The Bioequivalent and Effect of Nicotine Formulation Gum on Smoking Cessation†

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Objective: *To compare the absorption rate of nicotine in volunteer blood, and determine the clinical trial on smoking cessation.*

Material and Method: *This method using reverse phase C_{18} column and buffer pH 5.05 as the mobile phase, flow rate 0.9 ml/min. The UV-visible detector found the retention time of nicotine in gum and volunteer blood was 5.0756 min. The linear calibration curves of nicotine in human blood were obtained over the concentration range of 2.0-20.0 μg/ml. The coefficient variability for Nicotine gum 6.74% (2 mg/g). Extraction recovery was over 86% in blood, correlation coefficient of determination (r^2) > 0.9999 and the detection limit 0.0060 μg/ml.*

The 24 healthy volunteer men, 27 to 55 years of age, were habitual cigarette smokers. They were randomized into two groups,12 subjects chewed two 2 mg pieces, Nicomild-2 Sugar Free Gum (Millimed, Thailand), the other chewed two 2 mg, pieces, Nicorette Sugar Free(Pharmacia AB, Helsingborg, Sweden.)Volunteers' blood samples were withdrawn at 0, 15, 30, 40 min, concentration of nicotine in blood were measured by HPLC.

The 199 subjects were openly recruited under the project of "The smoking cessation for Phor Laung" (5-December). All of them received Nicomild-2 (nicotine polyestex gum) between November 2007 and December 2007.

Results: *The absorption rate of nicotine in volunteers' blood Nicomild-2 and Nicorette at 0, 15, 30,40 minutes were 0, 51.84, 26.73, 21.012 and 0, 56.603, 21.83, 15.183 (ng / min). Both of them were found to have maximum absorption rate at 15 minutes. When comparing the maximum absorption rate at 15 minute of Nicomild-2 (sugar free) with Nicorette (sugar free) didn't have significant differences detected. Treatment with nicotine polyestex gum were reported 65.3% (130/199) at 4 weeks compared with failure 30.15% (60/199)[65.3% vs 30.15%; p = 0.005]. The authors found 9 (4.5%) subjects successfully quit smoking free nicotine replacement therapy (NRT).*

Keywords: *Bioequivalent, Nicotine gum, Smoking cessation, Sugar free, Nicotine polyestex gum, Nicotine polacrilex gum, Nicomild-2, Nicorette, NRT*

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Nicotine is a major addictive substance in cigarette smoke, absorbed through the skin and mucosal lining of mouth and nose or inhaled in the lungs by both active and passive smokers. It is extensively metabolized to a number of metabolites, but the rate of metabolism varies among individuals[1,2]. The studies reported that nicotine has a relatively short half-life ($t_{1/2}$ = 1-2 h)[3,4]. Oral fluid specimens were determined as a biomarker[5] for tobacco smoking. The novel Nicomild-2 (nicotine polyestex gum) which has been approved for use by the Thai Food and Drug Administration (FDA) being effective and safe for smoking cessation[6]. Treatment with Nicomild-2 resulted in significantly greater abstinence rate at 3 months compared with placebo[7]. Glucose is monosaccharide that has limited use in subjects with diabetes mellitus[8,9] then sugar free gum is an aid for smoking cessation cases in some requirement in low intake sugar.

The aim of the present study was to determine the bioequivalent of nicotine polyestex gum: Nicomild-2

