RESEARCH ARTICLE

Design, Development, and Evaluation of Transdermal Patches Containing Donepezil Hydrochloride

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ABSTRACT

This study aimed to develop a donepezil hydrochloride (DH) transdermal drug delivery system to address non-compliance due to dementia in Alzheimer's patients. DH has a low dose, balanced hydrophilicity/lipophilicity, and low toxicity making it suitable for transdermal. DH transdermal patches were prepared using a polymer and plasticizer matrix system via box-Behnken design and evaluated for properties. Formulation B2 containing hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC), and xanthan gum was optimal, exhibiting a maximum of ~99.17% *in-vitro* drug release for 48 hours. *In-vivo* pharmacokinetic parameters studied in rabbits were superior to commercial DH tablets. The study demonstrates the potential for DH transdermal patches as an alternative to oral medication for Alzheimer's patients. The patches can provide sustained release for prolonged periods without requiring multiple doses. However, further confirmation is needed via *in-vivo* pharmacodynamic and human pharmacokinetic studies.

Keywords: Alzheimer's disease, Transdermal patches, Donepezil hydrochloride, Box-Behnken designs, *In-vivo* studies.

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INTRODUCTION

Alzheimer's disease causes acetylcholine decline, impairing cognition and physical abilities. Current treatments aim to slow the progression of the disease. Oral drugs rely on patient compliance but transdermal patches verify dosage and reduce errors in drug administration.[1,2] For dementia patients, transdermal patches are an attractive option as they offer advantages over other methods. Their non-invasive use improves compliance.[3,4] They provide consistent dosage, increasing bioavailability and decreasing liver metabolism. These benefits suit sustained, long-term delivery and can improve patient experiences.[5] Donepezil hydrochloride belongs to class I of the Biopharmaceutical classification system (BCS) with high solubility and high permeability. It is used in the management of Alzheimer's disease and suits transdermal delivery due to its long half-life, lesser dose, and minimal toxicity.[6] A sustained transdermal dosage could benefit Alzheimer's patients, given compliance challenges and disease progression.[7] This work aims to develop an effective, affordable, and stable DH transdermal patch that meets standards. A DH patch could avoid oral drug issues and realize transdermal benefits, impacting Alzheimer's management.

MATERIALS AND METHODS

The active ingredient, donepezil hydrochloride (DH), was obtained as a gift from Eisai Pharmaceutical India Pvt. Ltd. All of the polymers and excipients like ethyl cellulose (EC), hydroxypropyl methylcellulose (HPMC) 50 cps, xanthan gum, polyethylene glycol (PEG), propylene glycol (PG), dibutyl phthalate (DBP), dimethyl sulfoxide (DMSO), methanol were of laboratory-grade chemicals procured from SD Fine Chemicals Ltd. in Chennai, India.

Technology Employed

Transdermal patches containing donepezil hydrochloride were produced using the solvent casting method.[8] The solvent casting method involves dissolving polymers and components in a solvent, pouring the solution onto a casting surface, and allowing the solvent to evaporate, leaving behind the patch material containing the active drug. The glass slides provided a smooth, stable surface for casting the patches and facilitating solvent evaporation.

Preparation of Donepezil Hydrochloride Patches by Solvent Casting Method

Trial runs

Initial donepezil transdermal patch formulations were developed using a one-factor-at-a-time (OFAT) approach. HPMC between 100 to 150 mg, EC from 300 to 400 mg, and xanthan gum from 200 to 300 mg were tested based on the literature. The goal was to determine the ideal polymer concentrations for quality patches. The results from the trial

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runs are used for further optimization using Box-Behnken design.[9,10] The polymer solution was prepared by dissolving HPMC or ethyl cellulose in methanol, while xanthan gum used a water-methanol mixture to avoid precipitation. Co-solvents, plasticizers, and donepezil hydrochloride were added. The solution was cast on glass slides, dried, peeled off, and cut. Aluminum foil served as the backing layer with adhesive tape to adhere to the patch. The active side was covered until use (components of the patch are shown in Figure 1).

