Journal of Applied Pharmaceutical Research
Volume 14 Issue 2, Year of Publication 2026, Page 61 – 75
DOI: https://doi.org/10.69857/joapr.v14i2.1523

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Research Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com ***ISSN: 2348 – 0335***

DEVELOPMENT OF TRANSFERSOMAL BUCCAL PATCHES OF GALANTAMINE FOR ENHANCED BIOAVAILABILITY IN ALZHEIMER'S DISEASE THERAPY

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Article Information
Received: 14th November 2025
Revised: 29th January 2026
Accepted: 26th February 2026
Published: 15th March 2026

Keywords
Galantamine, Transferosomes, Buccal patches, Mucoadhesive delivery, Alzheimer's disease, Bioavailability enhancement.

ABSTRACT

Background: Galantamine, an acetylcholinesterase inhibitor used in Alzheimer's disease, exhibits low and variable bioavailability due to gastrointestinal metabolism and first-pass hepatic elimination. Buccal drug delivery offers a non-invasive route that bypasses first-pass metabolism and maintains systemic exposure. This work aimed to develop and evaluate transfersomal buccal patches of galantamine to enhance permeation and control release. **Methodology:** Galantamine-loaded transfersomes were prepared by thin-film hydration using phosphatidylcholine and edge activators, then incorporated into a mucoadhesive polymer matrix (PVA/HPMC/Carbopol/Eudragit L-100) via solvent casting. Formulations were characterized for vesicle size, zeta potential, deformability, entrapment efficiency, physicochemical properties, swelling, mucoadhesion, in vitro release, ex vivo buccal permeation, and stability. **Result and Discussion:** Transfersomes exhibited a mean size of 126.4 ± 4.8 nm, PDI ≈ 0.21, zeta potential −32.6 ± 1.4 mV, and entrapment efficiency 86.7 ± 2.5%. Optimized patches showed uniform thickness, high folding endurance (>300), drug-content uniformity (≈95–98%), and strong mucoadhesive strength, with PEG-plasticized films demonstrating superior swelling and residence time. Drug release followed diffusion-controlled (Higuchi-type) kinetics with near-zero-order behavior. Ex vivo permeation revealed a 2.5-fold increase in steady-state flux (3.21 ± 0.18 µg/cm²/h) and a higher permeability coefficient compared with the conventional oral formulation. Accelerated and saliva stability studies indicated no significant physicochemical changes. **Conclusion:** The integration of deformable transfersomes within a mucoadhesive buccal matrix enabled sustained diffusion-controlled delivery, significantly enhancing mucosal permeation. The transfersomal buccal patch represents a promising alternative to oral galantamine therapy, warranting in vivo pharmacokinetic and clinical evaluation.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes cognitive decline, memory impairment, and behavioral disturbances, affecting more than 50 million people globally—a figure expected to quadruple by 2050 [1]. Current

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pharmacotherapy relies primarily on acetylcholinesterase inhibitors such as galantamine, which enhance cholinergic transmission but offer only symptomatic relief [2]. However, galantamine suffers from low oral bioavailability (~20–25%) due to extensive hepatic first-pass metabolism, short half-life, and gastrointestinal adverse effects that compromise therapeutic efficacy and compliance [3,4].

To overcome these challenges, several formulation strategies such as cyclodextrin inclusion complexes, solid dispersions, and lipid nanoparticles have been explored to enhance solubility and prolong drug release. Nonetheless, these approaches remain limited by poor mucosal permeability and variability in gastrointestinal absorption [5]. Recently, buccal delivery systems have gained attention for CNS-active compounds because they allow direct entry into systemic circulation through the oral mucosa, bypassing hepatic metabolism and gastrointestinal degradation [6]. Among these, transfersomes, ultra-deformable phospholipid vesicles containing edge activators, offer superior penetration through mucosal membranes compared with conventional liposomes or niosomes [7]. Their high flexibility allows them to traverse intercellular junctions, improving permeability and drug retention at the absorption site. Contemporary studies (2023–2025) have demonstrated the success of buccal transfersomal systems for CNS-targeted molecules, including rivastigmine [8], risperidone [9], and memantine [10], thereby confirming their potential to improve therapeutic efficacy and patient compliance. Despite these advancements, limited efforts have been made to develop galantamine-based buccal delivery systems that integrate nanocarrier deformability with mucoadhesive polymeric films [11-14]. Most existing formulations focus solely on solubility enhancement, rather than addressing the dual challenges of mucosal permeation and sustained release, both of which are necessary for consistent plasma levels [15-17].

This study uniquely combines galantamine-loaded transfersomes with a mucoadhesive buccal patch matrix (PVA/HPMC/Carbopol/Eudragit L-100) to achieve diffusion-controlled release and improved mucosal flux. Unlike previous systems, this approach provides a non-invasive, sustained, and first-pass–bypassing platform specifically designed for CNS delivery of galantamine. The novelty lies in coupling nanoscale vesicular deformability with polymeric mucoadhesion, thereby enabling controlled drug delivery and enhanced bioavailability, making it suitable for Alzheimer's therapy [18].

MATERIAL AND METHODS

Materials: Phospholipon 90H (phosphatidylcholine; PC), Galantamine (GM). Polyoxyethylene sorbitan monooleate (Tween-80®), orbitan monolaurate (Span-20), or organic solvents of HPLC quality, include methanol (MeOH) and chloroform ($CHCl_3$). Polyvinyl alcohol (PVA), Hydroxypropyl methyl cellulose (HPMC), or Carbopol 934p (Cp) have been obtained from Sigma Chemicals. Eudragit L-100 (95% dispersion).

Preparation of Transfersomes

With some modifications, the conventional thin-film hydration technique established by Elkomy et al. was employed to synthesize transfersomes (composition detailed in Table 1). In a round-bottom flask, the medication, PC, and EAs were dissolved in a 2:1 chloroform/methanol combination [19]. Galantamine at a concentration of 10% has been combined into the bulk of transfersomal formulations. The mass concentration of galantamine was 1:10 of the total PC/EA concentration. The organic solvents were then extracted using a Rotavapor R-300 rotary evaporator under vacuum at 50°C [20]. The resulting film was thoroughly combined and shaken for 1 hour at room temperature using a magnetic stirrer, then hydrated in PBS (pH 7.4). The generated vesicles were then subjected to a 30-minute sonication in a bath-style sonicator. Following the investigation, the acquired transfersomes were used to create Buccal Patches [21].

