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Research Article

Polymeric Transdermal Drug Delivery System of Ramipril and Repaglinide: *In-Vitro* and *Ex-Vivo* Evaluation

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Abstract

The current project was designed with the aim to develop a transdermal drug delivery system in the form of matrix type transdermal patches integrated with Ramipril and Repaglinide. Different formulations were prepared by varying concentrations of HPMCK4M and Eudragit L100 (EL100) by solvent casting method. Oleic acid and Propylene glycol were employed as penetration enhancers and Polyethylene glycol 400 was used as plasticizer. Formulated patches were subjected to various evaluating parameters including pre-formulation studies FTIR, SEM and UV analysis and post formulation studies such as organoleptic evaluation, thickness, folding endurance, weight uniformity, flatness, pH determination, percentage moisture loss, drug content and permeation studies. FTIR revealed no interaction between drug and polymers. X-ray diffractometry (XRD) studies showed was that both drugs were of crystalline nature which was further confirmed by SEM. Surface (SEM) showed smooth surface of the patches. The results showed that all prepared patches having folding endurance more than 300 folds and showed 100% flatness. Percent drug content was excellent ranging from 90% to 105% for both drugs. *In vitro* and *ex vivo* permeation study was performed using Franz Diffusion cell. % drug permeated through skin was 44.05% to 87.76% for Repaglinide and 63.29% to 87.76% for Ramipril. Release behavior of the permeated drug was analyzed by the application of model dependent approaches. From the results, it was concluded that Korsmeyer-peppas model was found to be dominating in most of the formulations. It was also concluded that transdermal patches for the combination of Ramipril and Repaglinide can be prepared successfully using HPMCK4M along with Eudragit L100.

Keywords: *Transdermal Patches; Ramipril; Repaglinide; SEM; Ex-Vivo Permeation*

Introduction

Topical formulations that contain drug and showing 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 an advantageous route of drug administration because of sustained drug release and by-passing the drug from first pass metabolism [2]. Different transdermal delivery systems are developed for treating different diseases like hypertension, angina, motion sickness, pain, nicotine dependence; recent systems for contraception and urinary incontinence are the success of this approach [3]. Two major advantages were also apparent, first for those drugs which are given orally and they 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 is overcome by administering those drugs through transdermal route. The second is that when the drug is no

longer desirable, the therapy can be stopped by removing the patch, in other delivery systems rather than infusions, it is not possible to stop the therapy instantaneously [4].

Repaglinide in an oral anti-diabetic drug of Meglitinide class used to treat Non-Insulin dependent diabetes mellitus (NIDDM) by lowering the blood glucose levels. It has a very lower bioavailability and half-life of 56% and 1h respectively. Dose of Repaglinide is 0.5 mg to 4 mg and given 3 to 4 times a day. This can also be used for maintaining blood sugar levels in diabetic patients [5].

Ramipril is from the class ACE inhibitor and is used to treat hypertension and other cardiovascular diseases. Ramipril is a drug which acts on angiotensin coveting enzyme, and inhibits the conversion of angiotensin I to angiotensin II. It is used as a potent drug to treat Hypertensive issues. Absolute bioavailability of Ramipril is 28 - 35% and is poorly water soluble drug [6].

From studies, it was showed that total no. of people with diabetes was 171 million and it will rise to 366 million people by 2030. It is predicted that no. of adults with hypertension increased by 60% to a total of 1.56 million people by 2025. 70% of patients with diabetes affect with hypertension and it is almost twice in person as in those don't suffer with diabetes. Coexistence of both diseases varies across different ethnic and racial groups. Diabetes mellitus itself a risk factor for coronary artery disease, along with hypertension the risk is markedly increased [7].

Materials and Methods

Materials

Repaglinide was obtained as a gift sample from Wilshire Pharmaceuticals Ltd, Lahore, Pakistan and Ramipril was given by Standpharm Pharmaceuticals Ltd, Lahore, Pakistan for research purpose. Eudragit L100 was purchased from Obsons Pharmaceuticals Ltd, Lahore, Pakistan. HPMCK4M was received from Medipak Pharmaceuticals Ltd, Lahore, Pakistan. Oleic acid, polyethylene glycol400 and propylene glycol were obtained from Merck, Germany. All other ingredients used were of analytical grade.

