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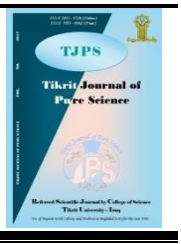

Determination of Montelukast Sodium by flow injection chemiluminescence

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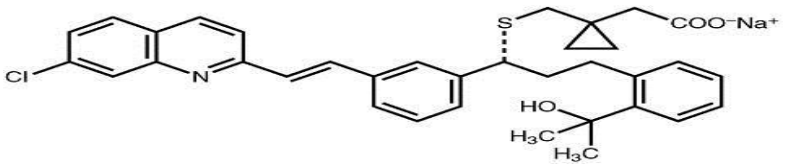
Abstract

This study includes determination Montelukast sodium by using flow injection chemiluminescence technique, the optimum concentrations were (150) ppm of magnesum ion, (5×10^{-4}) M luminol, (0.001) M hydrogen peroxide, linearity of concetraction (0.1-0.001) M that give the highest luminescence intensity, and correlation cofficient was (0.9054), The relative standard deviation RSD% (2.3) and detection limit (0.0001) M and relative error (0.018) ,the percent recovery (97%).

1-1 Montelukast drug

1-1-1 Definition [1]: The sicentific chemical name for this drug is 2-1-3-2-7-Chloroquinoli-2-Vinyl phenyl propyl thion methyl cyclopropyl acetic acid sodium .



The structural formula of Montelukast Sodium

While the common name according to the factoring companies is Singulair – Montelukast Sodium [2] and the molecular formula is $C_{35}H_{36}ClNO_3SNa$

1-1-2 drug proprties [1]

It is a white hygroscopic powder, freely soluble in water, it is odorless and melting point at 130° C and dissociated at same degree, where, the drug restricting chemical compound that called Leukotrienes which plays an intersting role in allergic response and inflammations, this restricting of that activity to prevent the bronchial constriction and improves the main symptoms of asthma.

1-1-3 drug uses

1- Laryngitis
2- Chronic asthma
3- Rhinitis

1-1-4 The techniquies that used for determination Montelukast Sodium

Guo[3] determined the Montelukast by indirect chemiluminescence and by quinine as receptor, where the tetra cerium oxidizing by sulpheric acid and the detection limit was 0.36 µmol per ml .

While, Song [4] was used photometric spectrum technique, promothymol used in determination at 420 nm and detection limit was 4mg/ml.

Liang [5] could to determination drug by fluorescence technique at linear limit 0.4-4 mg/l at detection limit reached to 0.04 mg/l. while, Zeng [6] was able to determine the drug by measuring the stability of photometric spectrum and TLC, using coated thin layer (silica gel 60 F 354) and acetonitrile / ethanol- water as a mobile phase and the detection limit was 2.1 gm/ml.

The researcher Zhou [7] was able to determine the drug by measuring chemiluminescence technique using cobalt ion as catalyst by chemiluminescence suppression .

1-1-5 the instruments and chemicals

1- pH meter model JENWAY350
2- Ultrasonic Cleaner model SARTORIUS-50 B
3- Sensitive balance model SARTORIUS
4- Hot plate with magnatic sterior model JENWAY, WITE. GERMANY
5- Unit of Flow injaction .
6- Chemiluminescence Unit System .

Table (1)the chemicals used in this study

Chemical name	Chemical formula	Purity %	Origin (company)
Luminol	$PHNH_2C_2O_2(NH_3)_2$	98	Fluka
Hydrogen peroxide	H_2O_2	48	BDH
Sodium carbonate	Na_2CO_3	99	BDH
Sulfuric acid	H_2SO_4	96	Fluka
Potassium permanganate	$KMnO_4$	98	BDH
Hydrochloric acid	HCl	96	Fluka
Magnesium Sulphate	$MgSO_4$	96	Fluka

2-1 Working conditions

2-1-1 Study of ion catalyst selection

The selection ofion catalyst in this technique was done by experimented numbers of ion catalyst (platinum, Zirconium, Manganese, and Thorium) to determine the ability of these ions in stimulation the luminol oxidation with hydrogen peroxide and it's ability to formation complexes with the drug which in turn leads to suppression or stimulation of chemiluminescence intensity for this substance.

