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Original Article

COMPARISON OF FT-NIR TRANSMISSION AND HPLC FOR GREEN APPROACH TO DETERMINE PARACETAMOL AND ITS DEGRADATION PRODUCT 4-AMINOPHENOL IN PARACETAMOL TABLETS

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ABSTRACT

Objective: Development and validation of Near infrared (NIR) spectroscopic method for determination of paracetamol and its major degradation product 4-aminophenol in paracetamol tablets and show the agreement between the NIR as a greener technique and the conventional high performance liquid chromatography (HPLC) method, official in British pharmacopeia (BP).

Methods: Calibration model for paracetamol and its degradation product 4-aminophenol was built by utilizing chemometric processing which is the most critical step in the development of specific and robust NIR models. It is based mainly on a partial least square regression fit on the transmission mode using paracetamol, 4-aminophenol and excipient materials of the drug products. The results obtained by NIR spectroscopy were compared with the compendial HPLC method in the BP.

Results: The chosen models had a root mean square error of the cross validation (RMSECV) values of 1.38, 1.42 and coefficient of correlation (*r*2) of 99.1, 99.05 for paracetamol and 4-aminophenol respectively, which indicates good fitness and accuracy of the model.

Conclusion: The present study showed that NIR could be used with high accuracy for determination of for parent drug and its major degradation product in paracetamol tablets. This proposed technique realizes many of green analytical aspects in developing eco-friendly analytical methods and may replace safely the conventional chromatographic technique without compromising efficacy.

Keywords: Paracetamol, 4-Amino phenol, FT-NIR transmission, GAC (green analytical chemistry), HPLC assay, Validation, PLS model.

INTRODUCTION

The trend of sustainable development requires chemistry to be "clean" or "green." In the 1990s, therefore, the concept of "Green Chemistry" was proposed, together with the "Twelve Principles of Green Chemistry."Presently, spectroscopic methods dominate the area of green analytical chemistry [1]. The pursuit in the field of green chemistry is growing dramatically and is becoming a grand challenge for chemists to develop new products, processes and services that achieve the necessary social, economic and environmental objectives due to an increased cognizance of environmental safety, checking environmental pollution, sustainable industrial ecology and cleaner production technologies worldwide [1]. The NIR region spans the wavelength range 12,500–4000 cm^{-1}. In this region, absorption bands correspond mainly to overtones and combinations of fundamental vibrations [2]. In the pharmaceutical sector, several qualitative and quantitative applications of NIR spectroscopy have been described during the manufacturing steps. At the beginning of the manufacturing process, NIR can be used for the identification of active substances and excipients [3–5].

Paracetamol is an old molecules, it is a synthetic non-opiate derivative of 4-aminophenol. Several methods for determination of the drug and its main degradation product have been reported such as spectrophotometric in dosage form [6, 7], fluorimetric in raw material and dosage forms [8], voltammetric in dosage forms and biological fluids [9], high-performance liquid chromatography [10–12], chemiluminescence [13, 14] and capillary electrophoresis [15] methods. However, using NIR for determination of paracetamol has been reported, but using this technique for simultaneous determination of the drug and its parent molecule is a quite new approach.

The aim of this study is to show the agreement between the NIR as a greener technique and the conventional HPLC–UV detection method, official in British pharmacopeia.

MATERIALS AND METHODS

Materials

All materials were supplied by SIGMA pharmaceuticals Corp., Egypt. The commercial samples of paracetamol 500 mg tablets were used and a placebo contains the same raw materials used in the production process, including microcrystalline cellulose, starch, sodium starch glycolate, polyvinylpyrrolidone, magnesium stearate and purified talc. The placebo was used to make serials of dilutions for establishing the calibration model. All materials are of pharmaceutical grade and all chemicals and reagents have been used in the HPLC method are analytical reagent of HPLC grade.

NIR spectroscopy

FT-NIR Spectrometer, MPA Flexible from Bruker Optics (Germany) was used. Pistol grip model with external trigger and LED status lights. It is equipped with two fiber optic probes, NIR probe for liquids "quartz" and NIR probe for solid. Includes 2 m fiber optic cable with Bruker quick connect. Fixed optical path length of 1 mm. NIR probe for solids, probe head length 80 mm, mounting of an integrating sphere for analysis of solid samples in diffuse reflectance and a measurement unit for analyzing highly scattering solid media in transmission. The spectrometer is equipped with a fast, PC-based data system with OPUS/IR FT-IR spectroscopy software package (version 5.0), which was provided by Bruker Optics. OPUS IDENT is a software package designed to identify substances by their NIR spectra while OPUS Quant is designed for the quantitative analysis. For this purpose, OPUS QUANT was used with a partial least square (PLS) fit method. In PLS, the calibration involves correlating the data in the spectral matrix *X* with the data in the concentration matrix *Y*. This means that the factoring of the spectral data is more suited for concentration prediction.

