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Research Article

Formulation Designing Factors for Development of Repaglinide Transdermal Therapeutic System

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ABSTRACT

Repaglinide, a blood-glucose-lowering drug, has a shorter half-life (~1 hour), low oral bioavailability (LOB) (~56 %) due to the first-pass metabolism, and required frequent dosing (Three to four times daily) to control blood glucose level. Repaglinide transdermal therapeutic system (TTS) was prepared to provide continuous drug delivery for a prolonged time. Designing factors for development are selection and optimization of product ingredients, optimization of drug load, types of TTS, matrix thickness, and optimization of drug delivery. During development, repaglinide TTS were evaluated for physicochemical characteristics and *ex-vivo* skin flux at different stages. Based on the pre-formulation study data, Durotak 87-2516® was selected as a pressure-sensitive adhesive. Different formulations of a drug in adhesive matrix and reservoir type repaglinide TTS were evaluated for *ex-vivo* skin permeation (flux) study. The skin flux results show that sandwiched reservoir type repaglinide TTS can provide average cumulative drug permeation and flux rate of $379.75 \pm 47.89 \mu\text{g}/\text{cm}^2$ and $4.62 \pm 1.00 \mu\text{g}/\text{cm}^2/\text{hr}$ respectively for sustain drug delivery over the time of 72 hours. Developed sandwiched reservoir type repaglinide TTS has the potential to sustain delivery of drug for 72 hours, which reduce frequent dosing and thereby improve patient compliance.

INTRODUCTION

According to the World Health Organization (WHO), the number of people with diabetes is 422 million, and that is one person in every eleven persons worldwide.^[1] The majority (about 80–90%) of diabetic patients have non-insulin dependent diabetes mellitus (DM). Currently, most physicians prefer oral anti-diabetic drugs for multi-doses daily. Limitations of most oral glucose-lowering drugs are LOB, adverse gastrointestinal effects, severe hypoglycaemia, and shorter half-life that results in increasing frequency of daily dosing. Moreover, the major challenge of oral delivery is to regulate drug delivery and absorption rate.^[2] The study conducted on type 2 diabetes patients shows that only 16.6 % of the patients were considered adherent to the prescribed anti-diabetic drugs.^[3]

The TTS provides numerous advantages compared to the conventional formulations or peroral sustain release formulations.^[4] Transdermal drug delivery system (TDDS) provides predetermined and controlled rate up to 1–7 days, reduces adverse or toxic effects owing to the optimization of drug plasma profiles, avoids the first-pass metabolism of the drug, better adherence to treatment; interruption or termination of treatment when necessary is possible, and dose dumping never occurs.^[5] Most of the research works of repaglinide transdermal patch carried out using cellulosic and eudragit polymers claiming sustain delivery in the range of 8–24 hours.^[6–8] Use of pressure-sensitive adhesive (PSA) polymers are well known in commercially available transdermal patches like Climara®, Duragesic® and Catapres®-TTS for dosing period in the range of 3–7 days. None of the research work explored pressure-

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sensitive adhesive for the development of repaglinide transdermal patch and repaglinide delivery beyond 24 hours. Thus, the objective of the research is to design a repaglinide transdermal therapeutic system using PSA to deliver a drug for 72 hours time period.

MATERIALS AND METHODS

Materials

The drug repaglinide base procured as a gift sample from Zydus Cadila (Ahmedabad, India). Pressure-sensitive adhesive (PSA) Durotak® 87-900A and Durotak® 87-2516 were procured as a gift sample from Zydus Technologies (Gujarat, India). Isopropyl Palmitate was supplied by signet Chemical Corporation Pvt. Ltd. (Mumbai, India). Oleic acid was obtained from the Croda Chemicals (India) Pvt. Ltd. (Mumbai, India). Scotchpak™ 9733, Cotran™ 9720, Scotchpak™ 9744, and Scotchpak™ 1109 were obtained from 3M India Ltd. (Mumbai, India). Silicon coated polyester film was received as gift samples from Saint Gobain (Bangalore, India). PET film XL was supplied by Kaygee-Loparex India Pvt. Ltd. (Gujarat, India).

Methods

Analytical Methods

- *Repaglinide Assay by High-performance Liquid Chromatography (HPLC) Method*

The HPLC system used for the analysis comprised of Shimadzu HPLC (Model: LC-20AT) with low-pressure gradient solvent delivery module and photo-diode array detector. A reverse-phase Synchronis C18 column having 60 mm × 4.0 mm diameter and 5 µm particle size was employed for the detection and quantification of repaglinide. The elution was ensured using a flow rate of 1.0 mL/min with the mobile phase consisting of methanol and pH 2.5 phosphate buffer in the ratio of (7:3). The column temperature was maintained at a temperature of 40°C and with a detection wavelength of 245 nm. The peak of repaglinide observed at the retention time of 5.627 minutes. The quantification of repaglinide was found to be linear in the concentration range of 0.5–150 µg/mL with the limit of detection and quantification of 0.2 µg/mL and 0.5 µg/mL, respectively. Spike recovery studies were performed at 50, 100, and 150% of target concentration levels to determine the accuracy of the method, and the results observed to be 99.4, 99.7, and 99.5%, respectively. The method was proved to be precise for both standard and sample solutions within the acceptable limits with relative standard deviation is less than 2%.

- *Peel Adhesion Testing*

The test sample placed at controlled room temperature for a minimum period of 24 hours in a conditioning chamber before the test. The sample then cut to a length

of approximately 25 mm and partially remove the release liner. Partial part of an adhesive matrix of the test specimen stick to steel plate of universal testing machine (see Fig. 1). Hand roller of 1 kg weight rolled over test specimen for twice in each lengthwise direction. The steel surface placed on the instrument by tightening the rotating screw. The strip portion of the test specimen attached to the upper jaw of the instrument. The force required pulling the test specimen from steel plate at 180° angle measured and recorded in g/mm.

