

Formulation and Evaluation of Mucoadhesive Buccal Tablets of Donepezil Hydrochloride for Alzheimer's disease

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ABSTRACT:

This project is aim to formulate and characterize mucoadhesive buccal tablets of Donepezil, utilizing different proportions of three polymers carbopol 934, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose. Eight batches of buccoadhesive Donepezil were prepared by the direct compression method. The compressed tablets were then evaluated for physicochemical parameters such as hardness, thickness, weight variation, drug content, friability, swelling index, surface pH, and ex vivo mucoadhesion. In vitro dissolution test was conduct for 12 hr according to Indian Pharmacopeia 2018, using the rotating paddle method in phosphate buffer of pH 7.4

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

I. INTRODUCTION

The oral drug administration is the most preferred drug delivery system .it is easy dosing, flexibility in scheduling doses, and improved patient adherence with the risk of administration challenges. However, it is does come with drawbacks like the metabolic effect breakdown in the gastrointestinal tract and a delayed onset of action. To address these challenges alternative approaches such, as drug delivery, sublingual drug and mucoadhesive buccal drug delivery system administration may offer solutions.

Mucoadhesive buccal tablets are pharmaceutical formulations made to attach to the mucous membrane of the buccal cavity (inner cheek) for an expanded period, allowing localized or systemic drug delivery or providing localized. The above tablets typically include active pharmaceutical ingredients along with mucoadhesive polymers that make easy adhesion to the mucosal surface.

The buccal route promotion like avoidance of first-pass metabolism, rapid onset of action and increases patient compliance because of easy administration. .

The buccal mucosa is one such mucosal site that has a high range of vascularization and accredits direct pump off of blood flow inside a jugular vein, that assists in circumventing the feasible metabolism of drugs by the liver and gastrointestinal route. The buccal delivery thus suggests the decrease of medication to the completion mucosal lining of the buccal cavity. uncomplicated drug intake, the chance of triggering abortion in the condition of accidental complicacy and urgent situation, the chance of integrating enzyme inhibitors, etc.

Different types of mucoadhesive polymers (natural, semi-synthetic, and synthetic) are used in the formulation for easy adhesion on the mucosal layer wherefore it is used to target a drug on a particular part of the body. In the early stages, when the mucoadhesive product communicates with the mucosal membrane, it accumulates and disperses, when it extends far down with the mucosal layer and after mucoadhesive substances are turned on by the existence of moisture and drug releases sustainly. There many advantage of mucoadhesive buccal drug delivery system such as it is aviod the gastrointestinal degradation , rapid onset of action , increases in bioavailabilty and drug release directly into blood stream

ALZHEIMER'S DISEASE

Alzheimer's disease is a brain disorderliness which gets terrible over time. It's designate by alternate in the brain that conduct to accumulation of certain proteins. Alzheimer's disease effect the brain to shrink and brain cells are finally die. Alzheimer's disease is the prevalent cause of dementia — its gradually decreases in memory, thinking ability, behavior changes and social skills. These changes may have an effect on

person's ability to function .More than 6.5 million population in the United States age 65 and oldlive accompanied by Alzheimer's disease. Among them, above 70% of 75 years elder and old. Above 55 million population of people suffering for dementia worldwide, approximately 60% to 70% are suffering for Alzheimer's disease.The first signs of the condition involve fail to remember recent events or conversations. Over time, it forward movement to server memory problems and fail to perform everyday tasks.Medicines can do increasememory or decrease the progression of indication. services and Programs help out support presons with the illness and their caretaker.There is no therapy that heal Alzheimer's disease. In modern stages, waiter loss of brain function can purposelose of water in body, poor diet or contamination.These difficulties maycause death.

Most commonly used drugs to treat the Alzheimer's disease there are

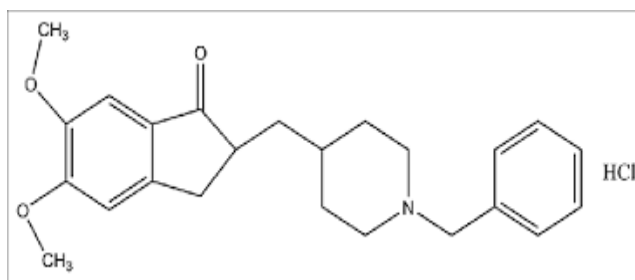
Memantamine

Galantamine

Donepezil

Rivastigamine

Donepezil hydrochloride, a piperidine derivative, is a centrally acting,fast, and resolvable acetylcholinesterase inhibitor mainlyused for treating Alzheimer disease. Acetylcholinesterase is a substance that crashes acetylcholine later than its free from the presynapse. By binding reversibly to acetylcholinesterase, donepezil inhibits acetylcholine hydrolysis, whereby improving acetylcholine availableness at the synapses and improving cholinergic transmission.



