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VALIDATION STUDY FOR PARACETAMOL DETERMINATION IN LIQUID PRODUCTS (PARACEROL) USING RAMAN SPECTROSCOPY

T. Kocaağa [1], F. Yıldırım [1], U. Kumrulu [1], E. Kumrulu [1], N. Mutlu [1], E. Sopacı [1], B. Demirdoğan [1] and D. Giray Dilgin [*2]

PolifarmaİlaçSan. ve Tic. AŞ [1], Ergene/Tekirdağ, Turkey.
Secondary Science and Mathematics Education Department [2], Faculty of Education, University of Çanakkale Onsekiz Mart, 17100, Çanakkale, Turkey.

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Correspondence to Author:
D. Giray Dilgin

Associated Professor in Analytical Chemistry, University of Çanakkale Onsekiz Mart, Faculty of Education, Secondary Science and Mathematics Education Department, 17100, Çanakkale, Turkey.

E-mail: didemgiray79@hotmail.com

ABSTRACT: In this study, Raman spectroscopy was used as an analytical quality control methodology to evaluate the paracetamol (PCT) quantity in a commercially available formulation in the pharmaceutical industry. The Raman Spectroscopy has been established for the validation and the quantification of PCT in a commercial product called Paracerol (Prc) Solution for I.V. Infusion containing 10.0 $mg.mL^{-1}$ PCT. The validation of the proposed method was performed by evaluating the specificity, linearity range, accuracy, precision, detection limit, quantification limit, and robustness parameters. The acceptable results for all parameters showed that the proposed method is valid. The Raman spectroscopic method was also compared with the HPLC method in terms of PCT determination and statistical tests such as t and F tests and the obtained results indicated that there is no any difference in the averages and precision results between the proposed Raman spectroscopy and HPLC methods. It has been reported that Raman spectroscopy can be applied in the pharmaceutical industry for the quality control analysis of the commercial formulation of PCT.

INTRODUCTION: Paracetamol (PCT) or acetaminophen (IUPAC name is N-(4-hydroxyphenyl) acetamide) has been widely used as an active pharmaceutical ingredient in analgesic and antipyretic drugs. It has been first prepared by Morse in 1878 1 and has been used as a drug since 1956 [2]. This important compound is often found as the main ingredient in numerous cold and flu medicines, and it is widely used to relieve many aches and pains, especially headache.

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The combination of PCT with other drugs such as opioid analgesics increases the effectiveness of its pain reliever and thus it can also be used in the treatment of more severe pain after surgery and for relieving of the pain of cancer patients [3].

In the market, PCT is available as an over-the-counter drug with different brand names and can be found in different forms such as tablets, liquids (as suspensions and solution), capsules, and suppositories. PCT can be taken with food or on an empty stomach. It is not listed as a nonsteroidal anti-inflammatory drug (NSAID) like other pain killers like aspirin and ibuprofen [3] for that reason; it is the most widely accepted drug. However, taking too much PCT than recommended doses (1.0 g/single dose and 4.0 g/day for adults) can lead to fatal liver damage, kidney problems, inflammation

in the pancreas, skin rashes, low blood sugar and even death [4]. Therefore, a lot of analytical methods such as chromatography [5-6], spectrophotometry [4, 7-10] and electrochemical methods [5, 11] have been developed for the determination and validation of PCT due to its great importance in human health.

The validation of the drug products is a very important process in the manufacture of pharmaceuticals. The compliance of the products includes the identity, purity, stability, potency of the drug etc. The quantitative analytical methods based on the structure and the properties of the active component of the drug formulation are utilized in drug industries. In the method development and validation for determination of a drug in the manufacture of pharmaceuticals, several analytical techniques such as chromatography (GC, HPLC), capillary electrophoresis (CE), spectroscopy (Uv-Vis, Fluorescence, NIR, NMR, AAS, ICP) and especially hyphenated methods (GC-MS, LC-MS, ICP-MS) have been widely used [12]. Among them the chromatographic techniques (especially liquid chromatography) have attracted a great attention in the validation of the drug formulation since these methods offer rapidity in process, better peak shape, higher resolution, accuracy, and precision and no isolation process [13]. Although the chromatographic methods exhibit these advantages, they are destructive methods as well as they require time consuming sample pre-treatment steps and use large volume of organic or inorganic solvents during sample preparation and analysis [14-16]. Therefore, there is a need to develop rapid and reliable alternative analytical methods containing green chemistry for the validation of the drug products.

