AJPS, 2012, Vol. 11, No.1

Simultaneous Determination of Paracetamol ,Chlorpheniramine Maleate and Ascorbic Acid in Tablet Dosage Form by HPLC .

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الخلاصة:

ان المستحضر المكون من خليط البراستول والكلورفينارامين واسكوربيك أسد ذو استعمال شائع في الطب كعلاج مضاد للرشح والانفلونزا . ومن الناحية الصيدلانية فان هذا المستحضر قد انتج بشكل حبوب من عدة مصانع وله شهره جيده في السوق الدوائيه ولكن لايزال هذا المستحضر المركب غير مسجل في دساتير الادويه العالميه ولم تثبت لة طريقة تحليل خاصة , الا ان دستور الادويه الامريكي(USP) قد ذكر طريقه لتحليل البراسيتول الداخل في تركيبة ادويه السعال بوجود مضادات الحساسيه وذلك باستعمال HPLC , ان تطبيق طريقه USP يتطلب تبديل ظروف الكروماتوكرافيا عند تحليل كل مركب من الخليط على انفراد كما ان هناك طرق تحليل منشورة تقتضي استخلاص المواد مسبقا وهو عمل مجهد وياخذ الوقت الطويل.

في هذا البحث عملنا على صياغة طريقه للتحليل لهذا المستحضر بواسطة استعمال HPLC وبتقنية الطور العكسي والمتكون من عمود الفصل ODS والطور الناقل المتكون من محلول فوسفات الأمونيوم عيار 0.1M وميثانول بنسبة 20 بالمائة.

لقد اعطى تحليل المستحضر ثلاث قمم في رسم الكروماتوغرافيا للدلاله على ثلاث مركبات والتي تم فصلها وحساب كمياتها في ان واحد وكان زمن ظهور المركبات هي 2,1 و 2,76 و6,6 دقائق لكل من اسكوربيك اسد، كلورفينارامين وبراستول وحسب الترتيب وعلية كان وقت انجاز التحليل بصورة كاملة هو 10 دقائق.

ان دقة وصحة الحسابات الكمية للمركبات في هذا المستحضر باستعمال هذه الطريقة قد اثبتت عمليا في هذا البحث.

Abstract:

The mixture of paracetamol, chlorpheniramine maleate and ascorbic acid is widely used in medicine as anti flu remedy .Pharmaceutically ,this mixture is prepared as a tablet by different manufacturers and it has good reputation in the market .However, this drug mixture is still non-official in pharmacopoiea, but the USP has described a non specific method of HPLC for the mixture of paracetamol with antihistamine and other antitussive drugs .

Application of the USP- HPLC method was found unreliable for the analysis of tablet containing this drug mixture of three components, since different chromatographic conditions should be applied for each component. Some workers also prescribed a method of analysis by specific procedure for each component individually after previous extraction, which rather long and tedious.

In this work; an HPLC method was developed by using the reversed phase mode of chromatography (ODS column) and a mobile phase consists of ammonium phosphate 0.1M and methanol 20% .the peaks of three components of the studied mixture were well separated and the retention times of ascorbic acid ,chlorpheniramine maleate and paracetamol were 2.10,2.76 and 6.60 Minutes respectively and the whole analysis was accomplished in 10 minutes. The accuracy and precision of this method were approved for the quantitative analysis of each component of the mixture.

Introduction:

The common cold remedy including the combination of three components; Paracetamol as (analgesic and antipyretic), Chlorpheniramine maleate as (anti-allergic for congestion) and ascorbic acid as(protective for mucous membrane) has been found with a beneficial effect in common cold[1]. This drug formula is widely used in medicine and for its safety ,it is considered as a drug over the counter in pharmacy .This drug mixture ,however, prepared in such concentrations of the components which rendered the detection of chlorpheniramine maleate rather difficult, because its concentration (2mg) is very low relative to the paracetamol concentration (350mg) in the formula.

The previous methods used for paracetamol in cough or cold medicines were included isolation of each component which then form a derivative to be detected spectrophotometrically [2-4]. In other methods, electrophoresis technique was applied [5-6].

The lake of accuracy in the these conventional techniques, let the workers to use the recent methods of chromatography in separation and quantitative analysis of the multi components medicines.Therefore, different liquid chromatographic methods have been described for analysis of the mixture of paracetamol with other components in which a simultaneous determinations of paracetamol and other components in cold products were obtained with high accuracy and precision by using different chromatographic techniques [7-17].

