



Development of Repaglinide Transdermal Drug Delivery System: A Novel Approach for the Management of Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder requiring effective and sustained glycemic control. Repaglinide is a short-acting insulin secretagogue used to improve postprandial glucose control. Its oral administration is associated with a short elimination half-life, variable systemic exposure, and substantial hepatic metabolism. Transdermal drug delivery system (TDDS) represents a potential alternative for improving drug delivery and reducing dependence on frequent oral administration; however, adequate skin permeation and an appropriate relationship between drug release and meal-related glucose control must be established. The present study proposes the development and systematic evaluation of a repaglinide-loaded transdermal drug delivery system intended to improve skin permeation, provide controlled drug release, and investigate its potential for managing T2DM. Repaglinide-loaded matrix patches will be prepared using a solvent-casting technique. Ethyl cellulose and HPMC and Polyethylene glycol glycerin as a plasticizer, and a selected skin-permeation enhancer will be investigated as formulation components. Preliminary compatibility and solubility studies will precede formulation optimization. Prepared patches will be evaluated for physical appearance, thickness, weight variation, folding endurance, tensile properties, moisture content, drug-content uniformity, in vitro drug release, ex vivo skin permeation, and stability. A factorial experimental design will be used to investigate the effects of selected formulation variables on drug release and permeation. Repaglinide transdermal delivery is a promising formulation-development research area. Its clinical value will depend on demonstrating reproducible delivery through human-relevant skin models, appropriate pharmacokinetics, glycemic efficacy, and acceptable local and systemic safety.

Keywords: Repaglinide; type 2 diabetes mellitus; transdermal drug delivery; matrix patch; HPMC, skin permeation.

1. Introduction

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by insulin resistance, progressive impairment of pancreatic beta-cell function, and persistent hyperglycemia. Long-term management requires individualized pharmacotherapy, dietary modification, physical activity, and regular monitoring of glycemic status. Although oral antidiabetic medicines are widely used, limitations associated with dosing frequency,

gastrointestinal administration, pharmacokinetic variability, and adherence continue to motivate the development of alternative drug delivery systems.

Repaglinide is a meglitinide-class oral antidiabetic agent that stimulates insulin secretion from pancreatic beta cells by modulating ATP-sensitive potassium channels. It is primarily used to control postprandial hyperglycemia in patients with T2DM. Its rapid onset and relatively short duration of action make administration in relation to meals important. Consequently, the development of a modified drug delivery system requires careful consideration of the relationship between drug exposure, meal timing, and the risk of hypoglycemia.

Repaglinide has limited aqueous solubility and undergoes substantial hepatic metabolism. These characteristics have encouraged investigation of formulation strategies intended to improve its dissolution, systemic exposure, and delivery efficiency.

1.1 Rationale for transdermal delivery

Transdermal drug delivery systems administer a drug across the skin into the systemic circulation. Potential advantages include avoidance of gastrointestinal administration, reduction of presystemic hepatic first-pass metabolism, controlled delivery, and the possibility of improved adherence.

However, the stratum corneum is a substantial barrier to drug permeation. Successful transdermal delivery depends on drug physicochemical properties, formulation composition, skin permeability, applied surface area, and the required delivery rate. Repaglinide's limited aqueous solubility and pharmacological action present additional formulation and therapeutic challenges.

A transdermal formulation should therefore not be considered clinically superior merely because it produces sustained release. It must provide an appropriate dose over a defined period and demonstrate that the resulting systemic exposure safely supports the intended therapeutic objective.

2. Aim and Objectives

To develop and evaluate a repaglinide-loaded transdermal matrix patch as an investigational drug delivery system for the management of type 2 diabetes mellitus.

2.2 Specific objectives

3. Materials and Methods

3.1 Materials

Repaglinide will be obtained from an authorized pharmaceutical supplier or as a characterized research-grade sample. Ethyl cellulose and HPMC and Polyethylene glycol, glycerin and other reagent and other reagents and solvents used were of analytical grade provided by L. N. Pharmacy College Deoria.

