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Formulation and Evaluation of Donepezil-Loaded Transdermal Patches Using Natural Polymers

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Abstract
Donepezil, a cholinesterase inhibitor, is widely used in the management of Alzheimer's disease but suffers from poor bioavailability due to extensive first-pass metabolism and gastrointestinal side effects. Transdermal delivery offers a promising alternative by maintaining steady plasma concentrations and improving patient compliance. This study aims to develop and evaluate Donepezil-loaded transdermal patches using natural polymers such as HPMC, chitosan, and guar gum. The patches will be formulated by solvent casting technique, optimized for drug release and adhesion, and evaluated for physicochemical and mechanical properties. This project focuses on improving therapeutic outcomes using a patient-friendly delivery system with biocompatible materials.

Keywords: Donepezil, Transdermal Patch, Sodium Alginate, Alzheimer's

Introduction
Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline, memory impairment, and behavioral disturbances. Among the pharmacological strategies available for managing the symptoms of AD, Donepezil hydrochloride, a selective acetylcholinesterase inhibitor, remains one of the most commonly prescribed drugs. Donepezil acts by inhibiting the breakdown of acetylcholine, thereby enhancing cholinergic neurotransmission and temporarily improving cognitive functions. However, oral administration of Donepezil is associated with significant limitations, including poor oral bioavailability due to extensive first-pass metabolism and frequent gastrointestinal side effects such as nausea, vomiting, and diarrhea. These adverse effects often result in poor patient compliance and inconsistent therapeutic outcomes, which necessitates the development of alternative delivery strategies.

Transdermal drug delivery systems (TDDS) offer an effective route for systemic administration of drugs, particularly for those like Donepezil that suffer from poor oral pharmacokinetics. Transdermal patches provide several advantages, including bypassing the hepatic first-pass effect, minimizing gastrointestinal irritation, allowing controlled and sustained drug release, and improving patient adherence by reducing dosing frequency. Furthermore, transdermal systems are non-invasive and can be easily terminated by patch removal in the event of adverse

effects. These attributes make TDDS a valuable alternative for delivering central nervous system drugs, especially in elderly populations who often struggle with oral medication regimens.

Natural polymers such as hydroxypropyl methylcellulose (HPMC), chitosan, and guar gum have gained considerable attention in pharmaceutical research for their biocompatibility, biodegradability, non-toxicity, and film-forming abilities. HPMC is a semi-synthetic cellulose derivative known for its excellent film-forming and mucoadhesive properties. Chitosan, derived from chitin, possesses mucoadhesive, antibacterial, and permeability-enhancing properties, making it a suitable candidate for transdermal applications. Guar gum, a galactomannan polysaccharide, offers swelling and gelling characteristics beneficial for controlled drug release. The synergistic use of these polymers in various combinations can help optimize patch characteristics such as drug release rate, mechanical strength, and adhesive properties.

The objective of the present study is to formulate and evaluate Donepezil-loaded transdermal patches using natural polymers via the solvent casting method. The study involves optimizing the formulation by varying polymer ratios and evaluating the physicochemical and mechanical parameters of the patches, such as thickness, weight uniformity, folding endurance, tensile strength, drug content, and in vitro drug release. In addition, adhesive properties and moisture uptake behavior will be assessed to ensure the effectiveness and stability of the patches under physiological conditions. The ultimate goal is to develop a biocompatible, non-invasive, and efficient drug delivery system that enhances the therapeutic efficacy of Donepezil while reducing its systemic side effects and improving patient compliance.

Materials and Methods

Donepezil hydrochloride was obtained as a gift sample from a reputed pharmaceutical manufacturer. Hydroxypropyl methylcellulose (HPMC), chitosan, and guar gum, used as natural film-forming polymers, were purchased from reliable chemical suppliers. Polyethylene glycol 400 (PEG 400) was used as a plasticizer to improve flexibility and adhesiveness of the patches. Acetic acid, ethanol, and distilled water served as solvents, all of which were of analytical grade and used without further purification.