Methods

Preparation of Ramipril and Repaglinide transdermal patches

Preparation of solutions

Preparation of Repaglinide and Ramipril Stock Solutions

For each patch, the required amounts of Repaglinide and Ramipril were 24.6 mg and 60 mg respectively. The stock solutions of both drugs were prepared separately. 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 strength of 15 mg/ml were prepared by mixing 750 mg of both Propylene glycol and Oleic acid in 50 ml of methanol separately. For this purpose, 750 mg of Oleic acid and Propylene glycol were weighed separately in 100 ml beaker and then 50 ml of Methanol was poured in both beakers. The beakers were properly sealed with Aluminium 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 Eudragit L100

Solvent casting technique was used for the preparation of transdermal patches. HPMC K4M was used in concentration of 9:1, 8:2, 7:3, 6:4, 5:5 and 4:6 with Eudragit L100. Accurate quantity of HPMC K4M was weighed and dissolved in 20 ml of Methanol and Chloroform 1:1 solution in 50 ml of beaker. For proper mixing, this solution was placed on hot plate magnetic stirrer for 30minutes. The stirrer was stirred at 300rpm at 30^0C. After mixing of HPMC K4M, accurate quantity of Eudragit L100 was added to the HPMC K4M solution and again allowed to stir for 30 minutes. After that the plasticizer, Polyethylene glycol 30%w/w of polymer was added to the polymeric solution. 1 ml solution from each Oleic acid and Propylene glycol stock solution was withdrawn and added to the polymeric solution. In final step,1 ml from each Repaglinide and Ramipril stock solutions was added to the polymeric solution. This solution was again mixed for 30 minutes, and beaker was removed from the magnetic stirrer. To remove any air bubble present in the solution the beaker was placed in sonicator at 37^0C 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 hours, 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 use.

Formulation	HPMCK4M (mg)	EL100 (mg)	Repaglinide (mg)	Ramipril (mg)	PEG400 w/w of polymer
HE1	450	50	24.6	60	30%
HE2	400	100	24.6	60	30%
HE3	350	150	24.6	60	30%
HE4	300	200	24.6	60	30%
HE5	250	250	24.6	60	30%
HE6	200	300	24.6	60	30%

Table 1: *Composition of transdermal patches of Repaglinide and Ramipril.*

- *Oleic acid and propylene glycol used 30%w/w of polymers*

Pre-formulation Studies

Drug-Drug and Drug-Polymer Compatibility Study

To check the drug-drug and drug-polymer compatibility FTIR was used. This study was performed on the Agilent technologies FTIR instrument. Scanning was done in the range of 650-4000cm-1. All the samples were run on the instrument and transmittance was taken of individual ingredient and of combinations to check the compatibility.

Surface Morphology

Light Microscopy

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

Scanning Electron Microscopy (SEM)

SEM was performed for both Repaglinide, Ramipril and also for the prepared patches. This was performed to assess the morphology of drugs and surface texture of prepared patches [8]. SEM photographs were taken from the Quanta scanning electron microscope at 500X, 1000X and 2000X.

X-Ray Diffraction (XRD)

X-Ray diffraction studies were performed for the drugs and the prepared patches. PHILIPS1710 XRD machine was used for this purpose. 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 [9]

Physicochemical Evaluation of transdermal patches

Organoleptic Examination

Color, flexibility, smoothness and transparency were observed in the organoleptic examination of transdermal patches [10]. Uniformity of patches, surface touch and strength during peeling were some other parameters which are also studied.

Thickness

Thickness of the prepared patches were evaluated by using a digital micrometer at 3 different points of the patch [11].

Folding Endurance

Folding endurance was determined by folding of a patch repeatedly at the same point until it broke. The number of times it took to break gave the value of folding endurance [12].

Weight uniformity

The prepared patches were dried at 60°C for 4 hours before testing. Patch was cut into 4 pieces with same dimensions from different parts and weighed on a digital balance. Individual weight and average weight of the patch was calculated to determine the weight uniformity [13].

Flatness

Measured length of strips was cut from prepared patches, and after some time the length of patches was again measured to check the non-uniformity in flatness. Constriction in the patch showed non-uniformity, if there was 0% constriction then it was considered to be 100% flatness [14].

pH determination

For the determination of pH, the patches are kept in distilled water for 1hour in a glass tube. Surface pH was noted by bringing the pH meter electrode near to the surface of patch and kept there for 1minute to equilibrate the reading [15].

Percentage moisture loss

The patches were weighed accurately and kept in a desiccators containing anhydrous Calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula [16].

% moisture loss= [Final weight- Initial weight/Initial Weight]×100

Drug content

Transdermal patch was cut into strips of 1 x 1 cm^2 area and dissolved into a measured volume of Methanolic phosphate buffer pH of 7.4. Then the solution was filtered through a filter medium and analyzes the drug contents with the suitable method [17]. For this purpose, the patch was dissolved into a 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 nm and 240 nm respectively.

