

Formulation Development, in Vitro Evaluation and Stability Study of Aceclofenac Tablet

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Abstract: The objective of the study was to develop film coated tablets of aceclofenac using wet granulation technique. Possible drug-excipient interaction was evaluated by HPLC (high performance liquid chromatography) and FTIR (fourier infrared spectroscopy). The tablets prepared were assessed for their physicochemical, in vitro dissolution at pH 1.2, 4.5, 6.8 and 7.5 and stability characteristics. Comparison with a commercial aceclofenac product was made in vitro and in vitro studies. There was no interaction between aceclofenac and used excipients. Furthermore, the physicochemical properties of the tablets were satisfactory. The dissolution profile of one of the formulated aceclofenac tablets (D07) was statistically similar ($p < 0.05$) to that of the commercial aceclofenac brand in all the dissolution media. The formulated products were stable and showed no changes in physical appearance, drug content, or dissolution pattern after storage at 40 °C/75% RH for 6 months. The results indicate that it is feasible to achieve a stable aceclofenac tablet formulation by using wet granulation technique.

Key words: Aceclofenac, film coated tablets, dissolution profiles, stability studies.

1. Introduction

The main purpose of solid dosage form is to make a drug available to the human body at a certain rate and define amount through the gastro intestinal tract so that the drug can produce pharmacological effects. But studies on bioavailability of drugs from a given dosage form revealed that, in many situations, solid dosage forms did not give the same therapeutic effects [1-3]. Aceclofenac FDA (US food and drug administration) from class 2 groups according to BCS (biopharmaceutics classification system) classification weak acid is a substance made. Rapidly absorbed after oral administration and the absolute bioavailability of approximately 100%. Formulation development of aceclofenac used, freely soluble in acetone, 96% ethanol-soluble, practically insoluble in water. Aceclofenac has an active lipophilic and practically insoluble in water.

NSAIDs (non-steroidal anti-inflammatory drugs) are considered to be the first-line drugs in the

symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosis spondylitis [4-6]. Aceclofenac is one of the emerging NSAID molecules for arthritis treatment. It is a newer derivative of diclofenac and has less gastrointestinal complications. The successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired. Aceclofenac is a newer derivative of the diclofenac group of NSAID that exhibits analgesic and anti-inflammatory activities. It directly blocks the prostaglandin synthesis and has less gastrointestinal complications [7-9]. It is a recommended first-line drug in the symptomatic treatment of rheumatoid arthritis, Osteoarthritis and ankylosing spondylitis. Aceclofenac, i.e., 2-{2-{2-(2,6 dichlorophenyl)amino} phenyl}acetyl oxy acetic acid, has a short biological half life of approx 4 h and a dosing frequency of 200 mg daily in two divided doses [10-12].

Aceclofenac is a phenyl acetic acid and the chemical structure is shown in Fig. 1 [13]. The solubility of Aceclofenac, a weakly acidic drug (pK_a 4-5), depends on pH. AC is highly soluble in basic

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conditions but relatively soluble in water and acidic pH conditions. It exhibits poor flow and compression characteristics [14-16]. Several methods are available in literature to determine the concentration of AC. Techniques used for analysis of AC include titrimetric, voltammetric, densitometric, colorimetric, spectrophotometric, spectrofluorometric, polarographic, HPLC (high performance liquid chromatography), capillary electrophoresis, and mass spectrometry. Different analytical methods have been developed for the simultaneous determination of AC combinations with various active molecules. Throughout the stability test, AC in plasma has proved stable at room temperature for at least 6 h [17].

2. Experiments

2.1 Materials

Aceclofenac (Suyash Laboratories Limited), Microcrystalline cellulose (JRS Pharma), Croscarmellose sodium (Vivasol) (JRS Pharma), Povidon K-30 (BASF), Glyceryl distearate (Type I) (Gattefosse), Ethanol (JT Baker), Advantia Prime (ISP) has been supplied. All other chemicals used were of pharmaceutical grade.

2.2 Methods

All excipients are tested on conformance to description and identification with an accompanying supplier's certificate of analysis. The analytical methods used to test the excipients are those described

in the European Pharmacopoeia.

