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TURBIDIMETRIC DETERMINATION OF MEBEVERINE HYDROCHLORIDE IN PHARMACEUTICAL FORMULATIONS USING TWO CONSECUTIVE DETECTION ZONES UNDER CONTINUOUS FLOW CONDITIONS

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Abstract. A simple, low cost and rapid flow injection turbidimetric method was developed and validated for mebeverine hydrochloride (MBH) determination in pharmaceutical preparations. The developed method is based on forming of a white, turbid ion-pair product as a result of a reaction between the MBH and sodium persulfate in a closed flow injection system where the sodium persulfate is used as precipitation reagent. The turbidity of the formed complex was measured at the detection angle of 180° (attenuated detection) using NAG dual&Solo (0-180°) detector which contained dual detections zones (*i.e.*, measuring cells 1 & 2). The increase in the turbidity of the complex was directly proportional to the increase of the MBH concentration in the range of 2.0-10 μmol/L with a limit of detection 0.35 μmol/L, 0.9981 (R^2), and 2.0-12 μmol/L with a limit of detection 0.4 μmol/L and 0.9973 (R^2) for measuring cells 1 and 2, respectively. The intra-day precision for three serial estimations of 5.0 and 9.0 μmol/L of MBH exhibited an RSD % of 0.23 % and 0.77 % and 0.68 % and 0.13 %, for cell 1 & 2, respectively. While the inter-day precision for three serials of three days exhibited an RSD % of 0.03 % and 0.77 % and 0.11 % and 0.07 %, for measuring cells 1 & 2, respectively. The accuracy of the developed method has expressed as an error % (*E*%) and a Rec % (recovery percentage), which was between 100.35 to 101.15 and 99.70 to 101.56 for cell 1 and cell 2, respectively. The present flow injection method has shown no interference effect from the common excipients and permits quantitively determination of 60 samples per hour. The developed method was successfully applied for the quantitative determination of MBH in different tablets containing 135 mg with excellent recovery percentage.

Keywords: mebeverine hydrochloride, flow injection, turbidimetric determination, dual detection zone, pharmaceutical preparations.

1. Introduction

Mebeverine hydrochloride (MBH) is chemically known as 4-[ethyl-[1-(4-methoxyphenyl)propan-2-yl]-amino]butyl 3,4-dimethoxybenzoate hydrochloride (Fig. 1). The drug is used for treatment of the musculotropic antispasmodic without any side effects on the normal gut motility.[1] Mainly this drug is used for treating both of gastrointestinal spasm and irritable bowel syndrome.[2] Its action on the smooth muscle of the colon reveals spasm with normal gut motility. Therefore, it represents the most prescribed drug which is currently available for treatment gastrointestinal spasm and irritable bowel syndrome. Officially in 2000, MBH has been registered in British pharmacopoeia.[3] In any drug design and development process, the oral bioavailability is considered as the most required property. Because any drug with high oral bioavailability can reduce the risk in the toxicity, highly achieve a desired pharmacological effect and elimination of the side effect, while lower oral bioavailability can cause higher inter-individual variability and low efficacy resulting in an unpredictable response of the drug. MBH possesses a poor oral bioavailability with some of the adverse effects even though MBH has a direct effect on the smooth muscle (colon), therefore, this drug is used for the site-specific drug delivery system which knows (model drug).[4,5] The colon disorders cause lots of diseases such as inflammatory bowel diseases (*e.g.*, irritable bowel syndrome, Crohn's disease, and ulcerative colitis), colon cancer and infectious diseases (*e.g.*, amoebiasis) are usually treated by conventional drug delivery systems, however, majority of these systems fail as the drug does not reach

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the target site with the desired concentration. This drawback has given a strong advantage for MBH to be used in treatment of some colon diseases effectively.[6] In the literature, several analysis methods have described the quantitative determination of MBH either in pharmaceutical or drug in bulk powder formulations. The following methods have been reported: chromatographic methods,[7-11] spectrophotometric methods,[12,13] electrochemical methods,[14,15] potentiometric,[16] RP-HPLC,[17,18] TLC,[19] voltammetry,[20] fluorescence,[21,22] and ion-selective electrode.[15,16] Molecularly imprinted polymer (MIP) is a fast-growing field in the applications of drug analysis especially in sensor.[14,23] Also, few of GC-MS, LC-MS and LC methods are reported to describe the stability behavior during the determination of MBH in tablet dosage or other samples.[23-26] In one of these reported chromatographic methods, MBH was found to be degraded and lose some of it due to using several of stress condition such as oxidative, photolysis, alkali, thermal and acidic.[26] In addition, great number of the reported methods have shown some drawbacks such as lack of robustness information, lack of peak purity, narrow linearity range, strict monitoring of pH of the mobile phase, non-stability, gradient elution, *etc*. Furthermore, the obtained data from the reported methods were not reliability ensured for the regulatory requirements. Therefore, in the present study, three critical aspects – robustness, narrow linearity range and lack of reliability were attempted to be developed by the authors.

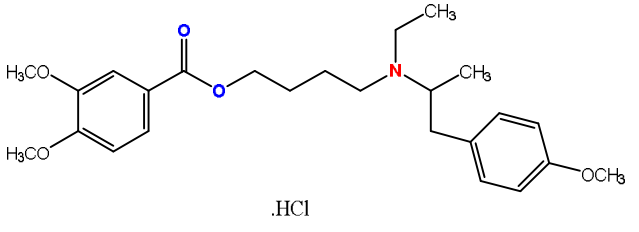

Fig. 1. The chemical structure of MBH

The turbidity concept is a widely used quantitative determination approach and lots of active ingredients have been determined using this technique such as cyproheptadine hydrochloride,[27,28] ephedrine Hydrochloride,[29] ciprofloxacin HCl,[30] paracetamol,[31] and sulfanilamide.[32] The main objective of the current study was to develop and validate an analysis method depending on turbidity concept combined with a flow injection technique, which allows simultaneous quantitative determination of MBH in pharmaceutical formulations for the same injected sample using two consecutive detection zones. These zones are supplied with white light emitter diodes (WLEDs) working as the light emitter while 3 solar cells working as the light detector. The first detection zone, the applied current of the WLEDs was set as 5 mA while 40 mA in the second detection zone was used. These zones were fabricated to be easily compatible and adapted with any flow injection system. Therefore, in the present work, a new, two-line manifold system for flow injection analysis is developed in which two consecutive detection zones (cells 1 & 2) for the same injected sample were applied using NAG dual & solo (0–180°) detector. This type of manifold is used for the chemical reactions when MBH is injected into the carrier streamline (distilled water) prior to mixing with the precipitation reagent line (sodium persulfate). The two lines are merged at Y junction point to form a white ion association complex due to the reaction between MBH and the sodium persulfate, the proposed mechanism of the reaction is shown in Fig. 2. The intensity of the complex is detected by two consecutive detection zones (cells 1 & 2). Thus, two peaks will be obtained for any injected sample. Therefore, a new manifold system for the flow injection spectrophotometric analysis was successfully presented and applied for the quantitative determination of MBH in different commercial tablets. The proposed method is simple, rapid, economic, and more sensitive than many reported earlier (Table 1).

