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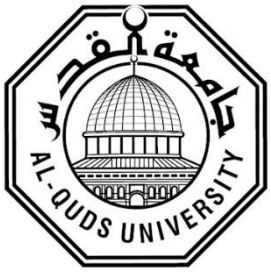

A new approach to Drug Delivery Using the E-Cigarette

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M.Sc. Thesis

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Dedication

I dedicate this thesis...

To my dear mom and dad

To my beloved husband, to my dear children, and to my brothers and sisters

To my beloved family big and small who supported and encouraged me through all the stages.

To my friends, my colleagues

To everyone who helped me complete this study

With respect and love.

Declaration

I certify that this thesis submitted for the degree of master in health policy and management, is the result of my own research, except where otherwise acknowledged, and that this thesis (or any part of the same material) has not been submitted for a higher degree to any other university or institution.

Signed Hadeel.Ik

Prepared by: Hadeel Ikbariah

Date: 06/05/2023

Acknowledgment

First, I thank God for helping me during my studies and completing this study. I would like to express my gratitude and appreciation to everyone who contributed to the success of this study.

Many thanks to my supervisor, Dr. Fuad Al-Rimawi, who guided me and gave his time until the completion of this study. For me, you are a leader, advisor, teacher, supervisor, and role model. Thank you very much.

Many thanks to Mr. Ibarhim Ayyad who gave me his great time and helped me collect the required samples. Really you are an asset to the university and the students.

and I sincerely hope that this study will be useful and informative for policy makers and strategic planners to pursue oral programs even though it would be impossible to name all of the individuals and events that contribute to the success of this thesis and the achievement of impressive knowledge and experience. I am very grateful to all who contributed to completing this study and helped make this happen

Search is possible.

Finally, my warm appreciation to my family, respectful parents, and siblings who have continuously supported me throughout my educational journey, what a treat it has been. I also wish a special thanks to my friends - for their supportive role and patient attitude, it was most welcome.

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Abstract

This study aimed to explore the potential use of e-cigarettes as a delivery method for the drug apomorphine, which is commonly used to treat patients with Parkinson's disease. The traditional method of administering apomorphine is through subcutaneous injection, which can be painful and difficult for patients. Therefore, finding alternative methods of delivering the drug is essential. In this study, a vacuum system was used to mimic inhalation and measure the concentration of apomorphine in the inhaled vapor. The drug mixture was prepared by dissolving apomorphine in methanol and then mixing it with E-liquid. HPLC analysis was conducted on cotton soaked with the collected vapor to determine the apomorphine concentration. Results showed that the concentration of apomorphine in the vapor increased with the number of inhalations and with increasing concentrations of apomorphine in the E-liquid. These findings suggest that e-cigarettes could be a promising alternative method for delivering apomorphine and other pharmaceutical drugs. Further research is necessary to explore the potential clinical applications of this approach.

Chapter one

Introduction

Parkinson's disease is a degenerative neurological disorder that affects millions of people worldwide. One of the primary symptoms of Parkinson's disease is a loss of dopamine in the brain, which leads to tremors, stiffness, and difficulty with movement. [1]
Apomorphine is a dopamine-receptor agonist that acts on the same receptors as dopamine, making it an effective treatment for Parkinson's disease. However, the current method of delivering apomorphine, subcutaneous injection, is painful, inconvenient, and difficult for patients. [2]

Recently, e-cigarettes have gained popularity as an alternative to traditional tobacco smoking. E-cigarettes are devices that vaporize a liquid (E-Liquid) containing nicotine, which can be inhaled by the user. The idea of e-cigarettes came from delivering nicotine to the smoker without the harmful chemicals present in tobacco smoking.

This thesis represents a step towards a new approach to drug delivery that can improve the lives of patients with Parkinson's disease and other conditions. By exploring the potential of e-cigarettes as a drug delivery device, we hope to provide a safer, more comfortable, and more efficient method of administering apomorphine and other pharmaceuticals.

In this thesis, we explore a new approach to drug delivery using the e-cigarette, with a particular focus on using e-cigarettes as a delivery method for apomorphine in patients with Parkinson's disease. By utilizing the e-cigarette as a drug delivery device, we aim to provide a more comfortable and efficient method of administering apomorphine, ultimately improving the quality of life for patients with Parkinson's disease.

The primary objective of this thesis is to investigate the feasibility and efficacy of using e-cigarettes asadelivery method for apomorphine. Additionally, we seek to contribute to the growing body of research on the potential uses of e-cigarettes as adrug delivery device for various pharmaceuticals.

1.1 Electronic Cigarette

The E- Cigarette was developed as a substitute for Tobacco smoking in order to reduce its harmful effects. Tobacco smoking involves inhaling burned tobacco leaves, which releases a combination of chemicals, including Nicotine, that the smoker craves [3].

The concept of E-cigarettes arose from the need to provide smokers with a source of Nicotine that contains fewer harmful substances than traditional tobacco smoking. There are several differences between tobacco smoking and E-cigarette smoking, including the contents of the smoke and the harm they cause to the human body. Through examining these differences, they can evaluate the advantages and disadvantages of using E-cigarettes as a substitute for tobacco smoking [4].

1.1.1 Composition of tobacco smoke and e-cigarette Aerosol

The Electronic Cigarette (E-Cigarette) is a device that allows the user to inhale nicotine without the harmful effects of tobacco combustion. Unlike traditional cigarettes, which release numerous harmful substances through the burning of tobacco, the liquid used in E-cigarettes typically contains propylene glycol, glycerine, nicotine, and flavorings [5].

A cigarette is a type of tobacco product that typically consists of tobacco leaves wrapped in a thin tissue paper. When a smoker inhales smoke from a cigarette, the tobacco is burned, releasing a mixture of approximately four thousand chemical substances. These chemicals include benzopyrene, tarry substances, carbon monoxide, acetone, butane, vinyl chloride, ammonia, arsenic, toluidine, formaldehyde, phenols, hydrocyanic acid, naphthylamine, carbinol, 2-benzoacridine, dichlorodiphenyltrichloroethane, dimethyl nitrosamine, cadmium, and urethane [5,6].

The harmful effects of these chemicals on the human body are well documented, and they can lead to a wide range of health problems, including respiratory issues, cardiovascular disease, and cancer. It is clear that smoking cigarettes poses a significant risk to the health of smokers and those around them. [7].

The lack of tobacco combustion in E-cigarettes is a significant advantage over traditional cigarettes, as it reduces the number of harmful chemicals that the smoker is exposed to. However, it is important to note that E-cigarettes are not completely without risk, as the long-term effects of inhaling the chemicals present in E-cigarette liquid are not yet fully understood [8].

The process of using an E-Cigarette involves heating the liquid to a temperature that allows it to transition from a liquid to a gaseous phase, which can then be inhaled into the lungs. While trace amounts of toxic substances have been found in E-cigarette vapors, the levels of these toxicants are typically 9-450 times lower than those found in normal cigarette smoke and do not exceed the authorized levels for use. These toxicants may originate from contaminated tobacco that was used in the production of nicotine for use in E-cigarettes [9,10].

1.1.2 Cigarette smoke and e-cigarette aerosol: harmfulness to health

The harmful effects of smoking are widely recognized and the addiction has been linked to numerous fatal diseases. Millions of people have had their lives cut short by smoking, and it can also lead to a loss of productivity and generate significant direct and indirect costs. In fact, tobacco has been responsible for more deaths than any war in the 20th century. The popularity of tobacco smoking has also led to a dramatic increase in the prevalence of cancer, with at least 40 different components of tobacco smoke contributing to the development of malignant tumors [11,12].

The devastating effects of smoking on health are clear, and efforts to reduce smoking rates and promote healthier alternatives such as E-cigarettes are important for improving public health [13].