3.2 Formulation development

Using the above mentioned method, formulation with repaglinide was made by mixing varying amounts of polymers and plasticizers. We made a 10% w/v polymeric solution by mixing ethyl cellulose and HPMC 15 cps in various amounts in a 50:50 mixture of dichloromethane and methanol. Also, varying amounts of propylene glycol (10% v/v) were added as a plasticizer. Then, 15% repaglinide was added, and the mixture was put on a petri dish that had been coated with PVA. Putting an upside-down funnel over the petri plate controlled how quickly the solvent evaporated. The solvent was left to evaporate at 500°C for duration of six hours.

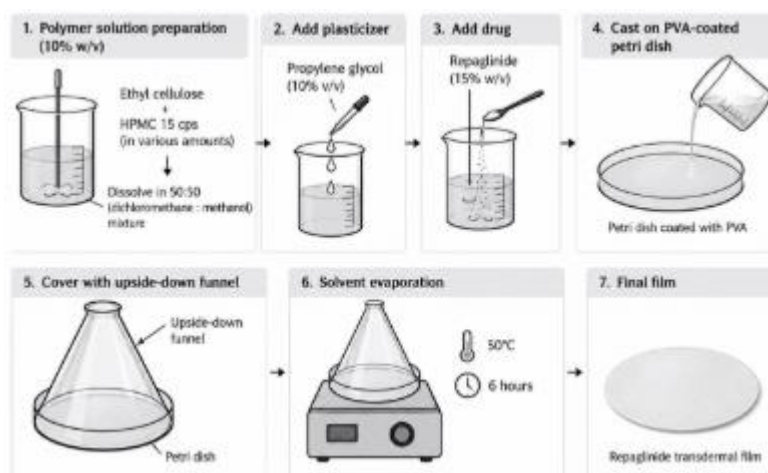


Fig 1. Preparation of TDDS

Table 1 :Polymer ratios in the Formulation

Formulation code	Polymer ratio EC:HPMC15cps	%Plasticizer Propylene glycol (V/V)	Glycerin (ml)	Drug (mg)
M2	7:3	15%	0.5	100
M3	7:3	20%		
M4	7:3	30%		
M7	8:2	15%		
M8	8:2	20%		

4 Evaluation of the transdermal patch

4.1 Physical appearance

Main focus was at the color, clarity, flexibility, and smoothness of all the transdermal systems

4.2 Thickness uniformity

The patch thickness was measured using a calliper that could measure to a precision of 0.01 mm. We took three separate measurements of the patch's thickness and averaged them. The outcomes can be seen in Table.

4.3 Folding Endurance

The manufactured patches were evaluated by hand for their folding endurance. The 3.14 cm² patch was sliced into thin sections. After then, the strips were folded at the same spot until they broke. Multiple foldings at the same spot without cracking the patches were used to determine the folding endurance rating . You can see the supplied value in Table

4.4 Weight uniformity

The desiccated areas were measured using an electronic balance .The mean of three observations was computed, and values of SDwere determined and presented in Table

4.5 Drug content

A 100 ml volumetric flask was used to hold the fragmented transdermal systems, which had a surface area of 3.14 cm² apiece. After that, 50 ml of MIPB with a pH of 7.4 was added, and the mixture was heated to 45°C for 15 minutes while being gently stirred. For 24 hours, the flask was left at room temperature and agitated occasionally.

Afterwards, 100 ml of MIPB was added to bring the pH to 7.4, and further dilutions were made using this solution [86]. Using a patch that did not contain any drugs, a control solution was also made. After filtering the solutions, a UV spectrophotometer was used to measure their absorbances at 222 nm. In Table, you can see the results.

