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Alizarin Red S as a Chromogenic Agent for the Determination of Meropenem in Pharmaceutical Formulations

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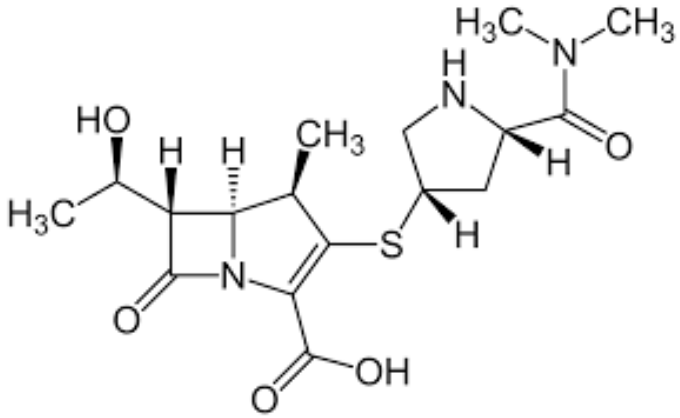
ABSTRACT

Alizarin red S (ALRS)reagent has been used for to determination of meropenem (MEP)by an easy, sensitive, and selective procedure based on an ion-pair formation reaction between ALRS and MEP in an aqueous: alcoholic medium in the ratio of 50:50 without adjustment of the acidity of the reaction medium. The linearity ranged from 1 to 50 µg /mL, molar absorptivity was 6.557 × 10^3 L.mol^{-1} .cm^{-1}., index of Sandell's, was 0.0584 µg.cm^{-2}, and the calculated LOD and LOQ were 0.02789 µg/mL, 0.0929 µg/mL respectively. The calculated range of relative error was from -1.022 to 0.34 % which indicates high accuracy, and the calculated range of the relative standard deviation was from 0.347 to 0.574% which indicates high precision. The method has been applied for the determination of MEP in dosage forms successfully in which the recovery ranged from 99.8 to 103.2%. The standard addition method proves no interfering effect caused by inactive ingredients involved in dosage forms of meropenem.

Keywords: Alizarin Red S, Meropenem, ion-pair, Chromogenc Agent.

INTRODUCTION

MEP is used to treat infections caused by Gram-positive and Gram-negative bacteria (Kayser *et al.*,1989) (Laith *et al*., 2022), infections caused by COVID-19 (Xu *et al.*, 2020) and severe skin infections (Fish, 2006) (Ku *et al.*, 2015). MFP is 3- [5-(dimethyl carbamoyl) pyrrolidin-2-yl] sulfanyl-6- (1-ydroxyethyl)-4-methyl-7-oxo- 1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic (National Center for Biotechnology Information, 2023). MEP may suffer from cleavage of beta lactam in a strong alkaline medium because of the weak bonds of sulfur between two five-member rings (Libin *et al*., 2018). Fig. (1) shows the chemical structure of meropenem, the chemical formula, and the atomic weight (The United States Pharmacopeia, 2007).



$C_{17}H_{25}N_3O_5S$, 383.464 g/mole (The United States Pharmacopeia, 2007)

Fig. 1: The chemical structure of MEP

A standard determination method was published in the United States Pharmacopeia which is based on gas chromatography provided with a flame ionization detection tool (The United States Pharmacopeia, 2007). UV with FT-IR and Raman spectra were recorded and used to follow the stability of MRP (Fayed *et al.*, 2019) (Cielecka *et al.*, 2013) (Jamieson *et al.*, 2020). The presence of many polar groups such as carboxylic and amino groups decrease the attachment of MRP to non-polar stationary phase and increase the affinity to relatively polar mobile phase in chromatographic methods (Roth *et al.*, 2017; Negi *et al*., 2017; Milla *et al.*, 2020; Sutherland and Nicolau, 2020), While spectrophotometric methods were limited because of the absence of strong functional groups. A spectrophotometric method-based oxidation of MEP by ferric ion followed by different color reactions has been published (Singh and Maheshwari, 2013). Charge -transfer reaction of MEP with 2,3 dichloro 5,6 dicyano 1,4 benzoquinone (DDQ) to form yellow colored complex measured at 345 nm was also used to determine MRP (Khalil and Ibrahim, 2020). A chromogenic reaction with a specific reaction 2,3-Dimethoxystrychnidin-10-one after oxidation with potassium iodate in 6 M of HCl produces a red color product measured at 520nm (Nakkella *et al.*, 2020). It also forms a chelating complex with gold ion (III) measured at 477 nm. (Qassim, 2015). Alizarin Red S is 3,4-Dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid with the chemical formula $C_{14}H_7NaO_7S$.It is a soluble sodium salt (Constantinescu *et al.*, 2018). Alizarin Red S may be used as a complexing agent (Justyna and Małgorzata, 2017) (Salim and Sammei, 2018) or proton transferee (Rabee and Nabeel, 2022), or ion pair formation (Sameer and Kanakapura, 2014).