Extensive research has demonstrated the negative effects of nicotine on health, particularly in relation to the development of leukemia and cancer in various organs throughout the body. Smoking is particularly damaging to organs such as the lungs, larynx, throat, esophagus, stomach, kidney, urinary bladder, pancreas, liver, nose, and uterine cervix, and has been linked to the development of cancer in these areas [14,15].

The popularity of tobacco smoking has had a significant impact on public health, with lung cancer being one of the most frequent and deadliest forms of cancer. In fact, lung cancer is responsible for approximately 30% of all cancer deaths [16]. This is due in large part to the numerous harmful chemicals found in cigarette smoke, many of which have been linked to the development of malignant cancer.

In addition to its carcinogenic effects, tobacco smoking also has numerous negative impacts on respiratory health. Chronic bronchitis, chronic obstructive pulmonary disease (COPD), emphysema, and bronchial asthma are just a few of the respiratory conditions that have been linked to tobacco smoking [17,18].

Furthermore, cigarette smoke has been shown to have significant negative effects on the cardiovascular system, including the development of atherosclerosis, arterial hypertension, ischemic heart disease, myocardial infarction, and aortic aneurysm. Additionally, smoking has been linked to a range of diseases of the nervous system, such as cerebral stroke, cerebral thrombosis, and subarachnoid hemorrhage [19,20,21].

In addition to its deadly impact on the human body, cigarette smoking also weakens the immune system, making individuals more susceptible to bacterial and viral infections, such as tuberculosis. Shockingly, cigarette smoking is responsible for more than 4 million deaths annually. [22,23]

Research has demonstrated that tobacco smoking has a negative impact on the development of diseases of the alimentary tract. These include chronic gastric and duodenal ulcer disease, gastroesophageal reflux, Lesniowski-Crohn disease, ulcerating inflammation of the large intestine, and intestinal hernia. [24,25,26]

In addition to its carcinogenic effects, tobacco smoking has been associated with the development of several other health problems. These include osteoporosis, parodontopathy, cataract, macular degeneration, and premature skin aging. Furthermore, cigarette smoking has been shown to have a negative impact on the reproductive system, increasing the risk of small birth weight in newborns, premature detachment of the placenta or rupture of the membranes, difficulty in becoming pregnant, and early onset of menopause. These adverse effects on reproductive health are particularly concerning and highlight the need for individuals to quit smoking in order to improve their overall health and well-being. [27,28,29].

E-cigarettes, in comparison to traditional tobacco smoking, are often considered to be a safer alternative due to the limited number of harmful substances they contain. The main harmful substance in tobacco is nicotine, which is known to have negative effects on the cardiovascular system. Nicotine causes blood vessels to constrict, increases blood pressure, raises heart rate, and increases the risk of blood clots. [30,31].

In addition, nicotine is a potent neurotoxin and may indirectly impact the growth of tumors by affecting the p53 gene, which inhibits uncontrolled proliferation of neoplastic cells. [32,33].

In summary, the negative impact of tobacco smoke on health far surpasses that of e-cigarette aerosol. Research has shown that e-cigarette aerosol results in significantly less cytotoxicity than tobacco smoke. [34].

While flavorings in e-cigarettes are considered safe when used in food products, there are concerns about their potential toxicity when inhaled. For example, benzaldehyde, a common ingredient in natural fruit flavors, has been found to cause respiratory irritation in animals and in occupational exposure studies. [35,36].

These findings underscore the far-reaching and damaging impact that tobacco smoking can have on overall health, beyond just its carcinogenic effects. It is clear that reducing or eliminating tobacco smoking should be a priority for public health efforts worldwide. While E-cigarettes may offer a potential alternative to traditional tobacco smoking, it is important to remember that their long-term health impacts are not yet fully understood, and more research is needed to fully assess their risks and benefits.

1.1.3 The principle of relying on E-cigarettes as a substitute of tobacco smoking

The principle of the lesser of two evils is based on the idea of using e-cigarettes as a replacement for traditional tobacco smoking, as nicotine is the addictive component in cigarettes despite its harmful effects. E-cigarettes were developed to deliver nicotine to the user without the many harmful chemicals present in tobacco smoke. [37]

1.1.4 The use of E-cigarette as a way of treatment of nicotine dependence

E-cigarettes are being considered as a potential option for nicotine replacement therapy due to their popularity, extensive research, and 25-year history of use in pharmacological treatment of tobacco dependence. [38]

To clarify, the use of E-cigarettes as a form of nicotine replacement therapy involves replacing the nicotine found in tobacco smoke with nicotine from e-cigarettes to help manage cravings during smoking cessation. The idea is to gradually reduce nicotine intake over time until the user can quit smoking altogether. [38]

Marketing information often highlights the potential of E-cigarettes to aid in smoking cessation or reduction, but the scientific evidence supporting this claim is limited and mixed, as indicated by several studies. [38,39,40].

One survey conducted in Poland also found that the use of e-cigarettes helped smokers to reduce the number of traditional cigarettes they smoked on a daily basis. The study conducted in Poland involved approximately 200 participants, of whom 66% reported quitting smoking altogether and 25% reported smoking less than 5 cigarettes per day after switching to e-cigarettes. [41].

The data obtained from previous studies are not substantial enough for the FDA (U.S. Food and Drug Administration) to recommend e-cigarettes as a nicotine replacement therapy. Studies consisting of randomized controlled trials and multiple cohort studies have shown varying associations between e-cigarette use and cessation rates. [42]

The objective of this work is therefore to use E-Cigarette as a new approach for delivery of Apomorphine to patients with Parkinson's disease.

1.1.5 Parts and the principle of action of the E-Cigarette

E-cigarettes work by vaporizing liquid nicotine, which is then inhaled by the user along with various flavors. These flavorings can simulate the experience of smoking traditional cigarettes, and some e-cigarette liquids offer a wide range of flavors, including fruit and mint [43].

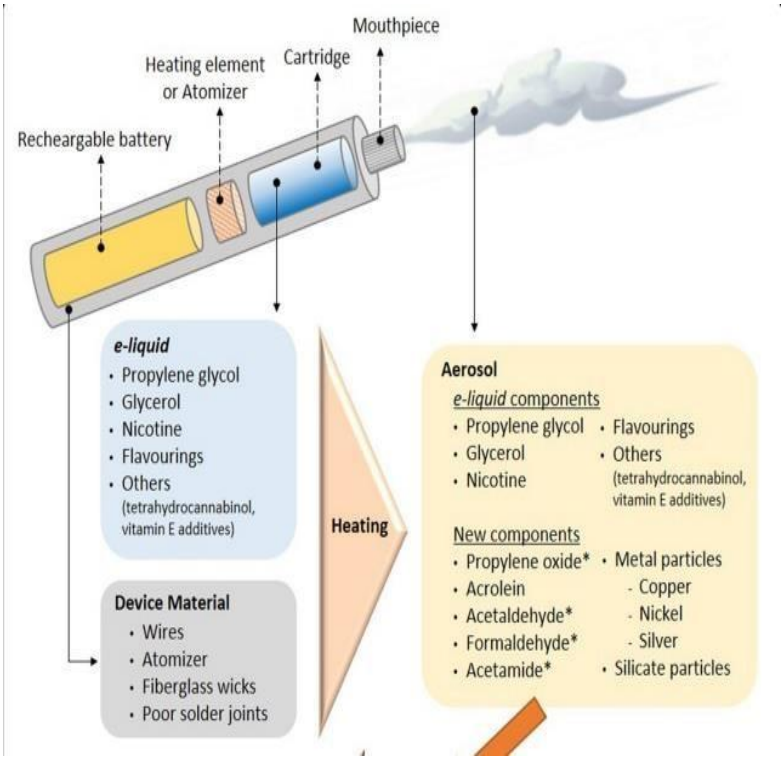


Figure 1: components of E-cigarette [44]