2-1-2 Selection the optimum concentration of magnesium ion Mg^{+2}

The magnesium ion was selected as catalyst, where a series of magnesium concentrations were injected into a range between 110- 150 ppm ,for finding the best concentration of Mg^{+2}, and found the best one was 150 ppm. Where is the weight 0.0742 gram with Magnesium sulfate and dissolved in distilled water in volumetric flask 100 ml capacity thus prepare 150 ppm of Magnesium sulfate .

2-1-3 Study of Luminol concentration

The effect of Luminal concentration on the intensity of chemiluminescence was studied by taken different concentration of Luminol ranging between ($5x10^{-4}$ – 10^{-6}) M , after injection 150ppm Mg^{+2} ion .

2-1-4 Study of hydrogen peroxide effect

The effect of different concentrations of hydrogen peroxide on the emission intensity was studied at rang (10^{-3} -10^{-6}) M, after fixing the concentration of Mg^{+2} and Luminol solution with injected 150 ppm Mg^{+2} ion.

2-1-5 Study of the acidity effect for Mg^{+2} ion on the luminscence intensity

Series of acid concentration ranging between (10^{-3}-10^{-5}) M was prepared, and the ion catalyst was dissolved in it, all that was done to show the acidic effect for ion catalyst on the emission intensity .

2-1-6 The volume effect of injection sample for ion catalyst

The effect of injector ion volume was studied, after fixing all chemical variables, by changing the length of curve tube in loop, where taken different volumes (150-400 µl) after injection 150ppm.

2-1-7 Study the effect of flow velocity rate

After fixing all chemical variables and the volume of injector ion, the effect of flow velocity rate of solutions on the emission intensity of chemiluminescence was studied by changing the flow rate from 2 to 4 ml/min.

2-1-8 Measurment the dilution degree The effect of dilution degree on the flow injection system was studied in case of presence and absence the ion exchanger columns by the following equation :**$D=H_0/H_{max}$**

H_0= represents the luminscent emission of Mg^{+2}ion in milli volt where it passes instead of the current .

H_{max}= represents the luminscent intensity of Mg^{+2} ion

2-1-9 Standard curve design to determining the montelukast drug

Series of montelukast solutions were prepared at different concentrations between (10^{-1}- 10^{-4} M) by diluted wih aqueous solution from Mg^{+2} at concentration 150ppm, then injected five times for each concentration simultaneously and recorded the average of five readings .

2-1-10 Measurment of accuracy and regulation in determination the montelkast drug

Theaccuracy and precision in determination montelukast drug were measured by measuring the relative standard deviation, relative error, and recovery, the optimum conditions for determination were obtained .

2-1-11 Applications

The optimum conditions that obtained were applied to determining drugs, where five tablets of drugs form were crushed and one tablet was weighted (2) gram (pioneer company pharmaceutical) As Sulaymaniyah, Iraq. then dissolved in Mg^{+2} ion at concentration 150 ppm using ultrasonic bath, which supplied with a water bath, in volumetric flask (100ml) for 10 min., then, the sample was filtered on the filter paper and the leach ate put in suitable volumetric flask and the volume completed with Mg^{+2} to gained the concentration of solution at (0.1-0.0001M), each concentrations were injected simultaneously and recorded the average of five readings.

3-1 Results and discussion

3-1-1 Selection the best concentration of magnesium

Magnesium ion was selected as best metallic ion to the drug determination, and has ability to oxidizing luminol with hydrogen peroxide . table (2) show the relationship between concentrations of series standard solution that prepared from Mg^{+2} ion at concentration 110-150 ppm with increasing of chemiluminescence intensity. 150 ppm was selected as best concentration to give it the highest chemiluminescence intensity, where sharp values in regular manner were obtained. While, at low concentration, the broad and not sharp were recorded, that mean , no irregularity of bands .