In this present work, we have developed an HPLC method by using reversed phase mode of chromatography with suitable UV detection which is rather simple and mostly available instrument in quality control and research laboratories.

Materials and methods:

Methanol BDH (HPLC grade), Ammonium Phosphate BDH (Reagent grade), Phosphoric Acid BDH (Reagent grade). Certified raw material of Paracetamol, Chlopheniramine Maleate and Ascorbic acid were obtained from Modern Drugs Industry (MDI Co. Iraq). Commercial product of Flu-out tablet B.N. (MDI Co.)

Apparatus: HPLC instrument; pump, detector, mixer, and software LC. (knauer Co.).

Chromatographic conditions: Column; ODS column, 30cm x 4.6mm, 5µm particle size.

Mobile phase: 20% Methanol in 0.1 M ammonium phosphate, pH is adjusted to 5.5 with phosphoric acid.

Flow rate; 1 ml/minute.

Injection volume; 20µL

Detection; UV at 214 nm.

Qualitative work:

A solution of appropriate concentrations of the three components ;Paracetamol,Chlorpheniramine and Ascorbic acid in distilled water was first prepared about 5mg of each in 100ml distilled water and then injected in to the chromatogram to detect their peaks and retention times.

Quantitative work:

Preparation of standard solution: Prepare a solution of 350mg of Paracetamol, 2mg Chlorpheniramine maleate and 100mg of Ascorbic acid in 100 ml distilled water, assure complete dissolution (standard solution 1). Dilute 10 ml of (solution 1) to 100 ml with distilled water, filter to be ready for injection into the chromatogram (solution 2). This solution (standard solution 2) was analyzed by five successive injections into the chromatograph and the average of the peaks area of each component was considered for calculations. In addition, several dilutions of (standard solution 1) were prepared and analyzed by this HPLC method to establish its precision.

Preparation of test solution (flu-out) tablet: Weigh 20 tablets of sugar-coated Flu-out and calculate the average weight. Powder the tablets and weigh a mount of tablet powder equivalent to 350 mg of Paracetamol according to the label, and dissolve it in 100 ml of distilled water with vigorous shacking until complete dissolution, then filter (test solution 1). Dilute 10 ml of (test solution 1) to 100 ml distilled water (test solution 2).

The final solution (test solution 2) was injected into the chromatogram and the average peak area for each component of the test mixture in replicate injections was reported then compared with that of corresponding standard solution for assay determination.

Results and Discussion

For qualitative analysis ;the results are shown in figure-1- where the three components in the standard preparation are well separated and identified by their retention times ; 6.58,2.76,and 2.1 minutes for ascorbic acid ,chlorpheniramine maleate,and paracetamol respectively .

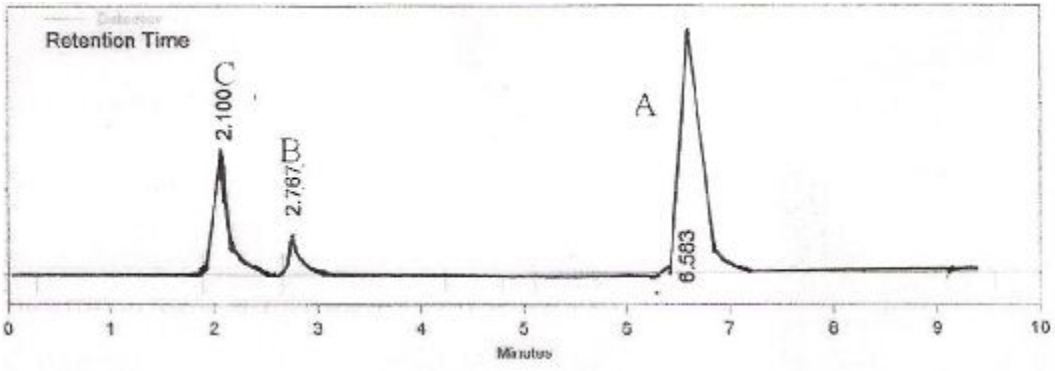


Figure-1: HPLC chromatogram of the mixture; paracetamol (A) at 6.58min Chlorpheniramine maleate (B) 2.76min., ascorbic acid (C) 2.10 min..