EXPERIMENTAL

Instruments

A double-beam Jasco V- 630spectrophotometer with 1.0 cm matched glass cell.

Chemicals and Prepared Solutions

MEP solution (250 µg /mL): This solution was prepared by dissolving 0.0250 g of MRP solution in a small amount of distilled water and then completing the volume to 100 mL in a volumetric flask. The solution must be kept in a brown bottle and re-prepared every three days.

ALRS (0.1%): This solution was prepared by dissolving 0.1000 g of solid pure compound (Fluka) in 50 mL of absolute methanol, then diluted to 100 mL with distilled water in a volumetric flask. The solution is kept in a dark brown bottle, and must be re-prepared each week.

Pharmaceutical Preparation

MER vials 1g / manufactured by Venus pharma/Germany: 0.0250 g of the vial powder has been dissolved in distilled water to prepare 250 µg /mL.

Nbaxo vials 1g / manufactured by acino/ Switzerland :0.0250g of the vial powder has been dissolved in distilled water to prepare 250 µg /mL.

Preliminary Investigation

0.5 mL of MEP (250 µg/mL) has been added into three 10-mL volumetric flasks and mixed with one mL (0.1%) Alizarin red S reagent, left for five minutes, then diluted with distilled water, methanol, and mixture of distilled water: methanol, then the absorption spectrum of the red colored solution has been taken against the blank solution. The results are shown in (Table 1).

Table 1: Select the solvent of the dilution

Solvent	Absorbance	λ_{max} (nm)
Water	0.2611	520
Methanol	0.3794	530
Water+ Methanol (50:50)	0.448	526

Table (1) shows that the mixture of 50:50 methanol: distilled water exhibited the best sensitivity. The reaction produces the red color of a new product with 526 nm. as a maximum peak against the yellow color blank prepared in the same way.

Selection of the Reaction Conditions

Parameters have been changed within a range to select the best reaction conditions:

1. Study the influence of ALRS amount

To five series of volumetric flasks, each one contains 0.5 mL of ALRS and increasing concentrations of MEP, series two contains 1mL of ALRS and increasing concentrations of MEP, series three contains 1.25mL of ALRS and increasing concentrations of MEP, and so on, all flasks have been left for five minutes, diluted by 50:50 methanol: water solution, then measured at 526 nm. against blank prepared according to the same criteria. The results are listed in (Table 2).

Table 2: Select the best amount of ALRS

Volume of 0.1%ALRS (mL)	Absorbance of product /(µg/mL) MEP					
	2.5	**12.5**	**25**	**37.5**	**50**	R^2
0.5	0.221	0.401	0.598	0.723	0.935	0.9897
1.0	0.241	0.413	0.612	0.788	0.981	0.9989
1.25	0.264	0.446	0.650	0.856	1.071	0.9997
1.5	0.295	0.489	0.693	0.883	1.133	0.998
2.0	0.311	0.509	0.711	0.895	1.170	0.9955

From (Table 1), the best determination coefficient between concentrations of MEP and ALRS was resulted by using 1.25 mL of 0.1% ALRS with good sensitivity, this factor has been fixed in all subsequent steps.

