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PREPARATION OF MIRTAZAPINE ORALLY DISINTEGRATING TABLETS WITH IMPROVED FORMULATION CHARACTERISTICS

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ABSTRACT
The present work aimed to formulate the taste-masked mirtazapine granular blend into a solid oral tablet dosage form which disintegrates in the mouth quickly and effectively releases the drug for its systemic absorption with immediate action for the treatment of depressive disorders. The taste-masked blend of mirtazapine containing different types of disintegrants prepared in our previous study was compressed by direct compression method using a rotary tablet compression machine with optimum parameters. The formulated tablets were evaluated for various quality parameters including appearance, thickness, hardness, disintegration time, weight variation, drug content, wetting time, water absorption ratio, in-vitro dispersion time, fineness of dispersion and dissolution. There was no significant difference in physical parameters for all the formulations F1-F3, F4-F6, F7-F9, F10-F12 and F13-F15, which contained pregelatinized starch, sodium starch glycolate, croscarmellose sodium, polacrilin potassium and crospovidone respectively in three concentration levels of 1.5%, 3.0% and 4.5%. Formulations containing croscarmellose sodium, polacrilin potassium and crospovidone (F7-F15) were observed to be having less disintegration time, wetting time, in-vitro dispersion time with increased water absorption ratio in compared to formulations with pregelatinized starch and sodium starch glycolate (F1-F6). The optimized formulation containing polacrilin potassium (F10-F12) shows the least disintegration time and increased rate of drug release compared to other formulations and market products. A compatibility study performed between mirtazapine and tablet excipients used in this study by FT-IR spectroscopy showed no interactions. Further stability studies were conducted as per ICH-described accelerated storage conditions. It can be concluded that the developed formulation of mirtazapine orally disintegrating tablets was stable to possess improved quality characteristics and the process of preparation was easily scalable for its commercial manufacturing.

KEYWORDS: Disintegration, polacrilin potassium, direct compression, stability.

INTRODUCTION
New developments in novel drug delivery systems (NDDS) are designed to improve patient compliance while improving drug molecule safety and efficacy. One such method is the use of "mouth-dissolving tablets," which dissolve in saliva and can be swallowed without water.[1] The use of mouth-dispersing tablets is advantageous, especially for older and pediatric patients who struggle to swallow traditional tablets and capsules.[2] Additionally, due to immature muscles and neurological systems, young patients may experience difficulties with intake. Furthermore, the usefulness of typical tablets or capsules taken orally is limited in patients who are traveling with limited or no access to water.[3] When a tablet is dissolved in the mouth, it dissolves and absorbs quickly, resulting in an immediate onset of therapeutic action. The medication is released, dissolved, or distributed in the saliva before being ingested and absorbed through the gastrointestinal tract. Furthermore, when manufactured as mouth-dispersing tablets, drug candidates that undergo pre-gastric absorption may exhibit enhanced oral bioavailability. It provides easy manufacturing, precise dosing and good stability.[4]

The drug mirtazapine is an antidepressant used for the treatment of moderate to severe depression. It is an atypical antidepressant having noradrenergic and specific serotonergic activity. It belongs to the chemical series called piperazinoazepines.[5] Other than depressive

characteristics, it also has anxiolytic, sedative, antiemetic, antiallergic and appetite-stimulating effects. It is also used to treat anxiety disorders, sleeplessness, nausea and vomiting, as well as to induce desirable weight gain.[6] It acts by blocking the histaminergic and muscarinic receptors and enhances serotonin neurotransmission at the 5-HT1 receptor. The absolute bioavailability of mirtazapine is about 50% and following oral administration, it reaches peak plasma concentration approximately in 2 hours.[7] It is usually prescribed to patients suffering from major depression and anxiety. A large number of geriatric patients were reported to be receiving this medication.[8] The oral bioavailability of mirtazapine is about 50%. Most of it (approximately 85%) is found attached to plasma proteins. Using the cytochrome P450 enzymes CYP1A2, CYP1D6, and CYP3A4, it is mostly metabolized in the liver through demethylation and hydroxylation.[9] The primary metabolite of it is desmethyl mirtazapine. The elimination half-life is 20–40 hours overall.[10] The medicine is conjugated in the kidney for excretion in the urine, where it is removed in approximately 75% of cases and feces in 15% of cases. In people with hypersensitivity to drugs, it is contraindicated.[11]

