International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.9, No.9, pp 200-207, 2016

To study the effect of iontophoresis on transdermal patch of Diltiazem HCl

Garala Jasmin[1]*, Dr. H. M. Tank[2]

[1] School of Pharmacy, RK University, Rajkot, Gujarat, India
[2] V. B. Manavar College of Pharmacy, Dumiyani, Rajkot, Gujarat, India

Abstract : Purpose: The objective of this study was to evaluate the effect of iontophoresis on transdermal patch of Diltiazem HCl prepared using different types of polymers.
Method: Transdermal patch of Diltiazem HCl was prepared by using different types of matrix forming polymers like Hypromellose K15M (5%), Eudragit RLPO (5%), Eudragit RSPO (5%), Ethyl cellulose (2%) and combination of Ethyl cellulose(1%)+Polyvinyl pyrrolidone K90 (0.5%) by solvent casting method. Polyethylene glycol or glycerin were used as a plasticizer. All prepared formulations were evaluated for its physico-chemical parameters like Appearance, Thickness, Weigh uniformity, Assay, Folding endurance, Percentage moisture absorbance, Loss on drying, Water vapor transmission per unit area and Water vapor transmission per unit area. Iontophoretic *in vitro* diffusion of Diltiazem HCl from prepared patches was studied using three chamber modified diffusion cell. Silver- silver chloride electrode was used for Iontophoretic study and a constant current of 0.3 mA/cm^2 for 6 hours was applied. Passive diffusion of drug was determined without application of electric current. Enhancement ratio was calculated to determine the effect of iontophoresis.
Results: Enhancement ratio 2.07 and 1.69 was observed with a patch prepared using ethyl cellulose and a combination of ethyl cellulose and polyvinyl pyrrolidone, respectively. Very less enhancement ratio was observed with Acrylate polymer.
Conclusion: The result indicates feasibility of iontophoresis to enhance transdermal drug delivery of Diltiazem HCl using cellulose polymers.
Key words: Iontophoresis, Diltiazem HCl, Transdermal patch, Invitro diffusion.

Introduction:

Transdermal delivery of drug (TDDS) is quiet popular method now a day for its easy application[1,2]. However, the rate limiting step for TDDS is permeation of therapeutic agent through intact skin. Various approaches are developed to increase the permeability of drug through skin. One of the novel mechanical approach to enhance delivery of drug through skin is iontophoresis[3]. It is non invasive technique, in which direct electric current is applied to increase diffusion of drug through skin[4,5]. Transdermal iontophoresis have merit over oral therapy as it bypass hepatic metabolism, easy discontinuation of therapy, less dose require, better control of drug therapy and better patient compliance[6,7].

Diltiazem, a calcium channel blocker, is used in the treatment of hypertension, angina pectoris and some types of arrhythmias. Hypertension is chronic disease, which requires prolong treatment with therapeutic agents. Diltiazem HCl is widely used for the treatment of hypertension[7]. Though Diltiazem is well absorbed from gastrointestinal tract, it under go first pass hepatic metabolism. This leads to significant difference between theoretical and practical bioavailability of drug. The elimination half-life of Diltiazem is 3-4.5 hours. Due to its shorter half life multiple oral administrations are required for the treatment. This makes Diltiazem a suitable candidate for administration by Iontophoretic transdermal formulation[8-12].

The purpose of present investigation was to provide the better delivery of the drug through skin at a controlled rate with the help of iontophoresis principle. Transdermal patches of Diltiazem HCl were formulated using various matrix forming polymers. The iontophoretic transdermal patches were evaluated for various physico-chemical parameters and *in-vitro* drug release. Passive and iontophoretic drug release was studied to evaluate effect of iontophoresis.

Materials and methods:

Materials

Active pharmaceutical ingredient (Diltiazem HCl) was obtained as a gift sample from Astra lifecare (India) Pvt. Ltd. All other chemicals/ingredients were analytical grade and were purchased commercially. Porcine skin of ear was obtained from local slaughter house.

Determination of λmax

A solution of Diltiazem HCl was prepared in phosphate buffer pH 7.4. Solution of Diltiazem HCl in phosphate buffer (5.0µg/ml) was scanned between 200 to 400 nm in UV/VIS spectrophotometer and λmax was determined.

Preparation of calibration curve

Calibration curve was prepared by measuring the absorbance of the solution in the range of 4-20 µg/ml at a wavelength of 237 nm, using phosphate buffer pH 7.4 as a blank solution.

