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Potentiometric Method to Determine Montelukast Sodium in its Tablets with In-line Monitoring of its Dissolution Behaviour

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Abstract- Direct drug determination without any pervious treatment steps is the most environmentally friendly method of analysis. Traditional analysis methods usually involve a pre-treatment step before analysis and this consumes time and organic solvents. This work describes direct potentiometric method by using ion selective electrode to determine Montelukast Sodium in its pure drug substance and in tablet formulation and for inline monitoring of its release from its tablet form without any sample pretreatment. A Sensor was fabricated using PVC based membrane containing tetradodecyl ammonium bromide (TDB) being as an anionic exchanger and 2-nitrophenyl-octyl-ether (2-NPOE) being a plasticizer. The validation of the proposed method was done according to International union of pure and applied chemistry recommendations, in which the proposed sensor show a linear dynamic range from 1.0×10^{-6} to 1.0×10^{-2} mol/L. The proposed sensor was applied to determine Montelukast sodium in bulk powder, tablets dosage form with no extraction. The sensor was also used as bench-top real-time analyser for in process tracking of Montelukast sodium concentration during monitoring of its dissolution behaviour, under U.S. Food and Drug Administration dissolution regulations, with clear discrimination from its common excipients. Results obtained by the proposed potentiometric method were compared with those obtained by the official HPLC method.

Keywords- Monitoring dissolution; Green approach; In-line potentiometric method; Montelukast Sodium

1. INTRODUCTION

Chemical sensors are used for fast and economical monitoring of different pharmaceutical compounds. The determination of drugs in pure powder and pharmaceutical dosage form by ion selective electrode (ISEs) have the ability to show both ion exchange and perm-selectivity of the sensor ions and the signal is generated due to selective partitioning of ionic species between these two phases. Ion selective electrodes show high selectivity and impart a great advantage over other techniques [1], where, they can be used through a wide concentration range also they demonstrate fast response to changes in concentration and can tolerate small changes in pH. In addition, they are uncomplicated, environmentally friendly, cost-effective in its setup and run [2]. Several reports have been published highlighting the importance of ion selective sensors contribution for the quantification of drugs [3-5].

Dissolution test technique is applied in order to detect pharmaceutical formulation problems and to compare in vitro and in vivo studies. Usually determination of different drugs in their dissolution media were carried out using traditional spectrophotometric or HPLC methods. At different time intervals samples are withdrawn then filtered and sometimes derivatized before being analysed. Dissolution systems automation was introduced but with several disadvantages either during UV- detection such as turbidity or in HPLC methods such as discontinues profiles. As the automation requires high-priced setup, time and solvent consumption, the development of a rapid in-line analytical method which is direct, simple and continuous is considered to be ideal to determine the drug concentration during dissolution testing.

Montelukast sodium (MLK) is an selective leukotriene receptor antagonist [6,7]. It belongs to a styryl-quinolines series with the chemical name, sodium salt of 2-[1-[[(1R)-1-[3-[2-(7-chloroquinolin-2-yl) ethenyl] phenyl]-3-[2-(2-hydroxypropan-2-yl) phenyl] propyl] sulfanyl methyl] cyclopropyl] acetic acid, (Fig. 1). It is used as a therapeutic agent for the treatment of bronchial asthma [8] by means of once daily oral administration.

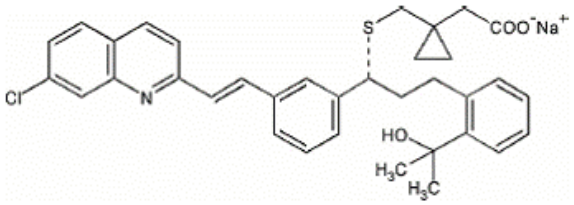

Fig. 1. Chemical structure of Montelukast Sodium

A literature survey revealed that several analytical methods were reported for the analysis of MLK including capillary electrophoresis [8-10], spectrophotometry [11-19], spectrofluorometry [20] high performance liquid chromatography (HPLC) [21-27], high performance thin layer chromatography (HPTLC) [28-30], and voltammetry [31-34]. Till date,

to best of our knowledge no potentiometric methods were reported for MLK determination. The main goal of this work was to determine MLK using ion selective electrode potentiometry. Applying this potentiometric method opens the field toward applying green cost-effective and simple in-line potentiometric method for continuous monitoring of MLK dissolution from its dosage form.

