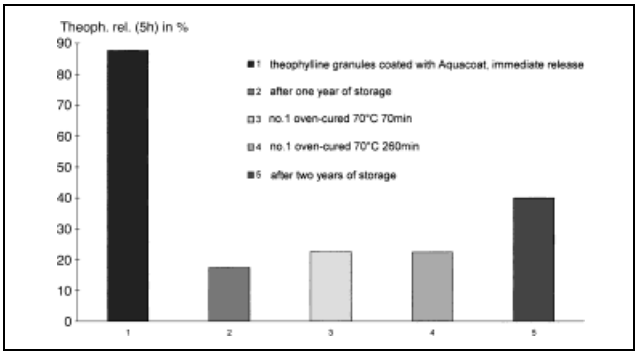

Fig. 1: Effect of storage and curing on theophylline release from coated granules

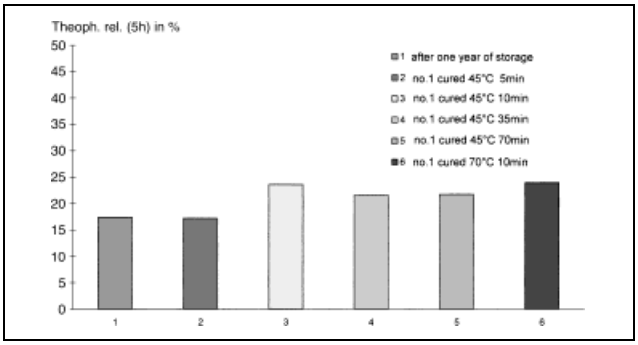

Fig. 2: Effect of storage and curing time on theophylline release from one year old coated granules

within five hours. The curing times of 70 min and 260 min caused no significant differences in drug release pattern.

Under normal conditions of storage (room temperature and humidity) the released amount of theophylline from coated granules within five hours was after one year about five times less than the released amount of new coated theophylline granules. After two years of storage (same conditions), surprisingly the released amount of drug within five hours was half of the release of the new coated granules (Fig. 1). This effect may be caused by aging of the material.

As can be seen in Fig. 2, oven-curing of the one year old granules did not show an effect by 45 °C and 5 min. By 45 °C and 10, 35 and 70 min, the theophylline release was slightly increased as well as at 70 °C and 10 min.

Experimental

A powder mixture of Emcocel® 50M (microcrystalline cellulose, Mendell Co. Inc., Carmel, NY, USA), theophylline (China), lactose hydrous (Sheffield Products, Norwich, NY, USA) and Ac-Di-Sol® (croscarmellose sodium, FMC Corporation, Newark, DE, USA) was used to produce granules in a fluid-bed rotor granulator (GPCG1, Glatt Air Techniques, Ramsey, NJ, USA) while continuously spraying a binder solution of 2.5% Plasdone® K-29/32 (polyvinylpyrrolidon, ISP Technologies Inc., Wayne, NJ, USA). After drying in the rotor granulator to a humidity of 2–4% the granules over 0.85 mm and under 1.7 mm were coated in the same granulator with a mixture of Aquacoat® (ethylcellulose aqueous dispersion, FMC Corporation, Newark, DE, USA) and 30% dibutyl sebacate (Sigma Chemical Co., St. Louis, MO, USA). The thickness of the layer was 4 mg/cm^2.

The dissolution test was made by USP basket-apparatus at 37 °C and 50 rpm. The medium was 900 ml of water. Samples were measured by UV spectrophotometry (Beckmann DU-70, Beckmann Inc., Fullerton, CA, USA).

The moisture content was determined using an automated gravimetric moisture content analyzer (Computrac, Max-50, Arizona Instruments, Tempe, AZ, USA).

The content uniformity was examined and the USP requirements were met for all batches.

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Effect of adhesive and drug reservoir on *in vitro* transdermal delivery of nicotine

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Transdermal delivery of drugs from polymeric devices has been around for over a decade and significant advances have been made in this field [1]. A complete design of a transdermal device or patch incorporates a drug-loaded matrix or reservoir totally covered by a rate-controlling membrane. The entire skin-contacting surface of the patch is coated with an adhesive [2]. Accordingly the topical permeability of a drug depends on the rate of release from its formulated product including drug reservoir, membrane and adhesive. The purpose of this investigation was to evaluate the influence of adhesive and drug reservoir on *in vitro* permeability of nicotine as a model drug. Transdermal delivery of nicotine into the systemic circulation has been shown to facilitate tobacco withdrawl by mitigating or even preventing abstinence symptoms and diminishing craving [3, 4]. Both natural rubber and silicone are used as the base of adhesive to determine the permeation of nicotine *in vitro*. A polysulfone hydrophobic membrane is employed as the rate-controlling membrane because of the good wetting of the membrane by the aqueous fluid beneath it [5]. In the drug reservoir of the *in vitro* diffusion cell, nicotine was incorporated into the hydrogel formulations including Carbopol polymer (polyacrylic acid), methylcellulose (MC) and hydroxypropyl cellulose (HPC).

