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VALIDATION OF PARACETAMOL IN QUALITY ASSURANCE AND QUALITY CONTROL

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ABSTRACT

For the measurement of paracetamol, Reverse Phase High Performance Liquid Chromatography (RP-HPLC) has produced a straightforward and repeatable technique. At a UV detection wavelength of 207 nm, paracetamol was separated on a C18 column [4.6 x 250 mm, particle size 5 µm] using an ortho phosphoric acid buffer with a pH of 3.5. Acetonitrile (ACN) and water wereeluted isocratically at several ratios and flow rates, until a final ratio of 25:75 v/v ACN and waterwas established at a flow rate of 1 mL/min. After checking for linearity, accuracy, precision, inter-day and intra-day fluctuation, and other statistical validity factors, it was discovered that the limitsof detection and quantification for paracetamol concentrations were 120 ng/mL and 360 ng/mL, respectively. The paracetamol recovery and assay trials showed percentages of 99 to 102%, suggesting that the suggested approach may be used for paracetamol quality control analysis. Thechemically 4-hydroxy acetanilide derivative paracetamol has analgesic, antipyretic, and mild anti- inflammatory properties1,2. It is also used to treat more severe pain in patients with advanced malignancies.3.In writing, a number of analytical methods including as colorimetric(4)techniques such as spectroflurimetric5 havebeen documented on the assay of paracetamol in relation to othermedications. Acetonitrile (ACN) was used as the solvent in the unique HPLC technique that was created in this work; it is an easy approach to examine, detect, and extract the paracetamol from the combination of substances and use it for ongoing quality evaluation in the scientific and pharmaceutical industries labs.

KEYWORDS: Simultaneous equation technique, UV visible spectrophotometer, RP-HPLC, andParacetamol Method development, Validation, Limits of detection and quantitation.

1. INTRODUCTION

As a counteranalgesic (pain reliever) and antipyretic (fever reducer), paracetamol (PARA) is commonly utilized. N-(4-hydroxy phenyl) ethanamide is its chemical name. It works by loweringprostaglandin synthesis. It may be used to relieve any type of discomfort, including headaches, tooth discomfort, etc.) in people with cancer. PARA is used in small doses for moderate discomfortor in conjunction with opioids (e.g., codeine), it has mild anti-inflammatory properties. PARA When liver illness is severe, it should not be used. Officially recognized by the Indian Pharmacopeia (IP), British United States Pharmacopeia (USP), and Pharmacopeia (BP). There are several techniques like as techniques for measuring paracetamol are published, including spectroscopy, HPLC, and HPTLC. Because of its antipyretic, analgesic, and anti-inflammatory properties, paracetamol (PCM), also referred to as acetaminophen, is one of the medications that is most commonly used. It is a prescription and over-the-counter (OTC) drug. Medication for thetreatment of fever, headaches, lumbar pain, and other general symptoms. In the regarding gastrointestinal distress, ulcer formation, and hemorrhaging, it is considered a superior substitute for aspirin. Prostaglandin synthesis is inhibited by cyclooxygenases I and II (COX-I and COX-II), respectively. Accountable for the analgesic, antipyretic, and anti-inflammatory qualities of PCM.In order to demonstrate that a process is under control, process validation studies look at the process under typical operating conditions. As long as no modifications are made, it is anticipatedthat the procedure will continue to be in charge once it has been certified. The process would needto be validated in case the equipment or systems used in it were modified, a problem arose, or the process itself had to be altered. More measurement is frequently needed for validation studies than is necessary for the regular procedure. In order to demonstrate the process's consistency, the validation must evaluate each step's ability to achieve the desired result. The method must continuously fulfill all specifications at every step of the procedure for at least three consecutive times in order to be deemed validated. It is crucial to predetermine the specification for the process that is being validated. Additionally, it is crucial that all of the crucial processing parameters for which specifications have been established are measured using equipment. These categories mayall be used for several different processes in manufacturing plants. Every process that has to be verified needs to be a distinct process that is well-explained in the SOP or master formula. Every piece of equipment, process parameter, and step specification needs to be specified in great detail.The equipment has to have its real working range, construction operational capacity, and identitycode number fully specified.

Processing parameters, such as time period, pH, volume, temperature, measurement specification, allowable range, etc., for each stage must be sufficiently comprehensive to allow for total reproducibility of the process every time it is carried out. It is necessary to define the controls, tests, and their specifications. Every stage of the product process has to have its purity profile specified.

