Vape as Another Drug Delivery System

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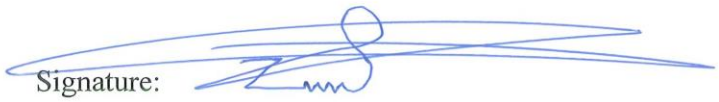

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Dedication

Praise be to God forever and ever

I dedicate this thesis to my **father** and **mother**, the creator of my personality, my strong pillar, the source of inspiration, wisdom, knowledge and understanding. They continue to inspire me every day with their determination and love. Words of thanks are not enough to express my love for you, who nourished and prepared the soil on which my guide was planted, the seeds of his knowledge.

Dear **brothers**, you are my happiness and all my life. Your support and leadership is what made me who I am.

For my family and all my friends, without whom I would not be able to succeed. Thank you all for helping me and giving me the life, I love today.

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Abbreviation

API	Active pharmaceutical ingredient
°C	Celsius degree
cm	Centimeter
cm^2	Square centimeter
COPD	Chronic Obstructive Pulmonary Disease
DW	Distilled water
g	Gram
HPLC	High Performance Liquid Chromatography
FP	Fluticasone propionate
FPF	Fine Particle Fraction
ICH	International Conference of Harmonization
JOD	Jordanian Dinar
LOD	Limit of detection
LOQ	Limit of quantification
µg	Microgram
mg	Milligram
ml	Millilitre
min	Minute
µl	Microlitre
mol	Mole
NGI	Next generation impactor
PG	propylene glycol
RD	Respirable Dose
RSD	Relative standard deviation
VG	vegetable glycerin

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Abstract

Background: The lungs are an attractive route for drug administration owing to its benefits over other drug delivery systems. The respiratory system has a large surface area, high vascularization, and thin blood – alveolar barrier. Several devices for pulmonary drug delivery are in use in the market such as Nebulizers, Pressurized metered-dose inhalers (pMDIs), and Dry powder inhalers (DPIs). Each of the devices has its merits and drawbacks which hindered the vast advancement of respiratory dosage forms. Recent studies reported that vaping devices have been extensively used for the delivery of nicotine and other illegal drugs and produced very effective outcome, making them a potential alternative for regular nebulizers, pMDIs, and DPIs. Therefore, the aim of this research project was to conduct an *in-vitro* evaluation of the performance of commonly used vapes to assess their effectiveness in delivering drugs to the respiratory system using fluticasone propionate (FP) as a model drug. **Methods:** HPLC methods for the analysis of nicotine and fluticasone propionate was employed and validated according to the ICH guidelines. **Results:** Aerodynamic deposition performance of the three vape devices was assessed using the NGI which showed the superiority of vape tank and vape coil over vape pod. The vape tank produced the highest amount of nicotine among the three marketed products, where the emitted dose, fine particle fraction of the nominated dose and the respirable dose were significantly higher than those of coil and pod (one way ANOVA, $p<0.001$). Despite similar nicotine content in each dose, the performance of the devices varied. Even with the presence of coil in the tank vape device, the amount vaporised and emitted dose from the device were larger in the case of tank with atomizer. The project then took a direction of developing FP e-liquid and assessing the *in-vitro* performance using the NGI. The performance of the developed E-liquid containing FP was assessed using the three previously tested devices and results were compared with the marketed FP pMDI. The aerodynamic performance of the formulation was tested on NGI and results of FPF ranged from 22.10% when the vape-pod was used to 50.38% in the case of vape tank. The marketed FP pMDi showed comparable results to that of vape-coil in terms of respirable dose. However, the FPF of

the nominated dose and RD usually, gave better presentation to the amount that reached the lower respiratory system with the vape tank achieving the highest of (50.38% and 50.38 µg, respectively). Statistical analysis showed a statistically significant difference among devices in delivering respirable dose (p=0.0001). Short stability study demonstrated the ability of the formulation to retain the content of FP. **Conclusions:** Such results are promising starting point for the possibility of utilizing the vape devices particularly vape tank using low temperature and wattage to deliver effective and user friendly dosage for respiratory drug delivery.

Chapter One

Introduction

1.1. Background

The respiratory tract has generated significant interest as an alternative drug delivery route owing to its benefits over other drug delivery systems. The respiratory system has a large surface area, high vascularization and thin blood–alveolar barrier (Liang *et al.*, 2015). Traditionally, the pulmonary route was employed for the treatment of local respiratory diseases such as asthma, chronic pulmonary infections, cystic fibrosis, or lung cancer. Recently, the pulmonary route is exploited for the systemic delivery of drugs such as insulin, human growth hormones, and oxytocin among others (Pilcer and Amighi, 2010; Sarasija and Patil, 2012). This is true for many biotherapeutics currently injected intravenously, such as growth hormones, glucagon or insulin, each of which could be delivered to humans by inhalation providing a more convenient less invasive yet efficient therapy (Palecanda and Kobzik, 2001).

The use of the pulmonary system as a drug delivery route offers many advantages, which include reduced systemic side effects and delivering higher doses of the active pharmaceutical ingredient (API) at the site of action. Further, the lungs are active port for the entry of drugs to the bloodstream due to the large absorptive surface area (~100 m^2), the very thin absorption membrane (0.1–0.2 μm) and the elevated blood flow (5 L/min), which rapidly distribute molecules throughout the body. Besides, medications administered via inhalation are not subject to first-pass metabolism (Patton, 2004). The alveolar epithelium of the lung is an absorption site for several therapeutics and macromolecules (Tuncer Degim and Celebi, 2006).

The treatment efficacy of pulmonary drug delivery mostly depends on the technique by which the API is delivered to the lung (Sarasija and Patil, 2012). Research in the area of pulmonary drug delivery has raised momentum in the last several years, with increased interest in using the lung

as area to delivering drugs systemically (Labiris and Dolovich, 2003). Advances in device technology have led to the development of more efficient delivery systems capable of delivering larger doses and finer particles into the lung (Labiris and Dolovich, 2003). Several devices for pulmonary drug delivery are in use in the market such as Nebulizers, Pressurized metered-dose inhalers (pMDIs), and Dry powder inhalers (DPIs). Each of the devices has its merits and drawbacks (Ibrahim, Verma and Garcia-Contreras, 2015).

Owing to the limitations encountered in commonly used devices for the delivery of inhalation medication, alternative techniques and /or devices need to be considered. For example, the use of nebulizers is associated with low efficiency, poor reproducibility, and time consuming. pMDIs have some disadvantages in terms of effectiveness and the need for patient coordination as well as the need for propellants. Most patients cannot use pMDIs correctly, even after repeated training. Deposition of the drug in the mouth and the oropharyngeal area is another drawback for the use of pMDIs (Pilcer and Amighi, 2010). Dry powder inhaler also has disadvantages pertinent dose uniformity and high cost (Yadav and Lohani, 2013).

A research conducted by Newman and colleagues (2017) reported that effective delivery of drugs to the lungs is adversely affected by the behavioral barriers of poor adherence and poor inhaler technique. Key enablers for effective inhalation are good inhalation devices, effective formulations that deliver the active pharmaceutical ingredient (API) to the lungs efficiently, enhanced inhaler technique and improved patient education and adherence. Owing to the advantages offered by the pulmonary route, the challenges that the route poses are worth addressing, and if successfully addressed, the pulmonary route offers huge opportunities, often fulfilling unmet clinical needs (Newman, 2017).

A vaping devices (Vapes) are relatively simple devices that are used to deliver tobacco products, particularly nicotine through the respiratory system. It enables the users to inhale nicotine and other flavoring materials via an aerosol. Vapes vary broadly in design and appearance, but largely operate in a similar manner and are comprised of similar components. It is consisted of battery, vape-chip and container for nicotine (see Figure 1.1.) (NIH, 2016).

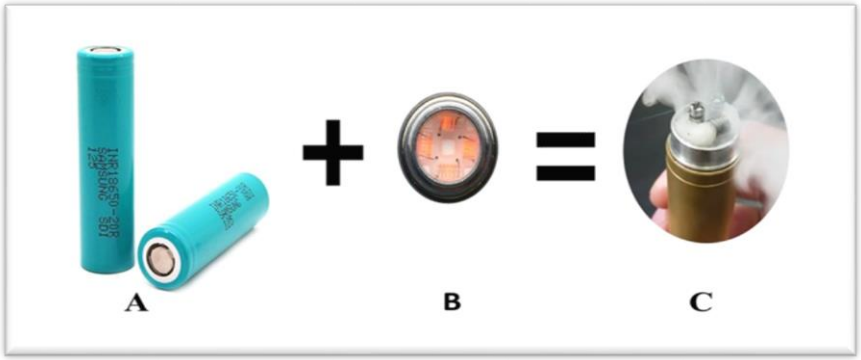


Figure 1.1: The main components of vapes. **(A)** Battery **(B)** Vape- chip and **(C)** Vape Container (adopted from (Ruthlessvapor, 2019).

Since their inception in early 2000, vapes gained high popularity particularly among youth and young adults due to its ease of use and availability. It has been used since 2003 for the delivery of nicotine. These devices are carrying several names such as "e-cigarettes," "e-cigs," "cigalikes," "e-hookahs," "mods," "vape pens," "vapes," and "tank systems."(NIH, 2016). The term vape will be employed to represent such products in this work. Several studies demonstrated the effectiveness of vapes in delivering nicotine as compared to cigarettes (Miech *et al.*, 2018). Further, the popularity of these devices among youth and young adults was the motive behind this project.

Developing inhalation dosage forms is a challenging project. Several challenges in developing inhalation therapies were reported, namely; the need to reduce the amount of carrier, the challenge

in breaking agglomerates, micronization related stability and handling issues (Catalant, 2018). Therefore, the use of alternative delivery systems is attractive particularly if it can deliver the medicine effectively to the lower parts of the respiratory system, come in an affordable convenient to use for all age groups, and provide stable formulation (Miech *et al.*, 2018).

As vapes are wildly available in the market (Yang and Lee, 2018), widely reported to be easy to use (Palazzolo, 2013), and are cost effective with an average cost of a vape is between $20-40 depending on which style and size, it presents an option for an alternative drug delivery system. It is expected that the use of vapes will enhance drug delivery to the lungs. Inhaled nicotine from vapes is easily absorbed from the large surface area of the lungs and is transported directly to the brain via the pulmonary venous system in 10–20 seconds. Therefore, presenting the possibility that delivery of API's could in turn also be potentially enhanced. Results as depicted from Figure 1.2 demonstrated the superiority of vapes in delivering nicotine over conventional cigarettes (Farsalinos *et al.*, 2015).

