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Application and Validation of Two Smart Spectrophotometric and a HP-TLC Densitometric Methods for Determination of Metoclopramide Hydrochloride/ Paracetamol in Raw Material and in Pharmaceuticals

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ABSTRACT

Currently the anti-emetic drug metoclopramide hydrochloride (MCP-HCl) is co-formulated with paracetamol (PCM). Three simple, economic and fast methods for determination of both drugs, simultaneously and without previous separation were developed. In first method (A), a third derivative spectrophotometric method was developed. The peaks amplitudes of third derivative spectra of MCP-HCl and PCM were measured at 334.5 and 299 nm, respectively. In second method (B), a ratio subtraction spectrophotometric method was developed. The peak amplitude of first derivative spectrum of MCP-HCl was measured at 321 nm at which PCM spectrum gives zero crossing point whereas the peak amplitude of ratio subtraction spectrum of PCM was measured at 292 nm. Both spectrophotomertric methods were linear within concentration range of MCP- HCl; 12-60 µg/mL and PCM; 35-165 µg/mL with high correlation coefficients. In third method (C), HP-TLC method was developed. The mobile phase composed of methanol, chloroform and conc. ammonia solution (10: 2: 0.15) gave typical chromatogram for MCP-HCl and PCM at R_fs 0.21 ± 0.02 & 0.59 ± 0.02, respectively and the UV scanning was carried out at 270 nm. The method was linear within range of MCP- HCl; 6-18 µg/mL and PCM; 5-50 µg/mL giving high correlation coefficients. Complete validation process of the established methods was performed according to ICH guidelines and USP requirements and gave relative standard deviation values for all the key validation parameters less than 2.00%.

Keywords: Metoclopramide-hydrochloride; paracetamol; spectrophotometry; HP-TLC densitometry; validation

INTRODUCTION

MCP-HCl is an anti emetic and a pro-kinetic agent. It is one of many active ingredients of pharmaceutical preparations concerned with gastroenterology, surgery, gynaecology, and cardiology [1]. Moreover, MCP-HCl is widely used in the treatment of drug induced nausea and vomiting, including anti-cancer drugs [2]. MCP-HCl, [monohydrate of 4-amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxy benzamide hydrochloride] [1], figure (1), is freely soluble in water and alcohol, sparingly soluble in methylene chloride and practically insoluble in ether [3]. USP monograph states that MCP- HCl should not be exposed to light [4]; it states an incompatibility with strong alkalis and strong oxidizing agents as well. Aubert *et al* investigated the effect of light on it and characterized the photolysis products [5]. Paracetamol (PCM) [N-(4-hydroxyphenyl)-Acetamide], figure (2), is soluble in boiling water, alkaline aqueous solution and organic solvents such as methanol and ethanol but slightly soluble in cold water and ether [3].

There are many analytical methods employed for the determination of MCP-HCl; for example fluorimetry [6], spectrophotometry [7, 8, 9], HPLC [10, 11, 12] and GC–MS [13]. Many methodology were found in

literature for analysis of PCM; spectrophotometry [14, 15], fluorimetry [16], IR [17], electrochemistry [18], chemomertry [19], HPLC [20, 21], GC [22]. There are few analytical assays reported in the literature to describe a parallel analysis of both drugs in mixture. Wadher SJ *et al* described ratio derivative spectrophotometry for analysis of this mixture [23]. Dudhane NP *et al* illustrated HPLC to analyse the same mixture [24]. This paper describes three simple, fast and economically effective methods for determination of both drugs, simultaneously without preliminary separation. Two of them are spectrophotometric, a third derivative spectrophotometric method (A) and a ratio subtraction spectrophotometric method (B). The third method is a highly selective HP-TLC densitomeric assay. A complete validation process was performed to ensure selectivity, accuracy, repeatability and reliability of the established method.

MATERIALS AND METHOD

Instrumentation: Dual beam UV-VIS Spectrophotometer (1601 Shimadzu) with two matched 1cm 3quartz cells and Bundled UV-PC personal spectroscopy software version (3.7) were used to process the absorption spectra. The spectral band width was 0.2 nm with wavelength scanning speed of 2800 $nm.min^{-1}$. A UV short wavelength 254 nm lamp (USA) was used for spots detection. A Camag Linomat 5 auto-sampler with Camag micro-syringe (100 µL); CAMAG, Muttenz, Switzerland, was used for spotting. A Camag Linomat scanner 3 densitometer model 3 S/N 130319 equipped with wincat software; CAMAG, Muttenz, Switzerland, was used for densitometric evaluation. Thin layer chromatography (TLC) plates pre-coated with silica gel60 F_{245} 0.25 mm thickness (E.Merk, Darmstadt, Germany).

