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RESEARCH ARTICLE

Enhancement of Dissolution of Aceclofenac Film Coated Tablet by Micronization Technique

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ABSTRACT

Aceclofenac is non-steroidal anti-inflammatory drug with marked anti-inflammatory and analgesic properties. It is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Aceclofenac is BCS class II drug with low solubility and high permeability. Micronization technique is used to increase the solubility and thus dissolution of Aceclofenac. The micronization was done using jet mill micronizer. The initial particle size of drug is 297.33 micron (D_{90}) which was reduced to particle size 121.87 micron (D_{90}) with single micronization, particle size 116.08 micron (D_{90}) with double micronization and 89.23 micron (D_{90}) with triple micronization of drug. It was observed that the solubility and thus dissolution of Aceclofenac was increased in principle media of 6.8 phosphate buffer and discriminating media 4.5 Acetate buffer with single, double and triple micronization. Thus, it can be justified that micronization is one of the good technique for enhancement of solubility of Aceclofenac by reduction of particle size of drug.

KEYWORDS

Aceclofenac, Dissolution, Micronization, Solubility.

INTRODUCTION

Oral dosage form is one of the most popular dosage forms of drug delivery system. For oral dosage form such as Tablets, solubility is main criteria for the drug to show its desired bioavailability. Many drugs are poorly water soluble which limits its use in many pharmaceutical dosage forms. Thus, solubility enhancement is an important step in formulation of poorly soluble drugs.

Aceclofenac is non-steroidal anti-inflammatory drug which is used in rheumatoid arthritis, ankylosing spondylitis with remarkable anti-inflammatory and analgesic activity.

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As per BCS classification, Aceclofenac is classified as class II low solubility and high permeability drug[1]. The solubility of Aceclofenac drug can be enhanced by micronization technique. Particle size reduction by micronization increases solubility dissolution and thus bioavailability of drug[2].

The bioavailability intrinsically related to drug particle size. The basic principle of micronization is to increase the dissolution velocity by increasing the surface area[3]. Micronization of Aceclofenac was carried out with Jet mill Midas Microniser. Film coated tablets were prepared with single, double and triple micronized drug and dissolution studies were carried out in 6.8 phosphate buffer and 4.5 Acetate buffer at different time point. The dissolution studies of these tablets shows increase in dissolution rate and thus drug release

with increasing number of micronization of drug.

MATERIALS AND METHODS

Material

Active Pharmaceutical Ingredient Aceclofenac was obtained as a gift sample from Ipca laboratories, Mumbai. Microcrystalline cellulose (FMC biopolymer), Sodium starch glycolate (DMV), Sodium Lauryl Sulphate, Stearic acid (Taurus chemicals), Magnesium stearate (Sunshine Pharma) were used in formulation. HPMC 5cps (DOW Chemicals), Titanium dioxide (Sachtleben pigment), PEG 6000 (Vasudha Chemicals) used for film coating. All solvents were of analytical grade and were used without further purification.

Equipments

Malvern Masteriser 2000 for particle size determination, Midas micronizer for particle size reduction, Weighing balance, Octagonal blender, Moisture balance, Density apparatus, Electromagnetic sieve shaker, Cadmach compression machine, Vernier caliper, Hardness tester, Friability tester, Disintegration apparatus, Mechanical stirrer ,Coating pan, Dissolution Apparatus, UV Spectrophotometer

Methods

Micronization of Drug and Particle Size Analysis

Particle size analysis of unmicronized and micronized Aceclofenac was measured using Malvern Masterizer 2000 that is based on laser diffraction technique. After determination of size of unmicronized particles, the drug was subjected to micronization using jet mill Midas micronizer. Milling performed at pressure of 30-40 psi and screw feeder speed of 30-40 rpm. After determination of Particle size of single micronized drug with Malvern technique, a part of single micronized drug was used for tablet formulation 1 and remaining single micronized drug was subjected to double micronization with jet mill Midas micronizer with same parameters so as to obtain double micronized drug. Determination of particle size of double micronized drug was done with Malvern technique. Again the part of double micronized drug was used for Tablet formulation 2 and remaining part of double micronized drug was subjected to triple micronization and particle size determination was done. Triple micronized drug so obtained was used for Tablet formulation 3.

Table 1: Particle size of Aceclofenac drug

Particle size range	Unmicronized drug (micron)	Single micronized drug(micron)	Double micronized drug(micron)	Triple micronized drug(micron)
D10	9.97	4.66	4.57	4.17
D50	113.98	25.74	22.77	18.18
D90	297.33	121.87	116.08	89.23

Preparation of Blend for Direct Compression

All excipients and API were weighed accurately according to formula (Table 2). Formulation 1 was designated for single micronized drug, Formulation 2 for double micronized drug and Formulation 3 for triple micronized drug.

The manufacturing process of Tablets for all three Formulations was same as follows.