Drug Permeation Studies

***In-Vitro* Drug Permeation**

In-Vitro drug release study was performed by 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 the 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 it with the help of magnet and hot plate magnetic stirrer for 30 min. This procedure was helpful in charging the membrane and the Franz cell and also to maintain the temperature at 37 ± 0.5^0C. After that the patch was placed over the synthetic membrane. Head and the receptor compartment were properly screwed with the help of a clipper. The solution of the receptor compartment was stirred at 250 rpm. 1 ml of sample was taken after 30minutes and after 1,2,3,4,5,6,7 and 8 hours from the starting time. Volume was making 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 - 250g was used to determine the *ex-vivo* release of drug. The rats were anaesthetized by using Chloroform and then the neck was dislocated as per guidelines approved by animal ethical committee. Hairs from the abdominal area were removed by using a sharp razor with the caution of damaging the skin by razor cut. Subcutaneous fat was removed with the help of sharp blade and Isopropyl alcohol swabs. After that the skin was washed with 0.9% NaCl solution and stored in this solution at 0 - 4^0C 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.

Results

FTIR of Repaglinide

FTIR spectra of Repaglinide showed peaks at 1090.2, 1209.5, 1181.6, 700.7 and 754.8cm^{-1}. First three peaks were due to the stretching of C-O and C-N. C-O confirmed that alcohols and esters were present and C-N confirmed the presence of aliphatic amines in the HPMC structure. The other two peaks present at 700.7 and 754.8cm^{-1} were due to the N-H wag and C-Hoop groups. N-H wag confirmed the presence of amines while the C-Hoop confirmed the presence of aromatics in the structure.

The peak at 1742.5cm^{-1} from the FTIR of Ramipril showed C=O stretch which confirmed the presence of Carboxylic acid group in the structure of Ramipril. The other peaks were observed at 1549.3 and 1183.4, from these the peak at 1549.3cm^{-1} was due to the N-H bend which is a sign of presence of amines in the structure. Peak at 1183.4cm^{-1} confirmed the presence of aromatic amines because of the stretching of C-N.

HPMC K4M showed three main peaks in the FTIR spectra. The peak at 941.2 was due to O-H bend and =C-H bend which confirmed the presence of alkenes and carboxylic acids groups in the HPMC structure. The peaks at 1045.5 and 1097.7cm^{-1} were due to the C-O stretch confirming the presence of alcohols and carboxylic acid groups.

FTIR spectra of Eudragit L100 showed two main peaks, one of them was at 1679.8cm^{-1} and the other at 1155.5 cm^{-1}. Peak at 1679.8 cm-1 was confirming the presence of carboxylic acid group while the peak at 1155.5 cm^{-1} was due to the C-O stretch

Ramipril and Repaglinide were properly mixed to determine the FTIR peaks of both drugs. The peaks of Ramipril were at 1742.5, 1549.3 and 1183.4 cm^{-1} and peaks of Repaglinide were at 754.8 and 700.7 cm^{-1} as the peaks observed in Ramipril and Repaglinide alone. There was not a little change observed in these peaks which showed that there is no interaction between the groups present in both drugs. So, this combination is considered to be suitable for dosage form development.

In case of Eudragit L100 the peak was observed at 1155.5 cm^{-1} and in case of HPMC it was present at 1097.7 cm^{-1} which showed the C-N stretch. When the peak of HPMC+EL100 combination was observed it was present at 1172.2 cm^{-1}. There was a small change observed in the peak, but the value lies between the ranges.

The FTIR peaks using combination of Ramipril, HPMC K4M and EL100 demonstrated that there was no change in the peak of Ramipril. The peak of Ramipril alone was at 1183.4 cm^{-1} and in combination it was also observed at the same position. There was a little bit change in the peaks of HPMC K4M and EL100, when compared with original ones. The peaks of HPMC K4M and EL100 were at 1045.5 and 1115.5 cm^{-1} and in combination these were observed at 1062.3 and 1153.6 cm^{-1} respectively. This showed that the values remain within limits and no interaction was found.

Repaglinide showed a little change in peak when it was used in combination with HPMC and EL100. The peak was at 1099.6 cm-1 while it was observed at 1090.2 cm^{-1} when taking alone, but the values remains within range. The peaks of HPMC and EL100 in combination also showed some deviation when compared within the peaks of HPMC and EL100 alone. The peaks of HPMC and EL100 were observed at 1067.9 and 1153.6 cm^{-1} respectively when using in combination but they were at 1045.5 and 1155.5 cm^{-1} when using alone. There was no interaction found in this combination because all the values lie within range.

