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DISPERSIVE LIQUID LIQUID MICRO EXTRACTION SPECTROPHOTOMETRIC DETERMINATION OF TELMESARTAN AND IRBESARTAN IN PHARMACEUTICALS SAMPLES

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ABSTRACT

The current work is characterized by simplicity, accuracy and high sensitivity Dispersive liquid - Liquid Micro Extraction (DLLME). The method was developed to determine Telmesartan (TEL) and Irbesartan (IRB) in the standard and pharmaceutical composition. Telmesartan and Irbesartan are separated prior to treatment with Eriochrom black T as a reagent and formation ion pair reaction dye. The analytical results of DLLME method for linearity range (0.2- 6.0) mg /L for both drugs, molar absorptivity were (1.67 × 105- 5.6 × 105) L/ mole. cm, limit of detection were (0.0242and0.0238), Limit of quantification were (0.0821and0.0711), the Distribution coefficient were (238 and 226) and the preconcentration factor were (25) for Telmesartan (TEL) and Irbesartan (IRB) respectively. The assay has been used successfully in a determination study of both in pure and pharmaceutical preparations.

Keywords: DLLME, microextraction, telmesartan, irbesartan, eriochrome black-T

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الاستخلاص الدقيق المشتت سائل سائل الطيفي لتقدير التلميسارتان والاربيسارتان في نماذج صيدلانية

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الخلاصة

يتميز العمل الحالي بالبساطة والدقة والحساسية العالية بطريقة الاستخلاص الدقيق المشتت سائل- سائل (DLLME) حيث تم تطوير الطريقة لتقدير التلميسارتان (TEL) والاربيسارتان (IRB) في التركيب القياسي والصيدلاني، اذ تم فصل التلميسارتان والاربيسارتان باستعمال الكاشف اريو كروم تي الاسود (EBT) وصبغة تفاعل الزوج أيوني، وقد بينت النتائج التحليلية لطريقة الاستخلاص الدقيق المشتت سائل- سائل (DLLME) ان مدى الخطية (0.2-6.0) ملغم/ لتر لكلا العقارين، وكانت الامتصاصية المولية (1.67×10^5 - 5.6×10^5) لتر/ مول. سم، بينما كان حد الكشف (0.0242 و0.0238)، والحد الكمي (0.0821 و0.0711)، و معامل التوزيع (238 و226) وعامل التركيز

المسبق 25 للتلميسارتان (TEL) وإيربيسارتان (IRB) على التوالي، وقد تم استخدام الفحص بنجاح في دراسة تحديد كل من المستحضرات النقية والصيدلانية.

الكلمات المفتاحية: الاستخلاص الدقيق المشتت سائل- سائل، التلميسارتان، الاربيسارتان، اريو كروم تي الاسود.

INTRODUCTION

Telmisartan can be represented chemically as 2-[4-[[4methyl-2-propyl-6-[1-(trideuteriiomethyl)benzimidazol-2-yl]benzimidazol-1-yl]methyl]phenyl]benzoic acid (Figure1-a), is an angiotensin II receptor antagonist, which is utilized to the manage the hypertension.

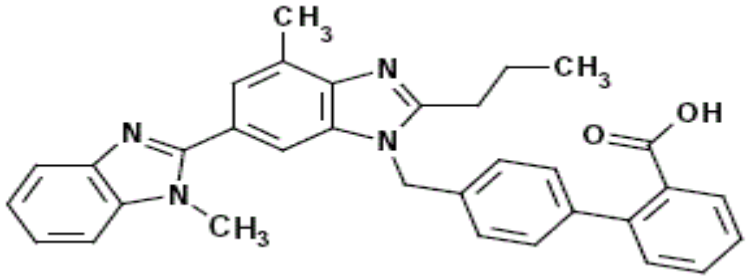

Figure (1a): Telmisartan

Chemically, the Irbesartan can be expressed as 2butyl-3-[[4-[2- (2 H-tetrazol-5yl) phenyl] phenyl] methyl]-1, 3-diazaspiro [4, 4] non-1en-4one(Figure1-b), is an angiotensin II receptor antagonist, which is fundamentally utilized to treat the hypertension.