Tensile Strength

The patch's tensile strength was assessed utilizing a tensile strength instrument, as depicted in Figure 4.8. This instrument has two grips: one stationary and the other adjustable. The patch, measuring 3.14 cm², was positioned between the grips. A force was subsequently increased incrementally until the film fractured. The findings are presented in Table.

Tensile strength = Tensile load at break / Cross sectional area

4.6 Percentage moisture content

Weighing each patch separately, we let them sit at room temperature for one day in a desiccator with fused calcium chloride. After that, we reweighed the patches and used the formula below to determine their moisture percentage. Table displays the results.

Percentage moisture content = [Initial weight-final weight/Final weight] ×100

4.7 Ex vivo drug permeation study

Table 4.17 presents the Ex vivo permeation of repaglinide utilizing goat ear skin. The necessary medication intake rate to get the effective plasma concentration of repaglinide was 117.31 µg/cm²/h. Formulation M8 exhibited the greatest permeation of repaglinide (301.825±1.05 µg/cm²) with a flow of 128.26±1.247 µg/cm²/h. This encompasses the partitioning of repaglinide into stratum corneum lipids, the partial extraction of stratum corneum lipids, and the phase separation inside the lipid lamellae of the stratum corneum. The M formulation had the largest flow over 24 hours across the preparations.

5. Results and Discussion

5.1 Physical appearance

Main focus was at the color, clarity, flexibility, and smoothness of all the transdermal systems

5.2 Thickness uniformity

The patch thickness was measured using a calliper that could measure to a precision of 0.01 mm. We took three separate measurements of the patch's thickness and averaged them. The outcomes can be seen in Table.

Table 2: Thickness uniformity

Formulation code	Mean ± S.D (mm) (n=3)
M2	0.21±0.001
M3	0.19±0.000
M4	0.1733±0.005
M7	0.18±0.000
M8	0.1866±0.005

5.3 Folding Endurance

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Table 3: Folding endurance

Formulation code	Mean ± S.D (n=3)
M2	157.66±7.505
M3	122.33±8.326

M4	82±6
M7	98±6.027
M8	72.66±4.932

5.4 Weight uniformity

The desiccated areas were measured using an electronic balance .The mean of three observations was computed, and values of SD were determined and presented in Table

Table 4: Weight uniformity

Formulation code	Mean ± S.D (n=3)
M2	0.0426±0.0016
M3	0.0336±0.0016
M4	0.0313±0.0015
M7	0.0333±0.0016
M8	0.0336±0.0015

5.5 Drug content

A 100 ml volumetric flask was used to hold the fragmented transdermal systems, which had a surface area of 3.14 cm² apiece. After that, 50 ml of MIPB with a pH of 7.4 was added, and the mixture was heated to 45°C for 15 minutes while being gently stirred. For 24 hours, the flask was left at room temperature and agitated occasionally. Afterwards, 100 ml of MIPB was added to bring the pH to 7.4, and further dilutions were made using this solution [86]. Using a patch that did not contain any drugs, a control solution was also made. After filtering the solutions, a UV spectrophotometer was used to measure their absorbances at 222 nm. In Table, you can see the results.

Table 5: Drug content

Formulation code	Mean ± S.D (n=3)
M2	19.33±0.00577
M3	20.66±0.364
M4	21.83±0.364
M7	18.66±0.0774
M8	19.93±0.00577

5.6 Tensile Strength

The patch's tensile strength was assessed utilizing a tensile strength instrument, as depicted in Figure 4.8. This instrument has two grips: one stationary and the other adjustable. The patch, measuring 3.14 cm², was positioned between the grips. A force was subsequently increased incrementally until the film fractured. The findings are presented in Table.

Tensile strength = Tensile load at break / Cross sectional area

Table 6: Tensile strength

Formulation code	Mean ± S.D (n=3)
M2	0.1995±0.0001
M3	0.2554±0.0038
M4	0.2968±0.0023
M7	0.2791±0.0013
M8	0.3880±0.0011

5.7 Percentage moisture content

Weighing each patch separately, we let them sit at room temperature for one day in a desiccator with fused calcium chloride. After that, we reweighed the patches and used the formula below to determine their moisture percentage. Table displays the results.

