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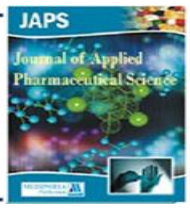

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Comparative in vitro dissolution study of Aceclofenac Marketed Tablets in Two Different Dissolution Media by Validated Analytical Method

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ABSTRACT

In this study five marketed brands of aceclofenac 100 mg tablets have been evaluated using dissolution test in two different media with the aim to assess bioequivalence and to select a proper dissolution medium. Other general quality parameters of these tablets like weight variation, hardness, friability, disintegration time were also determined according to established protocols. All the brands complied with the official specification for friability, uniformity of weight, disintegration time and drug content. UV spectroscopic and RP-HPLC methods were validated for the parameters like linearity, accuracy, precision and robustness. Potency was determined by using these two methods. Potency obtained from UV method and HPLC methods were found similar with paired *t* test. Dissolution test results were subjected to further analysis by difference factor (f1), similarity factor (f2) and dissolution efficiency (% DE). Higher drug release was found in phosphate buffer pH 6.8 than in 0.05% sodium lauryl sulphate solution. All brands were found similar in respect of drug release in phosphate buffer pH 6.8 but they differ in respect of drug release in 0.5% sodium lauryl sulphate. So phosphate buffer pH 6.8 may be a suitable media for dissolution study of aceclofenac tablets.

Keywords: Aceclofenac, method validation, similarity factor (f2), dissolution efficiency (% DE), dissolution comparison.

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 reveled that, in many situations, solid dosage forms did not give the same therapeutic effects. This is mainly due to the insufficient dissolution and subsequent absorption of the drug from the GIT. So, dissolution analysis of pharmaceutical solid dosage forms is a very important test of product quality (Hsu et al., 1989). Aceclofenac , [(2-{2,6-dichlorophenyl)amino} phenylacetooxyacetic acid] is a non-steroidal anti-inflammatory drug (NSAID) indicated for the symptomatic treatment of pain and inflammation with a reduced side effect profile, especially gastro-intestinal events that are frequently experienced with NSAID therapy. Aceclofenac is practically insoluble in water with good permeability (calculated log P = 2.170) and belongs to biopharmaceutics classification system (BCS) class II (low solubility, high permeability). Therefore, AC shows dissolution rate limited absorption that gives rise to difficulties in pharmaceutical formulations for oral delivery, which may lead to variable bioavailability. Therefore constant surveillance on marketed aceclofenac tablets by the government, manufactures and independent research groups is essential

to ensure availability of quality medicines. Quality assessment of locally available BCS class-II drug has been reported earlier (Oishi et al., 2011). But no such information is available on widely used BCS Class-II NSAID, aceclofenac. Aceclofenac tablet is not official in BP or USP till now, but products are available in the markets. No official method is available for dissolution study of aceclofenac tablets. So it is essential to check the dissolution profile of the marketed aceclofenac tablets to find out their bioequivalence. In this study an initiative was taken to test the dissolution profile of marketed aceclofenac tablets in two different dissolution media, phosphate buffer pH 6.8 and 0.5% sodium lauryl sulphate solution to find out suitable dissolution media. Other general quality assessments of these tablets like assay, weight variation, hardness, friability, disintegration time were also determined for total evaluation. Selective and sensitive analytical method for quantitative determination of drugs and their metabolites are essential for successful evaluation of clinical pharmacology, pharmacokinetics (PK), bioavailability (BA) and bioequivalence (BE) studies. As aceclofenac tablet is not official in BP or USP, official analytical methods are not available. Both UV (Gajanand et al., 2010) and HPLC (Venkatesh et al., 2009) methods for the analysis of aceclofenac have been reported. Most of the reported methods are applicable for multi-component dosage form and they are not free from limitations. Uttam et al., 2009 described an HPLC method where retention time of aceclofenac is 19.48 min which is not suitable for analysis of large number of samples due to higher solvent consumption. So development of analysis method for aceclofenac is still required. In this study we have validated both UV spectroscopic and RP-HPLC method and used them aceclofenac analysis and compare these two methods by paired *t* Test, so that one can test aceclofenac tablet with their available facility.