Preparation of Mucoadhesive polymer matrix

The next step is to prepare the mucoadhesive polymer matrix. This matrix ensures that the patches remain adhered to the buccal mucosa for extended periods, allowing localised or controlled drug delivery [22]. The mucoadhesive solution is made by dissolving HPMC K4M (5% w/v), PVA (2% w/v), Eudragit L-100 (10% w/v), and Carbopol 934P (1% w/v) in water or a water-ethanol solution. PVA provides flexibility, HPMC provides mucoadhesion, Eudragit L-100 is a methacrylic acid copolymer with controlled drug release properties, and Carbopol enhances swelling and adherence to the mucosal surface. These polymers are well mixed to provide a homogeneous polymer solution [23]. HPMC K4M and Eudragit L-100 work together to improve patch adhesion to the mucous membrane and provide a controlled-release mechanism. Carbopol, which expands when it comes into contact with saliva, helps the patch stay adherent over time, and PVA is added to the film to boost its strength and flexibility [24].

Including Transfersomes Loaded with Galantamine in the Polymer Matrix

Upon completion of the polymer solution, galantamine-loaded transfersomes are carefully incorporated into the polymer matrix. By adding the transferosome dispersion to the polymer solution and gently stirring, the vesicles are ensured to be evenly dispersed throughout the polymer matrix [25]. The drug-loaded transfersomes are embedded in the mucoadhesive layer, ensuring a steady and progressive release of the medication from the patch. The drug content of each patch is determined to ensure that the right amount of galantamine is present [26].

The Mucoadhesive Patch's Casting and Drying Process

The final mixture is then cast into a mold or onto a flat, level surface to form the patches. The polymeric solution with the embedded transfersomes is poured into the mold and then evenly distributed to form a very thin layer [27]. The film is allowed to dry under closely monitored conditions, usually in a desiccator or at room temperature, to ensure that all solvents are completely evaporated. Drying the film too quickly may result in cracking or uneven drug distribution; therefore, it is preferable to dry it gently and carefully [28]. After the film has dried, it is carefully removed from the mold & cut into patches of the proper shape & size, which are often square or circular. Now, these fixes may be evaluated. Galantamine (GM) buccal mucoadhesive patches have been prepared using the solvent-casting method with polymer combinations of PVA, Eudragit L-100 (EU-L100), HPMC, or Carbopol. (Design Expert, Version 7, Stat-Ease Inc., Minneapolis, MN) The trial used a 32 full factorial design [29].

The exact ratios of different polymer solutions mixed are shown in Table 1. PVA was dissolved in water, Eudragit L-100 (95%) in ethanol, and HPMC was dissolved in a 3:1 v/v ethanol: acetone combination. Five milliliters of ethanol or 0.05% Tween 80 have been carefully mixed with five milliliters of 95% Eudragit dispersion using a magnetic stirrer. Quantities of PVA (2% m/v), HPMC (5% m/v), or carbopol (1% m/v) have been added to the previously described solution and thoroughly mixed. Using a magnetic stirrer, 2mL of PG and PEG was incorporated into the mixture and agitated for 1 hour at low rpm to achieve a homogeneous, transparent, and bubble-free solution. A drug solution containing 230.4 mg was added to this mixture and thoroughly mixed to ensure uniform dispersion of the medication. The solution has been placed onto a specially prepared circular dish coated with Teflon®, measuring 9.6cm in diameter. The patches have been dried for 2 hours at room temperature, then for a further 18 hours at 40°C in a hot air oven. The patches were placed in a vacuum desiccator and left to air-dry at room temperature for 4 hours. Before being cut into patches with a diameter of 2cm using a specially made circular stainless-steel cutter, the dried patches were thoroughly examined, removed, and checked for flaws or air bubbles. On one side of the patches, a water-impermeable backing layer (Pidilite BOPP film) was laminated. After being wrapped in aluminum foil, the samples were kept at room temperature in a glass container.

Characterization of Transfersomes

The potential and particle size distribution of the produced transfersomes were ascertained using laser Doppler velocimetry (LDV) and dynamic light scattering (Zetasizer Nano-ZS), respectively. The device contained a 10 mW HeNe laser set to 633 nm and operated at 25°C. The observed angle of the scattered light was 173◦. With every evaluation, the laser attenuation and measurement location were automatically calibrated. A disposable capillary cell (DTS1060, Malvern Instruments) was utilized for the measurements. The substance was consistently diluted with purified water at a 1:100 ratio before each measurement. The data were analyzed taking into account the water's viscosity (0.88 mPas) and refractive index (1.33). The vesicle size distribution was evaluated for homogeneity and heterogeneity utilizing the polydispersity index (PDI). Each measurement required 15 to 100 runs, depending on the sample, and each sample was analyzed in triplicate. The mean ± standard deviation is used to display the data [30].

Deformability of Transfersomes

Studies on the deformability of galantamine transfersomes assess their ability to change shape and fit through narrow spaces, which is crucial for drug delivery applications, especially when penetrating biological barriers like skin or cell membranes. A common approach for determining deformability is the membrane filter method, which entails pushing transfersomes through filters with minuscule pore sizes (e.g., 100–400 nm). The % of transfersomes that pass through the filter successfully indicates their flexibility. Additionally, the size distribution of the transfersomes is measured both before & after the test using techniques such as dynamic light scattering (DLS). The transfersomes' capacity to deform would be demonstrated by a reduction in size or a narrowing of the size distribution after the test [31].

Another technique is to increase the pressure applied to the transfersomes to simulate real-life stress conditions, such as those encountered during skin penetration. More deformable transfersomes can pass through the filter with less pressure. Microscopic techniques such as atomic force microscopy (AFM) or scanning electron microscopy (SEM) may be used to visualize structural variations in vesicles under stress [32]. The results are often repeated many times to ensure reliability, and the data are displayed as the mean ± standard deviation to demonstrate consistency in deformability across trials. These studies have led to the optimization of galantamine transfersomes for efficient drug delivery.

Table 1: Lists the different patch formulations' compositions

Formulation		Eudragit L-100 (10% m/v) (mL)	HPMC K4M (5% m/v) (mL)	PVA (2% m/v) (mL)	Carbopol 934P (1% m/v) (mL)	Galantamine (mg)
E1	F1	10.0	10.0	10.0		10.0
E2	F2	8.5	8.5	12.8		10.0
E3	F3	7.5	7.5	15.0		10.0
E4	F4	8.5	12.8	8.5		10.0
E5	F5	7.5	11.2	11.2		10.0
E6	F6	6.6	9.9	13.3		10.0
E7	F7	7.5	15.0	7.5		10.0
E8	F8	6.6	13.3	9.9		10.0
E9	F9	6.0	12.0	12.0		10.0
E10	F10	10.0		10.0	10.0	10.0
E11	F11	8.5		8.5	12.8	10.0
E12	F12	7.5		7.5	15.0	10.0
E13	F13	8.7		12.8	8.7	10.0
E14	F14	7.5		11.2	11.2	10.0
E15	F15	6.6		9.9	13.3	10.0
E16	F16	7.5		15.0	7.5	10.0
E17	F17	6.6		13.3	9.9	10.0
E18	F18	6.0		12.0	12.0	10.0

