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# Stability-Indicating Spectrophotometric Determination of Aceclofenac Using Multivariate Calibration

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## Abstract

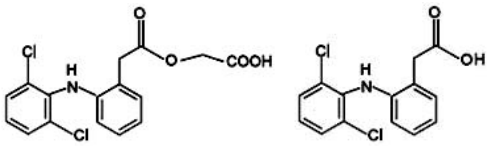
Two simple, rapid and inexpensive chemometric spectrophtometric methods were established for the stability-indicating determination of aceclofenac in presence of its degradation product; diclofenac. The applied chemometric techniques are multivariate methods including partial least squares (PLS) and concentration residual augmented classical least squares (CRACLS).The UV absorption spectra of the standard solutions of the training and validation sets in phosphate buffer of pH 6 were recorded in the range of 220-330 nm at 1.0 nm intervals. The developed methods were validated and successfully applied to the analysis of aceclofenac in pharmaceutical dosage forms and in bulk powder. The assay results obtained using the chemometric methods were statistically compared to those of a reference HPLC (high performance liquid chromatographic) method and a good agreement was observed.

**Keywords:** Stability-indicating; Chemometrics; Aceclofenac; Degradation; Dicolfenac; Multivariate

## Introduction

Aceclofenac is a phenylacetic acid derivative having the chemical name; 2-[(2,6-Dichlorophenyl) amino] benzene acetic acid carboxymethyl ester [1]. It has powerful analgesic and anti-inflammatory properties and an improved gastro-intestinal tolerance compared to other non-steroidal anti-inflammatory drugs (NSAIDs) [2,3].

The structural formulae of aceclofenac (I) and its main degradation product, diclofenac (II), are as follows:




(I)(II)

The BP (british pharmacopoeia) recommended an HPLC (high performance liquid chromatographic) method with UV (ultra-violet) detection for the determination of aceclofenac and diclofenac using phosphate buffer and acetonitrile as a mobile phase employing a gradient elution technique [1]. Several methods have been reported in the literature for the stability-indicating determination of aceclofenac in presence of diclofenac including spectrophotometric [4,5], spectrodensitometric [4-6], HPLC [5,7-9], capillary electrophoretic [10,11] and UPLC-MS methods [12,13].

Chemometric methods based on multivariate calibration such as classical least squares (CLS), partial least squares (PLS) and principal component regression (PrCR), based on computer assisted instrumentation have been increasingly applied for the analysis of multi-component mixtures [14-16]. Classical least squares (CLS) requires that the concentrations of all spectrally active constituents to be known and included in the calibration samples before a stable prediction model can be developed [17]. Because of this critical limitation, the use of principal component regression (PrCR) and partial least square (PLS) methods have become popular during the last years. PrCR and PLS methods can achieve excellent predictions for data sets even when some of the constituents concentrations have not been included in the calibration [18]. However, PrCR or PLS do not have the qualitative capabilities of CLS as they do not generate explicit estimated pure-component spectra. It was until the year 2000 when Haaland and Melgaard developed a family of augmented CLS techniques that have many advantages over PrCR and PLS [19-21]. Concentration residual augmented classical least squares (CRACLS) is a new algorithm that allows updating the model during prediction without recalibration. The CRACLS algorithm is based on CLS so it retains the qualitative benefits of CLS of estimating the pure components spectra and the flexibility of PLS modeling when spectrally active components are not explicitly included in the calibration. The components may be unknown, components with unknown concentrations, or other unidentified sources of spectral variation that are present in the calibration spectra.

The aim of the present study was to investigate the ability of chemometric methods to quantify aceclofenac in presence of its degradation product, diclofenac, as their spectra are highly overlapping, without any prior separation and to apply the optimized models in pharmaceutical preparations.

## Theory

The details of the CRACLS method are given in reference 21. For the convenience of the reader, a brief description of the theory will be given below.

