Release of Clonidine Hydrochloride from Pressure-Sensitive Adhesive Matrices Prepared by Emulsion-Type Acrylate Polymers

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The *in vitro* release characteristics of a model hydrophilic drug, clonidine hydrochloride, from pressure sensitive adhesive (PSA) matrices prepared by two coating methods, direct coating on a backing layer and transfer coating (coating on a liner layer and transfer of the resulting PSA onto a backing layer), with different drying temperatures were measured and evaluated. Hydrophilic polymer, polyethylene glycol (PEG), hydroxypropyl cellulose (HPC) or polyvinyl pyrrolidone (PVP) was added to the matrices to increase the drug release rate. A lower drying temperature showed a higher release rate. Each polymer increased the release rate compared to control (without polymer). A PSA matrix with HPC showed a low initial burst followed by a prolonged release, whereas those with PEG and PVP exhibited a high initial burst and a subsequent low release rate. The difference in the initial burst was related, to a considerable degree, to the affinity of the matrices against water. It was also related to the amount of drug on the matrix surface. The transfer coating and addition of HPC were useful in suppressing the high initial burst and in maintaining a high sustained release rate of the drug from the PSA matrices.

Key words *in vitro* drug release; PSA matrix; hydrophilic polymer; transfer coating; drying temperature

Topical formulations consisting of pressure sensitive adhesive (PSA) matrices have been prepared by dissolving or dispersing a drug in the PSA solution and casting or coating the solution on a backing film. Such formulations have been applied to several marketed transdermal delivery systems (TDS) containing nitroglycerin, estradiol and so on. Silicone polymers, natural and synthetic rubbers, and acrylate polymers have been used to make PSA.[1] These materials are sufficiently lipophilic to solubilize and disperse those lipophilic drugs which have been used in TDS.

The solubility of a selected drug in a PSA matrix is one of the most important factors determining the release properties of the drug from the matrix.[2–4] Lipophilic drugs are candidates for TDS due to their high intermutual solubilities. Some drugs in which a suitable pharmacological effect can be expected by the application of topical formulations, however, may be soluble in water and may be in a salt form. Low drug solubilities in PSA matrices are a major problem in the development of TDS. Thus, a logical approach would be to develop PSA matrices in which aqueous drugs can be solubilized or dispersed.

Emulsion-type acrylate polymers[5] were applied to overcome this problem. Most hydrophilic drugs are not soluble in conventional adhesive solutions, but are in a continuous phase for o/w emulsion-type acrylate polymers. A mixed solution containing an emulsion-type PSA and a hydrophilic drug can be coated on a film to make a PSA matrix containing a drug. The resulting TDS must be checked for the presence and distribution state of the drug in the matrix after drying the solvents together to determine the drug release and skin permeation profile from the matrix.

Clonidine hydrochloride was selected as a model drug in the present study.[6] *In vitro* release characteristics were measured from the emulsion-type polymers for the prepared PSA matrices containing the drug. Hydrophilic polymers such as polyethylene glycol (PEG), hydroxypropyl cellulose (HPC) and polyvinyl pyrrolidone (PVP) were used to increase the release rate.

Materials and Methods

Materials An o/w type emulsion (polymer/water = 50/50 by weight and anionic surfactant content $\leq 0.5\%$) of 2-ethylhexyl acrylate/methylmethacrylate copolymer (80/20 by weight) was generously supplied by Modern Plastic Industries Co. (Tokyo, Japan). Clonidine hydrochloride was purchased from Tokyo Chemical Industry Co. (Tokyo). PEG (polyethyelen glycol E-45, MW 600000—800000) was obtained from Meiwa Chemical Industries, Co. (Kyoto, Japan), and HPC (HPC-M, 150—400 cps) and PVP (PVP K-30, MW 40000) from Wako Pure Chemicals, Co. (Osaka, Japan). All other chemicals and solvents were of reagent grade or HPLC grade and were obtained commercially.

