

## Formulation and Validation of Vancomycin Liquid Fill Capsules

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**Abstract:** Enhanced systemic absorption of poorly permeable drugs like Vancomycin hydrochloride may be achieved by increasing their trans-epithelial and paracellular permeation across the gastrointestinal tract by using permeation enhancers like Macrogol. This was demonstrated by increase in Vancomycin apparent permeability coefficient across rat jejunal tissue in mucosal-to-serosal direction as measured in an *in vitro* system by at least 25%. This triggered a necessity to develop a newer formulation for Vancomycin hydrochloride, and to prepare permeable membrane with Macrogol and fill the liquid material in hard gelatin capsules. 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:** Hard gelatin capsules, manufacturing process, filling, deviations, Concurrent process validation.

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### Introduction

Vancomycin hydrochloride Capsules USP contains chromatographically purified Vancomycin hydrochloride, a tricyclic glycopeptides. It is derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*), which has the chemical formula  $C_{66}H_{75}C_{12}N_9O_{24} \cdot HCl$ <sup>1</sup>. 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<sup>2</sup>.

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. 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<sup>3</sup>.

Process validation is collection of data to have reproducibility in quality within the product specifications. Various process validation theories and procedures are put forward for various pharmaceutical dosage forms. Effective Process Validation contributes significantly to assuring drug quality. The basic principle of any process validation is that a drug that is manufactured should be fit for its intended use. This principle of process validation invokes the understanding that the Quality, safety, and efficacy are designed to the product. Quality cannot be addressed merely by in-process and finished-product testing. Quality of manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications. This will require systems for detecting unplanned deviations from the designed process, and there is a strong emphasis on the use of collected data, which is reviewed in a timely manner by adequately trained personnel in statistical process control techniques. The development of a data Collection Plan ensures that the information collected can be verified and the critical quality attributes are controlled throughout the process. This production data also should evaluate process stability and capability and the scrutiny should include both within batch as well as between batches<sup>4</sup>.

Any deviation observed in the validation protocol should be addressed through deviation handling procedure of the Quality management system and addressed through appropriate corrective and preventive action (CAPA). However when we take up process validation of special products like Vancomycin hydrochloride capsules which is filled as liquid filled capsules the validation of the dosage form achieves significance as the manufacturing process is new and innovative technique and very few companies in India are manufacturing this product. The capsules contain Vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) Vancomycin. Inactive ingredient includes Macrogol 6000 and the HGC for 125 mg capsule shell contains gelatin, F D & C Blue No. 1, titanium dioxide, iron oxide red and iron oxide yellow. The capsules are printed with black ink. The black imprinting ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide and potassium hydroxide<sup>5</sup>.

## Materials and Methods

### Process validation Protocol

Before starting the process validation study approved protocol is required. The parameters that need to be validated are required to be part of the protocol.

**Purpose of the study:** It explains the reason for conducting the process validation. To validate the critical control parameters during the manufacture and filling of Vancomycin hydrochloride Capsules.

**Scope of the process validation:** The scope of the study also gives the number of lots or the number of batches the validation study is planned. The scope of the study is the mixing time of the medicine preparation and product temperature during the filling activity. Three commercial batches are planned for validation study.

**Reason for revision:** This is mainly done in case of any typing error in the validation document. When validation is done for change of any equipment model name or specification or any lack of information in validation step is observed the protocol is revised<sup>6</sup>.

**Reason for validation:** The reason for validation could be new products introduction to the market or Changes in site of manufacturing or Change in batch size or Change in manufacturing formulae or Change in the manufacturing process or Changes in specification of input material or Change in vendor of active pharmaceutical ingredient or critical excipient or Abnormal trends, out of Specification (OOS) and or out of Trend (OOT).

**Responsibility:** This gives the people responsible for conducting the process validation study. The validation is done by the user department with representative from QA, QC, Engineering and production team. All the cross functional team heads will be responsible for any protocol preparation.

