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Preconcentration and determination of Metformine Hydrochloride in different samples by cloud point extraction coupling with uv-visible spectrophotometry

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Abstract:

This work was influenced the separation and preconcentration steps were carried out to determination of metformin (MET) in pharmaceutical preparations and human serum samples. Complex formation method and cloud-point extraction (CPE) coupling with UV-Visible spectrophotometry were used to investigated of study target.The results has showed the best optical characteristic for calibration curve and statistical data which were obtained under optimum conditions. The first method is based on the reaction of MET with nickel (II) in alkaline medium an absorption maximum $\lambda_{(max)}$ at 434nm. "Beer's low" is obeyed in the concentration range (10-100µg.ml^{-1}) with molar absorptivity of 3.9x10^{3} L.mol^{-1}.cm^{-1}.The limit of detection and quantitation values were 2.37 and7.11 µg.ml^{-1} respectively. The second method based on extraction of traces amounts of MET using the cloud-point extraction (CPE). This method implicated for using of a nonionic surfactant (Triton x-114) as an extraction medium which was entrap the hydrophobic complex formed between MET and nickel(ii) in basic medium as reaction system for designing the CPE procedure. The optimum conditions were similar the first method expect the amount of surfactant which was 0.5 ml. The concentrations range of calibration curve from 3.5to100 µg.ml^{-1} and molar absorptivity of 1.2x10^{4} L.mol^{-1}.cm^{-1}. In this method was access to less of concentrations in Limit of detection and quantitation which were 0.74and 2.22 µg.ml^{-1} respectively. The precise (RSD %) and accuracy (recovery %) of both methods were ranged between 0.24-0.47, 97.86-98.68 respectively. The data of two methods were appeared high acceptable with standered of British Pharmacopoeia through using statistic methods (f-test and t-test), that they may be used in analysis of MET.

Key words: UV-Vis spectrophotometry, new chelating agent, nickel (II), Cloud point extraction (CPE), Triton x-114

Introduction:

The chemically name of Metformin hydrochloride was 1,1 Dimethyl biguanide hydrochloride with a molecular formula of $C_{14}H_{12}ClN_5$ (Figure 1)[1-2].

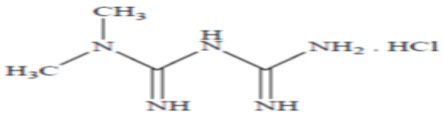

Fig.(1): chemical structure of metformin-Hcl

It is a medicine used to treat of secondary diabetes, which is not dependent on insulin through the inhibition of glucose and glycogenolysis in the liver[3-4]. It seems recently that this property alleviating hyperglycemia by improving insulin sensitivity and reducing its absorption in the digestive tract, and the prevention of cancer of the pancreas and liver disease [5-6].

Metformin (MET), was used as hydrochloric salt form being dissolved in aqueous medium, making it more effective in the treatment of patients with diabetes especially overweight people and those with normal kidney function[7-8] .It may be preferred by people who suffer from heart failure as evidence suggests[9].

It can be Contrary to all of sulfonylureas and insulin in addition to the significant reduction of sugar that it does not cause an increase in weight [10-11].

The MET was determination by various types of techniques in pharmaceutical formulas and human serum as spectrophotometric methods which were developed for analysis of drug[12-16]. HPLC methods were used to detect of MET with using low amounts of solvents[17-21]. Another different techniques for the determination of MET, which have been described, such as conductometric titration[22]., flow injection and chemiluminescence[23-26], capillary electrophoresis[27]. Cloud point extraction (CPE), a micelle-mediated process, has become one of the important separation and pre-concentration methods which were improving the sensitivity in determination of trace metal ions and acting as an alternative to liquid-liquid extraction. This particular technique was owing to several advantages including high performance and concentration factor, low cost, safety, environmentally friendly nature and Ingenuity offered [28-30].

In this study, new reagent nickel (ii) as complexing agent to investigate complication with MTF which was determined MET directly and also the cloud-point extraction methodology for preconcentration of super trace amounts of MET In serum using Triton x-114 as extranet coupling with vis-uv spectrophotometry. The purpose methods were applied for determination of MET in pharmaceutical preparation and human serum.

