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Formulation, Development and Characterization of Transdermal Patches of Sitagliptin Phosphate

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ABSTRACT

Sitagliptin is a dipeptidyl peptidase 4-(DPP-4) inhibitor with glucose controlling capabilities that was effectively used for treating diabetes in the past. However, the oral administration of this drug caused such severe side effects that it was removed from the market. Transdermal patches are innovative drug delivery systems and can be used for achieving efficient systemic effect by passing hepatic first pass metabolism and increasing the fraction absorbed. Transdermal patches of Sitagliptin phosphate (SIT) were prepared by the solvent casting evaporation technique using ethyl cellulose: HPMC, Eudragit RLPO, propylene glycol and permeation enhancer using different ratios. The physicochemical parameters such as flexibility, thickness, smoothness, weight variation, moisture content, hardness, folding endurance and tensile strength were evaluated for the prepared patches. The formulation exhibited flexibility, uniform thickness and weight, smoothness, good drug content (95.65to 99.45%) and little moisture content. The *in vitro* diffusion studies were carried out using modified Franz diffusion cell using egg membrane as the diffusion membrane and the formulation followed the Higuchi diffusion mechanism. The formulation containing ethyl cellulose: HPMC as polymers showed faster release rate compared to Eudragit: HPMC. The stability studies indicated that all the patches maintained good physicochemical properties and drug content after storing the patches in different storage conditions. Compatibility studies indicated that there was no interaction between the drug and polymers. Hence, the aim of the present study was to prepare the sustained release formulation (Transdermal patches) of the drug using different blend of polymers.

Keywords: Transdermal patches, Sitagliptin phosphate, Physicochemical parameters, *in vivo* study

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INTRODUCTION

According to the Center for Disease Control, diabetes is the seventh leading cause of death in the United States and over 29 million Americans currently have this disease, which translates to about 1 in every 11 people[1]. Two types of diabetes exist, including type 1 and type 2. Type 1 diabetes is usually present at birth and is caused by insulin deficiencies that prevent the pancreas from producing enough insulin. Patients with type 2 diabetes typically contract the disease over time. Type 2 diabetes is caused by insulin resistance and occurs when the pancreas produces insulin, though the body does not appropriately react to the protein[2]. Type 2 diabetes increases one's risk for many other health problems such as heart and blood vessel diseases, kidney damage, vision degeneration, nerve damage, and foot damage (even leading to amputation in some cases)[3]. Patients with type 2 diabetes continuously alternate between a hyperglycaemic and hypoglycemic state, which refers to high blood glucose and low blood glucose levels, respectively[4]. It is imperative for these patients to monitor their blood glucose levels in order to remain in good health. Oral drug delivery and liquid injections are currently the two most common forms of diabetes treatment[5]. However, both methods implicitly present limitations. Patients who take oral anti-diabetic medications typically require high dosages in order for sufficient efficacy due to low bioavailability in drugs of this class. Patients also tend to experience negative side effects, such as vomiting and digestive pain from taking high-dose oral anti-diabetic medications. Patients who take hypodermic insulin injections are required to inject themselves with insulin up to three times a day; this method is very painful and inconvenient for patients who are dependent on this life-saving protein[6]. A feasible treatment option for diabetes lays in transdermal drug delivery approaches. It has been shown that the skin is a barrier that can be exploited for drugs to enter the body, so transdermal patch or cream formulation has potential for development as an alternative to the typical diabetes treatments. Furthermore, the use of transdermal patches can provide

sustained drug release over hours and even days. This novel methodology for diabetes treatment would have the ability to enable patients to lead quality lives without the pain from the numerous hypodermic insulin injections or the negative side effects caused by oral anti-diabetic medications[7]. However, this delivery method possesses limitations of its own, such as the necessity of selecting a drug small enough (with appropriate chemical properties) to facilitate transdermal diffusion[8-11]. SIT is a dipeptidyl peptidase-4 (DPP-4) inhibitor. SIT works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretins GLP-1 and GIP, gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal[12]. The objective of present research was development of matrix type transdermal patches of SIT and to evaluate physicochemical, mechanical properties, *in vitro* drug release, *in vitro* permeation.

