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Prospective process validation for the manufacture of ketoprofen fast dissolving tablets

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ABSTRACT

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As validation is an integral part of current good manufacturing practice, nowadays, it is practiced in all pharmaceutical industries to assure that the manufacturing process is in control and products of high quality are obtained. Building of quality needs attention in the manufacturing process, from the raw materials to finalized product. The current research work is to perform prospective process validation for the manufacture of ketoprofen fast dissolving tablets (FDT) of 50 mg dose. Various trials and challenge studies were done to finalize critical process parameters. Three consecutive batches of ketoprofen FDT with the same batch size, procedure, equipment, and validation criteria were done and critical process parameters were monitored in each stage such as sifting, mixing, and compression. In-process quality control tests were performed for each batch. Friability, disintegration, dissolution, uniformity of dispersion, and assay were the major evaluation parameters considered. An average disintegration time was found to be 18–19 s and 97% of dissolution within 30 min, drug content ranging from 98.4% to 99.5% was achieved. All results complied with acceptance criteria. Evaluation results of all three batches were within acceptance criteria. The results concluded that current process validation was reproducible meeting all predetermined process variables.

Keywords: Fast dissolving tablets, ketoprofen, process validation, prospective process validation, quality, validation

INTRODUCTION

Validation plays an important role in all of the pharmaceutical industries as they are using highly expensive raw materials, equipment, and facilities which are more sophisticated, qualified personnel. With all these, product of high-quality meeting all the standards must be obtained. Implementing validation technique in the pharmaceutical industries helps to fulfill all the regulatory requirements and meets all the standards along with achieving the product at lowest cost which can be affordable to all people by reducing the cost of quality.[1]

Validation techniques are suggested to be implemented in all of the pharmaceutical industries which should be clearly explained and well known to all of the employees and if any new information is available, employees should be updated as soon as possible. All the important elements of the entire validation program of each of the pharmaceutical industry must be clearly stated or defined and documented in a validation master plan.[2]

Validation is a systematic approach to define, quantify, review, report, and reassess a number of crucial parts during production process requiring supervision for obtaining a standard manufactured product.[3] Validation is a necessary step in the production, storage, handling, and distribution of medicinal products. "Quality or value cannot be measured in products; it should be integrated or planned." Thereby, all the stages followed during the manufacturing process starting from the raw materials till to finished product must be controlled so that final product meets all specifications.[4]

Fast dissolving tablets (FDTs) are the tablets that disintegrate easily in mouth within few seconds of administration. They are also called as fast disintegrating, mouth or quick dissolving tablets. They normally disintegrate

or dissolve in the oral cavity without water. In these tablets, substances that cover the pungent taste of the drug play an important role as it enhances the patient compliance. As the drug is rapid dissolving, it will also lead to rapid absorption and hence immediate action of drug will be obtained. In general, the time required for the drug to melt or dissolve within the mouth should be below 1 min.[5] In the present work, process validation for FDT of ketoprofen has been undertaken. Ketoprofen comes from the class of nonsteroidal anti-inflammatory drugs which is widely used as antipyretic and analgesic.[6] The formulation FDT of ketoprofen has been obtained from an in-house research project and the process has been validated for the same initially at the research laboratory scale batch size.

MATERIALS AND METHODS

Drug Profile

Drug name: Ketoprofen.
Molecular formula: $C_{16}H_{14}O_{3.}$
Chemical name: 2-(3-benzoylphenyl) propanoic acid.
Molecular weight: 254.285 g/mol.
Category: Anti-inflammatory, anti-pyretic, and analgesic.
Melting point: 94°C.

Equipment and Instruments

Vibrator sifter with number 60 sieve of Vinsyst makes of model MA-134-102, tablet compression machine of Karnavati Engineering make, model Rimek 02007103, Vernier caliper, Monsanto hardness tester, friability tester (Roche), disintegration apparatus, USP TYPE-2 (paddle type) dissolution apparatus, and UV–visible spectrophotometer of Agilent makes. All instruments and equipment used during the manufacturing of ketoprofen FDT were qualified, calibrated, and maintained before use.

Prospective process validation for the manufacture of ketoprofen FDT was carried out with three consecutive batches and the batches were labeled as batch 1, batch 2, and batch 3.

Materials

Below are the active pharmaceutical ingredient and excipients used in experimental work. Batch size was 550 tablets and labeled claim is 50 mg/tablet.

Methods

Before conducting prospective process validation, validation protocol was prepared then approved by quality assurance personnel and following are the contents.