DONEPEZIL HYDROCHLORIDE

II. LITERATURE REVIEWS

S.NO	NAME OF THETITLE	NAME OF THE AUTHOR	YEAR	CONCLUSION
1	Human buccal startegies for the alzheimers disease treatment	G. Compisi. H. c. pederni R.saccone A.wolff		Mucosal and transmucosal delivery of drugs via the oral mucosal route is becoming more and it have significant advantage to the convectional route.
2	Drug delivery buccal startegies for the alzheimers disease treatment.	Antonio di Stefano, Sara laserna and piera sozia		The conventional oral formulation, a variety of druigs delivery startegies applied to the treatment of alzheimers disease;.potentialy alternative to conventional route orally disintegrating or sublingual formulation based drug delivery system Traditional oral based alzheimers therapies 1.Doneprazil,2.Galantamine, 3. Rivastigmine 4.

				Memantine
3	Characterisation of oral disintegrating filling containing Donepezil for Alzheimer disease	Kai bin lieu, Yvonne Tze fung tan, Kok khiang peh		A flexible Donepezil ODF formulation with the fast disintegration time, acceptability, palatability & stable over a period of 6 months was successfully developed. The results suggest that Donepezil ODF has the potential as an alternative dosage forms in treating alzheimers disease.
4	A review on bioadhesive buccal drug delivery system;current status of formulation and evaluation methods	China reddy.P Chaitanya.K.S.C. Madhusudhen rao.Y		Buccal adhesive system offer innumerable advantages in terms of accesability administration and with draw and high patient acceptability this drug delivery to mucosal membrane leads to an increased drug concentration gradient at the absorption site and improve bioability of systematically deliver to drugs and formulation in terms of there capability to promote drug absorption in Buccal route of administration has many advantages such as improving paitient compliance , by passing the GIT &hepatic first pass effect, subjecting table to 4 °C &75% RH ,results are within acceptable range it shows the potential formulation as a mucco adheshive buccal tablets buccal route.
5	Formulation and invitro evaluation of Donepezil Hcl rapid dissolving oral thin film	Keshi reddy Anji reddy and S.Karpagem		Prepared Doneprazil Hcl filim was showed better drug dissolution results compare to pure drug and marketed sample filimwas given satisfactory results in all evaluation parameters like disintegration time and drug content.

6	Formulation and evaluation of Orodispersable tablets of test	Dr.P.R.Radhika mekkena pavani		ODTS are developed to avoid the chocking problems which occur generally with the tablet dosage forms . The ODTS of various batches prepared by using various concentration of various super disintegrants like Sodium starch glycolate croscopolvidone and crocarmeuse sodium by direct compression method. The selected formulation was subjected for the short term stability studies for 60 days and the hardness, test, friability, drug content and disintegration were observed and found to be significant change in the results.
7	Preparation and evaluation of oral disintegrating film containing Donepezil for Alzheimer disease	Yjaopenj nen, Jiachenyan chao qin		The optimized Donepezil orally disintegrating film prepared by with the HPMC solvent it has satisfactory drug dissolution rate. In vitro disintegration time had acceptable physical and mechanical properties
8	Formulation and evaluation of mucoadhesive buccal tablets of Menemiac acid	Karen lu li, Agnes liamasares castillo		Buccal route of administration has many advantages such as improving patient compliance , by passing the GIT & hepatic first pass effect, subjecting table to 4 °C & 75% RH , results are within acceptable range it shows the potential formulation as a muco adhesive buccal tablets
9	Formulation & evaluation of mucoadhesive buccal tablets of Aceclofenac	Santhosh koirala, Prabin Nepal, Govinda ghimere		Study was conducted to formulate & evaluate mucoadhesive buccal tablet of Aceclofenac with a sustained released property & it is a alternative route prevent the first pass effective & to improve the bioavailability

