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Formulation and Evaluation of Mucoadhesvie 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 sustainlyThere 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 disorderlinesswhich gets terrible over time. It's

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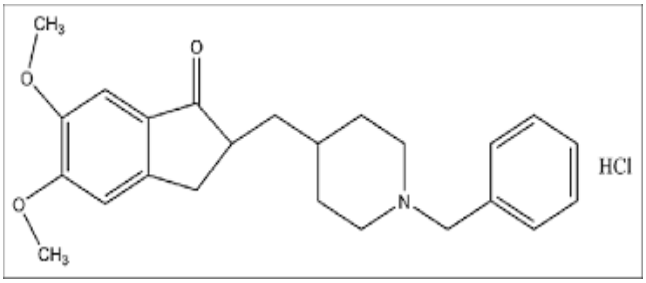
designate by alternate in the brain that conduct to accumulation of certain proteins. Alzheimer's disease effect the brain to shrink and brain cells are finally die. Alzheimer's disease is the prevalent cause of dementia — its gradually decreases in memory, thinking ability, behavior changes and social 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 imporving 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 oraly disintegranting or sublingual formulation based drug delivery system Traditional

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				oral based alzheimers therapies 1.Doneprazil,2.Galantammine, 3. Rivastigmine 4. Memantamine
3	Characterisation of oral disintegrating filling containg Donepezil for Alzheimer disease	Kai bin liew, Yvonne Tze fung tan, Kok khiang peh		A flexible Donepezil ODF formulation with the fast disintegration time, accepetability, palatability & stable over a period of 6 months was successfully developed. The results suggest that Donepzil 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 evalution 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 evalution of Donepezil Hcl rapid dissolving oral thin filim	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 evalution parameters like disintegrantion time and drug content.

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6	Formulation and evalution of Orodispersable tablets of test	Dr.P.R.Radhika mekkena pavani		ODTS are developed to evoid the chocking problems which occur generally with the tablet dosage forms . The ODTS of various batches prepared by using various concentration of various super disintegranrs like Sodium stexh glucolate crospovidone and crocermeuose 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 where observed and found to be signifant 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 nad acceptable physical and mechanical preporties
8	Formulation and evalution of mucoadhesive buccal tablets of Menemic acid	Karen lu li, Agnes liamasares castillo		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
9	Formulation & evalution of mucoadhesive buccal tablets of Aceclofenac	Santhosh koirela, Prabin Nepal, Govinda ghimere		Study was conducted to formulate &evaluate mucoadhesive buccal tablet of Aceclofenac with a sustainted released property &it is a alrnative route prevent the first pass effective & to improve the bioavailability

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10	Formulations and evalution of bilayered muccoadhesive buccal tablets of cervedicol	Grace rethnem and swetas		The formulato]ion 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 Doneprazil Hcl as an disease modifying agent in both pre clinical and clinical studies.
12	Current research is focused on the clinical role of Doneprazil 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

Db = M/ Vb

Where, M = mass of powder

Vb = bulk volume of thepowder.

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

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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 an 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 represntative 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 represented flow properties of powder . It can calculated in percentage and give as

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

Where, Dt = tapped density of the powder and

Db = bulk density of the powder

Relationship between % compressibility and flow ability

S.No	% compressbility	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

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

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Friability :

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

%Friability = Initial weight - Final weight / Initial weight ×100

Hardness :

Twenty tablets [n=20] take for the hardness test using a hardness tester. Then the force should apply from the movable probe of the hardness tester. Then the force is apply from the movable probe. The force to break the tablet should record.

Wetting time :

Wetting time is nearly associated to the inside structure of the tablets and to the hydrophicity of the additives. The process for wetting time is as following, take a piece of tissue paper double fold the tissue and it should spot in a petri plate (6.5cm is internal diameter) include 6ml of water hold in cosin (water soluble dye). The tablet should set on the paper and measure the complete wetting time of tablets in seconds.it should repeated for three times for every formulations to gest 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 aborption 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. May be there was no significant difference in the mean moisture absorption of the two batch.

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 0standard 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 to perform on petri dishes containing 1% agar gel. Four tablets were weigh and place in a petri dish. The petri dishes contained 4 tablets, and each is place in an incubator at 37 ºC + 1 ºC. After 0.5, 1, 1.5, 2, 2.5, 3 hours, excess water on the surface should carefully remove using the filter paper without pressing. The tablets is to weigh and the swelling index is calculated using the formula.

Swelling Index = Wi x Wf /Wi

Where Wi is the initial weight and Wf 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 :

Mocuadhesive buccal tablets of donepezil carried out by using USP dissolution apparatus I basket type by taking 900 ml 0f pH 6.8 buffer solution. Setting 50 rpm at a temperature of 37 ± 5 centigrade maintaines.Each time 5ml of sample withdrawn from medium as per predetermine sample intervals this replace with fresh medium. Sample is to dilute and assay by UV Spectroscopy at 230 nm. Studies is to conduct in triplicate

Distegration test

A 1000 mL beaker will be fill with 900 mLof distilled water and maintain at a temperature of 37 ± 0.5 °C. Six tablets place 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 record,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 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.

