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Quantitative Analysis of Dimetindene Maleate in Dosage Forms by Ion-pair Reversed- Phase HPLC

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Abstract:

The formulations of Dimetindene Maleate as capsule, drop and gel and their methods of analysis are still unavailable in international Pharmacopeia. In this work ion-pair reversed- phase HPLC method was developed for the determination of Dimetindene Maleate in its dosage forms, which can be used for the assay of capsule or tablet, drop and gel.

The separation of Dimetindene Maleate was performed in about 10 minutes with high efficiency using ODS column 25cm and a mobile phase consists of methanol 40 % in distilled water containing 0.02% 1-heptane sulfonate and adjusted with sulfuric acid to pH (3.5).The linearity of this HPLC method was proved and a straight line relationship was obtained between the peak areas and the different concentrations of Dimetindene Maleate standard solution in the range (1-8)µg/ml with confidence limit of 0.998 and the RSD was not more than 1.2%. In addition, this method was found to be suitable for stability study of dimetindene preparations and for dissolution test of capsules and tablets of dimetindene as well.

***Keyword**: Dimetindene Maleate, HPLC*

التحليل الكمي لمادة الدايمتندن ماليت في أشكال الجرعات الدوائية بواسطة الدمج الأيوني في الوسط العكسي للكروماتوغرافيا السائلة ذات الضغط العالي

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الخلاصة:

إن المستحضرات الصيدلانية لمادة الدايمتندن ماليت على شكل كبسول وقطرات فموية وكذلك على شكل جيلي للاستخدام الموضعي لازالت غير مسجلة في دساتير الادوية العالمية ولم تثبت لها طريقة تحليل دستورية بعد . في هذا البحث وضع ظروف فصل جديدة لطريقة الكروموتوغرافيا السائلة ذات الطور العكسي والأندماج الايوني تم لقد واستخدامها في تحليل مادة الدايمتندن ماليت في الكبسول والقطرات الفموية وفي مستحضر الجيلي .

لقد انجز فصل مادة الدايمتندن ماليت بهذة الطريقة خلال 10 دقائق وبكفائة عالية وذلك باستعمال عمود الفصل نوع اوكتادسيل سيلان بطول 25سم وكانت الطبقة المتحركة مؤلفة من 40% ميثانول في الماء واحتوائها على المادة الايونية 1-هبتان سلفونيت وتضبيط الحموظية الى (3,5) بواسطة حامض الكبريتيك (0,1عيارية). ان دقة وانضباط التحليل لهذة الطريقة قد اثبتت من خلال علاقة الخط المستقيم بين مساحات المنحني التابع للمادة ودرجات تركيزها في المستوى بين 1 الى 8 مايكروغرام من مادة الدايمتندن ماليت بالملليليتر من المحلول وكانت معامل التناغم للخط المستقيم هي 0,988 أما مقدار التذبذب القياسي النسبي فأقل من 1,2بالمائة بالإضافة إلى ذلك فان هذه الطريقة قد اثبتت قابلية لاستعمالها في دراسة ثبوتية مستحضرات الدايمتندن ماليت وكذلك في فحص الانحلالية للكبسول والحبوب لمنتجات الدايمتندن.

Introduction:

Dimetindene Maleate, an alkyl amine derivative, is antihistamine and it is used for the symptomatic relief of allergic conditions including urticaria, angioedema, rhinitis, and in pruritic skin disorders [1].It is also has a mild sedative effect and used in compound preparations for the symptomatic treatment of coughs and the common cold [2].

Date of acceptance: 30-3-2014

Dimetindene Maleate is prepared in different dosage forms including; capsule, tablet, oral drop and gel .It is also reported to be administered intranasally for allergic rhinitis [3].

Several methods of analysis have been reported for the analysis of Dimetindene Maleate in urine, plasma and in dosage forms by using different techniques. Aspectrophotometric method has been revealed for the determination of dimetindene and other antihistaminic drugs by using colorizing agents as p-chloranilic acid [4] or tetra-cynoquinondimethane [5]. to yield colored derivatives.

Capillary isotachophoresis technique was also used for determination of dimetindene in dosage forms [6].Capillary electrophoresis was also used for the determination of dimetindene enantiomers and its metabolites [7, 8].