The proposed methods were validated for the parameters like linearity, accuracy, precision and robustness as per ICH guidelines (ICH 1995). The linearity of an analytical method is its ability to elicit that test results are proportional to the concentration of drug in samples within a given range. Linearity of the method is generally determined by constructing calibration curves. The accuracy is the closeness of agreement between the true value and test result. Accuracy is determined by means of recovery experiments. The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple samplings of the same homogeneous sample under prescribed conditions. It is determined by calculating % RSD of various measurements at different time, lab, equipment or analyst.

MATERIALS AND METHODS

Reagents and Chemicals

Aceclofenac was provided by Aristo Pharma Limited, Dhaka, Bangladesh. Methanol was of HPLC grade and was purchased from E. Merck, Darmstadt, Germany. Other reagents were of analytical-reagent grade and purchased from E. Merck, India. Water was deionised and double distilled. Marketed formulations of aceclofenac tablet 100 mg (Five brands were denoted as A-1, A-2, A-3, A-4 and A-5) were purchased from local drug store in Dhaka city after checking their manufacturing license number, batch number, production and expiry date.

Validation of UV Spectroscopic Method

A double-beam Shimadzu (Kyoto, Japan) UV-Visible spectrophotometer, Model UV-1700 PC, equipped with 1 cm quartz cells, with a fixed slit width (1 nm), wavelength accuracy of +0.5 nm (with automatic wavelength correction) was used. The drug analyses data were acquired and processed using UV Probe software (Version 2.3, Shimadzu, Japan) running under Windows XP on a Pentium PC. For scanning, the wavelength range selected was from 300 nm to 220 nm with medium scanning speed. (Fig 1)

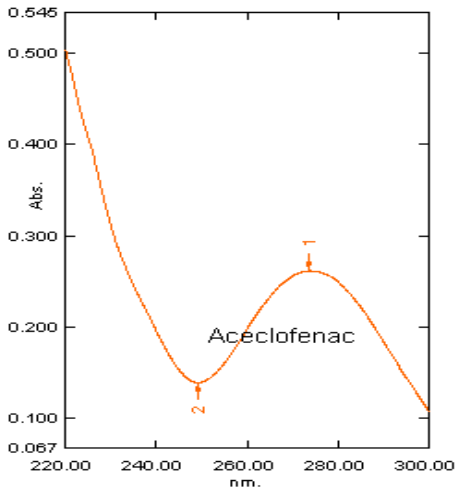

Fig: 1 Spectrum of aceclofenac.

The proposed method was validated for the parameters like selectivity, linearity, accuracy, precision and robustness as per ICH guidelines (ICH 1995).

Selectivity of the method was evaluated by comparing the spectrum of Standard aceclofenac with that of placebo product. Linearity of the method was determined by constructing calibration curves in pH 6.8 phosphate buffer. Stock solution of aceclofenac (100 mcg/ml) was prepared in pH 6.8 phosphate buffer diluted to get standard solution across the range of 4-16 mcg/ml.

Accuracy was determined by means of recovery experiments. Solution of known concentration of aceclofenac was prepared from placebo formulation and absorbance was measured and potency was calculated. The accuracy was assessed from the test results as the percentage of the drug recovered by the assay.

The precision of the method was investigated with respect to inter assay precision (repeatability), inter day precision (intermediate precision) and reproducibility (inter laboratory trial). Inter assay precision was determined by performing three repeated analysis of the four standard solutions (4, 8, 16 mcg/ml) on the same day from 9.00 am to 9.00 pm, under the same experimental conditions. Inter day precision of the method was assessed by carrying out the analysis of standard solutions on three different

days (inter day) in the same laboratory. For reproducibility the procedure repeated in another lab by using Shimadzu spectrophotometer model UV-1601. The relative standard deviation (% RSD) was calculated in order to assess the precision of the method. To determine the robustness drug was dissolved in phosphate buffer of pH 6.8 and 7.2. Percent recovery was calculated to examine the robustness.