Fabrication of transdermal patches[13-15]

As Diltiazem HCl is soluble in water, patch was prepared by solvent casting method using different type of sustained release polymers like

1. Hypromellose K15M – Hydrophilic cellulose polymer,

2. Eudragit RLPO – Acrylate polymer

3.Eudragit RSPO – Acryate polymer

4 Ethyl cellulose – Hydrophobic cellulose polymer

5. Combination of Ethyl cellulose (EC) and Polyvinyl pyrrolidone (PVP) K90 - Mixture of Hydrophobic and Hydrophilic polymer.

Polyethylene glycol and glycerin was used as plasticizers. Formulation of different patches was given in **table-1**. 2% drug solution was prepared in suitable solvent and poured in petridish in such a way that each patch contains 20 mg Diltiazem HCl per cm^2. Solvent was allowed to evaporate by keeping petridish in hot air oven at 50°C. After drying patches was wrapped in aluminum foil and stored in desiccator at room temperature[11].

Table 1: Formulation composition of transdermal patches using Diltiazem HCl

Formulation of Transdermal patches				
Code	**Drug**	**Polymer**	**Plasticizer**	**Solvent**
FDH	Diltiazem HCl (2.0 %)	Hypromellose K15M (5%)	Mecrogol 400 (1%)	Water + Methanol (10:90)
FDRL	Diltiazem HCl (2.0 %)	Eudragit RLPO (5%)	Mecrogol 400 (1%)	Water:Acetone:IPA (5:40:55)
FDRS	Diltiazem HCl (2.0 %)	Eudragit RSPO (5%)	Mecrogol 400 (1%)	Water:Acetone:IPA (5:40:55)
FDE	Diltiazem HCl (2.0 %)	Ethyl cellulose (EC) (2%)	Glycerine (2%)	Water + Methanol (10:90)
FDEP	Diltiazem HCl (2.0 %)	EC (1%) +PVP K90 (0.5%)	Mecrogol 400 (1%)	Water:Acetone:IPA (5:40:55)

Physicochemical evaluation of patch[16-20]

A. Appearance: All prepared patches were evaluated for Appearance, presence of any visual agglomerates of drug or polymer and entrapment of small air bubble in the patch.

B. Thickness: Thickness of the patch was measured using vernier calipers at three different locations for each patch and reported as a mean value with standard deviation.

C. Weigh uniformity: A patch of 1 cm^2 was cut uniformly and weighed individually same process was repeated for three different patches of each formulation and mean value were reported as weight uniformity with standard deviation.

D. **Assay**: Drug content of the patch was measured by adding a patch of 1 cm^2 in a beaker containing 100 ml of phosphate buffer pH 7.4 and stirred for 6 h. After 6 h solution was filtered using filter paper and amount of drug present in solution was determined using UV visible spectrophotometer with proper dilutions.

E. Folding endurance: A patch of approx. 2 cm^2 was cut and folded at the same place until it breaks. Number of times the patch folded to break the patch, were determined as a folding endurance value.

F. Percentage moisture absorbance: A physical ability of a patch to absorb moisture in high humid condition is determined by moisture absorbance test. A piece of patch was placed in a desiccator containing saturated solution of potassium chloride for 48 hours. Percentage moisture absorbance was determined using following formula.

% Moisture absorbance= (Final weight -Initial weight)/ Initial weight x 100

G. Loss on drying: A physical ability of a patch to loss moisture at high temperature is determined by percentage moisture absorbance test. A piece of patch was placed in a hot air oven for 2 hours at 60°C. Loss on drying was determined using following formula

% Loss on drying= (Initial weight –Final weight)/ Initial weight x 100

H. Water vapor transmission per unit area: A mouth of glass vial containing 1 gram of fused calcium chloride was covered with prepared patch with the help of adhesive tape. Glass vial was placed in a desiccator containing saturated solution of potassium chloride for 48 hours. Percentage weight gain by calcium carbonate was expressed as a water vapor transmission per unit area. It was determined using following formula

Water vapor transmission per unit area

= (Final weight – Initial weight)/ Area of glass vial mouth opening

I. Tensile strength: Test Patch of 4 cm x 1 cm was cut and fitted in two clips from both sides. One clip was fixed on a horizontal table and other clip was movable. A weight holder was fitted to the moving clip with the help of a metal wire in such a way that it would remain in hanging position. Weight in the weight holder was gradually increased until a patch breaks. The tensile strength was calculated using the following formula.

