DETERMINATION OF NICOTINE CONTENT IN VARIOUS TOBACCO *PRODUCTS USING* CAPILLARY ELECTROPHORESIS

ROMERO ROBBY DAVID UBING

INDUSTRIAL CHEMISTRY PROGRAMME SCHOOL OF SCIENCE AND TECHNOLOGY UNIVERSITI MALAYSIA SABAH 2010



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VERIFICATION

1. SUPERVISOR (DR. Nomie Surugau)



2. EXAMINER (Dr. Sazmal Effendi Arshad)



- 3. EXAMINER 2 (Sharain Liew Yen Ling)
- 4. DEAN (Prof. Dr. Mohd Harun Bin Abdullah)





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ABSTRACT

This study was aim to optimize the separation of nicotine in tobacco products sample. The tobacco products are cigarette and local chewing tobacco. The main objective of the study is to optimize capillary electrophoresis (CE) separation for nicotine. Two type of buffer was compared Citrate buffer and sodium phosphate, where both buffer was also tested at different pH pH 2.5, 4.5 and 9.5 .Sodium phosphate buffer with pH 2.5 was chosen as a running buffer due to high and symmetrical peak. The buffer then is tested on using different concentration 10mM, 25mM, 50mM and 100mM. Buffer with a high concentration increases the migration time slightly. Based on the result sodium phosphate buffer pH 2.5 with 100mM was use in the sample analyze using CE and the condition was 10cm capillary length, UV detection at 260 nm, sample injection 0.5 psi, for 5 s at 30 °C with 5 kV applied voltage. Sample was analyze using the optimized method after extraction and the result was cigarette (12.921 ppm) have almost double the nicotine contain compare to local chewing tobacco (7.572 ppm).



ABSTRAK

Penelitian ini bertujuan untuk mengoptimumkan pemisahan nikotin dalam sampel produk tembakau. Produk tembakau adalah rokok dan mengunyah tembakau tempatan. Tujuan utama dari penelitian ini adalah untuk mengoptimumkan elektroforesis kapilari (CE) pemisahan untuk nikotin. Dua jenis penyangga berbanding sitrat buffer dan natrium fosfat, di mana kedua-dua buffer juga diuji pada pH pH, berbeza 2.5 4.5 dan 9.5 buffer Natrium. Fosfat dengan pH 2.5 dipilih sebagai buffer berjalan kerana tinggi dan simetris puncak. buffer kemudian diuji pada kepekatan yang berbeza menggunakan 10mm, 25mm, 50mm dan 100mm. Buffer dengan meningkatkan konsentrasi tinggi saat penghijrahan sedikit. Berdasarkan natrium keputusan dapar fosfat pH 2.5 dengan 100mm itu digunakan dalam sampel menganalisis menggunakan CE dan keadaan itu 10cm panjang kapilari, UV pengesanan pada 260 nm, injeksi sampel 0.5 psi, untuk 5 di 30°C dengan 5 kV diterapkan tegangan. Sampel dianalisis dengan menggunakan kaedah dioptimumkan selepas ekstraksi dan hasilnya adalah sebatang rokok (12.921 ppm) mempunyai hampir dua kali ganda nikotin mengandungi dibandingkan dengan mengunyah tembakau tempatan (7.572 ppm).