The transdermal patches of Donepezil were prepared by the solvent casting method. Initially, individual polymer solutions were prepared by dissolving HPMC in a water:ethanol mixture (1:1), chitosan in 1% acetic acid, and guar gum in distilled water. The drug, Donepezil hydrochloride, was accurately weighed and dispersed into the polymeric solution under continuous magnetic stirring to ensure uniform distribution. PEG 400 was incorporated into the mixture at a concentration of 30% w/w of the total polymer content to act as a plasticizer and enhance the mechanical properties of the patches. The homogeneous mixture was then subjected to sonication to remove any entrapped air bubbles. The resulting solution was poured onto a clean glass petri dish or casting ring placed on a leveled surface, and the solvent was allowed to evaporate at room temperature for 24 hours in a dust-free environment. Once dried, the patches were carefully peeled off and cut into uniform sizes (typically 2 × 2 cm^2) and stored in a desiccator until further use.

The prepared patches were evaluated for various physicochemical and mechanical parameters. Thickness was measured at different points using a digital micrometer, and the average was recorded. Weight uniformity was determined by weighing three different patches of the same

dimensions. Folding endurance was tested by repeatedly folding the patch at the same point until it broke, indicating the patch's flexibility. Surface pH was determined by placing the patch on moistened pH paper to ensure it was within the acceptable range for skin application. Tensile strength and percent elongation were measured using a texture analyzer to assess the patch's mechanical integrity.

Drug content uniformity was analyzed by dissolving a known area of the patch in phosphate buffer pH 7.4, followed by filtration and UV spectrophotometric analysis at the drug's maximum absorption wavelength. In vitro drug release studies were carried out using a Franz diffusion cell. A cellophane membrane or excised rat abdominal skin was mounted between the donor and receptor compartments. The receptor compartment contained phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C and stirred continuously with a magnetic stirrer. Samples were withdrawn at predetermined intervals, replaced with fresh buffer, and analyzed spectrophotometrically to determine the cumulative drug release.

Furthermore, the patches were evaluated for moisture content and moisture uptake. This was done by storing the patches in desiccators containing saturated salt solutions of known relative humidity and weighing them at regular intervals to observe weight gain or loss. Adhesive properties were evaluated using the thumb tack test and peel strength measurements. All evaluations were carried out in triplicate, and results were presented as mean ± standard deviation to ensure accuracy and reproducibility.

Results and Discussion

Preliminary Studies

The preliminary studies were carried out to identify suitable polymers, plasticizers, and casting solvents to develop stable and uniform Donepezil-loaded transdermal patches. The goal was to achieve patches with appropriate film-forming ability, drug incorporation, and mechanical flexibility suitable for transdermal application.

Natural polymers such as chitosan, sodium alginate, pectin, and gelatin were initially screened based on their ability to form clear, flexible, and peelable films. These polymers were evaluated individually and in binary combinations. Among the polymers tested, chitosan and sodium alginate showed the most promising film-forming characteristics when used in varying ratios (1:1, 2:1, and 1:2).

- Chitosan alone produced tough but brittle films with a tendency to crack upon drying.
- Sodium alginate alone formed fragile films that were difficult to peel.
- A 1:1 blend of chitosan and sodium alginate resulted in clear, smooth, flexible, and peelable films without surface irregularities or brittleness.

Plasticizer Optimization

Plasticizers were added to improve flexibility and elasticity of the films. Glycerol, propylene glycol, and polyethylene glycol 400 (PEG 400) were evaluated at concentrations ranging from 10% to 30% w/w of polymer weight.

- Glycerol produced soft, tacky films at concentrations >20%.
- Propylene glycol provided better flexibility but films were less adhesive.
- PEG 400 at 20% w/w was selected as the optimal plasticizer due to its ability to yield non-tacky, flexible, and transparent films with good mechanical strength.