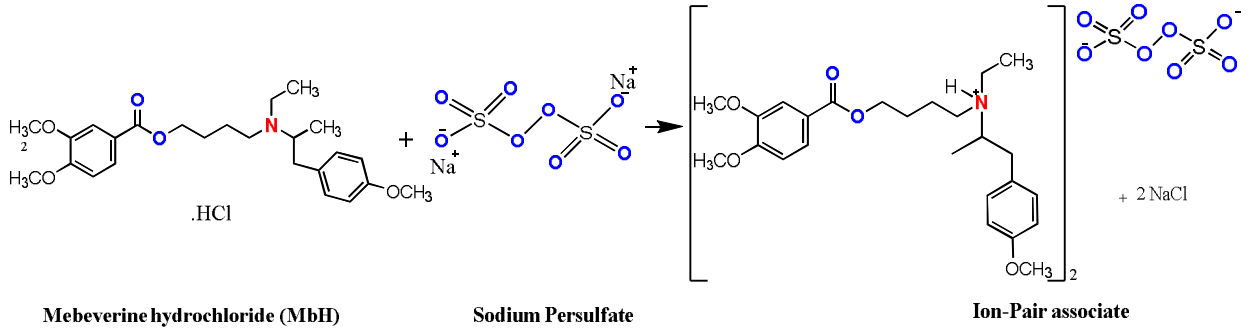

Fig. 2. The proposed mechanism of MBH reaction

Table 1. A comparison of determination methods for MBH the reported methods with the proposed methods

Reported methods	Linear range	Remarks	Ref
HPLC	1–40 μg mL^{-1}	Less sensitive	7
HPLC	5– 30 ng mL^{-1}	Narrow in linear range, but more sensitive	8
HPLC	10–100 ng mL^{-1}	Critical pH dependence, but more sensitive	21
Vis-spectrophotometry	2–28 μg mL^{-1}	Critical pH dependence and less sensitive	12
UV-Vis	2–25 μg mL^{-1}	Less sensitive	13
MIP	0.04–0.4 μg mL^{-1}	More sensitive	14
Potentiometry	1.86–930 μg mL^{-1}	Less sensitive	16
Fluorescence	230–4660 μg mL^{-1}	Less sensitive	22
LC	0.5–150 μg mL^{-1}	More sensitive	27
HPTLC	5–60 μg mL^{-1}	Less sensitive	28
Turbidity	0.9–4.66 μg mL^{-1}	Using a simple instrument and more sensitive	Proposed method (first detection zone)
Turbidity	0.9–5.66 μg mL^{-1}	Using a simple instrument and more sensitive	Proposed method (second detection zone)

2. Experimental

2.1. Materials

All of the standard materials used in the present study were of high purity (above 98 %), which are sodium persulfate, ammonium chloride, sodium chloride, potassium nitrate, potassium bromide, and sodium nitrite that were procured from Sigma Aldrich. The used solvents were of HPLC purity. All the dilutions and preparation of solutions were made using double-distilled water. Pure MBH (standard material) was provided from Samara Ltd., Iraq, while the commercial tablets were provided under their brand name from the local market.

2.2. Apparatus

A two-channel peristaltic pump (type Ismatec, model 796, Switzerland) supplied with Tygon pump tubing (0.8 mm i.d.) was used for the propulsion of the fluids. The manifold system was fabricated by the connection of all main parts which are peristaltic pump, injection valve, Y-junction point, and the detector unit. A Teflon tube (PTFE, 0.5 mm i.d) in different lengths was used to join and connect the manifold system parts together. The 6-way selection injection valve (Upchurch Scientific®, ceramic-to-ceramic interface and Medium Pressure) with the pressure rating of 34 bar and inside hole diameter 0.40" was used for sample injection. A methyl methacrylate was used to make Y-junction point (0.8 mm i.d.) which was used for mixing the reactants together. The turbidity of the formed complex was monitored using a homemade NAG Dual & Solo (0-180º) analyzer. The detector unit has been checked and validated based on the Central Organization for standardization and quality control (Patent No: N5490, International classification G01N33/0013, 6). It contains two identical detection zones (twin measuring cells, *i.e.*, cell no. 1 and cell no. 2), each one of them has 100 mm length, and in between them, there is a 20 mm without any detection. These zones are supplied with white light emitter diodes (WLEDs) working as the light emitter while 3 solar cells working as the light detector. The first detection zone, the applied current of the WLEDs was set as 5 mA while 40 mA in the second detection zone was used as shown in Fig. 3.

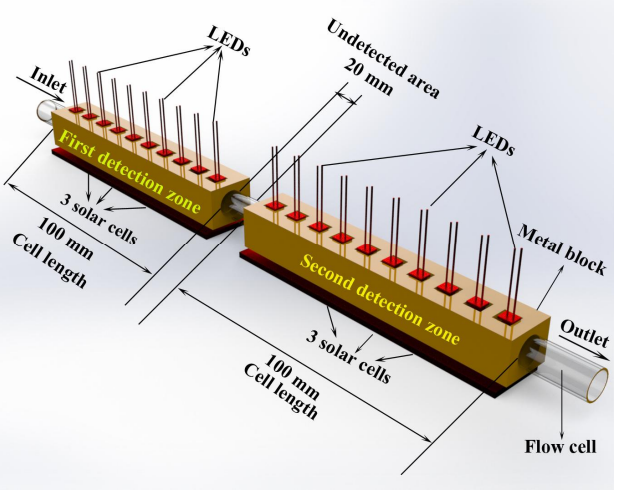

Fig. 3. A diagram shows the major components of the NAG Dual & Solo (0-180º) analyzer

The first & second measuring cells (*i.e.*, cell 1 & 2) are set for measuring the turbidity of the complex by attenuated light at 180º which is also known as turbidimetric detection. The detector is connected to readout system which is potentiometric recorder (1–500 mV, Graph C-1032, Siemens, Germany) and AVO-meter (0.00–2000 mV) for the Digital readout were used. The constructed flow injection manifold system which was used in the present method is shown in Fig. 4.