Materials and Methods:-

Apparatus

The absorption spectra and absorbance measurements of both analytes were carried out by using A shimadzu model UV-1800 equipped with 5-cm quartz cell was used to scan the absorption spectra for drug (metformin) ,Ni(II) solution and the MET-Ni(II) chelates in surfactant-rich phase against blank solution prepared under similar conditions without those drug. A portable pH –meter microprocessor (HANA-HI 98150 GLP Ph),Thermostated water bath shaker ,BS-11 digital ,JEIO TECH . Korea.And FTIR(Fourier Transform Infrared Spectrophotometer)

Materials and Reagents

All chemicals used were of analytical reagent grad unless otherwise is mentioned, metformin standerd powders (purity 99.9%) SDI. Triton X-114 (AMRESCO COMPANY), Nickel chloride hexahydrate (BDH), sodium hydroxide 0.2N.

Metformin hydrochloride standard solution (1000µg.ml^{-1})

This solution was prepared by dissolving 0.1gm of metformin hydrochloride in 100ml distilled water in a volumetric flask.

Nickel chloride hexahydrate standerd solution(1000µg.ml^{-1})

This solution was prepared by dissolving 0.4 gm of Nickel chloride hexahydrate in 100ml distilled water in a volumetric flask.

General CPE procedure for metformin

A typical cloud point experiment required the following steps: an aliquots of 10ml of a solution containing a known amount metformin, 0.5ml Triton x-114 10%(v/v),1ml sodium hydroxide,0.8ml Ni(II) of 1000µg/ml was mixed in 10ml volumetric flask and diluted to mark with distilled water and left to stand in a thermo-state bath at 60°C ,for 25min separation of the phase was achieved by centrifugation at 4000rpm for 4min.the phase was cooled down in an ice bath in order to increase the viscosity of the surfactant-rich phase and then the aqueous phase can be separated by using syring,subsequently,3ml of ethanol. This solution transferred to 1ml quartz cell. A blank solution was prepared in the same way.

Preparation of the pharmaceutical Sample

The proposed method was also used for the determination of Metformin content in three selected pharmaceutical containing metformin hydrochloride namely;(merc500mg-dialon500mg-awa500mg) The drug solution was prepared by accurately weighting 0.1 g of dried metformin hydrochloride into a 50 mL beaker and dissolved in minimum amount of distilled water with swirlin. The content of beaker was transferred quantitatively to 100 mL volumetric flask, and then diluted to mark with distilled water.and subjected to the general CPE procedure and metformin content was determination spectrophotometrically (434nm).

Preparation of the Serum Sample

Five adult volunteers were randomly designated to take orally a single tablet of (merc, glocophage 500mg), after two hours of administration, blood sample (5ml) was with drawn from the vein each subject by using medical syringe and then transferred immediately into centrifuging tubes. and 0.2 ml of each serum sample was transferred into10 ml volumetric flask and followed the general CPE procedure content in the complex determined spectrophotometric ally at 434nm.meanwhile,0.2 ml of each sample was transferred into 10ml volumetric flask metformin content was directly determination by traditional UV-Vis spectrophotometry at (232nm).

Results and Discussion

Absorption Spectra

Uv-vis spectra: The spectra of Ni-MET complexes show the absorption maxima of 434 nm with molar absorptivity of $1.2x10^4$ L.mol^{-1}.cm^{-1} (Figure 2). Whilst, the MET gave the absorption maxima of 238 nm (Figure 3).