2. REVIEW OF LITERATURE

2.1 Estimation of PCM in single-component dosage form:

Owing to its antipyretic and analgesic properties, PCM has been the preferred first-line therapy over all other analgesics in many countries. Overdosing on medication, however, can result in serious liver damage and possibly even death. The increasing prevalence of self-inflicted PCM overdoses necessitates further technique development for PCM calculation. Critchley et al. Developed an RP-HPLC method in 1994 to measure PCM and its main biomolecules in body fluids. Acetic acid, propane, and potassium dihydrogen orthophosphate at 0.1 M-2-01 in the proportion of (100:0.1:0.75) was employed as the mobile phase, and a wavelength of 254 nm wasutilized for UV detection. RSD were found that for urine and plasma PCM values of 5-500 µg/mLand 5-25 µg/mL, respectively, were 0.2-1.7% and 0.1-3.3% µg/mL, in turn.

In 1999, M.I.H. Helaleh et al. presented a kinetic method for detecting PCM in different formulations and pure forms. It is possible to successfully detect PCM using kinetics parameters thanks to the interaction of PCM with persulfate in an alkaline solution.

In 2004, M. de Los A. Oliva and colleagues developed a fluorescence spectrophotometric method for quantifying PCM in tablet form. In their method, ethyl acetoacetate and PCM reacted to create a coumarin molecule, with Serving as a catalyst is H2SO4. Excitation of the reaction product is observed at 446 nm in wavelength. At 478 nanometers, a robust excitation spectrum of fluorescence was observed for the reaction product. For the 0.1–0.4 equivalent µg/mL PCM, a rectilinear calibration curve was seen, and 57 ng/ml was the detection limit.

2.2 Estimation of DIC in single-component dosage form:

L.A. Carreira et al. developed a spectrophotometric method in 1995 for the quantitative assessmentof DIC in a variety of pharmaceutical formulations and in bulk using a europium (III) ion probe. The method was created by measuring the fluorescent EU (III) probe ion's transitions at 616 nm with extreme sensitivity. The fluorescent EU (III) probe ion's non-hypersensitive response is evaluated at 592 nm. To determine the ratio of intensity (R = I592), the percentage of bound probe ions/I616] was applied. ten as the relative stability constant was discovered in the molar combination of Eu (III) and Diclofenac (1:1). The relationship between bound Eu (III)Throughoutthe concentration range of (10–200) µg/mL, DIC was found to be linear, with a percent recovery of 100.22 %.

In 2002, L.G. Lala and colleagues devised a high-performance thin-layer chromatography (HPTLC) technique to ascertain the DIC content in serum from biological fluids. By extracting serum samples with ethyl acetate and marking them on Silica Gel 60 F254 plates using an 80:30:1 ratio, it was possible to ascertain the presence of DIC in the samples. Toluene, acetone, and glacial acetic acid make up the mobile phase, which is responsible for developing the plates. DIC was found by densitometric analysis at a wavelength of 280 nm and a retention factor of 0.58. In the

Plotting the standard curve for DIC in serum at a concentration range of 200–800 ng revealed that it was linear through FT-Raman spectroscopy is used.

Tablets and capsules containing solid dose forms, such as DIC, might be quantified by S. Mazurek et al. Principal component regression (PCR), counter-propagation artificial neural networks, partial least squares (PLS), and other methods were used to quantify DIC networks (CP-ANN). For the tablet dosage form, standard curves were created using unnormalized spectra. The spectra were then normalized using the intensity of a selected band from an internal standard. Not the same the dosage form in capsule form was prepared using preprocessing methods. The relative prediction standard errors (RSEP) values for the tablets and capsules' calibration and validation data sets were found to be within the range the percentage recoveries for the PLS, PCR, and of 2.4-3.8 %, 0.8- 1.9 %, 2.6-3.5 %, and 1.4-1.7% The results of CP-ANN approaches were 99.5-101.3%, 99.7- 102.0%, and 99.9-101.2%, in that order 29. Making use of the voltammetry method Hyphenated GC-MS detection using Linear Sweep Voltammetry (LSV).