2. Study the influence of the medium

From 0.5 to 1.0 mL of HCl (0.001M) and NaOH (0.001M) have been added to a series of 10 mL volumetric flasks containing 0.5 mL of MEP (250 µg/mL) and 1.25 mL of ALRS (0.1%), the flasks were left for five minutes, then diluted with a mixture of the same ratio of methanol, water and measured at 526 nm. The results in (Table 3) show that the presence of acid or base decreases to the sensitivity compared the measurements at the pH of the solution prepared without using them.

Table 3: Study the influence of the medium

Medium and pH	Absorbance* /mL of acid or base added				
	0.1	**0.2**	**0.3**	**0.4**	**0.5**
HCl	0.355	0.268	0.178	0.133	0.076
pH	6.35	6.12	5.83	5.57	5.23
NaOH	0.435	0.431	0.429	0.411	0.382
pH	6.93	7.13	7.34	7.5	7.73

*The absorbance without acid or base used =0.449, pH=6.7

3. Effect of solvent

1.25 mL of ALRS has been added to 0.5 mL of (250 µg/mL) MEP and diluted with different solvents to make 10 mL in volumetric flasks. Fig. (2) and (Table 4) show that no real shift in the spectrum of the colored product except in the case of acetic acid which decreases the sensitivity due to a change in final pH of the final solution, while the best sensitivity was observed by dilution with a mixture of methanol: water 50:50.

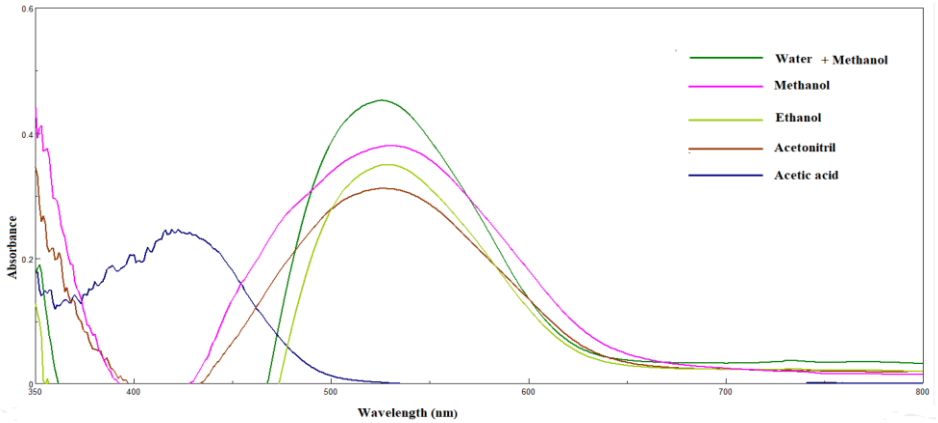


Fig. 2: The absorption spectrum of MEP-ALRS in different dilution medium

Table 4: Effect of solvents added.

solvent	Abs.	ʎ max (nm)	£ (l/mol.cm)
Water: methanol (50:50)	0.448	526	1.357×10^4
Methanol	0.379	530	1.163×10^4
Ethanol	0.349	528	1.058×10^4
Acetonitrile	0.311	525	9.433×10^3
Acetic acid	0.243	423	7.384×10^3

4. Study the time required to complete the reaction

Reaction components 0.5 mL of 250 µg/mL MRP and 1.25 mL of 0.1% ALRS are mixed together and get periods of standing time, then diluted by the mixture 50:50 water: methanol to produce 10 mL exactly and read the absorbance against blanks prepared in the same way. Table (5) indicates that between 5 to 20 minutes, the readings are close with a slight increase at five minutes which is followed in pre- and post-experiments.

Table 5: Study the time required to complete the reaction

Standing time(min)	0	5	10	15	20
Absorbance	0.3912	0.450	0.439	0.433	0.431

5. Study the effect of surfactant

2mL of 1x 10^{-3} M SDS, CPC and CTAB is added to the reaction mixture with different sequences to predict their effect on the reaction. Table (6) exhibits that SDS and CPC decrease the sensitivity, while CTAB cause in turbidity, this may be due to the formation of an insoluble salt in the reaction medium.

Table 6: The results of adding surfactant

Surfactant (1×10^{-3} M)	Absorbance /order of addition		
	I	II	III
SDS	0.351	0.332	0.320
CPC	0.379	0.351	0.338
CTAB	**Turbid**		

Absorbance without surfactant = 0.448, I MEP+ ALRS+ Surfactant, II MEP +Surfactant + ALRS, III Surfactant + MEP + ALRS.

