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ORIGINAL PAPER

Spectrofluorimetric Assessment of Metoclopramide Hydrochloride Using Terbium Doped in PMMA Matrix Optical Sensor

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Abstract A new, simple and accurate spectrofluorimetric method for the determination of metoclopramide hydrochloride was developed. The metoclopramide hydrochloride can remarkably enhance the luminescence intensity of the Tb^{3+} ion doped in PMMA matrix at λ_{ex}=360 nm in methanol at pH 6.9. The intensity of the emission band at 545 nm of Tb^{3+} ion doped in PMMA matrix is increased due to the energy transfer from metoclopramide hydrochloride to Tb^{3+} in the excited stated. The effect of different parameters, e.g., pH, temperature, Tb^{3+} concentration, foreign ions that control the fluorescence intensity of the produced ion associate was critically investigated. The calibration curve of the emission intensity at 545 nm shows linear response of metoclopramide over a concentration range of 5×10^{-5}–5.0×10^{-8} M with detection limit of 8.7×10^{-10} M. The method was used successfully for the determination of metoclopramide in pharmaceutical preparations and human serum. The average recovery of 99.48% with standard deviation of 0.32% and 96.98% with standard deviation of 0.4%, of pharmaceutical preparations and human serum respectively, were obtained which compared will with the results obtained from standard LC method of average recovery 99.04% and standard deviation of 0.6% and average recovery of 98.19% with standard deviation of 0.6% of pharmaceutical preparations and human serum, respectively.

Keywords Metoclopramide hydrochloride · Terbium · Optical sensor · Energy transfer · Luminescence Intensity · PMMA

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Introduction

Metoclopramide (MCP), 4-amino-5-chloro-2-methoxy-N-(2- diethylamino-ethyl) benzamide, is a dopamine-receptor antagonist active on gastrointestinal motility. It is used as an anti-emetic in the treatment of some forms of nausea and vomiting and to increase gastrointestinal motility. It is also used at much higher doses for the prevention of cancer chemotherapy-induced emesis [1].

In this perspective, the wide applications of MCP in both clinical and experimental medicine have prompted extensive interest in its determination. Current analytical methods employed for the determination of MCP can involve fluorimetry [2], spectrophotometry [3–10], chromatography [11–15], capillary electrophoresis [16, 17], differential scanning calorimetry (DSC) and X-ray diffraction [18], gas chromatography–mass spectrometry (GC–MS) [19], potentiometry [20], voltammetry [21], fast stripping continuous cyclic voltammetry [22], square wave anodic stripping voltammetric [23] and ^{1}H-NMR spectroscopy [24]. The chromatographic method is costly and also time-

consuming, limiting its application. Other methods often are typically less sensitive or have their own intrinsic disadvantages such as technical complexity or require expensive instrumentation.

Recently, Al-Arfaj developed a flow-injection (FI) method for the rapid and sensitive determination of MCP hydrochloride by using $Ru(dipy)_3^{2+}$ chemiluminescence (CL), [25] another electrochemiluminescence (ECL) sensor for the determination of MCP was developed based on $Ru(bpy)_3^{2+}$-doped silica (RuDS) nanoparticles dispersed in a perfluorosulfonated ionomer (Nafion) on a glassy carbon electrode (GCE) [26]. Most of these methods are coastly and lake from the simplicity and sensitivity. In this work, the metoclopramide hydrochloride concentration was determined by the terbium doped in the Polymethylmethacrylate (PMMA) matrix optical sensor. The absorption and emission spectra of metoclopramide hydrochloride and terbium were measured in the PMMA matrix. In comparison with other techniques, this method is simple, relatively free from interference with coexisting substances and can successfully be applied to the determination of the MCP drug in pharmaceutical tablets and in serum samples with satisfactory results.

Experimental

Chemicals and Reagents

All chemicals used are of analytical-reagent of higher grade. Pure standard of metoclopramide hydrochloride is either purchased from Sigma or supplied by the (National Organization for Drug Control and Research, Cairo, Egypt) Fig. 1. Pharmaceutical preparations, primpran, 10 mg (Aventis Company, Egypt), migracid, 5 mg (Cid Company, Egypt) are purchased from local market. Polymethylmethacrylate (PMMA) was delivered from Aldrich.