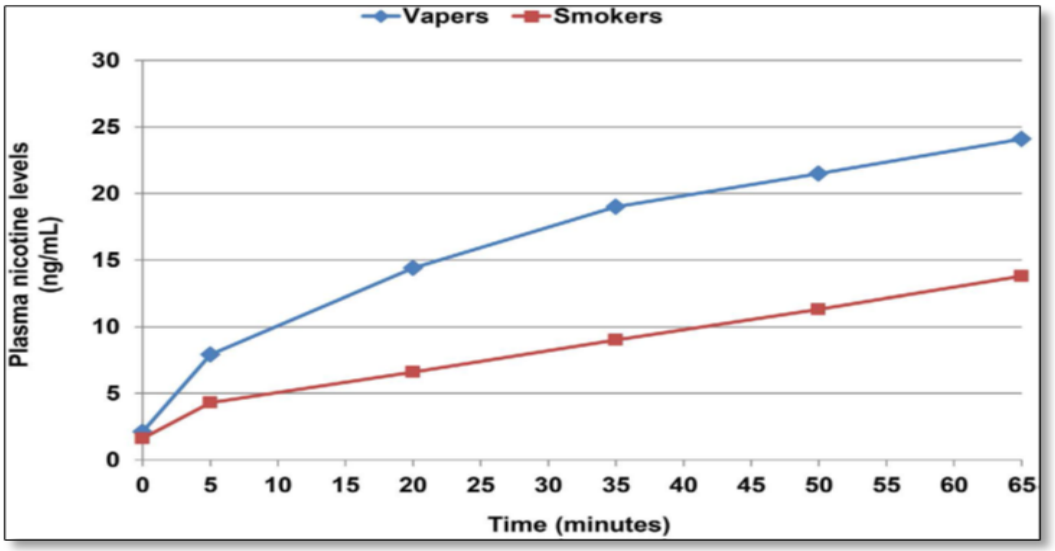


Figure 1.2: Plasma nicotine level following Vapes and conventional cigarette adopted from (Farsalinos *et al.*, 2015).

1.2. Study Aim and Objectives

The aim of this research project is to conduct an in-vitro evaluation of commonly used vapes using next generation impactor to assess their effectiveness in delivering active pharmaceutical ingredients (API) to the lower part of the respiratory system. Then the selected vape will be used as a delivery system using model drug (Fluticasone Propionate- FP). Specific challenges that will be tackled in this project pertinent to selection of the most effective device that delivers high amount of the drug into the lower parts of the lung. The specific objectives are as follows:

- Validation of analytical techniques for nicotine, and FP, using HPLC by applying the ICH guidelines (Validation of Analytical Procedures Q2 (R1)).
- *In-vitro* assessment of commercially available nicotine vapes using NGI (next generation Impactor).
- Development of formulation using FP to be delivered through the vape with targeted properties to compare the *in-vitro* performance in terms of fine particle fraction, emitted dose and respirable dose with a marketed pMDI.

Chapter Two

Literature Review

2.1. Introduction

Respiratory system consists of trachea that divides into two hollow tubes called bronchi, lung, and breathing muscles, which help the body to exchange gases between the air and blood. Most of the pulmonary system parts aid the distribution of air. Only the smallest, grape-like alveoli and the alveolar ducts are responsible for the actual gas exchange (Healthline, 2018).

Drug delivery to the lung offers multiple advantages when compared to other routes of drug administration due to the large surface area, less painful and convenience to patients (Liang *et al.*, 2015). The lung is a very attractive target for drug delivery where it offers a large surface area for drug absorption (Labiris and Dolovich, 2003). In addition, the alveolar epithelium is very thin (approximately 0.1–0.2 μm thick), permitting rapid drug absorption. Hence, the alveoli can be effectively targeted for drug absorption by delivering the drug as an aerosol with mass median aerodynamic diameter (MMAD) of less than 5 μm (Gilani, K.; Najafabadi, A.R.; Darabi, M.; Barghi, M. & Rafiee-Tehrani, 2004).

2.2. Pulmonary Drug Delivery Devices

Pulmonary drug delivery devices can be divided into three categories: nebulizers, pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs). Each class presents unique strengths and weaknesses. A good delivery device must generate an aerosol of suitable size, ideally in the range of 0.5–5 μm, and provides reproducible drug dosing. It must also protect the physical and chemical stability of the drug formulation. Further, the ideal inhalation system must be simple, convenient, inexpensive and portable (Telko and Hickey, 2005).

Nebulizers were the first device developed for inhalation therapy market. Nevertheless, it demonstrated several drawbacks such as low efficiency, poor reproducibility and requires extended duration for administration, handling and cleaning (Newhouse *et al.*, 2003). Nebulizers are used mostly in hospital settings and are not typically used for chronic-disease management because they are larger and less convenient, and the aerosol is delivered continuously over an extended period of time (Telko and Hickey, 2005). Nebulizers' formulations present the drug in the form of a liquid solution, which is often filled into the device at use. Corticosteroids and bronchodilators such as salbutamol are often used, and sometimes in combination with ipratropium. The reason for inhaling such drugs instead of ingesting them is to target their effects into the respiratory tract, which speeds the onset of action and reduces side effects, compared to other alternative routes (Thalberg, Lindholm and Axelsson, 2004). Nebulizers are not more effective than metered-dose inhalers with spacer (pMDIs) (Cates, Welsh and Rowe, 2013).

pMDIs were developed since 1950s for the use in the treatment of asthma. pMDIs are widely spared devices because they are relatively cheap and employed consistent technology to transfer APIs using propellants (Lavorini, Pistolesi and Usmani, 2017). pMDIs have some disadvantages in terms of effectiveness and ease of use. Most patients cannot use pMDIs correctly, even after repeated training by healthcare professionals (Crompton, 1982). The deposition of drugs in the mouth and the oro-pharyngeal area is another disadvantage (Pilcer and Amighi, 2010). Misused pMDI is a repeated drawback and is associated with poor asthma control for inhaled corticosteroid-treated asthma patients (Giraud and Roche, 2002).

DPIs do not require the use of propellants as pMDIs which were developed in a bid to overcome the limitations of nebulizers and pMDIs (Labiris and Dolovich, 2003). The development of DPIs has been motivated by the desire for alternatives to pMDIs, to reduce emission of ozone-depleting

and greenhouse gases (chlorofluorocarbons and hydrofluoroalkanes, respectively) that are used as propellants, and to facilitate the delivery of macromolecules and products of biotechnology (Telko and Hickey, 2005). DPIs have several types such as (Aerolizer, Diskus, Flexhaler, Handihaler, Neohaler, Pressair, Rotahaler**)**. DPIs provide better physicochemical stability and deep lungs deposition using the patient's respiration (Frijlink and Boer, 2004). Although most patients are capable to produce, enough flow to turn on a DPIs efficiently however, there are few cases where patients were not capable of producing enough air flow activate the DPI device such as children, elderly and patients with severe airflow limitation. For this reason, DPIsare not used for patients under the age of five years. Further, DPI are relatively expensive to produce and entail dose uniformity challenges (Borgström, Asking and Thorsson, 2005). Comparison between the three commonly used devices is depicted in Table 2.1.

Table 2. 1: Summary of commonly used respiratory devices, their advantages and disadvantages.

Device	Advantages	Disadvantages	References
Nebulizers	Effective in delivering drugs that cannot be delivered with pMDIs and DPIs.	Difficult to clean	(Le Brun *et al.*, 2000; Máiz Carro and Wagner Struwing, 2011)
		Solution characteristics challenges	
		Gas flow used to power nebulizer	
	Fast, quiet, portable	Expensive	
	Deposited directly into the respiratory tract and thus higher drug concentrations can be achieved in the bronchial tree and pulmonary bed	Not available when needed. Limited to hospital use. Not user friendly, large device difficult to carry.	
	High doses possible	Variable dose (depends on device, technique, fill volume, viscosity)	
		Not all drug formulations available	
		Nosocomial gram -negative infections possibility	
PMDIs	Widely Spread in the markets	Low effectiveness	(Newhouse, 2009)
	Relatively cheap	Deposition of the drugs in the mouth and the oro-pharyngeal area	
	Wide particle size range potentially available from 5 μm to 10 μm.	Require the use of propellants-environmental hazard	
	Can be employed for local or systemic drug administration.	The excipients (e.g., oleic acid) may cause cough and bronchoconstriction	
	Lack of preservatives compared with nebulizers	Stability problem of drug in solution and/or suspension.	
		Requires patient coordination.	
DPIs	Environmental sustainability, Little or no patient coordination required Formulation stability	Deposition efficiency dependent on patient's inspiratory airflow Potential for dose uniformity problems Development and manufacture more complex	(Telko and Hickey, 2005)
	DPIs have been motivated by the desire for alternatives to pMDIs, to reduce emission of ozone-depleting and greenhouse gases not use propellant	DPIs are not used for patients under the age of five years	
	Physicochemical stability and deep lungs deposition	Expensive	

2.2.1. Fluticasone propionate

Fluticasone propionate have a chemical formula ($C_{25}H_{31}F_3O_5S$), molecular weight of 500.58 g/mol, melting point between 272℃ to 273 ℃ and a boiling point of 568.3 ± 50.0 ℃ with enthalpy of vaporization of 98.0±6.0 kJ/mol (40 kJ/mol for water). It is not soluble in water (0.0114 mg/mL) but slightly soluble in alcohol such as methanol, and soluble in acetonitrile (Fisher-Scientific, 2020).

Fluticasone propionate was patented in 1980 and approved for medical use in 1990. Fluticasone is a synthetic trifluorinated glucocorticoid receptor agonist used for antiallergic, anti-inflammatory and antipruritic effects (Coutinho and Chapman, 2011). It is used for long-term prevention of bronchospasm in patients with asthma and Chronic Obstructive Pulmonary Disease (COPD) (Wedzicha *et al.*, 2016). It can be administered by nasal inhalation using a metered-dose nasal spray pump for hay fever and nasal polyps. Nasal and oral inhaler dosage forms have little corticosteroid side effects compared with tablet formulation because of the low dose compared with oral and limited systemic blood absorption (Giavina-Bianchi *et al.*, 2008).

Common side effects when used as nasal dosage form include nasal irritation, headache, stomach upset, nausea, vomiting and diarrhea. Unusual side effects include fever, sore throat, and cough, vision problems, severe swelling, hoarse voice, and difficulty breathing or swallowing (Barnes, 2010). When used in inhalers, side effects may include upper respiratory tract infection, throat irritation, thrush, cough, and headache. Rare side effects include swelling of the face/neck, depression, tiredness, and shortness of breath (Calverley *et al.*, 2007; Kariyawasam and Scadding, 2010)(Calverley *et al.*, 2007; Kariyawasam and Scadding, 2010). Fluticasone propionate is available as a nebulizer, pMDI and DPI (see Table 2.2).

Table 2. 2: Fluticasone propionate dosage forms that are available in the market.

Type of Device	No of doses /container	Dose	Indication	Brand name	Cost (JOD)	Manufacturer	Reference
pMDI	60,120 puffs	50, 125 and 250 µg/ puff	Asthma, and COPD	Flixotide Evohaler®	7.94 to 28.52	GlaxoSmithKline (GSK)	(GSK, 2020c) (JFDA, 2020)
DPI	60 puffs	100 and 250 µg/ puff	Asthma, and COPD	Flixotide Diskus®	7.62 to 15.11	GlaxoSmithKline (GSK)	(GSK, 2020a) (JFDA, 2020)
Nebulizer		0.5mg /2ml	Asthma, and COPD	Flixotide Nebulas®	Not available in Jordon	GlaxoSmithKline (GSK)	(GSK, 2020b)

2.2.2. Vapes

Although e-cigarettes have been around for more than a decade, vaping rose in recent years, mostly among youth and young adults. E-cigarettes are now the most frequently used tobacco product among adolescents. Almost 2.1 million youth and young adults were reported as e-cigarette users during 2017. Which is higher than the rate of traditional combustible cigarettes. One popular vape device that comes in multiple flavors, which delivers high levels of nicotine. The market's vape size exceeded the $10 billion in value (Jones, 2019).

Vaping is inhaling and exhaling the vapor produced by the heated nicotine liquid (often called “juice”) of an electronic cigarette (e-cigarette or e-cig) (Martinelli, 2020). Although vapes have some risks associated with vaping, it appears to be a little severe than traditional combustible cigarettes (e.g., absence of tar). Some of the reported risks during vaping are 1) high levels of nicotine, 2) because of this high nicotine level, vaping is extremely addictive (Martinelli, 2020),

3) the long-term side effects are not known yet (Jones, 2019), 4) some sweeteners and flavors of the e-cigarettes are irritants and potentially may cause inflammation of the airways (Jones, 2019).