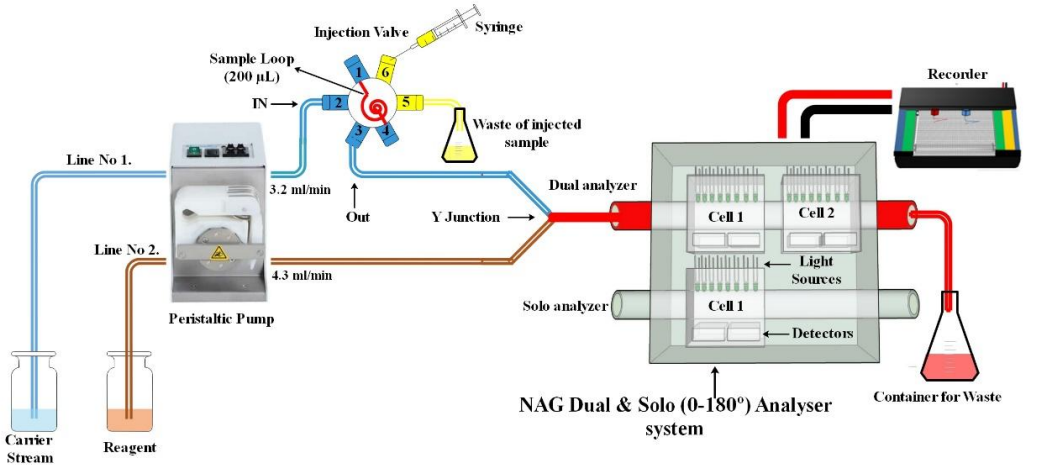

Fig. 4. A diagram shows the flow manifold system used in the determination of MBH

2.3. Standard and Sample Solutions

The stock solution of MBH (50 µmol/L) was prepared by weight of 5.285 g of MBH and dissolving in a 250 mL conical flask using double-distilled water (D.W.). Further dilutions of the stock solution of MBH were performed by dissolving appropriate volumes of the stock solution using D.W. to prepare a range of 0.25-25 µmol/L of standard solutions. During the proposed analytical procedure of MBH, the stability of MBH was monitored using UV-Vis and the results showed there is no decomposition in MBH during the proposed method.

2.4. Preparation of Samples Solutions (Tablets)

Three different commercial companies of 135 mg of MBH (Colofac ® (Abbott, France), Colospasmin ® (EIPICO, Egypt), and Duspalina ® (Asia, Syria) were investigated in the present study. Sample solutions were prepared by weighing twenty tablets and then powdering and mixing. The average weight of the tablet was accurately dissolved in double distilled water, mechanically shaken for 20 min and filtered. The residue from the filtration was washed four times with the distilled water and transferred to a volumetric flask and diluted to the mark with distilled water. A series of injected sample concentrations were prepared from the tablets stock solution by appropriate dilutions. All of the above steps were repeated for each type of commercial tablet.

2.5. Recommended Procedure

The flow injection manifold system in Fig. 3 was used for the determination of MBH using two consecutive detection zones (cells 1 & 2) for the same injected sample. A series of physical and chemical parameters precipitation reagent concentration, salts effect, flow rates, mixing coil, purge time, light intensity, and volume of the sample were optimized inside the manifold system. Both carrier stream and reagent (sodium persulfate, 5 µmol/L) lines solutions were propelled at 3.2 mL min^{-1} & 4.3 mL min^{-1} flow rates for both carrier stream and reagent lines, respectively, using the peristaltic pump. 200 µL of the sample volume of MBH is injected into the injection valve and loaded, remained into the loop. After loading of the sample, the position of the injection valve is changed from rotating to the injection mode. By switching the injection valve mode, the injected sample is transported by the waterline and merged with the reagent at the mixing point (Y-junction), the white and turbid product will be formed and transported to the detection zones by the stream for the detection. After passing of the formed product through the detection zones, the turbidity value of the formed product will be recorded on a chart paper represented by two peaks (for cell 1 & 2, respectively). These two peaks are responsible for the determination of injected sample concentration by treating them mathematically. Fig. 5 shows the shape of the peaks obtained from the recorder. The concentration of MBH is determined by plotting the calibration graph (peaks height 1, 2).

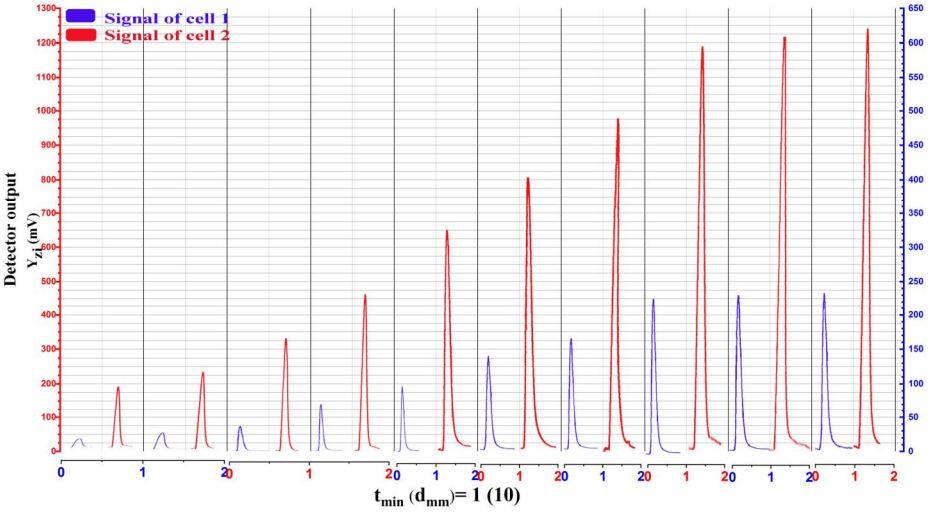

Fig. 5. The typical peaks obtained from the analysis of MBH using a range of concentrations (0.5-20 µmol/L) under flow optimized conditions