Table (2) the relationship between Mg^{+2} concentration and the intensity of chemical luminescence emission

The intensity Elevated of chemilumienscence emission (milli volt)	Mg^{+2} concentration (ppm)
200	110
220	120
240	130
270	140
290	150

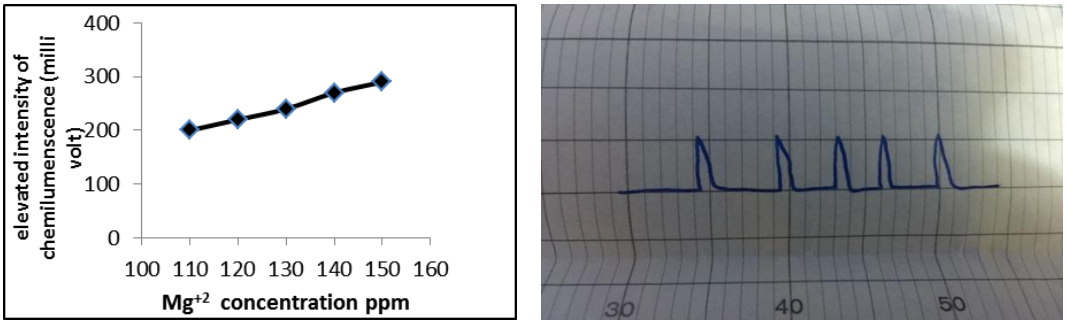


Figure (1) relationship between the intensity of chemiluminescence emission and Mg^{+2} concentration

3-1-2 Selection the best concentration of Luminol

After the selection best concentration of Mg^{+2} ion, the effect of Luminol concentration on the emission intensity of chemiluminescence was studied by changing the luminol concentration at range ($5x\ 10^{-4}$ - 10^{-6} M) and the results were obtained as shown in table (3) recorded after fixing all chemical variables. it was observed that the luminescence increase with the increasing of luminol concentration (the donor molecule to luminesce) and the recorded that, $5x10^{-4}$ M was the best concentration to give it the highest intensity. according to the previous studies [8] the decrease may be happened in chemiluminescence intensity duo to the increasing in luminol concentration. That may be leading to increasing in the numbers of donor molecules as luminescence light in surrounding that leading to free collisions between the reacting molecules, some of it which entered in collision and producing excited molecules and the excess of it will reacting with molecules of reactants in surrounding, and luminol excited molecules causing loss in energy as thermal energy– non radioactive - and thus chemiluminescence emission reduce.

Table (3)relation between Luminol concentration and Intensity of chemical lumeinscence

Luminol concentration M	Intensity of chemical lumeinscence (milli volt)
10^{-6}	**110**
$10^{-6}5\times$	**130**
10^{-5}	**150**
$10^{-5}5\times$	**170**
10^{-4}	**180**
$10^{-4}5\times$	**200**

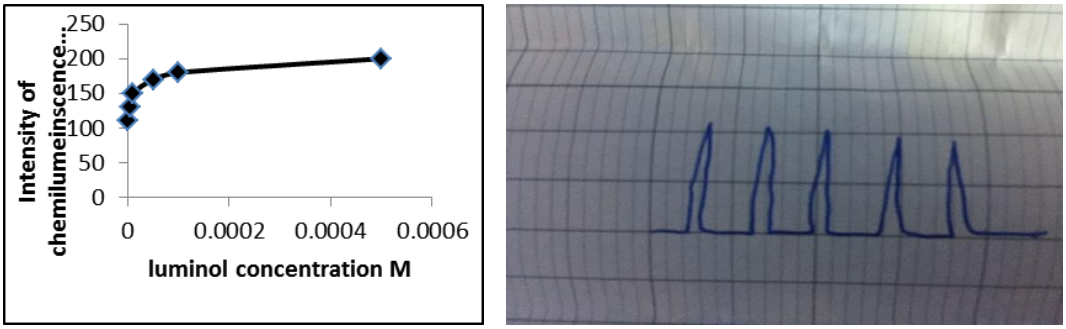
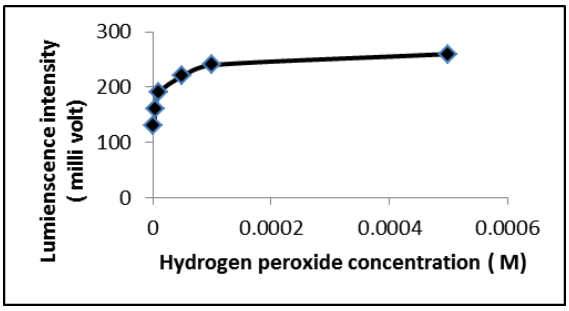


