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Formulation and Development of Orodispersible Tablet of an Antialzheimer Drug Donepezil HCL with Extended-Release Profile

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory impairment, with no definitive cure currently available. Donepezil HCl, an acetylcholinesterase inhibitor, is widely used for symptomatic treatment in mild to moderate AD. However, conventional oral dosage forms often pose challenges in elderly patients due to dysphagia and non-compliance. This study aims to formulate and evaluate an orodispersible tablet (ODT) of Donepezil HCl incorporating an extended-release (ER) profile to address both rapid onset and sustained therapeutic action. The formulation employed co-processed super-disintegrants—crospovidone and croscarmellose sodium—prepared by solvent evaporation in various ratios. Direct compression was selected for tablet preparation using excipients like mannitol, microcrystalline cellulose, and aspartame. Pre-compression and post-compression evaluations, including bulk and tapped density, angle of repose, hardness, friability, disintegration time, and drug content, confirmed acceptable pharmaceutical quality. In vitro drug release studies demonstrated an initial burst followed by a controlled release profile. The developed dual-action ODT of Donepezil HCl offers improved patient compliance and may serve as a promising approach for effective Alzheimer's therapy.

Keywords: Donepezil HCl, Orodispersible tablets, Extended-release, Alzheimer's disease, Co-processed super-disintegrants, Direct compression

1. INTRODUCTION

Alzheimer's disease (AD) dementia refers to a particular onset and course of cognitive and functional decline associated with age which ultimately results in death. It was first described by Alois Alzheimer in 1906 when he described the case of Auguste Deter, a 51-year-old woman with cognitive disturbance, disorientation, delusions, and other behavioural changes whom he first saw in 1901[1]. there are still no disease-modifying treatments. Here an overview of current thinking in AD, with respect to epidemiology, genetics, pathology and pathogenesis, is provided before its clinical presentation, current treatment options and future therapeutic strategies are considered[2]

Epidemiology-Dementia – acquired progressive cognitive impairment sufficient to impact on activities of daily living – is a major cause of dependence, disability and mortality. Current estimates suggest that 44 million people live with dementia worldwide at present. This is predicted to more than triple by 2050 as the population ages, when the annual cost of dementia in the USA alone may exceed US$600 billion[3].

Pathology- The cardinal features of Alzheimer pathology are amyloid plaques and neurofibrillary tangles (NFTs) (Fig. 1). In addition, neuropil threads, dystrophic neurites, associated astrogliosis and microglial activation are seen, and cerebral amyloid angiopathy frequently coexists[4]. The downstream consequences of these pathological processes include neurodegeneration with synaptic and neuronal loss leading to macroscopic atrophy. Mixed pathology frequently occurs particularly in older individuals and includes vascular disease and Lewy bodies[5]. Indeed, even in fAD cases Lewy body pathology often coexists, the mechanism for which remains uncertain[6]. TDP-43 pathology is increasingly recognized as an important co-pathology Neurofibrillary tangles are primarily composed of paired helical filaments consisting of hyperphosphorylated tau. Tau pathology typically begins in the allocortex of the medial temporal lobe (entorhinal cortex and hippocampus) before spreading to the associative isocortex. Primary sensory, motor and visual areas tend to be relatively spared. Neuronal and synapse loss typically parallel tangle formation, and as such the clinical features and severity of AD are better correlated with NFT pathology, whilst b-amyloid pathology reaches a plateau early in the symptomatic phase of the disease[7]

