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Formulation And Invitro Evaluation Of Orodispersible Films Of Donepezil Hydrochloride And Determination Of Percentage Purity By Orthogonal Polynomials

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ABSTRACT

The current project aims to increase the bioavailability of Donepezil Hydrochloride (an anti Alzheimer drug which is extensively metabolized by hepatic first pass). Although the drug is known to be majorly eliminated by the renal route in humans, the drug also is known to undergo hepatic first pass considerably.The drug has been successfully formulated into a novel drug delivery system “Mouth Dissolving Films”. Almost all of the drug is dissoluted out in the mouth and is absorbed by the mucosal membrane itself. The films have been formulated by the incorporation of superdisintegrants Sodium Starch Glycollate and Doshion P-544 for the instant release of the drug.The films have been formulated also by incorporating suitable plasticizers and flavourants for the patient compliance. The rate of drug release from the formulations has been compared with that of a conventional dosage form ARICEP. (A market tablet of 5 mg from Eisai Pharma) and was found to be almost superior with that of the tablet. Also owing to the change in the site of absorption an increase in the bioavailability of the drug is anticipated. The amount of drug release has been estimated by conducting comparative dissolution studies. The two dosage forms of the drug, the tablet and the film were subjected to the dissolution test and the rate and amount of drug release was calculated and found to be comparable. The assay of the drug has also been counterchecked and calculated by the implementation of a mathematical tool “The Orthogonial Polynomials” establishing its significance of applicability in drug content calculation.

Key words: Mouth dissolving films, orthogonal polynomials, bioavailability, novel drug delivery system, hepatic first pass**.**

INTRODUCTION:

Amongst the various forms of drug delivery, oral route is perhaps the most popular to the patient as well as the clinician. However, oral administration of drugs has few short commings

such as liver metabolism and enzymatic degradation within the GI tract, that restrict oral administration of certain classes of drugs like peptides and proteins. As a result, other absorptive mucosa are considered as potential sites for drug administration. Tranmucosal routes of drug delivery offer many advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoiding of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug. (1-2). Also mouth dissolving films have become a drug delivery route of choice for patients on dialysis were the water intake is regulated. Further for patients who do not have the sense of drug administration because of dementia of Alzheimer's these films prove out to be very useful.

The oral cavity comparated to other routes of administration is highly acceptable by patients. The buccal mucosa is more permeable when compared to the mucosal lining of the gut with ample blood supply, it shows short recovery times after stress or damage (3-5), and the lack of Langerhans cells (6) renders the oral mucosa tolerant to potential allergens. Furthermore, oral transmucosal drug delivery bypasses hepatic first pass effect and prevents pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive site for systemic drug delivery.

Plasticizer (7-8) is a critical ingredient of the fast dissolving buccal films formulation. The mechanical properties such as the tensile strength , elongation of the films can be enhanced by the addition of the plasticizer. It also helps to improve the flexibility of the film and reduces the brittleness of the film. The pour of polymer also gets better by the addition of the plasticizer. The selection of the plasticizer will depend upon its compatibility with the polymer and also on the type of solvent used in its casting. Plasticizers are exemplified with glycerine, sorbitol, propylene glycol, polyethylene glycol, triacetin, di-butylpthalate, triethyl citrate, acetyl triethyl citrate and other citrate esters. Typically the plasticizers are used in the concentration ranges of 0-20% w/w of the dry polymer weight (9) . Inappropriate use of the plasticizer may result to film cracking, splitting, peeling of the film and it may also affect the absorption rate of the

Hydroxypropylmethyl cellulose (HPMC) is known for its good film-forming properties and has excellent suitability. (10,11) maltodextrin is classified as a complex carbohydrate, but behaves like a simple carbohydrate in the body. It has a role of film-forming agent, solubilizer, and imparts sweetness to the formulation. (12,13)

For the fabrication of films, glycerol was used as a plasticizer and mannitol was used as a sweetener. (14)

The percentage purity of the drug in the dosage form could be calculated by the implementation of the statistical tool, the orthogonal polynomials (15). The polynomial coefficient of second degree could be implemented if the UV curve of the drug shows the polynomial coefficient as quadratic. Also six points of equal intervals of wavelength have to be considered. The assay of the drug by the implementation of the quadratic polynomials assures that the drug in the formulation will not interact with the other components. The orthogonal polynomial thus omit the interfering absorbances from other components of the formulation. The table of the polynomial coefficient provides the values for the respective points selected (16).

