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Process validation of mefenamic acid tablets by spectroscopic method

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ABSTRACT

Mefenamic Acid is anti-inflammatory drug used to treat pain. The focus of this research work was the validation of mefenamic acid tablets to ensure their quality and efficacy by applying various physical and chemical parameters such as weight variation, % age assay, friability, disintegration time (DT), hardness and loss on drying (LOD) by comparing with standards parameters of British Pharmacopoeia (BP) and United States Pharmacopoeia (USP). The validation was conducted during the preparation process as it was easy to remove any shortcomings during the process rather than after the completion of the manufacturing process. Further, the validation is also necessary to achieve batch-to-batch consistency during the product manufacturing. This method is precise, accurate and very simple to analyse mefenamic acid tablet. This qualitative data can help for further improvement of the mefenamic acid drug efficiency.

Keywords: Hardness, Friability, Disintegration time, Loss on drying, UV-VIS spectroscopy, IR spectroscopy.

INTRODUCTION

Common observation is that the substandard pharmaceutical products are more harmful than goods to the human health (Johnston and Holt, 2014). The quality of a pharmaceutical product is determined by comparing its various parameters with the standards to obtain the quality product that gives the required results (Pramod *et al.,* 2016). The products do not fulfill the parameters at standard level are low quality products and may not effective at the required level. To ensure the quality of a product, various control variables are evaluated during the process along with its various physical and chemical characteristics, including disintegration time (DT), loss on drying (LOD), hardness, dissolution, assay % age and identification by using SOP's and standards given in the British Pharmacopeia (BP) and United State Pharmacopeia (USP) (Wazade *et al.,* 2012).

Pharmaceutical Process Validation is one of the most significant parameters of CGMPs (Current Good Manufacturing Practice) which ensures that a particular process is consistent in producing the same quality product again and again (Aleem *et al.,* 2003). The term 'process validation' is broadly used for various activities that include a precise series of analytical tests and inspections of facilities, equipment and procedure used for the manufacturing of a particular drug product by ensuring that it qualifies the pre-determined specifications. The main aim of the validation process is to ensure that all the individual items of the system work together as per requirement under pre-defined protocol. So, it plays a vital role in the pharmaceutical industry for development and manufacturing of drug product (Jatto and Okhamafe, 2002).

Mefenamic acid is non-steroidal anti-inflammatory drug (Renata *et al.,* 2016). Mefenamic acid is used to treat mild to moderate pain from various conditions. (kumar *et al.,* 2018). Due to its dual action on prostaglandins, it has anti-inflammatory, anti-pyretic (fever reducing) and analgesic (pain killer) activities in the biological system. Hence, it is used to treat pain in various conditions involving arthritis, menstrual cramps and inflammation (swelling with redness) etc. (Shirvani

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et al., 2015). In order to ensure its effectiveness to control pain, it is highly important to evaluate the product quality prior to putting it in the proposed use. The present study was aimed to evaluate the product quality of mefenamic acid tablets by applying various in-process quality control (QC) parameters.

MATERIALS AND METHODS

Sample collection

The manufacturing of mefenamic acid (Trade name: Amnic Tablets 250 mg) tablets involves preparation of paste, wet mixing, drying, granulation and compression. The sample was collected at granulation and compression stages due to the criticality of these two phases in tablet quality. In order to check the reproducibility of the test results, samples of three consecutive batches (No. 6792, 6793 & 6794) of *Jawa Pharmaceuticals* Lahore, Pakistan, of mefenamic acid tablets were collected and evaluated.

Sampling at granulation stage

A sampling rod was used to collect samples of mixed grains (10 g for each batch) from four different corners (top right corner, top left corner, middle right corner and middle left corner) of the V-mixer and the physical and chemical tests were performed. The grains were kept in air tight polythene bags in order to ensure that it stays free from any moisture present in the surrounding (Chowhan, 1979).

