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

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ABSTRACT

This study investigates the stability of paracetamol pediatric oral suspension (120mg/5ml) in simulated in-home storage conditions at temperature ranging from (2-8C^0) representing refrigerator condition. Samples from suspension were assayed and tested for related substance (degradants) using B.P pharmacopeia HPLC method. The study was performed in day zero, seven, fourteen, thirty and forty five. The instrument employs column ® C8, 100 x 4.6 mm, 3.5 µm particle size. The mobile phase consisted of methanol, tetrabutylammonium hydroxide (40 %) and sodium orthophosphate buffer. The results showed that the drug assay content remains within the limits up to day fourteen. Furthermore, the half live was found to be 36.8 days.

Keywords: Paracetamol, 4-amino phenol, degradation, HPLC

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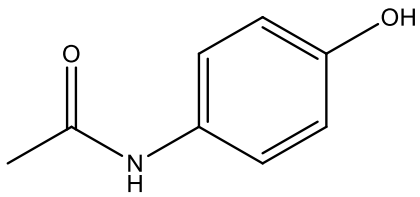
INTRODUCTION

Paracetamol or acetimenophen (N-acetyl-p-aminophenol) is a common over the counter (OTC) analgesic and antipyretic drug and for the relief of headaches and other minor aches and pains. It has also weak anti-inflammatory properties. International Union of Pure and Applied Chemistry (IUPAC) name of paracetamol is N-(4-hydroxyphenyl) ethanamide N-(4-hydroxyphenyl) acetamide. Paracetamol is a synthetic derivative of *p*-aminophenol[1].

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[2].



paracetamol

Figure 1: Paracetamol chemical structure

Pharmaceutical suspensions are uniform coarse dispersions of solid drug particles in a vehicle in which the drug has minimum solubility. Particle size of the drugs may vary from one formulation to another depending on the physicochemical characteristics of the drug and the rheological properties of the formulation.

Many bitter tasting and or/insoluble drugs are formulated as suspension e.g. antacid oral suspensions antibacterial oral suspension anthelmentic oral suspension to mask the taste or to enhance the stability or to achieve controlled or sustained release. Additional advantage of pharmaceutical suspensions is the fact that many patients, especially geriatric and pediatric patients have difficulty in swallowing whole tablets or capsules:

This study investigates the stability of paracetamol suspension (120mg/5ml) stored in a fridge at a temperature ranging from (2-8 C^0) for different periods and the effect of the storage condition on the drug content.

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),tetrabutyl ammonium 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 fridge with fluctuating temperatures between 2-8°C 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 tests

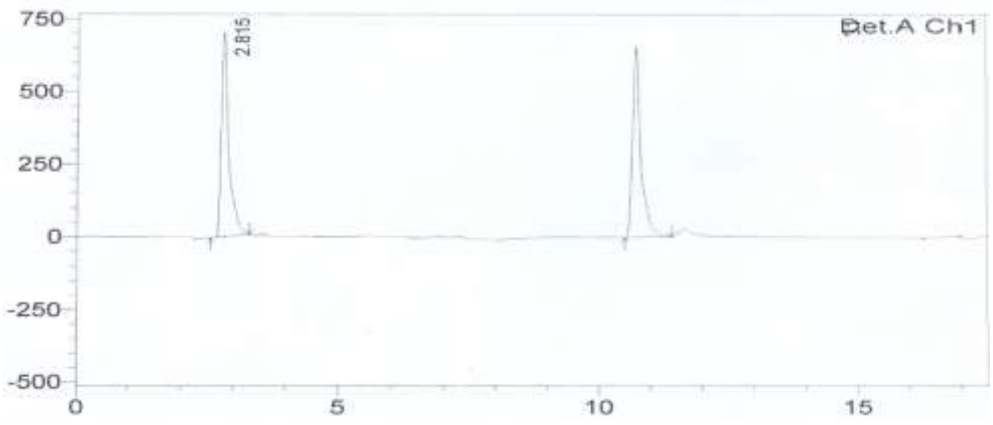


Figure 2: Paracetamol standard solution(duplicate analysis)

