RJC

RASĀYAN *J. Chem.*
Vol. 15 | No. 4 |2938-2945| October - December | 2022
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

BAYESIAN REGRESSION OF OVERLAPPING IBUPROFEN-PARACETAMOL UV SPECTRA

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ABSTRACT

Bayesian regression has been successfully applied to predict a full spectrum of ibuprofen and paracetamol binary mixture. The Bayesian regression models were constructed using 25 ibuprofen and paracetamol mixture with concentration combinations of 6, 8, 10, 12, and 14 ppm for each ibuprofen and paracetamol. The models were validated using synthetic test solutions to acquire the model's accuracy and precision. The intercept, slopes, and model mean squared error indicated that paracetamol prediction on the test and sample solution was more reliable than ibuprofen. The recovery ranges and mean squared error for both the test solution and pain relief tablet confirm that the models have good accuracy in predicting ibuprofen and paracetamol binary mixture in the pharmaceutical drug. The measurement was carried out at wavelengths ranging from 220 to 270 nm.

Keywords: Bayesian regression, Ibuprofen, Paracetamol, Spectrophotometry.

RASĀYAN *J. Chem.*, Vol. 15, No.4, 2022

INTRODUCTION

Many drugs contain multi-component mixtures that are often difficult to analyze compared to others. This is due to overlapping spectra or the presence of other compounds at different concentrations. Analysis of pharmaceutical mixtures using various chemometric methods from UV-Vis spectra has been reported in many studies.[1–5] The quality of the data resulting from this analysis must be able to demonstrate the quality of the process and its fitness for its purpose by providing a measure of the result's reliability. One measure for this purpose is the measurement of uncertainty. Although uncertainty cannot replace method validation, it can provide more complete information regarding samples.[6-8] Bayesian regression is a suitable strategy for validating quantitative analysis methods and evaluating measurement uncertainty. The Bayesian analysis is capable to evaluates the analytical measurements' reliability. The Bayesian regression method offers several advantages i.e. (a) maintaining a balance between the accuracy and complexity of the model when dealing with overfitting, (b) providing a prediction distribution by showing prediction intervals, and (c) eliminating cross-validation steps that are computationally intensive.[9,10] Based on the above rationale, this research was carried out to investigate the reliability of ibuprofen and paracetamol binary mixture determination using Bayesian regression. In this study, 25 UV spectra of the ibuprofen-paracetamol calibration solution at a wavelength ranging from 220 to 270 nm were analyzed using Bayesian regression based on multivariate modeling. The Bayesian regression model was validated using external sample sets before being applied to analyze commercial pharmaceutical formulation samples.

EXPERIMENTAL

The chemicals used in this study were paracetamol (87.5-92.5%, Sigma Aldrich), ibuprofen (99.8-101.0%, Sigma Aldrich), methanol pa (Merck), and commercially available pain relief tablets that contain a mixture of 350 mg of paracetamol and 200 mg of ibuprofen. All the chemicals were used without further purification. The paracetamol and ibuprofen were analyzed using a Genesys 10S spectrophotometer using a 10 mm quartz cell. The measurement was carried out at a wavelength of 220 - 270 nm. The application of Bayesian regression was carried out using the PyMC3 software package.[11] Paracetamol 1000 mg/L stock solutions were prepared by dissolving 0.1143 gr paracetamol in 100 ml methanol. Ibuprofen 1000 mg/L

