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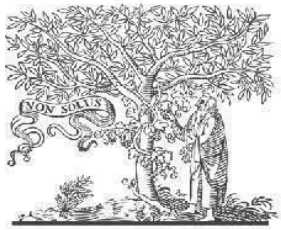

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DEVELOPMENT AND ASSESSMENT OF MUCOADHESIVE BUCCAL TABLETS CONTAINING DONEPEZIL HYDROCHLORIDE FOR ALZHEIMER'S DISEASE

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Abstract
This project aims to develop and characterize mucoadhesive buccal tablets of Donepezil using varying proportions of three polymers: carbopol 934, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose. Eight batches of buccal Donepezil tablets were prepared via the direct compression method. The tablets underwent evaluation for several physicochemical parameters including hardness, thickness, weight variation, drug content, friability, swelling index, surface pH, and ex vivo mucoadhesion. In vitro dissolution testing was conducted over 12 hours following the Indian Pharmacopeia 2018 guidelines, employing the rotating paddle method in phosphate buffer of pH 7.4.

Keywords: Donepezil Hydrochloride, Mucoadhesive, Alzheimer's disease, Buccal tablets, Polymers.

Introduction

Oral drug administration remains the most preferred method due to its ease of dosing, flexible dosing schedules, and enhanced patient adherence despite challenges such as metabolic breakdown in the gastrointestinal tract and delayed onset of action. Alternative drug delivery systems like sublingual and mucoadhesive buccal drug delivery offer potential solutions to these drawbacks.

Mucoadhesive buccal tablets are formulated to adhere to the mucous membrane of the buccal cavity (inner cheek) for prolonged periods, facilitating localized or systemic drug delivery. These tablets typically contain active pharmaceutical ingredients combined with mucoadhesive polymers that enable them to adhere to the mucosal surface.

The buccal route offers advantages such as bypassing first-pass metabolism, rapid onset of action, and improved patient compliance due to ease of administration. The highly vascularized buccal mucosa facilitates direct absorption into the bloodstream, thus avoiding metabolism by the liver and gastrointestinal tract.

Various types of mucoadhesive polymers (natural, semi-synthetic, and synthetic) are utilized in formulations to ensure adherence to the mucosal layer and targeted drug delivery to specific body parts. Upon contact with the mucosal membrane, these mucoadhesive products swell and disperse, ensuring sustained drug release.

The mucoadhesive buccal drug delivery system offers several advantages, including avoidance of gastrointestinal degradation, rapid onset of action, increased bioavailability, and direct drug release into the bloodstream.

Alzheimer's Disease

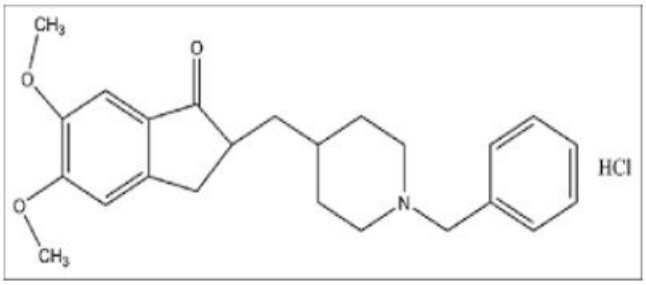
Alzheimer's disease is a progressive brain disorder characterized by changes in the brain that lead to the accumulation of specific proteins. This disease causes the brain to shrink and ultimately results in the death of brain cells. It is the most common cause of dementia, resulting in a gradual decline in memory, cognitive abilities, behavioral changes, and social skills. These changes can significantly impact a person's daily functioning.

In the United States, more than 6.5 million people aged 65 and older live with Alzheimer's disease, with over 70% of them being 75 years old or older. Globally, approximately 55 million people are affected by dementia, and 60% to 70% of these cases are attributed to Alzheimer's disease.

The initial signs of Alzheimer's disease typically include forgetting recent events or conversations. As the disease progresses, individuals may experience severe memory loss and difficulty performing everyday tasks. While medications can help improve memory and slow the progression of symptoms, there is currently no cure for Alzheimer's disease.

In advanced stages, complications such as dehydration, poor nutrition, or infections can further contribute to the decline in brain function and may lead to complications that can be life-threatening.

Commonly used drugs to treat Alzheimer's disease include Memantine, Galantamine, Donepezil, and Rivastigmine. Donepezil hydrochloride, a piperidine derivative, is a centrally acting and reversible acetylcholinesterase inhibitor primarily used to treat Alzheimer's disease. Acetylcholinesterase is an enzyme that breaks down acetylcholine after its release from the presynapse. By binding reversibly to acetylcholinesterase, donepezil inhibits the breakdown of acetylcholine, thereby increasing its availability at the synapses and improving cholinergic transmission.



DONEPEZIL HYDROCHLORIDE

Materials and Methodology

Drugs and Chemicals

The materials used in this study include Donepezil hydrochloride, Carbopol, Hydroxypropyl methylcellulose (HPMC), Sodium carboxymethylcellulose (SCMC), Magnesium stearate, Microcrystalline cellulose powder 200 (MCCP 200), and Talc. All substances and analytical reagents were of pharmaceutical grade.

