CHAPTER IV
DISCUSSION AND CONCLUSION

DISCUSSION

Various nicotine-TDS preformulations will discuss as follows :

1. **Preformulation of drug reservoir for nicotine -TDS**
   - A. Non-aqueous base preformulation
     1. Effect of solvents/vehicles on stability of nicotine
     2. Effect of solvent/vehicles on *in-vitro* release and skin permeation of nicotine through membrane, adhesive and skin
   - B. Aqueous base preformulation
     1. Study the effect of pH values on preformulation of nicotine-TDS
        - 1.1 Effect of pH values on partition coefficient
        - 1.2 Effect of pH values on the stability of nicotine
        - 1.3 Effect of pH values on the release and skin permeation of nicotine through membrane, adhesive and skin
     2. Study the effect of antioxidant on the stability of nicotine

2. **Evaluation of nicotine-TDS formulations**
   - 2.1 Physical characteristics evaluation of formulas
   - 2.2 *In-vitro* evaluation of formulas
     - 2.2.1 Nicotinell®-TTS
     - 2.2.2 Formulas of nicotine in mineral oil
     - 2.2.3 Formulas of nicotine with carbomer 934
     - 2.2.4 Formulas of nicotine with pluronic F-127
     - 2.2.5 Formulas of nicotine with EVA copolymer
   - 2.3 Comparison between non-aqueous base, aqueous base and matrix systems

CONCLUSION

DISCUSSION

1. Preformulation of Drug Reservoir for Nicotine-TDS

A. Non-aqueous Base Preformulation

1. Effect of Solvents/Vehicles on the Stability of Nicotine

In general, no additive is necessary to assist in transdermal administration of nicotine because nicotine base is very highly lipid soluble and is quickly and completely absorbed into the systemic circulation. However, should it be designable to increase or decrease the rate of permeation, then nicotine base can be carried by a suitable solvent such as propylene glycol, glycerin, mineral oil, polyethylene glycol 400, simethicone and silicone oil. The results for this investigation of the stability of nicotine in various vehicles were shown that stability of nicotine in mineral oil > silicone oil > simethicone > glycerin ~ propylene glycol > polyethylene glycol 400. These revealed that nicotine in mineral oil exhibited more stable than other vehicles.

2. Effect of Solvents/Vehicles on the Release and Skin Permeation

Nicotine base was added to various vehicles at 5% w/w concentration and the release and skin permeation time interval was 12 hours. The release and skin permeation time profiles showed in Figures 20-23. The fluxs of nicotine release and skin permeation could be ranked in the following order; silicone oil > simethicone > mineral oil > glycerin > polyethylene glycol 400 > propylene glycol. From the release and skin permeation rate of nicotine from each vehicles which observed from the slope of Q_s as a function of time plot, it was found that nicotine in silicone oil exhibited superior release and skin permeation rate than the others. Since the nicotine concentration was the same in all vehicles, the difference in flux presumably reflect differences in the membrane, skin/vehicles partition coefficient.

In conclusion, nicotine in mineral oil, silicone oil and simethicone showed the release and skin permeation-time profiles higher than propylene glycol, polyethylene glycol 400 and glycerin. From the stability data, nicotine in mineral oil also exhibited very stable than other vehicles thus mineral oil was the most suitable vehicles for nicotine TDS.

B. Aqueous Base Preformulation

1. Study the Effect of pH Values on Preformulation of Nicotine-TDS

1.1 Effect of pH Values on Partition Coefficient

The present work sought to investigate the partitioning character of nicotine. As lipophilic phase in partitioning experiments, n-octanol was chosen because it have polar and non-polar properties can simulate skin lipids. Nicotine is also a small molecule (MW:162.23) and therefore not hindered by bulk effect which have been associated with the poor permeability of large molecules such as steroid. Finally, nicotine is a diacidic base with pK_a values reported in separate references as 6.16 and 10.96 (Aungst, 1988), 3.04 and 7.84 (Sifton, 1994) and 3.4 and 8.2 (Cordell, 1981). Therefore, when the vehicle pH is below 10, as in these experiments, nicotine is mostly ionized. The measured apparent partition coeffecients as a function of pH as shown in Figure 24. The profile of n-octanol/buffer partition coefficient versus pH increase in the lipophilicity by increasing the pH value or increasing ionization with decreasing pH. The apparent partition coefficient describes the partitioning characteristics of a molecule without separating the effects of drug association or dissociation. Determination of the true partition coefficient which considers only the partitioning of the unionized base between the two phases.