The peaks of FTIR showed no interaction between the combinations of both drugs along with HPMC K4M and EudragitL100. The value observed were 1183.4 cm^{-1}, 700.7 cm^{-1} for Ramipril and Repaglinide respectively. For HPMC K4M and EudragiL100 the values were 1045.5 and 1155.5 cm^{-1} which were same when the values observed alone.

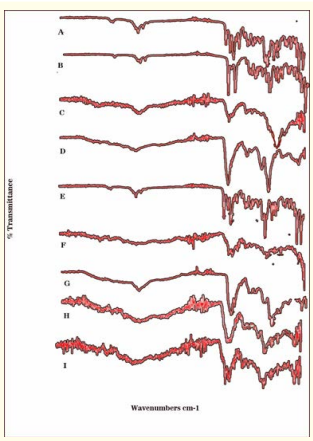

Figure 1: *FTIR spectra of Repaglinide (A), Ramipril (B), HPMCK4M (C), Eudragit L100 (D), Repaglinide + Ramipril (E), PMC K4M+EL100 (F), Ramipril +HPMC K4M +EL100 (G), Repaglinide + HPMC K4M + EL100 (H), Ramipril + Repaglinide + HPMCK4M+ EL100 (I).*

Surface Morphology

Optical microscopic studied were conducted and images were taken at 40X, as illustrated in figure 2, a uniform and complete blending of drug and excipients, surfaces of formulations HL3 (Figure 2C) and HL5 (Figure 2E) were seemed more smooth as compared to other formulations (Figure 2).

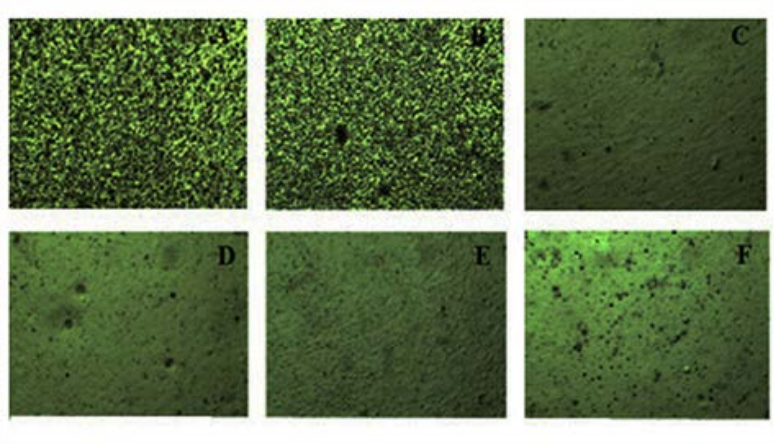

Figure 2: *Illustration of Optical Microscopic studies depicting the surface morphology of variable concentration based polymeric patches; A, HL1, B, HL2, C, HL3, D, HL4, E, HL5, F, HL6.*

Surface morphology at micro level [18] was observed by using scanning electron microscope at 2000X for both drugs and selected formulation HL4. Illustrations in figure 3A and 3B were the evident of crystalline structure of Ramipril and Repaglinide [19] which were diminished when they were formulated in patch formulation (Figure 3C). The claim of conversion of crystalline drugs into an amorphous form was strengthen by the x-ray difractograms (Figure 4C).

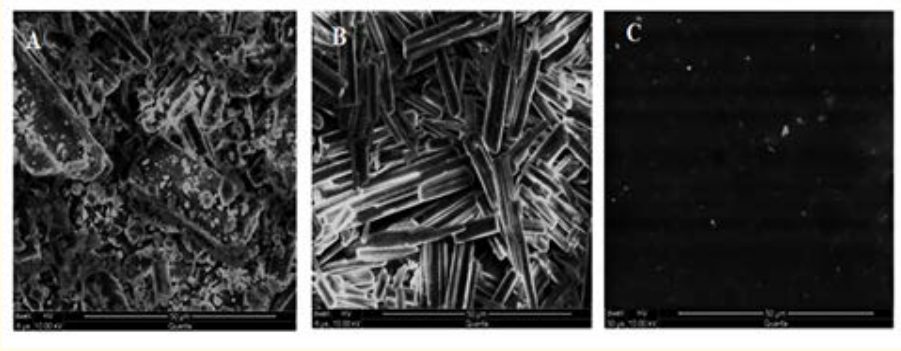

Figure 3: *SEM of Ramipril at 2000X (A), SEM of Repaglinide at 2000X (B) and SEM of HL4 at 2000X (C).*

X-ray Difractometry

X-Ray diffraction studies were performed for drugs and selected formulations. The presence of numerous distinct peaks in the XRD spectrum of the selected powdered Repaglinide (Figure 4A and B) showed that drug was present as crystalline form with major diffraction peaks appearing at at diffraction angles [20]. The powder X-Ray diffractogram of pure Ramipril showed numerous distinctive peaks that indicated a high crystallinity [21]. Crystalline nature of both drugs was also confirmed by Scanning Electron Microscopy figure 3A

and 3B. The selected formulation was also subjected to x-ray diffractometric analysis revealing that there was no sharp peak appeared in the difractogram, Figure 4C was the evident of that drugs and excipients were mixed thoroughly which may be the cause of decreased in crystallinity of the drugs [22].

