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Research Article

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Determination of Telmisartan and Estradiol Valerate using Magnetic Iron Oxide Nanoparticles Modified with Cetyltrimethylammonium Bromide followed by Spectrophtometry and HPLC

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ABSTRACT

Two novel, fast, and simple spectrophotometric and HPLC procedures were developed for the determination of telmisartan and estradiol valerate by magnetic solid-phase extraction (SPE) using magnetic Fe_3O_4 nanoparticles (MNPs) modified by cetyltrimethylammonium bromide (CTAB) as an extractor and methanol was used as desorption. Effects of different parameters influencing the extraction efficiency of drugs were investigated and optimized. Spectrophotometric method was monitored at λ_{max} 230 and 209 nm with detection limit 0.016 and 0.087 µg mL^{-1} for telmisartan and estradiol valerate, respectively. HPLC method was developed with detection limits 1.63 and 7.02 ng mL^{-1} for telmisartan and estradiol valerate, respectively. Finally, the proposed method has been effectively employed in extraction and determination of the drugs in pure form, in pharmaceutical formulations. Telmisartan can be extracted and determined in mixture with hydrochlorothiazide, and also estradiol valerate can be analyzed in mixture with norgestrel by the two cited methods.

Keywords: Magnetic nanoparticles; Telmisartan; Estradiol valerate

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INTRODUCTION

Telmisartan[4¢-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl]biphenyl-2-carboxylic acid] [1] is an angiotensin II receptor antagonist used in the management of hypertension [2]. Different techniques were reported for the determination of telmisartan including: spectrophotometric [3], HPLC [4,5], HPTLC [6,7] methods. Estradiol valerate [3-Hydroxyestra-1,3,5(10)-trien-17b-yl pentanoate] [1] is the most active of the naturally occurring oestrogens. Estradiol is primarily used as menopausal hormone replacement therapy and may also be used as replacement therapy for female hypogonadism or primary ovarian failure [2]. Several analytical methods were reported for determination of estradiol valerate including spectrophotometric [8-10], gas chromatography [11], capillary electrophoresis [12], liquid chromatography [13,14], flow injection chemiluminescence [15] and electrochemical methods [16,17].

Magnetic iron oxide nanoparticles (MNPs) have been recently used as solid phase extraction sorbent for preconcentration of many organic and inorganic compounds because of their unique and small size and superparamagnetic properties. Several studies used surfactants to modify the surface of MNPs such as CTAB [18-21] and sodium dodecyl sulfate (SDS) [22,23]. In the present study, we employed iron oxide magnetite nanoparticles (MNPs) modified with cetyltrimethylammonium Bromide (CTAB) for preconcentration and determination of telmisartan and estradiol valerate followed by spectrophotometric and HPLC detection.

EXPERIMENTAL SECTION

Instrumentation

A strong magnet of Nd-Fe-B was used for magnetic separations. A JEOL-1010 Transmission Electron Microscope at 80 KV, Japan was employed for Transmission Electron Microscopy (TEM) examination at Regional Center for Mycology and Biotechnology (RCMB) at Al-Azhar University. A Shimatzu UV and visible recording spectrophotometer (UV 260) with matched 10-20 quartz cell was employed for all spectrophotometric absorbance measurements. Agilent Technologies 1200 series chromatographic apparatus equipped G1354A isocratic quaternary pump with on-line Agilent G1322A vacuum degasser, autosampler injector and 100 µgl volume injection loops. Separation was carried out on Thermo Hypersil (250 mm × 4.6 mm I.D, 5µmparticle size column) for telmisartan and Agilent Zorbax ODS ® 5 µ C18(250 × 4.6 mm I.D., 5 µm particle size) for estradiol valerate using UV lamp(Germany) and G1315D photodiode array detector (DAD) connected to a HP computer loaded with Agilent Chemstation software. Digital analyzer pH meter (USA) was used.

Materials and Reagents

Chemicals used were of the highest purity:

1. Telmisartan (obtained from Sigma Pharmaceutical Industries).
2. Estradiol valerate (obtained from Chemical Industrial Development (CID)).
3. Ferric chloride (anhydrous)(Riedel-De Haen AG Seelze Hannover, Germany) and Ferrous sulphate. $5H_2O$ (Euclid).
4. Hydrochloric acid and sodium hydroxide (1.5 M) (El Nasr Pharmaceutical Chemicals CO).
5. Cetyltrimethylammonium bromide (1% w/v) (Sigma Aldrich).
6. Phosphate buffer (pH=3.5): Dissolve 68 g of potassium dihydrogen orthophosphate in 1000 ml of water and adjust the pH of the solution to 3.5 with orthophosphoric acid [1].
7. Acetonitrile, methanol and water (Fisher chemical® HPLC gradient grade).