According to the equation 16, for nicotine the $K_{a,2}$ ($1x10^{-8.2}$) value was used. By ploting $K (1+K_a/[H_3O^+])$ versus $K_a/[H_3O^+]$ (Figure 25), a straight line is obtained with good correlation of determination ($r^2 = 99992$), slope equal to 8.1345 (corresponds to the true partition coefficient) and the intercept is 1.18779 (corresponds to the ion pair partition coefficient). In order to confirm this result, by using Equation 17, it possible to draw the curve describing the theoretical profile by plotting log (k/k_u) as a function of pH for nicotine with a $pK_{a,2}$ of 8.2 would yield a slope of zero at pH values above $pK_{a,2}$ according to equation 18, below $pK_{a,2}$ equation 19 holds with a slope of plus unity and an intercept of $-pK_{a,2}$. At pH values close to $pK_{a,2}$ equation 17 applies with no simplifying assumptions (Figure 26). The experimental profile of nicotine is nearly the theoretical curve.

1.2 Effect of pH Values on the Stability of Nicotine

Nicotine was degraded rapidly when expose to air or oxygen by oxidative mechanism. Oxidative decomposition leading to color development. Nicotine solutions, when stressed with high temperature develop a yellow to brown color. The factors accelerated the decomposed reaction are solvent, pH, ionic strength, light, oxygen and temperature, etc. This part was studied the effect of pH values on the stability of nicotine in aqueous solutions. Nicotine stability was also measured by using aqueous vehicles at pH range between 2-10 with other factors held constant and accelerated by kept in high temperature (45 °C) for 4 weeks. Data are summarized in Tables 11-12 and Figures 27-28. These studies demonstrated that the rate of reaction in aqueous solutions were dependent on the solution pH, at pH above 6.5 nicotine was stable in aqueous solution more than pH below 6.5. These studies were able to recognize possible catalysts in formulation mixtures and to minimize their effects on drug-product stability.

1.3 Effect of pH Values on the Release and Skin Permeation of Nicotine Through Membrane, Adhesive and Skin

Nicotine is dibasic, with pK_a values reported in separate references. Therefore, when the vehicle pH is below the pK_a nicotine is mostly ionized. The profile of octanol/buffer partition coefficient versus pH values reflected the increasing ionization with decreasing pH. Skin penetration fluxs using aqueous buffer vehicles also showed a similar profile (Figure 30).

The fluxs of nicotine through EVA copolymer membrane and adhesive. Nicotine vehicles at pH 6.5, 8.5 and 10.5 the fluxs were 0.0924 ± 0.0018 mg/cm^2/hr, 0.1121 ± 0.0042 mg/cm^2/hr and 0.1091 ± 0.0039 mg/cm^2/hr, respectively. The release fluxs of nicotine depend on pH of nicotine vehicle. At pH 8.5 and 10.5 nonsignificant different in drug release characteristics had been observed. All of the laminate plus skin showed that the skin permeation fluxs increased with the pH, the flux at pH 6.5, 8.5 and 10.5 were 0.0511 ± 0.0017 mg/cm^2/hr, 0.0823 ± 0.0034 mg/cm^2/hr and 0.084 ± 0.0068 mg/cm^2/hr, respectively. These suggests that the fluxs of nicotine free base in aqueous solution significantly increased drug permeation when pH of the solution increased. This may be due to the difference in ionized and unionized form of nicotine in various pH values. When the vehicle pH higher than pK_a nicotine became unionized, thus it was penetrated rapidly. There was no

difference in the absence and presence of skin. Although the membrane and adhesive laminate can control the delivery of nicotine through skin, however, vehicles of more extreme pH would probably be too irritating to be acceptable for clinical application. Therefore, from this study the suitable pH was approximately 8 - 8.5.