The basic CLS model is

$$A = CS + E_A \quad (1)$$

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where **A** is the *nxp* matrix of the absorbance spectra from the *n*samples at the *p* wavelength, **C** is the *nxm*reference concentration matrix containing *m* components, **S** is the *m* x *p* matrix of pure-component spectra, and $\mathbf{E}_A$is the *nxp*matrix of spectral residuals (contains errors due to non linearity or if $\hat{\mathbf{S}}$ does not include all the pure-component spectra or other sources of spectral variation). The calibration step requires determining the least-squares estimate for $\hat{\mathbf{S}}$, this estimate is given by:

$$\hat{S} = (C'C)^{-1}C'A \quad (2)$$

This estimate will provide accurate estimates of the pure-component spectra only if the system is linear and **C** contains all the chemical and non-chemical components which contribute to spectral variation in the sample spectra. If the concentration matrix does not contain all spectral variation sources, the estimated pure-component spectra will be contaminated by other sources of spectral variation. These contaminated estimated pure-component spectra are then used during CLS prediction to approximate the original reference concentrations as follows:

$$\hat{C} = A\hat{S}'(\hat{S}\hat{S}')^{-1} \quad (3)$$

The *n* x *m* concentration residuals matrix, $\mathbf{E}_C$, then is given by:

$$E_C = \hat{C} - C \quad (4)$$

To accommodate unmodeled components, equation (1) can be rewritten as:

$$A = CS + C_uS_u + E \quad (5)$$

where$\mathbf{C}_u$ and $\mathbf{S}_u$ represents the concentrations and pure spectra of the unmodeled components, and **E** represents the remaining error after removing unmodeled spectra. $\mathbf{S}_u$ can be decomposed into a sum oftwo terms:

$$S_u = DS + G \quad (6)$$

where DS represents the part of $\mathbf{S}_u$ that projects into the factor space spanned by **S**, and **G** is the part of $\mathbf{S}_u$ that is orthogonal to **S**. Inserting (6) into (5) gives:

$$A = (C + CuD)S + C_uG + E \quad (7)$$

The predicted concentration obtained by applying the above equation is :

$$\hat{C} = C + C_uD \quad (8)$$

and the residual concentration, defined in (4) ,is

$$E_C = C_uD \quad (9)$$

The original concentration matrix, **C**, can be augmented by inserting any one column of $\mathbf{E}_C$ matrix as new column in **C**. the augmented **C** matrix is used again to calculate $\hat{\mathbf{S}}$ matrix again. The new $\hat{\mathbf{S}}$ matrix is used to predict $\hat{\mathbf{C}}$. A new $\mathbf{E}_C$ is computed, and a vector of the new $\mathbf{E}_C$ is added to the previously augmented $\hat{\mathbf{C}}$. This process is iterated until no further improvement in prediction is achieved.

## Experimental

### Apparatus

The spectrophotometric measurements were performed using a double-beam Shimadzu UV-Visible spectrophotometer model UV-1601 (SHIMADZU, Japan) connected to an IBM compatible PC. The bundled software was UVPC Personal Spectroscopy Software, version 3.7. The spectral bandwidth was 1.0 nm. Absorption spectra of samples were recorded using 1 cm quartz matched cuvettes on a fast scan speed between 220 - 330 nm. A Consort P-901 pH-meter was used for pH measurements.

All computations were performed in Matlab for Windows TM version 5.3 Math works Inc. 1999 with our own written codes. The PLS procedure was carried out using Solo® software 5.2.2, Eigenvector Research, Inc. 2009.

### Materials and reagents

All the chemicals used were of Analytical Reagents grade, and the solvents were of spectroscopic grade.

- Aceclofenac was kindly provided by Bristol Myers Squibb, Egypt.
- Diclofenacsodium, was kindly provided by Sedico (Egypt) and taken as standard degradation product.
- Orthophosphoric acid (Riedel-deHäen, Sleeze, Germany).
- Methanol (Sigma-Aldrich, Germany).
- Sodium hydroxide (Winlab, UK).
- Sodium dihydrogen phosphate (El-Nasr Pharmaceutical Chemicals Company (Adwic), Egypt).
- Bristaflam®tablets were purchased from the local market (Bristol Myers Squibb, Egypt). Each tablet contains 100 mg of aceclofenac.

### Preparation of solutions

Stock solutions of 0.4 mg/mLof each of aceclofenac and its degradation product, diclofenac, were prepared in methanol. Working solutions were prepared by diluting the stock solutions with methanol as appropriate. The stock solutions were found to be stable for one week if kept in the refrigerator.

### Preparation of training set

Multilevel multifactor design was used for the construction of the calibration and validation set [22]. A training set of 15 synthetic mixtures with different concentration ratios of aceclofenac and diclofenac was prepared by mixing different aliquots of working standard solutions in 10mL volumetric flasks then the volumes were completed with phosphate buffer of pH 6 (prepared by preparing a 0.2 M solution of sodium dihydrogen phosphate then pH was adjusted using orthophosphoric acid or 0.2 M sodium hydroxide). The resulting concentrations of aceclofenac and diclofenac were in the ranges 6-14 µg/mL and 0.6-1.4 µg/mL, respectively. Table 1 shows the concentrations of the prepared mixtures.