2.3 Estimation of CZ in single-component dosage form:

In 1978, J.T. Stewart et al. employed chemical derivatization using a variety of fluorogenic reagents to determine the fluorometric determination of CZ. Dansyl chloride, fluorescamine, 2,4-dihydroxybenzaldehyde, and salicylaldehyde were among the study's reagents. The fluorophor generated by CZ's basic hydrolysis came next. The method that proved to be the most sensitive was a fluorescamine reaction. Above the focus, In the range of 0.27-3.4 µg/mL, linear fluorescence was seen. The examination of CZ in a boosted and dosed form. It was found that human plasma and urine samples were accurate to within 1-4 percent.

An HPLC technique was created in 1993 by D.D. Stiff et al. to quantify CZ and its primary metabolite 6-hydroxyCZ in plasma. Using C18 solid phase extraction columns, the internal standard of CZ (5-fluorobenzoxazolone) was extracted from plasma. A 10-µm Waters C18, µ Bondapak column was utilized to analyze the extract. As a mobile phase, combine acetonitrile, tetrahydrofuran, and 0.1 M ammonium acetate (22.5:5.5:72). The detection of the test was carried out by UV at a wavelength of 283 nm, which offered enough sensitivity and specificity to concurrently. Quantify the levels of 6-hydroxyCZ and less than or equal to 100 ng/mL CZ in plasma.

In 1998, C.B. Eap et al. published a GCMS approach for the simultaneous measurement of CZ and 6-hydroxyCZ in plasma. When the calibration curves for CZ and 6-hydroxyCZ were drawn, it was discovered that they were linear in the range of 20 to 4000 ng/mL and 20 to 1000 ng/mL, respectively. The range of the percentage recoveries was 65-77% with coefficients of variance both within and between days being less than 9%.

2.4 Estimation of PCM and DIC in combined dosage form:

A normal-phase HPTLC technique for identifying DIC and PCM in a pharmaceutical formulation and bulk drug powder was created in 2006 by V.V. Dighe et al. On silica gel 60 F254 HPTLC plates, the analysis was performed with a mobile phase of toluene–ethyl acetate–methanol–formic acid, 5.0 + 4.0 + 1.0 + 0.01 (v/v) at 260 nm. The DIC and PCM standards showed linear responses within the concentration ranges of 30-800 ng/µL and 300-2000 ng/µL, in that order, using aceclofenac as the internal reference. In order to evaluate the recovery studies. The average recovery from the pharmaceutical formulation was found to be 99.57 percent, indicating the accuracy of the approach for DIC and 100% for PCM, in that order.

Using gabapentin as an internal reference and a Quality by Design (QbD) methodology (IS), P. Bhatt et al. described the development and validation of an LC-MS/MS technology for measurement of PCM and diclofenac in human plasma in 2018. The protein precipitation techniquewas used for sample preparation and extraction, followed by chromatographic analysis. The calibration range for diclofenac and PCM was determined to be 40–2555 ng/mL and 205–13060 ng/mL, respectively. All of the validation study's requirements, including linearity, accuracy, precision, selectivity, sensitivity, and stability, were satisfied by the developed method for PCM and diclofenac estimation.

A spectrophotometric approach for measuring PCM and DIC in pharmaceutical formulations and in pure form was proposed by M.M. Sebaiy et al. in 2020. The H-Point assay was used to test both drugs simultaneously without first separating them. In terms of accuracy, precision, repeatability, and robustness, the procedure parameters were assessed in accordance with ICH guidelines and found to be within allowable bounds.

3. MATERIAL AND METHOD

Every reagent utilized was of the quality of analytical reagent. A sonicator (Digital Citizen Ultra Sonic Cleaner) for degassing HPLC grade ACN and ortho phosphoric acid 88% (S.D. FineChem Limited, Mumbai, India), pure paracetamol medication, and reverse osmosis and ultra pure water(Nanopure Human Corporation, Korea) are examples of water purification systems.

3.1 Chromatographic system:

The Agilent 1200 series immediate pilot software, ChemStation Plus and EZChrom Elite, is the core of the RP-HPLC system and is approved for use in pharmaceutical QA/QC. It is made up of the following: thermostated column compartment G1316B with C18 column [4.6x250mm, pore size 5µm], high performance autosampler G1367C, thermostat for high performance auto- sampler G1330B, binary pump G1312B, diode array detector SL G1315C, micro vacuum degasser G1379B, and thermostat. It is the most adaptable setup for full spectrum UV-visible detection for peak purity analysis and spectral confirmation, with the highest gradient and low flow rate accuracy and precision, high speed, and many wavelengths. The chromatographic and integrated data were recorded in computer system.