Authentic powder & pharmaceutical products:

- MCP-HCl and PCM USP grade powders were supplied by PCCA.
- Migura® tablets batch no 310190 (5 mg MCP-HCl and 500 mg PCM / tab), Memphis Pharm. & Chemical Ind. was obtained from Egyptian market.
- Methanol of analytical grade (ADWIC) was used as main solvent in preparation of standard solution.
- The mobile phase was consisted of methanol, chloroform, conc. ammonium hydroxide solution of analytical grade (ADWIC) in ratio (10: 2: 0.15; v/v/v).

Standard solutions: Stock standard solution of MCP-HCl (3mg/mL) and of PCM (5mg/mL) were prepared in distilled water. The working standard solutions of MCP-HCl (60 & 120 µg/mL) and of PCM (120 & 500 µg/mL) were prepared in distilled water. A series of mixture solutions of MCP-HCl and PCM in ratios 0.5: 9.5, 1: 9, 2: 8 and 3: 7 were prepared freshly in distilled water. Mixture standard solution of MCP-HCl and PCM (2 & 5mg/ml, respectively) was prepared in methanol. A series of mixture solutions of MCP-HCl and PCM in ratios 0.3: 9.7, , 2: 8 and 2.5: 7.5, 3.5: 6.5 and 5: 5 were prepared freshly in methanol. N.B. These ratios were selected to be around the concentration ratio of already present MCP-HCl: PCM ratio in pharmaceutical products

Application Aqueous Solution of Migura® Tablets: Weigh accurately 10 tablets of migura® and finely grind them. Transfer accurately a weight of the powder, equivalent to 5 mg of MCP-HCl and 500 mg of PCM into a beaker. Add about 50 mL distilled water into the beaker and sonicate for 10 min. Filter into a 100 mL volumetric flask and wash the residue three times each with 10 mL water and then complete volume to the mark to get an stock application solution of MCP-HCl: 50 µg/mL & PCM: 5000 µg/mL. Transfer 4, 5 & 6 mLs of the stock application solution into three 10 mL volumetric flasks and complete to volumes with same solvent to get working application solutions of MCP-HCl (20, 25 & 30 µg/mL). Carry out the procedures on the prepared solutions as under MCP-HCl/ linearity to determine MCP-HCl. Transfer 1, 2 & 3 mLs of the stock application solution into three 100 mL volumetric flasks to get working application solutions of PCM (50, 100 & 150 µg/mL). Carry out the procedures on the prepared solutions as under PCM/ linearity to determine PCM.

Application Methanolic Solution of Migura® Tablets: Weigh accurately 10 tablets of migura® and finely grind them. Transfer accurately a weight of the powder, equivalent to 25 mg of MCP-HCl and 2500 mg of PCM into a beaker. Transfer 20 mL distilled water into the beaker to disintegrate the tablets, frequently add 15 mL of methanol then sonicate for 10 min. Filter into a 50 mL volumetric flask and wash the residue three times each with 4 mL methanol. Then, complete to volume with methanol to get application solution (A) (50 mg/mL of PCM and 0.5 mg/mL of MCP-HCl), suitable for determination of MCP-HCl. Transfer 2 mLs of application solution (A) into a 100 mL volumetric flask and complete to volume with methanol to get application solution (B) (1 mg/mL of PCM and 0.01

mg/mL of MCP-HCl), suitable for determination of PCM. Spot 15, 16 & 17 µLs of the prepared solutions in triplicate onto TLC plate and develop likely as mentioned under the linearity then calculate the concentration of the drug from regression equation.

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Procedures

Method A: The third derivative spectrum of working standard solution of both drugs were recorded, using Δλ = 8 and scaling factor = 1000. The peaks amplitudes of MCP-HCl and PCM spectra were measured at λ_{max} = 334.5 and 299 nm, respectively.

Method B: The first derivative spectrum of MCP-HCl working standard solution was recorded, using Δλ = 4 and scaling factor = 10, and the peaks amplitudes of the spectra were measured at λ_{max} = 321 nm. The zero order spectrum of PCM working standard solution was recorded and divided by spectrum of MCP-HCl working standard solution (35 µg/mL), a divisor, giving new spectrum called ratio spectrum. The plateau value appeared in the ratio spectrum was subtracted from the ratio spectrum giving what is called ratio subtraction spectrum. The peak amplitude of the ratio subtraction spectrum was measured at λ_{max} = 292 nm.

