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Formulation and Evaluation of Transdermal Drug Delivery System of Nateglinide for Controlled Release Application

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Abstract:

The present study aimed to develop and evaluate transdermal patches of Nateglinide for controlled and sustained drug delivery. Transdermal drug delivery systems (TDDS) offer a non-invasive alternative to conventional dosage forms by improving bioavailability and reducing dosing frequency through bypassing hepatic first-pass metabolism. In this study, various polymer-based matrix patches were formulated using agar, HPMC K-100, guar gum, ethyl cellulose, and Eudragit RS, along with suitable plasticizers. The prepared formulations were evaluated for physicochemical and mechanical properties including thickness uniformity, weight variation, moisture content, swelling behavior, tensile strength, folding endurance, surface pH, and drug content uniformity. In vitro drug release studies were performed using the paddle over disk method in phosphate buffer (pH 7.4) for 24 hours. The results demonstrated uniform film characteristics with thickness ranging from 0.401 to 0.631 mm and drug content between 94.95% and 102.32%, indicating uniform drug distribution. Swelling studies showed significant hydration capacity, while mechanical testing confirmed adequate tensile strength and excellent folding endurance across all formulations. Surface pH values remained within the skin-compatible range, ensuring safety for dermal application. In vitro release studies revealed sustained drug release up to 24 hours, with formulation F8 exhibiting the highest release (89.03%).Overall, the developed transdermal patches of Nateglinide showed promising results for controlled drug delivery, with optimized formulations providing sustained release, good mechanical strength, and acceptable skin compatibility, suggesting their potential for once-daily therapeutic application.

Keywords: Transdermal patches, drug delivery system, skin permeability, penetration enhancers, sustained release, microneedles, pharmaceutical innovation.

Introduction

Introduction to Transdermal Patches

Transdermal Drug Delivery Systems (TDDS) are an advanced drug administration approach in which medications are delivered across the skin into systemic circulation. This route offers several clinical and therapeutic advantages over conventional oral and parenteral administration. Most importantly, it bypasses hepatic first-pass metabolism, thereby improving bioavailability, reducing dosing frequency, and enhancing patient compliance. TDDS is also capable of maintaining consistent plasma drug levels through controlled and sustained drug release, which helps in minimizing dose-related toxicity and improving overall therapeutic efficiency.[1-3]

A transdermal patch is a specialized medicated adhesive formulation designed to deliver a predetermined amount of drug through the skin over an extended period. Depending on the design, the drug may be incorporated within a polymeric matrix or contained in a reservoir system separated by a rate-controlling membrane. Drug release is facilitated by diffusion and is influenced by skin temperature and polymer characteristics. Compared to oral, injectable, or topical routes, transdermal delivery provides a more controlled and non-invasive method of systemic therapy. However, its major limitation lies in the skin's natural barrier function, particularly the stratum corneum, which restricts permeation to drugs that are small in molecular size and possess adequate lipophilicity.[4-7]

The TDDS concept gained commercial significance in 1979 with the approval of scopolamine transdermal patches by the U.S. FDA for motion sickness treatment. Since then, TDDS has emerged as a patient-friendly, painless, and convenient alternative for systemic drug delivery. In this system, the patch is applied to clean and intact skin, where the drug gradually penetrates through the stratum corneum, followed by the epidermal and dermal layers, ultimately reaching systemic circulation via dermal capillaries. The large surface area of skin allows multiple potential application sites, contributing to its versatility in clinical use.[8-12]

Pharmacokinetically, transdermal delivery provides more stable plasma drug concentrations with reduced peak–trough fluctuations, thereby lowering the incidence of adverse effects. This makes TDDS particularly beneficial for patients who experience difficulty with oral administration, such as those with nausea, unconsciousness, or swallowing disorders. Additionally, its ease of application supports self-administration and improves long-term treatment adherence. Overall, TDDS enhances drug bioavailability by avoiding gastrointestinal degradation and hepatic first-pass metabolism, making it a highly effective controlled drug delivery system.[13-16]

Methodology

Materials and Instruments

The formulation and analytical work were carried out using standard laboratory instruments, including an analytical balance, digital pH meter, hot air oven, UV–Visible spectrophotometer, FTIR spectrophotometer, and HPLC system.

The chemicals and reagents employed in the study comprised Nateglinide (active pharmaceutical ingredient), agar, guar gum, ethyl cellulose, HPMC, Eudragit RS, diethyl tartrate, and dimethyl sulfoxide. All materials used were of analytical grade quality.

