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DEVELOPMENT AND CHARACTERIZATION OF FAST MELTING TABLETS OF DONEPEZIL HCL TREATING SENILE DEMENTIA OF THE ALZHEIMER TYPE (SDAT)

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ABSTRACT

The purpose of the present research was to design fast melting tablets of donepezil hydrochloride. FMT's were prepared by direct comperession using different superdisintegrants. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, in vitro and in-vivo dispersion, mouth feel and in vitro dissolution. All the formulations showed low weight variation with dispersion time less than 30 seconds and rapid in vitro dissolution. The drug content of all the formulations was within the acceptable limits. This work helped in understanding the effect of formulation processing variables on the drug release profile. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Keywords: *Fast melting tablets, Donepezil hydrochloride, Senile dementia of the Alzheimer type (SDAT), super-disintegrants & Korsemeyer-Peppas.*

Introduction

Over the past two decades, there has been an increased for novel drug delivery systems (NDDS) to improve safety, efficacy and patient compliance. The discovery and development of a New Chemical Entity (NCE) is highly expensive and time consuming affair. Hence the pharmaceutical industries are focusing on the design and development of new drug delivery system for the existing drugs, leading to improved bioavailability, reduced adverse effects and patient compliance. The patient acceptability and compliance are important in design of the NDDS; one such drug delivery system is mouth dissolving tablets which as gained acceptance and popularity in the recent times. The prime factor for the commercial success of FMT is, because of its significant impact on patient compliance of all age groups.[1]

'Mouth dissolving' (MD) or 'melt in mouth' tablets are a perfect fit for these patients as they immediately release the active drug, when placed on the tongue, by rapid disintegration, followed by dissolution of the drug. [2-4]

FMTs are prepared by various techniques, mainly direct compression,lyophilization and moulding. The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies[5]. Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants. [6]

Donepezil hydrochloride is a piperidine that is a cholinesterase inhibitor (ChE inhibitor). Senile

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dementia of the Alzheimer type (SDAT) has been linked to losses of presynaptic choliergic function in the nucleus basalis of the brain. Cholinegic agents - either agonists or enzyme inhibitors have been put forward as therapeutic agents. Donepezil HCL is one such candidate for a thereapeutic agent in SDAT. Alzheimer's disease is characterized by a decrease in levels of the neurotransmitter acetylcholine and neuronal cell death. Donepezil HCL is presumed to produce its clinical effect by enhancing cholinergic function in surviving neurones. Clinical trial results have demonstrated that administration of donepezil HCL (5 or 10 mg, once daily) significantly improves memory and cognitive function in patients with Alzheimer's disease. [7-9] The aim of the proposed work was to formulate and characterize fast melting tablets of donepezil HCL for rapid dissolution of drug and absorption, which may produce rapid onset of action in management of SDAT.

MATERIALS AND METHODS

Materials: Donepezil HCL was obtained from pharma intermediates, Crospovidone, Ac-Di-Sol, Sodium Starch Glycolate and Microcrystalline cellulose were obtained as gift sample from Arihant Trading Co., Mumbai. All other chemicals and reagent were of analytical grade.

Methods

Preparation of fast melting tablets of Donepezil HCL: The choice of superdisintegrant and optimization of concentration of superdisintegrant is a rationale to formulate a fast dissolving tablet Tablets are prepared by direct compression technique. Accurately drug was weighed and to this other excipients are added. All the ingredients are passed through sieve no 120. Tablets are punched by using 7/32 flat punches on sixteen station rotary tablet compression machine (Rimek, RSB press Cadmach, hmedabad, India).

Characterization of blend [10]

Angle of repose: Angle of repose was determined by using funnel method The response angle (θ) was calculated by formula.

$\tan \theta = 2h/D$

Bulk density: Apparent bulk density was determined by pouring pre-sieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is".

Tapped density: It was determined by placing a graduated cylinder containing a known mass of drug, excipient blend on mechanical tapping apparatus, which was operated for a fixed no of taps until the powder bed volume has reached a minimum using the weight of a blend in a cylinder and this minimum volume the tapped density was computed.

Percent compressibility and Hausner ratio: These were calculated by using below equations. (Aulton and Wells, 1988) % Compressibility: $\{(\rho t-\rho b)/\rho t\} * 100$; Hausner Ratio: $\rho t/\rho b$

Where, ρt= Tapped density & Pb= Bulk density

Characterisation of FMTof donepezil HCL

Weight variation: 20 tablets were weighed at a random using an electronic balance (Shimadzu, AUX 220, Shimadzu Corp, Japan) and average weight was determined. The individual tablets were weighed and was compared with average weight.