MATERIAL AND METHODS

Materials

SIT was received from pharmaceutical company, as a gift sample. Propylene glycol, HPMC, ethyl cellulose and eudragit RLPO purchased from Himedia Laboratory, Mumbai. Methanol, chloroform purchased from CDH chemical Pvt. Ltd. New Delhi. Dialysis membrane of Mol Wt cutoff 1200 was purchased from Himedia Laboratory, Mumbai**.** All other chemicals and reagents used were of analytical reagent grade.

Determination of λ_{max} of SIT

The λ_{max} of SIT was determined by analyzing the drug solution in double beam ultraviolet spectrophotometer (Labindia-3000+). Accurately weighed 10 mg of drug was dissolved in 10 ml of 7.2 pH buffer solution in 10 ml of volumetric flask. The resulted solution was 1000µg/ml of strength and from this solution 1 ml solution was pipette out and transfer into 10 ml capacity of volumetric flask and volume was made upto 10 ml with 7.2 pH buffer solution. This solution was scan at wavelength 400-200 nm on UV spectrophotometer. The higher absorption peak was obtained at 260 nm which was the λmax of drug.

Formulation of transdermal patches

SIT containing transdermal patch was prepared utilizing method given by (Manvi et al., 2003)[13] with slight modification. The casting solution was prepared by dissolving weighed quantities of HPMC (825, 850 and 875mg) and ethyl cellulose, Eudragit RLPO (125, 150 and 175mg) in 10 ml of methanol and chloroform at mixture in ratio 1:1. To the resulting solution, 0.5% w/w of propylene glycol as plastisizer and 10% w/w penetration enhancer was added in this solution. Then drug (300 mg) was added and mixed thoroughly to form a homogeneous mixture. The casting solution was then poured into glass mould/petri dish specially designed to seize the contents. The glass mould containing the casting solution was dried at room temperature for 24 hours in vacuum oven. The patch was removed by peeling and cut into round shape of 2.5 X 2.5cm^2. These patches were kept in desiccators for 2 days for further drying and enclose in aluminum foil and then packed in self-sealing cover [Table 1].

Table 1 Formulation design of sitagliptin phosphate transdermal patches

Formulation Code	Drug (mg)	HPMC (mg)	Ethyl cellulose (mg)	Eudragit RLPO (mg)	Total polymer weight (mg)	PEG 400 % w/w	Chloroform: Methanol (1:1v/v)
F1	300	875	125	-	700	1.0	10
F2	300	850	150	-	700	1.0	10
F3	300	825	175	-	700	1.0	10
F4	300	875	-	125	700	1.0	10
F5	300	850	-	150	700	1.0	10
F6	300	825	-	175	700	1.0	10

Dose calculations

- Width of the plate (mould) = 5 cm
- Length of the plate (mould) = 12 cm
- No. of 2.5 x 2.5 cm patch present whole(mould) = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug? = 25×12 = 300mg
- The amount of drug added in each plate was approximately equal to 300 mg.

Characterization of transdermal patches

The prepared transdermal patches were evaluated for the following parameters:

Physical appearance

All the transdermal patches were visually inspected for color, flexibility, homogeneity and smoothness.

Film thickness

The thickness of the patches was measured at five different places on a single patch of each formulation using a digital micrometer screw gauge and the mean values were calculated[14].

Weight variation

A set of three patches from each batch were weighed on a digital balance and the mean values were calculated. The tests were performed on films which were dried at 60°C for 4 h prior to testing[14, 15].

