Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 3, 2012

Research Article

PREPARATION AND EVALUATION OF TRANSDERMAL PATCHES OF METFORMIN HYDROCHLORIDE USING NATURAL POLYMER FOR SUSTAINED RELEASE

RAVI TEJA ALLENA*, HEMANT K S YADAV, SWETHA SANDINA, SARAT CHANDRA PRASAD M

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Mysore-570015, Karnataka, India Email: raviallena@gmail.com

Received: 05 Jan 2012, Revised and Accepted: 02 Apr 2012

ABSTRACT

The aim of the work was to develop a sustained release transdermal patch of metformin hydrochloride using a natural polymer like chitosan and a hydrophilic polymer like HPMC. Transdermal drug delivery can be efficiently used for the active agents which causes severe gastric irritation and undergo rapid first pass metabolism, hence the transdermal patches of metformin hydrochloride were prepared by using combination of chitosan and HPMC along with dibutyl phthalate as a plasticizer. The prepared formulations were evaluated for thickness, weight variation, drug content, folding endurance, moisture content, water-vapour transmission rate, tensile strength, *in vitro* permeation studies and stability studies. The drug-excipients compatibility studies were performed by Fourier Transform Infrared spectrophotometer (FTIR), DSC. The patches showed satisfactory folding endurance and tensile strength. *In vitro* dissolution test was carried for 24 hours and formulation F6 showed 95.89% drug release at the end of 24 hours. Release kinetics studies revealed that the drug release from formulation F6 followed zero order kinetics with release exponent value n=0.966, which shows that release pattern of patches follows Non - fickian diffusion mechanism. It was observed that the system with Chitosan: HPMC in the ratio 5:1 along with plasticizer was very promising in controlling release of metformin via transdermal drug delivery system.

Keywords: Chitosan, HPMC, Metformin HCl, Solvent evaporation method.

INTRODUCTION

Continuous intravenous infusion at a programmed rate has been recognized as a superior mode of drug delivery which not only bypasses the hepatic first-pass elimination but also maintains a constant, prolonged and therapeutically-effective drug level in the body. A closely monitored intravenous infusion can provide both the advantage of direct entry of drug into the systemic circulation and control of circulating drug levels. However such a mode of drug delivery entails certain risks and therefore necessitates hospitalisation of patients and close medical supervision of the medication. Recently there has been increasing awareness that the benefits of intravenous drug infusion can be closely duplicated, without its potential hazards, by continuous transdermal drug administration through intact skin. In response to this new idea several transdermal drug delivery systems (TDDS) have recently been developed, aiming to achieve the objective of systemic medication through topical application to the intact skin surface[1].

In recent years, developing nations have witnessed an explosive increase in the prevalence of diabetes mellitus predominantly related to life science changes and the resulting surge in obesity. The metabolic consequences of prolonged hyperglycaemia and dyslipidaemia including accelerated atherosclerosis, chronic kidney disease and pose enormous burden of patients with diabetes mellitus and on the public health system[2]. An estimated 20.8 million people currently has diabetes, of these, 6.2 million or about 1/3rd were undiagnosed. In 2005 alone, over 1.5 million new cases in adults were diagnosed. Globally the prevalence of diabetes for all ages is estimated to be 2.8% in 2000 and projected to 4.4% by 2030. The centres for disease control and prevention predicts the national incidence of diabetes will rise by 37.5% by the year 2025[3].

Metformin hydrochloride, an oral anti-diabetic drug frequently used as 1st line drug of choice in treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function[4]. Metformin is anti-hyperglycaemic and it does not cause insulin release in the pancreas. Metformin reduces glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat. Metformin is absorbed mainly from the small intestine and does not bind to plasma proteins[5].

Obstacle to more successful use of metformin HCl therapy is the high incidence of gastro-intestinal side effects and rapid first pass metabolism. These problems can be overcome by the preparation of transdermal patches of Metformin Hydrochloride.

