Comparison of enhancement of transdermal permeability of Carvedilol through physical and chemical methods

Sriram Pavani[a,b], Yamsani S. Kumar[b], Yamsani M. Rao[b]

[a]Department of Pharmacy, JNTU, Kukatpally, Hyderabad, Andhra Pradesh, [b]Department of Pharmaceutics, Vaagdevi College of Pharmacy, Hanamkonda, Telangana, India

Correspondence to Yamsani M. Rao, PhD, Department of Pharmaceutics, Vaagdevi College of Pharmacy, Hanamkonda, Warangal, 506001, Telangana, India
Tel: 9849466620;
e-mail: ymrao123@yahoo.com

Received 18 July 2014
Accepted 03 August 2014

Egyptian Pharmaceutical Journal
2015, 14:103–108

Background
The aim of the study was to overcome the difficulties raised in oral therapy; there is a need for the development of new drug delivery system that will improve the therapeutic efficacy. Because of its low dose and extensive hepatic metabolism, Carvedilol is a suitable candidate for transdermal administration.

Objective
The ultimate aim of this study was to administer Carvedilol through a transdermal patch and to evaluate by chemical method and iontophoresis by means of in-vitro drug release and ex-vivo permeation studies.

Materials and methods
The matrix type transdermal patches were prepared by solvent evaporation technique. Various formulations composed of hydroxypropyl methylcellulose (HPMC E15), Eudragit (ERL 100) in different ratios were prepared. All formulations consist of 15% v/w of dibutyl phthalate as plasticizer.

Results and conclusion
The prepared patches were characterized for various physicochemical parameters. The penetration-enhancing mechanism of iontophoresis was found to increase solvent flow through electro-osmosis and pore enlargement in the skin barrier, together with enhancement of electrochemical potential difference across the skin. The effect of chemical enhancer D-limonene and iontophoretic transdermal transport of drug using a current density of 1 mA/cm^2 was investigated. Increasing the applied current density from 0.5 to 1 mA/cm^2 resulted in a 2.2-fold increase in iontophoretic flux. Results demonstrated that iontophoresis exhibited a great ability to enhance the flux of drug in comparison with the chemical method. The optimized formulations F2 and F3 containing 8% D-limonene as chemical enhancer showed maximum skin permeation, 979.45 ± 3.16 and 900.57 ± 2.8 μg/cm^2, respectively, whereas formulations F9 and F10 with iontophoresis showed the skin permeation, 1048.7 ± 3.8 and 1476.7.7 ± 4.8 μg/cm^2, respectively, and obtained flux greater than F2.

Keywords:
Carvedilol, iontophoresis, permeation enhancer, transdermal

Egypt Pharm J 14:103–108
© 2015 Division of Pharmaceutical and Drug Industries Research, National Research Centre
1687-4315

Introduction

There is a need for new drug delivery system that will improve the therapeutic efficacy and safety of drugs more precise (i.e. site specific) thereby reducing both the size and number of doses. Because of its low dose, extensive hepatic metabolism, and lipophilic nature, Carvedilol is a suitable candidate for transdermal administration [1,2].

The drug enters the blood stream directly through the skin; the drug keeps diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood. Iontophoretic drug delivery is now an accepted method of drug therapy, which is gaining wide popularity especially in the area of pain relief, which requires long-term medication as in chronic pain, diabetes, hypertension, rheumatoid arthritis, etc.

Iontophoresis method involves the application of a low-level electric current either directly to the skin or indirectly through the dosage form to enhance permeation of a topically applied therapeutic agent with one or a combination of the following mechanisms [3]: Electrorepulsion (for charged solutes) or electro-osmosis (for uncharged solutes). Iontophoresis uses an electrode of the same polarity as the charge on the drug to drive ionic (charged) drugs into the body. Besides the typical advantages such as transdermal delivery, iontophoresis presents a unique opportunity to provide programmable drug delivery. This is because the drug is delivered in proportion to the current, which can be readily adjusted. Iontophoresis increases the penetration of ionic drugs into surface tissues by repulsion of ions at the active electrode. Negative ions are delivered by cathode and positive ions by anode [4,5].