Figure (2) relationship between luminol concentration and intensity of chemiluminescence

3-1-3 Selection the best concentration of hydrogen peroxide: The effect of hydrogen peroxide on chemiluminescence emission intensity was studied after fixing the concentration of ion catalyst and luminol at range (10^{-3} – 10^{-6} M), the (10^{-3} M) was selected as the optimum concentration to give it the highest chemiluminescence intensity with peaks , and noticed that a weak emission of chemiluminescence was obtained at low concentration of hydrogen peroxide due to the lack of light emitting – parts because to the concentration of oxidizing substances. the obtained results show in table (4).

Table (4) relationship between hydrogen peroxide concentration and Luminescence

Hydrogen peroxide concentration (M)	Lumienscence intensity (milli volt)
10^{-6}	**130**
10^{-5}	**160**
$10^{-5}5\times$	**190**
10^{-4}	**220**
$10^{-4}5\times$	**240**
10^{-3}	**260**



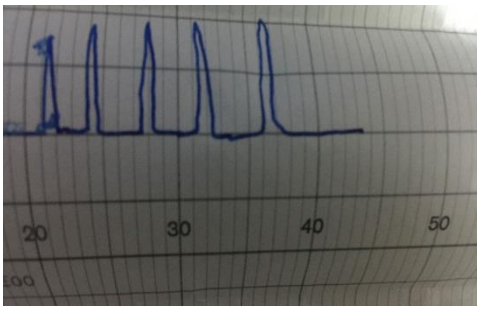


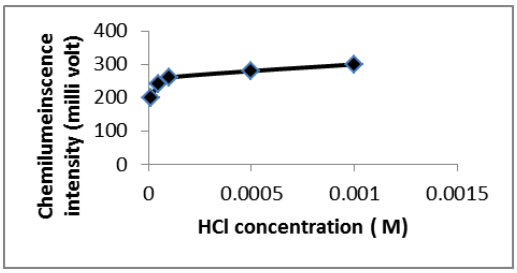
figure (3) relationship between hydrogen peroxide concentration and Luminescence intensity

3-1-4 Effect of catalyst acidity on the luminescence intensity

Table (5) shows the acidity effect for the solution that Mg^{+2} ions dissolved in it, so that at several concentration of hydochloric acid (10^{-3} - 10^{-5} M) were selected to dissolving Mg^{+2} ion in range 110-150 ppm with fixing the concentration of luminol and hydrogen peroxide. the 10^{-3} M was selected as optimum concentration to give it the highest intensity with sharp peaks that due to ability of hydochloric acid to releasing protons more than other acids, leading to increase the ability of ion catalyst to oxidizing the luminol and thus increasing the intensity of chemilumienscence emission [9].

Table (5) the effect of acidity on Mg^{+2} ion

HCl concentration (M)	Chemical lumeinscence intensity (milli volt)
10^{-5}	**200**
$10^{-5}5\times$	**240**
10^{-4}	**260**
$10^{-4}5\times$	**280**
10^{-3}	**300**



