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Formulation and Evaluation of Immediate Release Donepezil Tablets

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Abstract

The study was undertaken with an aim to develop an optimized formulation of anti-Alzheimer, Donepezil HCl by oral drug delivery. Preformulation studies were conducted to know the drug excipients compatibilities. Based on the results, suitable excipients were selected for formulation development. Tablets were prepared by using wet granulation method. During development of formula, flow properties of the blend and weight variation, hardness, thickness, disintegration time were evaluated for core tablets. Finished products were evaluated for assay and *in vitro* release studies. The developed trials were tested for *in vitro* dissolution profile and compared with the reference product. The *in vitro* dissolution profile of F-6 was nearly similar to that of reference. The optimized batch tablets were packed in HDPE containers and performed stability studies at 40°C/75%RH. Stability samples were evaluated initially and after two months. The results were compared with the predetermined specifications. All the results were found to be satisfactory. Hence the designed and developed formula of Donepezil was stable. The objective of the present project was successfully achieved by developing the product, giving the same release profile to that of innovators product.
Keywords: Donepezil HCl, tablets, immediate release, evaluation

Contents

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1. Introduction

The mean terminal disposition half-life was 81.5±22.0 h. The post-absorption phase of the plasma concentration–time curves for the 4.0 mg and 6.0 mg doses appeared to be biphasic, but the rate of donepezil clearance was independent of dose[1-3].The target of any drug delivery system is to deliver the drug at the site of action for getting and to maintain the desired drug concentration. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process [4]. However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drugs pharmacokinetic profiles, conventional drug therapy requires periodic doses of therapeutic agents. These

agents are formulated to produce maximum stability, activity and bioavailability. Oral DDS is the best wanted and preferred method of administering therapeutic agents for their systemic effects. In addition, oral medicine is measured as the first path investigated in patient acceptance and convenience in administration Oral dosage form is the most popular route for drug therapy [4-6]. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of excellent as they are easy to prepare, pack and shipment.

2. Materials and Method

Materials:

Donepezil was a gift sample from Hetro drugs ltd. Hyderabad, India. Lactose was procured from DMV International Delhi. Microcrystalline cellulose was procured from FMC Biopolymers' Bangalore, HPMC and Magnesium stearate were procured from Ferro Industries India. Opadry yellow was procured from Colorcon, India. All other chemicals used were of analytical reagent grade and double distilled water was throughout the experiment.

Methods: Donepezil HCl tablets were prepared using wet granulation method. Manufacturing process the following steps are involves [7-10].

Sifting: Accurately weighed quantities of Donepezil HCl, Micro Crystalline Cellulose and Maize starch were sifted through 40 mesh and collected in a Polybag. Dry sifted materials were mixed in RMG for 15min and then granulated using binder solution to get the granules of desired consistency.

Preparation of binder solution: Purified water was taken in to a beaker. HPMC was added to water and stirred continuously to get clear solution.

Granulation: Above Sifted materials were loaded in RMG & mixed for about 10 min with impeller at slow speed 150 rpm and chopper off. Binder solution was added to above step over the period of 2 min. Kneading was done with impeller slow speed 150 rpm and chopper for 60 sec. Then collect the granules.

Drying: The collected granules were dried in rapid drier.

Sifting: The dried granules were sifted through #20 mesh. Microcrystalline cellulose and maize starch were sifted through #40 screens and added to the above dried granules and blended for 10 min in octagonal blender. Magnesium stearate was sifted through #40 screen and added to blender and blended for 5 min. Lubricated blend was finally compressed using 9 mm punches. Formulation of Donepezil HCl immediate release tablet were shown in table 1.

Table 1: Formulation of Donepezil HCl immediate release tablet

Composition (mg)	**Formulations**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Donepezil HCl	10	10	10	10	10	10
Micro crystalline cellulose	36	36	34	34	34	34
Maize starch	5	10	10	10	10	10
Lactose	209	201.5	200.5	198.5	198.5	198.5
HPMC	6	6	6	8	8	8
Purified water	Qs	Qs	Qs	Qs	Qs	Qs
Micro crystalline cellulose (Avicel 102)	20	20	20	20	20	20
Maize starch	12	15	18	18	18	18
Magnesium stearate	2	1.5	1.5	1.5	1.5	1.5

Flow properties:

The formulation blends were evaluated for flow properties viz., angle of repose, bulk density, Carr's index and Hausner's ratio[11-13].

Drug excipients compatibility studies:

Binary mixture of drug and excipients were prepared by mixing as given below ratio and kept for stability in glass vials at 40˚C /75 RH and at 60˚C. They were observed for any physical change against control samples kept at refrigerated condition (2-8˚C).

Evaluation of the prepared formulations:

The prepared tablets from different batches were subjected to weight variation, thickness, hardness, friability and dissolution.

