Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 10, 2014

Original Article

INFLUENCE OF LOCALLY APPLIED HEAT ON THE PERFORMANCE OF TRANSDERMAL DICLOFENAC SODIUM PLASTERS

ICHIE SUZUKI[1], YASUNORI MIYAZAKI[*1,2], TOMONOBU UCHINO[1,2], YOSHIYUKI KAGAWA[1,2]

[1]Department of Clinical Pharmaceutics, School of Pharmaceutical Sciences, University of Shizuoka, 52-1Yada, Suruga-ku, Shizuoka 4228526, Japan, [2]Department of Clinical Laboratory, Shizuoka General Hospital, 4-27-1 Kita-andou, Aoi-ku, Shizuoka 4308527, Japan. Email: miyaza@u-shizuoka-ken.ac.jp

Received: 19 Aug 2014 Revised and Accepted: 20 Sep 2014

ABSTRACT

Objective: Applied heat to dermatologic preparations influences the medicine's performance, such as drug release rate and drug absorption. However, there is little information concerning the performance of non-steroid anti-inflammatory drug plasters at high temperature. Therefore, this study aimed to evaluate the effect of heat on drug dissolution and skin permeation from two kinds of Diclofenac sodium (DF) plasters *In vitro*, as well as transdermal absorption in healthy adult volunteers.

Methods: DF dissolution tests were performed using the paddle-over-disk method with 500 mL of phosphate-buffered saline at 32 and 41°C. DF permeation was studied at 32 and 41°C using a Franz-type cell with Yucatan micropig skin (YMP). Moreover, eight healthy volunteers were tested two times for each preparation while receiving a piece of DF plaster, and then the same plaster with a heat-generating pad over 4 hours maintained at 40-41°C; then, the residual amount of DF in the plasters was evaluated.

Results: Significant differences in the cumulative amount released from the preparations were seen between 32 and 41°C. The cumulative amount that permeated across YMP skin from all preparations at 32°Cwas also significantly higher than that obtained at 41°C. Furthermore, heat application on the plasters resulted in 1.4-fold higher absorption amount than without heat in the clinical study.

Conclusion: This study indicated that locally applied heat caused rapid and substantial drug release, resulting in increased transdermal absorption of DF compared with that upon the use of the plaster without heat.

Keywords: Diclofenac sodium, Plaster, Heated condition, Drug release, Skin permeation.

INTRODUCTION

Over-the-counter (OTC) medicines can be misused by patients as the medicines are increasingly used for self-medication [1]. Pharmacists can play a key role in safeguarding patients from potentially harmful adverse effects of OTC medications [2]. Therefore, it is necessary for pharmacists to understand the influence of the possible misuse of medicines. One concern about dermatologic preparations is the influence of temperature on the drug release rate from formulations. In the case of ethical medicines, the effects of locally applied heat on transdermal delivery systems were reported.

For example, locally applied heat could speed up the onset of steady-state fentanyl concentration in a fentanyl transdermal drug delivery system [3, 4]. Testosterone was also administered transdermally to treat hormone insufficiency, with heat showing a beneficial effect [5]. Nitroglycerin absorption through the skin was also improved significantly if heat was applied [6]. There was also a report about the risk of incidental exposure to external heat [7]. Roth noted that warming blankets should not be placed over areas treated with transdermal medications [8]. However, little is known about the topical use of external formulations.

Non-steroidal anti-inflammatory drug (NSAID) formulations are widely used for the treatment of acute and chronic musculoskeletal conditions [9, 10]. Patients are incidentally exposed to heated conditions, such as under a warming blanket, in a whirlpool, or in a sauna, after applying dermatologic preparations to their skin. The applied heat influences the medicine's performance, such as drug release rate and drug absorption. Besides, skin is damaged by repeated use of the plasters on the same site of the body. This is because the stratum corneum is stripped by the removal of adhesive preparations. Skin damage affects drug permeability to a large extent [11]. Therefore, we focused on NSAID preparations launched as not only ethical medicines but also OTC medicines. In this study, we used two kinds of DF plaster containing 15 mg/70 cm^2as a model NSAID. We aimed to reveal the effects of external heat on *In vitro* drug release and *In vitro* skin permeation from the plasters, and evaluated *In vivo* drug absorption under heated conditions.

MATERIALS AND METHODS

Materials

Voltaren AC tape (VT; DojinIyaku-kako Co., Ltd., Tokyo) and Fatas Z tape (FZ; Hisamitsu Pharmaceutical Co., Ltd., Tokyo) was used as model adhesive plaster preparations containing 1% DF. The excised skin of Yucatan micropigs (YMP; 5-month-old, female) was obtained from Charles River Laboratories (Japan). DF and methanol were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Methanol was of HPLC grade. All other chemicals were of reagent grade.