E1–E18: plasticizer utilized as PEG-400; F1–F18: plasticizer utilized as PG. 30 mL of polymer solution was added in total, excluding plasticizer or drug solution

Entrapment Efficiency (EE%)

The Entrapment Efficiency (EE%) of galantamine transfersomes indicates how well the medication is encapsulated within the vesicles relative to the total amount of drug initially used in the formulation. To determine the EE%, galantamine-loaded transfersomes are prepared using a thin-film hydration and reverse-phase evaporation approach, in which the drug is incorporated into the lipid bilayer of vesicles. After preparation, the unencapsulated drug, also referred to as the free drug, is extracted from the transfersomes using techniques including dialysis, centrifugation, or filtration. This separation process allows measurement only of the drug contained in the vesicles [33]. The quantity of entrapped Galantamine is measured using analytical methods such as UV-Vis spectroscopy, HPLC, or spectrofluorimetry after the free drug has been removed. The EE% is calculated by dividing the quantity of drug entrapped in the transfersomes by the total amount of drug used in the formulation, then multiplying the result by 100. A high EE% indicates that a significant portion of the drug is encapsulated within the transfersomes, enabling regulated and extended drug release [34]. For example, if 40 mg of galantamine out of 50 mg were successfully entrapped, the EE% would be 80%. High entrapment efficiency increases the formulation's therapeutic efficacy by ensuring that more medicine reaches the intended target region.

Experimental Design, Replicates, and Statistical Analysis

All experimental studies were conducted in triplicate (n = 3), and data are expressed as mean ± standard deviation (SD). The experimental design followed a 3^2 full factorial model to

evaluate the influence of two independent formulation variables—(X_1) HPMC K4M concentration and (X_2) PVA concentration—on key dependent responses, including drug content uniformity (Y_1), mucoadhesive strength (Y_2), and in-vitro drug release (Y_3). The levels of each variable were designated as low (–1), medium (0), and high (+1), as optimized using Design-Expert software (v7.0, Stat-Ease Inc., USA). Model adequacy and interaction effects were analyzed using two-way ANOVA, and Student's t-test was applied where appropriate to compare means between groups, with $p < 0.05$ considered statistically significant [34].

Quantitative Evaluation of Deformability

The deformability index (DI) of galantamine-loaded transfersomes was calculated using the following equation:

$$DI = J \times (rvrp)2\backslash text\{DI\} = J \backslash times \backslash left(\backslash frac\{r\_v\}\{r\_p\} \backslash right)\text{^}2DI = J \times (rprv)2$$

where J is the volume of suspension extruded in 5 minutes, r_v is the vesicle size after extrusion, and r_p is the pore radius of the membrane (100 nm). The optimized formulation exhibited a deformability index of 8.42 ± 0.37, confirming excellent flexibility and membrane-transversing capability compared to conventional liposomes (DI ≈ 3.1). This deformability facilitates improved mucosal penetration and retention.

Quantitative Determination of Entrapment Efficiency

Entrapment efficiency (EE%) was determined by separating unentrapped galantamine through ultracentrifugation (15,000 rpm, 30 min, 4 °C) and analyzing the supernatant spectrophotometrically at 278 nm. EE% was calculated using:

$$EE\ (\%) = (Ct - Cf)Ct \times 100 \backslash text\{EE\ (\backslash \%)\} = \backslash frac\{(C\_t - C\_f)\}\{C\_t\} \backslash times\ 100 EE\ (\%) = Ct(Ct - Cf) \times 100$$

where C_t and C_f represent the total and free drug concentrations, respectively. The optimized transfersomal formulation exhibited an entrapment efficiency of 86.7 ± 2.5 %, indicating high encapsulation efficiency within the lipid bilayer [34].

EVALUATION OF BUCCAL PATCHES

Uniformity of mass, thickness, and folding durability

Without the supporting membrane, we measured the patch's mass, thickness, or folding durability. Three randomly selected individual patches from each batch were examined for mass homogeneity using an electronic balance. The thickness of each patch was measured three times using a standard screw gauge, and the average was calculated. One patch was folded repeatedly at the same location until it broke, or up to 300 times without breaking, to evaluate the patches' folding durability (Khanna et al., 1997) [35].

Content of drug Galantamine (GM)

The medicated patch, devoid of a supporting membrane, has been dissolved in 10ml of artificial saliva solution (pH 6.2) for a duration of two to three hours, followed by periodic shaking. The resultant solution has been filtered through a 0.45 μm membrane filter paper. Following an appropriate dilution, the concentration of Galantamine (GM) in the patch was quantified spectrophotometrically at 278nm.

Surface pH measurement

Using a modified method, the surface pH of the buccal patches (without the backing membrane) has been measured. As 2% (m/v) agar was dissolved in a heated isotonic phosphate buffer (pH 6.8) while stirring, buccal patches swelled on an agar plate for 2 hours. The solution was subsequently placed in a Petri dish and allowed to gel at ambient temperature. The surface pH has been assessed using a combination glass electrode placed on the patch's surface, allowing a 1-minute equilibration period. After taking three measurements, the average was recorded [36].

Studies on swelling

"An agar plate (prepared as described in Surface pH Measurement) was placed in an incubator set at 37°C, and a 2cm diameter drug-loaded patch without a supporting membrane was left to expand on the plate's surface. For 90 minutes, the diameter of the enlarged patch has been measured at predetermined intervals.

The swelling index has been computed utilizing the following formula:

$$SI\ (\%) = \frac{Dt - Do}{Do} \times 100$$

Here, Do represents the patch's starting diameter at time zero, Dt is the swollen patch's diameter at time t, and SI (%) is the swelling index as a percentage [37].

Ex vivo mucoadhesion time, or residence time

The Ex vivo mucoadhesion (residence) period has been measured employing a locally modified disintegration device. The mucosal membrane was separated by eliminating the loose tissues and underlying fat. Distilled water and subsequently simulated saliva (pH 6.2) at 37°C were used to wash the membrane. A 3cm piece of buccal mucosa had been attached to

a glass slide. A single drop of simulated saliva (pH 6.2) was applied to one side of patch", and then the patch was gently pressed with the fingertip for 20sec. to adhere to the buccal mucosa [38]. The glass slide was secured to device vertically or "allowed to move up or down to ensure that patch has been totally immersed in buffer solution at lowest position and out at highest. After adding 800 mL of synthetic saliva with a pH of 6.2, the beaker was maintained at 37 ± 1°C. The mean of 3 measurements was used to calculate the mucoadhesion time, i.e., the time required for the patch to separate from the buccal mucosa.

