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Original Article

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF DONEPEZIL HYDROCHLORIDE

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ABSTRACT

Objective: The present study was aimed to develop the formulation and *in vitro* evaluation of Orodispersible tablets by wet granulation method using Donepezil HCl as a model drug to enhance patient compliance.

Methods: In the wet granulation method, a mixture of microcrystalline cellulose and hydroxypropyl methylcellulose were used along with superdisintegrants, i.e., croscarmellose sodium and crospovidone. The prepared granules were subjected to both pre and post-compression evaluation parameters including; FTIR spectroscopy, micromeritics properties, tablet weight variation, hardness, friability, drug content, disintegration time and *in vitro* drug release.

Results: FTIR studies indicated that there was nointeraction between the drug and the excipients used. The formulation containing high concentration of crospovidone and mixture as the best formulation F2 based on *in vitro* drug release characteristics of tablet formulation.

Conclusion: The results of this work suggested that orodispersible tablets of Donepezil hydrochloride with rapid disintegration time, fast drug release and good hardness can be efficiently and successfully formulated by wet granulation method.

Keywords: Orodispersible tablets, Donepezil, Superdisintegrants, Wet granulation method

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INTRODUCTION

Novel drug delivery system (NDDS) aims to improve safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance; one such approach is orodispersible tablets [1-4]. Donepezil hydrochloride is a new anti-alzheimer drug. Itisthepotentacetyl choline sterase inhibitor Chemically 2,3-Dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4piperidinyl*)* methyl)-1H-inden-1-one hydrochloride. Donepezil hydrochloride is apiperidine type reversible based inhibitor of the enzyme acetylcholinesterase (AChE) and has been approved for the symptomatic treatment of mild to moderate alzheimer's disease [5-6]. Donepezil hydrochloride is available in white crystalline powder which 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 [7]. The main object of the present study is to develop an orodispersible tablet of donepezil HCl by wet granulation method using different superdisintegrants like croscarmellose sodium and crospovidone along with microcrystalline cellulose and hydroxypropylmethylcellulose in different ratiosto achieve rapid dissolution of drug and absorption, quick onset of action, to leave minimal or no residue in mouth, to improve better patient compliance.

MATERIALS AND METHODS

Donepezil HCl was a gift sample from ESaiPharma, Parawada, and Visakhapatnam, India. HPMC, CCS, CP, MCC were procured from Merck Pvt limited. Analytical reagent grade chemicals were used in the following study.

Preparation of or dispersible tablets by wet granulation method

All the ingredients were weighed according to the formulation. Microcrystalline cellulose and intragranular portion of croscarmellose sodium or crospovidone were mixed in a mortar and then uniformly triturated for 5 min. Binder solution (isopropyl alcohol and water (90:10) ratio equivalent to 40% w/w of dry mix was added to donepezil hydrochloride and hydroxypropyl methylcellulose under stirring to get clear solution. Binder solution is added drop by drop to the mixture to obtain the wet mass and subjected to sieve #12 to obtain wet granules. Wet granules were then dried at room temperature. Dry granules obtained were passed through sieve #25. Extra granular portion of croscarmellose sodium or crospovidone and sodium saccharin were added granules. Finally, magnesium stearate and talc were added and then compressed into a tablet as shown in table 1.

Table 1: Formulation of donepezil HCl by wet granulation method

S. No.	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Donepezil HCL	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
HPMC	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg
CCS	I 8 mg	-	2 mg	6 mg	4 mg	6 mg	4 mg	-	-
	E 4 mg	-	1 mg	3 mg	2 mg	3 mg	2 mg	-	-
CP	I -	8 mg	6 mg	2 mg	4 mg	-	-	6 mg	4 mg
	E -	4 mg	3 mg	1 mg	2 mg	-	-	3 mg	2 mg
MCC	122 mg	122 mg	122 mg	122 mg	122 mg	125 mg	128 mg	125 mg	128 mg
Sodium saccharin	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Mg. stearate	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg
Talc	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg
Total	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg

Precompression studies

Fourier transform infrared spectroscopy (FT-IR)

The interaction between the drug and polymer was studied by FT-IR. To produce a stable product, the drug and polymer must be compatible with one another. Drug and polymer interactions were studied by using FT-IR (Shimadzu, Japan model–8400S) as per the method. IR spectral analysis of pure donepezil hydrochloride, croscarmellose sodium, crospovidone, sodium saccharin, microcrystalline cellulose was carried out. No change in peaks of mixture compared to pure drug indicates the absence of interactions.