3. Results and Discussion

Preformulation studies of pure drug

Particle size distribution: This was done by using Malvern analyzer. The results indicated that distribution of particles in 4.01µ range was 10%, distribution of particles in 10.67µ range was 50% and the distribution of particles in 22.53µ range was 90%.

Flow properties:

Preformulation studies of pure drug were conducted for Angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The results indicate that Angle of repose of pure drug is greater than 40 indicating poor flow properties. The carr's index was found to be 36% indicating very poor to passable. The Hausner's ratio indicates poor flowability. These results indicated the drug possessed poor flow properties. Hence magnesium stearate is used as lubricant in the formulation for good flow. Flow properties of Donepezil HCl blend was shown in table 2.

Flow properties:

Table 2: Flow properties of Donepezil HCl

Flow property	**Values**
Bulk density (g/ml)	0.226±0.001
Tapped density (g/ml)	0.353±0.001
Compressibility index (%)	36±0.15
Hausner's ratio	1.562±0.01
Angle of repose	44º±0.05

Drug excipients compatibility studies:

Drug excipients compatibility studies showed that there was no interaction or physical change between the drug and excipients. So the selected excipients were found to be compatible with the drug (table 3).

Table 3: Drug excipients compatibility study

Composition Details	**Ratio**	**Observations**						
		Storage condition /duration						
		Initial	**40°C/75% RH**			**60°C**		**2-8°C**
			1M	**2M**	**3M**	**15D**	**30D**	**3M**
Donepezil HCl	-	A white powder	NCC	NCC	NCC	NCC	NCC	NCC
API+Lactose	1:10	A white powder	NCC	NCC	NCC	NCC	NCC	NCC
AP+MCC	1:5	A white powder	NCC	NCC	NCC	NCC	NCC	NCC
API + maize starch	1:5	A white powder	NCC	NCC	NCC	NCC	NCC	NCC
API+HPC	1:1	A white powder	NCC	NCC	NCC	NCC	NCC	NCC
API+ Magnesium stearate	1:0.5	A white powder	NCC	NCC	NCC	NCC	NCC	NCC
API+ Ordinary yellow	1:1	A yellow powder	NCC	NCC	NCC	NCC	NCC	NCC

Tablet preparation and characterization:

In the present investigation, tablet formulations were prepared by Wet granulation method. Initially the tablets containing disintegrate tested for disintegration time. Maize starch is used as disintegrate in this formulation. The tablets were evaluated for hardness, friability, disintegration time, and *in vitro* drug release studies. If hardness of tablet decreases then the dissolution of tablet formulations increases. Hence hardness of F6 batch was decreased for better dissolution. In the friability study weight loss values of all the tablet batches was less than 1%. All the tablet formulations fulfilled the compendia requirements for disintegration time. The Physicochemical properties of the prepared tablets were represented in table 4.

Table 4: Physicochemical properties of the prepared tablets

Batch No.	**Average weight(mg)**	**Thickness (mm)**	**Hardness (kps)**	**Friability (%)**	**Disintegration time**
F1	287±3.7	4.62±0.30	6-7±2.10	0.63±0.35	8 mins
F2	288±3.7	4.68±0.30	5-6±2.10	0.57±0.35	6 mins
F3	290±3.7	4.59±0.30	4-6±2.10	0.48±0.35	6 mins
F4	292±3.7	4.54±0.30	7-8±2.10	0.44±0.35	5mins
F5	288±3.7	4.73±0.30	5-6±2.10	0.37±0.35	4mins
F6	289±3.7	4.86±0.30	3-5±2.10	0.31±0.35	3mins

Dissolution studies:

F1: The dissolution profile of this batch shows lower drug release than the reference tablets. In order to increase the dissolution profile of the tablets, it was decided to decrease the concentration of binder.

F2: The dissolution profile of this batch indicates the drug release of this batch releases the drug at lower rate. But the dissolution profile was still lower than the innovator. Based on this observation it was decided to decrease the concentration of binder.

F3: The dissolution profile of this indicates that the decrease of binder concentration and increase of drug release. But the dissolution profile of present batch was still lower than the innovator. Based on this observation it was decided to decrease the binder concentration.

F4: The dissolution profile of this batch indicates drug release profile of the sample still lower than the reference. Hence we are changing the binder Concentration.

F5: The dissolution profile of this batch will not match with reference. Hence we are increasing the coating rate and decrease the binder concentration.

F6: The dissolution profile of this batch indicates drug release profile of the sample will have nearly similar release profile of the innovator. Cumulative % drug release of drug formulation were shown in table 5.

Innovators product dissolution profile

Innovators product dissolution profile was shown in fig.1.