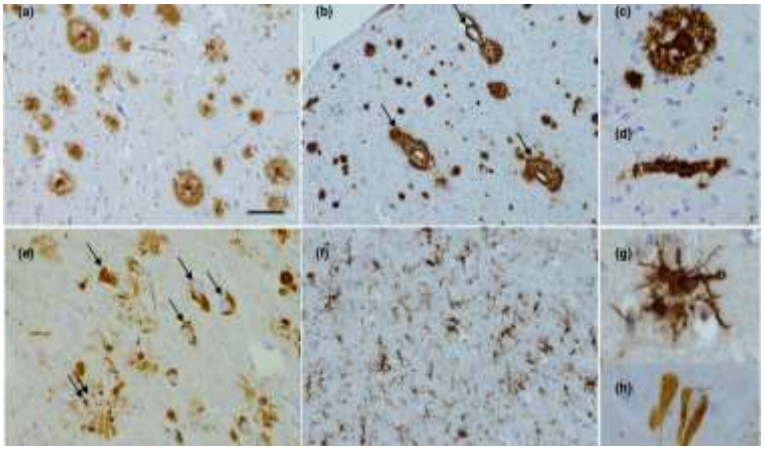


Figure 1 Pathology of Alzheimer's disease. Ab immunohistochemistry highlights the plaques in the frontal cortex (a) and cerebral amyloid angiopathy (CAA) where Ab accumulates within blood vessel (b, arrows). An Ab cored plaque is shown at higher magnification in (c) showing a central core. In severe CAA Ab accumulates within capillaries (d). Tau immunohistochemistry demonstrates both neurofibrillary tangles (e, arrows; h at higher magnification) and neuritic plaques (e, double arrow). Neuroinflammation is a prominent feature in Alzheimer's disease and this is evident by the number of reactive microglia (f; g at higher magnification). The bar represents 50 lm in a and f; 100 lm in b; 25 lm in c and e; 15 lm in d, g and h. Figure courtesy of Dr Tammaryn Lashley, Queen Square Brain Bank.

