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Formulation and biopharmaceutical evaluation of transdermal patch containing benztropine

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Abstract

Benztropine (BZ) is a potent muscarinic receptor antagonist that has been used for the treatment of Parkinson disease. However, the oral administration of BZ is often limited because of its many dose-related side effects. In this study, BZ was formulated into drug-in adhesive (DIA) patches in an attempt to overcome these problems. The effects of the formulation factors including pressure-sensitive adhesive (PSA), enhancer, the loading amount of the drug and patch thickness on the skin permeation of the drug were evaluated using excised rat skin. The optimized patch contained 10% BZ in Duro-Tak® 2525 as a PSA at a thickness of 100 μm. The pharmacokinetic characteristics of the optimized DIA patch were determined after the transdermal application to rabbits. The calculated relative bioavailability of BZ in the DIA patch was 54% compared to the oral administration of BZ mesylate. This suggests that the transdermal application of BZ in a DIA patch may be used for the treatment of Parkinson disease.

Keywords: Benztropine; Transdermal; Skin permeation; Pharmacokinetics

1. Introduction

Benztropine (BZ) is a potent muscarinic receptor antagonist that has been used for the treatment of Parkinson disease as well as to relieve the symptoms of the extrapyramidal syndrome induced by neuroleptic drugs such as the phenothiazine derivatives (Dollery, 1998; Brocks, 1999). However, the clinical application of BZ, is often limited on account of its dose-related adverse side effects such as tachycardia, paralytic ileus and urinary retention. The more serious side effects include forgetfulness, sedation, depression, and anxiety. In addition, as with other drugs used for Parkinson disease, its dose should be carefully adjusted and individualized according to the age and weight of the patients, as well as to the types of Parkinsonism being treated.

BZ is metabolized to *N*-oxide, *N*-desmethyl, 4-hydroxy and *N*-desmethyl-4-hydroxy-derivatives after its oral administration (He, 1994). The potential toxicity, metabolic behavior and the difficulties associated with self-administered injectable forms of BZ make the transdermal delivery of BZ an attractive alternative delivery route. Some studies have investigated the percutaneous absorption of BZ (Gorukanti et al., 1999; Bosman et al., 1998).

The aim of this study was to formulate drug-in adhesive (DIA) patches containing BZ using pressure-sensitive adhesives (PSA). There are many formulation factors for such a patch including PSA, enhancer, loading amount of the drug and the physical properties of the patch. This study examined their effects on the skin permeation of BZ using excised rat skin. The pharmacokinetic characteristics of an optimized DIA patch containing BZ were determined using rabbits.

2. Materials and methods

2.1. Materials

The following reagents were used as purchased without further purification: BZ mesylate (Fine Chemicals Corp., South Africa), HPLC grade acetonitrile and ethanol (J.T. Baker Co., USA), sodium 1-decanesulfonate, isopropyl myristate (IPM), polyethylene glycol 400 (PEG 400), propylene glycol (PG), polyoxyethylene-9-lauryl ether (POE), glycerin triacetate (Triacetin), tetraglycol, propylene carbonate (Sigma Chemicals Co., USA), diethylene glycol monoethyl ether (Transcutol®), propylene glycol monolaurate (PGML) (Gattefosse Co., France),

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Mygliol 812 (Sasol Co., German), and Myvacet (Eastman Chemical Products, Inc., USA). Duro-Tak® (DT) adhesives were obtained from National Starch and Chemical Co., USA. All other chemicals were of reagent grade. Water was purified with reverse osmosis and filtered in house.

2.2. Preparation of BZ from BZ mesylate

The BZ free base was prepared from BZ mesylate, which was available on the market. BZ mesylate solution (0.3 g/ml water) was titrated with 2N potassium hydroxide solution to pH 12. The aqueous phase was saturated with sodium chloride and extracted with diethyl ether. The ether layer was separated and washed with water, which was followed by the addition of anhydrous sodium sulfate. The ether was filtered and evaporated using a rotary evaporator (R-205, Büchi Labortechnik AG, Switzerland). The viscous colorless oil residue was transferred to an amber glass container and kept in vacuum evaporator until there was no weight loss. The final product, BZ, was identified using IR, NMR and HPLC.

2.3. Determination of partition coefficient of BZ

n-Octanol and water were saturated with each other for 24 h prior to the experiment. The BZ solution (100 μg/ml) was prepared using the *n*-octanol saturated with water. One milliliter of the solution was then transferred to a 10 ml centrifuge tube containing 1 ml of water saturated with *n*-octanol. The tube was gently shaken for 24 h at 25 °C and centrifuged at 3000 rpm for 10 min. After centrifugation, the BZ concentrations in each phase were determined using a validated HPLC method.