Box-Behnken design

The trial DH transdermal patch formulations were evaluated for quality parameters like physical appearance, folding endurance, swelling index, and drug release. HPMC 125 mg, ethyl cellulose 350 mg, and xanthan gum 300 mg produced optimal results in the trial runs and were used as low, middle, and high values to develop Box-Behnken design formulations.[11] The independent and dependent variables used in the study are shown in Table 1, while the patches' composition is shown in Table 2.

Analytical Studies

Construction of standard calibration curve

- *UV spectroscopy method*

Donepezil hydrochloride (DH) stock solutions of 10, 20, 30, 40, 50, and 60 µg/mL were prepared in pH 7.4 phosphate buffer. The absorbance of each concentration was measured at 271 nm in triplicate using a UV-Vis spectrophotometer (LAB INDIA UV 3000+, Mumbai) with buffer as blank.[12] A standard curve was generated by plotting absorbance versus DH concentration. Linear regression determined the equation of the best-fit line, slope, intercept, and regression coefficient (r^2) to assess linearity.[13]

- *RP-HPLC method*

Approximately 50 mg of donepezil hydrochloride (DH) standard was measured and dissolved in 35 mL solvent at room temperature. More solvent was added until 50 mL and mixed. A 5 mL portion was diluted in a 25 mL mobile phase for analysis within a specific concentration range (10 to 100 ng/mL). The mobile phase consisted of methanol, phosphate buffer, triethylamine, and phosphoric acid at pH 7.5. 20 µL of DH solution was injected into the HPLC system (Perkin Elmer series 200, Mumbai) with a UV detector at 271 nm.[14] The DH amount in an unknown sample was determined by measuring the peak area on the chromatogram versus a standard calibration curve. The peak area corresponds to a specific DH concentration, allowing its amount to be calculated.

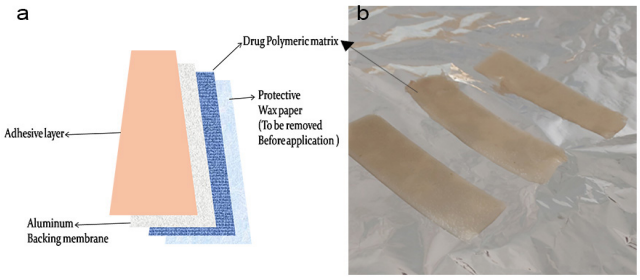

Figure 1: Components of the transdermal patch

- *Drug-excipient incompatibility studies*

Fourier transform infrared (FTIR) spectroscopy assessed potential interactions between donepezil hydrochloride (DH) and excipients in the transdermal patch. FTIR spectra of physical mixtures of pure DH and each excipient were obtained using the KBr pellet method over 4000 to 400 cm^{-1}. Spectra of the physical mixtures compared to pure components to determine peak shifts or changes and assess possible DH-excipient interactions.[13,15]

Evaluation of Prepared Transdermal Patches

Physical appearance

The formulated transdermal patches were evaluated for physical attributes, including appearance, color, clarity, flexibility, smoothness, and absence of air bubbles or drug precipitation. These characteristics largely determine patient acceptance and therapeutic effectiveness.[16]

Weight variation

10 patches were randomly selected and individually weighed to assess weight variation. The 10 weights were averaged to determine the average patch weight. The standard deviation was calculated to measure weight variability around the average.[17]

Thickness

The thickness of the transdermal patches was measured using a digital caliper (Mitutoyo 150, Maharashtra). For each patch, 3 thickness readings were taken at different points on a 2 by 2 cm section and averaged to determine the section's thickness. This process was repeated for all patches to obtain their thickness values. Averaging multiple measurements provided a more accurate assessment versus a single measurement per patch.[18]

Folding endurance

Folding endurance of the transdermal patches was evaluated by determining how many times a patch could be folded in

Table 1: Dependent and independent variables at various levels used in the Box-Behnken design

Factors	*Levels**			*Dependent variables (Response)*
Independent variables	Low	Medium	High	Y1= Folding endurance
A= HPMC 50 cps (mg)	125	137.5	150	Y2 = Tensile strength
B= EC (mg)	350	375	400	Y3 = swelling index
C= Xanthan gum (mg)	250	275	300	Y4 = % Drug release