MATERIALS AND METHODS

Metformin hydrochloride was obtained as a gift sample from Strides Arcolab Ltd., Bangalore. Chitosan was purchased from Sigma Aldrich, Bangalore. HPMC was obtained from Shreeji chemicals, Mumbai, India. Dibutyl phthalate was obtained from SD Fine Chemicals, Mumbai. All other chemicals and reagents used in the study were of analytical grade.

Preparation of the Transdermal Patches[6]

Matrix type transdermal patches of Metformin HCl were prepared by solvent evaporation technique using different proportions of polymers like Chitosan and HPMC in cylindrical glass mould with open end on both sides.

Table 1: Formulation chart of transdermal patches

Formulation Code	Drug (w/w)	Chitosan: HPMC Ratio	Dibutyl phthalate (v/v)	Ethanol: Dichloromethane
F1	20%	1:3	20%	1:1
F2	20%	1:5	20%	1:1
F3	20%	1:7	20%	1:1
F4	20%	1:9	20%	1:1
F5	20%	3:1	20%	1:1
F6	20%	5:1	20%	1:1
F7	20%	7:1	20%	1:1
F8	20%	9:1	20%	1:1

The backing membrane was cast by pouring 5% (w/v) PVA solution on bottom of the mould which was wrapped with aluminum foil followed by drying at 60°C for 6 h in an oven. Requisite ratios of the two polymers were weighed and they were then dissolved in ethanol: dichloromethane (1:1) as a solvent. Dibutyl phthalate (20%) of polymer composition was used as a plasticizer. The drug was added 20% w/w of the total weight of polymer, in the homogeneous dispersion, by slow stirring on a magnetic stirrer. On the PVA backing membrane casted earlier the uniform dispersion (3 ml each) was casted and dried at 40°C for 6 h. After drying patches were removed from the mold, wrapped with aluminium foil and kept in desiccators until they were used for further study. The formulation chart is given in Table 1.

Evaluation of Transdermal Patches

Drug polymer Interaction Study[7]

The physicochemical compatibility between Metformin HCl and polymers used in the films was studied by using Fourier transform-infrared (FT-IR- 8400, Shimadzu Co., Japan) spectroscopy. The pellatization was done by the KBr pellet method. The FT-IR spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for Metformin HCl and physical mixtures of Metformin HCl with polymers were compared.

Differential Scanning Calorimetry

About 5 mg of sample was weighed and crimped into an aluminium pan and analysed at scan range from 0 ºC - 300ºC at the heating rate of 5ºC/min under nitrogen flow of 25ml/min.

Scanning electron microscopy

Morphological details of the transdermal patches after swelling were determined by using a scanning electron microscope (SEM).

Folding endurance[8,9]

The prepared patches were measured manually for folding endurance. The folding of the patches was repeated at the same place till they broke. The accurate value of folding endurance was given by the number of times the patches could be folded at the same place without breaking.

Uniformity of thickness[8]

The uniformity of thickness of transdermal patches was measured by micrometer with least count of 0-0.1 mm. At five different points the thickness of the patch was measured and the average of five readings with the standard deviation was calculated.

Moisture content[10]

The prepared patches were marked, then individually weighed and kept in a vacuum desiccator containing diphosphorus pentoxide at room temperature for 24 h. The patches were individually weighed until they showed a constant weight. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

% of moisture content = (X-Y/Y) × 100

Where, X = initial weight, Y = final weight.

Moisture uptake[10]

The weighed patches were kept for drying in vacuum desiccator at normal room temperature for 24 h upto a constant weight and then exposed to 84% relative humidity (saturated solution of potassium chloride).

% of moisture uptake = (Y-X/X) × 100

Where, X = initial weight, Y = final weight.