**Validation approach:** This is to identify whether the study is prospective validation or Concurrent validation or Retrospective validation. In this case it is the Concurrent process validation as the commercial batches are used to monitor the processing parameter<sup>7</sup>.

**Manufacturing conditions:** It gives the conditions to be maintained in the area of manufacturing and any other special requirement for the stability of the product. In Vancomycin Capsules the area temperature should be maintained between 22°C to 25°C. The RH should be 40± 5%. Any excursion from the set temperature or humidity the production will be immediately suspended until the conditions are restored. This also gives detail if product is photo sensitive or any other environmental conditions to be maintained for moisture sensitivity<sup>8</sup>.

**Pack details:** This gives detail about the final product packing. It mentions about primary pack, secondary pack and tertiary pack and other details like product literature insert or any other specific information to packing.

**List of raw materials:** This gives the information on the label claim, the batch sizes, and the list of various active pharmaceutical ingredients, excipient required for manufacturing the batch. Each hard gelatin Capsule contains Vancomycin hydrochloride USP equivalent to Vancomycin 125 mg

**Batch Size:** 1, 20,000 Capsules.

### Batch formula

**Table 1:** Material ingredients

Name of the material	Spec	Quantity required
Vancomycin Hydrochloride	USP	15.375 kgs
Macrogol 6000	USP	21.825 kgs
Hard gelatin Capsules	USP	7.94 kgs ( 1,26,000)

### Equipments Required:

- Jacketed planetary mixer
- Jacketed kettle
- Liquid fill automatic capsule filling machine –AF 40(with line machines).
- Check weighing machine
- Blister packing machine.

**Reference documents:** Here the documents like Master Formula record (MFR), Batch manufacturing record (BMR) or Standard operating procedures (SOP) which are referred for this validation are mentioned.

### Manufacturing Process:

#### 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.

**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 start up 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<sup>9,10</sup>.

**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.

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.

**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.

## Results and Discussion

**Table 3:** Observations of 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	<b>115.4</b>	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	<b>117.1</b>	107.5	100.4	100.1
9	<b>89.9</b>	91.2	98.9	99.2
10	<b>115.8</b>	106.9	101.7	101.5

At the end of 35 minutes of mixing Vancomycin hydrochloride with Macrogol 6000, 3 sampling points in the planetary mixer – 1 and 9 found to contain less Vancomycin hydrochloride. Similarly the content of Vancomycin hydrochloride is above the Specified limit in 3 sampling points in the mixer - 3, 8 and 10. At the end of 40 minutes mixing the Vancomycin hydrochloride content is found to be better mixed than the earlier time limit. However sampling points 1, 3, 6, 8, 9 and 10 show more variation in the assay value of Vancomycin hydrochloride. At the end of 45 minute mixing time a uniform Vancomycin hydrochloride assay content is seen throughout the planetary mixer. All values were closer to the mid value. At the end of 50 minutes there is not much variation in Vancomycin hydrochloride content observed as compared to the 45 minutes mixing time. All 3 validation batches behaved in the similar way. Hence the mixing time of Vancomycin hydrochloride in Macrogol 6000 can be fixed at 45 minutes.

## Storage Temperature

**Table 4:** Storage condition

Storage tank temperature	Medicine character	Weight variation	Remarks
55° ±2°C	Poor flow property	Required weight not achieved	Lump formation of medicine, not flowing. Frequent stoppage
60° ±2°C	Poor flow property	Required weight not achieved	Material more sticky, small lumps observed
65° ±2°C	Flow uniform	Average weight achieved	Uniform, smooth and Free flowing
70° ±2°C	Flow uniform	Average weight achieved	Uniform, smooth and Free flowing