Drug Evaluation

Nateglinide was evaluated through several preliminary studies to determine its physicochemical characteristics and suitability for formulation:[17-19]

1. Organoleptic Evaluation

The drug was examined visually for its color, odor, and physical appearance.

2. Identification Studies

a. FTIR Spectroscopy: FTIR spectra of pure Nateglinide and drug–polymer mixtures were recorded and analyzed to determine possible interactions and compatibility.

b. UV Spectroscopy: A 100 mg sample of Nateglinide was dissolved in phosphate buffer (pH 7.4) and scanned over the wavelength range of 200–400 nm using a UV spectrophotometer with a 1 cm quartz cuvette. The λ_max obtained was compared with reported literature values for confirmation.

3. Calibration Curve Construction

A stock solution was prepared by dissolving 2.5 mg of Nateglinide in 25 mL of suitable diluent. Serial dilutions were then prepared, and their absorbance was measured at 258 nm. A calibration curve was plotted between absorbance and concentration, and the resulting regression equation was used for further drug release analysis.

4. Melting Point Determination

The melting point of Nateglinide was determined using the capillary tube method with a Thiele's tube containing liquid paraffin. The temperature at which complete melting occurred was recorded.

5. Solubility Analysis

Solubility studies were performed in methanol, distilled water, and phosphate buffer (pH 7.4). An excess quantity of drug was added to 5 mL of each solvent and equilibrated for 24 hours at room temperature. The solutions were then filtered and analyzed using UV spectrophotometry at 258 nm.

Preformulation Studies [20-24]

1. Melting Point Evaluation

The melting point was determined using a calibrated melting point apparatus. The experiment was performed in triplicate, and the average value was reported.

2. Drug–Excipient Compatibility Study

Compatibility between Nateglinide and selected polymers was assessed using FTIR spectroscopy. Spectra of the pure drug, individual excipients, and drug–polymer physical mixtures (1:1 ratio) were recorded in the range of 4000–400 cm^{-1} to identify any potential interactions or structural changes.

Formulation of Transdermal Patches

Polymer solutions were prepared in a 1:1 chloroform–methanol mixture. Drug, plasticizer, and permeation enhancer were incorporated sequentially with continuous stirring to obtain a homogeneous casting solution. The solution was degassed to remove trapped air and 3 mL was cast into circular glass moulds over a mercury surface. Films were dried at room temperature (24 h) and further in a hot air oven at 40–45 °C for 30 min to remove residual solvents. Ten formulations (F1–F10) were prepared using varying polymer ratios.

Table 1: Formulation Batches

Sr. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Nateglinide	10	10	10	10	10	10	10	10	10	10
2	Agar	50	--	--	7	7	3	--	--	--	6
3	HPMC K-100	25	10	75	--	--	--	12.5	--	--	--
4	Guar Gum	--	--	--	18	--	--	62.5	75	75	15
5	Ethylcellulose	--	65	--	36	68	52	--	--	--	30
6	Eudragit RS	--	--	--	14	--	21	--	--	--	24
7	Diethyl tartrate	40	40	40	40	40	40	40	40	40	40
8	Dimethyl sulfoxide	25	25	25	25	25	25	25	25	25	25
9	Total Weight (mg)	150	150	150	150	150	150	150	150	150	150

Evaluation of Transdermal Patches [25-29]

1. Thickness Uniformity

The thickness of each transdermal patch was measured at six different locations using a screw gauge. The average of all readings was recorded to ensure uniformity.

2. Weight Variation

Individual 1 × 1 cm² sections of the patches were weighed separately, and the mean weight was calculated to assess weight consistency across formulations.

3. Swelling Index

Samples of 1 × 1 cm² were immersed in phosphate buffer solution (pH 7.4). The weight gain was measured at 5-minute intervals for up to 30 minutes. The swelling index was then calculated based on the increase in weight relative to the initial weight.

4. Moisture Content Determination

The initial weight of the patches (W_1) was recorded. The samples were then placed in a desiccator containing fused calcium chloride until a constant weight (W_2) was achieved. The percentage moisture content was calculated using the formula:

% Moisture Content = $[(W_1 - W_2) / W_2] \times 100$.

5. Tensile Strength

Mechanical strength was evaluated using a tensiometer. The maximum force required to break the patch was recorded and divided by its cross-sectional area. Percentage elongation was also determined from the stress–strain relationship.