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(sugar free) and nicotine polacrilex gum: Nicorette (sugar free) in healthy volunteers who were habitual cigarette smokers. Subjects were admitted to study under submission by Ethics Committee Faculty of Medicine Srinakharinwirot University[10]. Nicomild-2 (sugar free) was supplied by Millimed (Thailand) in replacement of sugars by sweetener (non sugar) that had been proved as an aid in smoking cessation[11]. Determination of sugar was also carried out by the iodometric technique, which allows a distinction to be made between total sugars and total reducing content[12]. The developed method fitted to determine glucose, sucrose, total sugars in HPLC[13] with refractive index detector(RI) in the samples that contain nicotine[14]. However, the previous one report has included a HPLC technique for analysis of nicotine gum[15] and the rate of maximum absorption nicotine in effective time had been done by GC modified for use with a capillary column[16]. No evidence to determine the maximum rate absorption of nicotine in human blood among pharmaceutical formulations by using high-performance liquid chromatography. Hence, the authors lead to develop a simple, sensitive, selective separation on the bioequivalent of nicotine content in nicotine gum (sugar free) and clinical trial on smoking cessation.

Material and Method

Chemicals and reagents

Nicotine (Sigma,Switzerland), nicotine polacrilex gum sugar free (Nicorette, Pharmacia AB, Helsingborg, Sweden), nicotine polyestex gum sugar free (Millimed, Thailand), analytical grade of D-(+)-glucose, D-(-)-fructose and sucrose (Merck, Germany), n-hexane, methanol, ethanol, hydrochloric acid, perchloric acid, sulfuric acid, triethylamine, sodium phosphate (monobasic), sodium acetate, Rochelle salt, sodium carbonate, potassium iodide, potassium periodate, sodium hydroxide, sodium thiosulphate, anhydrous citric acid, copper sulphate, dipotassium oxalate, an HPLC grade of water, acetonitrile.

Preparation of calibration curve

Stock solutions for nicotine standard solutions were dissolved exactly weight (mg) of nicotine in methanol (HPLC grade) adjust in 25 ml dark volumetric flask. Solutions were stored at 4°C until evaluation requirement.

Samples calibration curve were created by using standard nicotine solution at the concentrations of 1.0, 5.0, 10.0, 15.0, and 20.0 mg/ml and an aliquot (20 ml) was analyzed by HPLC. The supernatant of blood blank with 1 ml were filtered through a 0.2-mm Nylon syringe filter (Alltech). The supernatants 20 ml, three replicated analyses were performed by HPLC.

Stock solutions of glucose, fructose, sucrose containing 100 mg/ml, five concentrations of each and mixed sugars being 0.1, 0.5, 5.0, 10.0, and 20.0 mg/ml were calibrated. and an aliquot (50 ml) was analyzed by HPLC.

Sample preparation

Nicotine gum (2 mg) was cut into small pieces and placed in a separatory funnel, dissolved in hexane (25 ml) and 0.1 M HCl (25 ml). Nicotine solution was extracted and discarded from hexane. The volumes were adjusted with mobile phase. Approximately 1 ml of solution was filtered through a 0.2-mm Nylon syringe filter. Nicotine content in these solutions was determined by HPLC.

For the determination of total sugars was also carried out by HPLC method, 2 ml of solution were mixed with 0.5 ml of 5% oxalic acid(w/v) and 5 ml of 95% ethanol. Then, the volume was adjusted to 20 ml water HPLC grade. Approximately 1 ml of solution was filtered through a 0.2-mm Nylon syringe filter. The determination of recovery extraction spiked with 100 ml of 20.0 mg/ml nicotine standard solution. Glucose, sucrose content in these solutions were determined by HPLC and Total sugar samples repeatedly confirmed appearance of total sugars and total reducing content by iodometric methodology.

Iodometric technique (Shaffer-Somogyi micro method)

Four pellets of nicotine gum (2 mg) were prepared similarly as above. Pipet 5 ml of samples test tube (25 x 200 mm) and add 5 ml of copper reagent (Shaffer-Somogyi carbonate 50 reagent). Prepared blank, place tubes in boiling water bath for 15 min. Add each tube 2 ml KI-$K_2C_2O_4$ solution (dissolved 2.5 g KI and 2.5 g $K_2C_2O_4$ in H_2O and adjusted to 100 ml by volumetric flask) and then 3 ml of 2 N H_2SO_4(56 ml/L). Mix until Cu_2O is dissolved, and let it stand in cold water bath following the titration with 0.005N $Na_2S_2O_3$using starch indicator.