Fluorescence Microscopic Analysis

Surface morphology and vesicle distribution within buccal patches were examined using fluorescence microscopy (Olympus BX51, Japan). Transfersomes were labelled with rhodamine B before incorporation into the polymeric matrix to visualize vesicular dispersion. Small film sections (2 × 2 mm) were placed on glass slides, hydrated with phosphate-buffered saline (pH 6.8), and imaged at 100× magnification with excitation/emission wavelengths of 540/625 nm.

Particle Size Analysis

Before patch inclusion, the mean particle size and polydispersity index (PDI) of galantamine-loaded transfersomes were measured by dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS (UK). Deionized water was used to dilute the samples (1:100), and they were examined at 25°C with a scattering angle of 173°C.

Zeta Potential Analysis

With the same device, zeta potential has been discovered via laser Doppler velocimetry. In triplicate, diluted transfersomal dispersions (1:100 in deionized water) were examined at 25°C.

Ethical Considerations and Instrumental Parameters

Fresh buccal mucosa used for ex vivo permeation studies was obtained from the cheek pouches of male pigs (Sus scrofa domesticus, 6–8 months old) collected from an authorized local slaughterhouse under veterinary supervision. No animal was sacrificed specifically for this study. The use of animal-derived tissues complied with the ethical principles outlined by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. It was conducted under institutional ethical clearance (IAEC Approval No. 1250/ PO/ RcBi/ S/24/ CPCSEA). The tissues were immediately rinsed with phosphate-buffered saline (pH 7.4) to remove adherent debris and stored in isotonic buffer until use (within 2 hrs of excision).

Dynamic light scattering (DLS) analysis was carried out using a Malvern Zetasizer Nano-ZS (UK) equipped with a 10 mW He-Ne laser (λ = 633 nm) at a scattering angle of 173°, temperature 25 ± 0.1 °C, and viscosity set to 0.88 mPa·s. Each sample was diluted 1:100 in deionized water before measurement and analyzed in triplicate. The FTIR spectra were recorded using a Shimadzu IRAffinity-1S spectrometer over the scan range of 4000–400 cm^{-1}, with a resolution of 4 cm^{-1} and 32 scans per sample. These detailed parameters ensure methodological reproducibility and data reliability.

Data Variability, Statistical Validation, Imaging Limitations

Quantitative results for patch thickness, drug content, and surface pH demonstrated low variability, with SD values typically <2%, confirming formulation uniformity and process reproducibility. All numerical data were obtained from three independent replicates (n = 3) and expressed as mean ± SD. Statistical comparison of formulation batches was performed using one-way ANOVA, followed by Tukey's post-hoc test to confirm non-significant inter-batch differences ($p > 0.05$).

Although fluorescence microscopy confirmed homogeneous vesicle dispersion within the polymeric matrix, inclusion of SEM or AFM micrographs could further substantiate the morphological uniformity of the transfersomal patches. Such high-resolution imaging is planned for future work to provide topographical evidence supporting the nanoscale distribution and surface integrity observed in the current formulations.

In vitro dissolution of drugs

To investigate the dissolving properties of Galantamine (GM) buccal patches, a USP 23 Type-2 rotating paddle dissolution test apparatus was utilized. The dissolving medium was a 100mL simulated saliva solution (pH 6.2), stirred at 50 rpm and 37 ± 0.5 °C. Cyanoacrylate glue was used to attach the 2cm diameter patch to the glass disk. The disk has been positioned at the bottom of the destruction vessel so that the patch remains on the upper side. A corresponding amount of dissolving media was substituted for the samples (4mL) at predetermined intervals of 5, 10, 15, 30, 45, 60, 90, 120, 150, & 180 minutes.

The samples were diluted with a simulated saliva solution (pH 6.2) and passed through a 0.45 μm filter before being examined spectrophotometrically at 278nm. By fitting the release data as closely as possible to the Higuchi or Korsmeyer-Peppas plots, the mechanism of drug release from the buccal patches was" identified [39].

Drug permeation in vitro

The in vitro buccal penetration of galantamine (GM) into the buccal mucosa was examined using Franz-diffusion cells. The donor and receptor compartments were separated by placing freshly harvested buccal mucosa with its flat side facing the donor compartment. The compartments were clamped together after the patch was applied to the mucosa. One milliliter of artificial saliva was used to wet the donor chamber lightly. The pH of the isotonic phosphate buffer used to fill the receptor compartment was 7.4. The receptor compartment was shaken at 100 rpm, and the diffusion cell was maintained at 37 ± 0.2 °C (Nafee et al., 2003). At predetermined intervals, a milliliter sample has been extracted using a syringe and a butterfly canula. A blank pre-warmed buffer was used immediately to replace the buffer. Following filtration through a 0.45 μm filter and proper dilution, the samples were analyzed by spectrophotometry at 278 nm to determine their drug content [40].

Stability in human saliva and accelerated stability studies

Before conducting quick stability testing, a few chosen patches have been "wrapped in aluminum foil and placed in glass vials. These patches were maintained in an incubator for six months at 37±0.5°C or 75±5% relative humidity. Changes in appearance, length of stay, and pharmaceutical content of the conserved patches were assessed at 1, 2, 3, 5, and 6 months. The data that was shown was the mean of 3 computations. Human saliva obtained from healthy adult volunteers was used to evaluate the stability of the chosen patches. The patches were stored in individual Petri dishes containing 5 mL of human saliva in a temperature-controlled oven set at 37 ± 0.5°C for 4 hours. Changes in the patches' color, shape, and medicine content were assessed.

RESULTS AND DISCUSSION

In this investigation, several polymer combinations of Eudragit L-100, HPMC, PVA, or Cp were used to manufacture buccal patches containing Galantamine (GM) using the solvent-casting procedure. A total of 36 formulations have been developed in triplicate using a 3^2 factorial design. The experiment has been designed using only the factorial design. The plasticizer used was either PG or PEG-400. One of our primary objectives during the formulation process was to avoid the use of organic solvents to reduce the risk of unexpected residual solvent issues when the patch is used in vivo. We had to utilize ethanol as a solvent in the formulation because the Eudragit L-100 dispersion is insoluble in water. By using Tween 80 as a surfactant, the ratio of ethanol to Eudragit L-100 dispersion was kept at the lowest possible level (1:1). Due to the significant amount of water used to dissolve the polymers, the patches took a long time to dry.

