Development of Transdermal Delivery System of Vildagliptin and Its Comparison with Oral Therapy

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ABSTRACT

Purpose: The long term oral therapy of vildagliptin is associated with potential hepatotoxicity and low patient compliance. This study aims at development of a drug in adhesive transdermal patch system of vildagliptin using pressure sensitive acrylic polymers and compare the pharmacokinetics with oral therapy. **Methods:** The prospective of different chemical enhancers in improving the transport of vildagliptin was assessed *ex vivo*. *In vivo* permeation studies in rats were performed using patch system contain sodium lauryl sulfate as enhancer. **Results:** Drug solubility varied among adhesive bases tested and maximum value (15% w/w) observed with Duro-Tak 87-2510. Incorporation of chemical agents significantly improved the permeation of vildagliptin, but not to the same extent. The highest flux value of vildagliptin was obtained by the addition of sodium lauryl sulfate (22.96 ± 3.58 $\mu g/cm^2/h$; $P<0.0001$), which is ~4 folds higher as compared to control. Pharmacokinetic profiles of vildagliptin were different for transdermal and oral delivery with significantly high bioavailability by transdermal delivery. The $AUC_{0-\alpha}$ in transdermal delivery (1018.43 ± 79.56 ng.h/mL) was ~14 folds higher ($P<0.0001$) as compared to oral administration. **Conclusion:** The current study concludes that the fabricated drug in adhesive transdermal system could be employed for the effective delivery of vildagliptin.

Key words: Transdermal, Adhesive, Vildagliptin, Enhancer, Flux, Pharmacokinetics.

INTRODUCTION

Diabetes mellitus is a complicated metabolic disorder characterized by hyperglycemia, abnormalities in lipids, carbohydrates, proteins metabolism which leads to postprandial and fasting hyperglycemia, dyslipidemia and hyperinsulinemia. Unprecedented increase in diabetes worldwide over the past few decades is a severe threat to world health and well-being.[1] Based on the World Health Organization (WHO) record, there are 366 million diabetic patients around the globe, and the prevalence is rapidly increasing which may lead to ~552 million people with diabetes by 2030.[2,3] Several hypoglycemic drugs are available for the treatment of type 2 diabetes which works by different mechanisms.[4] Despite the availability of large varieties of hypoglycemic agents, the treatment of type 2 diabetes remains elusive.[5] Recently, incretin based therapy has been approved by the US FDA for the management of type 2 diabetes.[6] Typically they act by inhibiting the enzyme, Dipeptidy peptidase-4 (DPP4) and improve glycemic control by increasing circulating levels of incretins, endogenous gut derived peptide hormones and suppress glucagon release in a glucose-dependent manner.[7] Among DPP inhibitors, vildagliptin is a selective, reversible, competitive inhibitor of DPP4 and is more effective. It possesses several advantages and overcomes the major issues such as hypoglycemia and weight gain, the normal side effects of other oral hypoglycemic agents.[8] However, its use has been restricted due to several adverse effects such as hepatotoxicity and regular hepatic function tests are recommended due to concerns about liver damage.[9] Vildagliptin possesses distinct physicochemical properties such as

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poor water solubility, small molecular mass and reasonable melting point which suggest its prospects to be delivered through the skin. Formulating a transdermal drug delivery product of this drug is likely to overcome the hepatic adverse effects and could maintain proper blood level for a prolonged period of time, which in turn would overcome the biopharmaceutical limitations that prevent the successful delivery of vildagliptin in oral therapy.[10] Extensive studies are being carried out to develop an alternative system which can surmount the existing issues and provide controlled and effective delivery of vildagliptin. Some novel approaches such as vesicular drug delivery systems were attempted, although produced limited results.[11]

Potential of transdermal systems to transport drugs into and across the skin membrane while bypassing first pass effect has attracted scientists worldwide. This drug delivery system has been accepted as an alternative administration path for oral delivery because of numerous advantages it possesses over conventional mode of drug delivery. Indeed, this approach increases the therapeutic efficiency of pharmaceutical actives by avoiding hepatic first-pass metabolism, deliver drug molecules in controlled manner, enhance absorption and improves patient compliance.[12] Moreover, it is an adhesive patch and offers a promising approach for developing a topical route to give local or systemic effects.[13] Advances in the field of adhesive science have paved way for developing optimized delivery systems which are capable of providing adequate skin adhesion, accommodate high drug load and greater drug delivery.[14] Transdermal patch system fabricated by using pressure sensitive adhesive has been known for a long time and has a number of advantages viz. small size, easy to formulate, comfortable to wear, prolonged delivery of active substances, no dose dumping, higher patient compliance etc.[15,16] Several research groups have demonstrated the feasibility of delivering active drug moieties through the skin using drug in adhesive transdermal systems.[17,18] The current study investigate the feasibility of developing a drug in adhesive transdermal system of vildagliptin and its comparison with oral therapy in animal model.

