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Extraction and preconcentration of methylphenidate from urine using silica-coated magnetic nanoparticles

Abstract

Magnetic nanoparticles (MNPs) have various applications including gas detectors, magnetic liquids, catalysts, magnetic storage systems, photomagnetic materials, magnetic resonance imaging, drug delivery systems, microwave devices, Fe3O4 silica-coated magnetic nanoparticles to adsorb analytes from biological samples. Methylphenidate is an amphetamine-like compound with urinary excretion that is prescribed to treat depression, symptoms of narcolepsy, and some patients with refractory hyperactivity. Initially, Fe3O4 magnetic nanoparticles were synthesized and coated with silica. To evaluate these nanoparticles, techniques such as Fourier transform infrared (FT-IR), scanning electron microscope (SEM), and X-ray diffraction (XRD) were used. The mean diameter of synthesized Fe3O4 and SiO2@Fe3O4 MNPs was about 45 nm and 72 nm, respectively. Two IR-FT absorption bands (636 and 656 cm cm^{-1}) have demonstrated the presence of MNPs.

By experiment on a real sample, the desorption yield was 91.5%, which indicates the effectiveness of the synthesized nanoparticles in extracting methylphenidate from the urine sample. Solvent type, extraction time, stirring speed, and ionic strength were investigated during the extraction process, and the optimal amount of each factor was determined using the Taguchi method, then the analyte extraction rate was measured under optimal conditions. The results showed that this method can successfully remove and extract methylphenidate from biological samples.

Keywords: *Magnetic nanoparticles, silica, methylphenidate, extraction.*

Keypoints

- Extraction of methylphenidate from urine by silica-coated MNPs is feasible and efficient.
- MNPs have a high potential for efficient recycling and reuse following the extraction process.
- Extraction of methylphenidate by MNPs can be an alternative to costly methods such as high-performance liquid chromatography

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Introduction

Methylphenidate (Ritalin) is a sympathomimetic medication with amphetamine-like properties that is prescribed to treat attention deficit hyperactivity disorder (ADHD), a behavioral-developmental disorder in children and adolescents, and to control the symptoms of narcolepsy in middle-aged and older adults (1). It has a stimulatory effect on the CNS by inhibiting the reuptake of norepinephrine and dopamine in presynaptic neurons. Like amphetamines, it mainly affects the cerebral cortex and subcortical structure (2). The World Anti-Doping Agency (WADA) has banned the use of Methylphenidate in athletes due to its potential to increase strength, ability, and endurance (3). In addition, there is the potential for methylphenidate abuse among adolescents, young adults, and students to improve concentration and alertness or for recreational purposes (such as euphoria) (4).

In the United States, methylphenidate administration increased by 260 percent between 1990 and 1995, indicating a significant increase in drug use (5). Another study by Musser et al. revealed a 16% increase in methylphenidate use among teenagers (6). As mentioned, there are serious concerns about the abuse potential of this drug among students, teens, and athletes. Consequently, it is very important to develop a new and sensitive identification method to determine the exact amount of drug consumption. Several studies conducted in various populations have shown that side effects such as decreased appetite, anxiety, arrhythmia, seizures, depression, hypertension, hyperhidrosis and insomnia are associated with methylphenidate use (7-9).

Today, a variety of methods such as spectrophotometry, gas chromatography (GC), gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), and liquid chromatography-mass spectrometry LC-MS) are used for drug analysis (10, 11). However, sample pretreatment must first be conducted using techniques such as solid-phase extraction (SPE), liquid-liquid extraction (LLE), solid-phase microextraction (SPME), and liquid-phase microextraction (LPME). Among the techniques mentioned, LLE and SPE are considered as more common preconcentration methods in sample preparation (12). However, these two methods are relatively time-consuming and also require an almost high volume of organic solvent which can be harmful to the environment and analytes. Therefore, techniques that use less or no solvent in their instructions, such as spectrophotometry, SPME, LPME, and