A research conducted by Breitbarth and co-workers (2018) revealed that e-cigarettes have been extensively used as a new route for administration of illegal drugs. Hence e-cigarettes and /or vapes could be a suitable alternative for regular nebulizers, pMDIs and DPIs (Breitbarth, Morgan and Jones, 2018).

In a study to compare the effect of vapes on the level of nicotine when compared to regular cigarettes, results revealed that regular cigarette smokers exhibited lower nicotine plasma levels at all time-periods; at 5-minutes the levels were lower by 46%, while during the subsequent period they were lower by 43% (at 65-minutes) to 54% (at 20-minutes) (Farsalinos *et al.*, 2015). Such alarming results provide an insight to the potential effect of vapes as quick onset and efficient drug delivery system. Table 2.3 summarizes all vapes types that are present in the market so far.

Table 2. 3: Types of the commonly used vapes highlighting it characteristics

Name	Description / advantages	Reference
1. Cig-A-likes	• First generation devices were called **cig-a-likes** due to the similar appearance of cigarettes. • Made of two parts: the battery and the cartridge. • Inside each cartridge, the atomizer coil heats the liquid nicotine mixture to produce the vapor each time a puff is taken. • The cartridges usually come filled with the e-liquid. • Each cartridge usually represents 1.5-2 packs of traditional cigarettes. • It usually lasts between about 300-400 puffs. • This type of vape is small and easy to use.	(Ruthlessvapor, 2019; Vaporferver, 2019).
2. Vape Pens	• The second-generation vape devices that are larger than the Cig-A-Likes to increase performance power in two areas: battery and atomizer. • Generally termed vape pens and are often used as a starter kit for people who are new to vaping. • It has a button to turn the battery on/off and used as a firing mechanism. • A chip regulates how long you can hit the device to prevent overheating. • It contains a container to refill the nicotine containing e-juice.	(Ruthlessvapor, 2019).

Name	Description / advantages	Reference
3. Mods (Box Mods)	• The Third generation of vapes that includes two types: A. **<u>Regulated Mods:</u>** contain a chip that regulates the electrical current as a safety mechanism. It also provides variable voltage to increase and decrease the power. B. **Unregulated Mods**: these devices do not have a chip to prevent overheating. Instead, they are limited by the resistance of the coil and the user's choice. They are given the term mechanical mods. Mechanical mods are not for beginner vapers since it takes a working knowledge of Ohm's law, electrical systems, and can be extremely dangerous if the battery is pushed to its limits. • Mods are metal tubes with a battery and an atomizer.	(Ruthlessvapor, 2019).
4. Pod mod	• Pod mods are the latest devices that are gaining popularity in the vaping community. • They are low wattage devices that are similar to a cig-a-like and are used with nicotine salt e-juices. • They are a new and improved version of the cig-a-like, and they are the latest device in the market • There are different types of pod mods: A. **Closed Pod Systems** are disposable devices with pods that are pre-filled with e-liquid. Like coffee pods, once the pods are finished, it is replaced. B. **Open pod Systems** are filled manually by buying the choice of nicotine salt e-liquid bottle. The cartridges are then replaced after an average refill of 4-5 times	(Ruthlessvapor, 2019).

The third generation of devices have a longer battery life, large different flavored liquids, modification options are primarily rechargeable, deliver more nicotine to the lung. This type will be investigated in this project along with the pod mod

Vapes popularity comes from provision of liquid nicotine with several flavor, with a claim that it does not contain carcinogenic substances as in combustible cigarettes. But nicotine that is present in e-liquids is a toxic alkaloid, highly addictive substances (Gomółka, Radomska and Bielska, 2016). Some e-liquid refills contain nicotine in varying amounts, but others may be nicotine-free (Martinelli, 2020). Harmful substance in an e-cigarette are not limited to nicotine alone, there are around 8,000 known e-liquid flavors available on the market today that contain aldehydes, organic ingredients often associated with aromas (such as those of berries), and other additives used for

flavoring that were not tested for suitability in inhalation. Hence the danger from using vapes.

Mode of action of vapes

Despite the toxicity encountered in vapes, the materials used in vapes such as vegetable glycerin and propylene glycol are FDA approved for use in pharmaceutical industry and both of them within the GRAS list (Generally Recognized as Safe) (FDA, 2019). Even though the use of materials that are in the GRAS list are understood to be safe for food and drug delivery system, it was not tested for smoking or vaping. The effects of these ingredients when subjected to heat or vaporization and found that they can cause the formation of formaldehyde and other cancer-causing chemicals (Healthline, 2019).

A recent study found that most people who intended to use vapes to support them stop the smoking habit, ended up continuing to smoke both traditional cigarettes and vapes (Baha, 2020).

Vapes heat nicotine, flavorings and other chemicals to create an inhalable aerosol (Figure 2.1) (Baha, 2020). An atomizer heats the liquid (often called "e-juice") to its boiling point and that becomes an inhalable vapor. That is why smoking e-cigarettes is often called “vaping.”(Dunworth, 2019). The definition of an atomizer is “a device for emitting water, perfume, or other liquids as a fine spray.” In vape terms, the word refers to any device that vaporizes e-liquid (Vaping 360, 2020).

Figure 2. 1 Mechanism of work of vapes adopted from (Dunworth, 2019; Vapeclub, 2020)

2.2.2.1. Vapes formulations

key element in vapes is the vape juice, which is the formulation that contains nicotine. Vape juice is mainly made of 1) propylene glycol (PG) with concentration of 50% or more, 2) vegetable glycerin (VG) where a 50/50 vapes juice is made (50% PG and 50% VG), a high VG E-Liquid – is made with 70% or more VG, 3) nicotine salt E-Liquid: nicotine salt e-liquids contain different types of nicotine salts (Dunworth, 2019; Vapeclub, 2020).

2.2.2.2. The designs of the Vape devices used in this project

There are different types of vapes from the third generation as was discussed in Table 2.1. The main types are listed below.

Vape box (box mods) with tank

This vape from (Greek vape) this device consists of a mouthpiece, a battery, a cartridge for containing the e-liquid or e-juice, and a heating component for the device that is powered by a battery (Figure 2.2). When the device is used, the battery heats up the heating component, which turns the contents of the e-liquid into an aerosol that is inhaled into the lungs and then exhaled. It has a screen and bottom for controlling the heating temperature and nicotine concentration. (Geek Vape, 2020).

Figure 2. 2. A graph highlighting the Vape Tank showing its components (Vape, 2020)

The advantages of this device include more battery power resulting in higher wattage capability, longer life of the device between charges, and better cloud production. The increased wattage and performance of box mods give the advantage of more vapor production per hit, and thus, bigger clouds (Vaping.com, 2020).

Vape box with Coil

The vape coil tank from (Greek vape) this device comes with 1ml tank form Maze company. This tank consists of two cotton and two heat-resistant metal wires for nicotine evaporation (Figure

2.3). This is installed on a regular vape (vape box) to give more nicotine smoke and is used a lot in young adults.

Figure 2. 3: A graph highlighting the Vape coil showing its components (Vaping.com, 2020).

The coils are wire that connect to a base, which in turn connect to the battery. When the battery is deployed, the wires heat up and vaporize the e-liquid. A single-coil atomizer head has just one single wire that is coiled up with the filament material running through it (Vaping.com, 2020). Key advantages include fast heat process, no burning taste upon dry hits, reduced chance of getting the unpleasant taste, easy to clean and produces more cloud when compared with regular tank (Vaping.com, 2020).

Vape pod (pod system)

The first pod systems were designed to look similar to cigarettes, which makes sense since they were designed to help users quit smoking – or at least cutback. These devices usually contain liquids that are made with salt-based nicotine. It has several merits such as these are easy to use, require low maintenance, user-friendly, and perfect for nicotine lovers, cheap price (Sunan, 2019).

It is a mini vape based on a two-part system: a pod filled with vape juice that snaps into a small battery. They are available in pre-filled or refillable designs. Some will have power buttons but often they're automatic (Figure 2.4) (Tobacco and vape mart, 2019). These systems are user-friendly and do not harm or hurt the throat as with traditional smoking. Moreover, you do not need to lit the fire or lighter because these are operated with an electronic battery (Sunan, 2019).

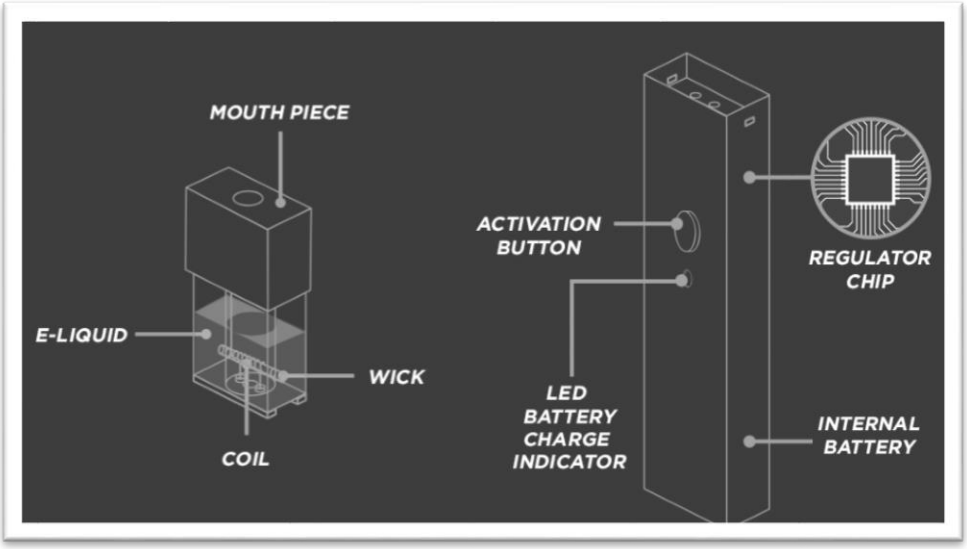


Figure 2. 4. A graph highlighting the Vape pod showing its components adopted from (Sunan, 2019)

Pod vape kits work like any other vape kit. E-liquid held in the dedicated pod is heated up by the battery, to the point it creates visible vapor. This vapor is then inhaled by the user. Inside each pod is a metal heating element known as a coil. It is the coil that converts that power supplied by the battery into heat. Wrapped around the coil is a piece of cotton, or a wick, which serves to soak up the e-liquid that's held in the pod (Vapeclub, 2020).

Chapter Three

Materials and Methods

3.1. Materials

Nicotine (hydrogen tartrate salt) was purchased from Sigma Aldrich (Pool, UK). Fluticasone propitiate was obtained from Acros Organics/ Thermo Fisher (Geel, Belgium). Dibasic potassium phosphate (K_2HPO4), potassium dihydrogen phosphate (KH_2PO_4), and ethanol were purchased from Honeywell International Inc. (NC, USA). Additionally, HPLC grade distilled water (DW), disodium hydrogen phosphate, sodium chloride, propylene glycol, glycerine and hydrochloric acid were purchased from AZ Chemicals, Inc. (ON, Canada). The vape devices that were used in this project are: 1**)** the vape box with tank (will be termed vape-tank in this manuscript) which was produced by Geek vape company and is marketed as Aegis ligand kit, 2) the vape box with coil, the coil was produced by Maze company and the coil was attached to the vape box with tank 3) the pod system which was produced by JustFog company and is given the brand name Mine Fit portable pod system. The three devices were purchased from the local market merchants. The nicotine e-liquid (vape juice) was produced by Johnny Creampuff - Lemon E-juice which contains 6 mg nicotine /ml as well as salt nicotine containing 30 mg nicotine/ ml (VCT Bold) produced by Ripe Vape company. Both e-liquids were purchased from the local market merchants.

