AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Solid Dispersion Method for Design of Donepezil Orodispersible Tablets: Formulation & Characterization

Naga Sai D[1], Krishna Veni V[1], Chandra Sekhar SB[2], Bhavani B*[1]
1.Koringa College of Pharmacy, Tallarevu, East Godavari
2.Drug Testing Laboratory, Karnataka

ABSTRACT

Donepezil HCl is an anti Alzheimer's drug of the acetylcholinesterase class. It is widely used in treatment of Alzheimer's disease and to control dementia. Orodispersable Tablets (ODTs) containing Donepezil HCl was prepared using super-disintegrant (croscarmellose sodium) by direct compression method using solid dispersion technique to mask the taste of the drug. Three types of excipient were used to mask the taste namely Mannitol, PEG 6000 and PVP K 30 in three different ratios (i.e. 1:1, 1:2, 1:3) using solvent evaporation method in solid dispersion technique. The optimized formulation shows the minimum disintegration time of 50 sec and release maximum amount of drug in 10 min. Short term stability studies indicated no significant changes in hardness, friability, *in vitro* disintegration time, drug content and *in vitro* drug release.

Keywords: Donepezil HCl, Solid dispersion, Oral dispersible tablet

*Corresponding Author Email: bhavani2008@gmail.com
Received 05 May 2019, Accepted 20 May 2019

Please cite this article as: Bhavani B *et al*., Solid Dispersion Method for Design of Donepezil Orodispersible Tablets: Formulation & Characterization. American Journal of PharmTech Research 2019.

INTRODUCTION

For the past two decades there is an enhanced demand for patients' compliance dosage forms. As a result, the demand for the technologies is been increasing three fold annually. Since the development cost of a new chemical or a drug molecule is very high, the pharmaceutical companies are focusing on development of New Drug Delivery Systems for existing drugs with an improved efficacy and bioavailability together with reducing dosing frequency to minimize side effects. The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance.

Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. The benefits in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market. Some drugs are absorbed from the mouth, pharynx and oesophagus when the saliva passes down into the stomach, in such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [1,2].

Many elderly persons have the difficulties in taking conventional dosage forms like solutions, suspensions, tablets, capsules etc. In some cases, such as motion sickness, sudden episodes of allergic attack or coughing and unavailability of water, swallowing tablets may become difficult. To fulfil these medical needs the pharmaceutical technologists have devoted considerable effort to develop a novel type of dosage form for oral administration, the Oro Dispersible Tablets, tablets that dissolve or disintegrate rapidly in the saliva without the need of drinking water. The Oro Dispersible Tablets usually dissolve in the oral cavity within 15 seconds to 3 minutes. The faster the drug is going in to the solution, the quicker the absorption and onset of clinical effect. Some drugs, which are soluble in saliva rapidly, absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach thus avoids first pass metabolism and enhance the bioavailability.

Solid dispersions (SDs) traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs [3]. Solid dispersion means the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state prepared by the fusion, solvent or solvent–fusion method. Solid dispersions prepared by

kneading and physical mixture method are widely and successfully applied to improve the solubility and consequently the bioavailability of poorly soluble drugs.

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 $C_{24}H_{29}NO_3HCl$ 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 [4,5]. 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 [6].

The aim of this study was to improve the dissolution rate of donepezil HCl and thereby increase solubility. Hence, solid dispersion by solvent evaporation technique was chosen to enhance the dissolution rate of donepezil.