Hardness and Friability: Hardness of tablet was determined by using a Monsanto tablet hardness tester (Cadmach Machinery Co, Ahmedabad, India). Friability of ten tablets from each formulation was determined using the Roche friabilator (Campbell Electronics, Mumbai, India).

Content uniformity test: This test is applicable to tablets that contain less than 10mg (or) less than

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10%w/w of active ingredient. The test for uniformity of content should be carried only after the content of active ingredient in a pooled sample of tablets has been shown to be with in accepted limits of the stated content. Ten tablets were taken and their content was determined by uv spectrophotometry.

Wetting time and water absorption ratio: A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was taken and weighed. Water absorption ratio (R) was determined using following equation. R=10* (wa-wb)/wb were wb is weight of tablet before water absorption and wa is weight of tablet after water absorption.

Thickness: Randomly 10 tablets were taken from each formulation and their thickness was measured using digital Vernier caliper (Mitutoyo Corp, Kawasaki, Japan).

In-vitro disintegration time: *In-Vitro* disintegration time for MDTs was determined using USP disintegration apparatus with pH 6.8 buffer as the disintegration medium. The time required for complete disintegration of the tablet was recorded.

Dissolution study: Dissolution rate was studied by using USP type II apparatus at 50 rpm. Distilled water, 900ml was used as dissolution medium. Temperature of dissolution medium was maintained at 37±0.5°c. Aliquot of dissolution medium was withdrawn at specific time interval and it was filtered. Absorption of filtered solution was checked by UV spectroscopy at required wavelength and drug content was determined from standard calibration curve. Dissolution rate was studied for all designed formulations and conventional marketed formulation.

Mechanism of i*n-vitro* drug release: The data obtained from *in vitro* dissolution studies were fitted to zero order, first-order and Korsemeyer- Peppas equation. The zero-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsemeyer-Peppas equation $mt/m¥ = k\ t^n$

where mt/m¥ is fraction of drug released, k is kinetic constant, t is release time and *n* is the diffusional exponent for drug release.[11]

Fourier transform infrared spectroscopy (FTIR): FTIR studies were performed on drug, excipients and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm^{-1}.

RESULTS & DISCUSSION

Physical properties such as bulk density, tapped density, percent compressibility index, hausner ratio, angle of repose are determined (Table-1) for the prepared tablet blend. The tablet blend batches in which microcrystalline cellulose was used as a diluent, the angle of repose is between 30° to 35°; this indicates the passable flowability. This property may be attributed due to the spherical shape of the particles. The percent compressibility index and hausner ratio are with in the limits. The prepared tablets were evaluated for hardness, friability, thickness, weight variation and content uniformity (Table-2) for all the batches were found to be with in the acceptable limits. All the formulations were found to pass the weight variation. Content of donepezil HCl from all the formulations was found to be in the range of 93% to 105%. The hardness was constantly maintained between 3-4 kg/ cm2 during compression. Friability for all the formulation shown less than 0.90% which is in the acceptable limits which indicates formulations have good mechanical strength. The wetting time was determined for all the formulations prepared. The wetting time for the optimized formulations is below one minute; this indicates quicker

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disintegration of the tablet. *In vitro* dissolution studies of the prepared FMTs was preformed in artificial saliva (pH 5.8) using USP dissolution apparatus type 2. At 5% superdisintegrant level the drug release at the end of 12 minutes were found to be 87.09, 72.04 and 58.78 % with Crosprovidone, Ac-Di-sol and SSG respectively (Figure-1). It was observed that as the concentration of superdisintergrant increased the drug release also increased. With reference to the type of superdisintergrant, the release rate was found to follow the order: Crosprovidone > Ac-Di-sol > SSG. Regression analysis was performed and regression values 'R2' were 0.990 to 0.995 for different formulations (Table-3). Slope values ($0.5<n<1.0$) suggest that the release of donepezil from fast dissolving tablets followed non-Fickian diffusion mechanism.

FTIR spectra of the drug, excipients and the optimized formulation were recorded in range of 4000-400 cm^{-1}. In the optimized formulations, the presence of all the characteristic peaks of the drug indicates lack of any strong interaction between the drug and the excipients.