Table 2. The optimum physical and chemical parameters with studied ranges

Studied parameter	Concentrations ranges		Optimum value
	From	To	
Sodium persulfate concentration (µmol/L)	10	80	60
H_2O concentrations (µmol/L)	---	---	D.W
HNO_3 concentrations (µmol/L)	10	50	No need
HCl concentrations (µmol/L)	10	50	No need
CH_3COOH concentrations (µmol/L)	10	50	No need
$NaNO_2$ concentrations (µmol/L)	10	50	No need
KNO_3 concentrations (µmol/L)	10	50	No need
NaCl concentrations (µmol/L)	10	50	No need
CH_3COONH_4 concentrations (µmol/L)	10	50	No need
NH_4Cl concentrations (µmol/L)	10	50	No need
Mixing coil length for the reagent (cm)	without	25	No need
Mixing coil for the product (cm)	10	40	20
The flow rate of water line (mL min^{-1})	1	7	3.2
The flow rate of reagent line (mL min^{-1})	1	7	4.3
Sample volume (µL)	32	400	250
Purge time (Sec)	3	Open valve	5-open valve

3. Results and Discussion

The MBH is found to be forming an ion association complex with sodium persulfate and the proposed mechanism of the reaction is illustrated in Fig. 2. The molar ratio between the drug and reagent was calculated to be 1 : 2 by conducting the mole ratio and Job's method. The formed complex is transported to the detector unit for the detection.

3.1. Effect of Chemical Parameters

In order to enhance the sensitivity of the proposed method represented by the height of the peak under initial flow conditions: sample volume 200 µL, MBH 7 µmol/L, flow rates of 3.2 mL min^{-1} and 4.3 mL min^{-1} for water and reagent lines, respectively, and open valve mode, a series of aqueous solutions and sodium persulfate concentrations were examined. The obtained results are demonstrated in Figs. 6-8. Table 2 shows the optimum chemical and physical parameters which were optimized during the experiments.

3.2. Effect of Physical Parameters

After determining all of the optimum chemical parameters, the sensitivity of the proposed method was investigated under different physical parameters inclu-

ding sample volume, purge time, flow rates and mixing coil. Under optimum chemical conditions (sodium persulfate 60 µmol/L and carrier solution (distilled water)) and keeping all of the other conditions constant, *i.e.*, open valve mode and 200 µL sample volume, the flow rates for both of water and reagent lines in the range of (1.0–7.0 mL min^{-1}) that are controlled by the peristaltic pump were examined. The results have shown that there was an increase in the heights of peaks synchronized with the increase in the flow rates of lines up to 3.2 & 4.3 mL min^{-1} for the water and reagent lines. The peaks at these rates were sharp and regular while applying flow rates above these rates resulting in decreasing the obtained response due to the sample segments passes fast in front of the detectors. Therefore, the rates 3.2 & 4.3 mL min^{-1} for the water and reagent lines were chosen to the optimum and used for further experiments as shown in Fig. 9. A series of sample volume ranging from (32–350 µL) were also investigated by keeping all other conditions constant. It was observed that there was a gradual increase in the heights of peaks with a regular response up to 250 µL (sample volume), more than that a decreasing in the response was noticed and therefore the 250 µL volume was chosen to be optimum volume as shown in Fig. 10. Introducing of mixing coil into the flow system was also investigated to ensure whether the coil will enhance the sensitivity of the proposed method or not. The role of the mixing coil in the flow system is critical and crucial, some of the reported methods have described that using of mixing coil enhances the completion and homogenization of the chemical reactions.

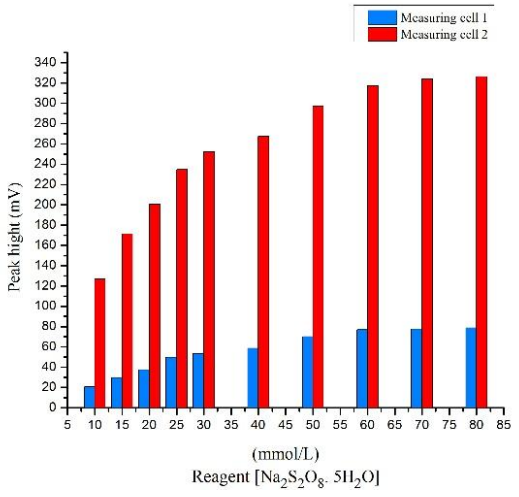

Fig. 6. The effect of sodium persulfate concentrations on the height of peaks using initial conditions: MBH 7 µmol/L, flow rates 2.8 & 3.2 mL min^{-1} for water and reagent lines, respectively, open valve mode and 200 µL sample volume

Therefore, a variable mixing coil length (10-40 cm) was applied in the manifold system. The placement of the mixing coil was after the Y-junction point, the results have illustrated that no significant differences were noticed during utilizing of the mixing coils. Therefore, the manifold system experiments were performed and continued without using it. The purge time of injected sample into flow system was also studied. Purge time can be defined as the required time that the injected sample needs to mix with the reagent and reach the detection cells. Finally, the required time that the sample needs to mix with sodium persulfate (reagent) and reaching the detector is known as the purge time. Purge time test allows us to determine how many runs can be performed by the instrument per hour (determine the capacity of the device). Therefore, 5–40 Sec in addition to an open valve mode were examined as shown in Fig. 11.