Pharmaceutical Preparations

1. Micardis® tablets containing 80 mg telmisartan per tablet(obtained from Boehringer Ingelheim, Germany).
2. Micardis® plus tablets containing 80 mg telmisartan per tablet and 40 mg hydrochlorothiazide per tablet (obtained from Boehringer Ingelheim, Germany).
3. Cyclo-progynova® white tablets containing 2 mg estradiol valerate per tablet and brown tablets containing 2 mg estadiol valerate + 0.5 mg norgestrel per tablets (obtained from Bayer Schering Pharma, Germany).

Standard Solutions

Solutions of 100 µg ml^{-1} of telmisartan and estradiol valerate were prepared by dissolving 10 mg of the pure drug in methanol then further dilution to 10 µgml^{-1} with methanol.

General Procedure

Procedure for synthesis and characterization of magnetic iron oxide nanoparticles (MNPS):

Magnetic iron oxide nanoparticles (MNPs) were prepared by the chemical co precipitation method [20] as follows: 6.24 gm anhydrous ferric chloride, 3.10 gm ferric sulphate and 1.7 mL of conc HCl were dissolved in 50mL of distilled water to prepare a stock solution. 500mL of 1.5 M NaOH solution was heated to 80°C in a beaker, the stock solution was added dropwise, and vigorous stirring was done by a stirrer (1000 rpm). After completion of the reaction, the obtained MNPs precipitate was separated from the reaction medium by magnetic field and washed with 500 mL water four times. Finally, the obtained MNPs were resuspended in 500 mL of distilled water. The pH of obtained suspension was 11.0. The obtained MNPs were stable up to one month. The average size of the prepared MNPs is about 8.98 ± 2.85 nm, which is estimated from TEM image (Figure 1).

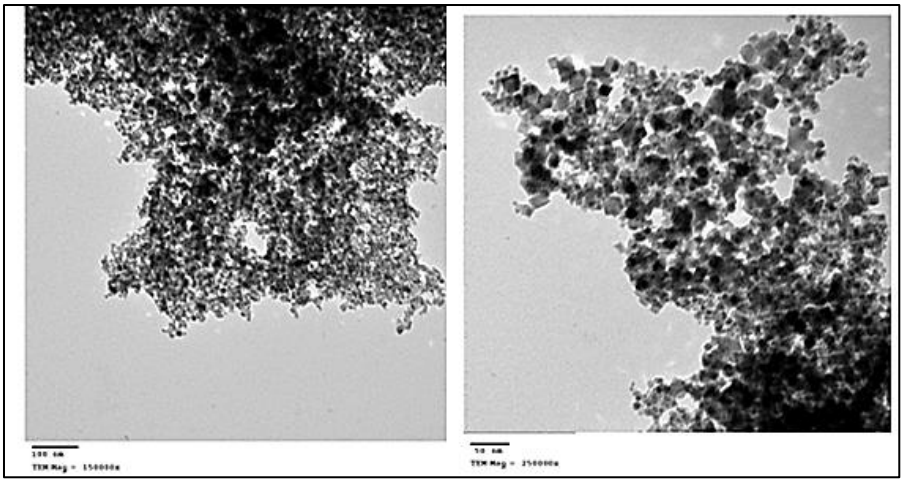
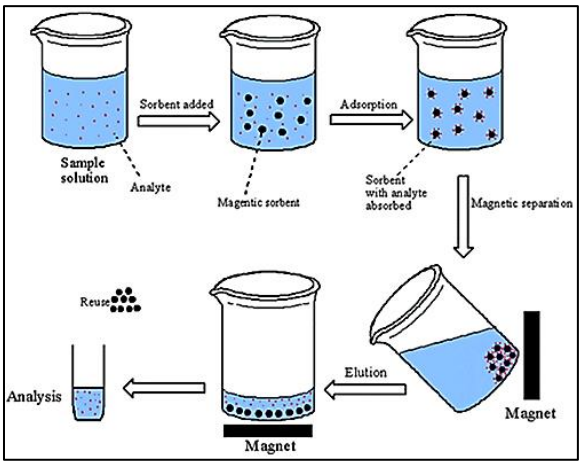