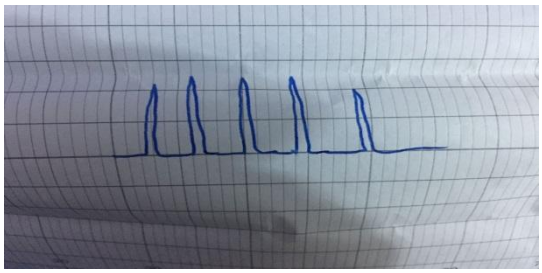


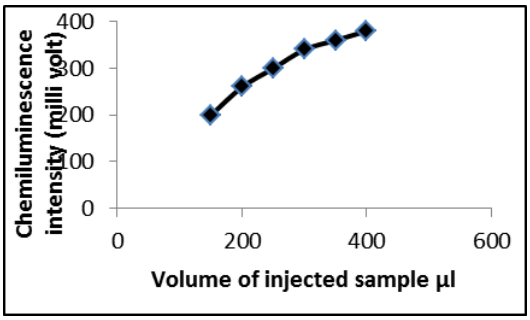
Figure (4) the effect of acidity on Chemilumeinscence intensity

3-1-5 effect of injected sample volume of ion catalyst

Effect of injected ion volume was studied after fixing all variables by changing the length of loop and noticed that the response was increase with increasing the volume of injected sample but the response represented at boarded peaks (more response) time, that result, of continuous emission, due to the length of sample part in the reaction phase versus the sensor (a saturation state happened for photo multiplying tube PMT), according to that, volume 350 µl was selected because it give the response with sharp and regular peaks but with sensitivity less than that resulting from larger volumes, therefore, the volume selection must be based on balance between the shape of response and it's intensity and the measured sensitivity, as well as the economy in the chemicals consumption.

Table (6) effect of Mg^{+2}volume on the chemiluminescence intensity

Volume of injected sample µl	Chemical luminescence intensity (milli volt)
150	200
200	260
250	300
300	340
350	360
400	380



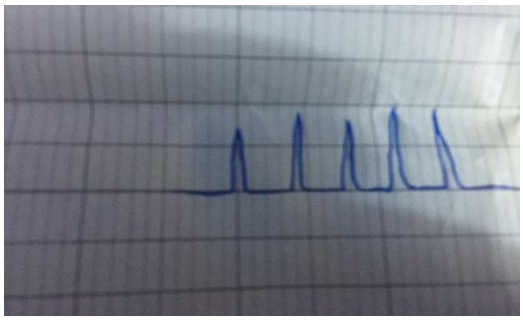


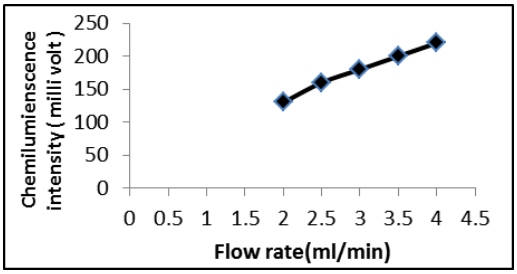
Figure (5) effect of injected volume on chemiluminescence intensity

3-1-6 Effect of ions flow rate

Effect of flow rate for solution on the intensity of chemical luminescence emission was studied, after fixing all chemical variables, by changing the flow rate from 2 to 4 ml/min for hydrogen peroxide and luminol, and noticed that the increasing of emission intensity happened with increasing the flow rate at beginning 2-4 ml/min because the high flow rate leading to rapidity lightness segment that exit from measurement cell (there was a little to recording a signal), therefore, 3-5 ml/min was selected because it's consuming less of chemicals, and perform the desired purpose .

Table (7) show the flow rate on chemiluminescence intensity

Flow rate (ml/min)	Chemiluminescence intensity (milli volt)
2	130
2.5	160
3	180
3.5	200
4	220



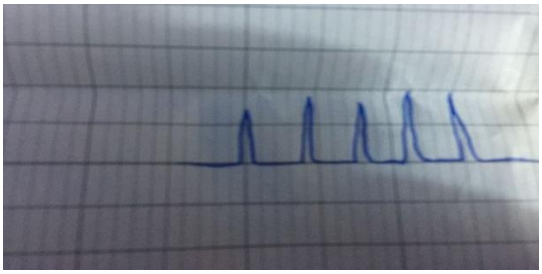


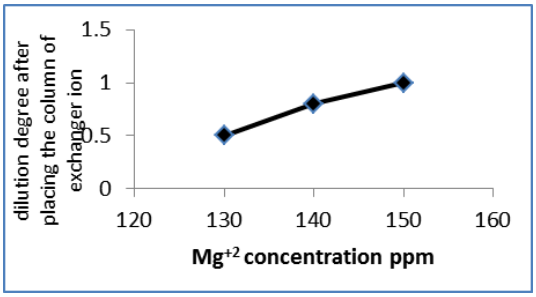
figure (6) show the flow rate on Chemilumienscence intensity