3.2 Chromatographic conditions:

Two solvents were utilized: solvent-A, which included ACN and was filtered through 0.2 µm filter paper, and solvent-B, which contained ultra pure water and was degassed with sonication after being filtered through a 0.25 µm PTFE (Poly Tetra Fluoro Thylene) filter (pH adjusted to 3.5 using88% ortho phosphoric acid). To design a procedure, several flow rates and sol-vent compositions were offered at ambient temperature (28°C). The diode array detector SL G1315C was used to conduct the detection at 207 nm.

3.3 Method:

Resolution In the mobile phase, 10 mg/mL of pure paracetamol was prepared. After the solution was sufficiently diluted to 50µg/mL, a technique was developed by experimenting with different solvent ratios and flow rates, as indicated by table 1 and figure 1's chromatograms.

Table 1: Acetonitrile and paracetamol ratios in mobile phase to resolve the paracetamol in HPLCcolumn in method development.

Percentage of solvents					
Solvent-A (ACN)	**Solvent-B (paracetamol)**	**Flow rate mL/min**	**Retention time**	**Area under curve**	**Recovery %**
80	**20**	1.00	2.3	17757573	67
75	**25**	1.00	2.4	18151358	69
70	**30**	1.00	2.5	18107126	68
65	**35**	1.00	2.5	18181695	71
60	**40**	1.00	2.6	18361607	71
50	**50**	1.00	2.6	17990113	67
45	**55**	1.00	2.9	18024389	68
40	**60**	1.00	3.0	17233768	68
25	**75**	0.75	4.8	31606579	120
25	**75**	1.00	3.6	26115406	100
25	**75**	1.50	2.6	16444904	63
25	**75**	2.00	2.1	13922706	52.99