Recently, vibrational spectroscopic methods (IR, NIR and Raman) have been taken a place as an alternative green analytical method in the pharmaceutical industry [14-20]. These methods have several advantages over the chromatographic methods such as label free, fast acquisition, solvent free, non-invasive, non-destructive, low-cost, minimization of the sample preparation step, direct measurement inside packaging material (glass, plastic *etc.*) and possibility to use probes [14-17]. Although IR and NIR are very useful techniques for the identification and validation of drug samples in the pharmaceutical industry, Raman spectroscopy has some superiorities over IR and NIR. For example, aqueous pharmaceutical formulations can be directly studied due to being Raman-inactive of water molecules and Raman spectra have higher chemically specificity and analysis speed than NIR [15, 17]. Moreover, Raman spectroscopy can give information at the molecular level to identify unknown solids or liquids of both organic and inorganic materials. It is also a practical method for identification and verification of known components and the determination of the impurities in pharmaceuticals. In this context, many studies based on Raman and FT Raman spectroscopic techniques have previously been carried out for the quantitative determination and validation of many drugs in liquid or solid pharmaceutical formulations [9, 10, 14-16, 19-36].

The Raman spectrophotometric determination of PCT in the pharmaceutical solution (Paracerol, Prc) has been described in this study. Although the PCT determination was studied [9, 33-35] in some solid and liquid pharmaceuticals, a detailed validation study has not been reported yet. Therefore, this study reports the validation based on using the parameters of sensitivity, selectivity, accuracy, reproducibility, repeatability, stability, linear range, and robustness and determination of PCT in Prc solution.

MATERIALS AND METHODS:

Apparatus: Thermo Scientific TruScan™ RM Handheld Analyzer was used to perform the Raman Spectroscopic measurements. It has a 785 nm excitation laser (250 mW) covering a range of 250–2875 cm^{-1}. Raman shifts have a spectral resolution of 8–10.5 cm^{-1} (FWHM) across the range. The principle of the technology is based on the optimization of the signal-to-noise ratio so that the analysis stops when this ratio is considered optimal inducing different acquisition parameters for each sample. Recently, a new upgrade known as TruTools™ was released, allowing the operator to set acquisition parameters, develop qualitative and quantitative chemometric models, and embed them into the spectrophotometer. As the need to quickly identify and quantify more materials increases, the pharmaceutical and biotechnology manufacturers require instruments that decrease laboratory sample testing and enable more at-line decisions. The Thermo Scientific™ TruScan™ RM analyzer with

TruTools™ embedded chemometrics package provides users with the flexibility to build customized qualitative and quantitative methods for complex material analysis problems. The HPLC experiments as a reference method were performed with the HPLC system UV detector. A column of C18 (300 × 3.9 mm, 10 µm) and a mobile phase solution that is a mixture of high purified water and methanol in a ratio of 3:1were used in the HPLC.

Reagent and Solutions: Paracetamol (%99.8) was supplied from Hebei Jiheng Pharmaceutical company and all other used chemicals such as Mannitol, L-cysteine hydrochloride, disodium phosphate were at analytical grade. The PCT serum solution (Prc) containing 10.0 $mg.mL^{-1}$ studied in the validation was produced by Polifarma company in Turkey. A placebo (Plc) solution was prepared by weighing precisely 3.85 g of mannitol, 25.0 mg of cysteine hydrochloride monohydrate, and 13.0 mg of disodium phosphate dihydrate to a 100 mL volumetric flask and diluting to volume with pure water.