2. Study the Effect of Antioxidant on the Stability of Nicotine

Oxidation reactions can be inhibited by agent that are

(a) chelating agents for metal ion initiators of free-radical oxidation reaction. Oxidative reactions are often initiated by metal ions such as Fe^{3+}, Cu^{2+}, Co^{3+}, Ni^{2+}, Mn^{3+}. These metal ion act as initiators because in their oxidative states they are capable of acting as free radicals. Chelating agents act in an auxiliary antioxidant by binding metal ions; thus removing them from solution. EDTA and citric acid are the most two useful agents.

(b) reducing agents; that is, substances that can reduce an oxidized drug such as sodium thiosulfate and ascorbic acid.

(c) preferentially oxidized compounds, that is, agents that are more readily oxidized than the agents they are to protect. Example of pharmaceutical oxidized compounds are sulfites and ascorbic acid, etc.

(d) chain terminator; that is, agents capable of reacting with radicals in solutions to produce a new species. The new radical may be intrinsically stable or may dimerize to form an inert molecule. The major water-soluble antioxidant that can act as chain terminator are the thiol species cysteine, thioglycerol, thioglycolic acid and thiosorbitol. Essentially all the lipid soluble antioxidants act as chain terminators are hydroquinone, octyl and dodecyl gallates, α -tocopherol and phenyl α-naphthylamine.

Compounds in all four categories are often classified as antioxidants (Connors, Amidon and Stella, 1986).

For study the effect of antioxidant on the stability of nicotine. The oxidative reaction of nicotine, will lead to change in color of the solution, reaction are complex and not yet understood. The chelating agent, sodium EDTA, probably the most use for complexing with trace metal ions that serve as catalysts for the oxidation reaction. The most commonly used aqueous antioxidants are the sodium salts of metabisulfite, bisulfite and sulfite. The choice of salt depends upon the pH of the system, the metabisulfite being used at low pH, the bisulfite at intermediate pH and the sulfite at higher pH. Thus, the suitable antioxidant for nicotine was sodium sulfite (Lachman, 1968 and Schroeter, 1961). The results indicated that 0.01-0.05 % w/w sodium EDTA showed the less effective for reduce color development of

nicotine in aqueous solution, sodium sulfite at concentration of 0.5% w/w more effective than 0.05 and 0.10 % w/w, and the combination of sodium EDTA and sodium sulfite showed more effective than using only sodium EDTA or sodium sulfite alone. Its was found that, the combination of 0.03% w/w sodium EDTA and 0.1% w/w sodium sulfite almost completely stopped color formation which are equivalent effective to 0.05% w/w sodium EDTA and 0.5 % w/w sodium sulfite for inhibit color development.

From these results, can concluded that to enhance the effectiveness of the antioxidant, approach, it is sometime useful to use more than one anti-oxidant. It has been found that a combination of two antioxidants often works well. This enhanced effectiveness is often referred to as synergism.

2. Evaluation of Nicotine-TDS Formulations

2.1 Physical Characteristics Evaluation of Formulas

Antioxidant was added in every formulations, for oil vehicles used 0.1% w/w BHA as antioxidant, in aqueous vehicles used 0.5% w/w sodium sulfite and 0.05% w/w sodium EDTA . Accelerated reaction was conducted by keeping at 45° C for 4 weeks. The results of the stability of nicotine formulation (Table 21) revealed that nicotine in aerosil gel was shown the least stable as compared with other formulations. No significant difference in drug stability characteristics were observed for all 14 formulations. Thus, nicotine in aerosil gel did not use to study *in-vitro* release and skin permeation. Selection the best formulation for nicotine-TDS, must evaluate by *in-vitro* release and skin permeation as compared to Nicotinell®-TTS.

2.2 *In-vitro* Evaluation of Formulas

In order to gain more insight of the release mechanisms of nicotine from the nicotine-TDS and their roles on transdermal delivery of nicotine, the drug release kinetics study was also investigated. The *in-vitro* release profiles of nicotine (2.5 mg/cm^2) across EVA membrane (~50 µm thickness) and hypoallergic acrylate adhesive into pH 7.4 isotonic phosphate buffer solution, throughout the course of 24 hours release study. The results are concluded in Appendices xvi-xxx and Tables 20-23. From *in-vitro* skin permeation experiment which used pig's skin as barrier, the skin permeation

profiles data of Nicotinell®-TTS and fourteen designed preparations are illustrated in Appendices xvi-xxx and Tables 24-26. All data were presented as average cumulative permeation of nicotine through a unit surface area of skin.