In vitro release study

In vitro release of DF from plasters was investigated at 32 ± 0.5°C and 41 ± 0.5° Caccording to the paddle-over-disk method (apparatus 5, USP30) [12]. Plaster specimens (5.5 cm^2) were fixed over the disk assemblies with instant glue. The disk assemblies were immersed in 500 mL of 50 mM phosphate buffered saline (pH7.4, PBS).

The paddle speed was set at 50 rpm. At predetermined times (0.5, 1, 2, 4, 6, 8, 12, and 24 h), sample (5 mL) was withdrawn and replaced with fresh medium. The concentration of DF was determined using HPLC as described below.

Extraction procedure of DF

After the release test was finished, each plaster was cut and placed into a 50-mL polypropylene centrifuge tube and 50 mL of methanol was added. The tube was shaken for 30 min and sonicated for 30 min, after which 10 µL of the solution was injected onto the column.

Determination of DF

The sample solution was filtered through a membrane filter (0.45 µmφ, Minisart RC15, Sartorius, USA) and injected into HPLC. The HPLC consisted of a solvent delivery pump (LC-10AS, Shimadzu Co., Kyoto, Japan), a column (TSKgel ODS-100V, 5 µm, 4.6φ×150 mm, Tosoh Co., Tokyo), a UV detector (SPD-10A, Shimadzu Co., Kyoto, Japan), and a column oven (CTO-10A, Shimadzu Co., Kyoto, Japan). The column temperature was maintained at 40°C. The mobile phase was made of methanol and a pH 2.8 phosphate buffer (50 mM) at a volume ratio of 13:3, and flowed at a rate of 1.0 mL/min [13]. UV absorbance was measured at 276 nm.

Calculation of release parameters

The cumulative amount of drug released per unit area is proportional to the square root of time [14], written as equation (1):

$$\frac{M_t}{M_\infty} = K_H \times \sqrt{t} \qquad \text{Eq. (1)}$$

Where Mt is the cumulative amount of drug at time t and M_∞ is the cumulative amount of drug released at infinite time, which should be equal to the initial loading amount. K_H represents the Higuchi constant, concerning the drug release rate.

***In vitro* skin permeation study**

In vitro experiments were performed according to the method given in a previous report [15]. Briefly, a Franz-type diffusion cell with an effective diffusional area of 0.385 cm² and downstream volume of 5 mL was used. The YMP skin was laid on the cell (the dermis side of the skin contacting PBS) that was filled with 5 mL of PBS maintained at 32 ± 0.5°C or 41± 0.5°C. The donor compartment of the cell was mounted with tape preparation and uncapped. Two hundred micro-liters of the sample was withdrawn periodically from the receiver compartment for 24 h and replaced with an equal volume of fresh PBS maintained at 32 ± 0.5°C or 41± 0.5°C. The concentration of DF was analyzed using HPLC as mentioned above.

Calculation of permeation parameters

The steady-state flux, J_{ss} (µg/cm²/h), permeability coefficient of skin, K_p(cm/h), partition coefficient from preparation onto stratum corneum, P, apparent diffusivity through skin, D_{ss}(cm/h), and lag time, t_{lag}(h), are defined by equations (2) and (3) in the polymer matrix diffusion-controlled system [16]:

$$J_{ss} = K_p \times C_d = \frac{P \times D_{ss} \times C_d}{L} \qquad \text{Eq. (2)}$$

$$t_{lag} = \frac{L^2}{6D_{ss}} \qquad \text{Eq. (3)}$$

Where L(cm)is the skin thickness and C_d(µg/cm³)is the concentration in the donor phase. In determining the above parameters, L was set at 20 µm, a value presumably representative of the thickness of YMC skin. $C_d$is practically equal to the drug concentration in the receptor compartment because the dissolved drug can be released from the matrix. Therefore, C_0, meaning the initial C_d, was 10 mg/cm³. Six experiments per group were performed. All data are expressed as the mean ± S. D.

***In vivo* absorption study**

Written informed consent was obtained from each volunteer before the study. The research on human subjects followed the guidelines as set out in the Declaration of Helsinki (1964) and associated amendments. The study protocol was approved by the Ethical Standards Committee of Shizuoka General Hospital.