Validation of HPLC Method

A Shimadzu (Japan) HPLC system consisting of a CMB-20 Alite system controller, two LC-20AT pumps, SIL-20A auto-sampler and CTO-10ASVP column oven were used. Ultraviolet detection was achieved at 273 nm with a SPD-20A UV-VIS detector (Shimadzu, Japan). The drug analyses data were acquired and processed using LC solution (Version 1.3, Shimadzu, Japan) software running under Windows XP on a Pentium PC. The mobile phase, methanol: water (40:60 v/v) pumped at a flow rate of 1.0 ml/min through the column (C_{18}; 250 mm X 4.6 mm, 5µ shim-pack, Japan) at 30^0C. The mobile phase was filtered through a 0.2µ nylon membrane filter and degassed prior to use under vacuum. Elusions were analyzed by UV detector at a sensitivity of 0.0001.

Stock solution of aceclofenac (100mcg/ml) was prepared in the mobile phase and diluted to get standard solution of 80%-120% of target concentration. The method was validated for the parameters like system suitability, selectivity, linearity, accuracy, precision and robustness.

The system suitability was assessed by six replicate analyses of standard solution at a 100% level to verify the resolution and reproducibility of the chromatographic system. This method was evaluated by analyzing the repeatability of retention time, tailing factor and theoretical plates (Tangent) of the column.

To determine the selectivity of the method standard samples of aceclofenac and placebo formulation injected in the system. The chromatograms were analyzed for retention time, peak area and peak shape to determine selectivity of the method.

Linearity was determined by means of calibration graph that was constructed with increasing amount of standard solutions (80%, 90%, 100%, 110% and 120% of target concentration). These standards were tested six times in agreement to the International Conference on Harmonization (ICH). The proposed method was evaluated by correlation coefficient of calibration graph.

Accuracy and precision were determined by performing four repeated analysis of the three standard solutions (90%, 100% and 110% of target concentration) on three different days. % Recovery was calculated to access accuracy and % RSD was calculated to access precision. The robustness of the method was assessed by altering the some experimental conditions such as by changing the flow rate from 1.1 to1.2 ml/min, amount of methanol (38% to 42%) and the temperature of the column (28 °C to 32 °C).

Test of physico-chemical parameters of aceclofenac tablets

The average weights for each brand as well as the percentage deviation from the mean value were calculated by weighing 20 tablets from each brand by an analytical weighing balance (AY-200, Shimadzu, Japan). The crushing strength was determined with an Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland). Twenty tablets of each brand were weighed and subjected to abrasion by employing a Veego friabilator (VFT-2, India) at 25 rev/min for 4 min. The tablets were then weighed and compared with their initial weights and percentage friability was calculated. Six tablets from each brand were employed for the disintegration test using a Tablet Disintigration Tester (Model: VDT-2, Veego, India). The disintegration time was taken as the time when no particle remained on the basket of the system.

Assay of aceclofenac tablets

20 Tablets were weighed and finely powdered. Powder containing about 48 mg aceclofenac was dispersed in 100 ml phosphate buffer (pH 6.8), shaken for 10 min, sonicated for 5 min and diluted up to 200 ml. The solution was again dilute with phosphate buffer to make a concentration of 12 mcg/ml. The solution was filtered and used for absorbance measurement in a double-beam Shimadzu (Kyoto, Japan) UV-Visible spectrophotometer (Model UV-1700 PC) to find out the potency. The samples were also prepared in mobile phase in the same way and injected in Shimadzu (Japan) HPLC system. Potency was calculated from peak area.

Dissolution test

The dissolution test was undertaken using tablet dissolution tester (TDT-08L, Electrolab, India) in 6 replicates for each brand. Dissolution media were USP buffer solutions at pH 6.8 (phosphate buffer solution) and 0.5% sodium lauryl sulphate solution. The medium was maintained at 37 ± 0.5°C. In all the experiments, 5 ml of dissolution sample was withdrawn at 0, 10, 20, 30, 40, 50 and 60 min and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by UV spectroscopic method. The concentration of each sample was determined from a calibration curve obtained from pure samples of aceclofenac.

Data analysis

The uniformity of weight was analyzed with simple statistics while the dissolution profiles were analyzed by difference factor (f1), similarity factor (f2), dissolution efficiency (% DE). Potency measured by two different methods was compared by paired *t* Test.