6. Folding Endurance

A film of dimensions 4 × 3 cm was repeatedly folded at the same point until it broke. The number of folds sustained before rupture was recorded as the folding endurance.

7. Surface pH Measurement

Patches were allowed to swell on agar plates or in a moist Petri dish for approximately 30 minutes. The surface pH was then measured using a calibrated digital pH meter to ensure skin compatibility.

8. Drug Content Uniformity

A film sample of 2 cm² was dissolved in methanol and subsequently diluted with phosphate buffer (pH 7.4). The resulting solution was analyzed spectrophotometrically at 240 nm. All measurements were performed in triplicate, and the average drug content was reported.

9. In Vitro Drug Release Study (Paddle Over Disk Method)

The patches were fixed onto glass slides using cyanoacrylate adhesive and placed in a

dissolution vessel containing 900 mL of phosphate buffer (pH 7.4) maintained at 37 ± 0.5 °C. The medium was stirred at 50 rpm.

At predetermined time intervals (1 hour up to 24 hours), 5 mL samples were withdrawn and replaced with fresh medium.

The collected samples were analyzed at 258 nm to determine cumulative drug release.

Results and Discussion

Analytical Evaluation

Descriptive and Identification Tests

Nateglinide appeared as a white, odorless powder with an amorphous nature upon visual examination. FTIR analysis showed its characteristic functional groups, including a broad O–H stretching band around 3210 cm^{-1}, C=O stretching of the carboxylic group near 1685 cm^{-1}, amide carbonyl absorption at approximately 1636 cm^{-1}, and aromatic C–C stretching around 1509 cm^{-1}. No additional or unexpected peaks were detected, indicating that the drug structure remained intact.

UV spectroscopic analysis demonstrated a maximum absorption wavelength (λmax) at 258 nm with an absorbance value of 0.9332. The calibration curve constructed over the concentration range of 5–25 µg/mL showed a strong linear relationship, confirming the method's reliability and suitability for quantitative drug estimation.