2. Experimental

2.1. Apparatus

Potentiometric measurements were accomplished using Ag°/AgCl double junction reference electrode; Orion 900200 (Thermo Fisher Scientific, Waltham, MA); 3.0 M KCl saturated with AgCl as an inner filling solution and 10% KNO3 as a bridge electrolyte and pH glass electrode; Jenway (UK) No. 924005-BO3-Q11C for adjusting pH was used. Digital ion analyzer (Jenway, United Kingdom) Magnetic stirrer, Bandelin Sonorox, Rx510S (Budapest, Hungary) were also used. VanKel VK 7000 USP II (Paddle) apparatus was utilized to perform the dissolution experiment. It consists of six vessels each containing 900 mL of 0.5% Sodium Dodecyl Sulfate (SDS) in water, thermostatically set at 37±0.5°C. The medium was agitated using a paddle at a rotation rate of 50 rpm.

KNAUER® smart line High-performance liquid chromatography (HPLC) furnished with Eclipse C-8 (100×4.6 mm, 3.5 µm) column, smart line pump 100 V5010 (KNAUER), KNAUER® photodiode array (PDA) detector, Injection switching values V7452 (KNAUER), smart line degasser V7620 (KNAUER), smart line column oven 4050 V7335 (KNAUER) were used.

2.2. Materials and reagents

Analytical grade chemicals and solvents were utilized. Polyvinylchloride (PVC) of high molecular weight, Tetradodecyl ammonium bromide (TDM), 2-nitrophenyloctylether (NOPE), tetrahydrofuran (THF), and acetonitrile HPLC grade were obtained from Sigma Aldrich, Egypt. Potassium chloride, hydrochloric acid, sodium hydroxide and potassium dihydrogen orthophosphate were obtained from El-Nasr Pharmaceuticals, Cairo, Egypt. Deionized water was obtained from an Elga Ultrapure Q apparatus. Phosphate buffer pH 8 was prepared by adding 46.8 mL of 0.2M sodium hydroxide to 50.0 mL of 0.2 M potassium dihydrogen phosphate then diluting to 500.0 mL with water.

2.3. Samples

2.3.1. Pure standards

MLK working standard was kindly supplied by EGYPHAR Pharmaceutical Industries, Obour city, Kaliobeya, Egypt and its purity was found to be 99.8% according to the official method [35].

2.3.2. Pharmaceutical formulation

Asmalair® tablets (Labelled to contain 10.4 mg Montelukast Sodium equivalent to 10 mg Montelukast, Batch No.1500617) were used. The tablets are manufactured by Hi Pharm for Manufacturing Pharmaceuticals and Chemicals, Cairo, Egypt, and were purchased from the local market.

2.4. Standard solution

MLK stock standard solution (1×10^{-2} mol/L) was prepared in 0.02 M phosphate buffer pH 8. Working standard solutions (1×10^{-7} to 1×10^{-3} mol/L) were prepared by suitable dilution of the stock solution by means of 0.02 M phosphate buffer pH 8.

2.5. Procedure

2.5.1. PVC membrane sensor fabrication and calibration

PVC membrane was fabricated in 5-cm diameter petri dish; 0.4 ml 2-NPOE was mixed with 190 mg PVC and 10 mg TDM to construct MLK sensor. The mixture was then dissolved by stirring with 6.0 mL of THF. The Petri dish was then covered with a Whatman No. 3 filter paper and left overnight at room temperature to evaporate the solvent obtaining master membrane with 0.1 mm thickness. A disk approximately 7 mm diameter was cut from the prepared PVC membrane and then firmed by the use of THF to an elastic PVC tip, which was fixed into the end of a glass electrode body. Equal volumes of 1×10^{-3} mol/L MLK and 1×10^{-3} mol/L potassium chloride (both prepared in 0.02 M phosphate Buffer pH 8) were mixed and used as an internal reference solution. Ag^{o}/AgCl wire (1 mm diameter) was used as an internal reference electrode when immersed in the internal reference solution. The sensor was conditioned by soaking in 1×10^{-3} mol/L MLK standard solution for 24 h and then stored in the same solution when not in use.

