RESEARCH ARTICLE

Prospective Process Validation for the Manufacture of Telmisartan Mini Tablets

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ABSTRACT

Failure in developing an effective process for the manufacturing of drug products may lead to severe consequences like product recalls and plant closure. As a result, process validation has gained a prime focus as an essential product development activity. In the limelight of this notion, the research goal of current work was to carry out prospective process validation for the manufacture of Telmisartan mini tablets along with a capsule containing them. Telmisartan mini tablets production was trialed and tested for results. The Formulation that gave promising results was considered and concluded for process validation. Protocol and batch manufacturing record (BMR) were prepared for three consecutive batches of the same size, method, equipment, and validation criteria. The critical process parameters were identified, mini-tablets were compressed by using the direct compression method and evaluated. The results of three consecutive batches were compiled with specifications. It indicated that the process employed here offers a high degree of assurance to produce quality products meeting pre-determined specification limits and quality attributes.

Keywords: Mini tablets, Process Validation, Prospective process validation, Quality attributes, Telmisartan.

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INTRODUCTION

Process validation is documentary evidence offering a high degree of assurance that a particular process can reliably deliver a product meeting its pre-determined specifications and quality standards.[1] It is the process carried out in all pharmaceutical industries to verify every step of manufacturing various dosage forms of drugs. The quality of drugs manufactured is very vital towards patient safety and hence regulatory bodies made process validation mandatory. The importance of process validation is enlisted below:

- It guarantees the manufacturing process and product quality.
- Process optimization can be achieved by maintaining the quality standard for maximum efficiency, facility, equipment, system, and process results in a product that achieves the lowest cost of quality requirements.
- It reduces rejections, reworks, re-test, re-examination, and thereby the cost of poor quality can be prevented.
- The validation process also improves safety operations.
- It ensures that the manufacturing process is appropriate and a product of the desired quality is consistently produced.

Process validation can be categorized as, prospective process validation, concurrent process validation, retrospective process validation, and revalidation.

Prospective process validation proves that the process can operate according to the predefined validation protocol prepared for pilot product trials and has documented robustness and reliability in the manufacture of predefined product specifications and current good manufacturing practice (cGMP) standards.[2-3]

Current work is on mini-tablets: the solid unit dosage form of size equal to or smaller than 3.0 mm (sometimes even up to 5 mm) in diameter. Mini tablets are one such multi particulate system that is filled in capsule and shows the benefit of tableting within the capsule. They offer high drug loading, low risk of dose dumping, less inter and intrasubject variability, a high

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degree of dispersion in the digestive tract and minimizes the risk of high local drug concentrations.[4-5]

Telmisartan, the antihypertensive drug, has a short half-life of about 1.5–2 hours, and therefore for long term use, it requires repeated administration in a particular period. Because of this, Telmisartan exhibits lower patient adherence, and higher incidences of side effects (such as nausea, vomiting), and development of tolerance. Instead of repeated administration, formulating it into a sustained release drug delivery is considered as an appropriate alternative. As per the technology point of view pellets, and granules are harder and more expensive to manufacture than tablets. Mini matrices were therefore developed to combine the physiological advantage of multi-unit dosage forms with the economic advantage of single unit dosage forms.[6-7]

So, Telmisartan sustained-release mini-tablets were formulated as per standard procedure, but the procedure was not evaluated previously for its consistency, and hence it became the objective of the current research. Therefore, the process validation of Telmisartan mini-tablet manufacture was considered essential to ensure drug consistency and patient health. The present work focused on identifying critical process parameters by questioning its upper and lower specifications and consequent evaluation through prospective process validation.

MATERIALS AND METHODS

Preliminary Studies of Raw Materials Used in the Manufacturing Process

These studies generally deal with physicochemical and various pharmaceutical properties related to drugs and excipients, and give an idea that any modification in the properties affects the nature of drug products to acquire better results. Hence all the raw materials used in the manufacturing process were tested as per respective pharmacopeia and the identity and purity of raw materials were confirmed.

