Research Article

Fabrication, Optimization and *In Vitro* Evaluation of Oral Disintegrating Tablets of Mirtazapine

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ABSTRACT

The aim of present work is to formulate Oral disintegrating tablets of Mirtazapine by direct compression method using super disintegrants such as Crosspovidone, Lycoat, SSG, Dehydrated banana powder and plantago ovata. It is extensively metabolized by liver and having oral bioavailability of 50%. To improve the oral bioavailability of Mirtazapine oral disintegrating tablets were formulated using different natural and synthetic super disintegrants. The dispersion time of tablets were reduced with increase in the concentration of super disintegrants. It also includes various invitro evaluation techniques to evaluate the performance of oral disintegrating tablets. From the results obtained, it was concluded that lycoat was found to be the best among the super disintegrants, the highest drug release was found to be 99.52% in F12 formulation at the end of 15min.

Keywords: Mirtazapine, Crosspovidone, lycoat, SSG, Dehydrated banana powder and plantago ovata. Oral disintegrating tablets.

INTRODUCTION

Mirtazapine is an atypical antidepressant which used primarily in the treatment of depression. Its antidepressant properties, mirtazapine, has anxiolytic, sedative, antiemetic, antiallergic and appetite, stimulant effects and is sometimes used in the treatment of anxiety disorders, insomnia, nausea and vomiting and to produce weight gain desirable[1].

Mirtazapine has elimination half -life of 20-40 hrs and the absolute bioavailability is about 50% mainly because of Gut wall and hepatic First pass metabolism which makes it more suitable for formulating as Oral disintegrating tablets to bypass the first pass metabolism[2].

The oral bioavailability of mirtazapine is about 50%. It is found mostly bound to plasma proteins, about 85%. It is metabolized primarily in the liver by demethylation and hydroxylation via cytochrome P450 enzymes, CYP1A2, CYP1D6, CYP3A4. One of its major metabolites is desmethyl mirtazapine. The overall elimination half-life is 20–40 hours. It is conjugated in the kidney for excretion in the urine, where 75% of the drug is excreted and about 15% is eliminated in feces[3].

MATERIALS AND METHODS

Materials

Mirtazapine purchased from Aurobindo pharma Ltd., Hyderabad, Crosspovidone, Lycoat, SSG, Dehydrated banana powder and plantago ovate, Aspartame, Microcrystalline cellulose (Avicel) Talc, Magnesium stearate and Hydrochloric acid were used. All the reagents used are of LR grade.

Methods

Oral disintegrating tablets of Mirtazapine were prepared by direct compression according to the formulae given in the table 1.2.

All the ingredients were passed through # 60 mesh sieve separately. The drug and microcrystalline cellulose (MCC) were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside[4].

Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#44mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm^2 for all batches. The weight of the tablets was kept constant for all formulations F1 to F15 (100mg).

Evaluation Parameters

Pre formulation studies

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve#20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below[5]. It is expressed in g/cc and is given by:

Where,

M = mass of the powder

Vo = bulk volume of powder.

Tapped density (D_t)

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 100times. Then the tapping was done for 100 times and the tapped volume was noted [5](the difference between these two volumes should be less than 2%). It is expressed in g/cc and is given by:

Dt=M/Vt

Where, M = mass of the powder

V_t= tapped volume of powder.

Angle of Repose (θ)

This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed[5].

tan θ = h/r

θ= tan-1(h/r)

Where,

θ= angle of repose, h= height of the heap, r = radius of the heap

The relationship between Angle of repose and powder flow is as follows:

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Compressibility Index:

The flow ability of powder can be evaluated by comparing the bulk density (Db) and tapped density (D_t) of powder and the rate at which it packed down[6]. Compressibility index is calculated by –

Compressibility index (%)= D_t-D_b / D_t ×100

Where,

D_b= Bulk density

D_t= Tapped density

Percent compressibility	Type of flow
5-15	Excellent
12-16	Good
18-21	Fare-passable
23-25	Poor
33-38	Very poor
>40	Extremely poor

Hausner's Ratio:

It is the ratio of tapped density to the bulk density[6]. It is given by- Hausner's ratio = D_t/ D_b

Where,

D_t= Tapped density

D_b= Bulk density.