- *Tack Testing*

The test sample placed at controlled room temperature for a minimum period of 24 hours in a conditioning chamber before test. After removing the release liner of a test specimen, it was placed on a platform of universal testing machine in such a way that the adhesive matrix side of the sample is facing upward direction. Testing speed of the instrument was 610 mm/min (24 inch/min) with dwell time of 1-second ± 0.01 second. Maximum force required to detach the instrument probe from the matrix recorded as tack value.

- *Shear Adhesion*

The sample was cut in size of 0.5-inch width and 1-inch length. After removing the release liner, it applied on the stainless steel plate in a way that it covers 0.5 × 0.5 inch. Hand roller of 1 kg weight rolled over test specimen for thrice in each lengthwise direction. Test specimen then loaded on a test panel of shear tested using clips. At the free end of the sample, the standard weight of 100 gm was attached. The time required to fall down the 100 gm weight was recorded as shear value.^[9]

Ex vivo Permeation Method

- *Skin Sample Preparation and Storage*

Human cadaver skin was immersed in water at 45 to 60°C for 60 seconds to isolate the stratum corneum from dermis using blunt forceps.^[10,11] Dermis sides of the skin samples

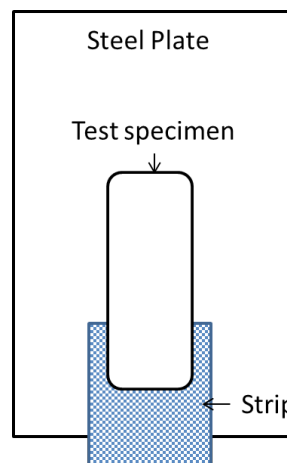


Fig. 1: Sample preparation for peel adhesion

were placed on a lint-free polyester net. Excess water from the skin samples was drained prior to immediate use or storage. Skin samples were either used instantly or stored frozen at -20°C on a lint-free polyester net until required for use. Skin permeability is not affected if stored at -20°C for twelve months.^[12]

• Skin Integrity Testing

Skin samples were placed at room temperature for 1-hour equilibrium, and then it was used for the transepidermal water loss measurement.^[13] The transepidermal water loss (TEWL) of the skin samples was determined under closed chamber conditions using VapoMeter (Delfin Technologies Ltd., Finland).^[14] For this, probe of the VapoMeter was placed over the top of the donor compartment using 9 mm adapter. The standard limit of $10 \text{ g.m}^{-2}.\text{h}^{-1}$ was used.^[15]

• Ex-vivo Skin Penetration Evaluation

Permeation studies through human cadaver skin samples performed in a modified Franz diffusion cell. The receptor compartment of modified Franz diffusion cells has 10 mL capacity with a surface area of about 2 cm^2 . Die-cut the transdermal system to the area of 3 cm^2 and remove the release liner from it. A patch was placed on top of the appropriate skin sample and ensured proper adhesion of the patch with no air gaps. The sample was applied to completely cover the cell opening of the receptor part of modified Franz diffusion cells and slightly overlap the edges of the cell opening. The donor part of the cells was placed on the top and clamped each cell. The receptor part of the cells was filled with flux media having pH 7.4 (phosphate buffer). The entire assembly magnetically stirred and maintained at a temperature of $32.5 \pm 0.5^{\circ}\text{C}$ for 72 hours. At predetermined time points, samples withdrawn by complete decantation (approx. 10 mL) from the receptor compartment using a dropper and refill the cells with fresh media at defined withdrawal time points. The samples were analyzed using the above HPLC method to detect the drug concentration permeate through the skin. The experiment was triplicated, and the mean result recorded. At the end of the permeation experiment, all the skin samples inspected for any visible damage or visual abnormalities. REPA permeated in $\mu\text{g}/\text{cm}^2$ at each time points were calculated, and a graph of cumulative permeation ($\mu\text{g}/\text{cm}^2$) vs. time (hours) was plotted. The slope of the graph for each time point calculated from linear regression curve obtained from the graph of cumulative permeation and reported skin flux ($\mu\text{g}/\text{cm}^2/\text{hour}$).^[16]

Pre-formulation Study Methods

• Solubility study of repaglinide in Permeation enhancers and Solvents

A saturated solution of drug in different enhancers and other organic solvents were prepared until drug particles

found in the undissolved form. Each saturated solution then incubated under continuous magnetic stirring at ambient temperature for 72 hours. The excess drug was removed by centrifugation, and the supernatant was filtered through a $0.45 \mu\text{m}$ filter. Quantify the drug present in the supernatant solution was analyzed by the HPLC method and the results were reported in mg/mL for each solvent.

• Drug-excipients Compatibility Study

Different excipients (PSAs and Oleic acid) were physically mix with repaglinide in 1:1 ratio, and then it filled in individual glass vials. These mixtures then stored at accelerated stability conditions ($40^{\circ}\text{C}/75\% \text{ RH}$) for up to 30 days. Each glass vial was analyzed for the repaglinide assay and repaglinide related compound A (i.e., (S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine N-acetyl-L-glutamate salt) using USP method of related substance test at the beginning and after 30 days.

• Drug Permeation Across the Backing Membrane

In this study, different grades of backing films (Scotchpak™ 9733, CoTran™ 9720, Scotchpak™ 1109) and release liners (Scotchpak™ 9744, PET 8310, and Loparex PET XL) were individually fixed between the donor and receptor parts of modified Franz diffusion cells. The drug contact layer of each backing and release liner was faced repaglinide solution as donor part and external surface faced to 7.4 pH phosphate buffer as receptor part. All the studied samples were stored at accelerated stability conditions ($40^{\circ}\text{C}/75\% \text{ RH}$) up to 168 hours. These samples were analyzed using HPLC method after 24 and 168 hours for repaglinide content in receptor compartment.

• Crystallization Study

Different concentrations of repaglinide (API) added to PSAs and mix well until homogeneous mixtures obtained. All formulations were kept at ambient temperature for one day to achieve equilibrium. These mixtures of API and PSA coated on Scotchpak™ 9744 and dried at 60°C drying temperature and residence time of 30 minutes to dry organic solvents that present in PSAs. The thickness of dried layer was set to 100 gm per square meter (GSM) for each trial formulation. Then, this dried layer was laminated again to the non-fluoro coated part of Scotchpak™ 9744 liner to achieve the final laminate. From this laminate, 10 cm^2 patches cut and stored at different stability conditions as follows: freeze-thaw cycle, accelerated stability, 90% RH, and controlled room temperature for 60 days. In the freeze-thaw cycle, samples were frozen to -20°C for one week and then thawed to 25°C for one week; this is called one freeze-thaw (FT) cycle. These samples were evaluated for the presence of the crystals using the microscope (Leica, GmbH). The compositions of the formulation provided in Table 1.