Percentage moisture content = [Initial weight-final weight/Final weight] ×100

Table 7: % moisture content

Formulation code	Mean ± S.D (n=3)
M2	7.751±1.342
M3	6.666±3.298
M4	7.842±1.697
M7	12.12±3.03
M8	9.09±0.00

5.8 Ex vivo drug permeation study

Table 4.17 presents the Ex vivo permeation of repaglinide utilizing goat ear skin. The necessary medication intake rate to get the effective plasma concentration of repaglinide was 117.31 µg/cm²/h. Formulation M8 exhibited the greatest permeation of repaglinide (301.825±1.05 µg/cm²) with a flow of 128.26±1.247 µg/cm²/h. This encompasses the partitioning of repaglinide into stratum corneum lipids, the partial extraction of stratum corneum lipids, and the phase separation inside the lipid lamellae of the stratum corneum. The M formulation had the largest flow over 24 hours across the preparations.

Table 8. Exvivo drug permeation profile

Time (h)	M2	M3	M4	M7	M8
0.5	2.944±2.451	1.472±2.335	1.472±1.993	5.889±2.431	2.944±2.31
1	7.361±1.243	5.889±1.236	7.361±2.043	16.195±2.488	11.778±1.242
2	16.195±1.253	13.250±0.943	14.723±1.632	35.335±2.153	27.974±0.936
4	30.918±0.253	27.974±0.492	23.557±2.142	58.892±3.021	48.586±2.044
6	47.114±1.256	45.641±1.23	38.280±1.223	85.394±1.243	73.616±2.431
8	67.726±2.41	71.254±2.31	55.948±2.419	113.368±2.482	111.896±1.24
12	104.534±1.25	103.28±2.11	82.449±2.134	147.232±1.243	153.121±2.443
16	156.066±2.032	199.202±3.21	135.453±1.253	188.457±2.043	219.375±1.324
24	207.903±1.022	288.955±1.04	197.290±1.257	239.988±3.054	301.825±1.05