HPLC conditions

An Agilent HPLC system (Series 1100, USA) was comprised of a quaternary pump with UV-Vis photodiode array detector. The chromatography was performed on a C_{18} column (125 mm x 4.0 mm i.d., 5 mm, Hypersil ODS, Agilent). Using the mobile phase

isocratic elution of sodium acetate: methanol: triethyl amine (88:12.0:0.5, v/v, apparent pH 5.05 adjusted with addition of glacial acetic acid) as with 0.9 ml/min flow-rate. The absorption wavelength was set at 259 nm.

The sugars were performed on a Spherisorb NH_2 column (250 x 4.6 mm i.d., 5 mm particle size). Acetonitrile: HCl 0.01 M (84:16,v/v) was used as the mobile phase at a flow rate of 1.0 ml/min.

Bioequivalent assay

The subjects were 24 healthy volunteers between 27 and 55 years old (39.45 $\pm$ 8.77) and body weight 64.166 $\pm$ 10.27 Kg. Volunteers were admitted to the present study under submission by the Ethics Committee Faculty of Medicine Srinakharinwirot University (Certify No. SWUEC 8-4/2008). They were randomized into two groups, 12 subjects chewed two 2 mg pieces, Nicomild-2 sugar free gum (Millimed, Thailand) and the other were chewed two 2 mg pieces, Nicorette sugar free (Pharmacia AB, Helsingborg, Sweden). Venous blood sample of volunteers (2 ml) were collected in disposable heparin tubes pre-dose at 0, 15, 30, 40 min after oral administration. After the addition of 200 ml of 35% perchloric acid samples were centrifuged at 4,000 x g for 4 min and supernatant were filtered through a 0.2-mm Nylon syringe filter (Alltech) with of the 20 ml supernatants. Three replicated analyses were performed by HPLC. The Extraction recovery supernatants spiked with 100 ml of 20.0 mg/ml nicotine standard solution.

Clinical trial

The 199 subjects were openly recruited under the project of "The Smoking Cessation for Phor Laung" (5-December) and approved by Bangkok Chest Hospital. All of them received Nicomild-2 (nicotine polyestex gum) between November 2007 and December 2007. To be eligible for the present study, subjects had to be 18 years of age or older with an average of 10 cigarettes or more per day for the past year smoking, and were interested in quitting smoking within the next 30 days. Exclusion criteria included pregnancy, previous use of other smoking cessation aids in the past month, a history or current diagnosis of coronary artery disease, stomach ulcers, and uncontrolled hypertension. Written informed consent was obtained from all participants. Dose of gum provided was based on the levels of nicotine dependence. The highly-dependent smokers were assigned to the 4-mg dose (2 pieces of 2-mg gum), and the others to the 2-mg dose (1 piece of 2-mg gum). Subjects set a target quit date; however, all of them were encouraged to completely stop smoking on the first day of treatment. They returned at 2, 4 weeks after their quitting date for follow-up visit.

Results and Discussion

Fig. 1 included: (a) a blank blood sample; (b) chromatogram of nicotine in mobile phase from Nicomild-2 sugar free gum (t_R = 4.021, C = 1.763 mg/ 1 g-gum); (c) Chromatogram of nicotine in human blood samples: 15 min after chewing Nicomild-2 (t_R = 4.968, C = 0.840 mg/1 g-gum); (d) Chromatogram of nicotine in human blood samples:15 min after chewed Nicorette (t_R = 5.076, C = 0.9753 mg/1 g-gum). This is in agreement with the authors' previous study[6,7], which found the retention time to be in the range of 4.0-5.02 minutes.