2.3 Assay of Aceclofenac Quantitative Determination of Aceclofenac

It was performed by HPLC. A gradient HPLC (Shimadzu Corporation, Kyoto, Japan) UV/VIS Detector Hichrom Kromosil100 5 C18 250 mm × 4.6 mm, 5 μ column was used. The mobile phase used was a mixture of Mobile Phase A/Mobile Phase B in a ratio of 3:2. The filtered from 0.45 μm mobile phase was pumped at a flow rate of 1.0 mL/min and the column temperature was maintained at 25 °C. The eluent was detected by a UV detector at 275 nm.

2.4 Dissolution Method

The solubility of Aceclofenac significantly increases with the pH of media. As the result of dissolution study pH 6.8 phosphate buffer media and the Pallet method have been selected. UV-Vis On-line Dissolution System was used in 75 rpm speed by a UV detector at 275 nm.

2.5 Preparation of Aceclofenac Tablet

The tablets were prepared by a wet granulation

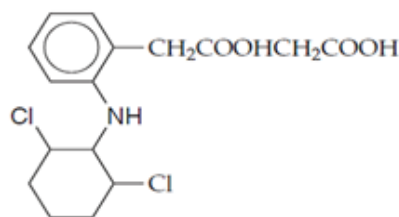


Fig. 1 Chemical structure of aceclofenac.

Table 1 Composition of formulation trials.

Ingredients	Using rate (%)					
	D 02	D 03	D 04	D 05	D 06	D 07
Aceclofenac	47.6	47.6	47.6	47.6	47.6	47.6
Microcrystalline cellulose (PH 101)	43.4	43.4	42.4	40.4	30.4	30.4
Crosscarmellose sodium	3.0	2.0	4.0	6.0	6.0	6.0
Povidon K-30	3.0	5.0	4.0	4.0	4.0	4.0
Microcrystalline cellulose (PH 102)	3.0	2.0	2.0	-	10.0	10.0
Glyceryl distearate (Type I)	37.0	37.0	37.0	2.0	2.0	2.0
Purified water*	47.6	47.6	47.6	37.0	37.0	-
Ethanol*	-	-	-	-	-	22.2

* Prepared according to the total powder are given as weight/weight. Granulation solvent is not included in the finished product.

technique. The composition of the tablet formulations are given in Table 2. 1/3 of Aceclofenac, microcrystalline sodium and crosscarmellose sodium were mixed in granulator for 5 min. The blend was granulated with the aid of PVP K-30 and ethanol/water.

The mass dried in a hot air oven at 40 °C until moisture is not more than 3.0%. The dried granules were sieved through a 600 µm sieve. 2/3 of crosscarmellose sodium was added to sieved granules and mixed in 15 rpm for 15 min. Glyceryl distearate was sieved through a 300 µm sieve and added to the blend and mixed in 15 rpm for 3 min. Prepared granules of Aceclofenac 100 mg were compressed as 210.0 mg ± 10%.

2.6 Physiochemical Characterization of the Tablets

Tablet weight variation was evaluated using 10 tablets with an electronic balance while tablet hardness and friability were determined for 10 tablets electronic friabilator for 4 min at 25 rpm, respectively.

2.7 In Vitro Evaluation

In vitro dissolution test was carried out in 900 mL of simulated pH 6.8 phosphate buffer. The dissolution medium was kept in thermostatically controlled water

bath, maintained at 37 ± 0.5 °C. The pre-weighed tablet was then introduced into the dissolution jar and the palette was rotated at 75 rpm. It was analyzed spectrophotometrically at 275 nm.

2.8 Stability Studies

Stability studies were conducted on a strip pack of one of the aceclofenac test formulation (D07) in order to assess its stability after storage at 40 °C/75% RH for 6 months. Samples were withdrawn at 1, 3 and 6 months and evaluated for the analysis results.