2.4. Preparation of DIA patches containing BZ

The DIA patches containing BZ were prepared with various PSA and enhancers. The amount of BZ in the patch was varied from 1 to 20%. A laboratory-coating unit (Labcoater LTE-S, Mathis, Switzerland) was used to prepare the DIA patches. An appropriate amount of BZ was dissolved in a suitable amount of ethanol, added to the PSA solution and mixed homogenously with a mechanical stirrer. The resulting drug–PSA solution was coated onto a fluoropolymer-treated polyester released liner (ScotchPak® 1022, 3M, USA) at a thickness of 100 μm. After the solvent had been removed, it was laminated with a polyester backing film (ScotchPak® 9732, 3M).

2.5. Determination of skin permeation of BZ

Skin permeation rates of BZ from various vehicles and DIA patches with different formulations were measured in order to evaluate the effects of the formulation factors on the skin permeation of BZ. Franz diffusion cells fitted with excised rat skins were used for this experiment. The rat skins were obtained from male Sprague–Dawley rats weighing 230 ± 20 g after the hair had been removed with an electric clipper (900, TGC Inc., Japan). A 3 cm × 3 cm patch of skin was excised from the dorsal region and the adhering fat and other visceral tissue was removed carefully. The excised rat skin was stored at −20 °C and used within 1 week after the skin harvest. The receptor compartment of the Franz diffusion cell was 11.5 ml and the effective diffusion area was 1.77 cm^2. Isotonic phosphate buffer (pH 7.4) containing 20% PEG 400 was used as the receptor medium, which was maintained at 37 ± 0.5 °C using a thermostatic water pump (WBC 1520, Jeio Tech Co., Korea) and stirred at a constant rate of 600 rpm during the experiment. At 2, 4, 6, 8, 12, 16 and 24 h after the transdermal application of the patch or solution containing BZ on the skin, 200 μl of the receptor medium was withdrawn and replaced with an equal volume of freshly prepared medium. The amounts of BZ permeated through skin into the receptor medium were determined using a validated HPLC method.

2.6. Data analysis

The cumulative amounts of BZ permeated through the skin were plotted as a function of time. From these graphs, the skin permeation rate of the drug was calculated from the slope of the linear portion of each plot. Only the linear portion of the plot with a correlation coefficient greater than 0.90 was used to calculate the slope.

2.7. Evaluation of physical properties of DIA patches

The prepared patches were cut into strips 2.54 cm wide and conditioned for 24 h at 23 ± 2 °C and 50 ± 5%RH. The samples were applied to an adherent plate made of stainless steel, smoothened with a 4.5 pound roller five times, and pulled from the substrate at a 180 °C angle at a rate of 300 mm/min. Adhesion/release tester (AR-1000, ChemInstruments, USA) was used for the determination of peel adhesion force. For the determination of tackiness, the prepared patches were cut into strips 10 cm × 1.5 cm and conditioned for 24 h at 23 ± 2 °C and 50 ± 5%RH, and mounted on loop tack tester (LT-100, ChemInstruments). Eight bank oven shear (HT-8, ChemInstrument) was used to determine shear strength, after the prepared patches were cut into strips 1 cm × 5 cm and conditioned for 24 h at 23 ± 2 °C and 50 ± 5%RH. The one side of patch 1 cm × 1 cm was attached on the panel and the other side was hung on a weight of 500 g.

2.8. Biopharmaceutical evaluation of DIA patches containing BZ

The pharmacokinetic characteristics of the DIA patch containing BZ was evaluated after its transdermal application to New Zealand white rabbits weighing 2.5–3 kg. The DIA patches with the optimized formula, covering an area of 2 cm × 2 cm (equivalent to 4 mg BZ), were applied to the shaved dorsal skin of rabbits with an overlay using adhesive tapes and removed 24 h later. The oral administration of BZ mesylate was used as the reference at a dose of 4 mg as BZ, using a different group of rabbits. BZ mesylate (5.24 mg, equivalent to 4 mg of BZ) was dissolved in 2 ml of water and administered to each rabbit using an oral feeding needle. The rabbits were fasted for over 10 h

prior to drug administration and allowed to have access to food 4 h after dosing.