Constructing the PLS model

In a first step a PLS regression model was built using calibration samples. The obtained model was chemo metrically validated by

leave-one-out cross validation. The final PLS model was described by a selected spectral region, spectra pretreatment and a number of PLS factors. To build the model, 87 different concentrations of tablet preparations were prepared ranged from 50 % to 100% of the labeled amount of the analyte of interest (paracetamol) and from 0.01% to 50 % of the degradation product (4-amino phenol) as demonstrated in table1 where Full cross-validation statistics obtained with calibration models for paracetamol and 4-aminophenol by using of 87 synthetic mixtures of the drug, degradation product and placebo. Each spectrum was the average of 32 scans and the spectrophotometer was operated at a resolution of 8 cm^{-1}.

Spectral data pretreatments

Calibration models were developed using full cross validation. The baseline can drift and maximum absorbance may change. Spectral pretreatments correct these interferences [16, 17]. In this study, reducing of baseline drift and enhancing spectral information has been achieved through chemometric processing include first derivative, second derivative, vector normalization, straight line subtraction and constant offset elimination. The NIR spectra were saved. Measurements were performed by the NIR fiber optic probe for solids. Before measurement, a measurement of the background must be taken and the detector signal shall be checked. In developing method, the measurement conditions shall be determined and saved to be recalled in each measurement time to avoid result variation and ensure high accuracy of the developed analytical procedure. Samples were measured into samples cavities of the equipment tray with keeping minimum illumination in the measurement place by using sample covers to ensure that there was no stray light during measurement. The measurement time for each sample was about 10 seconds per scan and the instrument was operated at a resolution of 8 cm^{-1}.

Reference method

According to the British pharmacopeia, the official HPLC method utilizing a stainless steel column (25 cm × 4.6 mm) packed with octylsilyl silica gel (5 µm) separation column at 35 °C and mobile phase composed mixture of 250 volumes of methanol containing 1.15 g of a 40% (w/v) solution of tetrabutylammonium hydroxide with 375 volumes of 0.05M disodium hydrogen orthophosphate and 375 volumes of 0.05M sodium dihydrogen orthophosphate. The flow rate to be adjusted at 1.5 ml/min and the detection wavelength was set at 254 nm [18].

RESULTS AND DISCUSSION

Method validation

Fig. 1 shows the raw spectra obtained with the calibration samples.

From these spectra, the Quant program selected five regions, automatically; it was between 12000 and 4000 cm^{-1}. All samples have been analyzed by the HPLC official method; Fig.2 shows the resulting chromatogram. As the HPLC reference method is official in the British pharmacopeia, the researcher has performed a verification study include the items of linearity, sensitivity, accuracy and precision for the compendial method while full cross validation has been performed for the proposed NIR method and the validation statistics obtained from the calibration models are recorded in table 1.

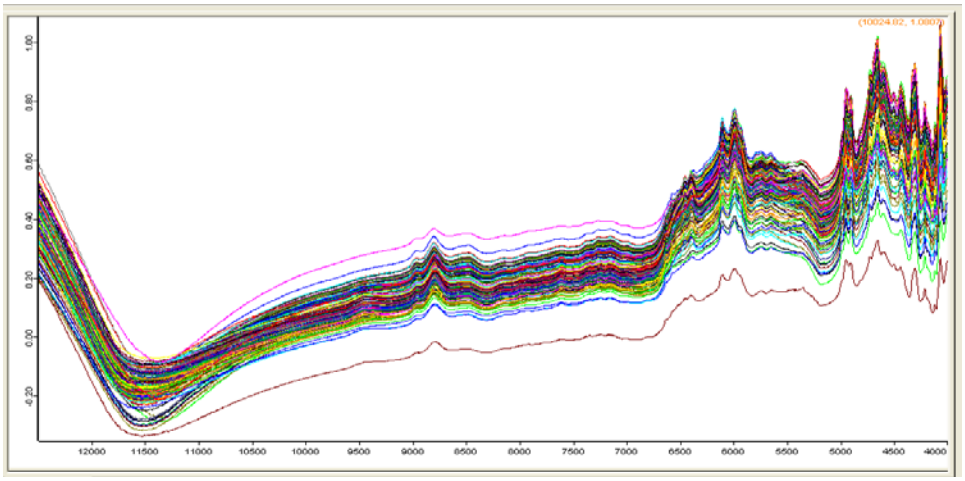

Fig. 1: The FT-NIR spectra for paracetamol and 4-aminophenol at different concentrations in synthetic mixtures with placebo

