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Research Article

An Extensive Comparison of Analytical Data Using Various Stability Condition of Non-Steroidal Anti-Inflammatory Drug (NSAID) For Paracetamol Infusion of Various Manufacturers of Branded (Innovator) Drug Product and Generic Drug Product

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1. Abstract:
This study aims to present comprehensive comparative analytical data on stability tests for non-steroidal anti-inflammatory drugs (NSAIDs), such as Paracetamol infusion. Pharmaceutical products from various manufacturers were bought from a medical supply store. Each of the medicinal products those were chosen were examined physically and maintained under various stability conditions. Intravenous paracetamol is an analgesic and antipyretic agent, recommended worldwide as a first-line agent for the treatment of pain and fever in adults and children. The drug products were kept for testing under two distinct stability conditions: 30°C(±5°C)/65%RH(±5%RH) and 40°C(±5°C)/75%RH(±5%RH). Samples were examined at various stability time intervals. Reverse Phase-High Performance Liquid Chromatography (RP-HPLC) was used to analyse the samples both qualitatively and quantitatively utilizing Indian Pharmacopeia (IP) techniques. According to Indian Pharmacopeia specifications, all drug product's assay and associated impurities were confirmed to be within permissible limits based on the analytical data. The data analysis reveals that all manufacturer-produced medications are stable under both stability scenarios and are safe for patients to take regardless of cost.

Keywords: Generic medicine, Branded medicine, Stability studies, Non-Steroidal Anti-Inflammatory Drugs

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2. Introduction:

Worldwide, the use of generic pharmaceutical medicines is growing yearly.[1,2] As a result, the nation's and each person's health budget is reduced.[3] Doctors, however, are also not recommending these medications based on their dependability and quality. However, the generic drugs are bio-equivalent to their innovative counterparts since they are manufactured in facilities that are similar to those of their innovative counterparts and adhere to approved manufacturing practices.[4] Non-steroidal anti-inflammatory drugs (NSAIDs) include Diclofenac, Ibuprofen, Aspirin, Ketorolac tromethamine, Flurbiprofen, and Indomethacin, among others. One of the most often used pharmaceutical medicines is paracetamol. The goal of the current study was to assess the quality of medication items for branded and non-branded drug products. Different manufacturers of paracetamol infusion were chosen from the market. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), are a class of pharmaceuticals used to treat pain, fever, inflammation, and blood clot prevention. Concerns over the potential long-term negative consequences of paracetamol use have grown during this time, first in the context of hypertension and more recently in other domains as well. Numerous cohort and observational studies, together with a small number of randomized controlled trials. Many of which contradict one another make up the body of evidence supporting the negative effects of long-term paracetamol usage.[5] Depending on the drug, dosage, and duration of usage, the most common side effects include an increased risk of gastrointestinal ulcers and bleeding, heart attacks, and kidney problems. [6] Drug goods from various manufacturers were bought from the market in order to conduct the analysis. For six months following purchase from a medical supply store, assay and related compounds were examined using High Performance Liquid Chromatography (HPLC) in two stability circumstances: Control room temperature (CRT) and Accelerated conditions (ACC).[7] The 2018 Inidan Pharmacopia was used as a guide for the analysis of every medication.[8]

3. Methods:

3.1 Selection of drug products: Paracetamol Infusion (10mg/mL) and was selected for carrying out study.

Table 1: Drug products used for analysis in Paracetamol Infusion

Paracetamol Infusion (10mg/mL)		
Brand Name	**Manufacturer**	**Price per Infusion (INR)**
Paracip Infusion	Cipla Limited	510.00
Lanol IV	Hetero Drugs Limited	372.00
Gerpyrin Infusion	Zydus Cadila	331.65

3.2 Quality Testing:

1. Description: Samples were taken in to glass container to check its colour and clarity.
2. Quantitative Identification: It was done by performing Assay by HPLC.
3. Qualitative Identification: It was performed by Related Substances by HPLC.

3.3 Comparison:

Analytical data of various manufacturers' drug products in respective brand were compared in all the analytical tests in above mentioned stability conditions.

3.4 Chromatographic Condition for Related Substances:

HPLC-DAC system from Waters Corporation with a quaternary pump, and an automated injector (ambient temperature) was used. A stainless steel HPLC column Symmetry C18 (250*4.0) mm, 5µm used with the 35°C column oven temperature. The mobile phase was composed Mixture of 25 volume of Methanol containing 0.115gm Tetrabutyl Ammonium Hydroxide (40% w/v) with 37.5 volume of 0.05M Disodium Hydrogen Phosphate and 37.5 volume of 0.05M Sodium Dihydrogen Orthophosphate in an isocratic condition with the 1.5 ml/min flow rate for 70 minutes. A 20 µL Injection volume was injected for analysis. UV detection wavelength 245nm was set for the analysis. [8]

Reference Solution and Sample Preparation:

Reference solution was prepared with the concentration of 0.02mg/mL each of 4-aminophenol and Paracetamol in mobile phase. Samples were prepared individually by using 2mL of sample in 100mL volumetric flask and diluted to mark with mobile phase. [8]

Formula for the Calculation of Highest Unknown Impurity and total impurity:

% Unknown impurities/total impurity=

$$\frac{Area\ of\ Impurity * Conc.\ of\ reference\ solution * 10 * dilution\ of\ sample * 100}{Area\ of\ Paracetamol\ in\ Reference\ Solution * Volume\ of\ sample * Label\ claim}$$

Table 2: Related Substances data comparison for Lanol drug product

Test	Results at different data station					Specification
	0 Month	3 Months		6 Months		
		CRT	ACC	CRT	ACC	
Related Substances	0.14	0.16	0.16	0.17	0.17	**Highest Unknown Impurities (NMT 0.25%)**
	0.16	0.20	0.19	0.20	0.20	**Total Impurities (NMT 1.0%)**

Table 3: Related Substances data comparison for Gerpyrin drug product

Test	Results at different data station					Specification
	0 Month	3 Months		6 Months		
		CRT	ACC	CRT	ACC	
Related Substances	0.13	0.15	0.15	0.16	0.16	**Highest Unknown Impurities (NMT 0.25%)**
	0.17	0.19	0.19	0.20	0.20	**Total Impurities (NMT 1.0%)**

Table 4: Related Substances data comparison for Paracip drug product

Test	Results at different data station					Specification
	0 Month	3 Months		6 Months		
		CRT	ACC	CRT	ACC	
Related Substances	0.10	0.12	0.12	0.14	0.14	**Highest Unknown Impurities (NMT 0.25%)**
	0.12	0.15	0.15	0.17	0.17	**Total Impurities (NMT 1.0%)**