Formulation of Donepezil Mucoadhesive Tablets

Mucoadhesive tablets were prepared using a modified direct compression method. The process involved weighing out precise quantities of each ingredient in their pure form. Donepezil was mixed with Carbopol first, followed by combining the remaining polymers with talc in a separate container. Both mixtures were blended together for 5 minutes after passing through a #40 sieve.

Microcrystalline cellulose powder (MCCP 200) and Aerosil were mixed separately for 2 minutes and then added to the preceding blend for another 5 minutes. Finally, magnesium stearate was incorporated, and the resulting mixture was compressed into tablets using a ten-station tablet punch, each tablet averaging 250 mg in weight. Eight batches were prepared and coded from B1 to B8, with each batch's formulation characteristics based on previous studies.

Performulation Studies

Bulk Density Bulk density, also known as poured density, was determined by pouring 20 g of powder into a 100 ml measuring cylinder (after passing through a standard sieve #42) and recording the initial mass. Bulk density (Db) is the ratio of the mass of the powder (M) to its bulk volume (Vb), expressed in g/ml:

Db=MVbDb = \frac{M}{Vb}Db=VbM

Tapped Density Tapped density represents the ratio of the total volume of the powder to its tapped mass. The powder was tapped for 750 times, and the tapped mass was recorded. If the difference between two volumes was less than 2%, tapping continued for 1250 times until the difference met the specified criteria. Tapped density (Dt) is calculated as:

Dt=MVtDt = \frac{M}{Vt}Dt=VtM

Where,

- M = mass of powder
- Vb = bulk volume of the powder
- Vt = tapped volume of the powder

Both bulk density and tapped density measurements are crucial for understanding the flow properties of the formulation and ensuring uniformity in tablet manufacturing processes.

Materials and Methodology

Friability

Twenty tablets (n = 20) from each batch were weighed and placed into the friabilator drum. After 100 revolutions, the tablets were removed, dusted, and reweighed. Friability (%) was calculated using the formula:

Friability(%)=(Initial weight−Final weightInitial weight)×100\text{Friability} (\%) = \left(\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \right) \times 100Friability(%)=(Initial weightInitial weight−Final weight)×100

Hardness

Twenty tablets (n = 20) were subjected to hardness testing using a hardness tester. The force applied by the movable probe to break each tablet was recorded.

Wetting Time

Wetting time was determined to assess tablet structure and hydrophilicity. A double-folded tissue paper was placed in a petri plate (6.5 cm internal diameter) containing 6 ml of water with a water-soluble dye. A tablet was placed on the paper, and the time taken for complete wetting was recorded in seconds. This process was repeated three times for accuracy.

Tablet Thickness and Diameter

Tablet thickness and diameter were measured to ensure they fell within acceptable ranges. All tablets had thickness values ranging from 3.71 mm to 3.80 mm.

Moisture Absorption Studies

Moisture absorption of the mucoadhesive buccal tablets ranged from 14.07% to 16.65%. Even after a stability test of 3 months, there was no significant change in the percent moisture absorption, indicating suitable moisture absorption capacity between batches.

Surface pH Study

The surface pH of the tablets was determined to ensure compatibility with the buccal mucosa pH (6.50 to 7.50). The tablets exhibited surface pH values within this range, suggesting they would not irritate the buccal mucosa.

Content Uniformity Test

According to USP standards, tablet content should be within 85% to 115%, with no individual unit outside 75% to 125% and a relative standard deviation ≤ 6%. All tablets met these criteria, with content uniformity falling within 85% to 115% and a relative standard deviation ≤ 6%.

Swelling Index Studies

Swelling studies were conducted using petri dishes containing 1% agar gel. Tablets were weighed and placed in the dishes, incubated at 37°C ± 1°C, and weighed at 0.5, 1, 1.5, 2, 2.5, and 3 hours after carefully removing excess surface water. The swelling index was calculated using the formula:

Swelling Index=WfWi×100\text{Swelling Index} = \frac{Wf}{Wi} \times 100Swelling Index=WiWf×100

where WiWiWi is the initial weight and WfWfWf is the final weight of the tablet.

Dissolution Rate

Dissolution testing of mucoadhesive buccal tablets of Donepezil was performed using USP dissolution apparatus I (basket type) in 900 ml of pH 6.8 buffer solution at 50 rpm and 37°C ± 5°C. Samples were withdrawn at predetermined intervals, replaced with fresh medium, diluted, and assayed by UV spectroscopy at 230 nm. The study was conducted in triplicate.

Disintegration Test

The disintegration test was conducted using a 1000 mL beaker filled with 900 mL of distilled water maintained at 37 ± 0.5 °C. Six tablets were placed in cylindrical tubes of the basket, ensuring discs were used to prevent floating. The time taken for complete tablet disintegration into small particles was recorded, with a maximum limit of 4 hours for buccal tablets.

Conclusion:

The type and proportion of polymers significantly influence drug release from buccal tablets due to their distinct swelling capacities. Formulations based on Carbopol exhibited superior mucoadhesive properties. Tablets containing over 5% Carbopol dissolved between 22% and 56% over a 12-hour period, highlighting the need for precise Carbopol ratios in sustained-release buccal formulations. Disintegration times varied with the polymer's pH sensitivity. Notably, significant differences in dissolution profiles were observed between buccal tablets tested using USP paddle and flow-through cell methods. Additionally, release profiles and kinetics occasionally differed across dissolution methods. However, the total amount of drug substance released from the tablets remained consistent regardless of the testing system employed.

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