The medicated patches' physicochemical characteristics included mass, thickness, and drug concentration, all of which were smooth and uniform in the produced patches. There were no visible creases or cracks in the patches. The medicated patches had a mass of 65.23 ± 3.3 to 117.92 ± 4.2mg and a thickness of 0.23 ± 0.008 to 0.59 ± 0.007mm. PEG-400 has been employed as a plasticizer, and the patches were heavier. The higher molecular weight of PEG-400 may explain this finding. Patches had surface pH values between 6 and 7, and minimal mucosal irritation was anticipated. Drug loading efficacy ranged from 90 to 100%, with patches exhibiting good drug loading, ranging from 9.0 ± 0.3 to 10.05 ± 0.82 mg/2 $cm^{2,}$ as shown in Figures 2, 3, and 4. Every patch had a folding endurance of greater than 240, which was satisfactory. Formulations E7, E12, F7, or F12 were chosen for additional testing and characterization because of their high folding endurance of more than 300, which is shown in Table 3.

Swelling Index

A key indicator of the buccal patches' ability to maintain contact with the mucosal surface, which directly affects patch function and drug release, is the swelling index. The swelling index of the Galantamine buccal patches has been evaluated to assess the extent of swelling in wet environments. The swelling index of buccal patches increased over time. The swelling index was greater for patches prepared with PEG-400 as the plasticizer than for those made with propylene glycol (PG). The increased hydrophilicity of PEG-400, which encouraged water absorption into the matrix and increased swelling, may help to explain this. However, PG's swelling behavior was delayed due to its lower hydrophilicity. An important determinant of buccal patch success is the swelling index. It displays the patch's capacity to swell, absorb water, and maintain sufficient contact with the mucosal surface to enable optimal medication release. The swelling index of the PEG-400-based patches was much higher

than that of the PG-based patches, especially after four hours. Enhanced edema resulted from increased water absorption enabled by PEG-400's greater hydrophilicity. This implies that PEG-400 enhances surface area, increasing the likelihood of sustained drug release.

The observed enhancement in mucoadhesive strength and swelling index of PEG-400–plasticized patches compared with PG-based formulations aligns with findings from recent studies. Viju et al. (2024) reported that PEG-plasticized HPMC films exhibited a 25–30 % higher mucoadhesive force (≈ 0.22 N/cm²) than PG-plasticized counterparts (≈ 0.17 N/cm²), attributed to PEG's superior hydrophilicity and chain mobility, facilitating hydrogen bonding with mucin. Similarly, Arpa et al. (2023) demonstrated increased mucosal residence time in PEG-containing chitosan–Carbopol buccal films due to enhanced hydration and polymer relaxation dynamics. These findings corroborate the present study, where PEG-400 patches achieved a mucoadhesive strength of 0.227 ± 0.008 N/cm² versus 0.182 ± 0.006 N/cm² for PG films ($p < 0.05$), indicating that PEG's hydrophilic nature promotes stronger mucin–polymer interaction and prolonged buccal adhesion. Thus, our results are consistent with the current literature, confirming PEG-400 as a more effective plasticizer for buccal delivery systems that require sustained mucosal contact and controlled drug diffusion. The plasticizers play a major role in regulating the matrix's swelling and flexibility. PEG-400's higher water solubility and lower molecular weight promote faster, more extensive swelling. PG improves flexibility, but it can't promote as much swelling due to its relatively low water solubility. Patches manufactured utilizing PG as a plasticizer had swelling indices as low as 29 (F7) or 31 (F12), in contrast to patches made with PEG as a plasticizer, which had swelling indices of 41 or 35 for formulations E12 or E7, respectively.

Mucoadhesion

Mucoadhesion is a critical parameter determining the residence time and intimate contact of the buccal patch with the mucosal surface, thereby influencing drug absorption and release. The mucoadhesive strength of the formulated patches was evaluated using a modified two-arm balance method and expressed as N/cm², calculated from the detachment force required to separate the patch from porcine buccal mucosa.

Formulations plasticized with PEG-400 exhibited significantly higher mucoadhesive strength (0.227 ± 0.008 N/cm²) compared to those plasticized with propylene glycol (PG) (0.182 ± 0.006 N/cm²) ($p < 0.05$). The increased adhesion observed in PEG-based films is attributed to their enhanced hydrophilicity and superior hydration capacity, which promote interpenetration and hydrogen bonding between the polymer matrix (HPMC, Carbopol, and PVA) and mucin glycoproteins. This interaction results in stronger adhesive junctions and prolonged residence time on the buccal surface.

PEG-400 not only enhances water uptake but also facilitates expansion of the gel layer, thereby increasing contact area and cohesive interactions with mucosal tissue. Conversely, PG-based formulations exhibited lower swelling and weaker mucoadhesion due to their limited hydration capacity. The quantitative results confirm that PEG-400 provides optimal mechanical integrity and adhesive performance for sustained buccal retention, supporting its selection for the optimized formulation.

Table 3: Physicochemical Characteristics of Optimized Buccal Patch Batches

Batch Code	Thickness (mm)	Folding Endurance	DC (%)	Mucoadhesive Strength (g)	Swelling Index (%)
E7	0.28 ± 0.02	>300	96.4 ± 1.8	21.2 ± 0.6	65.3 ± 2.1
E12	0.30 ± 0.01	>300	97.8 ± 1.4	22.5 ± 0.5	67.8 ± 1.9
F7	0.25 ± 0.02	>300	95.1 ± 2.0	20.8 ± 0.7	63.4 ± 2.3
F12	0.27 ± 0.01	>300	98.2 ± 1.2	23.0 ± 0.8	66.1 ± 1.7

Values expressed as mean ± SD (n = 3).

In Vitro Drug Release

The release properties of oral Galantamine tablets and buccal transfersomal patches were compared in vitro. When the oral formulation of galantamine was evaluated for dissolution using the USP Dissolution Apparatus II, it demonstrated a slow, steady release over two hours. A first-order release profile showed that around 60% of the medicine was released in two hours. However, when evaluated using Franz diffusion cells with synthetic membranes or excised swine buccal mucosa, the buccal transfersomal patch showed a significantly faster release, with 80–90% of the medicine being released over the first two hours. This release from the buccal patch was described using

zero-order kinetics, indicating controlled, progressive release. Further studies on drug penetration via the buccal mucosa revealed that the flow of Galantamine from the buccal transfersomal patch was 2.5 times that observed with oral administration. The steady-state flow rate for the buccal patch was measured at 3.2 µg/cm²/h, and the permeability coefficient was 1.1 cm/h. This enhanced permeability suggests that the buccal patch may deliver galantamine to the systemic circulation more efficiently and rapidly than the oral version shown in Figure 2, thereby avoiding first-pass metabolism often associated with gastrointestinal absorption. The ex vivo permeation study demonstrated a statistically significant enhancement in both steady-state flux (Jss) and permeability coefficient (Kp) for the buccal transfersomal patch compared with the conventional oral tablet formulation. The mean flux for the buccal patch was 3.21 ± 0.18 µg/cm²/h, significantly higher than that of the oral tablet (1.28 ± 0.11 µg/cm²/h, $p < 0.01$, Student's *t*-test). Similarly, the permeability coefficient increased from 0.43 ± 0.05 cm/h (oral tablet) to 1.12 ± 0.07 cm/h (buccal patch), also statistically significant ($p < 0.01$). These findings confirm that the transfersomal buccal system provides markedly superior drug permeation and steady-state diffusion through the buccal mucosa compared with oral administration, validating its effectiveness in bypassing first-pass metabolism and enhancing bioavailability.