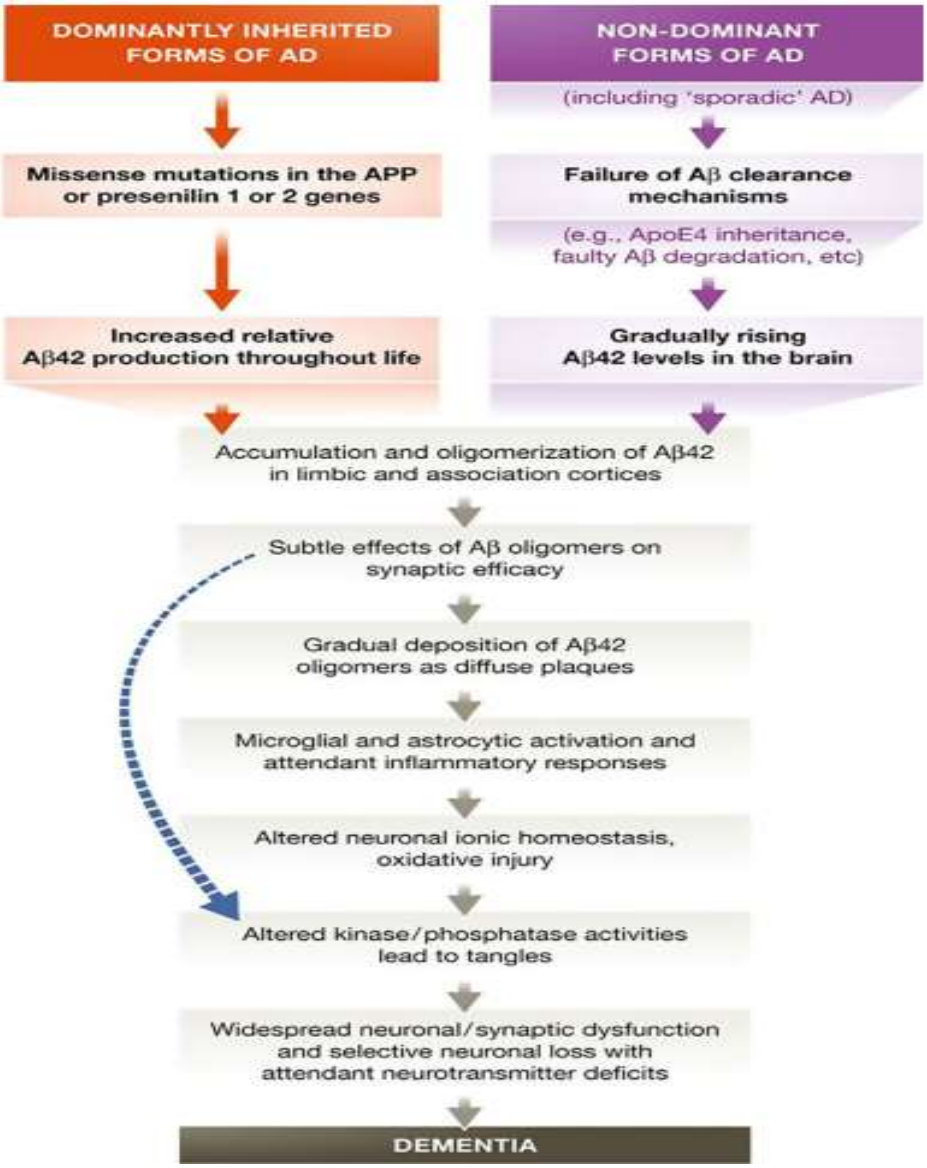


Fig. 2 An overview of the major pathogenic events leading to Alzheimer's disease as proposed by the amyloid hypothesis. The curved blue arrow indicates that Ab oligomers may directly cause synaptic and neuritic damage and induce tau hyperphosphorylation, in addition to activating damaging inflammatory cascades. The figure is reprinted from[8]

Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative disorder that severely affects memory, cognition, and behaviour, primarily in the elderly. With the rising global aging population, the burden of Alzheimer's disease is projected to increase substantially in the coming decades (Prince et al., 2013). Despite the availability of pharmacological agents like donepezil hydrochloride (HCl)—an acetylcholinesterase inhibitor—there is a significant need for improved drug delivery systems that address the limitations of existing therapies and enhance treatment outcomes[9].

Need for Improved Drug Delivery in Alzheimer's

Donepezil HCl is commonly prescribed for mild to moderate Alzheimer's and works by increasing acetylcholine concentrations in the brain, thereby improving cognitive function. However, conventional oral dosage forms, such as tablets and capsules, often present challenges in Alzheimer's patients, especially due to dysphagia (difficulty in swallowing), poor memory, and reduced coordination. These limitations lead to poor adherence and reduced therapeutic efficacy[10].

Challenges with Conventional Dosage Forms

Traditional dosage forms rely on the patient's ability to swallow and maintain regular intake, which becomes increasingly difficult in the cognitively impaired geriatric population. Furthermore, fluctuations in drug plasma levels can cause side effects or inadequate symptom control, necessitating frequent dosing and close monitoring[11].

Concept of Orodispersible Tablets (ODTs)

To overcome swallowing difficulties and improve medication adherence, orodispersible tablets (ODTs) have emerged as a suitable alternative. ODTs disintegrate rapidly in the oral cavity without the need for water, making them ideal for elderly patients or those with swallowing difficulties[13]. Additionally, the rapid onset of action associated with ODTs can provide quicker symptom relief compared to conventional formulations. ODTs are similar in appearance to conventional tablets; the rapid penetration of water through capillary action into the porous framework leads to their disintegration in the 30 s–3 min range. Different techniques are applied in order to prepare these tablets including direct compression, sublimation, phase transition process, moulding, cotton candy process, mass extrusion, melt granulation and others.

Classification of ODTs

Generally speaking, ODTs can be broadly classified in to three types.

Type I classification is based on dissolution potential of ODTs.

Type II classification is based on number of thin layers or multilayered thin films.

Type III classification is based on the nature of active ingredient present in ODT.

Type I Classification is based on dissolution potential:

Based on dissolution potential OTFs can be divided into three categories, namely: fast dissolving (1 to 30 seconds), moderately dissolving (1 to 30 minutes) and slow dissolving (> 30 minutes), refer figure 3.