2.2.1 Nicotinell®-TTS

Figure 53 showed schematic view of Nicotinell®-TTS. It contains natural, purified, nicotine free base as its ingredient. The drug release-time profile from Nicotinell®-TTS indicated that the release of nicotine seemed to follow the Higuchi's model, Q_s versus square root of time relationship was also obtained in this investigation. The release amount was clearly depicted from Nicotinell®-TTS with 1.9303 ± 0.0009 mg/cm^2.

The skin permeation-time profile of nicotine from Nicotinell®-TTS sustained permeation of nicotine over 24 hours. The skin permeation profile seemed to be Higuchi's model. The permeation amount and skin permeation rate were 1.8449 ± 0.0381 mg/cm^2 and 0.4478 ± 0.0028 mg/cm^2/h$^{1/2}$, respectively.

2.2.2 Nicotine-Mineral oil

A. Formula #1

Formula # 1 was 5% w/w nicotine in mineral oil. The release profiles of Formula #1 compared to Nicotinell®-TTS is shown in Figure 32. The release kinetic of Formula #1 was similar to Nicotinell®-TTS follow the Higuchi's model. The release amount was 2.3153 ± 0.1953 mg/cm^2 which is greater than Nicotinell®-TTS.

The skin permeation-time profile of Formula #1 compared to Nicotinell®-TTS shown in Figures 33-35. The skin permeation kinetic seemed to be Higuchi's model. The permeation amount and permeation rate were 1.8991 ± 0.0238 mg/cm^2 and 0.438 ± 0.006 mg/cm^2/h$^{1/2}$, respectively. It is interesting to note that Formula #1 has the skin permeation-time profile nearly Nicotinell®-TTS. Statistical analysis, by ANOVA, of the skin permeation rate of nicotine indicated that the differences between Formula #1 and Nicotinell®-TTS is statistically insignificant.

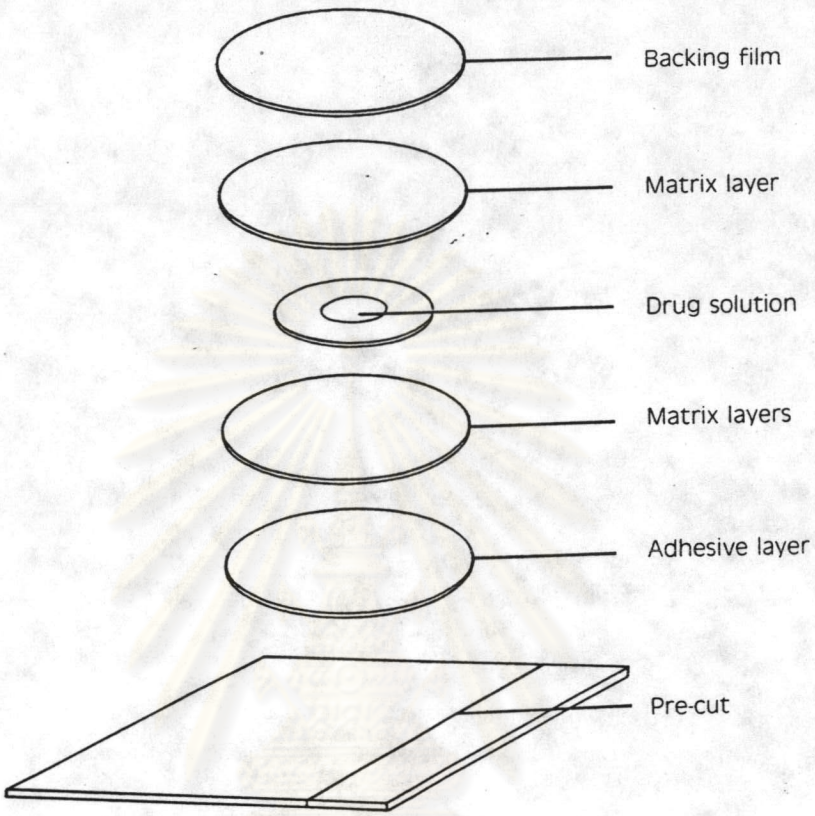

Figure 53 Schematic view of Nicotinell®-TTS.