MATERIALS AND METHOD

Materials

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

Methodology

Preparation of solid dispersion

For the formulation of ODTs, the most easy and economical method direct compression was selected. This is one the most widely used methods. Three approaches were designed to be used for this research work i.e, solid dispersions of drug with Mannitol, PEG 6000, PVP K 30 in three different ratios (1:1, 1:2, 1:3) as shown in Table 1. Solid dispersions of donepezil and polymer such as mannitol, PVP K30 and PEG-6000 were prepared by solvent evaporation method. The ratio of drug to polymer was taken as 1:1, 1:2 and 1:3. Composition of each ingredient is shown in Table 1. The drug and polymer were separately dissolved in sufficient quantity of methanol. The clear solutions of extract and polymer were mixed and then the solvent was evaporated in water bath at 50°C till dryness. The dried sample of dispersion was kept in desiccator until further study. To this dried dispersion required quantity of CCS, lactose, lubricant & glidant were added respectively and then pulverized using a mortar and pestle. Mixture was passed through 50-mesh

sieve (300 µm) and used for evaluation of micromeritic properties [7-8]. Then the final product under directly compressed into tablets.

Table 1: Formula for the preparation of donepezil orodispersible tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Donepezil	10	10	10	10	10	10	10	10	10
Mannitol	10	-	-	20	-	-	30	-	-
PEG 6000	-	10	-	-	20	-	-	30	-
PVP K30	-	-	10	-	-	20	-	-	30
CCS	60	60	60	60	60	60	60	60	60
Lactose	62	62	62	52	52	52	52	42	42
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total weight (mg)	150	150	150	150	150	150	150	150	150

Evaluation of prepared tablets

Pre compressional parameters

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 [9].

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 [10].

Compressibility index and Hausner's ratio

The compressibility index of the powder blends were determined by Carr's compressibility index or Carr's index (CI) & Hausner's ratio (HR) was also determined for each powder blend. Three determinations were done for each formula [11].

Post Compressional 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 [12].

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 [11].

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 [13].

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 [14].

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].

Stability studies:

The optimized formulation was subjected to stability studies at 40ºC±2ºC/75%±2%RH for period of one month. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at above specified condition in a heating humidity chamber for one month.

The tablets were analyzed for the hardness, disintegration time, and drug content and in-vitro drug release.

RESULTS AND DISCUSSION

Results

Pre compressional parameters:

The results were as shown in Table 2.

Loose bulk density:

LBD of the formulation blend plays an important role in the compression of the powder the LBD of the formulation was found to be in the range of 0.572 g/cm³ to 0.737g/cm³.

Tapped bulk density:

TBD also plays an important role in knowing the compressibility of the formulation blend and found to be in the range of 0.652g/cm³ to 0.788g/cm³. It was noted that the TBD of all the formulations where greater than their respective LBD thus indicating that all the powder formulation had a good compressibility.

Angle of repose (θ):

The angle of repose for the formulation blend was carried out and the results were shown in table no.19. it was concluded that the entire formulations blend were in the range 24.15 to 28.68 thus falling in the official limits range of 25º to 30º which indicates that all the formulation blend have Excellent flow property.

Carr's index:

CI was calculated on the basis of the LBD and TBD and the results were shown in table no.19. it was found to be in the range of 12.60 to 14.50 which lies in the official limits i.e. 11 to 15, indicating the granules blend has good flow property for compression.

Hausner's ratio:

HR was calculated on the basis of the LBD and TBD. It is a ratio between TBN and LBD and was found to be in the range of 1.12 to 1.18 thus indicating that formulation blend have good flowing property which is ideal for ODTs.

Post compressional parameters: The results were revealed in Table 3.

Thickness:

Thickness of all the tablets was found to be between 1.55 to 1.59 mm

Tablet hardness:

The crushing strength of the tablets of each batch ranged between 3.1 to 3.4 kg/cm³.

Friability test:

The values of friability test were in the range from 0.869% to 0.892%. The percent friability of all the formulations was less than 1% ensuring that the tablets were mechanically stable.

Weight variation test:

The percentage weight variations for all formulations were done. All the formulated tablets passed weight variation test as the percent weight variation was within the pharmacopeia limits as the formulation blend of all the formulations have a good flow thus the percent weight variation was in between ±7.5% of the average weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug content:

The percentage of drug content for all formulation was found to be 9.72 to 9.776 which lies in the IP limit.