Water vapour transmission rate[11]

5 mL capacity glass vials were thoroughly washed and dried in an oven up to a constant weight. Fused calcium chloride of about 1 g was taken in the vials and with the help of an adhesive tape the polymer films of 2.25 cm^2 were fixed over the brim. Vials were then weighed and stored in a humidity chamber at 80-90 % RH condition for a period of 24 h. At 24 h time intervals the vials were removed and weighed to note down the weight gain.

Percent flatness study[12]

From each transdermal patch the preparing strips were cut out, one from the centre and two from the either side. The variation in the length and the length of each strip was measured because of non-uniform in flatness which was measured by determining % of constriction, considering 0% constriction is equivalent to 100% flatness.

% of constriction = $l_1 - l_2/l_2$

Where, l_1 = initial length of each strip and

l_2 = final length of each strip.

Weight variation study[12,13]

Three randomly selected patches from each formulation were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.

Drug content study[14]

Drug content study was carried out using pH 7.4 phosphate buffer. Patches of $1cm^2$ were taken and crushed using motor and pestle and taken in 100ml volumetric flask. With the help of a teflon coated magnetic bead the medium was stirred for 5 h. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content at 233 nm spectrophotometrically.

Tensile strength[14]

Modified spring balance method was used for this study. From the centre of circular patch square strips of transdermal patch (3 × 3 cm) were cut. The patch was attached to hook at one end and in gradually increasing manner load was applied on the other end. Reading on the spring balance was noted at the point at which the patch tears from the centre that was divided by the area of transdermal strip to give tensile strength in g/cm^2.

***In vitro* permeation study**[15]

In vitro evaluation of transdermal patches was carried out in Franz diffusion cell. The skin with the patch attached was mounted and clamped carefully between the receiver and donor compartment of diffusion cells with the patch facing the donor side. The receiver was maintained at 37^0 C by thermostatically controlled water, which was circulated through a jacket surrounding each cell body, and the contents were stirred continuously at controlled speed. Normal saline containing 0.02 M sodium azide was used as receiver solution to optimize drug solubility and to arrest fungal growth, so that sink condition was maintained. At predetermined time, samples were withdrawn from the receiver and assayed for Metformin HCl spectrophotometrically at 233 nm after proper dilution with the elution medium.

Kinetics of drug release[16, 17, 18, 19]

The suitability of several equations to identify the mechanisms for the release of drug was tested with respect to the release data. The drug release data of the *in vitro* dissolution study was analyzed with various kinetic equations like zero-order (% release v/s time), first order (Log % retained v/s time), Higuchi model and korsmeyer peppas equation. Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots and are shown in table 5. The value of 'n' gives an indication of the release mechanism; when n = 1, the release rate is independent of time (zero-order) (case II transport), n = 0.5 for Fickian diffusion and when 0.5 < n <1.0, diffusion and non-Fickian transport are implicated. Lastly, when n > 1.0 super case II transport is apparent.

Stability Studies

Stability studies were carried out for optimized patch at 45^0C/75% RH in humidity chamber for 90 days. After 90 days the samples were analyzed for drug content and drug release.

RESULTS AND DISCUSSION

Polymers like Chitosan and HPMC were selected on the basis of their adhering property and non-toxicity. The FTIR study was carried out to determine the physical or chemical interaction between drug and polymers. IR spectra were recorded for metformin hydrochloride and the formulation. Pure metformin hydrochloride spectra showed sharp characteristic peaks at 3367.34, 3298.05, 3169.04, 2977.89, 1627, 1222, 1064.63, 636.47cm^{-1}. FTIR characteristic peaks of drug appear in the spectra of formulation at the same wave number indicating no modification or interaction between the drug and the polymers used. This proves the fact that there is no potential incompatibility of the drug with the polymers used in the formulations. Comparative study of FTIR graph is shown in figure 1.

