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Assessment of in-Home and in-Use Stability of Paracetamol Pediatric Oral Suspension through Simulate room temperature Storage Conditions

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ABSTRACT

This study examines the stability of paracetamol pediatric oral suspension (120mg/5ml) in simulated in-home storage conditions, temperature ranging from (30^0±5C/65±5RH) representing room condition. Samples from suspension were assayed for active pharmaceutical ingredient and tested for related substance (degradants) using B.P 2012 pharmacopeia HPLC method. The study was carried out in day zero, seven, fourteen, thirty and forty five. The instrument utilize column ® C8, 100 x 4.6 mm, 3.5 µm particle size. The flow rate was 1.5 ml/minute. The mobile phase consisted of methanol, tetrabutylammonium hydroxide and sodium orthophosphate buffer. The results obtained showed that the drug assay content was out of the limits from day zero Furthermore, the half live was found to be 35.06 days

Keyword: Paracetamol, 4-amino phenol, degradation, HPLC.

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INTRODUCTION

Stability studies are used to determine the quality of drug substances and drug product, shelf life for drug product and the optimal storage conditions.

In-use stability testing establishes where applicable the period of time during which a multi dose product can be used whilst retaining acceptable quality once the container is opened and the first dose is removed.

Suspensions may be defined as preparations containing finely divided drug particles (the *suspensoid*) distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility[1]

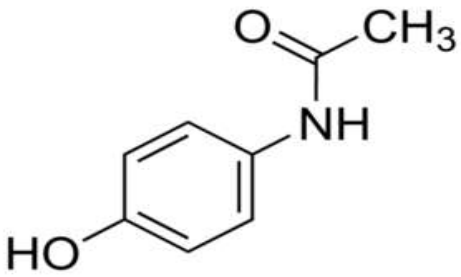

Figure 1: Paracetamol chemical structure

Paracetamol or acetaminophen is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer). It is commonly used for the relief of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies. In combination with opioid analgesics, Paracetamol can also be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients[2]

The chemical name for the compound is *para*-acetylaminophenol and *para*-acetylaminophenol. In some contexts, it is simply abbreviated as APAP, for acetyl-para-aminophenol

Systematic (IUPAC) name is *N*-(4-hydroxyphenyl)acetamide[3] [3] Paracetamol is synthesis by acetylation of 4-aminophenol [4]. 4-aminophenol is the main impurity present in preparation and synthesis of paracetamol or during storage of the drug[5].

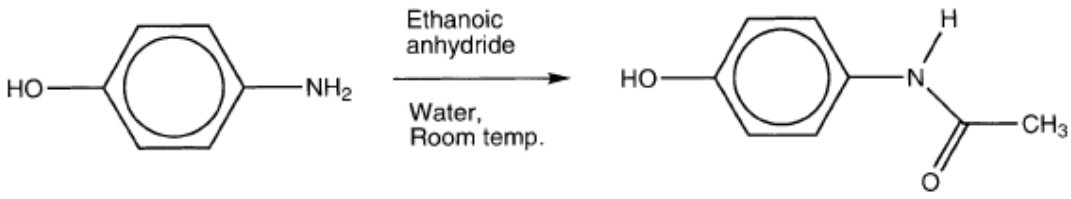

Figure 2: Paracetamol synthesis.

Paracetamol is an inhibitor of the synthesis of prostaglandins (PGs) by selectively inhibited cyclooxygenase -3 (COX-3), one of the PCOX-1 proteins (PCOX-1a) which is made from the COX-1 gene but retain intron in their mRNAs [6]

R.K. Gilpin and W. Zhou Studied the thermal degradation of acetaminophen using a conventional HPLC approach and electro spray ionization-mass spectrometry (ESI), paracetamol was stressed at temperatures between 160°Cand 190°C and the rate of decomposition was measured and the activation energy were determined. They found that the process occurs at much lower apparent activation energy. A comparison of the data shown that acetaminophen is significantly more stable in the dry state than in solution. [7]

Another study by Abd Al-Rahman Mahmoud Gamil was done in. The study aimed at comparing various conditions in Sudan with the internationally adopted conditions to investigate the optimal transportation and storage conditions. He tested the products initially, after transportation, after six months and lastly after 12 months by used of validated pharmacopoeial methods, Data loggers were measured and recorded temperature and humidity every 90 minutes during transportation and storage. , he reported that almost all utilized products showed significant alternation in the concentrations of the active ingredient. [8]

Dhia Elhag , Laila Fathi investigated the stability of paracetamol pediatric oral suspension in simulated in-home storage conditions at temperature ranging from (2-8^{0}C) Samples from suspension were assayed and tested for related substance (degradants) using B.P pharmacopeia HPLC method, they found that the drug assay content remains within the limits up to fourteen days. Furthermore, the half live was found to be 36.8 days [9]

Other numerous volume of literature had been devoted to the investigation of paracetamol formulation, its stability and identification of its degradations. [10-13]

MATERIALS AND METHOD

Paracetamol reference standard (99.5% purity), Yuxixing Company, China. (Expiration date 2017). Local brand of paracetamol suspensions (120mg/5ml) purchased from a reputable and registered pharmacy, aminophenol standard (98% purity). Methanol HPLC grade, (Chem-lab NV Company). Disodium dihydrogen orthophosphate.Sodium dihydrogen orthophosphate, (Tecno PharmChem Company). Tetrabutylammonium hydroxide, **(**Sigma-Aldrich Company**)** and cellulose filter paper**,** 0.45µm pore size, Ianjin Jinteng experiment equipment Co, China.