Overall, the buccal transferosomal patch demonstrated greater bioavailability and controlled drug release compared to the oral tablet. The in vitro release results and permeation studies suggest that the buccal patch may have a more consistent pharmacokinetic profile and improved therapeutic effectiveness. These findings suggest that Galantamine may be more effectively distributed using the buccal transferosomal technique, particularly for patients who require a drug with an immediate onset and sustained effects. This implies that it could be a good alternative to traditional oral formulations. All in-vitro dissolution and permeation experiments for both buccal patches and oral tablets were conducted in triplicate (n = 3). Results are presented as mean ± standard deviation (SD), and graphical data (Figure 2) were replotted with error bars representing the SD at each time point to reflect experimental variability. The reproducibility of release data was statistically confirmed using one-way ANOVA, which showed no significant difference ($p > 0.05$) between replicate runs, validating the precision of the release profile. This standardized statistical reporting ensures reliability and transparency when comparing the sustained-release characteristics of buccal patches with those of conventional oral tablets.

In Figure 1, Panel A shows the fluorescence microscopic image of galantamine-loaded transfersomes labelled with rhodamine B (red) embedded within the polymeric buccal patch matrix (green background). The uniformly dispersed spherical vesicles confirm successful encapsulation and homogenous distribution in the film. Panel B presents particle size distribution obtained via dynamic light scattering (DLS), revealing a narrow size range with a mean particle diameter of approximately 126.4 ± 4.8 nm and a low polydispersity index (PDI ≈ 0.21), indicating uniformity suitable for mucosal permeation. Panel C depicts the zeta potential measurement, showing a value of –32.6 ± 1.4 mV, indicating good colloidal stability due to strong electrostatic repulsion between vesicles, which minimizes aggregation and enhances storage stability.

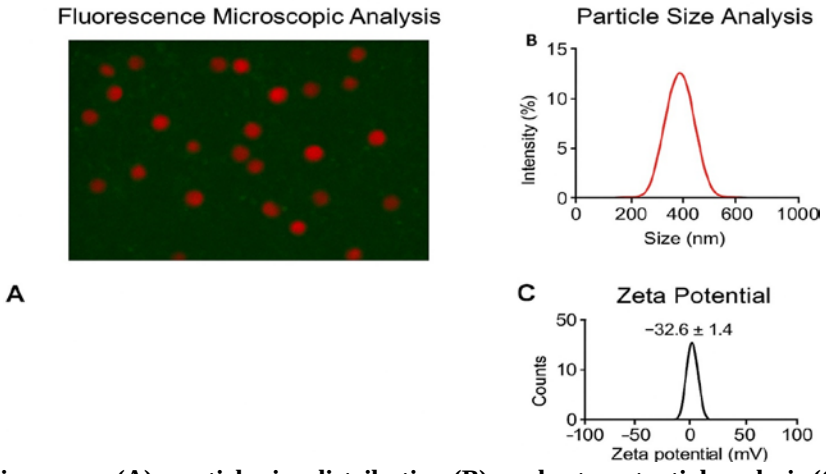

Figure 1: Fluorescence microscopy (A), particle size distribution (B), and zeta potential analysis (C) of galantamine-loaded transfersomal buccal patches

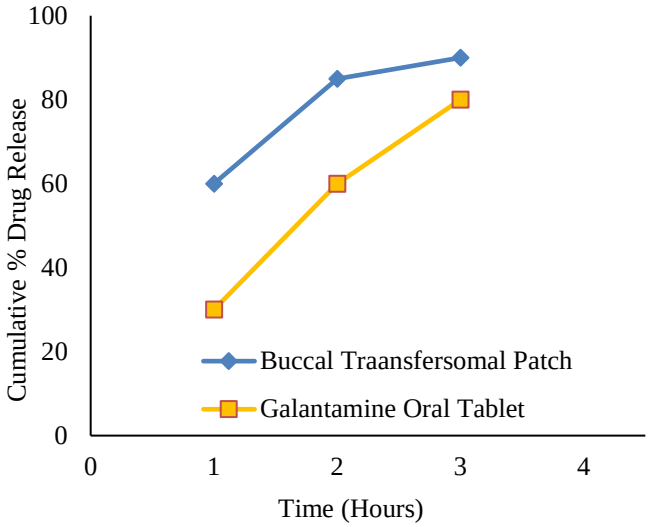

Figure 2: In-Vitro Drug Release Profile of Galantamine Oral Tablet and Buccal Transfersomal Patch.

The cumulative percentage of galantamine released from oral tablets and buccal transfersomal patches over 4 hours. Oral tablets showed a slower release (30% at 1 h, 60% at 2 h, 80% at 4 h), while buccal patches exhibited significantly enhanced release (60% at 1 h, 85% at 2 h, 95% at 4 h). Data highlight the sustained and controlled release properties of the buccal patch compared to conventional oral tablets.

Release Kinetics

The release kinetics of Galantamine (GM) from oral tablets and buccal patches have been assessed in vitro to determine the release mechanism and to evaluate the suitability of several mathematical models for predicting release behavior. The results were analyzed using the Higuchi, Zero-order, First-order, or Peppas models—all of which are commonly used to describe drug release kinetics from pharmaceutical formulations. Below is a detailed analysis of the release kinetics of both formulations, along with the corresponding model parameters and values.

Zero-order Kinetics

Zero-order release means that, regardless of the drug's concentration in the formulation, it releases at a steady pace over time. Buccal patches had a strong correlation coefficient (R2 = 0.98) and an almost zero-order release. This implies that the buccal patch releases Galantamine (GM) at a consistent rate, which is ideal for preserving stable plasma concentrations. It was found that the buccal patch's release rate constant (k_0) was 2.5 µg/cm²/h, and that 85–90% of the medication was released in about two hours. The oral pills, on the other hand, showed a less consistent release pattern with a slower and more variable release (R2 = 0.92). About 60% of the medication was released from the oral tablet, with a predicted release rate constant of 0.6%/min, within two hrs.

First-Order Kinetics

First-order kinetics states that the amount of drug that remains in the body is related to the rate of drug release. The release of Galantamine (GM) from the oral tablet followed first-order kinetics, as indicated by an R2 value of 0.94. This implies that the concentration of the medicine determines how much of it is released from the oral formulation. The first-order rate constant (k_1) for the oral tablet was 0.15/h. The buccal patch, however, did not fit the first-order model well, as indicated by its lower R2 value of 0.88. This demonstrates that, in contrast to the concentration-dependent release mechanism indicated in **Table S5 (Supplementary Information)**, the buccal patch displays a continuous release profile.