Distilled water and pure grade solvents from (Aldrich) are used for the preparation of all solutions and during the all determinations. A stock solution of metoclopramide hydrochloride (1×10^{-2} $molL^{-1}$) is freshly prepared and dissolved in methanol and stored at 4 °C when not in use.

A Tb^{3+} ion stock solution (1×10^{-2} mol L^{-1}) is prepared by dissolving $TbCl_3$ (delivered from Aldrich, 99.99%) with a small amount of methanol in 100 ml measuring flask, then diluting to the mark with methanol.

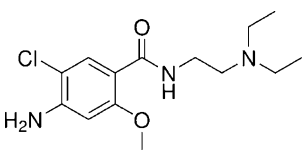

Fig. 1 Structure of Metoclopramide hydrochloride (MCP)

Apparatus

All luminescence measurements are carried out on Shimadzu RF5301 spectrofluorophotometer in the range (290–750 nm). The absorption spectra are recorded with a Unicam UV-Visible double-beam spectrophotometer from Helios Company. It employs a Tungsten filament light source and a Deuterium lamp, which has a continuous spectrum in the ultraviolet region. The spectrophotometer is equipped with a temperature-controller cell holder. (All measurements are measured at Photo Energy Center, Faculty of Science, Ain Shams Univ.).

General Procedure

Preparation of Tb Ion Doped in PMMA Matrix

Polymethylmethacrylate PMMA matrix was prepared by dissolving appropriate amount of PMMA in chloroform (5 gm PMMA/25 ml $CHCl_3$) at 30 °C with vigorous stirring for 15 min then Tb (0.02 gm/10 methanol) was incorporated into PMMA matrix at 30 °C under vigorous stirring for 15 min. The PMMA matrix was left to dry for 3 h at room temperature to obtain PMMA thin film. The thickness of the thin film was measured by micrometer and it was equal to 0.4 mm [27].

Preparation of Metoclopramide Hydrochloride Solutions

To 10 ml clean and sterilized measuring flasks, the standard solutions of metoclopramide hydrochloride are prepared by different additions of (5×10^{-4} mol L^{-1}) metoclopramide hydrochloride solution to give concentrations ranged from (5×10^{-5} to 5×10^{-9} mol L^{-1}) of metoclopramide hydrochloride. The solutions are diluted to the mark with methanol at room temperature. The above method is used for the subsequent measurements of absorption, emission spectra and effect pH. The luminescence intensity is measured at $\lambda_{ex}/\lambda_{em}$=360/545 nm.

Measurement Procedures of the Luminescence Spectrum of the Optical Sensor Tb^{3+} Doped in PMMA Matrix

After the preparation of the different standard solutions of metoclopramide hydrochloride in methanol as mentioned in above section, the optical sensor Tb doped in PMMA matrix will immersed in each standard solution of metoclopramide hydrochloride in the cell of the spectrofluorimetric device then the luminescence spectrum will be measured at the excitation wavelength 360 nm. The optical sensor must be rinsed after each measurement by methanol. Then draw the peak intensity at λ_{em}=545 nm on y axis against concentration of metoclopramide hydrochloride on x axis.

Validation

Selectivity

The selectivity was performed on the three different products of pharmaceutical tablets and human serum from 3 individual healthy donors receiving no medication for the assessment of potential interferences with endogenous substances at the linear range of the determination of metoclopramide hydrochloride.

Linearity

The linear range of determination of metoclopramide hydrochloride was processed according to the procedure described above for the construction of calibration curves. The different concentrations ranged from 5×10^{-5} to 5×10^{-8} mol L^{-1} calibration curve were obtained by plotting the peak intensity at λ_{em}=545 nm of Tb optical sensor on y axis against concentration of metoclopramide hydrochloride (MCP) on (*x*) axis. The linearity, LOD and LOQ were evaluated according to ICH guidelines [28] using the formulae:

$$\mathrm{LOD} = 3.3\,\mathrm{S/b}\ \text{and}\ \mathrm{LOQ} = 10\,\mathrm{S/b}$$

(where S is the standard deviation of blank luminescence intensity values, and b is the slope of the calibration plot).