Method C : Spot 5 µl of standard mixture solution of MCP-HCl and PCM (2 & 5mg/ml, respectively) onto a TLC plate using Camag Linomat auto-sampler with micro-syringe (100 µL). Develop the plate in a chromatographic tank previously saturated, for 30 min., with the mobile phase; methanol: chloroform: ammonia (60: 12: 0.9; v/v/v) by ascending chromatography through a distance of 15 cm at room temperature. Dry the plate in air then visualize the spots under UV lamp 245nm and scan them under the following conditions:

- Source of radiation: Deuterium lamp,
- Scan mode: Absorption mode,
- Slit dimension: 3 mm x 0.45 mm,
- Res µL t output: chromatogram and integrated peak area,
- Scanning speed: 20 mm/ s and
- Wavelength: 270 nm.

RESULTS AND DISCUSSION

Methods Development:

Method A: The absorption spectra of MCP-HCl and PCM showed major overlapping as shown in figure (3). In method A, recording third derivative spectra of their zero order spectra showed zero crossing for PCM spectrum and peak for MCP-HCl at **λ**= 334.5 nm. It showed zero crossing for MCP-HCl spectrum and peak for PCM at **λ**= 299 nm too, figure (4).

Method B: In the second method B, a ratio subtraction spectrophotometric method was developed. MCP-HCl could be determined by measuring its peak amplitude of the first derivative spectrum at 321 nm at which PCM first derivative spectrum give zero value. When the absorption spectrum of a PCM is divided by a spectrum of the same compound, a straight line of constant amplitude which parallel to the baseline will result. However, upon dividing the absorption spectrum of PCM by the absorption spectrum of MCP-HCl, a new spectrum, ratio spectrum, will outcome. So the MCP-HCl could be completely cancelled and the difference would represent the PCM only. PCM in a binary mixture can be determined from a calibration curve that relates the difference in amplitudes (ΔP_{1-2}) in the ratio spectrum at *292 nm* using a certain concentration of MCP-HCl as a divisor to the corresponding concentration of PCM. In the method, the first derivative spectra of the drugs showed zero crossing point of PCM spectrum and a peak of MCP-HCl spectrum at **λ**= 321 nm, figure (5). At this wavelength, peak amplitude of MCP-HCl could be measured to determine its concentration without interference of PCM spectrum. To determine concentration of PCM, dividing the absorption spectra of drugs mixtures, figure (6, A), by that of MCP-HCl, a divisor, resulted in new spectra called ratio spectra including a constant values corresponding to division of MCP-HCl spectra in the mixture by that of the divisor, figure (6, B). Subtraction of these values gave new spectra, ratio-subtraction spectra, corresponding to concentration of PCM in the mixture, figure (6, C). Multiplication of the ratio- subtraction curve by divisor curve gave the absorption spectra of the mixtures, figure (6, D).

Method C: To form a mobile phase able to develop both drugs' spots in well shaped band and with practically different R_f, mobile phases for quantitative or qualitative analysis of the drugs, reported in publication, had been checked up. It was noticed that both methanol and chloroform are used in analysis of both drugs so their mixture was the preliminary mobile phase. Many trials were done to get the most selective ratio mixture of methanol/ chloroform and it was found that their mixture in ratio 5: 1, respectively, is the optimum. This solvent developed both drugs' spots with reasonable different R_f but gave tailing band of MCP-HCl. Addition drops of conc. ammonia solution to the solvent adjusted the developed band of MCP-HCl.

The mobile phase composed of methanol, chloroform and conc. ammonia solution (10: 2: 0.15) gave typical chromatogram for MCP-HCl and PCM at R_fs 0.21 ± 0.02 & 0.59 ± 0.02, respectively, fig (7). UV spectra of both drugs show that both drugs have maximum absorbance at 245 nm and only MCP-HCl has absorbance peak at 270 nm. In other word, scanning of the developed band of each drug via densitometer gave higher sensitivity measurement for both drugs at 245 nm. But at 270 nm only PCM gave much less response than at 245 nm whereas MCP-HCl gave similar response. Scanning developed bands at 270 nm allowed determination of PCM high ratio mixtures without need to make more dilutions. So scanning of the developed bands was done at 270nm as refered in figure (8).

Methods Validation:

Linearity: The proposed methods linearity was studied and proved. Regression equations, correlation coefficients and concentration ranges of the linearity curves of both drugs by each proposed method were charted in table (I).

Selectivity: Selectivity of the proposed methods was tested by analysis of laboratory mixtures of the drugs in different ratios and it was found to be highly selective, as figured out in table (II & III).