Wetting time:

The values of wetting time were found in the range of 60 to 180 sec. The wetting time is least for formulation F1, so it will release the drug faster than other formulations.

***In vitro* disintegration test:**

This is the most important test with respect to ODT formulations. Among all formulations, F1 was selected as the best formulation as it gave the least *in vitro* disintegration time as given in table 4.

Table 2: Pre-compressional parameters for the prepared solid dispersions

Formulation code	Loose Bulk Density (gm/ml)	Tapped Bulk Density (gm/ml)	Angle of Repose(ºθ)	Carr's Index	Hausner's Ratio
F1	0.572±0.01	0.652±0.03	24.15±0.32	14.30±0.32	1.18±0.02
F2	0.589±0.03	0.663±0.01	24.75±0.46	14.23±0.56	1.17±0.03
F3	0.698±0.02	0.723±0.03	25.67±0.45	14.50±0.76	1.15±0.03
F4	0.584±0.01	0.661±0.02	24.35±0.27	12.60±0.57	1.12±0.03
F5	0.598±0.01	0.698±0.01	24.68±0.15	12.75±0.24	1.13±0.02
F6	0.628±0.03	0.735±0.01	25.96±0.16	13.27±0.54	1.15±0.01
F7	0.647±0.01	0.715±0.02	25.12±0.23	13.20±0.43	1.16±0.01
F8	0.688±0.02	0.759±0.01	27.75±0.14	14.40±0.33	1.18±0.01
F9	0.737±0.01	0.788±0.03	28.68±0.13	14.25±0.21	1.19±0.02

Table 3: Post-compressional parameters for the prepared tablets

Formulation code	Weight of the Tablet (mg)	Weight Variation	Uniformity of thickness (mm)	Hardness (kg/cm²)	Friability %
F1	147±1.23	0.67±0.01	1.55±0.03	3.1±0.03	0.879±0.02
F2	150±2.13	0.67±0.04	1.54±0.02	3.2±0.01	0.881±0.06
F3	150±1.65	0.67±0.02	1.59±0.03	3.1±0.02	0.892±0.06
F4	148±1.45	-6.04±0.03	1.57±0.04	3.2±0.01	0.872±0.050
F5	149±1.34	7.38±0.42	1.55±0.03	3.3±0.02	0.869±0.02

F6	150±1.32	0.67±0.02	1.56±0.02	3.1±0.02	0.818±0.07
F7	148±1.21	7.38±0.21	1.58±0.01	3.3±0.02	0.875±0.01
F8	147±1.43	-6.04±0.04	1.54±0.04	3.4±0.01	0.873±0.02
F9	150±1.11	0.67±0.02	1.55±0.03	3.1±0.01	0.878±0.02

Table 4: Disintegration time, wetting time & drug content for the prepared tablets

FC	Approach	Disintegration time (sec)	Wetting time (sec)	Drug Content (mg)
F1	Drug: Mannitol (1:1)	50±0.01	60±0.04	9.976±0.03
F2	Drug: Mannitol (1:2)	55±0.12	62±1.23	9.731±0.01
F3	Drug: Mannitol (1:3)	55±0.13	70±1.43	9.723±0.01
F4	Drug: PEG 6000 (1:1)	60±0.12	62±2.23	9.783±0.02
F5	Drug: PEG 6000 (1:2)	65±0.23	64±1.65	9.903±0.01
F6	Drug: PEG 6000 (1:3)	68±0.21	73±1.78	9.861±0.02
F7	Drug: PVP K 30 (1:1)	73±0.45	108±1.97	9.887±0.07
F8	Drug: PVP K 30 (1:2)	79±0.24	112±2.76	9.952±0.09
F9	Drug: PVP K 30 (1:3)	83±0.44	118±3.56	9.783±0.02

***In vitro* dissolution studies:**

All the selected formulations which pass the *in vitro* disintegration test were subjected to *in vitro* release studies using IP dissolution apparatus 1 in 0.1 N HCL. Depending on the *in vitro* disintegration test, *in vitro* dissolution test formulation F1 was selected as optimized formulation. F1 formulation released the maximum amount of drug 99.86% within 10 mins as shown in figure 1. These results are in tuned with those obtained for the disintegration time for the respective formulations.