MATERIAL AND METHODS

Materials

Vildagliptin was purchased from Crystal Pharma SAU (Boecillo, Spain). N-methyl-2-pyrrolidone (NMP), sodium lauryl sulphate (SLS), polyethylene glycol (PEG 400), menthol, ethyl acetate, acetonitrile and triethyl amine were purchased from Sigma Aldrich, St. Louis, MO. Polyester release liner (Scotchpak® 1022) and polyethylene monolayer backing membrane (CoTran™ 9720) were gifted by 3M, St. Paul, USA. Duro-Tak 87-4287, Duro-Tak 87-2287 Duro-Tak 87-9301 and Duro-Tak 87-2510 were graciously donated by the National Starch and Chemical Company, Bridgewater, NJ, USA.

Sample Analysis

The concentrations of vildagliptin in receiver fluid, vehicle or plasma were measured by high performance liquid chromatography (HPLC) system (LC-10ATVP; Shimadzu Corporation, Tokyo, Japan). The HPLC system consisted of a photodiode array detector. A Hypersil BDS C8 analytical column (4.6 X 150 mm, 5.0 µm particle size) was used in the current study. Chromatographic separation of vildagliptin was achieved by a mobile phase comprising of acetonitrile and triethylamine (0.3% v/v), adjusted with phosphoric acid (15:85) to pH 7. The column temperature was maintained at 25^{0}C while the flow of the mobile phase was regulated at 1.0 mL/min. Samples of 25 µL were injected and the area under the curve was measured at a wavelength of 207 nm. The calibration curve was linear in the range of 0.5-800 ng/mL. The retention time of vildagliptin was about 6.8 min.

Preparation of patches

Adhesive patches containing different concentrations of vildagliptin were fabricated using four different pressure sensitive adhesives and enhancers using solvent evaporation method. Appropriate quantity of drug and/or enhancers were dissolved in suitable solvents and added to the adhesives (National Starch and Chemical Company, USA) under constant stirring (for 3 h) using magnetic stirrer. The adhesive mix was applied on a polyester release liner (Scotchpak® 1022, 3M, St. Paul, USA) with an applicator at a thickness of ~300 µm. The product was air dried at room temperature for 2 h and kept in oven at 45^{0}C for 1 h to remove any residual solvents. The patches were punched to circular disc and a polyethylene monolayer backing membrane (CoTran™ 9720, 3M, St. Paul, USA) was laminated on the cast layer and kept in aluminium membrane.

The first step in formulating the drug in adhesive patch was to identify and select the appropriate adhesive. Four pressure sensitive adhesives (Duro-Tak 87-4287, Duro-Tak 87-2287 Duro-Tak 87-9301 and Duro-Tak 87-2510) were used to formulate the patches and the drug solubility was determined. In the next stage, the effect of different chemical enhancers (NMP, menthol, SLS and PEG 400) on the skin permeation was assessed.

Drug content

The amount of vildagliptin in formulated adhesive patches was assessed by weighing accurately a patch with area of 1 cm^2 and transferring it to 100 mL of ethanol. This was then sonicated for 1 h. The drug content was determined after filtering the solution using 0.22 μm Millex syringe driven filter unit, diluted with mobile phase and analyzed by HPLC.

Water absorption ratio

Water absorption capacity was assessed by placing a tissue paper (folded) in a petridish (i.d.=6.5 cm) having water (6 mL). Then the fabricated patch was kept over tissue and the time needed for complete wetting (entire patch was covered with solvent) is observed. After this, the patches were taken out and wiped with tissue to remove excess water and weighed. Below equation was used to measure the absorption ratio;

$$R = (Wa - Wb)/(Wb) \times 100$$

Where W_b and W_a are the weight of patch before and after water absorption, respectively.[19]

