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Different analytical methods for the determination of metronidazole –A review

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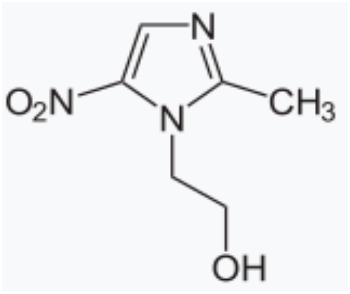
Abstract

Metronidazole is available in most areas of the world and is often used for treating bacterial infections in various parts of human body including the liver, brain, joints, vagina, skin, heart, respiratory tract, and stomach or intestines. Therefore, it is essential to develop simple and low-cost analytical methods for such a compound in order to advance quality control. In this paper, various analytical papers that identify metronidazole in commercial preparations and biological samples have been analyzed and reviewed. The reviewed literature included spectrophotometric, chromatography, and ion selective electrodes. ©2020 ijrei.com. All rights reserved

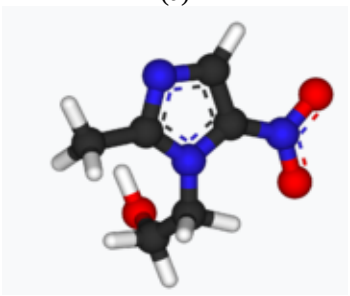
Keywords: Metronidazole, ISE, HPLC, Spectrophotometric

1. Introduction

Metronidazole is a 5-nitronimidazole derivative and is widely used for treating bacterial infections due to it's effectively towards anaerobic bacteria and anaerobic protozoa [2]. Topical metronidazole (Metrogel) is used to treat a skin condition known as rosacea. Its gel form is often used to treat vaginal bacterial infections [1]. It has the formula C6H9N3O3, shown in figure [1], and a molecular weight of 171.156 g·mol−1. Its chemical structure is [2- (2- methyl - 5 -nitroimidazole-1-yl) ethanol]. Metronidazole has a slight odor and is available in the form of crystalline powder of a light yellow to white color **[**1**]**. Several analytical methods were conducted by scholars to determine metronidazole. These methods included: Concentration range, limit of detection, recovery, life time, and type of column, mobile phase, slope, retention time, reduction peak current and the range of PH for metronidazole. The results of reviewing these methods in this study were listed in tables 1, 2, 3. In addition, there were other analytical methods for the determination of metronidazole, such as: Photo-Fenton Oxidation Technology [3], and Charge-Transfer Complexes Formation [4].



(a)



(b)

Figure 1: (a) 2D chemical structures of Metronidazole, (b) 3D chemical structures of Metronidazole.

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Table 1: Ion Selective Electrodes for Determination of Metronidazole.

Type of Ion pair for Electrodes	Results	Ref.
Electrochemical ultrasensitive sensor using carbonnano, multi-walled polydopamine/carboxylic - tubes (MWCNTs_COOH) nano composites using improved (GCE) glassy carbon electrode.	**Conc. Range:** 5 to5000 µ mol /dm^3. **Detection limit:** (S/N = 3)0.25 µmol / dm^3. **pH:** 5.0 to11.0. **Reduction peak current:** remained 95.2% of its initial value. **Recovery:** Between 93.4% and 118.3%. **Life time:**1 month.	[5]
(MNZ) metronidazole based on 1-butyl-3-methylimidazolium tetrafluoroborate as (IL) ionic liquid and (SWCNT) single walled carbon nanotube. Using IL in the paste, as a binder, increased the electrode response.	**Conc. Range:** Between 5.00×10^{-5} and 5.00×10^{-3} (mgL^{-1}). **Detection limit:** 1.238×10^{-5} (mgL^{-1}). **pH:** 2.0 to 10.0. **Reduction peak current:** –0.7 ± 0.05 V. **Recovery:** 90.33–108.0 %.	[6]
Quantitative and simultaneous (MT) metronidazole detection utilizing (PCHAGCE); (chromotrope 2B) poly, modified, activated glassy carbon electrode	**Conc. Range:** 1.0×10^{-5}- 4×10^{-4} mol/L. **Detection limit:** (S/N = 3) 3.3×10^{-7} mol/L. **pH:** 4.0-9.0. **Reduction peak current:** -0.58 V. **Recovery:** 99.0-103.0%. **Life time:** 2 weeks.	[7]
A sensor of amperometric metronidazole (MTZ) utilizing a recognition element (glycosylated metalloporphyrin) combined with a carbon paste electrode. For the preparation of a MTZ - sensitive active material, 5, 10, 15, 20 - tetrakis [2- (2, 3, 4, 6 - tetraacetyl - β - D -glucopyranosyl) - 1 - O - phenyl] porphyrin (T (*o*glu) PPH2) and its Mn (III) complex, MnT (*o*-glu) PPCl .	**Conc. Range:** From 2.9×10^{-3} to 5.8×10^{-8} (M/L). **Detection limit:** 5.8×10^{-8} (M/L). **pH:** 4.3. **Reduction peak current:** - 408 mV. **Life time:** 2 months.	[8]

Table 2: HPLC for determination of Metronidazole.

