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Spectrophotometric Method Development And Validation For Methamphetamine In Human Urine

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Abstract

Introduction: Methamphetamine (Meth) is a synthetic stimulant used as main component in many illegal drugs. its abusive use, moreover, can lead to immunodeficiency and neuropsychiatric disorders. Semi-permanent Meth abuse from repeated use from drug resistance and psychological dependence**. Aim of work:** Work aimed to development of a simple, sensitive and rapid spectrophotometric method for estimation of Meth in human urine. **Methodology:** The proposed method is based on the formation of an enamine which produced from (addition–condensation reaction) between meth and acetaldehyde then enamine react with sodium nitroprusside to produce an immonium intermediate. The intermediate subsequently reacts with water to form the blue complex. **Results:** The extraction recovery of Meth was 86.75%. The calibration curves were linear (r2 =1) in from 1 to 100 µg/ml. Limits of detection and quantification were 0.5 and 1 µg /ml respectively. Intra- and inter-assay precision was within 3.21–11.57% and 0.91–2.89% respectively. Intra- and inter-assay accuracy was within 1.68 to 3.75% and 0.69 to 1.15% respectively. **Conclusion:** Validation for the studied results indicate that the used method for Meth analysis can be successfully applied for its valid determination in screened positive urine for amphetamines.

Keywords: Urine screening; methamphetamine; spectrophotometric method; validation.

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1. Introduction

The authorities' campaign against illegal drug usage and drug trafficking includes identifying drug users and enrolling them in detoxification or replacement therapy programs. Toxicological analysis is needed to detect and quantify the parent substances or their metabolites in various biological matrices for drug users' diagnosis, therapy monitoring and assessment of substance use relapse during detoxification or replacement therapy [1].

Methamphetamine (Meth) is a synthetic and illegal drug which is described as (2S)-N-methyl-1-phenylpropan-2-amine hydrochloride by International Union of Pure and Applied Chemistry (IUPAC), **Figure (1)**. Physically, it is a white crystalline powder and has a shining appearance and it has a molecular weight 149.237 g/mol. The pKa of meth is 10.1 which is due to the basic nitrogen moiety in meth's chemical structure [2].

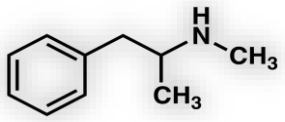

Figure 1. Chemical structure of methamphetamine.

Methamphetamine is a potent central nervous system stimulant through increasing the levels of monoamine neurotransmitters (dopamine, serotonin and norepinephrine) in the brain and it is mainly used as a recreational drug. It is structurally related to its metabolite amphetamine differing only by the presence of a methyl group. It is used medically in treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy as well as obesity [3], [4].

As a result of meth misuse, neuronal damage result from oxidative stress within mitochondrial membrane and dopamine pathway [5].

Methamphetamine problem is evidence of a considerably more hazardous condition than basic drug abuse-related self-destruction of an individual, which is often restricted to the abuser but extend to whole community. Meth usage causes people to become aggressive which lead to rise in crime rates and fatal automotive accidents. Therefore, there is an urgent need for drug testing for Meth at roadsides, workplaces, sports and criminal justice system [6].

Urine drug testing is one of the more objective tools available for tracking patient adherence to treatment, and it can expose possible drug abuse and misuse. of methamphetamine concentrations in urine of the chronic abusers was 1- 90 µg/ml. Identifying recent drug use from old drug consumption can be done by quantitative urinary results which can tell about patterns of drug use [7].

Various studies for Meth determination in blood, plasma, serum, urine and hair have been published using various methods, namely ultraviolet spectrophotometry, Raman spectroscopy, ion mobility spectrometry (IMS), capillary electrophoresis, gas chromatography–mass spectrometry (GCMS), chiral stationary phase liquid chromatography–mass spectrometry/mass spectrometry (CSP-LC-MS/MS), high performance liquid chromatographic (HPLC), liquid chromatography–mass spectrometry/mass spectrometry (LC-MSMS), liquid chromatography–mass spectrometry/mass spectrometry conducted with positive electrospray ionization (LC-ESI

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MS/MS) and molecularly imprinted polymer assisted paper spray ionization mass spectrometry (MIP-PSI-MS) [8],[9].