Donepezil Hydrochloride: the cholinergic hypothesis of Alzheimer's disease (17–19) has led to the growth of agents designed to increase cholinergic function in the central nervous system, such as inhibitors of acetylcholinesterase (AChE), the centrally active enzyme responsible for the catabolism of the neurotransmitter acetylcholine. Donepezil HCl (Aricep is a chemically unique, piperidine-based AChE inhibitor that has been proven in pre-clinical

studies to be a potent and relatively specific inhibitor of AChE (20) . Donepezil has been shown to be effective in randomized, controlled clinical trials of up . to 1 year in duration, showing significant benefits on cognition, global function and ability to perform activities of daily living (21–23). Due to its slow clearance (elimination half-life of 70 hrs) (24) , donepezil is effective as a single daily dose. It undergoes hepatic first pass in the liver by the cytochrome P450 isoenzymes CYP 3A4 and CYP 2D6. However, in vitro studies have revealed that the inhibitory effects of donepezil on these enzymes are very less, due to the low rate of binding relative to the therapeutic plasma concentrations of donepezil (25) . The majority of metabolites are eliminated in the urine (79% of recovered dose), suggesting elimination via the renal rather than the biliary route (26).

MATERIALS AND METHOD:

Composition:

Donepezil Hydrochloride, Hydroxypropyl methyl cellulose, Malto dextrin, Polyvinyl pyrolidone, Sodium starch glycolate, DoshionP-544, Polyethylene glycol-400, Glycerine, Mannitol, Ethanol, and water.

THE SOURCE OF THE MATERIALS:

HPMC was procured from LOBA chemicals (Hyderabad, India), Malto dextrin, Polyvinyl pyrolidone from HIMEDIA laboratories (Hyderabad, India), Sodium starch glycolate, Polyethylene glycol-400 from (SDFCL) (Hyderabad, India), Glycerine , Mannitol Ethanol, and water, from NICE chemicals (Hyderabad, India) ,Donepezil hydrochloride was a generous gift from EISAI PHARMA (India) .

PREPERATION OF MOUTH DISSOLVING FILMS:

The mouth dissolving films were prepared by the solvent casting method. HPMC K15 was hydrated in water for about 12 hours. Maltodextrin was then solubilised in uniformly dispersed HPMC to obtain a dispersion. Sodium Starch Glycolate, Polyvinyl pyrolidone, Mannitol, as sweetening agent and brilliant blue-fcf were dissolved in water to obtain a dispersion for Formulation 1 (F1) . The Formulation 2 (F2) also was prepared with a similar method except the SSG, which was replaced with Doshion.

To mask the bitter taste of the drug, inclusion complex of the drug was formed with hydroxyl propyl B cyclodextrin at 1:1 ratio by kneading method using ethanol as solvent for both the formulations F1 &F2.

The prepared alcoholic solutions and polymeric dispersions were mixed under constant stirring at 500 RPM with magnetic stirrer.until a homogenous thick viscous solution was obtained by adding PEG-400 and glycerine as plasticizer and humectant.

From the prepared homogenous thick viscous solutions, 20 grams of each mixture was taken and casted into 9cms glass Petri dishes. The dishes were kept at room temperature at about 15 minutes.

The petriplates were kept in hot air oven at 30-40 ^{0} C for final drying for about 2 days .the petriplates were allowed to equilibrate to the room temperature. The films were carefully peeled off from the petriplates and stored in an airtight plastic container.