### Preparation of validation set

A validation set of 10 synthetic mixtures with different concentration ratios of aceclofenac and diclofenac was prepared by mixing different aliquots of working standard solutions in 10 mL volumetric flasks then the volumes were completed with phosphate buffer of pH 6. The resulting concentrations lie in the same range as the training set but contain different concentration ratios. Table 1 shows the concentrations of the prepared mixtures.

### Analysis of dosage forms

10 Tablets were accurately weighed, finely pulverized and

| | Training Set | | Validation Set | |
|---|---|---|---|---|
| **Sample No.** | **Aceclofenac concentration (µg/mL)** | **Diclofenac concentration (µg/mL)** | **Aceclofenac concentration (µg/mL)** | **Diclofenac concentration (µg/mL)** |
| **1** | 6 | 0.6 | 6 | 0.8 |
| **2** | 6 | 1 | 6 | 1.2 |
| **3** | 6 | 1.4 | 8 | 1 |
| **4** | 8 | 0.6 | 8 | 1.4 |
| **5** | 8 | 0.8 | 10 | 0.6 |
| **6** | 8 | 1.2 | 10 | 1 |
| **7** | 10 | 0.8 | 12 | 0.6 |
| **8** | 10 | 1.2 | 12 | 1.4 |
| **9** | 10 | 1.4 | 14 | 0.8 |
| **10** | 12 | 0.8 | 14 | 1.2 |
| **11** | 12 | 1 | | |
| **12** | 12 | 1.2 | | |
| **13** | 14 | 0.6 | | |
| **14** | 14 | 1 | | |
| **15** | 14 | 1.4 | | |

**Table 1:** Composition of the Training and Validation Sets.

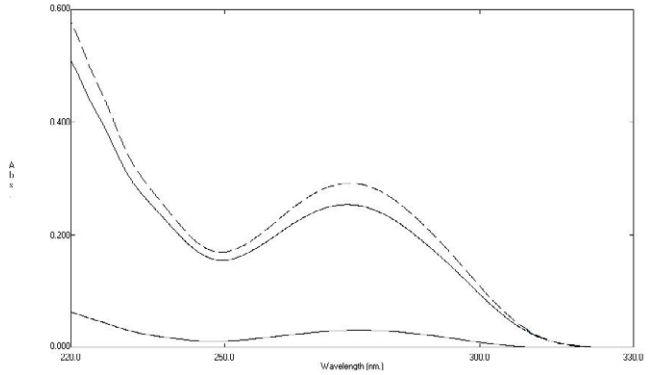


**Figure 1:** UV absorption spectra of : (A)Aceclofenac (10 µg/mL), (B)Diclofenac (1 µg/mL), (C) Binary Mixture, In phosphate buffer pH 6.

thoroughly mixed. An amount of pulverized tablets corresponding to 100 mg of declared active principle (calculated as aceclofenac free base) was weighed and transferred into a beaker. 80 mL of methanol were added and the mixture was sonicated for 30 min. in an ultrasonic bath and then filtered into a 100-mL volumetric flask and completed to the volume with methanol. Aliquots of this solution were diluted with phosphate buffer of pH 6 to give a repetitive concentration of 10 µg/mL of aceclofenac and the resulting solutions were preceded as in the previous section.

## Results and Discussion

The zero-order UV spectra (Figure 1) of aceclofenac and its degradation product diclofenac completely overlap with each other rendering it impossible to use the conventional spectrophotometric methods to analyze aceclofenac and diclofenac, in presence of each other. Mathematical models based on multivariate calibration, namely the partial least squares (PLS) and the concentration residual augmented classical least squares (CRACLS), were then applied to experimental data obtained from UV-spectra of mixtures composed of these drugs for their resolution. The analysis of these drugs in methanolic solutions was tested using different multivariate algorithms but no satisfactory results were obtained. Thus, the effect of the pH on the absorbance of both drugs was studied using phosphate buffer in different pH values ranging from 5 to 7.5. At pH 6 the best possible resolution of the overlapped spectra was observed giving the required results.

A training set was designed with 15 synthetic mixtures with different concentration ratios of aceclofenac and its degradation product, diclofenac. The ranges of the concentrations were selected, so that the ratio of the degradation product lies around 10% of the parent drug. The composition of these samples is summarized in Table 1. The absorbance data matrix for this training set was obtained by recording the absorbances within the wavelength range 220-330 nm at 1.0 nm intervals at 111 wavelengths. The training set of the two components was designed to give symmetric and orthogonal distribution in order to allow determination of aceclofenac and diclofenac in different concentrations accurately.