6. Study the effect of temperature

A series of volumetric flasks containing a reaction mixture under the above-selected conditions have been left for five minutes in water bathes of different temperatures (10,25,35,40,50 °C), the results have been expressed in Fig. (3).

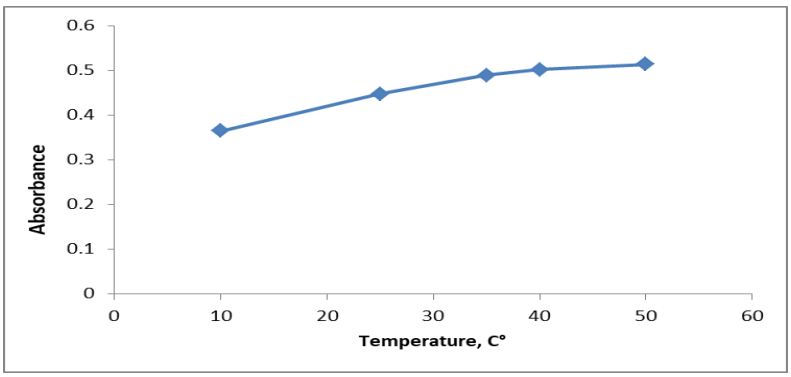


Fig. 3: Effect of temperature

Fig. (3) shows that there is no significant difference in absorbance between solution kept at 25 °C and other solutions.

7. Study the stability of the colored product

Table (7) shows the stability of two samples 12.5 and 25 µg/mL of MEP prepared according to the above selected conditions and procedure. The table shows that the reaction mixture requires five minutes after dilution to reach completion and stay stable for at least 55 minutes.

Table 7: Study the stability of the colored product

Time (min)	Absorbance of µg/ mL MEP	
	12.5	25
Immediately	0.394	0.587
5	0.443	0.643
10	0.447	0.649
15	0.449	0.650
20	0.450	0.652
25	0.449	0.649
30	0.452	0.650
35	0.448	0.651
40	0.449	0.649
50	0.450	0.652
60	0.447	0.651
Over night	0.429	0.636

The overall reaction conditions have been summarized in Table (8) to be used for the preparation of the final absorption spectrum (of 12.5 µg/mL MEP) (Fig. 4), the absorption spectrum of different concentrations (12.5-50 µg/mL MEP) (Fig. 5), and calibration curve (1-50 µg/mL). (Fig. 6).

Table 8: Summarization of the selected reaction conditions

Parameters	Optimum conditions
Reaction component	MEP and ALRS
Concentration of ALRS (%)	0.1
Amount of ALRS (mL.)	1.25
Medium of reaction	Water: methanol (50:50)
Final volume (mL.)	10
Reaction time (min.)	5
Development time (min.)	5
ʎ max (nm.)	526
Stability period time (min.)	50

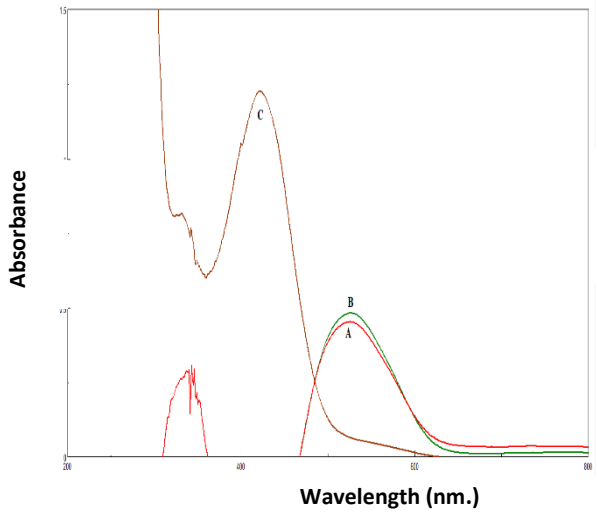


Fig. 4: The absorption spectrum of 12.5 µg/ml MEP sample prepared according to selected procedure conditions A:sample against blank, B:sample against distilled water and C: blank against distilled water.