3.4.1 Chromatograms of Initial Sample analysis:

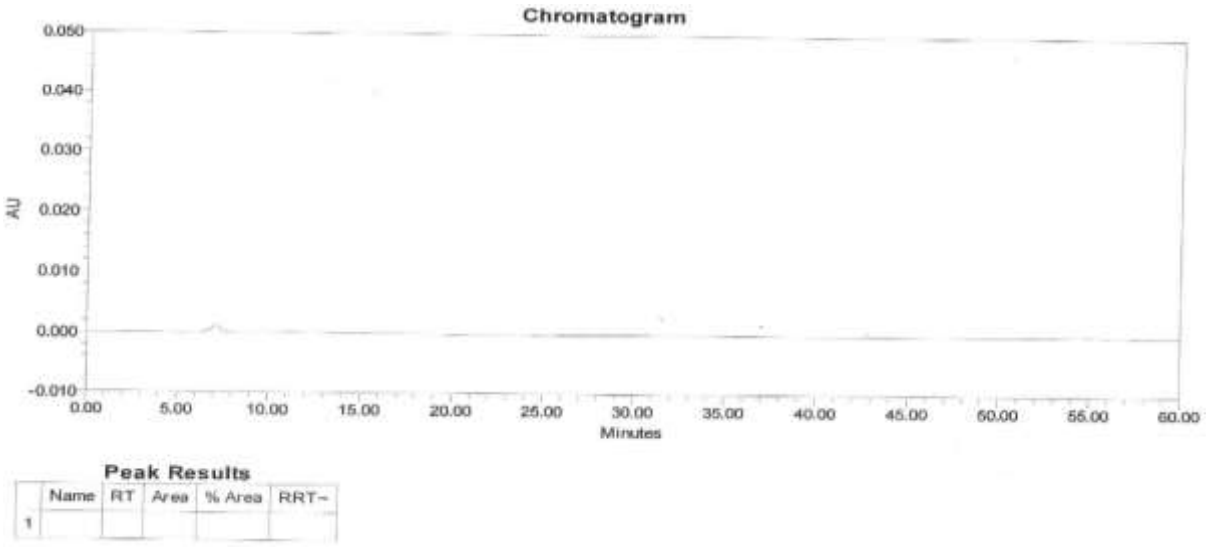


Figure 1: Blank Chromatogram

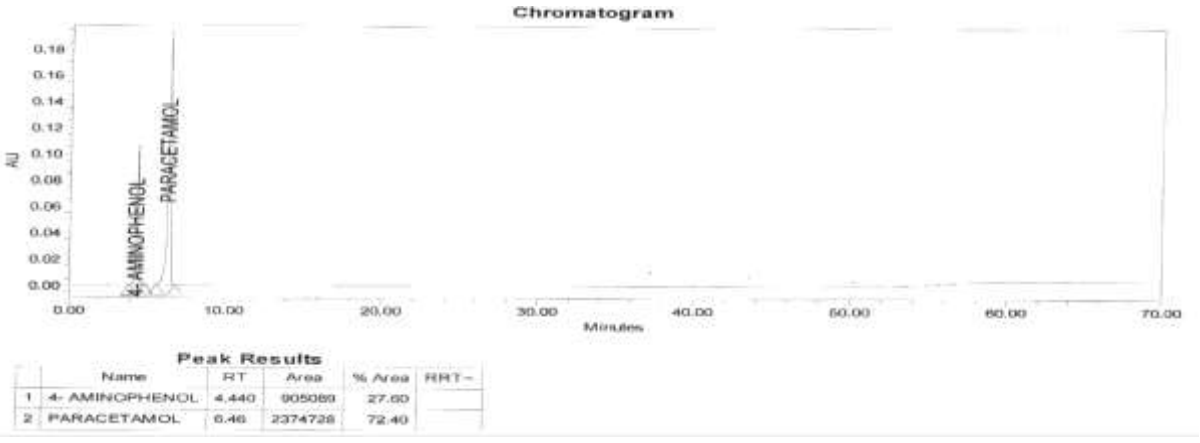
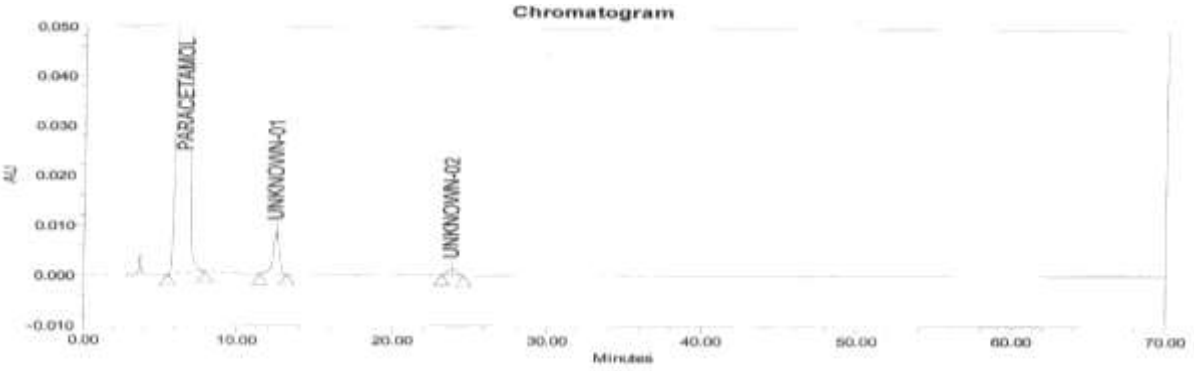


Figure 2: Reference Solution Chromatogram

Peak Results

	Name	RT	Area	% Area	RRT~
1	PARACETAMOL	6.64	91609544	99.59	
2	UNKNOWN-01	12.59	322184	0.35	1.89
3	UNKNOWN-02	23.92	53886	0.06	3.60

Figure 3: Chromatogram of Lanol drug product



Peak Results

	Name	RT	Area	% Area	RRT~
1	PARACETAMOL	6.64	91004622	99.70	
2	UNKNOWN-01	12.52	230628	0.25	1.89
3	UNKNOWN-02	23.82	45272	0.05	3.59

Figure 4: Chromatogram of Paracip drug product

Peak Results

	Name	RT	Area	% Area	RRT~
1	PARACETAMOL	6.63	90418283	99.57	
2	UNKNOWN-01	12.46	318038	0.35	1.88
3	UNKNOWN-02	23.73	74583	0.08	3.58

