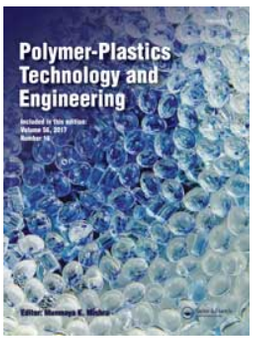


Polymer-Plastics Technology and Engineering

ISSN: 0360-2559 (Print) 1525-6111 (Online) Journal homepage: http://www.tandfonline.com/loi/lpte20

Fabrication and Characterization of Matrix-Type Transdermal Patches Loaded with Ramipril and Repaglinide Through Cellulose-based Hydrophilic and Hydrophobic Polymers: In Vitro and Ex Vivo Permeation Studies

Muhammad Zaman, Usman Khalid, Maria Abdul Ghafoor Raja, Waqar Siddique, Kishwar Sultana, Muhammad Wahab Amjad, Atta Ur Rehman & Mahtab Ahmad Khan

To cite this article: Muhammad Zaman, Usman Khalid, Maria Abdul Ghafoor Raja, Waqar Siddique, Kishwar Sultana, Muhammad Wahab Amjad, Atta Ur Rehman & Mahtab Ahmad Khan (2017) Fabrication and Characterization of Matrix-Type Transdermal Patches Loaded with Ramipril and Repaglinide Through Cellulose-based Hydrophilic and Hydrophobic Polymers: In Vitro and Ex Vivo Permeation Studies, Polymer-Plastics Technology and Engineering, 56:16, 1713-1722, DOI: 10.1080/03602559.2017.1289400

To link to this article: https://doi.org/10.1080/03602559.2017.1289400

Accepted author version posted online: 13 Feb 2017.
Published online: 19 Apr 2017.

Submit your article to this journal

Article views: 81

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=lpte20

POLYMER-PLASTICS TECHNOLOGY AND ENGINEERING
2017, VOL. 56, NO. 16, 1713–1722
http://dx.doi.org/10.1080/03602559.2017.1289400

Taylor & Francis
Taylor & Francis Group

Fabrication and Characterization of Matrix-Type Transdermal Patches Loaded with Ramipril and Repaglinide Through Cellulose-based Hydrophilic and Hydrophobic Polymers: In Vitro and Ex Vivo Permeation Studies

Muhammad Zaman[a], Usman Khalid[a], Maria Abdul Ghafoor Raja[d], Waqar Siddique[a], Kishwar Sultana[b], Muhammad Wahab Amjad[d], Atta Ur Rehman[c], and Mahtab Ahmad Khan[c]

[a]Department of Pharmaceutics, Faculty of Pharmacy, The University of Lahore, Pakistan; [b]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The University of Lahore, Pakistan; [c]Department of Pharmacology, Faculty of Pharmacy, The University of Lahore, Pakistan; [d]Department of Pharmaceutics, Faculty of Pharmacy, Northern Borders University, Rafha, Saudi Arabia

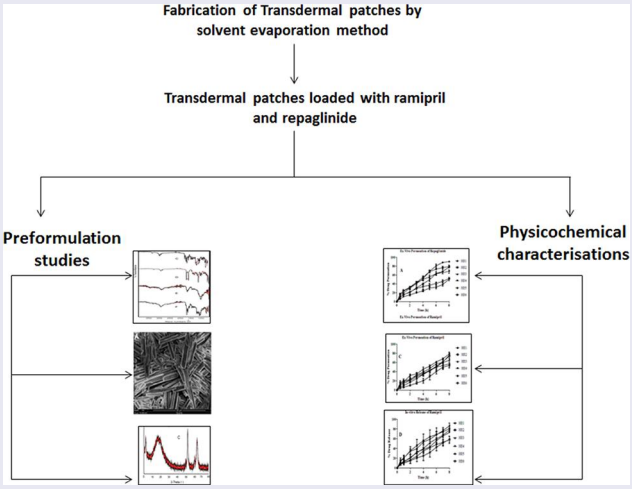
ABSTRACT

Transdermal patches loaded with ramipril and repaglinide were prepared with the ambition to develop matrix-type transdermal drug delivery system for enhanced permeability and hence improved bioavailability. Different formulations were designed by intermittent concentrations of hydroxypropyl methylcellulose K4M as hydrophilic polymer and ethyl cellulose as hydrophobic polymer. Solvent casting method was used for the fabrication of transdermal patches. Oleic acid and propylene glycol were used to enhance permeability along with polyethylene glycol 400 as plasticizer. Newly designed patches were then evaluated for various physicochemical and mechanical properties. Compatibility studies were performed by Fourier transformed infrared spectroscopy which did not reveal any interaction between drug and polymers. Crystalline nature of drugs was confirmed when they were subjected to X-ray diffraction study and surface morphological studies using scanning electron microscopy. Transdermal patches were of good mechanical strength with folding endurance of more than 300-fold and 100% flatness. Percent drug contents of ramipril and repaglinide ranged from 90 to 105%, i.e., analogous to official limits. In vitro and ex vivo permeation studies were executed using franz diffusion cell. The cumulative amount of drug permeated through skin was 55.22–112.72% for repaglinide and 73.14–91.46% for ramipril. The release behavior of the permeated drug was analyzed by the application of model-dependent approaches. The results showed that Korsmeyer–Peppas model was found to be dominating in most of the formulations and drugs followed diffusion mechanism. It could be concluded that hydroxypropyl methylcellulose K4M and ethyl cellulose has great potential for ramipril and repaglinide as a vector for transdermal drug delivery effectively because of the formation of smooth surfaces of patches, high folding endurance, and entrapment efficiency with the ability to release the drugs in sustained manner.

KEYWORDS

Fabrication; in vitro and ex vivo permeation; oleic acid; polyethylene glycol; solvent casting method; transdermal patches

GRAPHICAL ABSTRACT



CONTACT Muhammad Zaman m.zaman2157@gmail.com Department of Pharmaceutics, Faculty of Pharmacy, The University of Lahore, Lahore 54000, Pakistan.

Color versions of one or more of the figures in this article can be found online at www.tandfonline.com/lpte.