Spot tests were recommended by United Nations International Drug Control Programme since (1994), which are the simplest and quickest method for detecting the presence of the substance (include Meth) in the sample [10]. Ultraviolet–visible (UV–vis) spectrophotometry is an easy and simple widespread analytical method which can identify the concentration of analytes in a transparent fluid based on Lambert-Beer's law [11].

Colorimetric tests are commonly used in forensic science laboratories, but they are not sufficient to confirm the presence of meth. Quantification requires additional methods like spectrophotometry and chromatography. This article introduces an approach to developing semiquantitative colorimetric procedures for Meth utilizing color presumptive tests.

1. Material

A-Chemicals

Methamphetamine hydrochloride (purity >99 %) was purchased from Merck, Germany and a stock solution from Meth at (1mg/ml) concentration was prepared by dissolving 12.57 mg of methamphetamine hydrochloride in 10 ml (0.01M hydrochloric in methanol). HPLC grade methyl-tert-butyl ether (MTBE), was purchased from Merck, Germany. Ammonium hydroxide 33%, sodium nitroprusside powder was purchased from Egyptian Compony for Chemicals and Pharmaceuticals, Egypt and was prepared by dissolving 1 g in 99 ml deionized water. Sodium carbonate powder was purchased from Egyptian Compony for Chemicals and pharmaceuticals, Egypt and Sodium carbonate was prepared by dissolving 4 g in 96 ml deionized water, sodium hydroxide powder, sodium acetate powder, acetaldehyde liquid and hydrochloric acid were purchased from Egyptian Compony for Chemicals and pharmaceuticals, Egypt. Deionized water is obtained from human power one water deionizer, Sohag clinical toxicology laboratory. Multi-drug screen panel dip steak ABONtm (Abon Biopharm (Hangzhou) CO, Ltd). China.

B-Instrumentation:

Spectrophotometer, Specord 600, Analytik Jena, Germany in Clinical; Analytical balance, A&D Company, Limited - model (GR 200), Japan; Micropipettes, HTL – model (OP1000, OP100 and serial), China; Water deionizer, Human corporation – model (human power one), China. Centrifuge, Hettich Zentifugen – model (EBA20), Germany and Vortex, Germany industrial crop – model (VM300) at Toxicology Laboratory, Sohag University Hospitals, Egypt.

2. Methodology:

The current method based on extraction of Meth from previously positive amphetamine urine samples screened by rapid immunoassay dip steak (ABONtm), **Figure (2)**. Extraction was done by drevatization reaction to Meth followed by spectrophotometric determination and validation of the results.

A-Drevatization reaction of methamphetamine:

Methamphetamine reacts with acetaldehyde (through an addition–condensation reaction) and produces an enamine which further reacts with sodium nitroprusside to produce an immonium salt intermediate. The intermediate subsequently reacts with water to form the blue complex, **Figure (3)**. Modified from **Choodum et al, (2016)** [12].

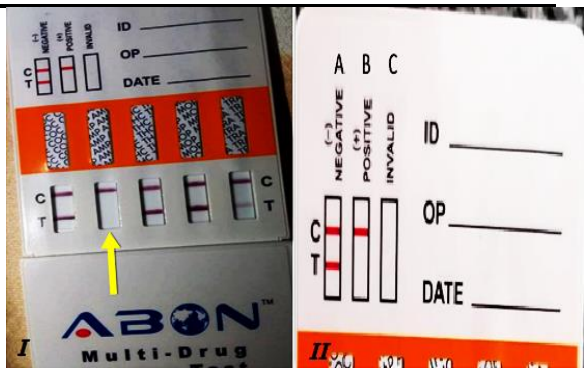

Figure (2): Rapid multidrug immunoassay screening; ***I***: Positive test for amphetamine (arrow) ***II***: Interpretation of the test; (A) Negative, (B) Positive, and (C) Invalid.