3.2. Methods

3.2.1. Preparations of phosphate buffer

USP method for the preparation of phosphate buffer pH 6.8 was employed. First, 27.22 g of potassium dihydrogen phosphate (KH_2PO_4) were accurately weighed and dissolved in 1000 ml of DW in a volumetric flask to form solution 1. Then 8 g of sodium hydroxide (NaOH) were accurately weighed and dissolved in 1000 ml of DW in volumetric flask forming solution 2 and

producing 0.2 M of NaOH. Then 125 ml from solution1 were added to 62.72 ml from solution 2 and further diluted to 500 ml with DW. The pH was measured using calibrated pH meter (Lohand Biological, China).

3.2.2. HPLC methods validation for the quantification of APIs

3.2.2.1 HPLC method for nicotine

Accurately weighed 100 mg of nicotine (hydrogen tartrate salt) was dissolved in 100 ml of phosphate buffer in volumetric flask forming 1 mg/ml stock solution. HPLC method for the quantitative analysis of nicotine in phosphate buffer solution was developed using Dionex Soften HPLC system from Thermo Fisher Scientific Inc.(MA, USA), with gradient pump, UV detector set at 254 nm and 5 µm Fortis C-18 analysis column (250 * 4.6 mm). The analytical method was based on a published method for the analysis of nicotine in pure form and from formulations (Tambwekar, Kakariya and Garg, 2003). The mobile phase consisted of phosphate buffer (pH 6.8, 19mM): methanol (35:65% v/v). Flow rate was set at 1 ml /min with sample injection volume of 50 µl. The HPLC method was validated according to ICH guidelines of specificity, accuracy, precision and linearity, limit of detection and limit of quantification (ICH, 2005).

3.2.2.2 HPLC method for fluticasone propionate

Fluticasone propionate stock solution was made from 10 mg of fluticasone propionate in 100 ml of acetonitrile (100 µg/ml). HPLC method was employed for the quantitative analysis of fluticasone propanoate in the solution. Dionex soften HPLC system of Thermo Fisher Scientific Inc. (MA, USA), with gradient pump UV detector set at 256 nm using 5 µm Fortis C-18 analysis column (250 * 4.6 mm). The method was developed using a mobile phase consisting of 60%

acetonitrile and 40 % DW. Pump flow rate was 1 ml/min with sample injection volume 10 µl and run time 10 min.

Validation of the method was done according to ICH guidelines in terms of specificity, accuracy, precision, linearity and limits of detection and limit of quantification. To investigate the specificity of the HPLC method, 50 µL each of the stock solution *(*fluticasone propionate 100 µg/ml), and mobile phase as a blank were separately injected to the HPLC and chromatograms developed

3.2.2.3 Linearity

A Beer-Lamberts calibration curve graph was constructed by plotting the mean peak area against the concentration of nicotine. Linearity was estimated by computing the regression line of the calibration curve for nicotine concentration that ranged from 7.8125- 250 µg\ml dissolved in the mobile phase or fluticasone propionate concentration that ranged from 7.8125- 62.5 µg\ml dissolved in the mobile phase. The correlation coefficient (R^2) was calculated for the two curves.

3.2.2.4 Accuracy

Aliquots of 50 µl of serial dilutions of nicotine solutions or 10 µl of serial dilutions of fluticasone propionate were injected into the HPLC system and the protocol described for linearity above was followed. The peak (AUC) for nicotine and fluticasone were recorded and the percentage recovery was calculated using the regression equation.

3.2.2.5 Precision

Precision was evaluated by developing the nicotine and fluticasone calibration curves in triplicates. Therefore, repeatability and intermediate precision were determined. The AUC was measured and recorded also relative standard deviation (RSD) was computed using equation 3.1

$$\boldsymbol{RSD = \frac{Standerd\ Deviation}{mean} \times 100} \ldots\ldots\ldots\ldots \boldsymbol{Eq\ (3.1)}$$

Also, precision was evaluated by preparing and measuring the 50 µg/m of nicotine and 62.5 µg/ml of fluticasone propionate ten times. Therefore, repeatability and intermediate precision were determined. The AUC was recorded and relative standard deviation (RSD) was computed using equation (3.1). Calibration curves were repeated (n=3) using freshly prepared stock solution and the RSD was calculated.

3.2.2.6 Limit of Detection (LOD) and Limit of Quantification (LOQ)

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

LOD and LOQ were determined based on the Standard Deviation of the Response and the Slope. The LOD and LOQ were calculated based on the following equation 3.2 and 3.3 respectively.

$$\boldsymbol{LOD = \frac{3.3 \times \sigma}{S}} \ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq\ (3.2)}$$

$$\boldsymbol{LOQ = \frac{10 \times \sigma}{S}} \ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq\ (3.3)}$$

Where σ is the standard deviation of the response whereas, S is the slope of the calibration curve (ICH, 2005).

3.2.3. Development of fluticasone propionate inhalation solution for use in the vape device

An accurately weighed 10 mg of fluticasone propionate (FP) was placed in a 10 ml beaker then dissolved in 1ml of acetone. The solution was then added to 30 ml of a mixture of 50:50 v/v of propylene glycol and glycerine and then mixed by magnetic stirrer for 30 minutes with hot plate set at 60 ℃ to ensure the acetone was evaporated. The solution was placed in tightly closed container in the refrigerator and maintained at a temperature of 2-6 ℃ until further use. The concentration of the final solution was 0.33 mg/ml. The amount of FP in each inhalation was calculated from the weight of the solution that was actuated, which resulted in 100 µg/inhalation of FP. The marketed FP pMDI contained 125 µg/ puff.

3.2.4. Assessment of aerodynamic particle size distribution of nicotine using next generation impactor (NGI)

The *in-vitro* deposition and aerodynamic particle size distribution analysis were conducted using the next generation impactor (NGI) (Copley scientific limited, Nottingham, UK.). Flow rate was set 60 L/min over 4 second to provide four litters of air at a pressure drop of 4 kPa. Aerosolization performance of nicotine was determined using three type of vapes (vape tank, vape coil and vape pod mod). The vapes were set on medium heat of 150 °C and 70 W for the vape tank and vape coil, while for the vape pod mod the temperature and wattage were fixed at 98-110 °C and could not be altered. Each e-liquid container was filled with 2 ml of nicotine juice and 6 actuations were made for analysis of fine particle fraction from emitted dose (FPF-ED) and nominated dose (FPF-

ND), emitted dose (ED) and concentration of nicotine in each puff. Samples were collected in each test by dissolving the content of each stage (including the mouthpiece, induction port, and the eight stages) with 10 ml of phosphate buffer. Each sample was then transferred into volumetric flasks and filtered through 0.22 µm membrane filter prior to HPLC analysis. Special adaptors were custom made to enable the vape tank and coil to fit into the induction tube of the NGI. Each vape was tested in triplicate with tests performed at room temperature (20-25 °C).

3.2.5 Assessment of aerodynamic particle size distribution of fluticasone propionate using next generation impactor (NGI).

The *in-vitro* deposition and aerodynamic particle size distribution analysis were assessed using the NGI (Copley scientific limited, Nottingham, UK). Flow rate was set 60 L/min over 4 second to provide four litters of air at a pressure drop of 4 kPa. Aerosolization performance of fluticasone propionate liquid was determined using three type of vape each one filled with 2 ml of (fluticasone liquid) and 6 actuations were made into the NGI to analyze the FPF, ED and the concentration of fluticasone in each inhalation . Samples were collected from each test by dissolving the content of each stage (including the mouthpiece, induction port, and the eight stages) with 10 ml acetonitrile. Each sample was then transferred into a volumetric flask, ultrasonicated for 10 mins and filtered through 0.22 um membrane filter prior to HPLC analysis. Samples were stored at 5°C in HPLC amber vials. Special adaptors were custom made to enable the vape tank and coil to fit into the induction tube of the NGI. Each vape was tested in triplicates with tests performed at room temperature (20-25 °C). The same process was used to examine the deposition and aerodynamic particle size distribution of the FP pMDI (Flixotide®).

3.2.5. Content uniformity

The HPLC method as described above was employed to assess content uniformity of FP liquids. A solution of FP was prepared by dissolving 1 ml of fluticasone solution in 10 ml of acetonitrile then injected into the HPLC.

3.2.6. Mass median aerodynamic dimeter (MMAD) calculation

MMAD was calculated using an online application (MMAD Calculator, 2020). The flow rate was selected to be 60 L/min through the NGI from the drop-down menu. The mass collected from each stage was then added from stage one to stage eight to calculate MMAD and geometric standard deviation (GSD).

Chapter Four

Results and Discussion

4.1 HPLC methods validation

4.1.1 HPLC Assay for nicotine

HPLC method for nicotine was validated according to ICH Q2(R1) guidelines (ICH, 2005). The standard nicotine peak was well resolved with retention time of 5.957 ± 0.5035 minutes. There was no interference from the solvent front which eluted at 2.587 ±0.020 minutes. The sample was run over 10 minutes to ensure that the peak appearing at 5.84 minutes is the only one related to nicotine as can be depicted in Figure 4.1.

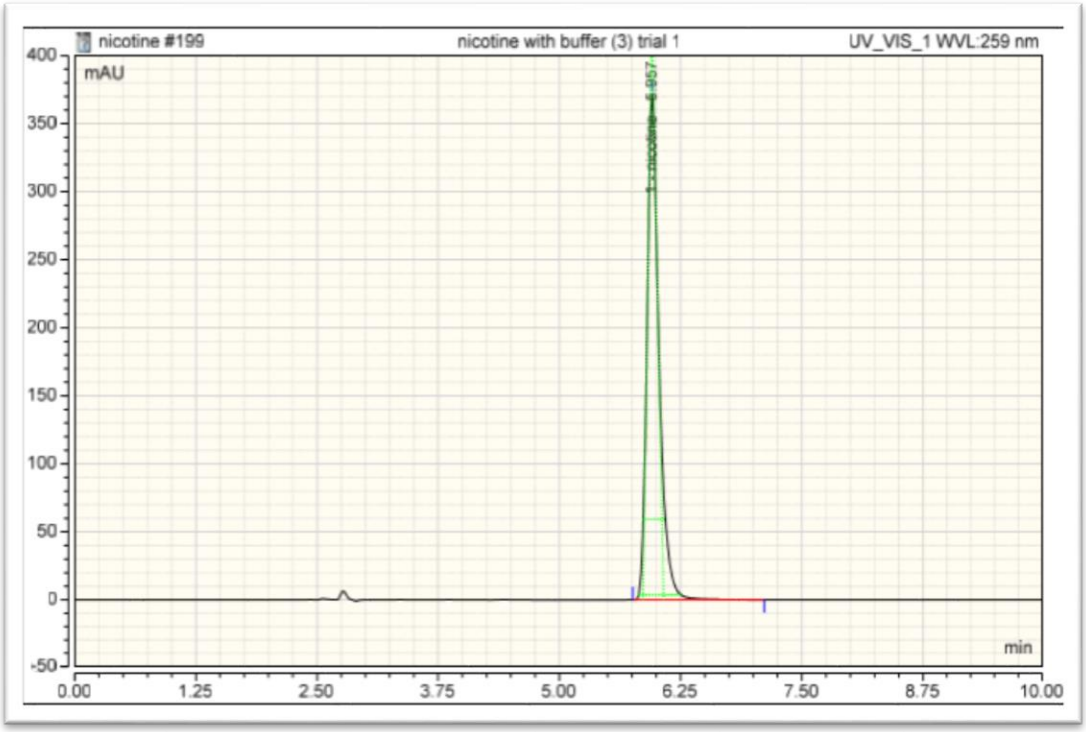


Figure 4. 1: HPLC chromatogram for nicotine with a retention time at 5.957mins.