RESULTS AND DISCUSSION

Validation of UV method

Validation result of UV spectroscopic method for aceclofenac analysis was summarized in table 1. The method was found selective as spectrum of standard aceclofenac coincide with that of placebo product indicating that excipients has no noticeable effect on the effectiveness of the method. The proposed method was found to be linear in the concentration range (4-16 mcg/ml). Correlation coefficient was 0.999 which proves the high linearity of the method. The method was found accurate as indicated by

results of recovery studies (%recovery was 99.5%-100.11%), highly precise (% RSD is less than 2%) and robust as no significant effect was observed in the recovery of drugs dissolved in different media.

Table 1: Data showing linearity, accuracy, precision and robustness of UV spectroscopic method.

Validation parameters		Concentration (mcg/ml)		
		4	8	16
Linearity	Range	4-16 mcg/ml		
	R2 (mean ± SD)	0.999 ±0.0003		
Accuracy	% Recovery ± SD	99.82 ± 0.31	100.11± 1.23	99.5± 0.52
Precision (%RSD)	Inter assay precision	0.35	0.27	0.095
	Inter day precision	0.59	0.43	0.25
	Reproducibility Lab-I	1.52	0.9	0.83
	Reproducibility Lab-II	1.38	0.84	0.83
Robustness % Recovery ± SD	Phosphate Buffer pH 6.8	100.04 ± 0.37	99.84± 1.26	99.65± 0.42
	Phosphate Buffer pH 7.2	99.94 ± 0.37	100.01± 1.13	99.57± 0.58

Validation of HPLC Method

The experiment was carried out according to the official specifications of USP, ICH- 1995, and Global Quality Guidelines. Table 2 represents system suitability tests results of this method. The system is found suitable in respect of retention time (% RSD 0.036), mean theoretical plate count (more than 3000), tailing factor (less than 1.5).

Table 2: Results of system suitability study.

Parameters	Average	SD	%RSD
Retention time	2.501	0.001	0.036
Area	304172.54	3456.850	1.136
Theoretical plates	4552.430	2.740	0.060
Tailing factor	1.172	0.003	0.289

Aceclofenac Peaks of standard solution and sample and placebo formulation were on same time (Fig. 2). Excipients did not change the retention time or interfere the analysis results. So the method is highly selective for aceclofenac.

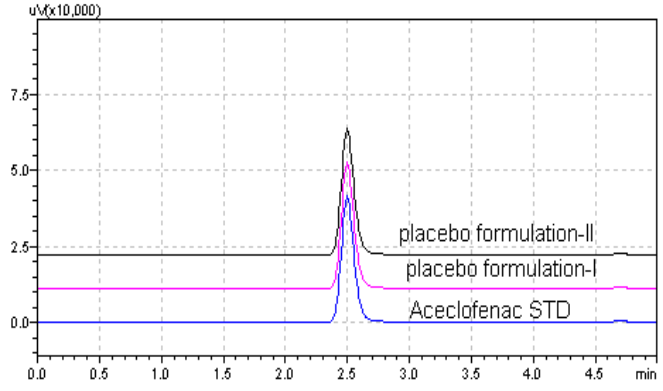

Fig: 2 Chromatogram of aceclofenac and placebo formulation.

Results of linearity, accuracy and precision were summarized in table 3. The method was found linear as regression co efficient of calibration curve is more than 0.999. Average % recovery was 99.74 ± 0.32and %RSD in precision was 0.45- 1.39. So the method is highly accurate and precise.

Table 3: Linearity, accuracy and precision results of HPLC method.

Validation parameters		Aceclofenac
Linearity (regression coefficient-R^2) (*Y = mX+C)	R^2 (mean±SD)	0.9997±0.0002
	%RSD **	0.02
	Slope (mean±SD)	20866.27±38.79
Accuracy	% Recovery	99.74 ± 0.32
	%RSD	0.320834169
Precision (%RSD)	Inter assay precision	0.45
	Inter day precision	0.52
	Reproducibility	1.39

* R^2 = regression coefficient. **Y = mX+C; where Y = peak area, m = slope, X = concentration (mcg/ml) and C = intercept.

Robustness study was performed by making a slight variation in flow rate, amount of methanol and column temperature. No significant effect was observed in the recovery of drugs. % recovery was 98% to 102%. On the other hand changes in retention time and theoretical plate were also negligible. So we can say that the method is robust.