To make a tablet that disintegrates quickly and has sufficient structural integrity, direct compression is considered to be the most appropriate and easiest method. The choice of appropriate excipients with good disintegration characteristics and compatibility is the most crucial consideration when using the direct compression method.[12] When choosing super disintegrants, several parameters should be taken into account because these agents affect more than just the rate of disintegration; they also affect friability, hardness and the feel of the tablet in the mouth. The individual or combined actions of disintegrants and water-soluble excipients determine the disintegration and dissolving characteristics of the direct compressible ODTs. The disintegrants play an important role due to their different types of mechanisms. To ensure a high disintegration rate, a suitable disintegrant type must be chosen at a sufficient concentration.[13]

The objective of the present study was to formulate and evaluate orally disintegrating tablets of mirtazapine by direct compression method and deliver the drug at a faster rate and to provide immediate onset of action in a shorter period with improved bioavailability.

MATERIALS

Mirtazapine was purchased from Neuland Laboratories, India. The excipients Polacrilin potassium (Vikram thermo), Citric acid (Sunil chemicals), Sodium bicarbonate (Nice Chemicals Pvt ltd, India), Mannitol (Quingdao Bright Moon Seawood Co. ltd, China), Microcrystalline cellulose (Ankit Pulps and Boards Pvt. ltd, Nagpur, India), Croscarmellose sodium (Prachin Chemicals, Ahmedabad, India), Pregelatinized starch (Universal Starchchem, India), Sodium starch glycolate (Vasa Pharmachem Pvt ltd, Ahmedabad, India), Crospovidone (International Fine Chemicals, Canada), Sucralose (Shandong Kanbo Bio chemical Technology, China), Strawberry powder flavor (International Flavours & Fragrances India ltd, Mumbai, India), Talc (Neelkanth Finechem, India) and Magnesium stearate (Nitika Pharmaceutical Specialities Pvt ltd, India) were purchased for the preparation of mirtazapine orally disintegrating tablets.

METHODOLOGY

Preparation of orally disintegrating tablets of Mirtazapine

The method of preparation of mirtazapine ODTs performed in two steps, which included the preparation of taste masked blend of mirtazapine with different disintegrants followed by the preparation of uncoated oral tablets by direct compression using a tablet compression machine (DB tooling).

For the manufacturing of the mirtazapine blend, as per our previous research work, the drug resin complex was prepared followed by mixing with other tablet excipients. The drug resin complex was prepared by mixing of drug with resin polacrilin potassium at the ratio of 1:1 in buffered (citric acid and sodium bicarbonate) purified water as a medium having pH 6.5. The complexation process continued for 12 hours followed by filtration, drying and passing through a 40# sieve. The drug resin complex blended with appropriate concentration of super disintegrants like pregelatinized starch, sodium starch glycolate, croscarmellose sodium, polacrilin potassium and crospovidone individually along with other excipients including mannitol, microcrystalline cellulose (MCC), sucralose, strawberry powder flavor, magnesium stearate and talc.[14]

The prepared blend of taste-masked mirtazapine was compressed into tablets by using the direct compression method. The 20-station rotary compression machine (Pacific tools) was set with DB tooling round punches with a diameter of 7.14 mm. The blend was loaded in the hopper and the machine was run at low rpm of 10. The tablet compression parameters were set at optimum to produce a tablet with an average weight of 100 mg with the necessary hardness and thickness. During the compression process, the tablets were collected at different time intervals and in-process quality checks were performed by keeping the target limits for the parameters as mentioned in below Table 1.

Table 1: In-process compression parameters for Mirtazapine tablets.

S. No.	In-process compression parameters	Target limit
1	Average weight	100 mg ± 7.5%
2	Thickness of the tablets	Not more than 3.5 mm
3	Hardness of the tablets	Not less than 4.0 kg/cm^2
4	Friability	Not more than 1%

The unit composition of the compressed tablets prepared using taste-masked drug resin complex with other tablet excipients is presented in Table 2.

Table 2: Unit composition of Mirtazapine orally disintegrating tablets.