Precision

The intraday precision of Tb optical sensor was evaluated by replicate (n=3) analysis of the pharmaceutical tablet samples and serum samples containing metoclopramide hydrochloride at three different concentrations of 1×10^{-5}, 1×10^{-6} and 1×10^{-8} mol L^{-1}. The intraday precision was evaluated at the above concentration levels for 3 days. The precision was estimated by the relative standard deviation (R.S.D. %).

Recovery

The average recoveries of metoclopramide hydrochloride were evaluated at three concentration levels of 1×10^{-5}, 1×10^{-6} and 1×10^{-8} molL^{-1} each one was repeated three times and from peak intensity of assayed samples comparison to the one of reference standards prepared in methanol, then recoveries were calculated using the formula:

$$\%\,\mathrm{Recovery} = \text{peak intensity serum}/\text{peak intensity methanol} \times 100$$

Stability

The processed pharmaceutical tablet samples and serum samples 1×10^{-5}, 1×10^{-6} and 1×10^{-8} mol L^{-1} treated as sample preparation were kept at room temperature for 24 h and then the stability was determined. The freeze–thaw stability was determined after three repeated freezing and thawing cycles on day 0, 15 and 30.

Determination of Metoclopramide Hydrochloride in Pharmaceutical Preparations

Ten tablets each of primpran 10 mg and migracid 5 mg are carefully weighed and ground to finely divided powders. Accurate weights equivalent to 10 mg primpran and migracid are accurately transferred to 50 ml beaker and dissolved in methanol and solutions are stand for about 10–15 min, filtered up using 12 mm filter papers then transferred to 100 ml volumetric flask and completed to the mark with methanol to give the test solution. The concentration of the drug is determined by immersing the PMMA film doped Tb^{3+} ion in the solution of the drug and concentration of each sample was obtained by the average of nine repeating times from the corresponding calibration graph. The reaction time between the MCP drug and MCP – Tb^{3+} optical sensor is 30 s.

Determination of Metoclopramide Hydrochloride in Serum Solution

A 1.0 ml of samples of serum collected from various real patients is centrifuged for 15 min at 4000 r/min to remove most of protein substances, then few drops of trichloroacetic acid (5%) to precipitate the residue of proteins were added, vortexes and centrifuged. The unknown amount of metoclopramide hydrochloride in human serum samples is determined using the standard addition (spiking) techniques as follow; a known volume of the treated serum of the real patient is transferred into a calibrated 10 ml measuring flask and diluted by methanol. The concentration of the drug is determined by immersing the PMMA film doped Tb ion in the serum sample for 30 s. The luminescence intensity of the test solution is measured before and after addition of 1.0 ml of previously prepared serum solution. The change in the luminescence intensity is used for determination of metoclopramide hydrochloride in serum samples.

Results & Discussions

Spectral Characteristics

Absorption Spectra

A preliminary investigation of the reaction of Tb^{3+} ion with metoclopramide hydrochloride (MCP) showed that Tb-MCP complex compound was formed between Tb ion

and MCP drug (Fig. 1) at pH 6.9 in PMMA matrix. The electronic spectrum of different concentrations of Tb ions with metoclopramide hydrochloride (5×10^{-4} M) displayed two characteristic bands at 276 and 310 nm as shown in (Fig. 2) curves (2, 3 and 4). Compared to those exhibited at 260 and 292 by MCP curve (1), there are a red shift by 8 and 9 nm, and the absorbance is also enhanced, which indicates that metoclopramide hydrochloride can form a binary complex with Tb^{3+} ion.