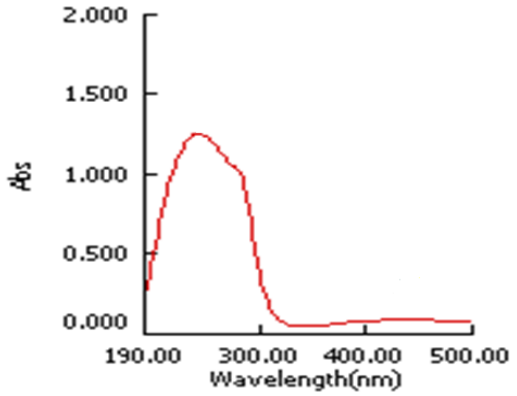

Fig. (2): The absorption spectra of complex Met-Ni(II)

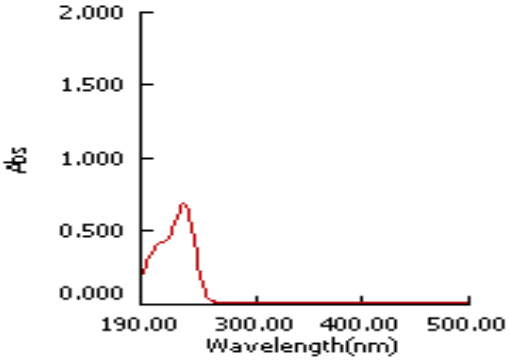

Fig. (3): The absorption spectra of metformin

The study of IR spectra: The important peaks of the IR spectra of the MET and the complex are summarized in Table (1) .The shifting and their intensities of the peaks confirming the modifying and formation of the complex.

Table (1): The important peaks of IR spectra for MET and Ni-MET compolex

Assignmet	Ligand	Complex
N-H) (υυ	3373_s	3363_w
(C=N)υ	$1583\text{-}1626_m$	$1612\text{-}1681_s$
$(N\text{-}CH_3)$υ	$1276\text{-}1419_m$	$1296\text{-}1425_m$
(Ni-N=C)υ	-	812

Optimization parameters for CPE of Metformin determination

All of the parameters in the CPE method such as:pH ,reagent concentration, percentage of surfactant(Triton-x114), heating time and temperature.

The Effect of pH:

An aliquot of 10ml solution containing 1ml (metformin) 200µg.ml^{-},Ni(II) 0.8 ml of 1000µg.ml^{-1},0.5 ml of Triton x-114 (10%), were mixed and varying pH range of (9-11.5) of sodium hydroxide (0.2N) were mixed and diluted to mark with distilled water according to general CPE procedure 10.5 value of pH was selected as the optimum pH for complete formation of complex. The results of pH were shown in the (Figure 4)

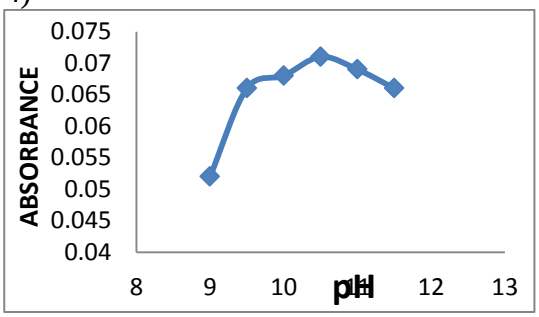

Fig. (4):pH effect on the absorbance on CPE

The effect of Ni(II) concentration

In the separated 10ml volumetric flasks, aliquots of 10ml of a solution containing of 200µg.ml^{-1} of metformin,0.5ml 10% Triton x-114 and varying amounts (0.4-1.2) ml of 1000µg.ml^{-1}, were mixed and diluted to mark with distilled water according to general CPE procedure. The optimum value of the concentration of nickel is 80µg.ml^{-1} because of the possibility of nickel atoms link with each bond metal Ni-Ni into force when metformin particles, the results were shown in the (Figure 5)

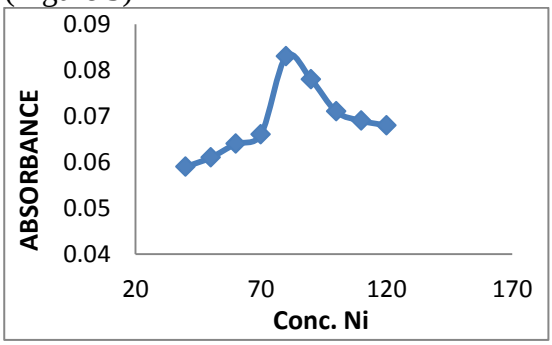

Fig. (5): The effect of Ni(II) concentration on the absorbance

The effect of TritonX-114 concentration

Different volumes of 10% Triton x-114 ranging from (0.1-1) ml were used in this study keeping other conditions are constant. The absorbance of each solution including different concentration of surfactant were measured and the results are shown in (Figure 6).0.5 ml of surfactant valium was suitable to optimum of formation cloud point.

