약제학회지(2010), 제 40 권 제 1 호
J. Kor. Pharm. Sci., Vol. 40, No. 1, 33-38 (2010)

Formulation and Evaluation of Transdermal Patch Containing Sibutramine

Robhash Kusam Subedi[1,*], Jun-Ho Jang[1,*], Jae-Il Kim[1], Young-Joon Park[2] and Hoo-Kyun Choi[1†]

[1]BK21 Project Team, College of Pharmacy, Chosun University, Gwangju, Korea 501-759
[2]Research center, Samil Pharm. Co. LTD., Anyang-Si, Gyeonggi-do, 431-060

(Received December 21, 2009 · Revised January 11, 2010 · Accepted January 14, 2010)

ABSTRACT – Sibutramine is a serotonin-norepinephrine reuptake inhibitor indicated for the management of obesity in conjunction with a reduced calorie diet. The oral administration of sibutramine is followed by its dose-related side effects. In this study, sibutramine was formulated into drug in adhesive (DIA) patches in an attempt to overcome these problems. The effects of different formulation variables including pressure-sensitive adhesive (PSA), loading amount of drug, thickness of matrix and enhancer on the skin permeation of the drug were evaluated using excised hairless mouse skin. In the acrylic adhesive with carboxyl functional group, low release of sibutramine was observed due to the strong interaction between carboxyl group of adhesive and amine group of sibutramine. The acrylic adhesive without functional group provided good adhesion force and allowed high drug loading. Changing drug load as well as thickness of the matrix was found to alter permeation rate. Crovol® PK40 and Crovol® A40, were found to be effective enhancers for sibutramine. The optimized patch contained 20% sibutramine, and 5% Crovol® A40 as permeation enhancer, in 80 μm thick Duro-Tak® 87-9301 matrix.

Key words – Sibutramine, transdermal drug delivery, pressure-sensitive adhesive penetration enhancement, antiobesity drug

Obesity is a chronic disease that impairs quality of life and causes premature mortality. It is a risk factor for non-communicable diseases such as non-insulin dependent diabetes, cardiovascular disease, various types of cancer, gallstones and certain respiratory disorders. Studies have demonstrated that modest weight loss (5-10%) is clinically beneficial in reducing post-prandial blood glucose, glycosylated haemoglobin, total plasma cholesterol, low density lipoproteins, triglycerides, uric acid and blood pressure.[1)] Lifestyle strategies like diet and exercise are often successful in affecting induction of weight loss, but they tend to fail in maintaining long-term weight loss. Prescribed and self-initiated diets, behavioral modification and exercise do not seem sufficient to address the obesity pandemic. The enormous problem of obesity requires adjunctive medical intervention.

Antiobesity agents like adrenergics (*e.g.*, phentermine, benzphetamine, phendimetrazine, diethylpropion, mazindol, and phenylpropanolamine) and the serotonergic agents (e.g., fenfluramine, dexfenfluramine) are known to have adverse effects like increased risks of cerebral vascular events, cardiac valve changes and pulmonary hypertension.[2,3)] Therefore, most of them are already withdrawn from the market while others have questionable efficacy/safety ratio. Newer drugs are being introduced among which rimonabant seems most prominent.[4)] It has been developed to treat obesity, a major risk factor for cardiovascular problems, and aid smoking cessation. Even though it is approved for sale in Europe, many concerns about reports of anxiety and depression in rimonabant users have kept the drug off the market in the United States. Every drug has to undergo post marketing survelliance before it can firmly be established in the market. Currently, sibutramine and orlistant are the most common antiobesity drugs. Sibutramine is a centrally acting serotonin-norepinephrine reuptake inhibitor structurally related to amphetamines. Clinical data have demonstrated that sibutramine, in conjunction with a low calorie diet, produces an initial and sustained weight-loss effect.[5)] Numerous studies on the mechanism suggest that sibutramine has two means of inducing weight loss, satiety and thermogenesis. In a clinical study, sibutramine was 1.5 times more effective than orlistant in decreasing body weight.[6)] However, sibutramine could slightly increase heart rate and blood pressure and should be cautiously used in patients with the risk of hypertension.[7)] It is well absorbed from the gastrointestinal tract, but undergoes extensive first-pass metabolism providing active metabolites M1 (mono-desmethylsibutramine) and M2 (di-desmethylsibutramine).[8)] In a clinical study, it was shown that bioavailability of sibutramine and M1 metabolite was increased under fed conditions.[9)] The change in pharmacokinetics could have paramount importance concerning safety of sibutramine.