Properties of tablets

All the brands had low tablet weight variation (SD < 2.89). Crushing strength of the tablets was in the range of 35to 116 N and percentage weight loss in the friability test was ≤ 0.2% in all the brands. Disintegration time (DT) of the tablets in all the brands showed 78.5-475.0 sec. Overall, the tablets were of good quality with regard to crushing strength, friability, weight uniformity and disintegration time (table 4).

Table 4: Physical properties of the aceclofenac formulations.

Brands	Thickness (mm) ± SD (n = 5)	Hardness (N) ± SD (n = 6)	Friability (%) (n = 20)	Weight (mg) ± SD (n = 20)	DT (Sec ± SD)
A-1	4.73 ± 0.027	35 ± 2.82	0.17%	256.84 ±2.49	475 ±7.73
A-2	4.07 ± 0.047	77 ± 4.9	0.15%	368.311±2.89	95.00 ±4.19
A-3	4.86 ± 0.047	45.50 ± 0.7	0.15%	261.77 ±2.13	79.80 ±4.6
A-4	3.53 ±0.0335	81.5 ± 2.21	0.19%	227.01±2.83	78.5 ± 7.71
A-5	4.83 ± 0.09	116 ± 2.38	0.11%	253.96 ±2.33	128.00 ±5.6

Potency of tablets

The validated UV spectroscopic and HPLC methods were used to determine the potency of commercially available aceclofenac tablets (table 5). Potency was found 98.73%-101.27% (UV method) and 100.19-103.42 (HPLC method). Potency calculated from UV method and HPLC method was compared by paired *t* Test at 0.05 significance level. The P-value was greater than the significance level, indicating that there was no statistically significant difference between the two methods.

Table 5: Potency of the aceclofenac tablets.

Brands	UV method		HPLC method		t-test	p
	Absorbance	Potency	Peak Area	Potency		
A-1	0.319	101.27	245678	100.96		
A-2	0.311	98.73	246747	101.40		
A-3	0.317	100.63	251648	103.42	2.6	0.056
A-4	0.315	100.00	245671	100.96		
A-5	0.314	99.68	246225	101.19		

In vitro drug release study

The release profiles of different brands of aceclofenac tablets are shown in Fig. 3 (Phosphate buffer pH 6.8 medium) and Fig. 4(0.5% sodium lauryl sulphate medium). All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results.

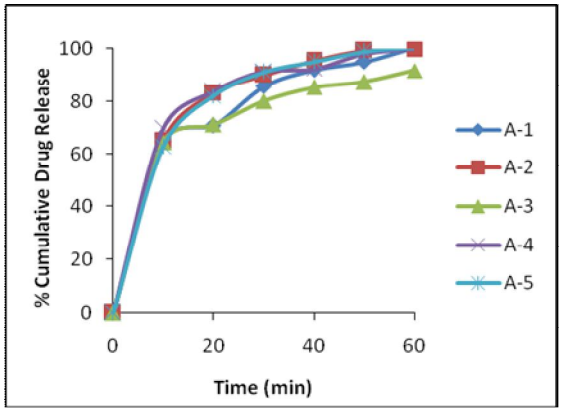

Fig: 3 Drug release from aceclofenac tablets (A-1 to A-5) in Phosphate buffer pH 6.8.

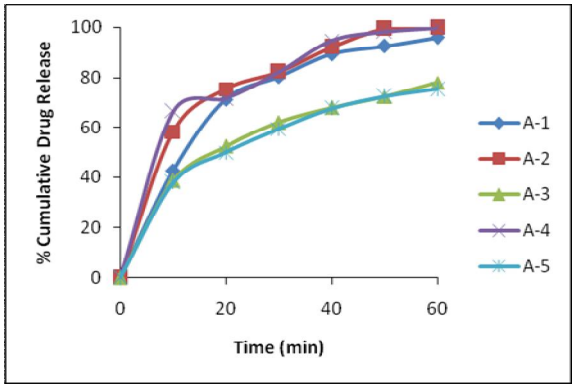

Fig: 4 Drug release from aceclofenac tablets (A-1 to A-5) in 0.5% SLS solution.

