

**Research Article****Formulation, development and characterization of transdermal drug delivery system for antidiabetic drug**

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**Abstract**

**Background:** The Transdermal Drug Delivery System is utilized for delivery of the drug through the intact skin into a systemic circulation. It is an alternative to oral drug delivery system and hypodermic injection. Saxagliptin belongs to the category of insulin-dependent antidiabetic drug which is used in the treatment of type 2 diabetes. **Objective:** The main aim of this research work is to formulate transdermal patch of Saxagliptin using a hydrophilic polymer which is intended to increase the bioavailability by penetrating poorly water-soluble drug through the surface of the skin and also making possible to avoid hepatic first pass metabolism. **Materials and Methods:** The present study was carried out to develop saxagliptin transdermal patch by using requisites ratio of a different polymer such as HPMC & PVP, along with Methanol, Dibutyl Phthalate and DMSO are used as a solvent, plasticizer and penetration enhancer respectively. Saxagliptin transdermal patch was prepared using solvent evaporation method. **Results:** The prepared transdermal films were evaluated for following parameters like thickness, weight variation, folding endurance, surface pH, tensile strength, percent flatness and drug content. *In vitro* drug permeation was determined by using Franz diffusion cell in phosphate buffer (pH 7.4). All the evaluation was done for six formulations F1 to F6. It was found that formulation F6 showed the best compatibility on the basis of the entire all evaluations test was performed. **Conclusion:** The obtained results conclude that the formulations can be promising therapeutic systems for the transdermal delivery of Saxagliptin to avoid the problem of the parenteral and oral route.

**Keywords:** Transdermal drug delivery system, patch, Saxagliptin, diabetes

**Introduction**

The transdermal delivery system is one of the best routes for new drug delivery system. Transdermal drug delivery gives more advantages over conventional delivery methods including oral and injection methods. The generally transdermal drug delivery system uses a patch containing drug substance enter via the skin, is convenient and painless, and avoids gastrointestinal toxicity (e.g. peptic ulcer disease) and avoids the therapeutic first pass metabolism. Transdermal drug delivery is rarely an old technology since 1800's and the technology is no longer just adhesive patches. The novel improvement in technology and the tendency to applying on the

skin without irritation to the site of action, the transdermal route is becoming a most widely accepted route of drug administration (Jamaandi et al., 2009).

The most suitable route of administration is an oral route but oral route have some problem like hepatic first-pass metabolism, poor bioavailability and tendency to produce rapid blood level spikes and this leads to frequent dosing, so to overcome this problem there is a need for the development of new drug delivery system. Transdermal drug delivery system supply predictable and extended duration of activity (Bagyalakshmi and Vmshikrishna, 2008).

The main aim of this research work is to formulate transdermal patch of Saxagliptin using a hydrophilic polymer which is intended to increase the bioavailability by penetrating poorly water-soluble drug through the surface of the skin and also making possible to avoid hepatic first pass metabolism. The adverse effect caused due to overdosing can be decreased and dose can be terminated immediately at the

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time of irritation or termination of therapy (Murthy et al., 2008). At present study most of the drugs are taken orally but, they are not found to be as effective to the patient. So to improve the activity of such drug through the TDDS (Das et al., 2006).

Diabetes mellitus is a fastly growing health problem in worldwide and an important cause of prolonged ill health and causes to early death. It is a chronic metabolic disorder characterized by a high blood sugar concentration (hyperglycaemia) caused by deficiency of insulin. The requirement for transdermal film of saxagliptin is additional justified suitable to the need for maintaining unfluctuating plasma concentrations, for the effective management of blood sugar for long period in diabetic patients (Aurora and Mukherjee, 2009).

The main target of transdermal formulation dosage form design is to increase the drug permeability through the skin into the systemic circulation & simultaneously decreases the retention and metabolism of the drug in the skin. The formulation of the transdermal patch by using various polymers, plasticizer, penetrant & solvent was prepared. This formulated transdermal patch is used for the treatment of type 2 diabetes (Vandana and Rachna, 2011)

## Materials and Methods

### Materials

Saxagliptin was obtained as a gift sample from MSN Laboratories, Hyderabad. HPMC and PVP are purchased from SD fine-chem. Limited, world road Mumbai, India. Dibutyl phthalate, DMSO, Methanol purchased from LOBA CHEMIE Tarapur MIDC, palghar, Maharashtra (India). All other chemicals were of analytical grade.

### Formulation of Saxagliptin Loaded Transdermal Patch

Formulations of Saxagliptin patch by using solvent evaporation technique. Formulation of the transdermal patch polymers was weighed in requisites ratio of HPMC and PVP. The polymer mentioned above is dissolved in methanol followed by addition

of Dibutyl Phthalate and DMSO in methanol and the mixture was homogenized. Addition of accurate quantity of Saxagliptin (10 mg) in polymeric solution and sonicate the mixture to avoid the lumps. The above solution was poured into polyurethane coated Petri plate used in bangles. After pouring a solution in Petri plate was kept for drying 24 hrs at room temperature. Inverted glass funnel was placed on petri plate for controlling solvent evaporation rate. After drying patch were removed & wrapped in aluminum foil and store in desiccators until further use (Manjusha et al., 2011) (Table 1).