Qualification of Equipment

A qualification is an act of proving and documenting that equipment or ancillary system are properly installed, work correctly, and leads to the expected results. It is a part of process validation, and two pieces of equipment used in the manufacture were qualified after preparing the qualification protocol.

Qualification was done into four phases for the Tablet compression machine and Sieve shaker, which is described as follows:

- *Design Qualification:* It was carried out by reviewing the equipment manual and then physically compared with the equipment.
- *Installation Qualification:* It was performed for both instruments and then checked if the equipment is installed properly in the appropriate room and environment and confirmed.
- *Operational Qualification:* Both instruments were operated without using raw material to confirm their working condition.
- *Performance Qualification:* This was done by operating both the equipment with a blended sample of the material.

Process Validation Protocol and Batch Manufacturing Record Preparation

Validation Protocol: It is a documentary outlining that how testing will be done, including test requirements, product specifications, manufacturing equipment, and decision points on what constitutes acceptable test results.[8]

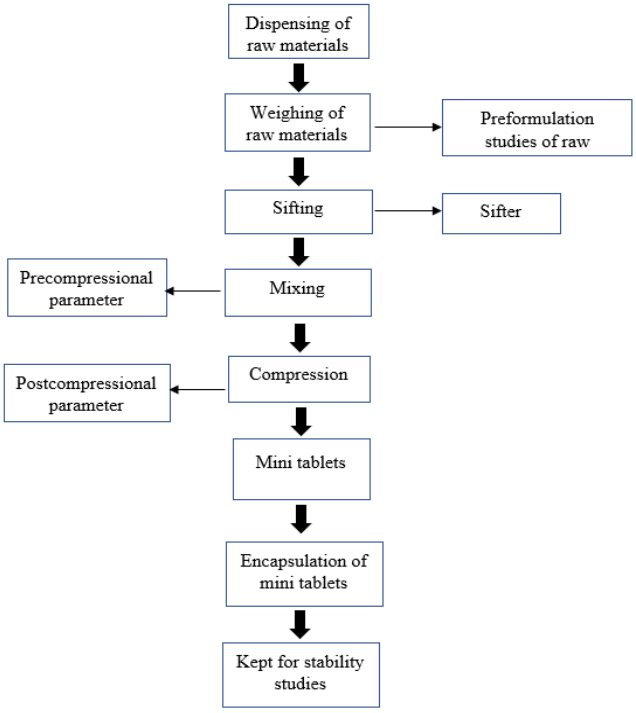
Prospective process validation protocol and BMR was prepared for by referring books, research, and review articles. This was achieved based on the results obtained during trials and challenge studies.

Following are the contents of the validation Protocol:

1. General information
2. Objective
3. Members involved in process validation
4. Formulation details
5. List of approved vendors (for the purchase of ingredients)
6. The detailed manufacturing process (flow chart)
7. List of equipment's
8. References for equipment qualification
9. Identification of description of critical steps and critical process parameters
10. Scientific rationale of critical steps and critical parameters
11. Sampling and testing plans
12. The validated analytical method for in-process and final product testing
13. Acceptance criteria

Process Validation

Three batches of 650 mini-tablets of the same size were manufactured as described in the BMR current versions of



Process flow chart: Telmisartan 80 mg mini tablets

Table 1: Blend uniformity results of three batches

	Mixing time									*Acceptance criteria*
Parameters	Batch 1			Batch 2			Batch 3			
	5 mins	10 mins	15 mins	5 mins	10 mins	15 mins	5 mins	10 mins	15 mins	95.0 %-105.0 % of labeled amount
% Assay (average)	95.38%	96.11%	96.23%	96.09%	96.19%	96.20%	96.16%	96.20%	96.20%	
SD	0.40	0.17	0.10	0.05	0.04	0.02	0.07	0.04	0.01	NMT 3%
% RSD	0.41	0.17	0.10	0.05	0.04	0.02	0.07	0.04	0.01	

Table 2: Pre compressional results of three batches

Sl. No	*Parameter*	*Batch 1*	*Batch 2*	*Batch 3*
1	Bulk density (g/cm^3)	0.47	0.46	0.45
2	Tapped density (g/cm^3)	0.48	0.47	0.46
3	Carr's index (%)	2.0%	2.12%	2.17%
4	Hausner's ratio	1.02	1.02	1.02
5	Angle of repose (°)	28.8	29.24	27.47

standard operating procedures (SOPs) were followed during the manufacturing process. The observations were recorded at the compression stage in the datasheets. The steps involved were represented in the below-mentioned flow chart and details were discussed further.

