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Evaluation of Polyvinyl Alcohol Hydrogel as Sustained-Release Vehicle for Transdermal System of Bunitrolol-HCl

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ABSTRACT

In order to evaluate a bunitrolol(β-blocker) preparation using poly(vinyl alcohol) (PVA) hydrogel for hypertension as a transdermal delivery system, in vitro release characteristics and the permeation of bunitrolol through rat skin from hydrogel and the bunitrolol plasma profile after application onto abdominal skin in rats were examined. The PVA hydrogel containing bunitrolol-HCl was prepared by a low temperature crystallization method. The release of bunitrolol from PVA hydrogel followed with Fickian diffusion (Higuchi model); the drug release profile versus square root of release time gave straight line over 60% of the total release process. The release rate and permeation through rat skins of bunitrolol from hydrogels affected with preparation at various physical and chemical states. Longer freezing times, higher polymerization and higher concentration of PVA resulted in lower permeation. These results had relations

with the results of release tests. Higher pH of preparation resulted in a higher permeation of bunitrolol, which did not have a relation with the results of release tests. The plasma concentration of bunitrolol after application of hydrogel preparation onto the abdominal skins were relatively high at early times and sustained a plateau level during 48 h in rats. In conclusion, transdermal delivery system using PVA hydrogel is favorable with prolonged action for low available drugs such as bunitrolol-HCl.

INTRODUCTION

The design of controlled-release dosage form for transdermal drug delivery is a new subject of considerable interest. The major advantages that transdermal drug delivery can offer are: avoidance of first-pass metabolism often associated with oral administration, sustained and more constant plasma concentration of drugs (1). Beta-adrenergic bloking agents (β-blocker) now occupy an important place in the treatment of angina pectoris, hypertension and other cardiovascular diseases. The transdermal delivery of β-blocker offers considerable advantages especially for treatment of chronic disease because many β-blockers have a first-pass metabolism and need a constant plasma level for a long period of time (2).

Hydrogel have been receiving a lot of interest as devices for the drug delivery systems (3-4). Novel poly(vinyl alcohol) (PVA) hydrogels, prepared by low temperature crystallization method, have porous and three dimensional network structure with high mechanical strength and high water contents (4). In the present study, PVA hydrogel, a

fully swollen hydrogel, was used as a controlled transdermal delivery system β-blocker, bunitrolol-HCl, for therapeutic of hypertension. In order to evaluate the hydrogel preparation as the following four topics were investigated; 1) the in vitro release characteristics of bunitrolol, 2) the drug permeation through rat abdominal skins, 3) the plasma concentrations of bunitrolol and 4) the change in arterial blood pressure after application of preparation onto the abdominal skins in rats.

MATERIALS AND METHODS

Materials PVA (degree of saponification; over 98.0 mol%, mean degree of polymerization; 1000, 1700 and 3210) was obtained from Unichika Ltd. (Osaka, Japan), bunitrolol-HCl from Nippon Boehringer Ingelheim (Kawanishi, Hyogo, Japan). All other chemicals were of reagent grade and were obtained commercially.

Preparations Hydrogel containing bunitrolol-HCl was prepared using low temperature crystallization method described by our previous paper (4). Briefly, PVA was dissolved in 1/15 M phosphate buffer (pH 6.5, pH 7.0 and pH 8.0) at about 100°C to have concentrations of 5, 10 and 15% w/w. Then bunitrolol-HCl was added in PVA solutions at room temperature with the final pH of those solutions being pH 6.5, pH 7.0 and pH 8.0. The PVA solutions containing bunitrolol-HCl were poured into glass syringes (ϕ 9.5 mm X 2.5 mm). The hydrogels containing bunitrolol-HCl were formed by freezing these PVA solutions at -20°C for 1 day to 8 days to allow crystallization of PVA, followed by thawing