Table 1: Composition for crystallization study

Formulation code	API: Durotak 87-2516 (% w/w)	Formulation code	API: Durotak 900A (%w/w)	Formulation code	API: BIO-PSA 87-4202 (%w/w)
PF1	1:99	PF8	1:99	PF15	1:99
PF2	3:97	PF9	3:97	PF16	3:97
PF3	5:95	PF10	5:95	PF17	5:95
PF4	6:94	PF11	6:94	PF18	6:94
PF5	7:93	PF12	7:93	PF19	7:93
PF6	8:92	PF13	8:92	PF20	8:92
PF7	10:90	PF14	10:90	PF21	10:90

Evaluation of Design Factors Affecting Drug Delivery

Designing factors for repaglinide TTS are selection and optimization of product ingredients (i.e., pressure-sensitive adhesive, a permeation enhancer, etc.), optimization of drug load in formulation matrix, selection of type of transdermal system, the thickness of formulation matrix, and optimization of sustain drug delivery for a certain period of the time.

- Pressure-sensitive Adhesive Types Versus Drug Delivery**

Repaglinide and respective PSAs were dispensed in a suitable size of stainless steel container and mixed using laboratory propeller stirrer (REMI, Mumbai) for 30 minutes to achieve homogeneous mixture (Blend). Then, this blend was coated on the flour-coated surface of Scotchpak™ 9744 (release liner) using a knife gap of 200 microns on the coating machine (Mathis, Switzerland) to produce uniform thickness wet matrix film. Coated matrix film along with Scotchpak™ 9744 dried at 60°C for 30 minutes to make it completely dry and uniform adhesive matrix film. After drying, dried adhesive matrix film along with release liner was laminated with Scotchpak™ 1109 (backing film) at lamination pressure of 3.0 bar using laminator (LL-100, ChemInstruments, Fairfield, Ohio). This final laminate cut to a specific size patch using a

10 cm² manual punching die tool to produce a repaglinide DIA system. The prepared formulations together with different concentrations of repaglinide and different pressure sensitive adhesives given in Table 2.

- Permeation Enhancer Versus Drug Delivery**

In this section of research, selected permeation enhancers (oleic acid, isopropyl palmitate, and propylene glycol) were incorporated in formulation FD-3 (patch using Durotak® 87-2516, 7% w/w of repaglinide) to enhance the drug delivery. The 5% w/w concentration of enhancers was selected based on its safety for human use. The prepared formulations together with different permeation enhancers given in Table 3.

- Matrix Thickness Versus Drug Delivery**

For this study, formulations contain different dry GSM or thickness were prepared, and concentrations of ingredients were constant. The prepared formulations together with different dried GSM provided in Table 4.

Repaglinide, Durotak® 87-2516, propylene glycol, and oleic acid were dispensed in suitable size of stainless steel container and mixed together using laboratory propeller stirrer (REMI, Mumbai) for 45 minutes to achieve homogeneous mixture (blend). Then, this blend

Table 2: Formulation trials for effect of drug concentration

Formulation code	Repaglinide (% w/w)	Adhesives
FD-1	3	97% Durotak® 87-900A
FD-2	5	95% BIO-PSA 7-4202
FD-3	7	93% Durotak® 87-2516

Table 3: Compositions with different permeation enhancers

Formulation code	Repaglinide (% w/w)	Durotak® 87-2516 (%w/w)	Permeation enhancers (%w/w)
FD-4	7	88	5% (Oleic acid)
FD-5	7	88	5% (Isopropyl palmitate)
FD-6	7	88	5% (Propylene glycol)

Table 4: Compositions with different dry GSM

Formulation code	Repaglinide (% w/w)	Durotak® 87-2516 (% w/w)	Propylene glycol (% w/w)	Oleic acid (% w/w)	Dry GSM
FD-7	7	85	5	3	75
FD-8	7	85	5	3	100
FD-9	7	85	5	3	125

was coated on a fluoro-coated surface of Scotchpak™ 9744 (release liner) using a different knife gap of 300–500 microns on the coating machine (Mathis, Switzerland) to produce uniform thickness wet matrix film and desired dry GSM formulations. Coated matrix film along with Scotchpak™ 9744 dried at 60°C for 30 minutes to make it completely dry and uniform adhesive matrix film. After drying, dried adhesive matrix film along with release liner was laminated with Scotchpak™ 1109 (backing film) at lamination pressure of 3.0 bar using laminator (LL-100, ChemInstruments, Fairfield, Ohio). This final laminate cut to a specific size patch using a 10 cm² manual punching die tool to produce a repaglinide DIA system with different dry GSM.

• Repaglinide Reservoir Type Tarsal Tunnel Syndrome

Repaglinide drug in adhesive TTS (100 dry GSM) was prepared in the same way as above and it is marked as Layer -1 (Active layer). On the another release liner (Scotchpak™ 9744), alone Durotak® 87-2516 was coated and dried in an oven at drying temperature of 60°C and residence time of 20 minutes to dry solvents traces. The thickness of placebo matrix is set to approximately 25 GSM. This dried placebo matrix, along with release liner was laminated with the rate-controlling membrane (CoTran™ 9705) at lamination pressure of 3 bar using a laminator. This is described as Layer-2 (placebo layer). Then, active layer and placebo layer were laminated together in a way that the rate-controlling membrane faces the active layer to produce the 5-layer laminate. In this process, one release liner of the active layer was removed simultaneously. Diagrammatic representation of the five layers system presented in Fig. 2. This laminate was cut using 10 cm² manual punching die tool for further evaluation.