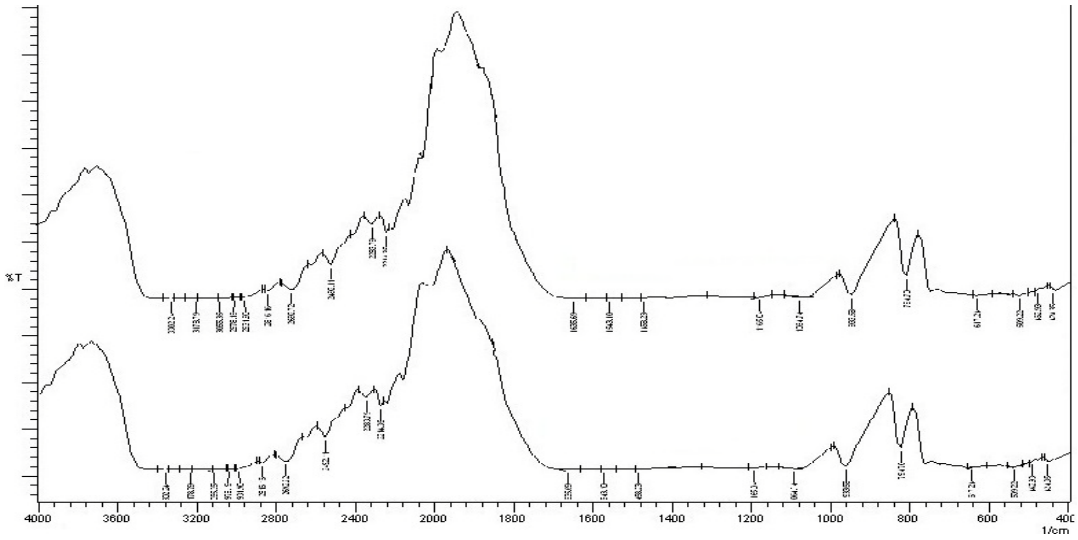

Fig. 1: Pure Metformin hydrochloride and Metformin hydrochloride with Chitosan and HPMC

The DSC thermograms of Pure Metformin HCl and Formulated Transdermal patches are represented in Figure 2. The DSC thermogram of Metformin HCl displayed the characteristic peak at 224^{0}C corresponding to its melting point. The drug peak appeared in the thermogram for all the drug-loaded films, confirming the chemical integrity of the drug. A slight shift in the Metformin HCl peak in the thermograms of the drug- loaded with polymer could be due to the presence of moisture in the film samples.

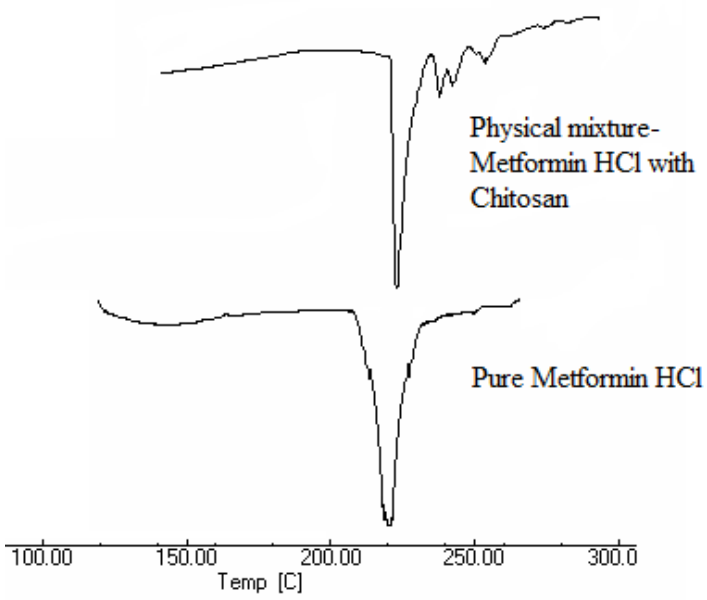

Fig. 2: DSC thermogram of Metformin and Physical mixture

Surface morphology shows that the drug release is by swelling of polymer and appearance is rugged. SEM photograph is shown in fig.3.