Methods	Results	Ref.
HPLC	**Column:** Eclipse XDB-phenyl column. **Mobil Phase:** (75:25:1, v/v/v) Sodium acetate (0.05 M): acetonitrile: glacial acetic acid, using phosphoric acid to adjust the pH ed to 4.0. **Detector:** UV detector, **λ:** 320nm. **Conc. range:**0.05 – 30µg/ml. **LOQ:** 0.05µg/ml. **t_R:** 4.06min.	[9]
RP-HPLC	**Column:** Column (C18,0.5µm), Shimadzu LC-10ATvp (HPLC), particle size (150×4.6mm). **Mobil Phase:** de-ionized water and HPLC grade methanol were mixed (ratio of 650:400 ml), using phosphoric acid to adjust the pH to 2.5. Using vacuum filtration unit, a 0.45 µ membrane was utilized to filter the mobile phase. Then, ultrasonic bath was used for degassing for 15 min. **Detector:** UV detector, **λ:** 254 nm. **Conc range:** 10-1000 µg/ml. **LOD:** 0.0158 µg ml^{-1}. **t_R:** 7.751±0.00025 min.	[10]
RP-HPLC	**Column:** (250 × 4.6mm) column, LiChrosorb® RP-18, packed with (5-µm) octadecylsilyl silica gel. **Mobil Phase:** A solution of (0.02:20:80 v/v/v) triethylamine, acetonitrile, and 0.3% o-phosphoric acid. **Detector:** ShimadzuSPD-20A ultraviolet-visible (UV/VIS) detector, **λ:** 290 nm. **Conc range:** 12.5 to 100.0 µg/ml. **LOD:** 0.125 µg/ml. **t_R:** 3.42 min.	[11]
RP-HPLC-DAD	**Column:** L-2300 column oven, prepared with a 250 × 4.6 mm2 (i.d.), ODS column (5µm). **Mobil Phase:** Phosphate buffer **(**50mM) adjusted with 1M HCl to a (4.27 ± 0.01) pH as mobile phase A-methanol. **Detector:** UV detector, **λ:** 242 nm. **Conc range:** 1-20 µg/ml. **LOD:** 0.02 µg/ml. **t_R:** 4.5min.	[12]

RP-HPLC	**Column:** 250 x 4.6 mm, 5 µ (Phenyl column). **Mobil Phase:** Instead of (ACN) Acetonitrile, Propylene Carbonate:Methanol 60:40 (Solvent-X) was used. **Detector:** UV-Vis detector. **λ:** 310 nm. **Conc range:** 1.0–2.4µg/ mL. **LOD:** 15ng/ml. **t_R:**5.2 min.	[13]
RP-HPLC	**Column:** (4.6 x150mm), particle size (5µ) (C-18 column), Water's X-bridge. **Mobil Phase:** a mixture of acetonitrile and phosphate buffer (pH 2.5) in (70:30, %v/v) ratio. **Detector:** UV detector. **λ:** 220nm. **Conc range:** 10-30µg/mL. **LOD:** 0.042µg/mL. **.t_R:** 3.157 min.	[14]
RP-HPLC	**Column:** The performance of isocratic elution on a (100mm×4.6 mm) Whatman® Partisil 5 ODS-3 column, (RP) plus Whatman® guard cartridge, particle size (5_m). **Mobil Phase:** Degassing and filtering of (0.45_m; Millipore) solution mixture of phosphate buffer. A pH of (4.7; 0.05 M) - methanol (95:5, v/v). The pH was adjusted to (4.0). **Detector:** UV detector. **λ:**254nm. **Conc range:** 0.13 and 300 µg/mL. **LOD:**0.1 µg/mL **t_R:**6.8 min.	[15]
HPLC	**Column:** *C8 ODS (250X4.6mm) column*. **Mobil Phase:** 200ml methanol, 300ml acetonitrile, 100ml THF, and (1.56gms/liter K2HPO4) 400 ml water. **Detector:** UV detector. **λ:** *254nm*. **Conc range:** (60-100) ppm. **LOD:** 0.1 ppm. **t_R:** 3.14 min.	[16]