Skin preparation

Skin membranes of Wistar rats were prepared by carefully removing the hair from the skin using a clipper. The skin with stratum corneum, epidermis and dermis layers was excised and the subdermal tissue was surgically removed, washed with physiological saline.[20] Then the skin was wrapped in aluminium foil and stored at -20^{0}C. The skin membrane was thawed prior to permeation studies. The membrane resistance was measured before the experiment as described in our earlier studies and the skin which had a resistance >20 kΩ.cm^2 was used.[21]

Ex vivo permeations tudies

The permeation of vildaglipt in across the full thickness dorsal rat skin was evaluated for a period of 12 h in a vertical Franz diffusion cell. The excised dorsal skin with specific integrity was clamped between two chambers with the dermis region of the skin facing receptor solution [phosphate buffered saline (PBS) pH 7.4]. Effective area for all experiments was 0.64 cm^2. Full thickness skin membrane was equilibrated for 1 h by placing PBS in both donor (1 mL) and receptor (5 mL) chambers.[22] After one hour, both donor and receptor fluid were removed and a circular transdermal patch (0.6 cm^2) was placed and pressed on the skin. The receptor compartment was filled with fresh PBS solution and continuously stirred at 600 rpm at 37 ± 0.5^{0}C. Permeation experiment was carried for a period of 24 h and receiver fluid was sampled at designated time points.

In vivo studies

In vivo experiments were carried out in male, 6-8 weeks old Wistar rats (200-250 g) which were maintained on a 12/12 h light/dark cycle in an animal facility with unlimited access to food and water (Institutional Animal Ethical Committee). Two groups of rats (six animals in each group) fasted for 12 h with free access to water were used in the study. For first group, the rats were anesthetized using phenobarbitone (30 mg/kg) administered intraperitoneally and the dorsal hair were trimmed carefully using electric clipper.[23] The application area of skin was cleaned with PBS and swabbed with tissue before applying the patch. The patch covering an area of 1 cm^2 (~4 mg vildagliptin) was placed on dorsal area and slightly pressed by fingers to provide adequate adhesion of patch to the skin membrane. The patches were removed after 12 h. For second group of rats, suspension of vildagliptin (4 mg/mL) was administered by peroral route (1mL dose) by gavage. Blood samples of ~200 μL were collected from lateral tail vein using dry heparinized tubes at 1, 2, 4, 6, 8, 10 and 12 h. Plasma samples (200 μL) were protein precipitated with equivalent amount of acetonitrile and 2-propanol. The calibration curve of vildagliptin in rat plasma was measured by adding various amount of vildagliptin (0.5-800 ng), the samples were vortex mixed for 2 min. Then the samples were centrifuged (12,000×g for 5 min) at room temperature. The upper clear layer (25 μL) was used for analyzing the drug content by HPLC.

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated using non-compartmental pharmacokinetic model. Different pharmacokinetic parameters like maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (T_{max}) were determined from the individual blood concentration time profile. The area under the time–concentration curve from time 0 to ∞ ($AUC_{0-\alpha}$) for each administration was calculated by the linear trapezoidal rule.

Data analysis

The data were expressed as mean of six trials. Total amount of vildagliptin transported per unit skin area was plotted against time and the slope of linear region of the plot was valued as flux.[24] Flux value was divided with drug concentration in the patch to determine permeability coefficient. Enhancement in permeation was measured as the ratio of vildagliptin flux with enhancer to the control. The data were tested by one-way

analysis of variance and t-test using GraphPad Prism (version 5, Graphpad software, San Diego, California, USA). A value of $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The major components of a transdermal patch include-pressure sensitive adhesive (incorporated with drug), backing membrane and release liner. The efficiency of such transdermal systems are generally optimized for adhesive matrix, drug loading and chemical permeation enhancers. Hence in the current study, drug in adhesive patch formulation containing vildagliptin were prepared and optimized by examining the influence of formulation factors such as pressure sensitive adhesives, solubility of drug in adhesives and type of skin permeation enhancers on the transport of vildagliptin across the rat skin membrane. The optimized patch formulation was further evaluated by *in vivo* pharmacokinetic study to hold promise for clinical application.