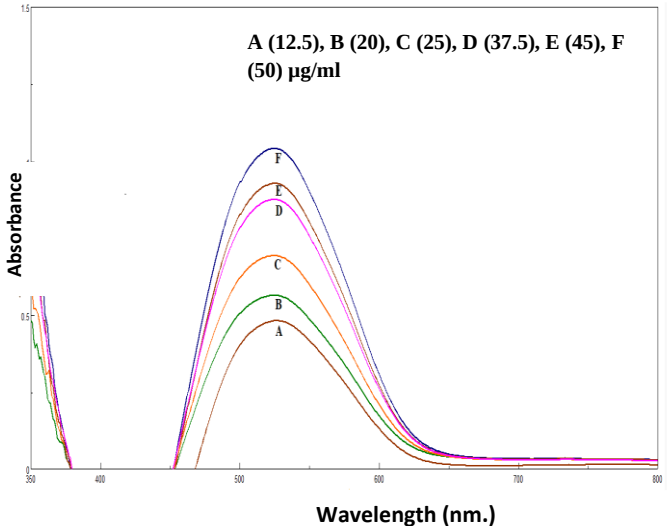


Fig. 5: The absorption spectrum of MEP sample prepared according to selected procedure conditions and measured against blank

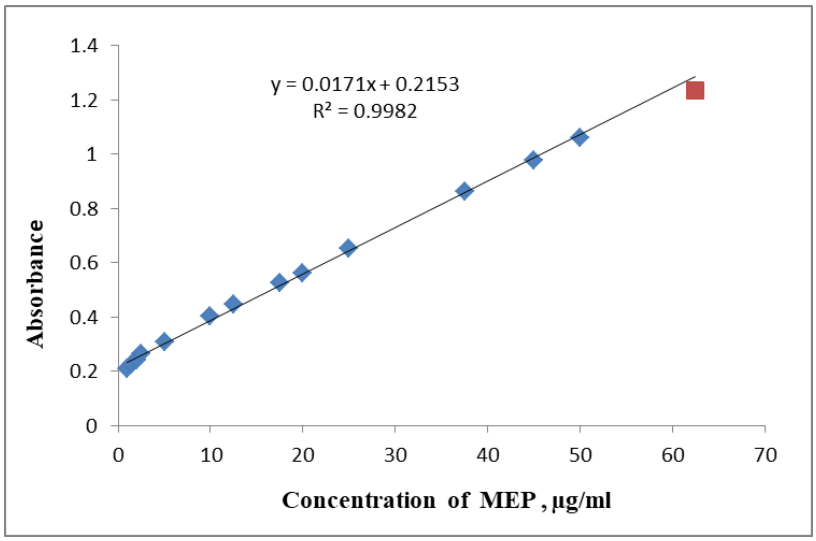


Fig. 6: The calibration curve for the determination of MEP according to the suggested new method

The calibration curve shows that the linearity range is from 1 to 50 µg/mL with molar absorptivity 6.557×10^3 $L.mol^{-1}.cm^{-1}$., index of Sandell's was 0.0584 $\mu g.cm^{-2}$, and the calculated LOD, and LOQ were 0.02789 µg/mL, 0.0929 µg/mL respectively.

8. Accuracy and precision of the present method

The accuracy of the method and precision have been checked for three concentrations 12.5,25, and 37.5 µg/mL with three replications of each concentration within the calibration, the calculated range of relative error was from -1.022 to 0.34 % which indicates high accuracy and the calculated range of the relative standard deviation was from 0.347 to 0.574% which indicate high precision. Table (9) list the results.

Table 9: The Accuracy and precision of the present method

Amount taken (µg/mL)	Amount found (µg/mL)	Recovery % *	Relative standard deviation* %	Relative error* %
12.5	12.47	99.82	0.574	-0.18
25	24.74	99.97	0.473	-0.03
37.5	37.63	100.34	0.347	0.34

* Average of five determinations

9. Study the reaction ratio between MEP and ALRS

Mole-ratio and Job methods (Christian, 2007) have been followed to evaluate the ratio of the reaction between MEP and ALRS, the two methods show that the reaction is 1:2 MEP to ALRS.