- Objective, scope, responsibilities.
  - List of members involved in validation.
  - Detailed formula of the formulation.
  - Authorized suppliers.
  - Guidance for production.
  - List of equipment used in production process.
  - Equipment qualification protocol number.
  - Identify and describe critical steps and critical parameters.
  - Scientific rationalization of critical steps.
  - How to take samples and test them.
  - Detailed analysis procedures (quality control [QC] test).
  - Statistical methods for the analysis of data.
  - Acceptance criteria.[7,8]

After the prospective process, validation protocol has been prepared and approved, batch manufacturing record (BMR) should be prepared. BMR is a written document of a batch which contains information of the entire manufacturing process that each and every step will be clearly defined and stated. It is used as a proof or evidence that lots or batches were correctly manufactured and approved by QC personnel. Each batch should contain separate BMR.

Validation Procedure

- Three consecutive batches were manufactured as described in the BMR.
- Current versions of standard operating procedures were followed.
- The observations were recorded at compression stage in the data sheets.

Manufacturing Process

Sieve integrity was checked before and after the process and each and every raw material was sifted through sieve number 60 separately. Accurately weighed and sifted ingredients (ketoprofen, CCS, MCC, and lactose) were mixed in a polybag for 15 min. At 6 min and 12 min, stopped for collecting sample then continued. Then, talc was added into the above mixture and mixed for 2 min. Then, magnesium stearate added into the above mixture and mixed for 2 min. Again, sample was collected of blend uniformity test. The above blended powder was compressed into tablets using tablet compression machine using 8 mm punches size and IPQC test was performed for tablets during the process and after compression taking tablets as composite sample.

Evaluation of Parameters

Evaluation of various parameters such as blend uniformity, tapped density, bulk density, Hausner's ratio, Carr's index, and angle of repose was performed on the blended powder and the compressed tablets (initial, middle, end tablets, and tablets as composite samples) were also evaluated for parameters such as general appearance, diameter, thickness, hardness, friability, disintegration, dissolution, and drug content.

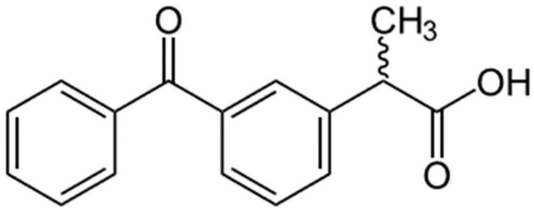
Table 1: List of ingredients AQ8

S. No.	Raw materials	Category	Quantity/ batch (g)
1	Ketoprofen	API	30
2	Croscarmellose sodium	Disintegrant	4.8
3	Microcrystalline cellulose	Binder	30
4	Lactose	Diluent	60
5	Talc	Glidant	0.9
6	Magnesium stearate	Lubricant	0.9

RESULTS AND DISCUSSION

Key variables of the production process that affects product output quality are generally known as critical process parameters. In the current work, critical process parameters were assessed in trail manufacturing of ketoprofen FDTs. It was found the optimal conditions were suitable and ketoprofen FDTs were found within acceptance criteria. Critical process parameters considered for current work along with reasons are mentioned in Table 3.

If there is any damage in sieve, blend may contain particles of different size which may affect flow property and, in turn, compression as well as content uniformity. It is essential to carryout sifting process for raw materials also, because it ensures all raw materials will fall in one particle size range and also ensures ease of missing and blending. Hence, first of all, sieving integrity was tested before and after use for all the three batches. No damage of the sieve was observed either before or after, no foreign material or particles were observed and also the integrity was found to be intact.



AQ7 **Figure 1:** Structure of ketoprofen.

Dry mixing was carried out and blend was taken to various QC tests. Content/blend uniformity was determined and results are mentioned in Table 4. Blend uniformity test was performed for all three batches at different sampling locations and results were recorded. According to the obtained results from all batches, it was found that the minimum assay % was 97.65% which was obtained in batch 2 at 6 min and maximum % assay was 99.32% which was obtained in batch 2 at 19 min. % RSD for all batches were <3% which indicates that all are within the acceptance limit. Therefore, dry mixing should be for totally 19 min as per results.

The obtained results for all three batches were within the acceptance limit and not much difference was observed between the batches, indicating that variation is minimal.