Quantitative analysis:

The results of prepared (Standard solution 1) which is filtered through Millipore filter and injected into the chromatogram are shown in figure -2. The peaks area of each component were measured and the relative standard deviations (RSD) in five successive injections for each component were not more than 1.2% .The precision of this method for quantitative determination was approved was, since the relationship of the concentrations of each component with peaks area was linear and the confidence limits were (r^2 = 0.999,0.996 and 0.998 for paracetamol, Chlorpheniramine Maleate and ascorbic acid respectively) .

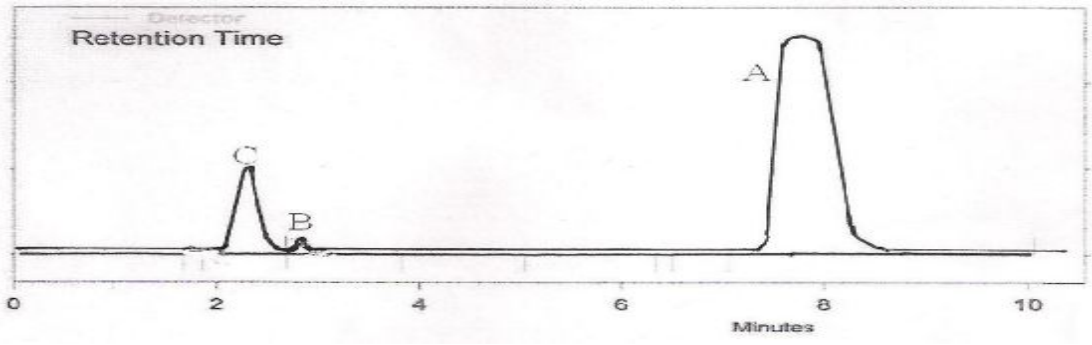
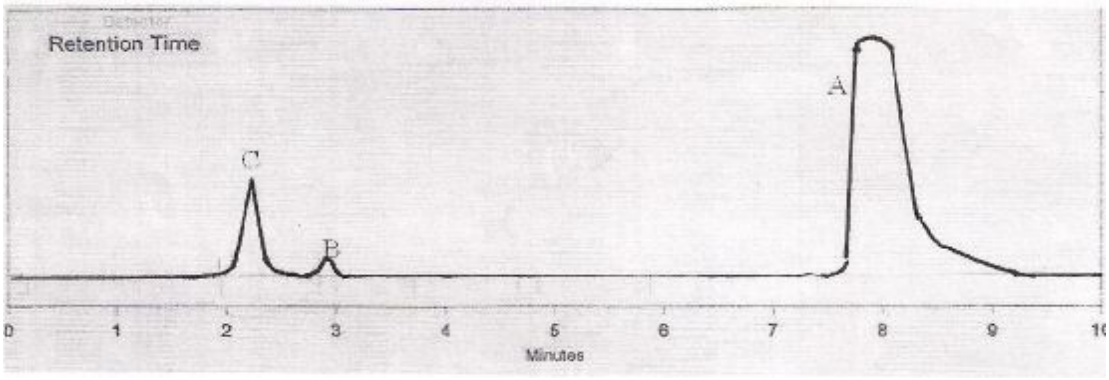


Figure-2: HPLC chromatogram of concentrated (standard solution1) which contains; Paracetamol 3.50 mg(A),Chlorpheniramine maleate0.02 mg(B),and ascorbic acid 0. 10 mg(C) per 1 ml distilled water.

Assay of flu – out tablet which contains this drug mixture was performed by injecting the prepared (test solution 1) into the chromatograme and the peak

area of each component was compared with that of standard (figure-3-) .The percents recovery were 100.1% , 99.8% and 99.7% for each of Paracetamol , Chlorpheniramine maleate ,and Ascorbic acid respectively.



Figur-3: Assay HPLC chromatogram of Flu-out tablet (testsolution1); paracetamol (A), chlorpheniramine maleate (B), ascorbic acid (C).

Analysis of diluted solution (test solution 2):

The result of chromatographic analysis of test solution 2 which is a tenth dilution of test solution 1 is shown in (figure- 4). This result demonstrated the ability of the HPLC method to detect all the components of this drug mixture even with very low concentration .This capability of detection is necessary, particularly in the dissolution test of flu-out tablet in which one tablet is dissolved in 1000 ml of distilled water and the concentration of chlorpheniramine maleate will be about 0.002 per ml.

