Formulation and Evaluation of Saxagliptin Trandermal Patches Of Anti Diabetic Drugs

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Abstract-

The transdermal drug delivery systems were developed to overcome the limitations associated with oral administration and to mimic the effects of intravenous infusion. The solubility of poorly soluble anti-diabetic drugs was enhanced by preparing solid dispersion using beta cyclodextrin as a carrier in the ratio of 1:2. The solid dispersions were evaluated by solubility study, scanning electron microscopy and X-ray diffraction studies which indicated the conversion of drug into amorphous form. The permeability of saxagliptin was enhanced by employing 4% sodium lauryl sulphate by co- surfactant method. The above mentioned physically modified drugs were formulated as transdermal delivery systems using hydroxy propyl methyl cellulose, ethyl cellulose and chitosan as rate controlling polymers. The formulated transdermal drug delivery systems were evaluated for physico-chemical properties and *in vitro* diffusion study and *in vivo* studies. Based on the evaluation criteria S4 (saxagliptin) which were on par with the aim and objective of the present investigation were optimized. Compatibility studies indicated that there was no chemical interaction between the drugs and polymers employed in the formulation. It was found that there was significant reduction in the blood glucose levels on transdermal administration for a prolonged period of time without hypoglycemic effect.

INTRODUCTION-

Diabetes mellitus is a common endocrine disorder of blood glucose metabolism, which has a number of deleterious health consequences and increases the risk of premature death in those affected. This disorder is categorized in two main forms.

Type I diabetes (juvenile onset diabetes) – In this form, there is deficiency of the hormone insulin, which is required to regulate blood glucose levels. Insulin replacement is the only option to manage type I which typically occurs in childhood or adolescence.

Type II diabetes (maturity onset diabetes) – In this form, the resistance to the glucose lowering impact of insulin causes the disorder of improper blood glucose regulation. Its onset and clinical effects are typically insidious and therefore the finding of elevated blood sugar or impaired glucose regulation is commonly incidental. Particularly in the early stages, blood glucose management could also be achieved by dietary measures alone or by the use of (oral hypoglycemic) drugs that increase the body's sensitivity to naturally occurring insulin.

Globally type II diabetes represents over 90% of all diabetes. Various investigations in virtually all continents of the globe have identified an alarming increase in the prevalence of type II malady in recent decades. It is estimated that there are currently some 190 million people with diabetes and that this range can increase to in excess of 300 million within the consecutive 20years. The World Health Organization (WHO) and others predict that India will be the leading country with highest number of people with diabetes within 20years, increasing from around 23million in 2000 to 57 million in 2025. Currently available oral hypoglycemic agents are categorized according to their

mode of action.

Drugs administered orally, produces wide range of fluctuations in plasma that leads to undesirable effects like toxicity or poor efficacy of drug. Some of the drugs may cause gastric disturbances, and some of them may undergo first pass metabolism. In such cases traditional route is not preferable. These limitations can be overcome by formulating transdermal delivery systems.

To overcome limitations of the oral route and to attain the advantages of intravenous drug infusion intravenous such as bypass hepatic "first pass" elimination, to maintain constant prolonged therapeutic and effective levels of drug in the body, which can be closely duplicated without its potential hazards is the transdermal administration through the intact skin.

2.0 DRUG PROFILE-

SAXAGLIPTIN:

Saxagliptin is a new oral antidiabetic agent of dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs used for the treatment of non-insulin dependent diabetes mellitus (NIDDM).

- **Chemical name:**

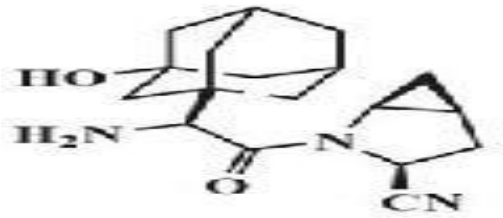
(1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile.

- **Molecular formula:**

The molecular formula of saxagliptin is $C_{18}H_{25}N_3O_2$.

