Volume in ml	Tapped density of materials in grams /ml			
		0.6	0.8	1	1.2
000	1.37	0.822	1.096	1.310	1.644
00	0.91	0.546	0.728	0.910	1.092
0	0.68	0.48	0.544	0.680	0.816
1	0.5	0.3	0.400	0.500	0.600
2	0.37	0.222	0.296	0.370	0.444
3	0.3	0.180	0.240	0.300	0.360
4	0.21	0.126	0.168	0.210	0.252
5	0.13	0.078	0.104	0.130	0.156

Industrial automatic capsule filling machine run at high speed , an output ranging from 75000 capsules to 1,20,000 capsules per hour. The tamping pins and the dosing disc play an important role in getting the capsules that are within the prescribed weight variation. The pharmacopoeia limits for capsules with average weight above 300 mg the weight variation should be within 7.5 % and for capsules with average weight less than 300 mg it is 10 % .Adequate lubrication is required for efficient plug ejection and to prevent filming in the dosing disc. The lubricant also reduces the friction of the sliding components which run at high speed of 50 to 120 strokes per minute.

3.2. Assurance of quality output

In industries the Quality assurance department takes care of the in process checks during the filling of the capsules. The various factors that are monitored during the hard gelatin capsule filling are

3.2.1. Weight variation

Proper lubrication and glidants facilitate uniform flow of granules or pellets from the hopper to the dosing disc. Periodic monitoring and recording of the average weight and uniformity of fill weight every 30 minutes during the filling reduces the weight variation problems

3.2.2. Disintegration time

Normally the pharmacopoeia limits says not more than 30 minutes

3.2.3. Locking length

This is an important check which assures the capsules are properly pressed and the locking system is intact.

3.2.4. Visual checks like telescopic capsule and dents

This happens due to improper machine setting with incorrect tamping pin sizes and pin configuration.

Hard gelatin capsules are finding wide acceptance in the formulation industry as it offers scope for many different formulations. Some of the formulations carried out in hard gelatin capsules are

- **Powder filling:** here the medicament will be in powder form or made granular if the flow is very poor using a granulation technique as is done in tablet granulation. Typical examples of this dosage form are multivitamin capsules, Piroxicam capsules, Tizanidine capsules, Ibuprofen capsule etc.
- **Tablets added to the Capsules along with powders**: this formulation is mainly done when the pharmacological action is required both in the buccal cavity as well as in the intestine. Tablets are enteric coated to get the dosage release in the intestine where the pH is more alkaline in nature;the powder form will give immediate release. Change part modification required to be done in the capsules filling machine where tablets can be introduced in every capsule.

Typical example of this dosage form is Rabiprazole enteric coated tablet added along with Atorvastatin powder in capsule form.

- **Pellets filling:** Sustained release formulation is designed in pellets form for capsule filling. An example of this formulation is the Domperidone Sustained Release Capsules. Pellets are coated with different thickness of cellulose to have different release profile. Say about 33 % pellets will have immediate release where as another 33 % will get released after 4 hours and another 33 % will get released after 8 hours. All pellets are coated separately and mixed to have uniformity and then filled. Caution to be taken in this dosage form with respect to particle size, more the difference in pellet size more will be variation in weight. Agglomeration of pellets will result in variation in release profile. Pellet filling is done with volumetric dosing plate and more care to be taken with respect to the moving parts in the capsule filling machine as any peel off to the surface of the pellets will affect the sustained release profile.
- **Liquid filled in Capsule:** The medicament will be in oily form and they are filled in hard gelatin capsule. Leakage of oil is associated with this dosage form. To arrest oil leakage band sealing of capsules with gelatin or cellulose is done.

  An example for this dosage form is Vitamin A & D capsules, Evening Prime Rose oil Capsules and Omega 3 fatty acid Capsules. As the nature of the drug is in oil form in earlier days they are filled in Soft gelatin Capsules. However with slight modification in the existing machine hard gelatin capsules are used for filling oils. Band sealing at the joints is an additional activity in this dosage form which is gaining popularity due to its uniqueness

and also transparent empty gelatin capsules are used for filling oils.