3. Results

3.1 Studies on API (Aceclofenac Active Pharmaceutical Ingredient)

The solubility of aceclofenac (mg/mL) was as follows: 0.1 M HCl (pH 1.2), 0.027 ± 0.010; pH 4.5 acetate buffer, 0.199 ± 0.010; pH 6.8 phosphate buffer 5.628 ± 0.010.

Figs. 2 and 3 show the spectra of the pure drug and

Table 2 Solubility of Aceclofenac.

Media	Solubility (mg/mL)	Dose/solubility
pH 1.2	0.027	3,700 mL
pH 4.5	0.199	502 mL
pH 6.8	5.628	17.8 mL

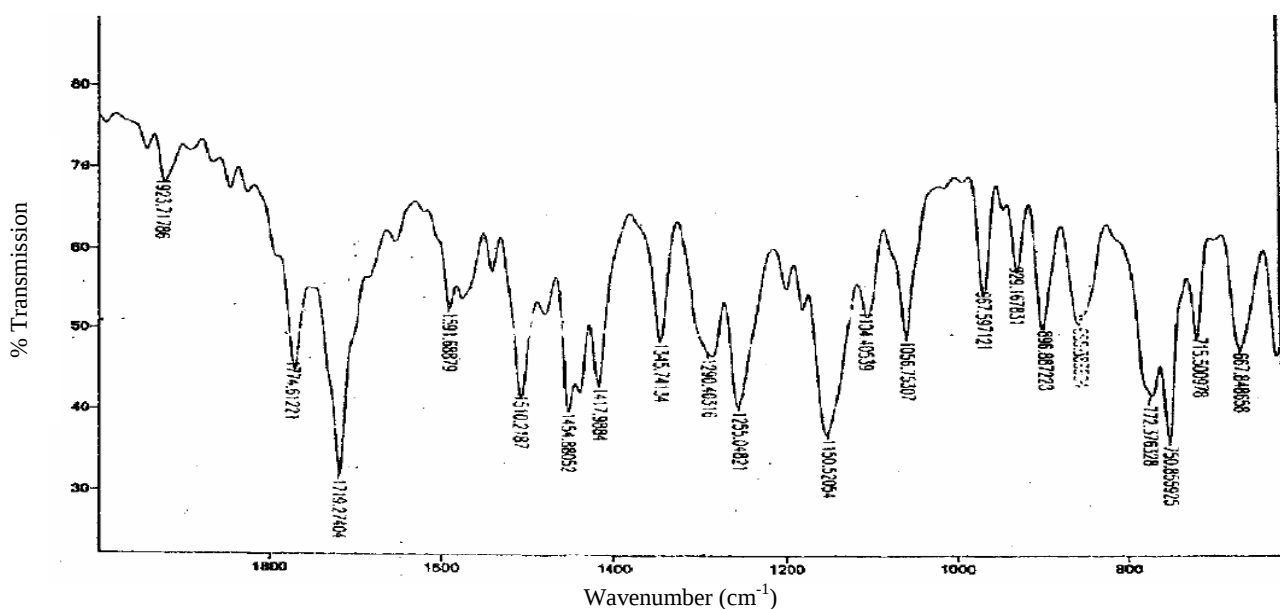


Fig. 2 FTIR spectrum of pure aceclofenac.