4.1.1.1 Specificity of nicotine

In order to assess the specificity of the HPLC method to the nicotine and that none of the excipients are interfering with the peak of it, stock solutions of all excipients in the formula were tested separately and the results were recorded and reported (see Figure 4.2). There was no interference between the excipients within the formulation and nicotine thus, this method was considered to be specific for the quantification of nicotine.

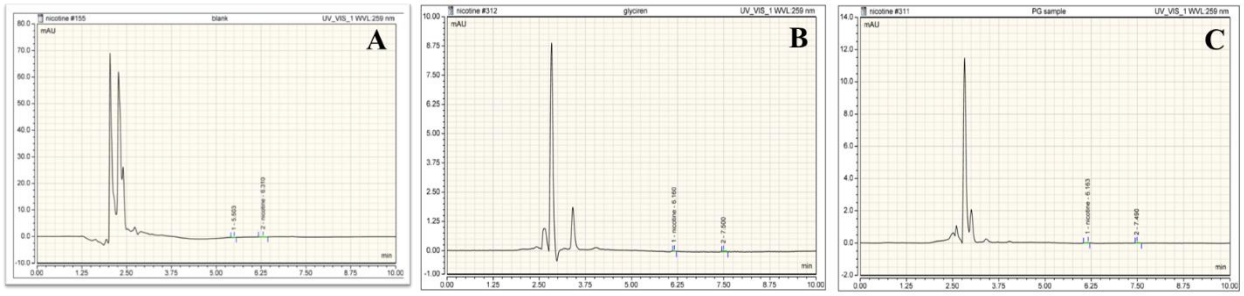


Figure 4. 2: HPLC chromatogram for **(A)** Blank samples (phosphate buffer), **(B)** Glycerin and **(C)** Propylene Glycol.

4.1.1.2 Linearity

A Beer-Lambert calibration curve was established by plotting AUC against nicotine concentrations that ranges from 7.8125- 250 µg/ml with coefficient of variation R^2= 0.9998 (Figure 4.3).

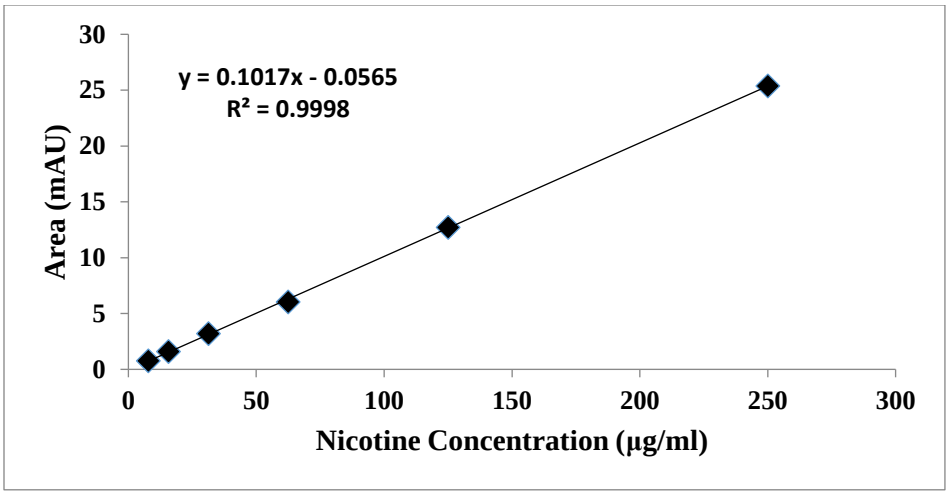


Figure 4. 3: Calibration curve of nicotine over concentration range from 7.8125- 250 µg/ml (mean ± SD, n=5).

4.1.1.3 Precision, accuracy, LOD and LOQ

The recovery method has been employed to investigate the precision of the HPLC assay procedure, that was performed by preparing one known concentration of 250 µg/ml of nicotine stock solution, ten samples were measure from the same solution and results showed an average of 100.51% ± 1.17% (RSD, 1.16%). The results showed the process is precise with RSD below 2%. Further, the Limit of detection (LOD) and limit of quantification (LOQ) of nicotine were then determined by using standard deviation of the response and the slope as stated in the ICH guidelines, was LOD=4.087 µg/ml and LOQ=13.623 µg/ml. The Accuracy of the method is the description of the closeness of the measured value to the true value for the sample. Therefore, the recovery experiments were employed to determine the intermediate precision and reproducibility as an indication of the accuracy of the method. Four different concentrations were prepared, three samples per concentration (see Table 4.1).

Table 4. 1: Percentage recovery of four concentrations of Nicotine repeated three times on three days to show the intermediate precision and reproducibility of the analytical technique.

A. Reproducibility				
Theoretical concentration of Nicotine (µg/ml)	**Intraday % Recovery (mean ± SD) (n=3)**	**Intraday %RSD (n=3)**	**Interday % Recovery (mean ± SD) (n=9)**	**Interday %RSD (n=9)**
250	100.01 ± 0.59	0.59	100.77 ± 1.65	1.64
125	102.90 ± 0.18	0.18	98.96 ± 4.21	4.25
62.5	100.07 ± 0.96	0.96	100.27 ± 1.51	1.50
31.75	99.77 ± 0.18	0.18	98.76 ± 0.87	0.88
B. Precision	**% Recovery**	**RSD**		
Concentration 50 µg/ml, n=10	100.51% ± 1.17%	1.16%		
C. LOD & LOQ		**µg/ml**		
LOD		4.087		
LOQ		13.623		

4.1.2 HPLC Assay for FP

Like the procedure employed for nicotine; HPLC assay validation of fluticasone propionate started with peak identification. The standard fluticasone peak was well resolved with a retention time of 7.203 ± 0.5035 minutes. There was no interference from the solvent front which eluted at 2.00 ±0.020 minutes (Figure 4.4). The sample was run over 10 minutes to ensure that the peak appearing at 7.203 minutes is the only one related to fluticasone propionate.

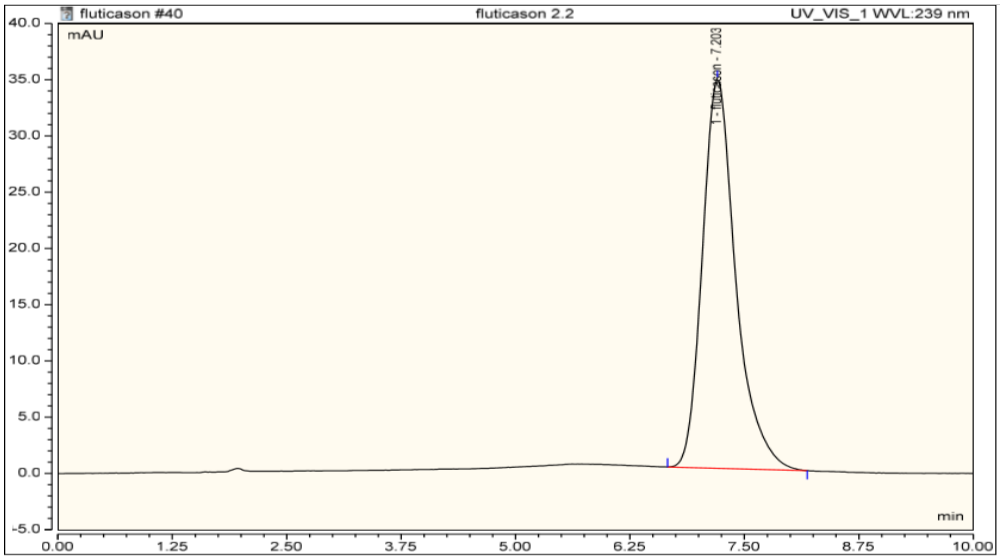


Figure 4. 4: HPLC chromatogram for fluticasone propionate, retention time (7.203 minutes) using HPLC.

4.1.2.1 Specificity of HPLC analytical method for FP

To assess the specificity of the HPLC method to FP and that none of the excipients are interfering with its peak, stock solutions of all excipients in the formulation were tested separately and the results showed no interference between the excipients in formula and FP. Thus, this method was specific in the quantification of FP despite the presence of other inactive ingredients in the formula.

4.1.2.2 Linearity

A Beer-Lambert calibration curve was established by plotting AUC against fluticasone propionate concentrations that ranges from 7.8125- 62.5 µg/ml (see Figure 4.5).

4.1.2.3 Precision, accuracy, LOD and LOQ

The Accuracy of the method is the description of the closeness of the measured value to the true value for the sample. Therefore, the recovery experiments were employed in order to determine the intermediate precision and reproducibility as an indication of the accuracy of the method. Three different concentrations were prepared, three samples per concentration. The results clearly as

depicted in Table 4.2 that illustrate the accuracy of the method. Recovery experiments were allocated to investigate the precision of the procedure, that was performed by preparing one known concentration of 62.5 µg/ml of FP standard solution, ten samples were measure and results showed 101.87 ± 1.94 and RSD of 1.90%. The results showed the process is precise owing to low RSD. The LOD and LOQ of cholecalciferol were then determined by using standard deviation of the response and slope as stated in ICH guidelines. Was LOD=2.04 µg/ml and LOQ=6.812 µg/ml.

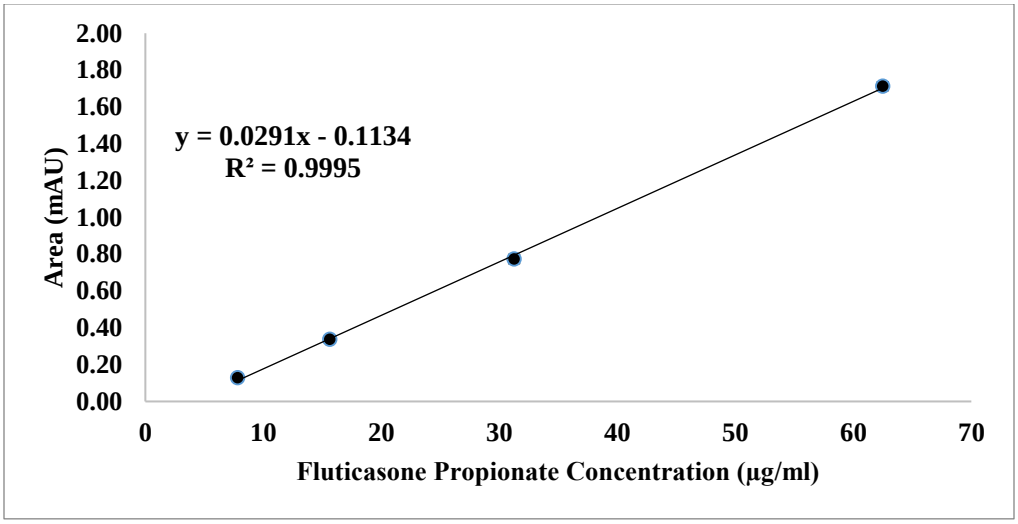


Figure 4. 5: Calibration curve of fluticasone propionate over concentration range from 7.8125- 62.5 µg/ml (mean ± SD, n=5).