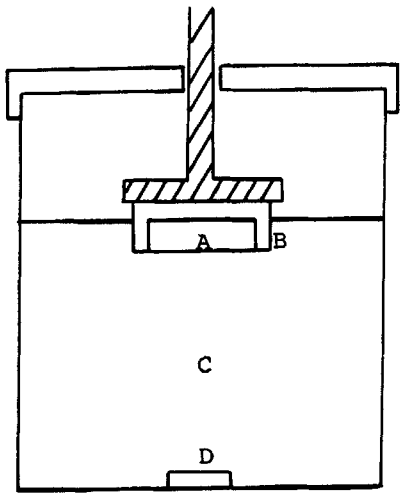

FIGURE 1

Release apparatus for hydrogel preparations.

A: Hydrogel preparations, B: Holder for preparation

C: Release Medium (37 °C), D: Stirring Bar (100 r.p.m.)

at 4-5°C for 2 days. The hydrogel preparations were stored to keep off aqueous evaporation at the room temperature and were used within 1 month.

Release Tests The release rate of bunitrolol-HCl from the hydrogel preparation was investigated by using a release apparatus (Fig.1). The dissolution fluid (300 ml) was 1/15 M phosphate buffer (pH 7.4) which was degassed and maintained at 37°C. One milliliter of each sample was removed at predeterminals and 1 ml of each fresh fluid was added to a vessel to maintain the original volume. The concentration of bunitrolol was assayed by fluorescence spectrophotometorically (excitation wavelength 295 nm and emmission wavelength 330 nm). Release rate data was treated using

mathematical relationships based on physical model (Fickian and Non-Fickian drug release model) (5-6).

In Vitro Percutaneous Permeation Tests Percutaneous permeation tests were determined by using the in vitro permeation cell procedure (Franz type) (7). Full thickness abdominal skins of male Wistar strain rats weighing about 250 g were used. The hair of abdominal area in rats was removed with electric hair clipper and electric razor without breaking the skin one day before the experiments. The extracted abdominal skin was mounted on the receptor phase compartment of diffusion cell (available diffusion area of 0.9 cm). The straum corneum side faced upward into the donor phase. The receptor phase containing 13 ml isotonic phosphate buffer (pH 7.4) at 37°C and was stirred with magnetic bar at 500 rev min. The hydrogel preparation was applied on the skin surface. One milliliter of each sample was removed at predeterminal and 1 ml of each fresh fluid was added to the cell to maintain the original volume. The concentration of bunitrolol was determined by the high performance liquid chromatographic (HPLC) method of Nagakura and Kohei (8).

In Vivo Percutaneous Absorption Tests Male Wistar strain rats weighing about 250 g, which had free access to diet and water, used in the in vivo percutaneous absorption tests. The hair of the abdominal area in rats was removed by the same method in the in vitro tests without breaking one day before the experiments. The hydrogels were applied onto the abdominal skin in rats under pentobarbital-Na anesthesia. The applied abdominal region was immediately occluded with a sheet of Parafilm (American CAN CO.) and a surgical adheisive tape.

In comparison, bunitrolol solution was administered orally to the rat stomach at a dose of 2 mg/rat with through a catheter. Blood samples (0.5 ml) were collected periodically from the inguinal vein. The plasma was separated immediately by centrifugation and stored frozen until assay. The concentration of bunitrolol was determined by HPLC method (8). In other rats under urethane anesthesia, the change in arterial blood pressure was directly measured with a pressure transducer after application of the hydrogel onto abdominal skin.

RESULTS

Release Tests The in vitro release tests of bunitrolol were carried out with hydrogel preparations, which were prepared at various physical and chemical states, freezing times, degrees of polymerization of PVA, concentrations of PVA, and pH of PVA solutions. Figure 2 shows the release profiles of bunitrolol from hydrogel preparations (5 and 15% w/w PVA, pH 7.0), which were prepared at various freezing times (-20°C). Freezing times did not affect the releases of bunitrolol from hydrogel preparation at 5% w/w PVA. However, the release of bunitrolol from hydrogel preparations at 15% w/w PVA were slower on longer freezing times.