Angle of repose

The angle of repose of the powder blend was determined by employing funnel method. Powder blend which was accurately weighed was taken in funnel and was allowed to flow through the funnel freely onto the surface. Angle of repose was calculated by measuring the diameter of the powder cone and three successive determinations were performed.

Bulk density

Weighed quantity of 2 g powder was introduced into a measuring cylinder. After determination of initial volume, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals and the tapping was continued until no further change in volume was noted. LBD and TBD were calculated. The determination was carried out in triplicate [8].

Compressibility index and hausner ratio

The compressibility index and hausner Ratio of the powder blend for each powder blend. Three determinations were done for each formula [9].

Post compression studies

Uniformity of weight

Individually twenty tablets were selected at random and weighed accurately. The average weight of individual tablets was compared for the determination of weight variation.

Hardness

The tablet hardness is the force required to break a tablet in a diametric compression force. In this Monsanto hardness tester was used for applies force to the tablet diametrically.

Friability

The friability (F) was measured using Roche friabilator (ERWEKA, Germany) and the test was performed for 20 tablets. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. Friability below 1% was considered acceptable [10].

Content uniformity

Donepezil HCl powder of 5 mg was extracted into methanol and filtered and the drug content was determined by measuring the UV-Visible spectrophotometer [11] absorbance at 230 nm after appropriate dilution with methanol.

Wetting time

A piece of double-folded tissue paper was placed in a Petri plate having an internal diameter 6.5 cm and containing 6 ml of water and the preweighed tablet was placed and the complete wetting time of the tablet was measured in seconds. The wetted tablet was then weighed.

***In vitro* disintegration time**

Disintegration test of the prepared tabletswas carried out at (37±2) °C in 900 ml of distilled water using a disintegration test apparatus. Disintegration time of six individual tablets were recorded and carried out at (37±2) °C in 900 ml of distilled water [12].

***In vitro* dissolution study**

Dissolution studies of donepezil HCl orodispersible tablets was studied in USP XXIII Type-II dissolution apparatus (Electrolab, Model-TDT 06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5 °C as dissolution medium and measured the absorbance at 230 nm against blank by UV-Visible spectrophotometer [11].

RESULTS AND DISCUSSION

FTIR studies

From the FT-IR spectra, the interference was verified and found that donepezil hydrochloride did not interfere with the excipients used. In comparison with the pure donepezil hydrochloride, the absorption peak of the spectra showed no shift and no disappearance of characteristics peaks suggested that there is no interaction between the drug and other additives. No degradation of donepezil hydrochloride molecule was observed during its formulation development; hence the drug excipient combinations used in the formulation development were compatible as shown in fig. 1 and 2.