http://doi.org/10.31788/RJC.2022.1546961

stock solution was prepared by dissolving 0.1002 gr ibuprofen in 100 ml methanol. Standard solutions with 25 concentration variations were prepared with ibuprofen and paracetamol concentration combinations of 6, 8, 10, 12, and 14 mg/L. The calibration was carried out using 25 standard solutions with 5 replications. Twenty commercial pain relief tablets were weighed and crushed into powder. An amount of powder that represents 200 mg ibuprofen (IB) and 350 mg paracetamol (PA) was prepared. The powder was dissolved in 100 ml methanol in a volumetric flask. The residue was rinsed with 10 ml of methanol. The solution was sonicated for 5 minutes to speed up the dissolution and centrifuged for 10 minutes at 340 rpm. Supernatants of 0.05 ml were diluted with methanol in a 25 ml volumetric flask. The absorbance of the solution was measured using a UV-Vis spectrophotometer at a wavelength of 220-270 nm. This measurement was repeated three times. The model fitting and posterior analysis were done using a Bayesian linear regression model with normal priors. The response variable (Y/μ) represents the concentration combination of predicted ibuprofen and paracetamol. The Y was assumed as normally distributed with expected alpha and beta values that were a linear function of 25 predictor variables,

$$Y_i \sim N(\text{alpha}, \text{beta}, \sigma^2)$$

$$\mu = \alpha + \beta_i X_i + \sigma$$

σ represents the observation error, N represents Normal distribution, and alpha and beta represent regression intercept and slope, respectively. A prior distribution for the unknown variables in the Bayesian model, generally, was a normal prior with a zero mean with a variance of 1 for both regression intercept and slope. This corresponded to *weak* information regarding the true parameter values. While, for the prior error term, a half-normal, HN(1), distribution was chosen.

$$\alpha \sim N(0,1)$$

$$\beta_i \sim N(0,1)$$

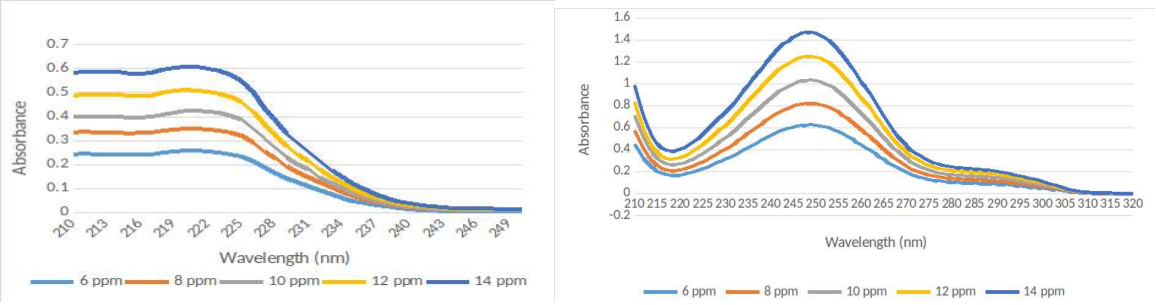
$$\sigma \sim HN(1)$$

DFT analysis was carried out using ORCA® 5.0.0[12] and the outputs were visualized using Avogadro® 1.2.0.

RESULTS AND DISCUSSION

Spectrophotometric Analysis and Construction of the Models

UV-Vis absorption spectra for each ibuprofen, paracetamol (Fig.-1), and the mixture of ibuprofen and paracetamol (Fig.-2) were measured in the range of 210–320 nm. Ibuprofen absorption peaks appear at wavelength ± 230 nm (Fig.-1(a)), while paracetamol has peaked at about 250 nm (Fig.-1(b)). This is in accordance with another research that has been done.[13,14]



(a) (b)

Fig.-1: The Individual Spectra of Ibuprofen (a) and Paracetamol (b)

Based on the DFT analysis of ibuprofen and paracetamol, it was shown that the electron transitions of ibuprofen occur at 218.74 nm and 237.47 nm, as shown in Fig.-3(a). But, the peak at 218 nm broadens and overlaps with the peak at 237.47 nm, Fig.-4(b). A similar phenomenon was observed for paracetamol, Fig.-3(b). The paracetamol peak at 241.7 nm broadens and becomes overlapped with the peak at 264.6 nm. As a result, the peak at 264.6 nm was not observed, Fig.-4(b). The overlapping of both ibuprofen and paracetamol UV spectra without peaks broadening was shown in Fig.-4(a).