The classic e-cigarette comprises three The basic comonents of E-cigarette include a battery, an evaporator, and a liquid container. The battery serves as a power source to the evaporator, which is composed of a heater and a container for the liquid. [45]

primary components: the battery, the evaporator, and the microchip. The battery provides the power source, while the evaporator, made up of a heater and a liquid container, generates the smoke through liquid nicotine evaporation. The microchip regulates the energy transfer, preventing the battery from overheating and controlling device operations. E-cigarettes can be operated either automatically, with an airflow sensor, or manually, by pressing a button. Moreover, these devices have additional features such as a battery status indicator, usually through a multicolor diode, and a device lock. [46]

The "click" system is a safety feature that is activated by pressing the battery button several times in quick succession, which activates the device lock. This ensures that brand-name e-cigarettes with their relatively complex design are generally safe for users. In addition to this safety feature, e-cigarettes also have a microchip that controls energy transfer, preventing the battery from overheating due to frequent use. The battery status indicator is another function that allows users to monitor the battery level of the device. Overall, the safety features of e-cigarettes make them a viable alternative to traditional cigarettes for those looking to quit smoking. [46]

1.2 Apomorphine

1.2.1 Background about Apomorphine

The primary source of apomorphine is through pharmaceutical companies that manufacture the drug for medical use. It is not available over-the-counter and can only be obtained with a prescription from a licensed healthcare provider. [47]

During the nineteenth century, Apomorphine was initially employed for treating behavioral issues in domesticated farm animals, and it continues to be utilized in veterinary medicine. It has had a chequered history in medical therapeutics, being successfully recommended as an emetic, a sedative, a treatment for narcotic and alcohol dependence and most recently for sexual dysfunction and impotence. It was first proposed as a treatment for movement disorders 150 years ago, but this indication was not pursued until the 1950s when Schwab in Boston confirmed its potential. [48]

Apomorphine is usually administered subcutaneously, but it can also be given by injection, infusion, or inhalation. It is not given orally because of its low bioavailability. When taken orally, the drug is rapidly metabolized by the liver, resulting in poor absorption and a low therapeutic effect. [49]

Apomorphine is synthesized from a precursor chemical called apocodeine. The synthesis involves a series of chemical reactions, including reduction, oxidation, and cyclization. The process yields a white crystalline powder that is highly soluble in water. [50]

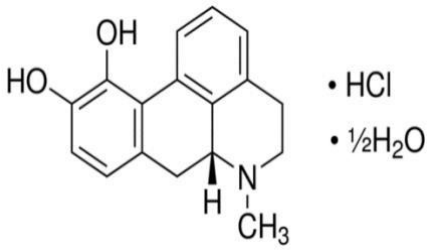
Like all medications, apomorphine has potential side effects. The most common side effects include nausea, vomiting, dizziness, and headache. These side effects are usually mild and resolve on their own, but in some cases, they can be severe and require medical attention. Other possible side effects of apomorphine include orthostatic hypotension, hallucinations, confusion, and sleepiness. [50]

George Cotzias conducted experiments with apomorphine in the 1970s after discovering that large doses of dopa improved Parkinson's disease. Cotzias was looking for other dopamine analogues that might have complementary effects. He carried out a series of scrupulous and fascinating experiments with apomorphine. [51]

1.2.2 Use of Apomorphine in Parkinson's disease

Studies have shown that apomorphine, when given through subcutaneous injection, is highly effective but short-lived. This drug is commonly used to treat "off" episodes in Parkinson's disease, and is administered by injection in a hospital or specialist clinic. Some of the main side effects include nausea, drowsiness, and reactions at the injection site. [52]

Apomorphine is a medication that acts on the same receptors as dopamine, making it a dopamine-receptor agonist. It is used to treat the "on-off effect" that some people with Parkinson's disease experience in later stages, where they can alternate between being able to move freely and having difficulty moving. Apomorphine can reverse these "off" episodes, but the effect lasts only about an hour. It is administered by subcutaneous injection, which may require frequent dosing, or as a continuous infusion using a cannula inserted under the skin. The main side effects include nausea, drowsiness, and injection site reactions. [53].



Molecular Formula $C_{17}H_{17}NO_2$ HCl · $1/2H_2$
Molecular Weight 312.79
color white to gray
Figure 2: Structure of apomorphine Hydrochloride Hemihydrate

Table 1: Information about Apomorphine medicine.

Type of medicine	Dopamine-receptor agonist
Used for	Parkinson's disease
Available as	Injection, pen injector, or pre-filled syringe

Parkinson's disease is a disorder of the brain. A small part of the brain, called the substantia nigra, is mainly affected. This area of the brain sends messages down nerves to control the muscles of your body. Messages are passed between brain cells, nerves and muscles by chemicals called neurotransmitters. Dopamine is the main neurotransmitter made by the brain cells in the substantia nigra. [54]

In Parkinson's disease, there is damage to some of the cells in the substantia nigra region of the brain, and as more cells become damaged over time, the amount of dopamine produced is reduced. This results in a low level of dopamine in the brain, which affects the messages that control muscles, causing them to become slowed and abnormal. This leads to the characteristic symptoms of Parkinson's disease, such as tremors, stiffness, and slow movement. [55]

1.3 Motivation for the study

The motivation for this study is to find an alternative and more convenient method for delivering Apomorphine to patients with Parkinson's disease. The current method of subcutaneous injection is difficult, painful, and inconvenient for patients.

By utilizing the e-cigarette as a drug delivery device, this study aims to provide a more comfortable and efficient method of administering the drug, ultimately improving the quality of life for patients with Parkinson's disease.

Additionally, this study seeks to contribute to the growing body of research on the potential uses of e-cigarettes as a drug delivery device for various pharmaceuticals.

1.4 Thesis Problem

Apomorphine is given by a subcutaneousn injection under the skin on lower abdomen or on the outer part of a thigh. This method to give this medicine is difficult and painful and inconvenient for the patient.

1.5 Thesis Objectives

The main objectives of my thesis is to find a new approach for delivery of Apomorphine to patients with Parkinson's disease by using E-Cigarette.

Chapter Two

2.Literature Review

The concept of using e-cigarettes for drug delivery has been a topic of interest for researchers for some time. E-cigarettes have been marketed as a safer alternative to traditional cigarettes, as they do not involve burning tobacco, but instead, vaporize a liquid that typically contains nicotine, flavorings, and other additives. However, some researchers have raised concerns that e-cigarettes may be used as a delivery system for illicit drugs, as they can be discreet and have the potential to aerosolize a variety of substances. [56]

This literature review aims to explore the current state of research on drug delivery using e-cigarettes and identify potential risks and benefits associated with this approach. [56]

Identification of amino-tadalafil and rimonabant in electronic cigarette products Hadwiger et al. (2010) identified amino-tadalafil and rimonabant in electronic cigarette cartridges using a high-pressure liquid chromatography-diode array detection and multi-mode ionization tandem mass spectrometry method. Amino-tadalafil is a drug analogue of the commercially approved tadalafil used for erectile dysfunction, while rimonabant was approved for weight loss in Europe but not the United States. The study found that some e-cigarette products labeled as containing no nicotine actually contained nicotine, and others contained significant amounts of rimonabant oxidative degradant, indicating poor quality control over these products. This research highlights the need for regulation of e-cigarette products to prevent the use of unapproved drugs and ensure quality control [56].