3-1-7 Dilution degree measurement

The dilution degree was calculated in presence and absent the ion exchanger columns because the flow injection technique is effects by dilution degree , all results that obtained from our study shown in table (8).

Table (8) the obtained results from measurement of dilution degree

Measurment case	Mg^{+2} Concentration ppm	Dilution degree	average of dilution degree
Befor placing the column of exchanger ion	130	2	2.4
	140	2.4	
	150	2.8	
After placing on the column of exchanger ion	130	0.5	0.76
	140	0.8	
	150	1	



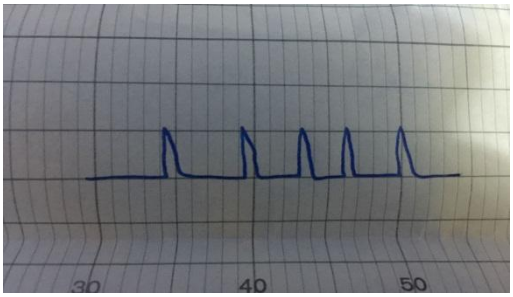


figure (8) the obtained results from measurment of dilution degree (after placing the column of exchanger ion)

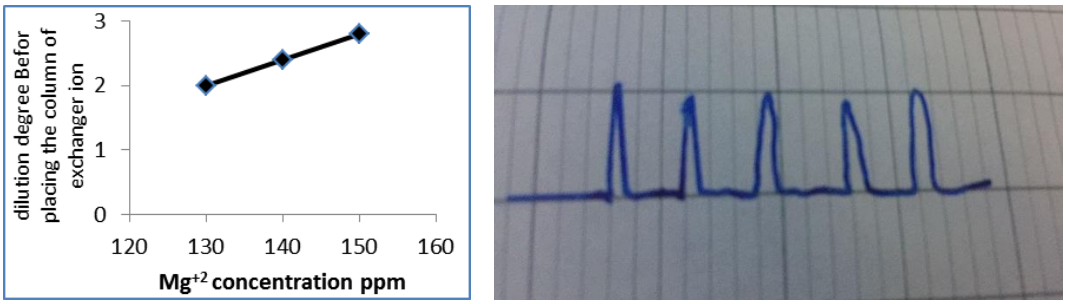


figure (7) the obtained results from measurment of dilution degree (before placing the column of exchanger ion)

3-1-8 Standard curve to determination the Montelukast drug

The relationship between the changing of drug concentration comparing with chemiluminescence intensity of magnisum ion at concentration 150 ppm, as shown in figure (9), it was noticed that there was increase in intensity of chemiluminescence due to functional role of druge. the linear equation was : Y=2535.2X + 657.32 , and detection limit was (0.0001M), correlation cofficient = 0.9054.

Table (9) the linear equation , linear range and detection limit for the Montelukast drug determination

Drug name	Linear equation	R^2 value	Linear range (M)	detection limit (M)
Montelukast	y=2535.2x+657.32	0.9054	0.1−0.001	0.0001