S. No.	Ingredients	Formulation code & Quantity in mg per tablet				
		F1 - F3	F4 - F6	F7 - F9	F10 - F12	F13 - F15
1	Drug-resin Complex (1:1)	32.5	32.5	32.5	32.5	32.5
2	Mannitol	15	15	15	15	15
3	Pregelatinized Starch*	1.5/3/4.5	-	-	-	-
4	Sodium starch glycolate*	-	1.5/3/4.5	-	-	-
5	Croscarmellose Sodium*	-	-	1.5/3/4.5	-	-
6	Polacrilin potassium*	-	-	-	1.5/3/4.5	-
7	Crospovidone*	-	-	-	-	1.5/3/4.5
8	Sucralose	0.2	0.2	0.2	0.2	0.2
9	Strawberry flavor	0.5	0.5	0.5	0.5	0.5
10	Talc	1	1	1	1	1
11	Magnesium Stearate	1	1	1	1	1
12	Micro crystalline cellulose	q.s to 100	q.s to 100	q.s to 100	q.s to 100	q.s to 100
Total weight of tablets		100	100	100	100	100

Note: *Three formulations were prepared using each of the disintegrants individually at three concentration level of 1.5%, 3% and 4.5%.

EVALUATION OF MIRTAZAPINE ORALLY DISINTEGRATING TABLET FORMULATIONS[15-17]

Drug excipients compatibility studies

Using Fourier Transform Infrared (FTIR) spectroscopy, the compatibility of mirtazapine and tablet excipients was studied at a 1:1 ratio. The drug and excipients taken in glass vials are physically mixed together using a capillary tube. After mixing thoroughly, the glass vials were sealed and stored at accelerated storage conditions. Shimadzu was used to record the FTIR spectrum between the wavelength of 600 and 4000 cm^{-1}, using KBr disc technique. The baseline correlation was done using dried potassium bromide and the spectrum of the dried mixture of the drug with potassium bromide was run followed by the drug with various excipients.

Post compression parameters

Visual appearance of compressed tablets

The physical appearance of the tablet was examined by various organoleptic properties. The general appearance of tablets, their visual identity and overall 'elegance' are essential for consumer acceptance. The visual inspection involves the measurement of attributes such as tablet's size, shape, color, presence or absence of odor, taste, surface texture, logo, score line, etc.

Thickness

The thickness of the tablet was measured by using a vernier caliper. To find the thickness, hold the tablet vertically against the jaws. Close the jaws until they touch the tablet and read the measurement on the main scale. Tablet thickness should be controlled within a ± 5% variation of the standard value. Randomly 10 tablets selected were used for the determination of thickness and the values were expressed in mm.

Hardness test

Hardness also known as crushing strength of tablets. Tablet requires a certain amount of mechanical strength to withstand the shock of handling on its manufacture, packaging, shipping and dispensing. Ten tablets were selected randomly from each of the batches and hardness was determined using a hardness tester, with results expressed in kg/cm^2 or Newtons.

Weight variation test

The weight variation test is carried out to ensure uniformity in the weight of tablets in a batch. Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablets was noted. The average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. Percentage deviation was calculated by using the following formula:

Percentage deviation = (Weight of tablet - Average weight of tablets / Average weight of tablets) x 100

According to USP, the specification limit and percentage deviation allowed for weight variation for tablets having

an average weight of 80 mg but less than 250 mg is ±7.5.

Friability test

The friability test is the loss of weight of a tablet during manufacturing or storage or transportation or handling due to the removal of fine particles from the surface. A Roche friabilator was employed to find the friability of the tablets. For tablets with a unit weight of less than 650 mg, take a sample of whole tablets equivalent to 6.5 g and load in the Roche friabilator. It is rotated at 25 rpm for 4 minutes for 100 revolutions and the loaded tablets were dedusted and weighed again. The percentage of weight loss was calculated using the formula and % friability of tablets less than 1% are considered acceptable.

Percentage friability = $[(W_0 - W_1) / W_0] \times 100$

Where, W_0 = Initial weight, W_1 = Final weight.

Estimation of drug content

From each formulation of mirtazapine ODT tablets, 10 tablets were taken randomly and powdered. A quantity equivalent to 15 mg of mirtazapine was transferred into a 100 ml standard flask, dissolved in 50 ml of ethanol. The volume was made up to 100 ml using 0.1N HCL. From stock solution 10 µg/ml solution was prepared. The drug content was estimated by measuring the absorbance of the solution at 316 nm using a UV-visible double-beam spectrophotometer.

Disintegration time

The disintegration test was carried out at 37°C±2°C in 900 ml of distilled water. The disintegration time of tablets from each formulation was determined using a disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was placed in each tube. The time taken in seconds for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

Wetting time

The wetting test is an important step in the disintegration process. Circular tissue paper of 10 c.m. diameter was placed in a petri dish with a 10 c.m. diameter. 10 ml of distilled water containing a yellow water-soluble dye (sunset dye), were poured into the tissue paper placed in the petri dish. A tablet was placed carefully on the surface of the tissue paper. The time required for the solution to reach the upper surface of the tablet was noted as the wetting time.