© 2017 Taylor & Francis

Introduction

Topical formulations that contain drug and have systemic drug action are known as transdermal drug delivery systems or transdermal therapeutic systems[1]. Transdermal delivery system is a painless delivery as compared to injections, so provide patient compliance. It provides a good alternative route of drug administration because of sustained drug release and bypassing the drug from first-pass effect[2]. Different transdermal delivery systems have been developed for treating different diseases like hypertension, angina, motion sickness, pain, nicotine dependence. Recent example of successful use of this systems is the management of urinary incontinency and contraception[3]. Different advantages are also apparent; including suitability for those drugs which are given orally and have a large first-pass effect, very low bioavailability, inconvenient dosage regimen, and due to metabolites formed by liver, sometimes, become the reason of toxicity/adverse drug action. This problem has been addressed by administering those drugs through transdermal route. There is another benefit of this route that when the drug is no longer desirable, the therapy can be stopped by removing the patch, in other delivery systems except infusions, it is not possible to stop the therapy instantaneously[4].

Repaglinide is an oral antidiabetic drug of meglitinide class used to treat noninsulin-dependent diabetes mellitus by lowering the blood glucose levels. It has a very lower bioavailability and half-life of 56% and 1 h, respectively. Dose of repaglinide is 0.5–4 mg and given 3–4 times a day. This can also be used for maintaining blood sugar levels in diabetic patients[5]. Ramipril is from the class angiotensin converting enzyme inhibitor (ACE) inhibitor and is used to treat hypertension and other cardiovascular diseases. Ramipril is a drug which acts on angiotensin converting enzyme and inhibits the conversion of angiotensin I to angiotensin II. Absolute bioavailability of ramipril is 28–35% and is poorly water-soluble drug[6]. These characteristics of both drugs made them suitable for being delivered through transdermal patches. From studies, it was observed that total number of people with diabetes was 171 million and it will rise to 366 million people by 2030. It is predicted that number of adults with hypertension will be increased by 60% to a total of 1.56 million people by 2025. Seventy percentage of patients with diabetes are also affected with hypertension and this proportion is almost twice as compared to those that do not suffer with diabetes. Coexistence of both diseases varies across different ethnic and racial groups. Diabetes mellitus itself is a risk factor for coronary artery disease, and along with hypertension, the risk is markedly increased[7]. Polymers with different characteristics have been used for many decades for the development of various dosage forms including gels, buccal films[8,9], modified release tablets[10], micro and nanoparticles. Cellulose-based polymers are considered safe and effective for the development of various dosage forms. Cellulose-based hydrophilic and hydrophobic polymers have been used extensively for the preparation of various dosage forms for sustained delivery of drugs[10–12].

In this study, matrix-type transdermal patches of hydroxypropyl methylcellulose K4M (HPMC K4M) and ethyl cellulose (EC) were synthesized and loaded with ramipril and repaglinide. The purpose of the study was to enhance the permeation of drugs and to avoid the first-pass metabolism of both drugs that will ultimately enhance the bioavailability.

Materials and methods

Materials

Repaglinide was obtained as a gift sample from ilshire Pharmaceuticals Ltd., Lahore, Pakistan and ramipril from Standpharm Pharmaceuticals Ltd., Lahore, Pakistan. Ethyl cellulose was provided by Arsons Pharmaceuticals Ltd., Lahore, Pakistan and HPMC K4M was a generous gift by Medipak Pharmaceuticals Ltd., Lahore, Pakistan. Oleic acid, polyethylene glycol 400, and propylene glycol were purchased from Merck, Germany. All other ingredients used were of analytical grade.

Methods

Preparation of ramipril and repaglinide transdermal patches

Preparation of solutions. Transdermal patches were prepared by solvent evaporation method. Stock solution of ramipril, repaglinide, oleic acid, and propylene glycol was prepared.

Preparation of repaglinide and ramipril stock solutions. For each patch, the required amounts of repaglinide and ramipril were 24.6 and 60 mg, respectively. Stock solutions of repaglinide with concentration of 24.6 mg/mL and of ramipril having concentration of 60 mg/mL were prepared in 50 mL of methanol. For proper dissolving of the drugs in methanol, magnetic stirrer was used. Both the beakers were sealed properly with aluminum foil to avoid methanol evaporation.

Preparation of oleic acid and propylene glycol stock solutions. Stock solution of oleic acid and propylene glycol having concentrationof 15 mg/mL was prepared by adding 750 mg of both propylene glycol and oleic acid in 50 mL of methanol separately. The beakers were properly sealed with aluminum foil to avoid evaporation of methanol. Magnetic stirrer was used for the proper mixing and solutions were saved for further use.

Preparation of transdermal patches of repaglinide and ramipril containing HPMC K4M and EC. The solvent casting technique was used for the preparation of transdermal patches according to the composition given in Table 1. HPMC K4M was used in concentration of 9:1, 8:2, 7:3, 6:4, 5:5, and 4:6 with ethyl cellulose. Accurate quantity of HPMC K4M was weighed and dissolved in 20 mL of methanol and chloroform 1:1 solution in 50-mL beaker. For proper mixing, the solution was placed on hot plate magnetic stirrer for 30 min. The stirrer was stirred at 300 rpm at 30°C. After mixing of HPMC K4M, accurate quantity of ethyl cellulose was added to the HPMC K4M solution and again allowed to stir for 30 min. After the plasticizer, polyethylene glycol 30% w/w of polymer was added to the polymeric solution. A total of 1 mL solution of each oleic acid and propylene glycol stock solution was added to the polymeric solution. At the end, 1 mL of each repaglinide and ramipril stock solutions was added to the polymeric solution. The solution was again mixed for 30 min, after that the beaker was removed from the magnetic stirrer. To remove any air bubble present in the solution, the beaker was placed in sonicator at 37°C until all the bubbles were removed. After sonication, the solution was poured in a Petri dish having a surface area of 26.74 cm^2. An inverted funnel was placed over the Petri dish to avoid uncontrolled evaporation of the solvent. After 48 h, the prepared patches were peeled off from the Petri dishes. The patches were properly wrapped in the aluminum foil and stored in desiccator for further characterizations.

Table 1. Composition of transdermal patches containing repaglinide and remipril.