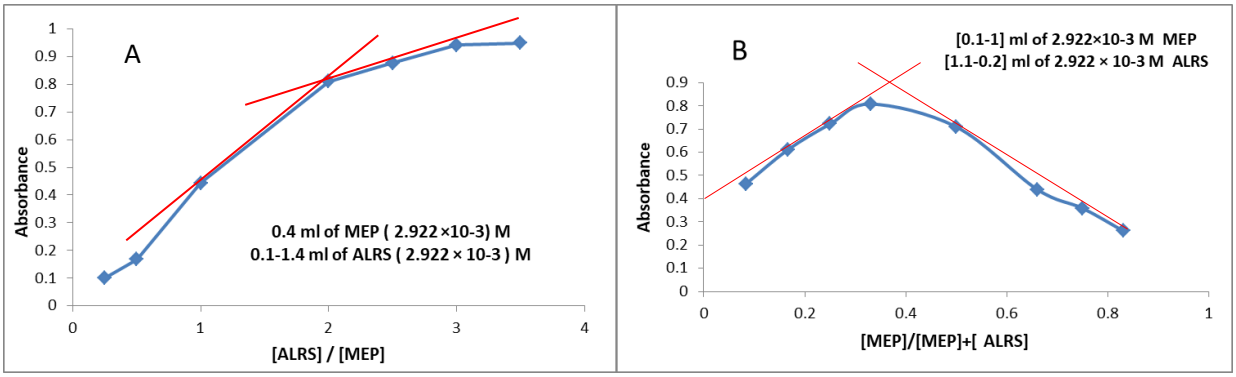


Fig. 7: A: Mole-ratio and B: Job methods to evaluate the reaction ratio between MEP and ALRS

According to the estimated reaction ratio between MEP and ALRS (1:2) and as the determination reaction take place at a slightly acidic medium pH 6.7, MEP undergoes protonation at two positions and therefore requires two negatively charged ALSR molecules to form the red ion-pair measured at 526 nm. (Rabee and Nabeel, 2022).

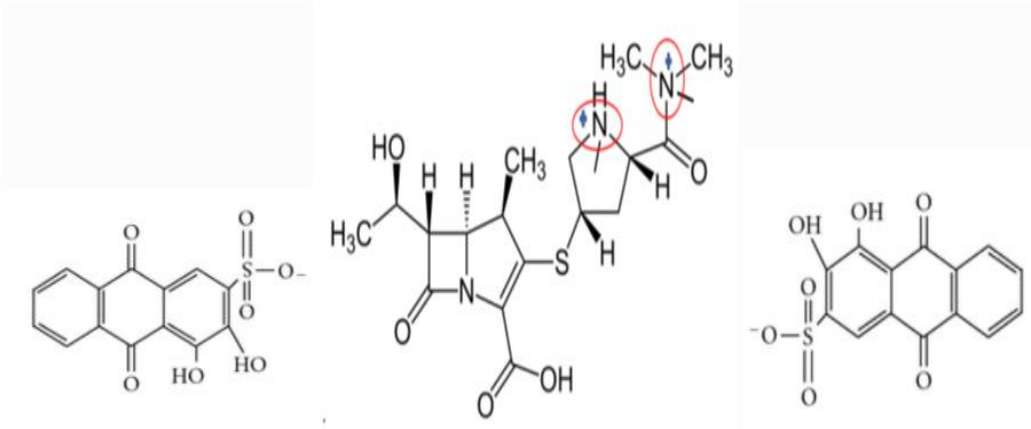


Fig. 8: The suggested reaction between MEP and ALRS

10. Stability constant of the colored ion-pair product

Equimolar (2.922x10^{-3}M) of the two reaction components MEP and ALRS has been mixed in two ratios, the first is the identical ratio (As) while the second is two-fold ratio excess of ALRS (Am) and measured at 526 nm. according to the reaction conditions against blank, then the degree

of dissociation α has been calculated and applied to the law of calculations of stability constant for 1:2 reactions. The results in (Table 10) show the high stability of the colored product with the average stability constant K equal to 3.1 x10^8 L.mol^{-1}.