Water absorption ratio

The weight of the tablet before keeping it in the petridish was noted (Wb). A fully wetted tablet from the petridish was taken and reweighed (Wa). The water absorption ratio R can be determined according to the following formula.

Water absorption ratio (R) = $[(Wa - Wb) / Wa] \times 100$

Where, Wb - Weight of tablet before wetting, Wa - Weight of tablet after wetting.

In-vitro dispersion time

In-vitro dispersion time was measured by dropping a tablet in a 50 ml beaker in 10 ml of water and the time required for the complete dispersion of the tablet was determined.

Fineness of dispersion

The fineness of dispersion test was done by using two tablets placed in a 200 ml beaker with about 100 ml of water in it. The system is stirred gently to obtain a smooth dispersion and allow it to pass through a sieve screen with a nominal mesh aperture of 710 mm (sieve no 22). No particles or lumps should remain on the mesh.

In vitro dissolution studies

The dissolution test was performed in the Schimadzu dissolution testing apparatus. Dissolution samples (1ml) were collected at predetermined time intervals and replaced with an equal volume of 0.1 N HCL fresh medium. The study was conducted for 15 minutes, the samples were then filtered and analyzed at 316 nm using a UV spectrophotometer. The dissolution conditions and parameters are given below.

Apparatus: USP Dissolution apparatus, Type II (Paddle)
Medium: 900ml of 0.1 N HCL
Rpm: 50; Temperature: 37°C ± 0.5°C
Sampling interval: 3, 6, 9, 12 and 15 minutes
Sample withdrawn: 1 ml

Accelerated stability studies

Accelerated stability studies are conducted as per ICH stability guidelines by accelerating the parameters such as temperature and humidity. The prepared formulation was stored at 40°C ± 2°C & 75% ± 5% RH for 3 months. Then the samples were withdrawn at a specified period and analyzed the stability indicating parameters such as hardness, disintegration time, in-vitro dispersion time and dissolution at every one-month interval.

RESULTS AND DISCUSSION

Drug excipients compatibility studies

FTIR study was performed by using Schimadzu 160A, Kyoto-Japan. The IR spectra of mirtazapine pure drug were recorded and shown in Figure 1. The IR spectrum of the drug excipient mixture which includes mirtazapine, polacrilin potassium, citric acid, sodium bicarbonate, mannitol, microcrystalline cellulose, sucralose, strawberry powder flavor, talc and magnesium stearate is shown in Figure 2. In Table 3 the wavelength (cm^{-1}) of major peaks observed for the pure drug mirtazapine and its mixture containing tablet excipients are recorded.

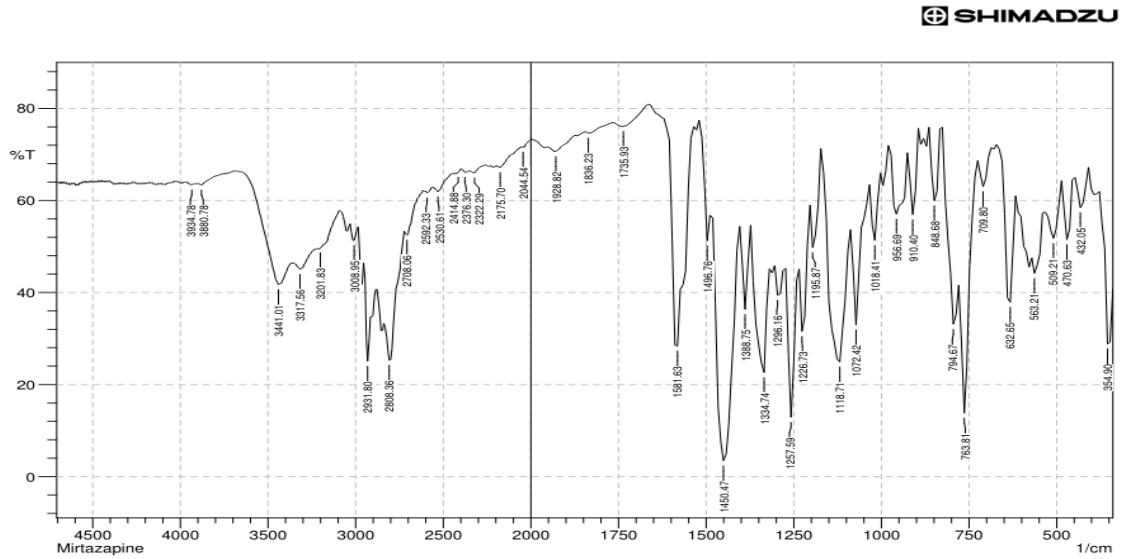

Figure 1: FTIR spectra of Mirtazapine.