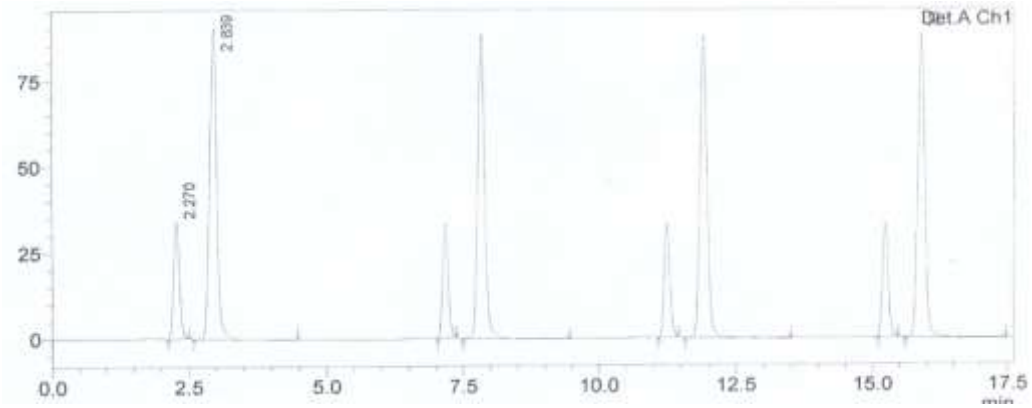


Figure 3: Related substances standard solution chromatogram (replicate analysis)

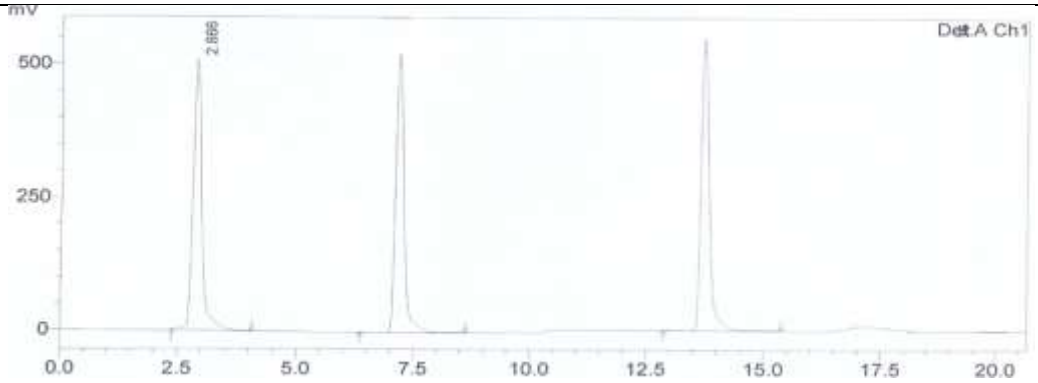


Figure 4: assay chromatogram (triplicate analysis)