Emission and Excitation Spectra

The Tb^{3+} ion react with metoclopramide hydrochloride (MCP) to form Tb^{3+}- MCP complex compound. Figure 3 shows the fluorescence excitation spectrum of Tb^{3+} (1×10^{-3} M) with metoclopramide hydrochloride 5×10^{-4} mol L^{-1} curve (1), where, the curves (2), shows emission spectrum of 5×10^{-4} mol L^{-1} MCP only. Where curve (3) shows no excitation or emission spectrum of 1×10^{-3} mol L^{-1} of Tb^{3+} only, On the other hand, Tb^{3+}- MCP complex show well defined emission spectra as shown in curve (4) for (1×10^{-3} mol L^{-1} of Tb^{3+} and 5×10^{-4} mol L^{-1} MCP complex in PMMA matrix at λ_{ex} /λ_{em}=360/545 nm.. Comparing curves 1 and 2 with curves (3 and 4) in Fig. 3, after the addition of metoclopramide hydrochloride into the Tb^{3+} ion in PMMA matrix indicate that metoclopramide hydrochloride can form a binary complex with Tb^{3+} ion. So it appears the characteristic peaks of Tb^{3+} ion ($^5D_4\rightarrow{}^7F_6$, $^5D_4\rightarrow{}^7F_5$, $^5D_4\rightarrow{}^7F_4$, and $^5D_4\rightarrow{}^7F_3$,), respectively. Thus, in the subsequent work, the concentration of MCP was determined through measuring the fluorescence intensity of the complex Tb^{3+} - MCP at 545 nm at the optimum experimental conditions.

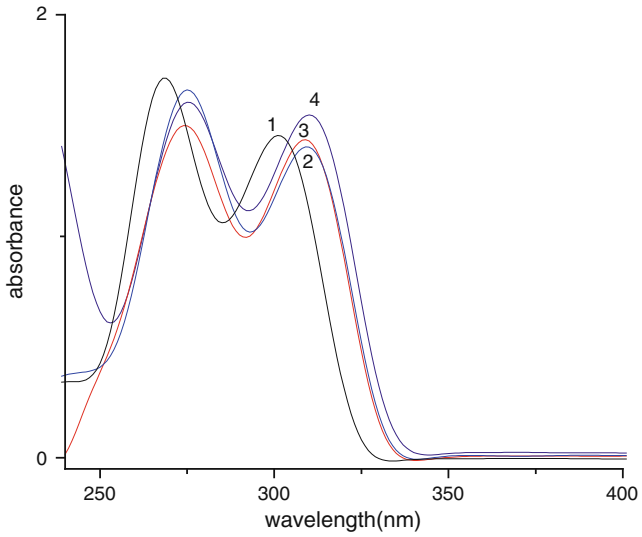

Fig. 2 The absorption spectra of 5×10^{-4} mol L^{-1} of MCP curve (1) in different molar concentration of Tb^{3+} doped in PMMA matrix curves (2, 3 and 4)

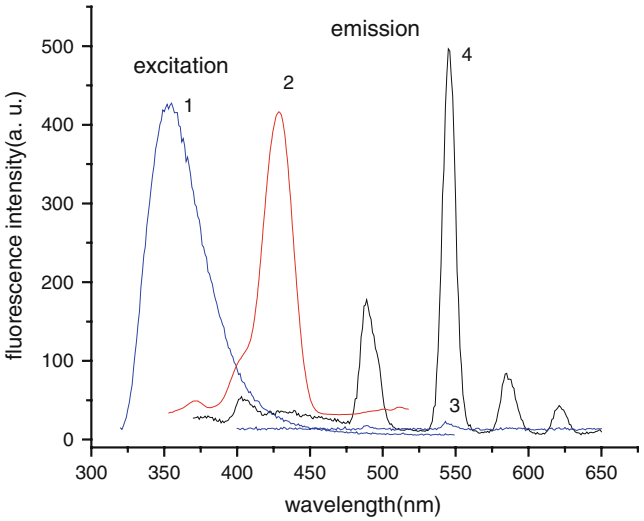

Fig. 3 The fluorescence excitation of (1×10^{-3} mol L^{-1} of Tb^{3+} with 5×10^{-4} mol L^{-1} MCP), curve (1), and emission spectrum of 5×10^{-4} mol L^{-1} MCP only, curve (2), and the excitation and emission spectrum of 1×10^{-3} mol L^{-1} of Tb^{3+} only curve (3), where curve (4) is the emission spectrum of (1×10^{-3} mol L^{-1} of Tb^{3+} and 5×10^{-4} mol L^{-1} MCP complex in PMMA matrix at λ_{ex} /λ_{em}=360/545 nm