METHODOLOGY FOR THE CHARACTERISATION OF FILMS:

The prepared films were evaluated for the parameters of thickness, folding endurance, content uniformity dissolution etc as per the methodology in references. The thickness of the film samples was measured by using a screw gauge at five locations (centre and four corners), the average thickness is calculated and recorded. Samples with air entrapped bubbles, nicks or tears and having mean thickness variation of greater than 5% are excluded from analysis. Folding endurance was performed by folding a film of approximate size 4 cm2 repeatedly at the same plane several times. The number of foldings

that create the first visible crack is recorded (17). Folding endurance indicates the brittleness of the film. The surface pH of fast dissolving film was determined in order to find out the possible any in-vivo side effect. A combined pH electrode was used for this function. Oral film was slightly hydrated with water. The pH was measured with the glass membrane electrode in contact with the surface of the oral film (18,19). Content uniformity parameter can be determined by dissolving known weight of film by homogenization in 100ml of simulated saliva of pH 6.8 for 30 min with continuous shaking. The drug concentration was then characterized spectrophotometrically at λmax of 231 nm(17).,Mechanical properties of the films were determined for the parameters of tensile strength and percent elongation. The tensile strength was determined by placing the extreme ends of films of size 20×20mm between two clamps of the tensile tester. To one of the clamps is attached the probe which holds the weights. the weight required to break the film was recorded. Percentage elongation is the parameter which is based on the tensile strength of the films. %elongation was measured by noting the increase in length of the film after the tensile strength measurement. Disintegration time was determined by immersing the films ten from each formulation into tubes of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in a beaker containing simulated saliva and the apparatus was operated until the film disintegrated. The time for total disintegration of the film was determined using a chronometer. The analysis were performed for 10 samples of each film. The dissolution study was performed using simulated saliva fluid as dissolution medium at 37±0.50C with 50 Rpm for 12 Mins. Samples of each preparation equivalent to 5 mg of drug were added to dissolution medium. A 5 ml aliquot was withdrawn at different time intervals (5, 10, 15,20,25,30,35,40,45and50).Samples are analyzed for its drug content spectrophotometrically by measuring the absorbance against blank at 231 Nm. Percent of Donepezil dissolved at various time intervals was calculated and plotted against time.

RESULTS AND DISCUSSION:

Thickness:

Test was carried out using an electronic micrometer.. The procedure was performed in triplicate and average with standard deviation was reported in (Table no. 1)

Table 1 . Evaluation results for thickness of the films:

SAMPLE NUMBER	F1(mm)	F2(mm)
1	0.120	0.140
2	0.060	0.100
3	0.080	0.120
4	0.100	0.160
5	0.060	0.120
Average	0.080	0.120
S.D	0.016	0.016
C.V	0.200	0.133

C.V= S.D/MEAN *100

Table no 1: Thickness was uniform at five different locations of the films and the average thickness of the films was determined. The result shows that the standard deviation was same for both the formulations and there was a negligible variation observed in C.V values.

Folding endurance:

evaluate the film for folding endurance, the film is cut and repeatedly folded at the same place till it broke. The maximum number of times the film could be folded at the same margin without breaking gives the value of folding endurance. The procedure was performed in triplicate and average with standard deviation was reported in (Table no.2)

Table 2 . Evaluation results for folding endurance of the films:

SAMPLE NUMBER	F1(Times)	F2(Times)
1	24	22
2	21	25

3	23	24
Average	22.6	23.6
S.D	1.24	1.24
C.V	0.54	0.52

Table-2 folding endurance was uniform for all the films and lies in the range of 22 ±0.054 to 23 ±0.052. The table also shows that the films do have enough required physical integrity for patient compliance.

Surface pH:

The procedure was performed in triplicate and average with standard deviation was reported in (Table.3)

Table3. Evaluation results for Surface pH of the films:

SAMPLE NUMBER	F1 **(pH scale)**	F2 **(pH scale)**
1	6.650	6.660
2	6.680	6.760
3	6.670	6.780
Average	6.660	6.730
S.D	0.012	0.052
C.V	0.180	0.770

The surface PH was uniform for all the formulation and the standard deviation along with coefficient of variation has been reported in the above tabular column.