The stock solution of PCT (20.0 $mg.mL^{-1}$) was prepared by weighing precisely 4.0 g of PCT to a 200 mL volumetric flask and diluting to the volume with pure water. Standard PCT solutions between 7.0 and 13.0 $mg.mL^{-1}$ PCT were prepared by diluting a known volume of stock PCT solution to 20 mL with pure water.

Validation of the Method: The proposed Raman spectroscopic method was validated according to the ICH guidelines [37] and according to the guidelines described by Ferenczi-Fodor *et al.* [38] for the following parameters: specificity, linearity range, accuracy, precision (system precision, repeatability, and intermediate precision), detection limit, quantitative limit, and robustness.

Specificity: The specificity of the method was checked by recording the spectra of the Plc solution, the standard solution, and the test solution, respectively.

Linearity and Range: The linearity of the proposed method was evaluated by analyzing five standard solutions of PCT (7.0; 9.0; 10.0; 11.0, and 13.0 mg mL^{-1}) prepared by diluting with pure water. The experiments were performed in three different analyses.

Accuracy: The accuracy of the method was evaluated by measuring the recovery after adding PCT to Plc solution such that the linearity range was in the low (8.0 $mg.mL^{-1}$), medium (10.0 mg mL^{-1}), and high (12.0 $mg.mL^{-1}$) levels. The experiments were performed in three parallel measurements containing three analyzes of each.

Precision: The system precision was evaluated by six consecutive measurements of the standard PCT solution of 10.0 $mg.mL^{-1}$. The repeatability was tested by measuring Prc solution (10 mg mL^{-1} PCT) for six times.

In addition, intermediate precision was tested by measuring six different Prc solution for infusion on different days by a different analyst in the same laboratory.

The precision was evaluated as the standard deviation (SD) or relative standard deviation percentage (RSD%), and the results were compared according to the acceptance criteria.

Limit of Detection (LOD) and Limit of Quantification (LOQ): The signal of Plc solutions that do not contain PCT was measured six times under the studied conditions.

Then the LOD and LOQ were calculated using 3.3 sbl/m, and 10 sbl/m equations, respectively, where sbl is the standard deviation of the response of Plc solution accepted as blank solution and m is the slope of the calibration curve.

Robustness: The robustness of the method was tested by evaluation of the signal of Prc solution for infusion based on the changes of parameters such as temperature and pH.

RESULTS AND DISCUSSION: The Raman spectrum of 10.0 mg mL-1PCT solution was recorded in **Fig. 1** to define the PCT peaks. It can be seen that the characteristic peaks of PCT were observed, such as phenyl-N bending mode at 1176 cm^{-1}, stretching of the hydroxyl group with respect to the phenyl moiety at 1240 cm^{-1}, CC, CN stretching, and CH bending at 1331 cm^{-1}, CH_3 bending at 1382 cm^{-1}, CC stretching and NH deformation at 1517 cm^{-1}, C-C stretching and NH deformation peak at 1620 cm^{-1}. Similar results were also obtained in the previous reported studies [9, 34].

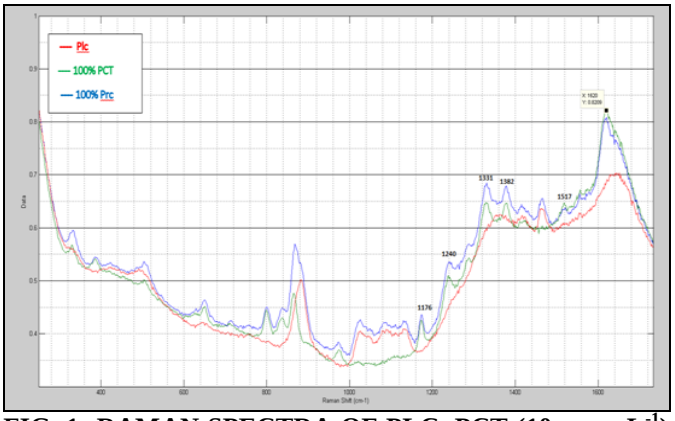

FIG. 1: RAMAN SPECTRA OF PLC, PCT (10 mg mL^{-1}) AND PRC SOLUTIONS FOR I.V INFUSION (CONTAINING 10 mg mL^{-1} PCT)