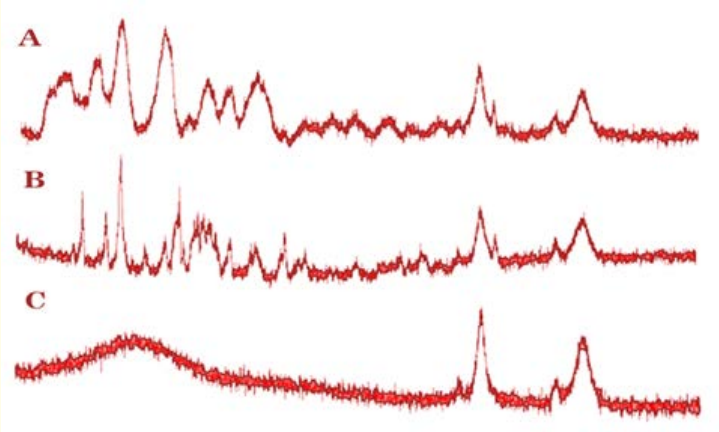

Figure 4: *X-Ray Diffraction of, Ramipril (A), Repaglinide (B) and selected formulation HL4 (C).*

Physicochemical characterizations of the prepared patches

Transdermal patches of Repaglinide and Ramipril were prepared followed by organoleptic evaluation and it was witnessed that patches were yellowish to colorless in the appearance with excellent uniformity in the texture showing good smoothness in touch. Flexibility of the patches admirable and they were transparent showing excellent strength on peeling (Table 2).

Formulation	Color	Uniformity	Surface touch	Smoothness	Flexibility	Transparency	Strength during peeling
HL1	Yellowish	Excellent	Smooth	Good	Very flexible	Transparent	Excellent
HL2	Yellowish	Excellent	Smooth	Good	Very flexible	Transparent	Excellent
HL3	Yellowish	Excellent	Smooth	Good	Flexible	Transparent	Excellent
HL4	Colorless	Excellent	Smooth	Good	Flexible	Transparent	Excellent
HL5	Colorless	Excellent	Smooth	Good	Very flexible	Transparent	Excellent
HL6	Colorless	Excellent	Smooth	Good	Very flexible	Transparent	Excellent

Table 2: *Organoleptic Evaluation of prepared patches.*

% moisture loss was calculated in it was concluded that the formulation having greater concentrations of HPMC showed greater moisture contents and vice versa. It may be due to the fact that as Eudragit L-100 is water insoluble, it has retained less moisture contents. Thickness of the patches was also observed and it was found that the patches were of uniform thickness with minor variation (± 0.007 to ± 0.014). Patches showed unanimously good mechanical strength with folding endurance > 300. Patches were of also uniform weight with negligible variation ranging from ± 0.0032 to ± 0.022 and 100% flatness. When patches were subjected to surface PH analysis, it was noticed that the ph of the patches has been fallen in the range of 6.18 ± 0.012 to 6.37 ± 0.008. When the patches were analyzed for drug contents, the analysis demonstrated that the selected formulations were quite capable of loading satisfactory amount of the drugs (95.99 ± 2.54 to 104.59 ± 2.91) suggesting their excellent drug loading capacity (Table 3).

Formulation	% moisture loss	Thickness (mm)	Folding endurance	Weight Variation (mg)	Flatness (%)	pH	Content Uniformity	
							% content Repaglinide	% content Ramipril
HL1	9.96	0.236 ± 0.013	>300	0.125 ± 0.0087	100	6.37 ± 0.008	103.00 ± 1.87	98.14 ± 1.30
HL2	8.57	0.272 ± 0.014	>300	0.112 ± 0.0170	100	6.31 ± 0.016	97.58 ± 0.72	99.24 ± 2.78
HL3	8.51	0.228 ± 0.013	>300	0.113 ± 0.0032	100	6.18 ± 0.012	102.42 ± 2.29	97.09 ± 1.70
HL4	5.55	0.258 ± 0.007	>300	0.120 ± 0.0135	100	6.34 ± 0.012	104.59 ± 2.91	98.23 ± 1.40
HL5	4.81	0.193 ± 0.010	>300	0.131 ± 0.0220	100	6.19 ± 0.012	95.99 ± 2.54	98.70 ± 2.83
HL6	4.29	0.241 ± 0.011	>300	0.126 ± 0.0101	100	6.23 ± 0.008	96.83 ± 3.03	99.82 ± 1.49