Uniformity of drug content:

The determination was done in triplicate for all the formulations and the mean with standard deviation was recorded and reported in (Table.4)

Table 4. Evaluation results for Uniformity of drug content of the films:

SAMPLE NUMBER	F1 (mg).	F2 (mg).
1	**0.240**	**0.230**
2	**0.260**	**0.260**
3	**0.240**	**0.230**
Average	**0.250**	**0.240**
S.D	**0.018**	**0.017**
C.V	**07.56**	**7.080**

The results indicate the drug was uniformly dispersed in almost all the portions of the formulation

Tensile strength:

Tensile strength was measured by using the following formula

Tensile strength= breaking force/elongated length.

The determination was done in triplicate for both the formulations and the mean with standard deviation was recorded and reported in (Table.5)

Table 5. Evaluation results for Tensile strengths of F1&F2

Sl. no	Sample	Tensile Strength N/cm2	Sample	Tensile Strength N/cm2
1	F1	86.40	F2	81.32
2	F1	85.80	F2	81.36
3	F1	86.80	F2	80.64
	F1	Mean :85.76	F2	Mean:81.10
	F1	S.D : 00.41	F2	S.D : 00.33
	F1	C.V :03.41	F2	C.V : 03.82

Percentage elongation:

Percentage elongation was measured by using the following formula

Percentage elongation= LF-LO/LO*100

Where LF is the final length and LO is the initial length.

The determination was done in triplicate for both the formulations and the mean with standard deviation was recorded and reported in (Table.6)

Table 6. Evaluation results for Percentage elongation

Sl no . Sample		Percentage elongation	Sample	Percentage elongation
1		5.321	F2	4.990
2	F1	5.294	F2	4.192
3	F1	5.381	F2	5.245
	F1	Mean : 5.330	F2	Mean: 4.821
	F1	S.D : 0.339	F2	S.D: 0.447

Disintegration time:

The time for total disintegration (minutes) of the film was determined using a chronometer.. At least 10 samples for the analysis were taken. The following (Table 7) shows the mean disintegration time of the films.

Table 7. Evaluation results for the Disintegration time of films

Sl. NO	Sample F1 SSG	Disintegration Time (sec)	Sample F2 DOSHION	Disintegration Time (sec)
1	F1	32	F2	20
2	F1	34	F2	28

3	F1	32	F2	21
4	F1	30	F2	22
5	F1	31	F2	21
6	F1	33	F2	29
7	F1	32	F2	21
8	F1	34	F2	28
9	F1	31	F2	20
10	F1	32	F2	29
	F1	Mean :32.1	F2	Mean:23.9
	F1	S.D : 0.894	F2	S.D :0.748
	F1	C.V	F2	C.V

Dissolution test:

It is explained as the quantity of drug substance that goes into the solution per unit time under standardized conditions of liquid/solid interface, solvent concentration and temperature. In vitro release studies were carried out in modified USP XXIII apparatus (paddle over disk) and the results are shown in (table 8,9&10).

Table 8. Dissolution test for Film formulation (SSG):

S N	Time (min)	Absorbance	Conc (µg)	Drug Release (mg)	% Drug release
1	02	0.142	1.571	1.41	28.2
2	04	0.159	2.28	2.052	41.04
3	06	0.191	3.14	2.826	56.52
4	08	0.231	3.44	3.0985	61.96
5	10	0.272	4.05	3.651	73.02
6	12	0.274	5.457	4.911	98.22

Table 9. Dissolution test for Film formulation(Doshion-100):

SN	Time (min)	Absorbance	Concentration (µg)	Drug Release (mg)
1	02	0.232	3.86	3.47
2	04	0.248	4.13	3.717
3	06	0.272	4.53	4.077
4	08	0.284	4.73	4.257
5	10	0.319	5.31	4.779
6	12	0.333	5.55	4.995

Table 10. Dissolution test for Marketed formulation:

SN	Time (min)	Absorbance	Concentration (µg)	Drug Release (mg)	% Drug release
1	5	0.229	3.81	3.429	68.58
2	10	0.235	3.91	3.519	70.38
3	15	0.268	4.46	4.014	80.28
4	20	0.273	4.55	4.095	81.9
5	25	0.299	4.98	4.482	89.64
6	30	0.331	5.51	4.959	99.18

Percentage purity of drug implementing Orthogonal Polynomials.