Materials and methods

Materials

The active pharmaceutical ingredient and other excipients used in this part were obtained from Origin Pharma Company (Hyderabad, India), Himedia Laboratories Pvt. Ltd (Mumbai, India), Finar Chemicals Limited (Ahmedabad, India), S.S Pharma (Hyderabad, India), and Merck Ltd (Mumbai, India). All chemicals used were of analytical grade.

Methods

Drug-excipient compatibility study

The IR spectra were recorded using an IR-spectrophotometer (FT-IR; Bruker, Mumbai, Maharastra, India) using KBr pellet method of pure drug Carvedilol, polymers [hydroxypropyl methylcellulose (HPMC) E15, ERL 100], and their physical mixtures used in formulations to study the possible interaction between drug and polymers.

Construction of standard graph of Carvedilol

The calibration curve is obtained by dissolving 100 mg of Carvedilol in 100 ml of methanol. From this stock solution (1000 μg/ml), further dilutions were made and absorbance was measured using UV-visible spectrophotometer (Shimadzu, Japan) at 241 nm against phosphate buffer pH 7.4 as blank (Fig. 1).

Preparation of Carvedilol transdermal patches

Matrix type transdermal patches containing Carvedilol were prepared by solvent evaporation technique using different ratios of HPMC E15, ERL 100 (Table 1). The polymers were weighed in requisite quantities by keeping the total polymer weight 480 mg and allowed for swelling for about 6 h in solvent mixture (1 : 1dichloromethane, methanol). 15% v/w dibutylpthalate was incorporated as plasticizer. Thereafter, the drug solution was added to the polymeric solution, casted on to Anumbra Petri plate, and allowed for air drying overnight. The entire sheet was cut into small patches with an area of 4.15 cm^2.

Evaluation of Carvedilol transdermal patches [6]

The films prepared by general procedure were evaluated for the following properties.

Thickness

The thickness of the film was measured at 10 different points using screw gauge. For each formulation, three selected films were used and average thickness was recorded.

Weight variation

Six films from each batch of an area of 4.15 cm^2 were weighed individually and the average weight was calculated.

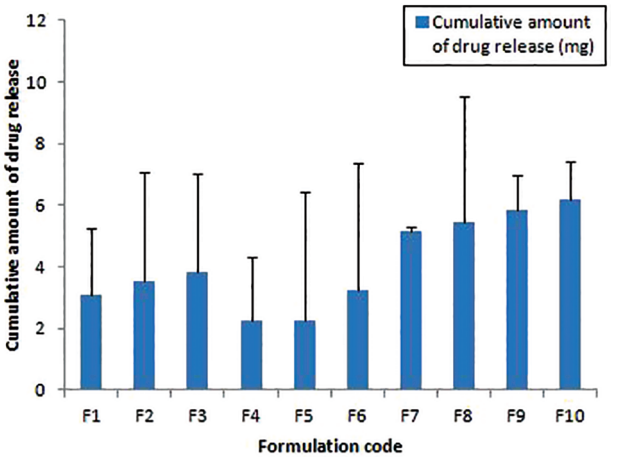
Folding endurance

Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at same place until it breaks. The number of times the strip could be folded at the same place without breaking gave the folding endurance number.

Drug content

Films from each formulation were taken, cut into small pieces, and were allowed to dissolve in a 100 ml solution containing 50 ml of methanol and dichloromethane. The solution was diluted suitably and the absorbance of the solution was measured

Figure 1



Standard graph of Carvedilol.