Tensile strength = (weight in kg x gravitational force) / cross sectional area of the patch

Skin preparation

Porcine skin was carefully removed from outer side of the ear with the help of scalpel. Other unwanted tissue attached to the skin was removed by using scalpel. Fat adhering to the skin was removed by washing the skin in water and / or alcohol. Before using the skin was hydrated in phosphate buffer pH 7.4 for 30 min.

Preparation of silver/silver chloride electrode

Pure silver circular plate was obtained from gold smith, was used as silver electrode. Silver chloride electrode was prepared by dipping silver plate in 0.1N HCl solution and a direct current of 1mA was applied for 6 h by using pure silver rod as a cathode.

Invitro permeation study[21-23]

In-vitro permeation of Diltiazem HCl from various formulations was determined using a tailor-made three chamber diffusion cell Figure-1. The dissuasion cell consists of three chambers, donor chamber containing drug formulation, receptor chamber containing buffer solution and reference chamber containing patch without drug. Porcine skin was sandwiched between slides as shown in figure 1. Prepared Diltiazim HCl patch was placed on porcine skin in donor chamber and silver electrode was placed above the patch. Similarly patch without drug was placed in reference chamber. Receptor chamber was filled with Phosphate buffer pH 7.4 and its temperature was maintained 37°C by placing it in a circulating water bath. DC current of 0.3mA/cm^2 was applied using DC current generator. 2ml sample was withdrawn from receptor chamber at every hour up to 6 h and analyzed for drug content by using UV visible spectrophotometer. Also Passive diffusion of the Diltiazem HCl from various patches was also determined without applying electric current.

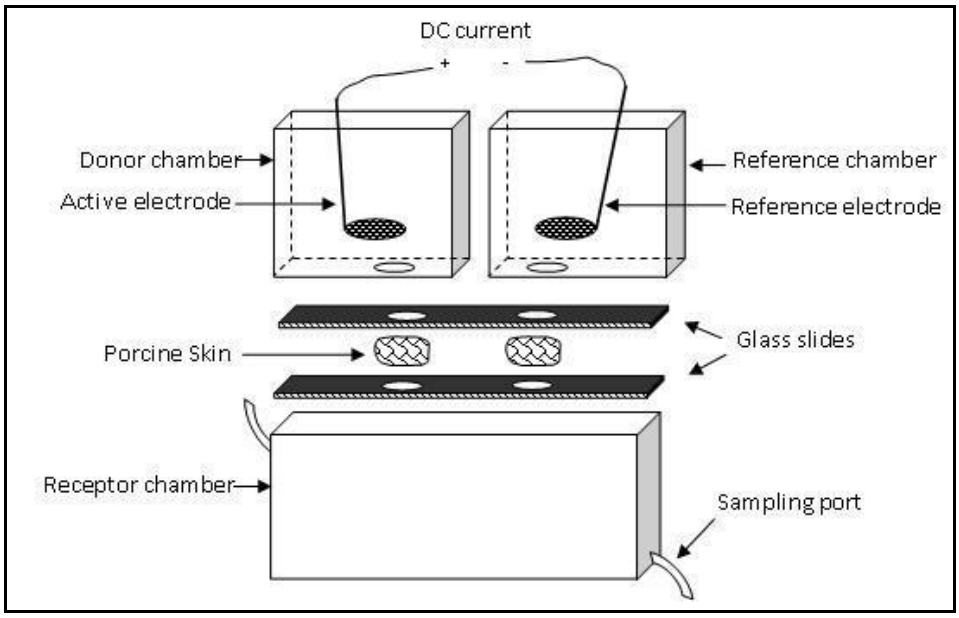

Figure-1 Three chamber diffusion cell for *in vitro* diffusion study.

3. Results and Discussions

The present investigation was performed to develop a patch of Diltiazem HCl for Iontophoretic delivery. Different patches of drug was prepared using controlled release polymers like Hypromellose, Eudragit RLPO, Eudragit PSPO, Ethyl cellulose and a mixture of ethyl cellulose and polyvinyl pyrrolidone by solvent casting method. Propylene glycol and glycerine was used as plasticizer. All prepared formulations were evaluated for its physico-chemical parameters like Appearance, Thickness, Weigh uniformity, Assay, Folding endurance, Percentage moisture absorbance, Loss on drying, Water vapor transmission per unit area, Water vapor transmission per unit area. The results of all these tests were found to be satisfactory, presented in Table-2 and Table-3.