Along with blend uniformity, other pre-compressional parameters, such as bulk density, tapped density, Carr's index,

AQ8 **Table 2:** Sampling plan and testing plan

S. No.	Step	Sample location	Sample quantity	Test to be performed
1	Mixing	1 point from top	105.5 mg from each location	Blend uniformity
		1 point from middle		
		1 point from bottom		
2	Compression	Draw tablets from initial, middle and near to end stage of the compression	50 tablets from each stage (initial, middle, and end stage)	General appearance
		Draw tablets as a composite sample from all containers for test parameters	50 tablets	Diameter
				Thickness
				Hardness
				Weight variation
				Friability
				Disintegration
				Dissolution
				Uniformity of dispersion
				Drug content

Table 3: Critical step and critical process parameters

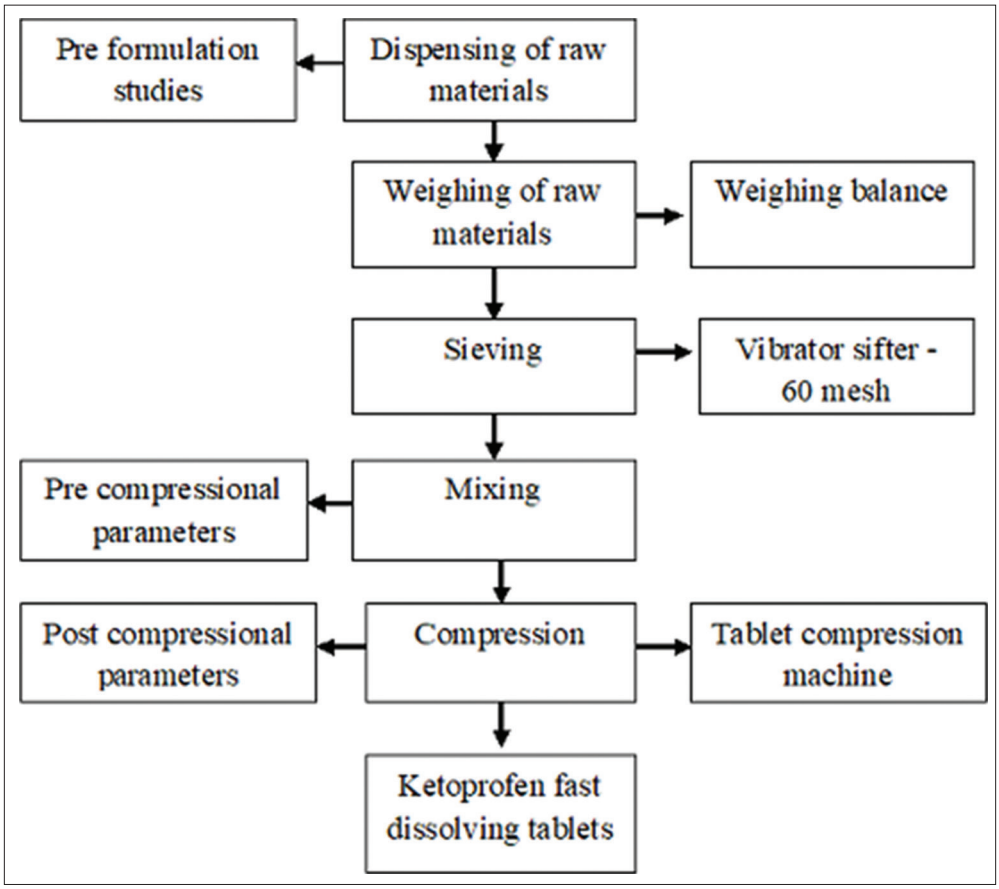
S. No.	Critical steps	Critical parameters	Scientific rationale
1	Sifting	Sieve size	To obtain uniform size of the powder
		Sieve integrity	To check whether there is any damage to the sieve
			Presence of any particle on the sieve
			To check whether there is presence of any foreign material in powder
2	Mixing	Mixing time	To check the content uniformity of powder
			To check the flow property of the powder
			To check the uniform mixing time
3	Compression	Compression force	To check the hardness and friability of the tablet
			To check the disintegration time of the tablet
			To check the thickness and diameter of the tablet

Table 4: Blend uniformity results

Value	Mixing time (batch 1)			Acceptance criteria
	6 min	12 min	19 min	
% assay (average)	98.04	99.03	98.51	95.0–105.0% of labeled amount
SD	0.33	0.57	0.77	
% RSD	0.34	0.58	0.78	NMT 3%
Value	**Mixing time (batch 2)**			**Acceptance criteria**
	6 min	**12 min**	**19 min**	
% assay (average)	97.65	98.8	99.32	95.0–105.0% of labeled amount
SD	0.57	0.51	0.68	
% RSD	0.58	0.52	0.68	NMT 3%
Value	**Mixing time (batch 3)**			**Acceptance criteria**
	6 min	**12 min**	**19 min**	
% assay (average)	97.88	98.57	98.64	95.0–105.0% of labeled amount
SD	0.44	0.50	0.38	
% RSD	0.45	0.51	0.39	NMT 3%

Table 5: Pre-compressional parameter results for all three batches

Batch No.	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
Batch 1	0.632	0.729	13.3	1.15	29.29
Batch 2	0.638	0.721	11.5	1.13	28.32
Batch 3	0.623	0.723	13.8	1.16	28.85



AQ7 **Figure 2:** Process flowchart.