Table 4. 2: Percentage recovery of four concentrations of fluticasone propionate repeated three times on three days to show the intermediate precision and reproducibility of the analytical technique.

Theoretical concentration of fluticasone propionate (µg/ml)	Intraday % Recovery (mean ± SD) (n=3)	Intraday %RSD (n=3)	Interday % Recovery (mean ± SD) (n=9)	Interday %RSD (n=9)
62.5	100.35 ± 1.31	1.31	100.71 ± 0.37	0.37
31.25	97.53 ± 2.79	2.86	98.77 ± 2.93	2.96
15.625	98.93 ± 0.72	0.73	100.60 ± 2.64	2.63
7.8125	106.61 ± 1.39	1.31	101.35 ± 1.78	1.76

4.2 In-Vitro comparison of the performance of marketed vapes in delivering nicotine using NGI

The first part of the investigations is focused on employing the NGI to assess the performance of commercially available vapes. A new adaptor was made to enable an airtight connection of the vape to the mouthpiece of the NGI (see Figure 4.6). Such custom-made tubing was essential to ensure effective process for vape tank and vape coil. Each vape was tested three times and in each test the inhaler was actuated 6 times to ensure adequate concentration of the nicotine within the NGI stages for quantification.

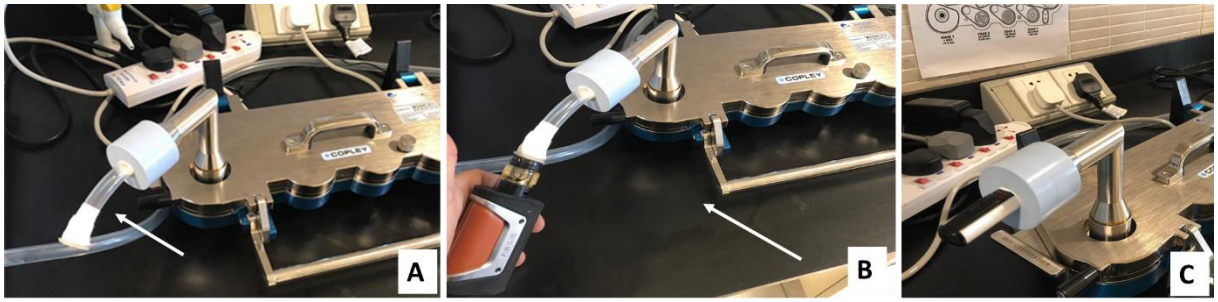
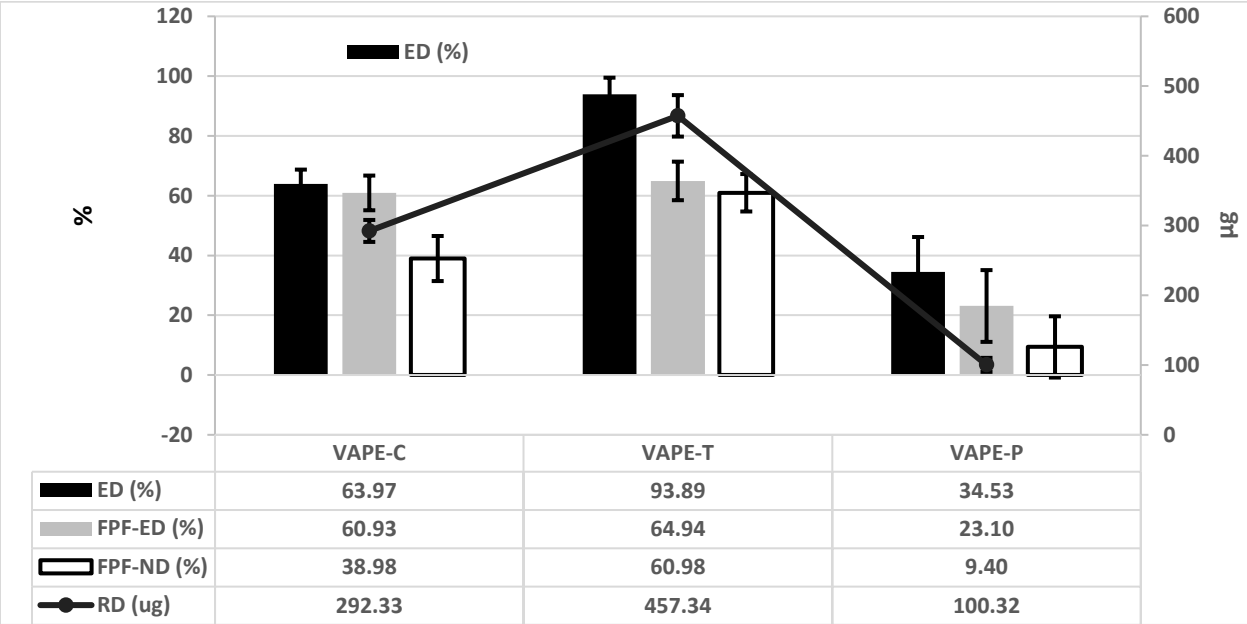


Figure 4. 6: Assembly for connecton of the vapes to the NGI equipment to enable testing it. (A) the adaptor to the mouth piece to be used with vape tank (white arrow) and vape coil, (B) the adaptor connected to the vape tank (white arrows), (C) the pod does not require special custom made adaptor and fits well in the mouth piece.

With the increase in the number of available nicotine delivery devices/ vapes, little is known about the efficiency in nicotine delivery among brands. Although other characteristics are vital such as taste, ease of use, puff resistance, cloud volume and user friendliness of the device as well as cost, the nicotine delivery effectiveness is paramount (Hajek *et al.*, 2017). Therefore, this study aimed at determining the efficiency of the most commonly utilized vapes. To effectively deliver a substance into the respiratory tract, the aerodynamic particle size of the aerosol needs to be less than 5 μm in size, which is termed the fine particle fraction (FPF) and is the most common method used to assess in vitro performance. Results for the key inhalation parameters (emitted dose

(%ED), FPF of emitted dose (%FPF-ED), respirable dose (RD) and FPF from the nominated dose (FPF-ND)) were assessed (triplicate NGI readings from the same batch) with results depicted in Figure 4.7. The ultimate aim of vapes is to deliver a high concentration of nicotine into the lower parts of the respiratory system.



	VAPE-C	VAPE-T	VAPE-P
ED (%)	63.97	93.89	34.53
FPF-ED (%)	60.93	64.94	23.10
FPF-ND (%)	38.98	60.98	9.40
RD (ug)	292.33	457.34	100.32

Figure 4. 7: Summary aerodynamic performance using NGI for three types of marketed nicotine vapes. Each puff contains 750 µg nicotine. **VAPE-C**: Vape Coil, **VAPE-T**: Vape Tank, **VAPE-P**, Vape pods. Results are presented as mean± SD, n=3. **ED**: %Emitted dose, **FPF-ED**: Fine Particle Fraction of Emitted Dose, **FPF-ND**: Fine Particle Fraction of Nominated Dose, **RD**: respirable Dose.

From the graph, the vape tank produced the highest amount of nicotine among the three marketed products, where the emitted dose, FPF-ND and the respirable dose were significantly higher than those of coil and pod (one way ANOVA, $p<0.001$). The theoretical dose was calculated based on the weight difference upon actuation. Using the density and weight difference upon actuation, each actuation should theoretically deliver around 750 ± 32.5 µg for nicotine tank and coil and 1070 ± 54.1 µg for nicotine pod. Despite similar nicotine content in each dose in vape tank and coil, the

performance of the devices varied. Even with the presence of coil in the tank vape device, the amount vaporised and emitted dose from the device were larger in the tank with atomizer.

Of the main reported challenges in nicotine delivery devices is the uniformity of delivered does, which is a critical quality attribute (DeVito and Krishnan-Sarin, 2018). The emitted dose, which represents the percentage of the nominal dose that is emitted from the device upon actuation. As can be noted from Figure 4.7, the emitted dose varied significantly between vape coil and vape tank (63.97 vs 93.89 respectively) despite the use of the same e-liquid. Similarly, the emitted dose of the vape -pod showed significantly lower value despite the use of higher nicotine concentration liquid. The vape pod, showed higher variation between actuations as can be seen from the large error bars. FPF from emitted dose represents the percentage of fine particles that can reach the lower part of the respiratory system. The higher the FPF the higher the possibility of systemic absorption of nicotine. Furthermore, a good representation of FPF is when the FPF from nominal dose is evaluated (FPF-ND) where the results showed higher levels of FPF-ND from vape tank (69.94%) which is high, whereas vape -pod revealed FPF-ND of only 9.4%. When the results are presented in terms of respirable dose which presents the mass of the nicotine that is in the micron size that would deliver to the lower parts of the respiratory system, the vape tank was superior followed by vape-coil followed by vape pod. Despite the popularity of vape pod and the very high nicotine concentration of the liquid, it showed undesirable performance when compared to vape coil and tank. In general, vapes operate by developing an aerosol made of humectant (glycerine and propylene glycol) nicotine and flavoring agent through the heat produced by the battery operated vaping devices (Kalkhoran and Glantz, 2016). The aerosolized liquid is then inhaled by the user. However, variations among amount of delivered nicotine is primarily dependent on the type of the vape. A study by Lechner and colleagues in 2015 reported that the second- generation

e-cigarettes are more effective in reducing symptoms of nicotine withdrawal than first- generation ones (Lechner *et al.*, 2015). The results support our finding that the second generation vape tank produces a higher RD. A study by Hajeck and coworkers in 2017 revealed that the most important parameter in nicotine delivery devices for smokers is the overall nicotine delivered and the speed of its absorption. If higher percentage is delivered to the lower parts of the respiratory system due to its smaller aerodynamic particle size, the faster the anticipated absorption and hence bioavailability of nicotine. The study also reported that earlier nicotine delivery devices were delivering less nicotine than cigarettes, however, recent devices particularly those entailing high power setting have superior nicotine delivery (Hajek *et al.*, 2017).

The aerodynamic particle size distribution parameters obtained using the NGI and three marketed vape devices with the cut-off diameter specifications of the NGI set at 60l/min were compared (Figure 4.8). From the figure, the three devices showed similar pattern of particle size distribution. Table 4.3 also, highlights the cutoff diameter of stages for the NGI showing that from stage 2-7 is the range that may produce deposition within the lower parts of the pulmonary system. The three vape devices had bi-modal aerodynamic particle size distribution the first part is the particles deposited extra-thoracic with particles exceeding 8 µm (particles deposited at the mouthpiece, induction tube and stage 1). Then little was deposited within the particle size rage of 1.66-4.46 µm (stages 2-4) indicating that the produced aerosols particle size was low where the greatest proportion was produced between the range of 0.34- 1.66 µm (stages 4-7). Although, the percentage of produced particles of vape-tanks and vape coil are higher, the trend of aerodynamic particle size distribution is similar.

Previous studies have described nicotine delivery from electronic nicotine delivery devices. First-generation devices have been reported to have relatively low nicotine delivery, and some studies

later showed that the second and third generation devices had increased plasma nicotine concentrations compared to those of first-generation ones. In this study an average voltage was used to produce temperature of around 150 °C (wattage 70 W) for the tank and coil vapes. While the vape pod had a set wattage that cannot be altered. Research results observed an increase in nicotine level with the increase in voltage of the device, but described the nicotine level as complex since individuals can adjust puff duration, velocity and voltage output (Peace *et al.*, 2018; Mulder *et al.*, 2019). However, the selection of low temperature was based on data obtained from literature that the mass of aerosol and the production of aldehydes, formaldehyde, acetaldehyde and acrolein is produced and increased with increasing voltage and temperature beyond 200 °C (Peace *et al.*, 2018).