## Characterization of medicated polymeric patch

### Physical appearance

All the transdermal patches were visually inspected for color, clarity, smoothness and flexibility.

### Surface pH

The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was determined by using pH paper.

### Thickness

The thickness of the film was measured by using Micrometer Screw Gauze. The thickness uniformity was measured at three different sites and an average of three readings was taken with standard deviation.

### Folding endurance

A 4 cm<sup>2</sup> area of the strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance.

### Flatness

For flatness determination, one strip was cut (2 cm<sup>2</sup>) from the center and two from each side of patches. The length of each strip was measured and the difference in length was measured by determining percent constriction. It was calculated by using following formula:

$$\% \text{ constriction} = \frac{L1 - L2}{L2} \times 100$$

Where, L1 = initial length of each strip,

L2 = final length of each strip.

### Weight uniformity

Five films were cut (2 cm<sup>2</sup>) from each batch and weighed on electronic balance for weight variation test. The test was done to check the variation of weight and thus to check the

**Table 1.** Composition of various formulations

Sr. No.	Name of Ingredient	Formulations					
		F1	F2	F3	F4	F5	F6
1	Saxagliptin(mg)	10	10	10	10	10	10
2	Methanol(ml)	10	10	10	10	10	10
3	Hydroxypropyl methyl cellulose(mg)	0	50	100	150	200	300
4	Polyvinyl Pyrrolidone (mg)	300	250	200	150	100	0
5	DMSO (ml)	0.8	0.8	0.8	0.8	0.8	0.8
6	Dibutyl phthalate(ml)	2	2	2	2	2	2

batch- to- batch variation.

### Tensile strength

To determine the tensile strength of transdermal patches, the polymeric films in the transdermal patch were sandwiched individually by corked liner iron plates. One end of the patch was kept fixed with the help of iron screen and another end was connected to a freely movable thread over a pulley. The weight increased slowly to the pan close with the hanging end of the thread. A pointer on the thread used to measure the elongation of the film. The weight just sufficient to break the film was noted, the tensile strength was calculated using the following equation.

Tensile strength = Maximum applied force/ Minimum cross-sectional area

$$= m \times g / b \times t \text{ kg/mm}^2$$

Where, m- Mass in kg; g- Acceleration due to gravity at 980 cm/sec

### Drug content

As with all controlled release drug delivery systems, the final product evaluated for a TDDS must include content uniformity determinations. This test involves the assay of individual units of a specified number of dosage forms in order to determine homogeneity in their content. The film which was used for weight variation was evaluated for their drug content individually. The drug-containing films were dissolved in sufficient quantity of methanol and volume was made up to 10 ml with phosphate buffer pH 7.4. From this 1 ml was withdrawn and diluted to 10 ml with solvent and the drug content was determined spectrophotometrically. Based on the concentration obtained and the dilution factor, the drug content in each film was calculated.

### In-vitro skin permeation study

In-vitro drug permeation studies were performed by using a franz diffusion cell (Area = 28.26 cm<sup>2</sup>) with a receptor compartment capacity of 60 mL. The Human Cadaver skin was mounted between the donor and receptor compartment of the franz diffusion cell. The prepared patches were applied on the skin &

covered with aluminium foil as a backing membrane. The receptor compartment of the franz diffusion cell was filled with phosphate buffer pH 7.4. The assembly was put on a magnetic stirrer and the solution was continuously stirred using magnetic beads at 50 rpm, and the temperature 37 ± 0.5°C was maintain throughout the study. The samples were withdrawn at fixed time intervals to check for drug content by spectrophotometrically. The receptor phases were replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal and the *in - vitro* drug permeation through human cadaver skin was determine (Samip et al., 2010).

### Results and discussion

In a preformulation study of saxagliptin the colour, odour, appearance and melting point was determined (Table 2).