Aceclofenac drug was passed through sieve no. 40. Microcrystalline cellulose, Sodium starch glycolate, Sodium lauryl Sulphate were passed through sieve no. 40. API and all above excipient were blended in a blender for 20 minutes. Stearic acid and magnesium stearate were sifted through sieve no. 40 and blended with above blend for 2 minutes.

Blend analysis for all three formulations such as Loss on drying (LOD), Bulk density, tapped density and sieve analysis were done (Table 3)

$$\text{Bulk density} = \frac{\text{Weight of powder in gms.}}{\text{Initial Volume in ml}}$$

$$\text{Tapped density} = \frac{\text{Weight of powder in gms.}}{\text{Final Volume in ml}}$$

Compressibility Index=$\frac{\text{Initial–final}}{\text{Initial volume}}$ X 100

Hausner's Ratio= $\frac{\text{Initial volume}}{\text{Final volume}}$

Table 2: Formulation of single micronized, double micronized, triple micronized Aceclofenac film coated tablet

Srno	**Ingredients**		
	Form. 1	**Form. 2**	**Form. 3**
1	Single micronized Aceclofenac	Double micronized Acecclofenac	Triple micronized Aceclofenac
2	Microcrystal line cellulose	Microcrystall ine cellulose	Microcrystal line cellulose
3	Sodium starch glycolate	Sodium starch glycolate	Sodium starch glycolate
4	Sodium lauryl sulphate	Sodium lauryl sulphate	Sodium lauryl sulphate
5	Stearic acid	Stearic acid	Stearic acid
6	Magnesium stearate	Magnesium stearate	Magnesium stearate
Film coating Ingredients			
7	HPMC 5cps	HPMC 5cps	HPMC 5cps
8	Titanium dioxide	Titanium dioxide	Titanium dioxide
9	PEG 6000	PEG 6000	PEG 6000
10	Purified water	Purified water	Purified water

Table 3: Granulator parameter of Formulation 1, 2 & 3

Parameters	**Form. 1**	**Form. 2**	**Form. 3**
Loss on drying(LOD)	1.47	2.43	3.14
Bulk Density	0.615	0.545	0.593
Tapped Density	0.762	0.691	0.777
Compressibility Index	19.231	21.129	23.684
Hausner's ratio	1.23	1.26	1.31

Table 4: Sieve analysis of Formulation 1, 2 & 3

Sieve no	**Form. 1**	**Form. 2**	**Form. 3**
	% Retained		
20	0.00	0.00	0.00
40	0.16	0.15	0.10
60	25.34	29.80	31.09
80	18.22	23.95	34.88
100	10.79	10.92	15.26
Fines	25.29	45.48	56.59

Compression of Tablets

Tablets of all three formulations were compressed with average weight of 200 mg. Standard concave punch, plain on both side were used for compression. Physical parameters of tablets such as weight variation, hardness, thickness, friability and disintegration time were performed.

Preparation of Coating Solution for Film Coating

HPMC 5cps, Titanium dioxide and PEG 6000 were weighed accurately. HPMC 5cps was added in sufficient quantity of water in beaker with continuous stirring with mechanical stirrer followed by addition of Titanium dioxide and PEG 6000. The stirring was continued for 45 minutes. After stirring solution was filtered through muslin filter.

Film Coating of Tablets

Compressed tablets were coated with Inlet temperature 50-55 °C, Bed temperature: 35-40 °C and Exhaust temperature 35-42 °C. Pan speed was kept between 7 to 8 RPM.

Drying of tablets was done for 15 minutes. Parameters of coated tablets were evaluated (Table no.5).

Table 5: Physical evaluation of Coated Tablets

Parameters	Form. 1	Form. 2	Form. 3
Weight in mg	215.9-220.1	215.8-217.9	216.4-218.9
Thickness in mm	3.99-4.03	3.98-4.14	3.99-4.20
Hardness in Newton(N)	78-92	72-85	75-85
Disintegration time	4.02-5.10	4.10-5.50	4.00-5.10

Preparation of Phosphate Buffer pH 6.8

250.0 ml of 0.2M Potassium dihydrogen phosphate and 112 ml of 0.2 M Sodium hydroxide were dissolved in Distilled water and volume made up to 1000 ml.

Preparation of Acetate Buffer pH 4.5

2.99 g of Sodium acetate and 14 ml of Acetic acid were placed in a 1000ml of volumetric flask and diluted with distilled water to 1000ml.

Dissolution Studies

Dissolution studies of Aceclofenac tablets were performed with USP Apparatus type 2 at 37± 2 °C with paddle speed of 50 rpm in 900 ml of dissolution medium.