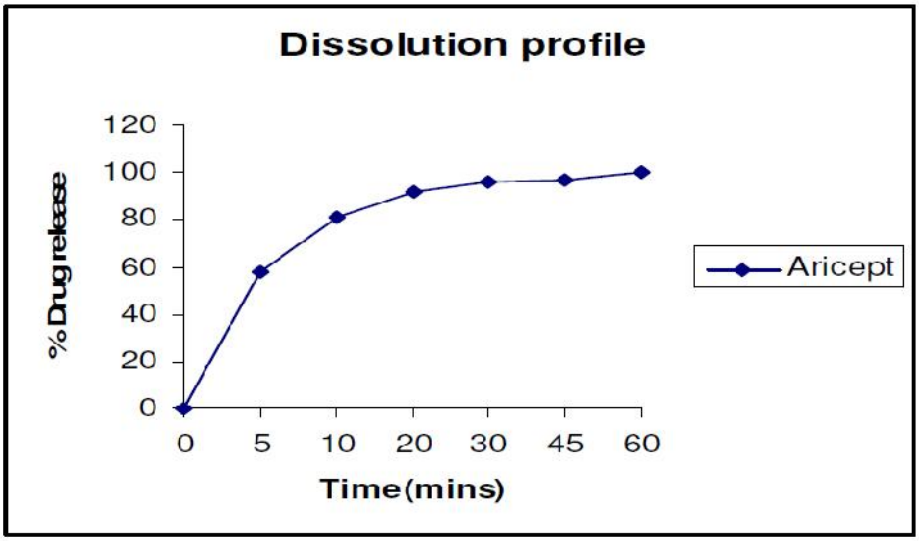

Figure 1: Innovators product dissolution profile

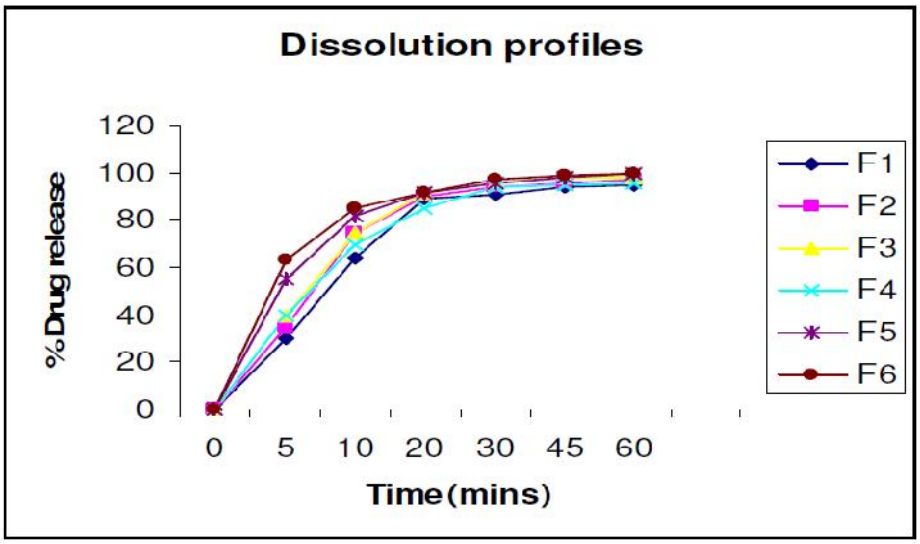

Figure 2: *In vitro* drug dissolution profile

Table 5: Cumulative % drug release of drug formulation

Time (min)	Cumulative % drug release of drug formulation					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
5	30	35	40	40	55	63
10	64	75	75	70	82	82
15	89	90	92	85	92	92
30	91	94	96	94	96	97
45	94	96	98	95	98	99
60	95	97	98	96	100	100

The results of *in vitro* release of tablets from batches 1-5 were shown in fig.2 and HPLC Chromatograms of dissolution was shown in fig.4. All formulation released more than 90% within 30 min. But the formulation 6 exhibited similar release profile to that of innovators product at each time point. Hence, this F-6 was considered as best formulation. Comparison of *in vitro* profiles of F6 and Innovator was shown in fig.3. The parameters after stability testing were represented in table 6 and shown in fig.5.