Linearity and lower limit of detection

The calibration curves (y = mx + b) were generated by a weighted linear least-squares regression of the standards. Nicotine in nicotine gums (sugar free) and nicotine in blood were validated over the

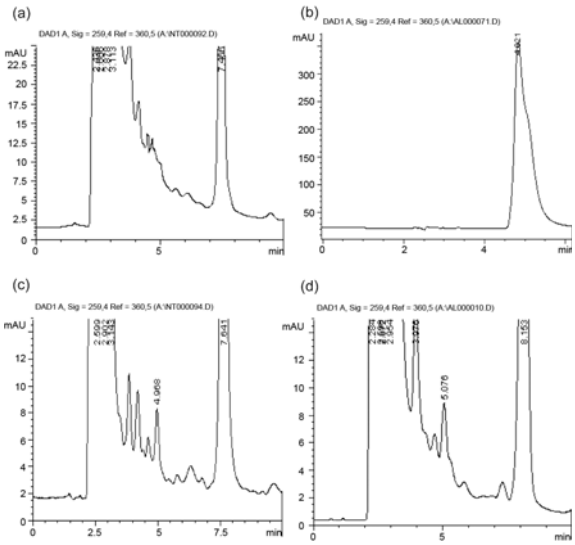

Fig. 1 (a) shows a representative chromatogram of a blank blood sample; (b) chromatogram of nicotine in mobile phase from Nicomild-2 sugar free gum (t_R = 4.021, C = 1.763 mg/1 g); (c) Chromatogram of nicotine in human blood samples: 15 min after chewed Nicomild-2 (t_R = 4.968, C = 0.840 mg/ml); (d) Chromatogram of nicotine in human blood samples: 15 min after chewing Nicorette (t_R = 5.076, C = 0.9753 mg/ml)

concentration range of 1.0-20.0 μg/ml. The correlation coefficient of determination (r^2) > 0.9999. Typical equation of calibration curves was y = 18.288x + 0.0107 and the detection limit 0.0060 μg/ml.

The linearity of all investigated sugar in the concentration range of 2.0-12 mg/ml. The correlation coefficient of determination (r^2) > 0.9999, equation of calibration curves was y = 122.39x-12.762 and the detection limit 4.68 mg/ml. All 5 ml of extracted nicotine gum samples were shown negative of cuprous oxide with Shaffer-Somogyi micro method.

Accuracy and precision

Two quality control samples (0.02, 20.0 μg/ml) were assayed for five samples in three independent batches of nicotine blood. Within-day and day-to-day accuracy and precision data are shown in Table 1. The data indicated that the recovery and precision (% CV) of nicotine were over 86% and < 6.0% respectively in blood concentration range evaluated.

The determination of nicotine contents and sugar contents in two brands of nicotine gum sugar free by HPLC technique are shown in Table 2. The means of nicotine not different significantly (t = 2.084, < p = 0.05). According to these methods of recovery the precision (% CV) were > 90%, and < 7.0% respectively. Two examination techniques of sugars with no detection HPLC and negative results by iodometric of Shaffer-Somogyi micro method. As a consequence, cuprous oxide precipitate were not found.

The maximum absorption rate in blood

The absorption rate of nicotine in volunteers Nicomild-2 and Nicorette at 0, 15, 30, 40 minutes were 0, 56.603, 26.721, 21.0122 (ng/min) and 0, 54.008, 21.835, 15.1825 (ng/min) respectively (Table 3). The above method for maximum absorption rate of nicotine concentration at 15 minutes and smoothly reduced about 40-50 minutes. The comparison of the maximum absorption rate at 15 minutes of Nicomild-2 (sugar free) versus Nicorette (sugar free) were not significant (Fig. 2) differences detection [t = 0.556 < p = 0.005].