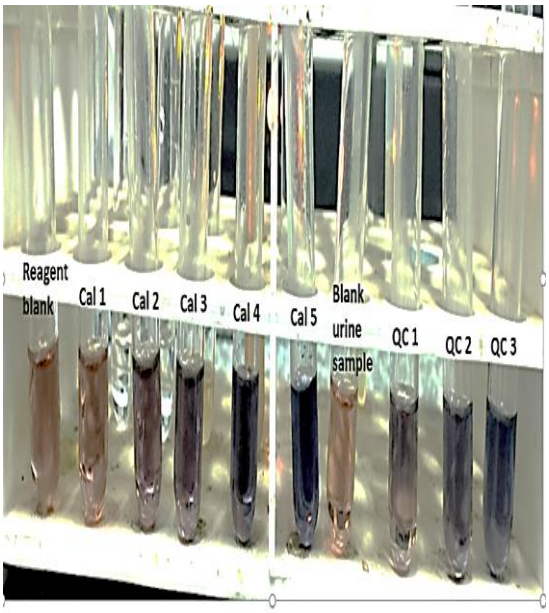

Figure (3). Gradient of blue coluor complex in Meth spiked samples for calibrators and quality controls (Cal: calibrator, Qc: quality control).

B-Optimization of reaction conditions:

The different parameters (drug concentration, reagent concentration and reaction time) affecting the development process were extensively studied to determine the optimum conditions for the assay procedures. The optimum values of the variables were maintained throughout the determination process.

C-Sample preparation:

For calibrator samples, a working solution of methamphetamine in methanolic HCl (0.01M) at a concentration of 200 µg/ml was created. For quality control (QC) samples, additional methanolic solutions were prepared: low quality control (LQC), middle quality control (MQC), and high-quality control (HQC). Calibrator and QC functioning solutions were created using various stock solutions. Calibration standards were created by serially diluting 200 µg/ml of methamphetamine with blank urine at concentrations of 1, 10, 30, 50, and 100 µg/ml. Quality controls were established by serial dilution of 200 µg/ml methamphetamine with blank urine at concentrations of 25

µg/ml (LQC), 40 µg/ml (MQC), and 75 µg/ml (HQC). All calibrators, quality control, blank urine and unknown samples were extracted by liquid extraction technique to separate Meth from urine matrix, to enhance drug selectivity and to increase recovered concentration Then the derivatization was performed by a modification from **Molins et al, (1994)** [13].

D- validation:

The Meth method in human urine was thoroughly and completely validated in accordance with USFDA requirements [14]. To assess method integrity, we looked at specificity, linearity, limits of detection (LOD) and quantification (LOQ), intra- and inter-assay precision, accuracy and extraction efficiency.

3. Results and discussion:

A- Derivatization and best Absorption spectrum:

In the current study best derivatization was obtained by taking 100 microliters from urine samples of Meth were taken in transparent Wasserman tube with 300 µl of mix solution which was prepared by adding 4ml of 1% sodium nitroprusside to 1ml acetaldehyde, followed by adding 600 µl of 4% sodium carbonate solution into each tube for total final volume of 1ml for each tube. A blue colour complex was developed which showed a maximum absorbance at 585 nm against blank, **Figure (4).** The present results agreed with the results recorded by **Choodum et al, 2014** [15].

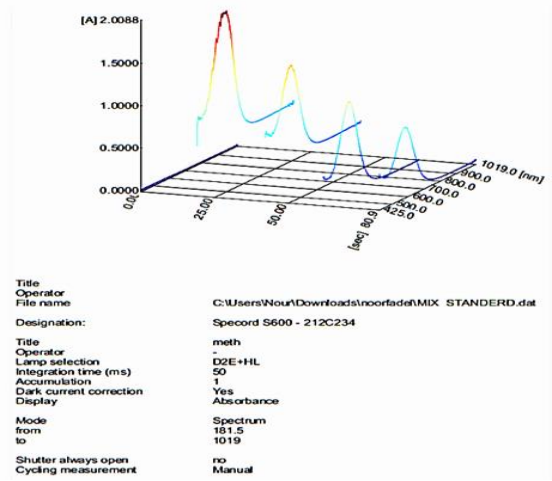

Figure (5). 3D graph showing spectrum absorption of increasing standard Meth concentrations by spectrophotometry.