Hausner's ratio, and angle of repose that are non-official tests for the powder flow properties, were evaluated for the blended powder. These tests are done to analyze flow property of blend. The results obtained all batches were within the acceptance limit and shown in Table 5. Obtained results of Carr's index, Hausner's ratio, and angle of repose indicate that the blend exhibited good flowability, compressibility, and free from lumps, respectively.

Compression Results

The blended powder was compressed into tablets using tablet compression machine at the optimum condition, using 8 mm punches. During the compression cycle, that is, at the initial, middle, and end stages, tablets' samples were collected and analyzed. Ketoprofen FDTs were of white color and round in shape. Diameter of the tablets was checked and found that average diameter was 7.99 mm and average thickness was 4.1 mm. It was done for confirmation purpose. Hardness of tablets was found in the range from 3.19 kg/cm^2 to 3.3 kg/cm^2. It indicates that the tablets withstand the stress of transport and tablets will be intact. All these tests were done at the initial, middle, and end stage compression as well as for composite sample taken after completion of tablet compression. Results for all batches are recorded in Tables 6 and 7. All results were found to be within the acceptance limit as per prospective process validation protocol.

Tablets were randomly selected, then in process, QC test was performed. The obtained results were, all the batches were within the limit as per validation protocol. The acceptance criteria for various QC tests were set in the validation protocol based on Indian Pharmacopoeia 2010 and 2014 edition. Acceptance criteria for uniformity of dispersion was set as per USP and for dissolution was based on literature[12] as many of

Table 6: Post-compressional parameter results for all three batches

Parameters	Acceptance criteria		Observations		
			Batch 1	Batch 2	Batch 3
Uniformity of weight	211 mg±15.825 (7.5%)	Initial	210.3 mg	210.65 mg	210.9 mg
		Middle	209.95 mg	209.60 mg	211 mg
		End	210 mg	210.55 mg	210.85 mg
Friability	Not >1%	Initial	0.29%	0.28%	0.31%
		Middle	0.26%	0.28%	0.33%
		End	0.31%	0.26%	0.28%
Disintegration	NMT 3 min	Initial	18 s	19 sec	21 s
		Middle	21 s	18 sec	18 s
		End	17 s	18 sec	19 s
Dissolution	NLT 80% in 30 min	Initial	97.73%	97.22%	97.88%
		Middle	97.70%	97.95%	97.23%
		End	96.97%	97.73%	96.95%
Uniformity of dispersion	The dispersed solution should completely pass through sieve number 22 (710 μm)	Initial	Complies	Complies	Complies
		Middle	Complies	Complies	Complies
		End	Complies	Complies	Complies
Drug content	95.0–105.0% of labeled amount	Initial	99.44%	99.10%	98.96%
		Middle	98.94%	98.46%	99.22%
		End	99.38%	99.28%	99.34%

Table 7: Tablets as composite sample results for all three batches

Parameters	Acceptance criteria	Observations		
		Batch 1	Batch 2	Batch 3
Uniformity of weight	211 mg±15.825 (7.5%)	210.1 mg	210.6 mg	211.15 mg
Friability	Not >1%	0.29%	0.28%	0.31%
Disintegration	NMT 3 min	19 s	18 s	23 s
Dissolution	NLT 80% in 30 min	97.12%	97.90%	97.99%
Uniformity of dispersion	The dispersed solution should completely pass through sieve number 22 (710 μm)	Complies	Complies	Complies
Drug content	95.0–105.0% of labeled amount	99.34%	99.46%	99.4%

the pharmacopoeias have not yet framed QC test parameters exclusively for FDTs.

CONCLUSION

FDT formulation is a current trend offering many advantages for children and geriatric patients. Ketoprofen is a commonly used NSAID available in various dosage forms. Recently, many researchers attempted to make ketoprofen FDTs and were successful. In that prospective standardizing, the manufacturing procedure will be vital contribution to scientific community, manufacturers, as well as society. In an attempt to standardize the manufacturing process, prospective process validation for ketoprofen FDTs was successfully performed. Observations and results obtained in each stage of the manufacturing process indicated that the process is capable enough for producing the desired quality tablets consistently and uniformly. It can be concluded that the manufacturing process of ketoprofen FDTs was efficient enough to provide a reproducibility of the process with acceptable and uniform results. Although the batch size was up to the research laboratory scale, method will be practical for the manufacture in large batch size as it only requires additional equipment and their qualification which can be included in the protocol after trials. These results prompted us to look into the large-scale manufacture in the near future.

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