The ibuprofen's highest electron transition energy, from the DFT study, was come from the transition of HOMO and LUMO orbitals that were shown in Fig.-5. It was shown that the transition at 218.74 nm was dominated by the electron transition of the ibuprofen aromatic ring. While transition at 237.47 nm was

dominated by electron transition of ibuprofen carboxyl groups beside from ibuprofen aromatic ring. Similar phenomena were also observed for paracetamol electron transitions, Fig.-6.[15]

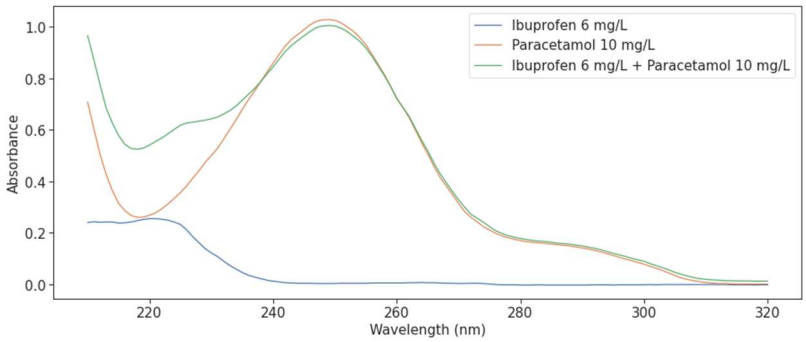
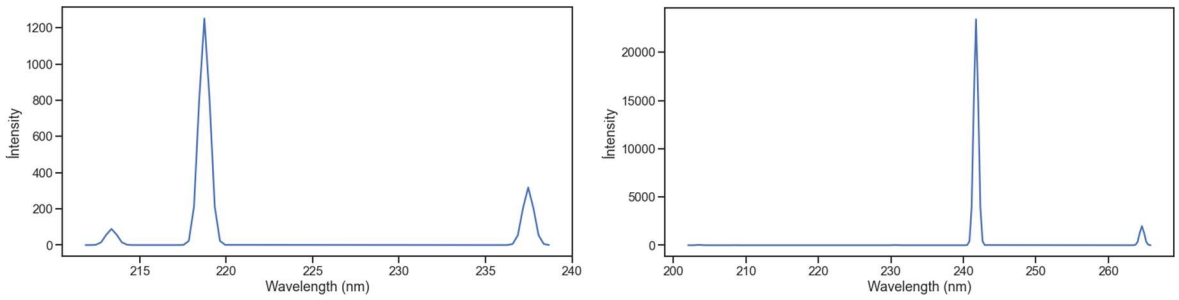
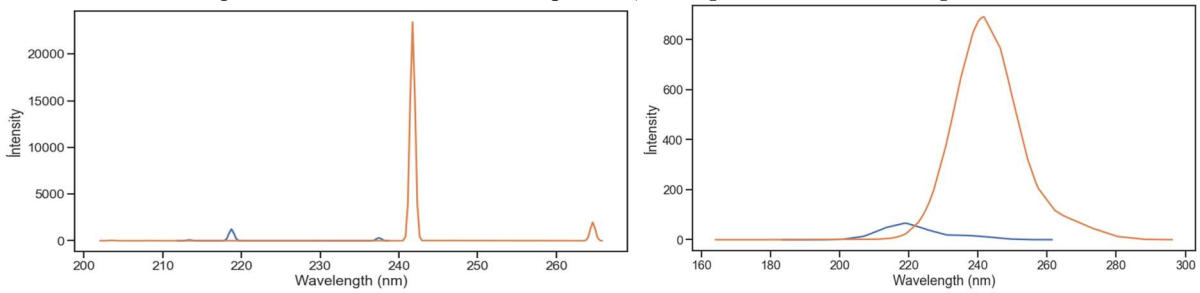


Fig.-2: The Individual Spectra of Ibuprofen (6 ppm) and Paracetamol (10 ppm) and Spectra of Ibuprofen and Paracetamol Mixture



(a) (b)

Fig.-3: The ORCA calculated ibuprofen (a) and paracetamol (b) UV spectra



(a) (b)