Instruments

HPLC Aligent's Shimadzu column ® C8, 100 x 4.6 mm, 3.5 µm particle size, UV detector LC 10AT VP shimadzue, Japan. sonicator SB2200, Shanghai Branson. China, electronic balance; JA 1003: Shanping, China. Data analysis was done by using the Lab Solutions analysis data system. In all the measurements, the injection volume was 50 µl.

Procedure

Samples were stored in a stability chamber with fluctuating temperatures between (30^0±5C/65±5RH) after reconstitution by using tap water and the measurements were performed on day zero, seven, fourteen, thirty and forty five.

Mobile phase preparation

250 volumes of methanol containing 1.15g of 40%w/v solution of tetrabutylammonium hydroxide.375 volumes of 0.05M disodium hydrogen orthophosphate and 375 volumes of 0.05M dihydrogen orthophosphate were mixed, filtered and degassed for 15 minutes.

Sample and standard preparation and procedure for assay tests

For standard preparation 0.012 g of paracetamol standard was accurately weighed and dissolved in 100 ml of mobile phase. For sample preparation, a quantity of paracetamol sample contained 24 mg (equal to 1ml of paracetamol 120 mg/5ml suspension) were accurately measured and dissolved in 100ml of mobile phase then diluted to 200 ml with mobile phase and filtered after sonication. A volume of 50 µl of solution was injected into HPLC system. Standard and sample solutions were immediately prepared before being used and were protected from light.

Sample and standard Preparation and procedure for related substances test

For standard preparation 0.00012 g of each paracetamol and 4-aminophenol were accurately weighed and dissolved in 100 ml of mobile phase to produce solution contained both substances as standard. For sample preparation 5ml of paracetamol suspension (120 mg/ 5ml) was dissolved in 100 ml mobile phase to produce 0.012%w/v solution and was filtered after sonication.

RESULTS AND DISCUSSION

Day zero chemical stability result

Figure 2: Paracetamol standard solution, day zero (duplicate analysis)

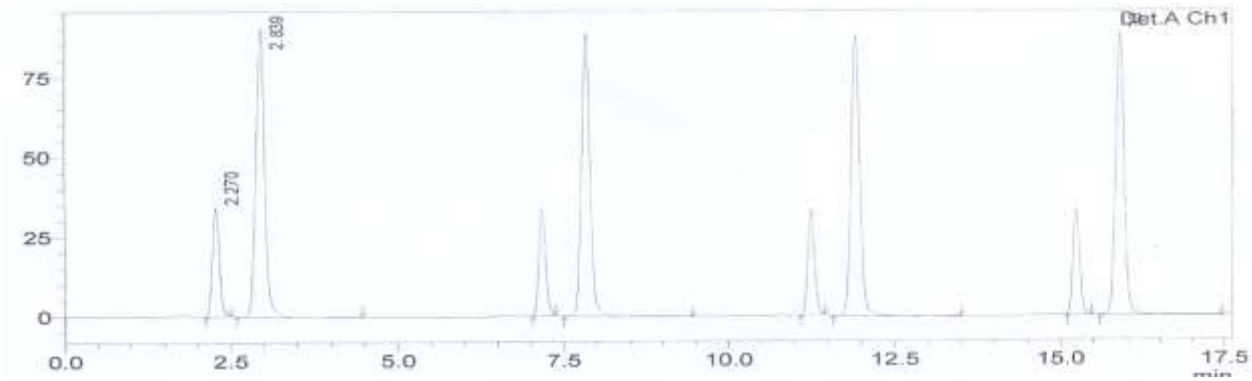

Figure 3: Related substances standard solution chromatogram, day zero (replicate analysis)