Preparation of PSA Matrix Clonidine hydrochloride (0.15 g) and a hydrophilic polymer (PEG, HPC, or PVP; 0.3 g for most experiments) were mixed thoroughly with an adequate amount of the PSA emulsion (total weight: 6.0 g). In direct coating,[7] this preparative solution was coated on polyethylene terephthalate (PET) film (as a backing film) by a Baker type applicator and dried in a vacuumed desiccator at room temperature (23 ± 3 °C) for 16 h, at 60.0 ± 0.5 °C for 90 min or 110.0 ± 0.5 °C for 60 min. The obtained matrix was attached to linear type (silicone-coated PET) and kept in the desiccator at room temperature until being used. In transfer coating,[8] the PSA solution containing PEG was used because high viscosity was required for the preparative solution at coating. PSA was coated on the silicone-coated PET film and dried at room temperature for 16 h. The obtained matrix was fastened to a backing film (PET) and kept in the desiccator at room temperature. The resulting PSA matrices were 100 ± 10 μm in thickness and contained 10 ± 0.2 mg matrix/cm^3. Lot-to-lot variations in the thickness and drug content were quite low.

Drug Release Experiment A PSA piece of 0.95 cm^2 was set in a diffusion cell with 2.5 ml distilled water at 37 °C according to our previous method.[2] At predetermined intervals, 0.5 ml samples were withdrawn to measure the drug release. The same amount of fresh water was added to keep the volume constant throughout the experiment.

***In Vitro* Skin Permeation Experiment** Abdominal skin excised from hairless rat (WBN/ILA-Ht, male, average weight 150 g, Life Science Research Center, Josai University, Saitama Japan) was excised after being shaven carefully. PSA matrix with and without PEG was affixed to the stratum corneum side of the excised skin, and the dermis side of the skin membrane was mounted to a diffusion cell, as above. Procedural details were the same as in our previous paper.[2]

Clonidine Assay Clonidine hydrochloride in the supernatant after

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centrifugation of the aqueous samples with *n*-amyl *p*-hydroxylbenzoate in methanol was determined by HPLC. The HPLC system consists of a pump (LC-6A, Shimadzu, Kyoto), autoinjector unit (SIL-6B, Shimadzu), system controller (SCL-6B, Shimadzu), column (Nucleosil 5C18, 4.6 × 250 mm, Nergel, Germany), column oven (CTO-6A, Shimadzu), UV detector (SPD-6B, Shimadzu) and integrator (CR-6A, Shimadzu). The elution solvent was 0.1% phosphoric acid : acetonitrile (45 : 55) containing 5 mM sodium dodecylsulfate, and its flow rate was 1.2 ml/min. The column temperature was maintained at 40 °C. Detection was done at UV 210 nm.

Assay of Water in PSA Matrix The PSA matrix (5 cm^2) 12 h after coating was immersed in 1 ml dioxane and ultrasonicated for 3 min to release water. After centrifugation at 0 °C, 2 μl of the supernatant was injected to gas chromatography (GC) with a thermal conductance detector (TCD-GC, GC-14A, Shimadzu). A glass column (3.0 mm × 3.1 m) packed with PEG 1000 with 10% Flusin T (60/80 mesh) was used. The carrier gas, helium, was flowed at 1.75 kg/cm^2. Detector and injector temperatures were maintained at 145 °C and the column temperature was increased from 95 to 145 °C at a rate of 40 °C/min.

FTIR Measurement of PSA Matrix Surface The PSA surface was examined by an attenuated total refraction (ATR) method using FTIR (JIR-5500, Nihondenshi, Tokyo) with an ATR unit (IR-ATR100, Nihondenshi). Repeated measurement (20 cycles) was done by fastening the PSA matrix to a ZnSe cell (52 × 20 × 20 mm, $\theta = 45°$). The ratio of absorbance at 1665 cm^{-1} specifically for clonidine against that at 1728 cm^{-1} for PSA was used as an index of the drug concentration at the matrix surface.

Results and Discussion

First, the effect of the drying condition on the clonidine release from a PSA matrix (without polymer) was measured. Figure 1 compares the release phenomena among three drying conditions. A lower drying temperature showed a higher release rate: only one-third against the initial loading was released over 24 h, even for the PSA matrix dried at room temperature, which showed the highest release. Therefore, the drying condition may be related to the amount of water remaining in the PSA matrix. Table 1 shows the amount of water in the matrices. A lower drying temperature resulted in a higher water content in the matrices.