Figure 3 (A) shows the release profiles of bunitrolol from hydrogel preparations (5% w/w PVA, pH 7.0) with various degrees of polymerization of PVA. Slower releases of bunitrolol were shown on higher polymerization of PVA.

Figure 3 (B) shows the effect of PVA concentrations in hydrogel preparations (pH 7.0) on the release profiles of bunitrolol. Slower releases of bunitrolol were shown on higher concentrations of PVA in hydrogel preparations.

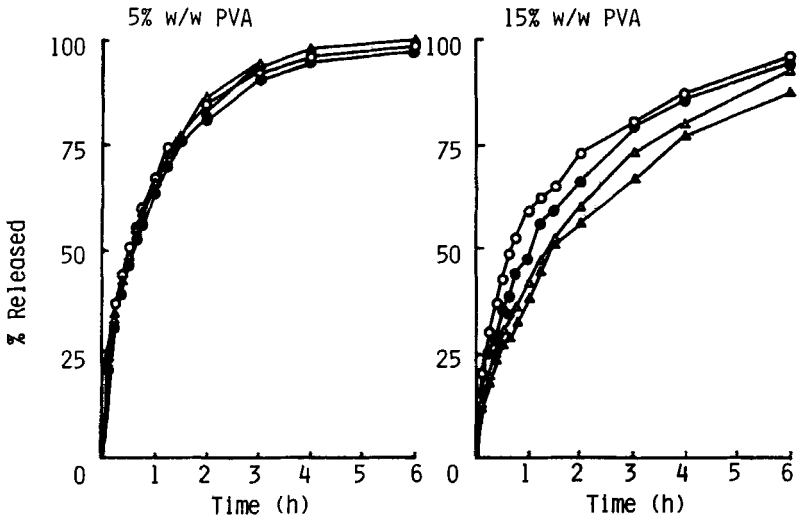

FIGURE 2

Release profiles of bunitrolol from 5% w/w (A) and 15% w/w (B) PVA hydrogels (pH 7.0) prepared at various freezing times.

Freezing times at -20°C: ○ 24 h, ● 48 h, △ 96 h, ▲ 192 h,

The degree of polymerization of PVA is 1700.

Each point represents the mean of 3 experiments.

Figure 3 (C) shows the release profiles of bunitrolol from hydrogel preparations (5% w/w PVA) prepared at various pH. Slower release of bunitrolol was shown with higher pH of hydrogel preparation.

Release rate from swelling polymeric hydrogel can generally be treated using Equ 1, $M_t/M_\infty = kt^n$, where M_t / M_∞ is the fraction of drug release at time, t, and k and n are constant and characteristic of polymeric system. The situation of n=1 corresponds to zero-order release kinetics, $1 > n > 0.5$ correpsonds to non-Fickian diffusion model and n=0.5 corresponds to Fickian diffusion (Higuchi model).