*Low and high levels of the polymer concentrations are chosen based on the initial trials where these levels have shown better performance individually. These concentrations are now used in combination to obtain desirable properties

Table 2: Formulation of DH transdermal patches using Box-Behnken design (with independent variables and their responses)

Formulation	*Independent Variables*			*DH (mg)*	*Dibutyl Phthalate (mL)*	*PG (mL)*	*PEG (mg)*	*DMSO (%)*	*Methanol (mL)*
	HPMC 50 cps (mg)	*EC (mg)*	*Xanthan Gum (mg)*						
B1	125	350	275	20	6	2	100	10	qs
B2	137.5	400	300	20	6	2	100	10	qs
B3	137.5	350	300	20	6	2	100	10	qs
B4	150	400	275	20	6	2	100	10	qs
B5	150	375	300	20	6	2	100	10	qs
B6	137.5	375	275	20	6	2	100	10	qs
B7	150	375	250	20	6	2	100	10	qs
B8	125	375	250	20	6	2	100	10	qs
B9	150	350	275	20	6	2	100	10	qs
B10	137.5	400	250	20	6	2	100	10	qs
B11	137.5	375	275	20	6	2	100	10	qs
B12	125	400	275	20	6	2	100	10	qs
B13	125	375	300	20	6	2	100	10	qs
B14	137.5	350	250	20	6	2	100	10	qs
B15	137.5	375	275	20	6	2	100	10	qs

the same place before breaking. This helps in the assessment of patch durability and flexibility.[19]

Tensile strength

A modified physical balance determined the transdermal patches' tensile strength. An egg membrane served as a model membrane moistened with a buffer solution. A 10 g preload applied for 5 minutes allowed the patch to adhere to the membrane. After preloading, the weight was removed and water was added until the patch detached. The water volume required indicates tensile strength, or adhesive strength important for adhering to skin.[20] Tensile strength is calculated by using the formula:

Where, F = The force required to break a transdermal patch, a = Width of the patch in centimeters, b = Thickness of the patch in centimeters, L = Length of the patch film in centimeters, I = Amount the patch film elongated just before breaking in centimeters

Surface pH

The transdermal patches were placed in sealed Petri dishes containing 5 mL of distilled water. The patches soaked in the water for 30 minutes to swell and absorb the water. After soaking, the pH of the water in each petri dish was measured using a pH meter. The pH of the water reflected the surface pH of the patch that soaked in it. An ideal surface pH close to the pH of the skin or neutral pH provides compatibility and tolerability.[21]

Swelling index

The swelling of a patch can impact adhesion, flexibility, and drug release. The swelling properties of the transdermal patches were evaluated by placing a pre-weighed patch in a pre-weighed stainless steel wire mesh and immersing it in 15 mL of buffer solution. The weight increase of the patch was measured at regular intervals until the constant weight reached.[21] The degree of the swelling property was determined by using the formula,

Drug content uniformity

A 2 by 2 cm section was dissolved in 100 mL pH 7.4 buffer solution to measure the drug entrapped in the patch. The solution was shaken for 24 hours to completely dissolve the patch and then filtered. The drug concentration in the filtrate was determined using a spectrophotometer at 271 nm. The patch drug content was calculated from the concentration and volume of the solution.[22]

In-vitro drug release (permeation) Studies

Permeation studies measured the rate at which the drug moves from the patch into the skin and bloodstream. A Franz diffusion cell with two compartments separated by a membrane was used. The transdermal patch was placed in the donor compartment facing the membrane. The receptor compartment contained a pH 7.4 buffer to mimic physiological conditions. Samples were taken from the receptor compartment at intervals, analyzed for drug concentration, and replaced with fresh buffer.[23] The permeation data can also be plotted as %drug release versus time to compare drug delivery across the batches.

Drug release kinetics

In-vitro drug release data from the transdermal patch was fit to zero order, first order, Higuchi and Korsemeyer-Peppas kinetic models.[24,25] Fitting the data to the models evaluated the release kinetics and mechanism from the patch. The best-fit model indicates the likely release mechanism, providing information about how the drug is released from the patch system.