- **Molecular weight:** 315.417 g/mole

- **Chemical structure:**



- **Solubility characteristics, partition coefficient and pKa value:**

Saxagliptin may be a white to light weight yellow or brown powder.

Saxagliptin is sparingly soluble in water, slightly soluble in ethyl acetate, soluble in methanol, isopropanol, acetonitrile and acetone.

❖ The pKa value of saxagliptin is 7.9.

- **Melting point:**

The melting point of saxagliptin was found to be 205-207˚C.

- **Mechanism of action:**

Saxagliptin is a reversible, competitive, DPP-4 inhibitor with nanomolar potency. Saxagliptin demonstrates selectively for DPP-4 versus other DPP enzymes, with greater than 75 fold selectivity over DPP-8 and DPP-9. Saxagliptin has extended binding to the DPP-4 active site, prolonging its inhibition of DPP-4 by showing the inactivation of incretin hormones.

The log partition coefficient (log P) in n-octanol–water is 0.98

3.0 MATERIAL AND METHODS-

The following chemicals and equipment were employed in the present research project. The materials and equipment used for the formulation of saxagliptin transdermal patches were listed in **Table: 3.1,3.2** respectively.

Table No. 3.1: **List of chemicals**

S.No.	Materials	Supplier
1	Saxagliptin	SMS Pharmaceuticals Ltd.
2	Ethyl cellulose	LobaChemiPvt.Ltd.
3	Hydroxypropyl methyl cellulose	LobaChemiPvt.Ltd.
4	Chitosan	LobaChemiPvt.Ltd.
5	Tween 80	LobaChemiPvt.Ltd.
6	Propylene glycol	Fischer Scientific
7	β –Cyclodextrin	Sigma Aldrich
8	Methanol	Merck Life Sciences Pvt.Ltd.
9	Potassium dihydrogen orthophosphate	LobaChemiPvt.Ltd.
10	Sodium hydroxide	LobaChemiPvt.Ltd.
11	Chloroform	LobaChemiPvt.Ltd.
12	Acetic acid	LobaChemiPvt.Ltd.

Table No. 3.2: List of equipment

S.No.	Equipment	Manufacturer
1	Electronic balance	Sartorius, Mumbai
2	Digital screw gauge	Sartorius, Mumbai
3	Hot air oven	Remi
4	Magnetic stirrer	Remi
5	Tensile strength and elongation testing apparatus	Lab India
6	UV spectrophotometer	Shimadzu
7	FTIR spectrophotometer	Bruker – Alpha
8	Sonicator	VJ Instruments, Mumbai
9	Digital pH meter	Remi

10	Melting point apparatus	Remi
11	DSC	Q 20
12	One touch glucometer	Johnson & Johnson
13	HPLC	Shimadzu

3.1 Preparation of standard calibration curve for saxagliptin at 274nm:

100mg of saxagliptin was weighed accurately into a 100mL volumetric flask and dissolved in few mL of phosphate buffer saline of pH 7.4 with sonication. The volume was finally made up to 100mL with phosphate buffer saline of pH 7.4 to attain a concentration of 1000µg/mL (SS-I). 10mL was pipetted from the stock solution – I into a 100 mL volumetric flask and the volume was finally made up with phosphate buffer saline of pH 7.4 to attain a concentration of 100µg/mL (SS-II). From SS - II, working standard solutions were prepared.

From (SS-II) aliquots of 0.5mL, 1.0mL, 1.5mL, 2.0mL and 2.5mL were pipetted out into labelled 10ml volumetric flasks and the volume was made with phosphate buffer saline of pH 7.4 to attain a concentration ranging from 5-25µg/ml. The resulting solutions were analyzed using UV spectrophotometer at 274 nm against the respective parent solvent as a blank. The calibration curve was plotted for absorbance values and concentration for the estimation the drug.