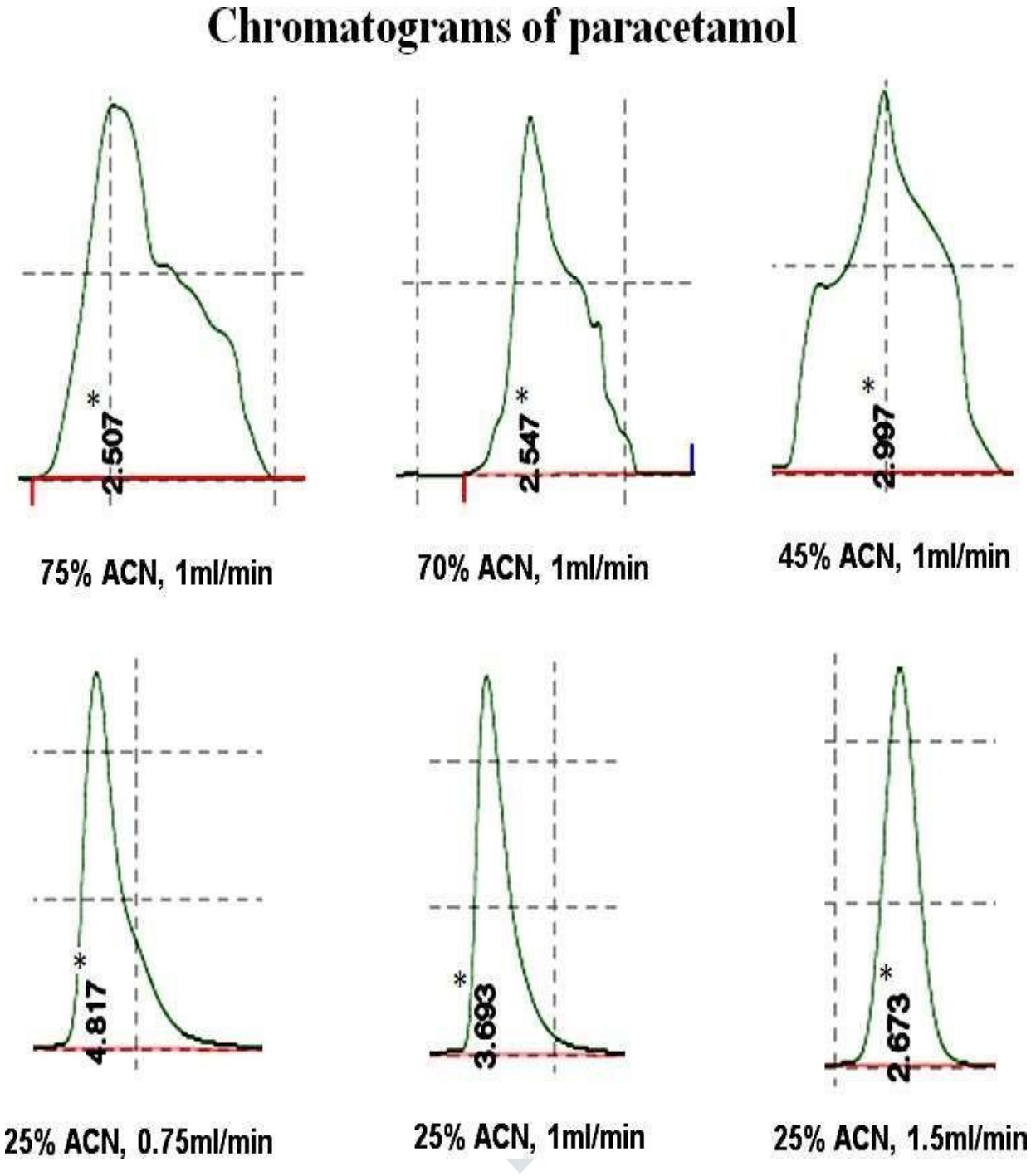

Fig. Chromatograms of paracetamol in varied ACN% and flow rates while method development.

*Retention time.

3.4 Validation of the method:

The following parameters were used to validate the improved HPLC technique.

3.5 Linearity:

The aliquots that followed were made using a 10 mg/mL standard stock solution of paracetamol; aliquots containing concentrations of 100, 50, 25, 12.5, and 6.25 µg/mL were created using serialdilution. A 200 µL solution was put into the autosampler tray, and 20 µL was injected into the column. For every concentration, all measurements were made three times over. The area under the curve versus concentration

calibration curves were noted.

3.6 Accuracy:

The accuracy investigations involved the preparation of 10, 35, and 55 µg/mL concentrations, which were then injected using a standard stock solution of 10 mg/mL of paracetamol. The acquired area under the curve was examined and the recovery percentage was calculated.

3.7 Precision:

Repeatability, intra-day, and inter-day precision were used to assess and validate the method's accuracy. Six injections of a paracetamol concentration at a concentration of 80 g/mL were made on the same day to verify repeatability, and one injection and analysis at various times that same day was made for intraday precision. Similar to this, separate days were used to assess a different concentration for the inter-day precision.

3.8 Limit of detection (LOD) and limit of quantification (LOQ):

The signal (S) to noise (N) ratio was used to independently calculate the LOD and LOQ of paracetamol. The LOD and LOQ concentrations of paracetamol were verified and recorded by the S/N ratio, where 3 and 9 were displayed.

3.9 Analysis of the marketed drug:

Ten Crocin (paracetamol) pills were weighed and finely powdered. We determined and weighed the average weight of a single pill. In a volumetric flask, 100 mL of mobile phase were added to the weighed fine powder of paracetamol tablets, and the mixture was shaken for 30 minutes. After 20 minutes of ultrasonication, the solution was filtered through 0.2 µm filter paper. To analyze the medication content in the tablet, several dilutions were created.

4. RESULT AND DISCUSSION

The goal of the developed and approved paracetamol technique was to provide chromatographic conditions that could determine the amount and quality of paracetamol in pharmaceutical formulations. RP-HPLC was used to fully separate paracetamol on a C18 column using isocratic elution of ACN and water as the mobile phase. Broadening, fronting, and tailing of peaks were seen when the ACN percentage was decreased starting at 80% by a decrement of every 5%. The peak was well-defined and distinct due to the greater ACN concentrations in the mobile phase and the corresponding drop in the percentage of ACN. The odd peaks may indicate that the paracetamol was not effectively dissolved in a greater concentration of ACN, which prevented the chromatographic column from correctly resolving the paracetamol and even caused a drop in the paracetamol recovery % (Table 1). The peak occurs when the ACN concentration progressively drops. Significantly less widening, fronting, and tailing occurred. As the flow rate increases from 0.75 mL/min to 1.50 mL/min, the retention time also decreases with fluctuations in the paracetamol recovery (Table 1). Ultimately, proper resolution was achieved at a flow rate of 1 mL/min and a retention time of 3.6 minutes. It is clear that the mobile phase flow rate in chromatography plays a significant role in resolving the paracetamol.