• Repaglinide Sandwiched Reservoir Type Tarsal Tunnel Syndrome

Sandwiched reservoir type TTS prepared by replacing the placebo layer with an active layer in above reservoir type TTS. Therefore sandwiched reservoir type TTS contains two active layers, where rate-controlling membrane sandwiched between them. The repaglinide concentration in both active layers is 12 % w/w, and dry gram per square meter (GSM) is 62.5 GSM. This laminate was cut using 10 cm² manual punching die tool for further evaluation. Diagrammatic representation of the five layers system presented in Fig. 3.

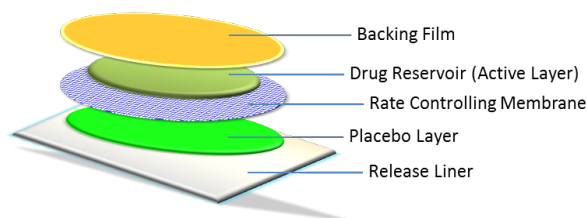


Fig. 2: Repaglinide reservoir type TTS

RESULTS AND DISCUSSION

Pre-formulation

Various formulation factors are involved at different development stages of the transdermal drug delivery system. Designing factors for repaglinide TTS are selection and optimization of product ingredients (i.e., pressure-sensitive adhesive, backing film, release liner, permeation enhancers, etc.), optimization of drug load in formulation matrix, selection of a type of transdermal system, the thickness of formulation matrix, optimization of system wear characteristics, and optimization of sustain drug delivery for a certain period of the time. The optimized formulation was selected based on solubility study, transmission study, crystallization study, drug excipients compatibility, etc., and skin flux results.

Solubility

Solubility study data plays an important role in the selection of the pressure-sensitive adhesive, flux media, and permeation enhancers. For various pressure-sensitive adhesives (PSA), polymers are dispersed in the organic solvents (i.e., ethyl acetate, heptane, hexane, etc.). Therefore, the solvent of PSA, which dissolves the drug, would be more appropriate for the development. The solubility of the repaglinide in the different permeation enhancers and solvents shown in Table 5. Repaglinide has a higher solubility in oleic acid compared to the isopropyl palmitate, which indicates that oleic acid is a suitable permeation enhancer for the repaglinide to improve the skin flux rate if needed. Based on the solubility of a drug in ethyl acetate, PSA containing ethyl acetate are suitable for designing the TTS. Moreover, phosphate buffer pH 7.4 is appropriate for the flux media due to higher drug solubility, and it can provide sink condition.

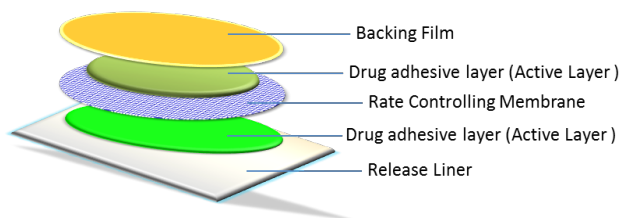


Fig. 3: Repaglinide sandwiched reservoir type TTS

Table 5: Solubility of Repaglinide

Solvent Name	Solubility (mg/mL)
Oleic acid	22.25
Isopropyl palmitate	0.88
Ethyl acetate	Freely soluble
Dichloromethane	Freely soluble
Methanol	Freely soluble
Phosphate buffer pH 7.4	Freely soluble



Drug-excipients Compatibility

Repaglinide compatibility study performed with Durotak® 87-2516, Durotak® 87-900A, and oleic acid. The results of the physical and chemical testing (repaglinide assay and repaglinide related compound A) are mentioned in Table 6.

Data of Table 6 shows that there is no change in physical appearance as well as there is no significant change in the assay and related compound of beginning and after 30 days for all three ingredients. The data shows that drug is compatible with Durotak® 87-2516, Durotak® 87-900A, and oleic acid.

Drug Permeation Across Backing Membrane

Backing film and release liner provide physical integrity to the system, maintenance of the physical dimensions, and shape of the formulation during shelf life as well as during the in-use period. The selected backing film and release liner should not absorb any significant quantities of drug, not allow significant permeation or transmission of drug through it into the environment or headspace of packaging. Therefore, the transmission study is essential for the selection of the backing film and release liner. The results of the repaglinide transmission study for different backing films and release liners shown in Table 7.

Data of Table 7 shows that CoTran™ 9720 shows significant drug transmission, and Scotchpak™ 9733 and Scotchpak 1109 do not show any significant transmission after 168 hours. Drug contact side for CoTran™ 9720 is polyethylene, and for other two backings is polyester. The data shows that polyethylene has a tendency to absorb and transmit the repaglinide. Therefore, the backing containing the polyester layer (Scotchpak™ 1109) selected for further development. For the release liner, none of them shows drug transmission and hence, Scotchpak™ 9744 selected for the TTS.

Crystallization

Supersaturated state of API in the adhesive matrix used to intensify the drug delivery rate in the transdermal system.^[18,19] The unique merits of the supersaturated system are more straightforward delivery system design and low skin toxicity compared to other penetration enhancement strategies. A major formulation challenge associated with the supersaturated system is physical instability of formulation, which may lead to crystallization due to higher thermodynamic activity.^[17] The results for the crystallization study provided in Tables 8–10.

Table 6: Drug excipients compatibility study

Tests	Drug: Oleic acid		Drug: Durotak® 87-2516		Drug: Durotak® 87-900A	
	T0	After 30 days	T0	After 30 days	T0	After 30 days
Appearance	Whitish	Whitish	Transparent	Transparent	Transparent	Transparent
Repaglinide assay (% LC)	96.56	97.34	101.35	99.52	98.67	97.62
Repaglinide related compound A	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected

Table 7: Results of repaglinide transmission study

Material grades	Composition	Repaglinide transmission (mg)	
		24 hours	168 hours
Backing film			
Scotchpak™ 9733	Polyester and ethylene-vinyl acetate copolymer	0.052	0.091
Cotran™ 9720	Polyethylene monolayer film	1.345	8.395
Scotchpak™ 1109	Pigmented polyethylene and aluminum vapor coated polyester	0.002	BQL
Release liner			
Scotchpak™ 9744	Fluoropolymer coated polyester film	BQL	BQL
Polyester film, 75 micron	Silicone coated polyester film	BQL	BQL
Silicon coated polyester film (8310)	Silicone coated polyester film	BQL	BQL