Drug content uniformity

The patches (2.5*2.5 cm (Equivalent to 6.25 mg of drug) were taken into a three separate 10 ml volumetric flask and dissolved in methanol (10ml) with the help of mechanical shaker. The solution was centrifuged to separate out any particulate matter. 1ml of sample was withdrawn and transferred in volumetric flask (10 ml of capacity). The sample was dilute upto the mark with distilled water and analyzed by UV spectrophotometer at 260.0 nm using the

placebo patch solution as blank and the drug content was calculated[14, 15].

Folding endurance

A strip of 2.5 cm × 2.5 cm was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed and the values were reported[16].

Tensile strength

The tensile strength of the patch was evaluated by using the tensiometer (Erection and instrumentation, Ahmedabad). It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2×2cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

$$Tensile\ Strength\ (s) = \frac{Applied\ force\ (m * g)}{Cross\ sectional\ area(b * t)}$$

Where,

S = tensile stress in 980 dynes/cm^2

m = mass in grams

g = acceleration due to gravity (980 dynes/cm^2)

b = breadth of strip in centimetres

t = thickness of strip in centimetres

Percent moisture content

Weighed individually the films (1cm^2) and kept them in desiccators containing calcium chloride at room temperature for at least 24 hrs. Film was weighed again; the difference in weight (initial and final weight) gives moisture content.

$$\%\ Moisture\ content = \frac{Intial\ weight - final\ weight}{\text{Intial weight}} \times 100$$

Percent moisture uptake

Weighed individually the films and kept them in desiccator containing calcium chloride at room temperature for at least 24 hrs. remove the films from desiccators and exposed to 4% relative humidity (Rh) using saturated solution of potassium chloride in a another desiccator until a constant weight is achieved.

$$\%\ Moisture\ uptake = \frac{final\ weight - Intial\ weight}{\text{final weight}} \times 100$$

Compatibility studies

In the present study, compatibility studies were carried out to assess any incompatibility between the drug and polymers. The IR studies were performed to check the compatibility with excipients. Spectra of the pure drug and the formulated patch were taken individually by the potassium bromide pellet method[17].

Stability studies

The stability studies of the formulated transdermal patches were carried out on prepared films at different temperature and humidity: 25-30°C (60%RH) and 45-50°C (75%RH) over a period of 60 days. The patches were wrapped in aluminum foil and stored in a desiccator for stability study. The patches were characterized for drug content and other parameters at regular intervals (0, 15, 30, 45 and 60 days) [18].

In Vitro skin permeation study

The *in vitro* skin permeation study was carried out by using a Franz diffusion cell (receptor compartment capacity: 80 ml: area: 2.5*2.5 cm (Equivalent to 6.25 mg of drug). The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. The temperature of receptor compartment was maintained at 32±0.5ºC. The samples were withdrawn at different time intervals and analyzed for drug content 250 nm using UV-visible spectrophotometer after suitable dilution with diluents[19]. At the same time receptor phase was replaced with an equal volume of buffer solution at each time interval.

Kinetic study

To know the mechanism of drug release from these formulations, the data were treated according to first order (log percentage of drug to be released vs time), Higuchi's (percentage of drug released vs square root of time), and zero-order (percentage of drug released vs time) Korsmeyer-Peppas model (log percentage of drug to be released vs log time) patterns.

RESULT AND DISCUSSION

The λmax of the drug was found to be 260 nm. The calibration curve of the drug displayed a high linearity with an r^2 value of 0.998 where a linear relationship was observed within the concentration range. All the patches prepared with different polymer concentration were found to be flexible, smooth, opaque, non-sticky and homogeneous in nature [Table 2]. This may be due to the presence of plasticizer. Marginal difference in thickness was observed among each group indicated that more the amount of polymer higher the thickness values [Table 4]. All the six patches have showed good folding endurance, and [Table 2] indicated that the patches have good flexibility. All the formulation show lowest moisture content i.e. less than 4%. Moisture in this value is required to provide strength and flexibility to the patches. In all formulations formulation F3 contain minimum moisture contain 2.5±0.2and moisture uptake was less in F3 as compared to other formulation [Table 3]. The effect of concentration of polymers was observed on the percentage elongation and tensile strength. It was found that as the concentration of polymers increased, the percentage elongation and tensile strength were also increased within the patches. There was no significant difference in the drug content among the patches [Table 4] indicated content uniformity. The maximum drug content was found in formulation F3, 99.45±0.85%.