Second, the effect of the addition of hydrophilic polymers on the release profiles was investigated. Figure 1 also shows the release phenomena for three matrices containing 5% PEG, HPC or PVP (drying condition: room temperature for 16 h). Each polymer increased the release rate compared to the control (without polymer), suggesting the usefulness of such hydrophilic polymers in enhancing the release rate of hydrophilic drugs from PSA matrices. The greatest effect was found by PEG. Time courses of the drug release were different among the polymers added: the PSA matrix with HPC showed a low initial burst followed by a prolonged release, whereas those with PEG and PVP exhibited a high initial burst and a subsequent low release rate. The water amount in the matrices (Table 1) was increased by the addition of hydrophilic polymers. No linear relation, however, was recognized between the water content and the release rate or the amount of clonidine hydrochloride from the matrices, probably due to the different physicochemical properties of the polymers. The effect of concentration of the hydrophilic polymer was also investigated. A higher concentration showed a higher release for every polymer (data not shown). To investigate the relationship between the release rate and skin permeation rate of clonidine hydrochloride from the matrices, the effect of the hydrophilic polymers on the skin permeation of clonidine hydrochloride from PSA matrices was determined using PEG as a model (Fig. 2). It is clear that PEG increased the skin permeation. PEG may accelerate the dissolution of the drug in the matrices.

Figure 3 compares the release pattern of clonidine hydrochloride from the matrices prepared by direct and transfer coatings. The amount of drug released from the transfer coating-matrix was lower than from the matrix

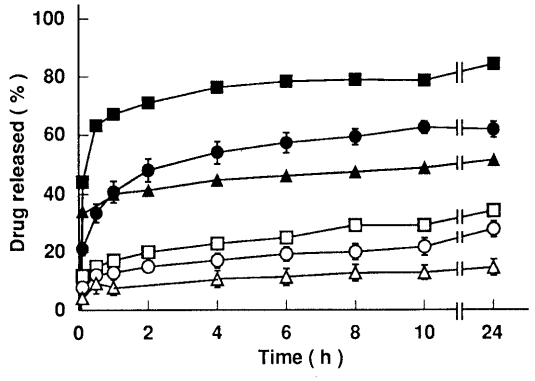

Fig. 1. Effect of Drying Temperature and Addition of Hydrophilic Polymers on the Release Profile of Clonidine Hydrochloride from PSA Matrix

□, room temperature for 16 h without polymer; ○, 60°C for 90 min without polymer; △, 110 °C for 60 min without polymer. ■, room temperature for 16 h, PEG; ●, room temperature for 16 h, HPC; ▲, room temperature for 16 h, PVP. Each point represents the mean ± S.E. of 5 experiments.

Table 1. Effect of Drying Temperature and Hydrophilic Polymers on the Water Content of PSA Matrices

Condition	Water content (%)[a]
Room temp. for 16 h; without polymer	1.018 ± 0.106
60 °C for 90 min; without polymer	0.944 ± 0.335
110 °C for 60 min; without polymer	0.443 ± 0.025
Room temp. for 16 h; with PEG	1.926 ± 0.184
Room temp. for 16 h; with HPC	1.851 ± 0.042
Room temp. for 16 h; with PVP	2.926 ± 0.179

a) Mean ± S.D. of 5 determinations.

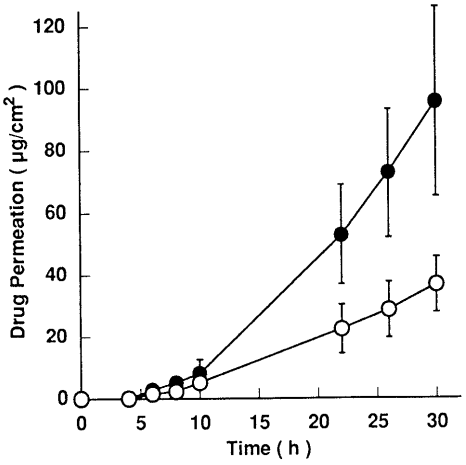

Fig. 2. Permeation Profiles of Clonidine Hydrochloride from PSA Matrices with and without PEG through Excised Hairless Rat Skin

○, without PEG; ●, with PEG. Each point represents the mean ± S.E. of 3 experiments.