S.no.	**Concentration(µg/ml)**	**Absorbance (Mean ± S.D)**
1	5	0.22±0.012
2	10	0.441±0.055
3	15	0.667±0.025
4	20	0.888±0.036
5	25	0.997±0.011

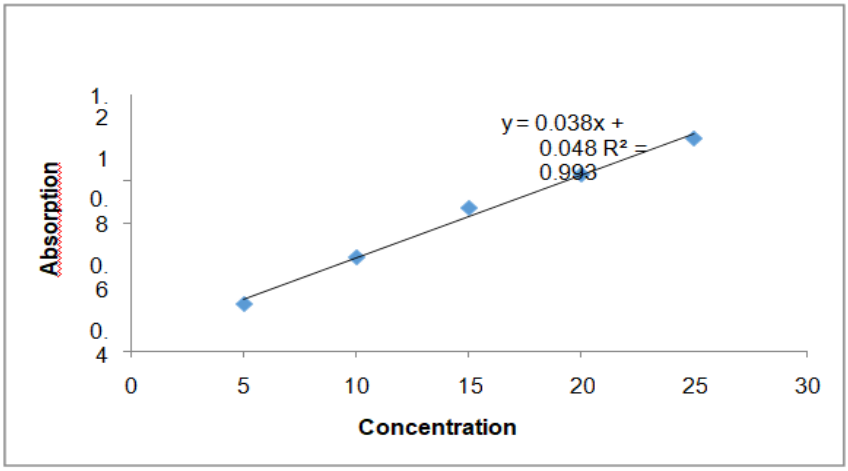


Fig.6.1 Calibration curve for the estimation of saxagliptin

3.1 Preformulation studies:

Preformulation studies like solubility, partition coefficient, and melting point were carried out as per the given procedure prior to the development of transdermal system.

❖ **Solubility measurement:**

The solubility of Saxaliptin was determined in pH 7.4 phosphate buffer, water, methanol, alcohol(95%), chloroform, isopropanol, ethyl acetate, ether, acetone and acetonitrile. Glimepiride was added in an excess amount to 10 mL of all the above mentioned solvents. The samples were stirred for 24 hrs at 37˚C and filtered through
0.45 micron whatmann filter paper and the absorbance value was measured using UV spectrophotometer.

❖ **Partition coefficient:**

The lipophilicity of a molecule can be predicted from its oil-water partition coefficient value. This can be used to anticipate its capability to bypass the biological membranes. Partition coefficient was determined by shake flask method which was widely used.

A saturated solution of Saxaliptin in 5 mL of n-octanol was prepared by incorporating the drug in minute amounts. The above solution was clarified using whatmann filter paper. 3mL of the saturated solution was mixed with 2mL of fresh n-octanol. 5mL solution of n-octanol containing Saxaliptin was added to 15mL of water. Then the two phases were set aside for equilibration at 37°C for 24hrs. Necessary dilution was made and the concentration of drug in organic phase and aqueous phase was determined by UV spectroscopy. The ratio of drug concentration in each phase which is the apparent partition coefficient(K_p) was calculated by the following equation.

$$K_p = C_{org} / C_{aq} \quad \text{Eq 3.1}$$

Where,

C_{org} – Drug concentration in organic phase

C_{aq} – Drug concentration in aqueous phase.

❖ **Determination of melting point :**

The determination of melting point of the selected drug was carried out by taking a required quantity of the drug substance in a capillary tube closed at one end. The tube was mounted in digital melting point apparatus and temperature at which the drug melted was recorded.

Compatibility studies of drug and polymers:

❖ **FTIR studies:**

Fourier transform infrared spectroscopic technique can be applied in the qualitative analysis of the drugs and related substances either in pure form or in mixture and to establish the structure of the compound. An elaborate information about the structure of molecular compounds can be provided by IR spectra as it is related to covalent bonds. In order to ascertain this, comparison was done between the spectrum of the pure compound and the substance. The compatibility of the drug with the polymers and the identity of the drug can be confirmed with infrared spectra.

Infrared spectra of drug, polymers, alone and in formulation were depicted. Then it was further investigated for any potential interaction between drug and polymer.