B. Formula #3

Formula #3 was nicotine 20 % w/w in mineral oil adsorbed on non woven (content rayon 70-80 % and acrylic monomer 20-30 %) that was able to blot the nicotine solution but did not catch nicotine. The release-time profiles of nicotine from Formula #3 compared to Nicotinell®-TTS is given in Figure 36, indicated that the release of drug tended to be First order kinetic and the amount of drug release was 2.0195 ± 0.1036 mg/cm^2, which is greater than Nicotinell®-TTS.

The skin permeation-time profile of Formula #3 compared to Nicotinell®-TTS is shown in Figures 37-39. The skin permeation pattern of drug from this formula seemed to be Higuchi's model according to the

maximum correlation coefficient in Table 28. The amount and the rate of drug permeation was 1.8243 ± 0.0186 mg/cm^2 and 0.441±0.0113 mg/cm^2/h$^{1/2}$, respectively. Statistical analysis, by ANOVA, of the skin permeation rate of nicotine indicated that the differences between Formula #3 and Nicotinell®-TTS is statistically insignificant.

2.2.3 Nicotine-Carbomer 934

The release-time data and release-time profiles of nicotine from four permeations of nicotine-TDS using carbomer 934 gel at concentration 0.3, 0.5, 1.0 and 1.5% w/w are illustrated in Appendices xiv-xxii, Table 21, and Figure 40. All preparations, exactly, can sustained the release of nicotine over 24 hours. The maximum release amount was observed from Formula #4 and 5 to be 1.9672 ± 0.0219 and 1.9769 ± 0.0521 mg/cm^2, respectively, while the minimum was 1.2248 ± 0.0426 mg/cm^2 from Formula #7. They could be ranked in the following order; Formula #4 ~ Formula #5 > Formula #6 > Formula #7. The drug release-time profile from the preparations containing this polymer indicated that the release of drug depended on the concentration of polymer. Increasing the concentration of polymer effected decreasing of drug release. Maximum correlation coefficient in Table 27 indicated that the release of drug seemed to follow the First order kinetic in the concentration of carbomer 934 0.3, 0.5 and 1% w/w and Higuchi's model kinetic in the concentration of 1.5% w/w.

The cumulative skin permeation-time data and profiles of nicotine from four preparations of nicotine-TDS using carbomer 934 gel matrix as drug carrier are presented in Appendices xix-xxii, Table 25, and Figures 41-43. The preparations composed of 0.3, 0.5, 1,0 and 1.5 % w/w of carbomer 934, these presented the amount of drug permeations to be 1.9094 ± 0.277 mg/cm^2, 1.6760 ± 0.0559 mg/cm^2, 1.1325 ± 0.0618 mg/cm^2 and 0.9149 ± 0.0029 mg/cm^2, respectively. The skin permeation pattern of drug from this polymer seemed to be the Higuchi's model in the concentration of 0.3, 0.5, 1.0 and 1.5% w/w according to the maximum correlation coefficient in Table 28.

As these results, they were indicated that the concentration of polymer obviously affected the amount of drug release and skin permeation. The skin permeation time profiles of Formula # 4-7 compared to Nicotinell®-TTS revealed that the release profiles of Formula #4 and 5 were similar to

Nicotinell®-TTS. Statistical analysis, by ANOVA, of the skin permeation rate indicated that the different between Formula #4 and Nicotinell®-TTS is statistically insignificant but the different between Formula #5 and Nicotinell®-TTS is statistically significant.