Table 2: Physicochemical properties of Diltiazem HCl patches

Formula Code	Thickness (µm)	Weigh uniformity (mg)	Assay (%)	Folding endurance
FDH	273.67 ± 11.68	80.03 ± 4.50	96.92 ± 1.67	>300
FDRL	151.67 ± 26.39	83.50 ± 5.07	97.33 ± 4.14	237 ± 20
FDRS	131.00 ± 15.13	86.53 ± 3.30	101.84 ± 1.29	238 ± 31
FDE	96.33 ± 19.16	65.57 ± 1.90	97.11 ± 1.48	16 ± 9
FDEP	175.00 ± 7.00	53.20 ± 3.29	98.87 ± 0.39	172 ± 30

Table 3: Physicochemical properties of Diltiazem HCl patches

Formula Code	Percentage moisture absorbance (%)	Loss on drying (%)	Water vapor transmission (mg/cm^2)	Tensile strength (kg/cm^2)
FDH	82.67 ± 9.67	1.58 ± 0.54	85.44 ± 6.10	0.116 ± 0.007
FDRL	29.23 ± 6.99	0.81 ± 0.04	23.76 ± 3.79	0.123 ± 0.011
FDRS	17.23 ± 1.46	0.95 ± 0.09	48.07 ± 3.33	0.106 ± 0.010
FDE	2.73 ± 0.93	0.51 ± 0.08	12.68 ± 0.71	0.228 ± 0.018
FDEP	12.47 ± 0.70	1.38 ± 0.39	18.62 ± 2.79	0.145 ± 0.010

In vitro passive and Iontophoretic diffusion of drug was studied and results of the same was presented in table-4 and Table-5 respectively.

Table 4: *In vitro* passive diffusion of the Diltiazem HCl

Polymer used	Hypromellose	Eudragit RLPO	Eudragit RSPO	Ethyl cellulose	EC + PVP
Formula code	**FDH**	**FDRL**	**FDRS**	**FDE**	**FDEP**
Time (hr)	**Cumulative amount of drug release (µg/cm^2)**				
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	18.60 ± 0.49	18.02 ± 0.99	18.96 ± 2.60	18.40 ± 1.12	16.61 ± 1.90
2	20.25 ± 1.71	20.84 ± 2.68	23.15 ± 2.62	24.12 ± 3.86	17.47 ± 1.43
3	24.11 ± 1.18	22.23 ± 3.03	26.78 ± 1.27	26.51 ± 4.04	19.28 ± 1.07
4	24.70 ± 2.66	24.55 ± 1.85	42.63 ± 9.35	29.24 ± 6.08	26.13 ± 3.15
5	26.01 ± 2.10	32.23 ± 4.20	52.67 ± 6.03	30.13 ± 6.81	27.75 ±3.33
6	26.61 ± 2.17	36.03 ± 4.39	55.04 ± 5.78	32.69 ± 5.77	29.66 ± 5.35

Table 5: *In vitro* Iontophoretic diffusion of the Diltiazem HCl

Polymer used	Hypromellose	Eudragit RLPO	Eudragit RSPO	Ethyl cellulose	EC + PVP
Formula code	**FDHI**	**FDRLI**	**FDRSI**	**FDEI**	**FDEPI**
Time (hr)	**Cumulative amount of drug release (µg/cm2)**				
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	26.41 ± 4.28	21.41 ± 2.69	23.58 ± 2.52	35.28 ± 4.28	27.34 ± 4.29
2	34.70 ± 1.17	22.83 ± 2.80	26.73 ± 2.94	54.52 ± 2.12	28.98 ± 3.74
3	35.42 ± 3.45	23.71 ± 3.44	30.32 ± 2.03	57.30 ± 1.73	32.22 ± 4.35
4	38.00 ± 1.99	25.14 ± 3.41	48.10 ± 5.24	59.68 ± 3.25	43.01 ± 3.34
5	39.86 ± 2.42	39.03 ± 4.00	57.57 ± 2.66	62.52 ± 4.85	46.06 ± 4.38
6	42.19 ± 1.97	43.07 ± 4.41	60.72 ± 5.50	67.37 ± 7.87	50.39 ± 3.33

Steady state flux of the drug release was obtained by plotting cumulative amount of Diltiazem HCl release in receptor chamber verses time. Steady state flux was calculated by calculating Slop of the plot.

Steady state flux (Jss) = dQ/dt = slop of the plot.