Especially during long-term use, the potential adverse effects

†본 논문에 관한 문의는 이 저자에게로
*These authors equally contributed to this work
Tel : 062)230-6367, E-mail : hgchoi@chosun.ac.kr
DOI : 10.4333/KPS.2010.40.1.033

like nausea, dry mouth, rhinitis, constipation and possible increases in blood pressure and heart rate justify the need for safer and more effective dosage of sibutramine. Development of a transdermal drug delivery system (TDDS) offers a possible mode to overcome some of the drawbacks of systemic sibutramine oral therapy as: (a) this route improves compliance of the patient, (b) ensures essentially constant drug input, and (c) bypasses the gastrointestinal tract and hence the variation in bioavailability. In our knowledge, no study has so far investigated the percutaneous absorption of the drug. Furthermore, TDDS system allows easy termination of dosing in case of adverse effects, for example, significant rise in blood pressure. Hence, TDDS for sibutramine could present an attractive alternative to the presently available mode of administration.

Skin is an excellent barrier to the ingress of many compounds and poses a major problem for therapeutic TDDS. Various physical (stripping of stratum corneum, iontophoresis, phonophoresis), chemical (lipophilic analogs, permeation enhancer) and biological (prodrugs, skin metabolism inhibitors) approaches could be utilized to overcome the impermeability of skin. Among these techniques, the chemical enhancer approach is most commonly included in the TDDS to facilitate the penetration of the drug administered.[10] It is well known that the enhancing properties of chemical enhancers depend on the physicochemical properties of drugs and the combination with the excipients in the formulations.[11]

The aim of this study was to evaluate DIA type patches containing sibutramine. Different formulation factors like effect of PSA, drug amount, thickness of matrix and enhancer were studied. In vitro diffusion studies were performed across hairless mouse skin to assess the permeation of the drug.

Materials and Methods

Materials

Sibutramine was purchased from Cipla limited (Pune, India). Propylene glycol caprylate/caprate (Labrafac® PG), PEG-8 glyceryl linoleate (Labrafil® 2609), PEG-8 glyceryl caprylate/caprate (Labrasol), Polyglyceryl-3 oleate (Plurol olieque® CC497), Propylene glycol mono laurate (Lauroglycol® FCC), Caprylic/capric triglyceride (Labrafac® CC) and Polyoxy glycerate (Labrafil® 1944) were obtained from Gattefosse (Gennevillers, France). Polyethylene glycol 300 (PEG 300), PEG sorbitan monooleate (Tween 80®) and Sorbitan monooleate (Span 80®), were purchased from Junsei Chemical (Tokyo, Japan). Super refined oleyl alcohol (Novol®), Isopropyl myristate (IPM®), Isopropyl palmitate (IPP®), PEG-12 palm kernel glycerides (Crovol® PK40), PEG-60 almond glyceride (Crovol® A70) and PEG-20 almond glyceride (Crovol® A40) were obtained from Croda (Parsippany, NJ, USA). (R)-(+) Limonene, Cineole, Lauryl alcohol, Brij 52®, Brij 97® and Brij 30® were purchased from Sigma Chemical (St. Louis, MO, USA). Acrylic, poly isobutylene (PIB) and Styrene-butadiene-styrene (SBS) PSA solutions, in organic solvents, were obtained from National Starch and Chemical Company (Bridgewater, NJ, USA). Silicone PSA (BioPSA® 7-4302) was obtained from Dow Corning (Midland, MI, USA). All other chemicals were of reagent grade or above and were used without further purification.

Methods

Preparation of Patch Containing Sibutramine

Drug solution was prepared by dissolving sibutramine in ethyl acetate. After adding enhancer and PSA to the drug solution, the mixture was stirred using a teflon-coated magnetic bar. The resulting drug-PSA solution was coated onto the release liner. After the solvent had been removed, it was laminated with a polyester backing film (ScotchPak® 9732, 3M, USA).