In the study of **Molins et al, (1994)** Meth was determined in urine sample by spectrophotometric technique using sodium 1,2-naphthoquinone-4-sulphonate as reagent. In this study limit of detection in urine 0.9 µg/ml but current study detection limit 0.5 µg/ml also. In addition, the aforementioned approach some error in Meth concentration due to presence of amphetamine as methamphetamine metabolite in samples and reagent can react with amphetamine in contrast to the current method.

In the article reported by **Bachri et al, (2021)** a spectrophotometric method has been developed and applied to measure methamphetamine and other drugs in Ecstasy tablet at high level(LOD =21.99µg/ml) without derivatization [8] in contrast current method meth was determined in urine sample with derivatization at low level(LOD =0.5µg/ml) .Also **Choodum et al, (2015)** detected Meth in illicit tablets by using A sol-gel colorimetric sensor with a color analysis application on a mobile phone [16]. At high level (LOD from 207 to 600 µg/ml).

B-Effect of the concentration of drug:

The absorbance spectrum was measured for various concentrations of Meth solutions in the range of 1-100 µg/ml with addition previously mentioned reagent at wave length of 585 nm against blank. The obtained results obeyed Beer's law**, Figure (5).**

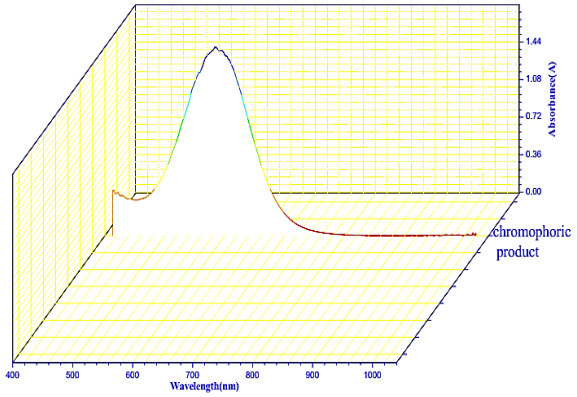

Figure (4). Spectrum and maximum (at 585nm) absorbance of Meth with reagent.

C-Urine sample preparation

200µL of 33% ammonium hydroxide and 4.0 ml of Methyl-Tert-Butyl Ether (MTBE) were added to 2 ml of urine specimens. The tubes were then vortexed for 5 minutes, pH checked, then centrifuged at 4000 rpm for 5 minutes. The organic layer was transferred to a new 5-ml clean glass tube and dried in the nitrogen stream. to the dry tube 300 µl of 1% sodium nitroprusside) and 1ml acetaldehyde were mixed and kept at room temperature for 10 minutes. At 585 nm, the absorbance of the solution in each tube was measured in comparison to the reagent blank. The calibration graph was created by graphing absorbance versus final Meth concentration. The regression equation was calculated, scheme is shown in **Figure (6).**

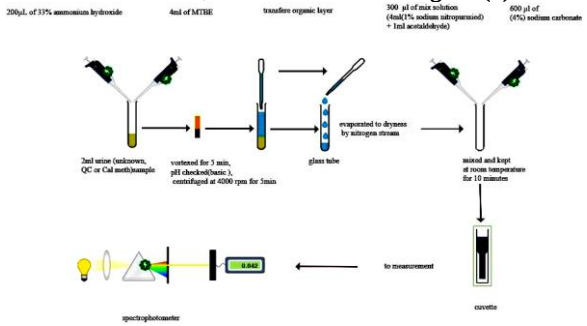

Figure (6). Illustration scheme for Meth extraction from urine and complex formation for spectroscopic identification.

In a method reported by **Kim et al, (2020)**, the

extraction Meth from urine sample was performed using ethyl acetate as the organic solvent and potassium hydrogen carbonate to pH adjust before analysis by GC-MS [17].