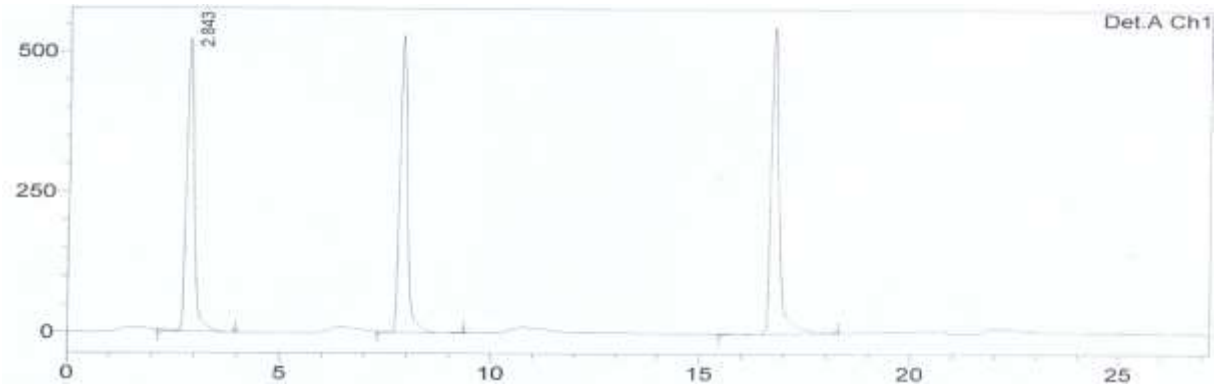

Figure 4: day zero assay chromatogram

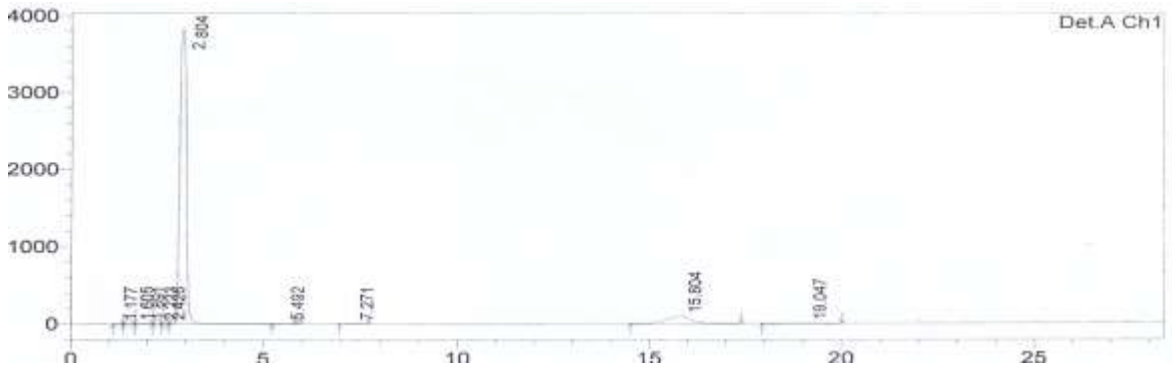

Figure 5: day zero related substances chromatogram

Day seven chemical stability result

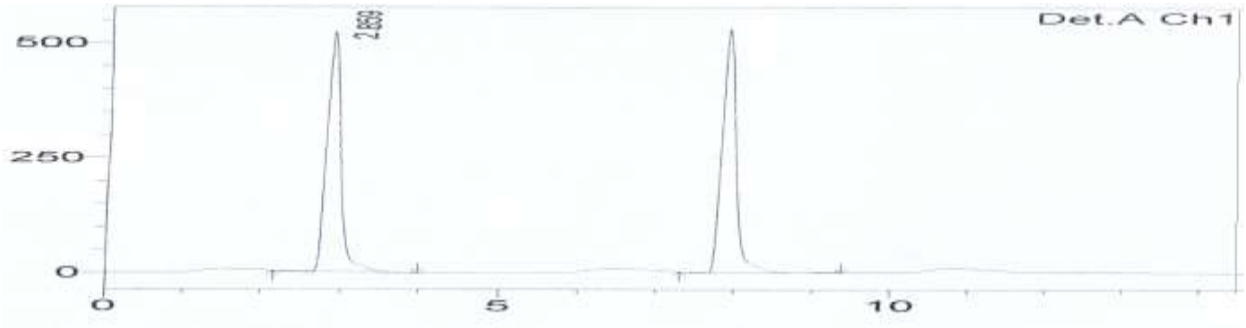

Figure 6: day seven standard solution assay chromatogram

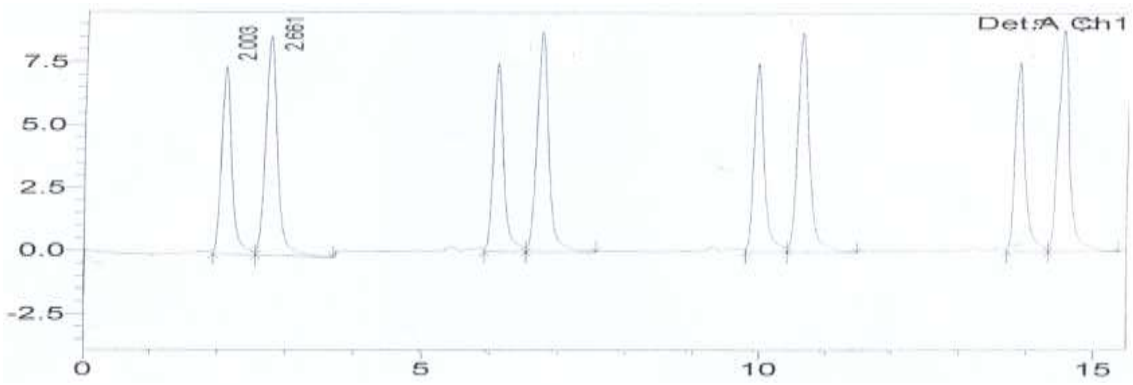

Figure 7: day seven related substances Standard chromatogram

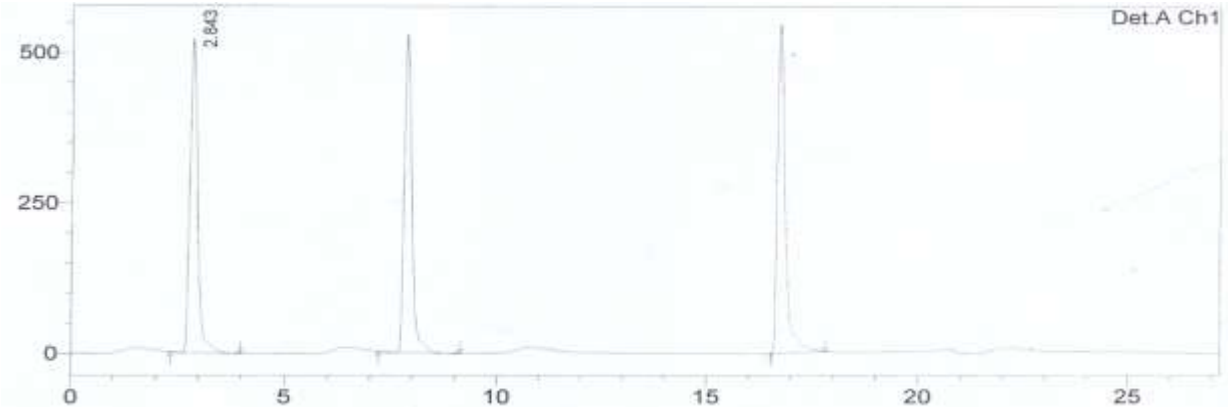