The thickness of the transdermal patches for 8 different polymer ratios varied from 198µm to 215 µm. The maximum difference between the thicknesses of patches was 0.09 mm, which indicates that all the prepared patches were of nearly uniform thickness. The results are given in table-2.

The weight variations of the patches were in the range of 236 mg cm^{-2} to 260 mg cm^{-2} for 8 formulations, difference in weight variation was due to addition of polymer in different ratios which influence weight of patches. The results are given in table-2.

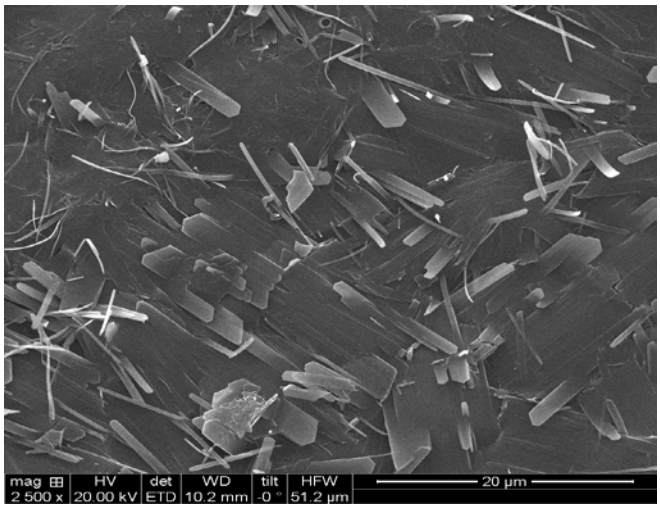

Fig. 3: SEM photograph Of Metformin HCl Transdermal patch

The drug content varied due to polymers which were added in different concentrations. As the polymer concentration increases, the bond formation between the drug molecules and polymer molecules increases which will retard the drug release. Drug content of all batches were well within the range between 91.04 and 94.05±2.98%. The results are given in table-2.

Test results indicated that all the patches can withstand to rupture and would maintain their integrity with general folding when used. The folding endurance values lie in between 151 and 167 and was measured manually. The value was found to be high in patches containing higher amount of the HPMC. The prepared transdermal patches showed good tensile strength and there was no sign of cracking in prepared transdermal film. This might be due to the addition of the plasticizer, dibutyl phthalate. Mechanical properties of a polymer matrix were improved by the use of polymers.

Tensile strength lies in between 182 g/cm^2 and 202 g/cm^2, the difference in values were due to composition of polymer used. Also there was an increase in the tensile strength with increasing concentration of chitosan and HPMC. Highest tensile strength was observed in F4 and this might be due to the highest concentration of hydrophilic polymer used and as the concentration decreased from F4 to F1 tensile strength got decreased. The results are given in table-2.

Table 2: Evaluation of Transdermal Patches

Formulation code	Thickness (µm)	Weight variation (mg cm^{-2})	Drug content (%)	Folding endurance	Tensile strength (g cm^{-2})	% flatness
F1	200±0.031	245±1.42	91.04±3.25	151±02	184.54±0.096	100±1.28
F2	215±0.002	236±1.36	91.96±3.16	158±03	189.85±0.105	99±1.37
F3	198±0.012	255±1.05	92.54±2.96	161±02	196.11±0.089	100±1.19
F4	204±0.071	248±1.40	93.76±2.85	167±02	202.11±0.112	100±1.22
F5	210±0.002	260±1.66	91.42±3.26	164±03	182.75±0.099	98±1.35
F6	210±0.051	239±1.85	92.65±3.08	159±03	179.15±0.095	99±1.19
F7	199±0.042	241±1.35	93.27±3.15	155±02	192.78±0.108	97±1.27
F8	202±0.097	254±1.57	94.05±2.98	154±02	200.44±0.109	98±1.21

Mean ± SD (n= 3)

For F1 to F4 transdermal patches, hydrophilicity increased due to increase in the HPMC ratio, this resulted in increased moisture content. For F5 to F8 patches hydrophobicity increased by increasing the chitosan ratio, and resulted in decreased moisture content. The results are given in table-3.