Two milliliters of blood samples were collected from the marginal ear vein of the rabbits at 0, 2, 4, 6, 8, 12, 16, 24, 36, 60, 96 and 132 h after the transdermal application of the patches, and 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 60, 96 and 132 h after the oral administration of the BZ mesylate solution. The blood was transferred immediately into polypropylene tubes containing a small amount of sodium heparin, and centrifuged at 3000 rpm for 5 min. The obtained plasma was stored at −20 °C until analysis.

The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were compiled from the plasma concentration of BZ versus time profile. The area under the plasma concentration–time curve (AUC) up to 132 h was calculated using the linear trapezoidal rule. The relative bioavailability of the BZ patch, compared to the oral administration of BZ mesylate, was calculated according to the AUC values obtained.

2.9. HPLC determination of BZ

The concentrations of BZ in the vehicle, receptor medium or rabbit plasma were determined using a validated HPLC method with a slight modification (Raje et al., 2002). The HPLC system consisted of an isocratic pump (L-7100, Hitachi, Japan), a UV detector (L-7400, Hitachi), an automatic injector (L-7200, Hitachi) and an integrator (L7000, Hitachi). The column used was a Luna C_{18} column (4.6 mm × 150 mm, 5 μm particle size, Phenomenex, USA). The mobile phase was a mixture of acetonitrile and 0.03 M phosphate buffer (pH 3) containing 0.01 M sodium 1-decanesulfonate (40:60). Its flow rate was 1.2 ml/min. The detection wavelength was 259 nm for the permeation study and 199 nm for the pharmacokinetic study. The lower limit of quantitation for the permeation study was 1 μg/ml, while that for the pharmacokinetic study was 1 ng/ml. For the permeation study, the samples were diluted with the mobile phase, and 100 μl was injected onto the column. For the pharmacokinetic study, 60 μl of internal standard solution (desipiramine 0.5 μg/ml), 150 μl of triethylamine, 4 ml hexane were added to 600 μl of plasma and vortexed for 1 min. After centrifuged at 3000 rpm for 5 min, the organic phase was taken and evaporated to dryness at 40 °C under a gentle stream of nitrogen. The residue was reconstituted with 300 μl of the mobile phase and 200 μl of the final solution was injected onto the column.

2.10. Statistics

Each experiment was repeated at least three times. The mean values and standard deviations are presented. Student's *t*-test was used to compare the pharmacokinetic parameters with the level of significance set at $P < 0.05$.

3. Results and discussion

3.1. Preparation of BZ from BZ mesylate

The diffusion behavior of the drug molecules is one of the most important physicochemical properties when determining the feasibility of a transdermal delivery system for a drug. It is generally accepted that the lipophilic free acid or free base form of a drug has a higher partition coefficient than the corresponding hydrophilic salt form. Therefore, the former has higher skin permeability than the latter. In this regard, the free base form of BZ was prepared using an acid–base titration and extraction procedure because only the mesylate form of BZ is available on the market. The prepared product was identified as BZ using IR, NMR and HPLC with a high level of purity (>99.5%). The efficiency of the conversion was 95%. The log $P_{o/w}$ of BZ was 2.21 ± 0.03 ($n = 3$).

Table 1
Skin permeation rates of BZ from 2% BZ solutions in the neat vehicles through the excised rat skins

Vehicles	J_s[a] (μg/cm²/h)	Vehicles	J_s[a] (μg/cm²/h)
Isoamyl alcohol	15.24 ± 1.56[b]	Mygliol 812	23.58 ± 3.45
Hexanol	12.31 ± 1.17	Triacetin	6.36 ± 3.08
Octanol	16.86 ± 0.90	Propylene carbonate	6.24 ± 2.56
Decanol	28.26 ± 1.21	Soya oil	24.27 ± 3.95
PG	7.82 ± 3.09	Triethanolamine	3.24 ± 0.86
PEG400	2.88 ± 1.83	Transcutol®	0.48 ± 0.09
PGML	1.73 ± 0.66	POE	0.47 ± 0.06
IPM	52.34 ± 10.86	Tetraglycol	2.52 ± 2.27
Myvacet	71.48 ± 3.34	Oleic acid	0
Ethyl oleate	38.29 ± 8.16		

[a] Skin permeation rate.
[b] Mean ± S.D. ($n = 3$).

3.2. Effect of vehicles on skin permeation of BZ

The importance of the vehicle in the percutaneous absorption of a drug has been well documented (Rolf, 1988; Ghosh and Banga, 1993; Yamashita et al., 1993). The vehicle can act as a plasticizer, which can increase the solubility and mobility of a drug in a patch. In particular, it can improve the permeation rate of the drug. In this study, the effect of various vehicles on the permeation of BZ through excised rat skin was evaluated.