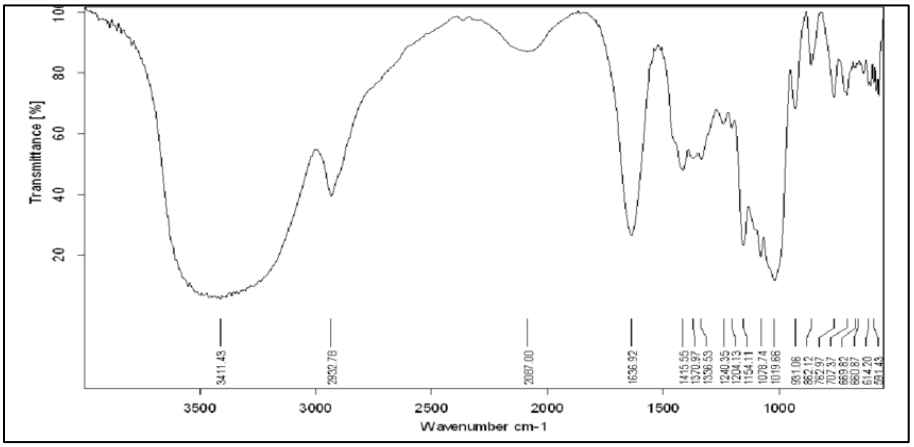

Figure 1: FTIR Spectrum of Nateglinide

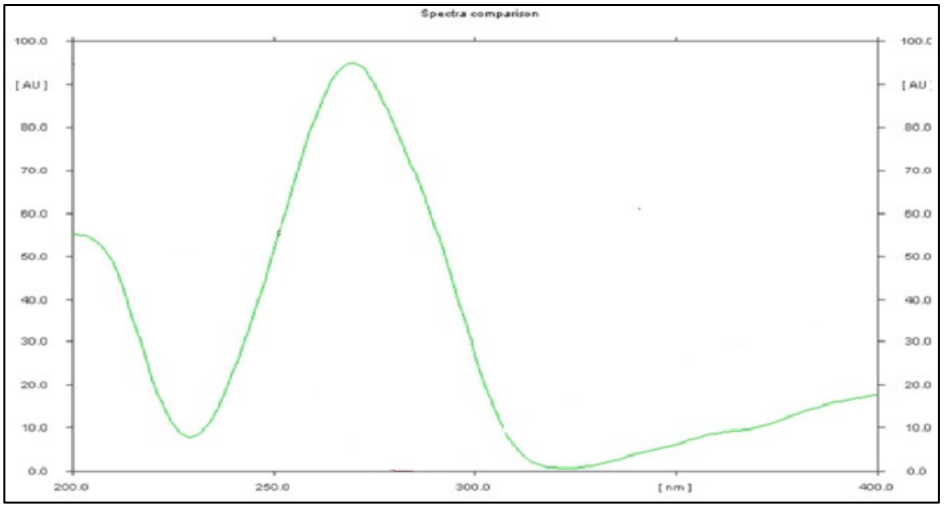

Figure 2: UV Spectra of Nateglinide

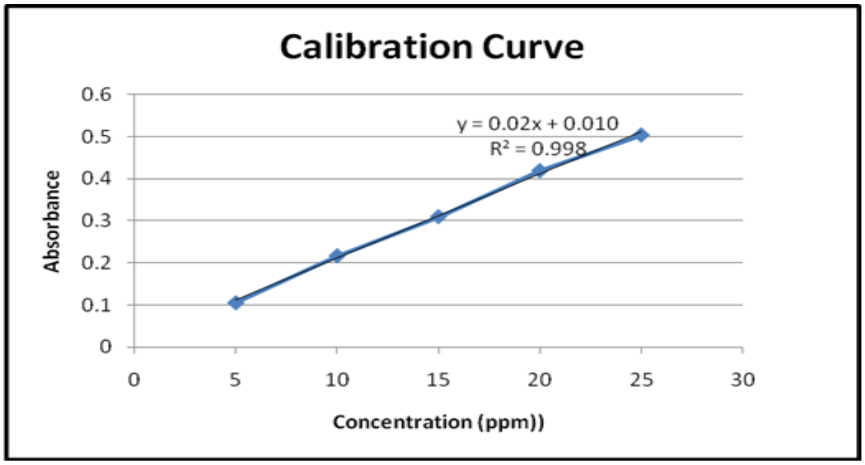

Figure 3: Calibration Curve of Nateglinide

Melting Point and Solubility

The melting point of pure Nateglinide (129.5°C) matched reported literature values, indicating purity. The drug was slightly soluble in water, sparingly soluble in alcohol, and soluble in pH 7.4 buffer, suggesting potential for moderate aqueous permeation.

Preformulation Studies

Melting Point of Formulations

Drug–excipient mixtures (F1–F10) exhibited melting points in the range 127.4–135.5°C, showing no significant deviations from the pure drug, implying the absence of incompatibility or degradation during mixing.

Evaluation of Transdermal Patches

Table 2: Evaluation of Transdermal Patches

Formulation	Thickness (mm)	Weight (mg)	Moisture Content	Swelling Index (% at 30 min)	Tensile Strength (kg/mm^2)	Folding Endurance	Drug Content	Surface pH
F1	0.564	30.48	3.3 %	106.48 %	0.45	>200	96.09 %	5.7
F2	0.510	32.72	4.7 %	116.75 %	0.29	>200	98.46 %	5.4
F3	0.523	34.32	3.6 %	184.62 %	0.63	>200	96.26 %	5.2
F4	0.544	36.81	4.2 %	149.35 %	0.27	>200	97.94 %	4.6
F5	0.526	32.02	6.4 %	191.16 %	0.62	>300	102.32 %	5.3
F6	0.595	31.74	5.6 %	234.75 %	0.76	>300	97.84 %	5.8
F7	0.532	30.95	4.7 %	288.94 %	0.53	>200	99.45 %	6.4
F8	0.401	28.32	5.3 %	126.32 %	0.32	>300	98.74 %	5.1
F9	0.572	29.10	5.6 %	109.65 %	0.79	>300	95.05 %	5.6
F10	0.631	30.07	5.8 %	156.84 %	0.23	>400	94.95 %	6.1

Thickness and Weight Uniformity

The prepared patches exhibited thickness values ranging from 0.401 mm (F8) to 0.631 mm (F10), while the weight varied between 28.32 mg (F8) and 36.81 mg (F4). The low degree of variation among formulations indicated a consistent casting process and homogeneous distribution of polymers. An increase in polymer concentration was generally associated with a corresponding rise in both thickness and weight of the films.

Moisture Content

The percentage moisture content was found to be in the range of 3.3% (F1) to 6.4% (F5). Formulations containing a higher proportion of hydrophilic polymers exhibited greater moisture retention, which may contribute to

improved flexibility of the patches. However, such formulations may require careful optimization to prevent microbial contamination due to increased moisture levels.