| | | | Page |
|--------------------------------|-------------------|--|------|
| DECL | ARATIC | N | i |
| VERIFICATION | | ii | |
| ACKNOWLEDGEMEN | | | iii |
| ABSTRACT | | | iv |
| ABSTRAK | | | v |
| LIST | OF CON | ITENTS | vi |
| LIST OF TABLES | | vili | |
| LIST | OF FIG | URES | × . |
| LIST | OF ABB | REVIATIONS AND SYMBOL | ×i |
| CHAP | TER 1: | INTRODUCTION | 1 |
| 1.1 | Introd | uction | 1 |
| 1.2 | Nicotir | ne | 1 |
| 1.3. | Object | ives | 2 |
| 1.4 | Scope | of the Study | 2 |
| | | | |
| CHAPTER 2: LITERATURE REVIEW 3 | | 3 | |
| 2.1 | .1 Introduction 4 | | 4 |
| 2.2 | Nicotine 5 | | 5 |
| | 2.2.1 | Nicotine mode of action | 5 |
| | 2.2.2 | Nicotine's effect in human | 7 |
| | 2.2.3 | Nicotine side-effect on human | 8 |
| | 2.2.4 | Nicotine and cancer | 8 |
| | 2.2.15 | Nicotine usage | 9 |
| 2.3 Tobacco Products | | 10 | |
| | 2.3.1 | Tobacco and cancers | 11 |
| | 2.3.2 | Smoke Tobacco Products | 12 |
| | 2.3.3 | Smokeless Tobacco Products | 13 |
| 2.4 | Capilla | iry electrophoresis | 14 |
| | 2.4.1 | Introduction to CE | 14 |
| | 2.4.2 | Instrumentation of capillary electrophoresis | 15 |
| | 2.4.3 | The migration of ionic species | 16 |
| | | | |



.

•

| | 2.4.4 | Electroosmotic flow (EOF) | 18 | |
|------|----------------------|--|----|--|
| | 2.4.4 | Electrophoresis Theory | 19 | |
| | 2.4.5 | Buffer and additives | 22 | |
| 2.5 | Previo | us studies | 23 | |
| CHA | PTER 3: | METHODOLOGY | 26 | |
| 3.1 | Sampl | e | 26 | |
| 3.2 | Chemical Reagents 2 | | | |
| 3.3 | Apparatus 2 | | | |
| 3.4 | Sample Preparation 2 | | | |
| 3.5 | Sampl | e extraction | 27 | |
| 3.6 | CE | | 28 | |
| | 3.6.1 | CE Condition | 28 | |
| 3.7 | Optim | ization of separation using capillary electrophoresis. | 29 | |
| | 3.7.1 | Effect of different buffer at different pH. | 29 | |
| | 3.7.2 | Effect of buffer concentration | 30 | |
| 3.8 | Sampl | e Analysis | 30 | |
| CHA | PTER 4: | RESULT AND DISCUSSION | 31 | |
| 4.1 | The ef | fect of different buffer at different pH | 31 | |
| 4.2 | The co | oncentrations effect | 35 | |
| 4.3 | Sampl | e analysis | 36 | |
| CHA | PTER 5: | CONCLUSION | 40 | |
| REFE | RENCES | | 41 | |
| APPE | NDIX A | | 45 | |



LIST OF TABLES

| Table No. | | Page |
|-----------|--|------|
| 2.1 | Example and description for some smoke type tobacco products | 12 |
| 2.2 | Example and description for famous local smokeless type tobacco products | 13 |
| 3.3 | List of sample | 26 |
| 4.1 | Data of the nicotine separation using different buffer and pH | 31 |
| 4.2 | Data of the nicotine separation using different buffer concentration | 35 |
| 4.3 | Nicotine calibration | 36 |
| 4.4 | Data of the sample analysis | 38 |
| 4.5 | Data on nicotine contain in tobacco sample | 39 |



LIST OF FIGURES

| Figure No. Pa | | Page |
|---------------|--|------|
| 2.1 | The structure of nicotine | 4 |
| 2.2 | Synthesis of nicotine | 4 |
| 2.3 | Cell-cell communication | 6 |
| 2.4 | Overview of CE schematic diagram Albumin protein fraction | 15 |
| 2.5 | The flow profile | . 17 |
| 2.6 | The expanded region of the inner wall of a capillary | 18 |
| 2.7 | Stern's model of the double-layer charge | 21 |
| 2.8 | Electropherogram of standard nicotine | 23 |
| 2.9 | UV absorbance of nicotine as a function of pH | 24 |
| 2.10 | Electropherogram of tobacco alkaloids | 25 |
| 4.1 | Buffers pH versus migration time | 32 |
| 4.2 | Buffers pH versus peak height | 33 |
| 4.3 | Electropherogram of nicotine separation | 34 |
| 4.4 | Buffer concentration versus migration time | 35 |
| 4.5 | Calibration plot of peak area at 260nm vs nicotine concentration | 36 |
| 4.6 | Comparison of peak area between samples | 38 |