Fig-3 Types of OTFs based on dissolution potentia

Type II: Classification based on number of thin layers or multilayered thin films:

Accordingly, based on number of thin layers, OTFs can be broadly divided into three categories, namely: Mono- layered, Bi-layered, Sandwiched or multilayered, refer below figure-4

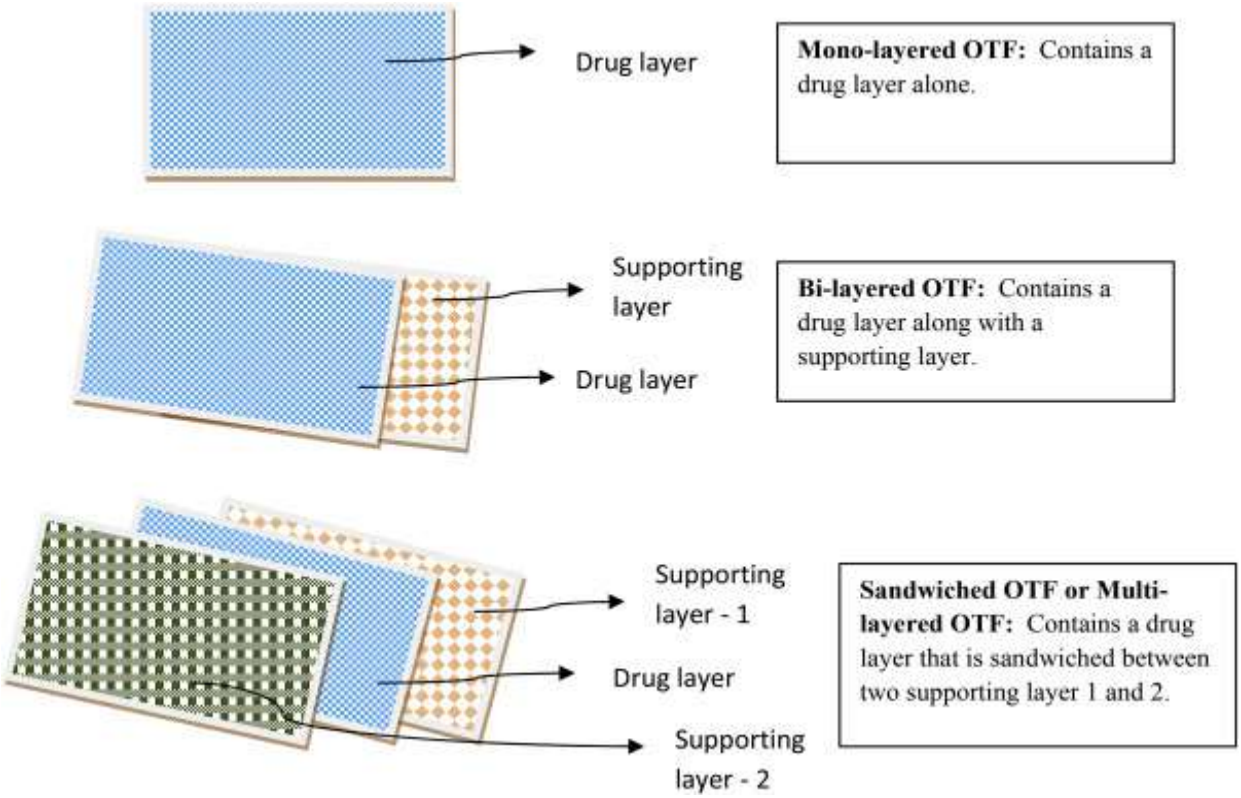
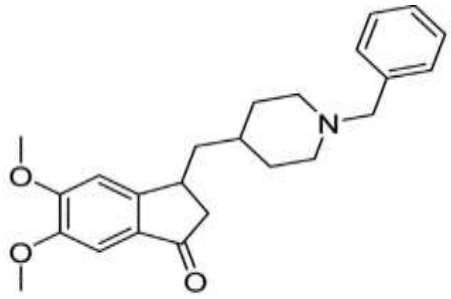


Fig. – 4 Mono- layered, Bi-layered, Sandwiched or multilayered OTF

Rationale for Extended Release in Alzheimer's Treatment

While ODTs offer fast onset, Alzheimer's therapy also requires prolonged and stable plasma concentrations to maintain consistent symptom control. The integration of extended-release (ER) features within an ODT allows for both rapid onset and sustained drug action. This dual-release approach can reduce the dosing frequency, maintain therapeutic plasma levels over an extended period, and improve patient compliance[14]. Donepezil, with its long half-life (~70 hours), is a suitable candidate for such a system, making it possible to develop once-daily formulations with reduced side effects[12].