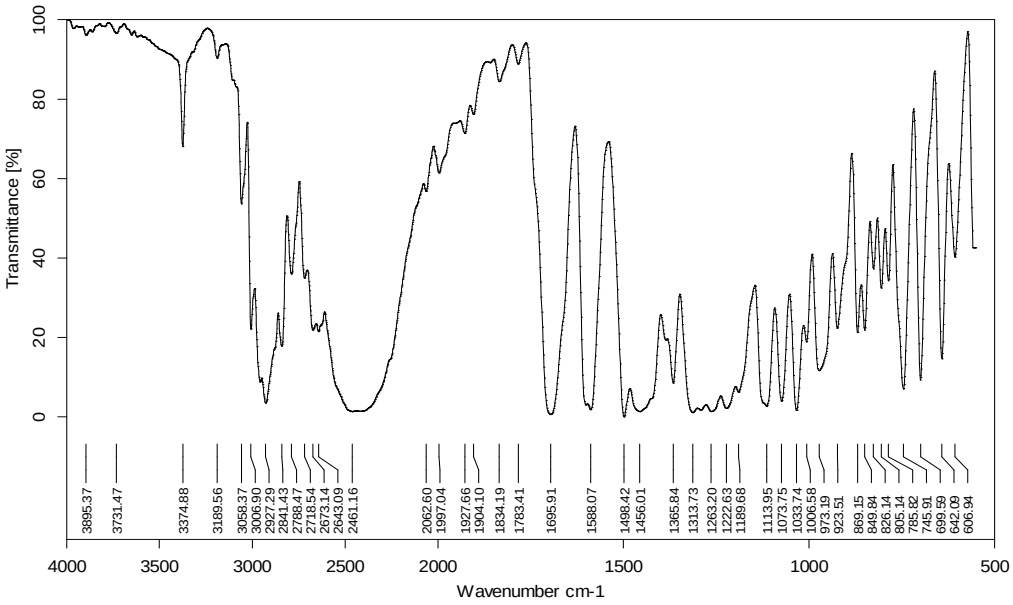

Fig. 1: FTIR spectrum of donepezil hydrochloride

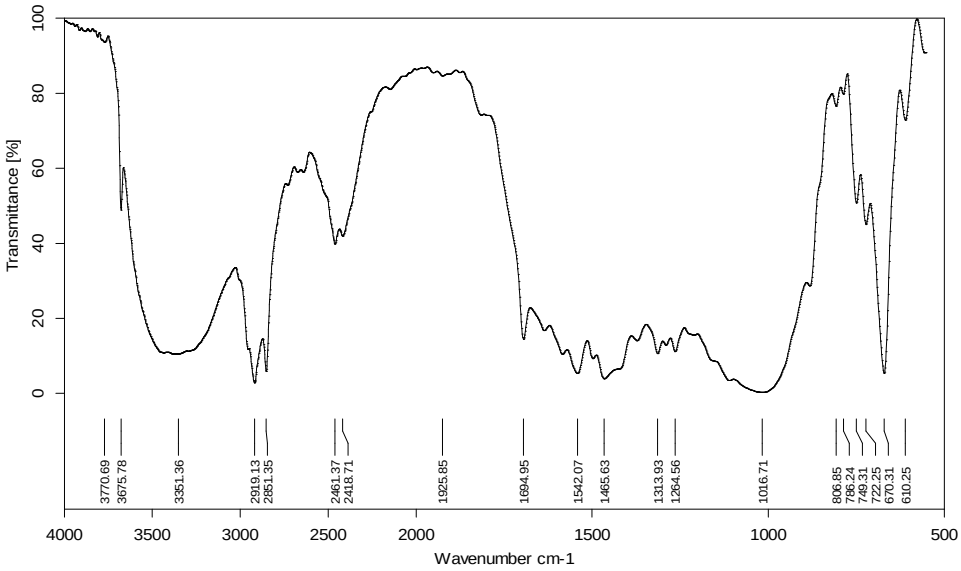

Fig. 2: FTIR spectrum of donepezil hydrochloride+excipients

Table 2: Precompression studies

Formulation	Loose bulk density (g/ml)	Tapped bulk density (g/ml)	Angle of repose (θ)	Carr's index	Hausner's ratio
FI	0.572±0.025	0.652±0.032	24.15±0.025	14.30±0.023	1.18±0.024
F2	0.589±0.023	o.663±0.036	24.75±0.024	14.23±0.024	1.17±0.034
F3	0.698±0.025	0.723±0.042	25.67±0.024	14.50±0.025	1.15±0.034
F4	0.584±0.035	0.661±0.032	24.35±0.026	12.60±0.024	1.12±0.035
F5	0.598±0.026	0.698±0.041	24.68±0.024	12.75±0.026	1.13±0.034
F6	0.628±0.027	0.735±0.034	25.96±0.026	13.27±0.024	1.15±0.034
F7	0.647±0.028	0.715±0.034	25.12±0.027	13.20±0.034	1.16±0.034
F8	0.688±0.025	0.759±0.031	27.75±0.028	14.40±0.045	1.18±0.035
F9	0.737±0.35	0.788±0.035	28.68±0.024	14.25±0.023	1.19±0.035