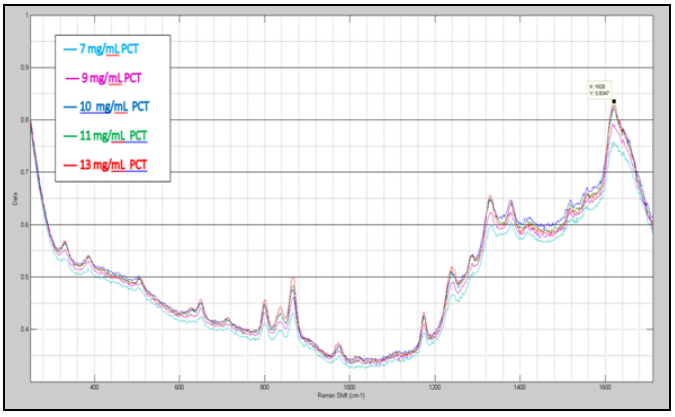

FIG. 2: RAMAN SPECTRA OF PCT SOLUTIONS OF DIFFERENT CONCENTRATIONS IN THE RANGE FROM 7.0 TO 13.0 mg mL^{-1}

Validation of the Raman Spectroscopic Method for Prc Solution:

Specificity: The specificity demonstrates the ability of the analytical method to measure accurately and selectively the analyte in the presence of components that may be expected to be present in the sample matrix. It was already mentioned that Raman spectroscopic and especially chromatographic methods were used and validated for PCT drugs and solutions. However, our literature survey shows that the Raman spectroscopic method has not been used to validate a PCT drug solution, Prc. For this purpose, the Raman spectra of the Plc, standard (100% or 10 mg mL^{-1} PCT) and test solutions (100%) were recorded under same conditions, and they were shown in **Fig. 1**. It was observed that the excipients present in the Prc formulations did not interfere with the PCT peak. These results indicate that an acceptable specificity was obtained for the Raman spectroscopic determination of PCT in Prc formulations.

Calibration and Linearity Range: The calibration curve demonstrates that the analytical method is capable to obtain test results which are directly proportional to the analyte concentration in a sample. In this context the Raman spectra of various concentration of PCT in the range from 7.0 to 13.0 mg mL^{-1} were given in **Fig. 2**. The calibration curve for the real values versus predicted concentration was presented in **Fig. 3**. This figure shows that a linear relationship exists between real concentration and experimentally obtained PCT concentration in the range from 7.0 to 13.0 mg mL^{-1}.

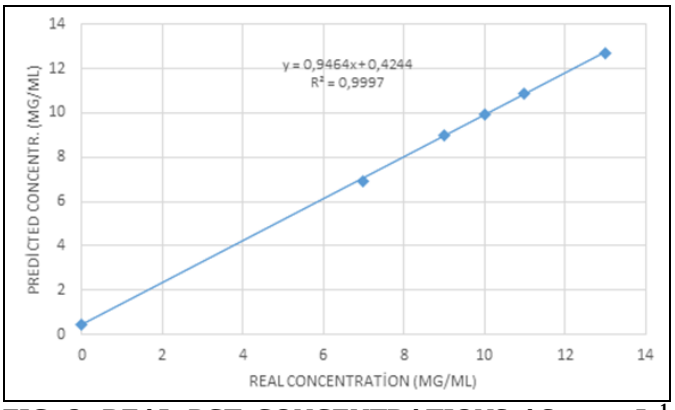

FIG. 3: REAL PCT CONCENTRATIONS AS mg mL^{-1} *VS.* CALCULATED CONCENTRATIONS RESULTING FROM PARTIAL LEAST SQUARES ANALYSIS

Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a true conventional value or as an accepted reference value and the value found. After the addition of a known amount of PCT to Plc solution, the recovery results were used to evaluate the accuracy of the proposed method. The recovery values given in **Table 1** for three different concentrations of PCT were obtained in the range between 100.4% and 101.9%. The low RSD values (RSD<2%) indicate that the proposed method has a high accuracy for PCT determination in Prc solution.