In-vivo studies

Healthy New Zealand rabbits were used as the animal model following protocol #1271 approved by the Institutional Animal

Ethics Committee, ensuring the ethical use of animals in research. The rabbits were divided into groups receiving DH tablets or optimized transdermal patch B2. The DH dose in tablets and patches was calculated based on the rabbit equivalent dose.[26] For oral administration, tablets were crushed and given with water using a syringe. The patch was applied to shaved rabbit skin. Blood samples were collected over 48 hours and centrifuged. The plasma was stored until analysis. Plasma samples were prepared by adding acetonitrile to precipitate proteins and centrifuging the supernatant. The supernatant was concentrated, reconstituted in the mobile phase, and analyzed by HPLC-UV at 271 nm. DH concentration was determined from the peak area.

Stability studies

The transdermal drug delivery system stability impacts therapeutic effectiveness and compliance. To evaluate patch (formulation B2) stability, patches were wrapped in foil and stored at 4, 45, and 60°C for 30 days. At intervals, patches were evaluated for physical appearance and drug content uniformity (process described earlier).[27]

RESULTS

Standard Calibration Curve

UV-visibile spectroscopy

A standard calibration curve for donepezil hydrochloride (DH) was generated in pH 7.4 buffer using UV-vis spectroscopy at 271 nm. The curve was linear ($r^2 = 0.999$) over 10 to 60 µg/mL. The equation of the line was y = 0.009x + 0.068 with a slope of 0.009 and an intercept of 0.068. The calibration curve (Figure 2a) estimated unknown DH concentrations in the transdermal patch during drug content uniformity testing and *in-vitro* drug release studies.

RP-HPLC method

The reverse-phase high-performance liquid chromatography (RP-HPLC) method was linear for donepezil hydrochloride (DH) from 10 to 100 ng/mL, with r2 of 0.999. The equation of the line was y = 59.02x + 492.2 with a slope of 59.02 and an intercept of 492.2 The lowest detectable DH amount was 3.41 ng/mL. The lowest precisely quantifiable amount was 10.35 ng/mL. The calibration curve (Figure 2b) estimated unknown DH concentrations in plasma samples during the *in vivo* drug release study. The chromatogram of the drug sample is shown in Figure 3.

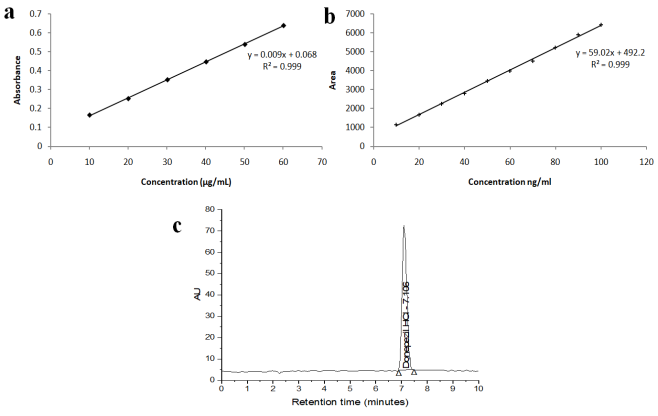

Figure 2: Standard calibration curve of DH a. using UV spectroscopy in pH 7.4 phosphate buffer b. using RP-HPLC method in pH 7.4 phosphate buffer

Drug excipient incompatibility studies

The FTIR spectra of DH-excipient physical mixtures were compared to pure component spectra. The DH characteristic peaks at 1680, 1264, 1032, 747, and 1316 cm^{-1} were present in the mixtures without peak shifts, indicating no DH-excipient interactions. The FTIR results (Figure 4) showed DH compatibility with the excipients in the transdermal patch.