Precision: Obtained results upon analysis of 3 samples of each drug, separately, through three hours during the day and through three different days, showed repeatability and reproducibility of the proposed methods and verified their high precisions as referred in table (IV, V & VI).

Accuracy: Accuracy of the methods was proved by application of standard addition technique on MCP-HCl and PCM standard solutions, separately. Obtained recoveries percentages, standard deviations and relative standard deviations percentages reflected the high accuracy of the methods as referred in table (VII, VIII & IX).

Applicability: Applicability of the suggested assays were confirmed by analysis the drugs in migura® tablets and they gave high recovery percent, table (X).

CONCLUSION

The established assays can determine MCP-HCl and PCM in their binary mixture, simultaneously, in high selectivity and simplicity without preliminary separation. The range of linearity was wide for both drugs. The precision and accuracy of the method was found to be perfect. Applicability of the methods on migura® tablets gave excellent results for both drugs.

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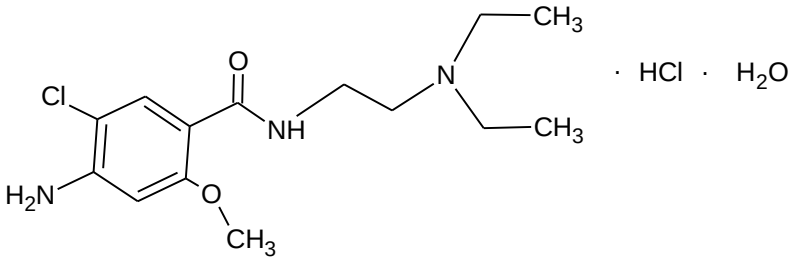

Fig. 1: Structure of MCP-HCl Monohydrate

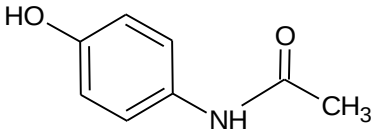

Fig. 2: Structure of PCM

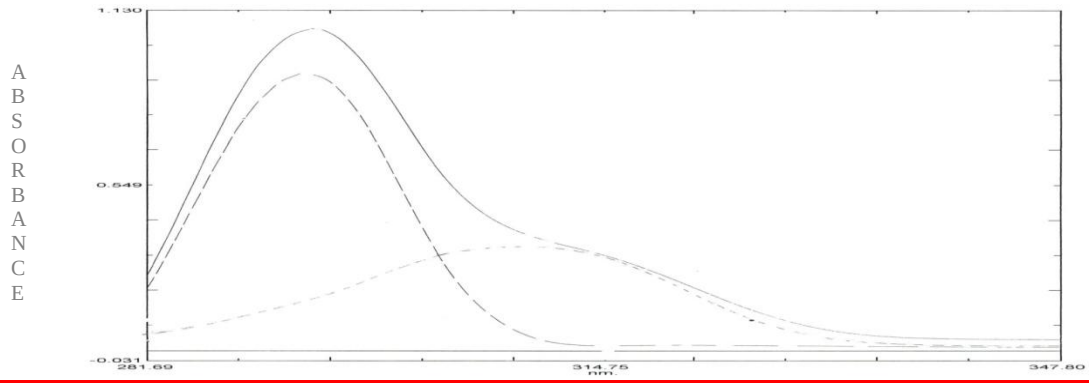

Fig. (3): Zero order spectra of MCP-HCl (35 µg/mL) (…..), PCM (140 µg/mL) (----) and MCP-HCl / PCM mixture (30: 70) (⁻), using water as a blank.

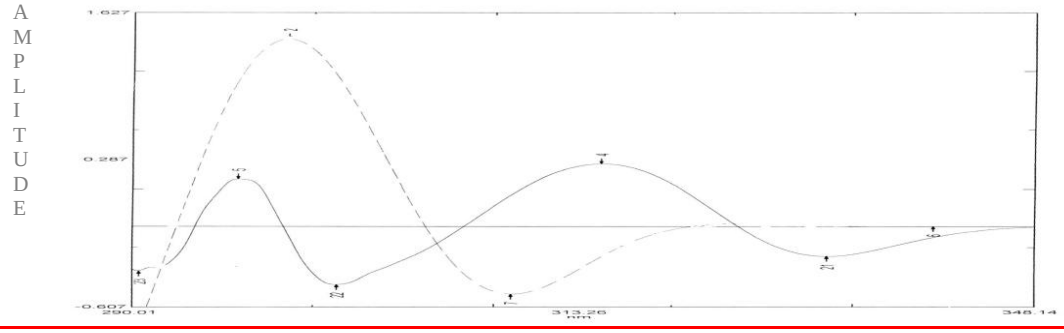

Fig. (4): The third derivative spectra of MCP-HCl (35 µg/mL) (—) and PCM (140 µg/mL) (---) aqueous solutions.