Evaluation of physical parameters of granules

The physical parameters of granules of three selected batches/samples at granulation stage were evaluated as below:

Table I: Parameters for physical analysis at granulation stage

Sr. No.	Physical Parameters	IH Specifications*	Status
1	Physical form	Granules	Pass
2	Color	White	Pass
3	Moisture Contents	Not more than 2-4%	Pass

IH Specifications*= In House specifications of Jawa Pharmaceutial Industry

Content of mefenamic acid (% Assay)

100 mL of ethanol was taken in a titration flask and gently warmed on a hot plate. 2 - 3 drops of phenol red were added as an indicator. A yellow color appeared. Neutralized this solution using 0.1 N NaOH until a purple color appeared. The first sample of batch No. 6792 (powdered grains of mefenamic acid tablet 508.9 mg containing 250 mg of active drug) was added in the above solution, bright yellow color (showing that the solution became acidic again) appeared. After that, mixture was sonicated for about 15 minutes and then it was stirred for 10 minutes. Finally, titrated it against 0.1 N NaOH until a purple coloration appeared (end point). The %assay for mefenamic acid (limit BP 95-105%) was calculated by following formula:

$$\%\ \text{Assay} = \frac{\text{Volume used (mL)} \times \text{Factor}}{\text{Amount of active drug}} \times 100$$

Where;

Factor = Molecular weignt of mefenamic acid × Molarity of titrant

Factor = 241.3 g/mol × 0.1 mol/L

Factor = 24.13 g/L

Identification of active drug (mefenamic acid) in granules

The presence of active drug in granules was confirmed by UV-VIS and IR spectrophotometers as follows: -

Using UV-VIS Spectrophotometer

Preparation of standard stock solutions

Accurately measured 200.08 mg of sample powder (containing 100 mg of the active mefenamic acid) in a 100 ml volumetric flask (1000 ppm of mefenamic acid) and the volume was made up to the mark by using 0.1N NaOH. The final concentration of standard stock solution was made to 1000 µg/mL of mefenamic acid.

Preparation of working standard solution

1 ml of the standard stock solutions was taken in a 100 mL of volumetric flask and made the volume up to the mark using distilled water to get 10 ppm dilution of the sample (which is required for getting UV-Vis spectra of mefenamic acid). The final concentration of the working standard solution was now 10 µg/mL of mefenamic acid.

Selection of wavelength

The appropriate wavelength for the estimation of mefenamic acid was selected from the UV spectrum. 200 – 400 nm was used to scan the standard solution of mefenamic acid and the λ_{max} was found to be 285 nm against 0.1N NaOH.

Using IR Spectrophotometer

A quantity of powdered tablet containing 0.25 g of mefenamic acid was extracted two times with 30 mL ether each time. The combined extract was washed with water and it was evaporated to dryness at 105 °C. A sufficient quantity of dried residue was dissolved in the minimum quantity of absolute ethanol and evaporated to dryness on a water bath. The final product was run in IR spectrophotometer and the infrared absorption spectrum obtained from it was compared with the reference spectrum of mefenamic acid.

The coincidence of physical and chemical parameters at granulation stage with that of British Pharmacopoeia (BP) and United States Pharmacopoeia (USP) and showed that the granules are suitable to be compressed in the form of core mefenamic acid tablets.

Sampling at compression stage

About 20 tablets were taken from the bulk storage for each batch (No. 6792, 6793 and 6794) and both chemical and physical QC parameters were performed as weight variation, friability, disintegration time (DT), hardness and loss on drying (LOD) to ensure the product quality.

Evaluation of physical parameters of compressed tablets

The physical properties of three selected batches of mefenamic acid tablets were characterized by weight variation, friability, disintegration time (DT), hardness and loss on drying (Table II).

Table II: In-process product specification (during compression)

Sr. No.	Physical Parameters	Specification (IH/BP/USP)	Status
1	Physical Form	Core	Pass
2	Color	White	Pass
3	Shape	Round	Pass
4	Disintegration Time	Not more than 30 minutes	Pass
5	Friability	Not more than 1 %	Pass
6	Hardness	8-10 kg cm^{-2}	Pass
7	Weight/Tablet	Reference to the approved range mentioned in the batch analysis report	Pass
8	Loss on drying	2-4%	Pass

Disintegration time

The disintegration test was carried out by placing one tablet in each tube of the basket-rack. Water was taken in the beaker as an immersion fluid. The temperature was set at 37 °C using a thermometer and the tester was run. The tablets started to disintegrate. After the complete disintegration of tablets, the tester was turned off immediately making sure that all the tubes were free from any remnants of the tablet. The disintegration time was noted and compared with the BP/USP specifications.