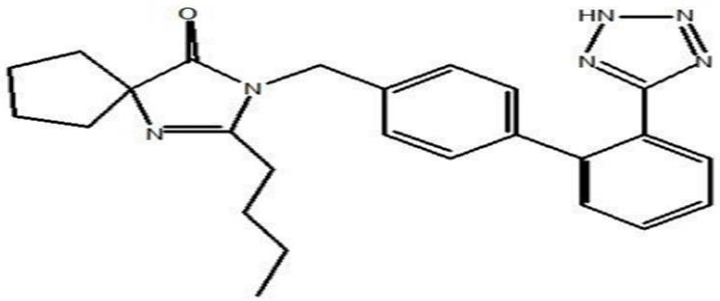

Figure (1b): Irbesartan

The Literature survey has shown a number of the analytical approaches for quantitatively determining the telmisartan **(Qin 2009; Patil *et al*., 2009; Shen *et al*., 2005; Froestl 2012; Wankhede *et al*., 2007; Lakshmi, 2010)** and the irbesartan **(Albero *et al*., 2002; Bae *et al*., 2009; Erk 2003; Sane 2002)** in the pharmaceutical formulations and the biological fluids. Through the literature survey, there are many spectrophotometric methods for determining the pharmaceutical formulations such as, oxidization reactions **(Hassan 2017; Mohammed 2019)**, dispersive and charge transfer methods **(Hassan 2019**), flow injection analysis (**Intisar 2019).**

The objective of this research is developing rather a sensitive, simple, low cost, and validated extractive visible spectrophotometric approach for estimating the telmisartan and the irbesartan in the pharmaceutical and the pure formulations. Due to the fact that the majority of

earlier approaches have involved tedious preparation of the sample, low cost equipment, and critical reaction conditions, which is why, the authors made an effort toward developing a simpler approach that involves no heating for producing color and in addition to that, inexpensive. The suggested approach was extended for routine quality control analyses of the Irbesartan and telmisartan pharmaceutical formulations.

MATERIAL AND METHODS

Instruments

A Shimadzu UVvisible double beam spectrophotometer, UV160 (Japan), which is equipped by matched 1.0 cm path-length quartz cuvettes 10mm matched cells of the quartz has been utilized for absorbance and the spectral evaluations. Irbesartan, Telmisartan and reagents have been obtained from the Sigma-Aldrich. Tablet formulation Boehring Ingelhem International GmbH Germany) with 150mg of the irbesartan and the TELMA, which contains 50mg of the telmisartan have been procured from the local pharmacy. All utilized chemicals have been of an analytical grade and solutions have been prepared freshly with the double distilled water.

Standard Solution Preparation (1000 µg.mL^{-1})

100 mg of every one of the drugs has been precisely weighed then transferred into 100 mL volumetric flasks. Add 5 mL of the methanol to dissolve the drug to each flask and volume has been made up to mark with the distilled water.

Prepare a solution of Eriochrome black-T (0.10%)

100 mg of the eriochrome black-T has been dissolved in 100 mL of the distilled water.

Buffer solution pH 3.50

0.40 gm of the anhydrous sodium acetate was weighed and dissolved in 84 mL of the distilled water and adequate 15 mL of glacial acetic acid for adjusting the value of the pH to 3.50 and this volume has been completed to 100 mL with the distilled water.

On the other hand, the solutions of other reagents have been prepared by the dissolution of required amounts in the distilled water.

A-Ion pair reaction of EBT and cooling with Temesartan or Irbesartan

1 mL (1000 µg/mL) standard solution of irbesartan and telmisartan have been transferred into 20 mL calibrated flasks To each flasks 2.50 mL of pH 3.50 buffer (for both drugs) and 1 mL of 0.10% of the eriochrome solution for the telmisartan and 3 mL for the irbesartan has been added and the total aqueous phase volume in every one of the flasks has been adjusted to 20 mL and transferred into a 60 mL separating funnels Then 10 mL of the chloroform has been added and contents have been shook for 2 min. Both phases have been left to separate and separated chloroform layer absorbance has been evaluated at 510 nm for the two drugs against reagent blank which has been similarly prepared **(Tulja 2012).**