magnetic solid-phase extraction (MSPE) have a special place (13). In general, fewer solvent requirements, cleaner sample preparation, and greater selectivity are the benefits of solid-phase extraction compared to liquid-phase extraction (14, 15). In SPE, separation is based on the distribution constant of the analyte between the mobile phase and solid adsorbent. There are different types of this technique depending on the extraction process, size, and shape of the adsorbent bed and adsorbed material. In SPE with different adsorbents, it is not always possible to optimally retain the analyte and isolating and concentrating any single compound can be challenging and time-consuming (16). MSPE is a new alternative to SPE that uses a magnetic adsorption phase to extract analytes from the sample. Magnetic nanoparticles (MNPs) are a desirable alternative to conventional adsorbents in solid-phase extraction that may overcome the aforementioned limitations. Due to their small size, MNPs have a specific surface area and high adsorption capacity, as well as excellent selectivity to analytes, which increase the efficiency of the extraction process. Other advantages of MSPE are the short extraction time and facilitating adsorbent separation from the sample medium without the need for processes such as centrifugation or filtration (17).

MNPs have a magnetic core mainly made of cobalt, nickel, iron, or oxides of these elements. Due to the unique magnetic properties of iron oxides, Fe3O4 and Fe2O3-γ are often used as the core of MNPs. However, pure iron oxides are prone to clumping, which reduces their magnetic properties (18). In addition, the nanometer size of MNPs is not sufficient to isolate analytes in high-volume samples. To overcome these limitations, the magnetic core of MNPs is coated with suitable inorganic (such as silica, alumina, and manganese oxide) or organic (such as surfactants, Chitosan, and polyamidoamines) coats. A suitable coating prolongs the life of the adsorbent and prevents its oxidation. In addition, modification of organic or inorganic coatings with appropriate functional groups can increase the adsorption property and ultimately improve the extraction efficiency (19). Silica is one of the most common materials in the magnetic core coating of magnetic nanoparticles due to its high availability, unique properties, and ease of modification with different functional groups (organic and inorganic particles). In addition, a silica coating has high thermal and mechanical stability, which makes it possible to extract at high temperatures (20).

Methylphenidate is often excreted by the kidneys, and direct analysis of urine samples is virtually impossible due to the complexity of the urinary environment, which results in decreased sensitivity and selectivity (17). Because small amounts of unchanged methylphenidate are excreted in the urine, it can only be measured using expensive methods such as Liquid chromatography-mass spectrometry (LC-MS). Therefore, it is very important to use a new technique that can extract and pre-concentrate small amounts of it from urine. In previous studies, various methods such as enzyme-linked immunosorbent assay (ELISA) (21), HPLC (22), and liquid chromatography-electrospray ionization mass spectrometry (23) have been used for methylphenidate determination. The measurement of methylphenidate in urine samples by liquid chromatography-tandem mass spectrometry (LC-MS/MS) was assessed and confirmed by Paterson et al (24). MSPE is expected to pre-concentrate and determine methylphenidate in urine samples faster, more accurately, and with a lower solvent requirement compared to most of the above methods.

Methods

Chemicals

The chemicals used in the MNPs manufacturing process, including hydrochloric acid, ammonium hydroxide, ammonia solution 25%, ethanol, isopropanol, tetraethyl orthosilicate (TEOS), iron (II) chloride tetrahydrate ($FeCl_2.4H_2O$), iron (III) chloride hexahydrate ($FeCl_3.6H_2O$, purity 97%), were all purchased from Merck Chemicals Co. (Darmstadt, Germany). The products used in the MSPE, including methanol, acetonitrile, and acetone, also originated from the same company. Deionized water was produced in the laboratory by the authors.

Standard solutions and real samples

To prepare the sample solution, we transferred 10 mg of Ritalin made by Novartis (Basel, Switzerland) to a 100 ml volumetric balloon and volumized with deionized water. It was then placed in an ultrasonic water bath for 5 minutes and stirred for 40 minutes after placing a magnet inside the balloon. The 100 ppm solution was then diluted to 2 ppm, 4 ppm, 6 ppm, 8 ppm, and 10 ppm. Based on the calibration curve, a set of designed experiments were conducted at a concentration of 10 ppm. All the above processes were performed at room temperature. To obtain a real sample, a urine sample was taken from a healthy young man and maintained at -20° C until use.