Figure 8: day seven assay solution chromatogram

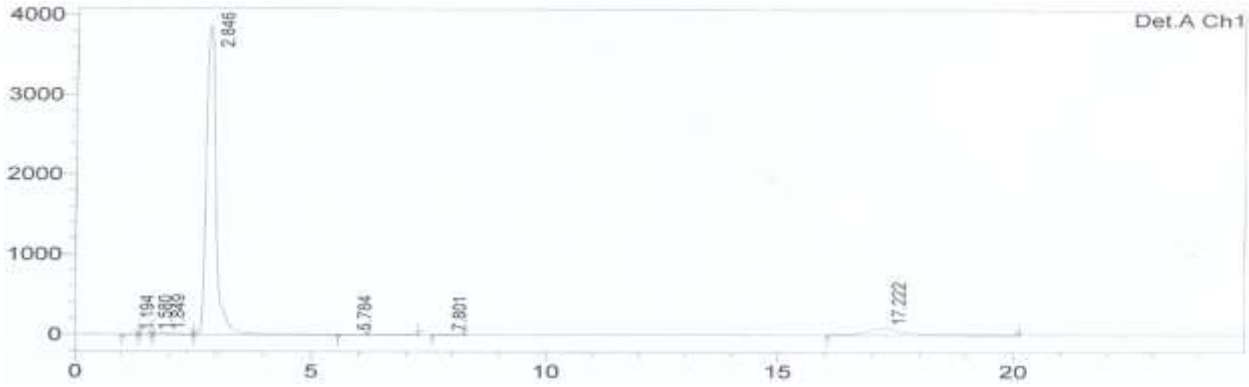

Figure 9: day seven related substances chromatogram

Day fourteen chemical stability result

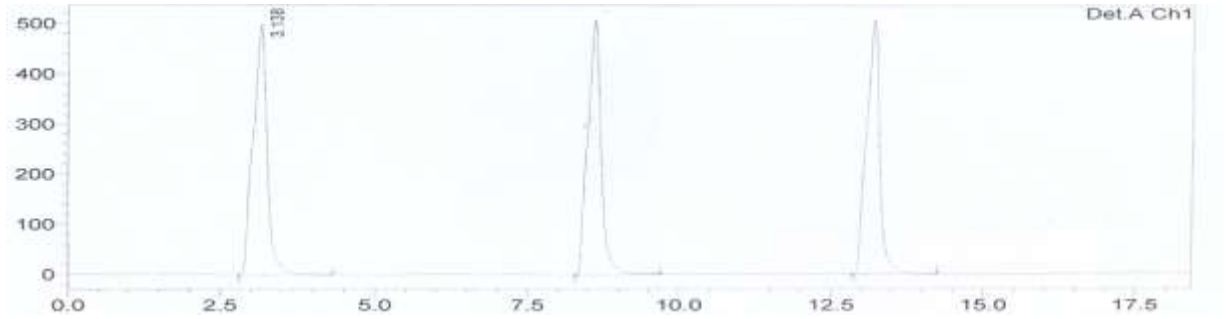

Figure 10: Day fourteen standard solution assay chromatogram

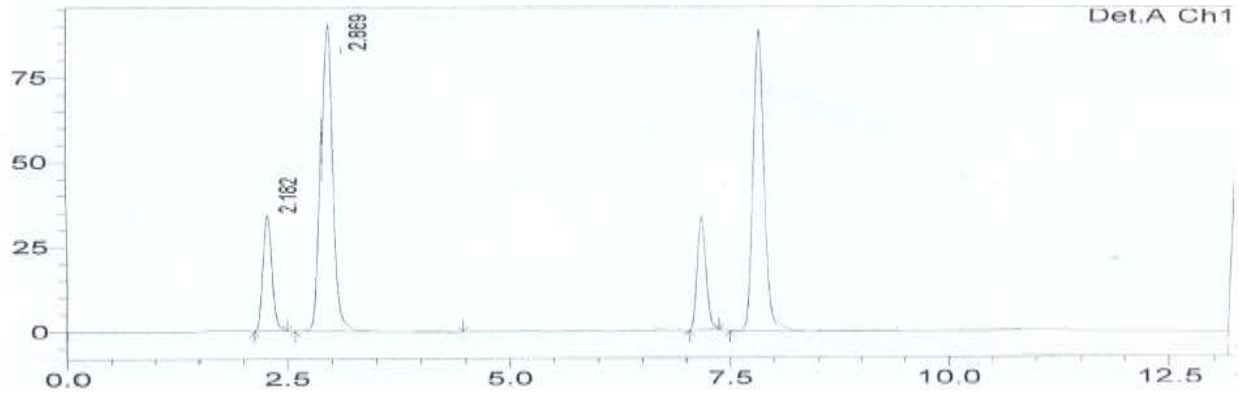

Figure 11: Day fourteen related substances Standard chromatogram

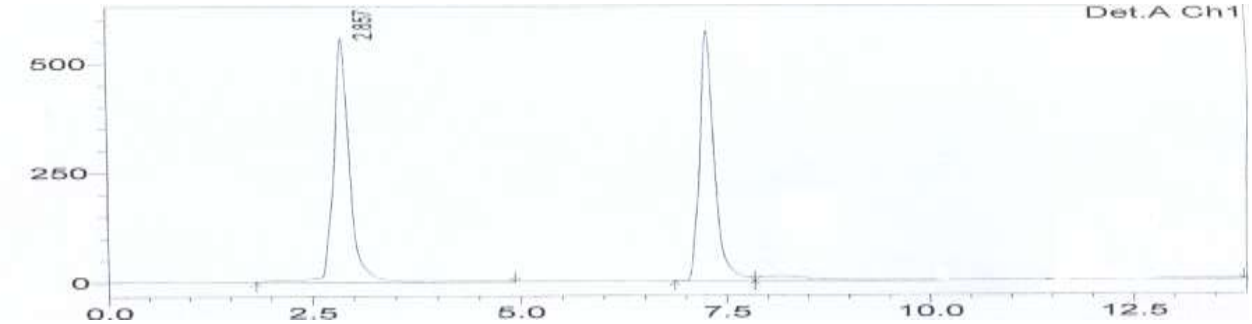

Figure 12: Day fourteen assay chromatogram (duplicate analysis)