Precompression studies

Angle of repose (θ): All formulation showed angle of repose within 28 ° which indicates excellent flow of powder mixture as shown in table 2.

Bulk density

Loose bulk density and tapped bulk density for all formulations varied from 0.572 gm/cm^2 to 0.737 gm/cm^2 and 0.652 gm/cm^2 to 0.788 gm/cm^{2}respectively. The values were within acceptable range with minimum difference found between loose bulk density and tapped bulk density.

Compressibility index

Compressibility of all formulations lies within the range of 12.60 to 14.40, which showed good compressibility.

Post compression studies

Uniformity of weight

The average weight of the formulation was 150 mg. All the tablets passed weight variation testas the % weight variation was within the Pharmacopoeial limits of±10%. The weights of all the tablets were found to be uniform.

Hardness test

Hardness test was performed by Monsanto tester. It was found to be within 2.9 kg/cm^{2}to 4.9 kg/cm^2. The lower standard deviations values indicated that the hardness of all the formulations was almost uniform and possess good mechanical strength. Superdisintegarnts like croscarmellose sodium and crospovidone were added for fast disintegration in the saliva as shown in table 3.

Table 3: Post compression studies

Formulations	Uniformity of weight(mg)#	Hardness (kg/cm²)*	Friability (%)#	Wetting time (sec)	Drug content	Disintegration time (sec)
F1	150.12±0.24	4.2±0.2	0.03±0.13	27±0.9	97.21±3.86	19±3.86
F2	149.47±0.3	3.9±0.3	0.04±0.21	26±0.5	99.08±3.12	14±3.12
F3	149.9±0.3	3±0.3	0.2±0.35	22±0.5	97.45±2.88	16±2.88
F4	150.28±0.47	2.6±0.4	0.34±0.34	24±0.2	99.35±2.54	38±2.54
F5	149.89±0.38	3.0±0.3	0.05±0.21	21±0.3	98.614±3.12	26±3.12
F6	150.34±0.52	2.9±0.1	0.57±0.31	29±0.4	101.45±2.64	48±2.64
F7	150.±0.99	3.3±0.4	0.37±0.24	28±0.5	98.317±3.15	59±3.15
F8	150±0.30	3.4±0.2	0.36±0.25	22±0.4	99.478±2.14	32±2.14
F9	150.01±0.26	2.6±0.3	0.23±0.31	27±0.1	99.57±1.95	44±1.95

Friability

All formulations possess good mechanical strength as the values were found well within the approved range (<1%).

Content uniformity

The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 97.21±3.86 mg to 99.08±3.12 mg to 99.35±2.54 mg to 101.45±2.64 mg. The results indicated that, in all the formulations, the drug content was uniform. The percentage drug released by each tablet in the *in vitro* release studies were based on the mean content of the drug present in the respective tablet.

Wetting time:

Wetting time of the tablet containing Croscarmellose sodium and crospovidone was 27 seconds. Wetting time of the tablet containing crospovidine was 20 sec. The disintegration time of the formulation in the oral cavity increases with an increase in the wetting time. To shorten the disintegrations time in the oral cavity, the addition of the disintegrant having a property of quick water uptake in the formulation would be preferable. It was considered that the rapid disintegration would be due to its wettability. All superdisintegrants have high water absorption capacity and wicking property, which leads to faster swelling of the disintegrants. The Tablet containing croscarmellose sodium significantly swelled and loosed on shape. Observed results suggested that the disintegrants added to tablet formulation might cause the penetration of water in the tablet, and the penetration rate of water would be altered. This parameter also duplicates disintegrant ion time in oral cavity as tablet is kept motionless on tongue: hence the correlation between wetting time and disintegration time in oral cavity can also be made.