Water vapour transmission studies were performed for all 8 different patches were found to be within the range of 0.426 to 0.503mg cm^{-2} h^{-2}. F8 showed least water vapour transmission due to the higher concentration of Chitosan. As the hydrophobic polymer increased, it did not allow transmitting water and finally resulted in least transmission rate. F4 has showed highest value due to highest amount of hydrophilic polymer used. The results are given in table-3.

Moisture uptake was found to be in range of 0.117 to 2.374%, which implies that the increase in hydrophilicity of the HPMC the moisture uptake was increased. Hydrophobicity was increased from F5 to F8 formulations, which resulted in rapid decrease in the moisture uptake. The results are given in table-3.

Table 3: Evaluation of transdermal patches

Formulation code	Moisture content (%)	WVTR (mg cm^{-2} h^{-2})	Moisture uptake (%)
F1	1.210±0.59	0.485±0.005	1.198±1.076
F2	1.258±0.62	0.491±0.008	1.578±0.971
F3	1.352±0.49	0.496±0.003	1.891±0.957
F4	1.854±0.55	0.499±0.009	2.374±0.768
F5	1.011±0.68	0.503±0.018	0.982±0.854
F6	0.985±0.71	0.468±0.012	0.735±1.029
F7	0.825±0.51	0.457±0.002	0.581±0.669
F8	0.754±0.68	0.429±0.006	0.117±1.014

Mean ± SD (n= 3)

The drug release rate decreased when the concentration of hydrophilic polymer was increased and sustained release was observed in case of F6 and F7 formulations. The cumulative percentage drug release of F4 was found to be 52.22±0.19 % at 24 h. This is due to the highest amount of hydrophilic polymer used which degraded the drug present in it. Formulation F7 showed the highest drug release and this might be due to the polymers used in the formulation. The formulation, F6 [Chitosan : HPMC in 5:1] was considered as a best formulation, since it shows sustained *in vitro* drug release of 95.89 ± 0.28 % at the end of 24 h with optimum polymer concentration. The formulation F5 showed the next highest release after F6. This showed that the formulations with increased concentrations of chitosan resulted in sustained release of the drug upto a certain level and further more decreased due to excess polymer concentration which resulted in high encapsulation of drug. Formulations (F1, F2, F3 and F4) with increased HPMC polymer concentration, showed a constant decrease in the cumulative drug release due to drug degradation by the excess moisture content and uptake. The results are given in table 4.

Table 4: *In vitro* drug release studies

Time in hours	% Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
1	3.98±0.18	3.89±0.54	2.98±0.29	3.22±0.52	3.65±0.16	5.22±0.26	4.86±0.41	4.22±0.01
2	6.19±0.24	6.12±0.29	7.16±0.47	4.41±0.46	5.66±0.25	10.94±0.34	8.36±0.24	11.22±0.12
4	13.57±0.15	13.17±0.34	12.15±0.32	11.55±0.15	12.95±0.06	22.83±0.19	19.56±0.12	19.61±0.08
6	19.48±0.49	18.42±0.39	17.62±0.35	17.23±0.29	20.63±0.22	37.45±0.09	29.25±0.27	29.11±0.11
8	28.11±0.55	27.56±0.25	27.17±0.27	25.62±0.17	29.22±0.35	49.18±0.14	42.77±0.05	42.77±0.20
12	40.69±0.37	39.58±0.18	36.12±0.16	38.62±0.36	38.68±0.18	73.25±0.28	57.25±0.16	60.11±0.05
16	45.17±0.28	43.62±0.11	41.62±0.08	42.97±0.29	42.72±0.27	82.74±0.35	72.25±0.22	74.17±0.17
24	92.18±0.37	87.19±0.27	69.18±0.24	52.22±0.19	84.91±0.39	95.89±0.28	97.14±0.19	93.42±0.25