Various nicotine loading amounts are incorporated into pH 7.0 McIlvaine buffer for the *in vitro* permeation study through a polysulfone membrane combined with natural rubber or silicone adhesive. The profile of nicotine flux and the permeability coefficient is shown in the Table. There is an ascendant trend for nicotine to increase its flux from the nicotine concentration of 3 to 9% either through a natural rubber adhesive or through a silicone adhesive. After the calculation of the correlation coefficient between the drug concentration of 3 to 9% and flux, a linear relationship ($r = 0.999$ for natural rubber; $r = 0.998$ for silicone adhesive) was observed. No significant difference was found between the flux from drug re-

Table: Flux and permeability coefficient of nicotine in pH 7.0 buffer through various adhesives

Adhesive		Nicotine concentration in pH 7.0 buffer (%)			
		3	6	9	12
Natural rubber	Flux[a] ($\mu g/cm^2/h$)	71.30 ± 10.37	125.18 ± 12.45	182.45 ± 13.87	188.65 ± 35.27
	Permeability C[b]	1.19 ± 0.17	1.04 ± 0.10	1.01 ± 0.08	0.79 ± 0.15
Silicone	Flux	71.49 ± 5.90	113.84 ± 14.85	165.45 ± 35.19	168.99 ± 14.26
	Permeability C	1.19 ± 0.10	0.95 ± 0.12	0.92 ± 0.20	0.70 ± 0.06

[a] Flux is calculated by the slope of the linear portion of cumulative amount-time curve
[b] Permeability coefficient = Flux/Nicotine loading amount (mg) in pH 7.0 buffer

servoir with 9% and 12% nicotine concentration. Thus, the loading amount of 9% may act as a maximum concentration to achieve an effective permeability of nicotine since the higher loading amount may restrict its absorption amount only to the level of 9%. The flux of nicotine through rubber adhesive was slightly higher than that through silicone adhesive, although there was no significant difference (t-test, $p > 0.05$) between the flux of these two adhesives. As a consequence, the 9% nicotine loading amount was added to the hydrogels, used for the formulation of nicotine to deliver through a polysulfone membrane and rubber adhesive for the *in vitro* permeation study.

As shown in the Fig., both viscosity and nicotine flux of cellulose gel are higher than those of Carbopol® gel. Since there is 20% propylene glycol in the Carbopol hydrogel formulation, the pH 7.0 buffer content of the Carbopol hydrogel (67.7%) was lower than that of the

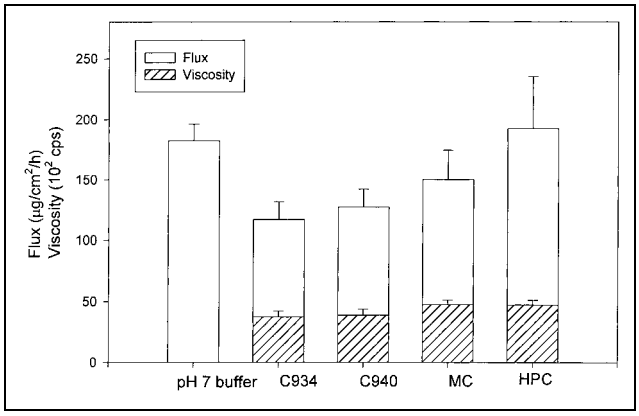

Fig.: *In vitro* flux of nicotine and viscosity from various hydrogel formulations. Values are the mean for three determinations

cellulose hydrogel (89.0%). The hydrophobic nicotine molecules may partition into the polymer phase rather than into the water phase. This would explain why increasing the water content in the vehicle would lead to an increased flux for nicotine since it would decrease the concentration of nicotine in the hydrogel phase and hence increase its partitioning into the skin. This result was consistent with that of a previous study which shows that increasing the water content in the Myverol® gel greatly increases the apparent flux of nicotine [6].

The highest permeability of nicotine was observed in the HPC hydrogel. There was no significant difference between the nicotine flux from HPC gel and pH 7.0 buffer solution, indicating a lack of a significant diffusion barrier property of HPC. Comparisons with earlier work on nicotine clearly demonstrate that the choice of vehicle can contribute to the performance of these types of transdermal drug delivery systems.

Experimental

1. Materials

Nicotine was purchased from Sigma Co. (USA). Natural rubber was supplied by Tong-Ho Co. (Taiwan). Px 1150® terpene polymer was from Yasuhara Co. (Japan). Dow Corning 355® silicone adhesive was obtained from Dow Corning Co. (USA). Polysulfone membrane was obtained from Gelman Co. (USA). Methylcellulose (MC) and hydroxypropyl cellulose (HPC) were purchased from Tokyo Kasei Co. (Japan). Carbopol 934® and 940® were supplied by B. F. Goodrich Co. (USA).

2. Preparation of adhesive

Nicotine and polymers (10% natural rubber, 10% polyisoprene and 4% Px 1150® terpene polymer) were accurately weighed and then dispersed in cyclohexane. This mixture was stirred for 24 h until the polymer was dissolved and the solution well mixed. Then the mixture was poured uniformly onto the impermeable backing membrane (Scotchpak 1009®) by constant volume in a glass ring. The adhesive film was kept at room temperature for 2 h to evaporate excess organic solvent. Finally, the release liner (Scotchpak 1022®) was covered on the film to protect it.

3. Preparation of hydrogels

The Carbopol 934® or 940® hydrogel was composed of Carbopol polymer (0.3%), triethanolamine (3%), propylene glycol (20%) and pH 7.0 buffer (76.7%). Cellulose hydrogel was composed of cellulose polymer (2%) and pH 7.0 buffer (98%). Nicotine was participated in the hydrogel in a concentration of 9%. The determination of hydrogel viscosity was done according to the previous study [7].

4. In vitro permeation study

Excised male Wistar rat was employed as the skin barrier. The flux of nicotine was determined using a modified Franz diffusion cell. Details of the *in vitro* permeation experiment were described earlier [8].

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