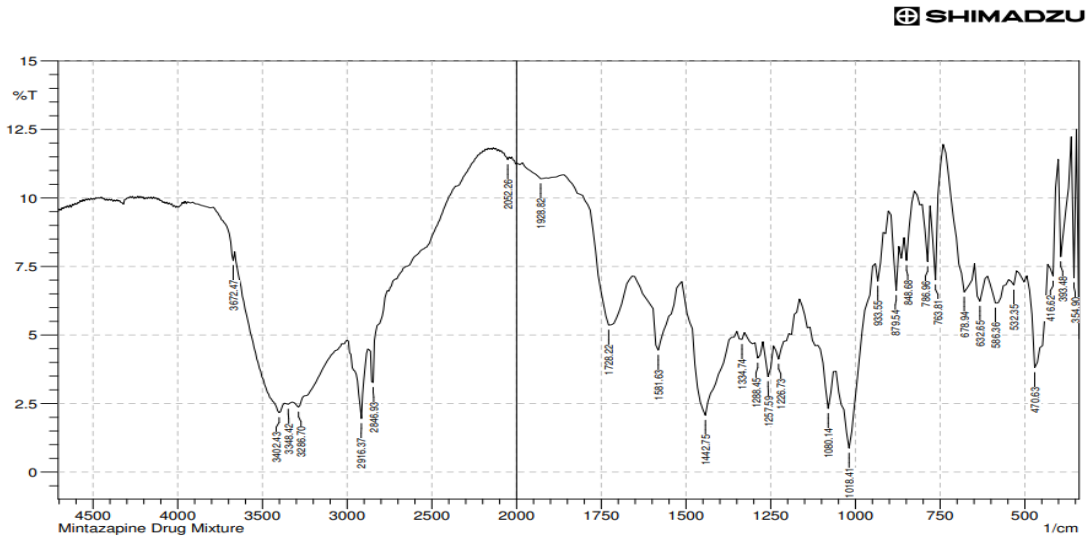

Figure 2: FTIR spectra of Mirtazapine drug with excipients mixture.

Table 3: Comparative FT- IR spectra of pure drug and drug excipients mixture.

S. No.	Functional group	Standard IR Spectral wavelength (cm^{-1})	Pure Drug	Drug mixture
1	N-H Stretching	3350 - 3500	3441	3402
2	C-H Stretching (CH3 group)	2800 - 3000	2931	2916
3	N-H bending	1500 - 1600	1581	1581
4	Pyridine ring	1400 - 1500	1450	1442
5	C-N Aromatic	1250 - 1350	1334	1334
6	Pyrazine ring	1000 - 1200	1072	1018
			1118	1080
7	Pyrazine ring	700 - 800	763	786
8	Pyrazine ring	600-700	632	678

The drug-excipient mixture has all the major peaks present in the pure drug IR spectra, hence it was proven that the drug is compatible with other excipients used in the formulation.

Evaluation of directly compressed tablets

Visual appearance

The appearance of all formulations (F1-F15) was examined visually and found to be a white, round shape with smooth surfaces and free of any cracks, depressions

and pinholes.

Tablet compression parameters

The prepared tablets were evaluated for various compression quality parameters such as thickness, hardness, weight variation and friability. The results are described in Table 4.

Table 4: Compression parameters.