Differential scanning calorimetry (DSC):

Differential scanning calorimetry is a widely used analytical technique in which the heat flow to or from a reference standard was monitored as a function of time or temperature, while the sample is subjected to a controlled temperature program. The main principle involved was the determination of the enthalpy of caloric process by measuring the flow of heat between the samples and reference standard with linear or isothermal heating or cooling: calibration of the heat capacity with standards of heat of fusion. Thermal properties of the pure drug, optimized formulations and optimized formulations subjected to stability studies were evaluated by differential scanning calorimetry. The analysis was performed from a temperature range of 30 to 300˚C at an increase rate of 5˚C/ min under nitrogen flow of 25 mL/min.

3.2 Preparation of transdermal patches of saxagliptin:

Transdermal drug delivery systems of saxagliptin were developed by solvent evaporation method using different grades of polymers in varying ratios. The polymers ethyl cellulose, hydroxy propyl methyl cellulose and chitosan were weighed in requisite quantities and dissolved in 50mL of methanol and 0.1N acetic acid to form polymer solution. To the above solution weighed quantity of saxagliptinwas then added and stirred by using a magnetic stirrer until drug dissolved. Finally required quantities of plasticizer and permeation enhancer were added to the above dispersion. The solution was poured on a film former and dried at ambient temperature for 24 hours. The solvent was evaporated to leave stable, flexible patches.

S. N.	Formulation	Drug	EC	HPMC	Chitosan	Propylene Glycol	SLS	Solvent mixture
1	S1	20mg	100mg	50mg	-	20%	4%	50ml
2	S2	20mg	100mg	100mg	-	20%	4%	50ml
3	S3	20mg	200mg	100mg	-	20%	4%	50ml
4	S4	20mg	300mg	100mg	-	20%	4%	50ml
5	S5	20mg	-	-	50mg	20%	4%	50ml
6	S6	20mg	-	-	100mg	20%	4%	50ml

4.0 RESULTS AND DISCUSSION

4.1 Preparation of standard calibration curve for saxagliptin at 274nm

Saxagliptin showed absorption maxima at 274nm in phosphate buffer saline of pH 7.4. The spectrophotometric determination exhibited linearity range of 5 to 25µg/ml. The absorption data points were considered for linear regression analysis. The equation of straight line y= 0.0387x+0.0487 was generated for the calculation of amount of the drug. The coefficient of determination (R^2) was found to be 0.9939.

The present analytical method developed was suitable for estimation of saxagliptin as it obeyed Beer's law in the concentration range of 5-25 µg/mL.

4.2 Preformulation studies:

Saxagliptin was soluble in water, chloroform, acetone, acetonitrile, methanol, ethanol, ether, alcohol (95%) and slightly soluble in ethyl acetate.

The melting point of saxagliptin was recorded as 170˚C which complied with pharmacopoeial standards.

The partition coefficient of saxagliptin was determined in n-octanol and water.

The logarithmic value of partition coefficient (log P) was recorded to be 1.2.

The calculated steady state permeability coefficient (K_p) of the drug diffused through the dialysis membrane was found to be 0.2×10^3 cm/hr. The intrinsic membrane permeability of saxagliptin was very low. Hence the permeability of saxagliptin needed to be enhanced.

4.3 Compatibility studies:

The FTIR spectra of pure drug saxagliptin, EC, HPMC, chitosan and optimized formulation were shown in **Fig.**

The FTIR spectra of the pure saxagliptin showed peak at 3433.12 cm^{-1} due to N-H stretch; 2919.18 cm^{-1} due to C-H stretch; 3330-2500 cm^{-1}due to OH stretch; 1519.77 cm^{-1} due to C-N; 1033 cm^{-1} due to C-O stretching confirming the drug structure.