It is well known that the adhesive layer of transdermal product plays significant role in releasing and controlling the delivery of active drugs in a system. First phase of the study investigated the influence of pressure sensitive adhesives on the release of vildagliptin and its permeation across the rat skin. In the current investigation different acrylic polymers were selected as they are considered to be relatively less expensive than silicone and polyurethane pressure sensitive adhesives [14]. Described herein before, four renowned acrylate adhesives (Duro-Tak 87-4287, Duro-Tak 87-9301, Duro-Tak 87-2287 and Duro-Tak 87-2510) were selected based on the literature where their potential and suitability in developing transdermal systems of several drug molecules are demonstrated.[14-18] Pressure sensitive adhesives containing carboxylic acid groups were not examined as there is a possible interaction between the drug and adhesive. The properties of the selected adhesives are described in Table 1. The properties of adhesives used were different from one another with respect to functional groups, presence or absence of vinyl acetate and viscosity. The solubility of vildagliptin in the selected adhesives were examined to incorporate the highest possible amount of drug. For this, different concentrations (1-20% w/w) of drug was incorporated into the adhesives and patches were fabricated by solvent evaporation method. The prepared patches were examined regularly using optical microscopy for drug crystallization by storing at 25^{0}C for three months. It was observed that solubility varied among adhesive bases tested and was 15% (w/w), 11% (w/w), 10.5% (w/w) and 7.5% (w/w) of vildagliptin with Duro-Tak 87-2510, Duro-Tak 87-4287, Duro-Tak 87-9301 and Duro-Tak 87-2287, respectively. The maximum solubility of vildagliptin was determined as the prepared patches do not show any crystallization even after storage for three months. However, in all the cases, a higher drug levels lead to drug crystallization, which was observed after a week. Although we have not directly examined the exact mechanism, the variation in solubility of vildagliptin in different adhesives is probably due to difference in properties of adhesives (Table 1).

Drug content is an important quality control parameter for transdermal patches, and the assessment (per cm^2 area) in all the formulated patches shown higher drug content in the range of 94-97%. In addition, the water absorption ratio of patches were in the range of 16-24%, suggesting adequate water intake capacity by the prepared patches. Figure 1 illustrates the amount of vildagliptin permeated across the skin membrane and reaching the receiver compartment. This typical permeation profile substantiates the potential of transdermal delivery of vildagliptin. Remarkably, drug was detected in receiver fluid in the first sampling period itself (1 h) indicating very short or no lag time. As expected, Figure 1 demonstrates that the rate of drug permeation from the tested formulations decreases in the following pattern, Duro-Tak 87-2510>Duro-Tak 87-4287>Duro-Tak 87-9301 >Duro-Tak 87-2287. It is evident that this observed variation in vildagliptin flux values is approximately dose proportional (drug content in patches were different) throughout the study period (12 h). The observed flux values of vildagliptin were 22.96 ± 4.17 μg/cm^2/h, 13.33 ± 2.86 μg/cm^2/h, 11.02 ± 2.54 μg/cm^2/h and 5.06 ± 1.53 μg/cm^2/h with Duro-Tak 87-2510, Duro-Tak 87-4287, Duro-Tak 87-9301 and Duro-Tak 87-2287, respectively ($P<0.001$), in the current experimental condition. The difference in flux observed here substantiate the well-known theory that higher the drug concentration, greater the flux. In addition, the cumulative amount of drug permeated at the end of study period (12 h) from different patches was statistically significant ($P<0.0005$). The above data indicate that the permeation of vildagliptin is influenced by the adhesives tested, under similar conditions. Indeed, the permeation of drug moieties across the biological barriers is directly influenced by the rate and extent of drug release from the matrix. It should be emphasized that the release rate of a drug in an adhesive matrix is primarily governed by its solubility in the polymer as well as its diffusion coefficients in polymer. The difference in flux values observed here suggest that the rate of release of vildagliptin from the tested adhesives

Table 1: Comparison of properties of selected acrylate pressure sensitive adhesives

Adhesive	Functional Group	Vinyl acetate	Cross linker	Viscosity (cP)
Duro-Tak 87-4287	-OH	Present	Absent	8000
Duro-Tak 87-2287	-OH	Present	Absent	18000
Duro-Tak 87-9301	None	Absent	Absent	9500
Duro-Tak 87-2510	-OH	Absent	Absent	4250

Table 2: Mean pharmacokinetic parameters of vildagliptin in plasma after transdermal application using optimized drug in adhesive patch and oral administration in Wistar rats (n = 6).