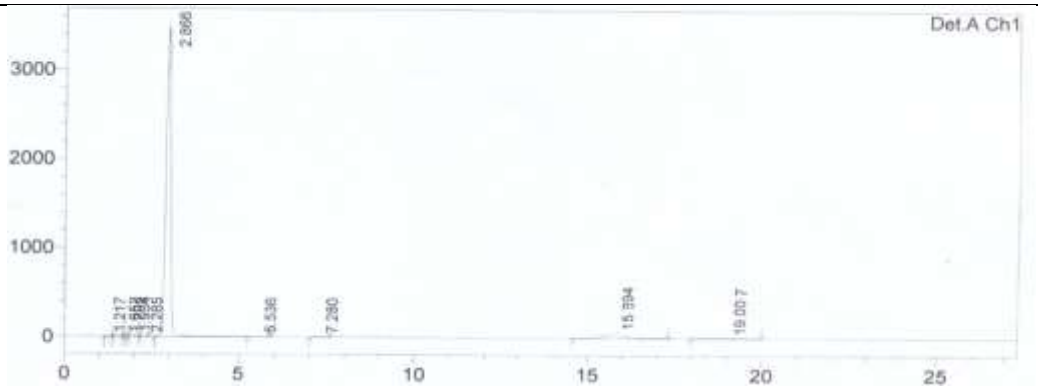


Figure 5: sample related substances chromatogram

Day seven Chemical Stability tests

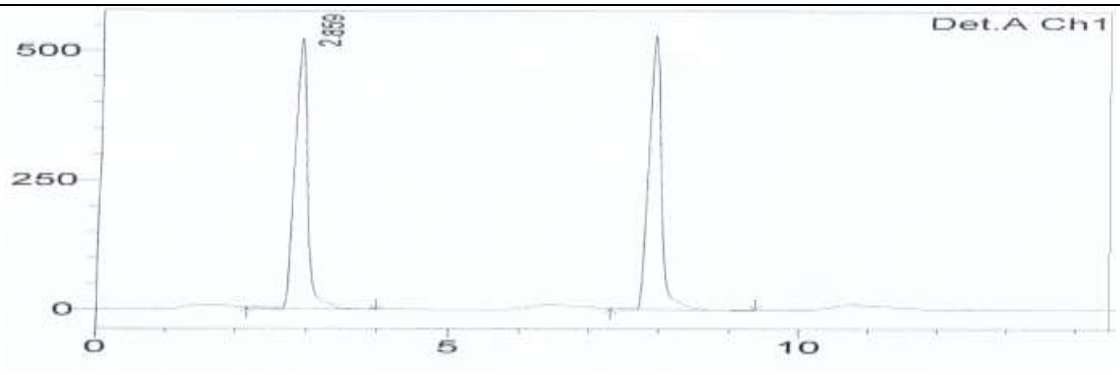


Figure 6: day seven standard solution assay chromatogram (duplicate analysis)

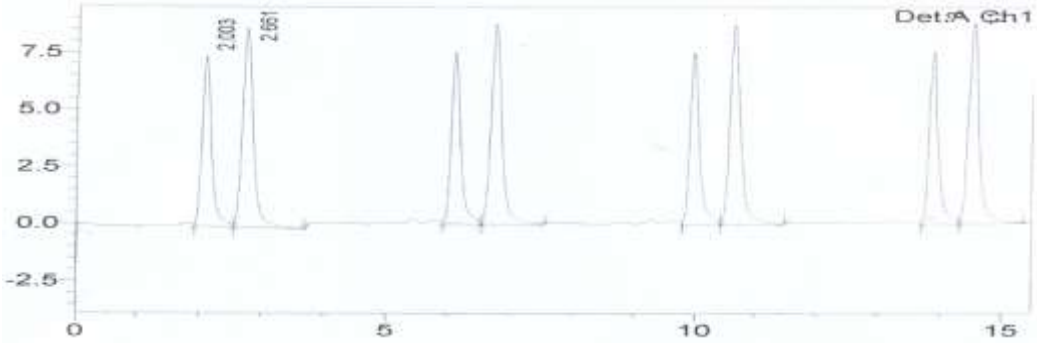


Figure 7: Related substances standard chromatogram (replicate analysis)

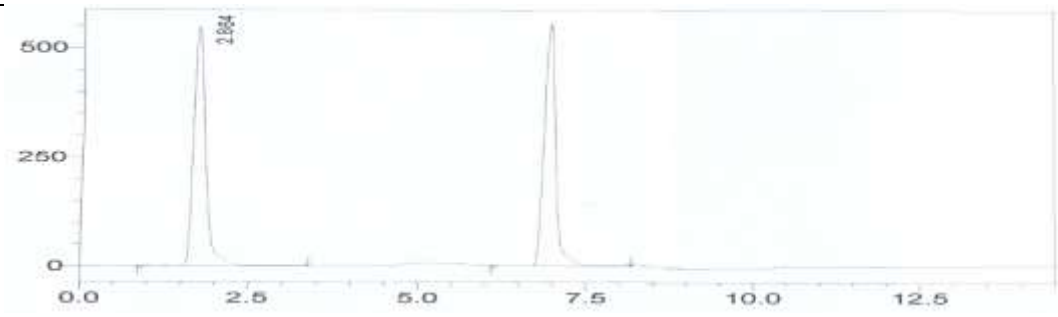


Figure 8: assay chromatogram(duplicate analysis)