2.2.4 Nicotine-Pluronic F -127

The influence of concentration of polymer on the drug release of the preparations containing Pluronic F-127 was exhibited. Higher concentration of this polymer produced lower amount of drug released. The formulations containing 1, 5 and 10 % w/w pluronic F-127 could present the amount of drug release of 1.0186 ± 0.0272 mg/cm^2, 1.0512 ± 0.0398 mg/cm^2 and 0.7527 ± 0.0159 mg/cm^2, respectively. The cumulative release time data of nicotine from three preparations (Formula #8, 9, 10) were presented in Appendices xxiii-xxv and Table 22. According to the high relationship between the drug released and the square root of time, it could be implied that the release pattern of drug from this polymer tend to be the Higuchi's model kinetic.

The release of drug depended on the concentration of polymer. Increasing the concentration of polymer affected decreasing the drug released. From the release of Formula # 8, 9, 10 compared to Nicotinell®-TTS (Figure 44) revealed that all of the Formulas were shown lower release pattern than the Nicotinell®-TTS. This suggests that Pluronic F-127 could not use for nicotine carrier.

2.2.5 Nicotine-EVA copolymer

The release-time data of nicotine from preparations of nicotine-TDS using EVA copolymer as drug matrix carriers are illustrated in Appendices xxvi-xxix and Table 23. All preparations can sustain the release of nicotine over 24 hours. The formulations composed of 5, 10, 15 and 20 % w/w EVA copolymer presented the amount drug release of 1.8139 ± 0.0123 mg/cm^2, 1.3323 ± 0.0137 mg/cm^2, 1.1500 ± 0.020 mg/cm^2 and 0.8976 ± 0.0169 mg/cm^2, respectively. Maximum correlation coefficient in Table 27 and the release pattern of drug from this polymer may be the Higuchi's model. These results were indicated that the concentration of polymer obviously affected the amount of drug release, increasing the polymer concentration significantly decreasing the amount of drug release. A typical release profile depicting the effect of

increasing polymer on drug release compared to Nicotinell®-TTS as shown in Figure 45. This suggests that nicotine-5% w/w EVAco (Formula #11) shown the release profile similar to Nicotinell®-TTS.

Due to the reason of nicotine-5% w/w EVAco film was very thin (~70 μm) and difficult to prepare, nicotine-10% w/w EVAco film (~140 μm) was easy to prepare and the film thickness was suitable to use as drug reservoir for TDS. Nicotine-10% w/w EVAco presented the amount drug release less than Nicotinell®-TTS thus Formula #15 used 10% w/w EVAco and added 10% w/w mineral oil in order to increase nicotine release rate. The release-time data and profiles of Formula #15 compared to Nicotinell®-TTS is shown in Appendix xxx, Table 23 and Figure 49. The amount drug release was 2.1236 ± 0.0109 mg/cm²/day and the release of drug seemed to follow the First order kinetic.

The skin permeation kinetics of nicotine delivered by the nicotine-EVA copolymer TDS were investigated. The results are given in Appendices xxvi-xxix, Table 26 which indicated that the skin permeation of drug depended on the concentration of EVA copolymer. Increasing the amount of polymer affected decreasing of drug permeation. The drug permeation from preparations composed of 5, 10, 15 and 20 % w/w of this polymer were 1.9363 ± 0.0159 mg/cm²/day, 1.2222 ± 0.0188 mg/cm²/day, 1.1435 ± 0.0118 mg/cm²/day and 1.0782 ± 0.0459 mg/cm²/day, respectively. Maximum correlation coefficient in Table 28 and the permeation profiles compared to Nicotinell®-TTS shown in Figures 46-48, indicated that the permeation of drug from this polymer seemed to follow Higuchi's model and Formula #11 (5% w/w EVAco) shown the profile similar to Nicotinell®-TTS. Statistical analysis, by ANOVA, of the skin permeation rate of nicotine indicated that the different between Formula #11 and Nicotinell®-TTS is statistically insignificant.

The skin permeation data and profile of Formula #15 is shown in Appendix xxx, Table 26 and Figures 50-52 indicated that the skin permeation amount was 1.8443 ± 0.0123 mg/cm²/day and the maximum correlation coefficient seemed to follow to First order kinetic. The profile was similar Nicotinell®-TTS, by ANOVA, indicated that the different between Formula #15 and Nicotinell®-TTS is statistically insignificant.