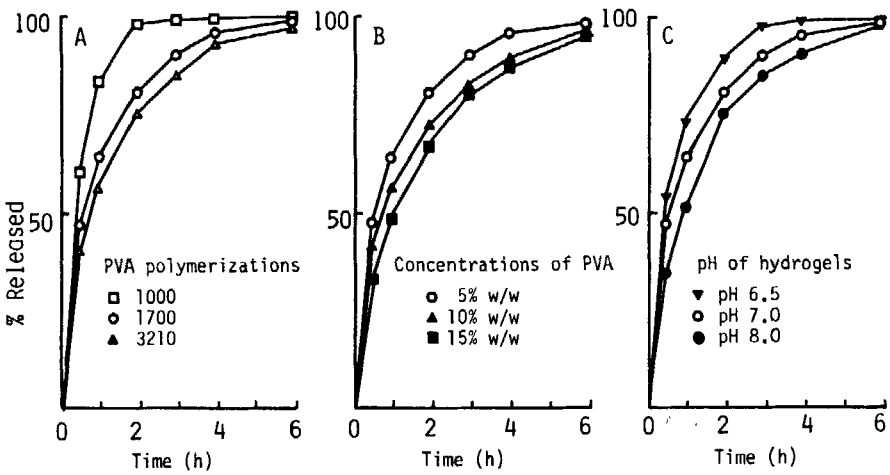

FIGURE 3

Release profiles of bunitrolol from PVA hydrogels prepared at various physical and chemical states, degrees of polymerization of PVA (A), concentrations of PVA (B) and pH of PVA solutions (C).
Freezing time is 48 h.
Each point represents the mean of 3 experiments.

The kinetic parameters for bunitrolol released from hydrogel preparations are summarized in Table I. The derived n values, obtained by using values of $M_t / M_\infty \leqq 0.6$, approached 0.5. The bunitrolol release from hydrogel preparations accorded with the well-known Fickian diffusion model. Therefore, if cumulative amounts of released bunitrolol from hydrogel preparations were plotted as a function of square root of time, these release profiles would show one straight line between these relationships.

Permeation Tests The permeations of bunitrolol through rat skins from hydrogel preparations at various states were

Table I
Kinetic Parameters for Bunitrolol HCl Release from Hydrogel Preparations

Bunitrolol HCl Hydrogel Preparation	$\frac{M_t}{M_\infty}$	Release Exponent n	Kinetic Constant $k(\%\cdot min^{-n})$	Correlation Coefficient r
5% PVA (1000, 7.0)	0.6	0.505	11.089	0.996
5% PVA (1700, 7.0)	0.6	0.506	8.475	0.999
5% PVA (3210, 7.0)	0.6	0.509	7.807	0.997
10% PVA (1700, 7.0)	0.6	0.504	7.991	0.998
15% PVA (1700, 7.0)	0.6	0.503	6.362	0.998
5% PVA (1700, 6.5)	0.6	0.494	10.221	0.997
5% PVA (1700, 8.0)	0.6	0.519	6.789	0.999

Values in parentheses are degree of polymerization and pH of preparation.

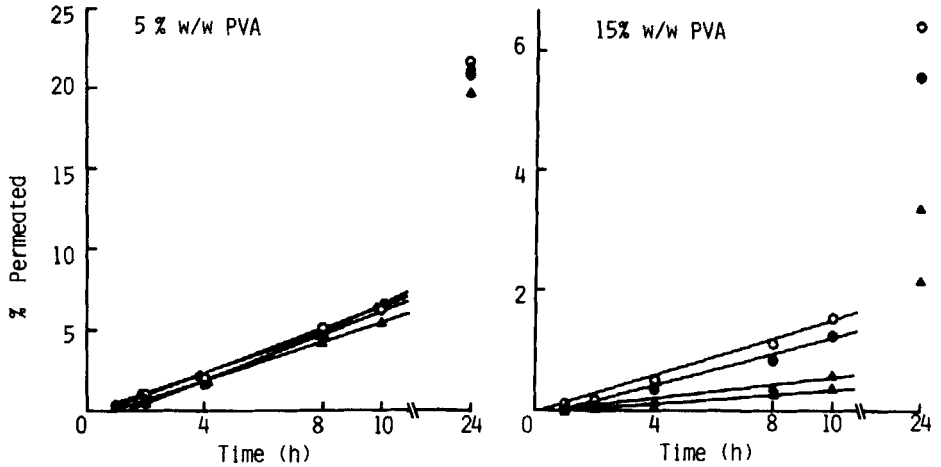

FIGURE 4

Permeation profiles of bunitrolol from 5% w/w (A) and 15% w/w (B) PVA hydrogel (pH 7.0) prepared at various freezing times.

Freezing times at -20°C: ○ 24 h, ● 48 h, △ 96 h, ▲ 192 h,

The degree of polymerization of PVA is 1700.