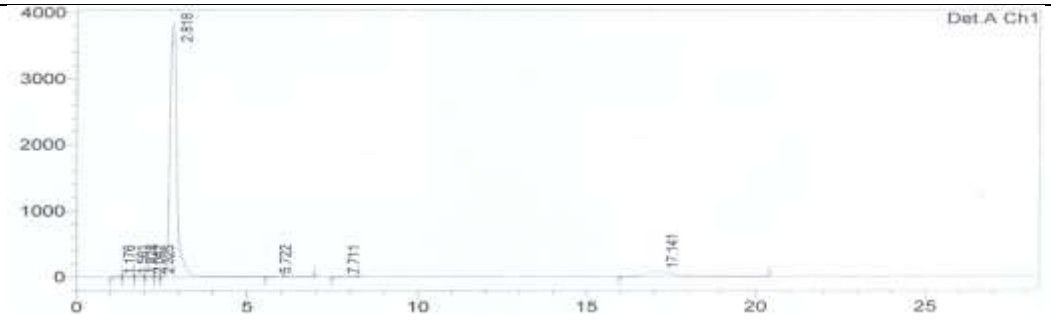


Figure 9: related substances chromatogram

Day fourteen Chemical Stability tests

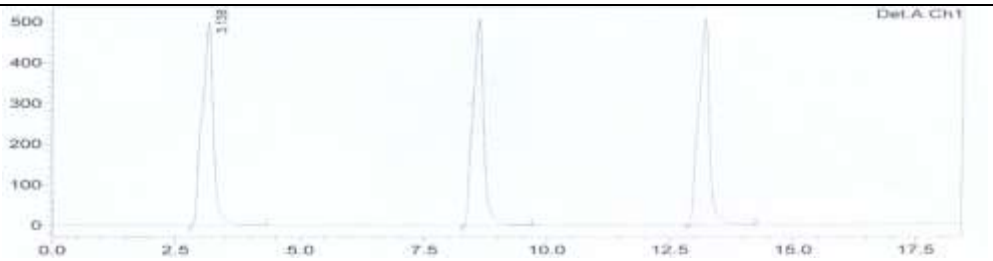


Figure 10: Day fourteen standard solution assay chromatogram

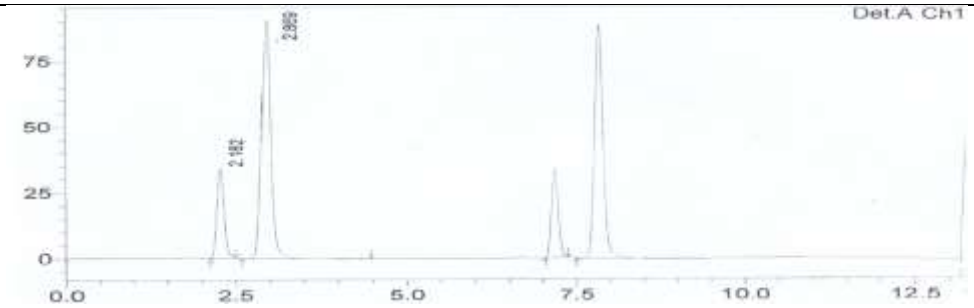


Figure 11: Related substances Standard chromatogram(duplicate analysis)

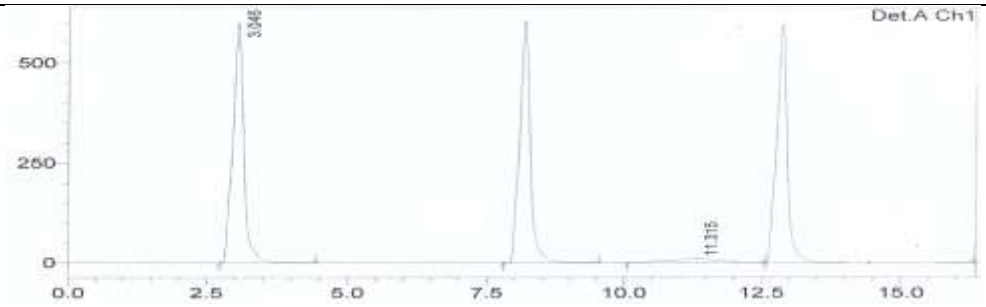


Figure 12: Assay chromatogram (triplicate analysis)