Fig.-4: The Calculated Ibuprofen and Paracetamol UV Spectra Without Peaks Broadening (a) and With Peaks Broadening (b)

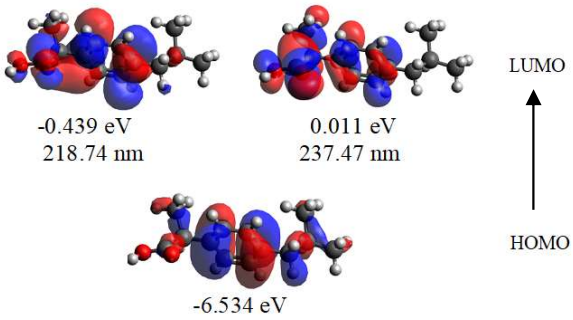


Fig.-5: HOMO and LUMO Orbitals of Ibuprofen Electron Transitions

Bayesian inference was carried out by assuming that regression slope and intercept were normally distributed with an error that was half normally distributed. NUTS inference for 5000 samplings produces a linear model with an intercept of -0.253 with a standard deviation of 0.292 for ibuprofen. The linear model intercept for paracetamol was 0.215 with a standard deviation of 0.072 (Fig.-7).

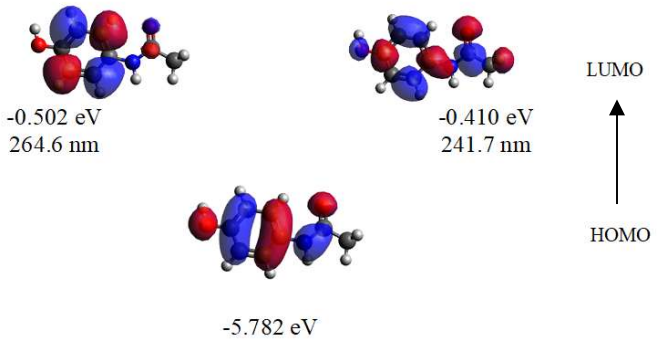


Fig.-6: HOMO and LUMO Orbitals of Paracetamol Electron Transitions

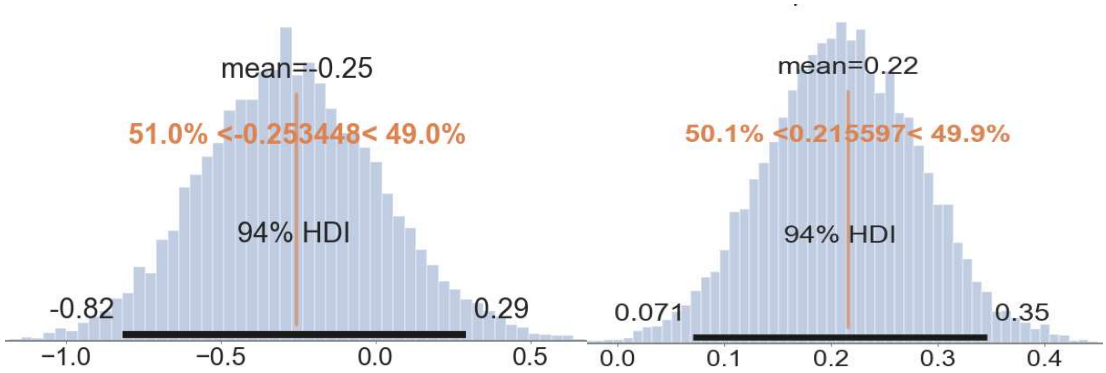


Fig.-7: Posterior Plot of Ibuprofen (a) and Paracetamol (b) Intercepts

The slopes for 50 absorbances data were spread from -1 to 4 with a standard deviation of 1.585. The slopes of paracetamol were spread at about -1 to 1 with a standard deviation of 0.2077. The slope deviation for paracetamol was smaller than that of ibuprofen. This was confirmed by the trace plot of ibuprofen and paracetamol shown in Fig.-8. The slopes of ibuprofen have non-zero values at 220 - 230 nm. Thus, the absorbance that correlated with ibuprofen concentration was located at these wavelengths. The slopes of paracetamol were contributed from the absorbance at around 227 nm and 252 nm (Fig.-9). Thus, the linear model for paracetamol was more reliable than that for ibuprofen as shown in Fig.-10.