Friability

Before carrying out the friability test, any loose dust from the tablets was removed. 10 tablets were accurately weighed, and they were placed in the drum. The rotation time was set for 4 minutes at 25 rpm (specification for friability). After that, the tablets were taken out from the drum. They were dedusted properly and weighed again.

%age friability of the tablets was found by the following formula:

$$\text{Percentage friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where;

Initial weight = W_1, Final weight = W_2

Hardness

10 tablets from each batch were taken. The crushing strength was found for each individual tablet by placing them one by one between the jaws of the hardness tester. The average hardness value was recorded for each batch (Johnston and Holt, 2014).

Loss on drying (LOD)

The test was carried out by evenly distributing the powdered sample of the compressed tablets on the heating pan of the device. The % age weight loss was automatically recorded by the instrument which was read directly from the screen later on.

Identification of active drug (mefenamic acid) in compressed tablets

Both chemical assay and identification test were carried out for compressed tablets following the same procedure as for granules at mixing stage.

RESULTS AND DISCUSSION

Physio-chemical testing of drug products is an important step before releasing the batch in market for human use. Three successive batches 6792, 6793 and 6794 of Amnic tablet 250 mg (mefenamic acid) were tested by applying various quality control parameters (physical and chemical tests) at mixing and compression. The results obtained are as follows:

Physical analysis

Any fluctuation in the physical characteristics of the compressed tablet (e.g., texture, color and shape of the tablet) might affect the patient's compliance and acceptability of drug and results in medication error. The results of QC parameters showed that the physical appearance of tablets met the IH parameters of the Pharmaceutical industry (Table III).

Table III: Physical parameters of tablets at lubrication stage

Batch No.	Tests	IH Specification	Results	Result status
6792	Physical form	Granular powder	Complies	Pass
	Color	Pure white	Complies	Pass
	LOD	2-4%	2.5%	Pass
6793	Physical form	Granular powder	Complies	Pass
	Color	Pure white	Complies	Pass
	LOD	2-4%	2.1%	Pass
6794	Physical form	Granular powder	Complies	Pass
	Color	Pure white	Complies	Pass
	LOD	2-4%	2.9%	Pass

All of three tablet samples were pure white in colour. The appearance of active salt of mefenamic acid was observed as granular powder.

Weight variation test

This test is carried out to ensure good manufacturing practices (GMP), content uniformity and suitable tablet mass (Yoshida and Sakai, 1999). The USP and BP have provided the range for the acceptable weight variation of individual tablet. According to which, for tablets weighing 130 mg or less, the weights of not more than two tablets should differ from the average weight by ±10.0 and none of them should deviate by more than twice of that percentage (Table IV, Lachman *et al.,* 1986) .

Table IV: Individual weight of 10 tablets of different batches

Sr. No.	Batch No.					
	6792		6793		6794	
	Individual weight (mg)	% variation	Individual weight (mg)	% variation	Individual weight (mg)	% variation
1	506	-0.550	503	0.0397	499	-0.47
2	511	0.432	505	0.437	502	0.297
3	512	0.628	507	0.835	501	-0.079
4	504	-0.943	500	-0.556	498	-0.678
5	507	-0.353	505	0.437	503	0.319
6	504	-0.943	503	0.039	505	0.717
7	513.2	0.864	508	1.034	501	-0.079
8	515	1.218	503	0.039	501	-0.079
9	512	0.628	503	0.039	504	0.518
10	508	-0.157	512	1.829	500	-0.279
Average	508.8		502.8		501.4	
Results	Complies		Complies		Complies	

Average weight of tablet for batch no. 6792, 6793 and 6794 was calculated as 508.8, 502.8 and 501.4 respectively.

Disintegration time (DT)

This test is carried out to evaluate the time required for a tablet to disintegrate completely in the body. It is highly important for the therapeutic effect of tablet. Disintegration time is influenced by the type of excipients used in the tablet formulation. The tablets having high hardness values and too much binder may have a high disintegration time. All the batches were found to have disintegration time within the pharmacopoeial specifications (British Pharmacopoeia BP) which sets a disintegration range of less than 15 minutes for core tablets (Table V).

Table V: Disintegration time of amnic tablets for different batches

Batch No.	Sample No.	Disintegration time	Results
6792	1	5 minutes 3 sec.	Complies
	2	5 minutes 9 sec.	
	3	4 minutes 56 sec.	
6793	1	4 minutes 45sec	Complies
	2	5 minutes 23 sec	
	3	5 minutes 34 sec	
6794	1	4 minutes 53 sec	Complies
	2	5 minutes 17 sec	
	3	5 minutes 27 sec	

The average disintegration time for mefenamic acid tablet was observed as 5 minutes for each batch which was in accordance with the limits as provided by US pharmacopeia.