Parameter	Transdermal	Oral
T_{max} (h)	4.0	6.0
C_{max} (ng/mL)	12.44 ± 3.16	19.46 ± 5.47
AUC_{0-o} (ng.h/mL)	1018.43 ± 79.56	73.46 ± 18.06

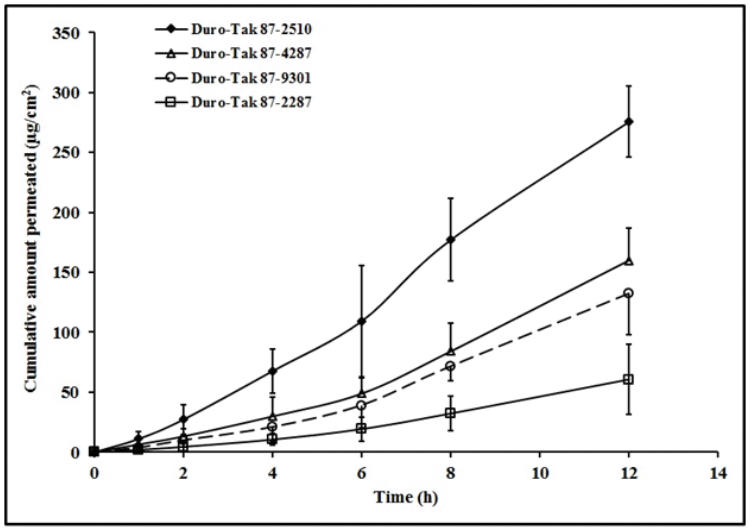

Figure 1: Comparison of the amount of vildagliptin permeated at different time intervals across the rat skin membrane from patches prepared with different pressure sensitive adhesives. All values are mean ± SD (n=6).

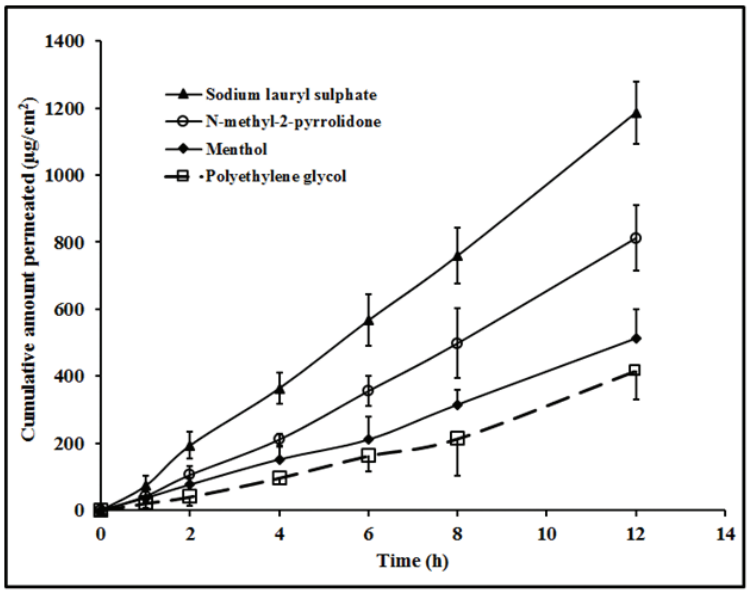

Figure 2: Comparison of the amount of vildagliptin permeated at different time intervals across the rat skin membrane from patches with different permeation enhancers. All values are mean ± SD (n=6).