10	Formulations and evaluation of bilayered mucoadhesive buccal tablets of cervedicol	Grace rethnem and swetas		The formulation of carvedilol mucpedhesive tablets can be an effective alternative route to prevent the frist pass effect and to improve bioavaibility through the mocusal membrane also hence Patient acceptability by fascinating extend released of durg.
11	Donepezil-an updated review of changes in dosage forms design	Lalinthip sultha Pitaksakul,crpspim R,dess		Current research is focused on the clinical role of Donepezil Hcl as an disease modifying agent in both pre clinical and clinical studies.
12	Current research is focused on the clinical role of Donepezil Hcl as an disease modifying agent in both pre clinical and clinical studies.	Varsha V.nair, Pablo Cabrera , Mijuel.O.jara		Buccal delivary of drug and biologic has studied using various manufacturing technicaues.The buccal route of administration bypasses frist pass metabolism

III. MATERIALS AND METHODOLOGY

DRUGS AND CHEMICALS

Donepezilhydrochloride, Carbopol. Hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (SCMC). Magnesium stearate, micro crystalline cellulose powder 200 (MCCP 200), and talc. Every substances and analytical reagents used were of pharmaceutical grade.

FORMULATION OF DONEPEZIL MUCOADHESIVE TABLETS

Mucoadhesive tablets should be prepared by acquiring anearlierly initiated method with slight qualification . Direct compression method is used to compress the tablet , utilising varying quantity of various polymer grades.every small particles in pure form is to completely weigh. Mix the Donepezil with CP. Then in a separate pouch left over polymers are mix it with talc. Then above two mixtures in the blender for 5 min after passing through a #40 sieve.Mix MCCP 200 and aerosil in a different pouch for 2 min. Then mix it with the foregoing mixture for 5 min. ultimately magnesium stearate should be add and the resultant mixtures were on the mix and the blend is compressed it into tablets having an average weight of 250 mg,by

using a ten station tablet punch. Prepare Eight batches and code it from B1 to B8. The featuresof formation of each batch will be acquired from the former study

PERFORMULATION STUDIES

BULK DENSITY

Bulk Density is also known as poured density. Bulk density is calculated by pouring the 20 g powder into a 100 ml measuring cylinder (before that powder passes from standard sieve # 42) and initial mass should be recorded .this is the ratio of total volume of powder to the bulk mass of powder. . The initial mass is called the bulk volume. From that the bulk density is measured by following given formula . It is expressed in g/ml and is given by

$$D_b = M / V_b$$

Where, M = mass of powder

V_b = bulk volume of the powder.

Tapped density:

Tapped density is the ratio of total volume of the powder to the tapped mass of the powder. The mass is calculated by tapping the powder for 750 times and the tapped mass will be recorded, if there is any difference among two volumes less than 2%. If the difference is greater than 2% than

continues the tapping for 1250 times and tapped volume should be recorded. Tapping would continue up to the difference among successive masses is smaller than 2 % (in a bulk density instrument). It is expressed in g/ml and calculated given by following formula

$$Dt = M / Vt$$

Where, M = mass of powder

V = tapped volume of the powder.

Angle of repose (θ):

The friction force of a movable powder can be measure by the angle of repose (q). It is a representative of the flow properties of the powder. It is defined as maximum possible angle between the surface of the pile of powder and the horizontal

plane and it can be measured by the following formula.

$$\tan(\theta) = h / r$$

$$\theta = \tan^{-1}(h / r)$$

Where, θ = angle of repose.

h = height in cms

r = radius in cms.

The powder blend is acceptable to flow through the funnel fixed to a stand at exact height . The angle of repose then measured by calculating the peak and diameter radius of the heap of powder forms.Careful to observe that the powder particles roll and slip over each other around the sides of the funnel. Relationship among angle of repose and powder flow property of powder is given below

Angle of Repose represents of Powder Flow Properties:

S.NO	Angle of repose	Flow types
1	<20	Excellent
2	20-30	Good
3	30-40	Passable
4	>34	Very poor

Carr’s index (or) % compressibility:

It’s representes flow properties of powder . It can calculated in percentage and give as

$$Dt - Db$$

$$I = \frac{Dt - Db}{Dt} \times 100$$

Dt

Where, Dt = tapped density of the powder and

Db = bulk density of the powder

Relationship between % compressibility and flow ability

S.No	% compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-25	Poor
5	33-38	Very Poor
6	<40	Very very Poor

Hausner ratio :

Hausner ratio is expressed by the following formula

$$\text{Hausner ratio} = Dt/Db$$

Where,Dt = tapped density

Db =bulk density

It represent the less than 1.25 is good flow properties than greater than 1.25

EVALUATION OF TABLET PROPERTIES:

Different quality control parameter of all the batches of mucoadhesive Donepezil tablets were weighe analysed by adopting the method described in Indian Pharmacopeia

Weight variation :

Take twenty tablets [n = 20] from every batch weigh by using digital balance and the average weight tablet to be calculated.