Table 2 Physicochemical properties of the prepared transdermal patches

F. Code	Flexibility	Smoothness	Transparency	Stickiness
F1	Flexible	Smooth	Opaque	Non-sticky
F2	Flexible	Smooth	Opaque	Non-sticky
F3	Flexible	Smooth	Opaque	Non-sticky
F4	Flexible	Smooth	Opaque	Non-sticky
F5	Flexible	Smooth	Opaque	Non-sticky
F6	Flexible	Smooth	Opaque	Non-sticky

*Average of three determinations

Table 3 % Moisture content and moisture uptake of different formulations

S. No.	F.Code	% Moisture Content	% Moisture Uptake
1.	F1	3.5±0.2	4.8±0.1
2.	F2	3.6±0.1	4.3±0.2
3.	F3	2.5±0.2	2.9±0.3
4.	F4	3.8±0.3	3.9±0.2
5.	F5	3.5±0.1	4.1±0.2
6.	F6	3.4±0.2	4.8±0.1

*(n=3±SD)

Table 4 Thicknesses folding endurance and drug content of different formulations

S. No.	Formulation Code	Thickness (mm)*	Folding Endurance*	% Drug Content
1.	**F1**	145±5	156±5	98.85±0.45
2.	**F2**	148±6	189±6	95.65±0.65
3.	**F3**	150±4	192±4	99.45±0.85
4.	**F4**	154±5	173±5	97.85±0.45
5.	**F5**	152±2	130±2	98.98±0.65
6.	**F6**	154±4	125±3	96.65±0.74

*(n=3±SD)

In vitro drug release study of formulation was showed in [Table 5 and Fig. 1]. The release kinetics of the transdermal patches followed Higuchi diffusion mechanism [Table 6,7 and Fig 2-5]. Stability studies showed that, there is no significant change in physical characteristics and drug content. Based on these results it was concluded that the formulated transdermal patches were found to be physically and chemically stable during the study period (60 days)

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Table 5 *In Vitro* % permeation profile of sitagliptin in formulation F1-F6

Time	% of Drug Release					
(hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0.5	33.25	30.45	28.56	39.98	45.56	49.85
1.0	45.58	40.23	35.65	48.89	52.45	55.65
2.0	66.69	60.32	45.89	69.98	70.23	70.23
4.0	78.89	72.23	55.89	82.23	85.56	89.98
6.0	89.98	85.85	69.98	90.23	93.32	98.89
8.0	98.89	90.45	75.56	99.23	99.45	99.69
10.0	-	98.89	88.98	-	-	-
12.0	-	-	96.65	-	-	-

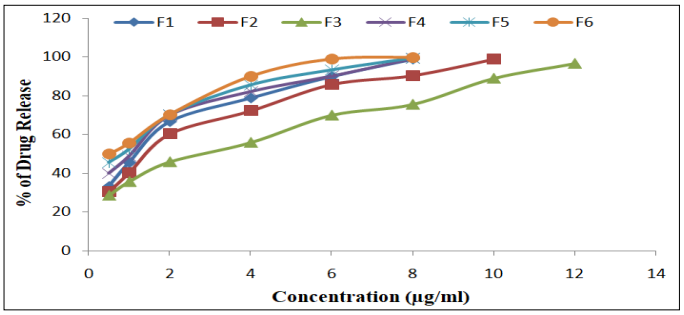

Figure 1 *In Vitro* % permeation profile of sitagliptin in formulation F1-F6

Table 6 *In Vitro* Drug Release Data for optimized formulation F3

Time (min)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
0.5	0.707	-0.151	08.43±0.45	0.926	91.57	1.962
1.0	1.000	0.000	16.53±0.23	1.218	83.47	1.922
2.0	1.414	0.151	28.26±0.45	1.451	71.74	1.856
4.0	1.732	0.239	35.68±0.65	1.552	64.32	1.808
6.0	2.000	0.301	46.35±0.52	1.666	53.65	1.730
8.0	2.236	0.349	54.23±0.47	1.734	45.77	1.661
10.0	2.449	0.389	62.45±0.65	1.796	37.55	1.575
12.0	2.828	0.452	69.38±0.32	1.841	30.62	1.486