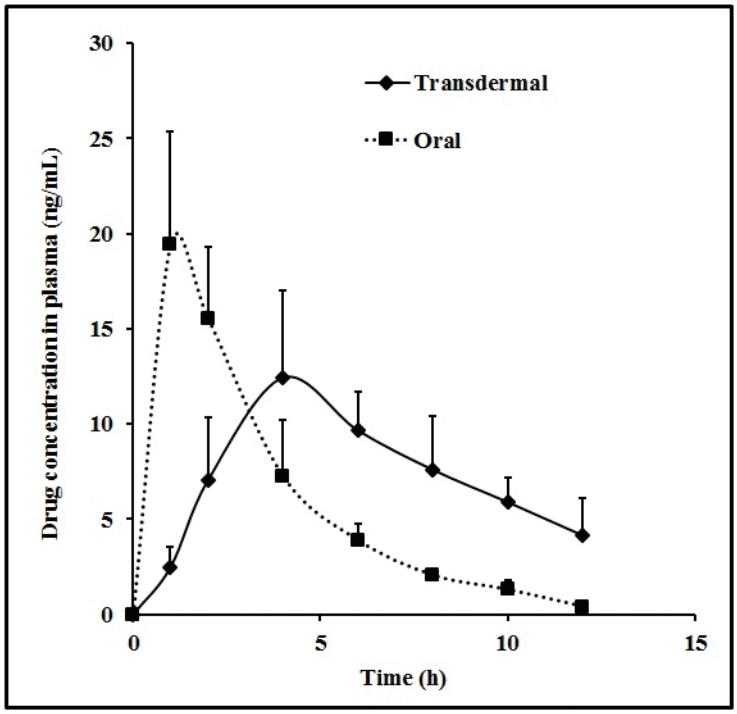

Figure 3: Comparison of concentration time profiles of vildagliptin in plasma (ng/mL) at different time intervals after transdermal (optimized patch) and oral administration in Wistar rats. All values are mean ± SD (n=6).

varies and the drug release is likely to be high from Duro-Tak 87-2510 patch. Thus it is speculated that the higher release of vildagliptin (Duro-Tak 87-2510 patch) may be likely due to hydrophilic nature of the adhesive, although the actual mechanism need to be investigated. Based on these results, Duro-Tak 87-2510 was selected for further studies. Moreover, the drug content in the selected vildagliptin patch was ~4 mg/cm^2, while the thickness was in the range of 270-315 μm.

The observed flux values in the above experiment indicate the intrinsic permeation potential of vildagliptin is moderately low (K_p =1.53×10^{-3} cm/h) to deliver therapeutically relevant concentration of drug. Thus to hold promise for further *in vivo* investigations, permeation enhancers which are most commonly employed and known to be potent and safe were selected (NMP, menthol, SLS and PEG 400). These enhancers were incorporated in the selected patch (fabricated using Duro-Tak 87-2510 adhesive, contain 15% (w/w) of vildagliptin and showed higher permeation) to screen their potential to improve transdermal delivery of vildagliptin. The mode of action of these chemical enhancers to augment the transport of drugs across the skin barrier is reported in the literature.[25,26] Indeed, the use of such chemical agents in adhesive patches seems to be most effective approach to overcome the barrier properties of stratum corneum, which in turn leads to higher permeation.[25,27] The concentration of enhancers was fixed at 5% w/w, which is reported to be safe and effective *in vivo*. The permeation profiles of the patches containing different chemical enhancers are depicted in Figure 2. The profile observed in Figure 2 signify the use of chemical agents, wherein the drug permeation was enhanced considerably, but not to the same extent. The highest flux value of vildagliptin was observed by the addition of SLS (22.96 ± 3.58 μg/cm^2/h; P<0.0001), which is ~4 folds higher as compared to flux value observed with control (patch with no enhancers), among chemical enhancers tested.This substantial improvement in permeation of vildagliptin by SLS may be due to its renowned property to fluidize intercellular lipid bilayer of stratum corneum which in turn reduce the barrier resistance.[28] In addition, it is likely that the negatively charged SLS possibly will surge the membrane charge and improve the permeation of vildagliptin, which is positive in charge. On the other hand, the observed enhancement in vildagliptin flux values with enhancers like NMP, menthol and PEG 400 were ~3, ~2 and ~1.5 folds, respectively as compared with control. Based on the higher flux values, the patch contain SLS as enhancer was selected for *in vivo* investigation.

Figure 3 compares the mean plasma concentration time curves of vildagliptin following transdermal administration of optimized formulation and oral administration of suspension (4 mg of vildagliptin in 1 mL) in Wistar rats. The observed mean pharmacokinetic parameters of vildagliptin such as C_{max}, T_{max} and $AUC_{0-\alpha}$ is listed in Table 2. It can be seen that the pharmacokinetic profiles

of vildagliptin were different for transdermal and oral delivery (Figure 3). In case of transdermal administration, drug permeation was slow in the initial hour (~2.5 ng/mL) while in oral delivery the C_{max} (~20 ng/mL) was achieved in the first hour itself. The short T_{max} value in oral therapy (Table 2) indicate that vildagliptin absorption is rapid from the gastro intestinal tract. Followed by the quick absorption, the drug level declined rapidly in oral administration (Figure 3). However in transdermal application, drug level in the systemic circulation continued to increase until 4 h (T_{max}) with a C_{max} value of 12.44 ± 3.16 ng/mL, although lower than the oral therapy ($P<0.0001$). Thereafter, the plasma drug concentration decline slightly till the end of the study period (12 h). The overall mean value of $AUC_{0-\alpha}$ in transdermal delivery (1018.43 ± 79.56 ng.h/mL) was ~14 folds higher ($P<0.0001$) as compared to oral administration (Table 2), demonstrating improved bioavailability of vildagliptin by transdermal delivery. Indeed, this noticeable enhancement in AUC values (in case of transdermal application) signifies increased rate and extent of vildagliptin delivery from the newly formulated patch.