The BZ concentration in each vehicle was fixed to 2%, because BZ was miscible with all of the neat vehicles studied. Table 1 shows the permeation rates of BZ through the excised rat skins. Among the vehicles examined, Myvacet had the highest enhancing effect on the permeation rate of BZ through the skin, followed by IPM and ethyl oleate. Generally, the lipophilic vehicles had higher permeation rates of BZ through the skin than the hydrophilic vehicles such as PEG 400. Oleic acid had no effect on the skin permeation of BZ, possibly due to an interaction between the amine moiety of BZ and the carboxylic acid of oleic acid. Many studies have shown that several fatty acid esters increased the fluidity of the lipid portions of stratum corneum by disrupting lipid packing, and thereby enhancing the permeability of drugs through the skin (Golden et al., 1987; Friend et al., 1989). IPM enhanced the skin permeation rate of progesterone, estradiol, indomethacin and methyl nicotinate (Leopold and Maibach, 1996), tacrine (Kim et al., 2000) and BZ (Gorukanti et al., 1999). IPM is known to act as a fluidizer of intercellular lipids, and affects the lipid-rich phase in the stratum corneum, thereby reducing its barrier function. Ethyl oleate has

Table 2
Skin permeation rates of BZ from the patches made with different PSAs containing 5% BZ through excised rat skin

PSAs			J_s[b] (μg/cm²/h)
Trade name[a]	Chemical description	Functional group	
DT2510	Acrylate	−OH	11.36 ± 2.45[c]
DT2516	Acrylate–vinylacetate	−OH	12.22 ± 0.99
DT2287	Acrylate–vinylacetate	−OH	12.41 ± 2.24
DT2525	Acrylate–vinylacetate	−OH	14.31 ± 2.49
DT6430	Polyisobutylene rubber	−None	8.18 ± 1.36
DT9301	Acrylate	−None	5.80 ± 2.36
DT4098	Acrylate–vinylacetate	−None	7.68 ± 2.65
DT2051	Acrylate–vinylacetate	−COOH	0
DT2353	Acrylate	−COOH	0

[a] Duro-Tak series made by Nation Starch and Chemical Co., USA.
[b] Skin permeation rate.
[c] Mean ± S.D. (n = 6).

the same enhancement mechanism as IPM (Golden et al., 1987). Myvacet may enhance the skin permeation of BZ like other fatty acid esters. Therefore, Myvacet and IPM were selected for the preparation of patches containing BZ.

Alkanols also enhanced the skin permeation of BZ to some extent. Their mechanism is known to involve the disruption of densely packed lipids that fill the extra cellular spaces of the stratum corneum (William and Barry, 2004). The enhancement effect of alkanols increased with increasing carbon-chain length (Wu et al., 1997; Walters and Brain, 2001; Kim et al., 1992). The results also showed that decanol (C-10) had greater enhancement effect than the others.

3.3. Effect of PSAs and enhancers on skin permeation of BZ

The selection of an appropriate PSA is the most important factor in designing a transdermal drug delivery system (Tan and Pfister, 1999). For the formulation of a DIA patch containing BZ, the effect of different types of PSA on the skin permeation of BZ was evaluated using excised rat skins. The BZ concentration in the PSAs was fixed to 5% and each DIA patch was prepared with a thickness of 100 μm. Table 2 shows the skin permeation rates of BZ from the DIA patches made from the different PSA. The skin permeation of BZ depends on the functional group of PSA employed. Whereas the PSAs containing carboxylic acid did not show any skin permeation, the PSAs containing a hydroxyl group produced a high skin permeation rate of BZ. The PSAs containing no functional groups showed relatively high skin permeation of BZ. Other studies have also reported that different functional groups in acrylate PSAs could have different release rates (Guyot and Fawaz, 2000; Chedgzoy et al., 2002). The presence of carboxylic acid groups can increase the hydrophilicity of the matrix, which decreases the diffusivity of lipophilic BZ. In addition, the lack of skin permeation from the patches made from the PSA containing a carboxylic acid might be due to an interaction between the amine moiety of BZ and the carboxylic acid of the PSA. Other skin permeation studies of lidocaine, aminopyrine, ketoprofen and tacrine from various PSAs produced similar results (Kokubo et al., 1994; Cho and Choi, 1998; Kim et al., 2000). Therefore, the chemical nature of the adhesive must be considered before selecting the adhesive matrix because the interaction between a drug and PSA can have a significant effect on the rate of drug release.