Table 10: The stability constant of the colored ion-pair of MEP and ALRS

Volume of MEP (2.922×10^{-3} M) (mL)	Abs		α	K (L/mol)	Average value of K (L/mol)
	As	Am			
0.3	0.393	0.609	0.3545	4.6×10^8	**$10^8\times3.1$**
0.6	0.7891	1.1699	0.3254	1.6×10^8	

11. Application of the method

The present method has been applied for the determination of MEP in pharmaceutical preparations by taking three different concentrations 12.5,25, and 37.5 µg/mL and following the reaction procedure to calculate the recovery % and the relative standard deviations. as well as the "t" value test for the purpose of determining the efficiency of the proposed method, and for five determinations of pharmaceutical solutions by applying the following mathematical relationship to find the experimental "t" value (Christian, 2007).

$$\pm t = (\bar{x} - M)\frac{\sqrt{N}}{S}$$

where $\bar{x}$ is the main of readings, M is the amount of standard meropenem, N is the number of readings of the proposed method, and S is the standard deviation that can be calculated by applying the following relationship, where Xi is the reading:

$$S = \sqrt{\frac{\sum(Xi - \bar{x})^2}{N - 1}}$$

The calculated t-experimental has been listed in (Table 11).

Table 11: Determination of MEP in pharmaceutical preparations

Drug content	MEP-taken (µg/mL)	MEP -found (µg/mL)	Recovery * %	Relative standard deviation*%	t-exp.
Meropenem vials 1g/ (Venus pharm/Germany)	12.5	12.46	99.68	0.583	−1.035
	25	24.77	99.08	0.385	-1.666
	37.5	37.55	100.13	0.313	0.958
Nbaxo vials 1g / manufactured (acino/ Switzerland)	12.5	12.37	98.96	0.259	-1.690
	25	24.65	98.6	0.359	-2.47
	37.5	37.55	100.13	0.334	0.894

* Average of five determinations

Standard Addition Method

To improve the ability of the application to pharmaceutical preparations without any interferences caused by inactive ingredients, the standard addition method has been followed for two concentrations of MEP 12.5 and 25 µg / mL as shown in Fig. (9 A and B) respectively. The results in (Table 12) show a high recovery ranging from 102.0 to 103.2%.

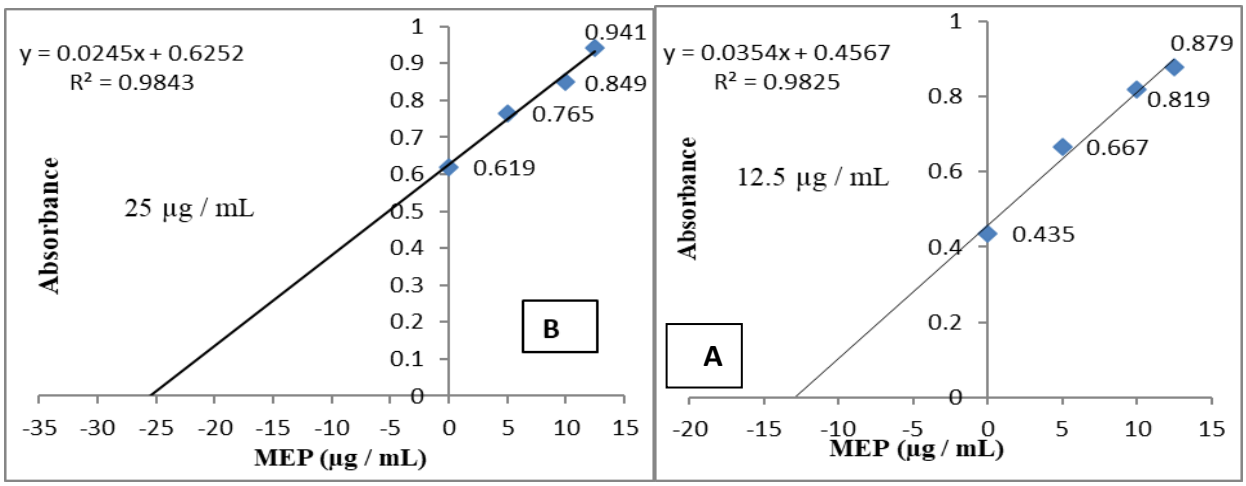


Fig. 9: The standard addition method

Table 12: The results of standard addition method

Drug content	MEP taken(µg/mL)	MEP found(µg/mL)	Recovery %
Meropenem vials 1g/ (Venus pharm/Germany)	12.5	12.90	103.20
	25.0	25.51	102.00

Comparison of the Method

Table (13) shows a wide range of application, higher sensitivity, lower detection limit and lower determination limits, and show higher stability.