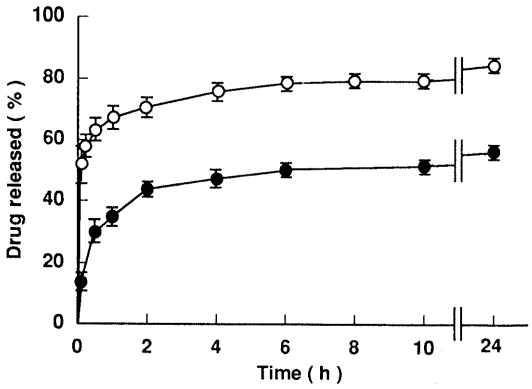

Fig. 3. Release Profiles of Clonidine Hydrochloride from PSA Matrices with PEG Prepared by Direct and Transfer Coatings

○, direct coating; ●, transfer coating. Each point represents the mean ± S.E. of 5 experiments.

Table 2. Index for the Amount of Clonidine Hydrochloride on the Surface of PSA Matrices

Preparation method[a]	Index[b]
Direct coating; without polymers	0.2350
Direct coating, PEG	0.4951
Direct coating; HPC	0.1712
Direct coating; PVP	0.3207
Transfer coating; PEG	0.1965

a) Each PSA was dried at room temperature. *b*) Absorbance ratio at 1665 cm^{-1} for clonidine against that at 1728 cm^{-1} for PSA. Mean ± S.D. of 5 determinations.

directly coated. The major difference in the amount released was in the initial burst. No significant difference was found in the release rate after 0.5 h.

The difference in the distribution of clonidine hydrochloride in the matrices between the two preparation methods, direct and transfer coatings, with and without the hydrophilic polymers, was evaluated by ATR-FTIR. This technique enables one to semiquantitatively distinguish the drug amount on the matrix surface. Table 2 summarizes the obtained index, showing the amount of clonidine hydrochloride on the matrix surface. The addition of PEG and PVP increased the index, whereas HPC decreased the value. The two former polymers showed a large initial burst, but HPC did not. The initial burst may be related to the amount of drug on the matrix surface. In addition, the value for the transfer coating with PEG was lower than that for the direct coating with PEG, suggesting a higher drug concentration on the dry surface of the matrices.

The effect of the hydrophilic polymers can be viewed as follows by dividing it into two stages, the initial burst period and the later release profiles. The high initial burst was probably due to high distribution of the drug on the release surface of the matrices, which was found by scanning electron microscopy with a light element X-ray detector (data not shown).[9] This localized distribution of the drug was confirmed from the release profiles from those matrices containing PEG prepared by transfer coating, which had only a small initial burst (Fig. 3). In contrast, little initial burst was found from the matrices containing HPC (Fig. 1). These matrices showed a similar amount of clonidine hydrochloride on the release surface as those without any hydrophilic polymers. HPC matrices also showed a large release at the later period. The exact difference in the characteristics and morphology of the HPC matrices from PVP and PEG, however, was not clear. Further experiments with various polymers may clarify the effect of hydrophilic polymers and elucidate a criterion by which to select additives for the PSA matrices. The affinity of PSA to water was also a very important issue for determining drug release. A higher water affinity or content generally resulted in a greater release rate.

It is still difficult to understand the implication of the *in vitro* release test compared to the *in vitro* skin permeation test and *in vivo* absorption test.[10] The *in vitro* release rate of a drug is seldom proportional to the skin permeation rate. Rank order of the release rate from different vehicles may not be the same as that of the absorption rate. If the skin permeation rate is much lower than the release rate from vehicles, only a slight change in the release rate does not influence the skin permeation rate. The release phenomenon, however, is very important in determining the thermodynamic activity of drugs in vehicles[4] and in optimizing vehicle formulation for better topical delivery or in quality control of batched manufacturing.[11] It is thus important to follow the *in vitro* release profiles when considering and comparing corresponding *in vivo* situations.

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