Table 1 Composition of Carvedilol transdermal patches

Formulation code	Drug (mg)	HPMC E15 (mg)	ERL 100 (mg)	D-limonene (%)	Current (mA/cm^2)
F1	60	480	–	8	–
F2	60	420	60	8	–
F3	60	300	180	8	–
F4	60	240	240	8	–
F5	60	180	300	8	–
F6	60	360	120	8	–
F7	60	420	60	–	0.5
F8	60	300	180	–	0.5
F9	60	420	60	–	1
F10	60	300	180	–	1

Note that 15% v/w DBP was used as plasticizer and 8% v/w of D-limonene as penetration enhancer to the total polymer weight. Each patch (4.15 cm^2) contains 6.2 mg of Carvedilol. DBP, dibutyl phthalate; ERL 100, Eudragit L100; HPMC E15, hydroxypropyl methylcellulose E15.

using UV-visible spectrophotometer at 241 nm against blank.

Moisture absorption studies

The weighed patches were placed in desiccator containing saturated solution of aluminum chloride, which maintains 84% RH. After 3 days, the patches were taken out and weighed. The percentage moisture absorption was calculated.

Moisture content determination

The patches were weighed accurately and placed in a desiccator containing calcium chloride at 40°C for 24 h. Thereafter, the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated using the following formula:

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100.$$

Measurement of mechanical properties

Mechanical properties of the films were evaluated using a microprocessor-based advanced force gauze (Ultra test tensile tester, Mecmesin, UK) equipped with a 25 kg load cell. Film with dimensions 60 × 10 mm free from physical imperfections was held between two clamps positioned at a distance of 3 cm. During measurement, the top clamp at a rate of 2 mm/s pulled the strips to a distance until the film broke. The force and elongation were measured when the film broke [7].

In-vitro release studies

The *in-vitro* drug release studies were carried out using USP paddle over disk apparatus.

Preparation of rat abdominal skin

The male albino rats were killed using anesthetic ether. The hair of test animals were carefully trimmed (<2 mm) with a trimmer taking precaution not to damage the skin, and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by heat separation technique, followed by removal of epidermis [8]. The epidermis was washed with water, wrapped in aluminum foil, and stored at 4 ± 1°C. At the time of use, the epidermis was rehydrated by immersing in water for 1 h at room temperature.

Ex-vivo permeation studies

Franz diffusion cell with a surface area of 4.15 cm^2 was used for ex-vivo permeation studies. The rat skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment; transdermal patch was placed over the skin. The receiver phase with pH 7.4 PBS was stirred at 500 rpm on a magnetic stirrer. The amount of drug permeated was determined by withdrawing sample at appropriate time intervals for 24 h; the volume was replenished with an equal volume of pH 7.4 buffer. The absorbance was measured at 241 nm spectrophotometrically. Cumulative amounts of drug permeated in μg/cm^2 were calculated and plotted against time. Drug flux (μg/h/cm^2) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface.

The target flux is calculated using the following equation:

$$J = \frac{C_{SS}\text{Cl}_T\ \text{BW}}{A}$$

where A represents the surface area of the transdermal patch (i.e. 3.14 cm^2), BW the standard human body weight of 70 kg, C_{ss} the steady state concentration at the therapeutic level (0.0023 mg/l), and the Cl_T the total clearance (0.52 l/h/kg); the calculated target flux was 26.6 μg/h/cm^2 [9].

Preparation of Ag/AgCl electrodes and iontophoresis

Pure silver wire with 0.5 mm diameter was used as the anodal electrode, and silver chloride (AgCl) electrode was prepared by dipping Ag wire in silver chloride powder; this coated silver wire–AgCl electrode was used as cathodal electrode. These were connected to a power source. The receptor compartment was filled with PB pH 7.4 and tissue integrity test was conducted using methyl red solution in the donor compartment for about 3 h. After this, skin was washed thoroughly and kept in place between the compartments. Thereafter, patch was placed above the skin. The anodal (Ag) electrode was placed in the donor compartment above the skin touching the patch and the cathodal electrode was inserted in the receptor compartment and a current of 0.5 mA/cm^2 was maintained for about 2 h; thereafter, iontophoresis was discontinued and passive diffusion was continued for 24 h. The sampling method and time points were the same as in the in-vitro release studies (Fig. 2).