Figure 1: TEM image for MNPs nanoparticles

Extraction Procedure

Add appropriate volumes of the drug's stock solutions (10 µl in 100 mL of distilled water), then 1 or 2 mL of the MNPs suspension were added for telmisartan or estradiol valerate, respectively. Then, 0.5 or 1 mL of 1% CTAB solution were added for telmisartan or estradiol valerate, respectively, and the mixtures were shaken for 5 min to enhance the drug's adsorption efficiency and then by use of a strong magnet, MNPs placed at the bottom of the beaker was separated quickly from sample solution and the supernatant water was decanted. The entire steps of the process are shown in Scheme 1. Finally the drugs were desorbed with 5mL methanol from MNPs for spectrophotometric measurements and 1ml methanol for HPLC procedure at appropriate conditions (Table 1 and Figures 2-4).



Scheme 1: Illustration of adsorption and desorption procedure using MNPs modified with CTAP [22]

Table 1: Analytical parameters for determination of telmisartan and estradiol valerate using MNPs followed by spectrophotometric and HPLC detection

Parameter	Telmisartan	Estradiol valerate
Volume of MNPs	2 ml	1 ml
Volume of CTAB (1% w/v)	1 ml	0.5 ml
Extraction time	5 min	5 min
Desorption time	5 min	5 min
Desorption solvent (spectrophotometry)	Methanol (5 ml)	Methanol (5 ml)
Desorption solvent (HPLC)	Methanol (1 ml)	Methanol (1 ml)
For spectrophotometric method		
Beer's law limits (µg ml^{-1})	0.05 - 0.45	0.3 - 1.4

λ max	230 nm	209 nm
For HPLC method		
Beer's law limits (ng ml^{-1}**)**	5-90	20-500
Mobile phase for HPLC	Acetonitrile: Phosphate buffer	Acetonitrile: Water
	70:30:00	90:10:00
Flow rate	1.2 ml	1.2 ml
UV- detection at	230 nm	209 nm
Injection volume	10 µl	10 µl
Temperature	Room temp	Room temp
Retention time	3.40 min	5.82 min

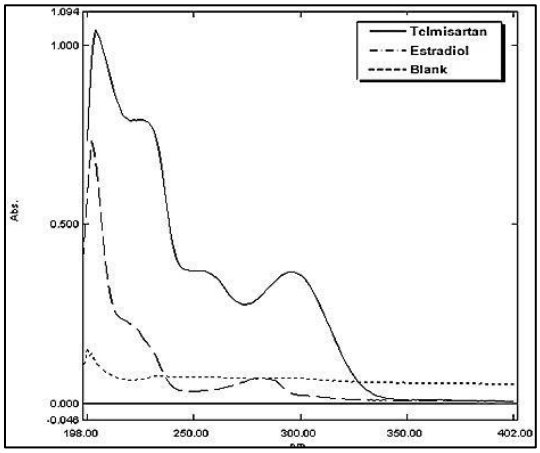


Figure 2: Absorbance spectra of -0.3 µg ml^{-1} telmisartan, -1 µg ml^{-1} estradiol valerate

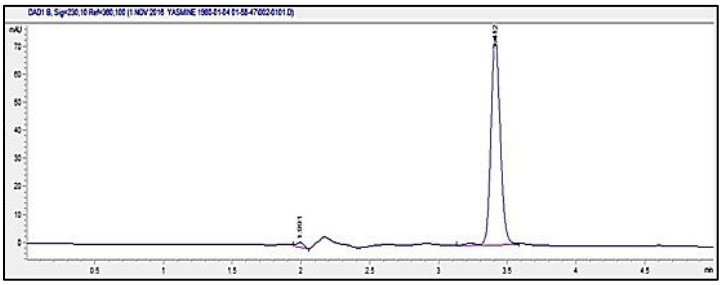


Figure 3: Chromatogram of 60 ng ml^{-1} telmisartan

Assay of Pharmaceutical Preparations

Ten tablets were weighed and pulverized into fine powder. Specific quantity of powdered tablets equivalent to 10 mg pure drug were dissolved in methanol. Solutions were filtered and diluted to 100 ml with methanol then further dilution to 10 µg ml^{-1} with methanol. Procedures were completed as in general procedures (Figures 5 and 6).