Table 3: *Evaluation studies of transdermal patches containing Reapglinide and Ramipril.*

In-vitro and *Ex-vivo* permeation studies

In-vitro and *ex-vivo* drug permeations are important parameters and assist in predicting the *in-vivo* behavior of the drug. Prepared patches were subjected to these important evaluation parameters.

In-vitro permeation showed that in initial 1h, maximum amount of Repaglinide and Ramipril was released by HL3 (13.90 and 19.57% respectively) however the maximum amount of Repaglinide which was 114.53% and of Ramipril which was 97.76% has been released by HL1 in studied duration of 8h.

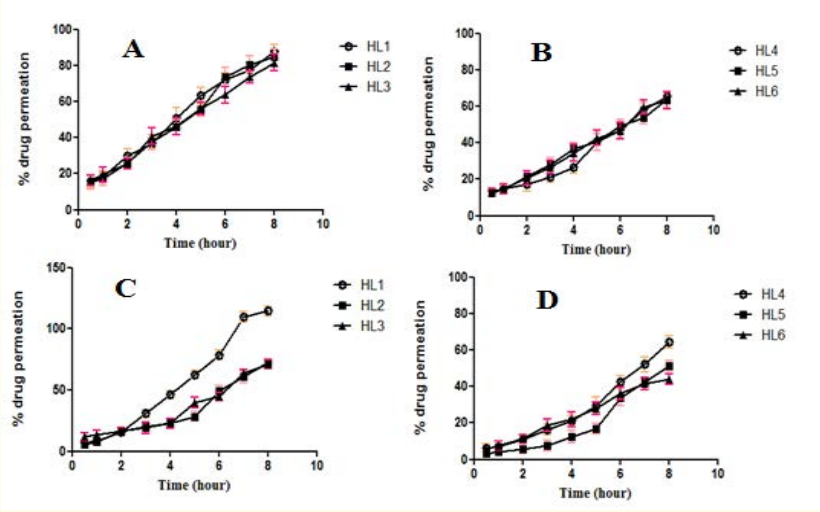

Figure 5: In-vitro drug permeation studies showing drug permeation of Ramipril (A and B) and Repaglinide (C and D).

Ex-vivo permeation studies showed that HL1 composed of 450 mg of HPMC and 50 mg of Eudragit L-100, released about 20% of both drugs, HL2 released 10% of Repaglinide and 24% of Ramipril, similarly a trend of decreased in drug release was observed with increased in Eudragit L-100 suggesting its greater drug retarding ability as compared to HPMC K 4M. Maximum amount of the Repaglinide (98.27%) that was permeated in 8 h was from HL1 and the maximum amount of Ramipril (91.96%) was permeated from HL2. HL6 and HL5 released the least amounts of Repaglinide (48.50%) and Ramipril (52.77%) respectively (Figure 6).

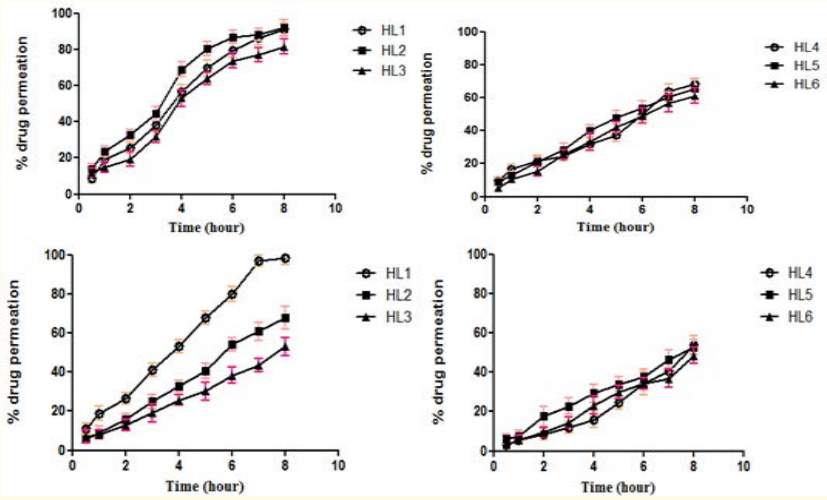

Figure 6: *Ex-vivo drug permeation studies showing permeation of Ramipril (A and B)and Repaglinide (C and D).*