Diffusion Procedure

A flow-through diffusion cell system was used, comprising of a multi channel peristaltic pump (IPC-24, ismatec, Switzerland), a fraction collector (Retriecer IV, ISCO, NE, USA), a circulating water bath (Jeio-Tech, South Korea), and flow-through diffusion cells. Each flow-through cell had two arms, which allowed the receiver cell medium to be pumped to a fraction collector. The diffusion cell temperature was maintained at 37°C by circulating water through the outer part of jacketed receiver cell. The surface area of receiver cell opening was 2 cm^2, and its volume was 5.5 mL. Skin was excised from hairless mice that were sacrificed under anesthetic condition with diethyl ether. Subcutaneous fat was removed with scissors and scalpel. Each of the flow-through diffusion cell components were connected via silicone rubber tubing with an internal diameter of 0.015 inches. The receiver cell was filled with buffer solution (pH 6.0) and the media stirred by teflon-coated magnetic bar. The excised skin was mounted onto each receiver cell. And O-ring and cell top were placed on the top of each skin. These components were then clamped. The samples were collected every 4 hr for 24 hr and assayed by HPLC.

Analytical Method

Sibutramine was analyzed by an HPLC system (Shimadzu Scientific Instruments, MD), consisting of a UV detector

(SPD-10A), C18 column (4.6 × 100 mm, 5 μm, Gemini), a pump (LC-10AD), and an automatic injector (SIL-10A). The method previously described with modification was used.[12] Briefly, the wavelength of the UV detector was 222 nm, the column temperature was maintained at 30°C, the flow rate was 1.2 mL/min and injection volume was 20 μL. The mobile phase was consisted of acetonitrile/50 mM phosphate buffer (40/60%).

Results and Discussion

Effect of Adhesive Matrix

TDDS can be broadly classified into reservoir and matrix type systems. In the former system, maintenance of drug delivery rate is easier through the rate controlling membrane. But any damage in the membrane could result in dose dumping and the high cost of production. Therefore the recent trend is gradually being directed to the matrix system that offers greater versatility and lower manufacturing costs.[13] PSA is one of the important formulation variables in the matrix based TDDS. The effect of PSA matrix on the permeation of sibutramine was investigated using silicone, SBS, PIB and acrylic adhesive matrixes. Initially, patches containing silicone and acrylic adhesives with different functional groups were screened at 5% drug load. The permeation of sibutramine from the matrices showed the rank order of: BioPSA® 7-4302>Duro-Tak® 87-9301> Duro-Tak® 87-2287> Duro-Tak® 87-4098> Duro-Tak® 87-2516> Duro-Tak® 87-2510> Duro-Tak® 87-2074 (Table I). Patches formulated in silicone matrix, which do not contain any functional group, showed the highest flux rate than those in acrylic adhesives with different functional groups. Similar sibutramine flux rate was obtained in Duro-Tak® 87-9301 and Duro-Tak® 87-2287 matrices. However, Duro-Tak® 87-9301 matrix provided higher adhesive force than Duro-Tak® 87-2287. The results clearly indicate that the nature of adhesive and functional group of acrylic adhesive significantly affect the permeability of sibutramine and suggest that the functional group of the adhesive must be considered before the selection of proper adhesive matrix. Various studies have demonstrated that different functional groups in acrylic PSAs impart different physicochemical properties to the matrix that could result in different release rates.[14,15] The initial step for drug permeation through the skin is released from the adhesive matrix, followed by partitioning into the skin and diffusion across the skin. The release of drug from the matrix is dictated by the affinity drug possesses towards the functional group present in the matrix. The permeation rate was the lowest in the adhesive formulation containing carboxyl functional group (Duro-Tak® 87-2074). This is due to the interaction between amine group of sibutramine and carboxyl group of adhesive.[16]