Figure 5: Chromatogram of Gerpyrin drug product

3.4.2 Chromatograms of 3M Accelerated condition Sample analysis:

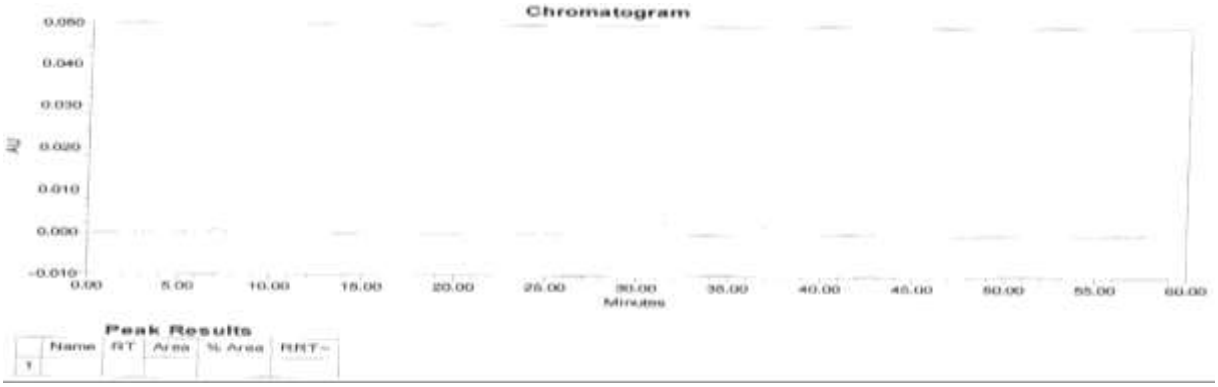


Figure 6: Blank Chromatogram

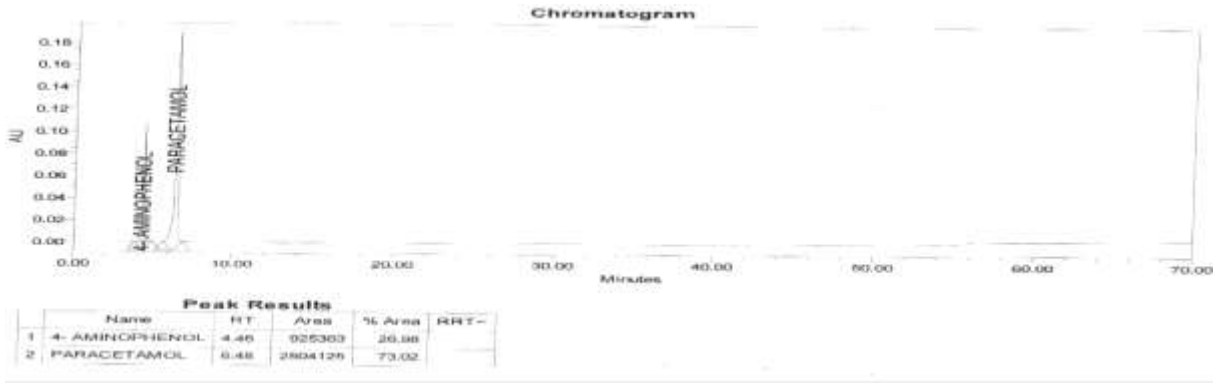


Figure 7: Reference Solution Chromatogram

Figure 8: Chromatogram of Lanol drug product

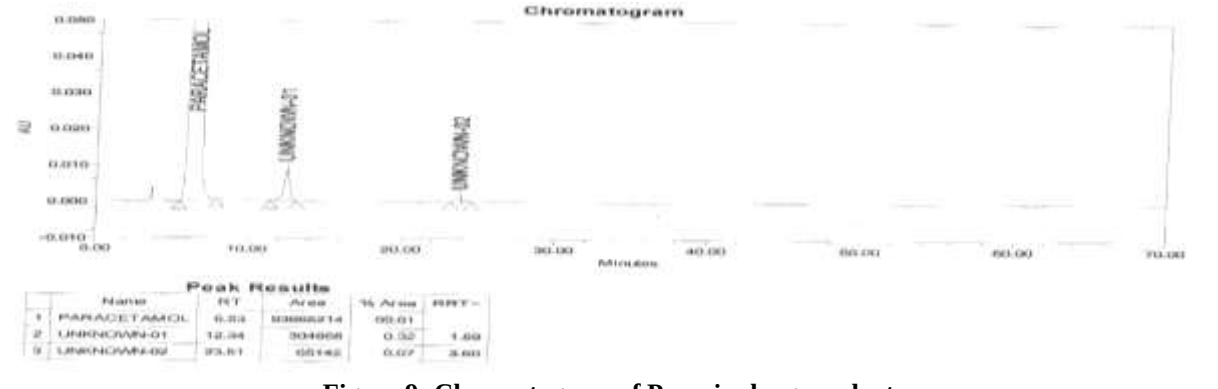


Figure 9: Chromatogram of Paracip drug product

Figure 10: Chromatogram of Gerpyrin drug product

3.4.3 Chromatograms of 3M Long term condition Sample analysis:

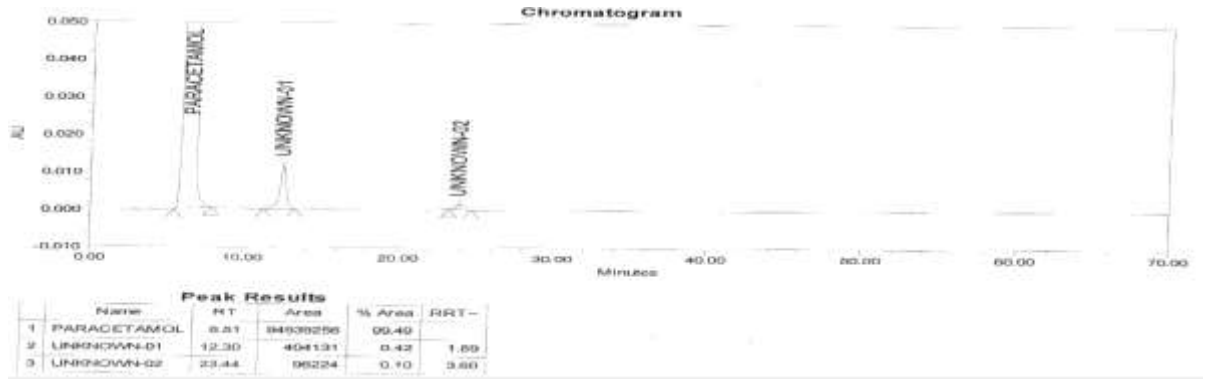


Figure 11: Chromatogram of Lanol drug product

Figure 12: Chromatogram of Paracip drug product

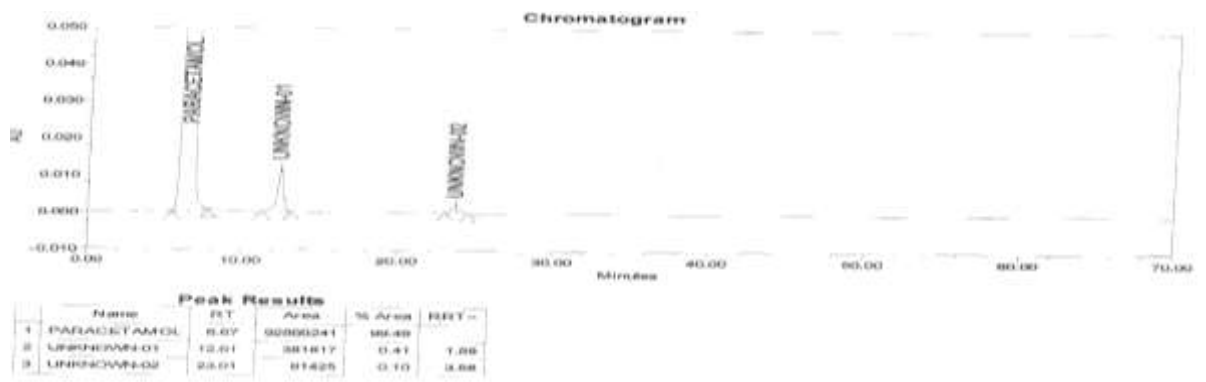


Figure 13: Chromatogram of Gerpyrin drug product

3.4.4 Chromatograms of 6M Accelerated condition Sample analysis:

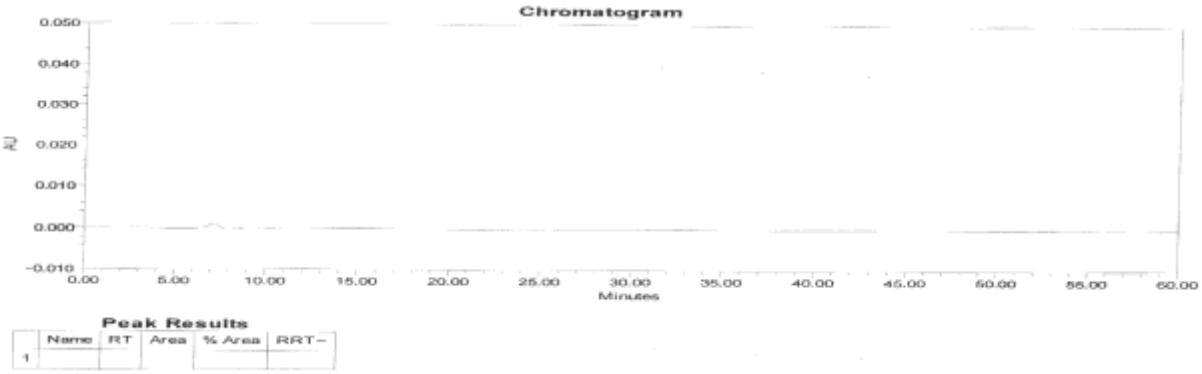


Figure 14: Blank Chromatogram

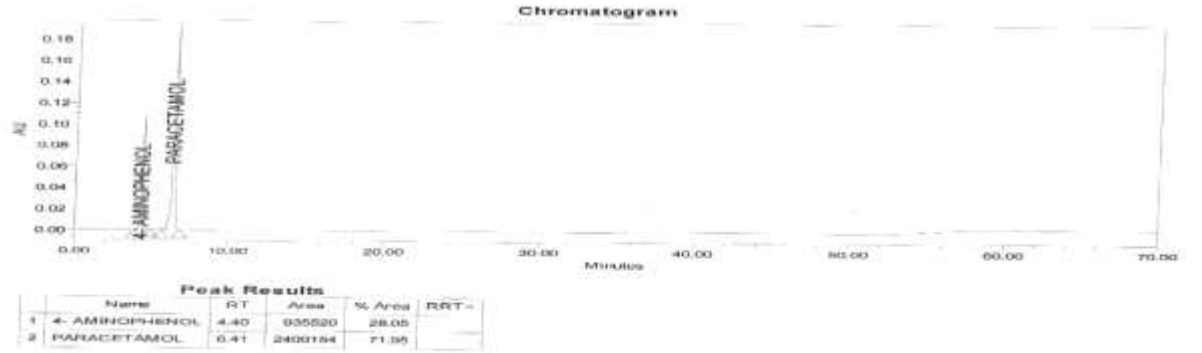


Figure 15: Reference Solution Chromatogram

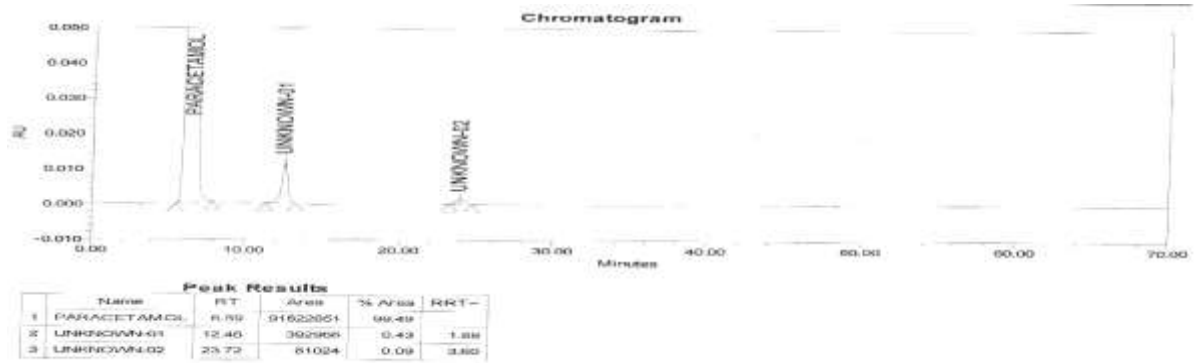


Figure 16: Chromatogram of Lanol drug product

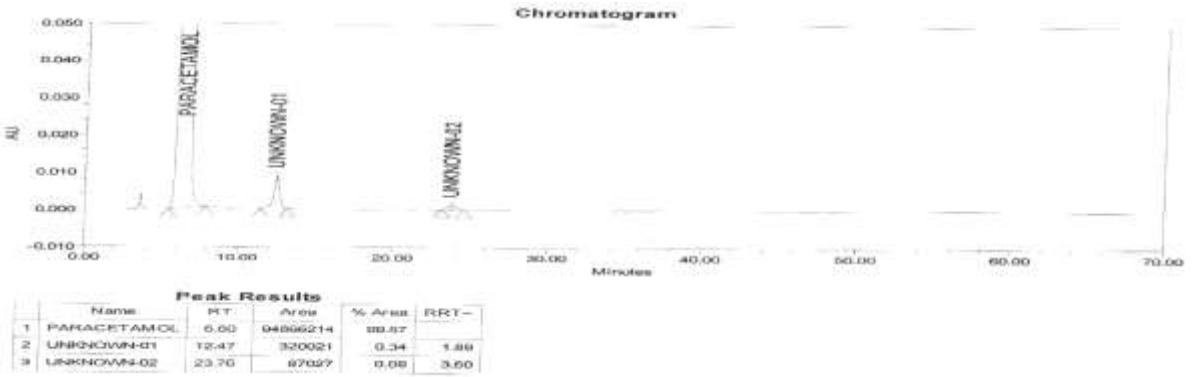


Figure 17: Chromatogram of Paracip drug product

Figure 18: Chromatogram of Gerpyrin drug product

3.4.5 Chromatograms of 6M Long term condition Sample analysis:

Figure 19: Chromatogram of Lanol drug product

Figure 20: Chromatogram of Paracip drug product

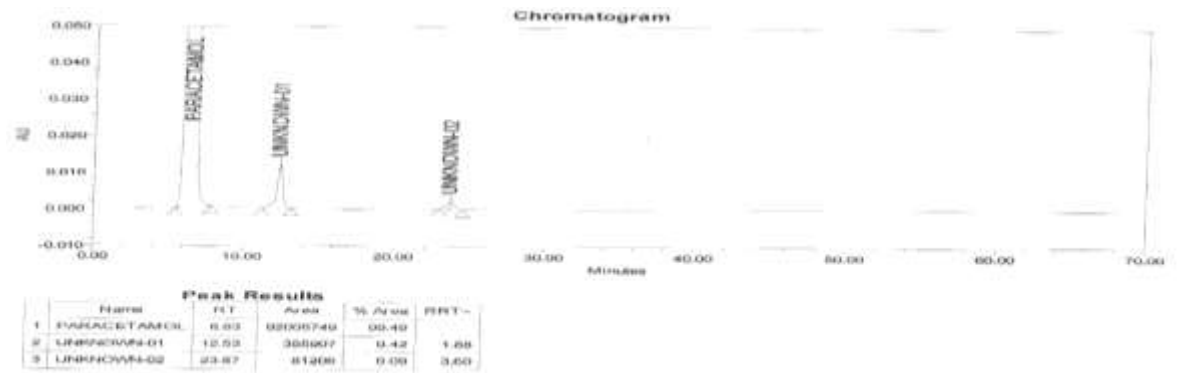


Figure 21: Chromatogram of Gerpyrin drug product

3.5 Method of analysis for Assay:

HPLC-DAC system from Waters Corporation (Model Alliance 2998 USA) with a quaternary pump, and an automated injector (ambient temperature) was used. A stainless steel HPLC column Symmetry C18 (200*4.0) mm, 10µm used with the ambient column oven temperature. The mobile phase was composed Mixture of 0.01M Sodium butane sulfonate in mixture of 85 mL of water, 15 mL of methanol and 0.4 volume of formic acid in an isocratic condition with the 2.0 ml/min flow rate for 15 minutes. A 20 µL Injection volume was injected for analysis. UV detection wavelength 245nm was set for the analysis. [8]

Reference Solution and Sample Preparation:

Reference solution was prepared with the concentration of 0.01% each of 4-aminophenol and paracetamol in mobile phase. Samples were prepared individually by using 1mL of sample in 100mL volumetric flask and diluted to mark with mobile phase. [8]

Table 5: Assay data comparison for Lanol drug product

Test	Results at different data station					Specification
	0 Month	3 Months		6 Months		
		CRT	ACC	CRT	ACC	
Assay	99.58	99.47	99.51	99.43	99.45	**90.0% to 110%**

Table 6: Assay data comparison for Gerpyrin drug product

Test	Results at different data station					Specification
	0 Month	3 Months		6 Months		
		CRT	ACC	CRT	ACC	
Assay	99.40	99.32	99.35	99.27	99.29	**90.0% to 110%**

Table 7: Assay data comparison for Paracip drug product

Test	Results at different data station					Specification
	0 Month	3 Months		6 Months		
		CRT	ACC	CRT	ACC	
Assay	99.79	99.75	99.76	99.62	99.60	**90.0% to 110%**

Formula for the Calculation of Assay

$$\textbf{\%Assay} = \frac{\text{Area of Impurity} * \text{Conc.of reference solution} * 100}{\text{Area of Paracetamol in Reference Solution} * \text{Conc.of sample solution}}$$