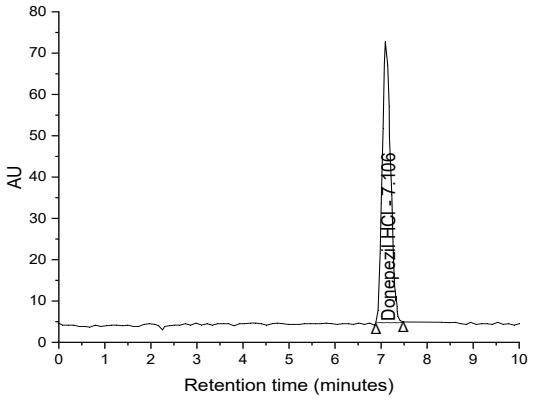

Figure 3: Chromatogram showing the retention time and peak area of DH obtained by the RP-HPLC method

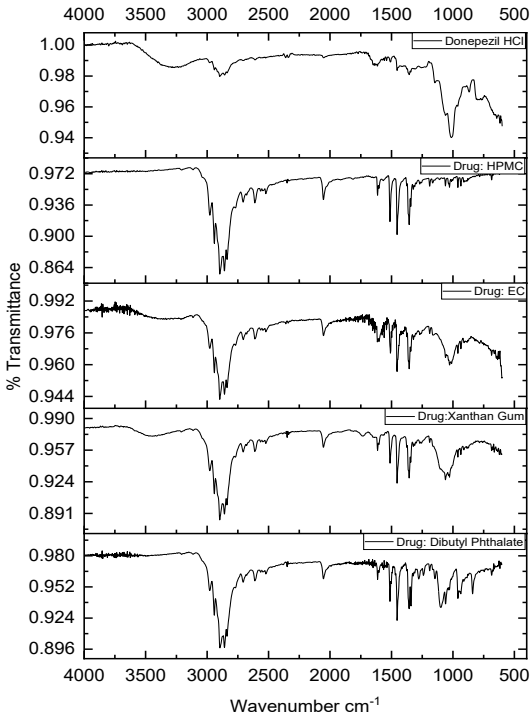

Figure 4: FTIR spectrum of i. pure drug ii. Drug: HPMC iii. Drug: EC iv. Drug: Xanthan Gum, and v. Drug: Dibutyl Phthalate in 1:1 concentrations (From top to bottom)

Evaluation of Prepared Transdermal Patches

Weight variation

The transdermal patch formulation weight variation ranged from 0.81 ± 0.33 g to 1.64 ± 0.46 g. Formulations containing higher ethyl cellulose (EC) showed lower weight variation while those with more hydroxypropyl methylcellulose (HPMC) showed higher variation. Weight variation can impact dosage uniformity, so lower variation is desirable.

Thickness

The developed transdermal patch formulations had thicknesses ranging from 1.01 ± 0.07 to 1.68 ± 0.10 mm. Formulations with higher EC and xanthan gum showed lower thickness while those with more HPMC showed higher thickness.

Folding endurance

The folding endurance of the transdermal patches, indicating mechanical strength, ranged from 139 ± 1.99 to 212 ± 4.33. Formulations with more EC showed higher folding endurance followed by those with xanthan gum and HPMC. The higher EC folding endurance may be due to its greater elasticity, improving mechanical strength beyond the yield point under stress.

Tensile strength

The tensile strength of the prepared formulations ranged from 0.7 to 4.2 kg/cm^2 (results shown in Table 3). These values indicate the elasticity and ruggedness of the patches and serve as a measure of their durability against wear and tear during usage.

Surface pH

The transdermal patch formulations ranged from 7.39 ± 0.13 to 7.84 ± 0.12, indicating a neutral pH. A neutral pH is desirable to avoid irritation to the skin or interference with skin functions. The skin surface pH is slightly acidic, so a neutral patch pH avoids irritation issues due to pH differences.

Swelling index

The transdermal patch swelling index, indicating moisture absorption ability, ranged from 1.46 to 3.15. Formulations with xanthan gum showed the highest swelling index followed by those with EC and then HPMC. A higher swelling index indicates greater moisture absorption, desirable for patch comfort and tolerability.

Drug content

The drug content of the prepared patches ranged from 95.7% ± 0.76% to 99.55 ± 0.28% (Table 3). The formulation containing EC showed the highest drug content, followed by those with xanthan gum and HPMC. Higher drug content is desirable to ensure the target dose is delivered.