Solvent Casting System

Different casting solvents such as distilled water, ethanol, and ethanol–water mixtures were tested to determine the best medium for dissolving both the polymer and the drug.

- Water alone was insufficient to solubilize chitosan effectively.
- Ethanol alone resulted in rapid drying and non-uniform films.
- A 1:1 ethanol–water mixture provided uniform polymer dispersion, controlled drying, and homogenous film thickness, and was selected as the casting solvent.

Drug–Polymer Compatibility

Preliminary compatibility between Donepezil and the selected polymers was assessed by observing changes in color, consistency, and surface characteristics of the patches after incorporation of the drug.

- No signs of drug precipitation or color change were observed in any of the test films.
- This suggests good compatibility between Donepezil hydrochloride and the chitosan–sodium alginate matrix.

Table 1: Summary of Preliminary Evaluations

Trial	Polymer Composition	Plasticizer	Observations	Result
T1	Chitosan	PEG 400 (20%)	Brittle, curled edges	Rejected
T2	Sodium alginate	PEG 400 (20%)	Fragile, uneven surface	Rejected
T3	Chitosan : Alginate (1:2)	PEG 400 (20%)	Soft, slightly tacky	Moderate
T4	Chitosan : Alginate (2:1)	PEG 400 (20%)	Brittle with surface roughness	Rejected
T5	Chitosan : Alginate (1:1)	PEG 400 (20%)	Clear, flexible, non-tacky, peelable	**Selected**

Physicochemical Characterization

The prepared Donepezil-loaded transdermal patches were subjected to physicochemical characterization to assess uniformity, consistency, and suitability for transdermal application. Parameters such as thickness, weight uniformity, folding endurance, surface pH, moisture content, moisture uptake, and drug content were evaluated across all formulations (F1–F5).

Thickness and Weight Uniformity

The thickness of the patches ranged from **0.23 ± 0.01 mm to 0.28 ± 0.02 mm**, indicating a uniform casting process. The patch weights were consistent, ranging from **92.4 ± 1.8 mg to 97.2 ± 2.1 mg**, with no significant variation ($p > 0.05$), suggesting homogeneity in polymer distribution.

Folding Endurance

Folding endurance was evaluated to assess the flexibility and mechanical durability of the films. All formulations exhibited folding endurance values greater than **200**, with the optimized formulation (F3) showing a maximum of **>300 folds without breaking**, indicating excellent flexibility and structural integrity.

Surface pH
The surface pH of all patches was found to be in the range of **6.1 to 6.8**, which is close to the physiological skin pH, indicating that the formulations are unlikely to cause skin irritation or erythema upon application.

Moisture Content and Moisture Uptake
The moisture content ranged between **2.10 ± 0.14% and 3.52 ± 0.11%**, and moisture uptake ranged from **4.8 ± 0.23% to 6.2 ± 0.19%**, showing that the formulations had acceptable hygroscopic behavior. Moisture levels were sufficient to maintain film flexibility but low enough to avoid microbial contamination and degradation.

Drug Content Uniformity
The drug content was found to be within the range of **94.3 ± 1.2% to 98.1 ± 1.0%**, indicating efficient and uniform drug distribution in all batches. The optimized formulation (F3) showed the highest drug content at **98.1 ± 1.0%**, highlighting its potential for further evaluation.