Post-compression parameters

Shape of Tablets

Directly compressed tablets were examined under the magnifying lens for the shape of the tablet[7].

Tablet Dimensions

Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually[8].

Weight variation test

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed[8].

Average weight of a tablet	Percentage deviation
130 mg or less	±10
>130mg and <324mg	±7.5
324 mg or more	±5

In all formulations, the tablet weight is 150 mg, hence 7.5% maximum difference allowed.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined[8].

Friability Test

The friability of tablets was determined by using electro lab friabilator. It isexpressed in percentage (%). Ten tabletswere initially weighed (W_I) and transferred into friabilator.Thefriabilator was operated at 25rpm for 4minutes or run up to 100 revolutions. The tablets were weighed again (W_F). The % friability was then calculated by

%F = 100 (1-W_I/W_F)

% Friability of tablets less than 1% was considered acceptable.

Test for Content Uniformity

Tablet containing 30mg of drug was dissolved in 50ml of

6.8 pH buffer in volumetric flask. The drug was allowed to dissolve in the solvent. The solution was filtered; 2mlof filtrate was taken in 10ml of volumetric flask and diluted upto mark with distilled water and analyzed spectrophotometrically at 232 nm. The concentration of Mirtazapine was obtained by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch[9].

In vitro Dispersion Time

Tablet was added to 10ml of distilled water at 37±0.5^{0}C. Time required for complete dispersion of a tablet was measured[9].

In vitro Dissolution Study

In vitro dissolution of Mirtazapine Oral disintegrating tablets was studied in USPXXIV dissolution test apparatus. 900ml Phosphate buffer 6.8 (simulated fluid) was used as dissolution medium. The stirrer was adjusted to rotate at 50rpm. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment.

One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 232 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Mirtazapine released was calculated and plotted against time[10].

Drug Kinetics

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Qv/st), first order[Log(Q0-Q)v/st], Higuchi's square root of time (Qv/st$^{1/2}$) and KorsemeyerPeppas double logplot (logQ v/slogt) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t[11]. In short, the results obtained from invitro release studies were plotted in four kinetics models of data treatment as follows.

Cumulative percentage drug release Vs. Time (zero order rate kinetics)

Log cumulative percentage drug retained Vs. Time (first order ratekinetics)

Cumulative percentage drug releaseVs. √T (Higuchi's classical diffusion equation)

Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

RESULTS AND DISCUSSION

Determination of melting point

The melting point of Mirtazapine was found to be 114-116°C which was determined by capillary method.

Solubility

Solubility of Mirtazapine was carried out at 25^{0}C using 0.1 N HCL, 6.8 phosphate buffer, 7.4 pH buffer and purified water. From the solubility studies results obtained in various buffers we can say that 6.8 pH buffer solution has more solubility when compared to other buffer solutions.

Determination of absorption maximum (λmax)

Determination of Mirtazapine λ-max was done in pH 6.8 buffer medium for accurate quantitative assessment of drug dissolution rate.

Standard Calibration Curve of Mirtazapine in 6.8 pH buffer

Standard calibration curve of Mirtazapine was drawn by plotting absorbance v/s concentration. The λmax of Mirtazapine in 6.8pH buffer was determined to be 232 nm. The absorbance values are tabulated in Table 1.1. Standard calibration curve of Mirtazapine in the Beer's range between 5-30µg/ml is shown in Fig.1.1.

Drug-Excipient Compatibility Study

Compatibility studies were performed using FT-IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristic absorption peaks of Mirtazapine were obtained at different wave numbers in different samples. The peak so obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. From the drug and excipients interaction studies it was identified that the pure drug and the optimized formulation have no interactions when compared with the pure drug functional groups.

Micromeritic Properties

The angle of repose of different formulations was ≤ 30.68 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.39g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.45g/cm^3 to 0.61g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.53-15.51 and Hausner's ratio from 1.12-1.18 which reveals that the blends have good flow character.

Evaluation Studies

Weight Variation Test

The percentage weight variations for all formulations

were given. All the formulated (F1 to F15) tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test

The measured hardness of tablets of all the formulations ranged between 3-4 kg/cm^2. This ensures good handling characteristics of all batches.