Based on the initial screening at 5% drug load, several adhesives were selected for further testing at 10% drug load. The adhesives included in this testing were silicone, acrylic adhesives without functional groups, PIB, and SBS. The results are shown in Table I. The flux rates obtained with PIB and SBS matrices were quite low, indicating higher solubility of the drug in these matrices. With similarity as the case with 5% drug load, silicone matrix showed the highest flux. Although all the matrixes contained the same drug load, this wide variation in the flux could be due to the different thermodynamic activity of the drug in each matrix. Although sibutramine exhibited the highest thermodynamic activity in silicone matrix, patches containing 10% drug load in silicone matrix had poor adhesion properties and were too soft to be used. Furthermore, silicone matrix could not accommodate drug load higher than 10%. Among the PSAs screened at 10% drug load, Duro-Tak® 87-9301 matrix resulted in better flux than PIB and SBS matrices with high adhesive force. Adhesion of TDDS to the skin is a critical factor directly related to drug delivery and therapeutic effects. Since drug absorption process is determined by partitioning of drug between TDDS and skin, complete skin contact over the entire delivery surface for the labeled application period is essential.[17] If the TDDS lifts or partially detaches, the effective area of TDDS/skin contact, and thus the drug absorption, changes in an unpredictable manner. This could even cause therapeutic failure. Only a constant TDDS/skin contact over the whole application period allows a consistent delivery and absorption of the drug. Hence, poor

Table I–*Effect of pressure sensitive adhesives (PSA) on the permeation rate of sibutramine at 5% and 10% drug loads in 80 μm matrix. Values are expressed as mean ± standard deviation. (n=3)*

PSA Trade name	Functional group	Flux (μg/cm²/h) 5% drug load	Flux (μg/cm²/h) 10% drug load
Duro-Tak® 87-2074	-COOH/-OH	0.21±0.24	
Duro-Tak® 87-2510	-OH	0.59±0.24	
Duro-Tak® 87-2287		0.91±0.02	
Duro-Tak® 87-2516		0.84±0.11	
Duro-Tak® 87-9301	None	0.92±0.11	1.91±0.24
Duro-Tak® 87-4098		0.88±0.06	
BioPSA® 7-4302		1.77±0.21	3.40±0.79
PIB		-	1.07±0.25
SBS		-	1.05±0.21

adhesion results in improper dosing of patients, increases the patient's cost if need to be replaced and also pose a safety issue. Considering both the permeation and adhesive properties, Duro-Tak® 87-9301 matrix was selected for further study.

Effect of Enhancer

To reversibly overcome the barrier properties of stratum corneum, which limits the permeation of drug molecules, penetration enhancers are commonly employed in the transdermal systems.[10] Enhancers can also act as a plasticizer, increasing the mobility of the drug in the matrix. Table II shows the effect of enhancers in Duro-Tak® 87-9301 matrix with 10% drug load. Among the enhancers screened, except Span 80®, IPM® and PEG 300, all others significantly enhanced the flux of sibutramine. All the formulations had good adhesion characteristics and no cold flow could be observed.

In order to get sufficient flux, drug loading was further increased to 20% and various enhancers were studied at the level of 5% and the results are shown in Table III. Crovol® PK40 was found to be the most effective enhancer. Span 80®, Brij 52® and IPM®, among others, could significantly enhance the permeation of sibutramine. Similar results were obtained in previous studies with meloxicam and piroxicam salts with ethanolamine.[18,19] It was reported that non-ionic surfactants with medium HLB value (10) and appropriate alkyl chain (18) and an ethylene oxide chain are capable of effectively modifying the properties of stratum corneum and thus promote the delivery of drug. The close relationship observed between permeation enhancement and lipid bilayer fluidization in several studies suggests that lipid lamellae is the major site of the action of non-ionic surfactants.[20]

Crovol® PK40 is a PEG glyceryl fatty acid ester that consists of a hydrophilic portion (polyethylene oxide chain) and a hydrophobic portion (alkyl chain). Many studies have been conducted to study the effects of the alkyl and polyoxyethylene chain lengths of surfactants on the transdermal absorption.[21] It was interesting to note that, the enhancement ratio brought about by Crovol® A70, which belongs to the same chemical class as Crovol® PK40, was 1.29 as compared to 1.73 for Crovol® PK40 (Table III). The difference between these two enhancers lies in the ethylene oxide chain length. The ethylene oxide chain lengths of Crovol® PK40 and Crovol® A70 are 12 and 60, respectively. To investigate the effect of ethylene oxide

