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Formulation and Development of Orodispersible Tablet of Donepezil Hydrochloride by Effervescent Method

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ABSTRACT

Background: The present study was aimed towards the formulation and *in vitro* evaluation of Orodispersible tablets by effervescent method using Donepezil HCl as a model drug to enhance patient compliance. Donepezil is a centrally acting reversible acetyl-cholinesterase inhibitor, its main therapeutic use in the palliative treatment of Alzheimer's disease.

Method: In the effervescent method, mixture of sodium bicarbonate and citric acid were used along with superdisintegrants, i.e., sodium starch glycolate, croscarmellose sodium and crospovidone. The prepared powder mixtures were subjected to both pre and post compression evaluation parameters including; FTIR spectroscopy, micromeritics properties, tablet weight variation, hardness, friability, drug content, wetting time, disintegration time and *in-vitro* drug release.

Results: FTIR studies indicated that there was no interaction between the drug and the excipients used. The hardness and friability test reports revealed that the tablets had a good mechanical strength and resistance. The formulation containing high concentration of crospovidone and mixture of effervescent emerged as the best formulation based on *in vitro* drug release characteristics compared to commercial conventional tablet formulation.

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

Key words: Orodispersible tablets, Donepezil, Alzheimer disease, Superdisintegrants, Effervescent.

Introduction

In spite of remarkable advancements in drug delivery, the oral route remains the faultless route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance. Patient ease and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self administration even without water or chewing. Recent advances in technology have presented viable dosage alternatives for patients who have difficulty in swallowing tablets or capsules. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Recent advances in novel drug delivery systems (NDDS) aim 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. It is the potent acetyl cholinesterase inhibitor 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[5,6]. 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 [7].

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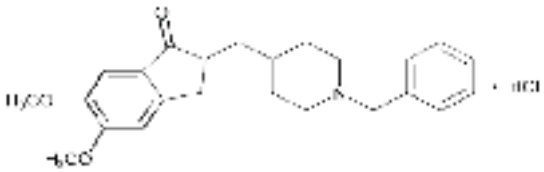


Aim and Objective

The main object of present study is to develop a orodispersible tablet of donepezil HCl by effervescent method using different superdisintegrants like sodium starch glycolate, croscarmellose sodium and crospovidone along with sodium bicarbonate and citric acid in different ratios were used to get high tablet hardness, fast oral disintegration rate to achieve rapid dissolution of drug and absorption which may generate quick onset of action, to leave minimal or no residue in mouth, to improve the quality of life and better patient compliance.

Materials

Donepezil HCl was a gift sample from Actavis Pharmaceuticals, Chennai, India. Sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone (CP) were gift samples from Wockhardt Research Centre, Aurangabad, India. Directly compressible mannitol (Pearlitol SD 200) were generous gifts from Strides Acrolabs, Bangalore, India. All the other chemicals used were of analytical reagent grade.

Methods

Preparation of orodispersible tablets by effervescent method

Orodispersible tablets of donepezil HCl were prepared by effervescent method [6] according to the formulae. Sodium bicarbonate and citric acid were preheated at a temperature of 80° to remove fascinated/enduring moisture and were thoroughly mixed in a mortar to get a uniform powder and then added to other ingredients. The ingredients after shifting through sieve No. 44 were thoroughly mixed in a tumbling cylindrical blender (fabricated in our laboratory). The blend thus obtained was directly compressed using 8 mm round flat beveled edge punches to get tablets of 100 mg weight on 10-station rotary tablet machine (Clit, Ahmadabad). A batch of 50 tablets were prepared for all the designed formulations which is illustrated in table 1[12].

Table 1:
Composition of donepezil HCl tablets

Ingredients	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Donepezil HCl	05	05	05	05	05	05	05	05	05	05
Sodium bicarbonate	15	15	15	15	15	15	15	15	15	15
Citric acid	10	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	-	03	06	09	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	03	06	09	-	-	-
Crospovidone	-	-	-	-	-	-	-	03	06	09
Aspartame	04	04	04	04	04	04	04	04	04	04
Mannitol	40	40	40	40	40	40	40	40	40	40
Microcrystalline cellulose	21	18	15	12	18	15	12	18	15	12
Magnesium stearate	03	03	03	03	03	03	03	03	03	03
Purified talc	02	02	02	02	02	02	02	02	02	02
Total	100	100	100	100	100	100	100	100	100	100

PRE COMPRESSION STUDIES

Fourier transform infrared spectroscopy

It was used to study the interactions between the drug and polymer. The drug and polymer must be compatible with one another to produce a stable product. Drug and polymer interactions were studied by using FT-IR (Shimadzu, Japan model – 8400S) as per the method. IR spectral analysis of pure norfloxacin, guar gum, xanthan gum, norfloxacin with xanthan gum, norfloxacin with guar gum were carried out. The peak and patterns produced by the pure drug were compared with combination of pure drug and polymer [13].