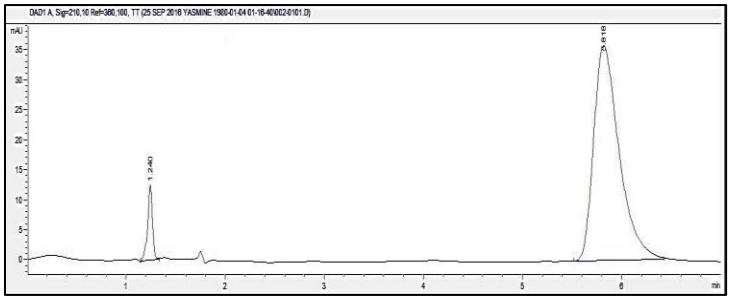


Figure 4: Chromatogram of 50 ng ml^{-1} estradiol valerate

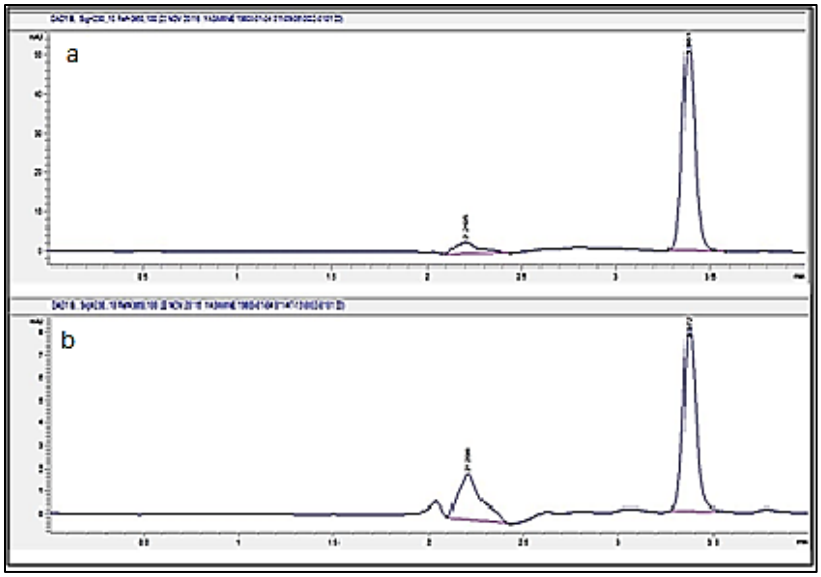


Figure 5: Chromatogram of a) 40 ng ml^{-1} telmisartan in micardis tablet b) 10 ng ml^{-1} telmisartan in micardis plus tablet

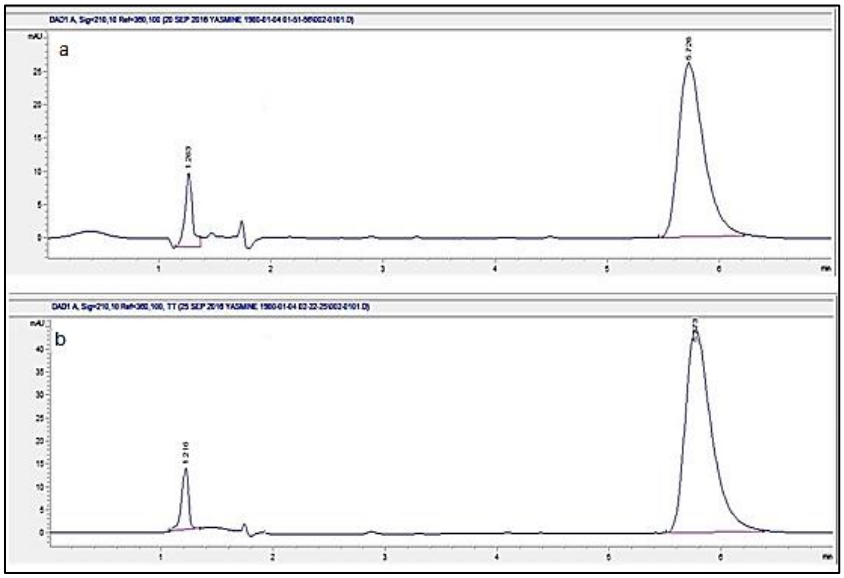


Figure 6: Chromatogram of a) 40 ng ml^{-1} estradiol valerate in white tablets b) 50 ng ml^{-1} estradiol valerate in brown tablets

RESULTS AND DISCUSSION

Magnetic iron oxide nanoparticles (MNPs) have been recently used as solid phase extraction sorbent for preconcentration of many organic and inorganic compounds because of their unique, small size and superparamagnetic properties. In this study MNPs modified with CTAB was used as sorbent for preconcentration of telmisartan and estradiol valerate followed by spectrophotometric and HPLC measurements at λ_{max} 230 and 209 for telmisartan and estradiol valerate, respectively. The average size of MNPs was confirmed by TEM image which indicates nanopaticles formation of cubic shaped nanoparticles in size of 8.98 ± 2.85 nm. Optimum conditions affecting the reaction were studied.