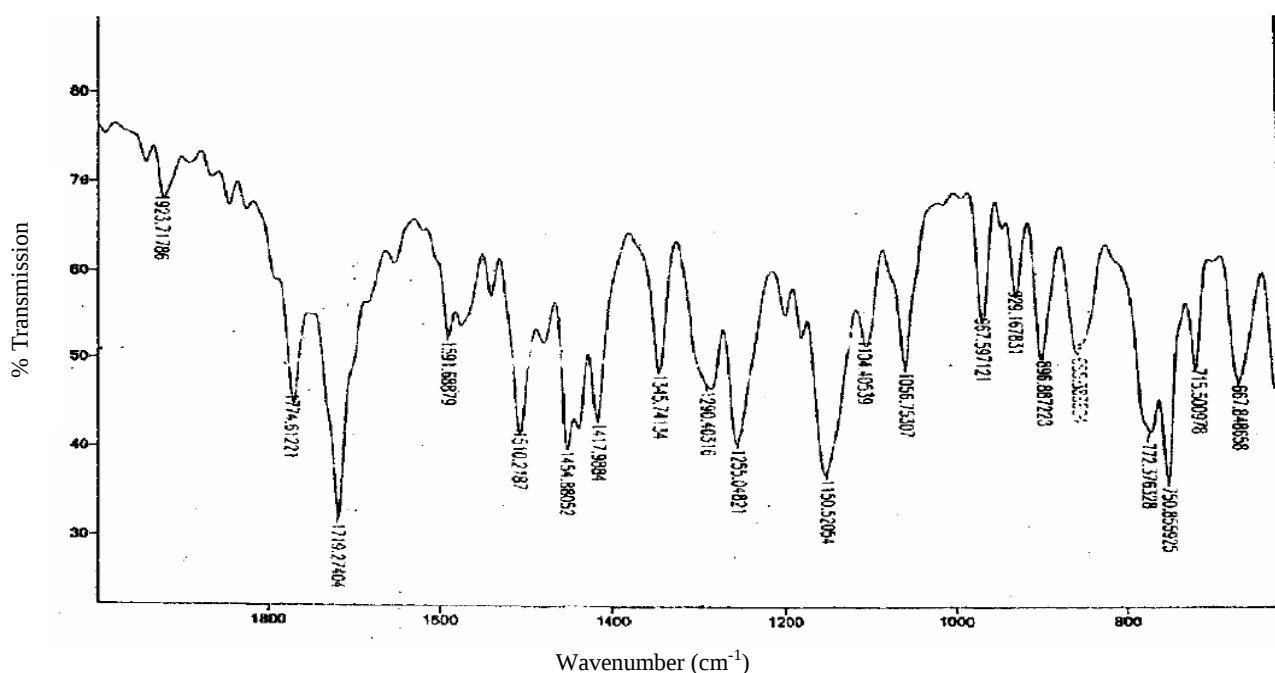


Fig. 3 FTIR spectrum of aceclofenac tablet.

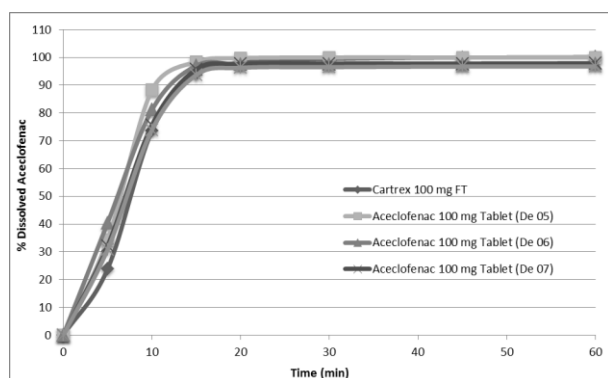


Fig. 4 Comparative dissolution profile of aceclofenac tablet trials in pH 6.

tablet formulation (D07), respectively. The spectrum for pure aceclofenac showed major peaks. Formulation D07 spectrum also showed similar peaks at the above wave numbers.

3.2 Calculation of Similarity Factor

The similarity factor (f_2) was also calculated using below Eq. (1).

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (1)$$

where, n = no. of full points, R_t = the reference profile at the time point, t , and T_t = the test profile at the same point.

The similarity factor (f_2), when the drug release

data for D07 and the reference product were compared in various dissolution media were as follows: pH 1.2, $f_2 = 76.4$, pH 4.5, $f_2 = 79.5$, pH 6.8, $f_2 = 72.2$. f_2 value between 50 and 100 suggest that two dissolution profiles are similar. Drug release from D07 in pH 6.8 media was similar to that of the reference tablet thus indicating that both formulations behaved in a similar manner in this dissolution media.

3.3 Physicochemical Properties of the Formulated Tablets

Tablet thickness was in the range 3.6-3.9 mm; diameter, 11.0 mm; and hardness, 10.0-14.0 kg/cm². Tablet friability and coefficient of weight variation of all the tablet batches were in the ranges 0.5 to 0.8% and 1.4 to 3.5%, respectively. Drug content was satisfactory and uniform (> 99%) for all the batches of tablet formulations.