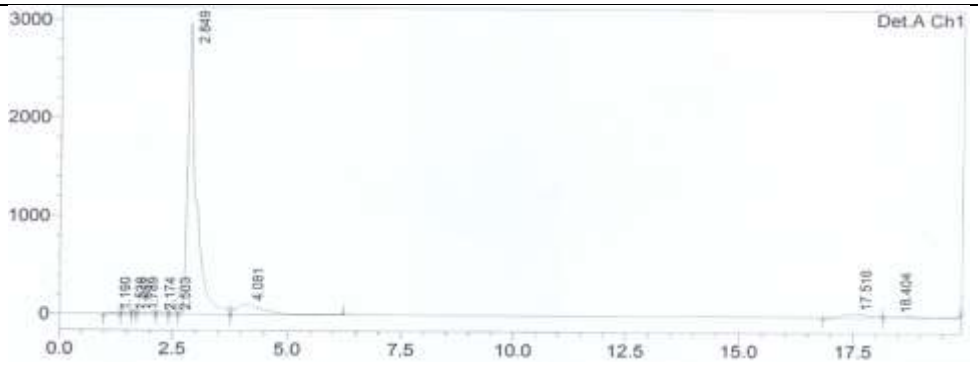


Figure 13: Related substances chromatogram

Day thirty Chemical Stability tests

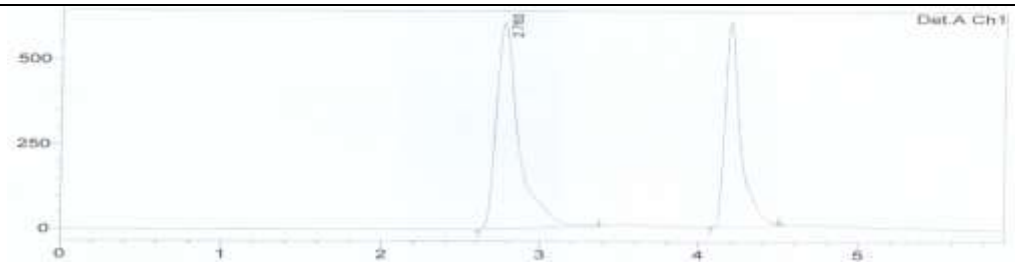


Figure 14: Standard solution assay chromatogram (duplicate analysis)

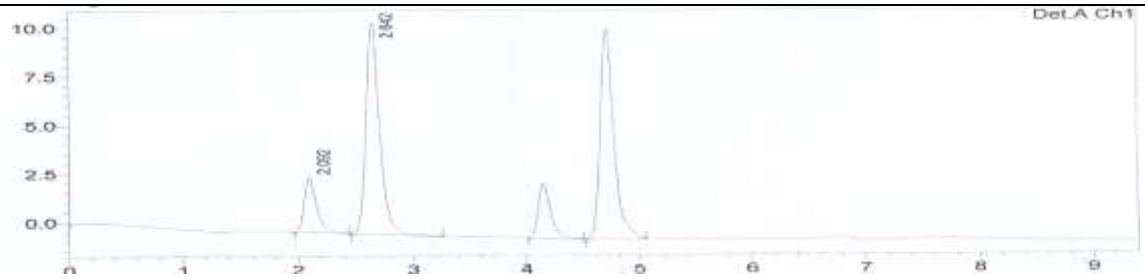


Figure 15: Standard solution related substances chromatogram (duplicate analysis)