Each point represents the mean of 5 experiments.

examined by using the in vitro Franz type cell procedure. The profiles of cumulative amounts of permeated bunitrolol showed one straight line with short lag times as a function of time on every hydrogel preparation (Fig. 4-5). Figure 4 shows the permeation profiles of bunitrolol through rat skins from hydrogel preparations (5 and 15% w/w PVA, pH 7.0), which were prepared at various freezing times (-20°C). Freezing times did not affect the permeation of bunitrolol through rat skin from hydrogel preparations of 5% w/w PVA. However, the permeation of bunitrolol from hydrogel preparation of 15% w/w PVA was lower with the longer freezing times.

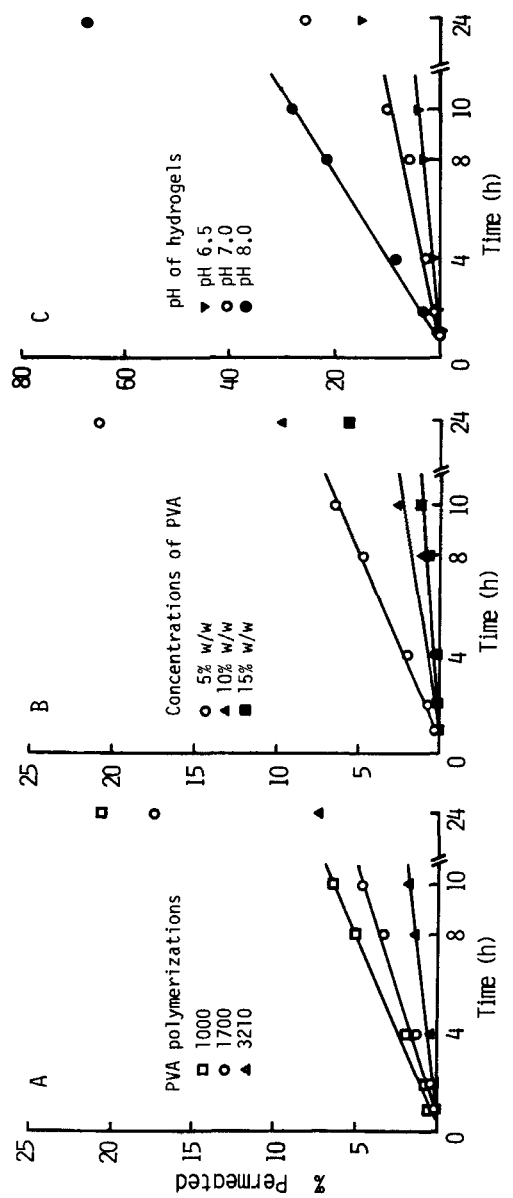

FIGURE 5

Permeation profiles of bunitrolol from PVA hydrogels prepared at various hysical and chemical states, degrees of polymerizations of PVA (A), concentrations of PVA (B) and pH of PVA solutions (C). Freezing time is 48 h.

Each point represents the mean of 5 experiments.

Figure 5 (A) shows the permeation profiles of bunitrolol through rat skins from hydrogel preparations (5% w/w PVA, pH 7) using various degrees of polymerization of PVA. Lower permeations of bunitrolol were shown on hydrogel preparations at higher polymerization of PVA. Figure 5 (B) shows the effect of PVA concentrations in hydrogel preparations (pH 7.0) on the permeations of bunitrolol through rat skins. Lower permeations of bunitrolol were shown on hydrogel preparations at higher concentrations of PVA. Figure 5 (C) shows the permeation of bunitrolol through rat skins from hydrogel preparations (5% w/w PVA) prepared at various pH. The permeations of bunitrolol, a basic compound (pKa = 9.7) were pH dependent and increased with rising of pH.