Table 3: Spectrophotometric methods for determination of Metronidazole

Methods	Results	Ref.
Two Spectrophoto-metric methods	**Sample:** metronidazole. **Conc range:** 5-55 µg/ml and 5-60 µg/ml**.** **Slope:** 0.0228 and 0.0174. **r^2:** 0.9996 and 0.9997**.** **%Re:** 99.15 and 99.54. **λ_{max}:** 510 nm and 480.	[17]
Spectrophoto-metric	**Sample:** metronidazole. **Conc range:** 2.0-40.0 µg/mL. **Slope:** 4.38×10^{-2}. **r^2:**0.9988. **LOD:** 0.76 µg/mL, **λ_{max}:** 326 nm.	[18]
UV Spectrophoto-metric	**Sample:** metronidazole. **Conc range:** 2-20 µg/ml. **r^2:**0.998. **%Re:** 98-102%. **LOD:** 0.763µg/ml. **λ_{max}:** 320 nm.	[19]
UV Spectrophoto-metric	**Sample:** metronidazole. **Conc range:** 2-10µg/ml. **r^2:** 0.9987. **%Re:** 102.459, **λ_{max}:** 277nm.	[20]
UV Differential Spectrophoto-metric	**Sample:** metronidazole. **Conc range:** 2-14µg/mL. **r^2:**0.999**.** **%Re:** 99.93. **LOD:** 0.15µg/ml, **λ_{max}:** 324 nm.	[21]

Novel UV spectrophoto-meter	**Sample:** metronidazole and furazolidone. **Conc range:** between 10 to 50 µg/mL, and between 5 to 25 µg/mL. **r ^{2}:** 0.9992, 0.9996. **%Re:** 98.16 and 98.44. **Slope:** 0.0277 and 0.0600**.** **LOD:** 0.323 µg/ml, 0.443 µg/ml. **λ_{max}:** 319 and 364 nm**.**	[22]
UV-visible Spectrophoto-metric	**Sample:** metronidazole. **Conc range:** 1 to 15µg/ml. **r ^{2}:** 0.9994. **%Re:** 98.80. **LOD:** 0.4277 µg/ml**.** **λ_{max}:** 320 nm.	[23]
Extractional spectrophoto-metric	**Sample:** metronidazole. Tinidazole, ornidazole and secnidazole. **Conc range:** 2.50–22.50, 2.50–30, 7.50–35 and 5–30 µgml^{-1}. **Slope:** 3.15×10^{-2} ,4.56×10^{-2}, 5.14×10^{-2} and 4.66×10^{-2}. **r ^{2}:** 0.9995, 0.9995, 0.9995 and 0.9996. **LOD:** 5.33×10^{-2}, 5.16×10^{-2}, 5.01×10^{-2} and 4.67×10^{-2} µg/ml. **λ_{max}:** 419, 418, 420 and 416 nm.	[24]

2. Conclusions

In tables 1, 2, and 3, a variety of theoretical studies of three analytical methods for calculating metronidazole were included. It turns out from reviewing these studies that, the best way to calculate metronidazole is (HPLC) high performance liquid chromatography. This method gave a wide range of concentrations that were specified in ng/ml and µg/ml, as well as low detection limit plus the most commonly used solvents are acetonitrile and methanol. As for spectrophotometric and ion selective electrodes, these methods are low cost considering quality control analysis compounds in pharmaceutical preparations. In addition, they are easy to use in terms of their application in calculating metronidazole in pharmaceutical samples.

References

[1] British pharmacopoeia; "Medicinal and Pharmaceutical Substances," published by The Stationery Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA); Vol. 1 & 2; pp. 1406-1407; 2014.

[2] Lamp, Kenneth C., Freeman CD, Klutmam NE. "Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials." Clinical pharmacokinetics 36.5 (1999): 353-373.

[3] Shemer, Hilla, Yasemin Kaçar Kunukcu, and Karl G. Linden. "Degradation of the pharmaceutical metronidazole via UV, Fenton and photo-Fenton processes." Chemosphere 63.2 (2006): 269-276.

[4] Adegoke, O. A., O. E. Umoh, and J. O. Soyinka. "Spectrophotometric determination of metronidazole and tinidazole via charge transfer complexation using chloranilic acid." Journal of the Iranian Chemical Society 7.2 (2010): 359-370.

[5] Tursynbolat, Satar, Yrysgul Bakytkarim, Jianzhi Huang, Lishi Wang. "Ultrasensitive electrochemical determination of metronidazole based on polydopamine/carboxylic multi-walled carbon nanotubes nanocomposites modified GCE." Journal of pharmaceutical analysis 8.2 (2018): 124-130.

[6] Saghravanian, Maliheh, Mahmoud Ebrahimia, Zarrin Es'haghib, and S. Ali Beyramabadia. "Experimental sensing and density functional theory study of an ionic liquid mediated carbon nanotube modified carbon-paste electrode for electrochemical detection of metronidazole." South African Journal of Chemistry 70 (2017): 29-37.