Table 8: Crystallization results in Durotak 87-2516

Repaglinide: Durotak 87-2516	Freeze-thaw cycle		90 % RH		40°C/75%RH	
	2 cycles	5 cycles	30 days	60 days	30 days	60 days
F1 (1:99)	-	-	-	-	-	-
F2 (3:97)	-	-	-	-	-	-
F3 (5:95)	-	-	-	-	-	-
F4 (6:94)	-	-	-	-	-	-
F5 (7:93)	-	-	-	-	-	-
F6 (8:92)	+	+++	++	+++	-	-
F7 (10:90)	+	+++	++	+++	+++	+++

- : No crystal; + : < 10 % area; ++: 10-40% area; +++: 40-70% area; ++++: >70% area

Table 9: Crystallization results in Durotak 87-900A

Repaglinide: Durotak 87-900A	FT cycle		90 % RH		40 °C/75%RH	
	2 cycles	5 cycles	30 days	60 days	30 days	60 days
F8 (1:99)	-	-	-	-	-	-
F9 (3:97)	-	-	-	-	-	-
F10 (5:95)	+	++	++	+++	-	-
F11(6:94)	+	+++	++	+++	-	-
F12 (7:93)	++	++++	+++	++++	+	++
F13 (8:92)	++	++++	+++	++++	+	++
F14 (10:90)	++	++++	+++	++++	++	++++

Table 10: Crystallization results in BIO-PSA 7-4202

Repaglinide: Durotak 87-900A	FT cycle		90 % RH		40°C/75% RH	
	2 cycles	5 cycles	30 days	60 days	30 days	60 days
F15 (1:99)	-	-	-	-	-	-
F16 (3:97)	-	-	-	-	-	-
F17 (5:95)	-	-	-	-	-	-
F18 (6:94)	+	+++	++	+++	-	-
F19 (7:93)	++	++++	+++	++++	+	++
F20 (8:92)	++	++++	+++	++++	+	++
F21 (10:90)	++	++++	+++	++++	++	++++

It can be seen from the Tables 8 and 9 that repaglinide does not show any crystal up to 7% w/w in Durotak® 87-2516 in all stability conditions while show crystals at 8% w/w concentration in a freeze-thaw cycle and 90% RH condition. On the other side, repaglinide starts showing crystal for 6% w/w concentration in Durotak® 87-900A in a FT cycle and 90% RH condition. This indicates that repaglinide has a higher solubility in Durotak® 87-2516 compare to the Durotak® 87-900A and therefore, drug is less prone to crystallization in Durotak® 87-2516. The presence of hydroxyl functional group in Durotak® 87-2516 forms the H-bond with repaglinide and it would prevent the crystallization of drugs. Hence maximum saturation solubility of the drug in acrylates adhesive Durotak® 87-2516 and Durotak® 87-900A is 7% w/w and 3% w/w, respectively. Data of Table 10 shows that repaglinide starts showing crystal for 6% w/w concentration in BIO-PSA 7-4202 in freeze-thaw cycle and 90% RH condition. At the same time, there are no crystals in accelerated stability conditions. This indicates that the highest drug solubility in BIO-PSA 7-4202 is 5% w/w. It was observed that the maximum solubility of repaglinide depends on chemical composition of PSA types.

Physicochemical Characterization of the Repaglinide Tarsal Tunnel Syndrome

Physical Characterization

The surface area of the TTS is critical factor that decides drug delivery rate and extent from a TTS. Therefore, poor adhesion properties of the TTS can lead to a reduction in efficacy of the system. Adhesion characteristics of the transdermal system are described by: a) "Peel" defines

the force required to take out the transdermal system from a substrate. b) "Tack" is referred to the ability of the transdermal system to form the initial bond with a substrate under light pressure and shorter contact time. c) "Shear adhesion" relates to the resistance of the transdermal system to flow during wear period.^[18]

The transdermal system should stick quickly to skin at a minimum applied pressure, and therefore low-tack transdermal systems are preferred. Shear adhesion property of the transdermal patch ensures proper patch placement to skin throughout the wear period despite torsional strains arising from body movements and cloth. Peel force of the system should be optimized for easy removal of the patch from the skin (painless), without leftover residue on skin and causing physical harm to skin.

Different formulations were tested for the matrix weight, drug content, peel, tack, shear adhesion, and patch thickness. The results of all tests for all formulations mentioned in Tables 11 and 12.

The Data of Table 11 show that formulation FD-1 which has 3% of drug content shows slightly higher peel and tack value compare to formulations FD-3 having 7% of drug. Thus, as drug concentration increase in the formulation matrix, adhesive force decreases (peel and tack value) and cohesive force (shear) value increases. This indicates that drug substance has antiplasticizer effect due alteration of TG value of the pressure sensitive adhesive of the system.^[19] Conversely, as GSM of matrix increase, a continuous increase in the peel was naturally associated with decrease in shear adhesion. However, there is no impact of GSM on the tack force. Peel and tack value of the reservoir system drastically increased and this is due to the placebo adhesive in contact layer.



Table 11: Results of repaglinide TTS

Tests	Pressure sensitive adhesive types versus drug delivery			Permeation enhancer versus drug delivery		
	FD-1	FD-2	FD-3	FD-4	FD-5	FD-6
Matrix weight, mg	52.5	49.3	50.9	47.5	53.3	49.4
Patch thickness, μ	179 $\pm$ 2.6	174 $\pm$ 1.9	176 $\pm$ 2.2	172 $\pm$ 2.6	182 $\pm$ 1.9	175 $\pm$ 2.2
Drug content (assay), % label claim	100.5 $\pm$ 2.2	95.3 $\pm$ 2.8	98.5 $\pm$ 1.8	96.5 $\pm$ 2.9	98.3 $\pm$ 3.8	102.5 $\pm$ 3.2
Peel, gm force	2359 $\pm$ 16.3	190 $\pm$ 5.3	1809 $\pm$ 13.9	538 $\pm$ 11.3	756 $\pm$ 19.1	629 $\pm$ 18.6
Tack, gm/19.6 mm ²	859 $\pm$ 8.9	16 $\pm$ 3.3	658 $\pm$ 10.3	238 $\pm$ 12.9	547 $\pm$ 18.3	435 $\pm$ 34.2
Shear adhesion, minutes	124 $\pm$ 6.9	46 $\pm$ 6.3	179 $\pm$ 18.3	46 $\pm$ 7.3	67 $\pm$ 7.3	32 $\pm$ 3.3
Average cumulative permeation, $\mu\text{g}/\text{cm}^2$	55.71 $\pm$ 14.89	126.35 $\pm$ 16.56	191.76 $\pm$ 18.08	234.23 $\pm$ 5.20	226.56 $\pm$ 16.99	300.58 $\pm$ 30.93