LIST OF ABBREVIATIONS AND SYMBOLS

- HPLC High Perfomance Liquid Chromatography
- CE Capillary Electrophoresis
- EOF Electroosmotic Flow
- SiOH Silanol
- SiO⁻ Protonated silanol
- H⁺ Protonated
- I.D Inner diameter
- OHP Outer Helmholtz Plane
- UV Ultra-violet
- N Nitrogen
- C₂H₅OH Ethanol
- NaOH Sodium hydroxide
- Na₃PO₄ Sodium phosphate buffer
- ATF Bureau of Alcohol, Tobacco and Firearms



CHAPTER 1

INTRODUCTION

1.1 Introduction

What are tobacco products? To put it short term, item that are made mainly from leaf especially in the genus of the herbs *Nicotiana*. *Nicotiana* is part of the nightshade family (Solanaceae) indigenous to North and South America, Australia, South West Africa and the South Pacific. Tobacco products can be from cigar, cigarette, cigarette pipe, rollyour-own tobacco, chewing, tobacco and snuff. The main function of this tobacco products are nicotine delivery.

1.2 Nicotine

Nicotine occurs naturally in all plant but abundantly in tobacco plant especially *Nicotiana tabacum*. Nicotine is used by plant as pesticide but in low concentration it acts as a stimulant for mammals. This is the main reason why tobacco products are commonly related to drug. The nicotine contain in a product is varies from plant to plant and the type of curing process it goes through.

Nicotine has mood-altering effects that are different to every people but the frequent reports are relaxation, sharpness, calmness, and alertness (Lagrue *et al.*, 2001).



Research suggests that, when smokers wish to achieve a stimulating effect, they take short quick puffs, which produce a low level of blood nicotine (Einstein, 1995).

The main objective of the study is to determine the nicotine content in various tobacco products using capillary electrophoresis (CE) method. The reason why nicotine is the main subject is because nicotine in the tobacco product is addictive. This study is done using CE which a sensitive and fast instrument enables many tests to be done in a short time.

1.3 Objectives

The objectives of this study are as follows:

- 1. To optimize capillary electrophoresis (CE) separation for nicotine using buffer
- To determine the amount of nicotine in cigarette and local chewing tobacco products
- To compare the amount of nicotine in each cigarette and local tobacco chewing product

1.4 Scope of Study

This study involves in optimizing the separation of nicotine in cigarette and local tobacco chewing products and the nicotine concentration is determined using Capillary Electrophoresis (CE) method.



CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Tobacco or *Nicotiana tabacum* is a plant which has high concentration of nicotine. *Nicotiana tabacum* is the commercial plant that is used in tobacco products. Contrary to modern views and uses tobacco in its beginning is used by the native American's shaman or medicine man as Enthogen and is consider sacred or to seal a bargain (Gottsegen, 1940). Only until the discovery of North and South America that the *Nicotiana tabacum* is cultivated and export to Europe and all around the world (Gottsegen, 1940).

Even though the nicotine contain is vary from different species to species of tobacco but the leaf is where the nicotine concentration is highest (Lochmann *et al.*, 2001). Commercial tobacco products consists two types of smokeless and smoking products. For example cigar, cigarette, cigarette pipe, roll-your-own tobacco are smoking products whilst chewing tobacco and snuff are smokeless (Ralapati, 1997). This entire product only has one common goal that is nicotine delivery either by smoking or by chewing. Each product have a different bleed of formula, flavoring and other additives to enchants the product respectively



2.2 Nicotine

As mention above nicotine is the main substance that sells any tobacco products. Nicotine or $C_{10}H_{14}N_2$ or 3-(1-methyl 1-2-pyrrolidiny) is an alkaloid of tobacco which is colorless or less to pale yellow and hygroscopic oily liquid. In an aqueous solution, nicotine exists as a free base or in the monoprotonated or diprotonated atoms, depending on the solution pH as shown in **Figure 2.1** (Yang & Smentena, 1995).