From this *in-vitro* permeation studies, it could be concluded that formulations which could give permeation of nicotine similar

to Nicotinell®-TTS are as follows : Formula #1, Formula #3, Formula #4, Formula #5, Formula #11 and Formula #15. The skin permeation rates were calculated from the slope of drug permeation profile of Q_s versus $t^{1/2}$ (Table 31). Table 32 showed the one-way analysis of variance (ANOVA) of the permeation rate.

According to the ANOVA Table, VR = 26.4732 was more than critical value of F (0.95, 6, 24) = 2.64, revealed that the differences between each formulation (among group mean square) more different than within formulation (within group mean square). It can concluded that the mean of seven formulations were singnificant difference.

Duncan's new multiple range test for testing the difference in value of a pair of permeation rate is shown in Table 33 indicated that the differences between Nicotinell®-TTS and Formula #1, 3, 4, 11 and 15 showed statistically insignificant but the different between Nicotinell®-TTS and Formula #5 was statistically significant. The rank order of drug skin permeation rates from TDS was obtained as follow : Formula #15 > Formula #11 > Nicotinell®-TTS > Formula #3 > Formula #4 > Formula #1 > Formula #5. Formula #5 significant more slow permeation rate than the other formulations.

Table 29 The skin permeation rates of nicotine from transdermal patches.

Formula #	Skin permeation rate ($mg/cm^2/h^{1/2}$)			
	1	2	3	X ± SD
Nicotinell®	0.4505	0.4449	0.4481	0.4478 ± 0.0028
1	0.441	0.431	0.442	0.4380 ± 0.0061
3	0.4537	0.4374	0.4319	0.4410 ± 0.0113
4	0.4381	0.4511	0.4262	0.4385 ± 0.0125
5	0.3854	0.3641	0.3879	0.3791 ± 0.0131
11	0.4588	0.459	0.4474	0.4551 ± 0.0066
15	0.4492	0.4591	0.4576	0.4553 ± 0.0053

Table 30 Analysis of variance of drug skin permeation rates of nicotine transdermal patches.

ANOVA TABLE

Source	df	SS	MEAN SQUARE (MS=SS/df)	V.R.
Among Group	k-1=6	0.0125	2.08×10^{-3}	26.4732
Within Group	N-k=21-7 =14	0.0011	7.857×10^{-5}	
Total	20	0.0136		

Critical value (F) = 2.64 α = 0.05

SS = Sum of square
MS = Mean square
df = Degree of freedom
V.R = Variance ratio

Table 31 Comparison of means of skin permeation rates of nicotine transdermal patches using Duncan's new multiple range test.

Formulation	Difference between mean	LSR	Dtatistical significant	Formulation	Difference between mean	LSR	Dtatistical significant
F7-F1	0.0721	0.01735	S	F5-F1	0.0687	0.01673	S
F7-F2	0.0173	0.01725	S	F5-F2	0.0098	0.01673	NS
F7-F3	0.0168	0.01704	NS	F5-F3	0.0093	0.01627	NS
F7-F4	0.0143	0.01673	NS	F5-F4	0.0068	0.0155	NS
F7-F5	0.0075	0.01627	NS	F4-F1	0.0619	0.01673	S
F7-F6	0.0002	0.01550	NS	F4-F2	0.003	0.01617	NS
F6-F1	0.0760	0.01725	S	F4-F3	0.0025	0.0155	NS
F6-F2	0.0171	0.01704	S	F3-F1	0.0594	0.01617	S
F6-F3	0.0166	0.01673	NS	F3-F2	0.0005	0.0155	NS
F6-F4	0.0141	0.01627	NS	F2-F1	0.0589	0.0155	S
F6-F5	0.0073	0.01550	NS				

F1 = Formula #5
F2 = Formula #1
F3 = Formula #4
F4 = Formula #3
F5 = Nicotinell®-TTS
F6 = Formula #10
F7 = Formula #15