4.1 Linearity:

As seen in figure, the approach produced a linear response to the paracetamol medication within the concentration range of 6.25 - 100 µg/mL with r2= 0.999. Table 2 illustrates that the paracetamol was recovered in the range of 98.8 to 102.0 % for different concentrations.

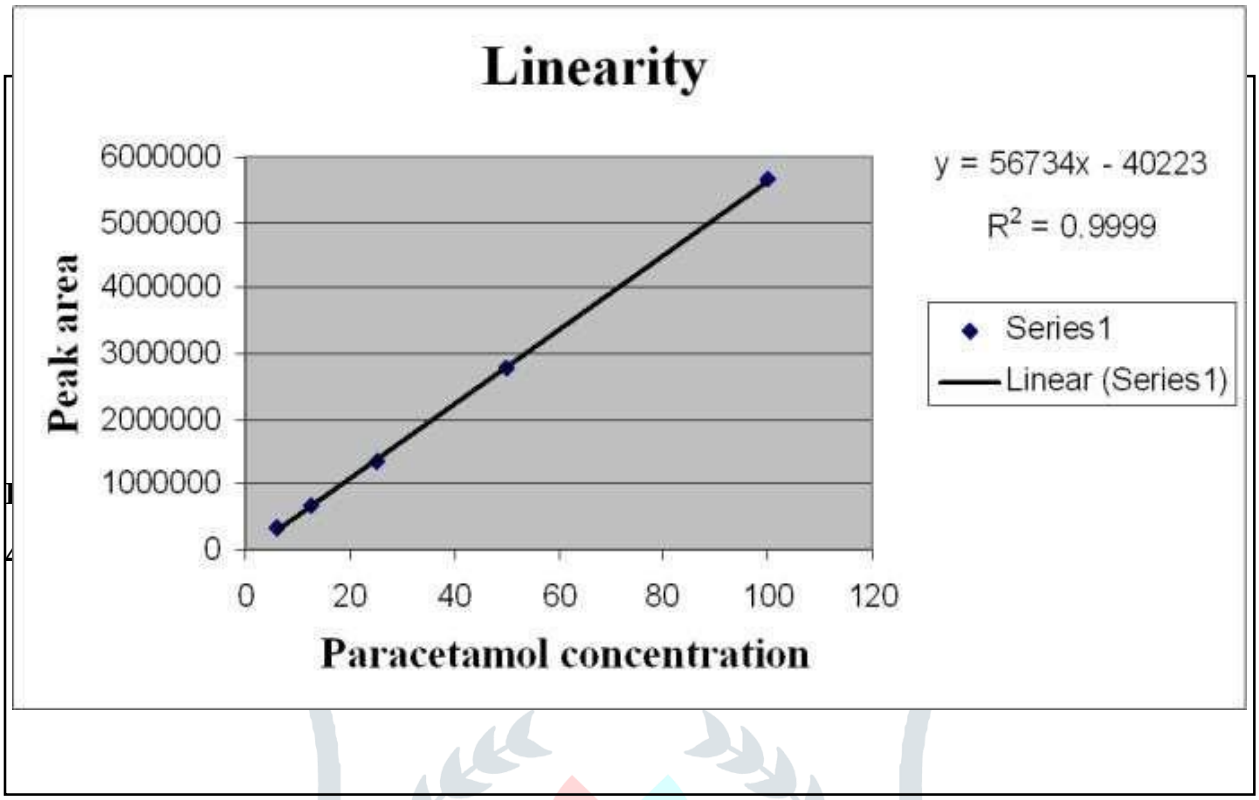

Table 2: Recovery percentage of paracetamol in accuracy studies

Concentration (µg/mL)	**Area**	**Amount Recovered**	**Recovery (%)**
10	520309	09.87	98.9
35	1963625	35.30	100.7
54	3143687	56.10	102.2

4.3 Precision:

Table 3 displays the repeatability, intra-day, and inter-day precision values. Because the RSD values were less than 3%, the accuracy was satisfactory. Less than 0.1% was the t-test value for inter-day accuracy, showing significant precision.