The absorbance readings of the standard donepezil hydrochloride solution were scanned from 231 nm to 261 nm at 2 nm intervals using 0.01N hydrochloric acid as blank. The excitation wavelength to measure the absorbance reading was set at 231 nm as the excitation maxima occurred at this wavelength. The quadratic polynomial coefficient was calculated for six points of 2 nm intervals for every segment from 231 nm to 261 nm.

The quadratic polynomial coefficient (P2f) was maximum for the segment 231 to 241 nm and hence was chosen for the method.

$P2f = +(5)\ A_{231} - (1)\ A_{233} - (4)\ A_{235} - (4)\ A_{237} - (1)\ A_{239} + (5)\ A_{241}$…Eq 1

Where A is the value of absorbance and the subscript denotes the wavelength at which it is measured and the figures in the brackets taken from standard texts on numerical analysis.(21,22)

The amount of drug content in the film formulation was calculated by using the equation 2. Vt / Vs x Ws/ Wt x A.W/D x 100 = % of the label claim. ?Eq 2 Where Ws and Wt are the weights of the standard drug and the sample preparation. A.W is the average weight of the tablet and D the labeled drug content, all the weight being reported in the mg. Vt and Vs are the values of quadratic polynomial coefficient calculated for the test and standard respectively using using -- Eq 2.

Table 11: Percent Recovery &Reproducibility for market&film

Formulation	% Recovery	% Reproducibility.
Tablet formulation.	98.7	99.0
Film formulation	98.3	98.6

Thus the assay of the drug could also be again given by :

$$\frac{\text{Polynomial coefficient}_{(film)}}{\text{Polynomial coefficient}_{(tablet)}} \times 100 \quad \text{-----Eq3}$$

Assay of the drug in film formulation -1.48/-1.48×100 = 100%.

CONCLUSION

From the results of evaluation of the films it is evident that almost all of the drug gets solubilised within less than half time when compared to that of the tablet dissolution time. Also the study compares the role of two superdisintegrants SSG and Doshion P 544D. The study concludes that the later is more superior than the former as the rate and extent of drug release with Doshion is more comparatively.Since the site of absorption of the drug is oral cavity a reduction in the dose and administration frequency could be anticipated. Also consequently the adverse effects of the drug. Although similar works have been taken up by many formulators but differently the present study has introduced the roles of superdisintegrants like the Doshion and the SSG. It is evident from the literatures of other studies that the disintegration times of their films range from about 40 seconds to 50 seconds. Present study has come up with films having disintegration times in the ranges of 20-34 seconds.The fast dissolving films in comparison to the tablet thus have proven to be more advantageous in terms of administration, quick dissolution and absorption and less metabolic distruction. The parameters like good folding endurance of the film ensures a proper strength of the formulation. Drug uniformity content and surface PH show that the film formulation is very compatible with human physiology. There is a further scope in the above study as a correlation between the rate of drug release, absorption and metabolism is yet to be established. Also the amount of drug that gets possibly flushed with the saliva is yet to be established.

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REFERENCES:

1. Aungst, B.J., Rogers, N.J., and Shefter, E., Comparison of nasal, rectal, buccal, sublingual and intramuscular insulin efficacy and the effects of a bile salt absorption promoter, The J. Pharmacol. Exp. Ther., 244:23-27, 1988.
2. Aungst, B.J. and Rogers, N.J., Site dependence of absorption-promoting actions of Laureth-9, Na salicylate, Na2EDTA, and Aprotinin on rectal, nasal, and buccal insulin delivery, Pharm. Res., 5:305-308, 1988.
3. Rathbone, M.J. and Hadgraft, J., Absorption of drugs from the human oral cavity, Int. J. Pharm., 74:9-24, 1991.
4. de Vries, M.E., Bodde, H.E., Verhoef, J.C., and Junginger, H.E., Developments in buccal drug delivery, Crit. Rev. Ther. Drug Carr. Sys., 8:271-303, 1991.
5. Squier, C.A., The permeability of oral mucosa, Crit. Rev. Oral Biol. Med., 2:13-32, 1991.
6. Bodde, H.E., De Vries, M.E., and Junginger, H.E., Mucoadhesive polymers for the buccal delivery of peptides, structure-adhesiveness relationships, J. Control. Rel., 13:225-231, 1990.
7. P Sakellariou; RC Rowe. Prog. Polym. Sci, 1995, 20, 889-942.
8. GS Banker. J. Pharm. Sci, Jan 1966, 55, 81-88.
9. LME McIndoe; RC Rowe; PJ Sheskey; SC Owen. In Handbook of Pharmaceutical Excipients, Pharmaceutical press, London, 2006, p. 128 - 130.
10. Amin A, Mishra R. Formulation development of taste-masked rapidly dissolving films of cetrizine hydrochloride. *Pharm Technol*. 2009;33(2):48–56.
11. Rowe R. 4th ed. London: Pharmaceutical Press; 2003. Handbook of Pharmaceutical Excipients.
12. Cilurzo F, Cupone I, Minghetti P, Selmin F, Montanari L. Fast dissolving films made of

maltodextrins. *Eur J Pharm Biopharm.* 2008;70:895–900. (PubMed)

13. Dzija M, Barkalow D, Chapdelaine A, Zyck D. Edible film formulations containing maltodextrin US PATENT 2003/0035841. 2003
14. Dixit R, Puthli S. Oral film technology: Overview and future potential. *J Control Release.*2009;139:94–107. (PubMed)
15. Determination of Piroxicam content in dissolution test using orthogonal polynomials. The eastern pharmacist ,April 1996.p129.
16. Spectroscopic determination of ciprofloxacin hydrochloride by orthogonal polynomial function method. The eastern pharmacist, January 1993, p123.
17. Davies P, Maloney AJF. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet. 1976;2:1403. (PubMed)
18. Perry EK, Perry RH, Blessed G, Tomlinson BE. Necropsy evidence of central cholinergic deficits in senile dementia. Lancet. 1977;1:189. (PubMed)
19. Bowen DM, Benton JS, Spillane JA, Smith CC, Allen SJ. Choline acetyltransferase activity and histopathology of frontal neocortex from biopsies of demented patients. J Neurol Sci. 1982;57:191–202. (PubMed)
20. Rogers SL, Yamanishi Y, Yamatsu K. E2020: the pharmacology of a piperidine cholinesterase inhibitor. In: Becker R, Giacobini E, editors. Cholinergic Basis for Alzheimer Therapy. Boston: Birkhäuser; 1991. pp. 314–20.
21. Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer's disease: a 15-week, double-blind, placebo-controlled study. Arch Intern Med. 1998;158:1021–31. (PubMed)
22. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology. 1998;50:136–45. (PubMed)
23. Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, Rogers SL, Friedhoff LT. The effects of donepezil in Alzheimer's disease – results from a multinational trial. Dement Geriatr Cogn Disord. 1999;10:237–44. (PubMed)
24. Mihara M, Ohnishi A, Tomono Y, Hasegawa J, Shimamura Y, Yamazaki K, Morishita N. Pharmacokinetics of E2020 – a new compound for Alzheimer's disease, in healthy male volunteers. Int J Clin Pharmacol Ther Toxicol. 1993;31:223–9. (PubMed)
25. ARICEPT® (donepezil hydrochloride tablets) Teaneck, NJ: Eisai Inc; 2000. US Package Insert December.
26. Tiseo PJ, Perdomo CA, Friedhoff LT. Metabolism and elimination of ^{14}C-donepezil in healthy volunteers: a single-dose study. Br J Clin Pharmacol. 1998;46(Suppl. 1):19–24. (PMC free article) (PubMed)