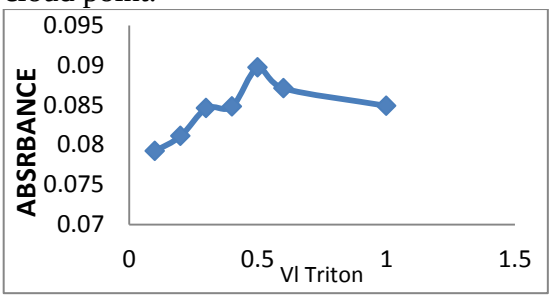

Fig.(6):The effect of Triton x-114 concentration on the absorbance

The effect of temperature and time

The effect s of the equilibrium temperature and the incubation time were examined optimized other conditions .The temperature was varied from (20-80)°C in a search of optimum value and the results are shown in (Figure 7). Also, time from (5-40)min in a search of optimum values and the results were depicted in (Fig.8). the 40 °C and 25 min were best optimum for formation cloud point.

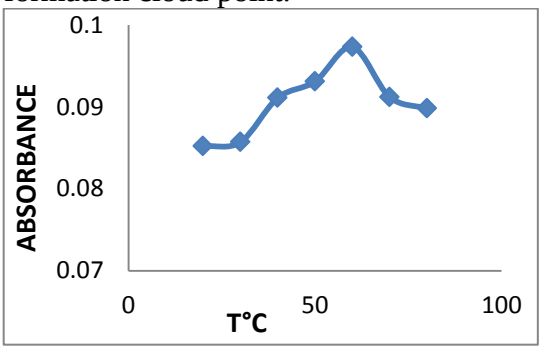

Fig.(7):The effect of temperature on the absorbance

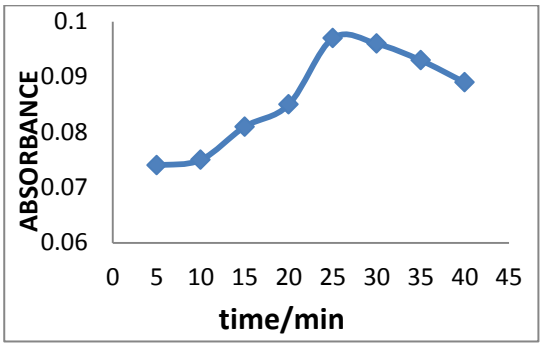

Fig.(8):The effect of incubation time on the on CPE

Optimization parameters for direct of Metformin determination

A discrete variable here is the concentration of nickel reagent ($100\mu g.ml^{-1}$), temperature 60°C ,and incubation time 20min.

Stoichiometry of the Met-Ni(II) complex by Mole ratio method

A 1ml of $2x10^{-3}$ M of Ni(II) was pipetted into each of 7 ml volumetric flasks, then (0.5-3.5) ml of $2x10^{-3}$M solution of metformin were added in the presence of 0.2M sodium hydroxide (pH=10.5).The mixture solution were diluted to the mark with distilled water. The absorbance of the solution was measured by UV-Vis spectrophotometer at 434nm.The results are shown in Fig(9). The obtained results were indicated that the probable composition of complexes was 1: 2 which was refer in(Fig.10).