Table 13: Comparison of the methods

Analytical parameters	Present method	Literature method (Venkateswararao *et al.*, 2013)
Method	Ion –pair	Ion –pair
Reagent	Alizarin red S	Bromothymol and bromocresol
Temperature (°c)	At room temperature	––––––––––
λmax (nm)	526	420 418
Medium of method	Slightly acidic 6.7 pH	pH 3
Color of the dye	Red	-Blue -purple
Linearity, µg.mL^{-1}	1-50	10-50 12.5-62.5
Sandell's sensitivity, µg/cm^2	0.0584	0.6548 0.7854
LOD(µg/mL)	0.02789	1.188 1.986
LOQ(µg/mL)	0.0929	3.96 6.57
Molar absorptivity (L.mol^{-1}.cm^{-1})	6.557 × 10^3	1.018x10^3 1.43×10^3
Pre-separation	Non	Solvent extraction
Stability of the color	55	––––––––––
Application of the method	Injection powder	Injection powder

CONCLUSION

A sensitive, selective, and simple method for the determination of MEP is created using an ion-pair reaction procedure with ALRS by a single analysis step, adjustment of the acidity or temperature of the reaction medium is not required. The linearity ranged from 1 to 50 µg /mL, with molar absorptivity of 6.557×10^3 L.mol^{-1} .cm^{-1}., the range of relative error was from -1.022 to 0.34 % which indicates high accuracy, and the calculated range of the relative standard deviation was from 0.347 to 0.574% which indicates high precision. A successful determination of MEP in dosage forms has been applied in which the recovery ranged from 99.8 to 103.2%. The method has been validated by t-test and standard addition method. The method reduces the use of reagents, reduces the time of analysis.

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الاليزارين الأحمر بوصفه كاشفا كروموجينيا لتقدير الميروبينيم في المستحضرات الصيدلانية

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الملخص

تم استخدام الاليزارين الأحمر بوصفه كاشفا كروموجينيا لتقدير الميروبينيم في مستحضراته الصيدلانية وذلك من خلال تطبيق طريقة حساسة وانتقائية تعتمد على تكوين مزدوج ايوني بين المركبين في مزيج من محيط مائي وكحولي بنسبة 50:50من دون الحاجة الى تهيئة محيط للتفاعل سواء حامضي او قاعدي. أظهرت الطريقة مدى من الخطية تراوح بين 1 الى 50 مايكرو غرام/ مللتر. كانت قيمة الامتصاص المولاري مساوية الى 6577 لتر/ مول. سم. وقيمة دلالة ساندل للحساسية 0.0584 مايكروغرام/سم^{2}. كما ان قيم حد الكشف LOD و حد التقدير الكمي LOQ المحسوبة هي 0.02789 مايكرو غرام/ مللتر و0.34 مايكروغرام /مللتر على التوالي. وكان الخطأ النسبي للطريقة بين −1.022الى + 0.34 % مما يدل على الدقة العالية للطريقة كما كانت قيم الانحراف القياسي النسبي تراوحت بين 0.347 الى 0.574 ممايدل على التوافق العالي بين القراءات. تم تطبيق الطريقة لتقدير الميروبينيم في المستحضرات الصيدلانية بنجاح حيث كانت نسبة الاسترجاع بين 99.8 الى 103.2وتم تطبيق طريقة الإضافة القياسية التي أظهرت عدم وجود تداخل من قبل المضافات غير الفعالة للدواء (مواد السواغ).

الكلمات الدالة: الاليزارين الأحمر، ميروبينيم، مزدوج ايوني، كاشف كروموجينيا.