Eight volunteers (four males, four females) between the ages of 22 and 49 (mean 29 years) were enrolled in the drug absorption studies. All formulations were tested on the volar aspect of a forearm of each subject. One 3×3 cm² square application site were demarcated using a skin marker pen on the forearms of the subjects. Plaster was cut into a 3 × 3 cm² square (1.93 mg of DF) and applied on the marked area. In the case of heat treatment, a heat-generating pad (Kubi-Hotton, Kobayashi Seiyaku Co., Tokyo) was put on the applied plaster. The temperature was maintained between 40 and 41° Cduring the absorption test for 4 h. After the absorption test, the plaster was analyzed for the residual amount of DF in it. DF was extracted from the plaster using methanol and detected by HPLC as mentioned above.

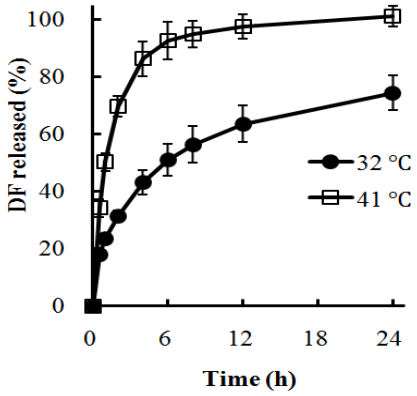
Statistical analysis

Statistical significance in the differences of the means was determined by Student's t test. A P-value of less than 0.05 was considered to indicate a statistically significant difference.

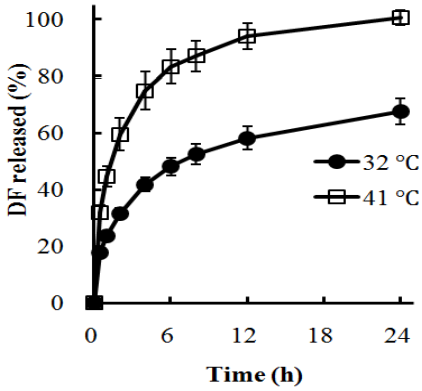
RESULTS AND DISCUSSION

***In vitro* study**

Initially, we examined the *In vitro* release of DF from the plasters using PBS as release medium. The release profiles from the two kinds of preparations are shown in Figure 1.



(A)



(B)

Fig. 1: Effect of temperature on DF release from the plasters, VT (A) and FZ(B)

The temperature of release medium greatly affected the DF release profiles, showing rapid and substantial release at 41°C. In both preparations, 100% of the DF loaded in the preparation was released at 24 h. Otto et al. reported that heat increased the diffusivity of drug molecules, resulting in faster release from gels containing DF [17]. Thus, heat enhanced DF release in this study.

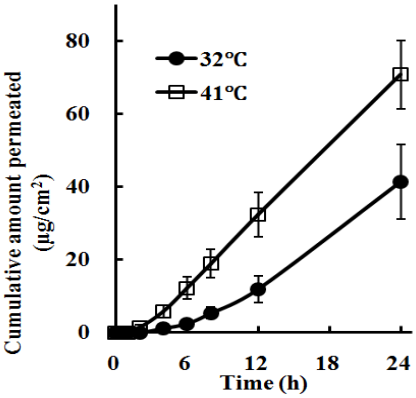
To investigate the difference in detail, we conducted kinetic analysis via the Higuchi equation using the release data below 60% release. The Higuchi constant is listed in Table 1.

Table 1: Higuchi constant ($h^{-1/2}$) of various DF preparations

Temperature (°C)	VT	FZ
32	0.20±0.02	0.18±0.01
41	0.50±0.03	0.42±0.04

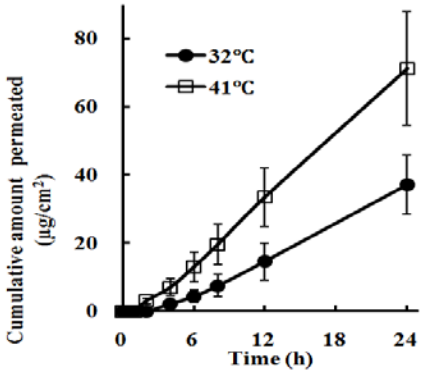
In both preparations, Higuchi constant increased significantly at high temperature($p< 0.05$). This was mainly because drug solubility and diffusion would be improved by high temperature. However, the extent of change differed significantly between the preparations($p< 0.05$). There are many potential factors that can explain these differences between the preparations. In many cases, the release of a drug can greatly depend on the solvent and structure of polymer matrix used in formulations. In this case, these preparations consisted of the same components, that is, ester gum HG, styrene-isoprene-styrene block copolymer, polyisobutylene, dibutyl hydroxy toluene,N-methyl-2-pyrrolidone (NMP),L-menthol, and four others [18, 19]. Therefore, the release of solvent, such as NMP and L-menthol, seemed to affect drug release.