Effect of Buffer pH

The pH of the solution plays an important role in the adsorption of drugs on the surface of MNPs. Thus the influence of solution pH on absorbance was studied over the pH range of 7.0-12.5. No buffer is required as the pH of reaction medium was found to be 9.5 that give the best adsorption efficiency (Figure 7).

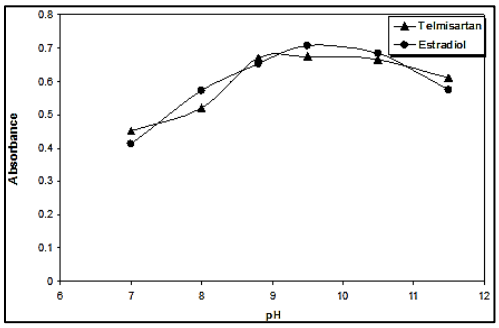


Figure 7: Effect of pH on extraction efficiency of -0.3 µg ml^{-1} telmisartan -1 µg ml^{-1} estradiol valerate

Effect of CTAB Volume

In the case of non-coated MNPs, 50% recovery or less of the drugs was adsorbed. Maximum extraction efficiency was obtained using 1 and 0.5 ml of 1% (w/v) CTAB for telmisartan and estradiol valerate, respectively (Figure 8).

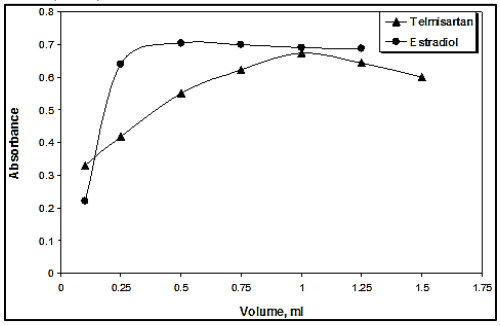


Figure 8: Effect of volume of CTAB (1% w/v) on extraction efficiency of -0.3 µg ml^{-1} telmisartan -1 µg ml^{-1} estradiol valerate

Effect of MNPs Solution Volume

Maximum recovery percentage was obtained using 2 and 1 ml of MNPs solution for telmisartan and estradiol valerate, respectively (Figure 9).

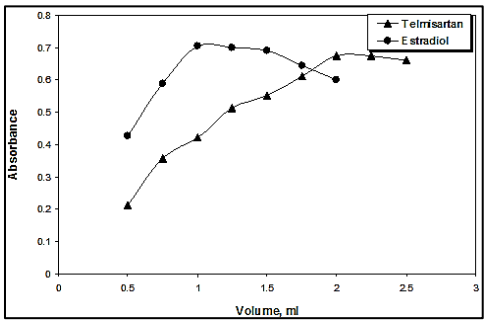


Figure 9: Effect of volume of MNPs on extraction efficiency of - 0.3 µg ml^{-1} telmisartan -1 µg ml^{-1} estradiol valer ate

Effect of Extraction Time

In order to obtain maximum extraction efficiency, extraction time was investigated in range from 1-15 min. So 5 min were chosen as best time obtained (Figure 10).

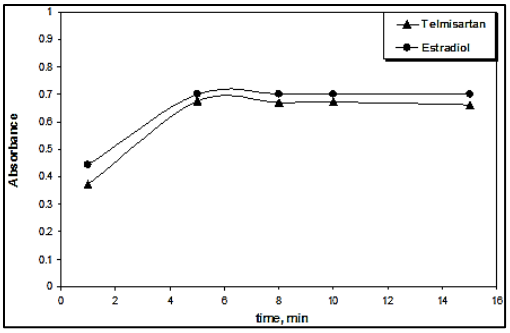


Figure 10: Effect of extraction time on extraction efficiency of -0.3 µg ml^{-1} telmisartan -1 µg ml^{-1} estradiol valerate

Effect of Desorping Solvent and Desorption Time

Different organic solvents were tried like methanol, ethanol and acetonitrile to find best desorbing solvent. Maximum absorbance values were obtained upon using methanol. Different desorption times were tried and it was found that 5 min is best time for complete desorption of the drugs from MNPs (Figure 11).