Donepezil

The chemical structures of Donepezil

It is the potent acetyl cholinesterase inhibit or Chemically 2,3-Dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)- 4piperidinyl*)* methyl)-1H-inden-1-one hydrochloride. It has an empirical formula of C24H29NO3HCl and molecular weight of 415.96. Donepezil hydrochloride was the first piperidine type reversible based inhibitor of the enzyme acetyl cholinesterase (AChE). It has been approved for the symptomatic treatment of mild to moderate Alzheimer's disease. Donepezil hydrochloride is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and n-hexane[17].

Objective and Scope of the Study

The primary objective of this research is to formulate and evaluate an orodispersible tablet of Donepezil HCl incorporating extended-release functionality, aiming to improve the management of Alzheimer's disease by ensuring quick onset and sustained therapeutic effect. The scope includes selection and optimization of suitable polymers, super-disintegrants, and excipients; evaluation of physicochemical properties; and in vitro release profiling. The goal is to develop a patient-friendly, effective dosage form that addresses both pharmacokinetic and compliance challenges in Alzheimer's therapy.

2. REVIEW OF LITERATURE

Jadhav et al. (2023) emphasized the growing importance of patient-centric drug delivery systems, particularly for neurodegenerative diseases like Alzheimer's. Their study demonstrated the effectiveness of combining super-disintegrants such as crospovidone and croscarmellose sodium with matrix polymers to achieve rapid onset and sustained release in Donepezil HCl orodispersible tablets. This dual-action approach significantly improved therapeutic adherence in cognitively impaired populations.

Project data (2025) further supported these findings through the development of co-processed super-disintegrants using the solvent evaporation technique. Various ratios (1:1, 1:2, and 1:3) of crospovidone and croscarmellose sodium were used to optimize disintegration time, flowability, and compressibility, confirming their essential role in orodispersible formulations prepared by direct compression.

Jadhav et al. (2013) investigated the use of hydrophilic matrix polymers such as hydroxypropyl methylcellulose (HPMC) in extended-release formulations. They found these materials particularly beneficial in modulating the release of central nervous system drugs, offering consistent therapeutic levels and reducing the risk of dose dumping.

Bhyan et al. (2009) reviewed the advantages of orodispersible tablets (ODTs), particularly for elderly and pediatric patients. Their research outlined various manufacturing techniques like direct compression, sublimation, and melt granulation. The study emphasized that ODTs enhance patient compliance by disintegrating quickly in the mouth, without requiring water.

Birks (2006) performed a systematic review on the efficacy and safety of acetylcholinesterase inhibitors in Alzheimer's disease. Donepezil was identified as having a favorable safety profile with better tolerability than other agents such as rivastigmine and galantamine, making it suitable for long-term therapy.

Katz et al. (2007) highlighted the challenges faced by caregivers and patients in managing Alzheimer's therapy with conventional oral tablets. Their findings indicated that difficulties in swallowing (dysphagia) and memory impairments often led to poor compliance, reinforcing the need for alternative formulations like ODTs.

Lane et al. (2018) described the neuropathological hallmarks of Alzheimer's disease, including amyloid plaques, neurofibrillary tangles, synaptic loss, and inflammation. Their work validated the amyloid cascade hypothesis, suggesting that β-amyloid oligomers initiate a chain of events that culminate in tau hyperphosphorylation and neuronal degeneration.

Prince et al. (2013) estimated that more than 44 million people worldwide suffer from dementia, with projections indicating a threefold increase by 2050. The rising healthcare burden underscores the importance of developing cost-effective and patient-friendly drug delivery systems to manage cognitive decline effectively.