Note: Results are mean $\pm$ SD

Table 12: Results of repaglinide TTS

Tests	Dry GSM versus drug delivery			Effect of rate-controlling membrane	
	FD-7	FD-8	FD-9	FD-10	FD-11
Matrix weight, mg	77.9	98.6	123.8	129.4	126.7
Patch thickness, μ	202 $\pm$ 2.6	254 $\pm$ 1.9	279 $\pm$ 2.2	253 $\pm$ 6.3	259 $\pm$ 4.4
Drug content (assay), % label claim	100.4 $\pm$ 1.9	97.9 $\pm$ 2.4	99.1 $\pm$ 2.8	101.4 $\pm$ 2.1	99.1 $\pm$ 3.1
Peel, gm force	745 $\pm$ 14.1	837 $\pm$ 17.2	1003 $\pm$ 12.3	1546 $\pm$ 24.1	776 $\pm$ 19.1
Tack, gm/19.6 mm ²	654 $\pm$ 16.1	715 $\pm$ 16.3	695 $\pm$ 21.2	1265 $\pm$ 19.1	614 $\pm$ 11.1
Shear adhesion, minutes	184 $\pm$ 8.9	124 $\pm$ 9.1	82 $\pm$ 7.3	384 $\pm$ 21.9	154 $\pm$ 14.9
Average cumulative permeation, $\mu\text{g}/\text{cm}^2$	284.84 $\pm$ 13.11	347.49 $\pm$ 77.90	374.32 $\pm$ 13.02	350.03 $\pm$ 39.76	379.75 $\pm$ 47.89
Average flux, $\mu\text{g}/\text{cm}^2/\text{hr}$	3.95 $\pm$ 0.58	4.79 $\pm$ 1.23	5.08 $\pm$ 0.55	4.06 $\pm$ 1.17	4.62 $\pm$ 1.00

Note: Results are mean $\pm$ SD

Ex vivo skin permeation (Flux)

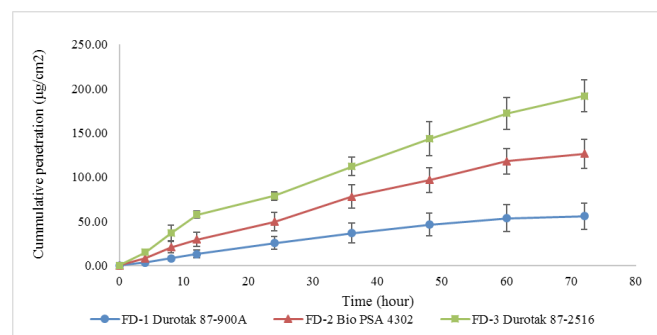
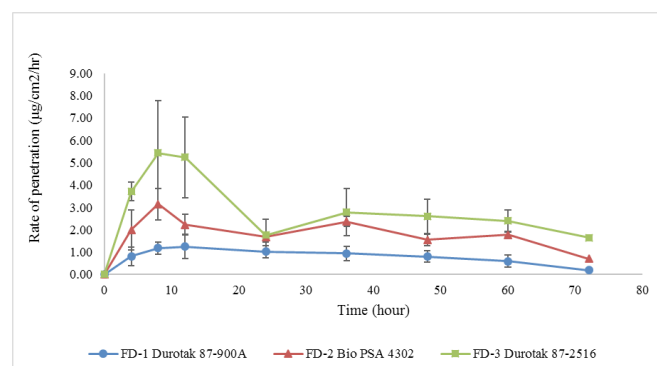
• Pressure Sensitive Adhesive Type's Versus Drug Delivery

Based on crystallisation study, maximum drug concentration of 7 % w/w in Durotak 87-2516, 3 % w/w in Durotak 87-900A and 5% w/w in BIO-PSA 7-4202 can be incorporated in TTS. Hence, preliminary formulation development trials were initiated to evaluate impact of these pressure sensitive adhesives on skin flux.

The average cumulative permeation of REPA through skin from FD1 3% API, FD2 5% API, FD3-7% API were found to be 55.71 $\pm$ 14.89, 126.31 $\pm$ 16.56, and 191.76 $\pm$ 18.08 $\mu\text{g}/\text{cm}^2$, respectively. Batch FD-3 showed significantly higher cumulative drug delivery compared to the other two batches, as presented in Fig. 4. The average flux of FD-1, FD-2 and FD-3 found to be 0.76 $\pm$ 0.26, 1.71 $\pm$ 0.34, and 2.84 $\pm$ 0.88 $\mu\text{g}/\text{cm}^2/\text{hr}$ respectively, where the maximum skin flux achieved in FD-3, as presented in Fig. 5. The higher permeation of REPA from batch FD-3 can be imputed to the higher drug concentration (7% w/w). To obtain maximum delivery of repaglinide, patch FD-3 selected for further development. Flux rate of the FD-3 was decreasing after 12 hours of the continuous and it reaches to the level of 1.65 $\pm$ 0.28 $\mu\text{g}/\text{cm}^2/\text{hr}$ at 72-hour time point. These data indicate that studied formulation trials are not able to provide controlled delivery of repaglinide over a period of 72 hours. This suggests modification in formulation design by adjusting the matrix thickness (GSM) and the addition of permeation enhancers.