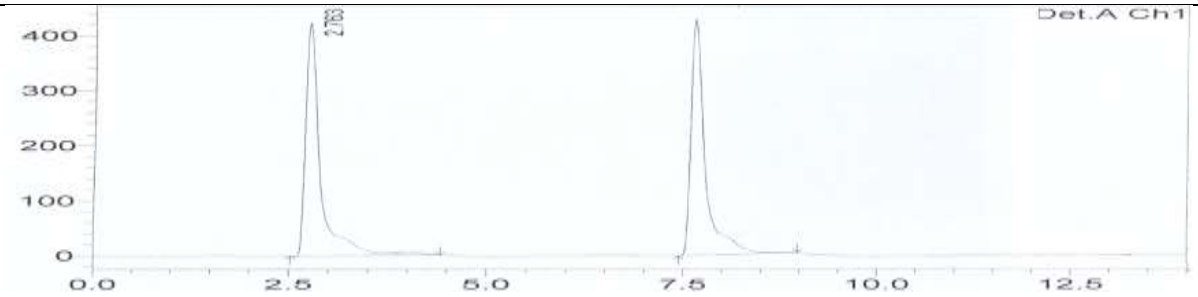


Figure 16: Assay chromatogram

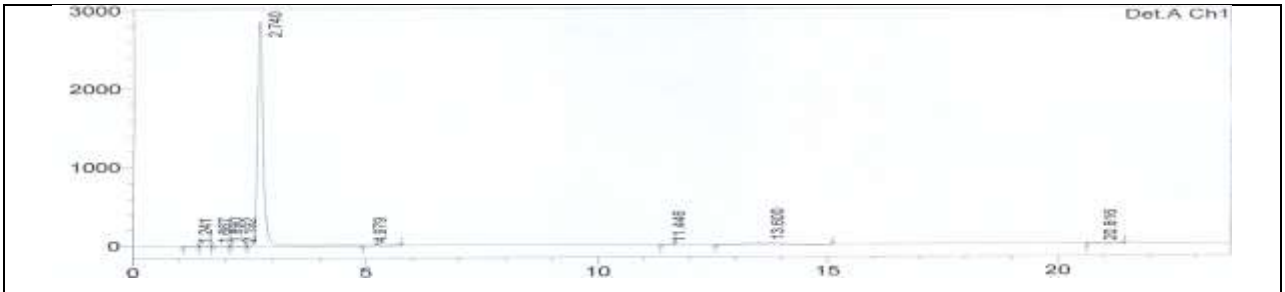


Figure 17: Related substances chromatogram

Day forty five tests

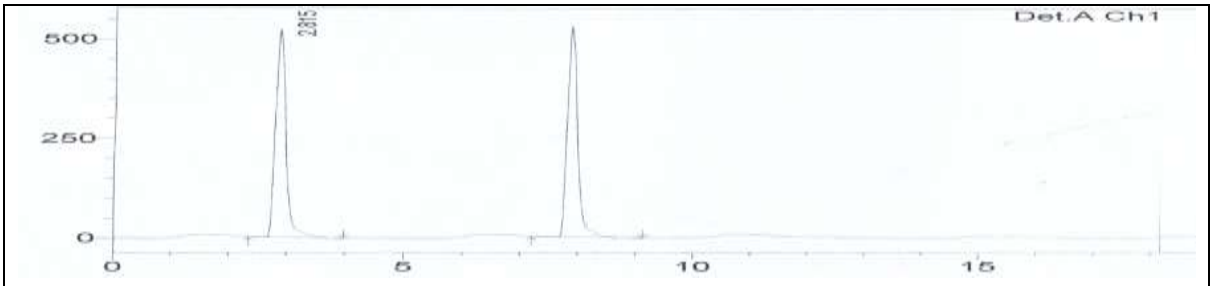


Figure 18: Standard solution assay chromatogram (duplicate analysis)

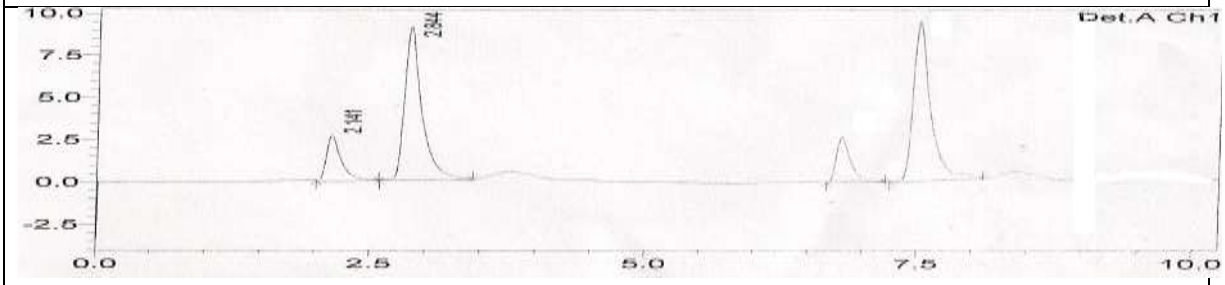


Figure 19: Standard related substances chromatogram (duplicate analysis)