CLS method was tested to determine its ability to evaluate these drugs in synthetic mixtures and in pharmaceutical dosage forms, however, no reliable results were obtained at all ranges of wavelengths tested and erroneous results were obtained when comparing true and predicted concentrations of the drugs in the validation set. Thus, CLS could not resolve the overlapping peaks of aceclofenac and its degradation product, diclofenac. Afterwards, two multivariate calibration methods, namely the partial least squares (PLS) and the concentration residual augmented classical least squares (CRACLS) were performed on experimental data obtained from UV-spectra of mixtures of these drugs in synthetic mixtures and in pharmaceutical dosage forms.

The multivariate calibrations were computed with the PLS and CRACLS algorithms using mean-centered data for the absorbance data matrix and the corresponding concentration data matrix of the training (calibration) set.

### Optimization of the PLS method

Determining how many factors (latent variables) to be used in the calibration is a key step in factor based techniques. Only those factors that contain analytical information must be kept. The discarded factors should contain only noise.

The Solo® software offers some indicators that could be used for determining the optimum number of latent variables. The cross validation procedure leaving out one sample at a time was applied to the mean centered data. The root mean squared error of cross-validation (RMSECV) was determined. Genetic algorithms use this approach to locate the variable number which gives the lowest RMSECV. It is calculated as follows:

$$\mathrm{RMSECV}_k = \sqrt{\frac{\sum_{i=1}^{n}\sum_{j=1}^{q}\left(C_i - \hat{C}_{-i,k}\right)^2}{n}}$$

Where:

$C_i$ is the measured concentration for sample *i*. $\hat{C}_{-i,k}$ is the predicted concentration for sample *i.i* represents the sample number whereas *j* represents the measurement variable number. *n* is the number of samples, and *q* is the number of variables [23].

The root mean squared error of calibration (RMSEC) was also determined. It is calculated as follows:

$$\mathrm{RMSEC} = \sqrt{\frac{\sum_{i=1}^{n}\left(C_i - \hat{C}_i\right)^2}{n-(q+1)}}$$

Where:

$C_i$ is the measured concentration of the $i$th sample, $\hat{C}_i$ is the predicted concentration for the $i$th sample, using a model with $q$ variables, and $n$ is the number of samples in the calibration set [18].

To develop the PLS model, Haaland's method [23] was used to calculate the optimum number of latent variables to be used in the models. Three latent variables was found to be the optimum rank for this binary chemometric model according to RMSECV and RMSEC indicators (Figures 2 and 3).

The predicted concentrations of aceclofenac and diclofenac in each sample of the validation set were compared with their known concentrations, and the root mean square error of prediction (RMSEP) was calculated. The RMSEP was used as a diagnostic test for examining the errors in predicted concentrations. It indicates both precision and accuracy of predictions [18], as shown in Table 2. The small values of the RMSEP indicate the negligible error of prediction and the high predictive ability of the proposed methods.

Also a linear relationship with a slope approaching one when plotting the predicted concentrations versus the measured ones indicates the precision of the methods (Figures 4 and 5).