2.3 Comparison between Non-aqueous Base, Aqueous Base and Matrix Systems

Three formulation systems; non-aqueous base, aqueous base and matrix systems; were formulated for nicotine-TDS reservoir. In non-aqueous base formulations used mineral oil as solvent/vehicle. Formula #1 was 5 % w/w nicotine in mineral oil, Formula #3 was 20 % w/w nicotine adsorbed on non woven. Both Formulas had skin permeation rate similar to Nicotinell® -TTS but Formula #1 was liquid reservoir if some damages occur to the membrane, dumping effect of nicotine may be occurred. In aqueous base formulations used carbomer 934 as gelling agent, only Formula #4 (5 % w/w nicotine - 0.3 %w/w carbomer 934) had skin permeation rate similar to Nicotinell®-TTS but 0.3 %w/w carbomer was likely liquid solution more than gel, thus the dumping effect may be occurred if membrane tear. In matrix reservoir systems, Formula #11 (5 %w/w EVAco) and Formula #15 (10 % w/w EVAco -10 % w/w mineral oil) were skin permeation rate paralleled to Nicotinell ®-TTS. However, Formula #11 was very thin and difficult to prepare, thus it was not suitable for drug reservoir. Form these three formulation systems the two best systems in this study for drug reservoir were Formula #3 (20 % w/w nicotine adsorbed on a non woven patch) and Formula #15 (5 % w/w nicotine-10 % w/w EVAco-10 % w/w mineral oil), respectively.

CONCLUSION

Nicotine is a pyridine alkaloid and extracts from tobacco. Nicotine replacement therapy offer an effective approach to act in smoking cessation and good candidate for development of its transdermal therapeutic system. *In-vitro* experiments were performed to characterize nicotine skin penetration and some factors affecting skin penetration. The results of this preliminary can be summarized as follows:

(1) In non-aqueous preformulation, effects of six non-aqueous solvents/ vehicles, they are propylene glycol, polyethylene glycol 400, glycerin, mineral oil, silicone oil and simethicone, on stability could be ranks in the following orders : mineral oil > silicone oil > simethicone > glycerin ~ propylene glycol > polyethylene glycol 400 and the ranks order of drug release and skin permeation was obtained as follows : silicone oil > simethicone > mineral oil > glycerin > polyethylene glycol 400 > propylene glycol revealed that mineral oil seemed to be the best vehicles for nicotine.

(2) In aqueous preformulation, effects of pH values on octanol/buffer partition coefficient, It can conclude that increasing lipophilicity of nicotine by increasing the pH value or increasing ionization with decreasing the pH values.

(3) Nicotine was very stable in aqueous solution when the pH value of the solution was alkaline.

(4) *In-vitro* release and skin permeation of nicotine in aqueous solutions at pH 10.5, 8.5 and 6.5 are as follows : pH 10.5 > pH 8.5 > pH 6.5

(5) For aqueous antioxidant, 0.05% w/w sodium EDTA and 0.5% w/w sodium sulfite were the most effective concentration for nicotine in aqueous solution.

(6) Development of nicotine-TDS was formulated in 3 systems; (1) nicotine-mineral oil (2) nicotine-gelling agents (ie. carbomer 934 and pluronic F-127) and(3) nicotine-EVA copolymer; these indicated that increasing polymer concentration decreasing nicotine release and skin permeation.

(7) The skin permeation kinetics of all formulas appeared to be Higuchi's model excepted for nicotine-10% w/w EVAco-10% w/w Mineral

oil was first order kinetic release.

(8) Statistical analysis; by ANOVA, of the *in-vitro* skin permeation rate of nicotine indicated that the differences among Nicotinell®-TTS, nicotine - mineral oil, nicotine - 0.3% w/w carbomer 934, nicotine - 5% w/w EVA copolymer, and nicotine - 10% w/w EVAco - 10% w/w mineral oil were statistically insignificant.

Consequently, It was concluded that mineral oil was suitable solvent/ vehicles for nicotine, carbomer 934 was the useful gelling agent, EVA copolymer was the useful matrix-carrier for nicotine-TDS that could be deliver nicotine in a controlled and continuous manner for over 24 hours. from the five Formulas (#1, 3, 4, 11, and 15) that have permeation rates similar to Nicotinell®-TTS, can be concluded that Formula #3 (20% w/w nicotine adsorbed on a non woven patch) and Formula #15 (5 % w/w nicotine -10 % w/w EVAco - 10 % w/w mineral oil) were the best formulation for nicotine-TDS because they easy to prepare and good apparent more than other formulas.