REFERENCES:

[1]. Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A, Pandey J, Parajuli-Baral K. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon. 2021 Mar 1;7(3).

[2]. Li KL, Castillo AL. Formulation and evaluation of a mucoadhesive buccal tablet of mefenamic acid. Brazilian Journal of Pharmaceutical Sciences. 2020 Jun 21;56:e18575.

[3]. Liew KB, Tan YT, Peh KK. Characterization of oral disintegrating film containing donepezil for Alzheimer disease. AapsPharmscitech. 2012 Mar;13:134-42.

[4]. AnjiReddy K, Karpagam S. Micro and nanocrystalline cellulose based oral dispersible film; preparation and evaluation of in vitro/in vivo rapid release studies for donepezil. Brazilian Journal of Pharmaceutical Sciences. 2020 Nov 6;56.

[5]. Pavani M. Formulation and Evaluation of Orodispersible Tablets of Taste Masked Nizatidine (Doctoral dissertation, Nandha College of Pharmacy, Erode)Seltzer B. Donepezil: a review. Expert Opin Drug Metab Toxicol. 2005 Oct;1(3):527-36.

[6]. Kumar A, Sidhu J, Goyal A, Tsao JW. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jun 5, 2022. Alzheimer Disease.

[7]. Morant AV, Vestergaard HT, Lassen AB, Navikas V. US, EU, and Japanese Regulatory Guidelines for Development of Drugs for Treatment of Alzheimer's Disease: Implications for Global Drug Development. Clin Transl Sci. 2020 Jul;13(4):652

[8]. Larkin HD. First Donepezil Transdermal Patch Approved for Alzheimer Disease. JAMA. 2022 May 03;327(17):1642.

[9]. Szigeti K, Hafeez MU. Exploring the role of donepezil in dementia with Lewy bodies. Drugs Today (Barc). 2015 Oct;51(10):579-90.

[10]. De-Paula, V.J.; Radanovic, M.; Diniz, B.S.; Forlenza, O.V. Alzheimer's disease. Sub-Cell. Biochem. **2012**, 65, 329–352.

[11]. Blass, J.P. Alzheimer's disease. Dis. A Mon. Dm **1985**, 31, 1–69.

[12]. Terry, R.D.; Davies, P. Dementia of the Alzheimer type. Annu. Rev. Neurosci. **1980**, 3, 77–9

[13]. Szigeti K, Hafeez MU. Exploring the role of donepezil in dementia with Lewy bodies. Drugs Today (Barc). 2015 Oct;51(10):579-90

[14]. Cacabelos R. Donepezil in Alzheimer's disease: From conventional trials to pharmacogenetics. Neuropsychiatr Dis Treat. 2007 Jun;3(3):303-33

[15]. Yiannopoulou KG, Anastasiou AI, Kyrozis A, Anastasiou IP. Donepezil Treatment for Alzheimer's Disease in Chronic Dialysis Patients. Case Rep Nephrol Dial. 2019 Sep-Dec;9(3):126-136.

[16]. Park, C.R., Munday, D.L., 2002. Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. Int. J. Pharm. 237 (1), 215– 226.

[17]. Kassem, M.A., ElMeshad, A.N., Fares, A.R., 2014. Enhanced bioavailability of buspirone hydrochloride via cup and core buccal tablets: formulation and in vitro/in vivo evaluation. Int. J. Pharm. 463 (1), 68–80.

[18]. . Yie W Chein. Oral Drug Delivery Systems: Novel Drug Delivery Systems", Marcel Dekker, New York, 2nd edition, 2005;50:139-196.

[19]. Thomas Wait-Yip Lee and Joseph R Robinson, "Controlled Release Drug Delivery Systems", In the Science and Practice of Pharmacy, 2001;1:20th edition, 903.

[20]. Jain NK. Controlled and Novel Drug Delivery. CBS Publishers & Distributors, New Delhi, 3rd edition. 2007;353-380.

[21]. Hetangi Rathod. Floating Drug Delivery System: Innovative Approach of Gastroretention. International Journal of Pharmaceutical Sciences Review and Research. 2010;.4(3):183-192.
[22]. Shweta Arora. Floating Drug Delivery Systems: A Review", AAPS PharmSciTech. 2005;6(3): E372-E390.
[23]. Brayfield A. (14 January 2014). Aspirin. Martindale: The Complete Drug Reference. Pharmaceutical Press. Retrieved 3 April 2014.
[24]. Available from: http//www.drugbank.com/nicotinicacid/htm.
[25]. Ramdas T Dolas. Novel Sustained Release Gastroretentive Drug Delivery System. A Review International Journal of Pharma Research and Development. 2011;2(11):26-41. Samar EI Samaligy. Floating systems for oral controlled release drug delivery. Dissertation work, Berlin, 2010.
[26]. Jagadeesh Nadigoti and Shayeda. Floating Drug Delivery Systems. International Journal of Pharmaceutical Sciences and Nanotechnology. 2010;2(3):595-604.