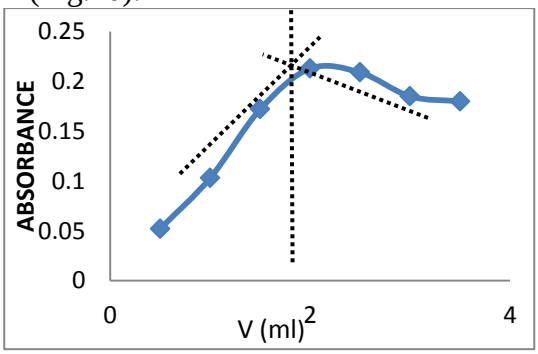

Fig. (9): Mole ratio plot complex between Ni(II) and metformin

Fig. (10): The probable chemical structures of the complex

Preparation of Calibration Curve to Determination of MET by Direct method and CPE

Under optimum conditions established, two calibration curves were constructed, once for direct determination of metformin and another for cloud point extraction. Tables 1 and 2 are summarized the statistical data of the two curves which were showed all figures of merit for target analyses.

The calibration curve for direct determination of metformin was linear over the concentration range of 10-100µg.ml^{-1} (r=0.9979, 10 points). The limit of detection (LOD) of 2.37µg.ml^{-1} and the quantitative of limit of 7.11µg.ml^{-1} (Table1). The calibration curve for determination of metformin by cloud point extraction CPE was linear over the range of 3.5-100µg.ml^{-1} (r=0.9978, 10 points). The preconcentration factor obtained was of 50 fold resulted in achieving the limit of detection (LOD) of 0.74µg.ml-1 and the quantitative of limit of 2.22µg.ml^{-1} (Table 2).

Table (2): Analytical figures of the spectrophotometric direct determination of metformin

(nm) $_{max}$ λ	434
Regression equation	y=0.0024x+0.001
Correlation coefficient	0.9989
Linearity percentage % R^2	99.79 %
Dynamic range (µg.ml^{-1})	(10-100)
Slope (b)	0.0024
Intercept(a)	0.001
Molar absorptivity (L.mol^{-1}.cm^{-1})	3.9x10^3 =ε
Sandells Sensitivity (mg.cm^{-2})	0.04
Limit of Detection(µg.ml$^{-1)}$	2.37
Limit of Quantitation(µg.ml^{-1})	7.11
RSD%(n=5) at 80 µg.ml^{-1}	0.68

Table (3): Analytical figures of merit of the spectrophotometric determination of metformin by CPE

Parameter	Value
(nm) $_{max}$ λ	434
Regression equation	y=0.0072X+0.0028
Correlation coefficient	0.9987
Linearity percentage % R^2	99.78 %
Dynamic range (µg.ml^{-1})	(3.5-100)
Slope b	0.0072
Intercept a	0.0028
Molar absorptivity (L.mol^{-1}.cm^{-1})	1.2x10^4 =ε
Sandells Sensitivity (mg.cm^{-2})	0.013
Limit of Detection(µg.ml$^{-1)}$	0.74
Limit of Quantitation(µg.ml^{-1})	2.22
RSD%(n=5) at 40 µg.ml^{-1}	0.63
Preconcentration factor	200
Enrichment factor	193
Distribution ratio	29.41

Application of direct method and CPE to determination of MET in pharmaceutical preparations.

The two methods were used for the determination of Metformin content in three selected pharmaceutical containing metformin hydrochloride namely;(Glugophag 500mg,dialon 500mg, awa 500mg)**,** the results are tabulated in Table 3and 4.

Table (4): Direct method to determination of metformin in pharmaceutical preparations

Name Drug.	Taken Conc. µg.ml^{-1}	Found Conc. µg.ml^{-1}	Recovery %	Found mg
Glugophage 500mg	50	49.23	98.4	492
	25	24.47	97.88	489
Dialon 500mg	50	51	102	510
	25	25.7	102.8	512
Awa 500mg	50	48.75	97.5	487.5
	25	24.58	98.32	491.6

Table (5): Determination of metformin by CPE in the pharmaceutical preparations.

Name Drug.	Taken Conc. µg.ml^{-1}	Found Conc. µg.ml^{-1}	Recovery %	Found mg
Glugophage 500mg	50	49.37	98.74	493.7
	25	24.21	96.84	484.2
Dialon 500mg	50	49.18	98.36	491.8
	25	24.58	98.32	491.6
Awa 500mg	50	48.93	97.86	489.3
	25	24.55	98.2	491

Determination of Accuracy and Precision for proposed methods

The accuracy and precision of the proposed method were checked by analyzing three replicate of three different concentrations .the accuracy was determination by calculating the relative error percentage, while the precision was tested by calculating the percentage relative standard deviation (RSD%).the results indicated good accuracy with reasonable precision of the proposed method which were range between -1 and -2.5 that were showed in Table 5 and 6.