The thickness of the patches was found to be in the range 0.234 ± 0.020 to 0.308 ± 0.030 mm. The surface pH of all the formulation was found to be in the range of 6.14 ± 0.09 to 6.52 ± 0.07 which coincide with a pH range of skin and hence can be concluded that no skin irritation should be occur. The folding endurance of transdermal patches was measured manually. The folding endurance of the patches was found to be in the range of 112 ± 11.50 to 190 ± 14.97. The patches would not break and would retain their integrity with general skin folding when applied on the skin. The weight uniformity of formulated patches was found to be in the range of 20.58±0.46 to 24.89±0.56 mg. The Flatness studies showed that some of the formulations had the differences in the length before and after their cuts. It

**Table 2.** Organoleptic Characterization of Saxagliptin

Properties	Result Observed	Reported Result
Colour	White	White
Odour	Odorless	Odorless
Appearance	Fine powder	Fine powder
Melting Point	226°C-229°C	228°C

**Table 3.** Evaluation of Medicated Polymeric Patch

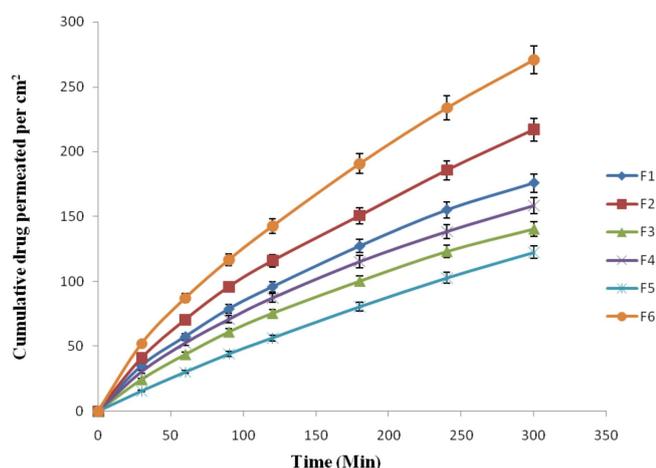
Formulations	Thickness (mm)	Surface pH	Folding Endurance	Tensile Strength(kg/cm <sup>2</sup> )	Percent flatness	Weight Uniformity (mg)
F1	0.283±0.015	6.25±0.20	145±11.53	1.165±0.05	101±0.05	20.98±0.58
F2	0.234±0.020	6.29±0.25	173±12.00	1.164±0.04	100±0.1	24.44±0.24
F3	0.253±0.036	6.38±0.18	112±11.50	1.163±0.07	101±0.06	22.46±0.58
F4	0.241±0.010	6.14±0.09	155±10.66	1.165±0.05	100±0.10	20.58±0.46
F5	0.308±0.030	6.35±0.14	121±13.79	1.167±0.08	101±0.17	24.53±0.30
F6	0.302±0.020	6.52±0.07	190±14.97	1.821±0.06	100±0.17	24.89±0.56

indicates percent constriction and almost 100 % flatness in all formulations. The tensile strength of the patches varies with the concentration of polymers. It was found to be between  $1.163 \pm 0.07$  to  $1.821 \pm 0.06$  kg/cm<sup>2</sup>. The results are shown in (Table 3). In comparisons of all formulation F6 show the best results.

The drug content varied between  $94.06\% \pm 0.62$  to  $98.69\% \pm 0.20$  of the drug incorporated in the formulations. Formulation F6 shows maximum drug content ( $98.69\% \pm 0.20$ ). *In - vitro* skin permeation study for transdermal patch, was performed for 7 hrs using excised human cadaver skin. Transdermal flux for different patches formulation was calculated and was found in the range of  $4.76 \pm 0.080$  to  $26.41 \pm 0.035$  µg/cm<sup>2</sup>/hr. Flux for F6 formulation was 6 times greater than that of the F5 formulation (see Table 4 & Figure 1). The F6 formulation is considered as the best and optimized formulation from thickness, surface pH, weight uniformity, flatness, drug content, folding endurance and *in vitro* permeation study results.

**Table 4.** *In vitro* drug permeation study

Sr. No.	Formulations	Drug Content(percent)	Flux (µg/cm <sup>2</sup> /hr)
1	F1	96.88 ± 0.36	18.72 ± 1.035
2	F2	97.18 ± 0.25	21.77 ± 1.432
3	F3	94.23 ± 0.45	12.91 ± 1.251
4	F4	94.06 ± 0.62	16.84 ± 1.652
5	F5	95.46 ± 0.54	4.76 ± 0.980
6	F6	98.69 ± 0.20	26.41 ± 1.735



**Figure 1.** Cumulative drug permeated per cm<sup>2</sup> of various transdermal patch

### Conclusion

Transdermal drug delivery system was developed by using Saxagliptin as a drug. The rationale behind choosing this drug was that all physicochemical properties of the drug were suitable for administering the drug via transdermal route. The transdermal patches were prepared by a solvent evaporation

method. The prepared patches were evaluated for thickness, surface P<sup>H</sup>, weight uniformity, flatness, drug content, folding endurance and *in-vitro* permeation study across excised human cadaver skin.

The formulated patches had good appearance and physical characteristics (no cracks, uniform thickness, mass and drug content) and showed high characteristics. The optimized HPMC (100%) patches (Formulation F<sub>6</sub>) showed the highest *in - vitro* drug permeation flux and drug content. The obtained results suggested that the formulations can be promising therapeutic systems for the transdermal delivery of Saxagliptin to avoid the problem associated with parenteral and oral route.

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**Conflicts of interest:** None

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