Dispensing of the Raw Materials

Suitable environmental conditions and room temperature were observed during dispensing stages of different raw materials. Dispensed raw materials need to be verified that all the materials should bear quality control approved label and stored in quarantine before proceeding any further steps.

Weighing

Ensure that the weighing balance is clean and check the balance is adjusted to zero. Different spatulas or scoops were used to avoid mix-ups or cross-contamination and store in an airtight container.

Sifting

Sifting was performed to achieve uniform particle size. Accurately weighed ingredients were passed through 60 # sieve and calculated for the sample retained on the sieve and the sifted sample. The sieve integrity was checked before and after each use. The formula for the sieve analysis:

sample retained %=(sample retained)/(sample taken)×100

Blending

The sieved material was transferred to the polybag and mixed for about 15 minutes. The sample was collected at 5, 10, and 15 minutes to perform the blend uniformity test described in Table 1, and later blend was stored into an airtight container to perform Precompressional parameters.

Compression

Ensured that the tablet compression machine was clean before and after use. Multi tooling punch was used to compact small mini tablets by using a previously stored powder blend. Mini tablets were collected at different stages during compression at initial, middle, and end stages to perform post compressional parameters. The post compressional parameter was for composite samples. Fixed parameters and specifications were followed during the compression stages.

Pre Compressional Parameters Enlisted Below

Blend uniformity, angle of repose, bulk density and tapped density, compressibility index, and Hausner's ratio are the parameters performed considering required specification limits in Table 1.

Postcompressional Parameter Given Below

Appearance, weight variation test, hardness, thickness, percentage friability, drug content, *in-vitro* disintegration, In vitro dissolution studies, and stability studies were performed for three batches as per set acceptance limits as described in Table 2.

Consolidation of Results and Preparation of the Validation Report

Manufacturing, evaluation results, and their comparison with acceptance criteria were collectively summarized in the final validation report.

RESULTS AND DISCUSSION

The dose of Telmisartan mini-tablets was each tablet containing Telmisartan 20 mg.

All raw materials were subjected to identification tests and assay to confirm purity. All of them have passed the tests and the assay result was within the acceptance criteria.

Based on a literature survey and by referring books and articles, prospective process validation protocol, batch manufacturing record (three batches) BMR, qualification protocols for the equipment were formatted, and specifications were set based and trial runs of Telmisartan mini-tablets manufacture. Protocols were prepared, and the result data of all the batches were recorded.

Critical process parameters for the Telmisartan mini-tablets manufacturing process were identified as sifting, mixing, and compression.

As sifting was found to be one of the critical processes, sieve integrity was considered as a critical process parameter and found to be intact before and after the sieving process. The quantity of blend powder at the initial as well as at the end of the process was weighed, calculated, and noted down in BMR of each batch.

To verify the mixing process's efficiency, powder blend samples were taken from different points in each batch and were subjected to blend uniformity test. Samples at various

time intervals 5, 10, and 15 minutes were tested for blend uniformity and the results of all batches shown between 95–105% drug content i.e., within the acceptance limit. Pre compressional parameters were analyzed for the powder blend and the results of all three lots were compared with acceptance criteria and found to be within limits.