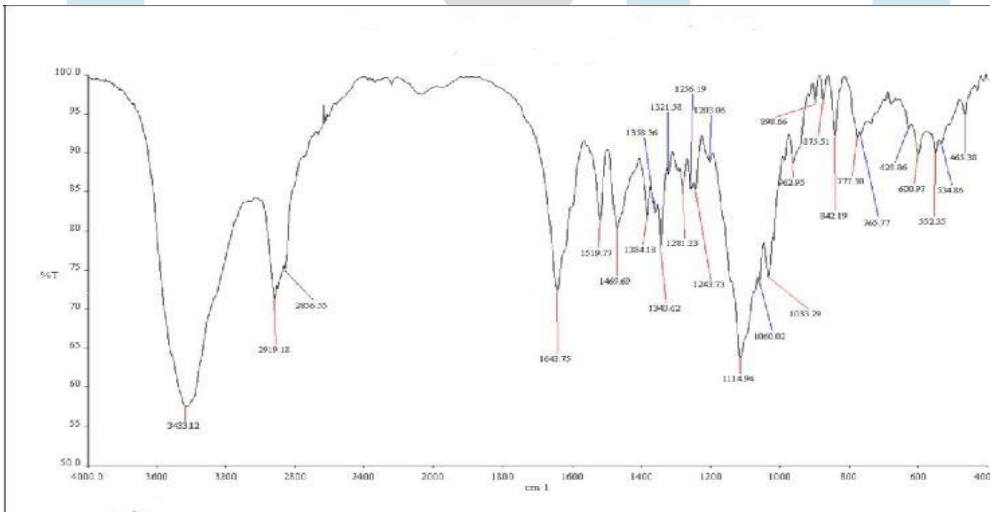


Fig 7.1: FT-IR spectra of saxagliptin

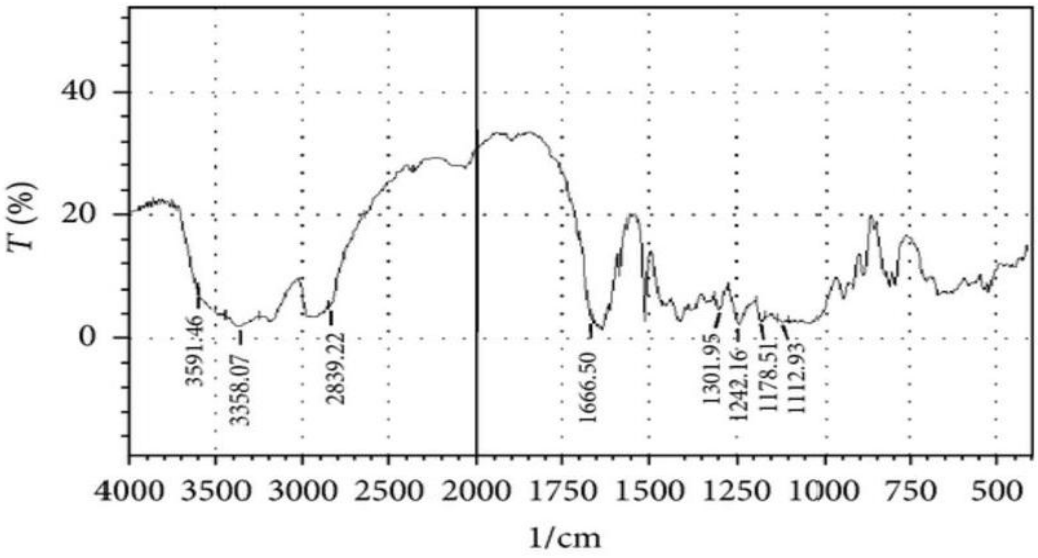
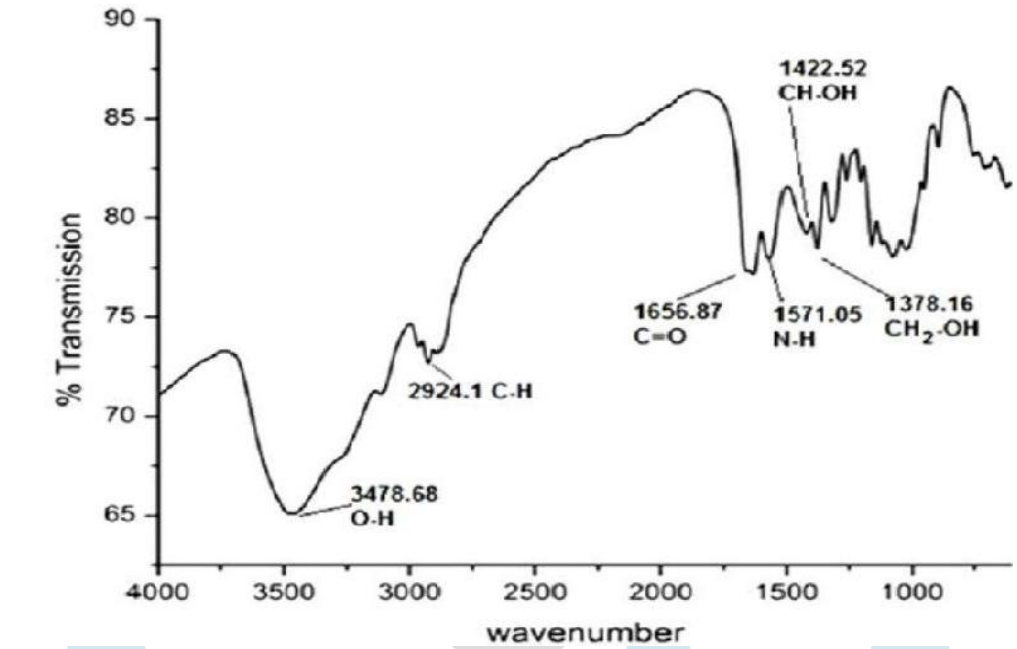