Formulation	HPMC K4M (mg)	EC (mg)
HE1	450	50
HE2	400	100
HE3	350	150
HE4	300	200
HE5	250	250
HE6	200	300

EC, ethyl cellulose; PEG 400, polyethylene glycol 400; PEG, polyethylene glycol.

Note: Constant quantities of repaglinide (24.6 mg), ramipril (60 mg) PEG 400 (30%) oleic acid (3%) and propylene glycol (3%) were used in all the formulations.

Pre formulation studies

Drug–drug and drug–polymer compatibility study

To evaluate the drug–drug and drug–polymer compatibility, Fourier transformed infrared spectroscopy (FTIR) was used. This study was performed on the Agilent technologies FTIR instrument. Scanning was performed in the range 650–4,000 cm^{-1}. All the samples were run on the instrument and transmittance was taken of individual ingredients and of combinations to check the compatibility.

Surface morphology

Light microscopy

A small portion (1 × 1 cm^2) of each patch was cut and placed over a glass slide to observe under the lens. 40× power lens was used to observe the surface of patches.

Scanning electron microscopy

Scanning electron microscopy (SEM) was performed for both repaglinide, ramipril and also for the prepared patches. This was performed to observe the morphology of drugs and surface texture of prepared patches[13]. SEM photographs were obtained from the Quanta scanning electron microscope at 500×, 1000×, and 2000×.

X-ray diffraction

X-Ray diffraction (XRD) studies were performed for drugs and prepared patches using PHILIPS1710 XRD. In pharmaceutical industry, X-ray diffraction is mainly used for

1. To identify drug substance forms, including an unknown material.
2. Applied to quantify crystalline content in an amorphous formulation.

Used to identify two related drug forms in a solid formulation[14].

Physicochemical evaluation of transdermal patches

Organoleptic examination

Color, flexibility, smoothness, and transparency were observed in the organoleptic examination of transdermal patches[15]. Uniformity of patches, surface smoothness, and strength during peeling are some other parameters which were also studied.

Thickness

Thickness of the prepared patches was evaluated using a digital micrometer at three different points of the patch[16].

Folding endurance

Folding endurance was determined by folding a patch repeatedly at the same point until it broke. The number of times it took to break gave the value of folding endurance[17].

Weight uniformity

The prepared patches were dried at 60°C for 4 h before testing. Patch was cut into four pieces with same dimensions from different parts and weighed on a digital balance. Individual weight and average weight of the patch were calculated to determine the weight uniformity[18].

Flatness

Measured length of strips was cut from prepared patches, and after some time, the length of patches was again measured to check the nonuniformity in flatness. Constriction in the patch showed nonuniformity, if there was 0% constriction, then it was considered to be 100% flatness[19].

pH determination

For the determination of pH, the patches were kept in distilled water for 1 h in a glass tube. Surface pH was noted by bringing the pH meter electrode near to the surface of patch and kept there for 1 min to equilibrate the reading[20].

Percentage moisture loss

The patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula[21]:

$$\text{Moisture contents}\,(\%) = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 10.$$

Drug content

Transdermal patch was cut into strips of $1 \times 1\ \text{cm}^2$ area and dissolved into a measured volume of methanolic phosphate buffer pH of 7.4 (methanol 50% v/v). Then the solution was filtered through a filter medium and drug contents were analyzed using the suitable method[22]. For this purpose, the patch was dissolved in 100 mL of media; from this, 1 mL of sample was withdrawn and further diluted to 10 mL with media. Absorbance was taken for ramipril and repaglinide at 210 and 240 nm, respectively.

Drug release permeation studies

In vitro drug release

In vitro drug release study was performed using a franz diffusion cell having a capacity of 13 mL. Cellulose acetate synthetic membrane having pore size of 0.22 µm was used as a barrier between the receptor compartment and patch. Franz cell was thoroughly washed before use and filled up with methanolic phosphate buffer 7.4. Then the membrane was placed on the franz cell and operated with the help of magnet and hot plate magnetic stirrer for 30 min. This procedure was helpful in charging the membrane and franz cell and also to maintain the temperature at 37 ± 0.5°C. After that, the patch was placed over the synthetic membrane. Head and receptor compartment were properly screwed with the help of a clipper. The solution of receptor compartment was stirred at 250 rpm. A total of 1 mL of sample was taken after 30 min and after 1, 2, 3, 4, 5, 6, 7, and 8 h from the starting time. Volume was adjusted up to 3 mL of each sample and was analyzed on UV Spectrophotometer.

Ex vivo drug permeation

Abdominal skin from healthy male albino rats having weight of 200–250 g was used to determine the ex vivo release of drug. The rats were anesthetized using chloroform and then the neck was dislocated as per guidelines approved by the animal ethical committee, The University of Lahore. Hair from the abdominal area were removed using a sharp razor with the caution of damaging the skin by razor cut. Subcutaneous fat was removed with the help of sharp blades and isopropyl alcohol swabs. After that, the skin was washed with 0.9% NaCl solution and stored in this solution at 0–4°C if the skin was used after some time. Before using, the skin temperature was normalized and cut according to the size of franz cell. The remaining method was adopted as performed for in vitro drug release.

Application of kinetic models

Different kinetic models, zero-order, first-order, higuchi model, hixcon crowell cube root, and Korsmeyer–Peppas model were applied to observe the release pattern and behavior of drugs.