The dissolution medium used for Aceclofenac drug was Phosphate buffer pH 6.8 and Acetate buffer pH 4.5. A 10ml of sample was withdrawn at interval of 5, 10,15,30,45 and 60 minutes. The same volume of fresh medium was replaced to maintain constant volume. The samples were suitably diluted with phosphate buffer pH 6.8 and analysed using UV Visible Spectrophotometer at 275 nm.

RESULT AND DISCUSSION

Particle size range of unmicronised Aceclofenac was recorded as 297.33 micron for 90% of the particles. With single micronisation particle size of 90% of the particles were found to be reduced up to 121.87 micron. Again with double and triple microniation particle size of 90% of drug particles can be reduced up to 116.08 micron and 89.23 micron. Thus with jet mill microniser particle size of drug can be reduced to considerable limit (Table no 1). Physical parameters of tablets which prepared from single, double and triple micronized drug were found satisfactory (Table no 5).

The solubility of drug increases with reduction of particle size. The dissolutions of film coated tablets with triple micronized drug in Phosphate buffer pH 6.8 and in Acetate buffer pH 4.5 were highest as compare to film coated tablets of single and double micronized API. The dissolution of formulation 3 was 97.1 % in Phosphate buffer pH 6.8 (Table 6) and 61.1 % in Acetate buffer pH 4.5 (Table 7) in 60 minutes. The dissolution of formulation 2 was 89.8 % in Phosphate buffer pH 6.8 (Table 6) and 45.2 % in Acetate buffer pH 4.5 (Table 7) in 60 minutes which was less than formulation 3. The dissolution of Formulation 1 was least amongst three formulation which was 67.9 % in Phosphate buffer pH 6.8 (Table 6) and 35.5 % in Acetate buffer pH 4.5 (Table 7).

Table 6: Dissolution studies in 6.8 Phosphate buffer

Time in min	Form. 1	Form. 2	Form. 3
5	20.1	15.4	18.5
10	31.2	28.7	32.8
15	39.2	34.9	61.7
30	44.1	51.4	72.5
45	62.5	72.3	88.2
60	87.9	89.8	97.1

Table no 7: Dissolution studies in 4.5 Acetate buffer

Time in min	Form. 1	Form. 2	Form. 3
5	13.2	18.1	28.0
10	18.6	25.2	35.2
15	22.1	30.2	42.8
30	29.1	36.5	51.6
45	33.8	42.3	55.6
60	35.5	45.2	61.1

This shows that micronisation helps to increase solubility and therefore dissolution of poorly soluble active ingredients. The comparison of dissolution data of three formulations were shown in figure 1 and figure 2.

CONCLUSION

Poor solubility of drug is major problem to achieve desired bioavailability of drug. Different solubilisation techniques help to increase solubility have been established for poorly soluble drug like Aceclofenac. Micronisation is one of the best technique to increase solubility of drug. Formulation of film coated tablet with triple micronisation gave best results of dissolution. Thus it can be concluded that micronisation technique can be efficiently use to enhance solubility and thus dissolution of Aceclofenac.

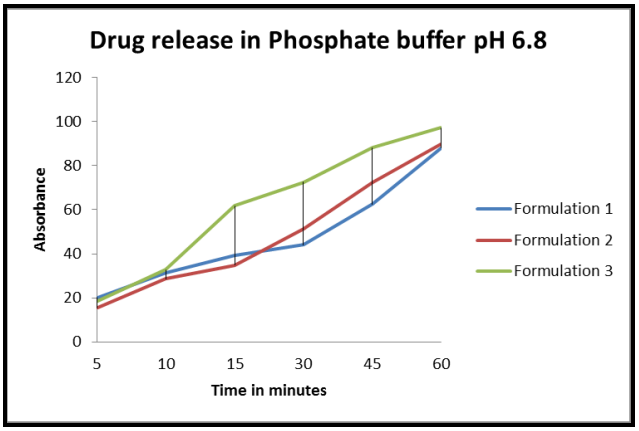

Figure 1: Drug release in Phosphate buffer pH 6.8

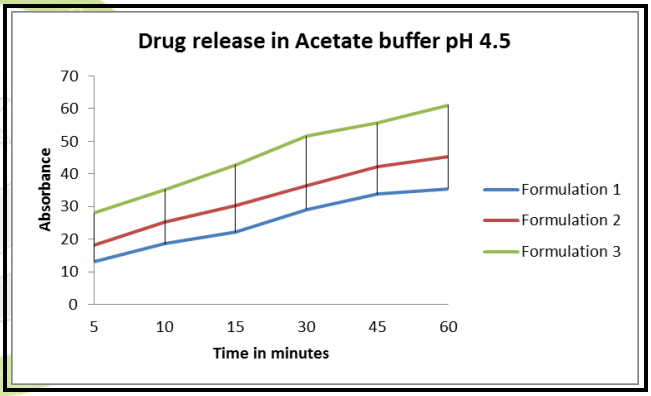

Figure 2: Drug release in Acetate buffer pH 4.5

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