Calibration was done in a series of 25-mL volumetric flasks by transferring aliquots of MLK working solutions then immersing the electrode in conjunction with a double junction Ag^{0}/AgCl reference electrode in each solution and the potential was measured. Washing of the electrode between measurements was done using 0.02M phosphate buffer pH 8. The calibration plot was obtained by plotting the developed potentials versus Logarithmic concentration of MLK. The subsequent measurements of unknown samples were determined using the regression equation obtained from the calibration plot. The electrochemical performance of the sensor was evaluated according to International Union of Pure and Applied Chemistry (IUPAC) recommendations [36].

2.5.2. Effect of pH and temperature on electrode response

pH study was performed by recording the changes occurring in the potential by a gradual increase and decrease in the pH ranging from 2 to 11. The pH effect on the potential values

was studied by adding 2N HCl and 2N NaOH to adjust the pH of a 1.0×10^{-3} and 1.0×10^{-4} mol/L MLK solution. At each pH value the potential obtained was recorded. Temperature study was done by recording the changes occurring in the potential by gradual increase in the temperature from 25 to 37°C.

2.5.3. Sensor selectivity

The proposed sensor selectivity was studied in the presence of some interfering substances by measuring the response and then calculating the potentiometric selectivity coefficients ($K^{pot}_{MLK,\ interferent}$). The selectivity coefficient had been calculated to determine to which extent a foreign substance would affect the electrode response to their primary ion. Then the selectivity coefficients were evaluated according to IUPAC guidelines by the separate solutions method (SSM) using the following equation [37] (Equation 1):

$$-\log\left(k^{pot}_{\text{primary ion, interferent}}\right) = (E1 - E2) / S \quad (1)$$

where $E1$ is the potential measured (millivolts) in 1.0×10^{-3} mol/L of MLK solution; $E2$ is the potential measured in 1.0×10^{-3} mol/L of the interfering substance solution; and S represents the slope of the proposed sensor (millivolt/concentration decade).

2.5.4. Potentiometric determination of Montelukast Sodium in its pharmaceutical formulation Asmalair® tablets

Ten tablets were weighed then finely powdered. An accurately weighed portion of the powdered claimed to contain 1.0×10^{-3} mol/L MLK was transferred to a 25-ml volumetric flask and completed to volume with 0.02 M phosphate buffer pH 8. Then the potential was recorded after immersing the proposed sensor together with the reference electrode in the solution and MLK concentration was determined using the corresponding regression equation.

2.5.5. Determination of percent dissolution of Montelukast Sodium from Asmalair® tablets by the proposed potentiometric method

Both the prepared sensor and the reference electrode were introduced jointly in the dissolution vessel. The potentiometric readings were recorded at 0, 2, 5, 10, 15, 20, 25, 30 min and then converted into percentage dissolution using the transpose of Nikolskii–Eisenman equation, as follows [38] (Equation 2):

$$C_{analyte} = C_{st}\left(10^{E/S} - 1\right) \quad (2)$$

where $C_{analyte}$ is the analyte concentration; C_{st} is a constant; E is the potential in millivolts; and S is the slope of the investigated sensor. The dissolution profile was obtained relating the

percent dissolution to the time.

2.5.6. Determination of percent dissolution of Montelukast Sodium from Asmalair® tablets by the official HPLC method [35]

At different time periods of 0, 5, 10, 20, 30 min, samples were withdrawn from the dissolution vessel, filtered, diluted with 0.02M phosphate buffer and injected into HPLC system. Peak areas were recorded at 255 nm and utilized to determine the corresponding MLK concentration. After calculating the percentage dissolution, the dissolution profile was drawn relating the percent dissolution to the time.

3. RESULTS AND DISCUSSION

ISEs achievement abilities depend on using ion exchangers which depend greatly on the ion exchanger nature and their lipophilicity [39], the solvent mediators type [40] and the used additives [41,42].