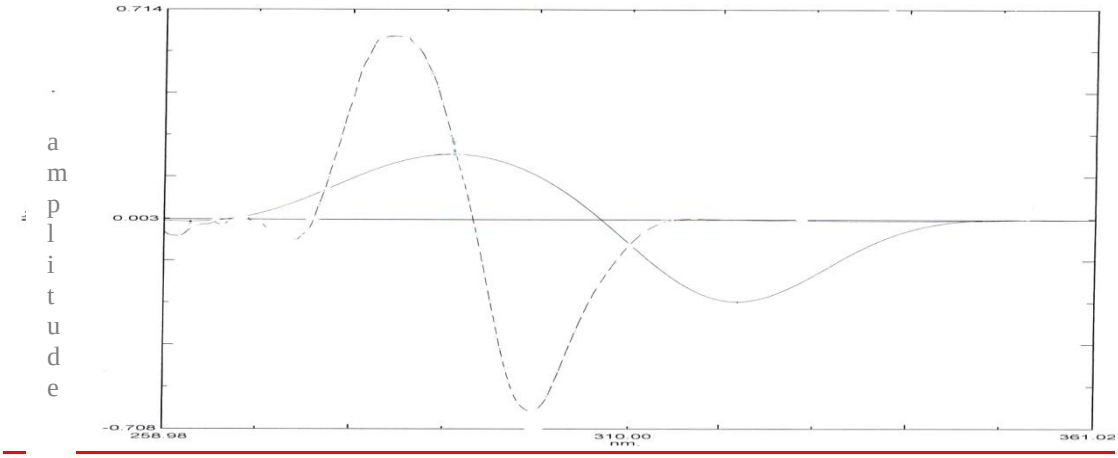

Fig. (5):
The first order spectra of MCP-HCl aqueous solution (35 µg/mL) (—) and PCM aqueous solution (140 µg/mL) (---).