The chromatographic methods were more sensitive in detection of dimetindene and its metabolites in plasma and urine .Gas-chromatography was used for determination of dimetindene in serum and urine with a limit of detection 10µg/L [9]. High-pressure liquid chromatography were also applied on determination of dimetindene in plasma and urine [10,13], in which special detection device might be used as fluorescence detector to detect the conjugated derivative of dimetindene metabolites and also by using a modified type of column attached to pre-column to be suitable for extraction of biological fluid which render these method inconvenient for determination of dimetindene in dosage forms. Other study applied HPLC on a group of antihistamines to determine the relation of retention data with their pharmacological relevant classify-cation of antihistamines[14], which apparently not specific work for dimetindene. The only work of using HPLC on dosage forms has been discussed by Matysova et.al, 2009 who applied a hydrophilic interaction liquid chromate-graphy (HILIC) technique with the using of a specific column for this technique (Se Quant ZIC) to determine the dimetindene in topical gel[15] which apparently unpractical and lack of simplicity for routine analytical work. It is worth mentioning here, that some recent works in 2013 published papers described the use of HPLC in determination of dimetindene and its impurities [16] and also by using the TLC densitometric method [17].

The aim of this study is to develop a simple method of HPLC, with high efficiency and suitability for routine work to assay Dimetindene Maleate in its dosage forms. In addition, it is necessary that the developed method should designed to be able to detect the degradation products of dimetindene maleate in stored product and so sensitive to analyze the very small amount of dimetindene maleate of tablet or capsule under the dissolution test.

Materials and methods:

Dimetindene Maleate USP standard was obtained from Al-Haditha Co. for drug manufacturing, Feneistil capsule 4mg/cap, Feneistil drop 1mg/ml and Fenistil gel 0.1% dimetindne maleate (mediterranean pharm. ind, Co. Syria), Acetic acid (BDH, Reagent grade). Methanol (BDH, HPLC grade), sulfuric acid (BDH reagent grade), Acetone (Analar), 1-heptane sulfonate (BDH).

Apparatus: HPLC instrument with UV-detector (Knouar Co., Germany). Tablet Dissolution tester apparatus USP with 6 vessels (knouar Co.) Stability chamber (Laboratory size, Beckman Co.).

Procedure: Column ODS type, 5 µm particle size, 250 x 4.6 mm dimension. Mobile phase; methanol 40% in water, containing 0.02% 1-heptane sulfonate and adjusted to pH 3.5 with sulfuric acid solution

Date of acceptance: 30-3-2014

The solvent was degassed by ultrasonic then filtered. Detection; by UV at 260 nm, Flow rate; 1 ml/minute.

Quantitative determination; Preparation of standard solution; 100 mg of standard dimetindene maleate was accurately weighed and dissolved in 100 ml diluents (40% Methanol in Water) ,using volumetric flask (V.F). This solution is then diluted 100 times to obtain a concentration of (10µg /ml). Filter solution through 0.45 µm membrane filter and inject 20µL of this solution into the HPLC system.

Preparation of test solution:

Capsules: Each Fenistil capsule contains 4mg dimetindene maleate. Weigh the contents of 20 capsules and transfer amount of powdered capsules equivalent to 50 mg of dimetindene maleate to 50 ml V.F by using diluents (40% Methanol in water) and complete solution to volume to obtain a concentration of sample about 10µg /ml. This solution is then filtered through membrane filter size (0.45µm) and 20 µL of the final solution is injected in the HPLC system.

Oral Drops: Fenistil oral drop contains dime-tindene maleate 1mg/ml. So 5 ml of Fenistil drop was diluted to 50 ml with diluents solution .Transfer 10 ml of the resulted solution to 100 ml and complete to volume with diluents to obtain a concentration of dimetindene maleate about 10µg/ ml according to the labeled amount of the drop.

Gel: Fenistil gel 0.1% Weigh an amount of gel equivalent to 10mg of dimetindene maleate (10 gm of Fenistil gel) and transfer to 100 ml V.F. by the aid of 50 ml diluents, shake well and use ultra sonic operation for 10 minutes, complete to volume with diluents then filter. Dilute the resulted solution 10 times with the same diluents to obtain a solution containing dimetindene maleate about 10µg/1 ml.