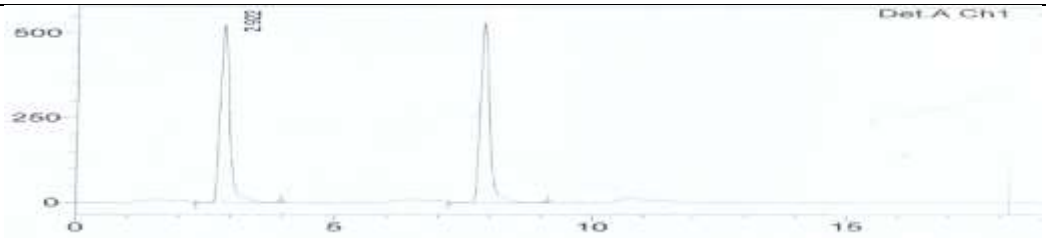


Figure 20: Assay chromatogram (duplicate analysis)

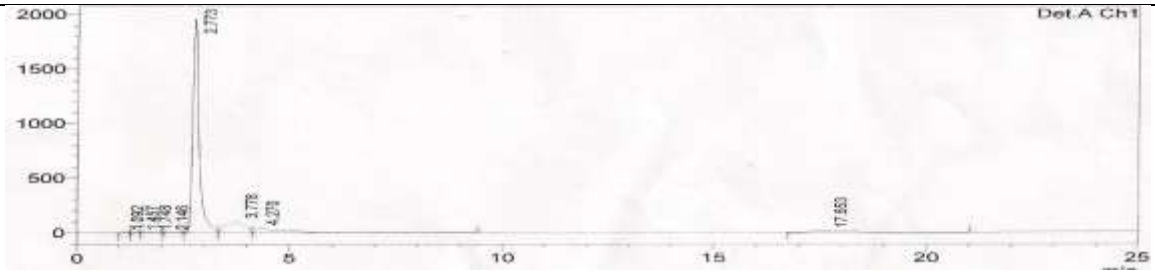


Figure 21: Related substances chromatogram

Day zero standard solutions

The duplicate analysis of paracetmol standard solution for assay test 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 2.87 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[3] 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 99.3%. The B.P monograph states that the content% of paracetamol pediatric suspension (120 mg/5 ml) limits are 95%-105%. Accordingly, the samples passed the assay content test.

For day zero, standard 4-aminophenol showed retention time at 2.27 minute. The chromatogram of the related substances showed a peak corresponding to 4-aminophenol at 2.22 minutes. 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. Standard 4-aminophenol shown retention time at 2.18 minutes but it passed the test because the corresponding peak area was lower than the standard peak area.

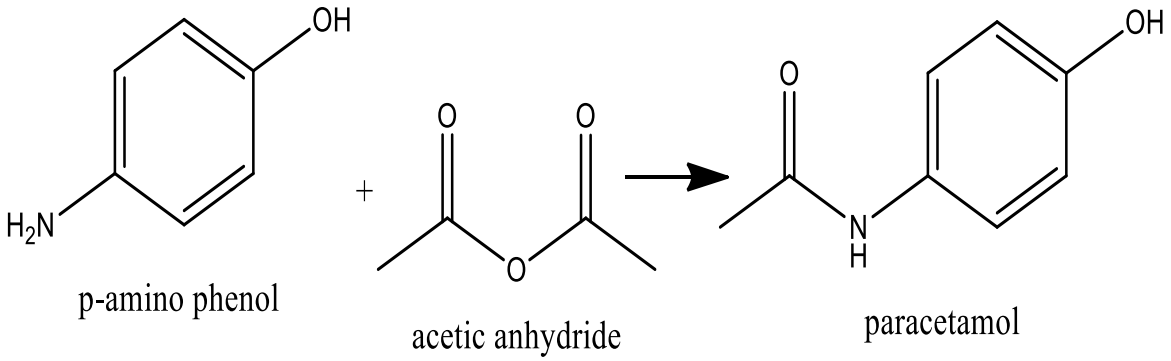
Following the same argument and for convenience, the test results from day zero to day forty five are summarized in Table1.