Kinetic modeling of permeated data

Data of both drugs gathered through *in-vitro* and *ex-vivo* permeation studies was further assessed by the application of various kinetic models which have been applied to predict the mechanism and pattern of drug released [23-25]. Data of Ramipril obtained from *in-vitro* analysis was subjected to kinetics models and it has been found the goodness of fit favored the Korsmeyer peppas model in all 6 formulations, suggesting uniformity in drug permeation. Formulations other than HL2 showed values of co-efficient of correlation greater than 0.9, signifying the dominancy of diffusion pattern of drug release. However, values of 'n' was the evidence of non-fickian type of drug diffusion in HL1, HL3, HL4, HL5 and HL6 (n < 0.50), while HL2 released the drug following super case II transport as the value of 'n' was greater than 0.89. Hixson Crowell Model is an important predictor of even or uneven exhaustion of drug reservoir. Greater values of coefficient of correlation (0.9552 to 0.9780) for this model proposed the uniform degradation of patches (Table 4).

Formulations	Zero order	Ko	First order	Higuchi model	Korsmeyer-peppas model	Value of n	Hixon- Crowell model	Best fit model
				Ramipril				
HL1	0.8437	0.195	0.9590	0.9012	0.9760	0.773	0.9613	Korsmeyer-peppas
HL2	0.9388	0.191	0.9043	0.8136	0.9400	0.945	0.9196	Korsmeyer-peppas
HL3	0.9263	0.171	0.9665	0.9301	0.9858	0.717	0.9680	Korsmeyer-peppas
HL4	0.9223	0.134	0.9596	0.9248	0.9801	0.718	0.9552	Korsmeyer-peppas
HL5	0.9497	0.137	0.9628	0.9170	0.9891	0.759	0.9780	Korsmeyer-peppas
HL6	0.9619	0.138	0.9461	0.8893	0.9817	0.817	0.9665	Korsmeyer-peppas
				Repaglinide				
HL1	0.9862	0.096	0.9832	0.8565	0.9890	0.924	0.9869	Korsmeyer-peppas
HL2	0.8550	0.089	0.7992	0.5962	0.9785	1.943	0.8175	Korsmeyer-peppas
HL3	0.9268	0.139	0.8522	0.7062	0.9612	1.403	0.8773	Korsmeyer-peppas
HL4	0.9453	0.118	0.8815	0.7159	0.9825	1.140	0.9033	Korsmeyer-peppas
HL5	0.9565	0.228	0.7821	0.7224	0.9889	1.359	0.8355	Korsmeyer-peppas
HL6	0.9200	0.137	0.8512	0.7349	0.9309	1.203	0.8754	Korsmeyer-peppas

Table 4: *Kinetic modeling of in-vitro permeation data of Ramipril and Repaglinide.*

For Repaglinide same pattern and mechanism of drug permeation was observed as all the formulations have been following Korsmeyer peppas model. Higher values of R2 for zero order kinetics were suggesting good sustained effect of the polymers with the ability to release the drugs in controlled manner. Hixson Crowell models was followed by HL1 and HL4, indicating uniform degradation of these patches during 8h of the studies. Values of 'n' were higher than 1 indicating super case II transport of the drug from the formulations.

Data gathered from *ex-vivo* analysis conducted for 8h was also analyzed for mechanism and pattern of the drug permeation across the rat skins. Best fit model for Ramipril was Korsmeyer peppas model with the exception of HL3 which has followed Hixson Crowell Model, although the R2 values for Korsmeyer peppas model were greater than 0.9 but lesser than that of Hixson Crowell model. All the formulation showed controlled permeation of the drug with their independence over initial concentrations of the drug in the reservoir, as they showed R2 values greater than 1st order kinetics. Values of 'n' were the indication of non-fickian type of drug diffusion from HL1, HL3, HL5 and HL6 while from HL2 and HL4 the diffusion was super case II type. In case of Repaglinide, the best fit model was Korsmeyer peppas models for all the studied formulations. Permeation of the drug was found independent from the initial concentration from all the formulations except HL3 as the values of R2 for zero order kinetics were better than the values of correlation coefficient of 1st order kinetics. Permeation mechanism of drug from HL1, HL3, HL4 and HL6 was super case II as the values of 'n' for Korsmeyer peppas model were greater than 0.9. While other 2 formulations were following non-fickian type of drug permeation (Table 5).