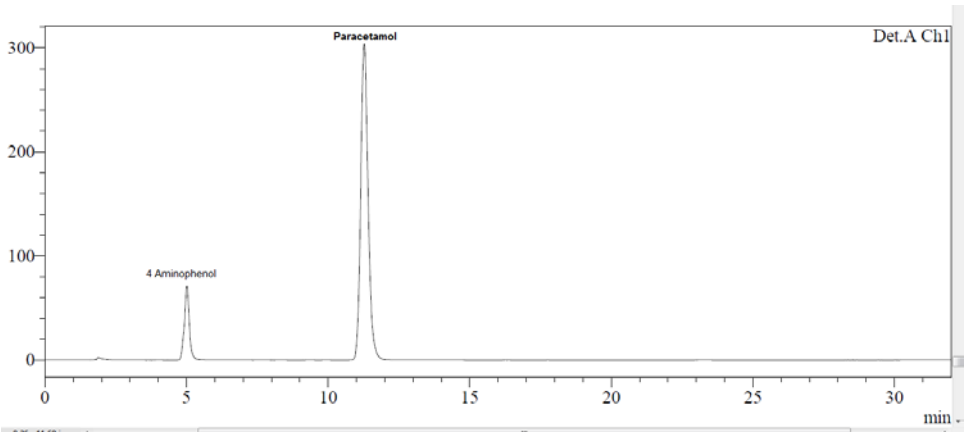

Fig. 2: The resulting chromatogram for paracetamol and its major degradation product (4-aminophenol) under typical chromatographic conditions described in BP

Table 1: Full cross-validation statistics obtained with calibration models for paracetamol and 4-aminophenol by using 87 synthetic mixtures of the drug, degradation product and placebo