Total abstinence rate and adverse reactions

The number of subjects who successfully stopped smoking is shown in Table 4. At the end of the treatment phase (4 weeks after the quitting date), the success was significantly better than the failure (70% vs. 30%, p = 0.005). All adverse reactions reported one or more times by the subjects in any given treatment group are shown in Table 5. The present results are in

Table 1. Results of accuracy, the within day and day-to-day precision evaluation experiments of nicotine (0.02, 20 μg/ ml) in blood

Samples	Concentration (μg/ml)	
	0.02	20.0
Within-day (n = 5)		
Mean	0.0198	17.21
SD	0.0011	0.821
% CV	5.05	4.77
% recovery	89.90 ± 5.76	92.01 ± 5.97
Day-to-day (n = 5)		
Mean	0.0201	16.240
SD	0.0012	0.897
% CV	5.97	5.52
% recovery	86.01 ± 5.76	8.01 ± 5.72

Table 2. Content of nicotine and sugar in nicotine gum sugar free (n = 6)

Nicotine gum samples	Nicotine (mg/g)	Glucose (mg/g)	Sucrose (mg/g)	Fructose (mg/g)
Nicomild-2				
Mean	1.8916	ND	ND	ND
SD	0.1276			
% CV	6.74			
% recovery	98.01 ± 5.72			
Nicorette				
Mean	1.753	ND	ND	ND
SD	0.1019			
% CV	6.23			
% recovery	92.01 ± 5.97			

ND = not detected

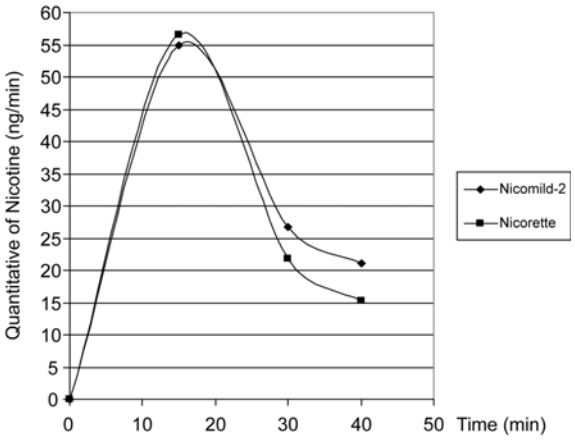

Fig. 2 The comparison of nicotine absorption rate: Nicomild-2 vs. Nicorette

Table 3. The comparison maximum absorption rate of nicotine in blood of volunteer samples: the bio-equivalent assay (n = 12)

Nicotine gum samples 4	0 min (mg/ml)	15 min (mg/ml)	30 min (mg/ml)	40 min (mg/ml)
Nicomild-2				
Mean	0.7960	0.8491	0.8019	0.8405
SD	0.0772	0.0959	0.0659	0.0447
% CV	9.6984	11.294	8.22	5.31
Rate of absorption (ng/min)	0	56.603	26.721	21.0122
Nicorette				
Mean	0.6334	0.8101	0.6551	0.6073
SD	0.0698	0.0717	0.0682	0.0841
% CV	11.01	8.84	10.4	13.84
Rate of absorption (ng/min)	0	54.008	21.835	15.1825

Table 4. Total abstinence rates at the end of treatment (4 weeks)

Outcomes	Study groups	p-value
	Nicomild-2, No. (%)	
Success	139 (70.0)	0.005[a]
Failure	60 (50.0)	

[a] Chi-square test (χ^2, df = 1 $\geq$ 7.88, p = 0.005)

Table 5. Adverse reactions reported at least once during the treatment

Adverse reactions	Study groups
	Nicomild-2, No.(%)
Dizziness	22 (11.05)
Sore mouth	15 (7.50)
Dyspepsia	8 (4.02)
Dyspnea	2 (1.00)

accordance with previous studies that used nicotine polyestex gum[6,7]. All of them had reported the superior success rates of Nicomild-2 compared with placebo.