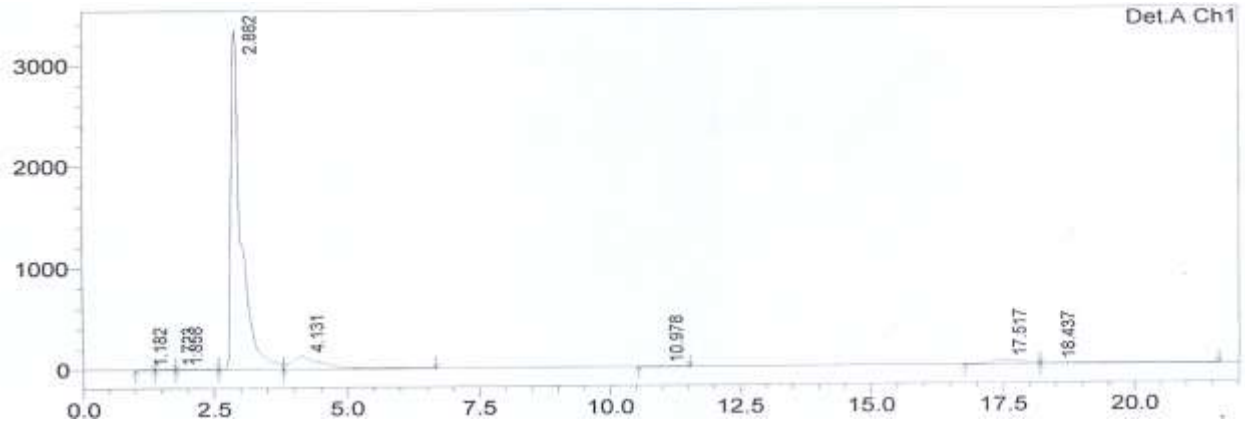

Figure 13: Day fourteen related substances chromatogram

Day thirty chemical stability results

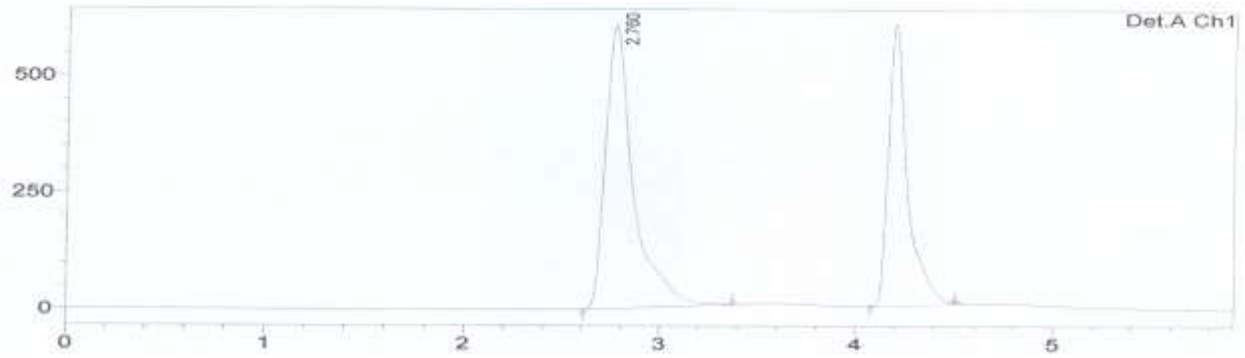

Figure 14: Day thirty standard solution assay chromatogram

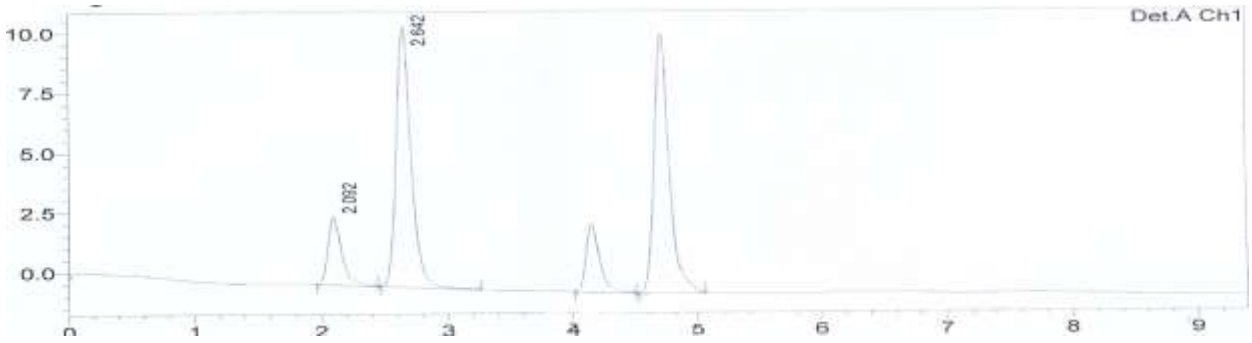

Figure 15: Day thirty related substances Standard chromatogram