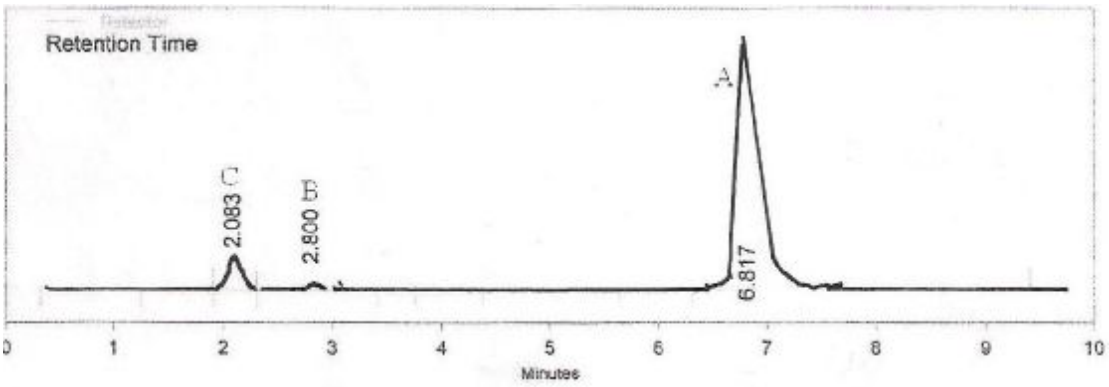


Figure-4:HPLC chromatogram of diluted solution of Flu-out tablet; paracetamol 0.35 mg (A), Chlorpheniramine maleate 0.002 mg (B), and Ascorbic acid 0.01mg (C) per 1 ml water .

The detection of chlorpheniramine maleate in this particular concentration was optimized by using stop- integration technique at the end of second peak as shown in (figure -5).

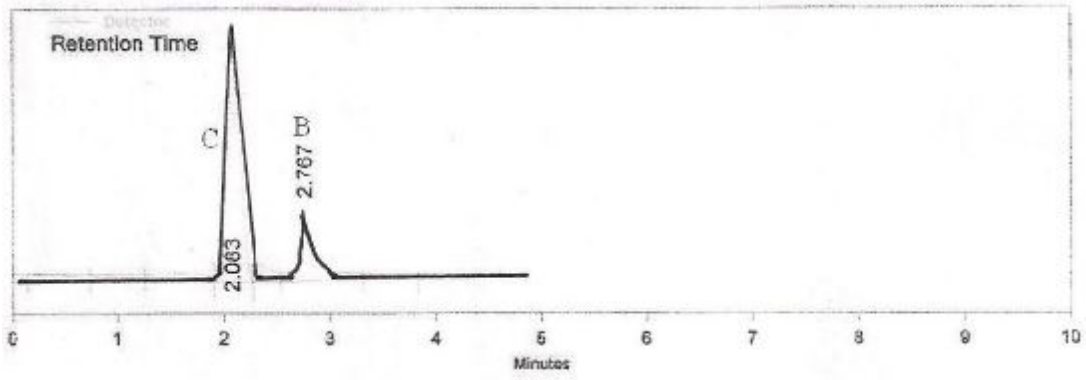


Figure-5:HPLC of the three component mixture, using stop integration technique. The peak C (Ascorbic acid 0.01mg/ml), peak B (Chlorpheniramine maleate 0.002mg/ml).

This technique, in fact, renders the HPLC UV-detector at suitable sensitivity.

For the quantitative determination of chlorpheniramine maleate in its low concentration and prevent the effect of high concentration of paracetamol on the level of detection, therefore the results will be more reliable and accurate.

Conclusion:

The new developed HPLC method used in this work was rapid, accurate and precise for the quantitative simultaneous determination of the three components;Paraacetamol,Chlorpheniramine maleate and Ascorbic acid which formulated as tablet and commonly known as Flu-out for cold remedy ,in addition this method was found suitable for the dissolution test of Flu-out tablet where the concentration of Chlorpheniramine maleate is very low (0.002mg/ml). Applications of this method for the detection of the degradation products of the three components in flu-out tablet and its suitability for stability study are considered of future work.

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