Bahmanabadi et al, (2017), applied an extraction method with n-hexane and potassium hydroxide to extract Meth from oral fluid [18]. **Molins et al, (1994)**, reported that Meth was extracted from urine sample by n-hexane and ammonium hydroxide [13].

The current method uses MTBE as extraction solvent these results were disagreed with results recorded by **Ridha et al, (2022)** who used Cloud Point Extraction technique in their study to extract palladium from water and soil sample in this technique water was used instead organic solvents since the volume of a surfactant-rich layer is around 10-100 times smaller than the size of an aqueous layer [19].

In article reported by Issa et al (2019) Benzethonium Chloride in pharmaceutical formulation was determination by spectrophotometric methods, these methods are based on ion-pairs formation of the drug with some chromotropic acid azo dyes, Contrary to the current method these methods use methylene chloride to extract final product were formed after add reagents while current method use MTBE to extract target analyt from urine sample before reagents were added [20].

Liquid -liquid extraction technique used in current method perform by large volume of organic solvent comparing with volume of solvent used in air-assisted liquid–liquid microextraction technique which reported by **Azooz et al, (2022)** [21]. Current method for methamphetamine determination was compared with previous analytical methods, **Table (4).**

D- Validation:

a-Sensitivity and specificity

Sensitivity was estimated by determining limits of detection (LOD) and quantification (LOQ) for methamphetamine. The LOD and LOQ of the method were determined by analyzing validation samples (n=5), where the LOD was set to 0.5 µg/ml and LOQ was set to 1.0 µg/ml. on the other hand, specificity was evaluated by assaying of six different human blank urine. No endogenous absorbance was observed in blank urine selected wave length, **Figure (7).**

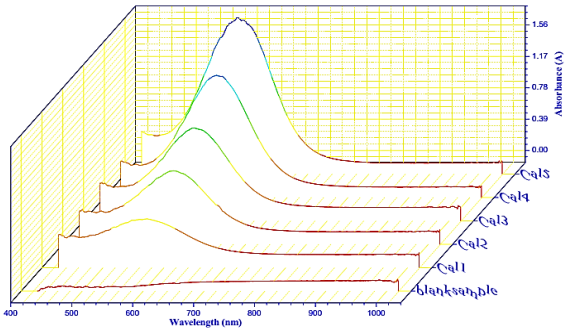

Figure (7). Spectrum and maximum absorbance of different Meth calibration levels against blank urine sample

b-Linearity

Linearity of the Meth solution was studied and calibration plots were constructed with obtained results, **Figure (8).** The linearity of calibration graphs was proved by the high values of the correlation coefficient and the small values of the y-intercept of the regression equation. The apparent molar absorptivity's of the resulting colored complexes and relative standard deviation of response factor for proposed spectrophotometric method were also calculated. The obtained results like Beer's law limit, Sandell's sensitivity, molar absorptivity and correlation coefficient were reported in **Table (1).**

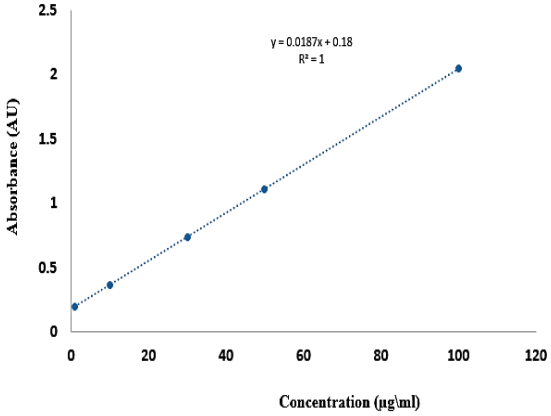

Figure (8). Methamphetamine calibration curve**.**

c-Accuracy and precision

Precision and accuracy of the method were evaluated at three concentrations, Low, middle and high quality controls (LQC, MQC and HQC) over the linear dynamic range by five replicates of each one for three times in three different days. Intra- and inter assay precision by measuring relative standard deviation (RSD%) which was ranged from 3.21 to 11.57% and 0.91.16 to 2.89%, respectively. Intra- and inter assay accuracy by measuring bias% which was ranged from 1.68 to 3.75% and 0.69 to 1.15% respectively, **Table (2)**.