Exp.	4-Amino phenol					Paracetamol				
No.	True	Prediction	Difference	F Value	F Prob	True	Prediction	Difference	F Value[a]	F Prob[b]
1.	0	0.509	-0.509	0.128	0.278	100	100.4	-0.365	0.0688	0.206
2.	0	-0.2537	0.254	0.0317	0.141	100	100.8	-0.751	0.292	0.41
3.	0.6	-0.6348	1.23	0.758	0.614	99.4	98.45	0.953	0.472	0.506
4.	0.8	-0.3979	1.2	0.713	0.599	99.2	99.35	-0.149	0.0114	0.0848
5.	0.9	1.401	-0.501	0.124	0.274	99.1	98.52	0.578	0.173	0.321
6.	1	0.8788	0.121	0.00724	0.0676	99	98.76	0.244	0.0308	0.139
7.	1.5	0.8175	0.682	0.23	0.367	98.5	97.53	0.967	0.486	0.512
8.	2	1.622	0.378	0.0706	0.209	98	98.12	-0.125	0.00807	0.0714
9.	2.5	2.963	-0.463	0.106	0.254	97.5	98.12	-0.622	0.2	0.344
10.	3	3.596	-0.596	0.175	0.323	97	96.54	0.464	0.111	0.261
11.	1	-0.4804	1.48	1.09	0.701	99	100.5	-1.49	1.17	0.717
12.	0.1	-0.05473	0.155	0.0118	0.0862	99.9	99.83	0.0741	0.00284	0.0424
13.	0.1	0.1293	-0.0293	0.000422	0.0163	99.9	101.1	-1.23	0.792	0.624
14.	0.1	-0.3529	0.453	0.101	0.249	99.9	101.4	-1.52	1.21	0.725
15.	0.2	-0.01942	0.219	0.0237	0.122	99.8	100.5	-0.66	0.226	0.364
16.	0.2	-0.3188	0.519	0.133	0.284	99.8	99.43	0.369	0.0705	0.209
17.	0.2	0.5424	-0.342	0.0578	0.189	99.8	100.5	-0.684	0.242	0.376
18.	0.3	0.6514	-0.351	0.0609	0.194	99.7	100.2	-0.507	0.133	0.284
19.	0.3	1.128	-0.828	0.339	0.438	99.7	99.23	0.466	0.112	0.262
20.	0.3	-0.5046	0.805	0.32	0.427	99.7	100.1	-0.355	0.0651	0.201
21.	0.4	0.4264	-0.0264	0.000344	0.0148	99.6	98.65	0.949	0.468	0.504
22.	0.4	0.4618	-0.0618	0.00188	0.0345	99.6	100.3	-0.715	0.265	0.392
23.	0.4	2.472	-2.07	2.17	0.855	99.6	98.53	1.07	0.599	0.559
24.	0.5	1.471	-0.971	0.467	0.504	99.5	98.91	0.593	0.182	0.329
25.	0.8	1.752	-0.952	0.449	0.495	99.2	98.53	0.669	0.232	0.369
26.	0.8	3.978	-3.18	5.28	0.976	99.2	96.5	2.7	3.93	0.949
27.	0.8	-0.3367	1.14	0.641	0.575	99.2	100.4	-1.15	0.693	0.593
28.	1.1	-0.1098	1.21	0.727	0.604	98.9	101	-2.05	2.24	0.862
29.	1.1	3.948	-2.85	4.19	0.956	98.9	96.77	2.13	2.4	0.875
30.	1.1	1.996	-0.896	0.398	0.47	98.9	97.9	0.997	0.517	0.526
31.	1.4	0.1965	1.2	0.719	0.601	98.6	98.94	-0.342	0.0605	0.194
32.	1.4	4.379	-2.98	4.61	0.965	98.6	95.78	2.82	4.32	0.959
33.	1.4	2.643	-1.24	0.768	0.617	98.6	97.16	1.44	1.08	0.698
34.	1.8	2.475	-0.675	0.225	0.364	98.2	98.04	0.157	0.0127	0.0895
35.	1.8	1.734	0.0658	0.00213	0.0367	98.2	98.33	-0.133	0.00918	0.0761
36.	2.1	0.1965	1.9	1.82	0.819	97.9	99.14	-1.24	0.805	0.628
37.	2.1	1.67	0.43	0.0914	0.237	97.9	99.62	-1.72	1.56	0.785
38.	2.3	0.0232	2.28	2.63	0.892	97.7	98.2	-0.498	0.128	0.279
39.	2.3	2.47	-0.17	0.0143	0.0948	97.7	97.38	0.32	0.053	0.182
40.	2.5	2.458	0.0421	0.000874	0.0235	97.5	98.92	-1.42	1.05	0.693
41.	2.7	1.2	1.5	1.12	0.708	97.3	99.68	-2.38	3.04	0.915
42.	2.9	0.6771	2.22	2.51	0.883	97.1	98.69	-1.59	1.33	0.748
43.	2.9	0.4589	2.44	3.04	0.915	97.1	97.63	-0.527	0.144	0.294
44.	2.9	0.8888	2.01	2.04	0.843	97.1	99.19	-2.09	2.33	0.869
45.	3.1	4.337	-1.24	0.761	0.615	96.9	95.87	1.03	0.554	0.541
46.	3.1	2.031	1.07	0.567	0.546	96.9	98	-1.1	0.626	0.569
47.	3.6	5.244	-1.64	1.35	0.752	96.6	94.7	1.9	1.91	0.83
48.	3.6	2.857	0.743	0.273	0.397	96.6	95.28	1.32	0.914	0.658
49.	4.1	2.648	1.45	1.05	0.692	95.9	94.99	0.911	0.431	0.487
50.	4.1	2.747	1.35	0.912	0.658	95.9	98.26	-2.36	2.99	0.913
51.	5.1	6.148	-1.05	0.544	0.537	94.9	94.82	0.0772	0.00308	0.0441
52.	5.6	4.998	0.602	0.179	0.327	94.9	93.02	1.88	1.87	0.825
53.	5.6	6.35	-0.75	0.278	0.401	94.6	93.61	0.994	0.513	0.524
54.	7.6	5.796	1.8	1.63	0.795	92.4	94.12	-1.72	1.55	0.784
55.	8.6	7.784	0.816	0.329	0.432	91.4	90.84	0.561	0.163	0.312
56.	2	3.09	-1.09	0.589	0.555	98	95.34	2.66	3.82	0.946
57.	2	4.611	-2.61	3.5	0.935	98	94.71	3.29	5.97	0.983
58.	4	5.348	-1.35	0.905	0.656	96	93.49	2.51	3.37	0.93
59.	4	5.002	-1	0.497	0.517	96	95.48	0.524	0.142	0.293
60.	6	4.471	1.53	1.17	0.717	94	94.78	-0.782	0.317	0.425
61.	8	9.408	-1.41	0.987	0.677	92	91.95	0.0485	0.00122	0.0277
62.	10	10.64	-0.64	0.202	0.346	90	89.13	0.872	0.395	0.469
63.	10	8.691	1.31	0.852	0.641	90	92.69	-2.69	3.92	0.949
64.	12	9.784	2.22	2.49	0.882	88	87.8	0.205	0.0216	0.117
65.	12	11.73	0.27	0.0361	0.15	88	89.26	-1.26	0.834	0.636
66.	14	14.97	-0.966	0.462	0.501	86	85.5	0.498	0.129	0.279
67.	18	19.1	-1.1	0.6	0.559	82	81.82	0.183	0.0172	0.104
68.	20	22.01	-2.01	2.03	0.842	80	79.74	0.264	0.0362	0.15
69.	20	21.89	-1.89	1.8	0.817	80	77.76	2.24	2.67	0.894