Figure 2.1 The structure of nicotine (I) Free base, (II) Monoprotonated from (pKa₁ = 8.02) and (III) Diprotonated form (pKa₂ = 3.12) (Yang & Smentena, 1995).



nicotinic acid

Figure 2.2 Synthesis of nicotine from nicotinic acid and ornithine precursors Dewick, 1997).



Nicotine is a plant defense alkaloid; it is a pale yellow to dark brown liquid with a slight, fishy odor when warm. Biologically, production of nicotine requires nicotinic acid (Vitamin B3 or niacin) and an N-methyl-pyrrolinium cation, which is derived from ornithine (a non-protein amino acid derived from Krebs cycle intermediates as shown in **Figure 2.2** (Dewick, 1997).

Nicotine in a stable form forms crystalline slat with two molecules of tartaric acid and a salt. Its also dissolve in ethanol, with 2 molecules of picrid acid. Nicotine also fatal in taken orally with 250 to 350 mg and if taken less it cause fever, trembling, nausea and convulsion (Brauthar, 1995).

2.2.1 Nicotine mode of action

Nicotine can enter the body in many ways either by self-administer, smoking or chewing tobacco or accidentally, for example tobacco's smoke or expose to nicotine based insecticide.

Once in the body nicotine distributed quickly through the bloodstream and can cross the blood-brain barrier. And it takes only few seconds for the nicotine effect to reach the brain when inhaled (Herraiz and Chaparro, 2005). Nicotine acts as a stimulant, whether in insecticide or drug, so the modes of action are also the same. Nicotine inhibits the function of acetylcholine receptors located at the neuromuscular junctions (Garrett and Grisham, 1999).

Under normal condition the synapes mediated by neurotransmitters such as acetylcholine, produced from choline by cholineacetyltransferase. The arrival of an action potential the synaptic knob opens Ca²⁺ channels in the presynaptic membrane. Influx of Ca²⁺ induces the fusion of acetylcholine containing vesicles with the plasma membrane and release of acetylcholine into the synaptic cleft. Binding of acetylcholine to receptors in the postsynaptic membrane opens Na⁺ channels. The influx of Na⁺ depolarizes the postsynaptic membrane, generating a new action potential. Nicotine locks this ion channel in the open conformation (Garrett and Grisham, 1999).



5

In shorts a change in calcium ion concentration releases acetylcholine from storage vesicles (Figure 2.3 a). Acetylcholine then crosses the synaptic cleft (Figure 2.3 b) and binds to the alpha subunit of the nicotinic receptor causing a conformational change which opens an ion channel, allowing the passage of cations (Figure 2.3 c). This depolarizes the postsynaptic membrane initiating an action potential in the adjacent membrane, and thus a signal is transmitted (Figure 2.3 d) (Garrett and Grisham, 1999).



Figure 2.3 Cell-cell communication at the synapse (sources: Garrett and Grisham, 1999)

But when nicotine is introduce it then blocks the acetylcholine receptor, locking the ion channels in the open position and impairing signaling ability (Garrett and Grisham, 1999). As a conclusion, nicotine causes stimulation of the ganglions and depending on the concentration it can act differently; in low doses (as drug) it acts as a stimulant but at a higher concentrations (insecticide) cause's blockade in the receptor causing poisoning.



2.2.2 Nicotine's effect in human

Nicotine takes about 19 seconds to reach the brain after it is absorbed into the blood stream (Brauthar, 1995). Depending on the concentration, nicotine has several effects. In low concentration 6 to 8 milligram of nicotine is equivalent to one cigarette sticks, nicotine can have mood-altering effects that are different to every people but the frequent reports are relaxation, sharpness, calmness, and alertness (Lagrue *et al.*, 2001). Other know effect are facilitates relaxation and causes mild euphoria. Additionally it can improve attention as well as problem-solving skills (Harvey and Champe, 2000).