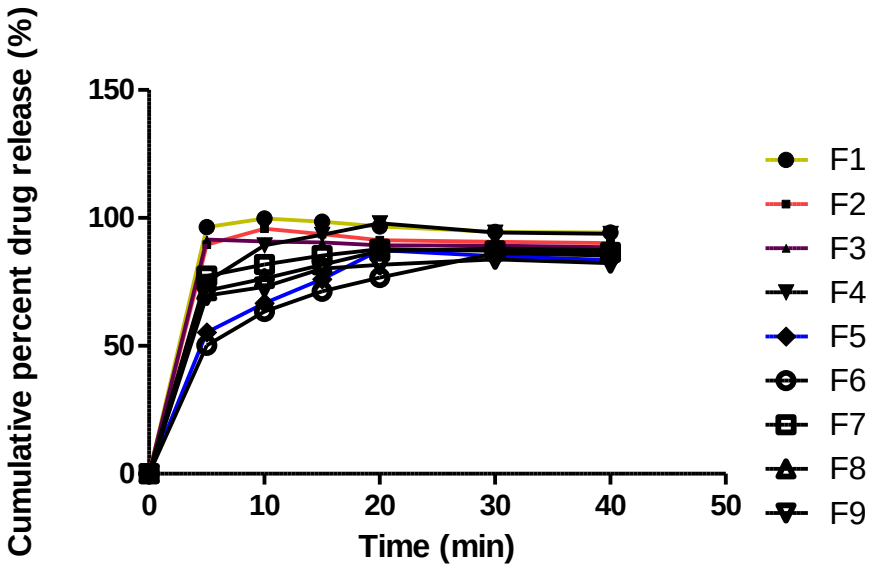

Figure 1: Drug release profiles of prepared oral disintegrating tablets of donepezil HCl

Accelerated stability studies:

The selected formulation F1 was subjected to accelerated stability studies and the formulation where evaluated for appearance, hardness, friability, drug content, *in vitro* disintegration time and *in vitro* dissolution test. The formulations were stored at different conditions. All the formulations were analyzed after every 15, 45, and 90 days. All the formulations (Table 5) show no change in all the above parameters thus successfully passes the accelerated stability study which was conducted for 90 days.

Table 5: Stability studies of prepared tablets

FC	Time (days)	Hardness (kg/cm²)	Drug Content (%)	Dissolution (%)	DT (sec)	Friability	Appearance
F1	15	3.1±0.03	9.76±0.22	96.4±0.98	90±1.2	0.877±0.02	White
F1	45	3.1±0.08	9.74±0.41	96.4±0.35	90±0.9	0.875±0.04	White
F1	90	3.1±0.03	9.74±0.51	96.2±0.63	90±1.4	0.875±0.01	White

DISCUSSION

For present study, we have selected Donepezil HCL, a noncompetitive acetylcholine esterase inhibitor, which was used as anti-Alzheimer's disease. This drug was selected as drug candidate as it is not available in such a dosage form and also with the objectives such as to improve the patient compliance, and to develop a new dosage form for children and elderly.

In the present study, Oro Dispersible Tablets (ODTs) of Donepezil HCL was prepared by using three different solid dispersions in three different ratios. The basic approach followed in this study was to achieve rapid dispersion and instantaneous dissolution of the tablet along with good mouth feel, taste, and excellent mechanical strength The superdisintegrant use here was CCS along with other excipients like lactose, mannitol, PVP K 30, PEG 6000.