70.	22	22.39	-0.386	0.0736	0.213	78	77.6	0.402	0.0834	0.227
71.	24	23.62	0.38	0.0713	0.21	76	78.54	-2.54	3.46	0.934
72.	26	25.21	0.79	0.309	0.42	74	72.42	1.58	1.31	0.744
73.	30	29.51	0.494	0.12	0.271	70	70.36	-0.363	0.0682	0.205
74.	30	31.25	-1.25	0.774	0.619	70	69.73	0.268	0.0372	0.152
75.	34	35.7	-1.7	1.44	0.767	66	66.27	-0.27	0.0376	0.153
76.	34	34.35	-0.354	0.0618	0.196	66	66.12	-0.117	0.00713	0.0671
77.	36	34.56	1.44	1.04	0.689	64	63.29	0.707	0.259	0.388
78.	36	34.08	1.92	1.85	0.823	64	66.73	-2.73	4.02	0.952
79.	38	39.14	-1.14	0.642	0.575	62	60.4	1.6	1.34	0.749
80.	38	36.11	1.89	1.79	0.816	62	63.5	-1.5	1.17	0.718
81.	40	41.24	-1.24	0.768	0.617	60	57.69	2.31	2.85	0.905
82.	42	41.21	0.786	0.305	0.418	58	58.77	-0.771	0.308	0.42
83.	44	47.15	-3.15	5.2	0.975	56	55.6	0.398	0.0818	0.224
84.	44	42.14	1.86	1.74	0.809	56	56.36	-0.355	0.0653	0.201
85.	48	45.08	2.92	4.43	0.962	52	55.11	-3.11	5.29	0.976
86.	50	47.84	2.16	2.37	0.872	50	51.3	-1.3	0.877	0.648
87.	48	50.48	-2.48	3.13	0.92	52	50.6	1.4	1.02	0.684

[a] F Value: reducing such value indicates that the spectra are efficiently represented by the PLS vectors [b]F Prob: indicates the probability that a standard is a spectral outlier.

Linearity of the reference method

The linearity of calibration curves (peak area vs. concentration) were checked over the concentration ranges from 5-100 µg/ml and from 0.5-10 µg/ml for paracetamol and 4-aminophenol respectively in the drug-matrix solutions, each concentration level was injected 3 times (n=3) and the average peak area was calculated. The resulting curve was found to be linear with correlation coefficients of better than 0.999 in most cases; the limits of detection LOD and the limits of quantitation LOQ, were calculated for the calibration curves as three and ten times of the noise levels for LOD and LOQ, respectively[19]. Table 2 lists the linearity parameters of the calibration curves.

Sensitivity and accuracy of the reference method

The accuracy of an analytical method is the closeness of test results obtained by that method to the true value [19]. The accuracy of the method was tested by analyzing different samples at various concentration levels ranged from 30.30 to 70.70 and 7.28 to 3.12 µg/ml for paracetamol and 4-aminophenol respectively added to drug-matrix used in tablet formulation, each concentration level was injected 3 times (n=3) and the average peak area was calculated. The results were expressed as percent recoveries of the. Table 3 shows that the overall percent recoveries was 100.03 % and 100.26% for paracetamol and 4-aminophenol respectively, with relative standard deviation (RSD) lower than 2% in all cases.