Skin permeation studies were performed using YMP skin, which has a structure similar to that of human skin [20]. *In vitro* DF permeation through YMC skin was examined for 24 h because the plasters are ordinarily used once a day. The permeation profiles from the plasters are shown in Figure 2.



(A)

In vitro skin permeation was increased at high temperature in all formulations compared with that at normal temperature. The overall amounts of DF permeated in 24 hat 41°C were approximately 2-fold larger than those at 32°C. The permeation rate at 41°C also increased compared with that at 32°C. In addition, DF permeation through the receiver cell was first observed at about 4 h from the test started at 32°C, while DF was detected in the receiver cell as early as about 2 h at 41°C. Obata et al. Reported that heat application caused disorder of the intracellular lipid lattices in stratum corneum, influencing drug permeability [21]. Therefore, this was due to not only improved release but also change of diffusivity in the skin structure. However, no significant difference between the preparations was observed.



(B)

Fig. 2: Permeation profiles of DF through excised YMP skin from the plasters, VT(A) and FZ(B)

For each diffusion cell, the cumulative amount of DF permeated per unit area was plotted against time, and from the slope of the linear portion of the plots (4-24 h), DF steady-state flux was obtained. Thereafter, penetration parameters were calculated from the penetration data according to Eq. (2) and (3), and are presented in Table 2.

Although both preparations showed similar values of *Jss*, the *Ds* and *P* values differed between the preparations. The diffusivity and solubility are important factors for determining permeability. In both cases, the diffusivity in the skin was suggested to bea major factor enhancing DF permeability (Table 2). As a result, the skin permeation was enhanced by heat in both preparations.

Clinical study

Determination of residual drug in applied transdermal patches is useful for evaluating its transdermal absorption rate in individuals when the drug concentration in muscle cannot be detected directly [22]. In the present study, the effects of heat treatment on the transdermal absorptivity of DF in plasters for 4 h were examined. The percentage of residual DF in the applied plasters was calculated using 100% as the residual DF content extracted from each plaster that was not applied. The effect of heat treatment on the transdermal absorption rate of DF in each plaster is shown in Figure 3.

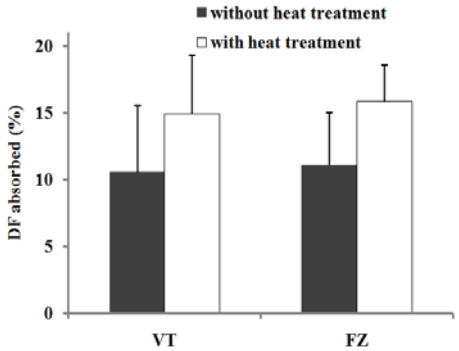


Fig. 3: Absorbed amount of DF from various plasters, VT and FZ, after 4 h of application to human

The transdermal absorption amounts of DF from both preparations with the heat treatment were significantly increased compared with those without the heat treatment. It is worth mentioning that the plasters were applied for only 4 hours to safeguard the volunteers.

If patients apply a plaster to damaged skin caused by the repeated application of plasters, drug absorption could increase markedly under heated conditions. This fear was reported in the case of tulobuterol patch [23].

Table 2: Effect of temperature on the permeation parameters of DF from theplasters through YMP skin

Preparation	Temperature (°C)	J_{ss} (μg/cm²/h)	D_S (× 10^{-7}, cm²/h)	P (—)
VT	32	2.20 ± 0.57	1.21 ± 0.12	3.70 ± 1.2
VT	41	3.25 ± 0.43**	4.07 ± 2.6*	2.12 ± 1.1
FZ	32	1.83 ± 0.38	1.83 ± 0.56	2.09 ± 0.48
FZ	41	3.22 ± 0.74**	10.4 ± 15	1.79 ± 1.2

* $p< 0.05$ and ** $p< 0.01$

CONCLUSION

In this study, we demonstrated that DF release from OTC plasters and DF permeation across YMP skin were enhanced at high temperature. In addition, DF absorption from the plasters was suggested to be increasedby locally applied heat in clinical study. Although the plasters were applied on normal skin of healthy volunteers, not but on damaged skin, the absorption amount increased significantly after only 4-hours application.