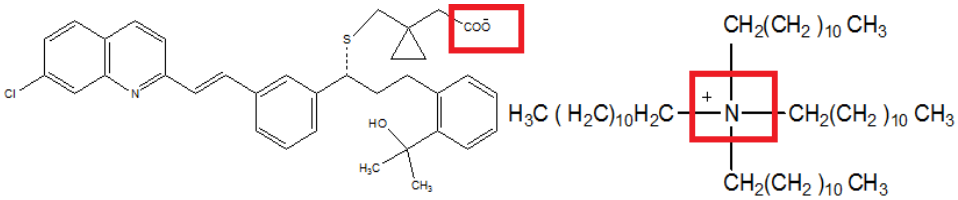

Fig. 2. Structure of ion-pair complex formed between Montelukast and Tetradodecyl ammonium bromide

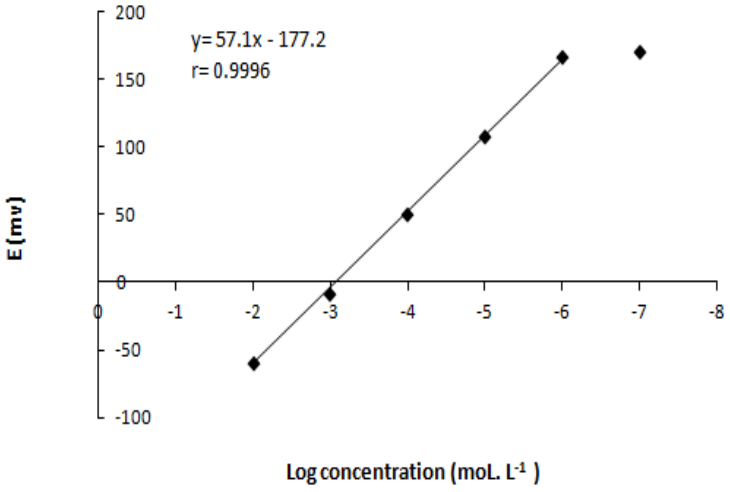

Fig. 3. Profile of the potential in millivolts versus log concentrations of MLK in mol/L

Developing this sensor arises from the evidence that MLK behaves as anionic species because of the presence of a carboxylate group in its structure (Fig. 1) and its pK_a value of 4.4 gives it the property of being an anion in neutral and basic media this suggests the use of anionic exchanger to form the ion pair in the MLK based sensor.

Table 1. Electrochemical response characteristics of the investigated sensor

Parameter	**Sensor**
Slope, mv/decade [a]	57.1
Intercept, mv [a]	-177.2
Correlation Coefficient	0.9996
LOD, mol/ L [b]	7.94×10^{-7}
Response time, s	5
Working pH range	6-10
Concentration range, mol/L	1×10^{-6} - 1×10^{-2}
Stability, days	30

[a] Average of three determination three determination
[b] LOD (according to IUPAC definition: measured by intersection of the extrapolated arms of non-responsive and Nernstian segments of the calibration)

Tetradodecyl ammonium bromide (TDB) was used to prepare MLK sensor and the membrane was soaked in 1.0×10^{-3} mol/L MLK solution replacing the main replaceable counter ion (Br^-) with MLK (Fig. 2). IUPAC recommendations [36] were used for evaluating the Sensor electrochemical performance characteristics (Table 1).

A constant potential reading within±1 mv from day to day in the concentration range from 1.0×10^{-6} to 1.0×10^{-2} mol/L was obtained (Fig. 3). The evaluation of ion-selective electrode requires the determination of the dynamic response time, it is the time needed for the sensors to reach values within ±1 mv by increasing MLK concentration by 10-fold (Table 1). The proposed sensor response was examined over a wide pH range from 2 to 11.

Fig. 4A displays the profile of potential versus pH for 1.0×10^{-3} mol/L and 1.0×10^{-4} mol/L showing a pH range 6-11 for MLK to be the best for obtaining a constant potential where a complete dissociation and formation of ionisable coo^- group was formed. Below this pH 6 a gradual decrease in the potential was observed due to the formation of un-ionisable form of MLK which will not be easily sensed by the ISE thus pH 8 was found to be the ideal pH to

determine MLK present in its ionisable form. Also, pH 8 permits monitoring of MLK dissolution in its dissolution medium (0.5% SDS in water) described by the U.S. Food and Drug Administration (FDA; [43]) which has a pH of 8.