Table 2: Linearity of calibration curve for Paracetamol and 4-Aminophenol in drug-matrix preparation. Number of points in the regression line are 6 for each case

item	Calibration range (µg/ml)	Correlation coefficient	Slope	Slope 95% confidence interval for the slope[a]	Intercept	Slope 95% confidence interval for the intercept[a]	LOQ (µg/ml)	LOD (µg/ml)
Paracetamol	5-100	0.9999	0.810	±0.0334	0.159	±1.221	0.347	0.104
4-Aminophenol	0.5-10	0.9998	0.774	±0.0612	1.555	±2.545	0.325	0.0975

[a]Confidence intervals of the slope and the intercept = (SD of the slope or intercept x *t*), the value of *t* at 3 degree of freedom and 95% confidence level is 1.33.

Table 3: Accuracy of the proposed HPLC method for the determination of paracetamol and 4-Aminophenol in drug matrix solution

Paracetamol			4-Aminophenol		
Quantity added in µg/ml	Quantity found in µg/ml	Recovery (%)	Quantity added in µg/ml	Quantity found in µg/ml	Recovery (%)
30.30	30.41	99.72	7.28	7.35	100.12
40.40	41.02	99.40	6.24	6.17	100.18
50.50	49.93	99.20	5.20	5.28	100.39
60.60	59.95	100.55	4.16	4.21	100.99
70.70	71.02	99.56	3.12	3.08	100.18
	Average	100.03		Average	100.26
	% R. S. D	1.13		% R. S. D	1.35

Precision of the reference method

According to and ICH [19] guidelines, the precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

Analysis repeatability

It was evaluated by carrying out the analysis of the six homogenous solutions of the same test samples. The determinations were carried out one after the other under conditions as similar as possible.

The relative standard deviation was calculated from the results of the obtained observations as shown in table 4**.**

Intermediate precision

The intermediate precision of the method was checked by determining precision on a different day using the same number of samples and same concentration range as in repeatability. The relative standard deviation was calculated from the results of the obtained observations. In all cases, the RSD was lower than 2 as shown in table 4.

Table 4: Intra-day and Inter-day precision

Exp. No.	Repeatability on day 1		Repeatability on day 2 (Intermediate precision)	
	Paracetamol	4-Aminophenol	Paracetamol	4-Aminophenol
1	99.684%	100.269%	100.751%	99.265%
2	98.362%	100.784%	99.865%	98.568%
3	99.765%	99.235%	98.782%	100.257%
4	100.045%	98.036%	99.638%	100.226%
5	98.062%	100.478%	99.105%	99.078%
6	100.361%	100.785%	100.784%	98.681%
Mean	99.380%	99.931%	99.821%	99.346%
SD	0.858	0.995	0.755	0.675
RSD	0.864%	0.996%	0.756%	0.679%

Predictability of the proposed NIR method

The coefficient of correlation ($r2$) and root mean square error of the cross validation (RMSECV) are essential tools to evaluate the predictability of the obtained chemometric model of the proposed NIR method [20]

$$\text{RMSECV}(\%) = \sqrt{\frac{\sum_{i=1}^{n}(C_{\text{HPLC}} - C_{\text{NIR}})}{\sum_{i=1}^{n} C_{\text{HPLC}}}}$$

Where C_{HPLC} is the amount of paracetamol or 4-aminophenol measured by the reference method, C_{NIR} is the amount of paracetamol or 4-aminophenol as measured by the proposed method and n is the number of samples. The chosen model had a RMSECV value of 1.38, 1.42 and coefficient of correlation ($r2$) of 99.1, 99.05 for paracetamol and 4-aminophenol as illustrated in fig. 3 & 4, which indicates good fitness and accuracy of the model.