Swelling Behavior

After 30 minutes of exposure to phosphate buffer (pH 7.4), the swelling index values showed considerable variation, ranging from 106.48% (F1) to 288.94% (F7). Formulations such as F6 and F7 demonstrated enhanced swelling characteristics, which can be attributed to their higher hydrophilic polymer content. This increased water uptake is expected to facilitate improved drug diffusion from the matrix.

Mechanical Properties

The tensile strength of the patches varied from 0.23 kg/mm² (F10) to 0.79 kg/mm² (F9). Formulations F6 and F9 displayed superior mechanical strength, indicating good structural integrity. Folding endurance values were above 200 for all formulations, with F10 exhibiting the highest flexibility (>400 folds). These results suggest that an appropriate balance between polymers and plasticizers effectively enhanced the mechanical performance of the patches.

Drug Content Uniformity and Surface pH

Drug content analysis revealed values within the range of 94.95% to 102.32%, confirming uniform drug distribution across all formulations and compliance with acceptable pharmacopeial standards.

The surface pH of the patches ranged from 4.6 (F4) to 6.4 (F7), which falls within the physiological skin pH range (4.5–6.5), indicating that the formulations are unlikely to cause skin irritation.

In Vitro Drug Release

Sustained drug release was observed for up to 24 hours across all formulations. The highest cumulative release was recorded for F8 (89.03%), followed by F5 (86.44%) and F4 (85.33%). Formulations with an optimal combination of hydrophilic and hydrophobic polymers demonstrated better hydration and diffusion properties, resulting in enhanced drug release profiles. In contrast, F7 and F9 exhibited comparatively slower initial release, likely due to a more compact matrix structure. Overall, all formulations were capable of providing extended drug release suitable for once-daily administration.

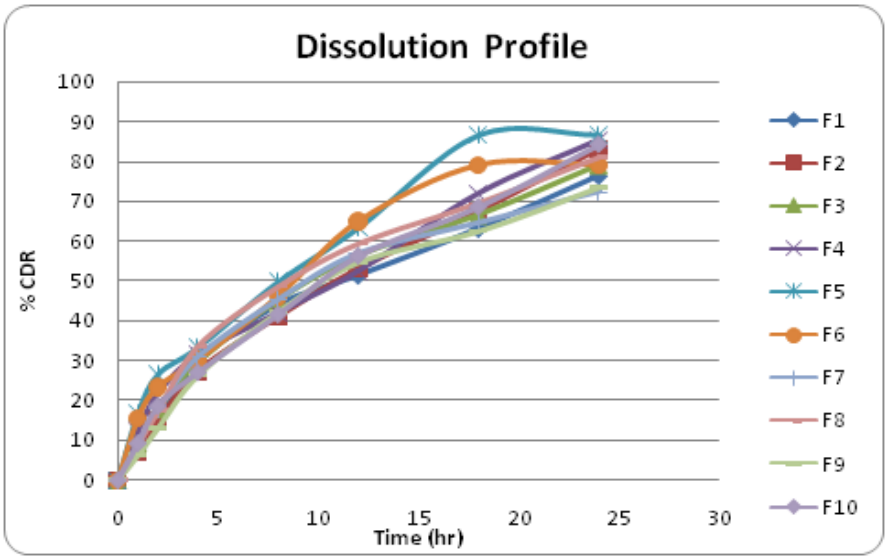

Figure 4: Dissolution Profile

Conclusion

The present investigation successfully formulated and evaluated sustained-release transdermal patches of Nateglinide using a combination of natural (agar, guar gum) and synthetic polymers (HPMC, Eudragit RS, and ethyl cellulose). Among all batches, formulation F8 emerged as the most promising, exhibiting superior mechanical strength, uniform drug content, and an optimal 24-hour sustained-release profile (89.03% cumulative release).

Drug release kinetics indicated a diffusion-controlled mechanism with anomalous transport, reflecting the combined influence of drug diffusion and polymer relaxation.

This transdermal approach offers significant advantages over conventional oral therapy, including bypassing hepatic first-pass metabolism, enhancing bioavailability, and improving patient compliance through reduced dosing frequency. The findings support the potential of this delivery system for diabetes management, warranting further studies—such as ex-vivo permeation, skin irritation, and in-vivo pharmacokinetics—to confirm clinical applicability and safety for eventual commercialization.

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