Multi tooling punches were used for tablet compression, required compression force was set to achieve mini-tablets as mentioned in the pre-planned protocol. Then mini-tablets were punched, (Figure 1) and tablets were segregated at different stages (initial, middle, and end). Post compressional parameter evaluation as mentioned in the prospective process validation protocol, was performed, and results were found within the required acceptance limit. Tablets as a composite sample were

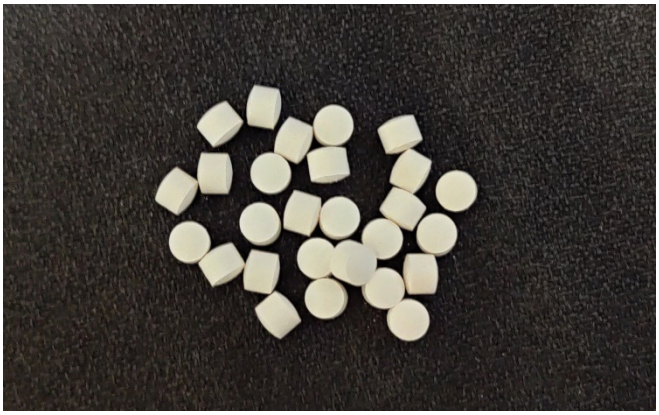


Figure 1: Telmisartan mini tablets

Table 3: Post compressional parameter of three batches

		Observations			
Parameters	*Acceptance criteria*		*Batch 1*	*Batch 2*	*Batch 3*
General appearance	Round in shape, white in color, biconvex and plain uncoated tablets	Initial	Complies	Complies	Complies
		Middle	Complies	Complies	Complies
		End	Complies	Complies	Complies
Diameter	4 mm ± 5 %	Initial	3.95 mm	3.96 mm	3.95 mm
		Middle	3.93 mm	3.94 mm	3.97 mm
		End	3.94 mm	3.95 mm	3.97 mm
Thickness	3 mm ± 5 %	Initial	3.05 mm	3.02 mm	3.03 mm
		Middle	3.05 mm	3.01 mm	3.02 mm
		End	3.03 mm	3.02 mm	3.04 mm
Hardness	3–6 kg/cm^2	Initial	4.07 kg/cm^2	3.97 kg/cm^2	3.96 kg/cm^2
		Middle	3.96 kg/cm^2	3.93 kg/cm^2	3.98 kg/cm^2
		End	4.18 kg/cm^2	4.0 kg/cm^2	3.95 kg/cm^2
Weight variation	60 mg ± 6 (10 %)	Initial	60.0 mg	60.3 mg	59.85 mg
		Middle	60.05 mg	59.9 mg	59.70 mg
		End	60.3 mg	59.9 mg	59.85 mg
Friability	Not greater than 1%	Initial	0.29 %	0.15%	0.09%
		Middle	0.26 %	0.21%	0.06%
		End	0.31 %	0.01%	0.09%
Disintegration	uncoated tablets should retain intact NLT 1 hours in acidic buffer (pH 1.2) medium	Initial	Tablet remain intact for 1 hour	Tablet remain intact for 1 hour	Tablet remain intact for 1 hour
		Middle	Tablet remain intact for 1 hour	Tablet remain intact for 1 hour	Tablet remain intact for 1 hour
		End	Tablet remain intact for 1 hour	Tablet remain intact for 1 hour	Tablet remain intact for 1 hour
Dissolution	• Not less than 45 % and NMT 75 % in 3 hours • Not less than 80 % in 10 hours of the drug in the medium	Initial	Min 55.0 % Max 88.29 %	Min 54.74 % Max 87.78 %	Min 56.98 % Max 89.64 %
		Middle	Min 52.89 % Max 81.98 %	Min 57.10 % Max 87.17 %	Min 55.10 % Max 88.93 %
		End	Min 59.51 % Max 83.66 %	Min 54.80 % Max 88.96 %	Min 53.82 % Max 88.23 %
Drug content	95.0–105.0 % of labelled amount	Initial	98.74 %	99.37 %	99.29 %
		Middle	98.8 %	99.02 %	99.16 %
		End	98.83 %	98.83 %	98.00 %