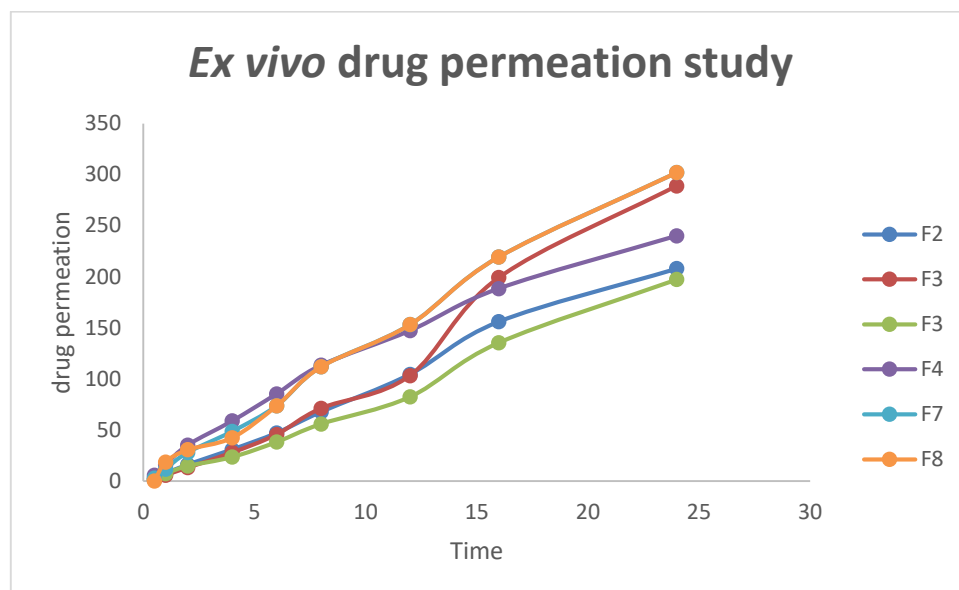


Fig. 2 Exvivo drug permeation profile

5.9 In –vitro Drug Release Studies

At specified times, a 1 mL aliquot of the dissolving medium was extracted and subsequently filtered. To preserve sink conditions, the dissolving medium was then substituted with MIPB 7.4. The absorption of the filtered solution was evaluated via UV spectroscopy at a wavelength of 222 nm, and the drug content was determined by reference a standard calibration curve. The dissolution testing was conducted in duplicate. Thus, the percentage of drug released was computed and graphed as a function of time to enable an investigation of the drug release profile.

Table 9: In vitro release data of the transdermal patches of repaglinide from batch M8

Time (min)	Abs	Release (mg.)	Cumulative	% Cumulative release
0	0	0	0	0
15	0.112	0.141772	2.126582	8.506329
30	0.158	0.2	3.141772	12.56709
60	0.256	0.324051	5.202532	20.81013
120	0.398	0.503797	8.222785	32.89114
180	0.583	0.737975	12.38101	49.52405
240	0.468	0.592405	10.79367	43.17468
300	0.658	0.832911	14.99367	59.97468
360	0.998	1.263291	15.82658	63.30633

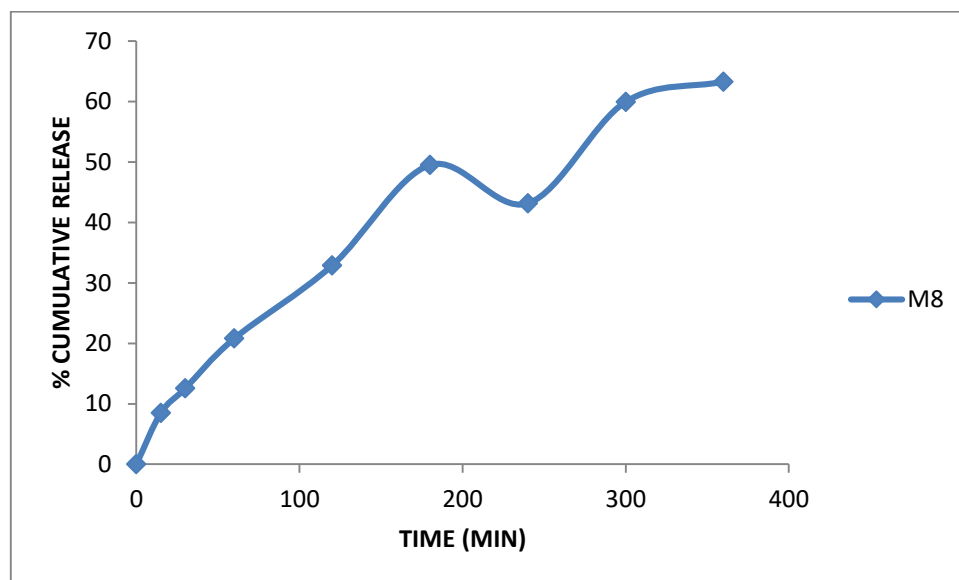


Fig3:% Cumulative release profile of batch M8 in MIPB (pH 7.4)

7. Conclusion

The development of a repaglinide-loaded transdermal drug delivery system is a scientifically relevant formulation-development approach for investigating controlled drug administration in T2DM. Polymeric matrix patches offer a platform for studying the effects of formulation composition on mechanical performance, drug release, and skin permeation.

Patches M2 to M8 were made with plasticizer, and they turned out well. Consistent with the aforementioned findings, this study performed an encouraging pilot trial to see whether transdermal patches containing EC and HPMC 15cps may increase the bioavailability of Repaglinide. M8 formulation show better result among all formulation.

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