Results

Fourier transform infrared spectroscopy

Two peaks were observed in the FTIR spectrum of ethyl cellulose (Figure 1, graph A). The peak observed at frequency 1,049 cm^{-1} was due to the C-O stretch and another peak was found at 3,350 cm^{-1} indicating the

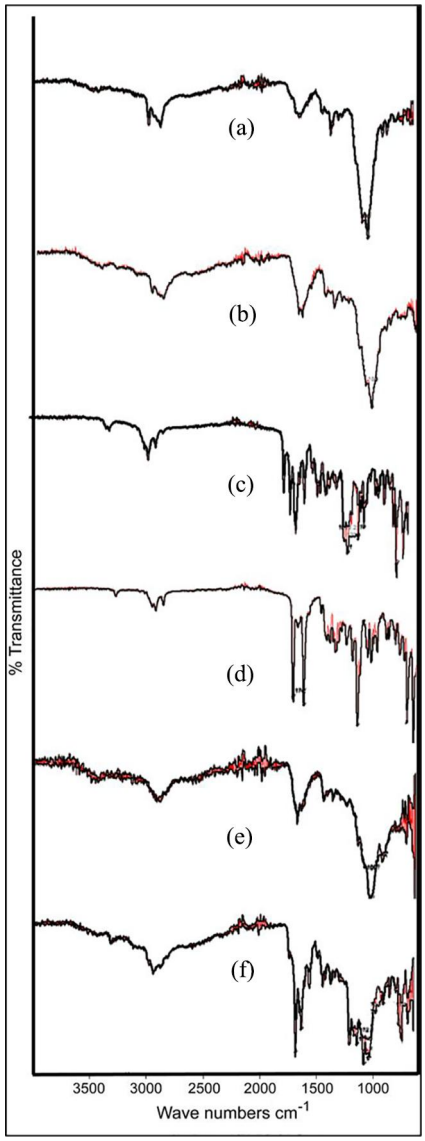


Figure 1. FTIR spectra of EC (a), HPMC K4M (b), ramipril (c), repagline (d) physical mixture of EC and HPMC K4M (e), and physical mixture of EC, HPMC K4M, ramipril and repaglinide (e). *Note*: HPMC K4M, hydroxypropyl methylcellulose K4M; EC, ethyl cellulose; FTIR, Fourier transformed infrared spectroscopy.

presence of O-H of alcohol group in the structure of ethyl cellulose. HPMC K4M (Figure 1, graph B) showed three main peaks in the FTIR spectrum. The peak at 941 was due to O-H bend and O-H stretch bands appeared at around 3,300 which confirmed the presence of alcohol groups in the HPMC structure. The peaks at 1,045 and 1,097 cm^{-1} were due to the C-O stretch.

Fourier transformed infrared spectroscopy spectrum of repaglinide (Figure 1, graph C) showed peaks at 1,090, 1,209, 1,181, 700, and 754 cm^{-1}. First three peaks were observed due to the stretching of C-O and C-N. The peak at 1,742 cm^{-1} from the FTIR of ramipril showed C=O stretch which confirmed the presence of carboxylic acid group in the structure of ramipril. Another important peak in the C=O region appeared around 1,670 cm^{-1} due to the presence of amide in the molecule. The other peaks were observed at 1,549 and 1,483 cm^{-1} revealing the presence of aromatics in the structure. Peak above 3,000 cm^{-1} confirmed the presence of amines because of the stretching of C-N.

In case of ramipril (Figure 1, graph D), there were two significant bands which appeared in the C=O region one at 1,667 cm^{-1} and other at 1,747 cm^{-1} indicating the presence of amide and carboxylic acid in the structure. The peak for C=O of ester group was found to be overlapped somewhere in the carboxylic region. N-H and O-H stretch bands were observed around 3,000–3,500 cm^{-1}.

Ramipril and repaglinide were properly mixed to determine the FTIR peaks of both drugs. There was a little or no change observed in these peaks which showed that there is no chemical interaction between the groups present in both drugs. So, this combination is considered to be suitable for dosage form development. FTIR peaks of HPMC and EC mixture were observed which showed two peaks. The peak present at 1,097 cm^{-1} was observed in both FTIR of HPMC and EC alone. The other peak present at 1,047 cm^{-1} showed a very little change. In case of HPMC, it was present at 1,045 cm^{-1}, while at 1,049 cm^{-1} in case of EC. No interaction was found between EC and HPMC because of no significant change in peaks. Formulated patch was also analyzed by FTIR, and in the combination of repaglinide, HPMC K4M, and EC, there was no change observed in the peaks of repaglinide and ramipril (Figure 1, graph E). A little change was observed in the peak of HPMC K4M which was at 1,067 cm^{-1} in combination and at 1,045 cm^{-1} when observed alone (Figure 1, graph E). The values of HPMC K4M were found to be within limits, so there was no interaction observed between different components of this combination.

Surface morphology

Optical microscopy

Results of optical microscopy revealed smooth surface of the patches with evenly distributed drugs and other excipients. Patch formulation HE2, with (Figure 2f) and without drug (Figure 2e) was observed under the microscope and a noticeable difference in the appearance of both patches was depicted in the Figure 2.

Scanning electron microscopy

In Figure 2a and b, crystals of both drugs repaglinide and remipril could be clearly observed indicating crystalline nature of both drugs. However, the SEM photograph of transdermal patch of optimized