Angle of repose (θ°)

The angle of repose of powder blends were determined by the funnel method. Accurately weighed powder blends were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex

of the heap of the powder blends . The powder blends were allowed to flow through the funnel freely onto its surface. The diameter of the powder cone was measured and angle of repose was calculated. Three determinations were performed [6].

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was determined, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated. The determination was carried out in triplicate [13].

Compressibility index and Hausner ratio

The compressibility index of the powder blends were determined by Carr's compressibility index or Carr's index (CI). Hausner ratio (HR) was also determined for each powder blend .Three determinations were done for each formula [12].

POST COMPRESSION STUDIES

Weight variation

Twenty tablets were selected at random and weighted individually. The individual weights were compared with the average weight for determination of weight variation[8].

Hardness

The tablet hardness is the force required to break a tablet in a diametric compression force. monsanto hardness tester was used in this study. This tester applies force to the tablet diametrically. The test was performed on six tablets and the average was calculated [9].

Friability

The friability (F) of a sample of 20 tablets were measured using Roche friabilator ((ERWEKA, Germany). Twenty tablets were weighed, rotated at 25 rpm for 4 min. 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

For content uniformity test, ten tablets were weighed and powdered. The powder equivalent to 5 mg of donepezil HCl was extracted into methanol and liquid was filtered. The drug content was determined by measuring the absorbance at 230 nm after appropriate dilution with methanol. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations [9].

Wetting time

A piece of tissue paper folded double was placed in a petri plate (internal diameter is 6.5 cm) containing 6 mL of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in minutes [7].

Disintegration time

In vitro disintegration time of the prepared tablets were carried out at (37 ± 2) ºC in 900 mL of distilled water. Using a disintegration test apparatus. Disintegration time of 6 individual tablets were recorded and carried out at (37± 2) ºC in 900 mL of distilled water [10].

***In vitro* dissolution study**

In vitro dissolution 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° as dissolution medium [8].

RESULTS AND DISCUSSION

Table - 2
Pre compression studies

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Mean Carr'x index %	Hausner'sratio
F1	0.50±0.005	0.64±0.02	30.6±0.28	14±2.41	1.16±0.03
F2	0.53±0.007	0.63±0.01	29.1±0.25	15±1.67	1.18±0.02
F3	0.54±0.020	0.63±0.009	29.7±0.23	14±2.39	1.10±0.09
F4	0.57±0.25	0.66±0.19	29.3±0.23	15±0.31	1.25±0.14
F5	0.55±0.07	0.65±0.01	27.7±0.35	15±1.39	1.14±0.03
F6	0.49±0.31	0.55±0.15	27.3±0.25	18.9±0.41	1.23±0.16
F7	0.48±0.42	0.52±0.27	26.4±0.55	15.7±0.28	1.18±0.13
F8	0.49±0.40	0.58±0.3	29.6±0.43	19.8±0.09	1.24±0.19
F9	0.50±0.16	0.62±0.22	27.2±0.09	20.1±0.31	1.24±0.07