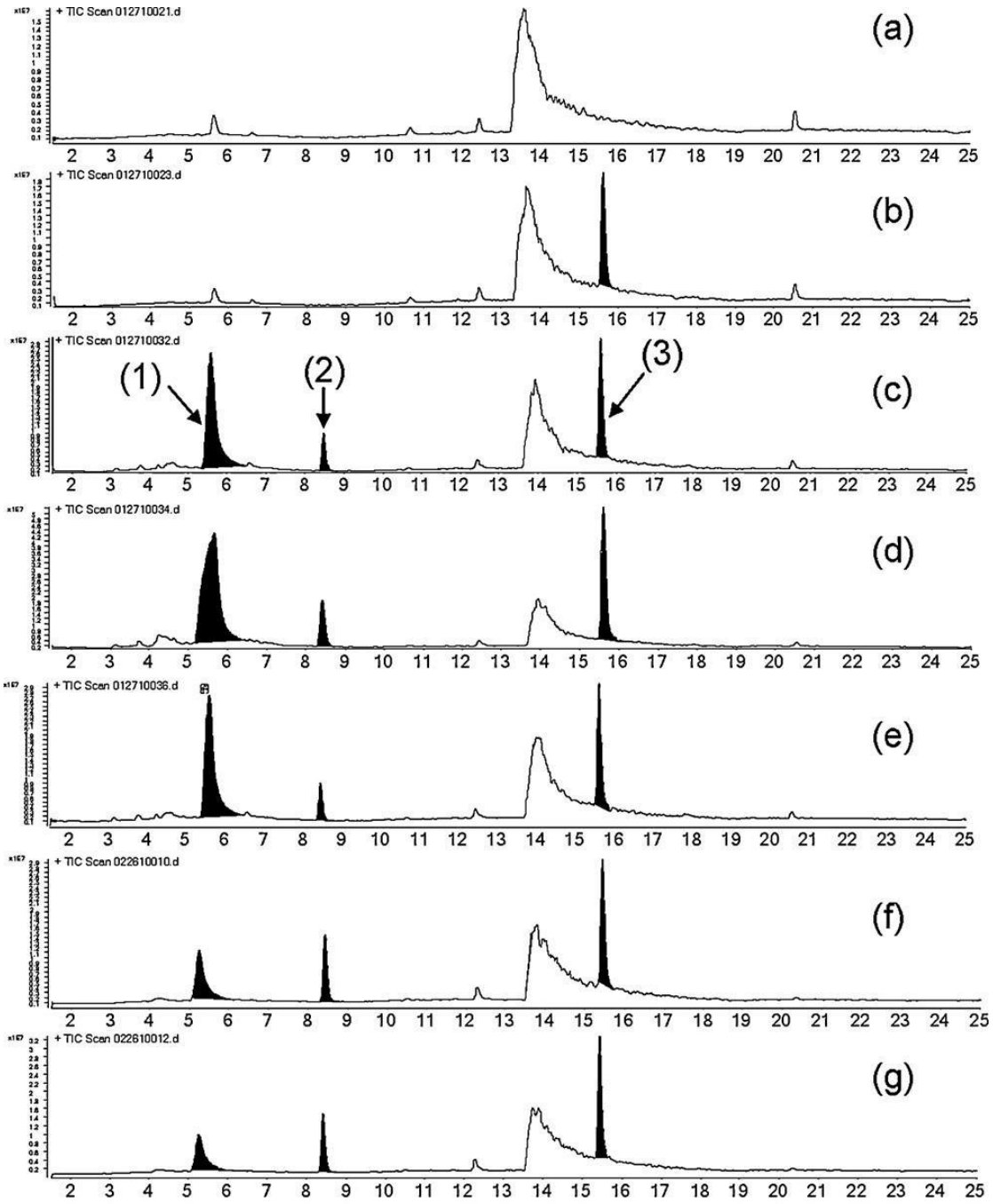


Figure 3: (a) blank solvent, (b) 10_g/mL rimonabant, (c)–(e) extracts from cartridges labeled as containing rimonabant, (f)–(g) e-cigarette refill liquid sample extracts. (1) Nicotine (5.4 min), (2) rimonabant oxidative degradation impurity (8.5 min), and (3) rimonabant (15.5 min)[65]

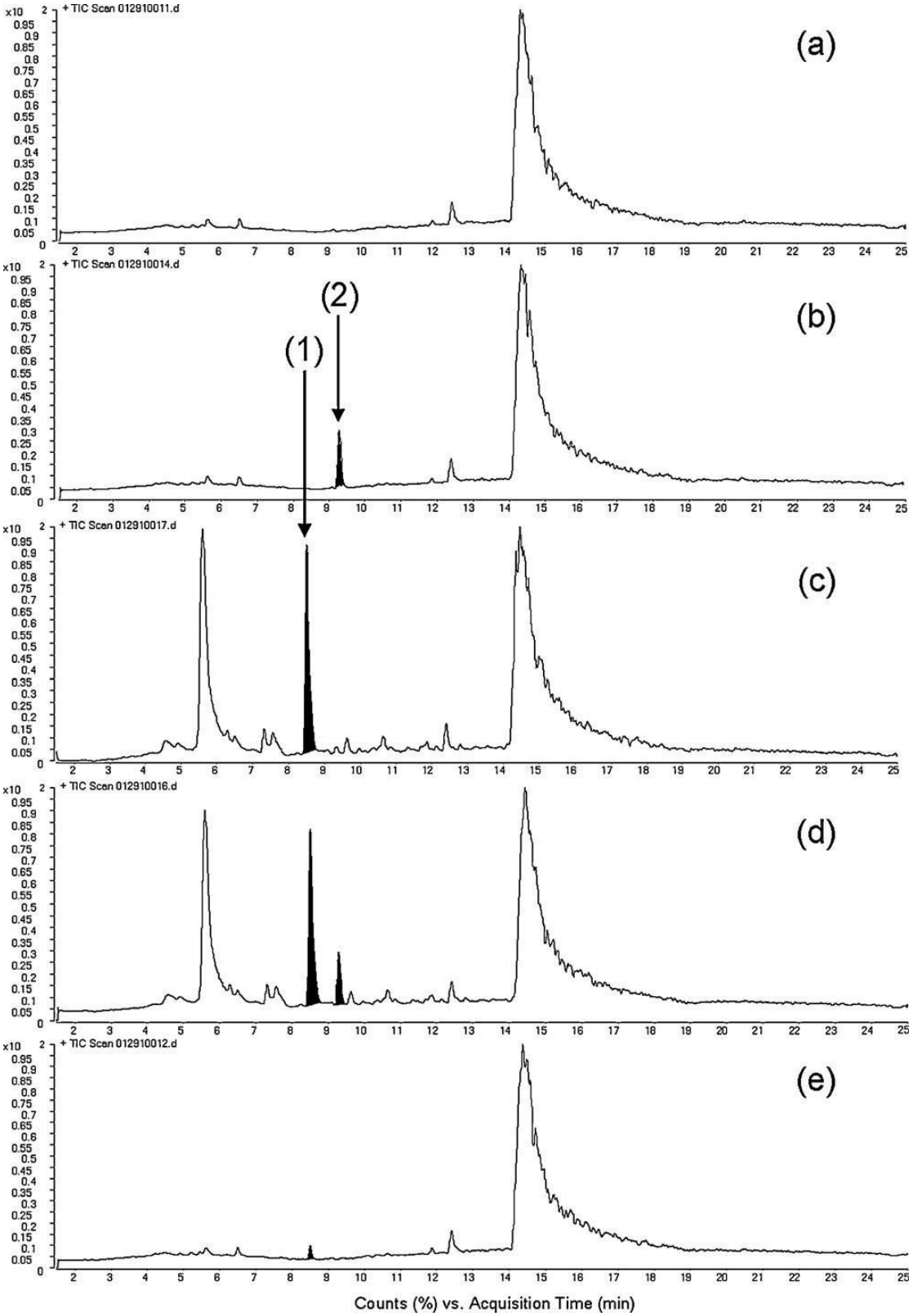


Figure 4: (a) blank, (b) tadalafil standard solution, (c) e-cigarette sample solution labeled as containing Cialis (blocks the action of a certain enzyme, which can result in increased blood flow to the penis, causing an erection.), (d) ecigarette solution spiked with tadalafil, (e) 10_g/mL amino -tadalafil. (1) Aminotadalafil, retention time at about 8.5 min, (2) Tadalafil, retention time at about 9.3 min[56].