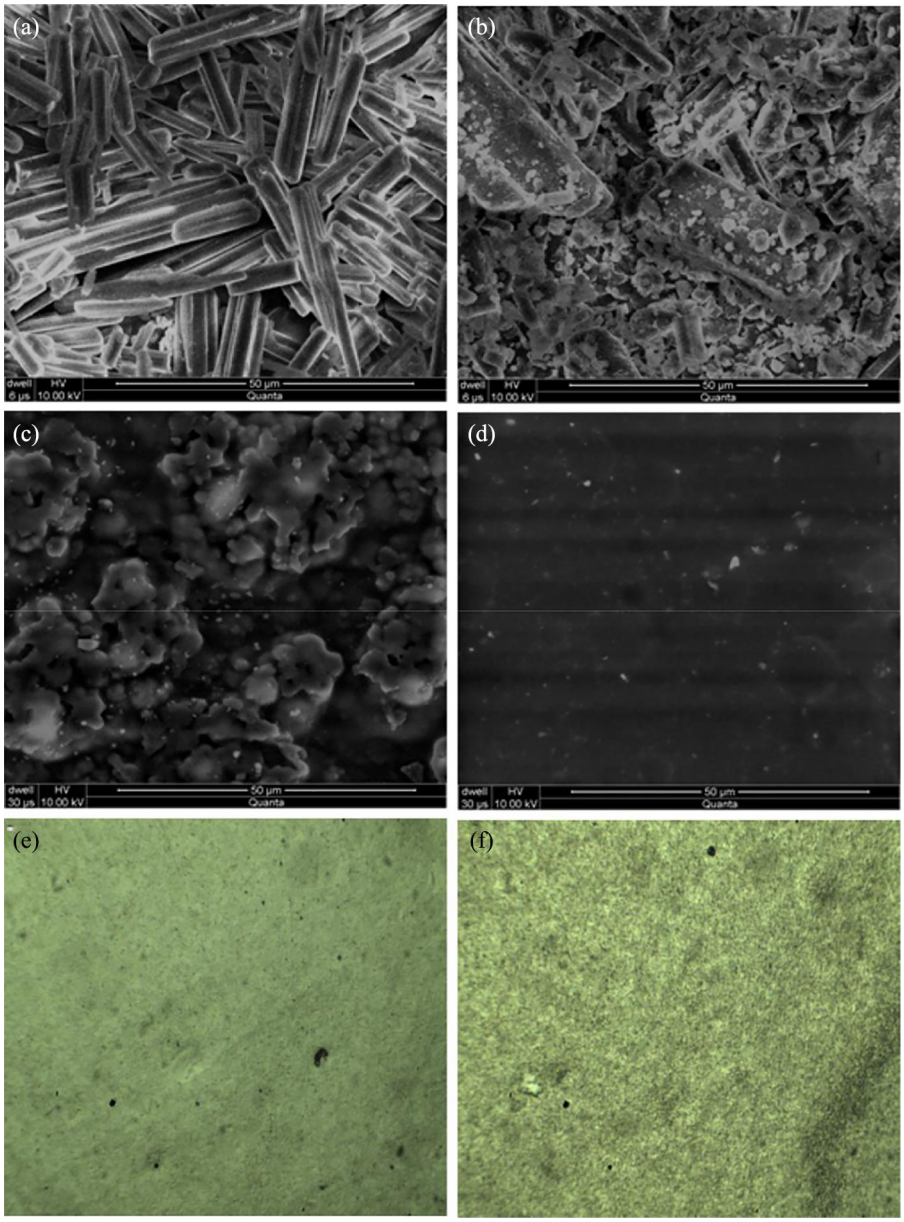


Figure 2. SEM [remipril (a), repiglinide (b), and HE2 (c)] and OM [HE1 (d), HE2 (e), and HE3 (f)] photographs showing surface morphology of the repaglinide, remipril, and formulated patches. *Note*: SEM, scanning electron microscopy; OM, optical microscopy.

formulation HE2 containing repaglinide and remipril showed that crystallanity of both drugs had been decreased and they were converted into almost amorphous drugs. Furthermore, good integrity of the patch with uniform mixing of drugs in polymeric mesh could also be observed in Figure 2c. For comparative analysis, patch formulation HE2 with (Figure 2c) and without drug (Figure 2d) was observed by SEM to observe the difference between both patches.

X-ray diffraction

The X-ray diffractogram of ramipril had sharp peaks at diffraction angles (2Ø) at 15°, 16°, 17°, 21°, 24°, 26°, 27.5°, 43.6°, and 51.2°, respectively, showing a typical crystalline nature of the drug (Figure 3a). In Figure 3b, repaglinide showed characteristics peaks at 15°, 16.8°, 17.3°, 22°, 25.3°, 30°, 45°, and 52.7°. In Figure 3c, crystallanity of drugs seemed to be decreasing describing uniform distribution in the polymeric matrix.

Organoleptic evaluation of prepared patches

Different organoleptic properties were studied. It was observed that all patches were colorless, uniformity of the patches was good, and smoothness and flexibility were good, but with an increase in EC concentration, smoothness decreased from good to satisfactory. Patches were found to be transparent with excellent peeling strength.

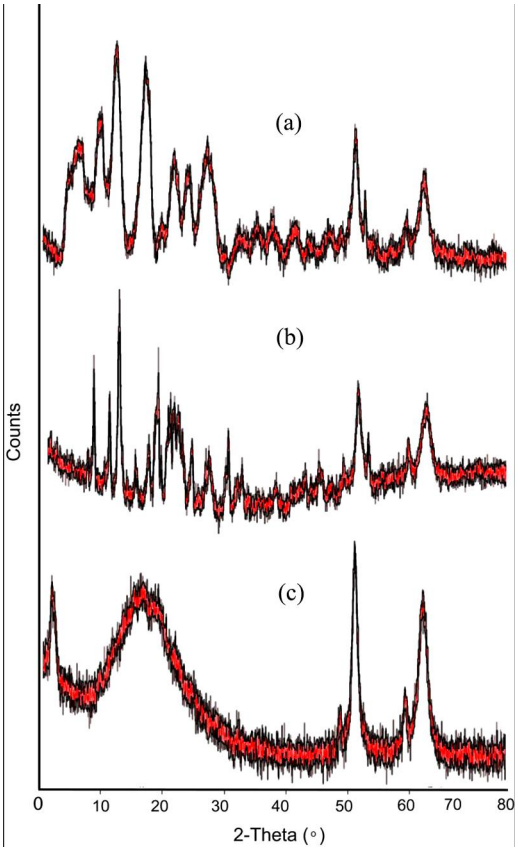


Figure 3. XRD spectra of ramipril (a), repaglinide (b), and HE2 (c).

Percent moisture was found to be decreasing with an increase in concentration of EC. It was revealed that moisture-retaining ability of HPMC K4M was greater as compared to EC. Thickness was uniform with standard deviation of 0.004–0.010. Folding endurance was greater than 300 suggesting good mechanical strength. Flat patches had pH in the range of 6.13–6.39 and exhibited uniform weight.

Drug contents were also satisfactory and they were in the range 94.01–99.07% for repaglinide, while for ramipril, they were 94.45–102.87% (Table 2).

In vitro drug release

Results obtained through the release studies performed using synthetic membrane showed that 92.64% of repaglinide and 86.55% of ramipril were released from the transdermal patches of HE1 formulation. A comparable amount of both drugs repaglinide (85.52%) and ramipril (83.73%) was released from HE2. Similarly, HE3, HE4, HE5, and HE6 released 77.39, 71.47, 60.10, and 57.41% repaglinide and 78.16, 72.90, 57.72, and 58.7% remipril, respectively (Figure 4).