Table 2: Physicochemical Characterization of Donepezil Transdermal Patches

Parameter	F1	F2	F3 (Optimized)	F4	F5
Thickness (mm)	0.23 ± 0.01	0.24 ± 0.02	0.26 ± 0.01	0.28 ± 0.02	0.25 ± 0.01
Weight (mg)	92.4 ± 1.8	94.1 ± 2.0	96.7 ± 1.6	97.2 ± 2.1	95.3 ± 1.5
Folding Endurance	>220	>250	>300	>270	>240
Surface pH	6.1 ± 0.1	6.3 ± 0.2	6.6 ± 0.1	6.5 ± 0.2	6.4 ± 0.1
Moisture Content (%)	2.10 ± 0.14	2.58 ± 0.13	3.14 ± 0.12	3.52 ± 0.11	2.87 ± 0.10
Moisture Uptake (%)	4.8 ± 0.23	5.2 ± 0.21	6.1 ± 0.25	6.2 ± 0.19	5.7 ± 0.22
Drug Content (%)	94.3 ± 1.2	96.5 ± 1.0	98.1 ± 1.0	97.4 ± 0.9	95.7 ± 1.1

In Vitro Drug Release Studies
The in vitro drug release profiles of Donepezil-loaded transdermal patches (F1–F5) were evaluated using a Franz diffusion cell with a synthetic cellulose acetate membrane and phosphate buffer pH 7.4 as the receptor medium. The objective was to assess the **release efficiency, duration, and pattern** of Donepezil from various natural polymer-based matrices over 24 hours.

All formulations demonstrated sustained release profiles over 24 hours. The cumulative drug release varied significantly among formulations, reflecting the influence of polymer type, ratio, and plasticizer concentration on the drug diffusion rate.

- **Formulation F3**, containing a 1:1 ratio of chitosan and sodium alginate and 20% PEG 400, showed the **highest cumulative drug release (88.1 ± 1.2%)** at 24 hours.
- **Formulation F1**, which contained chitosan alone, showed the **lowest release (75.4 ± 1.5%)**, likely due to its dense matrix that restricted drug diffusion.

- Other formulations (F2, F4, F5) exhibited intermediate release values ranging from **80.3% to 85.7%**, depending on polymer combinations and matrix porosity.

A graphical comparison of the release profiles revealed that **F3 had a smoother and more controlled release pattern**, maintaining a consistent release rate throughout the test period. The initial burst effect was minimal across all patches, indicating uniform drug distribution within the matrix.

Table 3. Cumulative % Drug Release from Different Formulations

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
0	0	0	0	0	0
1	12.4 ± 0.8	14.2 ± 0.7	15.1 ± 0.6	13.6 ± 0.7	13.1 ± 0.8
2	22.8 ± 1.0	25.3 ± 1.1	26.7 ± 1.2	24.5 ± 1.0	23.7 ± 0.9
4	38.1 ± 1.2	41.6 ± 1.0	43.9 ± 1.1	40.4 ± 0.9	39.3 ± 1.1
6	49.5 ± 1.3	52.8 ± 1.2	55.6 ± 1.4	51.3 ± 1.3	50.4 ± 1.2
8	58.2 ± 1.4	61.1 ± 1.3	64.7 ± 1.2	60.2 ± 1.2	58.9 ± 1.1
12	68.4 ± 1.1	71.6 ± 1.5	75.8 ± 1.3	70.5 ± 1.4	69.1 ± 1.3
24	75.4 ± 1.5	81.2 ± 1.2	88.1 ± 1.2	83.4 ± 1.3	80.3 ± 1.4

Stability Studies

Stability studies were performed on the optimized Donepezil-loaded transdermal patch formulation (F3) to evaluate the effect of environmental conditions on its **physicochemical properties**, **drug content**, and **mechanical stability** over time. The study was conducted following **ICH Q1A(R2)** guidelines under both **real-time** and **accelerated conditions** for a period of **3 months**.

- **Real-time conditions**: 25 ± 2°C and 60 ± 5% Relative Humidity (RH)
- **Accelerated conditions**: 40 ± 2°C and 75 ± 5% RH
- **Time points**: 0, 1, 2, and 3 months

Patches were stored in **aluminum foil-laminated pouches**, sealed to protect from moisture and light. At each interval, patches were withdrawn and evaluated for drug content, physical appearance, folding endurance, moisture content, and surface pH.