Mean ± SD (n= 3)

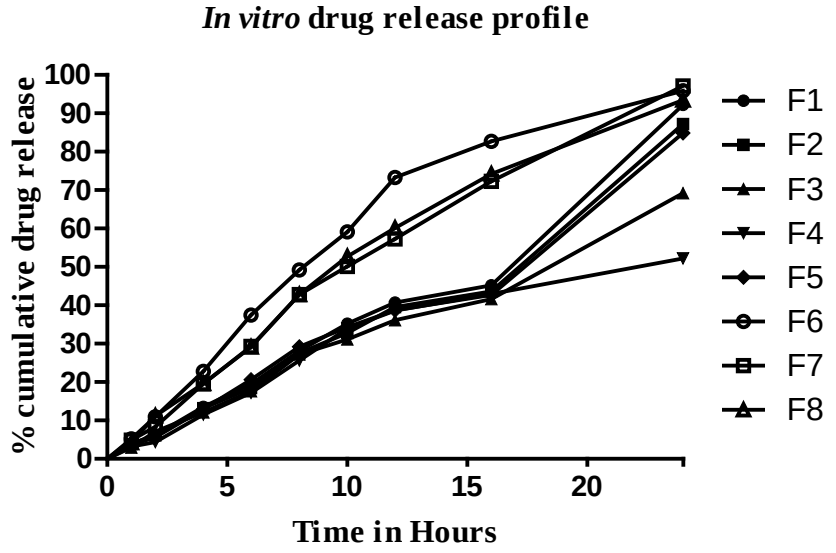

Fig. 4: Cumulative % drug release

The drug release kinetics studies showed that all formulations were governed by Peppas model and mechanism of release was non-Fickian mediated. Regression analysis of the *in vitro* permeation curves was carried out. The slope of the curve obtained after plotting the mean cumulative amount released per patch versus time was taken as the *in vitro* release for Metformin Hydrochloride.

Table 5: Release kinetics

Formulation	Zero order	First order	Korsermayer-Peppa's	
	R^2	R^2	n	R^2
F1	0.964	0.852	0.979	0.989
F2	0.989	0.847	0.969	0.990
F3	0.988	0.824	0.959	0.992
F4	0.922	0.851	0.980	0.973
F5	0.970	0.824	0.990	0.988
F6	0.920	0.827	0.966	0.981
F7	0.981	0.846	0.986	0.992
F8	0.966	0.828	0.979	0.986

K values are release rate constants according to the models considered; R^2 values are determination Coefficients; and *n* is the exponent of the korsmeyer-peppas model.

All the formulations were selected for stability studies and observed for physico-chemical changes like colour, appearance, flexibility, drug content and % drug release. As per the ICH guidelines temperature and humidity values were selected and the tests were carried out. Patches were analysed at different intervals like 15, 30, 60 and 90days. The drug content was in the range of 90.15±0.94 to

95.21±1.39% and the drug release was in the range of 48.57±0.27 to 90.37±0.51%. The results indicate that all the formulations were stable in the required storage condition.

CONCLUSION

Controlled release transdermal patches can be prepared using solvent evaporation technique using natural polymer Chitosan and a semi-synthetic polymer HPMC with Metformin Hydrochloride. This system can be efficient for the drugs which have the similar properties as that of Metformin HCl i.e. which causes gastric irritation and having high first pass metabolism, and freely water soluble in nature. The prepared patches showed good compatibility, flatness and thickness. The patches showed significant folding endurance and tensile strength. The moisture content and moisture uptake were found to be optimum. The prepared patches showed optimum drug content and sustained drug release. The results presented in this study suggest that applying transdermal patches containing Metformin HCl can achieve sustained drug delivery without gastric irritation. These findings show that Metformin HCl transdermal patches will have a good prospect for treating type 2 diabetes.