- **Semisolid capsule**: This is a new technique where thermoplastic components are filled in hard gelatin capsule. Example for this dosage form is the Vancomycin Hydrochloride Capsules. In this dosage form the medicine will remain in liquid form at a temperature of 50°C- 60°C .The liquid fill preparation is filled in hard gelatin capsules which solidify as the temperature falls below 50°C. There is no requirement of band sealing as the liquid will solidify taking the shape of the gelatin capsules [7].

3.3. Process validation of formulations in Hard gelatin Capsules

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced for its intended use. This principle of process validation incorporates the understanding that the following conditions exist:

- Quality of the product, safety, and efficacy of the dosage form are designed into the product.
- Quality cannot be adequately assured merely by in-process checks and finished-product analysis.

The manufacturing process is controlled to assure that the finished product meets all quality attributes including all finished product specifications.

3.4. Approach to process validation

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages [8].

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 –Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Before commencing the commercial production a manufacturer should gain a high degree of assurance in the performance of the manufacturing process such that it will consistently produce the quality. The active pharmaceutical ingredients and drug products meeting these attributes relating to identity, strength, quality, yield and other finished product specification. The information and data obtained from the first three process validation batches should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions.

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that result in products with the desired quality attributes. Therefore during the preparation of the process validation report the manufacturer should

- Understand the sources of variation.
- Detect the presence and degree of variation.
- Understand the impact of variation on the process and ultimately on product attributes.
- Control the variation in a manner commensurate with the risk it represents to the process and product.

After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change [9].

3.5. Documentation

Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle.

Before starting the process validation study a protocol is prepared which highlights the reason for the study, the scope of the study, sampling procedure, the critical control parameters to be captured and the finished product specification. They also identify the organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to the market. A process validation report will be prepared in line with the protocol and the

summary and conclusion will give the validated critical control process parameters to be followed for commercial run.

The various critical control parameters that are required to be documented in the Capsule manufacturing are preparation of medicament for filling purpose.

- Preparation of granules, which are done in the granulation area like that of tablet granulation using Rapid mixer granulator, Fluid bed drying, multi mill and finally blenders for lubrication of the granules.
- In case of preparation of sustained release pellets conventional coating pans are used for spray coating.
- When enteric coated tablets are added to granules or pellets in hard gelatin capsules the tablets preparation is separately carried out in the compression cubicles and coated in coating pans and separately loaded in hopper to be fed inside the capsules along with powder or pellets.
- For filling liquids the fill preparation are prepared by filtering and mixing the various oils in planetary mixer. Band sealing is important in liquid filled hard gelatin capsules. Band sealing is done separately but immediately after the filling of capsules are completed.
- For manufacturing of Semisolid fill preparation thermoplastic components are kept in hot condition along with the medicament and will remain in liquid form at a temperature of 50°C to 60°C. The liquid fill preparation is filled in hard gelatin capsules which solidify as the temperature falls below 50°C. Vancomycin Hydrochloride Capsules are manufactured using this procedure.

3.6. Manufacturing process

3.6.1. Medicine fill preparation

Required quantity of Macrogol 6000 taken in the jacketed planetary mixer and steam passed through the outer jackets. The temperature is raised to 80°C and maintained until the Macrogol 6000 is completely in molten state. The temperature reduced to 70°C and weighed quantity of Vancomycin hydrochloride added to the Macrogol 6000. The planetary mixer is mixed for 45 minutes until a smooth molten paste of the medicine is obtained. Unload the medicine in a jacketed kettle, weigh the medicine and transfer to the filling area. The vessel should be maintained at 65°C to 70°C throughout the filling period.

3.6.2. Capsule filling

The machine set with 2 size capsule change part for Vancomycin hydrochloride 125 mg capsules. The hoppers and the plungers are maintained at 65°C throughout the filling period to avoid any solidification during the filling period at the nozzle or in the product hopper. As the medicine is of high value machine initial setting should be carried out with empty capsules. After machine setting for locking length and capsule loading on the filling plates, line clearance from quality assurance obtained to start the filling process. The fill medicine is transferred to the hopper from the kettle to the product hopper. Any leftover in the kettle has to be kept under closed condition and at 65°C to avoid solidification of the material. The empty capsules are loaded to the empty capsule hopper and startup of the capsule filling machine done. Due to the viscous nature of the medicine the machine is run at a speed of 6 SPM to 12 SPM (3600 capsules to 7200 capsules per hour) Discard the initial few rotations of the filled capsule until the material is uniformly filled in the capsule. Collect 10 capsules and check the average weight. Suitable adjustment carried out until the required weight is achieved. Once the weight is set the disintegration of the capsules checked (NMT 30 minutes).The locking length of the capsules checked. Once all the parameters are within the product specification QA will give approval for filling activity to commence. The filled capsules after closing is allowed to tumble through the mini capsule sorter and empty capsule sorter and collected in double poly bag lined HDPE drums. The capsules have to be kept in open condition until the Capsules cools down to room temperature.