***In vitro* disintegration time**

The internal structure of tablets such as pore size distribution, water penetration in to tablets and swelling of disintegration substance suggested mechanism of disintegration. All the formulations showed disintegration time less than 30 seconds. Disintegration time, which is affected by the hardness of the tablet, is related to the nature of the disintegrant agent that allows the tablet to break up in to smaller fragments upon contact with physiological fluid. The content of the superdisintegrant agent ranges between 1% to 6% w/w. This parameter appears to be the main factor responsible for the difference in the disintegrating time.

***In vitro* dissolution studies**

All the nine formulations were subjected for *in vitro* dissolution studies using tablet dissolution test Lab India D S8000. The samples were withdrawn at different time intervals and analyzed at 230 nm. Cumulative drug release and cumulative % drug retained were calculated.

Percentage drug release of formulations

The cumulative drug release of donepezil hydrochloride released as a function of time (t) following zero-order for formulations F1, F2, F3, F4, F5, and F6, F7, F8, F9. The log % drug undissolved Vs time (min) for formulations F1, F2, F3, F4,F5 and F6, F7,F8, F9 followed first-order kinetics. Donepezil hydrochloride orodisintegrating formulations F2, F8, F9 was found to be 99±2.89, 99±0.96, 99±2.14 release and for F1, F6 and F7 formulations 99±2.6, 99±3.08 and 99±0.97 and F3, F4,F5 formulations was found to release 99±3.08, 98±1.65, 99±1.6 of donepezil hydrochloride respectively at end of 20 min in table 4. In all formulations, the drug release was nearly 100 % within 20 min. Oro-disintegrating tablets are designed to disaggregate in the oral cavity and release the active agent to dissolve remarkably fast in the saliva. The release of the drug from all the formulations containing the crospovidone as superdisintegrant was found to be 4.8% after 5 min as shown in fig. 3 to fig. 8 The association with microcrystalline cellulose promotes the release, with respect to pure drug despite the favorable pH of the dissolution medium and also could limit the contact of the drug with mouth mucosa, besides preventing dumping as a possible side effect. The presence of the superdisintegrants CCS and CP in the formulations F2, F3 produced tablets that dissolved fastly. It was in fact, reported that a close association between a drug and superdisintegrants enables the formation of a state suitable to improve the dissolution rate in the present case.

Table 4: Drug release (%) of formulations

Time (min)	Percentage drug released (x±sd)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	48±3.4	57±4.52	52±3.65	40±3.67	47±1.35	28±0.9	24±2.4	33±0.96	26±0.96
5	88±2.4	94±2.85	89±2.43	79±2.44	88±2.35	60±1.65	52±3.1	68±1.65	61±1.25
10	96±2.8	99±2.84	96±3.62	89±2.14	96±2.51	80±2.43	76±1.6	88±1.44	86±2.45
15	98±2.5	99±1.89	99±1.60	98±0.96	98±1.65	96±1.60	92±0.96	99±2.14	96±2.14
20	98±5	99±2.84	99±3.08	98±1.65	99±1.6	99±3.80	98±0.97	99±0.96	99±2.14