3.5.1 Chromatograms of Initial Sample analysis:

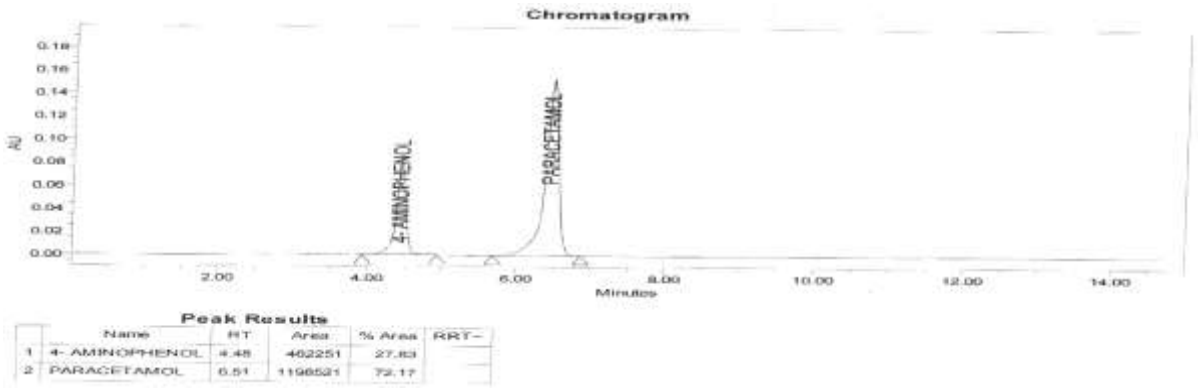


Figure 22: Reference Solution Chromatogram

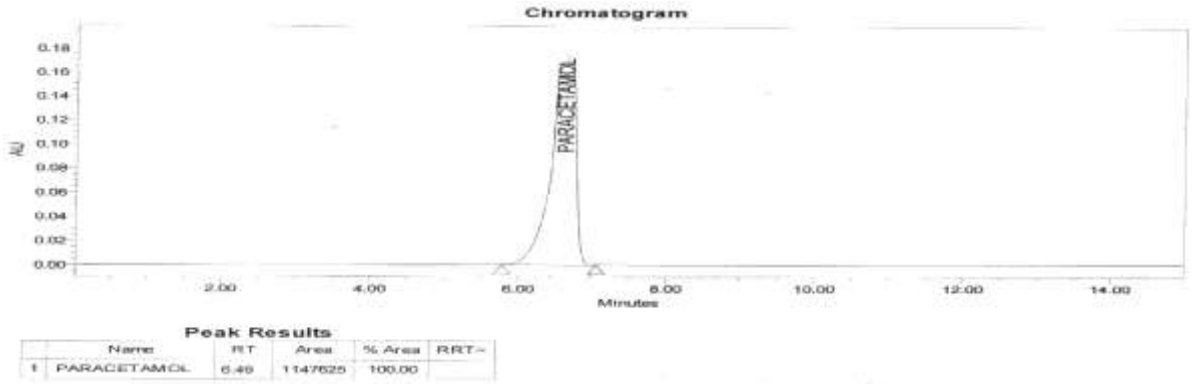


Figure 23: Chromatogram of Lanol drug product

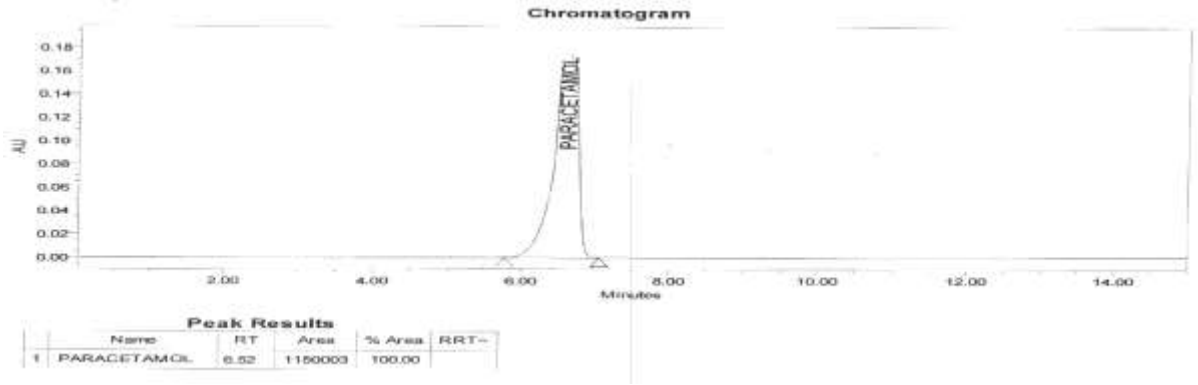


Figure 24: Chromatogram of Paracip drug product

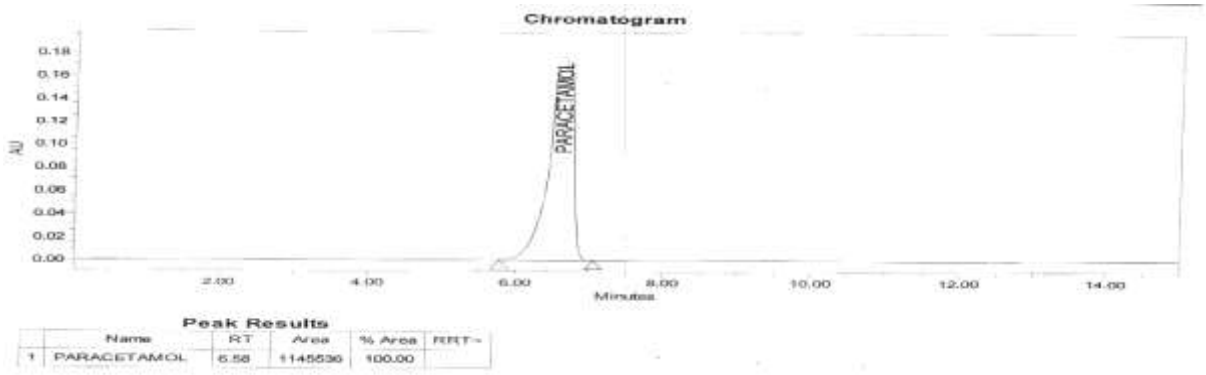


Figure 25: Chromatogram of Gerpyrin drug product

3.5.2 Chromatograms of 3M Accelerated condition Sample analysis:

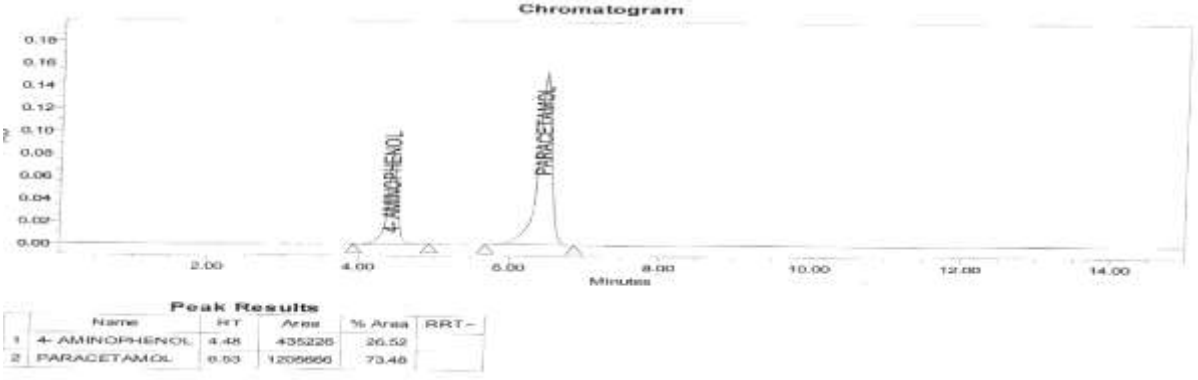


Figure 26: Reference Solution Chromatogram

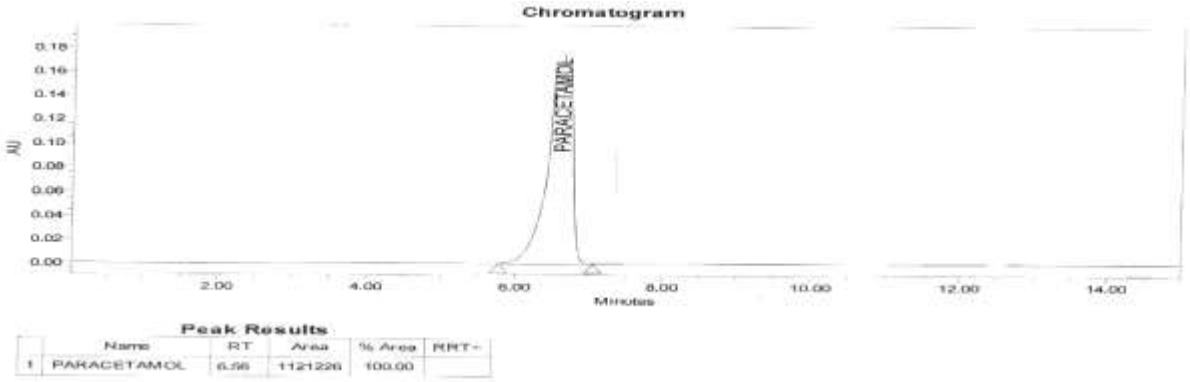


Figure 27: Chromatogram of Lanol drug product

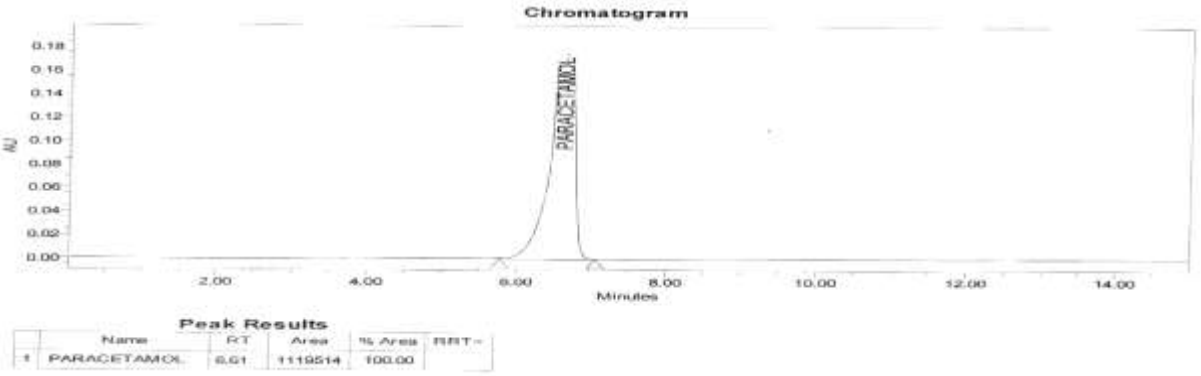


Figure 28: Chromatogram of Gerpyrin drug product

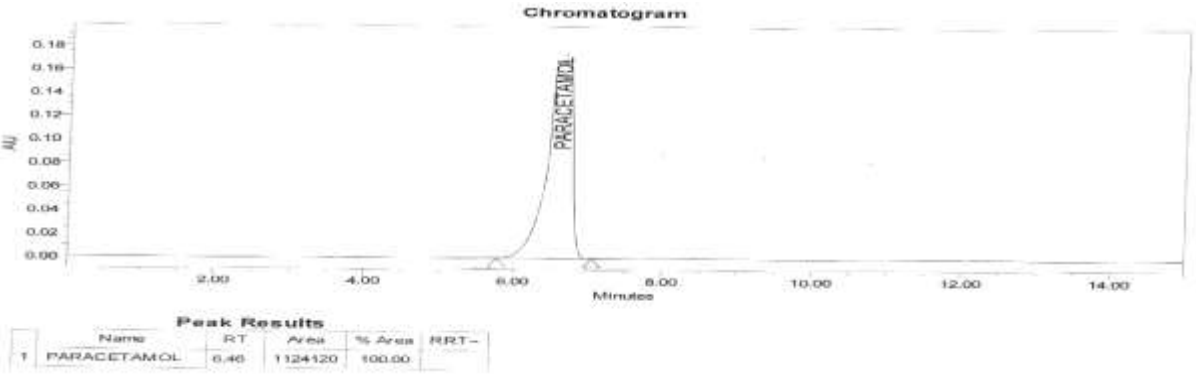


Figure 29: Chromatogram of Paracip drug product

3.5.3 Chromatograms of 3M Long term condition Sample analysis:

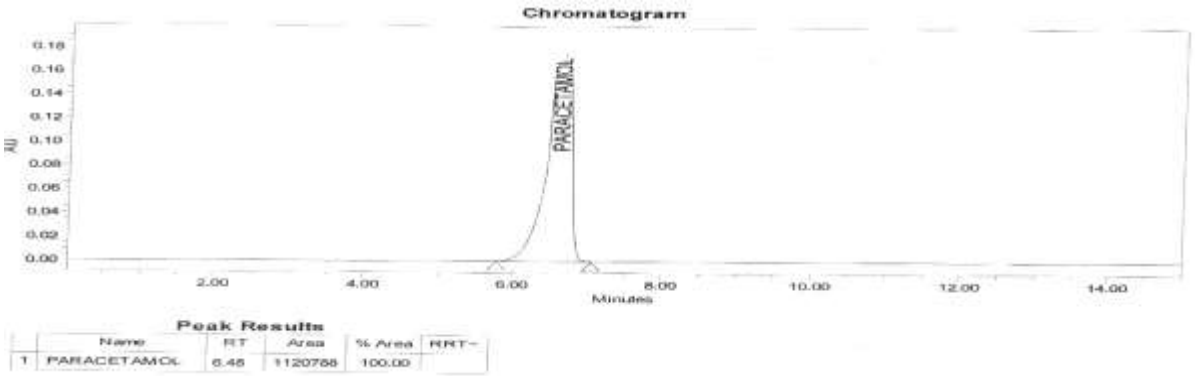


Figure 30: Chromatogram of Lanol drug product

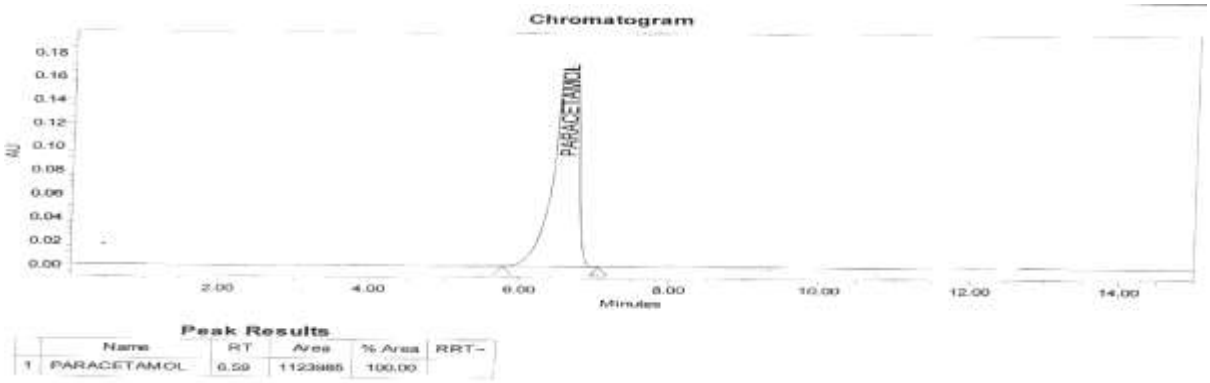


Figure 31: Chromatogram of Paracip drug product

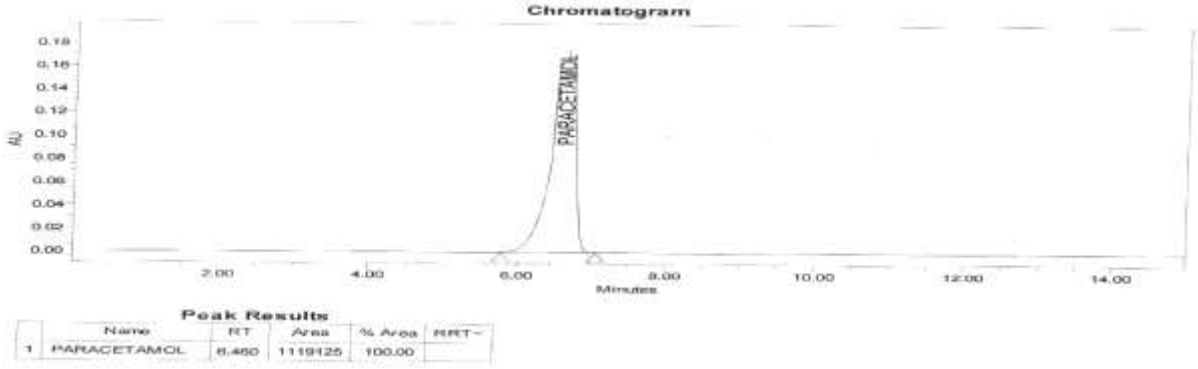


Figure 32: Chromatogram of Gerpyrin drug product

3.5.4 Chromatograms of 6M Accelerated condition Sample analysis:

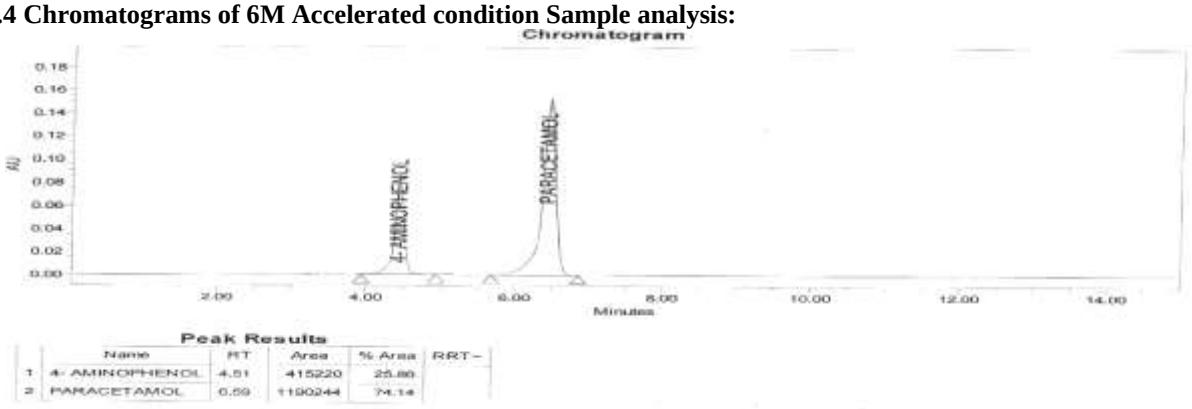


Figure 33: Reference Solution Chromatogram

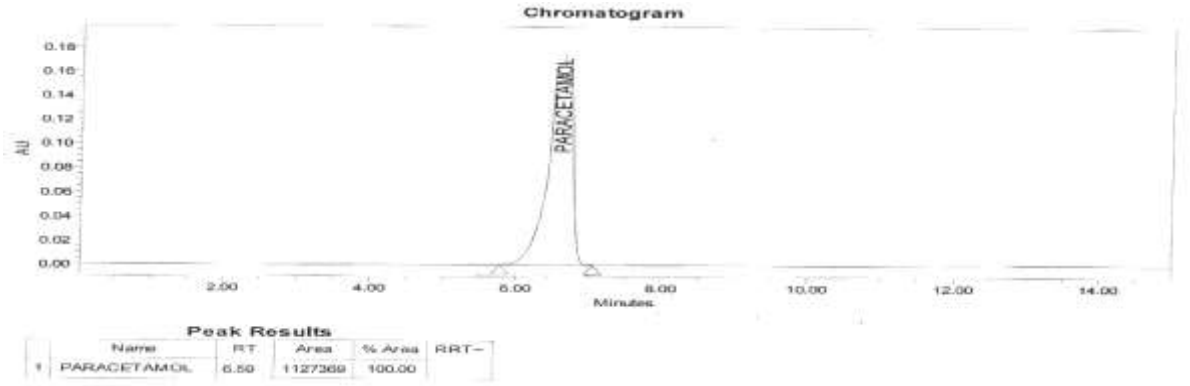


Figure 34: Chromatogram of Lanol drug product

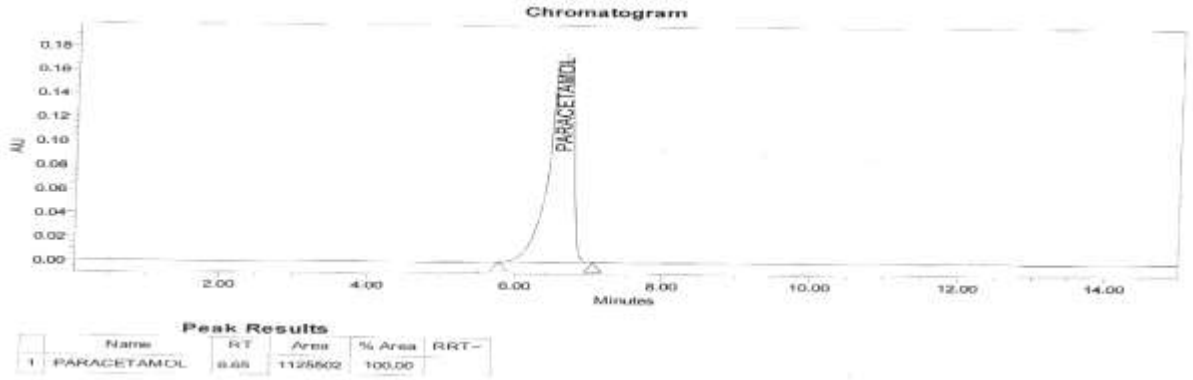


Figure 35: Chromatogram of Gerpyrin drug product

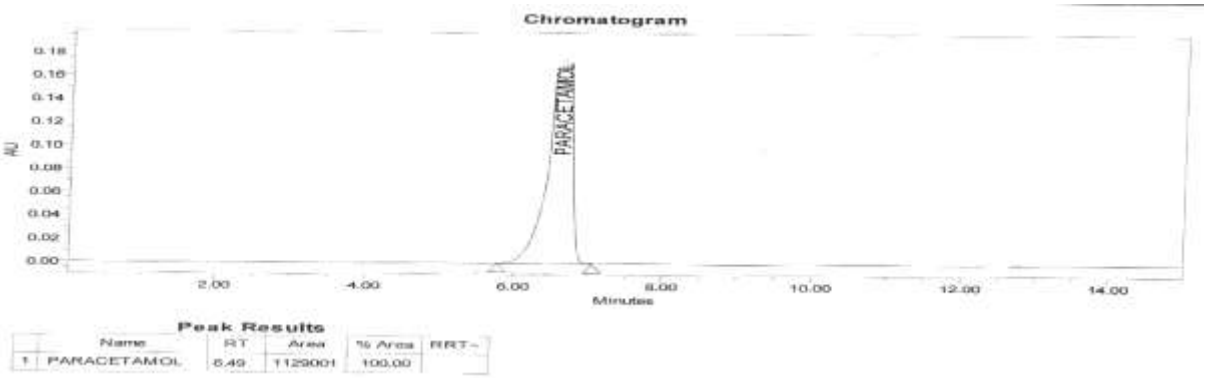


Figure 36: Chromatogram of Paracip drug product

3.5.5 Chromatograms of 6M Long term condition Sample analysis:

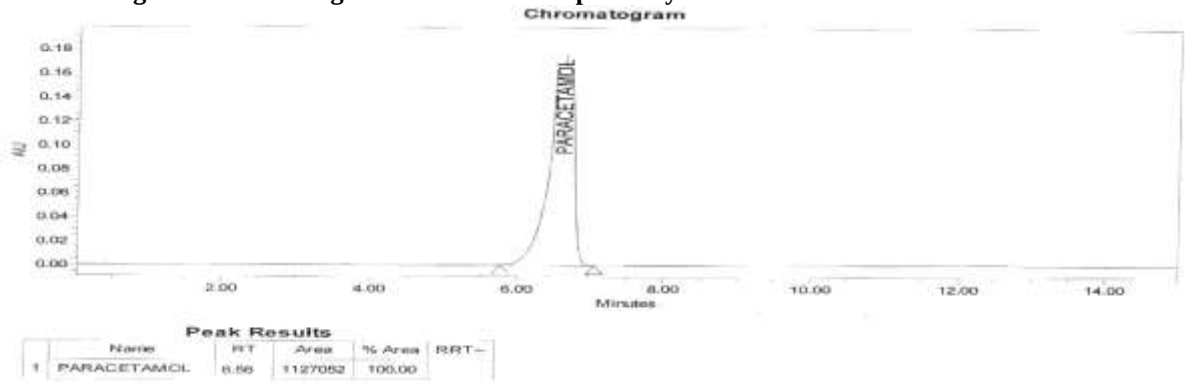


Figure 37: Chromatogram of Lanol drug product

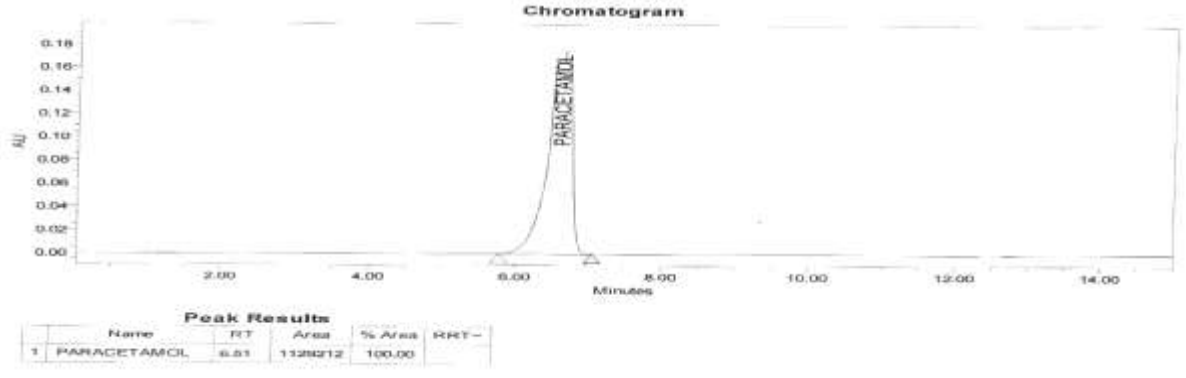


Figure 38: Chromatogram of Paracip drug product

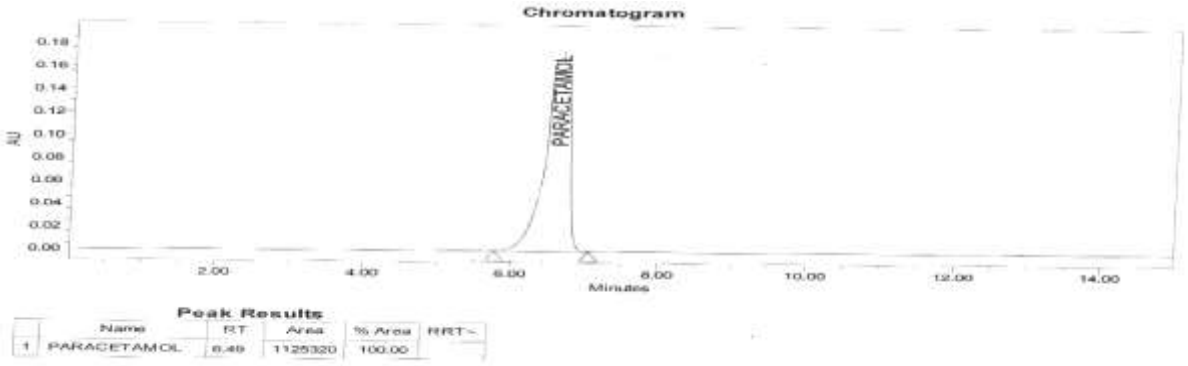


Figure 39: Chromatogram of Gerpyrin drug product

3.6 Results:

After being stored for six months under various stability conditions, three different manufacturers of pharmaceutical drug products with 10 mg/mL strength underwent qualitative and quantitative analysis and with the following findings:

1. Description: All samples were clear and colourless liquid when taken in glass container,
2. Quantitative Identification: Assay by HPLC shows data which were within the specification.
3. Qualitative Identification: Related Substances by HPLC performed and data for Unknown Impurities and Total Impurities were within the specification.

3.7 Discussion:

This Study was conducted to corelate data for the Branded (Innovator) manufacturer to the generic drug product manufacturer of the same therapeutic molecule and chemical strength of Paracetamol. [9] Analysed drug products were also compared with the final price to purchaser (MRP). In India, medicine prices are set in one of the two ways. Medicine prices are under the purview of Department of Pharmaceuticals which itself is under ministry of chemicals and fertilizers. The Drug Price Control Order (DPCO) identifies active pharmaceutical ingredients (APIs) for which a pricing formula is used to set the MRP. There are only 74 bulk drugs which are under price control and are called scheduled medicines. [10] For all other medicines called "non-scheduled