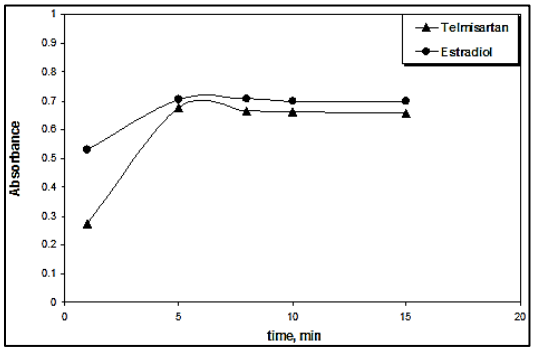


Figure 11: Effect of desorption time on absorbance of -0.3 µg ml^{-1} telmisartan -1 µg ml^{-1} estradiol valerate

Method Validation

Linearity:

Under the described experimental conditions standard calibration curves with good linearity for telmisartan and estradiol valerate were constructed by plotting absorbance against concentration for spectrophotometric measurements and area under curve against concentration for HPLC. A linear correlation was found. Range of concentrations, correlation, coeffiecient, intercepts and slope for the calibration curve were calculated. Also relative standard deviation, analytical standard error, detection and quantification limits were calculated and listed in Tables 2 and 3.

Application:

The validity of proposed methods was assessed by their application to the determination of the cited drugs in their pharmaceutical preparations. Also telmisartan was extracted and assayed in the presence of hydrochlorothiazide and estradiol in presence of norgestrel because MNPs adsorp the cited drugs only leaving the other (Tables 4 and 5). Student's t-test and F-test (at 95% confidence level) were applied to the results obtained compared with that obtained from reported method [3] for telmisartan and official method [1] for estradiol valerate. Results showed that there are no significant differences between the proposed and official methods. Results of different statistical treatment of the data are shown in Table 6.

Accuracy and precision:

Accuracy and precision were carried out by six determinations at two different concentrations of the four drugs in the same day (intra-day), and in six different days (inter-day). Percentage relative standard deviation (RSD%) as precision and percentage relative error (Er%) as accuracy of the suggested method were calculated. The percentage relative error calculated using the following equation:

$$Er\% = [(founded - added) / added] \times 100$$

The results of accuracy and precision (Table 7) show that the proposed methods have good repeatability and reproducibility.

Table 2: Spectral data for determination of telmisartan and estradiol valerate using MNPs followed by spectrophotometric and HPLC detection

Parameter	*Spectrophotometric method*		*HPLC method*	
	Telmisartan	*Estradiol valerate*	*Telmisartan*	*Estradiol valerate*
Linearity range	0.05-0.45 ng ml^{-1}	0.3-1.4 ng ml^{-1}	5-90 ng ml^{-1}	20-500 ng ml^{-1}
Limit of detection LOD	0.016 ng ml^{-1}	0.087 ng ml^{-1}	1.63 ng ml^{-1}	7.02 ng ml^{-1}
Limit of quantification LOQ	0.048 ng ml^{-1}	0.263 ng ml^{-1}	4.88 ng ml^{-1}	18.47 ng ml^{-1}
Regression equation*				
Slope (b)	1.8827	0.7277	4.147	1.2868
Intercept (a)	0.12	-0.0216	39.7706	-1.7707
Correlation coefficient (r)	0.9998	0.9999	0.9999	0.9999

Note: ** A= a + bc

Table 3: Determination of telmisartan and estradiol valerate using MNPs followed by spectrophotometric and HPLC detection