Stability studies

The stability studies were conducted according to the international conference on harmonization guidelines; the patches of optimized formulation were wrapped in aluminum foil and stored for 3 months; and the samples

were withdrawn at intervals of 1, 2, and 3 months and analyzed for drug content.

Results and discussion

Drug-excipient compatibility studies

The Fourier transform infrared spectroscopy studies were carried out for pure drug along with excipients. The results are summarized in Figs. 3 and 4 and Table 2. From the results, it could be seen that there is no interaction as the major peaks remained the same.

Weight, thickness, folding endurance, and drug content

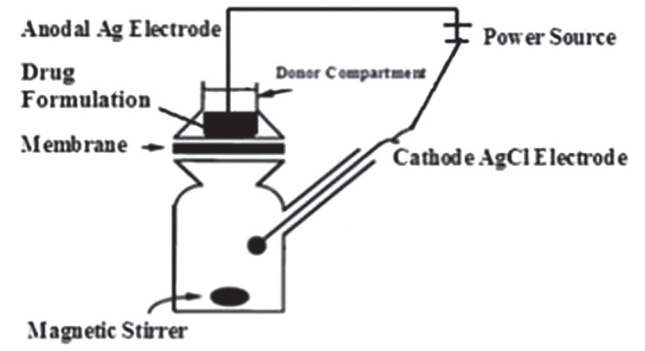
The results are shown in Table 3. Results of weight variation test indicated uniformity in weight of patches, as evidenced by SD values, which were less than 2.0 for all formulations. The weight of the patches ranged from 38.4 ± 1.13 for formulation F5 to 43.4 ± 1.13 for formulation F2; the weight of the patches decreased with decrease in HPMC E15 concentration. The thickness increased with increase in HPMC E15. The folding endurance numbers for the formulations prepared with penetration enhancers were in the range of 141–222. The folding endurance number gives the mechanical property of the patches; high folding endurance number indicates high mechanical property. The folding endurance number was increased with increasing HPMC E15 content. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. The drug content ranged from 5.72 ± 0.75 to 6.01 ± 0.53.

Table 2 Comparative Fourier transform infrared spectroscopy values

IR spectra	Peak of functional groups [wavelength (cm^{-1})]			
	N–H stretching	O–H stretching	C–H stretching	N-H bending
Carvedilol	3347	3628	3067	1502
Carvedilol+HPMC E15	3527.7	3347	3101.2	1576.2
Carvedilol+HPMC E15+ERL 100	3700.3	3668.4	3169.22	1590

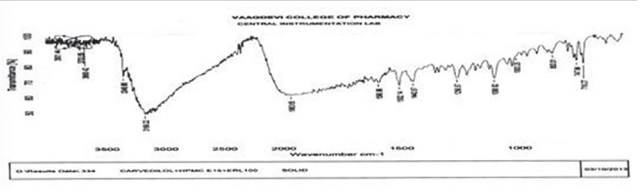
ERL 100, Eudragit L100; HPMC E15, hydroxypropyl methylcellulose E15; IR, infrared.

Figure 2



Franz diffusion cell with iontophoresis.

Figure 4



Fourier transform infrared spectroscopy of drug with excipients.

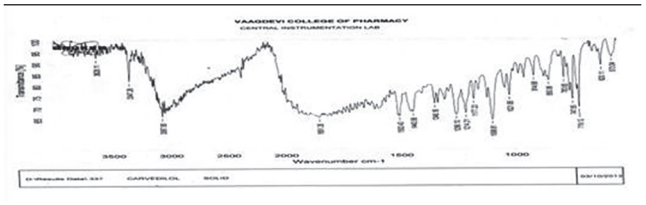
Moisture content and moisture absorption studies

The results of moisture content and moisture absorption studies are shown in Figure 5. The moisture content in the patches ranged from 4.5 to 6.8%. The moisture absorption in the formulations ranged from 5.18 to 15.82%. The results revealed that the moisture absorption and moisture content were found to increase with increasing concentration of hydrophilic polymer HPMC E15. The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film.