Preparation of iron oxide nanoparticles

Magnetic cores were synthesized by the co-precipitation method. This was achieved by mixing 0.85 ml of HCl, 25 ml of water, 5.20 g of $FeCl_3.6H_2O$, and 3.83 g of $FeCl_2.4H_2O$. The prepared solution was added dropwise to the sodium hydroxide solution, which was obtained by adding 15 g of sodium hydroxide to 250 ml of water, stirring at constant speed. Fe3O4 nanoparticles were synthesized in a nitrogen (oxygen-free) atmosphere. The synthesized Fe3O4 nanoparticles were separated by an external magnetic field washed with water and dried in a 100°C oven. The resulting solid was ground well to

obtain a homogeneous powder. The nanoparticles were stored in closed containers at room temperature. The mean diameter of Fe_3O_4 MNPs was about 45 nm.

Preparation of Fe3O4 / SiO2

The silicate coating of magnetic iron oxide nanoparticles was carried out following the Stöber method (25). Initially, 120 mg of the Fe3O4 nanoparticles prepared in the previous step was added to 250 ml of isopropanol. A solution containing 150 ml of water, 150 ml of isopropanol, and 6 ml of ammonium hydroxide was prepared and added to the previous mixture and stirred. Then 150 µl of TEOS was added to the final mixture and stirred well for 3 hours. SiO2@Fe3O4 nanoparticles were separated by an external magnetic field and dried at 65 ° C after washing with ethanol. The resulting solid was ground well to obtain a homogeneous powder.

Optimization of experimental conditions

The SiO2@Fe3O4 MNPs absorb methylphenidate with maximum efficiency when adsorption-affecting parameters are optimized. Therefore, it was necessary to optimize all effective parameters in this study. Various effective variables of methylphenidate adsorption by SiO2@Fe3O4 nanoparticles included MNPs quantity, pH, ionic strength, solvent type, sample volume, cycles, and duration of vortex application. A univariate (or conventional) approach can be used to optimize variables, where only one-factor changes and the others remain unchanged. At each stage, the optimized factor value is used in subsequent experiments. In addition to not evaluating the interactions between variables, this method is also time-consuming and costly due to the large number of experiments required to optimize the variables. Another approach to optimizing variables is to use the experimental design method by chemometry. To design the experiment, first, the independent variables must be carefully selected and the method of experiment design according to the experimental field must be selected and then subjected to mathematical statistical analysis of experimental data by the software. There are several methods for optimizing independent variables in experimental design approaches, including the Taguchi method, the mixed design method, and the response surface methodology (RSM). Extraction parameters in the present study, including solvent pH (6, 8, and 10), vortex duration (5, 10, 15 minutes), ionic strength (2, 5, and 8%), sample volume (2.5, 5, and 7.5 ml), vortex speed (400, 700, and 1000 rpm), type of solvent (methanol, acetone, and acetonitrile) amount of nanoparticles (0.03, 0.04, and 0.05 mg), were entered into Taguchi software to achieve optimal values and levels. Analysis of variance (ANOVA) was also used to validate the model. In addition, alignment curves and statistical analysis were provided by design-expert software (version 7.0) to show the interaction of independent variables with the dependent variable (response), which in this study is the efficiency of methylphenidate extraction.

Extraction process

After diluting the real sample in a 5: 5 ratio with deionized water, 10 mg of methylphenidate was added. The optimum amount of SiO2@Fe3O4 nanoparticles (0.003 g) was then added to the sample whose pH and electrolyte concentration were adjusted. The adjustment was made for pH at optimum (pH = 6) by adding HCl and NaOH, and for electrolyte concentration at optimum 2% by adding NaCl. After extraction under optimal conditions, the amount of methylphenidate extracted from urine was examined by ultraviolet-visible (UV-Vis) absorption spectroscopy.

Results and discussion

Characterization of MNPs

To characterize SiO2@Fe3O4 MNPs, various methods including scanning electron microscopy (SEM), X-ray diffraction (XRD) and Fourier transform infrared (FT-IR) were used, the details of which are given below. The morphology of Fe3O4 nanoparticles is shown by field emission scanning electron microscopy (FESEM) in Figure 1a. Accordingly, Fe3O4 nanoparticles form spherical, cohesive structures with an almost uniform distribution of about 72 nm. The sphericity of SiO2@Fe3O4 MNPs is a desirable parameter for adsorption, in other words, the symmetrical shape of these particles allows them to absorb contaminants at all points on the surface.