Statistics	**Spectrophotometric method**				**HPLC method**			
	Telmisartan		**Estradiol valerate**		**Telmisartan**		**Estradiol valerate**	
	Taken	**Recovery***	**Taken**	**Recovery***	**Taken**	**Recovery***	**Taken**	**Recovery***
	$\mu\gamma\ \mu\lambda^{-1}$	%	$\mu\gamma\ \mu\lambda^{-1}$	%	ng ml^{-1}	%	ng ml^{-1}	%
	0.05	100.92	0.3	101.97	5	99.97	20	100.14
	0.1	98.79	0.5	99.38	15	100.04	50	101.32
	0.15	100.92	0.7	99.45	20	101.55	70	101.88
	0.2	101.45	1	99.84	40	100.21	100	99.46
	0.3	98.26	1.2	99.93	60	98.56	300	98.89
	0.35	99.55	1.4	100.28	70	99.98	500	100.37
	0.45	100.68			90	100.54		
Mean ± S.D.	100.08 ± 1.217		100.14 ± 0.952		100.15 ± 0.887		100.34 ± 1.117	
N	7		6		7		6	
V	1.48		0.906		0.788		1.248	
S.D.	1.217		0.952		0.887		1.117	
R.S.D.	1.216		0.95		0.887		1.113	
S.E.	0.46		0.389		0.338		0.456	

Table 4: Determination of telmisartan and estradiol valerate in their pharmaceutical formulations using MNPs followed by spectrophotometric detection

Telmisartan						**Estradiol valerate**					
Micardis tablets			**Micardis plus tablets**			**Cyclo-progenova white tablets**			**Cyclo-progenova brown tablets**		
(telmisartan alone)			**(**In mixture with hydrochlorothiazide**)**			(estradiol valerate alone)			(In mixture with norgestrel)		
Taken	**Added**	**Recovery* %**	**Taken**	**Added**	**Recovery* %**	**Taken**	**Added**	**Recovery* %**	**Taken**	**Added**	**Recovery* %**
ng ml^{-1}			ng ml^{-1}			ng ml^{-1}			ng ml^{-1}		
0.05	-	99.86	0.05	-	98.79	0.3	-	103.79	0.3	-	99.22
	0.05	98.79		0.05	100.92		0.3	98.76		0.3	100.59
	0.1	101.45		0.1	101.98		0.4	100.18		0.5	100.48
	0.15	100.92		0.15	98.79		0.7	98.47		0.7	101.61
	0.25	100.07		0.25	99.22		0.9	101.02		0.9	98.58
	0.3	98.79		0.3	100.74		1.1	100.64		1	98.75
	0.4	100.79		0.35	98.79						
Mean ± S.D.	100.13 ± 1.128		100.07 ± 1.327			99.81 ± 1.139			100.00 ± 1.301		
V	1.273		1.761			1.296			1.693		
S.D.	1.128		1.327			1.139			1.301		
S.E.	0.461		0.542			0.509			0.581		

Table 5: Determination of telmisartan and estradiol valerate in their pharmaceutical formulations using MNPs followed by spectrophotometric and HPLC detection

Statistics	Telmisartan				Estradiol valerate			
	Micardis tablets		Micardis plus tablets		Cyclo-progenova white tablets		Cyclo-progenova brown tablets	
	(telmisartan alone)		(In mixture with hydrochlorothiazide)		(estradiol valerate alone)		(In mixture with norgestrel)	
	Taken	Recovery*	Taken	Recovery*	Taken	Recovery*	Taken	Recovery*
	ng ml^{-1}	%	ng ml^{-1}	%	ng ml^{-1}	%	ng ml^{-1}	%
	10	99.42	5	101.42	20	99.36	20	100.14
	20	101.55	10	101.59	50	99.12	70	101.88
	35	100.75	20	101.55	70	101.99	100	98.52
	40	101.45	40	99.61	300	99.15	300	99.67
	50	99.46	70	98.77	500	100.52		
Mean ± S.D.	100.64 ± 1.187		100.59 ± 1.312		100.03 ± 1.240		100.05 ± 1.397	
V	1.408		1.721		1.538		1.953	
S.D.	1.187		1.312		1.24		1.397	
S.E.	0.531		0.587		0.554		0.699	

Table 6: Statistical data for determination of telmisartan and estradiol valerate using MNPs followed by spectrophotometric and HPLC detection

Item	Telmisartan			Estradiol valerate		
	Reference method [3]	Spectrophotometric method	HPLC method	Official method [1]	Spectrophotometric method	HPLC method
Mean ±S.D.	100.56 ± 0.901	100.08 ± 1.217	100.15 ± 0.887	99.93 ± 1.017	100.14 ± 0.952	100.34 ± 1.117
N	5	7	7	5	6	6
V	0.811	1.48	0.788	1.034	0.906	1.248
S.D.	0.901	1.217	0.887	1.017	0.952	1.117
t		0.744 (2.228)*	0.784 (2.228)*		0.352 (2.262)*	0.631 (2.262)*
F		1.825 (4.530)*	1.029 (4.530)*		1.141 (5.190)*	1.207 (5.190)*