Comparison of release profile of F6 with Innovators product

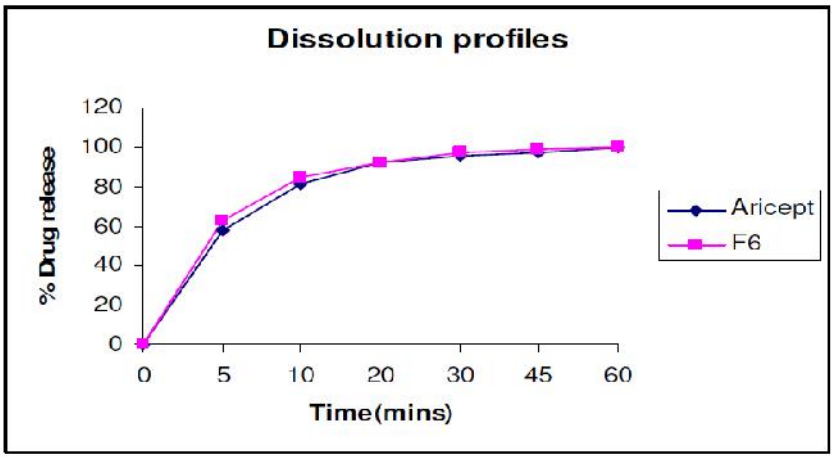

Figure 3: Comparison of *in vitro* profiles of F6 and Innovator

Chromatograms of optimized formulation

Dissolution chromatograms:

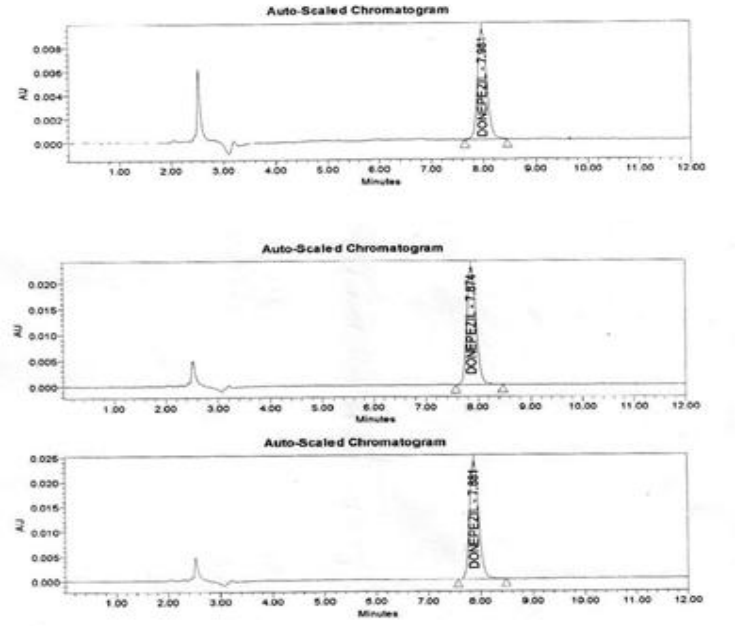

Figure 4: HPLC Chromatograms of dissolution

Assay chromatograms:

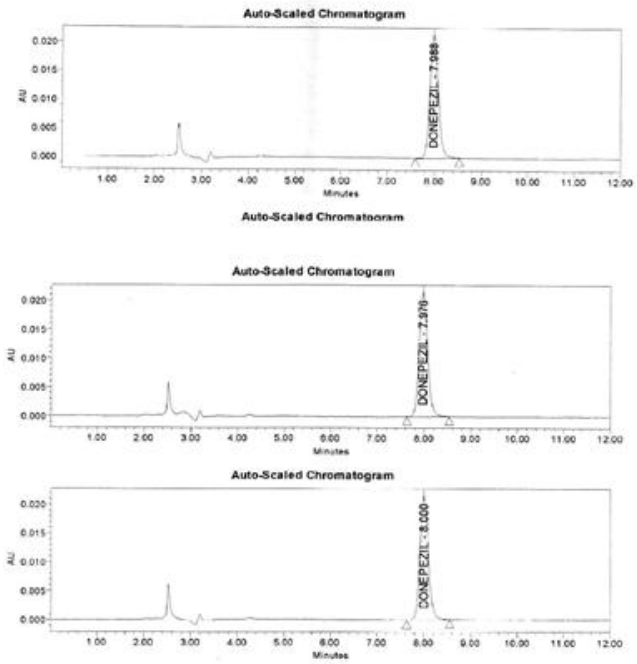

Figure 5: Stability studies of the optimized batch

Table 6: Accelerated stability studies

Test	Specification	Initial	After 1 month	After 2 month
Description	Yellow. Round tablet	Complies	complies	Complies
Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in of the chromatogram the standard preparation as obtained in the assay.	Complies	complies	Complies
Dissolution (0.1 N HCl)	100% release within 60 min	100%	99%	98%
Related substances (%)	NMT 1.5%	Complies	complies	Complies
Assay (by HPLC)	NLT 97% and NMT 101.5%	99.3	99.5	99.7

4. Conclusion

Donepezil hydrochloride immediate release oral dosage forms which is used as an anti-Alzheimer drug was found to have good drug release profile as that of innovator. Donepezil hydrochloride tablets also proved to have good evaluation parameters which were checked. After looking to the evaluation of the formulations F6 was found to be the best. It shows better % cumulative drug release compared with innovator. Hence it can be concluded that F6 is the best among the six formulations. Further detailed investigation is required to know the kinetics of these formulations.

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