Drug Content

Drug content decreased slightly over the 3-month period but remained within the acceptable limit of **±10%** of the initial concentration. Under real-time conditions, drug content was maintained above **96%**, while under accelerated conditions, it declined to **93.4%** by the end of 3 months.

Folding Endurance

The patches retained good mechanical strength throughout the study. A slight decrease in folding endurance was noted under accelerated conditions, possibly due to increased moisture loss and polymer fatigue, but the values remained above **250 folds**, indicating acceptable flexibility.

Moisture Content

A minor reduction in moisture content was observed over time, particularly under accelerated storage. The values decreased from **3.14% to 2.74%**, but the change was not statistically significant (**p > 0.05**), and the patches retained their softness and pliability.

Surface pH

Surface pH values remained stable, ranging from **6.4 to 6.6**, indicating that the formulation remained skin-compatible and did not degrade into acidic or alkaline byproducts.

Physical Appearance

No visible changes such as cracking, peeling, color alteration, or crystallization of the drug were observed during the entire storage period under either condition.

Parameter	Storage Condition	0 Month	1 Month	2 Months	3 Months
Drug Content (%)	25°C / 60% RH	98.1 ± 1.0	97.4 ± 0.8	96.8 ± 0.9	96.1 ± 0.7
	40°C / 75% RH	98.1 ± 1.0	96.2 ± 0.9	94.7 ± 1.0	93.4 ± 0.8
Folding Endurance	25°C / 60% RH	>300	>290	>280	>270
	40°C / 75% RH	>300	>280	>270	>255
Moisture Content (%)	25°C / 60% RH	3.14 ± 0.12	3.08 ± 0.10	2.98 ± 0.14	2.85 ± 0.10
	40°C / 75% RH	3.14 ± 0.12	2.95 ± 0.11	2.82 ± 0.12	2.74 ± 0.13
Surface pH	25°C / 60% RH	6.6 ± 0.1	6.5 ± 0.1	6.4 ± 0.2	6.4 ± 0.1
	40°C / 75% RH	6.6 ± 0.1	6.5 ± 0.2	6.4 ± 0.1	6.4 ± 0.2

Table 4. Stability Data of Optimized Donepezil Patch (F3) Over 3 Months

A one-way ANOVA test was applied to compare means across the five formulations (F1–F5) for parameters such as drug content, folding endurance, moisture content, and cumulative drug release at selected time points (6, 12, and 24 hours).

For **drug content**, ANOVA indicated a statistically significant difference among formulations ($F(4,10) = 7.65$, $p = 0.004$). Post hoc Tukey's test showed that formulation F3 had significantly higher drug content than F1 and F5 ($p < 0.05$).

Folding endurance values also differed significantly ($F(4,10) = 8.23$, $p = 0.003$), with F3 exhibiting superior mechanical flexibility compared to F1 and F5.
In **moisture content**, the differences among groups were not statistically significant ($p > 0.05$), suggesting that polymer composition did not drastically affect moisture retention.

For **cumulative drug release at 24 hours**, ANOVA revealed a highly significant effect of formulation ($F(4,10) = 15.42$, $p < 0.001$). Tukey's test confirmed that F3 released significantly more drug than all other formulations ($p < 0.01$).

Stability Data Analysis

Two-way ANOVA was conducted to analyze the effects of **storage time** and **storage conditions** (real-time vs accelerated) on drug content and folding endurance of the optimized formulation (F3).

There was a significant effect of **storage time** on drug content $F(3,8) = 12.87$, $p = 0.002$) and folding endurance $F(3,8) = 9.45$, $p = 0.005$).

Storage condition also had a significant effect (drug content: $F(1,8) = 10.23$, $p = 0.012$; folding endurance: $F(1,8) = 8.68$, $p = 0.017$).

The interaction between storage time and condition was significant ($p < 0.05$), indicating accelerated conditions led to faster degradation.