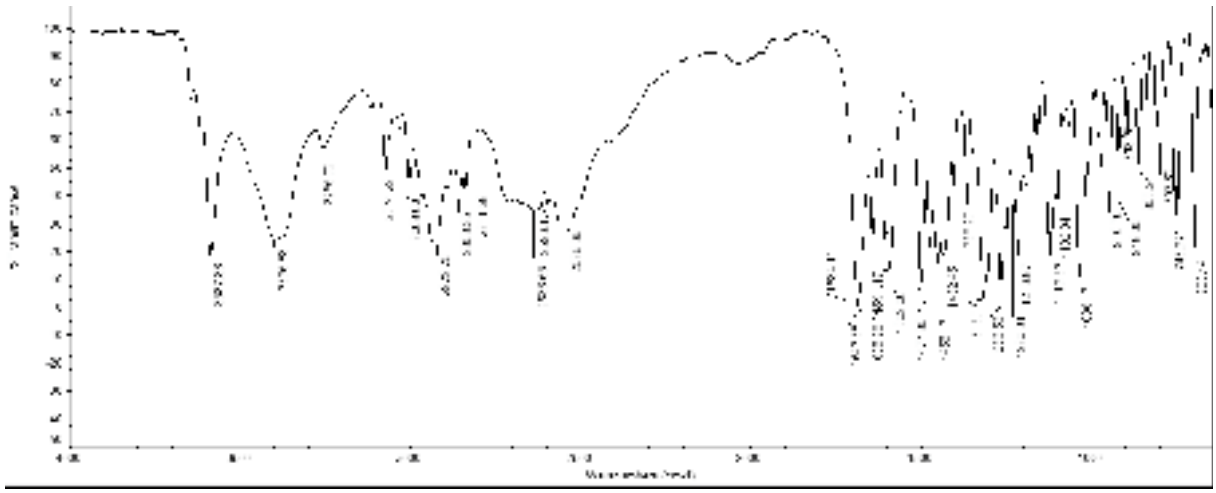
Table - 3
Post compression studies

Formulation	Weight variation (gm)	Hardness (kg/cm2)	Friability %	Drug content %	Wetting Time (sec)	Disintegration time (sec)
F1	2.2±0.42	2.4±0.13	0.58±0.13	97.28	22±0.9	27±2.1
F2	3.2±0.31	2.5±0.14	0.53±0.25	96.41	21±1.3	23±2.6
F3	4.2±0.48	3.6±0.12	0.74±0.32	96.86	16±1.7	18±2.7
F4	2.5±0.51	3.2±0.27	0.33±0.21	96.92	31±1.3	33±2.1
F5	3.8±0.47	3.0±0.23	0.48±0.37	97.85	23±1.5	26±1.3
F6	2.3±0.63	2.8±0.48	0.67±0.13	98.13	30±1.7	32±1.7
F7	3.9±0.71	3.3±0.17	0.36±0.42	97.79	16±0.8	17±2.3
F8	2.1±0.18	3.4±0.27	0.58±0.31	98.24	13±1.6	14±2.8
F9	3.3±0.49	3.8±0.65	0.75±0.33	98.78	10±0.6	10±2.3

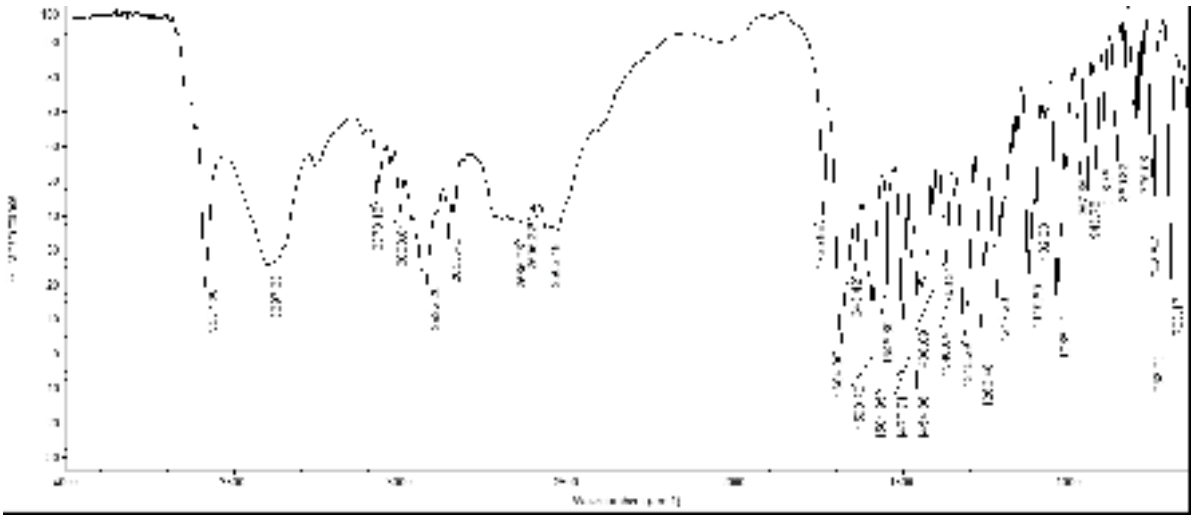
Table - 4
***In vitro* drug release study**