Percutaneous Absorption of Bunitrolol The percutaneous absorption of bunitrolol from hydrogel preparations were examined on the application onto the abdominal skins in rats. Figure 6 shows the bunitrolol concentration in plasma after application of hydrogel preparations at various pH in rats. The bunitrolol plasma concentrations were relatively high at early times after application. It did not show a sharp peak and sustained a plateau level during 48 h. These plateau levels were about 7.18, 13.22 and 19.64 ng/ml with hydrogel preparations at pH 6.5, pH 7.0 and pH 8.0, respectively. In comparison, Fig. 7 shows the bunitrolol concentration in plasma after oral administration of bunitrolol-HCl (dose; 2 mg/rat) in rats. The bunitrolol in plasma was rapidly eliminated after sharp peak at 30 min after administration. The bioavailabilities of the percutaneous administrations of hydrogel preparations at pH 6.5, pH 7.0 and pH 8.0 (AUC_{0-48h}), relative to oral administration of bunitrolol-HCl ($AUC_{0-\infty}$), were 371%, 656% and 954%,

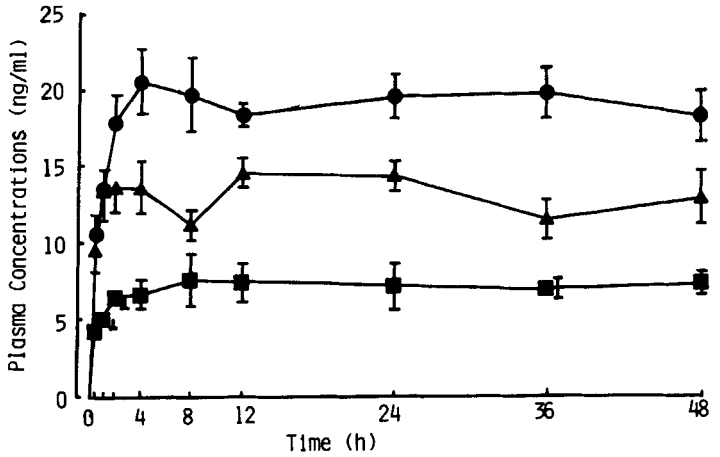

FIGURE 6

Plasma concentrations of bunitrolol after application of hydrogel preparations (5% PVA) at various pH onto the abdominal skins in rats.

pH of PVA hydrogel: ■ pH 6.5, ▲ pH 7.0, ● pH 8.0.

Each PVA hydrogel containing 2 mg of bunitrolol HCl.

Each point represents the mean ± S.E. of 5 animals.

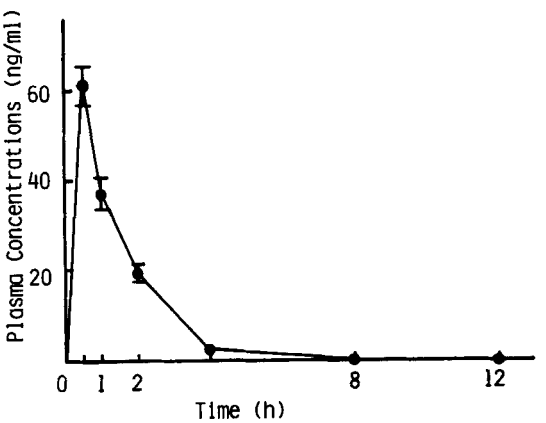

FIGURE 7

Plasma concentrations of bunitrolol after oral administration of bunitrolol-HCl solution (dose;2mg/rat) in rats.

Each point represents the mean ± S.E. of 5 animals.