Table (6): The accuracy and precision of the direct determination of metformin

Name and Taken Conc.	Found µg.ml^{-1}	E_{rel}	Er %	RS % n=3	$t_{cal} = \frac{\lvert\bar{X}-\mu\rvert}{S_d} \times \sqrt{n}$
Glugophage 500mg	19.69	-	-2.5	1.23	t_{cal}=3.6
20µg.ml^{-1}	19.58 19.23 Ave:19.5	0.5			3.6<4.303
Dialon 500mg	30.74	-	-1	2.99	t_{cal}=1.74
30µg.ml^{-1}	29.36 29.15 Ave:29.7	0.3			1.47<4.303
Awa500mg	39.71	-	-	0.9	t_{cal}=3.02
40µg.ml^{-1}	39.46 38.95 Ave:39.3	0.7	1.75		3.02<4.303

Table (7): The accuracy and precision for the determination of metformin by CPE

Name and Taken Conc.	Found µg.ml^{-1}	E_{rel}	Er %	RSD % n=3	$t = \frac{\lvert\bar{X}-\mu\rvert}{S_d} \times \sqrt{n}$
Glugophage 500mg	14.78 14.82	-	-	0.47	t_{cal}=4.193
15µg.ml^{-1}	14.91 Ave:14.83	0.17	1.13		4.193<4.303
Dialon 500mg	19.83 19.79	-	-	0.96	t_{cal}=2.73
20µg.ml^{-1}	19.48 Ave:19.7	0.3	1.5		2.73<4.303
Awa 500mg	24.67 24.71	-	-	0.24	t_{cal}=2.105
25µg.ml^{-1}	24.79 Ave:24.72	0.3	1.12		2.105<4.303

Compared between proposed method and slandered of British Pharmacopoeia[31]

In this work, it can be concluded that the nickel (ii) as agent beside CPE-Spectrophotometry gave satisfactory analytical for MET when were compared with standered of British Pharmacopoeia[31]. All results of statistic methods (T-test and F-test) were calculated from this comparison confirm the absence of a significant difference, which were facilitates the application of these methods in the analysis of MET in various samples. These date tabulated in Figures

Table (8): Comparison of direct method with standard British pharmacopeia method[31] for the determination of MET in pharmaceutical preparations.

Name and Taken Conc.	Proposed Method µg.ml^{-1}	Standard method [31]	$t_{cal} = \frac{\bar{D}}{S_d} \times \sqrt{n}$	$F_{cal}=S_1^2/S_2^2$
Glugophage 500mg	14.31	14.82	$\bar{D}$=0.37	S^2_1=26.52
15µg.ml^{-1}			S_D=0.214	S^2_2=24.55
Dialon 500mg	19.4	19.69	$t_{cal\,(n=3)}$=0.934	F_{cal}=1.08
20µg.ml^{-1}			t_{tab} at95% df 2=4.303	F_{tab} at95% df 2=19.01
Awa 500mg	24.61	24.73	0.934<4.303	1.08<19.01
25µg.ml^{-1}				

Table (9): **Comparison of CPE with standard British pharmacopeia method[31] for the determination of met in blood serum of five adult Volunteers after two hours of taking orally a single tablet (merc, glocophage 500mg)**

Sample NO.	Proposed Method µg.ml^{-1}	Standard method[31] µg.ml^{-1}	$t_{cal} = \frac{\overline{D}}{S_d} \times \sqrt{n}$	F=s^2_1/s^2_2
1	15.23	13.42	D=0.41 S_D=0.836 $t_{cal(n=5)}$=1.095 t_{tab} at 95% 4=2.776 df 1.095<2.776	S^2_1=21.75 S^2_2=20.2 F_{cal}=1.076 F_{tab} at 95% df 4=6.39 1.076<6.39
2	20.37	20.72		
3	12.24	12.01		
4	23.54	22.13		
5	14.32	15.29		

Study of Interferences

The results showed that no interferences where found in the presence of up to (200, 20)µg.ml^{-1} of the studied excipients (lactose, sucrose, starch, glucose, valine, and glycine) in the determination of metformin. Table9 was showed no noticeable changes in result.