* Average of three determinations

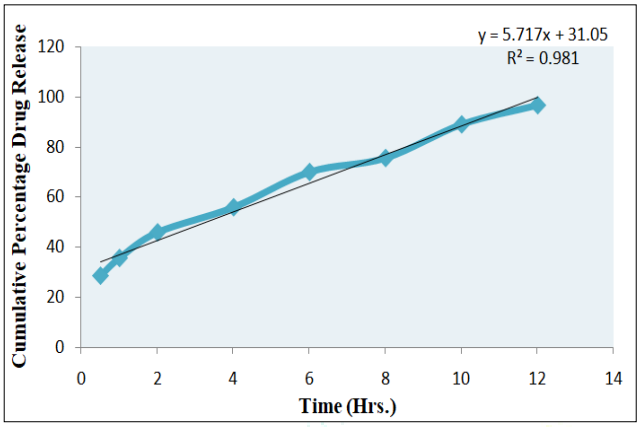

Figure2 Graph of zero order release kinetics

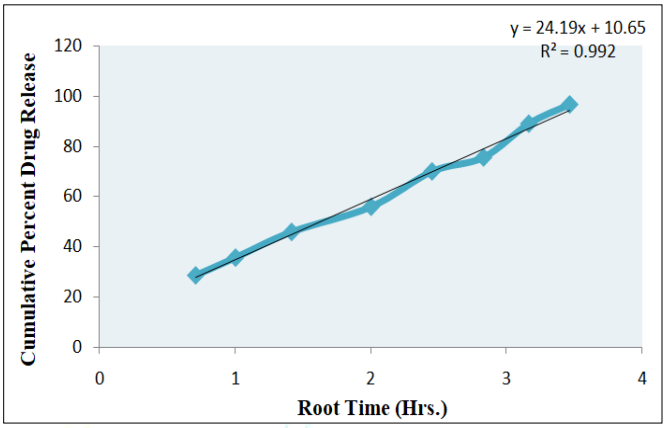

Figure 4 Graph of Higuchi release kinetics

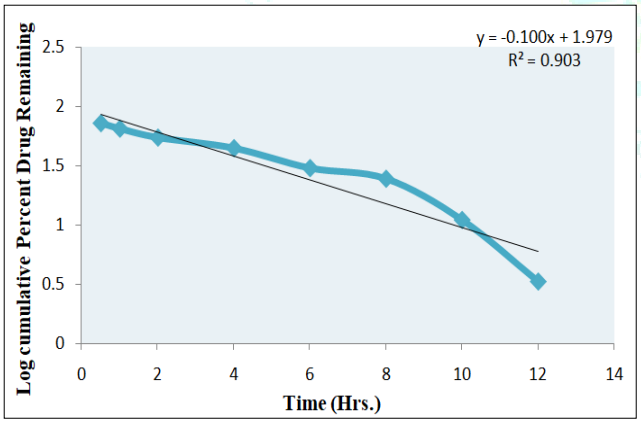

Figure3 Graph of first order release kinetics

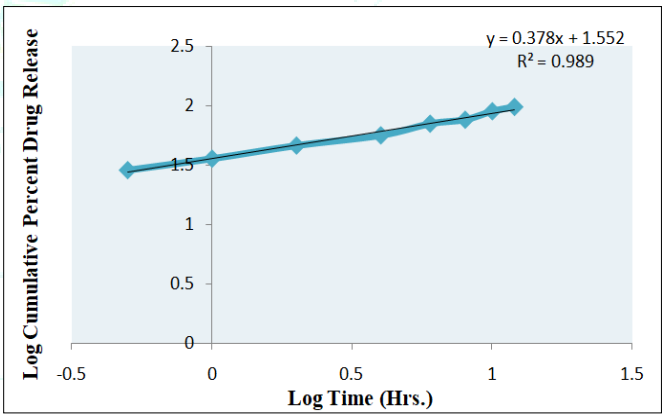

Figure5 Graph of Peppas release kinetics

Table 7 Kinetic data of Sitagliptin transdermal patches

Formulation code	Regression coefficient			
	Zero order	First order	Higuchi	Peppas
F3	0.981	0.903	0.992	0.989

CONCLUSION

The transdermal patches of SIT prepared by solvent casting method using a combination of ethylcellulose, eudragit, in various ratios of plasticizers and permeation enhancers were studied. All the formulations showed good physicochemical properties such as thickness, weight variation, drug content and folding endurance. The in vitro release data showed that drug release from the patch has been affected by the type and concentration of the polymer. From this data, optimized formulations were screened. Formulation F3 were considered as the best formulations. Based on the encouraging results, the SIT transdermal patch can be used as a controlled drug delivery system and frequency of administration can be minimized. Though the efforts were made for the development of SIT transdermal patch, long-term pharmacokinetic and pharmacodynamic studies are needed to undertake the establishment of the usefulness of these patches. Further, these findings may help the industry to scale up for commercial production. Transdermal dosage form of SIT may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.

REFERENCES

1. National Diabetes Statistics Report. Centers for Disease Control and Prevention. 2017.
2. Diabetes: Differences between Type 1 and 2-Topic Overview. WebMD.