Permeation Enhancer versus Drug Delivery

It is ostensible from Fig. 6 that the presence of permeation enhancers significantly improves extent of repaglinide drug delivery through the human cadaver skin though the permeation rate is divergent. Fig. 7 compares the

**Fig. 4:** Effect of PSAs on cumulative permeation**Fig. 5:** Effect of PSAs on rate of permeation (flux)

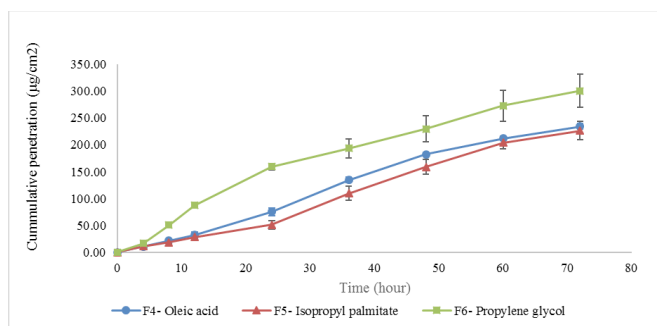


Fig. 6: Comparison of the cumulative amount of repaglinide permeated from formulations containing various permeation enhancers. All values are mean $\pm$ SD (n = 3).

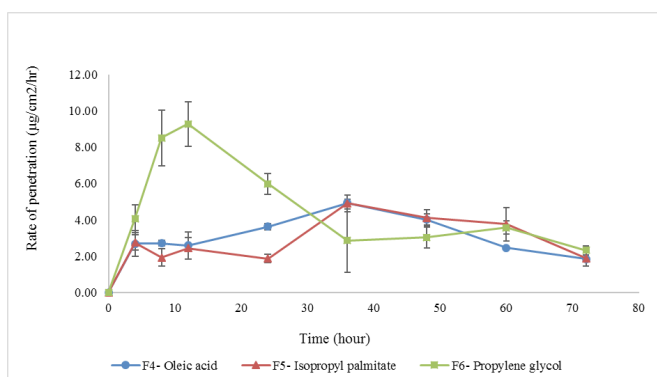


Fig. 7: Comparison of the skin flux (rate of penetration) of repaglinide permeated from formulations containing various permeation enhancers. All values are mean $\pm$ SD (n = 3).

penetration rate of repaglinide for different permeation enhancers intended to enhance drug permeation. Effectiveness of permeation enhancement for repaglinide from higher to lower side as propylene glycol > Oleic acid > isopropyl palmitate.

A formulation containing propylene glycol show superior flux profile ($4.4 \pm 0.78 \mu\text{g}/\text{cm}^2/\text{hr}$; $p < 0.0001$), which almost double than flux achieved with formulation F3 (without permeation enhancer). The total quantity of repaglinide transported in 72 hour was $234.23 \pm 5.20 \mu\text{g}/\text{cm}^2$, $226.56 \pm 16.99 \mu\text{g}/\text{cm}^2$, and $300.58 \pm 30.93 \mu\text{g}/\text{cm}^2$ when treated with oleic acid, isopropyl palmitate and propylene glycol, respectively.

The greatest skin flux of repaglinide observed (8–9 $\mu\text{g}/\text{cm}^2/\text{hr}$ at 8 and 12 hours) when formulation contains propylene glycol among various formulations evaluated in this study under similar experimental conditions. Besides, propylene glycol shows higher flux from 0 to 24 hours' period when compared with the rest two permeation enhancers. Then, flux decreases to about $3 \mu\text{g}/\text{cm}^2/\text{h}$ and consistent during a period of 36 to 60 hours, followed by again fall to $2.3 \mu\text{g}/\text{cm}^2/\text{hr}$ at 72 hours.

In summary, propylene glycol increase flux of repaglinide up to 24 hours and oleic acid increase flux after 24 hours to 60 hours. In the presence of propylene glycol, most of the drug was delivered at a higher flux rate up to 24 hours, and that lead to a decrease in concentration

gradient and lower flux for further time point. At last time point of 72 hours, flux value decrease with all three studied enhancers and that is also due to depletion of drug in adhesive matrix due to lower GSM.

Matrix Thickness versus Drug Delivery

The average cumulative permeation of REPA through skin from F7- 75 GSM, F8-100 GSM, F9-125 GSM were found to be 284.84 ± 13.11 , 347.49 ± 77.90 , and $374.32 \pm 13.02 \mu\text{g}/\text{cm}^2$ respectively. Formulation F9 showed significantly higher cumulative drug delivery compared to rest two formulations, as presented in Fig. 8. The average flux of F7, F8 and F9 found to be 3.95 ± 0.58 , 4.79 ± 1.23 , and $5.08 \pm 0.55 \mu\text{g}/\text{cm}^2/\text{hr}$ respectively, where the maximum skin flux achieved from F9, as presented in Fig. 9. Data shows that as dry GSM (matrix thickness) increases in the formulation, cumulative amount permeated, and rate of drug permeation are increased. There is a slight increase in flux for formulation having 100 GSM compares to 75 GSM, but significantly increases in a formulation having 125 GSM. In F7 formulations, the rate of permeation maintains up to 36 hours and then starts decreasing after 48 hours. While for F8 and F9 formulations, the rate of permeation is higher up to 12 hours compared to F7

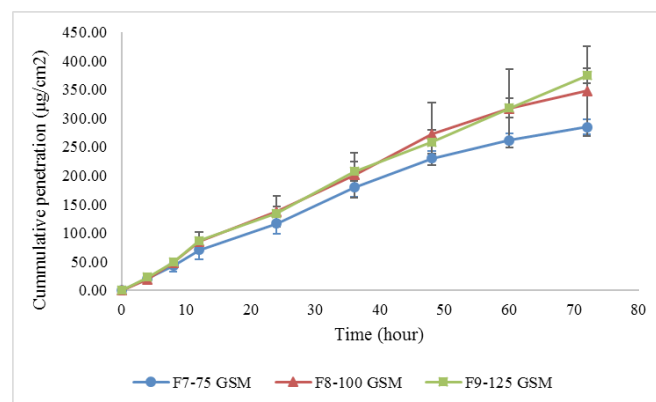


Fig. 8: Comparison of the cumulative amount of repaglinide permeated from formulations having different GSM. All values are mean $\pm$ SD (n = 3)