When the training models were applied to the prediction of the

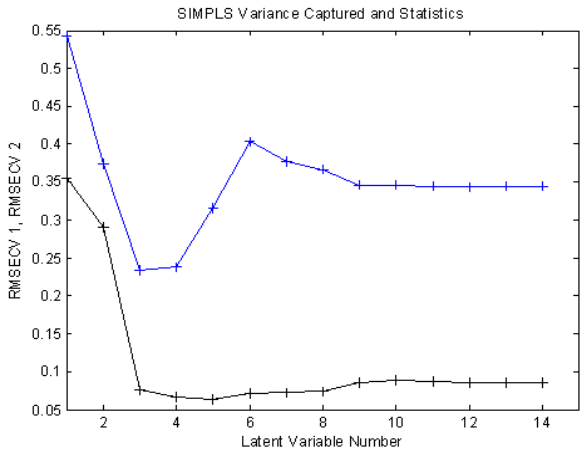


**Figure 2:** A plot of RMSECV versus number of latent variables for the PLS model.

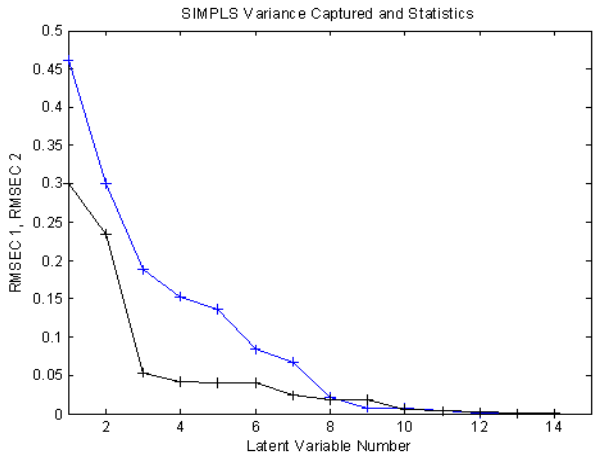


**Figure 3:** A plot of RMSEC versus number of latent variables for the PLS model.

| Validation Mixture No. | % Recovery | | | |
|---|---|---|---|---|
| | PLS | | CRACLS | |
| | Aceclofenac | Diclofenac | Aceclofenac | Diclofenac |
| **1** | 96.81 | 116.70 | 101.46 | 102.26 |
| **2** | 96.68 | 124.19 | 102.47 | 92.87 |
| **3** | 91.29 | 130.94 | 98.14 | 126.59 |
| **4** | 99.88 | 93.91 | 97.76 | 114.30 |
| **5** | 99.41 | 86.80 | 101.76 | 97.89 |
| **6** | 98.76 | 104.75 | 101.85 | 92.19 |
| **7** | 101.35 | 93.72 | 99.36 | 117.98 |
| **8** | 97.84 | 93.57 | 101.45 | 104.98 |
| **9** | 98.28 | 107.17 | 100.51 | 109.85 |
| **10** | 95.99 | 108.66 | 97.25 | 119.52 |
| $\overline{X}$ | 97.63 | 106.04 | 100.20 | 107.84 |
| **± S.D.** | 2.75 | 14.52 | 1.92 | 11.76 |
| **R.S.D.** | 2.82 | 13.69 | 1.92 | 10.90 |
| **RMSEP[a]** | 0.367 | 0.184 | 0.126 | 0.142 |