Ex vivo permeation studies

Permeation data of ex vivo studies that were performed using rat abdominal skin, described that HE1 released 90.5% repaglinide and 79.03% ramipril. From HE2, permeated amount of remipril and repaglinide was 78.5 and 79.5%, almost equal amount of both drugs were permeated that made this formulation to be considered as optimized. Other formulations HE3, HE4, HE5, and HE6 released 78.59, 68.14, 51.22, and 52.5% repaglinide and 76.52, 66.12, 57.10, and 53.14% ramipril, respectively (Figure 4).

Application of kinetic models

When kinetic models were applied to observe the permeation pattern of ramipril, it was found that the values of R^2 were highest in case of Korsmeyer–Peppas model suggesting it as best fit model. In case of Hixon–Crowell, all values were found to be in between 0.91 and 0.97, only HE5 showed the value which was lower than 0.9. Formulations HE1, HE4, HE5, and HE6 showed lower values, when zero-order kinetic model was applied. It was observed that R^2 values of higuchi model were higher than 0.9, indicating diffusion pattern of drug release. The value of HE5 was lower than 0.9 in case of first order. For repaglinide, the values of R^2 of zero-order kinetics were higher than 0.95 for all formulations. First-order kinetics and higuchi model showed comparatively lower values of R^2. In the Hixcon–Crowell model, the values of R^2 were also higher than 0.9 for formulation except HE3. It was observed from the value of n that only HE1 and HE2 followed case 2 transport, while all the other showed super case 2 transports. However, Korsmeyer–Peppas model was best fit. Data from in vitro studies were also evaluated by kinetic models. HE2 (data of ramipril) and HE3 (data of ramipril) followed Hixcon–Crowell cube root and first order, respectively, while the rest of the formulations

Table 2. Results of various evaluation parameters of transdermal patches.

Formulation	Moisture loss (%)	Thickness (mm)	Folding endurance	Weight variation (mg)	Flatness (%)	pH	Content uniformity	
							Repaglinide	Ramipril
HE1	8.67	0.186 ± 0.004	>300	0.123 ± 0.0098	100	6.13 ± 0.012	94.01 ± 1.25	96.51 ± 2.91
HE2	6.93	0.230 ± 0.005	>300	0.115 ± 0.0012	100	6.15 ± 0.008	99.73 ± 1.62	100.06 ± 2.69
HE3	7.91	0.215 ± 0.006	>300	0.151 ± 0.0167	100	6.27 ± 0.012	96.63 ± 1.33	94.45 ± 3.01
HE4	5.99	0.237 ± 0.010	>300	0.111 ± 0.0019	100	6.12 ± 0.008	99.07 ± 1.28	102.40 ± 2.04
HE5	4.41	0.234 ± 0.014	>300	0.117 ± 0.0035	100	6.22 ± 0.012	95.73 ± 0.70	102.87 ± 1.59
HE6	3.33	0.224 ± 0.004	>300	0.119 ± 0.0047	100	6.39 ± 0.012	96.53 ± 2.39	100.54 ± 1.80

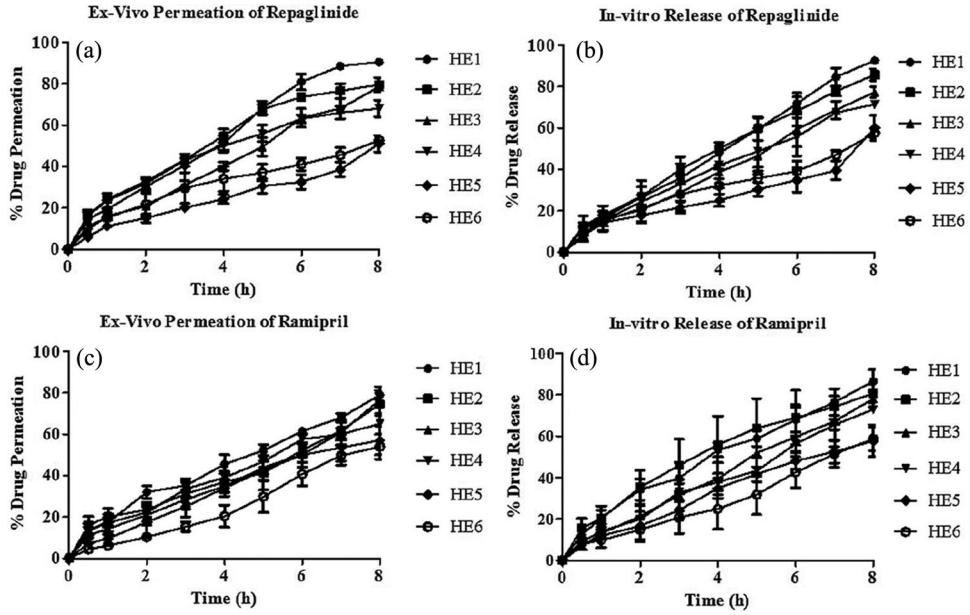


Figure 4. Graphs showing cumulative amount of repaglinide and remipril through silicon membrane and rat abdominal skin. (a, b) describe permeation through silicon membrane and rate skin, respectively, while (c, d) show permeation of remipril through silicon membrane and rat skin, respectively.

Table 3. Kinetic modeling of permeation data of through rat abdominal skin.

Formulation no.	Zero order	Ko	First order	Higuchi model	Korsmeyer–Peppas model	Value of *n*	Hixon–Crowell model	Best fit model
					Ramipril			
HE1	0.8418	0.206	0.9369	0.9529	0.9758	0.622	0.9224	Korsmeyer–Peppas
HE2	0.9810	0.193	0.9093	0.9503	0.9942	0.681	0.9841	Korsmeyer–Peppas
HE3	0.9323	0.181	0.9557	0.9333	0.9905	0.720	0.9731	Korsmeyer–Peppas
HE4	0.8827	0.164	0.9296	0.9279	0.9665	0.674	0.9263	Korsmeyer–Peppas
HE5	0.8203	0.162	0.8824	0.9179	0.9406	0.626	0.8750	Korsmeyer–Peppas
HE6	0.8838	0.167	0.9870	0.9655	0.9979	0.648	0.9789	Korsmeyer–Peppas
					Repaglinide			
HE1	0.9811	0.124	0.9377	0.7735	0.9943	1.188	0.9731	Korsmeyer–Peppas
HE2	0.9845	0.130	0.8223	0.9340	0.9847	1.172	0.9418	Korsmeyer–Peppas
HE3	0.9690	0.243	0.8493	0.8636	0.9762	0.880	0.8966	Korsmeyer–Peppas
HE4	0.9781	0.125	0.9832	0.8592	0.9840	0.895	0.9874	Korsmeyer–Peppas
HE5	0.9831	0.127	0.9852	0.8833	0.9935	0.861	0.9899	Korsmeyer–Peppas
HE6	0.9838	0.181	0.9201	0.8391	0.9842	0.971	0.9485	Korsmeyer–Peppas