Table 4: Results of tablets as composite samples of three batches

		Observations		
Parameters	*Acceptance criteria*	*Batch 1*	*Batch 2*	*Batch 3*
General appearance	Round in shape, white in color, biconvex & plain uncoated tablets	Complies	Complies	Complies
Diameter	4 mm ± 5 %	3.95	3.95	3.97
Thickness	3 mm ± 5 %	3.03	3.01	3.0
Hardness	3-6 (kg/cm^2)	3.94	3.96	3.95
Weight variation	60 mg ± 6 (10 %)	60.05	60.35	60.00
Friability	Not greater than 1%	0.04 %	0.12 %	0.09 %
Disintegration	uncoated tablets should retain intact NLT 1 hours in acidic buffer (pH 1.2) medium	Tablet remain intact for 1-hour	Tablet remain intact for 1-hour	Tablet remain intact for 1-hour
Dissolution	Not less than 45 % and NMT 75 % in 3 hours Not less than 80 % in 10 hours of the drug in the medium.	Min 60.68% Max 87.40%	Min 58.64% Max 89.22%	Min 53.64% Max 89.26%
Drug content	95.0 % -105.0 % of labelled amount	98.84%	99.59%	99.43 %

Table 5: Disintegration test of minitablets during stability studies of three batches

	Tablet condition	
Batch No.	*HCL 1.2*	*Phosphate buffer*
1	Remained intact for 1-hour	Tablet showed slight disintegration at 3rd hour
2	Remained intact for 1-hour	Tablet showed slight disintegration at 3rd hour
3	Remained intact for 1-hour	Tablet showed slight disintegration at 3rd hour

Table 6: Dissolution Test results during stability studies of three batches

Day	*Acceptance criteria*	*Time*	*Observations*		
	3 hours, not less than 45% *10 hours, not less than 80 %*		*% CDR*		
			Batch 1	*Batch 2*	*Batch 3*
Initial		3 hours 10 hours	57.68 % 89.81 %	56.58 % 87.96 %	56.64 % 85.36 %
30th Day		3 hours 10 hours	53.97 % 86.67 %	55.69 % 88.19 %	55.43 % 84.65 %
45th Day		3 hours 10 hours	52.86 % 86.68 %	51.49 % 83.78 %	-

Table 7: Drug content of minitablets during stability studies of three batches

	Drug Content %		
Day	*Batch 1*	*Batch 2*	*Batch 3*
Initial	99.58 %	99.14 %	99.34 %
30th Day	99.3 %	98.65 %	98.98 %
45th Day	98.5 %	97.45 %	97.85 %

also taken from three batches, and results for all the batches complies with the specification as described in Table 3.

Telmisartan mini-tablets were also subjected to stability studies for about 45 days found that degradation was minimal, as described in Tables 4 to 6.

The results of all batches were compiled in the validation report and found that the adapted manufacturing procedure is consistent and gives telmisartan mini-tablets of good quality.

Stability studies were done based on standard parameters i.e., at room temperature and normal humidity. After specified days, capsules were tested for drug content and found less degradation in the first thirty days. The results obtained after 45 days have shown minor degradation of drug content but even acceptable. Details are mentioned in Table 7.

CONCLUSION

The end product's quality can never be assured by only finished testing of the product but it should be installed during the development cycle itself. The manufacturing process needs to be consistent so that the end product meets the specification limits. Prospective process validation has been performed for the 80 mg Telmisartan mini tablets. Mini tablets were punched using the direct compression method. Based on the pre-planned protocol manufacturing process was found proficient and reproducible for all the batches. All the parameters were found within the acceptance limit at different stages like sifting, mixing, and compression. Pre compressional and post compressional parameter evaluation results were found within the specification limits. Thus there was no deviation or changes were recorded during the manufacturing process. A validation report of three batches of (Telmisartan mini-tablet) was prepared. It shows that the end product was stable and

meeting pre-determined specifications and quality attributes. Hence, we can conclude that the process employed for the manufacture of mini-tablets was validated and complies with the pre-determined specifications.

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