Hardness

Sufficient tablet hardness is essential to ensure damage resistance during handling, packaging and transportation. In order to withstand mechanical shocks of handling during its manufacture, packaging and transport, the tablet requires a certain amount of strength, or hardness.

In addition, tablets should be able to withstand reasonable abuse when in the hands of the consumer. Adequate tablet hardness is a necessary requisite for consumer's acceptance. All the brands had shown their hardness less than the value specified by USP (Table VI, Uddin *et al.,* 2017). Hardness of amnic tablet (mefenamic acid) was calculated as 7.84 $kgcm^{-2}$, 9.87 $kgcm^{-2}$ and 9.28 $kgcm^{-2}$for batch 6792, 6793 and 6794 respectively.

Table VI: Average hardness of compressed tablets

Sr. No.	Hardness ($kgcm^{-2}$)		
	Batch No.		
	6792	**6793**	**6794**
1	8.12	9.55	8.92
2	9.07	9.88	9.84
3	8.80	8.97	9.95
4	7.58	9.90	11.33
5	6.02	9.92	8.69
6	6.69	10.73	10.32
7	6.29	9.99	7.48
8	8.11	9.66	8.76
9	8.45	9.65	9.27
10	9.29	10.46	8.19
Average	7.84	9.87	9.28
Result	complies	complies	complies

Friability test

Shocks and frictional forces can cause the tablets to get damaged or break. With this test, it is possible to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. The United State Pharmacopoeia states that the friability value of tablets should be less than 1% (Uddin *et al.,* 2017). All the batches were found to meet this specification (Table VII).

Table VII: Percentage friability of amnic tablets

Batch No.	Initial weight (g)	Final weight (g)	% Friability	Status
792	5.089	5.048	0.80	pass
793	5.112	5.098	0.46	pass
794	5.095	5.079	0.31	pass

Percent friability of sample tablets was 0.80, 0.46 and 0.31 for batch no. 6792, 6793 and 6794. It is observed that the % friability value of tablets is less than 1% which is within the range provided by US pharmacopeia.

Loss on drying (LOD)

The moisture content of tablets is important because it can affect the tablet hardness and disintegration time. The results of LOD at different stages met the B.P criteria (i.e., 2-4%) which ensured the product quality (Table VIII).

Table VIII: Loss on drying (LOD) of tablets

Batch No. 6792			
Processing stage	**OD limit**	**Observed LOD**	**Result**
Wet granulation	0-30%	22.2%	Complies
Drying	-4%	2.08%	
Final mixing	-4%	2.4%	
Batch No. 6793			
Processing stage	**OD limit**	**Observed LOD**	**Result**
Wet granulation	0-30%	24.22%	Complies
Drying	-4%	2.30%	
Final mixing	-4%	2.76%	
Batch No. 6794			
Processing stage	**OD limit**	**Observed LOD**	**Result**
Wet granulation	0-30%	23.79%	Complies
Drying	-4%	1.55%	
Final mixing	-4%	1.81%	

LOD limit for batch 6792, 6793 and 6794 at final mixing level was 2.4%, 2.76% and 1.81% and found to fall within the range of 2-4% provided by British pharmacopeia.

Chemical analysis

Uniformity of contents

To ensure the consistency of dosage units, each unit in a batch should have active drug content within a narrow range around the label claim. According to U.S.P and B.P (Shah *et al.,* 2010), the content uniformity should be within a range of 95-105%. All the results of uniformity of contents lie within the specifications (Table IX).

Table IX: Uniformity of contents of amnic tablets different baches

Batch No.	Sample No.	NaOH used (mL)	% Uniformity contents B.P Limit (95-105%)	Results
6792	1	10.0	96.52	Complies
	2	10.3	99.41	
	3	10.1	97.48	
	4	9.8	94.58	
6793	1	10.5	101.34	Complies
	2	10.9	105.20	
	3	10.7	103.27	
	4	10.6	102.31	
6794	1	10.1	97.48	Complies
	2	10.4	100.38	
	3	10.4	100.38	
	4	10.6	102.31	

Uniformity of content for batch 6792, 6793 and 6794 was between 94.58 to 105.20 % and found to fall within the range of 95-105 % provided by British pharmacopeia.