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	Aricept
2	15.7	19.6	14.9	24.8	28.4	28.3	22.3	26.2	27.9	13.6
4	21.4	23.3	21.9	27.9	33.3	30.9	28.9	29.4	30.5	19.8
6	24.9	29.7	26.6	30.1	37.4	39.6	33.6	35.6	37.8	27.4
8	33.9	36.1	31.4	36.8	42.1	48.7	47.1	47.9	49.3	33.9
10	46.2	43.6	40.7	42.5	48.8	61.4	57.2	58.3	58.6	44.2
12	50.8	63.1	57.2	49.6	61.9	77.9	74.3	76.1	77.9	60.3
14	64.7	67.3	63.4	69.2	68.8	82.5	81.7	82.7	83.4	67.9
16	73.8	72.2	69.9	79.9	79	90.6	90.9	92.5	93.7	76.6
18	82.5	80.6	82.1	88.7	92.8	98.3	95.3	97.2	98.8	89.5

FT-IR Report for Donepezil HCl



FT-IR Report for Donepezil and Excipients



From the FT-IR spectra the interference was verified and found that donepezil did not interfere with the excipients used.

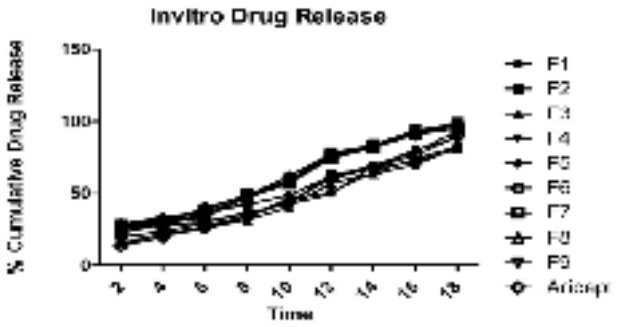
Effervescent method was established to manufacture orodispersible tablets of Donepezil HCl. Orodispersible tablets of donepezil were successfully prepared using effervescent and superdisintegrants of sodium starch glycolate, croscarmellose sodium and crospovidone in each formulation. Weight variations of all the formulations were observed which were within the acceptable limit for uncoated tablets as per United States Pharmacopoeia.

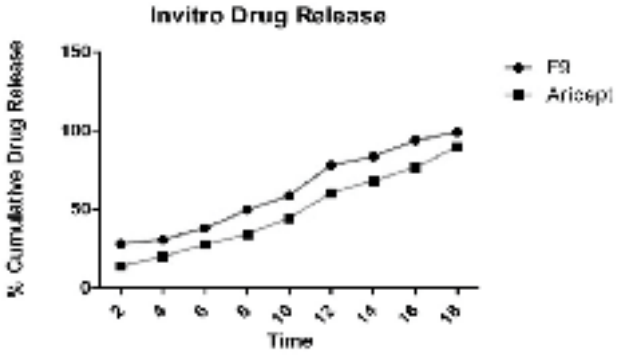
One of the primary requirements of immediate release preparation is faster disintegration. It is well known to formulation scientists that the tablets with higher crushing strength show longer disintegration time. Since mechanical integrity is of paramount importance in successful formulation of fast disintegrating tablets. The hardness of tablets were determined and was found to be in the range of 2.4 to 3.8 kg/cm^2. But friability was observed between 0.58 to 0.75%, which was not within the acceptable limit.

The wetting time for all the formulations were found to be (10±0.6) to (22±0.9) seconds. The tablets were subjected for evaluation of *in vitro* disintegration time. *In vitro* disintegration time for formulations F9 was 10 secs.

Based on the *in vitro* drug release study, F9 was identified as the best formulation among all the other formulations and *in vitro* release profiles was more than 98% within 20 minutes.

The formulation F9 contains high concentration of crospovidone and effervescent substance which causes the rapid disintegration. It causes the maximum *in vitro* dispersion within 10 sec, hence the formulation F9 was optimized after conducting the reproducibility study.





in vitro release rate of formulation F9 was compared with marketed product Aricept. F9 shows rapid drug release than marketed product and its graphically illustrated.

Conclusion

The results of this study revealed that the amount of sodium bicarbonate, citric acid, sodium starch glycolate, croscarmellose sodium and crospovidone significantly affect disintegration time, hardness and percentage friability. Thus it is concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Effervescent method would be

an effective alternative approach compared with the use of more expensive adjuvant in the formulation of fast dissolving tablets.

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