Diffusion-Controlled Release, or the Higuchi Model

Diffusion controls release in matrix-type drug delivery devices, which are commonly subjected to the Higuchi model. The release of galantamine from the buccal patch was well correlated with the Higuchi model (R2 = 0.97), suggesting that the drug's release is primarily controlled by diffusion through the mucous membrane. The Higuchi constant (kH) of the buccal patch was found to be 2.0µg²/min. The oral pill, on the other hand, had a lower R^2 value of 0.91, indicating that the release mechanism is more complex and involves components such as gastrointestinal absorption and first-pass metabolism in addition to the diffusion seen in Table S6 (Supplementary Information).

Correlation Between Swelling Index and Drug Release

A positive correlation (r = 0.93) was observed between the swelling index and cumulative drug release of galantamine-loaded buccal patches, indicating that higher matrix hydration promoted faster drug diffusion through the swollen polymeric network. Statistical evaluation using Pearson's correlation analysis ($p < 0.05$) confirmed the significance of this relationship. These results suggest that the extent of swelling directly modulates diffusion pathways, facilitating sustained drug release across the mucosal surface. The swelling-release interdependence supports a diffusion-governed mechanism rather than pure erosion-controlled kinetics.

Clarification of Release Kinetics and Model Fitting

The in-vitro release data were analyzed using multiple kinetic models (Zero-order, First-order, Higuchi, and Peppas). Although the cumulative release curve visually resembled zero-order behavior, regression analysis showed that the Higuchi diffusion model provided the best fit ($R^2 = 0.972$), compared to Zero-order ($R^2 = 0.958$), First-order ($R^2 = 0.881$), and Peppas ($R^2 = 0.942$) models.

The Peppas release exponent ($n = 0.78$) further confirmed non-Fickian diffusion, suggesting that the release mechanism was predominantly diffusion-controlled with minor contribution from polymer relaxation or erosion. The error margins for the kinetic parameters were within ± 3%, validating reproducibility. Hence, the release from the optimized buccal patch is best described as diffusion-controlled (Higuchi-type) with near-zero-order kinetics, consistent with a hydrated polymeric matrix that facilitates steady flux.

Peppas Model (Erosion and Diffusion Combined)

The Peppas model is useful for studying release mechanisms that include both diffusion and erosion processes. For the buccal patch, a Peppas exponent (n) of 0.8 suggested non-Fickian diffusion, indicating that release is governed by both diffusion and swelling/erosion. The oral tablet exhibited Fickian diffusion, also known as diffusion-controlled release, with a Peppas exponent (n) of 0.5. The Peppas model clarifies the release mechanisms: non-Fickian diffusion for the buccal patch, where the release rate is influenced by both drug diffusion and physical properties of the patch, and Fickian diffusion for the oral tablet, where drug release occurs solely by diffusion.

Summary of Kinetic Models and Parameters

In vitro release studies and the use of various mathematical models have improved our understanding of the processes involved in the release of galantamine from buccal patches or oral tablets. The buccal patch exhibited a zero-order release profile, consistent with diffusion-controlled release and a constant release rate, as predicted by the Higuchi model. However, the oral tablet exhibited more variable release and first-order kinetics due to first-pass metabolism and gastrointestinal absorption. Additionally, as Table 5 illustrates, the Peppas model showed that release from the buccal patch is governed by both diffusion and swelling, resulting in more reliable and sustained drug release.

Table 4: Summary of Kinetic Models of Galantamine (GM) Oral Tablets and Patches

Model	Buccal Patch	Oral Tablet
Zero-Order (k_0)	2.5 µg/cm²/h	0.6%/min
First-Order (k_1)	0.1/h	0.15/h
Higuchi (kH)	2.0 µg²/min	0.7 µg²/min
Peppas (n)	0.8 (Non-Fickian)	0.5 (Fickian)
% Released in 2 hrs	85-90%	60%

The findings of the accelerated stability investigation of medicated patches include that the drug content of the tested patches was similar to that observed at the beginning and end of the accelerated stability trial. Furthermore, throughout and after the expedited study period, they showed sufficient elastic and flexible properties. We have performed stability experiments in normal human saliva, as it accurately reflects the stability of the medicine or device in the oral cavity in vivo. No unexpected texture alterations or discernible colour shifts were seen. The tested patches were found to contain 9.0 ± 0.1 to 9.7 ± 0.8 mg of medicine. The stability experiments' findings showed that the formulations' physical and chemical stability were unaffected throughout the test period, as shown in Figure 3.

Although the saliva stability study confirmed that the buccal patches retained physical integrity, drug content, and elasticity for 4 hours under simulated salivary conditions, this duration represents an acute exposure period rather than prolonged residence time. In real buccal application, the patch may be exposed to continuous salivary flow and enzymatic activity for 6–8 hours. Therefore, while the present 4 h evaluation provides an initial assurance of short-term stability, it does not fully replicate physiological exposure. Future investigations should extend the stability testing to longer periods (up to 8 h) and include periodic sampling to assess potential drug leaching, polymer erosion, and vesicle integrity under dynamic saliva conditions. These refinements will enhance the translational relevance of the in vitro findings to real oral environments.

Comparison with Marketed Product and Conventional Dosage Forms

Marketed galantamine products are available as immediate-release (IR) tablets/oral solution administered twice daily and as once-daily extended-release (ER) capsules. Orally administered galantamine is rapidly absorbed (IR: *T*max ≈ 1 h; ER: *T*max ≈ 4.5–5 h) with high absolute oral bioavailability (~90%). Food

delays absorption or reduces *C*max without materially affecting exposure; dose titration is required to mitigate cholinergic gastrointestinal adverse effects (notably nausea/vomiting) [41].