B-DLLME method

2 mL aliquot of the formed ion pair-dye (containg 2.0-60.0 µg of Telmesartan or Irbesartan) transferred into 10 mL calibrated flask complete the volume to mark with the distilled water and the content of the flask has been quantitatively transferred to a 15mL centrifuge tube on the other hand 2 mL of organic solvents mixture methylene chloride (as extraction solvent): ethanol (as dispersive solvent) (1:3, v/v) was quickly injected into the aqueous phase of the ion pair-dye solution by a syringe. The processes of injection enhance the cloudy sample formation that facilitates the separation of the solution. After centrifuging the mixture for 4 min at 4000 rpm for both druges, the absorbance of collected organic phase has been measured at 510 nm for Telmesartan or Irbesartan**.**

RESULT AND DISCUSSION

Experimental conditions were developed to achieve full extraction of the drug formed ion pair dye using the dispersion of liquid micro extraction. Verification includes the type and size of organic solvents and dispersal, extraction time, ion strength, duration and centrifuge speed. The study found that the time of extraction and ionic strength of the aqueous phase does not important role in the extraction of the drug. The selection of disperser solvent and extraction solvent is an important step In the DLLME technique,. Generally, the suitable extraction should have a high affinity to analysts, higher density, low solubility in water, , and lower miscibility than the aqueous sample **(Konieczna *et al.*, 2016)**. The study demonstrated that ethanol has the best properties for serve as a dispersive solvent Among other solvents (acetonitrile, methanol, ethanol and acetone). In DLLME The sensitivity and preconcentration factor are highly dependent on the volume of organic phase **(Poormoghadam 2015)** therefore, the volume and the type of organic solvent used for extraction were studied. The results shown in (Figure 2 and 3) indicate that dichloro methane shows the greatest ability to extract among other solvents when mixed with ethanol (as a dispersed solvent) in a ratio of 1:3, the total volume of the mixture should be 2 mL. The increase in the volume of dichloro methan in the mixture ratio leads to a decrease in the absorption value of the extracted dye This is because of the dilution effect, which leads to a decrease in the concentration of the solution. It was also found that absorption increases with an increase in the volume of ethanol to 1.5 mL, and then decreases after that, the reason may be an increase in the solubility in the aqueous phase **(Kalhor *et al.*, 2016)**. Different centrifugation durations and speeds were studied (Figure 4 and 5). 4 min at 4000 rpm for both drugs was optimum.

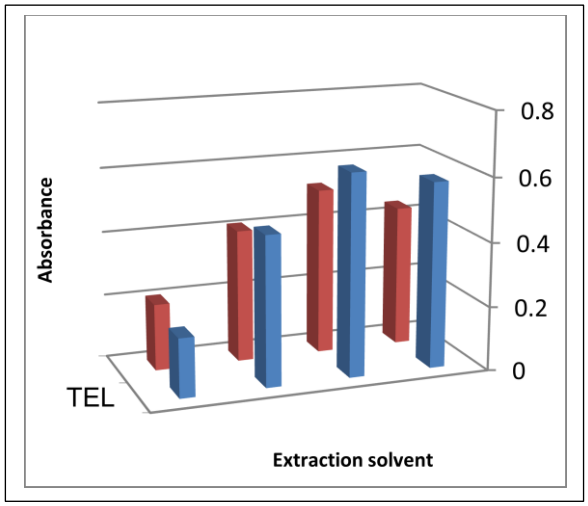

Figure (2): Effect the type of Extraction solvent.

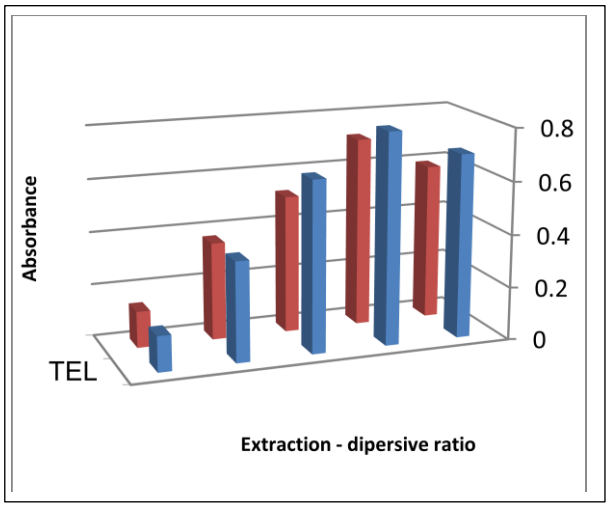

Figure (3): effect of extraction-to-dispersive solvents ratio.