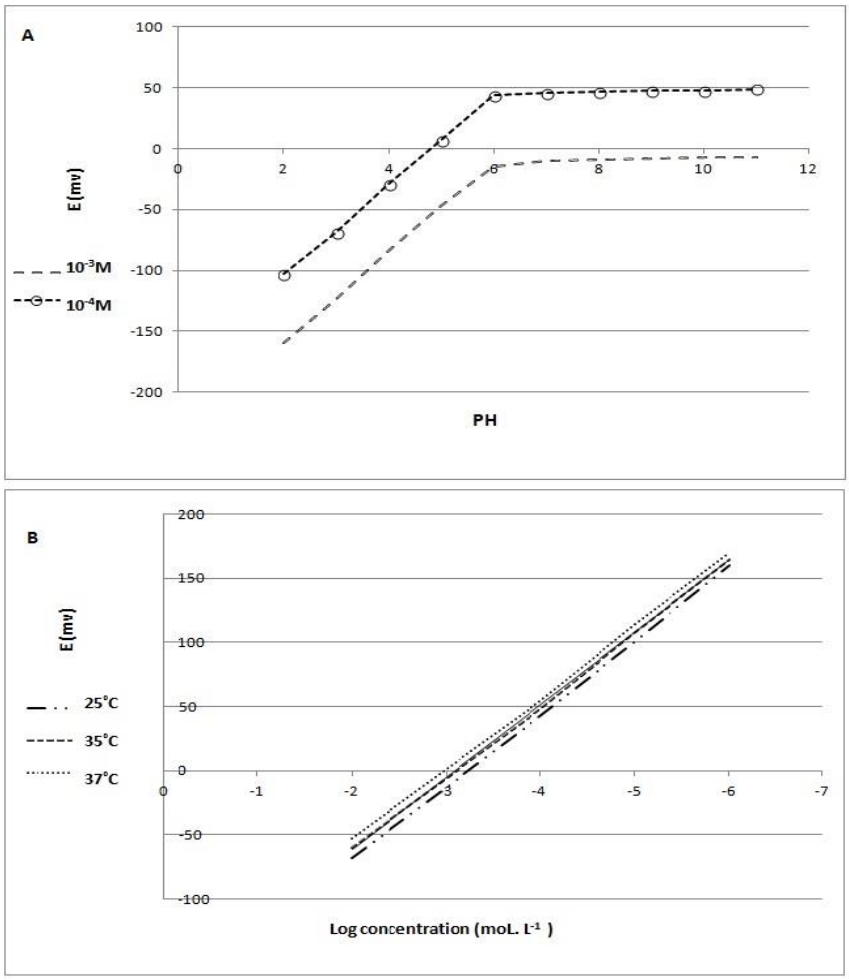

Fig. 4. A) Effect of pH on the performance of MLK sensor in 10^{-3} and 10^{-4} mol L^{-1} MLK, **B)** Effect of temperature on MLK sensor in 10^{-3} mol L^{-1} MLK

Temperature study was done by recording the changes occurring in the potential by gradual increase in the temperature from 25 to 37 ^{o}C. Parallel calibration plots of relatively similar slopes were obtained indicating that the proposed PVC sensor is thermally stable (Fig. 4B).

Selectivity coefficient calculated from the SSM [37] is considered as a reliable measurements reflecting the degree at which the sensor will be affected by the existence of excipients, inorganic and organic related substances. The obtained results prove good electrode selectivity towards measuring MLK concentration (Table 2).

Table 2. Potentiometric selectivity coefficients (K^{pot} Montelukast Sodium) of the proposed sensors using the separate solutions method

Interferent, 10^{-3} mol/L	**K_{Sel}**
Glucose	3.6×10^{-5}
Urea	4.56×10^{-5}
Talc	7.15×10^{-5}
Starch	3.29×10^{-5}
(NH4SCN)	6.34×10^{-3}
KCl	1.65×10^{-3}
NaCl	5.47×10^{-4}
KBr	4.78×10^{-3}

3.1. Method Validation

The proposed method validation was done according to ICH guidelines [44] (Table 3). Accuracy is confirmed by evaluating the recovery of three known MLK concentrations in 0.02 M phosphate buffer pH 8. Satisfactory results are obtained as shown in Table 3. The method Precision is determined by measuring the potential in mV of three different concentrations five times within same day and on 5 different days, where the SD was lower than 2 as shown in Table 3.