Effect of Experimental Conditions

Effect of the Amount of Metoclopramide Hydrochloride

The influence of the amount of MCP on the luminescence intensities of the Tb^{3+} ion doped in the PMMA matrix is studied. The luminescence intensity of Tb^{3+}- MCP complex was increased upon increasing the concentration of metoclopramide hydrochloride till 5×10^{-4} mol L^{-1} then becomes constant. The experimental results showed that the luminescence intensity reached maximum and remained constant when metoclopramide hydrochloride solution is 5×10^{-4} mol L^{-1} in the methanol preparations (Figs. 4 and 5).

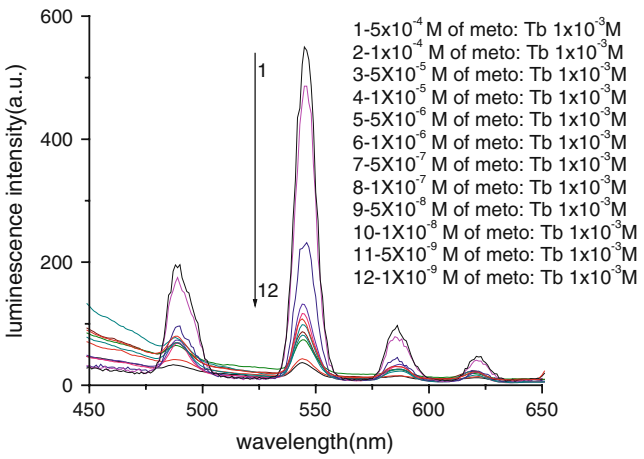

Fig. 4 Luminescence spectra of 1×10^{-3} mol L^{-1} of Tb^{3+} doped in PMMA in the presence of 5.0×10^{-5} to 5.0×10^{-9} mol L^{-1} of MCP in methanol at λ_{ex}=360 nm

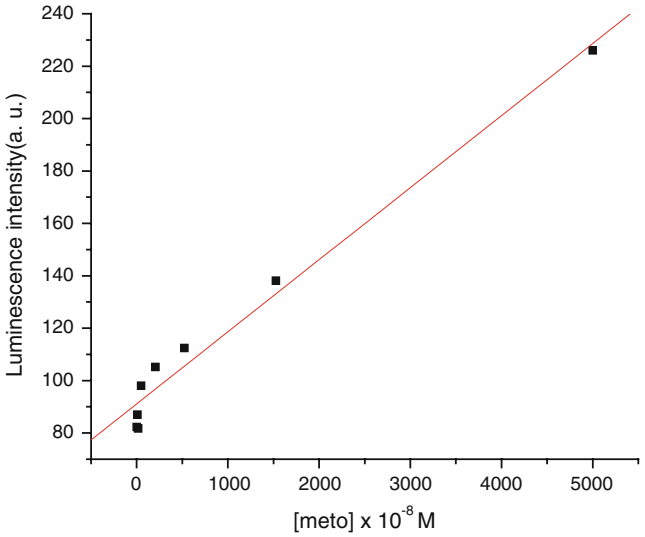

Fig. 5 Linear relationship of 5.0×10^{-5} to 5.0×10^{-9} mol L^{-1} of MCP in methanol and the luminescence intensity of Tb^{3+} doped in PMMA matrix at λ_{ex}=360 nm

Effect of the Amount of Tb^{3+}

The influence of the amount of Tb^{3+} ion on the luminescence intensities of Tb-metoclopramide hydrochloride in PMMA matrix is studied under the conditions established above. The luminescence intensity of Tb^{3+}- MCP complex at 545 nm was increased upon increasing the concentration of Tb^{3+} up to 1×10^{-3} mol L^{-1} then becomes constant. The above data reveals that the composition ratio for the Tb^{3+} to metoclopramide hydrochloride in the Tb^{3+} - MCP system is 2:1. Thus, 1.0×10^{-3} mol L^{-1} of Tb^{3+} ion concentration is used for further study in the PMMA matrix.