In-vitro drug release studies

In-vitro drug release from the transdermal patches were evaluated to determine the effects of polymer types and concentrations on release kinetics. Formulation B2, with middle HPMC level, highest EC level, and highest xanthan gum level, showed the slowest release with 27.95% in 8 hours (Figure 5a). The sustained release from B2 may be due to the polymers' combined effects and the high EC concentration, which can act as a stronger diffusion barrier. For EC, the

Table 3: Results of evaluation parameters of formulations B1 to B15

Formulation Code	*Wt. Variation (gm)**	*Thickness (mm)**	*Folding Endurance (No of Folds)**	*Tensile Strength (Kg/cm^2)*	*Surface pH**	*Swelling Index*	*Drug content (%)**
B1	1.32 ± 0.77	1.14 ± 0.03	151 ± 2.81	1.1	7.7 ± 0.1	1.87	95.7 ± 0.76
B2	0.98 ± 0.65	1.21 ± 0.08	212 ± 4.33	4.2	7.7 ± 0.15	3.15	99.55 ± 0.28
B3	1.32 ± 0.49	1.23 ± 0.07	157 ± 3.2	1.4	7.82 ± 0.21	2.01	97.64 ± 0.75
B4	1.1 ± 0.6	1.18 ± 0.07	198 ± 3.6	3.5	7.67 ± 0.1	2.95	97.84 ± 0.22
B5	1.29 ± 0.23	1.39 ± 0.07	185 ± 2.8	2.9	7.84 ± 0.12	2.74	98.19 ± 0.28
B6	1.27 ± 0.57	1.68 ± 0.1	179 ± 4.19	2.6	7.39 ± 0.13	2.68	99.2 ± 0.43
B7	0.81 ± 0.33	1.48 ± 0.04	161 ± 3.31	1.6	7.58 ± 0.05	2.28	98.89 ± 0.33
B8	1.05 ± 0.92	1.53 ± 0.07	169 ± 1.85	1.9	7.61 ± 0.17	2.31	99.19 ± 0.53
B9	1.29 ± 0.61	1.67 ± 0.07	139 ± 1.99	0.7	7.69 ± 0.14	1.46	95.93 ± 0.4
B10	1.22 ± 0.96	1.26 ± 0.08	189 ± 1.81	3.2	7.76 ± 0.17	2.81	97.54 ± 0.55
B11	1.52 ± 0.55	1.01 ± 0.07	179 ± 1.71	2.6	7.71 ± 0.09	2.68	97.58 ± 0.58
B12	1.39 ± 0.91	1.37 ± 0.12	204 ± 1.99	3.9	7.79 ± 0.06	3.02	96.8 ± 0.77
B13	1.44 ± 0.69	1.53 ± 0.05	174 ± 2.08	2.2	7.82 ± 0.12	2.59	96.22 ± 0.33
B14	1.64 ± 0.46	1.48 ± 0.08	142 ± 1.98	0.9	7.76 ± 0.19	1.64	96.19 ± 0.33
B15	1.35 ± 0.59	1.68 ± 0.03	179 ± 4.51	2.6	7.79 ± 0.13	2.68	98.14 ± 0.5

* Mean ± SEM, n = 3 observations

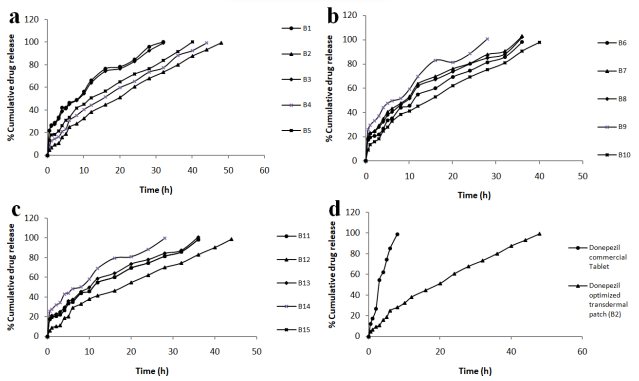

Figure 5: *In-vitro* drug dissolution of a. formulations B1 to B5, b. B6 to B10, c. B11 to B15 and d. marketed DH tablet and optimized patch