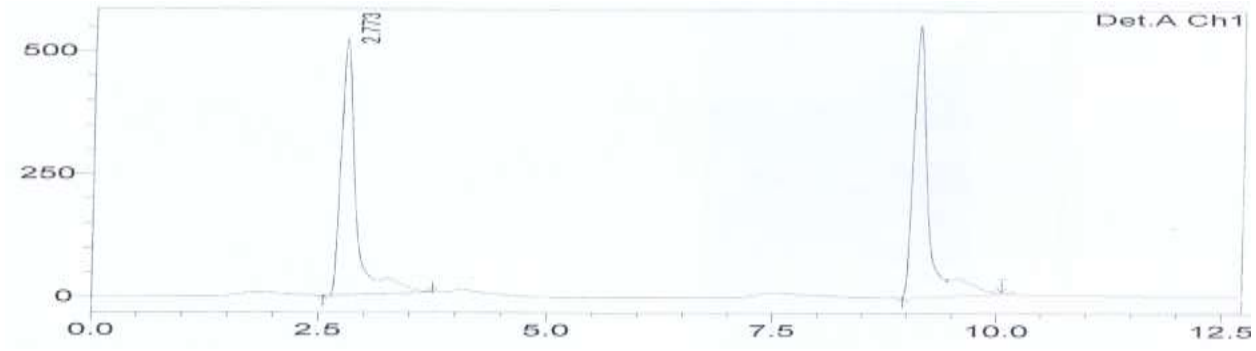

Figure 16: Day thirty assay chromatogram (duplicate analysis)

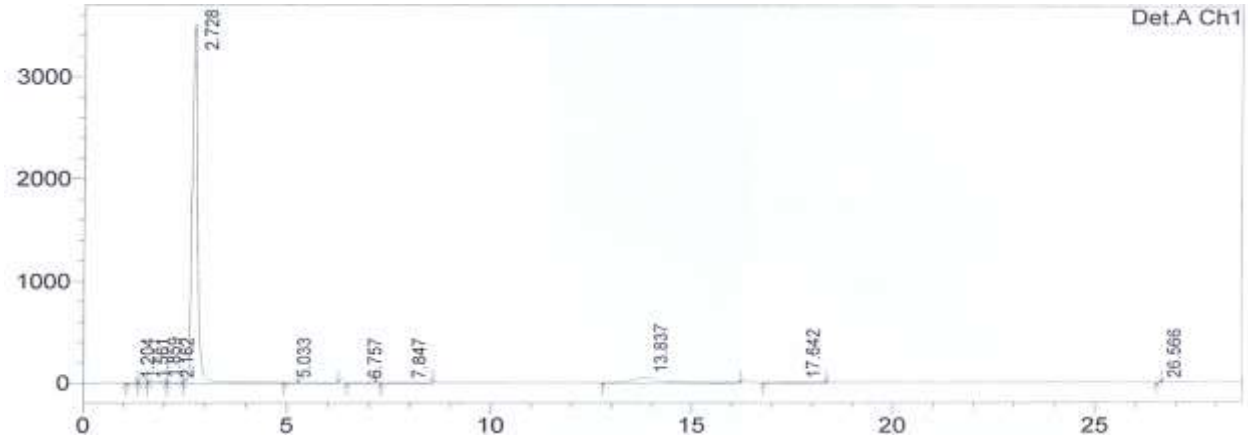

Figure 17: Day thirty related substances chromatogram

Day forty five chemical stability results

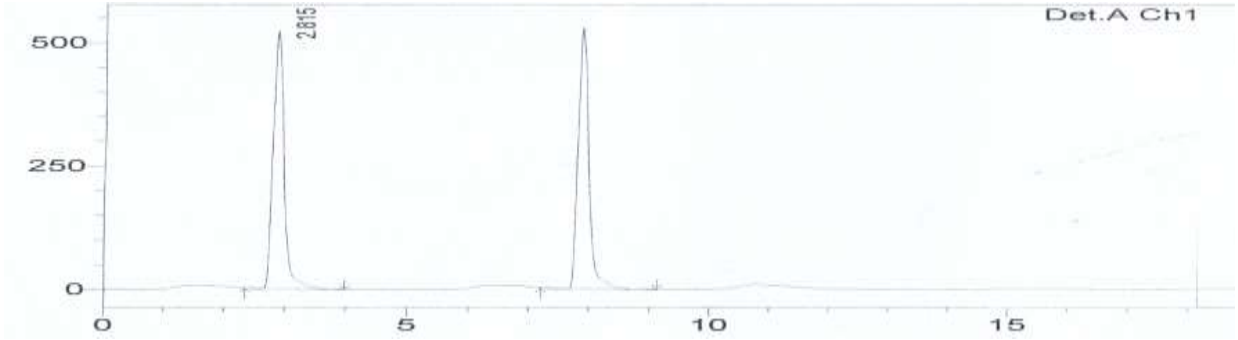

Figure18: Day forty five standard solution assay chromatogram (duplicate analysis)