One major concern associated with misuse/abuse of OTC medicines is the potential for an overdose. The package insert indicates that patients are limited to use two pieces of the plaster a day. However, excess absorption caused by heat could lead to unexpected side effects. Prevention of misuse and understanding the extent of the influence of heat would benefit patient safety. Therefore, the information from this study should be valuable for pharmacists to understand the risk of applied heat and draw patients' attention to this in advance.

CONFLICT OF INTERESTS

This research has no conflict of interest.

REFERENCES

1. Wazaify M, Shields E, Hughes CM, McElnay JC. Societal perspectives on over-the-counter (OTC) medicines. BMC Fam Pract 2005;22:170-6.
2. Chui MA, Stone JA, Martin BA, Croes KD, Thorpe JM. Safeguarding older adults from inappropriate over-the-counter medications: the role of community pharmacists. Gerontologist 2013;doi: 10.1093/geront/gnt130.
3. Shomaker TS, Zhang J, Ashburn MA. Assessing the impact of heat on the systemic delivery of fentanyl through the transdermal fentanyl delivery system. Pain Med 2000;1:225-30.
4. Ashburn MA, Ogden LL, Zhang J, Love G, Basta SV. The pharmacokinetics of transdermal fentanyl delivered with and without controlled heat. J Pain 2003;4:291-7.
5. Shomaker TS, Zhang J, Ashburn MA. A pilot study assessing the impact of heat on the transdermal delivery of testosterone. J Clin Pharmacol 2001;41:677-82.
6. Klemsdal TO, Gjesdal K, Bredesen JE. Heating and cooling of the nitroglycerin patch application area modify the plasma level of nitroglycerin. Eur J Clin Pharmacol 1992;43:625-8.
7. Frölich MA, Giannotti A, Modell JH. Opioid overdose in a patient using a fentanyl patch during treatment with a warming blanket. Anesth Analg 2001;93(3):647-8.
8. Roth JV. Warming blankets should not be placed over transdermal medications. Anesth Analg 2002;94(4):1043.
9. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain: a meta-analysis. BMC Fam Pract 2004;5:10.
10. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. BMC Musculoskelet Disord 2004;5:28.
11. Awa K, Satoh H, Hori S, Sawada Y. Prediction of systemic exposure of ketoprofen tapes by *In vitro* test and pharmacokinetic model analysis: comparison between brand-name and generic formulations. Yakugaku Zasshi 2012;132(1):135-44.
12. The United States Pharmacopeial Convention. The United States pharmacopeia, 30th ed. Rockville; 2007.
13. Arellano A, Santoyo S, Martín C, Ygartua P. Enhancing effect of terpenes on the *In vitro* percutaneous absorption of diclofenac sodium. Int J Pharm 1996;130:141-5.
14. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci 1961;50:874-5.
15. Caon T, Costa AC, de Oliveira MA, Micke GA, Simões CM. Evaluation of the transdermal permeation of different paraben combinations through a pig ear skin model. Int J Pharm 2010;391(1-2):1-6.
16. Melero A, Garrigues TM, Almudever P, Villodre AM, Lehr CM, Schäfer U. Nortriptyline hydrochloride skin absorption: development of a transdermal patch. Eur J Pharm Biopharm 2008;69(2):588-96.
17. Otto DP, de Villiers MM. The experimental evaluation and molecular dynamics simulation of a heat-enhanced transdermal delivery system. AAPS Pharm Sci Tech 2013;14(1):111-20.
18. Package insert of Voltalen AC tape. Novartis Pharm Co; 2013.
19. Package insert of Fatas Z tape. Hisamitsu Pharm Co; 2013.
20. Fujii M, Yamanouchi S, Hori N, Iwanaga N, Kawaguchi N, Matsumoto M. Evaluation of Yucatan micropig skin for use as an *In vitro* model for skin permeation study. Biol Pharm Bull 1997;20(3):249-54.
21. Obata Y, Utsumi S, Watanabe H, Suda M, Tokudome Y, Otsuka M, *et al*. Infrared spectroscopic study of lipid interaction in stratum corneum treated with transdermal absorption enhancers. Int J Pharm 2010;389(1-2):18-23.
22. Ohtani M, Matsumoto M, Namiki M, Yamanura Y, Sugiura M, Uchino K. Evaluation of pharmaceutical equivalency between genuine and generic ketoprofen tape. J Pharm Sci Tech Jpn 2011;71(2):120-5.
23. Watanabe T, Satoh H, Hori S, Miki A, Ohtani H, Sawada Y. Model analysis of tulobuterol patch formulations to explain the influence of drug release rate and transdermal transfer rate on the plasma concentration profile. Yakugaku Zasshi 2011;131(10):1483-92.