d-Recovery

The extraction recovery of Meth in urine was determined at the three concentration levels LQC, MQC and HQC. It was calculated by comparing standard curve, **Table (3)** shows the recoveries of three quality control samples of Meth for LQC, MQC and HQC 87.32, 84.80 and 88.13 % respectively. The mean recoveries of the three quality controls were 86.75 %.

Table (1): Performance data and statistical parameters of the drug complex.

Item	λmax (nm)	Molar absorbance ($L.mol^{-1}$ cm^{-1})	Beer's law limit (µg/ml)	Sandell's sensitivity (µg/cm^2)	Correlation coefficient (r^2)	LOD (µg/ml)	LOQ (µg/ml)
Result	585	5.46×10^3	1-100	0.0273	1	0.5	1

Table (2): Intra- and Inter assay precision and accuracy for Meth concentrations in human urine samples.

Nominal concentration (µg /ml)	Found concentration (µg /ml)	Precision (% RSD)	Accuracy (% Bias)
Intra-assay (n = 5)			
LQC (25)			
Day 1	23.68	7.11	1.68
Day 2	24.60	10.88	2.68
Day 3	25.07	11.57	2.90
LQC (40)			
Day 1	40.39	5.87	2.37
Day 2	42.10	6.95	2.93
Day 3	39.92	3.21	1.28
LQC (75)			
Day 1	76.26	3.70	2.82
Day 2	74.98	4.66	3.50
Day 3	76.06	4.93	3.75
Inter-assay (n = 15)			
LQC	24.45	2.89	0.71
MQC	40.80	2.81	1.15
HQC	75.77	0.91	0.69

Table (3). Absolute recovery data of Meth

Parameter	Add concentration (µg /ml)	Found concentration (µg /ml)	Recovery %
LQC	25	21.83	87.32
MQC	40	33.92	84.8
HQC	75	66.1	88.13
Mean			86.75

Table (4): Comparison of some previous analytical methods developed for determination of methamphetamine.

Sample type	Technique	Derivative	LOD (µg/ml)	LOQ (µg/ml)	References
Meth tablet (yaba)	Built -in digital camera of iPhone 4.0	Sodium nitroprusside & acetaldehyde	11	44	[15]
Meth tablet (yaba)	Built -in digital camera of iPhone 4.0	Sodium nitroprusside & acetaldehyde	207 to 590	-----	[16]
Amphetamine street sample	Built -in digital camera of iPhone 4.0	Sodium nitroprusside& acetaldehyde	1010	1010	[22]
Ecstasy tablet	UV-Vis Spectrophotometer	With out	21.99	66.66	[8]
Urine	HPLC -fluorescence detection	9-fluorenylmethyl chloroformate	0.015	0.05	[23]
Urine	GC- mass spectrometry	Without	0.36	1.09	[24]
Urine	GC-mass spectrometry	Dimethylformamide	0.007	0.023	[25]
Odor-adsorbent material	HPLC-ultraviolet detector	Without	1	3	[26]
Manufactured Meth sample	UV-Vis Spectrophotometer	Without	50	50	[27]
Urine	UV-Vis Spectrophotometer	Sodium nitroprusside & acetaldehyde	0.5	1	current

4. Conclusions

In the present reported method, the drug methamphetamine was estimated in spiked urine samples then applied on patients samples after preliminary tests use of rapid screening immunoassay for amphetamine for minimizing number of suspected samples. The linearity of the proposed method was good from the result of correlation coefficient. The developed method is simple, specific, accurate, precise and reproducible. Specificity and selectivity, LOD, LOQ, molar absorptivity and Sandell's sensitivity values indicate that the proposed analytical method can be successfully utilized for the estimation of methamphetamine in biological fluid samples.

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