Disintegration test

It was found between 24 – 76 seconds ensuring that all the cores of different formulations were rapid disintegrating type.

Friability Test

The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

In vitro Dissolution Study

The in-vitro dissolution study of Mirtazapine tablet is tested in phosphate buffer 6.8(simulated fluid). The invitro drug release study of oral disintegrating tablets from each batch ($F_1$to F_{15}) was carried out in phosphate buffer 6.8 (simulated fluid) for 30mins and the values are shown in Table. The plot of % Cumulative drug release V/s time (mins) were plotted. From the invitro dissolution data, it was found that the drug release study from formulations containing Plantago ovata as super disintegrant (F_1-F_3). F1 formulation shows maximum drug release at the end of 93.62% at the end of 30mins. Whereas F2 formulation shows maximum drug release at the end of 99.85% at the end of 25mins, while F3 formulation shows maximum drug release at the end of 98.26% at the end of 25mins. While the Formulations containing crosspovidone as super disintegrant (F_4-F_6) showed 98.41, 92.63, 98.63% of drug release respectively at the end of 30,25 and 25mins respectively. Whereas the Formulations containing dehydrated banana powder as super disintegrant (F_7-F_9) showed 97.72, 99.65, 97.51% of drug release respectively at the end of 30, 30 and 25mins. Whereas the Formulations containing lycoat as super disintegrant (F10-F_{12}) showed 97.34, 98.52, 98.05% of drug release respectively at the end of 25, 20 & 15mins. Whereas the Formulations containing SSG as super disintegrant (F13-F_{15}) showed 97.63, 99.41, 99.42 % of drug release respectively at the end of 30, 25 and 20mins. From the in vitro dissolution studies it was observed that the increase in the super disintegrant concentration proportionally decreases the time taken for the dissolution. It was observed from the results that, formulations containing lycoat as super disintegrant showed maximum dissolution rate 99.52%of drug release in F12 in 15minutes.The invitro release profiles of all the formulations (F1toF15) are shown in tables 1.5 and 1.6.

Drug release kinetics

From the drug release kinetics it was observed that the optimized formulation follows Zero order drug release based up on the regression value i.e., R^2 value, and drug release was found to be super case II transport mechanism.

Comparison with Marketed Product

The Optimized formulation dissolution profile was compared with marketed conventional tablets of Mirtazipine 15mg and the optimized formulation showed good dissolution rate in less time when compared with marketed preparation. The comparative profiles of both marketed and optimized preparations are given in Fig 1.2.

CONCLUSION

In the present work, Oral disintegrating tablets of Mirtazapine were prepared by direct compression method using superdisintegrants such as lycoat, Plantago Ovata, Dehydrated Banana powder, crosspovidone, SSG. The flow properties of polymer and drug were found to be good. FT-IR studies revealed that there is no chemical interaction between Mirtazapine and the excipients used in the study. Formulated tablets has shown satisfactory result for various physico-chemical evaluation of tablets like tablet dimension, hardness, friability, weight variation, in vitro dispersion time, and drug content. The in-vitro dissolution study of Mirtazapine tablet is tested in phosphate buffer 6.8(simulated fluid).From the in vitro dissolution studies it was observed that the increase in the super disintegrant concentration proportionally decreases the time taken for the dissolution. It was observed from the results that, formulations containing lycoat as super disintegrant showed maximum dissolution rate 98.06%of drug release in F12 in 15minutes.The optimized tablets are compared with marketed conventional tablets of mirtazapine which showed release for 25 minutes. From this it has been concluded that oral disintegrating tablet of mirtazapine showed good release within short period of time.

Table 1: Calibration data of Mirtazapine in 6.8pH buffer at λ_{max} 232 nm

Concentration µg/ml)	Absorbance
0	0
5	0.101
10	0.194
15	0.301
20	0.399
25	0.481
30	0.592