Among the PSAs possessing a hydroxyl functional group, DT-2525 showed the highest skin permeation rate of BZ. Therefore, DT-2525 was selected as the PSA of choice for the DIA patch containing BZ.

In order to develop a matrix-type transdermal delivery system for a drug, an appropriate vehicle is often needed to enhance the permeation rate and/or to increase the solubility of the drug in the patch. Since both Myvacet and IPM showed high skin permeation rates of BZ, they were used as enhancers to improve the skin permeation of BZ from the DIA patches. The effects of Myvacet, IPM and their mixtures at different ratios on the skin permeation of BZ from the DIA patches were investigated using excised rat skins. The concentrations of both BZ and the enhancers were fixed to 5%. Table 3 shows the skin permeation rates of BZ from the DIA patches containing the enhancers. The skin permeation rates of BZ from the DIA patches containing Myvacet, IPM and their mixtures were almost the same. They did not show any significant increase in the permeation rate of BZ through the skin compared with the DIA patch without the enhancer (Table 2). Therefore, no enhancer was added to the DIA patch containing BZ.

Table 3
Skin permeation rates of BZ through excised rat skins from the patches containing 5% BZ and 5% vehicles (mixture of Myvacet and IPM at different ratios) in DT-2525

Myvacet: IPM	J_s[a] (μg/cm²/h)
10:0	15.25 ± 1.31[b]
8:2	14.19 ± 1.87
5:5	14.29 ± 1.57
2:8	15.47 ± 0.71
0:10	14.53 ± 1.85

[a] Skin permeation rate.
[b] Mean ± S.D. (n = 6).

3.4. Effect of loading amount of BZ on skin permeation of BZ

In order to evaluate the effect of the loading amount of the drug in the patch on the skin permeation of BZ, DIA patches containing different amount of BZ were prepared with DT-2525 and the skin permeation rates of BZ from these patches were determined using excised rat skins. The amount of BZ in the patch was varied as 1, 2.5, 5, 10 and 20%. Fig. 1 shows the skin permeation rates of BZ from the patches as a function of the loading amount of BZ. The skin permeation rate of BZ increased linearly with increasing the amount of BZ in the DIA patch. According to Fick's law, skin permeation of a drug is usually proportional to the drug concentration in the PSA when the drug concentration is below saturation. There was good linearity between the skin permeation rate of BZ and the loading amount of BZ in the DIA patches (r = 0.9981). The linearity indicates that the skin permeation of BZ was essentially a passive diffusion process.

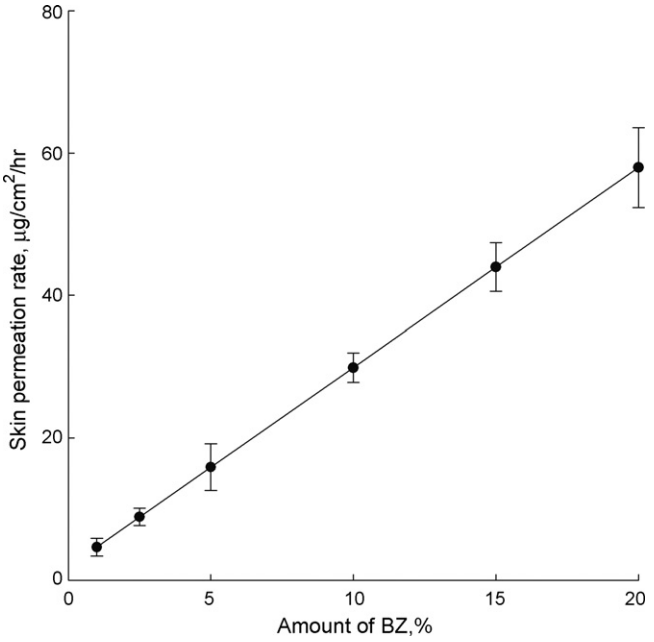

Fig. 1. Effect of the amount of BZ in the DIA patches made with DT-2525 on the skin permeation rate of the drug. Mean ± S.D. ($n = 6$).