followed Korsmeyer–Peppas model. F3 and F9 showed Hixon–Crowell as the best fit model and from the values, it was observed that first order was considered to be the best fit model in case of F4. Remaining formulations followed Korsmeyer–Peppas as a best fit kinetic model. Formulations F4, F6, and F9 showed lower values for zero-order kinetics, remaining formulations showed the values 0.9. All formulations showed higher values for first-order kinetics. Formulations F2, F3, F7, F8, F10, and F11 in case of higuchi model showed lower values and the remaining formulations showed the values higher than 0.9. The values observed from Hixon–Crowell model showed that all formulations followed Hixon–Crowell kinetic model. The value of *n* from Korsmeyer–Peppas model demonstrated that the formulations HE2 (data of repaglinide) and HE4 (data of repaglinide) followed super case 2 transports while remaining followed case 2 transport (Table 3).

Discussion

Compatibility studies performed by FTIR of both drugs and polymer-loaded drugs showed that there was no interaction between drugs and polymers. X-ray diffractometry was used to observe the crystallanity or amorphous nature of ramipril and repaglinide. It was observed that both drugs were of crystalline nature which was further confirmed by SEM. Crystallanity of the drugs was decreased when drugs were added with excipients in dissolved form to fabricate the patches. Surface morphology was studied by optical microscopy and SEM which showed smooth surface of the patches

Table 4. Kinetic modeling of permeation data of through synthetic membrane.

Formulation no.	Zero order	Ko	First order	Higuchi model	Korsmeyer–Peppas model	Value of *n*	Hixon–Crowell model	Best fit model
					Ramipril			
HE1	0.9650	0.209	0.9784	0.9075	0.9914	0.793	0.9813	Korsmeyer–Peppas
HE2	0.9786	0.221	0.9562	0.8664	0.9841	0.893	0.9694	Korsmeyer–Peppas
HE3	0.9684	0.192	0.9690	0.8846	0.9855	0.831	0.9868	Hixon–Crowell
HE4	0.7563	0.149	0.9826	0.9213	0.9360	0.592	0.9690	First order
HE5	0.9318	0.145	0.9785	0.9355	0.9916	0.717	0.9730	Korsmeyer–Peppas
HE6	0.8758	0.140	0.9691	0.9637	0.9935	0.642	0.9673	Korsmeyer–Peppas
					Repaglinide			
HE1	0.9803	0.104	0.9717	0.8580	0.9837	0.915	0.9771	Korsmeyer–Peppas
HE2	0.9891	0.148	0.9333	0.9650	0.9947	1.049	0.9537	Korsmeyer–Peppas
HE3	0.9878	0.183	0.9492	0.8616	0.9913	0.915	0.9713	Korsmeyer–Peppas
HE4	0.9634	0.141	0.8985	0.7632	0.9749	1.198	0.9223	Korsmeyer–Peppas
HE5	0.8952	0.112	0.9440	0.9394	0.9796	0.676	0.9331	Korsmeyer–Peppas
HE6	0.9771	0.139	0.9168	0.8600	0.9814	0.905	0.8451	Korsmeyer–Peppas

with uniform mixing of ingredients. Physicochemical properties of all formulations were satisfactory. From results, it was concluded that all prepared patches having folding endurance more than 300-fold which was the evidence that cellulose derivatives form good and mechanically stable patches and showed 100% flatness[23]. Thickness of the patches was ranging from 0.186 ± 0.004 to 0.237 ± 0.010 mm. The values of pH, weight uniformity, and percentage moisture loss were in the range 6.12 ± 0.008–6.39 ± 0.012, 0.111 ± 0.0019–0.151 ± 0.0167 mg, and 3.33–8.67%, respectively. Percentage moisture content of the formulations decreased when there was an increase in concentration of hydrophobic polymers (EC)[23]. Percent drug content was satisfactory and was observed to be ranging from 90 to 102% for both drugs. In vitro drug release and ex vivo permeation studies were performed using franz diffusion cell. Ex vivo permeation studies of the patches showed drug release ranging from 51.22 to 90.5% for repaglinide and 53.14 to 83.03%, while in vitro drug release study showed that % drug permeated through skin from the patches containing HPMC K4M and EC was 57.41–92.64% for repaglinide and 58.7–86.55% for ramipril. Drug retardation was dominated by the increased concentration of EC as Figure 2 described that formulations having greater concentration of EC, released lesser amount of both drugs[11,24]. HE2 was considered the best and optimized formulation due to better results as compared to other formulations. They released approximately equal amount of both repaglinide and ramipril which was the indication that both drugs will exhaust at the same time. Patches were transparent and colorless with good uniformity, smoothness, and peeling strength. pH was found to be compatible with skin; thickness was uniform with smaller standard deviation of 0.005. Moreover, drug contents were excellent, approximately 100% for both remipril and repaglinide. From the permeation data, it was noted that the percentage of drug permeated decreased as the concentration of HPMC K4M was decreased and the concentration of EC was increased. Retarding in permeation of the drug was due to the hydrophobic nature of EC. Rapid release of drug from the formulations having higher ratios of HPMC K4M was due to the hydrophilic nature of polymer. Kinetic models were applied on permeation data which showed Korsmeyers–Peppas as the best fit model for almost all formulations (Table 3). Exception was observed, when permeation data of ramipril that were permeated across synthetic membrane from two formulations HE3 and HE4, which were analyzed by kinetic models and it followed Hixon–Crowell cube root and first-order kinetics (Table 4).