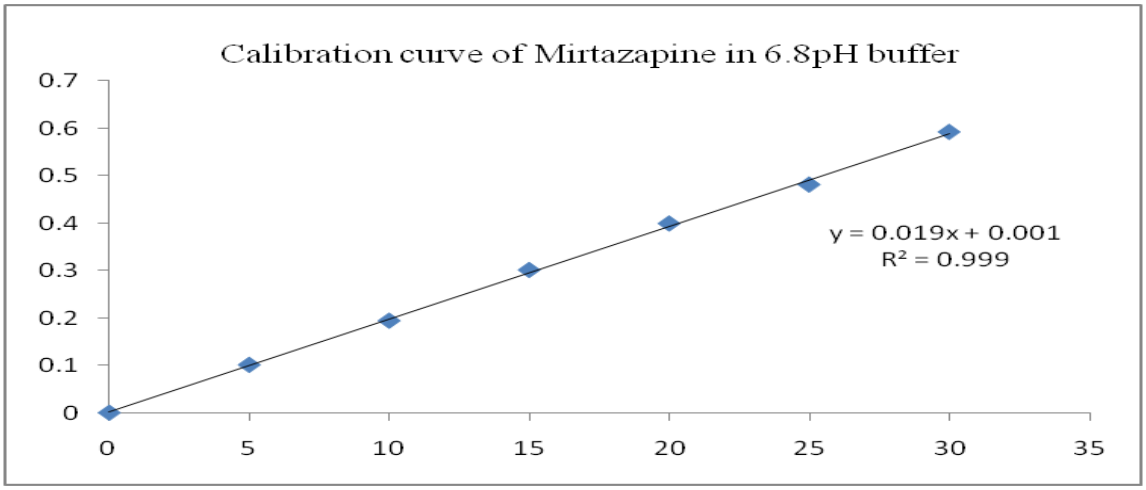

Figure1: Standard calibration curve for Mirtazapine in 6.8pH buffer at λmax 232 nm.

Table 2: Formulation table of Mirtazapine Oral Disintegrating Tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Mirtazapine	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
PlantagoOvata	2	4	6	-	-	-	-	-	-	-	-	-	-	-	-
Crosspovidone	-	-	-	2	4	6	-	-	-	-	-	-	-	-	-
Dehydrated Banana powder	-	-	-	-	-	-	2	4	6	-	-	-	-	-	-
lycoat	-	-	-	-	-	-	-	-	-	2	4	6	-	-	-
SSG	-	-	-	-	-	-	-	-	-	-	-	-	2	4	6
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M.C.C	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Table 3: Pre Compression parameters

Formulation Code	Derived properties		Flow properties		
	Tapped Density (mean±SD)	Bulk Density (mean±SD)	Angle of Repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.54±0.32	0.47±0.48	26.38±0.15	12.96±0.62	1.15±0.62
F2	0.52±0.31	0.46±0.15	27.42±0.14	11.32±0.59	1.13±0.26
F3	0.49±0.45	0.42±0.2	29.02±0.65	14.08±0.26	1.16±0.15
F4	0.52±0.26	0.46±0.65	27.26±0.52	11.54±0.14	1.13±0.15
F5	0.59±0.15	0.51±0.25	30.68±.15	13.56±0.26	1.16±0.26
F6	0.57±0.26	0.51±0.64	29.26±0.26	10.53±0.32	1.12±0.48
F7	0.49±0.14	0.43±0.23	27.02±0.15	12.24±0.15	1.14±0.65
F8	0.61±0.26	0.52±0.17	30.62±0.48	14.75±0.62	1.17±0.59
F9	0.45±0.32	0.39±0.15	28.02±0.26	13.33±0.67	1.15±0.36
F10	0.51±0.48	0.42±0.25	26.24±0.17	18.30±0.65	1.22±0.62
F11	0.52±0.67	0.45±0.49	29.24±0.59	13.46±0.47	1.16±0.34
F12	0.54±0.64	0.48±0.64	28.56±0.14	11.11±0.64	1.13±0.26
F13	0.56±0.95	0.49±0.65	28.65±0.36	12.50±0.15	1.14±0.48
F14	0.53±0.41	0.47±0.15	29.49±0.59	11.32±0.26	1.13±0.32
F15	0.51±0.16	0.45±0.14	26.47±0.32	11.76±0.14	1.13±0.62