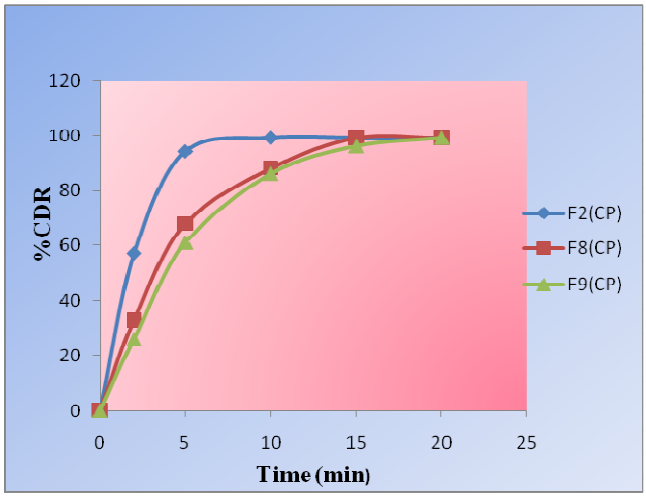

Fig. 3: Dissolution profile for F2, F8, and F9

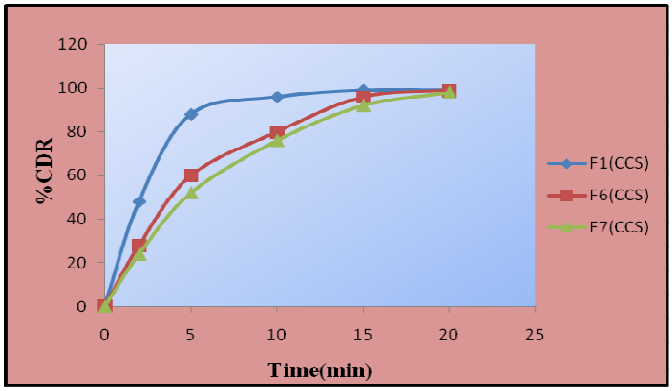

Fig. 4: Dissolution profile for F1, F6, and F7

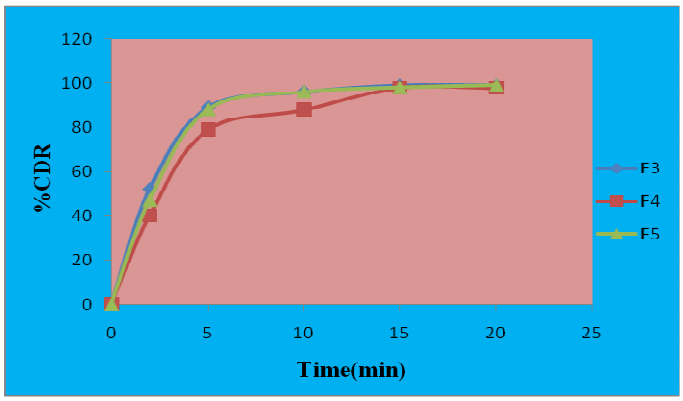

Fig. 5: Dissolution profile for F3, F4, F5 (CCS=CP)

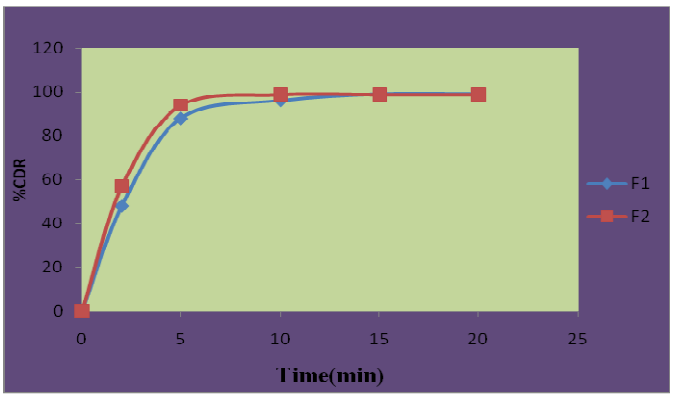

Fig. 6: Dissolution profile for F1 and F2 (CCS=CP 12 mg)