Precision: The precision of an analytical method is described as the harmonization of the results obtained from the replications of a homogenous sample. This protocol includes system precision, repeatability, and intermediate precision. The system precision is tested at the same conditions and in a short time interval. It is the measurement of the system performance parameter that is

independent of errors occurred at the sample preparation stage. The results of the standard solution of 10.0 mg mL^{-1} obtained from six consecutive injections were presented in Table 2. The repeatability is tested under the same conditions over a short interval of time. It is the measurement of the system performance dependent on the errors that occurred at the sample preparation. The results of six different Prc solution for I.V infusion drug product (containing 10 mg mL^{-1} PCT) were given in **Table 2**. The intermediate precision determines the effects of the changes on the results of a homogenous sample analyzed on a different day by a different analyst. It is not necessary to make each of the changes at the same time. The results of six different test solutions (Prc 10.0 mg mL^{-1} Solution for I.V. Infusion) analyzed in the same laboratory on a different day by a different analyst were also presented in **Table 2**. The obtained RSD values are smaller than 1% in all precision studies indicating that the proposed method is highly precise for PCT determination.

TABLE 1: ACCURACY RESULTS OBTAINED FROM DIFFERENT CONCENTRATIONS OF PCT (8.0, 10.0, AND 12.0 mgmL^{-1})

Theoretical value (mg mL^{-1})	Found value (mg mL^{-1})	Mean	SD	RSD %	Mean (n=9)	Recovery %	SD (n=9)	RSD% (n=9)
8.0 (1)	8.10	8.08	0.029	0.36	8.15	101.9	0.075	0.92
	8.05							
	8.10							
8.0 (2)	8.28	8.23	0.042	0.51				
	8.20							
	8.22							
	8.18	8.13	0.046	0.57				
8.0(3)	8.09							
	8.12							
10.0 (1)	10.10	10.12	0.049	0.48	10.17	101.7	0.073	0.72
	10.18							
	10.09							
10.0 (2)	10.29	10.25	0.059	0.58				
	10.18							
	10.27							
10.0 (3)	10.14	10.13	0.036	0.36				
	10.09							
	10.16							
12.0 (1)	11.97	12.06	0.079	0.66	12.05	100.4	0.071	0.59
	12.12							
	12.09							
12.0 (2)	12.02	12.01	0.031	0.26				
	11.98							
	12.04							
12.0 (3)	11.97	12.07	0.100	0.82				
	12.08							
	12.17							

TABLE 2: PRECISION RESULTS OBTAINED FROM 10.0 mg mL^{-1} STANDARD PCT AND PCR TEST SOLUTIONS CONTAINING 10.0 mgmL^{-1} PCT (N=6)

System Precision				Repeatability		Intermediate precision	
Standard solutions	Results mg mL^{-1}	RSD%	Test solution	Results mg mL^{-1}	RSD%	Results mg mL^{-1}	RSD%
St1	10.01	0.58	1	9.77	0.44	9.91	0.42
St2	10.08		2	9.73		9.91	
St3	10.09		3	9.82		9.87	
St4	10.04		4	9.83		9.82	
St5	10.06		5	9.84		9.90	
St6	10.18		6	9.83		9.94	

LOD and LOQ Values: LOD and LOQ were calculated using 3.3 sbl/m, and 10 sbl/m equations, respectively, where sbl is the standard deviation of the response of Plc solution accepted as blank

solution and m is the slope of the calibration curve. The LOD and LOQ were found to be 2.2 and 7.3 mg mL^{-1}, respectively. All results obtained in the validation studies are presented in **Table 3**.