3.2. Determination of MLK concentration and monitoring of its release from Asmalair® tablets

Potentiometric determination of MLK in its pharmaceutical formulation Asmalair® tablets was successfully accomplished using the proposed sensor without any sample pre-treatment or extraction steps. The proposed method results were statistically compared to the results obtained by the official HPLC method [35], where, the calculated student *t* and F values were found to be less than the theoretical ones showing no significant difference between the proposed and official method regarding both accuracy and precision as shown in (Table 4).

The proposed sensor has the ability to determine MLK in its dissolution medium with monitoring of MLK release from its tablets. The entire concentration range during dissolution process requires accurate description from zero concentration at the beginning of the process to the maximum concentration released at the end of the process.

The conversion of the obtained potential at the beginning (zero MLK concentration) to percent dissolution can be performed by using the transpose of Nikolskii-Eisenman equation [38], (Equation 2). The equation has the ability to converts the measured potential in millivolts to concentration values using the slope (S), and a constant value called (C_{st}). At the same conditions of the dissolution test, the slope (S) was obtained from the calibration curve measured prior to the dissolution test.

Table 3. The proposed sensor assay validation sheet

Parameter	**Sensor**
Accuracy [a]	98.42%
Precision (RSD%)	
Repeatability [b]	±0.83
Intermediate precision [c]	±1.25
Robustness [d]	±0.87
LOD, mol/L [e]	7.94×10^{-7}
Linearity	
Slope	57.1
Intercept	-177.2
Correlation coefficient	0.9996
Range, mol/L	1×10^{-6}– 1×10^{-2}

[a] The accuracy (n=5), average % recovery of three concentrations (10^{-6}, 10^{-4}, and 10^{-2} mol/L) of MLK.
[b] The intraday precision (n=5) RSD of three concentrations (10^{-6}, 10^{-4}, and 10^{-2} mol/L) of MLK repeated five times within a day.
[c] The interlay precision (n=5) RSD of three concentrations (10^{-6}, 10^{-4}, and 10^{-2} mol/L) of MLK repeated five times on three consecutive days.
[d] Robustness (n=3), RSD of determinations of three concentrations (10^{-6}, 10^{-4} and 10^{-2} mol/L) of MLK under variation of pH of the solvent (±0.2) and temperature.
[e] Limit of detection (measured by interception of the extrapolated arms of Fig. 3).

Table 4. Montelukast determination in Asmalair® tablet by the proposed potentiometric method and the official HPLC method [35]

Pharmaceutical dosage form	**Potentiometric method**	**HPLC method [35[a]]**
Recovery ± SD%	99.60 ± 1.031	99.34 ± 0.429
Student's *t*-test [b] (2.770)	0.8571	
F value [b] (4.296)	0.6024	

[a] USP method for Montelukast Sodium is a HPLC method
[b] The values in parenthesis are the corresponding theoretical values at P= 0.05

The constant value (C_{st}) was calculated from the obtained potential acquired by inserting the electrode in solutions of known concentration of MLK by the end of the dissolution testing. The dissolution curve was plotted as percentage dissolution versus time (Fig. 5) after converting the produced potential into concentration using the average value of C_{st}. Regardless the linearity range of the sensor [38]; this equation can be applied through the entire concentration range from 0 to 100% MLK.