3.4 In Vitro Drug Release

The results of the in vitro drug release studies in simulated gastric and intestinal fluids are presented in Table 3. As shown in Table 3, drug release data for the reference tablets and test formulation D07 in

Table 3 Comparative in vitro release profile of a test aceclofenac tablet formulation (D07) and reference product at pH 1.2, 4.5 and 6.8.

Product	Dissolution medium	Drug release (%)					
		5 min	10 min	15 min	20 min	30 min	45 min
D07	pH 1.2	4.1 ± 1.4	14.7 ± 1.4	28.6 ± 1.3	39.3 ± 1.1	52.6 ± 1.5	64.6 ± 2.0
Reference		3.9 ± 0.9	14.3 ± 4.4	30.4 ± 5.5	42.7 ± 4.6	56.8 ± 4.0	68.3 ± 3.7
D07	pH 4.5	10.7 ± 1.6	32.7 ± 2.7	50.2 ± 2.2	60.7 ± 2.1	73.3 ± 2.3	83.5 ± 2.6
Reference		11.8 ± 1.9	35.5 ± 5.3	53.3 ± 3.9	63.2 ± 3.5	74.2 ± 4.1	80.7 ± 5.0
D07	pH 6.8	26.9 ± 2.0	66.1 ± 2.2	91.5 ± 2.3	96.6 ± 1.7	96.8 ± 1.7	96.8 ± 1.7
Reference		23.8 ± 4.5	73.6 ± 9.1	94.1 ± 3.3	98.1 ± 3.2	99.5 ± 3.1	99.9 ± 3.1

Table 4 Stability results of a test Aceclofenac tablet formulation (D07) in accelerated condition.

Shelf life Parameters	Limits	Initial	1 st Month	3 rd Month	6 th Month
Appearance	White, round, biconvex, coated tablets	Complies	Complies	Complies	Complies
Weight	(216.0 mg ± %7.5)	214.6	215.9	216.6	218.2
Hardness	For information	11.6 kp	14.2 kp	14.2 kp	15.8 kp
Moisture	NMT 4.0%	1.9	2.1	2.6	2.5
Disintegration	NMT. 15 min/37 °C distilled water	9	7	6	7
Assay	(90.0 mg/tb-105.0 mg/tb)	98.3	96.3	98.0	95.5
Dissolution	NLT 85% in 30 min.	100.9	100.9	98.7	97.8
Related substances	NMT 0.2%	0.06 (RRT:1.39)	0.06 (RRT:2.2)	0.16 (RRT:2.25)	0.17 (RRT:2.35)
Unknown unique Imp	NMT 2.0%	0.07	0.43	1.4	1.4
Imp A Total Imp	NMT 3.0%	0.15	0.59	1.7	1.7

different pH media were similar, indicating both exhibited similar characteristics.

3.5 Accelerated Stability Studies

Appearance, weight, hardness, moisture, dissolution assay, dissolution and impurities values were determined to be within target limits of the shelf-life period. The results obtained from accelerated stability studies indicate that D07 tablets did not show any physical changes after 6 months. The results are presented in Table 4. These data were not significantly different ($p < 0.05$). Furthermore, there was also no significant change ($p > 0.05$) in the drug release profile of the formulation over.

4. Discussion

The available literature on the solubility profile of aceclofenac indicates that the drug is freely soluble in

acetone and practically insoluble in water. In the present study, aceclofenac showed pH-dependent solubility; as pH was raised from 1.2 to 7.5, solubility improved considerably.

There was no interaction between aceclofenac and the excipients used, thus indicating that the choice of excipients for the aceclofenac tablets was suitable. Furthermore, all the formulations showed satisfactory results in critical quality parameters.

5. Conclusions

All analytical and stability study results are supported that the quality parameters of developed formulation is significantly similar with the reference product and aceclofenac 100 mg tablet is a stable, generic, pharmaceutical product. The formulation method employed is simple and should be adaptable for commercial scale up.

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