[a]RMSEP is the root mean standard error of prediction

**Table 2:** Assay results of aceclofenac and diclofenac in validation mixtures by the proposed multivariate methods.

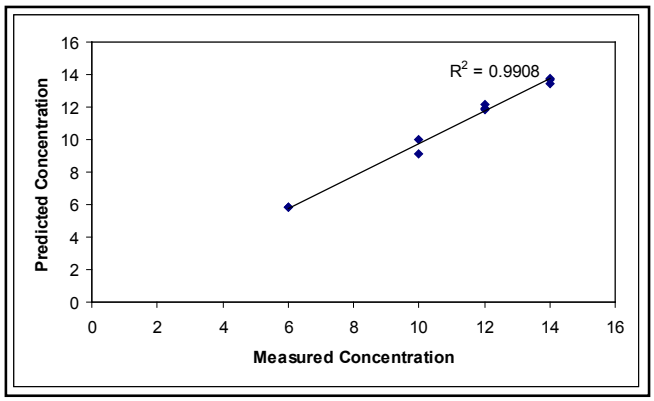


**Figure 4:** A plot of the measured versus the predicted concentration of aceclofenac in µg/mL using PLS method.

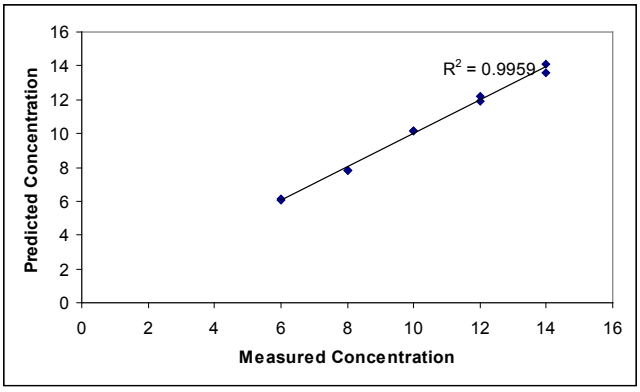


**Figure 5:** A plot of the measured versus the predicted concentration of aceclofenac in µg/mL using CRACLS method.

| Parameter | PLS | CRACLS | Comparison[5] |
|---|---|---|---|
| % Recovery | 96.81 | 101.46 | 99.72 |
| | 96.68 | 102.47 | 99.64 |
| | 91.29 | 98.14 | 100.96 |
| | 99.88 | 97.76 | 98.58 |
| | 99.41 | 101.76 | |
| | 98.76 | 101.85 | |
| | 101.35 | 99.36 | |
| | 97.84 | 101.45 | |
| | 98.28 | 100.51 | |
| | 95.99 | 97.25 | |
| $\overline{X}$ | 97.63 | 100.20 | 99.72 |
| S.D. | 2.75 | 1.92 | 0.97 |
| Variance | 7.56 | 3.68 | 0.94 |
| Students *t*-value | 1.46 | 0.47 | |
| Variance ratio *F*- value | 8.04 | 3.91 | |

Tabulated *t*- and *F*-values at $p$=0.05 are: 1.782 and 8.812, respectively[22]

**Table 3:** Assay of aceclofenac in synthetic mixtures using the proposed and comparison methods.

| Parameters | Aceclofenac® 100 mg / tab | | |
|---|---|---|---|
| | PLS | CRACLS | Comparison[5] |
| % Recovery | 91.27 | 88.25 | 94.62 |
| | 89.65 | 89.37 | 91.99 |
| | 93.99 | 92.66 | 95.68 |
| | 89.81 | 94.92 | 93.48 |
| | 95.72 | 89.97 | |
| $\overline{X}$ | 92.09 | 91.03 | 93.94 |
| S.D. | 2.67 | 2.71 | 1.58 |
| Variance | 7.15 | 7.35 | 2.50 |
| Students *t*-value | 1.21 | 1.889 | |
| Variance ratio *F*- value | 2.860 | 2.94 | |

Tabulated *t*- and *F*-values at $p$=0.05 are 1.895 and 9.117, respectively[22]

**Table 4:** Assay of Aceclofenac in formulations using the proposed and comparison methods.

validation set, good results were obtained, with a mean accuracy, expressed as percentage recovery ± R.S.D of 97.63 ± 2.82 and 106.04 ± 13.69 for aceclofenac and diclofenac, respectively

## Optimization of CRACLS method

CRACLS models were built for Aceclofenac and diclofenac in presence of each other. To test the prediction ability of the new method, the model was challenged with the spectra of the validation set. Recoveries are shown in Table 3. The prediction was found to improve as the augmentation number increases. The RMSEP continues to improve as the number of augmentation increases. Three iterations were enough to reach stable predictions. Increasing the number of augmentation does not lead to overfitting, after a sharp decrease the RMSEP decreases gradually till it reaches a constant value. Haaland's method [23] was also used to calculate the optimum number of iteration be used in the models. No significant difference in RMSEP was obtained between the optimum number of iterations and subsequent iterations.

When the training models were applied to the prediction of the validation set, good results were obtained, with a mean accuracy, expressed as percentage recovery ± R.S.D of 100.2 ± 1.92 and 107.84 ± 10.90 for aceclofenac and diclofenac, respectively.

## Statistical analysis

The produced models were used for analysis of aceclofenac in pharmaceutical formulation. The results were compared with the comparison HPLC method [5] which depends on the determination of aceclofenac in presence of diclofenac by reversed phase HPLC using methanol: water (60:40 v/v) as mobile phase at a flow rate of 1 mL/min and UV detection at 275 nm. The linearity range was 1-50 µg/mL [5], where no significant difference for both accuracy and precision was observed as indicated by *t*-test and *F*-test (Table 3).

# Applications

## Dosage form analysis

The proposed methods were successfully applied to the assay of aceclofenac in commercial tablets (Bristaflam®). The average percent recoveries of a certain defined concentration were based on the average of five replicate determinations. The results shown in Table 4 are in good agreement with those obtained with the comparison method [5]. Therefore, the proposed method can be used for the quality control of the tablets.

# Conclusion

Chemometric spectrophotometric methods (PLS and CRACLS) have been developed in this study for the stability indicating assay of aceclofenac in presence of its degradation product diclofenac in synthetic binary mixtures and in pharmaceutical dosage forms. The CRACLS has prediction abilities comparable to PLS and yet has better qualitative characteristics than PLS. The assay results obtained were compared to those of a reported HPLC method and a good coincidence was observed as there was no significant difference between the methods compared. However, the chemometric methods are less expensive by comparison and do not require sophisticated instrumentation nor any prior separation step. The multivariate methods are characterized by being fast, easy, simple and they don't require any prerequisite for successful application.

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