Table 1. Showing the test results of the stability testing of paracetamol paediatric oral suspension

Day	Assay	Retention Time		Related Substances Test
		Paracetamol	4-aminophenol	
Zero	99.3%	2.87	2.27	Passed
7	97.7%	2.66	2.001	Passed
14	102%	2.18	2.17	Passed
30	91.3%	2.642	2.09	Passed
45	91.3 %	2.844	2.141	Passed

From Table 1, it is clear that paracetamol suspension starts to degrade from day thirty.

The sources of 4 hydroxy amino phenol(p amino pheno) in paracetamol could be the manufacturing process (see the scheme below) to moisture or it could be due to moisture and humidity.



p-amino phenol acetic anhydride paracetamol

It has been reported that oral solutions may lose their flavour and taste, while precipitation and discolouration may also be evident. Suspensions may form a caked solid phase which results in a loss of dose uniformity. Sedimentation may also be due to microbial contamination. However, Different techniques can be used to investigate the stability of paracetmol and each method can provide important information a bout the drug .e.g. sedimentation or electrokinetic methods.

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 22.

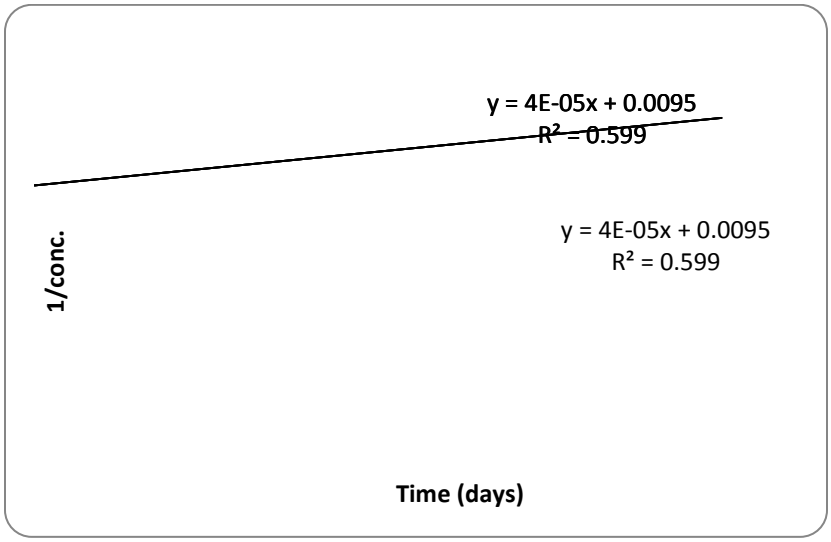


Figure 2 The plot of 1/conc. versus time

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

K=slope Where K=degradation rate

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

$t_{(1/2)} = 1/kC_0$ Where C_O =initial concentration $t_{(1/2)}$ =half life

$t_{(1/2)} = 1/4\times e^{-5} \times 0.993 = 36.8$ days.

A considerable volume of literature had been dedicated to the investigation of paracetamol formulation, and stability and identification of its degradations[4-13]. Many factors can contribute to the instability of drugs and these include the API; interaction between active ingredients and excipients, manufacturing process followed, type of dosage form, container/ closure system used for packaging and light, heat and moisture conditions encountered during shipment, storage and handling.

When paracetamol suspension is maintained under fridge temperature, it shows stability and the compound is very stable at room temperature. However, as the storage period is increased, signs of degradations starts to appear. Which is indicated by the prominence of p-aminophenol and in the presence of trace moisture, acetaminophen degrades more rapidly to p-aminophenol, which subsequently undergoes additional oxidative changes.

CONCLUSION

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

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