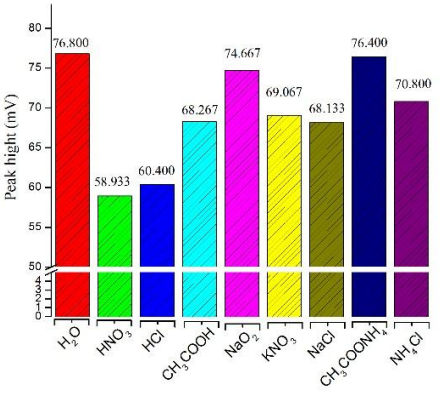

Fig. 7. The effect of using different aqueous mediums on the height of peaks for measuring cell 1 using initial conditions: MBH 7 µmol/L, sodium persulfate 60 µmol/L, flow rates 2.8 & 3.2 mL min^{-1} for water and reagent lines, respectively, open valve mode and 200 µL sample volume. Note: all of the used aqueous solutions were used instead of distilled water in this experiment

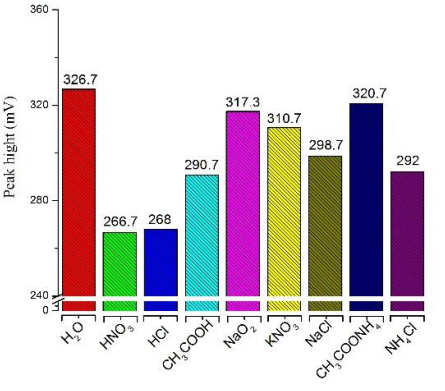

Fig. 8. The effect of using different aqueous mediums on the height of peaks for measuring cell 2 using initial conditions: MBH 7 µmol/L, sodium persulfate 60 µmol/L, flow rates 2.8 & 3.2 mL min^{-1} for water and reagent lines, respectively, open valve mode and 200 µL sample volume. Note: all of the used aqueous solutions were used instead of distilled water in this experiment

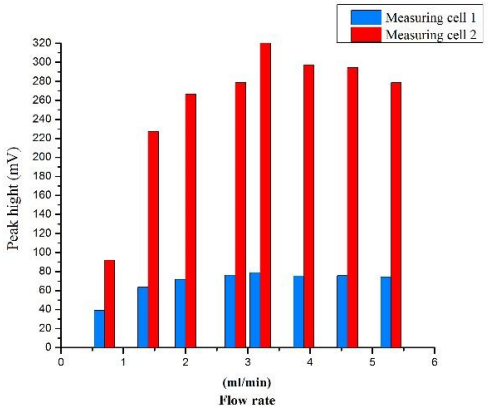

Fig. 9. The effect of flow rates on the height of peaks using initial conditions: MBH 7 µmol/L, sodium persulfate 60 µmol/L, open valve mode and 200 µL sample volume

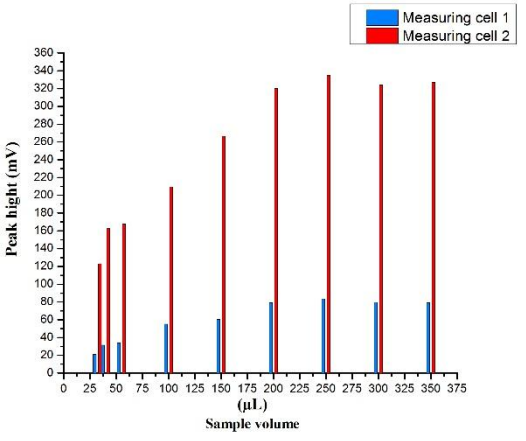

Fig. 10. The effect of using variable volumes of sample of the MBH on the height of peak using initial conditions: MBH 7 µmol/L, sodium persulfate 60 µmol/L, flow rates 3.3 & 4.3 mL min^{-1} for distilled water and sodium persulfate (reagent) lines, respectively, and open valve mode

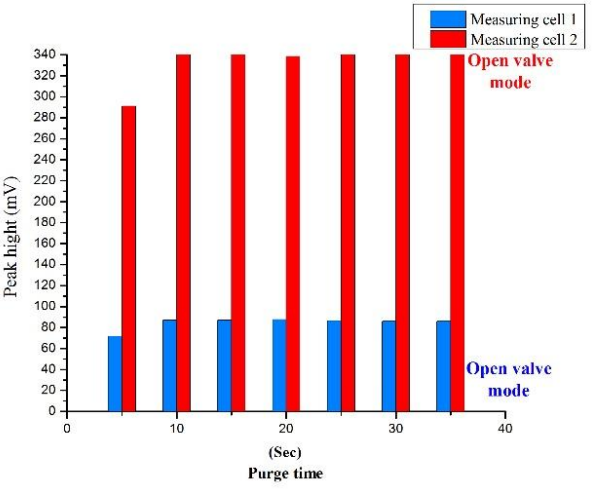

Fig. 11. The effect of the purge time the height of peak using initial conditions: MBH 7 µmol/L, sodium persulfate 60 µmol/L, flow rates 3.3 & 4.3 mL min^{-1} for distilled water and sodium persulfate (reagent) lines, respectively, and 250 µL sample volume

3.3. Effect of Interferences

In addition to the pharmaceutically active ingredient, each tablet contains some of the usual excipients, therefore, for the determination of 135 mg/tablet MBH the interfering effects of excipients have been conducted and all the obtained results are shown in Table 3. It was observed that there is no interference effect of drug excipients in various tablets. Thus, the developed method has found to be an appropriate assay for the quantitative determination of MBH in commercial tablets that contains different types of excipients in its formulations.

Table 3. The effect of the interferences on the determination of MBH (135 mg)

Excipients	Using 6.0µmol/L of MBH (measuring cell 1)			Using 6.0µmol/L of MBH (measuring cell 2)		
	Fold added (µmol/L)	MBH determined in (µmol/L±SD)	*%E*	Added (µmol/L)	MBH determined in (µmol/L±SD)	*%E*
Starch	1.5	5.98±0.02	-1.5	1.5	5.95±0.03	-0.83
Magnesium stearate	1.5	6.05±0.12	0.83	1.5	6.02±0.18	0.33
Sucrose	1.5	6.10±0.18	1.66	1.5	6.10±0.19	1.66
Lactose	1.5	5.99±0.15	-0.16	1.5	6.12±0.18	2.0
Gelatin	1.5	6.02±0.14	0.33	1.5	6.08±0.10	1.33
Calcium carbonate	1.5	6.12±0.16	2.0	1.5	6.05±0.14	0.83
All above	2	6.05±0.11	1.16	2	6.13±0.06	2.16

The proposed methods have been validated based on ICH guidelines (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use).[31] Therefore, the developed method was validated for linearity, accuracy, precision, repeatability, LOD and stability.