TABLE 3: METHOD-VALIDATION DATA FOR PCT DETERMINATION WITH RAMAN SPECTROSCOPY

Validation parameters	Obtained Results
Specificity	Specific
Linearity range	7.0-13.0 mg mL^{-1}
LOD	2.2 mg mL^{-1}
LOQ	7.3 mg mL^{-1}

Robustness: The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage. Some variations in the robustness parameters such as temperature, pH and the effects of these variations on the system suitability parameters and test results should be examined. In this study, the temperature of the analytical method was changed from 20 to 30 ºC and the pH of the solutions was changed from 5.0 to 6.0. The obtained results were given in **Table 4**.

The difference between the results obtained with the original method and the modified method should be less than 2.0%. These results show that the proposed method is robust.

TABLE 4: RESULTS OBTAINED FROM THE ROBUSTNESS OF THE PROPOSED METHOD

	Temperature (^oC)			pH		
Number of Samples	**20**	**25**	**30**	**5.0**	**5.5**	**6.0**
1 as mg mL^{-1}	10.354	10.381	10.216	10.280	10.417	10.121
2 as mg mL^{-1}	10.153	10.163	10.321	10.462	10.224	10.192
3 as mg mL^{-1}	10.220	10.164	10.158	10.391	10.219	10.270
Mean as mg mL^{-1}	10.242	10.236	10.232	10.378	10.287	10.194
SD	0.084	0.103	0.067	0.075	0.092	0.061
RSD%	0.816	1.002	0.659	0.722	0.896	0.597

Comparison of Method with HPLC: The results obtained from the Raman spectroscopic method was compared with a standard HPLC method to verify the proposed method for the PCT determination. The results obtained by the Student's t and F statistical tests of 73 samples are given in **Table 5**. The mean PCT concentration as $mg.mL^{-1}$ obtained by the proposed Raman spectroscopic and HPLC methods was found to be very close to the Prc solution for I.V. Infusion containing 10 mg mL^{-1} PCT.

In the evaluation of t-test, the Null Hypothesis (H0, (α=0.05) indicates that there is no significant difference between the mean values, while the Alternative Hypothesis (H1, (α=0.05) says the opposite. If t critical is higher than texp, H0 is accepted, and H1 is rejected. According to the results presented in Table 5, the evaluation of the t critical with texp at 95% confidence level demonstrated that there was no significant difference between the Prc solution (accepted real value) and the experimentally found PCT concentrations. In the evaluation of the F test, the Null Hypothesis (H0, (α=0.05) says that there is no significant difference between the variances, while the Alternative Hypothesis (H1, (α=0.05) says the opposite. If F critical is higher than Fexp, H0 is accepted, and H1 is rejected. According to the results presented in **Table 5**, there was no significant difference between the precisions (as standard deviations) of the proposed Raman spectroscopic and HPLC methods due to Fcritical > Fexp.

TABLE 5: COMPARISON OF THE STATISTICAL EVALUATION BETWEEN THE PROPOSED RAMAN SPECTROSCOPIC METHOD AND THE HPLC METHOD (N=73)

	HPLC Method	Raman Spectroscopy
Mean as mg mL^{-1}	10.04	10.08
Variance	0.032	0.026
t_{exp}	1.31	
$t_{crtical}$	1.98	
F	1.25	
$F_{critical}$	1.48	

CONCLUSION: In this study, a simple, sensitive, selective, and fast method for the determination of PCT was developed and validated based on Raman spectroscopy. A pharmaceutical solution containing 10.0 mg mL^{-1} of PCT was successfully quantified using the PLS models based on the Raman

Spectroscopy. The method demonstrated an acceptable accuracy, precision and stability over the applied concentration range with the linear concentration range from 7.0 to 13.0 mg mL^{-1}; the LOD and LOQ values were calculated as 2.2 and 7.3 mg mL^{-1} respectively. All these results confirmed that the Raman Spectroscopic method was successfully validated for the determination of PCT in Prc solution for I.V. Infusion.

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