The IR-FT spectrum of SiO2@Fe3O4 core-shell nanoparticles is shown in Figure 1b to investigate the surface functional groups as well as the success of synthesis. The presence of MNPs is characterized by two strong absorption bands at 636 and 565 cm^{-1} due to vibration fission of O-Fe at 567 cm^{-1}. In addition, the absorption band at 466 cm^{-1} is related to O-Fe vibration. The silica layer on the surface of MNPs is represented by the Si-O-Fe bond, but in Figure 1b this peak is not seen due to the overlap with the 570 cm^{-1} peak related to O-Fe vibration. However, the silane polymers present on the surface of MNPs are characterized by peaks at 954.80 cm^{-1} and 1095.60 cm^{-1}, which are related to the symmetric stretching vibrations of the Si-O-Si, OH-Si, and Fe-O-Si groups. The broad absorption band seen at 3400 cm^{-1} is related to water absorption and surface silanol groups.

The synthesized adsorbent was analyzed by XRD (Figure 1c). The peaks appearing in 2θ are equal to 30.4º, 35.6º, 43.3º, 57.3º, and 62.8º, which indicate the formation of magnetite (Fe2O4) in a pure phase. According to the IR-FT spectrum, which proved the presence of silica, and since no other peak (other than iron oxide peaks) is observed in XRD, the silica layer is amorphous and has no crystalline structure. The broad peak appearing at 2θ = 20-30º corresponds to amorphous SiO2.

According to the Vibrating-sample magnetometry (VSM) results (Figure 1d), superparamagnetic nanoparticles show very high magnetic strength due to the loop-back diagram with a magnetization of 15. Such a diagram proves the high magnetic property and even the maintenance of the magnetic state in the absence of the field.