Effect of pH

The pH of the medium has a great effect on the luminescence intensity of the Tb-metoclopramide hydrochloride complex compound. The luminescence intensity of the Tb^{3+} - MCP at different pH ranged from 2 to 10 using 0.1 M of HCl and /or NH_4OH was tested. The results obtained show that the maximum fluorescence intensity is obtained at pH 6.9. So, in the subsequent work, the pH of the tested solution was adjusted by 0.1 mol L^{-1} of HCl and /or NH_4OH to pH 6.9 before measurements.

Analytical Application

Linear Range and Limit of Detection

A linear correlation was found between luminescence intensity of MCP– Tb^{3+} complex at λem=545 nm and different concentrations of MCP in the ranges between 1000, 500, 170, 50, 10, 5×10^{-8} mol L^{-1} of the calibration curve were obtained by plotting the peak intensity of Tb^{3+} at λ_{em}= 545 nm versus the concentration of MCP and the graph was described by the regression equation:

$$Y = a + bX$$

(Where, Y = luminescence intensity of the optical sensor at λ_{em}=545 nm; a = intercept; b = slope and X = concentration in M). Regression analysis of luminescence intensity data using the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient (r). The values were presented in Table 4 showed that, the limit of detection (LOD) and quantitation (LOQ) which are statistically calculated according to ICH guidelines [28] using the formulae:

$$LOD = 3.3\,S/b \text{ and } LOQ = 10\,S/b$$

(where S is the standard deviation of blank luminescence intensity values, and b is the slope of the calibration plot) are 8.7×10^{-10} M and 2.6×10^{-9} M, respectively. The low value of LOD indicates the high sensitivity of the proposed method. The PMMA doped Tb^{3+} optical sensor displayed constant luminescence intensity from day to day and the

Table 1 Determination of MCP in pharmaceutical preparations and in serum using Tb^{3+}- MCP optical sensor

Drug	Added (x 10^{-8} mol L^{-1})	Found (x 10^{-8} mol L^{-1})	Average[a]	Average recovery % ± S.D. (%)	B.P. (LC)
Primpran, 10 mg (Aventis Co. Egypt)	5	5.02, 4.99, 5.1	1.002	100.2±0.21	98.98±1.0
	50	49.97,50.05,50.0			
	500	499.96,500.08,499.99			
Migracid, 5 mg (Cid Co. Egypt)	5	4.94, 5.14, 5.11	0.9877	98.77±0.43	99.1±0 .2
	50	50.02,50.03,50.05			
	500	499.92,499.96,499.91			
Serum sample	5	5.09, 5.03, 4.92	0.9698	96.98±0.40	98.19±0.1
	50	49.95, 49.99, 49.92			
	500	500.11,500.15,499.90			

[a] Average of nine measurements

Table 2 Freeze–thaw stability of MCP in pharmaceutical preparations and human serum (n=3) using Tb^{3+}- MCP optical sensor

Drug / serum	Normal concentration (10^{-6} mol L^{-1})	Found Average recovery ± S.D. (10^{-6} mol L^{-1})			S.D. (%)
		0 day	15 days	30 days	
Primpran, 10 mg (Aventis Co. Egypt)	10	10.1	10.13	10.15	5.70
	1	1.0	1.04	1.07	
	0.1	0.1	0.102	0.102	
Migracid, 5 mg (Cid Co. Egypt)	10	10.0	10.04	10.06	2.5
	1	1.0	1.02	1.06	
	0.1	0.1	0.102	0.103	
Serum sample	10	10.0	10.1	10.1	4.5
	1	1.03	1.05	1.05	
	0.1	0.101	0.102	0.103	

calibration slope did not change over a period of 3 months, this may be due to that PMMA is very stable in methanol.