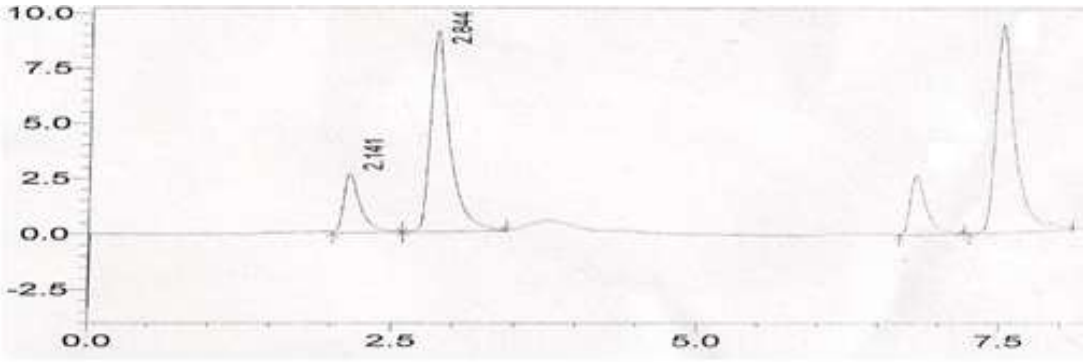

Figure 19: Day forty five related substances Standard chromatogram

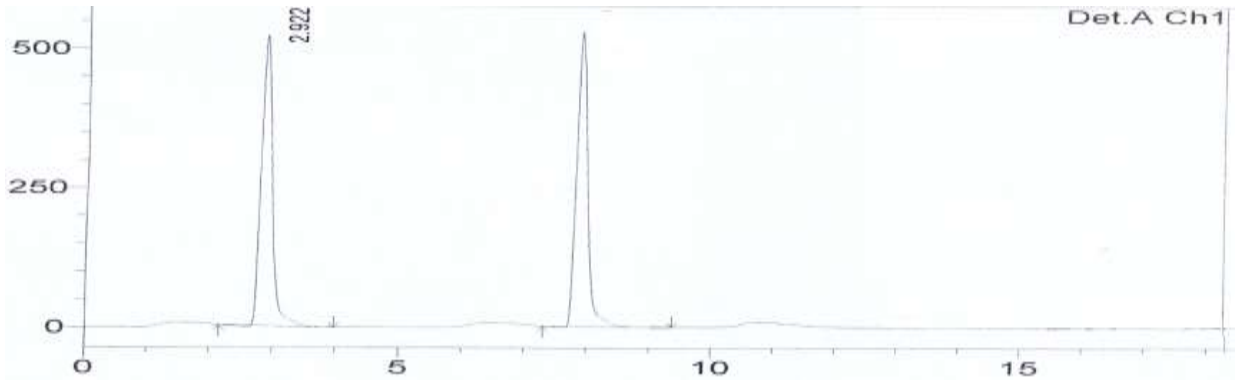

Figure 20: Day forty five assay chromatogram (duplicate analysis)

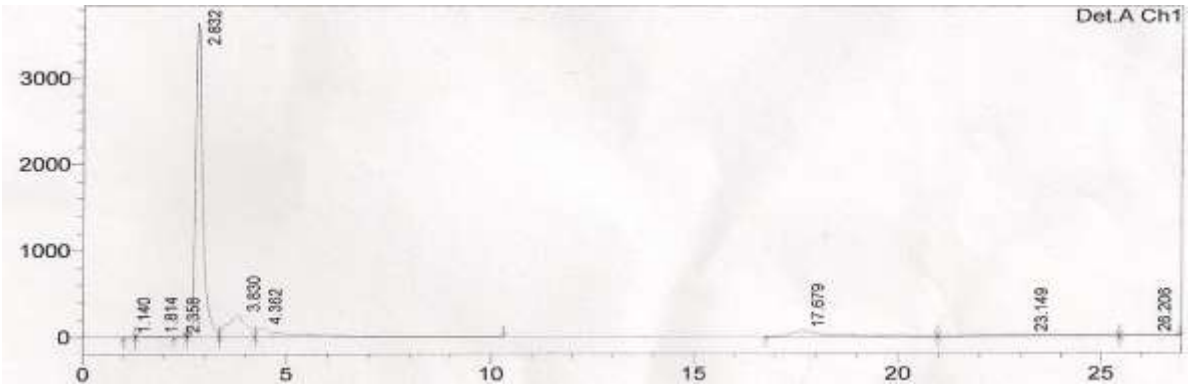

Figure 21: Day forty five related substances chromatogram

DISCUSSION

Day zero standard solutions

The duplicate analysis for assay test of paracetamol standard solution at day zero showed symmetrical peaks and no baseline sloping.

Related substances standard solution chromatogram (replicate analysis)

Standard related substances solution showed two peaks (replicate chromatograms were presented in one Figure) one correspond to paracetamol with retention time 2.843 minutes and the second peak correspond to 4-aminophenol with retention time 2.27 minutes. The resolution between

paracetamol and 4-aminophenol peaks was good. The B.P monograph[14] states that any peak area corresponding to 4-aminophenol in sample solution must not be greater than the peak area of 4-aminophenol in standard solution.

Day zero assay and related substances tests

*Sample assay chromatogram (*Triplicate analysis)

Assay test result at day zero was 94.5%. The B.P monograph states that the content% of paracetamol pediatric suspension (120 mg/5 ml) limits are 95%-105% and hence does not comply with the BP limit. This is may be due to the transporting condition or to the storage conditions of the bottle at the pharmacy from where the bottles were purchased, or due to manufacturing or sampling error.

Related substances solution chromatogram

The B. P 2012 monograph of paracetamol pediatric suspension (120 mg/5 ml) states that any peak area corresponding to 4-aminophenol in sample solution must not be greater than the peak area of 4-aminophenol in standard solution.

Following the same argument and for convenience, the test results from day zero to day forty five are summarized in Table 1.

Table 1: Results of the chemical stability testing of paracetamol paediatric oral suspension (120mg/5ml) at simulate room temperature.