Fig 4.1: FT-IR spectra of HPMC

Fig : 4.2FT-IR spectra of chitosan



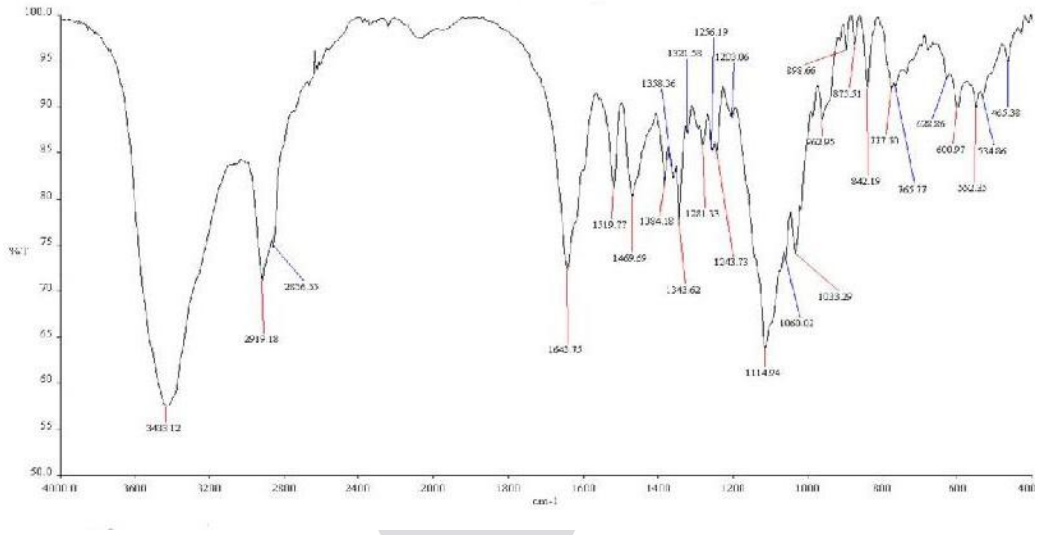
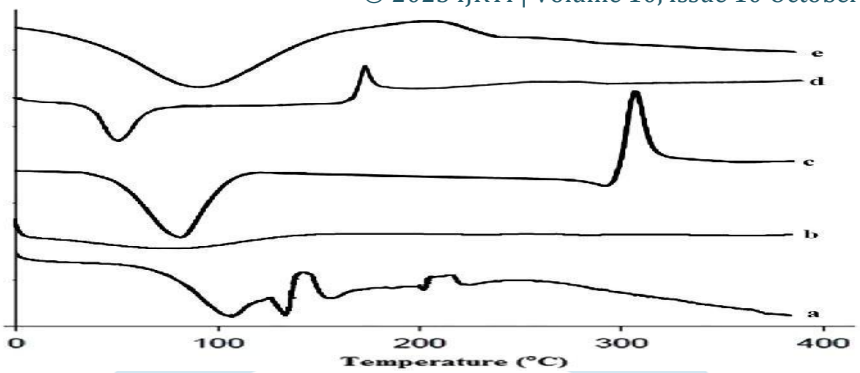