Steady state flux for passive and Iontophoresis diffusion was determined for all parch formulation. Enhancement of drug release due to iontophoresis was expressed by enhancement ratio and was calculated by using following equation.

$$\text{Enhancement ratio} = \frac{\text{Iontophoretic Jss}}{\text{Passive Jss}}$$

Enhancement ratio of all prepared formulation was calculated and presented in table 6.

Table 6: Enhancement ratio of prepared formulations

Polymer used	Hypromellose	Eudragit RLPO	Eudragit RSPO	Ethyl cellulose	EC + PVP
Formula code	**FDH**	**FDRL**	**FDRS**	**FDE**	**FDEP**
Passive flux	3.54	5.01	9.00	4.52	4.28
Iontophoretic flux	5.60	5.96	9.70	9.35	7.24
Enhancement ratio	1.58	1.19	1.08	2.07	1.69

Discussion

As λmax for Diltiazem HCl was found to be 237nm, estimation of Diltiazem HCl was done using UV/VIS spectophotometer at a wavelength of 237 nm. Calibration curve for Diltiazem HCl was a straight line with less SD value.

As Diltiazem HCl is water soluble in nature, the entire prepared patch was free from agglomerates of drug and polymers. Also there was no air entrapment was observed in all formulations. Patch prepared with ethyl cellulose and combination of ethyl cellulose and PVP was opaque while appearances of other formulations were transparent in nature.

The thickness value of prepared patches were ranged from 96.33 ± 19.16 µm to 273.67 ± 11.68 µm. Thickness of patches were uniform in all formulations and they were found to be flexible and smooth. A thickness of patches prepared with hydrophilic polymer (Hypromellose) was found more as compare to the thickness of hydrophobic polymer like ethyl cellulose.

The folding endurance gives the idea about breaking or creaking of patch during application. Folding endurance value of the all prepared patch formulation was ranged from 16 ± 9 to >300, which indicated prepared formulations have sufficient plasticizer to provide elasticity to the patch. However least value of folding endurance for ethyl cellulose indicates requirements of more plasticizer or change of plasticizer in the formulation is required. However during experimental use there was no breaking or cracking of patch was observed.

The weight variations of the patches were ranged from 53.20 ± 3.29 to 86.53 ± 3.30 and assay was also found to be uniform among the all formulations and ranged from 96.92 ± 1.67 to 101.84 ± 1.29. The results of weight variation and assay were found to be uniform with low SD value.

The percentage moisture absorption of the all patches was ranged from 2.73 ± 0.93 to 82.67 ± 9.67 percentages. Moisture absorption was found more with hydrophilic cellulose polymer Hypromellose and less with acrylic and ethyl cellulose polymer. Loss on drying value ranged from 0.51 ± 0.08 to 1.58 ± 0.54 percentages. Water vapor transmission and tensile strength was found to be 12.68 ± 0.71 to 85.44 ± 6.10 mg/cm^2 and 0.106 ± 0.010 to 0.228 ± 0.018 kg/cm^2 respectively.

In vitro passive permeation studies shows, passive diffusion was observed with all the formulation and a maximum of 55.04 $\mu g/cm^2$ passive permeation of Diltiazem HCl was observed after 6 hours in a patch prepared with acrylate polymer (Eudragit) and minimum of 26.61$\mu g/cm^2$ was observed with a patch prepared with cellulose polymer (Hypromellose). On application of electric current, iontophoretic diffusion of Diltiazem HCl was observed from 42.19 $\mu g/cm^2$ (Hypromellose patch) to 63.37 $\mu g/cm^2$ (Ethyl cellulose patch) in 6 hours.

2.07 folds enhancement in drug diffusion due to electric current was observed in a patch prepared with ethyl cellulose. And almost negligible enhancement in drug release was observed in a patch prepared with acrylate polymers.

Conclusion

As Diltiazem HCl is hydropholic in nature and having molecular weight, it is a suitable candidate for iontophoretic drug delivery. 2 fold enhancements in drug diffusion due to iontophoresis were observed in a patch prepared with ethyl cellulose. This indicates feasibility of iontophoresis to enhance transdermal drug delivery of Diltiazem HCl using cellulose polymers.