CONCLUSION

The *in vivo* data supported the *ex vivo* findings and suggest that the optimized drug in adhesive patch system can be a viable alternative approach to oral delivery of vildagliptin in patients with type 2 diabetes. However, vildagliptin level observed (C_{max}=12.44 ng/mL) under the current experimental condition (application area of patch is 1 cm^2) is well below the therapeutic range of vildagliptin (~100 ng/mL), suggesting a greater application area required to achieve the required drug concentration. Data observed in the current study demonstrate the potential of vildagliptin as promising candidate for developing a drug in adhesive transdermal delivery system consisting of Duro-Tak 87-2510 as pressure sensitive adhesive and SLS as enhancer, although need to be proved in human.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

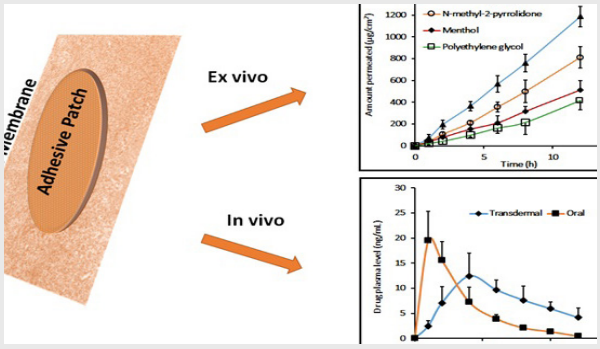
ABBREVIATION USED

$AUC_{0-\alpha}$: Area under the time–concentration curve from time 0 to ∞; C_{max}: Maximum plasma concentration; DPP4: Dipeptidy peptidase-4; HPLC: High performance liquid chromatography; NMP: N-methyl-2-pyrrolidone; PBS: Phosphate buffered saline; PEG 400: Polyethylene glycol; SLS: Sodium lauryl sulphate; T_{max}: Time to reach maximum plasma concentration; US FDA: United States Food Drug and Administration; WHO: World Health Organization.

SUMMARY

- The major concern in the oral therapy of vildagliptin is hepatotoxicity, hence regular hepatic function tests are recommended.
- Transdermal delivery system of vildagliptin is likely to overcome the hepatic adverse effects and maintain proper blood level for a prolonged period of time.
- *Ex-vivo* permeation studies showed significant enhancement in vildagliptin permeation in the presence of chemical enhancers.
- *In vivo* data suggest that the feasibility of delivering vildagliptin through skin.