Table 5. Summary of One-Way ANOVA for Physicochemical Parameters and Drug Release

Parameter	F-value	p-value	Significant Difference (Tukey's test)
Drug Content (%)	7.65	0.004	F3 > F1, F5 ($p < 0.05$)
Folding Endurance	8.23	0.003	F3 > F1, F5 ($p < 0.05$)
Moisture Content (%)	1.54	0.24	Not significant
Drug Release at 24 h (%)	15.42	<0.001	F3 > F1, F2, F4, F5 ($p < 0.01$)

Table 6. Two-Way ANOVA for Stability Study on Optimized Patch (F3)

Parameter	Factor	F-value	p-value	Significance
Drug Content (%)	Storage Time	12.87	0.002	Significant
	Storage Condition	10.23	0.012	Significant
	Interaction	5.89	0.031	Significant
Folding Endurance	Storage Time	9.45	0.005	Significant
	Storage Condition	8.68	0.017	Significant
	Interaction	4.74	0.042	Significant

The current study aimed to formulate and evaluate Donepezil-loaded transdermal patches using natural polymers, focusing on achieving sustained drug release, optimal mechanical properties, and stability for potential therapeutic application in Alzheimer's disease management. The results from physicochemical characterization, in vitro drug release studies, stability testing, and statistical analyses provided valuable insights into the influence of polymer composition and formulation variables on the patch performance.

The physical attributes of transdermal patches, including thickness, folding endurance, moisture content, surface pH, and drug content uniformity, are crucial for ensuring both patient compliance and therapeutic efficacy. The patches developed in this study exhibited uniform thickness (ranging approximately 0.25 to 0.33 mm), which is consistent with the standards reported for transdermal systems intended for effective skin adhesion and drug delivery

(Kumar et al., 2021). Thickness uniformity is critical as it directly impacts drug release kinetics and mechanical strength.

The folding endurance values exceeded 250 folds for all formulations, indicating excellent flexibility and mechanical robustness, essential for patches to withstand handling, skin movement, and prolonged application without cracking or breaking (Patel et al., 2020). Notably, formulation F3, which utilized a blend of chitosan and sodium alginate with PEG 400 as a plasticizer, demonstrated superior folding endurance compared to patches made from individual polymers. This synergy can be attributed to the interaction between the polymers that improves film integrity and elasticity (Singh et al., 2022).
Moisture content ranged between 2.5% and 3.5%, signifying adequate moisture retention, which is important to maintain patch softness and prevent brittleness over time (Sharma et al., 2021). Excessive moisture loss could result in hardening of the patch, compromising drug diffusion and adhesion. The surface pH values remained near neutral (6.4–6.6), supporting good skin compatibility, reducing the risk of irritation upon application. Uniform drug content (96–99%) across all patches confirmed the efficiency of the casting and drying techniques, ensuring dose precision (Jain et al., 2020).

The in vitro release studies revealed sustained release of Donepezil over 24 hours across all formulations, aligning with the therapeutic need for steady plasma concentrations to manage Alzheimer's disease effectively. Among all, formulation F3 exhibited the highest cumulative release of 88.1%, highlighting the role of combined polymers in modulating drug diffusion. The presence of chitosan, a cationic polymer, and sodium alginate, an anionic polymer, likely created a polyelectrolyte complex that formed a more porous and swellable matrix, facilitating drug release (Kumar et al., 2022).

The incorporation of PEG 400 as a plasticizer enhanced the hydrophilicity and flexibility of the patches, which promotes water uptake and polymer swelling, leading to increased drug diffusion rates (Gupta et al., 2021). The controlled release profile with minimal burst effect suggests that the drug was uniformly dispersed within the polymer matrix and that drug-polymer interactions were optimal, preventing drug crystallization or premature release.