Figure 3 shows the TICs obtained from the analysis of several rimonabant fortified e-cigarette sample extract solutions and a rimonabant standard solution. Peak 2 is due to a rimonabant impurity formed most easily under oxidative conditions. Peak 3 corresponds to rimonabant. As shown in Fig. 3, a comparison of the retention time of the peak of interest eluting at about 15.5 min in the e-cigarette solutions labeled as containing rimonabant (Fig. 3(c)–(g)) elutes at the same time as the rimonabant standard solution (Fig. 3(b)). Since a retention time match was obtained for the rimonabant standard and a peak in several samples, the UV, full scan mass spectra, and product ion mass spectra were extracted from for the peak of interest at 15.5 min.

Fig. 4 shows the total ion chromatogram (TIC) obtained from the analysis of one e-cigarette sample solution, an amino-tadalafil standard, and a tadalafil standard solution. As shown in Fig. 4, the peak at about 8.5 min in the chromatogram from the analysis of the e-cigarette solution labeled as containing Cialis TM (Fig. 4(c)) is not tadalafil. Tadalafil had a retention time of about 9.3 min (Fig. 4(b)) with this method. Therefore the UV spectrum, full scan mass spectrum and product ion mass spectrum were extracted from peak eluting at 8.5 min in the sample chromatograms.

E-cigarettes as an unintended illicit drug delivery system Breitbarth et al. (2018) conducted a review of literature and online forums to investigate the plausibility and risk of e-cigarette technology as an illicit drug delivery system. The review focused on a variety of illicit drugs, including cannabis, synthetic cannabinoids, synthetic cathinones, cocaine, GHB, heroin, fentanyl, MDA, MDMA, and methamphetamine. The review found evidence of e-cigarette use for each drug and explored the pharmacodynamics, typical methods of administration, required dosage for toxicity, and toxic effects of each drug. The authors concluded that e-cigarettes are a plausible and concerning method of illicit drug delivery, and there is a need for further research to explore the extent of this problem and potential solutions [57].

Blue Lotus Flower resin as a new type of electronic cigarette liquid Poklis et al. (2017) investigated the use of blue lotus flower resin as a new type of electronic cigarette liquid for a rebuildable dripping atomizer. Blue lotus flower resin contains apomorphine and nuciferine, with apomorphine having psychoactive properties and being primarily used to treat Parkinson's disease by stimulating dopamine receptors, while nuciferine is an alkaloid associated with dopamine receptor blockade. The study found that the nuciferine resin can aerosolize using the electronic cigarette and suggested potential implications for the use of blue lotus flower as a new type of electronic cigarette liquid. However, further research is needed to investigate its potential risks and benefits [58].

The study conducted by Justin L. Poklis and colleagues examined the use of Blue Lotus Flower (Nymphea caerulea) resin in a new type of electronic cigarette, the rebuildable dripping atomizer (RDA). The Blue Lotus Flower is known to contain the alkaloids apomorphine and nuciferine, with apomorphine being a non-selective dopamine agonist commonly used to treat Parkinson’s disease. Nuciferine, on the other hand, is associated with dopamine receptor blockade and is used as a sleep aid and anxiety reliever [59].

The researchers received a dark-brown resin material from a concerned parent, which had been confiscated from an adolescent with a reported history of marijuana use. The

resin was later identified as Blue Lotus Flower and was analyzed for content, along with four commercially available Blue Lotus products. Apomorphine was detected in two of the samples, and nuciferine was detected in all five samples. The confiscated resin was found to contain no apomorphine and 4300 ng/g of nuciferine. The researchers then showed that the nuciferine resin could be aerosolized using an RDA electric cigarette [59].

In another study, Samo Ribarič (2012) examined the pharmacological properties and therapeutic use of apomorphine. Apomorphine is a non-selective dopamine agonist that activates various dopamine receptors, serotonin receptors, and α-adrenergic receptors. In veterinary medicine, apomorphine is used to induce vomiting in dogs who have ingested poisons. In human medicine, it is used to treat addiction, erectile dysfunction, hypoactive sexual desire disorder, and Parkinson's disease. Apomorphine is commonly used in patients with advanced Parkinson's disease who have persistent and disabling motor fluctuations that do not respond to levodopa or other dopamine agonists, either on its own or in combination with deep brain stimulation [60].

In a review by Borkar et al. 2018 They focused on the research and development of an alternative delivery of apomorphine, aiming to highlight the potential for non-invasive treatment of apomorphine in PD, and proposed alternative methods such as sublingual delivery and transcutaneous delivery [61]

Recent studies suggest that apomorphine may have a new and potentially important therapeutic role in the treatment of Alzheimer's disease by reducing the rate of Aβ oligomerisation and consequent neural cell death. [61].

Role of apomorphine in the treatment of Parkinson's disease Allison Boyle and William Ondo (2015) discussed the current use of apomorphine in the treatment of Parkinson's disease, its delivery systems, and future research directions. Apomorphine is a drug that has been shown to be effective in managing the on/off symptoms of Parkinson's disease, but its use was limited in the past due to peripheral side effects. With the development of better delivery systems and medications to control side effects, the use of apomorphine has become more widespread. Currently, the major delivery systems for apomorphine are continuous subcutaneous infusions and intermittent subcutaneous injections, but other delivery routes are being investigated. This research highlights the potential benefits of improve patient compliance and quality of life. Several drug delivery systems have been developed to address this issue, including sublingual films, buccal tablets, and transdermal patches. In this article, the authors review the challenges and trends in apomorphine drug delivery systems for the treatment of PD. They discuss the advantages and disadvantages of different delivery routes and systems, as well as the current state of development and commercialization of these systems. The article highlights the need for continued research and development in this area to improve the effectiveness and accessibility of apomorphine therapy for parkison's disesase patients. [62].

Overall, the literature suggests that e-cigarettes have the potential to be used as a drug delivery system for both legal and illicit drugs. However, the quality control of e-cigarette products needs to be improved to ensure accurate labeling and the absence of harmful contaminants. Apomorphine, a drug commonly used to treat PD, is a promising candidate for alternative delivery methods beyond subcutaneous injections due to its lipophilic nature and extensive hepatic first-pass metabolism. Inhaled dry powder formulations of apomorphine may offer a more convenient and rapid delivery method compared to subcutaneous injections, but further research is needed to evaluate their safety and efficacy in PD patients.[63]

Chapter Three

Experimental

3.1 Chemicals

All chemicals were of analytical grade. Apomorphine , triethey amine, methanol, ethanol, acetonitrile , sodium hydoroxide and Potassium dihydrogen phosphate (KH2PO4) was obtained from Sigma Aldrich. Cotton. E-Cigarette (Joyetech) and the E-Liquid was purchased from a retail market in Ramallah. Purified water, and Syringe Millipore filter 30 mm diameter 0.45µm Nylon membrane were obtained from sigma Aldrich.

3.2 Instrumentation

3.2.1 High Pressure Liquid Chromatography

High Pressure Liquid Chromatography (HPLC-PDA) system consists of an alliance 2695 HPLC from (Waters), and waters Micromass® Masslynx ™ detector with Photo diode array (PDA) (Waters 2996). Data acquisition and control were carried out using Empower™ software (Waters). Analytes were separated on a 4.6 mm x150 mm C18 XBridge ®column (5 µm particle size) used in conjunction with a 4.6mmx20 µm XBridge ™ C18guard column. Microfilter was used with 0.45µm (Acrodisc® GHP, Waters).