Rogers and Friedhoff (1996) documented the pharmacokinetic profile of Donepezil HCl, noting its long elimination half-life of about 70 hours. This characteristic supports its use in extended-release formulations, reducing dosing frequency and enhancing therapeutic consistency.

Alzheimer (1906) first described the disease through the case of Auguste Deter, a patient exhibiting progressive cognitive decline. Selkoe and Hardy (2016) revisited the amyloid hypothesis 25 years later, emphasizing that although disease-modifying treatments remain elusive, symptomatic control through innovative drug delivery is essential in current therapeutic strategies.

3. MATERIAL AND METHODS

Material-

Donepezil HCl, super-disintegrants such as Croscarmellose sodium ,crospovidone, and sodium starch glycolate, along with other excipients like mannitol, aspartame, talc, and magnesium stearate were all provided by the college.

Methods-

While choosing the tablet formulation method, it is important to take into account the compressibility of the drug. The direct compression technique provides several benefits for pharmaceutical formulations, including: Direct compression is advantageous due to its cost-effectiveness, as it involves fewer processing steps, requires less manpower, and saves time. It also enhances product stability by minimizing exposure to moisture and heat. Furthermore, this method improves tablet performance by enabling rapid disintegration, which leads to faster dissolution. In the current study, the direct compression method was utilized for the formulation of orodispersible tablets.

Selection of Excipients

Excipients play a vital role in the formulation of any drug delivery system, significantly influencing its overall quality and therapeutic performance. For the development of orodispersible tablets, specific excipients were carefully chosen.

Diluents: Tablets formulated with crystalline cellulose, due to its insoluble nature, exhibited a gritty texture in the mouth. To address this issue, mannitol—a water-soluble diluent—was explored. However, tablets containing only mannitol often dissolved rather than disintegrated appropriately. Therefore, a combination of mannitol and microcrystalline cellulose was employed in this study to achieve a balanced diluent system.

A key requirement of orodispersible tablets is rapid disintegration with efficient dispersion, typically within seconds, using only the small amount of moisture present in saliva. This necessitates the inclusion of specialized disintegrants known as *super-disintegrants*. In this formulation, croscarmellose sodium and crospovidone were selected as super-disintegrants to fulfil this purpose.

Lubricants/Glidants: These are essential for minimizing friction during the tablet compression process and ensuring smooth ejection from the die cavity. In the current study, magnesium stearate and talc were utilized as lubricants and glidants.

Preparation of Co-processed Super-disintegrants

Co-processed super-disintegrants were formulated using the solvent evaporation technique. A mixture of croscarmellose sodium and crospovidone in varying ratios (1:1, 1:2, and 1:3) was dispersed in 10 ml of ethanol. The contents were thoroughly mixed in a 250 ml beaker and continuously stirred until most of the ethanol had evaporated. The resulting moist mass was passed through a #44 mesh sieve to form granules. These wet granules were then dried in a hot air oven at 60 °C for 20 minutes. Once dried, the granules were again sieved through a #44 mesh and stored in an airtight container for subsequent use.

Preparation of oro-dispersible tablets by direct compression method

Oro-dispersible tablets of Donepezil HCl were formulated using the direct compression technique, incorporating co-processed super-disintegrants such as croscarmellose sodium and crospovidone. Mannitol and microcrystalline cellulose were used as diluents, aspartame served as the sweetening agent, while magnesium stearate and talc functioned as the lubricant and glidant, respectively. All ingredients, except for the directly compressible granular excipients, were individually passed through a #60 mesh sieve. The weighed components were then blended in a geometrical order to ensure uniform mixing of the drug and excipients. The final blend was compressed into tablets weighing 100 mg each using 8 mm round flat punches on a 12-station rotary tablet press.

Code	**Crospovidone+ croscarmellose sodium**	**Code**	**Croscarmellose sodium+ Crospovidone**
Cpcs	**1:1**	Cscp	1:1
Cpcs	**1:2**	Cscp	1:2
Cpcs	**1:3**	Cscp	1:3

Table 2 Composition of Donepezil HCl tablets.