Table II–*Enhancement ratio of sibutramine flux from the patches containing Duro-Tak® 9301 adhesives, at 10% drug load and 5% enhancers in 80 μm matrix. Values are expressed as mean ± standard deviation. (n=3)*

	Enhancement ratio*
Control	1.00 ± 0.00
Labrafac PG®	1.30 ± 0.02
Labrafil 2609®	1.33 ± 0.27
Crovol® A40	1.71 ± 0.12
Labrasol®	1.22 ± 0.55
Plurol oleique®	1.30 ± 0.06
Tween80®	1.34 ± 0.24
Span80®	1.05 ± 0.35
Crovol® A70	1.46 ± 0.26
Novol®	1.37 ± 0.21
IPM®	0.77 ± 0.11
PEG 300	1.23 ± 0.14

*Enhancement ratio = Flux with enhancer/Flux without enhancer

Table III–*Enhancement ratio of sibutramine flux from the patches containing Duro-Tak® 87-9301, at 20% drug load and 5% enhancers in 80 μm matrix. Values are expressed as mean ± standard deviation. (n=3)*

	Enhancement ratio*
Control	1.00 ± 0.00
Labrafac PG®	1.19 ± 0.25
Labrafil 2609®	1.22 ± 0.07
Labrasol®	1.15 ± 0.30
Plurol oleique®	1.24 ± 0.26
Tween80®	1.36 ± 0.30
Span80®	1.30 ± 0.10
Crovol® A70	1.28 ± 0.17
Novol®	1.30 ± 0.26
IPM®	1.19 ± 0.25
PEG 300	1.16 ± 0.05
Brij 30®	1.03 ± 0.12
Limonene	0.88 ± 0.26
Crovol® PK40	1.66 ± 0.18
Brij 52®	1.32 ± 0.11
Brij 97®	0.93 ± 0.31
Cineole	0.89 ± 0.23
Labrafil 1944®	0.99 ± 0.27
IPP®	0.95 ± 0.35
Lauroglycol FCC®	1.02 ± 0.25
Labrafac CC®	0.94 ± 0.03
Lauryl alcohol	1.20 ± 0.53

*Enhancement ratio = Flux with enhancer / Flux without enhancer

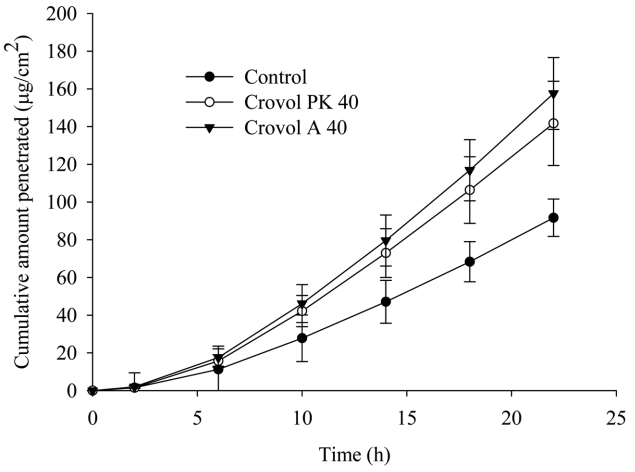

Figure 1–Effect of 5% enhancer on the permeation of sibutramine with 20% drug load in Duro-Tak® 87-9301 matrix. Values are expressed as mean ± standard deviation. (n=3)

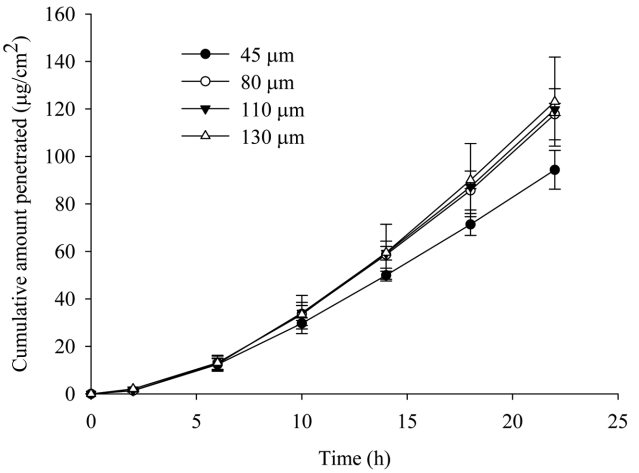

Figure 2–Effect of dried thickness on the permeation of sibutramine with 20% drug load and 5% Crovol® PK40 as enhancer in Duro-Tak® 87-9301 matrix. Values are expressed as mean ± standard deviation. (n=3)