Chemical analysis

Identification test (at granulation stage)

Identification of Mefenamic acid using UV-VIS Spectrophotometer

The presence of mefenamic acid in the samples was detected by UV-VIS spectroscopy. The spectra for standard 10 ppm dilution of mefenamic acid gave λ_{max} at 285nm. The same 10 ppm dilution was prepared for the compressed tablets of all the batches and λ_{max} was compared. All of the spectra were concordant with the standard and are depicted in Table X.

Table X: Relative absorbance and wavelengths for standard and granulated sample

Batch No.	Wavelength (nm)	Absorbance
Standard	285	0.410
	332	0.200
6792	285	0.331
	330	0.169
6793	285	0.363
	330	0.186
6794	285	0.367
	330	0.187

Identification of Mefenamic acid using IR Spectrophotometer

The FTIR spectrum of standard shows a weak peak at 3400 cm^{-1} which indicates the presence of a secondary amine in mefenamic acid structure. A relatively broad band in the range of 3200-2900 cm^{-1} is due to the presence of –OH. It also represents the intra and intermolecular hydrogen bonding due to –OH groups and also overlaps with the $–CH_3$ group. The peak at 1650-1750 cm^{-1} identifies C=O group. Likewise, a peak at 1000 cm^{-1} is due to the presence of a phenyl group.

The FTIR spectrum was scanned in the range of 4000-600 cm^{-1}. The spectra obtained for all the batches were found to be comparable with that of the standard.

Identification test (at compression stage)

Identification of Mefenamic acid using UV-VIS Spectrophotometer

The values of absorbance for all the batches at compression stage were also found to be comparable with the standard. The results are depicted in Table XI.

Table XI: Relative absorbance and wavelengths for standard and compressed sample

Batch No.	Wavelength (nm)	Absorbance
6792	285	0.342
	330	0.172
6793	285	0.359
	330	0.185
6794	285	0.380
	330	0.188

Identification of Mefenamic acid using IR Spectrophotometer

IR spectra for compressed tablets were also found to be comparable with the standard (fig 1 and 2)

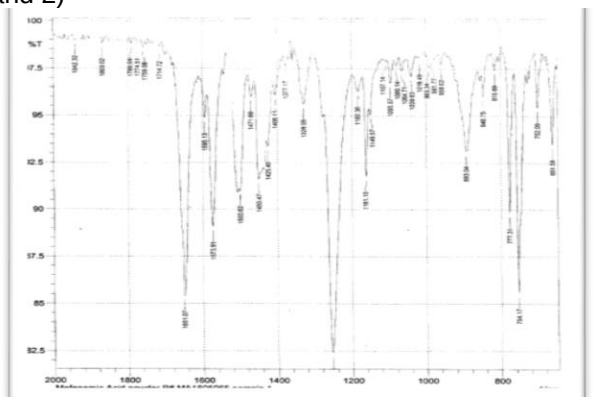

Fig. 1: IR spectra compressed mefenamic acid tablets

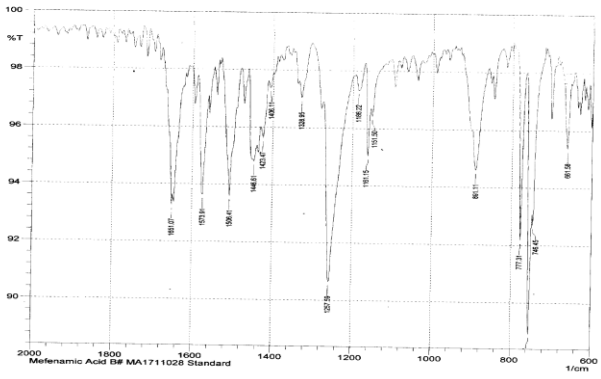

Fig. 2: IR spectra standard mefenamic acid tablets

CONCLUSION

From the present study, it is concluded that the process of mefenamic acid tablet formation is validated because all the batches met the specifications given by USP and BP in terms of weight variation, disintegration time (DT), loss on drying (LOD), hardness and friability. Moreover, the chemical analysis ensured the uniformity of contents which ensured the product quality. It also ensured that the tablets are suitable for intended use.

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