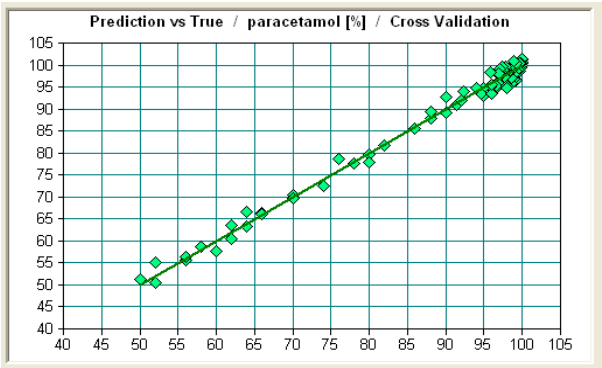

Fig. 3: Regression of the calibration samples for NIR proposed method in cross validation (paracetamol)

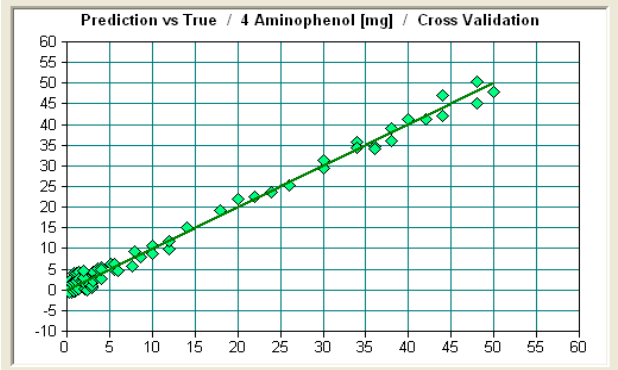

Fig. 4: Regression of the calibration samples for NIR proposed method in cross validation (4-aminophenol)

Agreement between the two methods for unknown samples

A simple plot of the results given by a method versus those of the other one is a useful mean to evaluate the validity of the proposed NIR method, however, the data points will usually be clustered near the line and it will be difficult to assess between method differences so that a plot of the difference between the methods against their mean is chosen. This plot of data may be more informative. Fig. 5& 6 shows the distribution of the differences against their mean.

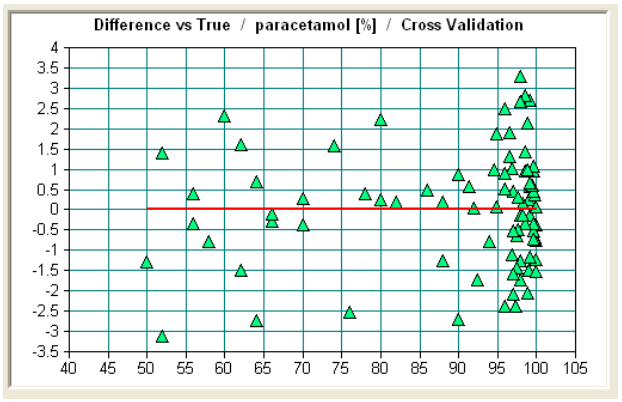

Fig. 5: Illustration of distribution of the differences against their mean in cross validation for paracetamol

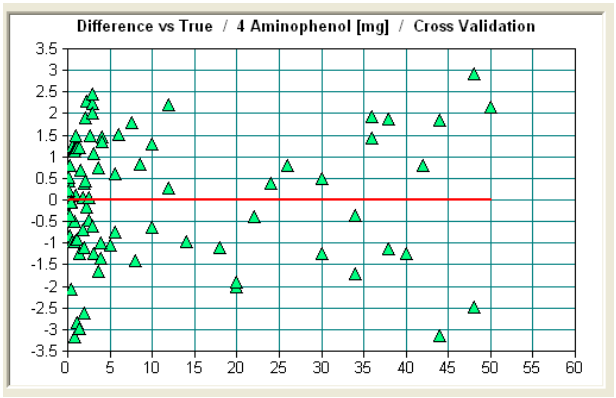

Fig. 6: Illustration of distribution of the differences against their mean in cross Validation for 4-aminophenol

CONCLUSION

NIR spectroscopy technique has several advantages making it one of the most favorable techniques according to the GAC principles. In

this study, it has been used as an alternative technique to HPLC with UV detector for the determination of paracetamol and its major degradation product 4-aminophenol in tablet dosage form. If an efficient calibration model has been established, it could be used easily for rapid and accurate analysis of a large number of samples. It is a non-destructive method, doesn't need to sample pre-treatment or toxic solvents and reagents and thus it fulfills the green analytical chemistry aspects and suitable for on-line, in-line and off-line production control purposes. Therefore, this technique can replace the conventional HPLC techniques in some applications safely for developing more eco-friendly analytical methods, realizing the green chemistry principles in a direct and clear way.

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CONFLICT OF INTERESTS

Declared None.

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