At 55°C the material was not flowing uniformly and more tendencies for lump formation in the tank was observed. Frequent stoppage of the capsule filling machine due to lumps in the medicine blocking the nozzle. Average weight not achieved continuously. When the temperature maintained at 60°C slight improvement in the flow observed, however lump formation is seen on the tank and average weight not achieved continuously. The temperature increased to 65°C and the medicine was found to be smooth and free flowing continuously through the pipes without any blockage. Required average weights were achieved. Temperature increased to 70°C, the medicine behaved same like 65°C with all the parameters found to be within normal limits. The material also smooth and free flowing, no lumps observed. All the 3 batches behaved the same with respect to temperature variation. The filled capsules solidify completely when the Capsules get tumbling to the polishing unit after getting ejected by the tamping pins. Temperature greater than 70°C will increase the solidification time of the medicine inside the hard gelatin capsules and that does not give the desired output.

Hence the Temperature of the medicine to be maintained between 65°C and 70°C during the entire time of filling. The validation process highlight the manufacturing process followed in studying the 2 process parameters.

## Conclusion

**Deviations Observed during the Process validation:** The process validation carried out as per the protocol however had some unexpected process deviations. These deviations were investigated to avoid recurrence of this kind of incident in the commercial batches. Three deviations were observed in the 3 process validation batches. Deviation was logged due to 1) change in locking length, 2) Weight variation and 3) hold time of medicine. Root cause analysis and risk assessment done for the deviation and suitable CAPA raised to close the deviation. As we go through the whole exercise of the process validation we could bring out some of the benefits we achieved through this study.

**Prevention based activity:** Process validation is done to have reproducible quality throughout the product life cycle. In this concurrent validation batches the products were subjected to long term and accelerated stability conditions to study the product behavior throughout its shelf life. As these are commercial batches the manufacturer releases the product to the market after QC clearance. All kind of precautions were taken in this process validation study. All parameters were well planned and executed as per the protocol. Both the process parameters gave very clear process clarity in terms of mixing time and product temperature. The deviations and subsequent root cause investigation has resulted in corrective and preventive action. This will avoid recurrence of such deviations in the future.

**Expensive activity but cost effective after validation:** As per the protocol excessive sampling done (in terms of number and quantity) during the mixing and holding time. All these analytical exercise result in huge analytical cost. Similarly more time is lost for frequent stoppages to understand the process variables. All these initial costs however give as valuable inputs. These costs can be recovered in the regular batches as the process parameters are validated and reproducibility of quality products with less process deviation is achieved.

## References

1. Gita Natarajan Shankar. Orally-Absorbed Solid Dose Formulation for Vancomycin, US Patent application number: 20090111736, April 30, 2009.
2. Rakesh Das, Tapan Kumar Pal, Bankim Chandra Nandy, Subhabrata Duttgupta. 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.
3. Vancomycin Hydrochloride capsules- Patient Counseling Information, Prasco Laboratories Mason, OH 45040 USA Rev. 07/12.
4. Pandita Rachna,Rana AC, Seth Nimrata, Bala Rajni. Introduction and general over view of pharmaceutical process validation. *International research journal of pharmacy*. 3(6), 2012: 60-64.
5. Stephen Brown, Gary Norman and Alyn McNaughton. Liquid-Fill Based Formulation: Advances and Challenges at Encapsulation Drug Delivery. *Innovations in Pharm. Technol.* 64-68.
6. Cole ET, Cadé D, Benameur H. Challenges and Opportunities in the Encapsulation of Liquid and Semi-Solid Formulations in Capsules for Oral Administration. *Adv Drug Deliv Rev.* 2008; 60(6):747-56.
7. 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.
8. N Vijaykumar, R Anusha Reddy. Liquid filling in hard gelatin capsules: A Review. *Journal of Pharmacy* 2013 1(1) 10-18.
9. Elsie Jatto, Augustine O. Okhamafe. An Overview of Pharmaceutical Validation and Process Controls in Drug Development. *Trop J Pharm Res*, 2002; 1 (2): 115-122.
10. Scott Bozzone, Process Validation of Solid Oral Dosage Forms, Part I General Principles Cork, Ireland IKEV Meeting June 1, 2001.

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