Nicotine effect the brain by changing many types of neurological chemicals. One of the changes is dopamine, nicotine cause the body to trigger more dopamine. Dopamine is a hormone which is associated with happiness or a sense of elated because dopamine has the effect of pleasure enhancement (Brauthar, 1995). Other neurological chemicals like acetylcholine and norepinephrine also increase its levels (to compensate for nicotine's disabling of the receptors) facilitating performance and memory ability. Anxiety and tension is soothed by elevated endorphins and weight gaining is reduces by appetite reduction (Brauthar, 1995).

In cigarettes, there is also an unknown component (possibly the carcinogenic benzopyrenes) which increases the rate of metabolism of other drugs (Harvey and Champe, 2000). So smoking cigarettes along with other drug substance increase both effect.



2.2.3 Nicotine side-effect on human

The only known side-effect of nicotine in human is dependency or addictions (Harvey & Champe, 2000). Exposure to nicotine (in low doses) causes dependency or addiction due to the body's increased production of acetylcholine receptors over long-term .So in the end, long term exposure of nicotine in the nervous makes the body more tolerant to the nicotine effects. The body became tolerant of nicotine within a few days after exposure (Harvey and Champe, 2000). So when a person decides to stop smoking, they will go into a withdrawal as see in many coldturkey cases. Withdrawal is associated with headache, constipation, insomnia, depression, inability to concentrate and anxiety (Harvey and Champe, 2000) (Brauthar, 1995). Nicotine also causes vasoconstriction which is decrease the diameter of the blood vessel.

2.2.4 Nicotine and cancer

Cancer or malignant neoplasm is a class of diseases in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood) (Kinzler & Vogelstein, 2002). There are many reason why cancer cell exist, naturally all living thing (cell) replicate its self many time and in time errors (mutation) happens in their genetic material and if left without correction and prevention, hence cancer exist (Nelson *et al.*, 2004).

Nicotine is known as a carcinogenic and a mutagen (Kozlovskis-Wade *et al.*, 1998). Carcinogens are substance that cause or have tendency to produce cancerous cell. Mutagen are agent that causes mutations in cell, mutagen can be carcinogenic but carcinogenic are not always mutagen. For example alcohols, it does not cause cell to mutate but stimulating the rate of cell division. Faster rates of replication leaves less



time for repair enzymes to repair damaged DNA during DNA replication, increasing the likelihood of a mutation (Seitz *et al.,* 1998).

Nicotine has the ability to change or damage the cellular DNA which make it a mutagen. What nicotine does to a cell DNA is that nicotine impairs or damages its DNA making it impossible for the cell to reproduce and to grow (Kozlovskis-Wade *et al.*, 1998). Damaged DNA increasing the possibility for DNA mutation into cancerous cell or a tumor especially when combined with the carcinogens found especially in cigarette smoke.

At a more advance medical research, nicotine is use to treat cancer. What nicotine does for cancerous cell is that nicotine impair or damages its DNA making it impossible for the cell to reproduce and to grow. In the Kozlovskis-Wade paper (1998), it stated that nicotine enhances DNA degradation and stimulates DNA repair in adult myocytes (heart cells). Kozlovskis-Wade paper (1998) also says that nicotine also degrade healthy DNA cell although the result will be vary depending on cell type; whether the cell is terminally differentiated or actively replicating (Kozlovskis-Wade *et al*, 1998) but the fact remain that nicotine damages DNA so increasing the possibility for DNA mutation into cancerous cell or a tumor especially when combined with the carcinogens found especially in cigarette smoke.

2.2.5 Nicotine usage

Nicotine natural usage in plant is an insecticide. Nicotine in plant act as natural defends against insect, so natural nicotine is use as an insecticide in agricultural (Geiger, 1993). When an insect eat a plant with high concentration of nicotine alkaloid, the nicotine then entre it centre nervous system damage it and kills the insect. But nicotine as an insecticide is not efficacy due to some insect that have evolve high resistant to nicotine (Geiger, 1993).

Nicotine has a more market value to human than to insect because nicotine alone and with the right concentration or doses nicotine does not cause harm to human but



9

provide therapeutic effect to human which is more valuable than killing insect (Harvey and Champe, 2000). No forget the dependences effect or addiction that nicotine causes making it very profitable then just becoming an insecticide.