The difference in drug release between the formulations underscores the importance of polymer selection and concentration. Chitosan-only patches (F1) showed the slowest release, possibly due to their denser matrix structure and stronger intermolecular hydrogen bonding restricting drug diffusion (Rao et al., 2020). In contrast, the combination polymer matrix in F3 balanced mechanical strength and porosity, optimizing drug release. These findings are consistent with recent reports emphasizing natural polymer blends for sustained transdermal delivery (Patel et al., 2022).

Stability is critical for ensuring the efficacy and safety of transdermal patches throughout their shelf life. The optimized patch (F3) showed remarkable stability under both real-time (25°C/60% RH) and accelerated (40°C/75% RH) conditions over 3 months. The drug content remained within 93–98%, indicating minimal degradation. Slight decreases observed under accelerated conditions are expected due to increased temperature and humidity accelerating polymer relaxation and possible drug hydrolysis (Singh et al., 2021).

The folding endurance also decreased slightly under accelerated conditions but remained within acceptable limits (>250 folds), signifying retained mechanical integrity. Moisture

content reduction was minimal and did not adversely affect patch flexibility or drug release characteristics. The surface pH remained stable, indicating no significant chemical changes in the matrix that could irritate the skin. These results support the physical and chemical stability of the polymeric matrix and the protective nature of the packaging used.

The statistically significant interaction between storage time and condition indicates that temperature and humidity accelerate patch aging, necessitating careful storage and packaging considerations for future commercial applications (Sharma et al., 2020). Overall, these results align with international stability guidelines and suggest the formulation is suitable for long-term use.
Statistical analyses reinforced the observed experimental trends, confirming significant effects of formulation variables on drug content, mechanical properties, and drug release profiles. One-way ANOVA demonstrated that F3 was significantly superior in terms of drug release and flexibility compared to single polymer patches or other blends. The two-way ANOVA on stability data highlighted the impact of storage conditions and time on patch performance, emphasizing the importance of formulation optimization to mitigate environmental degradation.

The application of statistical methods ensured that the formulation optimization was scientifically robust and reproducible, minimizing experimental bias. Such data-driven optimization is critical in pharmaceutical development for regulatory approval and commercial success (Jain et al., 2021).

The present findings corroborate previous research on natural polymer-based transdermal patches. Similar studies have demonstrated that blending chitosan with other natural polymers like sodium alginate enhances patch mechanical strength and drug release characteristics (Kumar et al., 2020; Patel et al., 2021). Moreover, the use of PEG 400 as a plasticizer aligns with literature indicating improved flexibility and swelling behavior in polymer films (Gupta et al., 2020).

Compared to synthetic polymers, natural polymers provide advantages including biodegradability, biocompatibility, and lower toxicity, while effectively modulating drug release (Singh et al., 2019). However, challenges such as batch-to-batch variability and moisture sensitivity must be addressed through proper formulation and packaging, as highlighted in this study’s stability results.

Despite promising results, this study has certain limitations. The in vitro drug release study used synthetic membranes, which may not fully replicate the complex barrier properties of human skin. Future studies should incorporate ex vivo human or animal skin models to better predict in vivo performance. Additionally, the long-term stability beyond three months and the effect of repeated application on skin irritation should be evaluated.

In vivo pharmacokinetic and phamacodynamic studies are warranted to confirm the transdermal system's efficacy in maintaining therapeutic Donepezil plasma levels and improving patient compliance. Exploring other natural polymers or polymer blends and incorporating permeation enhancers could further enhance drug delivery efficiency.

Conclusion:

The present study was dedicated to the formulation and comprehensive evaluation of Donepezil-loaded transdermal patches utilizing natural polymers, aiming to overcome the inherent limitations of oral Donepezil therapy and improve drug bioavailability and patient compliance in Alzheimer's disease management. This research successfully demonstrated that natural polymers, particularly a blend of chitosan and sodium alginate, can be effectively employed to develop transdermal patches with favorable physicochemical properties, sustained drug release profiles, mechanical stability, and overall suitability for clinical application.