medicines". The manufacturer sets the price and registers that price with the National Pharmaceutical Pricing Authority (NPPA) under Department of Pharmaceuticals. [1111] The medicines are sold at the printed MRP on their label and dispensing pharmacist cannot charge a price exceeding MRP printed on the pack, as per the provisions under paragraph 16 of the DPCO, 1995. [10,11] For scheduled medicines, the NPPA pricing formula sets the 8% mark-up for wholesalers and 16% for retailers.[11] For non-scheduled medicines, these markups are not set, but it is agreed by the partners of the trade that for branded medicines average mark-up would be around 10% and 20% for wholesalers and retailers, respectively.[11] Generic drug products were 30-35 % cheaper as compare to branded (Innovator) drug products. A systematic review of all products by analysing qualitatively and quantitatively shows similar data in outcome of the results. This study will be helpful in promoting the use of generic medicined as compare to branded (Innovator) medicines. In many countries generic medicine are promoted to purchase as it is low cost and provide similar effect to the patients.[12] Moreover, physicians' acceptance and willingness to prescribe generic drugs, as well as patient acceptance and compliance with generic drug use, play a vital role in promoting generic substitution. [13] Results of this study will also create impact on many countries and customers health budget. The rationale and significance of the generic medications policy is in its ability to stimulate competition, encourage innovation, and lower healthcare expenses. [14,15]

3.8 Conclusion:

The results of this study show that the three medicines of branded and branded-generic versions were of the same quality and met all requirements as per specifications. Therefore, general notion and doubt regarding the quality of the generic drug products need to be minimise by conducting this type of studies published them widely. Government should also interfere and generate more policies for controlling price of the drug products. Promotion and general awareness programmes must be initiate by the government for the consumption of generic drug products. Manufacturers can also exchange manufacturing technologies and manufacturing process to control prices of medicines and to serve nation by reducing health budget of country.

3.9 Ethical approval:

We hereby declare that this work is original and not copied from anywhere else. We approve that this work is not submitted in this language or any other language to any other journal nor it is submitted for simultaneous consideration.

3.10 Funding:

All expenses were done by research scholar. No fund was taken either from Institute or Industries.

3.11 Author contribution:

The research was written through contribution of all authors. Dr. Rohit H. Dave provided idea and revised this paper. Kushal P. Shah and Arvindsinh B. Sisodiya

contributed in literature review, analysis of data, structuring of manuscript, paraphrasing and removing plagiarism. All authors have given approval to the final version of the manuscript.

3.12 Declaration of competing interest:

The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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