Calculation:

Percent of dimetindene maleate in sample = (peak area of test solution/peak area of standard solution) X 100

Validation:

Accuracy was tested by measuring different concentrations of standard solution in the range between (1–8) µg/ml of dimetindene maleate in diluents solution was prepared. The resulted solutions were filtered through membrane filter and assayed by HPLC method which recorded the peaks areas of these different dilutions successsively.

Precision was also determined by measuring a definite concentration (0.4mg/ 100ml) of standard solution were injected (20µL injection volume) in the chromatogram by six successive applications and the peaks areas were recorded for determination of standard deviation.

Degradation products:

Sample of standard solution of dimetindene maleate in water was stored in stability chamber at 70˚C for one week. The stored solution was then analyzed by HPLC method to detect the presence of the resulted degradation products.

Dissolution Profile:

Generally, pharmaceutical analysis of solid dosage forms should include the dissolution test and since the dimetindene maleate is water soluble, therefore the suggested medium in this work was water 500ml which is set at a temperature 37˚±0.5 C and operated in a paddle type apparatus of 50 RPM for 45 minutes.

Procedure:

One Fenistil capsule containing 4 mg dimetindene maleate were immersed in each of 6 vessels of the system which was operated for 45 minutes, during that samples (about 10ml) were withdrawn every 10 minutes and replaced by new 10 ml water. Each 10 ml sample was filtered immediately

Date of acceptance: 30-3-2014

and analyzed by the HPLC method to determine the dissolved amount of dimetindene maleate in medium.

Results and Discussion:

Quantitative analysis: dimetindene maleate standard solution was well separated by this ion-pair reversed-phase high pressure liquid chromatographic method and the retention time were about 9.5 minutes (Fig.1).

The efficiency of separation was more than 5000 theoretical plates which contributed to ion-pair mode of chromatography by using 1-heptane sulfonate in a concentration of 0.02%.

Assay of dimetindene maleate of a definite concentration showed a percent of recovery of 99.9 ± 1.0 % (Fig. 2).

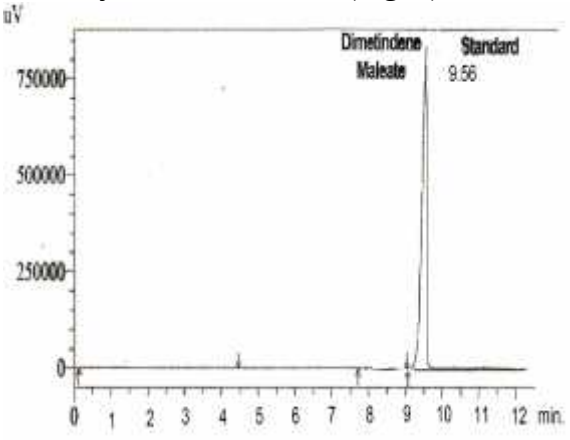

Figure-1: Chromatogram of dimetindene maleate standard solution.

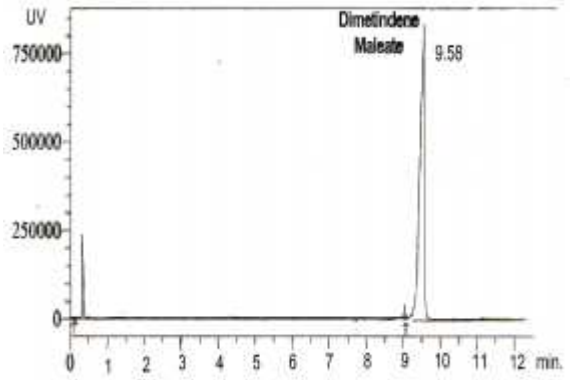

Figure-2: Chromatogram of dimetindene maleate, Fenistil oral drop.

Validation: the accuracy of this HPLC method is demonstrated by its constructed straight-line relationship between the peaks areas and the different concentrations of standard solution which has a correlation coefficient value of 0.998 (Fig. 3).