Fig 4.3: FT-IR spectra of optimized formulation (S4)

The absence of any chemical interactions between the drug and polymers was confirmed from FTIR analysis.

The DSC thermograms of pure drug saxagliptin and pure polymers HPMC, EC, chitosan and optimized formulation are shown in **Fig.** The slight shift observed in DSC thermograms of saxagliptinoptimized formulation was due to slight physical interaction between the drug and polymer without any chelation orchemicalinteraction. The unaltered peaks of saxagliptin in DSC thermograms of optimized formulation confirmed no



interaction.

Fig. 4.5: DSC thermogram of a. Saxagliptinb. HPMC c. EC d. Chitosan

Optimized formulation (S4)

4.4 Evaluation of formulated transdermal patches:

The formulated saxagliptin patches were evaluated for physical appearance, folding endurance, thickness, uniformity of weight, percentage drug content, percentage moisture content, tensile strength, elongation and *in vitro* permeation studies as per the procedure.

The physicochemical evaluation of the formulated saxagliptin patches revealed that the thickness was uniform throughout the entire length of the patch with low standard deviation values. The observed results were listed in **Table. 7.1.**

The weight of the saxagliptin patches was in the range of 0.098±0.085 gm to 0.478±0.013 gm. The results are presented in the **Table. 7.1**

Uniform reproducible controlled release of the drug from the patch was due tohomogeneous drug distribution which was one of the important characteristics of a transdermal system. The results revealed that the percentage drug content was almost uniform in the range of 90.45±0.02 to 97.36±0.01 in all the patches with low standard deviation values.

The increase in chitosan concentration had a renowned effect on the percentage moisture content of saxagliptin patches. The percentage moisture content results were in between 0.345 to 1.125.

The tensile strength of the patches was found to vary with the nature of the polymer, viscosity of solution and plasticizer. Polymer combination of EC and HPMC possessed high tensile strength when compared to the chitosan patches. The tensile strength results were in between 0.324±0.012 kg/mm^2 to 0.475±0.013 kg/mm^2 and the elongation was in between 13.45±0.855mm to 24.56±0.755mm.

Table:: Physico-chemical properties of saxagliptin patches

S.N.	Formulation code	Folding endurance	Thickness (mm)	Weight uniformity (gm)	Drug contet (%)	%moisturecontent	Tensilestrength (kg/m^2)	Elongation (mm)
1	S1	84±10.1	0.114±0.029	0.128±0.012	92.77 ±0.01	0.429	0.385±0.01	24.49± 1.086
2	S2	96±12.2	0.103±0.023	0.215±0.011	90.45 ±0.02	0.589	0.475±0.0134	22.35± 1.704
3	S3	202±7.5	0.181±0.011	0.308±0.034	94.48 ±0.01	0.345	0.424±0.0122	16.44± 1.151
4	S4	221±6.39	0.131±0.017	0.418±0.013	97.36 ±0.02	0.452	0.474±0.0093	24.56± 0.712
5	S5	185±8.08	0.102±0.028	0.068±0.085	94.72 ±0.05	1.001	0.324±0.0126	13.45± 0.855
6	S6	162±7.9	0.111±0.012	0.115±0.012	92.23 ±0.07	1.125	0.345±0.012	20.87± 0.923