References

1. Parasuram R. R., Guruprasad S., Nanoemulsion Based Emulgel Formulation of Lipophilic Drug for Topical Delivery. International Journal of PharmTech Research, 2016, 9(6): 210-223.
2. Anilkumar J. S., Amit L. S., Kevin C. G., Sac
3. hin A. K, Harinath N. M., Physical penetration enhancement by iontophoresis: a review. International Journal of Current Pharmaceutical Research,2010, l2: 1-7.
4. Lia S. K., Higuchia W. I., Zhua H., et al. In vitro and in vivo comparisons of constant resistance AC iontophoresis and DC iontophoresis. Journal of Controlled Release, 2003, 91: 327–343.
5. Harden J. L., Viovy J. L., Numerical studies of pulsed iontophoresis through model membranes. Journal of Controlled Release, 1996, 38: 129-139.
6. Burnette R.R., Ongpipattanakul B., Characterization of the permselective properties of excised human skin during iontophoresis. J. Pharm. Sci., 1987, 76: 765-773.
7. Naik S. R., Shanbhag V., Present Status of controlled drug delivery system. Indian Drugs, 30: 423-426.
8. Garala J., Tank H. M., Shiroya U., et al., Transdermal permeation enhancement by iontophoresis: a review. International Journal of Advances in Pharmaceutical Research, 2012, 3(7):1021-1032.
9. Teelavath M., Rao Patnaik K.S.K.,Design,Development and Pharmacokinetic Studies of Buccal Adhesive Diltizam Tablets of Natural Edible Mucoadhesives in Rabbit International Journal of PharmTech Research, 2014, 6(5): 1549-1561.
10. Timothy C., Fagan M. D., Diltiazem: 20 Years' experience in cardiovascular medicine. Clin Cardiol, 2003, 26:1-4.
11. Ekapol L., Kraisri U., Preparation and evaluation of diltiazem hydrochloride diffusion-controlled transdermal delivery system AAPS PharmSciTech, 2008, 9(2): 464-470.
12. Chaffman M., Brogden R. N., Diltiazem: A Review of its Pharmacological Properties and Therapeutic Efficacy. Drugs, 1985, 29(5): 387-454.
13. Pillai S. S., Muneer T. K., Panneerselvam T., et al., Controlled drug delivery of diltiazem hydrochloride as transdermal patches: a novel approach on formulation evaluation *in vitro* and *in vivo* parameters. Research in Pharmacy, 2011, 1(2): 17-19
14. Tous, Fathy M., Fetih G. and Sheryhan F. G., Preparation and Evaluation of Ketoprofen-loaded Calcium alginate beads. International Journal of PharmTech Research, 2014; 6(3):1100-1112.
15. Nabin K., Biswajit B. , Bhavesh B., Formulation, Optimization and Evaluation of Extended Release tablets of Levetiracetam . International Journal of PharmTech Research, 2014; 6(2): 476-486.
16. Shahenoor Basha SK., Sunita Sundari G., Vija K., Effect of Al_2O_3 on PVP based Polymer electrolyte films doped with $Mgcl_2$ $6H_2O$ For Solid State Battery applications International Journal of ChemTech Research,2016; 9(5):383-391.
17. S. Ramkanth, C. M. chetty, Y. Sudhakar, Development and evaluation of Transdermal drug delivery system of Atenolol. Int. J. Res. Pharm. Sci., 2012, 2(4): 692-697.
18. Gupta R., Mukherjee 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.
19. Bangale G. S., Rathinaraj B. S., Rajesh K. S., Shinde G. V., Design and evaluation of transdermal films of Atenolol. J. Chem. Pharm. Res., 2010, 2(3):593-6*0*4.
20. Khaja M., Syed M., Rao D. S., Design, development and evaluation of transdermal drug delivery of captopril, an antihypertensive drug. Indo. american Journal of pharmaceutical sciences, 2014, 1(5): 305-314.
21. Raghuraman V., Vijay P. P., Formulation and Evaluation of Gliclazide Transdermal Drug Delivery Application. International Journal of ChemTech Research, 2015, 8(8) :19-24.
22. Sophie C., Dominique D., Jean D., *et al*., Structural parameters involved in the permeation of propranolol HCl by iontophoresis and enhancers. J Control Release, 1999, 58:163–175.

23. Anne-Rose D., Ucakar B., Pre´at V., Transdermal Delivery of Timolol and Atenolol Using Electroporation and Iontophoresis in Combination: A Mechanistic Approach. Pharm Research, 2003, 20(12): 1946-51.
24. Sravanthi R.R., Rajalakshmi R., Krishna Moorthy S.B., Rupangada V., Ramya S. E., Mucoadhesive Buccal Films: An Innovative Drug Delivery System. International Journal of PharmTech Research, 2014, 6(5): 1665-1678.

*****