3.4. Validation of Proposed Method

3.5. Calibration Graphs

By injecting 2-10 µmol/L and 2-12 µmol/L of the standard solution of MBH into the manifold flow system and under using all the optimized operating conditions which are mentioned in Table 2, two calibrations curves were constructed, the first one for the nephelometry measurement cell and the second for the turbidity measurement cell. An excellent linear range was obtained between the obtained signals and the concentrations of MBH with excellent correlation coefficients as shown in Figs. 12, 13. All of the statistical parameters of the linear regression lines are tabulated in Table 4.

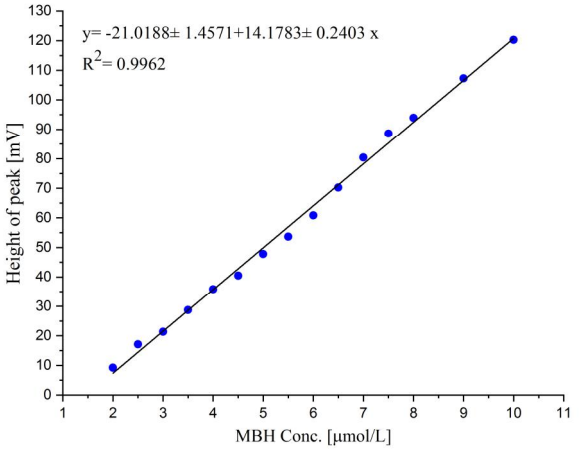

Fig. 12. The linear calibration curve for determination of MBH for measuring cell 1 using all of the optimum conditions: sodium persulfate 60 µmol/L, flow rates 3.3 & 4.3 mL min^{-1} for distilled water and sodium persulfate (reagent) lines, respectively, open valve mode and 250 µL sample volume

3.6. Limit of Detection

Development of precise, accurate, robust, and linear assays is one of the major requirements to development activities for drug substances and drug products. Therefore, determining the LOD of an assay that can reliably quantitate is a requirement of the authorities globally. LOD can be calculated according to the standard error of the responses (Y-intercepts) of regression lines. In this type, all the samples must be taken in the LOD and LOQ range of the whole range of the dynamic range for the sample. The calculations of LOD can be conducted as follows:

$$SD= SE/\sqrt{n-1}$$

$$LOD= 3* (slope/SD)$$

where the SE= the standard error of the response, n= the size of the sample.

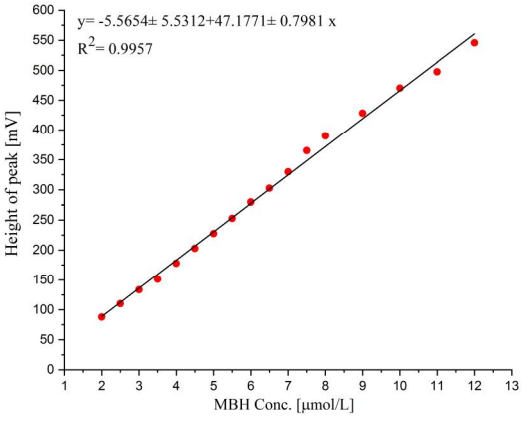

Fig. 13. The linear calibration curve for determination of MBH for measuring cell 2 using all of the optimum conditions: sodium persulfate 60 µmol/L, flow rates 3.3 & 4.3 mL min^{-1} for distilled water and sodium persulfate (reagent) lines, respectively, open valve mode and 250 µL sample volume

Table 4. The summary of linear regression of the proposed method

Parameter	Obtained value		
	Measuring cell 1	Measuring cell 2	Reference method[35]
Linearity (µmol/L)	2.0–10.0	2.0–12.0	10–32
Regression equation	14.1783x–21.0188	47.1771x–5.5654	0.0518x +0.9371
Slope	14.1783	47.1771	0.0518
Intercept	-21.0188	5.5654	0.9371
Correlation coefficient, r	0.9981	0.9978	0.9977
coefficient of determination, r^2	0.9963	0.9957	0.9955
LOD (µmol/L)	0.35	0.40	4.0

3.7. Repeatability

Repeatability measurements refer to the closeness of the obtained results with the same sample using the same operators, same measurement procedure, the same instrument, the same location, and the same operating conditions over a short period of time (usually one analytical run or one day). The repeatability measu-

rements are expected to give the smallest possible variation from the obtained results. Therefore, 3 of known concentrations [MBH] (3, 6 and 9 µmol/L) are used to determine the repeatability measurements. Each concentration of [MBH], 10 determinations were conducted as shown in Table 5.

Table 5. The evaluation of repeatability of the determination of MBH

[MBH] µmol/L	Peak height(mV) (n=3)	RSD%	Confidence interval at 95% $\bar{Y}_{zi}$ (mV) $\pm t_{0.05/2,n-1}\sigma n\text{-}1/\sqrt{n}$
	Measuring cell 1: Y=14.1783±0.2403-21.0188±1.4571[MBH] (µmol/L)		
	Measuring cell 2: Y=47.1771±0.7981-5.5654±5.5312[MBH] (µmol/L)		
3.0	21.922	1.16	21.922±0.1740
	135.932	0.65	135.932±0.5956
6.0	63.933	0.85	63.933±0.4371
	278.333	1.01	278.333±2.1853
9.0	107.200	0.73	107.200±0.5722
	420.733	0.56	420.733±1.7247

Table 6. The intra and inter day precisions of the proposed method for determination of MBH

Expected [MBH] µmol/L	Intra-day (n=5)			
	Measuring cell 1: Y=14.1783±0.2403-21.0188±1.4571[MBH] (µmol/L)			
	Measuring cell 2: Y=47.1771±0.7981-5.5654±5.5312[MBH] (µmol/L)			
	Peak height(mV) (n=3)	RSD%	Measured [MBH] µmol/L (n=3)	RSD%
5.0	49.8562±0.2455	0.2150	4.9988±0.0229	0.2313
	229.9231±2.5000	0.4420	4.9915±0.0712	0.6849
9.0	106.9232±1.9963	0.7475	9.02379±0.1862	0.7707
	419.733±1.1745	0.1100	9.0149±0.0334	0.1353

Expected [MBH] µmol/L	Inter-day (*n=3*)					
	Day 1 (*n=3*)		Day 2 (*n=3*)		Day 3 (*n=3*)	
	Measured µmol/L (n=3)	RSD%	Measured µmol/L (n=3)	RSD %	Measured µmol/L (n=3)	RSD%
5.0	4.9862±0.0208	0.2105	4.9931±0.0354	0.3573	5.00±0.0039	0.0393
	5.0350±0.0319	0.3116	5.0923±0.0092	0.0903	5.0862±0.0120	0.1183
9.0	9.0934±0.0474	0.1943	8.9833±0.1188	0.4815	8.9953±0.1895	0.7717
	8.9995±0.0502	0.2044	9.0845±0.0567	0.2319	8.9744±0.0189	0.0772