3.2.2 A vacuum system

A vacuum system was designedset up by the team of Dr. Hussein Hallak based on literature reports.

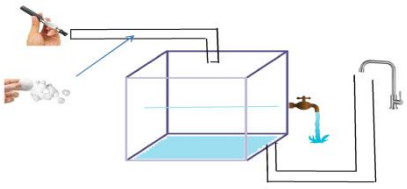


Figure 5: Vacuum system

3.2.3 pH meter

pH values were recorded using pH meter (model HANNA-HI11310).

Figure 6: PH meter

3.3.1 Samples Preparation

Two kinds of samples were prepared in which one is a blank and lead, another is experimental with unknown horizon. So after preparing the standard samples we have also made samples from the E-Liquid, Cotton and mix sample of the drug and E-Liquid with different Concentrations. In Every sample 1 to10 inhalations were taken. E-Liquid Sample was made by adding about 1ml of the E-liquid to 5ml of the mobile phase. This step was made to ensure that there's no interference between the drug and the components of the E-Liquid. Cotton sample was made by soaking a small amount of unused cotton in the mobile phase solution for about 30 minutes and then a solution sample has been taken. Mix sample (Drug mixture with E-Liquid) prepared by dissolving 0.5g of the drug (Apomorphine) with 5ml ethanol and then mixed with E-Liquid. To enhance the solubility we have sonicated the mixture for 5 minutes to obtain a less turbid Solution. The samples collected were analyzed for apomorphine drug using HPLC method.

3.3.2 HPLC method

- Buffer is prepared by dissolving 6.8 g KH_2PO_4 in one liter of water and adjusting pH to 2, then 0.2 mL of triethylamine is added.
- C18 column and a mobile phase of 16% acetonitrile and 84% of buffer at 1.3 ml/min flow rate was used.
- Wavelength of 275 nm and 20 microliter injection volume was used.
- Standard of 0.02 mg/ml of apomorphine in mobile phase was used.

Chapter Four

4. Results and Discussion

4.1 Development of HPLC method for analysis of Apomoprphine

HPLC method was developed for determination of apomorphine using different mobile phases of buffer and organic solvents (methanol and acetonitile). Different buffers were tested with different pHs with methanol and/or acetonitrile. C18 and C8 columns were used for the separation. The optimum conditions was found to be using phosphate Buffer (6.8 g KH2PO4 in one liter of water and adjusting pH to 2, then 0.2 mL of triethylamine is added) and a mobile phase of 16% acetonitrile and 84% of buffer at 1.3 ml/min flow. C18 column (25 cm and 4.6 um particles) at a Wavelength of 275 nm and 20 microliter injection volume was used.

4.2. Calibration Curve of Apomorphine

Different standards of apomorphine (in the concentration range of of 0.02-0.5 mg/ml, Table 2) in mobile phase was prepared and 20 uL was injected into the HPLC and analyzed using the HPLC method. Calibration curve was established by plotting peak areas vs. Concentration of apomorphine and a linear relationship was obtained with a good correlation coefficient (Figure 5). Figure 6 shows the chromatogram of apomorphine using the developed method with a retention time of 5.7 minutes.

Table 2: Calibration curve of apomorphine (peak area vs. Concentration).

Concentration	Peak area of apomorphine
0.02	12.3
0.04	225.1
0.06	37.5
0.10	63.5
0.12	74.5
0.15	91.3
0.20	128.5

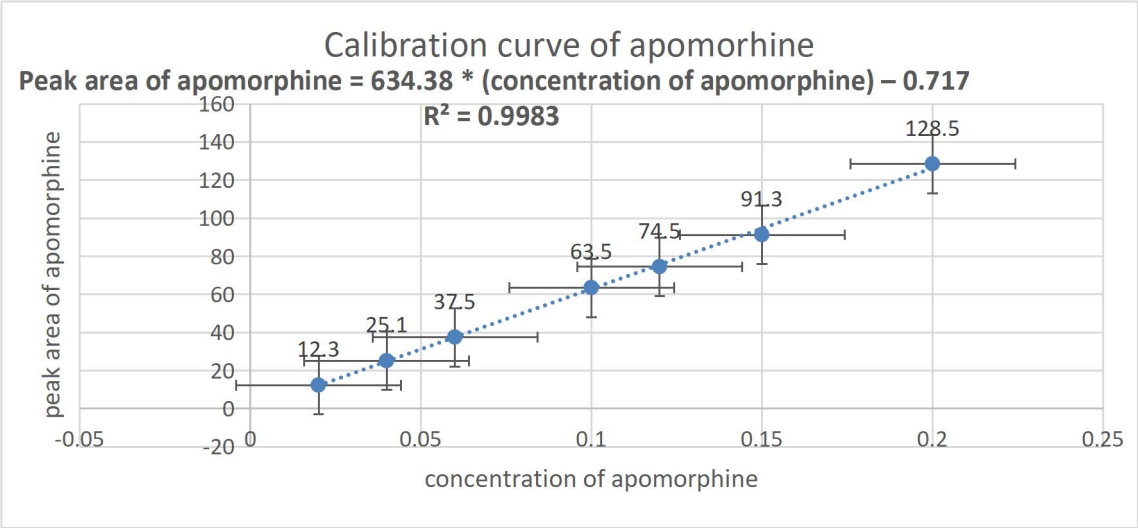


Figure 7: Calibration curve of apomorphine: peak area vs. concentration

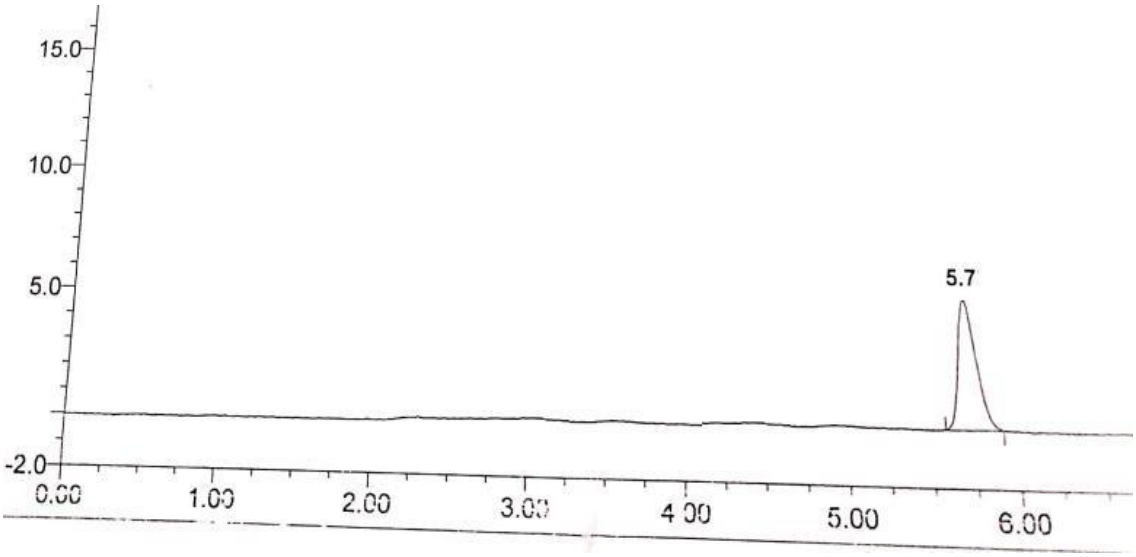


Figure 8: HPLC chromatogram of apomorphine using the developed chromatographic HPLC method. (x – axis : retention time)(y-axis : peak area of Apomorphine).