Mechanical properties

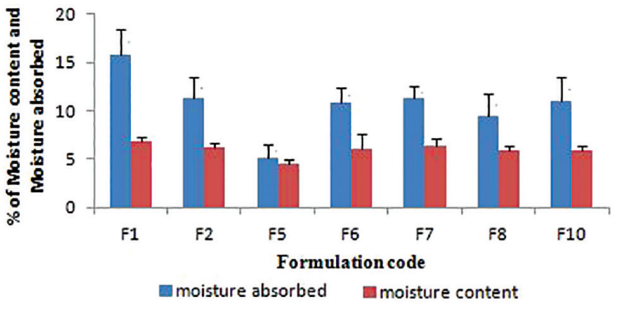
The results of mechanical properties (tensile strength, elongation at break, elastic modulus, and strain) are

Figure 3



Fourier transform infrared spectroscopy of pure drug.

Figure 5



Moisture content and moisture absorption of Carvedilol transdermal patches.

shown in Table 4. These observations indicate that the optimized formulations were found to be strong and flexible but not brittle. As the concentration of HPMC increased, tensile strength and elastic modulus also increased but elongation break value decreased.

Table 3 Weight, thickness, folding endurance, and drug content of Carvedilol transdermal patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (mg)
F1	40.83 ± 1.0	0.38 ± 0.75	222.06 ± 3.44	5.85 ± 0.76
F2	43.41 ± 1.13	0.38 ± 0.75	200.83 ± 3.45	5.98 ± 0.52
F3	42.22 ± 0.54	0.34 ± 0.75	193.52 ± 5.22	5.72 ± 0.75
F4	41.21 ± 0.75	0.33 ± 0.82	160.51 ± 4.96	5.81 ± 0.25
F5	38.43 ± 1.13	0.32 ± 0.89	141.74 ± 3.78	5.95 ± 0.57
F6	39.54 ± 0.86	0.34 ± 0.75	187.03 ± 3.94	5.73 ± 0.76
F7	42.62 ± 0.94	0.37 ± 1.05	217.02 ± 4.88	6.01 ± 0.53
F8	42.13 ± 0.44	0.35 ± 0.75	192.45 ± 3.98	5.72 ± 0.75
F9	42.57 ± 0.58	0.36 ± 0.72	206.45 ± 5.24	5.78 ± 0.76
F10	42.12 ± 0.65	0.35 ± 0.86	191.98 ± 4.64	5.71 ± 0.64

Table 4 Mechanical properties of optimized formulations

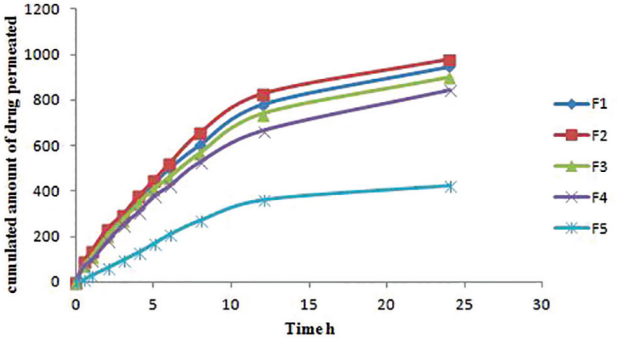
Formulation code	Tensile strength (kg/m^2)	Elongation at break ($\%mm^{-2}$)	Elastic modulus (kg/mm^2)	Strain
F2	1.73 ± 0.2	79.92 ± 3.07	3.65 ± 0.34	0.59 ± 0.02
F3	1.26 ± 0.25	80.7 ± 3.86	3.34 ± 0.41	0.55 ± 0.024