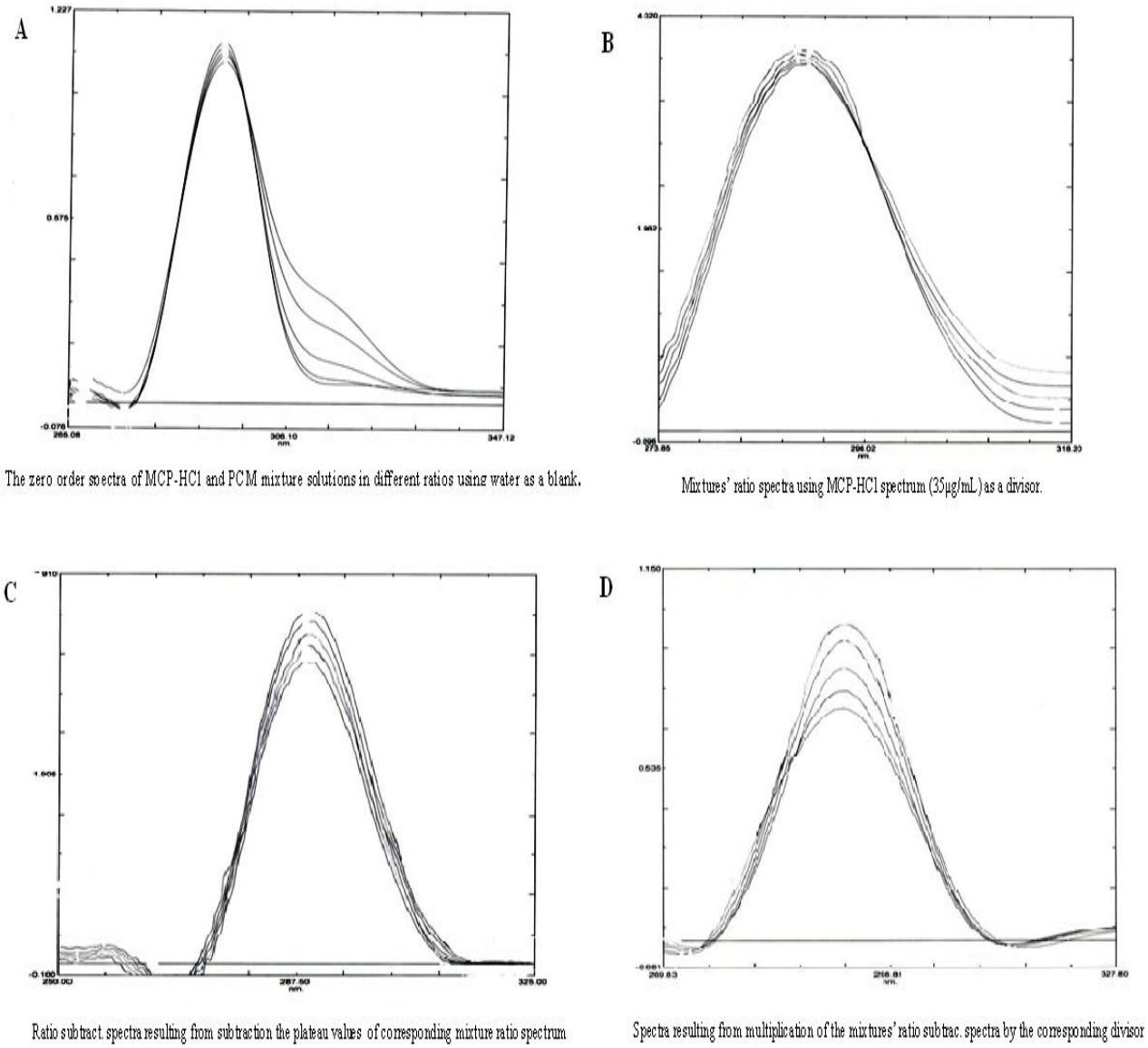

Fig. (6):

(A) The zero order spectra of MCP-HCl and PCM mixture solutions in different ratios using water as a blank.
(B) Mixtures' ratio spectra using MCP-HCl spectrum (35µg/mL) as a divisor.
(C) Ratio subtraction spectra resulting from subtraction the plateau values of corresponding mixture ratio spectra
(D) Spectra resulting from multiplication of the mixtures' ratio subtraction spectra by the corresponding divisor.

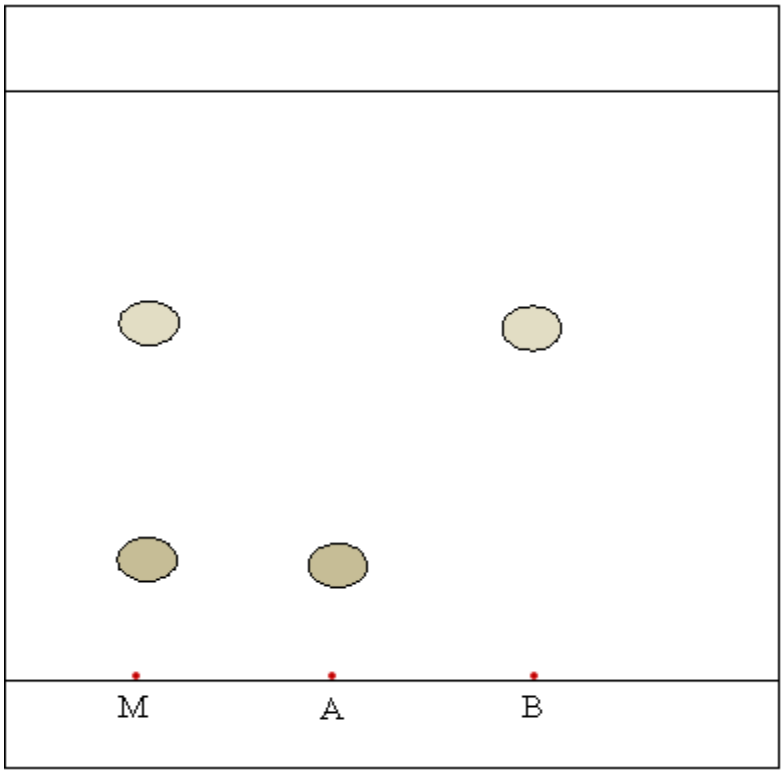

Fig. (7): Schematic representation of metoclopramide hydrochloride (A) and paracetamol (B) separation from their mixture (M) using methanol, chloroform and conc. ammonia solution (60: 12: 0.9) as a mobile phase.