Table(10): Percent recovery for 20µg.ml^{-1} of metformin in the presence of (20-200)µg.ml^{-1} of excipients.

Interference	Conc.µg.ml^{-1}	Recovery%
Lactose	20	7.57
	200	96.53
Glugose	20	98.22
	200	96.47
Sucrose	20	96.38
	200	96.71
Glycine	20	95.18
	200	93.25
Valine	20	94.76
	200	95.58
Starch	20	96.83

Conclusion

The developed methods were using Ni (ii) ions as new agent to form complex which was suitable and successfully validated to determination of trace and large amounts of MET in human serum and pharmaceutical samples. The procedure of preparation of complex in direct method or cloud-point extraction was simple, easy and rapid, which should be used for the assay of MET in present of excipients.

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اعادة التركيز والتقدير الطيفي للميتفورمين هيدروكلوريد في نماذج مختلفة بواسطة الاستخلاص بنقطة الغيمة والمزدوجة مع مطيافية الاشعة فوق البنفسجية والمرئية

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الخلاصة:

يتضمن هذا العمل انجاز خطوات فصل وتركيز لتقدير الميتوفورمين في نماذج من المستحضرات الصيدلانية وسيرم الدم البشري . استخدمت طريقتا تكوين المعقد كطريق اولى ونقطة الغيمة كطريقة الثانية المزدوجتان مع مطيافية الاشعة المرئية والفوق البنفسجية لتحقيق هذا الهدف. تم الحصول على افضل النتائج لمنحنى المعايرة والبيانات الاحصائية عند تطبيق الظروف الفضلى.

اعتمدت الطريقة الاولى على تفاعل الميتفورمين مع ايون النيكل الثنائي في الوسط القاعدي لتكوين معقد له اقصى امتصاص(λ_{max}) عند 434 نانومتر وقد لوحظ ان قانون بير يسري على الكميات التي تتراوح بين (-100 10) ميكروغرام /مل وان معامل الامتصاص المولاري ($3.9x10^3$) ل.مول$^{-1}$.سم$^{-1}$. وان حد الكشف وحدود التقدير الكمي كانت 2.37^1 و 7.11ميكروغرام/مل على التوالي.

اما الطريقة الثانية تشتمل على فصل وتقدير الكميات ذات التراكيز الواطئة للميتفورمين في نماذج من سيرم الدم لمتبرعين يتناولون الميتفورمين باستخدام طريقة الاستخلاص بنقطة الغيمة بوجود سطح انيوني من التريتون x-114 في وسط قاعدي تحت ظروف فضلى مشابه الى الطريقة الاولى ماعدا تركيز التريتون الذي كان حجمه0.5 ملليتر. وكان حدود التراكيز لمنحنى المعايرة من3.5 الى 100 ميكروغرام /مل وان معامل الامتصاص المولاري ($1.2x10^4$) ل.مول$^{-1}$.سم$^{-1}$. تم الوصول الى اقل تركيز في حدود الكشف وحدود التقدير الكمي والتي كانت 0.74 و 2.22 ميكروغرام بالملليتر على التوالي. كانت التوافقية والدقة لكلتا الطريقتين بدلالة الاسترجاعية والانحراف المعياري النسبي بمدى 97.86-98.68, 0.24-0.47 على التوالي. واظهرت نتائج الطريقتين متوافقة مع نتائج الطريقة القياسية لدستور الأدوية البريطاني باستخدام الطرق الاحصائية مثل اختبارT واختبارF مما يجيز لهما ان يستخدما في تحليل الميتفورمين.

الكلمات المفتاحية: جهاز الاشعة فوق البنفسجية – المرئية ، نيكل (II) ، تريتون x-114.