Note: *Theoretical values of t and F at p = 0.05

Table 7: The intra-day and inter-day accuracy and precision data for determination of telmisartan and estradiol valerate using MNPs preconcentration followed by spectrophotometry and HPLC detection

	Intra-day					Inter-day				
	Taken, µg/ml	Found, µg/ml	Recovery*, %	RSD, %	Er, %	Taken, µg/ml	Found, µg/ml	Recovery* %	RSD, %	Er %
Telmisartan (Spectrophotometric)	0.7	0.696	99.48	0.794	-0.52	0.7	0.695	99.23	1.006	-0.77
	0.8	0.801	100.18	0.582	0.18	0.8	0.802	100.21	0.961	0.21
Telmisartan (HPLC)	0.02	0.02034	101.71	1.012	1.71	0.02	0.02041	102.01	2.124	2.01
	0.09	0.09078	100.87	0.793	0.87	0.09	0.09036	100.4	1.078	0.4
Estradiol valerate (Spectrophotometric)	0.3	0.306	102.12	0.927	2.12	0.3	0.307	102.42	1.131	2.42
	1.2	1.195	99.6	0.597	-0.4	1.2	1.195	99.56	0.696	-0.44
Estradiol valerate (HPLC)	0.1	0.0991	99.14	0.428	-0.86	0.1	0.0991	99.14	1.235	-0.86
	0.5	0.499	99.82	0.69	-0.18	0.5	0.4999	99.98	1.088	-0.0

										2

Note: *Mean of six different experiments

System suitability:

System suitability test parameters of HPLC method involving column efficiency (number of theoretical plates, N), capacity factor (K) and tailing factor (T) were checked to ensure that the system was working correctly during the analysis. These parameters were calculated according to USP [24] and summarized as shown in Table 8.

Table 8: System suitability parameters of chromatogram for the determination of telmisartan and estradiol valerate by MNPs followed by HPLC method

Parameters	Telmisartan	Estradiol valerate
Retention time(tR)	3.4	5.82
Number of theoretical plates (N)	12693	3274
Tailing factor (T)	0.86	0.63
Capacity factor(K`)	1.62	3.48
Height equivalent to one theoretical plate (HETP)	0.0197 mm	0.076 mm

Robustness:

Robustness of HPLC procedure was examined where the influence of slight variations in one parameter chromatographic conditions while keeping all the others constant was evaluated. The studied variables included flow rate (1.2 ± 0.02) and acetonitrile content (70% ± 1) for telmisartan or (90 ± 1) for estradiol valerate was tested. Retention time and peak area were recorded upon these minor changes to indicate the robustness of the developed method as shown in Table 9.

Table 9: Robustness of the determination of telmisartan and estradiol valerate by MNPs followed by HPLC method

	Telmisartan		Estradiol valerate	
	90 ng ml^{-1}		500 ng ml^{-1}	
Parameter Variation	**Retention time**	**Peak area**	**Retention time**	**Peak area**
Flow rate(1.18 ml/min)	3.344	418	5.851	656
Flow rate(1.2ml/min)	3.404	415	5.818	645
Flow rate(1.22ml/min)	3.455	420	5.592	632
RSD of affected parameters	1.634	0.603	2.45	1.865
Acetonitrile content (71%)	3.358	419		
Acetonitrile content (70%)	3.404	415		
Acetonitrile content (69%)	3.442	412		
RSD of affected parameters	1.237	0.846		
Acetonitrile content (91%)			5.951	656
Acetonitrile content (90%)			5.818	645
Acetonitrile content (89%)			5.651	648
RSD of affected parameters			2.589	0.875

CONCLUSION

Application of MNPs modified with CTAB has been demonstrated in this work for pre concentration of the cited drugs followed by spectrophotometric and HPLC detection. The use of MNPs as solid phase extraction method has the advantage of high extraction efficiency with about 95-100% drug recovery. In this method magnet is used for drug extraction and so there is no need for time consuming filtration or centrifugation processes. In addition the adsorption and desorption of the cited drugs are very fast and could be completed in about 10 min These methods have the advantages of being very sensitive and selective in comparison with the previous reported methods as we are able to measure traces of the cited drugs even in the presence of other drugs in mixture with the cited drugs. These analytical methods can be applied for routine analysis of telmisartan and estradiol valerate in pure, pharmaceutical dosage forms and in mixture with other drugs.

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