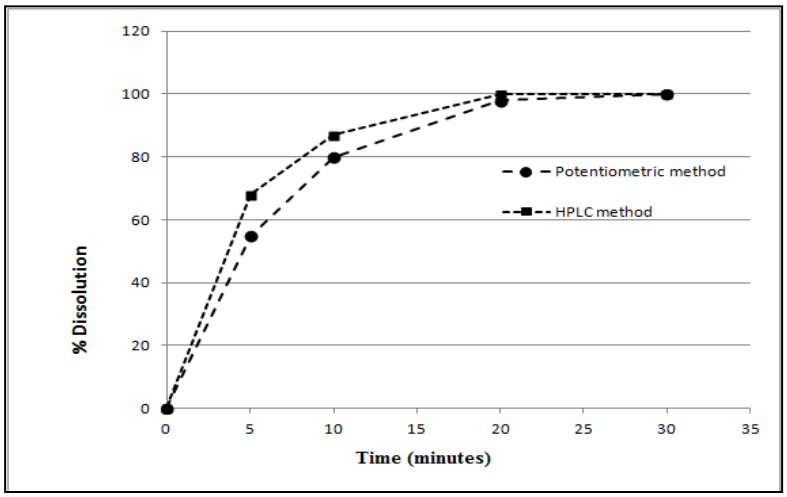

Fig. 5. Dissolution profile For Montelukast sodium tablets by in-line potentiometric and official HPLC procedure

3.3. Comparison of the proposed potentiometric method and the pharmacopeial method for MLK dissolution monitoring

USP describes HPLC method [35] as a general method for MLK determination while, the FDA describes the conditions for the dissolution testing for monitoring the dissolution of MLK [43]. Samples were withdrawn from dissolution medium at time periods of 0, 5, 10, 20 and 30 min, the curve obtained by the HPLC method was compared with that obtained from the potentiometric method, Fig. 5. In order to compare the dissolution profiles mathematically, many methods were stated [45,46].

Similarity and difference factors are the simplest methods to compare dissolution profiles, where only one value is obtained to describe the closeness of the two dissolution profiles. The factors are calculated from the following equations [46] (Equation 3,4):

$$f_1 = \left\{ \sum_{t=1}^{n} | R_t - T_t | / \sum_{t=1}^{n} R_t \right\} \times 100 \quad (3)$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\} \quad (4)$$

where f_1 is the difference factor, f_2 is the similarity factor, n is the number of dissolution sample times and R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively. The use of these factors was also recommended for dissolution profile comparison in the FDA guidelines for industry. According to these guides, generally, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) ensure sameness or equivalence of the two curves [46]. The factors were calculated for Asmalair® tablets dissolution profiles, where f_1 is 6.46 and f_2 is 55.05 indicating the similarity of both profiles.

Table 5. Penalty points for MLK determination using the proposed potentiometric method and the official HPLC method [35]

Reagents	**Proposed method**	**Official method[a]**
	Penalty points	**Penalty points**
NaOH	2	0
Potassium dihydrogen orthophosphate	0	0
Acetonitrile	0	6
Glacial acetic acid	0	2
NH_4OH	0	2
Water	0	0
Instruments		
Digital ion analyzer	0	0
Magnetic stirrer	0	0
HPLC	0	1
Occupational hazard	0	3
Water	3	8
Total penalty points	5	22
Analytical Eco-scale total score	95	78

[a]USP method for Montelukast Sodium is a HPLC method

3.4. Greenness Assessment of the proposed potentiometric method versus Official HPLC method [35]

Potentiometric measurements are simple, cost effective in its setup and run, time saving

and green methods with no hazardous effect on environment in comparison with classical methods for dissolution monitoring. Analytical Eco-Scale semi quantitative approach [47] was applied for greenness evaluation of the proposed potentiometric method and for comparison purposes. Analytical Eco-scale score was calculated for both the proposed potentiometric method and official HPLC method and it was found to be 95 and 78, respectively as shown in (Table 5). This indicates that the suggested potentiometric method is greener than the official HPLC one. Extending the results to all the reported methods can be done, as they all use hazardous organic solvents and produce a high amount of waste.

4. CONCLUSION

The electro-analytical methods are considered to be the greenest methods regarding to sample extraction and pre-treatment and also consumes less solvents. Fabrication of the electrode sensor in this study is simple and signifies a simple, sensitive and inexpensive sensor appropriate for determination of MLK in its tablet dosage form and its dissolution media. The dissolution curve attained by potentiometery proves that in-line potentiometric monitoring of MLK dissolution is an excellent shift from traditional analytical methods which require several tedious steps to a more simple and green methods. The green in-line potentiometric method offers many advantages over other classical reported methods for MLK determination.

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