There was one serious adverse event reported during or immediately after the treatment and stopped suddenly to use an active gum. Dizziness, Sore mouth, Dyspepsia and Dyspnea were found as the most common reactions seen during the treatment as shown in Table 5. Regarding its safety, adverse effects related to the use of Nicomild-2, tend to occur similarly the authors' previous study[6,7].

Conclusion

The method described in the presented paper can be used to determine the concentration of nicotine in sugar free chewing gum and in human blood. Validation experiments have shown that the assay has good precision and accuracy. Nicomild-2 (trade name) of the novel nicotine polyestex gum is effective and equivalent in maximum absorption of nicotine, nicotine contents in gum to Nicorette; additional safe for smoking cessation.

To the authors' knowledge, this is the first study to report the improvement in the resin for nicotine polyestex gum[6], which have removed any sugar as the pharmaceutical formulation of sugar free. However, the parameters of chemicals analysis data have been developed, revealed and investigated in the present report.

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การศึกษาชีวสมมูลและประสิทธิภาพของสูตรหมากฝรั่งนิโคตินในการช่วยเลิกบุหรี่

ยงยุทธ ตัณฑุลเวสส, ประพาฬ ยงใจยุทธ, วราดุล ฉัตรทอง, กวิตา ตัณฑุลเวสส

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบอัตราการดูดซึมนิโคตินในเลือดของอาสาสมัครและการศึกษาทางคลินิกในการช่วยเลิกบุหรี่*

วัสดุและวิธีการ: *เป็นการศึกษาแบบสุ่มโดยใช้อาสาสมัครจำนวนทั้งสิ้น 24 ราย แบ่งเป็น 2 กลุ่ม ๆ ละ 12 ราย แต่ละกลุ่มจะได้หมากฝรั่งนิโคตินสูตรไร้น้ำตาล 2 เครื่องหมายการค้า คือ นิโคมายด์-2 (ประเทศไทย) และนิโคเร็ตต์ (สวีเดน) อาสาสมัครจะได้รับหมากฝรั่งนิโคตินสูตรไร้น้ำตาลรายละ 2 ชิ้น (2 มิลลิกรัม/ชิ้น) เคี้ยวตามกรรมวิธีตามฉลากยากำกับเจาะโลหิต ที่เวลาเริ่มต้นก่อนเคี้ยว หรือ 0 นาที, 15, 30, 40 นาที สกัดแยกหาปริมาณนิโคติน โดยใช้เทคนิคโครมาโทรกราฟีของเหลวแบบสมรรถนะสูง*

ผลการศึกษา: *อัตราการดูดซึมสูงสุดที่เวลา 15 นาทีมีค่าไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ที่ระดับสูงมาก ($t = 0.556 < p = 0.005$) และปริมาณค่าเฉลี่ยนิโคติน ในหมากฝรั่งทั้งสองเครื่องหมายการค้า ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($t = 2.084 < p = 0.05$) โดยประสิทธิภาพของวิธี (% recovery) มากกว่า ร้อยละ 90 และค่าเที่ยงตรง (precision) น้อยกว่าร้อยละ 7 การศึกษาทางคลินิกพบว่าอาสาสมัครสามารถเลิกบุหรี่สำเร็จสูงกว่ากลุ่มที่เลิก ไม่สำเร็จอย่างมีนัยสำคัญทางสถิติ (65.3% vs. 30%; $p = 0.003$) และกลุ่มที่เลิกบุหรี่สำเร็จโดยไม่ใช้ยา (หมากฝรั่งนิโคตินทดแทน) พบจำนวน 9 ราย (4.5%)*

สรุป: *หมากฝรั่งนิโคตินทั้ง 2 เครื่องหมายการค้ามีค่าชีวสมมูล ไม่แตกต่างกัน ทั้งในปริมาณนิโคติน และอัตราการดูดซึมนิโคตินสูงสุดไปในทิศทางเดียวกัน และมีประสิทธิภาพและปลอดภัยในการช่วยเลิกบุหรี่*