ACKNOWLEDGEMENT

The authors wish to thank JSS College of Pharmacy, JSS University, Mysore for the support to carry out the research work.

REFERENCES

1. Yie W. Chien, Novel Drug delivery systems, M. Dekker, New York, 2011; 2nd ed, 50: 301-375.
2. Louis S Goodman; Laurence L Brunton, Goodman & Gilman's The pharmacological basis of therapeutics, McGraw-Hill Medical, New York, 2005; (11): 1613-1638.
3. Mary Anne Koda-Kimble, Llyod Yee Young, Applied Therapeutics, The clinical use of Drugs, Lippincott Williams, USA, 2009; 9: 50-2- 50-3.
4. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update) London: Royal College of Physicians 2008; ISBN 9781860163333, 86.
5. Louis S Goodman; Laurence L Brunton, Goodman & Gilman's The pharmacological basis of therapeutics, McGraw-Hill Medical, New York, 2005; 11th ed: 1638-1639.
6. Dey BK, Kar PK and Nath LK. Formulation design, preparation and *in vitro-in vivo* evaluation of propranolol hydrochloride transdermal patches using hydrophilic and hydrophobic polymer complex. Research J. Pharm. and Tech. 2009; 2(1): 155-60.
7. R.Herrman, Bioequivalence of a nifedipine extended release formulation compared to a standard formulation in steady state, Arzneimittel- Forschung, 1988; 46, 28.
8. Arora P. Mukherjee B. Design development of physicochemical *in vitro* and *in vivo* evaluation of transdermal patches containing diclofenac diethylammonium salt. Indian J. Pharm. Sci. 2002; 91(9): 2076-89.
9. Kevin c. Garala, anil j. Shinde, pratik h. Shah. Formulation and *in-vitro* characterization of monolithic matrix Transdermal systems using HPMC/Eudragit s 100 polymer blends, Int J Pharmacy and Pharmaceutical Sciences 2009; 1(1): 108-120.
10. Gupta R, Bajpal M and Bhattacharya A. Formulation and *in vitro* Evaluation of transdermal drug delivery system of tizanidine hydrochloride, Indian J. Pharm. Sci. 2008; 7(4): 208-13.
11. Sankar V, Benito DJ, Sivanand V, Ravichandran V, Velrajan G and Raghuraman S. Design and evaluation of nifedipine transdermal patches. Indian J. Pharm. Sci. 2003; 65(5): 510-15.
12. Sathyapriya, L.S., Jayaprakash, S., Prabhu, R.S., Abirami, A., Subramanian, K., Nagarajan, M., Int J Pharm Sci Tech 2008; 1: 22-28.
13. Saxena M, Mutalik S and Reddy MS. Formulation and evaluation of transdermal patches of metoclopramide hydrochloride, Indian Drugs. 2006; 43(9): 740-45.
14. Gupta SP and Jain SK. Effective and controlled transdermal delivery of metoprolol tartarate. Indian J. Pharm. Sci. 2005; 67(3): 346-350.
15. D. Thacharodi and K. Panduranga Rao. Development and *in vitro* evaluation of chitosan-based transdermal drug delivery systems for the controlled delivery of propranolol hydrochloride, Biomaterials. 1995; 16(2): 145-148.
16. Khan GM. Controlled Release Oral Dosage Forms: Some recent, advances in matrix type drug delivery systems. The Sciences. 2001; (1): 350-354.
17. Morkhade DM, Fulzele SV, Stturwar PM and Joshi SB. Gum copal and gum damar: novel matrix forming materials for sustained drug delivery. *Ind. J. Pharm. Sci.* 2006; 68: 53-58.
18. Higuchi T. Mechanism of rate of sustained-action medication. *J. Pharm. Sci*. 1963; 52: 1145-1149.
19. Peppas NA and Sahlin JJ. A simple equation for the description of solute release III.5 Coupling of diffusion and relaxation. *Int. J. Pharm*. 1989; 57: 169–172.