Day	Retention time		Assay test result	Related Substances Test
	Paracetamol	4-aminophenol		
Zero (0)	2.839	2.270	94.5%	Pass
Seven(7)	2.661	2.003	93.6%	Pass
Fourteen (14)	2.869	2.182	90.1%	Pass
Thirty (30)	2.642	2.092	86%	Pass
Forty five(45)	2.844	2.141	81%	Pass

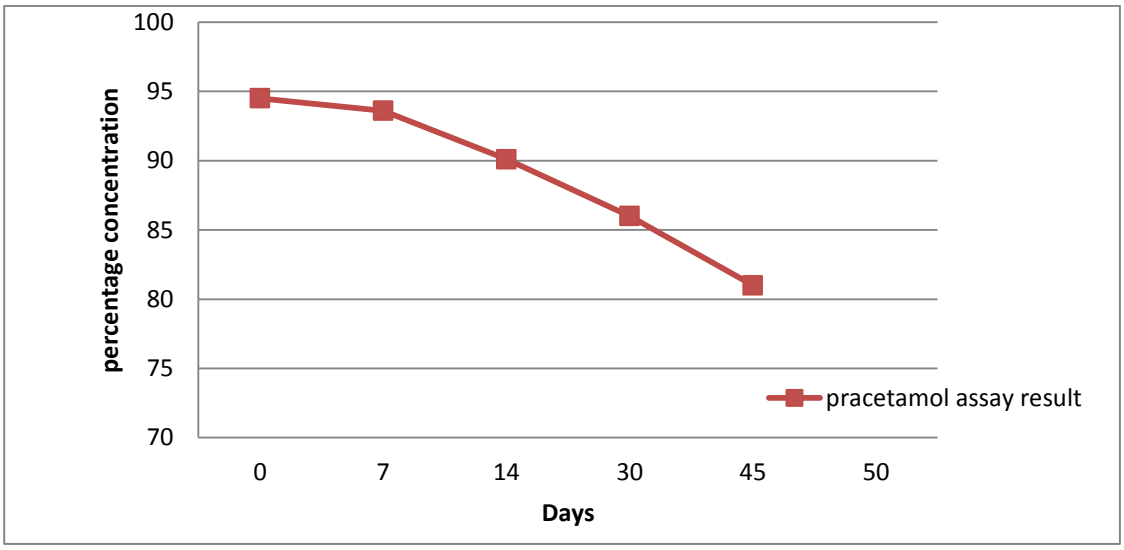

Figure 22: Degradation of paracetamol versus period of time

Kinetics study

Paracetamol concentration was measured over the period of the study and the reciprocal of concentration was measured Vs time. The produced curve is shown in Figure 23.

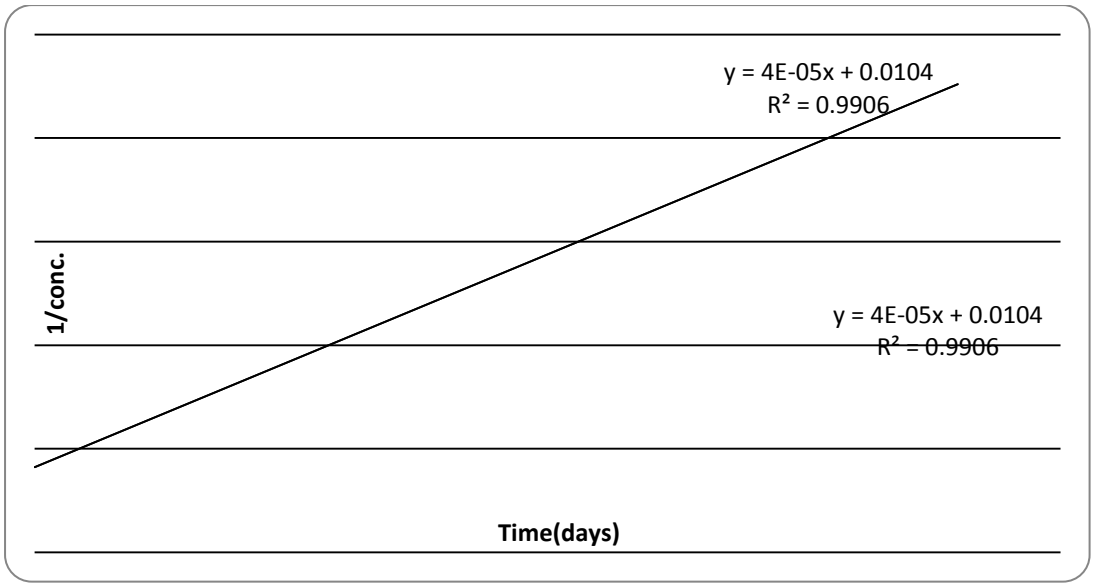

Figure 23: Paracetamol 1/conc. versus time plot

The plot above shows a straight line which indicates that paracetamol undergoes second order kinetics.

Also from the plot above and from straight line equation slope was found to be $4\times e^{-5}$ and from second order equations

K=slop

Where K=degradation rate

$K=4\times e^{-5}$ g/100ml /day.

$t_{(1/2)} = 1/kc_0$

Where C_O =initial concentration $t_{(1/2)}$ =half life

$t_{(1/2)} = 1/4 \times e^{-5} \times 0.945 = 35.06$ days.

When paracetamol suspension is stored at room temperature ranging from (30^0±5C/65±5RH), it shows a good stability. However, as the storage period is increased, degradations start to take place.

CONCLUSION

Paracetamol paediatric oral suspension (120 mg/5 ml) stability decreases with time. The content percent decreased according to the storage conditions such as humidity, temperature and the initial content concentration. Paracetamol undergoes second order reaction, and so initial concentration will have great effect in drug reactivity and its half life and shelf life. The presence of paracetamol degradant 4-aminophenol didn't exceed the B.P limit for the storage condition over the period of test.

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