Conclusion

Overall, the results suggest that suitably formulated fast melting tablets of donepezil HCL along with a super disintergrant can be achieved. The tablets exhibited good i*n vitro* dispersion and wetting properties. The FTIR studies are done for optimized formulation there is lack of interaction between the drug and the excipients. Thus the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Table 1: General Composition of Formulation Prepared by Direct Compression Method

Ingredients (mg per tablet)	F1	F2	F3	F4	F5	F6
Donepezil	10	10	10	10	10	10
Microcrystalline cellulose	94	94	94	94	94	94
Crospovidone	1.8	-	-	9.5	-	-
Ac-Di-Sol	-	1.8	-	-	9.5	-
Sodium starch glycolate(SSG)	-	-	1.8	-	-	9.5
Sodium saccharin	3	3	3	3	3	3
Talc	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2

Table 2: Characteristics of prepared FMTs of Donepezil

Code	Average Weight (mg)	Hardness (kg/cm2)	Friability (%)	Disintegration Time (sec)	Wetting Time (sec)	Water absorption ratio
F1	120.00±0.007	3.2±0.02	0.51±0.03	24±2.00	15±1.00	122±0.12
F2	121.68±0.101	3.0±0.10	0.05±0.07	29±2.00	23±0.00	116±0.09
F3	120.10±0.024	3.2±0.02	0.61±0.05	35±0.00	32±1.00	102±0.29
F4	129.08±0.105	4.0±0.01	0.15±0.03	10±1.00	08±0.00	158±0.97
F5	129.20±0.213	3.4±0.04	0.35±0.04	12±1.00	17±1.00	131±0.95
F6	129.38±0.199	4.2±0.00	0.75±0.01	21±2.00	19±2.00	125±1.05

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Table 3: kinetic models for release of Donepezil

Code	k0 (mg/min)	R2	k1 (min-1)	R2	n	R2
F1	1.623	0.987	0.041	0.943	0.935	0.991
F2	1.403	0.984	0.035	0.941	0.904	0.995
F3	1.387	0.982	0.033	0.955	0.902	0.993
F4	1.715	0.990	0.047	0.949	0.878	0.990
F5	1.698	0.989	0.041	0.965	0.905	0.992
F6	1.399	0.986	0.036	0.953	0.933	0.990

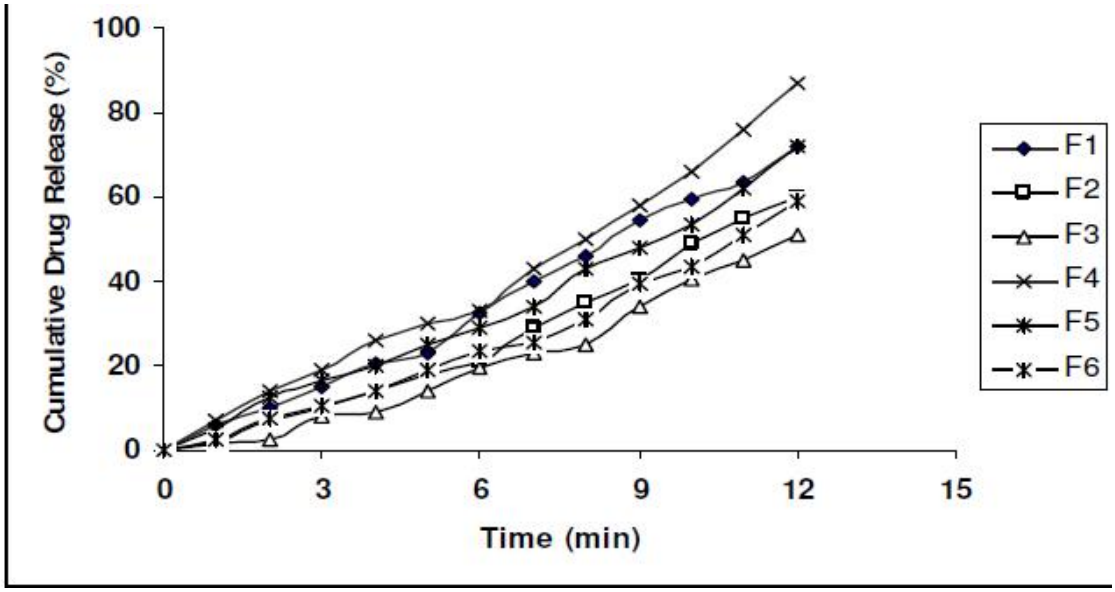

Figure 1: In Vitro release of Donepezil from fast melting tablets.

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