Pictorial Abstract



REFERENCES

1. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care. 2011; 34(6): 1249-57.
2. Kibiti CM, Afolayan AJ. Herbal therapy: A review of emerging pharmacological tools in the management of diabetes mellitus in Africa. Phcog Mag. 2015; 11(44): 258-74.
3. Naqvi A, Pandey A, Gupta V, Malasoni R, Srivastava A, Pandey RR, Satyanarayana M, Pratap R, Dwivedi AK. Assay method for quality control and stability studies of a new anti-diabetic and anti-dyslipidemic flavone (S002-853)*. Phcog Mag. 2015; 11(42): 53-9.
4. Chiabchalard A, Nooron N. Antihyperglycemic effects of Pandanus amaryllifoliusRoxb. leaf extract. Phcog Mag. 2015; 11(41): 117-22.
5. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs. 2005; 65(3): 385-411.
6. Holman RR. Type 2 diabetes mellitus in 2012: Optimal management of T2DM remains elusive. Nat Rev Endocrinol. 2013; 9(2): 67-8.
7. Attimarad M, Nagaraja SH, Aldhubaib BE, Nair A, Venugopala KN. Simultaneous determination of metformin and three gliptins in pharmaceutical formulations using RP HPLC: Application to stability studies on linagliptin tablet formulation. Indian J Pharm Edu Res. 2014; 48(4): 45-53.
8. Campbell RK. Clarifying the role of incretin-based therapies in the treatment of type 2 diabetes mellitus. ClinTher. 2011; 33(5): 511-27.
9. Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. Diabetes Care 2010; 33(2): 428-33.
10. Ghosh B, Iyer D, Nair AB, Sree HN. Prospects of iontophoresis in cardiovascular drug delivery. J Basic Clin Pharm. 2012; 4(1): 25-30.
11. Harsha SN, Al-Dhubiab BE, Alhaider IA, Attimarad M, Nair AB. Carbopol 934-P loaded with vildagliptin for diabetic delivery: *in vitro* and *in vivo* evaluation of nanoparticles. Curr Nanosci. 2013; 9(5): 642-47.
12. Nair AB, Vaka SR, Gupta S, Repka MA, Murthy SN. *In vitro* and *in vivo* evaluation of a hydrogel-based prototype transdermal patch system of alfuzosin hydrochloride. Pharm Dev Technol. 2012; 17(2): 158-63.
13. Tirunagari M, Jangala VR, Nandagopal A. Development and physicochemical, *in vitro* and *in vivo* evaluation of transdermal patches of zaleplon. Indian J Pharm Edu Res. 2013; 47(4): 49-58.
14. Ghosh A, Banerjee S, Kaity S, Wong TW. Current pharmaceutical design on adhesive based transdermal drug delivery systems. Curr Pharm Des. 2015; 21(20): 2771-83.
15. Jung E, Lee EY, Choi HK, Ban SJ, Choi SH, Kim JS, Yoon IS, Kim DD. Development of drug-in-adhesive patch formulations for transdermal delivery of fluoxetine: *In vitro* and *in vivo* evaluations. Int J Pharm. 2015; 487(1): 49-55.
16. Ren C, Fang L, Ling L, Wang Q, Liu S, Zhao L, He Z. Design and *in vivo* evaluation of an indapamide transdermal patch. Int J Pharm. 2009; 370(1): 129-35.
17. Nair AB,Kumria R, GuptaS, Al-Dhubiab BE. Development and evaluation of a novel drug in adhesive transdermal system of levodopa and carbidopa. J Pharm Innov. 2014; 9(40): 302-8.
18. Wolff HM, Irsan, Dodou K. Investigations on the viscoelastic performance of pressure sensitive adhesives in drug-in-adhesive type transdermal films. Pharm Res. 2014; 31(8): 2186-202.
19. Jacob S, Shirwaikar A, Nair A. Preparation and evaluation of fast-disintegrating effervescent tablets of glibenclamide. Drug Dev Ind Pharm. 2009; 35(3): 321-8.
20. Anroop B, Ghosh B, Parcha V, Kumar A, Khanam J. Synthesis and comparative skin permeability of atenolol and propranolol esters. J Drug Del Sci Tech. 2005; 15(2): 187-90.
21. Nair AB, Kumria R, Al-Dhubiab BE, Attimarad M, Harsha S. Noninvasive sampling of gabapentin by reverse iontophoresis. Pharm Res. 2015; 32(4): 1417-24.
22. Gerber GS, Fox LT, Gerber M, du Preez J, van Zyl S, Boneschans B, Plessis Jd. Stability, clinical efficacy, and antioxidant properties of Honeybush extracts in semi-solid formulations. Phcog Mag. 2015; 11(44): 337-51.
23. Nair AB. Quantification of uptake and clearance of acyclovir in skin layers. Antivir Ther. 2015; (in press, doi: 10.3851/IMP2970).
24. Nair A, Reddy C, Jacob S. Delivery of a classical antihypertensive agent through the skin by chemical enhancers and iontophoresis. Skin Res Technol. 2009; 15(2): 187-94.
25. Nair A, Vyas H, Shah J, Kumar A. Effect of permeation enhancers on the iontophoretic transport of metoprolol tartrate and the drug retention in skin. Drug Deliv. 2011; 18(1): 19-25.
26. Marwah H, Garg T, Goyal AK, Rath G. Permeation enhancer strategies in transdermal drug delivery. Drug Deliv. 2015; (in press, doi: 10.3109/10717544.2014.935532).
27. Khan AW, Kotta S, Ansari SH, Sharma RK, Kumar A, Ali J. Formulation development, optimization and evaluation of aloe vera gel for wound healing. Phcog Mag. 2013; 9, Suppl S1:6-10.
28. Murthy SN, Vaka SR, Sammeta SM, Nair AB. TranScreen-N: Method for rapid screening of trans-ungual drug delivery enhancers. J Pharm Sci. 2009; 98(11): 4264-71.