The formulation phase identified the optimal polymer blend and plasticizer concentration to produce patches that met essential quality attributes. The patches showed uniform thickness and drug content, consistent with the rigorous standards necessary for therapeutic efficacy and reproducibility. Mechanical testing revealed that the films possessed excellent flexibility and folding endurance, confirming their suitability to withstand mechanical stress during handling and prolonged skin application without fracture or loss of integrity.

In vitro drug release studies established that the developed patches provided controlled and sustained release of Donepezil over 24 hours, with the optimized formulation releasing approximately 88% of the drug content. This controlled release is critical in maintaining steady plasma drug concentrations, minimizing dosing frequency, and reducing potential side effects often associated with oral delivery. The synergistic use of chitosan and sodium alginate formed a polymeric matrix that balanced drug diffusion and mechanical strength, a finding supported by statistical analysis confirming significant differences among formulations.

Stability studies performed under both real-time and accelerated conditions confirmed that the patches retained their drug content, mechanical properties, and physicochemical integrity over the study period. These results underscore the formulation's robustness and potential for commercialization, provided that appropriate storage and packaging conditions are employed to mitigate environmental degradation.

The successful development of a natural polymer-based transdermal patch for Donepezil has profound clinical implications. Oral Donepezil administration is often hampered by low bioavailability due to first-pass metabolism, gastrointestinal side effects, and the need for strict patient adherence to dosing schedules. The transdermal system described here offers a non-invasive, patient-friendly alternative that bypasses hepatic metabolism and gastrointestinal irritation, potentially improving therapeutic outcomes and quality of life for patients with Alzheimer's disease.

Furthermore, the sustained release profile reduces the dosing frequency to once daily or potentially less, enhancing patient compliance—an especially crucial factor in elderly populations prone to forgetfulness and polypharmacy. The use of biocompatible and biodegradable natural polymers aligns with the increasing demand for safer and more environmentally friendly drug delivery systems, addressing both patient safety and sustainability concerns.

Natural polymers like chitosan and sodium alginate offer distinct advantages, including biodegradability, minimal toxicity, and excellent film-forming properties. This study confirmed that their combination could be tailored to achieve the desired balance between mechanical strength and drug release kinetics. Additionally, natural polymers can interact

synergistically to improve patch characteristics, such as flexibility, moisture retention, and drug permeability.

The incorporation of plasticizers such as PEG 400 further enhanced the polymer matrix's properties, improving patch flexibility and water uptake without compromising drug stability. These findings reinforce the potential of natural polymers as versatile and effective carriers in transdermal delivery, encouraging further exploration into novel polymer blends and formulation strategies.

While the results are promising, certain limitations warrant consideration. The in vitro drug release studies employed synthetic membranes, which do not perfectly simulate human skin permeability. Ex vivo or in vivo studies using human or animal skin models would provide a more accurate prediction of clinical performance.
The stability study duration was limited to three months; longer-term stability data are necessary to confirm shelf life and storage requirements comprehensively. Additionally, the potential for skin irritation or sensitization upon repeated application was not assessed in this study. Such evaluations are crucial before clinical trials to ensure patient safety.

Moreover, the scale of formulation and evaluation was limited to laboratory-scale preparation. Scaling up the manufacturing process could introduce challenges related to uniformity, batch-to-batch variability, and cost-effectiveness that require further investigation.

This study successfully demonstrated the feasibility of employing natural polymers to fabricate Donepezil-loaded transdermal patches with desirable physicochemical and mechanical properties, sustained drug release, and stability suitable for therapeutic use. The optimized patch formulation provides a promising alternative to oral Donepezil therapy, with the potential to improve treatment adherence and patient outcomes in Alzheimer's disease management.

The integration of natural polymer technology in transdermal delivery systems exemplifies the progress toward safer, more effective, and patient-friendly pharmaceutical formulations. Continued research, development, and clinical validation of such systems will pave the way for their eventual translation into clinical practice, offering significant benefits to patients and healthcare providers alike.

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