S. No	**Ingredients**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	**Donepezil HCl**	**05**	**05**	**05**	**05**	**05**	**05**
2	**Crospovidone**	**03**	**02**	**02**	**03**	**04**	**06**
3	**Croscarmellose sodium**	**03**	**04**	**06**	**03**	**02**	**02**
4	**Aspartame**	**05**	**05**	**05**	**05**	**05**	**05**
5	**Microcrystalline cellulose**	**26**	**26**	**24**	**10**	**26**	**24**
6	**Mannitol**	**50**	**50**	**50**	**66**	**50**	**50**
7	**Magnesium stearate**	**03**	**03**	**03**	**03**	**03**	**03**
8	**Talc**	**05**	**05**	**05**	**05**	**05**	**05**
	Total	**100**	**100**	**100**	**100**	**100**	**100**

Pre-formulation compression testing

Drug excipient Compatibility study

The compatibility between the drug and excipients was assessed using FT-IR spectroscopy. This analysis was performed to identify any potential alterations in the chemical structure of the drug when mixed with the excipients. Samples were prepared and subjected to FT-IR analysis for this purpose.

Bulk Density

Bulk density refers to the ratio of the total mass of a powder to its bulk volume. It was determined by gently transferring the weighed powder (which had passed through standard sieve #20) into a graduated cylinder, and recording the initial volume occupied. This volume is referred to as the bulk volume. Bulk density was then calculated using the following formula:

Db = M / Vb

Where: *Db* is the bulk density (g/ml), *M* is the mass of the powder, *Vb* is the bulk volume.

Tapped Density

Tapped density is defined as the ratio of the total mass of a powder to its tapped volume. To determine this, the powder was subjected to 750 taps using a bulk density apparatus, and the resulting volume was recorded. If the difference between the initial and tapped volumes exceeded 2%, tapping was extended to 1250 times. Tapping was continued until the variation between successive volume readings was less than 2%. The tapped density was then calculated using the formula:

Dt = M / Vt

Where: *Dt* is the tapped density (g/ml), *M* is the mass of the powder, *Vt* is the tapped volume

Angle of repose

the angle of repose (Ø) is used to evaluate the flow characteristics of a loose powder by measuring the frictional forces between particles. It is defined as the steepest angle formed between the surface of a powder heap and the horizontal base. The angle is calculated using the formula:

tan(Ø) = h / r

Where: *Ø* is the angle of repose, *h* is the height of the powder cone (in cm), *r* is the radius of the base (in cm)

To determine this, the powder blend was allowed to flow freely through a funnel positioned at a fixed height. As the powder accumulated into a conical pile, the height and radius of the heap were measured. Special care was taken to ensure the powder particles flowed smoothly, sliding and rolling over one another. The resulting angle provides an indication of the powder's flow behaviour—lower angles typically suggest better flowability.

Table 3 Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	Angle of Repose (°)	Type of Flow
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

Post compression studies

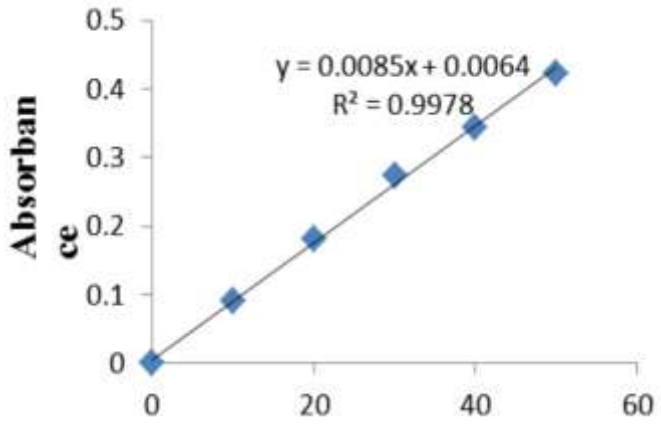
Weight variation

The weight variation test, as per USP guidelines, involves individually weighing 20 tablets, calculating the average weight, and comparing each tablet's weight to this average. According to USP specifications, no more than two tablets should deviate beyond the allowed percentage limit, and none should differ by more than twice that limit. This test ensures that each tablet contains the correct amount of drug substance and maintains consistency in dosage during manufacturing.