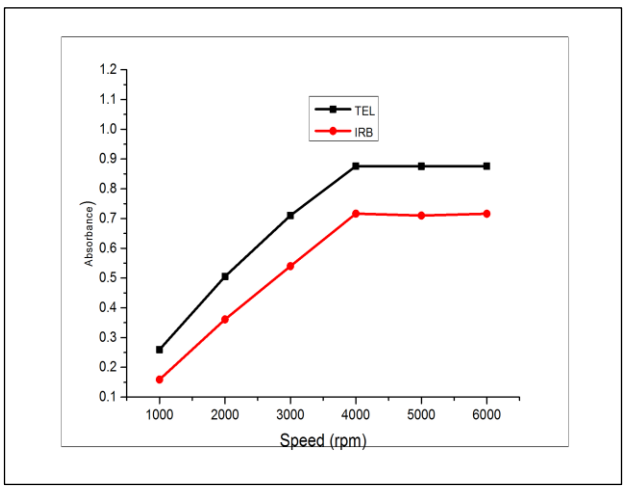

Figure (4): Effect centrifugation time**.**

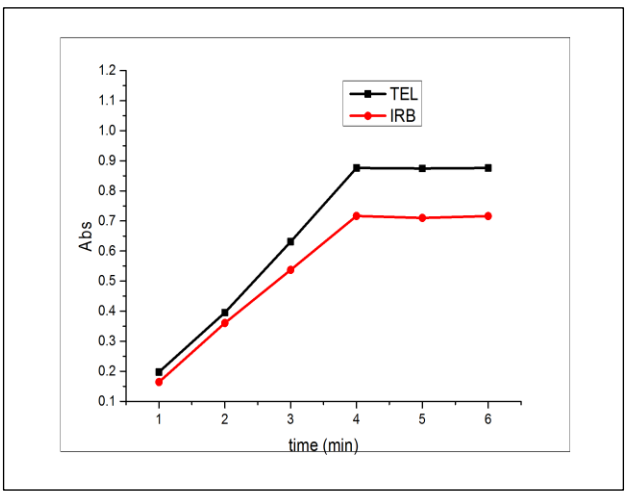

Figure (5): Effect of centrifuge speed**.**

Analytical accomplishment

Using optimization condition, which selected above to prepare the calibration curve at various concentration of ion pair dye for Telmesartan and Irbesartan respectively. The linearity was detected in the range of 0.2-6.0 mg/L with both drugs. In additional was obtained on the remained analytical data such as determination coefficient (r^2), distribution coefficient, enrichment factor, pre concentration factor, limit of detection (LOD=3×S/N) and limit of quantification (LOQ=10×S/N) as can be seen in (Figure 6) and (Table1).