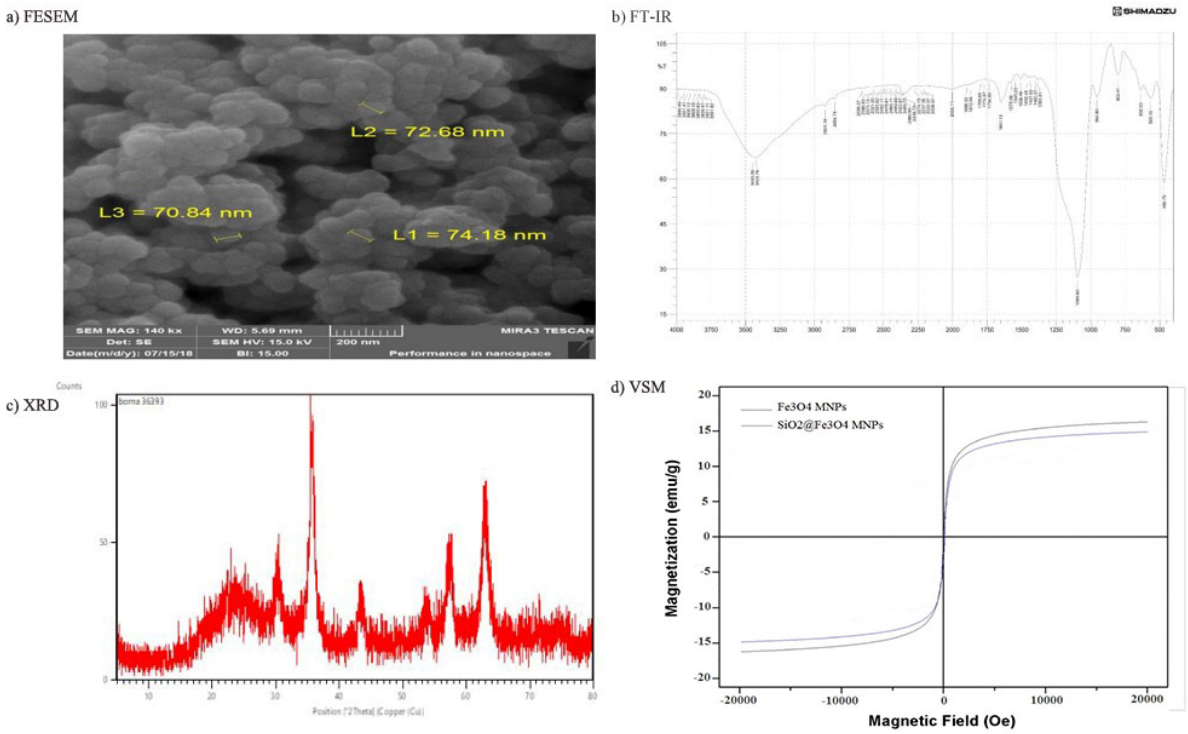

Figure 1. Characterization of SiO2@Fe3O4 MNPs. *a) Field emission scanning electron microscopy (FESEM), b) Fourier transform infrared (FT-IR), c) X-ray diffraction (XRD), d) Vibrating-sample* magnetometry *(VSM)*

Optimization results

By evaluating seven independent variables by Design Expert software version 7, the optimum experimental conditions were determined as follows: the amount of MNPs, 0.003 g; Sample volume, 2.5 ml; methylphenidate solution, 2.5 ml and 10 ppm; pH, 6; electrolyte concentration, 2%; Extraction time (sorption + desorption times), 5 minutes; Vortex speed, 400 rpm; Solvent type, methanol; Solvent volume, 2.5 ml (the first experiment in Table 1). The experiment was conducted on a real sample under mentioned conditions and the extraction or desorption yield was 91.5%.

Table 1. Experiments designed by Design Expert software and their extraction yield

No.	pH	Electrolyte concentration (%)	sample volume (ml)	adsorbent dosage (gr)	Extraction time (min)	Vortex speed (rpm)	Solvent type	Solvent volume (ml)	Desorption yield (%)
1	6	2	2.5	0.03	5	400	Methanol	2.5	93.2
2	8	5	5	0.03	10	700	Acetonitrile	2.5	28.5
3	10	8	7.5	0.03	15	1000	Acetone	2.5	97.8
4	6	8	2.5	0.04	10	1000	Acetonitrile	2.5	56.0
5	8	2	5	0.04	15	400	Acetone	2.5	25.0
6	10	5	7.5	0.04	5	700	Methanol	2.5	66.6
7	8	8	2.5	0.05	15	700	Methanol	2.5	0.0
8	10	2	5	0.05	5	1000	Acetonitrile	2.5	85.7
9	6	5	7.5	0.05	10	400	Acetone	2.5	50.0
10	10	2	2.5	0.03	10	700	Acetone	2.5	0.0
11	6	5	5	0.03	15	1000	Methanol	2.5	60.0
12	8	8	7.5	0.03	5	400	Acetonitrile	2.5	66.6
13	8	5	2.5	0.04	5	1000	Acetone	2.5	0.0

14	10	8	5	0.04	10	400	Methanol	2.5	36.3
15	6	2	7.5	0.04	15	700	Acetonitrile	2.5	50.0
16	10	5	2.5	0.05	15	400	Acetonitrile	2.5	11.1
17	6	8	5	0.05	5	700	Acetone	2.5	25.0
18	8	2	7.5	0.05	10	1000	Methanol	2.5	29.4

Taguchi method and quadratic model

The quadratic model proposed by the Taguchi experimental matrix was introduced after ANOVA as a suitable statistical model to show the relationship between dependent and independent variables. ANOVA results and model details are given in Table 2 and Table 3, respectively. According to Table 2, the introduced model is valid (p-value = 0.0053, F = 13.05) and all seven independent variables have a significant effect on the extraction of methylphenidate by MNPs (p-value < 0.05), which indicates the correct selection of variables. In addition, the mean squares and F values show that pH (variable C) has the greatest effect on the extraction yield. The best response for the variables of MNP amount and extraction time is shown in Figure 2. The interaction between sample volume and pH has a significant effect on the extraction of methylphenidate, and according to Figure 3, the best response is observed with a sample volume of 2.5 ml and a pH of 6.