Table7. The accuracy of the proposed method for determination of MBH

Nominal concentration of [MBH] (µmol/L)	Concentration found of [MBH] (n=3) (µmol/L)	RSD%	Accuracy as error %	Accuracy as recovery %
	Measuring cell 1: Y=14.1783±0.2403-21.0188±1.4571[MBH] (µmol/L)			
	Measuring cell 2: Y=47.1771±0.7981-5.5654±5.5312[MBH] (µmol/L)			
6.0	6.0215±0.0663	0.4408	0.3583	100.35
	5.9823±0.0306	0.2004	-0.2950	99.70
8.0	8.0923±0.05656	0.3309	1.1537	101.15
	8.1252±0.0328	1.5650	1.8584	101.56
Mean			0.7523	100.75
			1.0253	100.63

3.8. Precision and Accuracy

The (RSD) values of the inter-day and intra-day obtained from the developed method were found to be less than 0.8 % as shown in the Table 6. The accuracy of the developed method has expressed as an error % (E%) and a Rec % (a recovery percentage) which was between 101.15 to 100.35 and 101.56 to 99.70 for measuring cell 1 and measuring cell 2, respectively (see Table 7).

3.9. Stability

The stability of the formed product (analyte) with the temperature was examined using a range of temperatures. From the obtained results it was noticed that the formed product was stable at 288 and 298 K and no change in determination results were observed in comparison with freshly prepared analyte as shown in Table 8.

3.10. Tablet Properties

All of the physical characteristics of the pharmaceutical formulations (tablets) must be examined prior to the determination of them according to the USA pharmacopoeia requirements. Recently, there has been a growing concern about the photodegradation and lack of stability of active ingredients in pharmaceutical formulation, therefore, conducting of quantitative evaluation needs to be performed.[33-35] Therefore, content uniformity, friability, and the average weight of the selected tablets were examined. The USA pharmacopoeia reports the maximum limit for each of these physical characteristics such as 1.5 % for friability, 6 % for content uniformity, and ±5 % for the average weight. The results have shown that all of the examined tablets were in the range of official specifications and can be used in the experiments (Table 9).

Table 8. Thermal stability of validated determination of MBH

Variable	Conditions examined	Peak height (mV)				Recovery %
		Sample solution (6 µmol/L)	RSD %	Reference sample solution (6 µmol/L) at 283 K	RSD %	
		Peak height (mV) ofmeasuring cell 1				
		Peak height (mV) of measuring cell 2				
Solution temperature, K	288	63.1521	0.5597	63.933	0.5545	98.77
		277.5212	0.1725	278.333	0.0409	99.70
	298	63.7521	0.1647	63.933	0.5545	99.71
		278.2541	0.1479	278.333	0.0409	99.97

Table 9. The physicochemical characteristics of the selected tablets based on USA pharmacopoeia requirements

Tablet dosage (mg)	Average weight (mg) (*n=20*) Weight variation	Friability (%) (*n=20*)	Content uniformity (%), (*n=10*)		
			Lower	Higher	RSD %
135 France	410.97(428.30-392.20)	0.04	97.62	98.52	0.27
135 Egypt	308.70(317.85-299.20)	0.05	92.23	102.35	0.36
135 Syria	368.80(375.00-357.00)	0.05	95.34	99.25	0.45
Official limits	±5 %	Max. 1.5 %	85-115 %		≤6 %

3.11. UV Spectrophotometry Method (Reference Method)[37]

UV-Vis spectrophotometer type double-beam (Shimadzu, model 1601) with 1 cm quartz cell was used for conducting all the absorbance measurements. The absorption spectrum of MBH in the range of 190–400 nm was recorded and 262 nm was chosen to be the best wavelength of MBH as shown in Fig. 14. A series of MBH concentrations were prepared using distilled water in the range of (0.5–40 µmol/L). By conducting the statistical calculation, the drug has shown a linear range (10–32 µmol/L) with r = 0.9977, r^2 = 0.9955, LOD = 4.0 µmol/L, LOQ = 12.5 µmol/L at n = 12 (n= number of measurements).

3.12. Applications

Three different types of commercial pharmaceutical tablets containing 135 mg/tablet were quantified to assess the developed method using ion-pair association reaction and the flow injection system for the determination. All the obtained signals from each sample are conducted with triplicate analysis. All the obtained results are shown in Table 10. Also, the recovery percentages were studied by spiking an appropriate amount of the reference materials of MBH to the prepared solutions of tablets using standard addition method.

The recovery percentages of the samples were in the excellent agreement with the label claims and ranged from 99.83 to 103.08 for nephelometry and 99.77 to

103.13 for the turbidity measurements. All of the results are shown in Table 11.

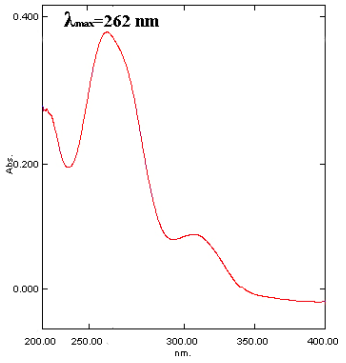

Fig. 14. The absorbance spectra of MBH

3.13. Data Analysis

F-test and one-sample t-test were carried out for the obtained results from the developed and reference methods. The statistical study was performed at 95 % confidence interval and 19 as a degree of freedom. The t-test analysis has shown that there is a significant difference between the results obtained by the methods and the label claims for the same batch, while the statistical evaluation (F-test) which is used for comparison between the developed and reference method has shown that there were no significant differences between all of the examined methods. All the statistical data are shown in Table 12.