chain length of glyceryl fatty acid ester on the flux of sibutramine, the enhancing effect of a structural analog with medium ethylene oxide chain length, polyoxyethylene (20) oleyl glyceryl ester (Crovol® A40), was also studied. Figure 1 shows a comparison between Crovol® PK40 and (Crovol® A40) in terms of penetration enhancement of sibutramine from the PSA matrix. Better permeation profile was observed with Crovol® A40, and the enhancement effect observed with both the enhancers was significantly higher than that from Crovol® A70. Hence, it can be inferred that, glyceryl fatty acid ester with medium ethylene oxide chain length (20) is most effective in promoting the sibutramine flux from the Duro-Tak® 87-9301 matrix.

Effect of Drug Loading and Thickness

Table IV shows the effect of drug loading in Duro-Tak® 87-9301 matrix. Permeation increased when drug loading increased from 10% to 20%. Beyond 20%, higher drug loading was not found useful. Furthermore, the effect of thickness at 20% drug loading in Duro-Tak® 87-9301 matrix, with 5% Crovol® PK40 as enhancer, was investigated. Figure 2 shows that the penetration rate of sibutramine increased when matrix thickness increased up to 80 μm. Further increase in the thickness could not significantly enhance the permeation. Moreover, at higher thickness patches were soft and exhibited cold flow. Therefore, matrix thickness of 80 μm was appropriate for the formulation of sibutramine in Duro-Tak® 87-9301 matrix.

Table IV–*Effects of drug load on the flux of sibutramine at 5% enhancer in Duro-Tak® 87-9301 matrix. 15% drug loading with 5% Crovol® PK40 was used as control, and the data is expressed as enhancement ratio with respect to the control. Values are expressed as mean ± standard deviation. (n=3)*

Drug concentration (%)	Flux ratio*
10.0	0.52 ± 0.03
12.5	0.67 ± 0.09
15.0	1.00 ± 0.00
17.5	1.03 ± 0.05
20.0	1.21 ± 0.08

*Flux ratio = Flux at different drug concentration / Flux at 15% drug concentration

Conclusions

Sibutramine was formulated into a transdermal patch to solve the problems associated with oral administration. The release of sibutramine from matrix was influenced by the nature and type of adhesive. In acrylic adhesive without functional group, high drug loading and high flux could be achieved using Crovol® A40 as an enhancer. Based on daily dose of 10 mg, bioavailability of 77%,[22] and the average flux of 5.87 μg/cm^2/hr, less than 55 cm^2 active patch area is required to deliver therapeutic amount of sibutramine daily. Although permeation rate of sibutramine has not been compared between hairless mouse skin and human skin, this study results showed that it may be feasible to develop transdermal drug delivery system for sibutramine.

References

1) D.J. Goldsetin, Beneficial health effects of modest weight loss.