Table 2. Results of analysis of variance (ANOVA) for quadratic model

Source	Sum of Squares	Df	Mean Square	F Value	p-value
Model	16154.78	12	1364.23	13	0.00
A-B	1808.64	2	904.32	8	0.02
B-C	3340.01	2	1670.00	16	0.00
C-D	3183.99	2	1592.00	15	0.00
E-F	1445.07	2	722.53	7	0.03
BC	6072.08	4	1518.02	14	0.00
Residual	515.89	5	103.18		
Cor Total	16670.67	17			

A: adsorbent dosage; B: sample volume; C: pH; D: solvent type; E: extraction time; F: vortex speed; G: ionic strength; BC: interaction between sample volume and pH

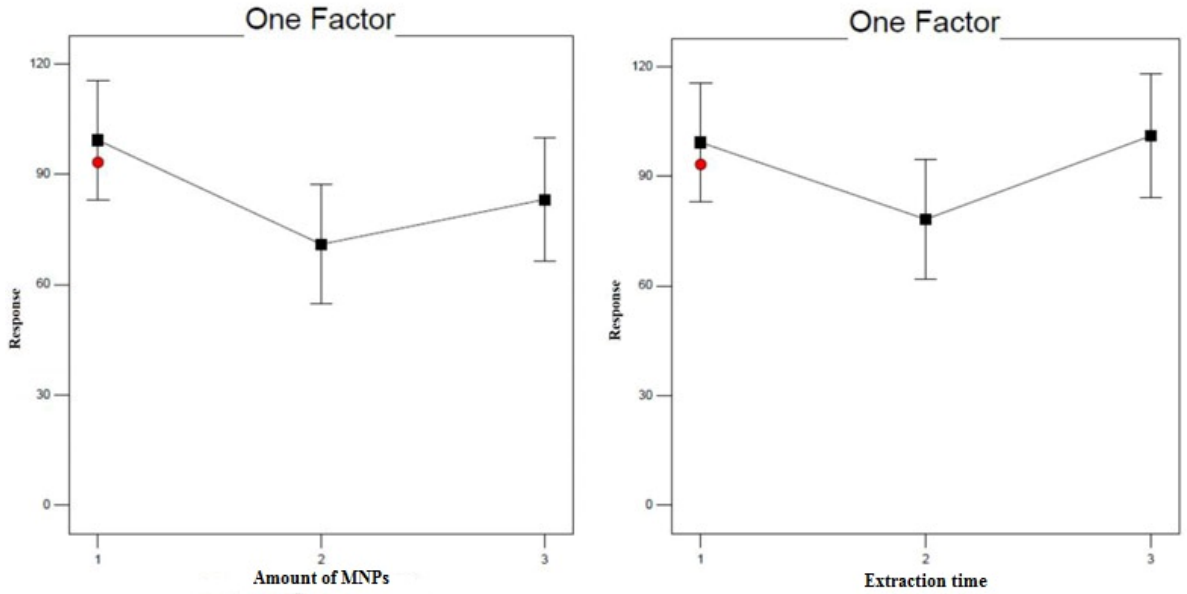

Figure 2. Evaluation of response rate in different values of variables, amount of MNPs, and extraction time.

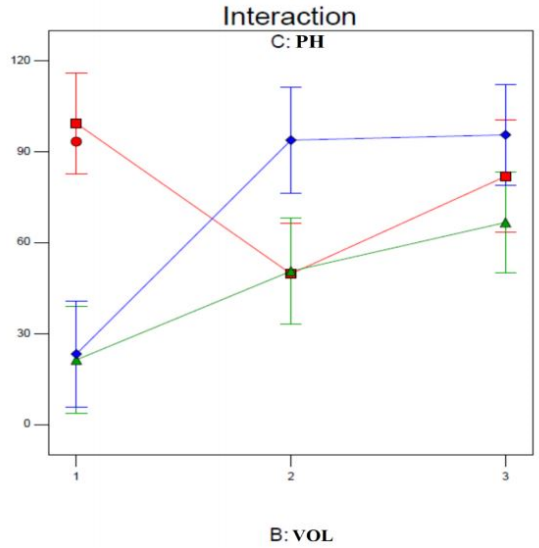

Figure 3. Effect of interaction between sample volume and pH on extraction of methylphenidate by MNPs

The details of the model shown in Table 3 indicate that the coefficient of determination (R2) equals 0.96. This means that the experimental and predicted values are well matched, and this model can be used to predict any similar situation in the future. On the other hand, the values of the adjusted coefficient of determination (Adj-R^2) and predicted coefficient of determination (Pre-R^2) (0.89 and 0.58, respectively) were very close to each other, which is another reason for the propriety of the model. Also, the Adeq Precision value (12.3) was larger than the threshold value (4), indicating that the proposed model could be used to design the experiment.