The tested e-liquid contain propylene glycol (PG), glycerin (GL) and flavoring agent. It is reported that PG and GL, the main carriers used in e-liquids, go through decomposition in contact with the atomizer heating-coil forming volatile toxic material, such as, formaldehyde, acetaldehyde and acrolein. These toxic chemicals are reported to produce adverse effect on human health upon inhalation at sufficient concentrations. A sharp increase in the generated toxic materials was observed when applying a battery-output that corresponds to 200–250 °C on the heating coil. For that reason, this study employed a battery -output that produces 150 °C only to minimize the magnitude of released volatile toxic chemicals (Geiss, Bianchi and Barrero-Moreno, 2016).

Table 4. 3: Cutoff aerodynamic diameter for stages of NGI apparatus set at 60L/min (adopted from (USP-31, 2008)

Stage	**Cut off diameter D_{50}**
1	8.06
2	4.46
3	2.82
4	1.66
5	0.94
6	0.55
7	0.34

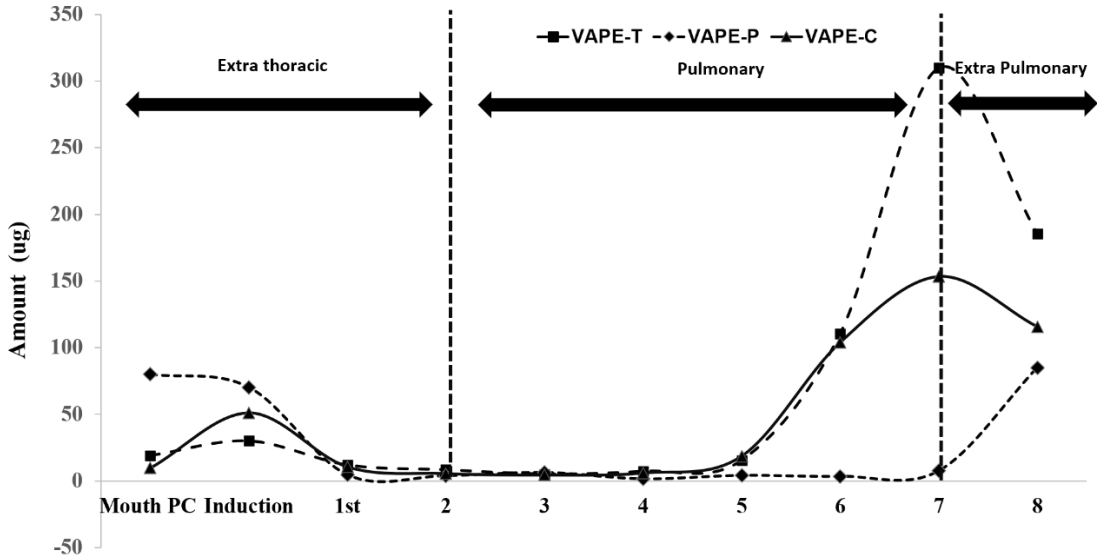


Figure 4. 8: *In vitro* comparison of aerodynamic particle size distribution of the marketed vapes products demonstrating the lung deposition of nicotine using NGI set at flow rate of 60l/min.

The mass median aerodynamic diameter (MMAD) values obtained for the three devices using the NGI set at 60l/min are depicted in Table 4.4. The results revealed that the MMAD values for vape coil and vape tank were similar while the MMAD produced from vape pod was lower. However, there is no statistically significant difference among them (one-way ANOVA, p= 0.33). Furthermore, examination of the geometric standard deviation (GSD) revealed that the vape tank produced aerosols with the lowest spread of particle size (GSD) while the vape pod produced the widest distribution with GSD approaching 4.8. The difference between device types is statistically significant (one-way ANOVA, p= 0.0005). Tukey post hoc test showed that the difference is between vape tank and vape pod (p=0.0005) and vape coil and vape pod (p= 0.0008) are significant whereas between vape coil and vape tank is not significant (p=0.9059).

Table 4. 4: MMAD and GSD values for the vapes

Device Type	Vape Coil	Vape- Tank	Vape- Pod
MMAD (µm)	**0.46 ± 0.09**	**0.42 ± 0.07**	**0.34 ± 0.11**
GSD	**1.65 ± 0.25**	**1.46 ± 0.19**	**4.8 ± 0.89**

The results of our research are in line with results obtained from the research of Mulder and coworkers which revealed that vape coil produced small aerosol particles with MMAD value of 0.3389 ± 0.009 µm (Mulder *et al.*, 2019).

4.3 Development and in-vitro comparison of the performance of fluticasone propionate containing vapes using NGI

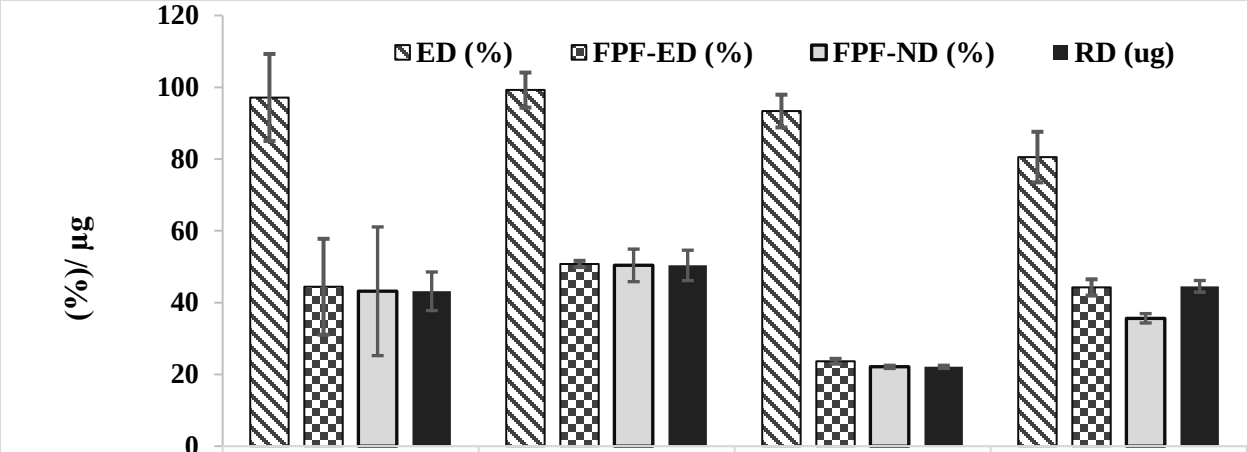
Development of an FP based vape liquid was commenced, and initial work was aimed at testing if FP could be delivered through a vape device. The three tested devices were compared to a marketed pressurized metered dose inhaler (pMDi) with FP.

The formulation was based on propylene glycol and glycerine as excipients. Propylene glycol is a commonly used liquid in pharmaceutical industry and has been employed in aerosolized drug delivery systems such as pMDIs and nebulizers (Montharu *et al.*, 2010). Further, glycerine is part of the GRAS list. A study revealed that the use of low volatility cosolvents such as propylene glycol can be applied to increase the residual aerodynamic particle size to a target range (Myrdal, Sheth and Stein, 2014). Therefore, the plan was to prepare FP liquid using 50:50 propylene glycol: glycerine. The concentration of FP was set at 0.33 mg/ml and each actuation contains 100 µg of FP while the marketed product concentration was 125 µg per actuation.

pMDi device is comprised of four basic functional parts which are the container, the metering valve, the actuator, as well as the mouthpiece. pMDi formulations contain a liquified propellant that delivers an energy source to expel the liquid formulation through the valve as a rapidly

evaporating droplets and as a dispersion medium for the formulation components (Newman, 2005). Nevertheless, there are several problems encountered in the use of pMDIs that set the motive behind this project. Poor coordination between actuation and inhalation processes may involve stopping inhalation when the aerosol hits the back of the throat which is termed cold-freeze effect as well as inhaling too fast may reduce efficient deposition into the lower parts of the respiratory system and hence increased local and systemic side effects (Virchow *et al.*, 2008). Thus, poor inhalation technique can noticeably reduce the percentage of the active that reaches the lung. Research results reported that 28-68% of the patients with asthma have problems using their pMDIs and DPIs sufficiently well to benefit from the dose (Rau, 2006). Therefore, development of device that is user friendly and does not depend on patient involvement and correct use of the device is of critical importance in maintaining optimal disease control (Giraud and Roche, 2002).

The performance of the developed e-liquid containing FP was assessed using the three previously tested devices and results were compared with the marketed FP pMDI. The aerodynamic performance of the formulation was tested on NGI and results are depicted in Figure 4.9



	FP-C	FP-T	FP-P	FP-M
ED (%)	97.17	99.23	93.38	80.56
FPF-ED (%)	44.42	50.77	23.66	44.23
FPF-ND (%)	43.16	50.38	22.10	35.63
RD (ug)	43.16	50.38	22.10	44.54

Figure 4. 9: Summary NGI performance for FP containing E-liquid using the three types of marketed nicotine vapes. Each puff contains 100 µg FP. **FP-C**: FP- Vape Coil, **FP-T**: FP- Vape Tank, **FP-P**, FP-Vape pods, **FP-M:** FP-marketed pMDI (containing 125 µg FP) . Results are presented as mean± SD, n=3. **ED**: %Emitted dose, **FPF-ED**: Fine Particle Fraction from Emitted Dose, **FPF-ND**: Fine Particle Fraction from Nominated Dose, **RD**: Respirable Dose.

The first parameter was the emitted dose, the total emitted dose as a percentage of the nominated dose was characterized using the NGI, results revealed that all the four devices delivered high emission ranging from 80.56% (FP from the marketed pMDi) to 99.23% (from FP-vape tank). Such results specify the efficiency of the vaping devices in emitting the desired dose. Despite the lower range of ED of pMDi when compared to vapes, the difference is not statistically significant 9one-way ANOVA, p 0.08). However, not all emitted dose contributes to the effectiveness of the dosage form. As discussed earlier, the aerodynamic particle size which needs to be below 5 µm is paramount (Mansour, Rhee and Wu, 2009). This is assessed using FPF -ED, FPF-ND and RD. FPF-ND ranged from 22.10% when the vape-pod was used to 50.38% in the case of vape tank. The marketed FP pMDi showed results that were better than the vape pod and coil but less than the vape tank. Statistical analysis demonstrated a significant difference among devices (one-way

ANOVA $p<0.05$). Further, the FPF of the nominated dose and RD usually, give also good presentation to the amount that reached the respiratory system with the vape tank achieving the highest of (50.38% and 50.38 µg respectively). The lowest was attributed to vape pod with FPF-ND of 22.10% and respirable dose of 22.10 µg. Statistical analysis using one way ANOVA followed by Tukey post-hoc test showed that there is a statistically significant difference among devices in delivering respirable dose ($p=0.0001$) and that the statistical significant difference was among vape coil and vape pod ($p=0.007$), vape tank and pod ($p=0.000$) as well as vape pod with the marketed product ($p=0.0004$). Interestingly, there was no statistical significant difference between vape tank and the marketed product or vape coil and the marketed product ($p>0.05$) and hence, it could be suggested to use the vape-tank or coil at low voltage and temperature to evaluate further the use of delivering drug to the lung. Although there was no significant difference among them, the dose employed in the vape was only 100 µg. However, the vape tank delivered the highest ED and FPF-ND and hence could be proposed to be used as it will provide an option of lowering content of FP while delivering higher percentage to the lower parts of the respiratory system.