Int. J. Obesity., **16**, 397-415 (1992).
2) L.B. Cannistra, S.M. Davis and A.G. Bauman, Valvular heart disease associated with desfenfluramine, *(letter). N. Engl. J. Med.,* **337**, 636 (1997).
3) W.N. Kernan, C.M. Viscoli, L.M. Brass, J.P. Broderick, T. Brott, E. Feldmann, L.B. Morgenstern, J.L. Wilterdink and R.I. Horwitz, Phenylpropanolamine and the risk of hemorrhagic stroke. *N. Engl. J. Med.,* **343**, 1826-1832 (2000).
4) L. Sjostrom, J-P. Despres and A. Golay, Weight loss in overweight/obese dyslipidemia subjects treated with rimonbant: the RIO-Lipids trial. *Int. J. Obesity.*, **28**(s28) (2004).
5) C.A. Luque and J.A. Rey, The discovery status of sibutramine as an antiobesity drug. *Eur. J. of Pharmacol.*, **440**, 119-128 (2002).
6) R. Padwal, S.K. Li and D.C.W. Lau, Long term pharmacotherapy for overweight and obesity: A systemic review and meta analysis of randomized control trials. *Int. J. Obesity.*, **27**, 1437-1446 (2003).
7) S.H. Kim, Y.M. Lee, H.J. Jee and C.M. Nam, Effect of sibutramine on weight loss and blood pressure: A meta analysis of controlled trials. *Obesity Res.*, **9**, 599-603 (2003).
8) N. Finer, Pharmacotherapy of obesity. *Best. Pract. Res. Clin. Endocrinol. Metab.*, **16**, 717-742 (2002).
9) Z. Abolfathi, J. Couture, F. Vallee, M. Lebel, M. Tanguay and E. Masson, A pilot study toevaluate the pharmacokinetics of sibutramine in healthy subjects under fasting and fed conditions. *J. Pharm. Pharmaceut. Sci.*, **7**, 345-349 (2004).
10) A.C. Williams and B.W. Barry, Penetration enhancers. *Adv. Drug Deliver. Rev.*, **56**, 603-618 (2004).
11) Y.-J. Cho and H.-K. Choi, Enhancement of percutaneous absorption of ketoprofen: Effect of vehicles and adhesive matrix. *Int. J. Pharm.*, **169**, 95-104 (1998).
12) I.D. Hind, J.E. Mangham, S.P. Ghani, R.E. Haddock, C.J. Garratt and R.W. Jones, Sibutramine Pharmacokinetics in young and elderly healthy subjects. *Eur. J. Clin. Pharmacol.*, **54**, 847-849 (1999).
13) R. Freynhfen, P. Busche, R. Savatowski, C. Konrad and S. Grond, Switching from reservoir to matrix systems for the transdermal delivery of fentanyl: A prospective, multicenter pilot study in outpatients with chronic pain. *J. Pain Symptom Mgmt.*, **30**, 289-297 (2005).
14) N.T. Hai, J. Kim, E-S. Park and S-C. Chi, Formulation and biopharmaceutical evaluation of transdermal patch containing benztropine. *Int. J. Pharm.*, **357**, 55-60 (2008).
15) S. Venkatraman and R. Gale, Skin adhesives and skin adhesion: 1. Transdermal drug delivery systems. *Biomaterials*, **19**, 1119-1136 (1998).
16) J.H. Kim, Y.J. Cho and H.K. Choi, Effect of vehicles and pressure sensitive adhesives on the permeation of tacrine across hairless mouse skin. *Int. J. Pharm.*, **196**, 105-113 (2000).
17) A.M. Wokovich, S. Prodduturi, W.H. Doub, A.S. Hussain and L.F. Buhse, Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. *Eur. J. Pharm. Biopharm.*, **64**, 1-8 (2006).
18) H.A. Cheong and H.K. Choi, Enhanced percutaneous absorption of piroxicam via salt formation with ethanolamines. *Pharm. Res.*, **19**, 1375-1380 (2002).
19) H.M. Ki, and H.K. Choi, The effects of meloxicam/ethanolamine salt formation on percutaneous absorption of meloxicam. *Arch. Pharm. Res.*, **30**, 215-221 (2007).
20) K.A. Walters and J. Hadgraft, "Pharmaceutical skin penetration enhancement". *Marcel Dekker, Inc.*: New York, 113-138 (1993).
21) E.S. Park, S.Y. Chang, M.K. Hahn and S.C. Chi, Enhancing effect of polyoxyethylene alkyl ethers on the skin permeation of ibuprofen. *Int. J. Pharm.*, **209**, 109-119 (2000).
22) F. Bucaretchi, E.M.D. Capitani, S.M. Mello, F. Lanaro, R.F. Barros, L.C.R. Fernandes and J.L.D. Costa, Serotonin syndrome following sibutramine poisoning in a child, with sequential quantification of sibutramine and its primary and secondary amine metabolites in plasma. *Clin. Toxicol.*, **47**, 598-601 (2009).