Table 4: Drug release kinetics of the optimized formulation B2

Mathematical model	*Rate order constant, $K^{\#}$ or release exponent**	*R^2 value*	*Drug release mechanism*
Zero order	2.275 mg/hr $^{\#}$	0.953	
First order	4.633 hr^{-1} $^{\#}$	0.984	First order
Higuchi model	15.03% $hr^{0.5}$ $^{\#}$	0.982	Non-Fickian Diffusion
Korsemeyer Peppas model	0.707*	0.991	

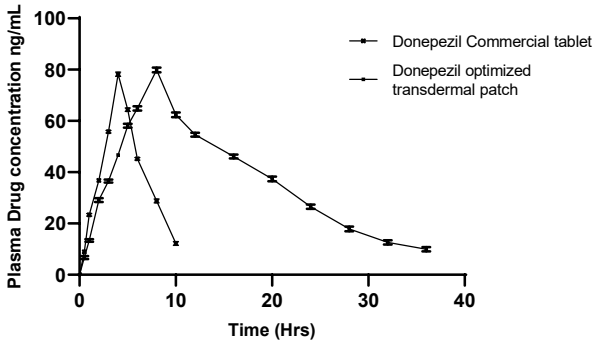

Figure 6: *In-vivo* drug release of DH commercial tablet and optimized transdermal patch

increasing concentration decreased release likely due to its nonpolar nature. For HPMC and xanthan gum, increasing concentration showed a biphasic effect, possibly due to polymer swelling enhancing both diffusion and retention. Compared to commercial tablets (98.76% release in 8 hours), the patch achieved superior sustained release (99.17% in 48 hours), demonstrating longer donepezil hydrochloride delivery to maintain therapeutic levels (Figure 5d). The release results and other evaluation data showed formulation B2 has the necessary properties for an effective transdermal patch.

Drug release kinetics

The *in-vitro* drug release data from formulation B2 was fitted to mathematical models to determine release order and mechanism. The first-order model showed a higher r2 value (0.984) than the zero-order model (0.953), indicating release kinetics is more linear with the first-order model

Table 5: Pharmacokinetic parameters

Formulation	*Cmax (ng/ml)*	*Tmax (h)*	*AUC $_{0-\infty}$ (ng h/ml)*	*MRT_{0-48} (h)*	*Half-life (h)*
Commercial Tablet	78.17	3.53	545.578	7.09	2.3
Optimized transdermal Patch	79.91	8	1429.80	16.92	8.19

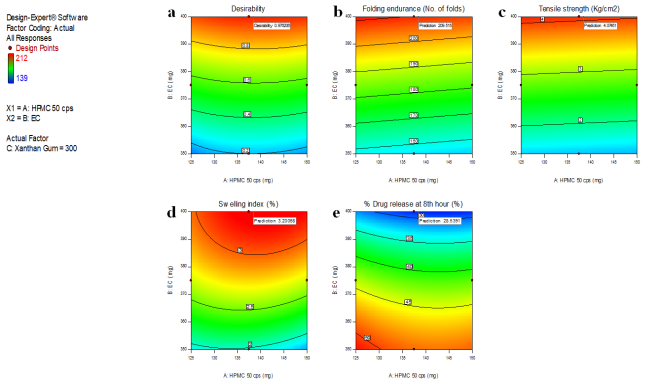

Figure 7: Contour plots of the optimized responses using Box Behnken Design a. desirability b. folding endurance (no. of folds) c. tensile strength (kg/cm^2) d. swelling index (%) e. % drug release at the 8^{th} hour

(results are shown in Table 4). The release exponent (n) from the Korsmeyer-Peppas model was 0.707, between 0.45 and 0.89. This indicates the release mechanism was non-Fickian diffusion. Therefore, the drug release from formulation B2 followed concentration-dependent kinetics and a non-Fickian diffusion mechanism.

In-vivo studies

In-vivo studies were conducted in rabbits to compare the plasma concentration profiles of donepezil hydrochloride from the optimized transdermal patch (formulation B2) and commercial tablets. The pharmacokinetic parameters are shown in Table 5 and the *in-vivo* drug release from the optimized formulation and commercial tablets is shown in Figure 6. The profile for formulation B2 showed the drug in the plasma for 36 hours, while the tablet profile spanned 8 hours.