Table 5 *In-vitro* drug release, *ex-vivo* skin permeation, and flux of transdermal patches

Formulation code	Cumulative amount of drug permeated ($\mu g/cm^2$) (Q_{24})	Cumulative amount of drug release (mg)	J_{ss} ($\mu g/cm^2/h$)
F1	946.8 ± 3.74	3.08 ± 2.16	11.56
F2	979.4 ± 3.16	3.52 ± 3.56	27.02
F3	900.57 ± 2.8	3.85 ± 3.18	26.41
F4	843 ± 3.8	2.26 ± 2.06	9.32
F5	423 ± 2.6	2.23 ± 4.22	6.51
F6	943.2 ± 2.8	3.22 ± 4.17	17.24
F7	1035.7 ± 4.8	5.16 ± 0.13	37.25
F8	1076.7 ± 4.8	5.45 ± 4.10	32.53
F9	1048.7 ± 3.8	5.82 ± 1.14	44.38
F10	1476.7 ± 4.8	6.21 ± 1.21	41.06

Q_{24}, cumulative amount of drug permeated at 24 h; J_{ss}, flux.

Figure 6



Cumulative amount of drug permeated from F1–F5 Carvedilol patches.

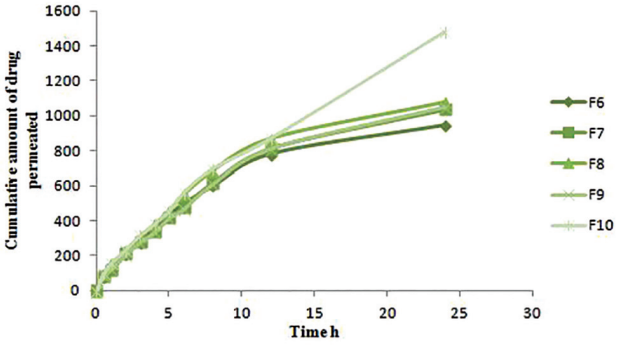
Ex-vivo permeation studies through rat abdominal skin from transdermal patches

The results of ex-vivo skin permeation of Carvedilol from patches are shown in Table 5. The formulations (area of 4.15 cm^2) F2 and F3 exhibited the greatest (979.4 ± 3.16 and 900.57 ± 2.8 $\mu g/cm^2$, respectively) cumulative amount of drug permeation, which were significantly different compared with other formulations in 24 h. As the proportion of HPMC increased, drug release and permeation were also increased. However, formulations F7, F8, F9, and F10 contained no chemical permeation enhancer; instead, current density of 0.5 and 1 mA/cm^2 exhibited the greatest (1035.7, 1076.7, 1048.7, and 1476.7 $\mu g/cm^2$, respectively) cumulative amount of drug permeated. These formulations exhibited the required flux. The results of drug permeated from transdermal patches through the rat abdominal skin confirmed that Carvedilol was released from the formulation and permeated through the rat skin, and hence could possibly permeate through the human skin (Figs. 6 and 7) [10,11].

In-vitro release studies

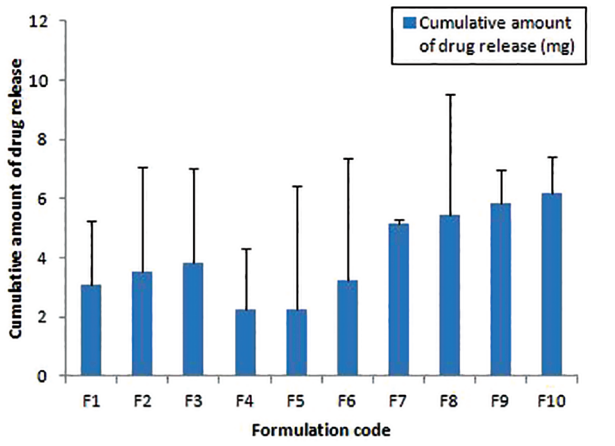
All transdermal patches were analyzed for their in-vitro release profiles to study the effect of polymer concentration on release kinetics. Drug release profiles from different formulations are shown in Figure 8. Formulation F2 exhibited maximum drug release in 24 h, which was significantly different among all the formulations. The increasing order of drug release with the chemical permeation enhancers was F5 < F4 < F1 < F6 < F2 < F3. The release data were fit into different kinetics to determine the release mechanism and n values.