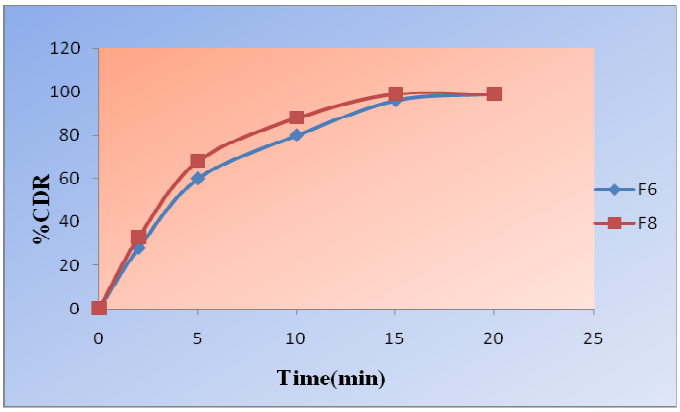

Fig. 7: Dissolution profile for F6, F8 (9 mg) formulation

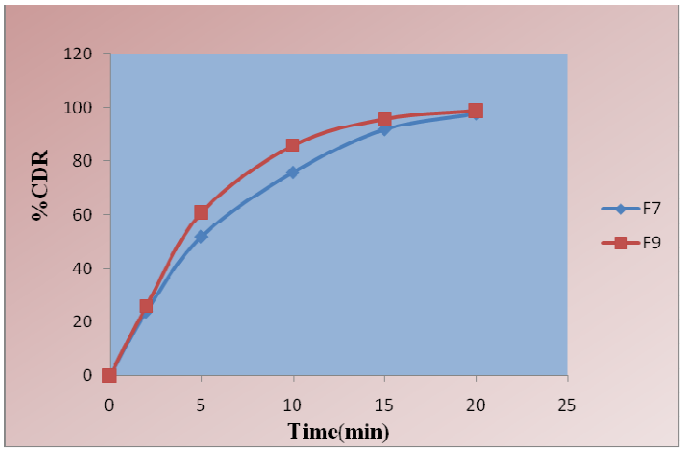

Fig. 8: Dissolution profile for F7, F9 (6 mg) formulation

Table 5: Dissolution efficiency$_{10}$, $T_{50\%}$, $T_{90\%}$

Formulations	DE_{10}	$T_{50\%}$	$T_{90\%}$
F1	71.2	3.34	13.17
F2	76.6	2.195	12.688
F3	72.6	2.998	13.075
F4	47	4.602	13.981
F5	70.95	3.425	13.252
F6	51	6.439	14.924
F7	48.8	7.196	15.598
F8	57.45	5.338	14.116
F9	52.4	6.152	14.651

Table 6: Correlation coefficient values of zero order and first order (R^2)

Formulations	Zero order	First order
F1	0.624	0.997
F2	0.5484	0.9876
F3	0.6045	0.9607
F4	0.7128	0.9466
F5	0.6248	0.9477
F6	0.8599	0.9715
F7	0.9009	0.9834
F8	0.7946	0.9978
F9	0.8385	0.9961

Dissolution efficiency

The formulations F2, F3, F1 and F5 got good dissolution efficiency values compared to F8, F9, F6, F4, and F7. This indicated increased dissolution rate in F2, F3, F1 and F5 compared to F8, F9, F6, F4, F7 formulations, as shown in table 5.

The correlation coefficient values in the analysis of release data as per different kinetic models were also studied.

Zero-order Correlation coefficient (R^2) of all the formulations (F1-F9) was found to be in the range from 0.624 to 0.8385 and first order Correlation coefficient (R^2) of all the formulations (F1-F9) is ranging from 0.997 to 0.9961. This indicated that all the formulations followed first-order release rate are shown in table 6.

CONCLUSION

An attempt was done to develop orodispersible tablets of Donepezil hydrochloride with an objective to improve bioavailability. FTIR spectra revealed that, superdisintegrants and excipients used were compatible with drug. The formulated tablets showed compliances for various physiochemical parameters viz. hardness, friability, weight variation, content uniformity and disintegration.

In vitro disintegration and wetting, studies indicated good results. Water absorption studies also indicated good absorptive in all formulation. *in vitro* release studies of drug for all the formulations revealed that 99% of the drug was released from the formulations within ten minutes. Formulation F2 showed faster drug released. The wet granulation technique may be utilized in preparing orodispersable tablets. Hence the overall objective of the investigation was fulfilled.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declare none

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