The FP NGI results were expected as the vape pods showed the lowest nicotine delivery due to the lower voltage employed. However, when comparing the voltage of the vape-tank and vape-coil, the wattage in the tank system was lower than that of the coil and yet it produced the best results in terms of all aerodynamic particle size distribution.

As for the marketed pMDI products, previous studies reported that pMDI in general with successful coordination of actuation with inhalation, accompanied by a slow and deep inhalation upon actuation that lasts approximately 2 seconds in a child and 5 seconds in an adult, around 10-20% of the emitted dose is deposited in the lung (Newman, 2005, 2017; Fredenberg *et al.*, 2011).

The high velocity and the large aerosolized particles causes 50-80% of the active dose to impact in the oropharyngeal region, whereas smaller particles deposit at the lower parts of the lung (Crompton, 1982; Virchow *et al.*, 2008),

Another issue that worth mentioning is the slight difference in the delivered nominal dose the e-liquid provided 100 µg per actuation whereas the marketed FP pMDi delivered 125 µg per puff. The amount of the FP that was delivered from the vape was calculated based on the weight difference before and after actuation as well as the weight of 1 ml of the e-liquid. The prepared e-liquid of FP contains 333 µg/ml each actuation delivered 0.3 ml representing 100 µg of FP.

Further analysis of the aerodynamic properties of the delivered dose between devices revealed that vape tank and vape coil demonstrate similar aerodynamic profile whereas the marketed FP pMDi showed particle size towards the higher margin 2.8-4.46 µg. The vapes had particle size ranging between 0.34- 1.66 µg. Apparently, the vapes produces aerosols with lower particle size and hence possibility of more deposition in lower parts of the respiratory system (see Figure 4. 10).

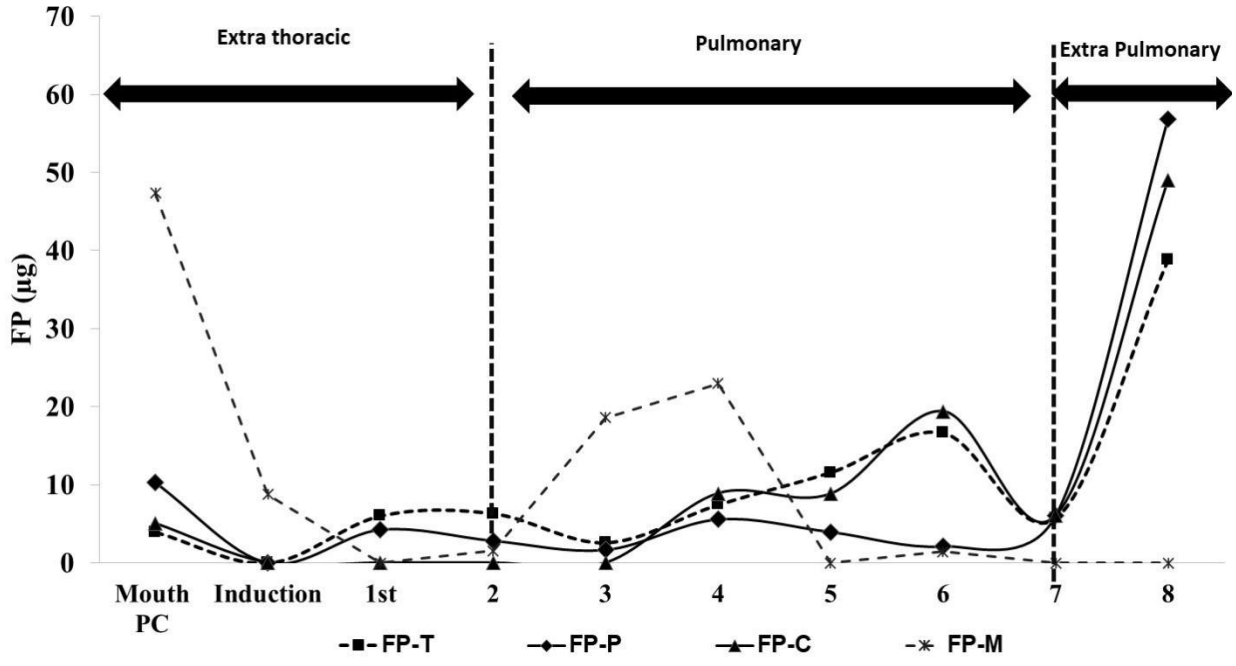


Figure 4. 10: *In vitro* comparison of aerodynamic particle size distribution of the FP vapes products and marketed FP pMDi demonstrating the lung deposition of FP using NGI set at flow rate of 60l/min.

4.4 Short Stability Study of the FP E-liquid

Short stability study was conducted to ensure the stability of the developed formulation in terms of content uniformity. The samples were stored at 2-6 ºC in amber vials for three months. Analysis of the sample each month was done using the HPLC method. Content of FP did not change overtime as can be seen in Table 4.5 indicating the stability of the formulation.

Table 4. 5: Results of short stability study for FP e-liquid with initial concentration of 0.33 mg/ml done over three months on samples that are stored at 2-6 °C.

Test month	% Recovery (mean ±SD, n=3)	RSD (%)
0 months	99.34 ± 1.99	2.0%
1 month	101.02 ± 3.25	3.22%
2 months	98.76 ± 0.73	0.74%
3 months	99.04 ± 3.32	3.35%

Chapter Five
Conclusions and Future Work

5.1. Conclusions

Vapes are nicotine delivery device, that became popular alternative for nicotine replacement owing to ease of use and cost effectiveness. The current project aimed at evaluating the *in-vitro* performance of three commercially available vape devices using the next generation impaction. Then a model drug was employed to assess the capability of vaping systems to deliver APIs into the lower parts of the lung. Results demonstrated the superiority of vape tank and vape coil over vape pod device in delivering higher FPF whereas the vape pod FPF did not exceed the 22% mark. Results of FP e-liquid demonstrated the capability of vape tank and coil to produce FPF, ED and RD that are superior to the marketed FP pMDI. Such results could be appealing to manufacturers as it provides a possible cost effective yet user friendly alternative to the commonly used inhalation devices.

5.2. Future work

This work is a promising preliminary study that requires several issues to be tackled as follows:

- Conducting a study to assess the stability of the compound upon heating and presence of degradants from glycerin and propylene glycol.
- Investigating the permeability of drugs through the pulmonary vesicles to predict the processing of drug transport across the lung mucosa membrane and in terms of toxicity.
- Exploring different formulation parameters for the preparation of vape juice to enhance dispersion parameters and allow for higher drug content, especially for poorly water-soluble APIs.
- Investigating the addition of flavoring agent to enhance patiently acceptance and improve bad taste of the drug.
- Collaborating with a 3D printing researcher to develop unit dose vapes.

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أستخدام السكائر الالكترونيه كطريق بديل لايصال الدواء

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أطروحة
مقدم لكلية الصيدلة كتنفيذ جزئي لمتطلبات درجة الماجستير في العلوم الصيدلية

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نبذه مختصره

تعتبر الرئه طريقه ملفته للانتباه في طرق ايصال الدواء بسبب فوائدها مقارنتاً بانضمه توصيل الدواء الاخرى. يمتلك الجهاز التنفسي مساحه سطحيه كبيره وعدد كبير من الاوعيه الدمويه. العديد من الاجهزه تستخدم في ايصال الدواء الى الرئه مثل البخاخات و اجهزه الاستنشاق بالجرعات المقننه (pMDI) و اجهزه الاستنشاق في المسحوق الجاف .لكل جهاز مزايا وعيوب هي التي اعاقه التقدم الهائل لاشكال الجرعات التنفسيه. ذكرت الدراسات الحديثه ان السجائر الالكترونيه (vape) قد استخدمت على نطاق واسع لتوصيل النيكوتين و المخدرات الغير مشروعه و انتجت نتائج فعاله للغايه وبالتالي يمكن التحقق من ان السجائر الالكترونيه كبديل لاجهزه الاستنشاق الاخرى. ان الهدف من هذا المشروع البحثي هو تقييم جميع انواع السجار الالكترونيه (vapes) المتاحه في الاسواق با ستخدام الجيل القادم من جهاز التاثير (NGI) لنتمكن من اختيار الجهاز المناسب لايصال ماده الفعاله (API) الى الجزء السفلي من الرئه من خلال استعمال ابخره السجاره الالكترونيه با اسخدام نموذج دواء معين الذي يمتلك خواص فيزيائيه مناسبه. تم استخدام طرق (HPLC) في تحليل بروبيونات النيكوتين والفلوتيكازون والتحقق منها وفقًا لإرشادات ICH. تم تقييم ادء الترسيب الديناميكي الهوائي لاجهزه السجائر الالكترونيه الثلاثه

(vape tank, vape coil, vape pod) با استخدام (NGI) التي اظهرت تفوق (vape tank) و(vape coil) على (vape pod). انتج (vape tank) اكبر كميه من النيكوتين من بين الثلاثه اجهزه حيث كانت الجرعه المرشحه والجرعه القابله للتنفس اعلى بكثير من تلك الموجوده في باقي الاجهزه. على الرغم من محتوى النيكوتين المتشابه في كل جرعة ، اختلف أداء الأجهزة. حتى مع وجود (coil) في جهاز(vape tank) ، فإن الكمية التي تبخرت والجرعة المنبعثة من الجهاز كانت أكبر في حالة (vape tank) مع البخاخة. ثم اتخذ المشروع اتجاهًا لتطوير سائل بروبيونات فلوتيكاسون (FP) وتقييم الأداء في المختبر باستخدام(NGI). تم تقييم أداء السائل الإلكتروني المطور الذي يحتوي على FP باستخدام الأجهزة الثلاثة التي تم اختبارها مسبقًا وتمت مقارنة النتائج مع اجهزه الاستنشاق بالجرعات المقننه (pMDI) FP المسوق.تم اختبار الأداء الديناميكي الهوائي للصيغة على NGI وتراوحت نتائج جزء الجسيمات الدقيقة من 23.69٪ عندما تم استخدام vape-pod إلى 50.85٪ في حالة vape tank. أظهر FP pMDi الذي تم تسويقه نتائج مماثلة لنتائج (vape coil). ومع ذلك ، فإن FPF للجرعة المرشحة و RD عادة ، يقدم عرضًا أفضل للكمية التي وصلت إلى الجهاز التنفسي السفلي مع تحقيق (vape tank)

على (50.38٪ و 50.38 على التوالي). أظهر التحليل الإحصائي وجود فرق يعتد به إحصائياً بين الأجهزة في تقديم جرعة قابلة للاستنشاق ($p = 0.0001$) وأن الاختلاف الإحصائي كان بين (vape coil) و (vape pod) ($p = 0.0010$)) ، (tank vape) و (vape pod) $p = 0$)، (0000 أيضًا كما جرب vape مع المنتج المسوق ($p = 0.0018$). ومن المثير للاهتمام ، أنه لم يكن هناك فرق إحصائي كبير بين خزان vape والمنتج المسوق ، وبالتالي ، يمكن اقتراح استخدام (vape tank) عند جهد ودرجة حرارة منخفضين لتقييم استخدام الدواء إلى الرئة.ا ظهرت دراسة الاستقرار القصيرة قدرة الصيغة على الاحتفاظ بمحتوى FP. هذه النتائج هي نقطة انطلاق واعدة لإمكانية استخدام أجهزة (vape tank) خاصة باستخدام درجة حرارة منخفضة والقدرة الكهربائية لتقديم جرعة فعالة وسهلة الاستخدام لتوصيل الأدوية التنفسية.