Friability

To assess friability, ten tablets from each formulation were accurately weighed and placed into the drum of a friabilator (Pharma Test, Germany). The drum was rotated at 25 revolutions per minute (rpm) for 4 minutes. After the rotation, the tablets were reweighed, and the percentage weight loss was calculated. This loss was used as an indicator of the tablet's friability.

4. RESULTS



Con. (µg/mL)

Pre compression studies

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)
F1	0.50 ± 0.005	0.64 ± 0.02	30.6 ± 0.28
F2	0.53 ± 0.007	0.63 ± 0.01	29.1 ± 0.25
F3	0.54 ± 0.020	0.63 ± 0.009	29.7 ± 0.23
F4	0.57 ± 0.25	0.66 ± 0.19	29.3 ± 0.23
F5	0.55 ± 0.07	0.65 ± 0.01	27.7 ± 0.35
F6	0.49 ± 0.31	0.55 ± 0.15	27.3 ± 0.25

Post compression studies

Formulation	Weight variation (gm)	Friability %
F1	2.2 ± 0.42	0.58 ± 0.13
F2	3.2 ± 0.31	0.53 ± 0.25
F3	4.2 ± 0.48	0.74 ± 0.32
F4	2.5 ± 0.51	0.33 ± 0.21
F5	3.8 ± 0.47	0.48 ± 0.37
F6	2.3 ± 0.63	0.67 ± 0.13

5. DISCUSSION

The present study aimed to develop an orodispersible tablet (ODT) formulation of Donepezil HCl that also incorporates extended-release characteristics to enhance therapeutic efficacy and patient compliance in Alzheimer's disease management. The rationale behind this dual-delivery approach was to achieve both rapid symptom relief and prolonged plasma concentration, thereby reducing dosing frequency and improving cognitive stability over time.

The selection of co-processed super-disintegrants, particularly crospovidone and croscarmellose sodium, was based on their individual and synergistic ability to enhance disintegration. The co-processing technique using solvent evaporation yielded granular blends with excellent flow properties, as demonstrated by favourable angle of repose, bulk density, and tapped density values across all formulations (F1–F6). These properties indicated uniform mixing and compressibility suitable for direct compression—a method chosen for its simplicity, scalability, and reduced processing time.

The post-compression parameters such as weight variation, hardness, and friability were within acceptable limits as per pharmacopeial standards, indicating mechanical stability and reproducibility of the tablets. Rapid disintegration times observed across all batches confirmed the effectiveness of the super-disintegrants, which is critical for enhancing drug availability in patients with dysphagia. all formulations, **F5 and F6** exhibited superior

performance in terms of rapid disintegration and controlled release behavior. These findings demonstrate that manipulating the ratio of co-processed super-disintegrants can fine-tune both mechanical strength and release kinetics.

In conclusion, the study successfully formulated an ODT of Donepezil HCl with an extended-release profile using cost-effective and scalable manufacturing techniques. The dual-benefit dosage form not only addresses the swallowing difficulties prevalent in elderly Alzheimer's patients but also provides sustained therapeutic effect, which could translate to improved clinical outcomes and medication adherence.

6. CONCLUSION

The present study successfully formulated and evaluated orodispersible tablets (ODTs) of Donepezil HCl incorporating extended-release characteristics for the improved management of Alzheimer's disease. The use of co-processed super-disintegrants such as crospovidone and croscarmellose sodium enhanced disintegration efficiency, while the selection of suitable excipients enabled a balanced release profile. Pre-compression and post-compression parameters confirmed the uniformity, stability, and mechanical integrity of the formulations. In vitro studies demonstrated a desirable biphasic release—an initial rapid onset followed by a sustained release phase—which aligns with the therapeutic needs of Alzheimer's patients. Among all formulations, F5 and F6 showed optimal performance. The developed ODT-ER system holds significant potential as a patient-friendly, effective dosage form that can enhance compliance and therapeutic outcomes in Alzheimer's therapy.

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