Table 4: Post compression parameters

Formula	Post compression parameters					
	Avg .Wt (mg)	Hardness (kg/cm²)	Thickness(mm)	Friability (%)	Disintegration time (secs)	Drug content (%)
F1	99.15±0.26	3.15±0.15	3.52±0.23	0.10±0.25	63±0.15	96.15±0.41
F2	98.15±0.22	3.15±0.26	3.63±0.14	0.63±0.23	56±0.96	81.42±0.96
F3	100.01±0.36	3.47±0.36	3.41±0.56	0.41±0.56	55±0.65	82.75±0.75
F4	100.2±0.15	3.63±0.10	3.52±0.45	0.85±0.75	76±0.25	95.63±0.63
F5	99.2±0.32	3.47±0.01	3.63±0.96	0.23±0.14	70±0.14	83.41±0.14
F6	98.8±0.63	3.72±0.16	3.41±0.85	0.62±0.25	66±0.15	86.26±0.20
F7	101.9±0.15	3.15±0.26	3.85±0.45	0.41±0.23	58±0.26	92.85±0.23
F8	99.5±0.36	3.42±0.30	3.52±0.25	0.52±0.14	53±0.32	94.63±0.16
F9	98.4±0.14	4.20±0.96	3.36±0.23	0.36±0.23	44±0.25	96.01±0.02
F10	100.2±0.35	3.15±0.10	3.04±0.14	0.04±0.52	36±0.16	99.20±0.85
F11	99.8±0.26	3.26±0.01	3.15±0.25	0.64±0.65	30±0.32	86.04±0.96
F12	98.7±0.14	3.14±0.16	3.20±0.26	0.17±0.63	24±0.32	95.06±0.75
F13	101.02±0.26	3.26±0.26	3.36±0.23	0.59±0.25	39±0.26	96.32±0.42
F14	99.4±0.15	3.78±0.30	3.85±0.15	0.65±0.14	35±0.26	97.34±0.63
F15	98.9±0.26	3.59±0.96	3.74±0.25	0.42±0.26	32±0.02	96.63±0.14

Table 5: Cumulative percent drug release of ODT of different formulations of Mirtazapine (F1toF9)

TIME (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	25.2±0.20	32.62±0.23	42.63±0.42	42.63±0.63	49.63±0.36	51.62±0.26	30.51±0.52	34.17±0.26	40.52±0.20
10	36.51±0.63	41.26±0.05	56.51±0.63	59.62±0.95	63.51±0.20	72.63±0.35	46.85±0.14	53.47±0.32	69.62±0.15
15	56.62±0.42	62.52±0.26	69.63±0.12	72.41±0.32	79.63±0.15	86.95±0.12	59.19±0.06	72.77±0.02	72.63±0.63
20	69.85±0.86	75.85±0.21	86.18±0.02	89.63±0.02	92.63±0.86	98.63±0.30	73.62±0.20	88.07±0.15	89.63±0.95
25	79.63±0.95	90.26±0.53	98.26±0.56	98.41±0.14			88.21±0.51	92.37±0.23	97.51±0.41
30	93.62±0.12	99.85±0.96					97.72±0.63	99.65±0.63	

Table 6: Cumulative percent drug release of ODT tablets ofdifferent formulations of Mirtazapine (F10toF15)

TIME (mins)	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0
5	49.63±0.26	51.63±0.36	58.3±0.23	33.52±0.02	45.62±0.20	52.63±0.36
10	69.52±0.20	72.61±0.45	76.95±0.63	53.95±0.21	59.62±0.53	63.74±0.25
15	79.3±0.09	85.63±0.30	99.52±0.14	69.84±0.36	72.84±0.61	89.63±0.01
20	86.04±0.42	98.52±0.02		76.85±0.45	86.43±0.42	99.42±0.02
25	97.34±0.38			89.61±0.21	99.41±0.52	
30				97.63±0.36		

Comparison with Marketed Product

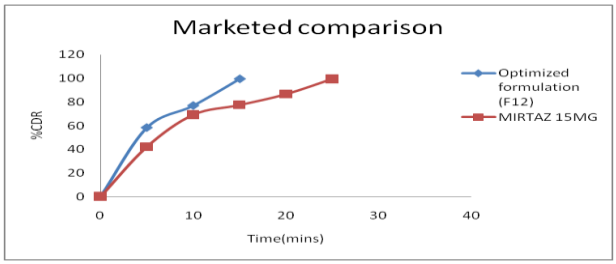

Figure 2: Comparative Dissolution graph of optimized formulation with marketed product

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