Table 3: Developed method was checked for precision with different intervals

Repeatability			
Injection No.	**Area**	**Amount Recovered**	**Recovery %**
1	4498501	80.00	100.00
2	4517340	80.33	100.40
3	4527683	80.69	100.86
4	4575290	81.35	101.68

5	4602753	81.83	102.28		
6	4624520	82.22	102.77		
Mean: 4559348, SD: 49642.59, RSD: 1.088					
Intra-day precision					
Time (hrs)	**Concentration (µg/mL)**	**Mean of area**	**SD**	**RSD**	
0	25	1352231	15349	1.13	
3	25	1357626	7423.9	0.54	
0	50	27796225	44542	1.60	
3	50	2767559	27159.2	0.98	
Inter-day precision					
Day	**Concentration (µg/mL)**	**Mean of area**	**SD**	**RSD**	**t-test**
1	100	5645864	17302.9	0.30	0.009
2	100	6526371	169296	2.59	
3	6.25	338998	335.16	0.09	0.0003
4	6.25	378366	1371.78	0.36	

4.4 LOD and LOQ:

The method's robustness yielded the mean, standard deviation (SD), and RSD within the givenbounds. Table 4 displays the results.

Table 4: Slight deviation from the optimized parameters to check the robustness of the method

Factor	Level	Retention time	Theoretical plates	Area	% content
Flow rate (mL/min)					
0.9	-1	3.98	9308	1341377	97.4
1.0	0	3.69	9272	1363085	98.9
1.1	+1	3.21	9231	1330170	96.6
Mean		3.62	9270.3	1344877	97.6
SD		0.38	38.52	16734.35	1.16
RSD		1.07	0.41	1.24	1.19
% of ACN in the mobile phase (v/v)					
24	-1	3.62	9227	1341608	97.4

25	0	3.69	9272	1363085	98.9
26	+1	3.71	9381	1338798	97.2
Mean		3.67	9293.3	1347830	97.8
SD		0.04	79.18	13285.43	0.92
RSD		1.28	0.85	0.98	0.94
pH of mobile phase					
3.4	-1	3.73	9260	1329658	96.5
3.5	0	3.69	9272	1363085	98.9
3.6	+1	3.62	9189	1332413	96.7
Mean		3.68	9240.3	1341719	97.3
SD		0.05	44.85	18554.9	1.33
RSD		1.51	0.48	1.38	1.36

4.5 Analysis of marketed drug:

Two distinct pill strips containing 250 and 500 mg of paracetamol each had labeled amounts of paracetamol that recovered 99.56% and 99.75%, respectively. There is less than 2% RSD. Table 5presents the findings, which indicate that the retention time was 3.6 minutes.

Table 5: Recovery studies of paracetamol in mar- keted drug

Labelled amount (mg/tablet)	**Amount found**	**Recovery (%)**	**SD**	**RSD**
250	248.92	99.56	0.76	0.30
500	498.72	99.74	0.9	0.18

4.6 System suitability studies:

As indicated in table 6, the system suitability parameters, including retention duration, capacity factor, theoretical plate number, peak purity, and resolution factor of the improved method, were linked to limited values.

Table 6: System suitability parameters of optimized method

S.NO	**System Suitability parameters**	**Associated values**
1	Retention Time	3.69
2	Capacity Factor	17.4
3	Theoretical Plate number	3631

5. CONCLUSION

To sum up, the validation process for Paracetamol QA and QC procedures is a thorough and methodical strategy that establishes trust in the dependability, precision, and coherence of the used techniques and procedures. The basis for guaranteeing the quality and safety of products containing paracetamol is laid by the successful validation, which eventually helps patients and healthcare professionals alike. In the ever-changing pharmaceutical landscape, frequent revalidation and continuous monitoring will be necessary to preserve the efficacy of the QA and QC procedures.

The validation results provide consumers trust in the general caliber of paracetamol goods by guaranteeing that they comply with legal specifications and industry norms. Both patient safety and the pharmaceutical manufacturer's reputation depend on this.

The equipment validation procedure ensures that the instruments used in the QA and QC procedures adhere to established guidelines and perform within approved bounds. This increases the overall dependability of the outcomes and guarantees the integrity of the data created during testing.

To further ensure that the manufacturing procedures used to produce paracetamol consistently result in goods that satisfy the necessary quality requirements, process validation has been done. To guarantee the manufacturing processes' repeatability, this involves verifying crucial process parameters.

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