4.3. Collection of samples

A vacuum system used as a device to mimic inhalation by the flow of water. The diagram of the vacuum system is shown below which was designedset up in the lab of Dr. Hussein Hallak.

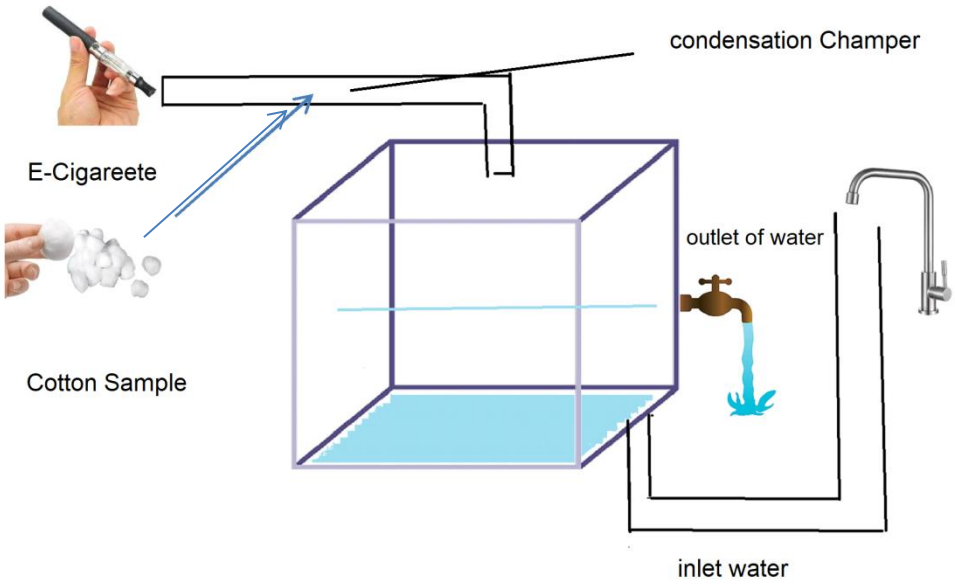


Figure 9: photo of the vaccumm system of e-cigarette which I used in this experiment

4.4 Analysis of the apomorphine in the inhaled solutions

A solution of 5 mg/ml of apomorhine was prepared in ethanol. Then 1 ml of this solution was mixed with e-cigarette liquid to obtain a solution with 1.0 mg/mL. This solution was used for the experiment to test the presence of apomorhine in the vaped vapor which is collected on cotton, and then soaked with 5 mL of mobile phase and analyzed using the HPLC method. Ten samples were collected with increasing number of inhalations (inhalation 1 to 10), and another control sample was also collected (e-cigartee liquid only without apomorphine). The concentration of apomorphine in vapor was calculated from the peak area of apomorhine in sample solution and using the calibration curve of apomorphine. Figure 10 shows a chromatogram of e-cigarette vapor (after 5 inhalations) and controlled sample (using e-cigarette liquid without apomorphine).

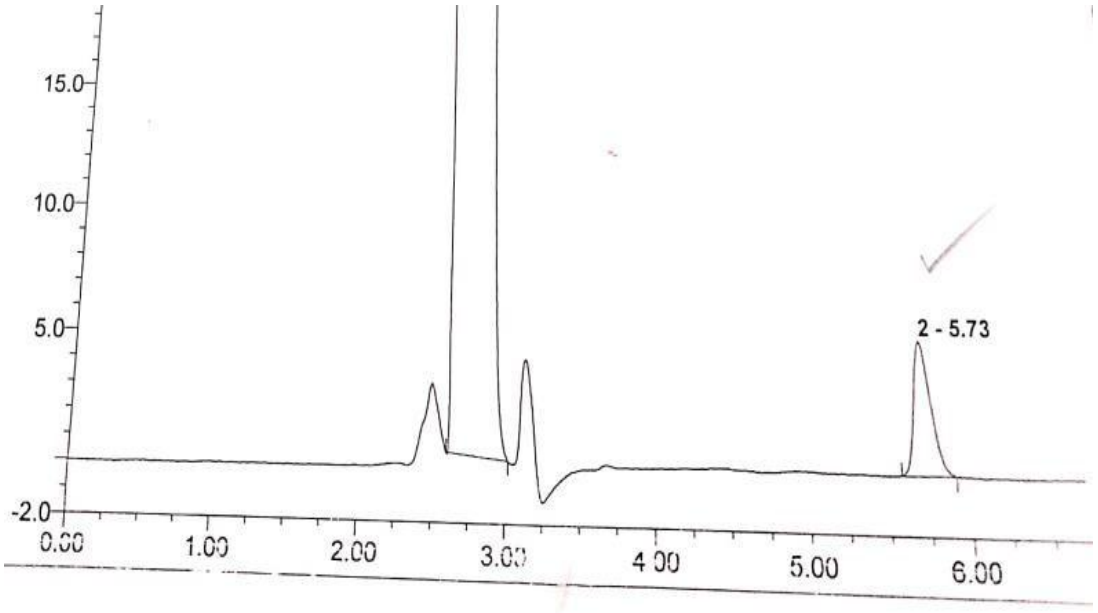
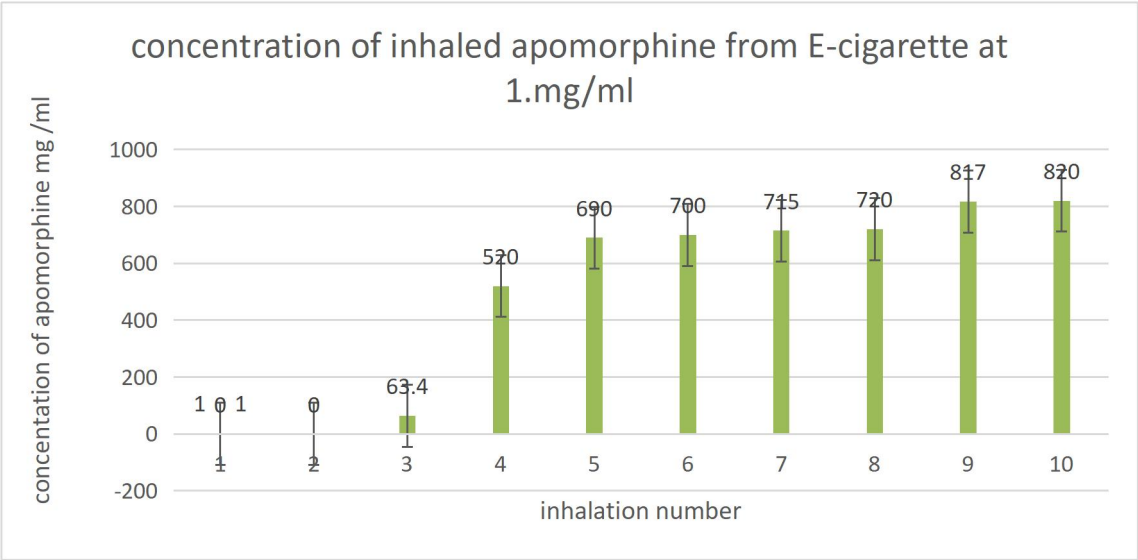


Figure 10: Chromatogram of apomorphine collected from the inhalation of e-cigarette liquid mixed with apomorphine drug (A) and a control sample (e-cigarette liquid without apomorphine). (x – axis : retention time)(y-axis : concentration of apomorphine).