Aceclofenac tablet is not official in BP or USP. There is no official dissolution medium available in the literature. Drug release from different brand was almost uniform. Around 80% drug was released within 30 min and almost 100% drug was released within 60 min from all the brands in phosphate buffer pH 6.8. Aceclofenac is a water insoluble drug but it is soluble in phosphate buffer pH 6.8. It's solubility in phosphate buffer is 1538.7 ± 1.215 mcg/ml (Soni et al., 2008). Due to the higher solubility in this media the entire drug dissolved with in 60 min. Drug release was found lower from all the brands in 0.5% SLS dissolution media. This is may be due to the lower solubility of aceclofenac in 0.5% SLS solution. (< 453.2 ± 1.295 mg/ml). Some of the brands (A-1, A-2, A-4) released relatively higher amount of aceclofenac than other brands (A-3, A-5). This may be due to the presence of some alkalizing agents in the formulation which increase the pH of the dissolution media and facilitate drug release. From the dissolution result it can be concluded that release of poorly water soluble drug from tablet formulation is dissolution media depended. On the other hand alkalizing agents present in the formulation may increase the drug release if the drug is soluble in higher pH. Similar result was also reported by Srivastav et al., 2011 in case of gliclazide, a poorly water soluble drug.

Comparison of dissolution data

Difference factor (f1), similarity factor (f2) and dissolution efficiency (%DE) were calculated and compare for dissolution data obtained from two dissolution media. Difference factor f1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. The following equations were used to calculate difference factor f1 and similarity factor f2.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

where n is the number of time points, Rt is the dissolution value of reference product at time t and Tt is the dissolution value for the test product at time t. Similarity factor f2 has been adopted by FDA (1997) and the European Agency for the Evaluation of Medicinal Products (EMEA, 2001) by the Committee for Proprietary Medicinal Products (CPMP) to compare dissolution profile. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100 (FDA, 1997).

Dissolution efficiency (DE) was also employed to compare the drug release from various brands. Dissolution efficiency is the area under the dissolution curve within a time range (t1 - t2). DE was calculated by using the following equation:

$$AUC = \sum_{i=1}^{i=n} \frac{(t_i - t_{i-1})(y_{i-1} + y_i)}{2}$$

Where *y* is the percentage dissolved at time *t*.

Table 6: f1, f2 and % DE of aceclofenac tablets.

Brand	Phosphate Buffer (pH 6.8)			0.5% SLS		
	f2	f1	%DE	f2	f1	% DE
A-1			78.26			72.41
A-2	58.34	6.49	84.39	53.94	8.76	77.63
A-3	67.75	4.03	75.32	38.42	22.03	55.85
A-4	55.95	7.70	85.39	45.59	11.04	78.01
A-5	58.94	7.01	84.04	36.53	24.20	53.99

Table 6 shows the f1, f2 and % DE of aceclofenac tablet in two different media. Brand A-1 was used as reference product to calculate f1 and f2. Drug release in phosphate buffer pH 6.8 was found similar with reference brand as f2 were greater than 50 and f1 were less than 15. But drug release in 0.5% SLS (sodium lauryl sulphate) was not similar with reference brand as f2 were smaller than 50. So we can conclude that use of 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5 °C, a paddle speed of 50 ± 5 rpm and a 60-min test, provided satisfactory results for all products.

Table 6 also shows the dissolution efficiency of different brands. Higher dissolution efficiency was found in case of Phosphate buffer pH 6.8 than 0.5% SLS media. % DE in two media was also compared by paired t test (Table 7). The P-value was lower than the significance level (0.05), indicating that there was statistically significant difference between the two dissolution media.

Table 7: Comparison of % DE of aceclofenac tablets.

Brand	% DE in		t value	p Sig. (2-tailed)
	PB pH 6.86.8	0.5% SLS		
A-1	78.26	72.41		
A-2	84.39	77.63		
A-3	75.32	55.85	2.93	0.04
A-4	85.39	78.01		
A-5	84.04	53.99		

CONCLUSION

The present study was undertaken with an aim to evaluate aceclofenac release in two different dissolution media in order to find out the suitable dissolution media for aceclofenac release study. The study indicates that use of 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5 °C, a paddle speed of 50 rpm and a 60-min test, may be used for dissolution study for aceclofenac tablets.

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