Figure 7



Cumulative amount of drug permeated from F6–F10 Carvedilol patches.

Figure 8



Cumulative amount of drug release from transdermal patches.

The Higuchi model was the appropriate model describing the release kinetics from all patches having the correlation coefficient between 0.962 and 0.994. The n value (0.22–0.41) indicates that the amount of drug released was due to Fickian diffusion [12,13].

Conclusion

Carvedilol transdermal films with chemical enhancer D-limonene (8% v/w) were prepared and evaluated for physicochemical and permeation characteristics. *Ex-vivo* permeation studies were carried out by iontophoresis with current density of 0.5 and 1 mA/cm^2 for optimized patches without chemical enhancer. The formulations containing D-limonene were found to meet the required flux, but the formulations with iontophoresis were found to be significant with flux greater than D-limonene.

Acknowledgements

The authors are thankful to Origin Pharma for providing gift sample of Carvedilol and also thankful to Vaagdevi College of Pharmacy, Warangal for providing facilities to conduct the study.

Conflicts of interest

None declared.

References

1 Packer M, Coats AJ, Fowler MB, Katus HA, DeMets DL. Effect of Carvedilol o survival in severe chronic heart failure. N Engl J Med 2001; 344:1651–1658.

2 Ashok Kumar J. Transdermal drug delivery system: an overview. Int J Pharm Sci Rev Res 2010; 3:49–54.

3 Eiichiro M, Sachihiko N, Kenji S, Yasunori M. Analysis of skin permeation enhancing mechanism of iontophoresis using hydrodynamic pore therapy. J Control Release 2000; 66:149–158.

4 Yan G, K Li, WI Higuchi. Evaluation of constant current alternating current iontophoresis for transdermal drug delivery. J Control Release 2005; 110:141–150.

5 Vinay V. Various penetration enhancement techniques in transdermal drug delivery. Int J Pharma Technol 2011; 3:2373–2401.

6 Yousuf M, Ahmad M. Ketotifenfumarate and salbutamol sulphate combined transdermal patch formulations: *in vitro* release and *ex vivo* permeation studies. In J Pharm Sci 2013; 75:569–577.

7 Jitendra B. Formulation, optimization and evaluation of matrix type transdermal system of Lisinopril dehydrate using penetration enhancers. Drug Invention Today 2010; 2:134–137.

8 Gupta R, Mukharjee B. Development and *in vitro* evaluation of diltiazem hydrochloride transdermal patches based on povidone ethyl cellulose matrices. Drug Dev Ind Pharm 2003; 29:1–7.

9 Sanjay K, Mangesh R, Rajesh R. Design, development and *in vitro in vivo* study of a colon specific fast disintegrating tablet. Pharm Dev Technol 2011; 16:449–456.

10 Cazares D, Balaguer C, Calatayud A. Transdermal iontophoresis of dexamethasone sodium phaosphate*in vitro* and *in vivo:* effect of experimental parameters and skin type on drug stability and transport kinetics. Eur J Pharma Biopharm 2010; 75:173–178.

11 Jennyfer C, Adriana G, David Q, Alicia C. Using transdermal iontophoresis to increase granisetron delivery across skin *in vitro* and *in vivo*: effect of experimental conditions and a comparison with other enhancement strategies. Eur J Pharm Sci 2010; 39:387–393.

12 Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv 1985; 60:110–111.

13 Arfat I, Zeeshan J. *In vitro* evaluation of transdermal patches of flurbiprofen with ethyl cellulose. Acta Poloniac Pharmaceutica 2014; 71:287–295.