Results showed that the concentration of apomorphine (in mg per liter or ppm) increases with increasing the number of inhalations. Table 3 shows the amounts of apomorphine found in the inhaled e-cigarettes mixed with apomorphine as a function of inhalations number. Figure 4 shows the accumulated concentration of apomorphine in the inhaled vapor as a function of inhalation number. As it is obvious from this figure, no apomorphine detected in the first 2 inhalations, while after this, apomorphine starts to appear with a content of 63.4 ppm after 3 inhalation and increasing until it reaches 820 ppm with 10 inhalations.

Figure 11: Concentration of inhaled apomorphine from e-cigarette liquid mixed with apomorhine at a concentration of 1.0 mg/ml.



4.5 Effect of concentration of apomorphine in the e-cigaretee liquid

The same procedure was followed as in the previous section but using two different concentration of apomorphine in the e-cigarette liquid (2 and 4 mg/mL) to study the effect of concentration of apomorphine in the e-cigartee liquid on the amount of apomorphine in the inhaled vapor. Results also showed that the amounts of apomorphine is increasing with the number of inhalations. For 2.0 mg/ml concentration no apomorphine detected in the first inhalations, while after this, apomorphine starts to appear with a content of 30 ppm after 2 inhalation and increasing until it reaches 980 ppm with 10 inhalations. For 4.0 mg/ml no apomorphine detected in the first inhalation, while after this, apomorphine starts to appear with a content of 50 ppm after 2 inhalation and increasing until it reaches 1038 ppm with 10 inhalations.

Also results showed that the amounts of apomorphine in the inhaled vapor of e-cigarette is higher when the concentration of apomorphine is increasing in the e-cigarette solution. Figure 9 shows the amounts of apomorphine in the inhaled vapor of e-cigarttecigarette as a function of apomorphine concentration in the e-cigarette liquid (2 and 4 mg/mL).

Figure 12: Concentration of inhaled apomorphine from e-cigarette liquid mixed with apomorhine at a concentration of 2.0 and 4.0 mg/ml.

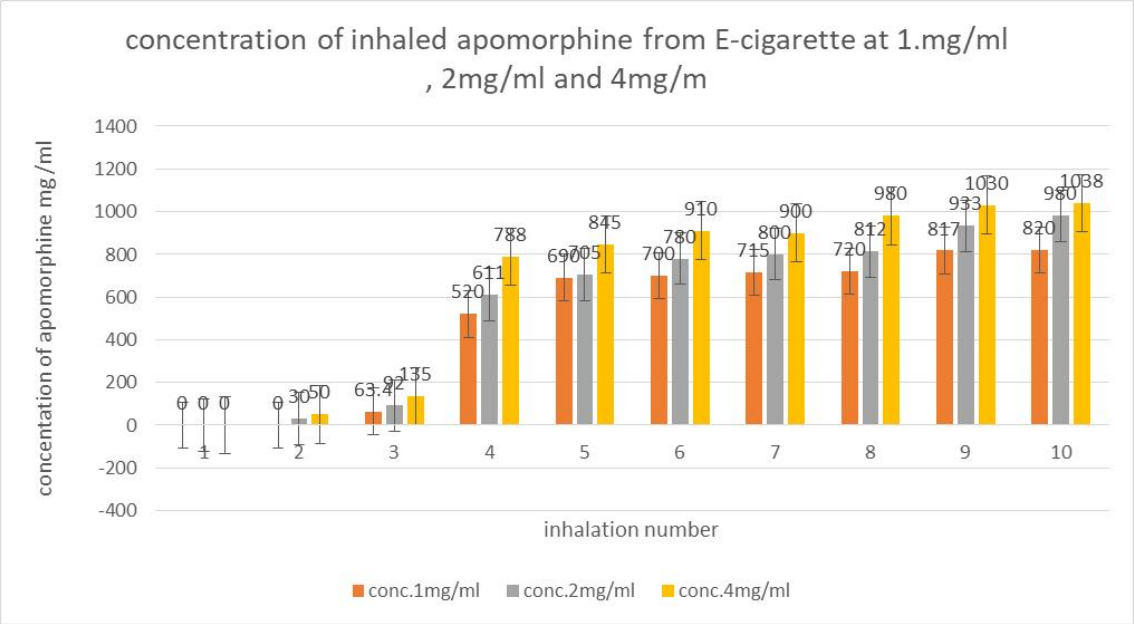


Figure 10: Concentration of inhaled apomorphine from e-cigarette liquid at a concentration of 1.0, 2.0 and 4.0 mg/ml.

4.6 Comparison of the poklis et al.2017 study and this study

The two studies have different objectives and methodologies. The Polkis et al. (2017) study aims to identify the presence of apomorphine and nuciferine in blue lotus products using DART-MS, GC-MS, and UPLC-MS/MS and to determine the potential of the Plume Veil 1.5 Clone RDA to aerosolize nuciferine. On the other hand, this study focuses on developing an HPLC method for the determination of apomorphine and establishing a calibration curve for the same.

Both studies detected apomorphine in blue lotus products, but this study did not detect nuciferine. Polkis et al. used different techniques to detect the two alkaloids, while this study developed an HPLC method to detect apomorphine. Polkis et al. also evaluated the potential of the Plume Veil 1.5 Clone RDA to aerosolize nuciferine, while this study did not investigate this aspect.

Overall, the two studies have different scopes and approaches, and they complement each other in contributing to the knowledge about blue lotus products and their alkaloid content.

Additionally, more research is needed to explore the potential benefits and risks of using E-Cigarettes as a drug delivery system for various medications, including their efficacy, safety, and potential side effects.

Chapter Five

Conclusions

Based on our study, we can conclude that the lesser of two evils principle holds true when it comes to nicotine delivery. E-Cigarettes can indeed be a substitute for tobacco smoking, and our findings suggest that they can serve as a reliable drug delivery system with further enhancements. Furthermore, our study also found that the concentration of apomorphine increased with an increasing number of inhalations.

This is promising news for patients with Parkinson's disease, as it suggests that E-Cigarettes may be a potential drug delivery system for this medication. However, it is important to note that our study was conducted in vitro, and further follow-up studies are needed to confirm our results using in vivo animal studies.

In conclusion, while our study provides promising initial findings, more research is needed to fully understand the potential of E-Cigarettes as a drug delivery system. Nonetheless, our results suggest that E-Cigarettes may offer a safer and more efficient way to deliver medications, and may offer hope for patients with conditions that require regular drug delivery.

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طريقة جديدة لتوصيل الدواء باستخدام السيجارة الالكترونية

اسم الطالب : هديل اكبارية

اشرف الدكتور : فؤاد الريماوي

الملخص

هدفت هذه الدراسة إلى استكشاف استخدام السجائر الإلكترونية كأسلوب لتسليم الدواء الأبومورفين الذي يستخدم عادة لعلاج مرض باركنسون. والطريقة التقليدية لإعطاء الأبومورفين هي عن طريق الحقن تحت الجلد، والتي يمكن أن تكون مؤلمة وصعبة على المرضى. لذلك، يجب العثور على طرق بديلة لتسليم الدواء. وفي هذه الدراسة، تم استخدام نظام شفط لتقليد الاستنشاق وقياس تركيز الأبومورفين في البخار المستنشق. تم إعداد خليط الدواء عن طريق ذوبان الأبومورفين في الميثانول ومن ثم خلطه مع سائل .E-liquid تم إجراء تحليل HPLC على القطن المشبع بالبخار المجمع لتحديد تركيز الأبومورفين. أظهرت النتائج أن تركيز الأبومورفين في البخار زاد مع عدد الاستنشاقات ومع زيادة تركيز الأبومورفين في سائل .E-liquid تشير هذه النتائج إلى أن السجائر الإلكترونية يمكن أن تكون طريقة بديلة واعدة لتسليم الأبومورفين وغيره من الأدوية الصيدلانية. ومن الضروري إجراء المزيد من البحوث لاستكشاف التطبيقات السريرية المحتملة لهذا النهج.