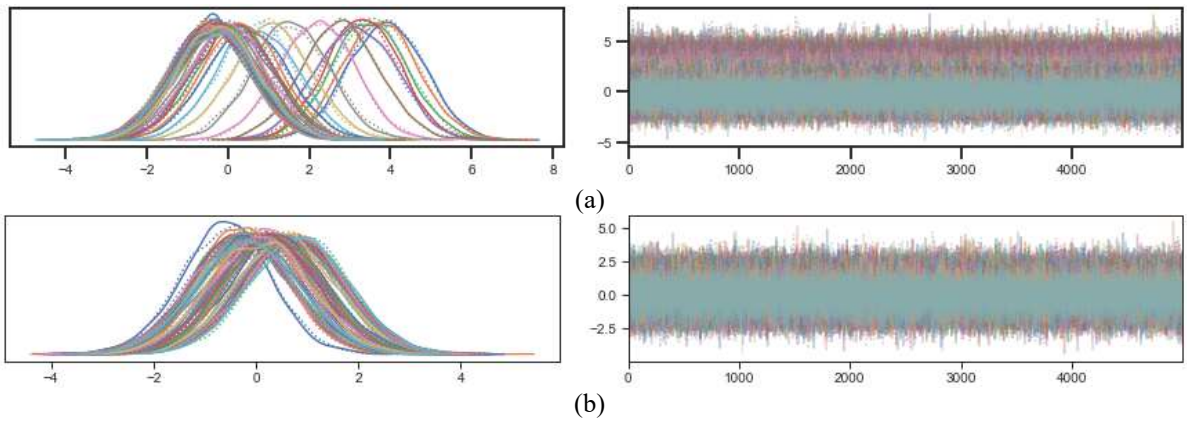
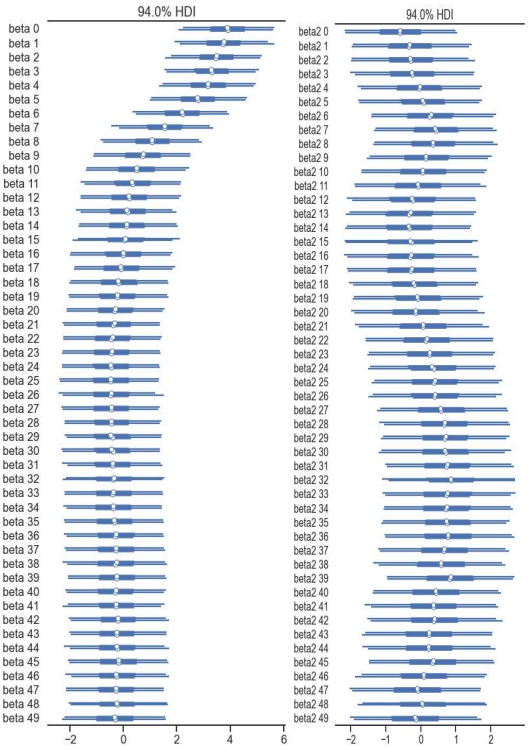


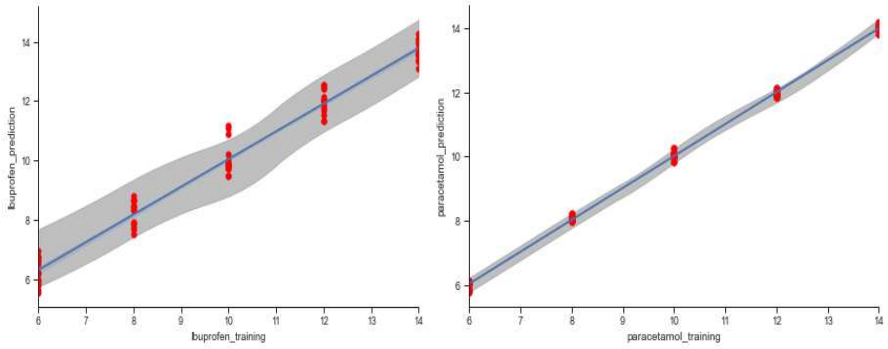
Fig.-8: Trace Plot of Ibuprofen (a) and Paracetamol (b) Slopes