[7] Li, Xiaobo, and Guangri Xu. "Simultaneous determination of ranitidine and metronidazole in pharmaceutical formulations at poly (chromotrope 2B) modified activated glassy carbon electrodes." Journal of food and drug analysis 22.3 (2014): 345-349.

[8] Gong, Fu-Chun, Xiao-Bing Zhang, Can-Cheng Guo, Guo-Li Shen and Ru-Qin Yu. "Amperometric metronidazole sensor based on the super molecular recognition by metalloporphyrin incorporated in carbon paste electrode." Sensors 3.4 (2003): 91-100.

[9] Ezzeldin, Essam, and Toqa M. El-Nahhas. "New analytical method for the determination of metronidazole in human plasma: application to bioequivalence study." Tropical Journal of Pharmaceutical Research 11.5 (2012): 799-805.

[10] Hussain, Shafique, and Muhammad Tayyab Ansari. "Quantitation of metronidazole in pharmaceutical suspension using high performance liquid chromatographic method." Pakistan Journal of Zoology 43.5 (2011).

[11] Maslarska, Vania, Boyka Tsvetkova, Lily Peikova, Stanislav Bozhanov. "RP-HPLC Method for Simultaneous Determination of Metronidazole and Ofloxacin in Synthetic Mixture." CBU International Conference Proceedings. Vol. 4. 2016.

[12] Elkhoudary, Mahmoud M., Randa A. Abdel Salam, and Ghada M. Hadad. "Development and optimization of HPLC analysis of metronidazole, diloxanide, spiramycin and cliquinol in pharmaceutical dosage forms using experimental design." Journal of chromatographic science 54.10 (2016): 1701-1712.

[13] Verma, Pratibha, Varsha Namboodiry, Soni Mishra, Ashok Bhagwat, Suvarna Bhoir "A stability indicating HPLC method for the determination of metronidazole using ecofriendly solvent as mobile phase component." Int J Pharm Pharm Sci 5 (2013): 496-501.

[14] Sivannarayana, P., and K. Rambabu. "Simultaneous assay of mupirocin and metronidazole in formulations using reverse phase-high performance liquid chromatography." International Journal of Bioassays 5.12 (2016): 5151-5155.

[15] Tavakoli, Naser, et al. "Development and validation of a simple HPLC method for simultaneous in vitro determination of amoxicillin and metronidazole at single wavelength." Journal of pharmaceutical and biomedical analysis 43.1 (2007): 325-329.

[16] Nandini R. Pai, and Deeptaunshu Atul Pusalkar. "Development and validation of liquid chromatographic method for Metronidazole." Der Pharmacia Sinica 5.1 (2014): 23-28.

[17] Thulasamma, P., and P. Venkateswarlu. "Spectrophotometric method for the determination of metronidazole in pharmaceutical pure and dosage forms." Rasayan J. Chem 2.4 (2009): 865-868.

[18] Nagwa A H.S. Ahmida, MOona A. Esmael, Eman A. Winse, N. El-Enany, and F. Belal. "Difference Spectrophotometric Method for the Determination of Metronidazole in Tablets." Asian Journal of Chemistry 21.1 (2009):755-762.

[19] Swetha Santhoshi Palla, Suresh T, D Sireesha, B Vasudha. "Development and Validation of UV Spectrophotometric Method for Estimation of Metronidazole in Tablet Dosage Form." International Journal of Pharma Research and Health Sciences 4.1 (2016): 968-971.

[20] Das, Joyani, and Manabendra Dhua. "UV-spectrophotometric assay method

development and validation of metronidazole in bulk and tablet formulation." J of Pharm Sci Tech 3 (2014): 109.

[21] Mastanamma, S. K., K. Sravani, and T. Anil. "UV differential spectrophotometric method for the estimation of metronidazole in bulk and pharmaceutical formulation." Rasayan J. Chem 8.3 (2015): 303-309.

[22] Jain, Ruchi, et al. "Novel UV spectrophotometer methods for quantitative estimation of metronidazole and furazolidone using mixed hydrotropy solubilization." Arabian Journal of Chemistry 10.2 (2017): 151-156.

[23] Sampson Opoku, Isaac Ayensu, Abena Amponsaa Brobbey, Kofi Aryee Adjavon. "Metronidazole Analysis: Method Development and Validation via Hydrotropic Solubilization." Human 12.4 (2018): 1-13.

[24] Darwish, Khaled M., Ismail Salama, Samia Mostafa, and Mohamed El-Sadek. "Extractional spectrophotometric analysis of metronidazole, tinidazole, ornidazole and secnidazole bases through acid-dye complexation using bromothymol blue dye." Pakistan journal of pharmaceutical sciences 25.1 (2012).

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