Friability :

Twenty tablets [n = 20] of each batch can be weighed and put into the friabilator drum. After 100 revolutions of friabilator, tablets are recorded. The tablets are then freed from dust and weighed. Friability was calculated from the Eq. [1]

$\% \text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$

Hardness :

Twenty tablets [n=20] are taken for the hardness test using a hardness tester. Then the force should be applied from the movable probe of the hardness tester. Then the force is applied from the movable probe. The force to break the tablet should be recorded.

Wetting time :

Wetting time is nearly associated to the inside structure of the tablets and to the hydrophobicity of the additives. The process for wetting time is as follows: take a piece of tissue paper, double fold the tissue and it should be spotted in a petri plate (6.5 cm is internal diameter) include 6 ml of water held in a cosine (water soluble dye). The tablet should be set on the paper and measure the complete wetting time of tablets in seconds. It should be repeated for three times for every formulation to get accurate.

Tablet thickness and tablet diameter :

All the tablets are within the acceptable range for tablet thickness with values ranging from 3.71 mm to 3.80 mm.

Moisture absorption studies:

Moisture absorption of the mucoadhesive buccal tablets is in the range of 14.07% to 16.65%. There was no significant change in the percent moisture absorption even after 3 months of stability test, which shows that the tablets have suitable moisture absorption capacity. Maybe there was no significant difference in the mean moisture absorption of the two batches.

Surface pH study :

The surface pH of the tablet should be close to the salivary pH so that the tablet will not irritate the buccal mucosa. The salivary pH is 6.50 to 7.50. Since the surface pH of the buccal tablet is within the limits of salivary pH, it shows that the tablet will not irritate the buccal mucosa.

The Content uniformity test :

According to USP, the tablet content should be within the range of 85% to 115% and no unit is outside the range of 75% to 125% and the relative standard deviation should be less than or equal to 6%. All fall within the range of 85% to 115% with a relative standard deviation of less than or equal to 6%.

Swelling index studies :

The swelling study is performed on petri dishes containing 1% agar gel. Four tablets are weighed and placed in a petri dish. The petri dishes contained 4 tablets, and each is placed in an incubator at $37 \pm 1 \text{ }^\circ\text{C}$. After 0.5, 1, 1.5, 2, 2.5, 3 hours, excess water on the surface should be carefully removed using the filter paper without pressing. The tablets are weighed and the swelling index is calculated using the formula.

$\text{Swelling Index} = \frac{W_f - W_i}{W_i} \times 100$

Where W_i is the initial weight and W_f is the final weight of the tablet (Chaudhari, Harsulkar, 2012; Hassam et al., 2009; Padsala, Desai, Swamy, 2014).

Appropriate swelling property of buccal formulations is needed for proper adhesion.

Dissolution rate :

Mucoadhesive buccal tablets of donepezil are carried out by using USP dissolution apparatus I basket type by taking 900 ml of pH 6.8 buffer solution. Setting 50 rpm at a temperature of $37 \pm 5 \text{ }^\circ\text{C}$ is maintained. Each time 5 ml of sample is withdrawn from the medium as per predetermined sample intervals and replaced with fresh medium. The sample is diluted and assayed by UV Spectroscopy at 230 nm. Studies are conducted in triplicate.

Disintegration test

A 1000 mL beaker will be filled with 900 mL of distilled water and maintained at a temperature of $37 \pm 0.5 \text{ }^\circ\text{C}$. Six tablets are placed in each of the cylindrical tubes of the basket. To avoid floating of the tablets, discs are used. The time taken to break the tablets into small particles is recorded. The limit for buccal tablets is 4 hours.

IV. CONCLUSION:

Polymer type and ratio affect the drug release from the buccal tablets due to their different swelling capacity. Carbopol based formulations showed the best mucoadhesive performance. Formulations containing more than 5% carbopol ratio dissolved 22–56% within 12 h time. This

finding shows that sustained release buccal tablet formulations must have appropriate ratios of carbopol. Disintegration times changed depending on the polymer's charges in different pH values. Significant variances between dissolution profiles for buccal tablets, using either USP paddle or flow through cell methods were found. In the same manner, the release profiles and sometimes release kinetics altered when different dissolution methods were used. The total amount of Drug substances released from the tablets was practically the same regardless of the system used.

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