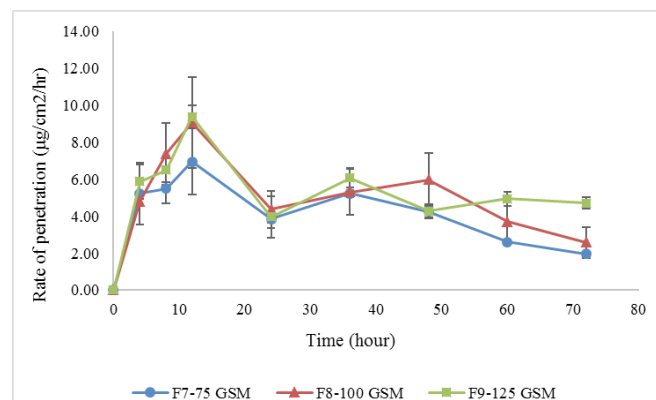


Fig. 9: Comparison of the skin flux (rate of penetration) of repaglinide permeated from formulation having different GSM. All values are mean $\pm$ SD (n = 3)



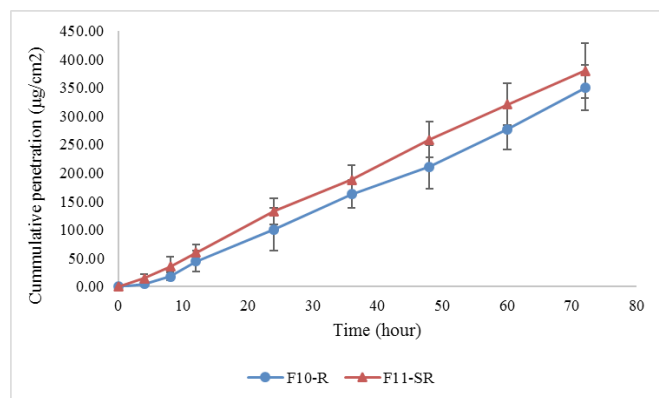


Fig. 10: Comparison of the cumulative amount of repaglinide permeated from patches prepared with sandwiched reservoir patch. All values are mean $\pm$ SD (n = 3)

formulation and decreases to a similar level of F7 at 24 hours. After 24 hours, F8 maintains the flux rate up to 48 hours, and further flux rate decreases and similar to F7 at 72 hours' time point. Interestingly, the flux rate of F9 after 24 hours maintains a similar value for up to 72 hours.

These data indicate that an increase in GSM of the transdermal system increases the delivery rate at later time points, and it is mostly due to the constant concentration gradient for the entire time. Hence, 125 GSM formulation (F9) is most suitable to achieve the desired drug delivery profile and rate. However, the flux rate is almost double at 12 hours' time point; further flux rate has fluctuated between 24 hours and 48 hours' time point.

This data shows that studied formulation trials still have scope of improvement to provide controlled and consistent delivery of repaglinide over 72 hours. Rate controlling membrane could be a critical element to achieve a controlled and consistent drug delivery. Therefore a further section is all about evaluation of the impact of rate-controlling membrane on drug delivery.

Reservoir and Sandwiched Reservoir Type Tarsal Tunnel Syndrome (Effect of rate-controlling membrane)

The average cumulative permeation of REPA through the skin from FD10 reservoir and FD11 sandwiched reservoir were found to be 350.03 ± 39.76 , and $379.75 \pm 47.89 \mu\text{g}/\text{cm}^2$ respectively. *Ex-vivo* drug permeation data revealed that formulation FD11 shows slightly higher flux compared to FD10, as displayed in Fig. 10. The average flux of FD10 and FD11 was 4.06 ± 1.17 and $4.62 \pm 1.00 \mu\text{g}/\text{cm}^2/\text{hr}$, respectively, as presented in Fig. 11. For FD10, the rate-controlling membrane provides controlled drug delivery. However, flux value for initial hours (up to 8 hours) are lower compared to rest time points, which can be due to the placebo layer in the skin contact part, and after 12 hours, flux rate is consistent up to 72 hours. While for FD11, flux value for initial hours (up to 8 hours) is increased compared to the FD10, and this can be due to active layer in skin contact part of FD11 instead of the placebo layer of FD10. The one can adjust patch size (cm^2) of the

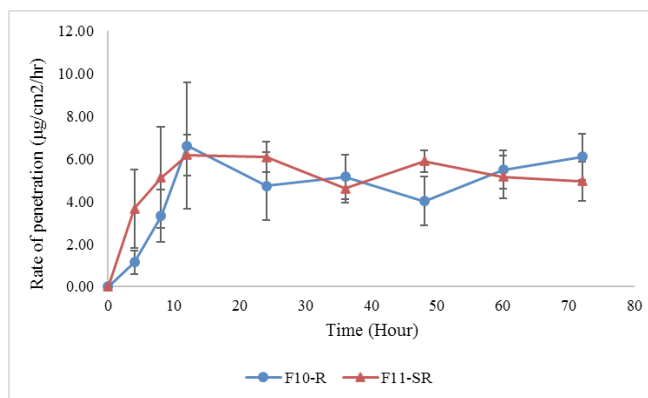


Fig. 11: Comparison of the skin flux of repaglinide permeated from patches prepared with sandwiched reservoir patch. All values are mean $\pm$ SD (n = 3)

formulation to achieve the desired dose of the repaglinide. Based on this data, sandwiched reservoir type TTS (FD11) consistently deliver repaglinide for the time of 72 hours.

CONCLUSION

The present research work demonstrates repaglinide TTS containing rate-controlling membrane can provide consistent delivery compared to a monolithic drug in adhesive type repaglinide TTS. Sandwiched reservoir type TTS where rate-controlling membrane sandwiched between two active layers of repaglinide can provide the sustain drug delivery up to a 72-hour time period, and hence, it can be considered as optimized formulation. Further development to study the *in-vivo* pharmacokinetic profile of the transdermal system, however, will be required.

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