3.6.3. Validation plan

This gives the plan about the sampling points in the planetary mixer, how much sample to be taken from each locations and the sampling temperature during filling [10].

Yield and reconciliation–Batches manufactured with tentative yield fixed for validation batches.

Table - 2: Yield

Stage	Tentative yield
Fill preparation	NLT 98 %
After Capsule filling	NLT 95 %
After check weighing	NLT 93 %
After packing	NLT 92

After evaluating yield trends from 10 batches Standard yield to be fixed.

Table - 3: Process validation mixing time

Planetary mixer sampling points	Assay after 35 minutes	Assay after 40 minutes	Assay after 45 minutes	Assay after 50 minutes
1	88.4	94.8	99.5	99.3
2	98.9	99.2	98.9	99.4
3	115.4	106.5	100.5	100.5
4	100.4	100.1	98.8	98.5
5	99.5	98.5	101.1	101.0
6	90.4	94.7	98.5	98.5
7	100.1	100.3	99.4	99.2
8	117.1	107.5	100.4	100.1
9	89.9	91.2	98.9	99.2
10	115.8	106.9	101.7	101.5

3.6.4. Documentation

All observation data like QC results, in process printouts which are validated during the study are collected and kept in the respective batch BMR.

4. CONCLUSION

The critical control parameters in hard gelatin capsules are mainly preparation of input material (Content uniformity), Average weight, uniformity of weight, disintegration test, locking length of capsules. During the filling of capsules all the physical parameters are documented at regular intervals. The goal of the manufacture is that every step in the manufacturing process is clearly built in the system in every step and not just tested in the end. An important aspect of process validation is training requirement of the personnel involved in documenting the results. The expectation from regulatory authorities is that all steps are clearly explained and controlled so that the production cycle does not change substantially over time between batches.

A well-executed process validation assures one and all that the process parameters are uniform and the integrity of the products assured.

5. REFERENCES

1. Sven Stegemann and Capsugel Bornem. Hard Gelatin Capsules-Today & Tomorrow at Capsugel. **Quality People & Product working together.** 2nd edition, 2002.
2. Guo M, Kalra G, Wilson W, Peng Y and Augsburger LL. A prototype intelligent hybrid system for hard gelatin capsule formulation development. **Pharm Technol N Am.** 2002; 26: 44–60.
3. Gita Natarajan Shankar. **Orally-Absorbed Solid Dose Formulation for Vancomycin,**. US Patent application number: 20090111736, April 30, 2009.
4. Vancomycin Hydrochloride capsules- Patient Counseling Information, **Prasco Laboratories Mason,** OH 45040 USA Rev. 07/12.
5. Kats P and Campbell C. FDA 2011 Process Validation Guidance: **Process Validation Revisited. Journal of GXP Compliance.** 2012; 16(4): 18-29.
6. Cole ET, Cade D and Benameur H. Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. **Adv Drug Deliv Rev.,** 2008; 60: 747–756.
7. Rakesh Das, Tapan Kumar Pal, Bankim Chandra Nandy and Subhabrata Duttagupta. Development of method of analysis for estimating the Vancomycin in blood Plasma by RP-HPLC method: Application to in vivo Studies. **Der Pharmacia Lettre**., 2010: 2(1) 201-210.
8. Guidance for Industry Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment, Office of Training and Communication, **Division of Drug Information, HFD-240, Center for Drug Evaluation and Research, Food and Drug Administration.**
9. Vijaykumar N and Anusha Reddy R. Liquid filling in hard gelatin capsules: A Review. **Journal of Pharmacy,** 2013; 1(1): 10-18.
10. Pandita Rachna, Rana AC, Seth Nimrata and Bala Rajni. Introduction and general over view of pharmaceutical process validation. **International research Journal of Pharmacy.** 2012: 3(6): 60-64.