Box-Behnken design of the formulations and the responses

Linear regression models were generated for folding endurance and tensile strength. Quadratic models were generated for swelling index and %drug release at 8 hours. The model equations:

Folding endurance = 174.53 -1.88 * A + 26.74 * B + 8.38* C

Tensile strength = 2.35 -0.050* A +1.34 * B + 0.39* C

Swelling index = 2.68 - 0.045 * A + 0.618 * B +0.181 * C +0.085 * AB +0.045 * AC -0.0075 * BC -0.138 * A^2 -0.216 * B^2 -0.061 * C^2

% Drug release at 8^{th} hour = 43.75 + 0.25 * A -8.07 * B -2.40 * C -0.097* AB -1.31 * AC - 2.15* BC+1.25 * A^2 -2.74 * B^2 +0.23 * C^2

Where A is the concentration of HPMC in mg, B is the concentration of EC in mg, and C is the concentration of

Table 6: Results of stability studies

Time (days)	*4℃*		*45℃*		*60℃*	
	*%Drug content**	*Appearance*	*%Drug content**	*Appearance*	*%Drug content**	*Appearance*
0	99.61±1.11	+++	99.8±4.36	+++	97.7±3.66	+++
5	99.61±2.12	+++	99.55±4.48	+++	97.36±3.83	+++
10	99.58±2.35	+++	99.48±3.67	+++	96.34±2.61	+++
15	98.32±3.46	+++	99.29±2.66	+++	96.34±4.3	+++
20	98.29±3.08	++	98.68±4.36	+++	96.29±2.4	+++
25	98.24±4.51	++	98.6±4.37	+++	96.2±4.13	++
30	97.61±2.94	++	98.41±3.74	+++	96.18±3.22	++

Average ± SD (n=3), +++: Good, ++: Slightly cloudy or wrinkled appearance

xanthan gum in mg. The model r^2 values indicated a good fit for experimental data. The *p-values* were <0.05, showing significant differences between formulations. The contour plot (Figure 7) showed predicted values close to experimental values, indicating model suitability. All the generated models showed ethyl cellulose had the greatest effect on responses, followed by xanthan gum, with HPMC having a minimal effect. The models and other evaluation data contribute to a mechanistic understanding of how the transdermal patch functions.

Stability studies

The results of the stability studies indicate that the optimized formulation B2 is intact throughout the study period of 30 days with acceptable drug content and physical appearance at different temperatures (4, 45, and 60℃). The results are shown in Table 6.

DISCUSSION

The study aimed to develop a long-acting donepezil hydrochloride (DH) transdermal patch to improve patient compliance with Alzheimer's treatment. Hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and xanthan gum were evaluated based on literature to achieve sustained release. Initial trial formulations used individual polymers at different concentrations to identify ideal concentrations for desirable patches. Based on the trial formulations, HPMC, EC, and xanthan gum ideal concentrations were selected as control points for optimized formulations combining all three polymers. A Box-Behnken design was used to efficiently develop optimized formulations by leveraging initial formulations' evaluation data. Formulation B2, with the highest EC amount followed by xanthan gum and then HPMC, showed the most promising results likely due to EC's nonpolar nature, lipophilicity, and longer chain. B2's physicochemical parameters and *in-vitro* drug release results were satisfactory. Stability studies showed the patch maintained consistent drug content under stressed temperatures. The study identified a transdermal patch formulation (B2) combining HPMC, EC, and xanthan gum that achieved sustained 48-hour DH release. Formulation B2 showed desirable properties suggesting potential as an effective transdermal patch for prolonged DH delivery to Alzheimer's patients.

CONCLUSION

This work shows donepezil hydrochloride can be delivered via a transdermal system using ethyl cellulose, xanthan gum, and hydroxypropyl methylcellulose. The patch provides controlled drug release, potentially allowing reduced dosing in Alzheimer's patients. The non-invasive patch increases compliance due to ease of application and removal. However, more studies are needed to further support this transdermal approach.

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