The observations have shown that the ODT formulations prepared by using the solid dispersion with mannitol are the best formulations in comparison with the other two dispersion methods. This is because the maximum *in vitro* disintegration time for ODT by solid dispersion with mannitol (1:1 ratio) was found to be 50 seconds. Also the least wetting time, least *in vitro* dispersion time, maximum *in vitro* drug release within 10 mins. Stability of F1 formulation was prepared and that showed no major change in physicochemical parameters, wetting time, *in vitro* disintegration time and *in vitro* drug release profile.

CONCLUSION

In the present study, an attempt was made to prepare ODTs of Donepezil HCL to increase its dissolution by its faster disintegration and patient compliance, as it can be swallowed with most

comfortable way. The ODTs of Donepezil HCL were prepared by direct compression method using solid dispersion technique. Optimization process was carried out and optimizes formula was prepared by using solid dispersion technique. In this technique three types of solid dispersions were prepared by using mannitol, PVP K 30 and PEG 6000 to mask the taste of the drug. The optimized formulation was found to be best in terms of cost effectiveness as only one superdisintegrant was used, disintegration time was found to be 60 sec with sufficient hardness and release maximum amount of drug in 10 min, It showed no significant change in physicochemical properties, drug content, disintegration properties and *in vitro* dissolution during stability studies for three months. Thus, the objective of the present investigation to design and prepared ODTs of Donepezil HCI was achieved successfully.

ACKNOWLEDGMENT

I would like to thank Chairman of Koringa College of Pharmacy for providing the research lab facilities.

REFERENCES

1. Anupama kalia, Shelly Khurana, Neena bedi. Formulation and evaluation of mouth dissolving tablets of Oxcarbazepine. International journal of pharmacy and pharmaceutical sciences. 2009;1(1):12-23
2. Habib W, Khankari R, Hontz J. Fast-dissolving drug delivery systems: Critical review in therapeutics. Crit rev ther drug carrier syst. 2000;17(1):61-72
3. Sachin Annasaheb, Nilesh B Chougule, Kailasam Koumaravelou, Formulation and evaluation of solid dispersion tablets of Andrographis paniculata extract, Pharmacogn J, 2018;10(5):1047-54.
4. Barner, E.L.and Grey, S.L. Donepezil use in Alzheimer disease, Ann.Pharmacother, 1998, 32:70-72.
5. The Merck Index, 14th edn, USA: Merck & Co,Inc, 2006. pp:578.
6. Sugimoto, H., Ogura, H. and Arai,Y. Research and development of donepezil hydrochloride, a new type of Acetylcholinesterase inhibitor, Jpn.J.Pharm, 2002 89:7-20.
7. Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Research in Pharmaceutical Science. 2010;5(1):49-56.
8. Weerapol Y, Tubtimsri S, Jansakul C, Sriamornsak P. Improved dissolution of *Kaempferia parviflora* extract for oral administration by preparing solid dispersion via solvent evaporation. Asian Journal of Pharmaceutical Sciences. 2017;12(2):124-33.

9. G.S. Banker, N.R.I. Anderson , L. Lachman, H.A. Lieberman, J.L. Kanig (Eds.), The Theory and Practice of Industrial Pharmacy (third ed.), Varghese Publishing House, Mumbai (1987), pp. 293–299.
10. Indian Pharmacopoeia. New Delhi: Controller of Publications; 1996. pp. 735–736.
11. Bi YX, Sunada H, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets by direct compression method. Drug Develop Ind Pharm. 1999;25: 571–581.
12. Bhagwati ST, Hiremath SN, Sreenivas SA. Comparative evaluation of disintegrants by formulating cefixime dispersible tablets. Indian J Pharm Edu Res. 2005;39: 194–197.
13. Kaushik D, Dureja H, Saini TR. Formulation and evaluation of olanzapine mouth dissolving tablets by effervescent formulation approach. Indian Drugs. 2004;41: 410–412.
14. Pathra CHN, Bhanoji Rao MK, Yadav KS and Prakash K. Influence of some cellulose ethers on the release of propranolol hydrochloride from guar gum matrix tablets. Ind J Pharm Sci. 2004; 66: 636 – 641.