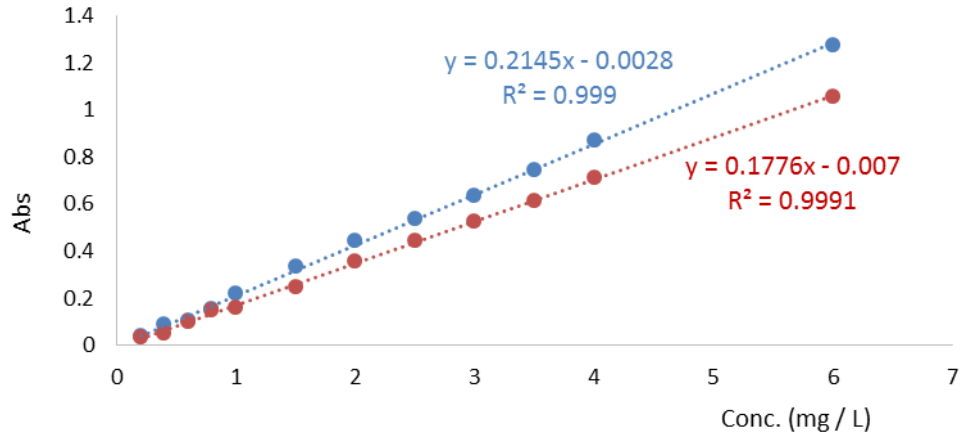

Figure (6): The calibration curve for Telmesartan and Irbesartan respectively after extraction them by DLLME method.

Table (1): The analytical results for TEL and IRB respectively at DLLME method.

Parameters	Result of TEL	Result of IRB
Linearity range (mg/L)	0.2-6.0	0.2-6.0
Molar absorptivity (ε) L/mole.cm	1.67×10^5	5.6×10^5
Slope	0.2145	0.1776
Intercept	0.0028	0.0070
Sandell's sensitivity (S) µg/cm^2	0.0047	0.0054
Coefficient of determination R²	0.9990	0.9991
limit of detection LOD	0.0242	0.0238
Limit of quantification LOQ	0.0821	0.0711
Distribution coefficient D	238	226
Enrichment factor EF **Preconcentration factor**	24.172 25	25.043 25

Accuracy and precision

The Precision and accuracy in an integrated method was estimated in terms of recovery and relative standard deviation % RSD. The samples have been evaluated by five replicates of three concentrations of TELand IRB dyes respectively and extracted by applying the DLLME method. Evaluated each sample was spectrophotometric method after separated the solution to two layers organic and aqueous and were the results as (Table 2)**.**

Table (2): Accuracy and precision results for TEL and IRB respectively at DLLME method.

Concentrations of Azo dyes	Amount of azo dye (mg/L)		(%) Relative Error	Recovery (100+%E)	(%) RSD (n=5)
	Taken	**Found**			
Telmesartan	1.000	0.997	-0.300	99.700	0.127
	3.000	3.005	0.500	100.166	
	5.000	4.998	-0.200	99.960	
Irbesartan	1.000	1.012	1.200	101.200	0.133
	3.000	3.004	0.400	100.133	
	5.000	4.998	-0.200	99.960	

Method Application

To investigating the suitability of proposed ion pair- DLLME approach, the content of TEL and IRB in commercial pharmaceuticals formulation were determined under the recommended procedures. The results in (Table 3) indicate that the recovery percent values are ranged between (99.633-100.360) and those for RSD% do not exceed 0.22 which proves that the proposed method is satisfactory.

Table (3): Application of the recommended procedures for the determination of TELand IRB in commercial pharmaceutical preparations.

Pharmaceutical preparation	**Concentration (mg/L)**		**Recovery (%)**	***RSD (%)**
	Taken	Found		
Telmesartan 80 mg tablet Hexal Germany	1.000	0.998	99.800	
	3.000	3.009	100.300	0.217
	5.000	5.013	100.26	
Telmesartan 40 mg tablet Medical Union Pharmaceuticals Egypt	1.000	1.002	100.200	
	3.000	3.010	100.33	0.189
	5.000	4.996	99.920	
Irbesartan 50 mg tablet Micro Labs Limited/India	1.000	1.011	101.100	
	3.000	2.989	99.633	0.220
	5.000	5.018	100.360	
Irbesartan 150 mg tablet Dar Al Dawaa / Jordan	1.000	0.999	99.900	
	3.000	3.002	100.066	0.202
	5.000	5.003	100.060	

* Average for 15 replicates.

CONCLUSION

In this work, a new analytical method was developed to determination TEL and IRB The method relies on the coupling of the aforementioned drugs with EBT and formed ion pair dye was extracted from the aqueous phase to dichloro methane and to determine the spectrophotometry. The proposed method is sensitive and highly selective . Where there is no interference with excipients and pharmaceutical preparations being dependent on DLLME,

which is simple and does not require complicated equipment. Finally, the analysis was performed according to the recommended conditions as it is not expensive, effective and harmless to the environment

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