Table10. The application results of the proposed method for the quantitative determination of MBH in tablets

Pharmaceutical preparations	Label claimed mg/tablet	Found (mean assay % of label claimed ± SD)		
		Reference method	Proposed method	
		UV	Measuring cell 1	Measuring cell 2
Colofac ® (Abbott, France)	135	100.01±0.09	103.89±0.09	101.99±0.16
Colospasmin ® (EIPICO, Egypt)	135	99.50±0.14	97.83±0.24	98.61±0.24
Duspalina ® (Asia, Syria)	135	102.95±0.19	102.53±0.42	101.07±0.06

Table 11. The results from the recovery determination of MBH

Method	Pharmaceutical Preparations	Added (µmol/L)	Found (µmol/L)	Rec[a] %	RSD[a]
Proposed Method (Cell 1)	Colofac ® (Abbott, France)	4.0	3.9952	99.88	0.24
		6.0	6.0232	100.38	0.12
		8.0	8.0563	100.70	0.42
	Colospasmin ® (EIPICO, Egypt)	4.0	4.1232	103.08	0.11
		6.0	6.0523	100.87	0.75
		8.0	8.1253	101.56	0.14
	Duspalina ® (Asia, Syria)	4.0	4.1235	103.08	0.12
		6.0	6.0956	101.59	0.22
		8.0	7.9865	99.83	0.43
Proposed Method (Cell 2)	Colofac ® (Abbott, France)	4.0	4.0563	101.40	0.44
		6.0	6.0825	101.37	0.32
		8.0	7.9856	99.82	0.62
	Colospasmin ® (EIPICO, Egypt)	4.0	4.0523	101.30	0.11
		6.0	5.9863	99.77	0.57
		8.0	8.1523	101.90	0.22
	Duspalina ® (Asia, Syria)	4.0	4.1252	103.13	0.52
		6.0	6.1232	102.05	0.14
		8.0	7.9856	99.82	0.38

3.14. Comparison Study between the Developed Method and the Reference Method

The comparison study between the two methods has been performed statistically by conducting one-way ANOVA test. This test provides information about whether there is an overall significant difference between the methods or not, depending on the p-value. If the P-value is bigger than 0.05, this means there is no difference between the methods. On the other hand, if the P-value (Sig) equal or less to 0.05 this means there is a significant difference among the three methods. By using SPSS software for conducting the ANOVA test, the overall significant difference between the methods has occurred as shown in Table 12.

Table 12. The statistical data analysis of the proposed method for determination of MBH in tablets

Type of MBH	One sample T-Test μ=0.135 (claimed value)				F test				One-way ANOVA (*P* value at 95 %)	
	Cell 1		Cell 2		Measuring cell 1 *vs.* reference method (UV)		Measuring cell 2 *vs.* reference method (UV)		P_{cal}	P_{tab}
	t_{cal}	t_{tab}	tc_{al}	t_{tab}	F_{cal}	F_{tab}	F_{cal}	F_{tab}		
Colofac ® (Abbott, France)	7.032>2.09		3.912>2.09		1.07<2.16		1.03<2.16		0.000096<0.05	
Colospasmin ® (EIPICO, Egypt)	5.034>2.09		3.187>2.09		1.04<2.16		1.02<2.16		0.018<0.05	
Duspalina ® (Asia, Syria)	10.751>2.09		4.069>2.09		1.01<2.16		1.04<2.168		2.87E-7<0.05	

4. Conclusions

Currently, the developed method is considered as a novel method since till now in the literature, there is no procedure that can determine the MBH drug in tablet preparations using two consecutive measuring cells, both calculating the turbidity for the same injected sample at the same time. The optimized operating parameters have allowed for obtaining good linear curves with excellent recovery percentages for the spiked sample analysis using standard addition method. The obtained results from the developed method show that flow injection manifold system for the same sample and a single detector which contains two consecutive measuring cells is found to be a proper method for simple, accurate, sensitive, selective, low-cost, and precise quantification of MBH in the tablet. The current flow injection manifold is a semi-automated system and in the future, it can be easily developed to the fully automated system and be used in the routine quality control analysis.

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ТУРБІДИМЕТРИЧНЕ ВИЗНАЧЕННЯ МЕБЕВЕРИНУ ГІДРОХЛОРИДУ У ФАРМАЦЕВТИЧНИХ ПРЕПАРАТАХ З ВИКОРИСТАННЯМ ДВОХ ПОСЛІДОВНИХ ЗОН ВИЯВЛЕННЯ В УМОВАХ НЕПЕРЕРВНОГО ПОТОКУ

Анотація. *Для визначення мебеверину гідрохлориду (МБГ) у фармацевтичних препаратах було розроблено і валідовано простий, недорогий і швидкий турбідиметричний метод впорскування. Розроблений метод ґрунтується на утворенні білого каламутного продукту у формі іонної пари в результаті реакції між МБГ і персульфатом натрію в замкнутій системі впорскування, у якій персульфат натрію використовують як осаджувач. Мутність утвореного комплексу вимірювали під кутом детектування 180° (ослаблене детектування) за допомогою детектора NAG dual&Solo (0-180°), який має подвійні зони детектування (тобто вимірювальні комірки 1 і 2). Збільшення мутності комплексу було прямо пропорційне збільшенню концентрації МБГ в діапазоні 2,0-10 мкмоль/л з межею виявлення 0,35 мкмоль/л, 0,9981 (R^2), та 2,0-12 мкмоль/л з межею виявлення 0,4 мкмоль/л і 0,9973 (R^2) для вимірювальних комірок 1 і 2, відповідно. Внутрішньодобова точність для трьох серійних оцінок 5,0 і 9,0 мкмоль/л МБГ показала RSD % на рівні 0,23 % і 0,77 % та 0,68 % і 0,13 % для комірок 1 і 2, відповідно, у той час як міжденна точність для трьох серій за три дні продемонструвала RSD % на рівні 0,03 % і 0,77 % та 0,11 % і 0,07 % для вимірювальних комірок 1 і 2, відповідно. Точність розробленого методу була виражена як % похибки (E%) і Rec % (відсоток відновлення), який становив від 100,35 до 101,15 та від 99,70 до 101,56 для комірки 1 і комірки 2, відповідно. Даний метод впорскування не показав ефекту інтерференції звичайних допоміжних речовин і дозволяє кількісно визначати 60 зразків на годину. Розроблений метод був успішно застосований для кількісного визначення МБГ в різних таблетках, що містять 135 мг, з відмінним відсотком відновлення.*

Ключові слова: *мебеверину гідрохлорид, впорскування, турбідиметричне визначення, подвійна зона виявлення, фармацевтичні препарати.*