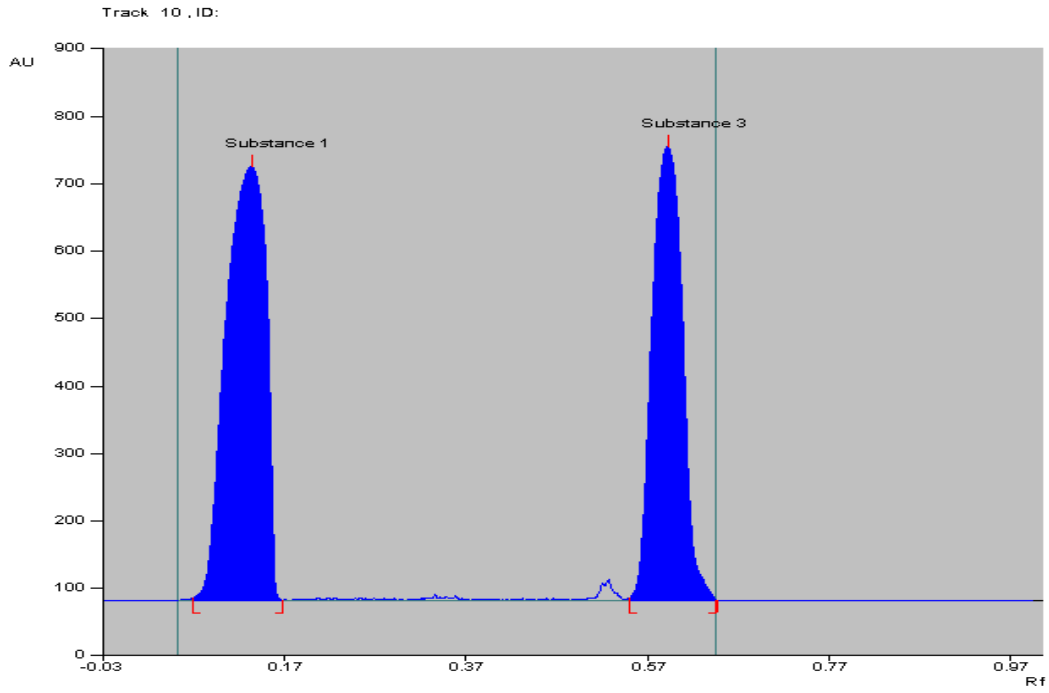

Fig. (8): Scanning profile of the TLC chromatogram of metoclopramide hydrochloride (substance 1) and paracetamol (substance 2) at 270 nm.

Table (I): Summary of linearity parameters of the proposed methods for determination of MCP-HCl and PCM in binary mixture

The Drug	Conc. Range	Calibration Equation	R^2
The third derivative method			
MCP-HCl (334.5 nm)	10 – 60 (µg/mL)	y = 0.52 x + 0.23	0.9998
PCM (299 nm)	35 – 165 (µg/mL)	y = 0.01 x + 00.00	0.9999
	The ratio subtraction method		
MCP-HCl (321 nm)	10 – 60(µg/mL)	y = 0.88 x + 0.26	0.9999
PCM (292 nm)	35 – 165(µg/mL)	y = 0.56 x + 00.35	0.9999
	The densitometric method		
MCP-HCl	6 – 18(µg/spot)	y = 0.02 x + 0.16	0.9999
PCM	5 – 50(µg/spot)	y = 0.005 x + 0.2	0.9997

Table (II): Data derived from analysis of MCP-HCl/ PCM lab. mixtures by the proposed spectrophorometric methods to prove selectivity

Metoclopramide Hydrochloride			Paracetamol		
(%) in lab. mixture	R % Third derivative	R % Ratio subtraction	(%) in lab. mixture	R % Third derivative	R % Ratio subtraction
10	96.76	100.42	90	100.08	100.47
20	100.59	100.40	80	100.08	100.34
30	99.60	98.41	70	100.11	100.21
40	99.19	101.28	60	100.06	100.75
Mean R%	99.03	99.82	Mean R%	100.08	100.41
SD (±)	1.409	1.116	SD (±)	0.016	0.185
RSD%	1.422	1.118	RSD%	0.016	0.184

Table (III): Selectivity of the HP-TLC densitometric method upon analysis of MCP-HCl and PCM. In laboratory mixtures

Drug (%) in the mixture solution		Recovery percentage (R %)	
MCP-HCl	PCM	MCP-HCl	PCM
50	50	100.34	100.72
40	60	100.86	101.45
35	65	100.95	100.86
25	75	99.90	100.79
20	80	100.21	100.21
Mean R%		100.45	100.81
SD		0.398	0.395
% RSD		0.396	0.392

Table (IV): Precisions of the third derivative spectrophorometric method for determination of MCP-HCl and PCM