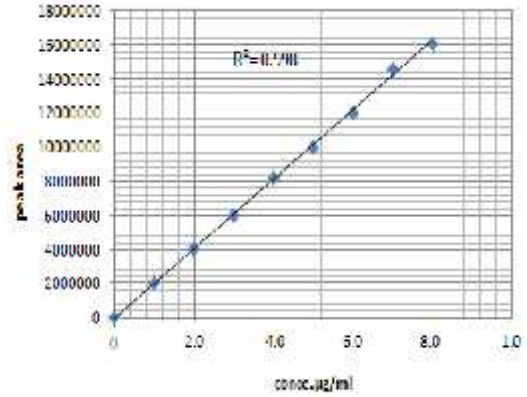

Figure-3: The relationship between the concentrations of dimetindene maleate and their peaks areas Y= 2035232.4 X - 36974.2.

The RSD value of repeated injections of a sample is not more than 1.2% and the least detection limit was on a concentration of 1µg/ml of dimetindene maleate.

The chromatogram of the prepared formulation of dimetindene maleate oral drop without the active constituent showed that all the excpients used in manufacturing of this dosage form have no interference with the retention time of the assay, since they are eluted in the first minute (Fig.4) and so for capsules and gel formulations.

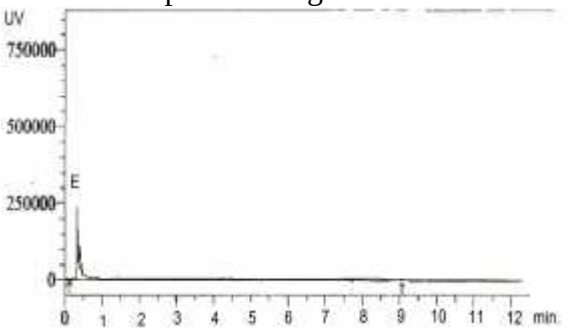

Figure-4: Chromatogram of excipients in repared oral drop (peaks E).

Date of acceptance: 30-3-2014

Degradation products; as it is shown in the chromatogram of the standard solution (Fig.1) that there was a single peak of the parent compound dimetindene maleate, however, the chromatogram of the same solution after degradation process give a secondary peak (B) in (Fig.5) which represent the presence of degradation product .In addition, the calculated percent of dimetindene maleate standard solution after degradation was about 5% less than the initial determination. It is worth to mention here, that the nature of degradation products of dimetindene needs identification and further study.

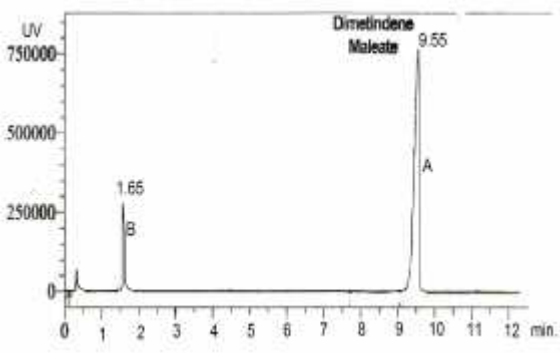

Figure-5: The chromatogram of degradation product (peak B).

Dissolution of Fenistil capsule: due to the high sensitivity of this HPLC method, the determination of dimetindene maleate 4mg per tablet in dissolution medium (500 ml) become more feasible (Fig.6).

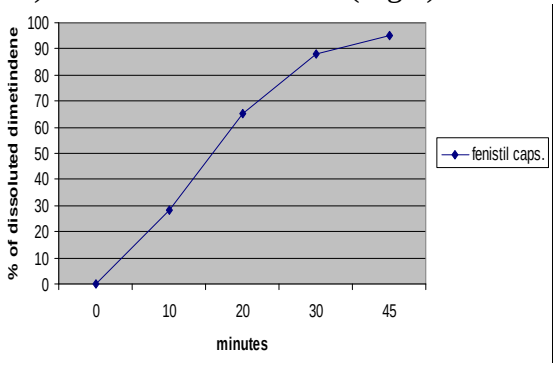

Figure-6: dissolution profile of Fenistil capsule

Conclusion:

The results of this work indicated that the developed ion-pair reversed –phase HPLC method showed good efficiency in separation and quantitative analysis of dimetindene maleate in its dosage forms including capsule, oral drop and gel with high accuracy and precision .The high sensitivity of the detection of this method permits the carrying of dissolution test for dime indene maleate capsule. In addition, this HPLC method was able to detect the degradation products of stored product of dime indene maleate.

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Date of acceptance: 30-3-2014

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