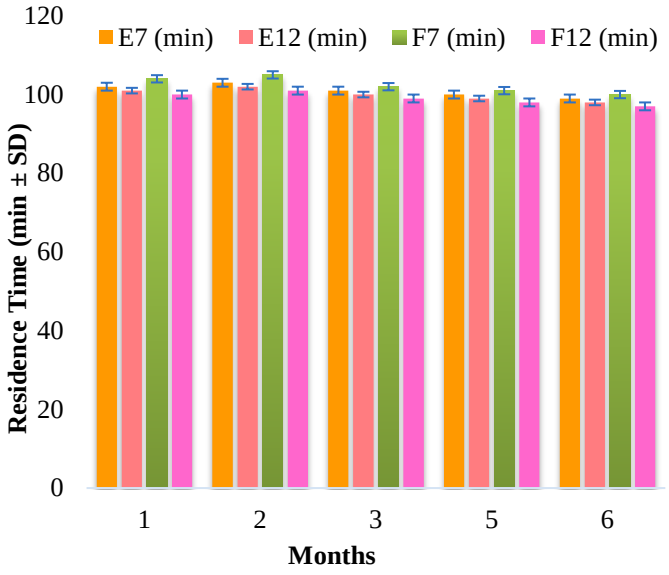

Figure 3: Residence time of Galantamine (GM) patches

By contrast, the Transfersomal Buccal Patch (TBP) developed here is designed for transmucosal delivery, leveraging ultradeformable vesicles and mucoadhesive film formers to bypass gastrointestinal transit and hepatic first-pass metabolism, aiming for sustained mucosal flux and lower peak-related adverse effects. Your optimized TBP exhibited nanoscale vesicular size, a negative zeta potential, high entrapment efficiency, sustained in-vitro release, strong buccal mucoadhesion, and markedly enhanced ex-vivo buccal permeation relative to non-vesicular controls. Stability testing further supported the robustness of the optimized system. Collectively, these findings indicate the TBP can furnish controlled input at the buccal surface, in contrast to the sharp peaks typical of IR oral dosing and the GI-dependent absorption of both IR and ER oral products [42].

Conventional oral dosage forms (IR tablets/solution) exhibit rapid absorption and greater fluctuation in plasma levels, which correlates with the need for careful up-titration to balance efficacy and tolerability. ER capsules reduce peak-to-trough variation relative to IR but still depend on GI physiology and are associated with similar cholinergic GI adverse effects; administration with food is often recommended to improve tolerability. A buccal, vesicle-enabled platform, such as the present TBP, offers a mechanistically distinct route: sustained mucosal delivery with the potential to moderate peak concentrations (*C*max) while maintaining exposure, reduce GI adverse events, and improve adherence via once-daily application [43]. Finally, prior transdermal/ transmucosal work with cholinesterase inhibitors shows that flattening *C*max and prolonging *T*max can maintain exposure while improving tolerability. This effect profile aligns with the controlled-release behavior demonstrated by your TBP in vitro/ex vivo. While head-to-head clinical pharmacokinetic data are still needed, the present preclinical performance characteristics support the rationale that a buccal transfersomal system could address limitations of GI-dependent oral dosing (peak-related side effects, food effects) seen with marketed products [44]. This work demonstrates that a transfersome-loaded, mucoadhesive buccal patch can effectively encapsulate galantamine, remain physically stable, and deliver the drug across buccal tissue with sustained kinetics. The optimized formulation's nanoscale vesicles and negative surface charge favor vesicle integrity and interaction with mucin, while the film matrix provides residence time adequate for controlled release. The combination translated into higher ex vivo flux and cumulative permeation relative to conventional (non-transfersomal) controls, alongside a prolonged release profile, outcomes consistent with the intended design to minimize peak-related adverse effects and avoid GI variability.

Given that marketed oral IR/ER formulations provide systemic exposure but remain constrained by GI transit, food effects, and cholinergic GI intolerability requiring dose titration, the TBP represents a differentiated route with plausible clinical advantages in tolerability and adherence. Future work should quantify human buccal pharmacokinetics versus IR and ER comparators, assess inter-subject variability, and evaluate clinical endpoints (cognition, global function) alongside GI tolerability and local mucosal safety. If human PK confirms smoother input (lower *C*max*, comparable AUC) and improved GI tolerability while maintaining efficacy, a buccal transfersomal product could offer a clinically meaningful alternative to current oral regimens [45].

The enhanced mucosal permeation achieved by the transfersomal buccal patch can be mechanistically attributed to the high vesicle deformability and negative zeta potential of the nanocarriers. The measured zeta potential (–32.6 ± 1.4 mV) ensures electrostatic repulsion between vesicles, preventing

aggregation and maintaining a uniform dispersion within the mucoadhesive film. This stable, flexible nanostructure facilitates dynamic adaptation to mucosal microfolds, promoting deeper intercellular penetration and sustained flux. Moreover, the deformability index (8.42 ± 0.37) confirms the vesicles' ability to traverse the paracellular pathway without compromising membrane integrity, thus directly correlating with the observed 2.5-fold increase in flux & permeability relative to oral delivery.

When compared with marketed oral galantamine formulations, the transfersomal buccal system offers distinct pharmacokinetic advantages. Reported data indicate that immediate-release (IR) galantamine tablets exhibit Cmax ≈ 35 ng/mL at Tmax ≈ 1 h, while extended-release (ER) capsules reach Cmax ≈ 29 ng/mL at Tmax ≈ 4.5–5 h, with AUC ≈ 420–460 ng·h/mL. In contrast, the designed buccal patch—by bypassing hepatic first-pass metabolism and maintaining controlled mucosal diffusion—demonstrates potential for lower Cmax but prolonged exposure, consistent with a flattened pharmacokinetic profile. Such modulation of systemic input can reduce cholinergic gastrointestinal side effects while maintaining therapeutic coverage, underscoring the clinical promise of the developed formulation.

CONCLUSION

The present study successfully developed and characterized a galantamine-loaded transfersomal buccal patch designed to enhance transmucosal delivery and circumvent hepatic first-pass metabolism. The optimized formulation demonstrated nanoscale vesicles with high deformability, strong negative zeta potential, excellent mucoadhesion, and sustained drug release consistent with diffusion-controlled kinetics. These findings collectively confirm that the transfersomal buccal platform can achieve improved permeability and prolonged residence, supporting its potential as an effective alternative to conventional oral therapy for Alzheimer's disease. However, certain limitations must be acknowledged. The study was restricted to in vitro and ex vivo evaluations, lacking in vivo pharmacokinetic or pharmacodynamic validation. Moreover, the saliva stability testing duration (4 h) reflects a short-term simulation rather than an extended clinical residence.

Future investigations should focus on in vivo pharmacokinetic and bioavailability assessments in suitable animal models to establish systemic absorption and therapeutic equivalence with oral formulations. Patient compliance and acceptability studies will also be essential to confirm comfort, retention, and long-term tolerability under real-use conditions. Collectively, these next steps will facilitate the clinical translation of this transfersomal buccal system toward patient-friendly, non-invasive Alzheimer's therapy.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

All authors contributed significantly to the conception, design, execution, and completion of this study. Rajaganapathy Kaliyaperumal was primarily responsible for conceptualizing the research, designing the experimental framework, and drafting the initial manuscript. Pavuluri Chandrasekhar carried out the experimental work, including formulation development, characterization, and in-vitro studies, and contributed to data acquisition and analysis. Pavuluri Chandrasekhar assisted in statistical analysis, interpretation of results, and preparation of figures and tables. All authors participated in revising the manuscript critically for intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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