➢ 7.4.1 In vitro release

In vitro release of saxagliptin across dialysis membrane from S1 and S2 formulation showed only 62.19% and 65.26% at the end of 24hrs. The slope of linear graph was considered to calculate the flux and it was found to be 36.09 and 38.27μg/cm^2/h × 10^{-2}, diffusion coefficient was 0.57 and 0.61 cm^2/h× 10^{-2} respectively. It was evident from the above result that there was a lower flux and lower diffusion rate through the dialysis membrane. However, at the end of 24hrs, *in vitro* release of saxagliptin across dialysis membrane from formulation S3, S4,S5 and S6 were 70.33%, 78.43%, 72.49% and 69.66% respectively. The flux for the formulation of S3,
S4, S5 and S6 was 38.57, 50.75, 43.93and 42.16 μg/cm^2/hr × 10^{-2}, diffusion coefficient was 0.72, 0.80, 0.73 and 0.71cm^2/hr × 10^{-2}. It was revealedfrom the above results that the S4 shows the prolonged outcome of drug from the patches.

In the formulation of S4, containing EC and HPMC in the ratio of 3:1, showed 78.43% saxagliptin release at the end of 24hr study. The flux and diffusion coefficient was found 50.75 μg/cm^2/h × 10^{-2} and 0.80 cm^2/h× 10^{-2} respectively.

The hydrophilic and swellablenature of the polymers which could affect the release of drug from the patches may be considered for the maximum release of drug from S4. The rapid diffusion of drug from the surface and consequent increase in the path length of diffusion may be the cause for controlled release of the drug from the

patch. The physicochemical properties of the formulation S4 depicted suitable formulation for the transdermal delivery. Basing on above criteria, S4 was hand picked as an optimal formulation.

Table:: In-vitro diffusion study of saxagliptin formulations S1-S6 through dialysis membrane

S.No.	Time(hrs)	S1	S2	S3	S4	S5	S6
1	1	12.84	14.92	17.43	20.72	14.66	12.45
2	2	14.68	17.22	20.38	24.46	18.44	15.32
3	3	17.19	20.89	23.57	28.48	21.18	19.14
4	4	20.46	24.45	26.81	34.54	25.42	23.14
5	5	23.69	28.38	30.53	39.17	30.88	28.54
6	6	27.44	31.42	35.61	44.22	34.54	33.12
7	7	30.45	35.39	39.21	48.41	39.64	37.85
8	8	33.29	39.44	46.58	51.88	44.26	41.25
9	12	45.09	51.77	54.81	65.27	56.02	54.21
10	24	62.19	65.26	70.33	78.43	72.49	69.66

5.0 SUMMARY AND CONCLUSION

The transdermal drug delivery systems were developed to overcome the limitations associated with oral administration and to mimic the effects of intravenous infusion. The solubility of poorly soluble anti-diabetic drug saxagliptin was enhanced by preparing solid dispersion using beta cyclodextrin as a carrier in the ratio of 1:2. The solid dispersions were evaluated by solubility study, scanning electron microscopy and X-ray diffraction studies which indicated the conversion of drug into amorphous form. The permeability of saxagliptin was enhanced by employing 4% sodium lauryl sulphate by co- surfactant method. The above mentioned physically modified drugs were formulated as transdermal delivery systems using hydroxy propyl methyl cellulose, ethyl cellulose and chitosan as rate controlling polymers. The formulated transdermal drug delivery systems were evaluated for physico-chemical properties and *in vitro* diffusion study and *in vivo* studies. Based on the evaluation criteria S4 (saxagliptin) which was on par with the aim and objective of the present investigation were optimized. Compatibility studies indicated that there was no chemical interaction between the drugs and polymers employed in the formulation.

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