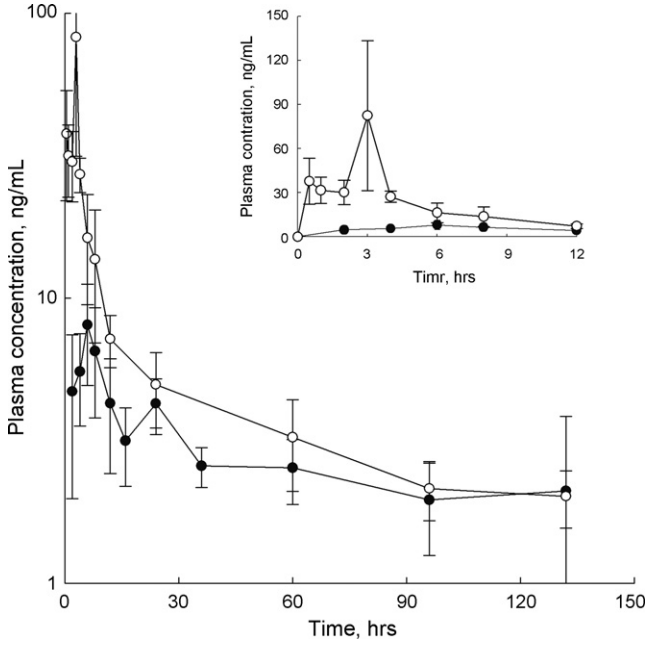

Fig. 2. Plasma concentration–time profiles of BZ following the transdermal application of the DIA patch containing BZ (●) and the oral administration of a BZ mesylate solution (◯) to rabbits at a dose of 4 mg. Mean ± S.D. ($n = 5$).

3.5. Evaluation of physical properties of DIA patches

The peel adhesion, tack and shear strength, which are the most important physical properties of a patch for the application, wearing and removal, were measured and the results are presented in Table 4. While the peel adhesion increased, the tack and shear strength decreased as the loading amount of BZ in the patch was increased. Except shear strength, the change of peel adhesion force and the tackiness was pronounced at 15% BZ in the patch. The DIA patches had a tendency to be soft at this amount of BZ. Therefore, 10% BZ was selected as the amount of BZ in the patch for further study.

3.6. Biopharmaceutical evaluation of DIA patch containing BZ

The pharmacokinetic properties of BZ after the transdermal application of the optimized DIA patch were evaluated using rabbits. The patch containing 10% BZ was made with DT-2525. Fig. 2 shows the plasma profiles of BZ after the transdermal application of the patch and the oral administration of the BZ mesylate solution. Table 5 summarized the pharmacokinetic parameters calculated from these profiles.

Table 4
Physical properties of the DIA patches containing different amounts of BZ in DT-2525

BZ (%)	Peel adhesion (g/12.5 mm)	Tack (g)	Shear strength (min)
5	980 ± 36[a]	1358 ± 35[a]	14.1 ± 1.0[a]
10	1214 ± 79	1310 ± 29	12.5 ± 1.7
15	1809 ± 63	1140 ± 48	11.1 ± 0.9

[a] Mean ± S.D. ($n = 5$).

Table 5
Pharmacokinetic parameters of BZ after the transdermal application of the BZ patch and the oral administration of BZ mesylate to rabbits at a BZ dose of 4 mg

Pharmacokinetic parameters	Administration route	
	Transdermal	Oral
C_{max} (ng/ml)	8.62 ± 2.51[a,*]	89.47 ± 42.84[a]
T_{max} (h)	7.2 ± 2.68[*]	2.5 ± 1.12
AUC (ng × h/ml)	365.95 ± 77.47[*]	677.43 ± 136.94
Relative bioavailability (%)	54.02	–

[a] Mean ± S.D. ($n = 5$).
[*] Significantly different from the oral ($p < 0.05$).

The peak plasma level of BZ after the transdermal application of the patch was 8.62 ng/ml after 7.2 h while it was 10 times higher after the oral administration of BZ mesylate. The plasma levels were maintained relatively constant (3–8 ng/ml) during the wearing of the patches (up to 24 h) after the transdermal application of the patch. After the patch was removed, the plasma level of BZ decreased slowly as a result of the long elimination half-life of BZ, 35 h (He, 1994). The calculated relative bioavailability of BZ after the transdermal application of the patch compared to the oral administration of BZ mesylate was approximately 54%.

4. Conclusions

BZ was formulated into a DIA patch in an attempt to solve the problems associated with its oral administration. The optimized patch was made from DT-2525 and contained 10% BZ at a thickness of 100 μm. The pharmacokinetic studies of the optimized DIA patch using rabbits showed that the relative bioavailability of the BZ patch was 54% compared to the oral administration

of BZ mesylate. This suggests that the transdermal application of BZ in a DIA patch can be used to treat Parkinson disease.

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