Conclusion

The purpose of the present study was to design and optimize a suitable transdermal patch formulation containing ramipril and repaglinide to enhance the bioavailability and patient compliance by reducing the number of doses. It was concluded from the present study that the combination of HPMC K4M along with EC are suitable polymers for developing the transdermal patches. Oleic acid and propylene glycol showed good effect in the permeation of both drugs. From the permeation data from rat skin, it was observed that the formulation HE2 showed good permeability. This formulation not only showed good permeability of drugs, but the values of all other parameters were also satisfactory. Both, polymers and excipients, used in the formulation of transdermal patches for incorporation of ramipril and repaglinide were not very expensive. So, a safe and cost-effective formulation can be developed.

References

[1] Brown, M.B.; Martin, G.P.; Jones, S.A.; Akomeah, F.K. Dermal and transdermal drug delivery systems: current and future prospects. Drug Delivery **2006**, *13*, 175–187.

[2] Karande, P.; Mitragotri, S. Enhancement of transdermal drug delivery via synergistic action of chemicals. Biochim. Biophys. Acta Biomembranes **2009**, *1788*, 2362–2373.
[3] Thomas, B.J.; Finnin, B.C. The transdermal revolution. Drug Discovery Today **2004**, *9*, 697–703.
[4] Wiedersberg, S.; Guy, R.H. Transdermal drug delivery: 30+ years of war and still fighting! J. Controll. Release **2014**, *190*, 150–156.
[5] Prajapati, S.T.; Patel, C.G.; Patel, C.N. Formulation and evaluation of transdermal patch of repaglinide. ISRN Pharm. **2011**, *2011*, 1–9.
[6] Senthilkumar, S.; Bharath, N.; Tamizhmani, T. Design and evaluation of transdermal films of ramipril. Int. J. Pharm. Sci. Lett. **2011**, *1*, 44–48.
[7] Lago, R.M.; Singh, P.P.; Nesto, R.W. Diabetes and hypertension. Nat. Clinic. Pract. Endocrinol. Metab. **2007**, *3*, 667–667.
[8] Hanif, M.; Zaman, M.; Chaurasiya, V. Polymers used in buccal film: A review. Design. Monomers Polym. **2015a**, *18*, 105–111.
[9] Hanif, M.; Zaman, M.; Qureshi, S. Thiomers: A blessing to evaluating era of pharmaceuticals. Int. J. Polym. Sci. **2015b**, *2015*, 1–9.
[10] Zaman, M.; Qureshi, J.; Ejaz, H.; Sarfraz, R.M., Ullah Khan, H., Sajid, F.R., Ur Rehman, M.S. Oral controlled release drug delivery system and Characterization of oral tablets: A review. Pak. J. Pharma. Res. **2016**, *2*, 67–76.
[11] Zaman, M.; Adnan, S.; Saeed, M.A.; Farooq, M., Masood, Z., Chishti, S.A., Qureshi, J.; Khan, R.S. Formulation and in-vitro evaluation of sustained release matrix tablets of cellulose based hydrophilic and hydrophobic polymers loaded with loxoprofen sodium. Indo. Am. J. Pharma. Res. **2013**, *3*, 7389–7398.
[12] Zaman, M.; Sarfraz, R.M.; Adnan, S.; Mahmood, A.; Hanif, M.; Qureshi, J.; Chaudhary, M.T.; Akram, M.A.; Bashir, I. Development and in-vitro evaluation of once daily tablet dosage form of loxoprofen sodium. Tropic. J. Pharm. Res. **2015**, *14*, 1557–1563.
[13] Jatav, V.S.; Saggu, J.S.; Sharma, A.K.; Sharma, A., Jat, R. K. Design, development and permeation studies of nebivolol hydrochloride from novel matrix type transdermal patches. Adv. Biomed. Res. **2013**, *2*, 1–6.
[14] Randall, C.S.; Rocco, W.L.; Rico, P. XRD: XRD in pharmaceutical analysis: A versatile tool for problem-solving. Am. Pharm. Rev. **2010**, *13*, 52.
[15] Can, A.S.; Erdal, M.S.; Güngör, S.; Özsoy, Y. Optimization and characterization of chitosan films for transdermal delivery of ondansetron. Molecules **2013**, *18*, 5455–5471.
[16] Alam, M.I.; Alam, N.; Singh, V.; Alam, M.S.; Ali, M.S.; Anwer, T.; Safhi, M.M. Type, preparation and evaluation of transdermal patch: A review. World J. Pharm. Pharm. Sci. **2013**, *2*, 2199–2233.
[17] Gairola, A.; Chaurasia, U.; Singh, A.; Saharan, V.A. Development and evaluation of transdermal patches of aceclofenac. Thai J. Pharm. Sci. **2014**, *38*, 90–97.
[18] Darwhekar, G.; Jain, D.K.; Patidar, V.K. Formulation and evaluation of transdermal drug delivery system of clopidogrel bisulfate. Asian J. Pharm. Life Sci. ISSN **2011**, *2231*, 4423.
[19] Mamatha, T.; Rao, J.V.; Mukkanti, K., Ramesh, G. Development of matrix type transdermal patches of lercanidipine hydrochloride: Physicochemical and in-vitro characterization. Daru J. Faculty Pharm. Tehran Univ. Med. Sci. **2010**, *18*, 9.
[20] Bharkatiya, M.; Nema, R.K.; Bhatnagar, M. Development and characterization of transdermal patches of metoprolol tartrate. Development **2010**, *3*, 130–137.
[21] Shivaraj, A.; Selvam, R.P.; Mani, T.T.; Sivakumar, T. Design and evaluation of transdermal drug delivery of ketotifen fumarate. Int. J. Pharm. Biomed. Res. **2010**, *1*, 42–47.
[22] Kumar, J.A.; Pullakandam, N.; Prabu, S.L.; Gopal, V. Transdermal drug delivery system: An overview. Int. J. Pharm. Sci. Rev. Res. **2010**, *3*, 49–54.
[23] Arun, R. Formulation evaluation and in vitro permeation studies of transdermal nifedipine from matrix types patches. Int. J. Pharm. Pharm. Sci. **2014**, *6*, 185–188.
[24] Ramasamy, C.; Wesley, J.; Koshy, B.M. Formulation of transdermal drug delivery system of metoprolol tartrate and its evaluation. Int. J. Pharm. Sci. Res. **2012**, *4*, 1939–1942.