The model error of 0.4997 with a standard deviation of 0.046 was observed for the ibuprofen linear model. Paracetamol linear model error was 0.1152 with a standard deviation of 0.01 as shown in Fig.-11. So, in general, the linear model for paracetamol was more reliable than the ibuprofen models.



(a) (b)

Fig.-9: Forest Plot of Ibuprofen(a) and Paracetamol (b) Slopes



(a) (b)

Fig.-10: Plot HPD of (a) Ibuprofen (b) Paracetamol Slopes

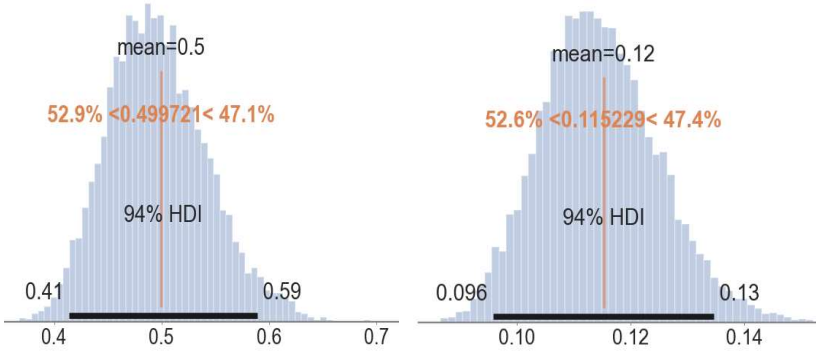
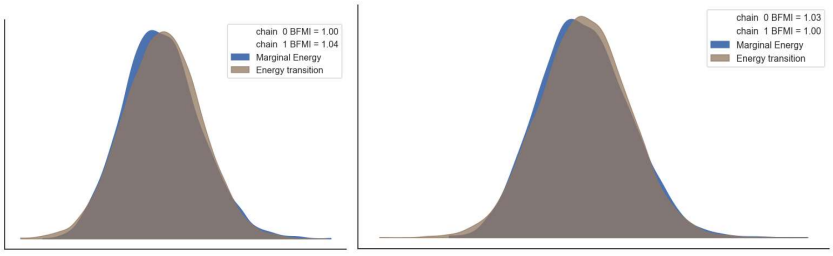


Fig.-11: Sigma of Ibuprofen Linear Regression

The BMFI (Bayesian Fraction of Missing Index) of both ibuprofen and paracetamol was at about 1. This indicated that the models converged very well (Fig.-12).



(a) (b)

Fig.-12: Energy Plot of (a) ibuprofen (b) Paracetamol Traces

Prediction of Validation/Test Sets

Ibuprofen and paracetamol at a ratio of 9 ppm: 9 ppm and 13 ppm: 7 ppm, respectively, were analyzed. The spectra of the test solution were shown in Fig.-13.