Table 3. Details of the quadratic statistical model resulting from Taguchi design

Std. Dev	10.16	R-Squared	0.96
Mean	43.42	Adj R-Squared	0.89
C. V. %	23.40	Pred R-Squared	0.59
PRESS	6685.97	Adeq Precision	12.30

Methylphenidate extraction and MNP recycling

Extraction recovery (ER) of methylphenidate was calculated to determine the adsorption of methylphenidate from aqueous samples by silicate-coated magnetic nanoparticles. The following equation was used for ER:

E.R.% = 100 = 100

$$\text{E. R. \%} = \left(\frac{C_0 - C}{C_0}\right) \times 100 = \left(\frac{A_0 - A}{A_0}\right) \times 100$$

In the above equation, A_0 is the UV-Vis absorption of methylphenidate in the initial solution, A is the UV-Vis absorption of remaining methylphenidate, C0 is the concentration of methylphenidate in the initial solution and C is the concentration of remaining methylphenidate. By placing the values in the above equation, the ER value for methylphenidate from aqueous solution was reported to be 91.5%, which is acceptable. Due to the lower cost of spectrophotometry than high-performance liquid chromatography (HPLC), the method proposed in the present study can be used to effectively and easily identify methylphenidate in aqueous solutions, including urine samples. In addition, the findings showed that it is possible to reuse MNPs after desorption. In other words, the adsorption of methylphenidate on the surface of SiO2@Fe3O4 MNPs is a reversible process, so adsorbent and desorbed methylphenidate can be recovered for re-use. Figure 4 shows that after 5 adsorption-desorption cycles, recycled nanoparticles have an adsorption capacity of 76%.

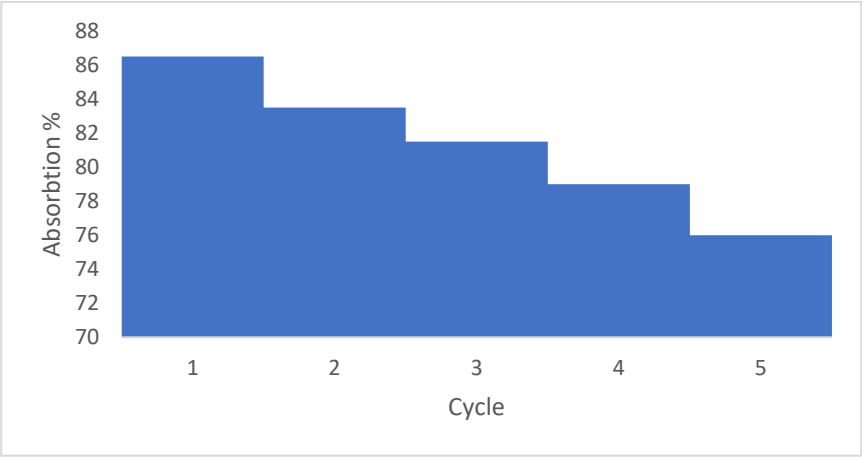

Figure 4: Adsorption of methylphenidate by Fe3O4 @ SiO2 nanoparticles in successive adsorption-desorption cycles

Conclusion

In the present study, a new, inexpensive, and effective method based on magnetic solid-phase extraction (MSPE) was introduced to extract methylphenidate from aqueous samples including urine. Taguchi method was used to design the experiment and achieve the optimal amount of factors affecting the absorption of MNPs. Advantages of extracting methylphenidate by SiO2 @ Fe3O4 MNPs over other methods such as LC-MS included easy and safe synthesis of MNPS, low time required for extraction due to superparamagnetic properties, and achieving quantitative and effective extraction with very low adsorbent due to high surface area of MNPs.

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