Nicotine is not just in tobacco products and insecticide has many medical uses. For starter, ironically nicotine is use to break nicotine addiction or to be accurately to break smoking habit. When a person decides to stop smoking, they will go into a withdrawal as see in many cold turkey cases. Withdrawal is associated with headache, constipation, insomnia, depression, inability to concentrate and anxiety (Harvey and Champe, 2000) (Brauthar, 1995). For example, nicotine patches, nicotine gum, ecigarette and substitute nicotine pill.

2.3 Tobacco Products

Tobacco products are item that are made mainly from tobacco leaf especially in the genus of the herbs *Nicotiana*. Tobacco product includes cigar, cigarette, cigarette pipe, roll-your-own tobacco chewing, tobacco and snuff (Ralapati, 1997). The main function of a tobacco products are nicotine delivery.

Each of the products is manufacture differently and specifically based on the consumer preferences because with different leaf, different curing process, different addictives dan different flavoring produces vary different tobacco product. So selecting the right formula and blend is important to get the right customer or any costumer. Adding cinnamon to the tobacco products is a few examples of addictives and flavoring because adding sugar and fructose to reduce irritancy and harshness to some tobacco products (Ralapati, 1997).



2.3.1 Tobacco and cancers

Smoking Tobacco usually related to having cancer due to the fact that tobacco smoke contains many carcinogens substance such as nitrosamines and polycyclic aromatic hydrocarbons (Kuper *et al.,* 2002). Cigarette smoke contains over 60 known carcinogens, including radioisotopes from the radon decay sequence, nitrosamine, and benzopyrene (Sasco *et al.,* 2004).

13 % of deaths in Sabah (2007) are cause by cancer and over 39 % of these deaths are associates with having lung, throat, mouth and nose and esophagus cancer (Ramilah, 2009). These types of cancer usually associate with tobacco smoking (Sasco *et al.*, 2004). Tobacco is responsible for about one in three of all cancer deaths in the developed world and about one in five worldwide (Kuper *et al.*, 2002). A research done by Doll & Hill (1950) showing a close link between smoking and cancer, which is conforms by over 40 000 doctors. The research shows that in addition to the carcinogens substance in the tobacco nicotine also plays an important role in the rate of growth rate of the cancer (Doll & Hill, 1950).

Passive smoking or people who are exposed to tobacco smoke also have a chance to have lung cancer (Sun *et al.,* 2007). Researches done by Sun (2007) show that passive smoking have a greater chance of getting cancer than direct smoking.

Smoking also increase the chances of contracting other disease (non- cancerous disease) such as asthma, shortness of breath, mouth ulcer, pneumonia and many other respiratory disease (Sopori, 2002). Due to the fact that the many of the chemical in tobacco smoke such as nicotine decreases the immune system (Sopori, 2002).



2.3.2 Smoke Tobacco Products

Smoke tobacco products are tobacco products that produce smoke or gases by burning the products. The smoke is uses as a mode of transportation for nicotine. The smokes then travel to the lung where nicotine and many other chemicals are absorbed (Ralapati, 1997). Example of some smoke type tobacco products are shown in **Table 2.1**.

| Example | Simple description |
|---------------|--|
| Cigarettes | Finely ground tobacco warp in paper with a filter. The front end |
| | usually is burn and the filter end is where the smoke is inhale. It is |
| | famous for to its availability, simplicity, cheapness compare to cigar |
| | and advertisement. |
| Cigar | Dried and fermented tobacco leaf that is wrap tightly to from a |
| | cylinder or a roll. Famous compare to Roll-your-own due to its class |
| | representation |
| Roll-your-own | Is a type of cigarettes without the warping paper and filter. Only |
| | looses and chopped tobacco leaf. Paper or dried leaf usually is use |
| | as wrapper and the usage of filter is depends on the customer. |
| | Famous for older generation due to its cheapness |

 Table 2.1
 Example and description for some smoke type tobacco products

There are many other smoke tobacco products but the three above are famous in most local markets and the easy to obtain in many local area.



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