Formulations	Zero order	Ko	First order	Higuchi model	Korsmeyer-peppas model	Value of n	Hixon- Crowell model	Best fit model
Ramipril								
HL1	0.9525	0.210	0.9438	0.8594	0.9653	0.850	0.9643	Korsmeyer-peppas
HL2	0.9495	0.227	0.9208	0.8387	0.9537	0.903	0.9348	Korsmeyer-peppas
HL3	0.8764	0.189	0.9570	0.9182	0.9618	0.681	0.9755	Hixson- crowell
HL4	0.9921	0.142	0.9855	0.8650	0.9959	0.913	0.9937	Korsmeyer-peppas
HL5	0.9675	0.148	0.9497	0.8839	0.9844	0.831	0.9770	Korsmeyer-peppas
HL6	0.9655	0.134	0.9925	0.9119	0.9954	0.786	0.9937	Korsmeyer-peppas
Repaglinide								
HL1	0.9329	0.095	0.8826	0.6938	0.9847	1.512	0.8997	Korsmeyer-peppas
HL2	0.9772	0.112	0.9885	0.8926	0.9929	0.834	0.9888	Korsmeyer-peppas
HL3	0.9051	0.142	0.9587	0.8255	0.9955	1.029	0.9757	Korsmeyer-peppas
HL4	0.9865	0.107	0.9692	0.8407	0.9868	0.972	0.9775	Korsmeyer-peppas
HL5	0.9847	0.220	0.9147	0.8671	0.9903	0.896	0.9528	Korsmeyer-peppas
HL6	0.9843	0.095	0.9646	0.8035	0.9863	1.074	0.9729	Korsmeyer-peppas

Table 5: *Kinetic modeling of ex-vivo permeation data of Ramipril and Repaglinide.*

Discussion

Drug-drug and drug-excipients compatibility studies were conducted using a reliable method known as FTIR. Individual as well as blend and prepared formulations have preserved their characteristic peaks indicating chemical stability and chemical compatibility of the selected ingredients. XRD was used to observe the crystallinity or amorphous nature of Ramipril and Repaglinide and their transition into an amorphous substances while formulating in patch formulation. Both drugs were found crystalline in nature [26,27] and their crystallinity was masked due to entrapment of these drugs in to polymeric mash which may have been the clue of excellent drug loading abilities of the selected polymers [28]. Surface morphology of the patches advocating their reasonable smoothness and crystallinity of the drugs (Figure 3). Physicochemical evaluations were resulted in a suitable patch formulation as the results of studied parameters were quite satisfactory. Patches showed negligible variation in their weights and thickness having surface Ph in the range of 6 to 6.5. Prepared

patches were transparent with %100 flatness and satisfactory mechanical strength with > 300 folding endurance. Uniformity in the thickness and weight has great link with uniformity in the drug contents and it may be the reason that formulations showed drug contents (95 - 105%) in the Pharmacopoeia limits [29]. Preservation of suitable moisture contents are necessary to maintain reasonable flexibility in the patches and in the current study it was observed that prepared formulations have restored a satisfactory level of the moistures. Moisture may be retained in the patches due to the presence of plasticizer i.e. Polyethylene glycol as well as because of hydrophilic nature of the HPMC. This claim was further strengthen by the fact that formulations with comparatively greater HPMC concentrations have retained more moisture contents.

In vitro and *ex vivo* permeation studies were conducted using Franz Diffusion Cell and a common trend was observed that was evident from the literature that sustained effect was directly linked with polymeric contents [30]. Although HPMC is considered as one of the better drug retarding polymer but due to Ph dependent solubility and its hydrophobic nature the Eudragit L-100 showed dominating effect over drug release from the patches. Patches were prepared with the aid of Oleic acid and Propylene glycol used as permeation enhancer and they have played their role effectively as in 8 h of the study duration up-to 100% drug was permeated across the synthetic membrane and more than 90% across the rat abdominal skin.

Kinetic modeling of released and permeated data suggested that the dominating model was Korsmeyer peppas followed by diffusion as a dominant pattern of drug permeation.

Conclusion

Current study was design with the prime objective of developing a transdermal drug delivery systems i.e. transdermal patches to enhance the bioavailability of Repaglinide and Ramipril. The project was succeeded as about %100 of the drug permeation was achieved in 8h. Suitable and compatible combination of the ingredients was selected which have been converted into the patches of smooth and uniform surface with good mechanical strength and durability. Prepared patches have shown reliable ability of the drug loading and desirable extent of moisture retention. Conclusively, the transdermal drug delivery systems for the controlled and sustained delivery of Ramipril and Repaglinide were prepared successfully.

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Conflict of interest

All authors have nothing to disclose.
Certification from R and D department.

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Volume 4 Issue 1 July 2017