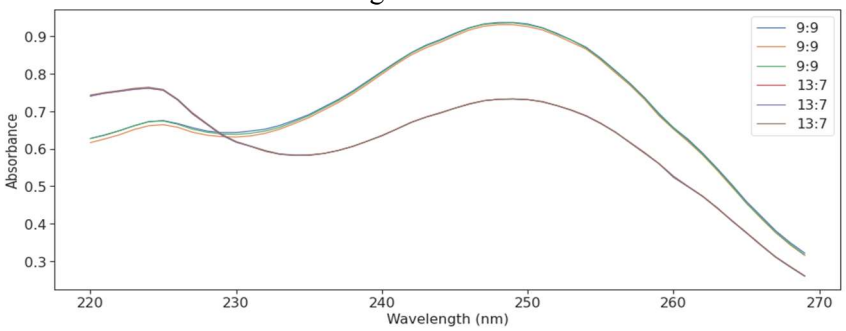


Fig.-13: The Spectra of the Test Solution

The predictive ability of the model was tested on a synthetic mixture of ibuprofen and paracetamol. Two sets of solutions containing ibuprofen and paracetamol in the same concentration range were used in the calibration set. The calibration model obtained was applied to predict the sample. The trueness and precision results were compared in terms of percent recovery and standard deviation. The quantification of ibuprofen using the Bayesian regression method was good, showing a recovery ranging from 97.90% to 100.63% with a cumulative standard deviation of 0.9454 (Table-1). The recovery value of paracetamol in the mixture also gave good results, 100.14% - 100.95% with a standard deviation of 0.3986 (Table-2). The mean squared error for the prediction of ibuprofen was 0.0079 and that of paracetamol was 0.0037.

Table-1: Ibuprofen Test Solution Prediction

Ibuprofen	Ibuprofen Prediction
9.0	9.0443
9.0	8.8106
9.0	9.0426
13.0	13.0197
13.0	13.0277
13.0	13.0825

Table-2: Paracetamol Test Solution Prediction

Paracetamol	Paracetamol Prediction
9.0	9.1063
9.0	9.0551
9.0	9.0857
7.0	7.0182
7.0	7.0101
7.0	7.0122

Analysis of Commercial Pain Relief Tablet

Commercial pharmaceuticals containing ibuprofen and paracetamol were analyzed by using the models applied for the test solution. The spectra of commercial pain relief tablets containing paracetamol and

ibuprofen solution were shown in Fig.-14. The results were summarized in Table-3 for ibuprofen and Table-4 for paracetamol.

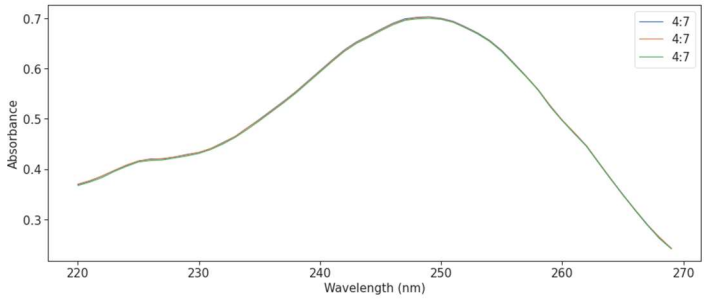


Fig.-14: The Spectra of Commercial Pain Relief Tablets

The experimental results were in agreement with the values on the label of the formulations. The mean squared error for ibuprofen in pain relief tablets was 0.0689 and 0.0001 for paracetamol.

Table-3: Ibuprofen in Pain Relief Tablet Prediction

Ibuprofen	Ibuprofen Prediction
4.0	4.2643
4.0	4.2869
4.0	4.2337

Table-4: Paracetamol in Pain Relief Tablet Prediction

Paracetamol	Paracetamol Prediction
7.0	7.0161
7.0	7.0075
7.0	6.9975

CONCLUSION

Bayesian regression has been successfully applied to predict a full spectrum of ibuprofen and paracetamol mixture. The Bayesian regression models indicated that paracetamol prediction on the test and sample solution was more reliable than ibuprofen. Although, in general, both components can be predicted very well based on the models developed. The mean squared error between the designed concentration and the predicted concentration in the test solution confirms that conclusion. The recovery ranges for ibuprofen and paracetamol were relatively narrow and lies at around 100%.

ACKNOWLEDGEMENT

The authors gratefully acknowledge financial support from the Institute Tektology Sepuluh Nopember for this work, under the project scheme of the Publication Writing and IPR Incentive Program (PPHKI).

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[RJC-6961/2022]