3. Preventing and Managing Diabetes Complications. NIH Medline Plus. 2012; 7: 12.
4. Hypoglycemia (Diabetic) & Hyperglycemia. Health Central. 2015.
5. Mitragotri S. Recent development in needle-free drug delivery. Natl Acad Engr 2008; 38.
6. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol 2008; 26: 1261-1268.
7. Peterson Timothy A. Transdermal drug formulation and process development. Formulation, Fill & Finish 2003; 18-21.
8. Guy RH, Hadgraft J. editors. New York: Marcel Dekker. Transdermal Drug Delivery. 2003.
9. Williams A. London: Pharmaceutical Press. Transdermal and Topical Drug Delivery. 2003.
10. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov 2004; 3: 115-124.
11. Bronaugh RL, Maibach HI. Editors Vol Edn 4th New York: Marcel Dekker. Percutaneous Absorption. 2005.
12. http://www.drugbank.ca/drugs/DB01261
13. Manvi FV, Dandagi PM, Gadad AP, Mastiholimath VS, Jagadeesh T. Formulation of a Transdermal drug delivery system of ketotien fumarate. Indian J Pharm Sci 2003; 65 (3):239-243
14. Gattani SG, Gaud RS, Chaturvedi SC. Formulation and evaluation of transdermal films of chlorpheniramine maleate. Indian Drugs 2007; 44:27-33.
15. Rao RP, Divan PV. Influence of casting solvent on permeability of ethyl cellulose free films for transdermal use. East Pharma 1997; 40: 135-7.
16. Kusum DV, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Devel Indust Pharm 2003; 29:495-503.
17. Pandit V, Khanum A, Bhaskaran S, Banu V. Formulation and evaluation of transdermal films for the treatment of overactive bladder. Int J Pharm Tech Res 2009;1:799-804
18. Sankar V, Johnson DB, Sivanad V, Ravichadran V, Raghuram S. Design and evaluation of nifedipine transdermal patches. Indian J Pharm Sci 2003; 65:510-5.
19. Rao RP, Divan PV. Influence of casting solvent on permeability of ethyl cellulose free films for transdermal use. East Pharma 1997; 40: 135-7.