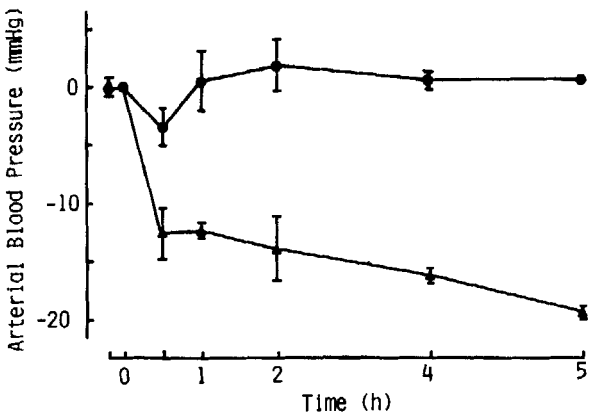

FIGURE 8

Change in arterial blood pressure after application of hydrogel preparations (5% w/w PVA, pH 7.0) onto the abdominal skins in rats.

▲ Hydrogel preparation containing drug, ● Hydrogel preparation without drug.

Each hydrogel preparation containing 2 mg bunitrolol HCl.

Each point represents the mean ± S.E. of 3 animals.

respectively. Thus, the percutaneous administration of hydrogel preparations could avoid the first-pass eliminations of bunitrolol on the oral administration.

Figure 8 shows the change in arterial blood pressure after application of hydrogel (pH 7.0) onto the abdominal skins in rats. The arterial blood pressure decreased 13 mmHg 30 min after application compared with initial level. This hypotensive effect increases slowly until 6 h after application.

DISCUSSIONS

PVA hydrogel, prepared by low temperature crystallization method in this study, is a non-erodible, non-dissolving and fully swollen matrix (4). Furthermore, this hydrogel has porous and three-dimensional network structure with high mechanical strength and high water contents. The bunitrolol-HCl preparation using this hydrogel was designed for controlled transdermal delivery system.

Several basic studies have shown that drug release from hydrogel depends on the nature of hydrogel used particularly the degree of crosslink, the side of water channel and the drug equilibrium between the polymer phase and external water phase. In this in vitro release tests, the release of bunitrolol from hydrogel preparations followed the Fickian diffusion (Higuchi model), which the drug release profile versus the square root of release time gave straight line over about 60% of the total release process (5). Bunitrolol-HCl completely dissolved in water phase of hydrogel. This result is in agreement with the release of indomethacin, which dispersed in hydrogel as previously described. These may be caused by characteristics of hydrogel which is a non-erosible and fully swollen matrix.

The release rates of bunitrolol from hydrogel preparations were affected with preparation at various physical and chemical states, freezing times, degrees of polymerization of PVA, concentrations of PVA, and pH of hydrogels. Longer freezing times, higher polymerization and higher concentrations of PVA resulted in higher network system and lower drug release rates. On the other hand, lower pH of hydrogels resulted in a higher ionized molecules of bunitrolol, a basic drug (pKa= 9.7), in hydrogel and higher bunitrolol release.

In the in vitro permeation tests, bunitrolol released from hydrogel permeated through the rat skins at a zero-order rate. The permeation rates of bunitrolol were affected with hydrogel preparations at various physical and chemical states. Longer freezing times, higher polymerizations and higher concentrations of PVA resulted in lower permeation. These had relation with the results of release tests. However, in the case of changed pH of hydrogels, higher pH of hydrogel preparation resulted in higher permeation of bunitrolol, which did not have relation with the result of release tests. Furthermore, the bunitrolol plasma concentrations after application of hydrogel preparations at various pH onto abdominal skins increased with rising of pH in rats. These data suggested the preferential absorption of unionized form.

The bioavailability of orally administered bunitrolol is considerably low and varies individually (9). The variations in blood levels as well as the extensive drug metabolism during absorption and first passage through the liver. The bunitrolol in plasma was rapidly eliminated after sharp peak at 30 min after oral administration of bunitrolol-HCl (2 mg/rat) in rats. On the other hand, the bunitrolol plasma concentration after application of hydrogel preparations onto abdominal skin in rats sustained a plateau level during 48 h. Thus, these findings suggest that the elimination of bunitrolol during the absorption process in the transdermal delivery system is almost negligible, and that the transdermal delivery system, which can be controlled by hydrogel, is useful for the development of new dossage forms of low available drugs such as bunitrolol.

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