Determination of MCP in Pharmaceutical Preparations and in Serum Solution

The reliability of the proposed method Tb^{3+} - MCP optical sensor for the determination of metoclopramide hydrochloride was assessed by determining MCP in powder form and in pharmaceutical preparations. For the assay of metoclopramide hydrochloride, the samples must be diluted appropriately within the linear range of determination of metoclopramide hydrochloride and the sample solution is analyzed by the method developed above, using the standard calibration method. The results obtained in Table 1 showed that the average recovery and standard deviation (S.D) are 98.98% and 0.3%, respectively. Data obtained by liquid chromatography method of British Pharmacopoeia [B.P. 2000] of average recovery 98.49% and standard deviation of 0.6% are also presented for comparison and show a good correlations with those obtained by the proposed method. The developed method can be easily performed and offers good precision and accuracy when applied for the determination of metoclopramide hydrochloride in pharmaceutical preparations.

The proposed method is also, applied for the determination of metoclopramide hydrochloride in human serum sample. Proteins in human serum interfere seriously for the system. So, 1.0 ml serum is centrifuged for 15 min at 4000 r/min to remove most of protein substances. Then 100 micron of the serum of real patients is added to 9.8 ml of methanol then analyzed by a standard addition method as mentioned above. The experimental results in Table 2 show that an average recovery of 96.98% with standard deviation of 0.4%, which indicates that the developed method can be easily performed and offers good precision and accuracy when applied to human serum sample.

Stability

No significant loss of metoclopramide hydrochloride (S.D., 0.3%) was observed after storage of pharmaceutical tablet samples and serum samples at room temperature for at least 24 h Table 1. Pharmaceutical tablet samples and serum samples were stable over at least three freeze–thaw cycles Table 2, indicating that the pharmaceutical tablet samples and serum samples can be frozen and thawed at least three times prior to analysis (S.D ., 4.2%).

The comparison of the proposed Tb^{3+} - MCP optical sensor for the determination of MCP with other published

Table 3 Comparison of the proposed Tb-MCP optical sensor with some existing methods for the determination of MCP

Method	Linear range (mol L^{-1})	Detection limit (mol L^{-1})	References
Chemiluminescent method	1.4×10^{-8}–1.0×10^{-6}	2.8×10^{-9}	[25]
Spectrophotometric method	1.4×10^{-5}–7.0×10^{-5}	1.4×10^{-6}	[8]
Flow injection-spectrophotometric method.	1.4×10^{-3}–2.4×10^{-1}	1.4×10^{-4}	[10]
Square wave anodic stripping voltammetric method	1.9×10^{-10}–7.6×10^{-10}	1.7×10^{-10}	[23]
HPLC method	2.8×10^{-6}–2.8×10^{-5}	1.4×10^{-6}	[29]
Potentiometric PVC matrix membrane sensor.	1×10^{-2}–6×10^{-5}	4×10^{-5}	[20]
Optical sensor Tb^{3+} doped in PMMA matrix	5.0×10^{-9}–5.0×10^{-5}	2.7×10^{-10}	Present work

spectrophotometric [8, 10, 25] potentiometric [20, 23] and chromatographic [29] methods indicate that the developed method has good stability, lower limit of detection (2.7×10^{-10} mol L^{-1}) and wide linear range of application (5×10^{-9}–5.0×10^{-5} mol L^{-1}) as shown in Table 3. Also, the proposed method avoids potential background fluorescent emission interferences from the biological background. So, this method may provide a new kind of luminescent sensor for the determination of bio-molecular systems

Conclusion

The Tb^{3+} ion doped in PMMA matrix has high sensitivity and selectivity characteristic peaks in the presence of metoclopramide hydrochloride. The intensities of these peaks are enhanced by increasing the concentration of metoclopramide hydrochloride, due to energy transfer from metoclopramide hydrochloride to the Tb^{3+} ion and it can be used for determination of metoclopramide hydrochloride in pharmaceutical preparations and in serum samples. The proposed Tb^{3+} - MCP optical sensor provide a new kind of luminescent sensor for the determination of bio-molecular systems and has advantages over other published methods in terms of lower limit of detection (8.7×10^{-10} mol L^{-1}) and wide linear range of application (5×10^{-9}–5.0×10^{-5} mol L^{-1}).

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