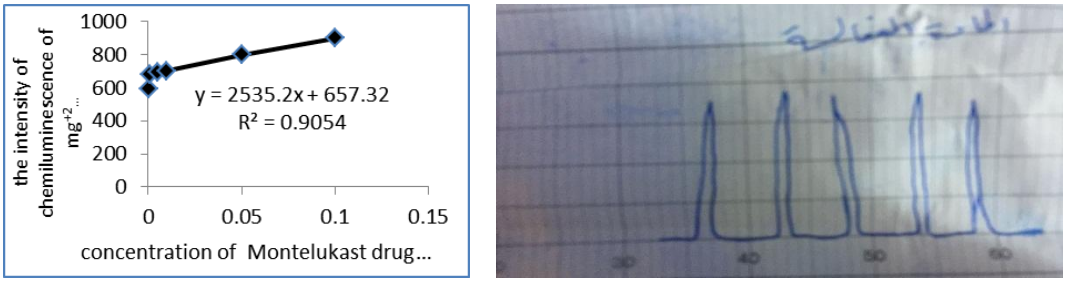


Figure (9) standard curve of montelukast drug

3-1-9 Measurment of accurcy and precision in drug detremination

After fixing the optimum conditions to determination the drug , the accuracy and precision were calculated by calculation the recovery and recovery rate was (97-99%), the relative standard deviation (RSD) ranging at (2.2-2.9 %) , while the relative error was (0.9 - 0.18).

Table (10) The obtained results from accuracy and precision measurement

Drug name	**Prepared amount (M)**	**RE %**	**RSD %**	**Recovary %**
Montelukast (pioneer company pharmaceutical) As Sulaymaniyah , Iraq	**10^{-4}**	**0.9**	**2.2**	**97**
	10^{-3}	**0.12**	**2.5**	**98**
	10^{-2}	**0.15**	**2.8**	**98.5**
	10^{-1}	**0.18**	**2.9**	**99**

3-1-10 Applications

The optimum conditions for drug determination were applied and series of concentrations were prepared and the relative error, recovery, and relative standard deviation were calculated, the results shown in table (11).

Table (11) the recovery, and relative standard deviation(RSD) and relative error(RE) of drug

Drug name	**Recovary %**	RSD %	**RE %**
Montelukast	**95**	**2.3**	**0.019**

Table (12) T calculated values of drug

Drug name	**T tabled test at 95%**	**T calculated teset**
Montelukast	**2.45**	**19.2**

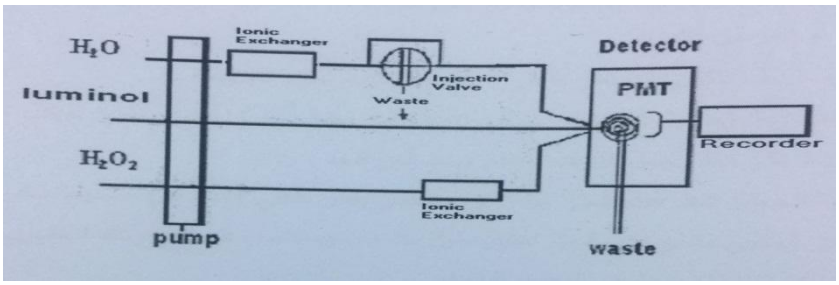


Diagram represents the flow injection process

Picture showing flow injection device

Conclusions

A simple and accurate method for estimating Montelukast sodium was developed by flow injection chemiluminescence technique. 150 ppm was tested as the highest concentration of magnesium ion 5×10^{-4} and as the best concentration of luminol (0.001) M where the concentration of hydrogen peroxide was higher than luster intensity and was linear at concentration (0.905), while the relative standard deviation (2.3), the detection unit (0.0001) M, the relative error (0.018), the retrieval rate of less than 97%.

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تقدير المونتيلوكاست صوديوم بأستخدام تقنية الحقن الجرياني– البريق الكيميائي

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الملخص

يتضمن البحث تقدير المونتيلوكاست صوديوم بأستخدام تقنية الحقن الجرياني– البريق الكيميائي وقد تم اختبار 150 جزء من المليون كأفضل تركيز لايون المغنيسيوم5×10^{-4}وكأفضل تركيز للومينول (0.001)M حيث اعطى تركيز بيروكسيد الهيدروجين اعلى شدة بريق وكانت خطية عند تركيز (0.1 – 0.001) M وبمعامل ارتباط (0.905)، بينما كان معدل الانحراف القياسي النسبي (2.3) وحد كشف (0.0001)M، والخطأ النسبي (0.018)، ونسبة استرجاع لاتقل عن 97%.