Metoclopramide Hydrochloride			Paracetamol		
Mean R % *	SD (±)	RSD %	Mean R % *	SD (±)	RSD %
Intra-day precision					
100.00	0.00	0.00	100.74	0.834	0.828
100.01	0.708	0.708	100.30	0.170	0.169
100.01	0.122	0.122	99.99	0.378	0.378
Inter-day precision					
100.76	0.054	0.053	99.99	0.662	0.662
100.00	00.00	00.00	100.00	0.622	0.662
100.00	0.244	0.244	100.00	0.234	0.233

Table (V): Precisions of the ratio subtraction spectrophorometric method for determination of MCP-HCl and PCM

Metoclopramide Hydrochloride			Paracetamol		
Mean R % *	SD (±)	RSD %	Mean R % *	SD (±)	RSD %
Intra-day precision					
100.00	0.00	0.00	100.74	0.834	0.828
100.01	0.708	0.708	100.30	0.170	0.169
100.01	0.122	0.122	99.99	0.378	0.378
Inter-day precision					
100.76	0.054	0.053	99.99	0.662	0.662
100.00	00.00	00.00	100.00	0.622	0.662
100.00	0.244	0.244	100.00	0.234	0.233

Table (VI): Precision of the HP-TLC densitometric method for determination of MCP-HCl and PCM.in mixture

Metoclopramide Hydrochloride				Paracetamol			
Conc. of sample (µg/spot)	Mean R % *	SD (±)	RSD%	Conc. of sample (µg/spot)	Mean R % *	SD (±)	RSD%
Intra-day precision (n=3)							
10	100.94	1.22	0.71	25	99.99	0.64	0.64
14	99.99	1.14	0.38	45	99.99	1.41	1.41
16	99.99	1.07		50	99.99	0.89	0.89
18	99.99	0.99	0.32				
Inter-day precision (n=3)							
12	99.99	1.80	1.80	35	100.00	1.03	1.03
14	100.14	0.56	0.56	40	100.00	1.74	1.74
16	99.99	0.85	0.85	45	100.00	0.66	0.66
18	99.99	0.27	0.27				

Table (VII): Application of standard addition technique on standard solutions of MCP-HCl and PCM by the third derivative spectrophorometric method

Metoclopramide Hydrochloride			paracetamol		
Claimed mount taken (µg/mL)	Standard added (µg/mL)	R %	Claimed mount taken (µg/mL)	Standard added (µg/mL)	R %
12.50	00.00	100.80	100.00	00.00	99.50
	3.50	100.08		25.00	100.00
	10.00	98.63		65.00	100.00
	16.00	100.40			
Mean		99.97	Mean		99.83
S.D (±)		0.818	S.D (±)		0.235
RSD%		0.818	RSD%		0.236

Table (VIII): Data derived from application of standard addition technique on standard solutions of MCP-HCl and PCM by the ratio subtraction spectrophorometric method

Metoclopramide Hydrochloride			paracetamol		
Claimed mount taken (µg/mL)	Standard added (µg/mL)	R %	Claimed mount taken (µg/mL)	Standard added (µg/mL)	R %
30.50	00.00	100.27	100.00	00.00	100.66
	3.50	100.01		25.00	100.21
	10.00	99.79		45.00	100.44
	15.50	99.76		65.00	100.32
Mean		99.95	Mean		100.40
S.D (±)		0.204	S.D (±)		0.166
RSD%		0.204	RSD%		0.166

Table (IX): Accuracy of the HP-TLC densitometric method for determination of MCP-HCl and PCM by applying standard addition technique

Metoclopramide Hydrochloride			Paracetamol		
Claimed mount taken (µg/spot)	Standard added (µg/spot)	R %	Claimed amount taken (µg/spot)	Standard added (µg/spot)	R %
5.00	5.00	98.15	5.00	5.00	99.75
	10.00	99.94		10.00	100.64
	15.00	100.78		15.00	99.51
Mean		99.62	Mean		99.97
S.D (±)		1.094	S.D (±)		0.484
RSD%		1.098	RSD%		0.484

Table (X): Data derived from analysis of migura® tablets (0.05 mg MCP-HCl & 5 mg PCM/ tab) by the proposed methods

Migura® Tablets B. NO 310190	R%	SD (±)	RSD%
Third derivative method			
MCP-HCl (334.5 nm)	99.89	0.33	0.33
PCM (299 nm)	100.42	0.92	0.89
Ratio subtraction method			
MCP-HCl (321 nm)	104.00	0.55	0.52
PCM (292 nm)	97.27	0.45	0.46
HP-TLC Densitometric method			
MCP-HCl	99.62	1	1
PCM	99.97	0.484	0.484

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