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)
F1	3.38±0.01	4.6±0.29	99.25±5.47	0.32±0.02
F2	3.38±0.02	4.3±0.28	99.25±4.47	0.32±0.01
F3	3.36±0.01	4.6±0.38	100.23±5.38	0.31±0.01
F4	3.41±0.05	4.2±0.27	98.75±5.52	0.28±0.01
F5	3.40±0.07	4.2±0.27	100.70±3.51	0.28±0.02
F6	3.40±0.02	4.1±0.17	98.75±3.52	0.26±0.01
F7	3.36±0.06	4.5±0.49	98.90±5.47	0.25±0.02
F8	3.37±0.01	4.4±0.49	100.90±2.51	0.25±0.03
F9	3.36±0.04	4.5±0.50	100.95±5.51	0.26±0.01
F10	3.48±0.02	5.3±0.24	99.85±4.37	0.20±0.01
F11	3.48±0.03	5.6±0.45	100.85±5.37	0.20±0.01
F12	3.46±0.01	5.2±0.26	99.80±4.38	0.21±0.01
F13	3.43±0.08	5.2±0.33	99.75±5.45	0.22±0.03
F14	3.45±0.05	4.9±0.25	100.74±5.45	0.22±0.01
F15	3.45±0.06	5.2±0.24	99.75±5.45	0.23±0.01

Note: All values are expressed as mean ± SD, n=6.

The thickness of the tablets was measured and was found in the range between 3.36±0.01 mm and 3.48±0.03 mm, and hence there is no significant difference. The hardness of the tablets was measured and the values were found in the range between 4.14±0.17 to 5.25±0.45 kg/cm^2. These showing all batches of the prepared tablets had acceptable mechanical strength with sufficient hardness. In all the formulations the weight variation values of tablets range from 98.75±5.52 to 100.95±5.51 mg, which was within the acceptable variation limit of the tablet. Similarly, percentage friability values of the prepared mirtazapine orally disintegrating tablets showed less than 1% weight loss which is within the acceptable limit. Hence all the tablet formulation trials complies the friability test.

Disintegration study

The disintegration (DT) study results of mirtazapine ODTs are shown in Table 5.

Table 5: Disintegration study of Mirtazapine orally disintegrating tablets.

Formulation code	DT (sec)		Formulation code	DT (sec)
F1	63.28±0.23		F9	21.65±0.16
F2	50.00±0.18		F10	20.28±0.14
F3	38.93±0.17		F11	14.15±0.21
F4	55.17±0.20		F12	10.75±0.18
F5	41.68±0.19		F13	34.86±0.25
F6	32.35±0.25		F14	20.10±0.12
F7	39.77±0.18		F15	15.38±0.17
F8	26.18±0.12			

Note: All values are expressed as mean ± SD, n=6.

The disintegration test results of mirtazapine orally disintegrating tablets range from 10.75±0.18 to 63.28±0.23 seconds. The formulations F1, F2 and F3 have the disintegrant pregelatinized starch at a concentration of 1.5, 3.0 and 4.5% and show disintegration times of 63.28±0.23, 50.00±0.18 and 38.93±0.17 seconds, respectively. Similarly, the other formulations F4-F6 containing sodium starch glycolate show disintegration times of 55.17±0.20 to 32.35±0.25 seconds, respectively. Formulations F7-F9, F10-F12 and F13-F15 which contain croscarmellose sodium, polacrilin potassium and crospovidone respectively show minimum disintegration times of 21.65±0.16, 10.75±0.18 and 15.38±0.17 seconds, respectively at higher disintegrant concentration and 39.77±0.18, 20.28±0.14 and 34.86±0.25 seconds, respectively at lower disintegrant concentration. Hence, increasing the concentration of disintegrant impart better disintegration. Also, formulation containing polacrilin potassium (F10-F12) showed reduced disintegration time in comparison

to other disintegrants. The disintegrant mechanism plays an important role in the fast disintegration of mirtazapine tablets.

Drug content (Assay)

The Drug content of mirtazapine orally disintegrating tablets is given in Table 6.

Table 6: Drug content of Mirtazapine orally disintegrating tablets.

Formulation code	Drug content (%)		Formulation code	Drug content (%)
F1	98.85±0.17		F9	99.85±0.22
F2	98.85±0.15		F10	100.50±0.21
F3	98.82±0.18		F11	100.50±0.23
F4	98.92±0.25		F12	100.52±0.20
F5	98.95±0.18		F13	99.98±0.18
F6	98.95±0.18		F14	99.97±0.15
F7	99.86±0.21		F15	99.97±0.13
F8	99.85±0.25			

Note: All values are expressed as mean ± SD, n=6.

The drug content of mirtazapine in all formulations was found in the range of 98.82±0.18 to100.52±0.20 %, which was within the acceptable USP limits.

Wetting time, water absorption ratio, in-vitro dispersion time and fineness of dispersion

The prepared tablets were evaluated for wetting time, water absorption ratio, in-vitro dispersion time and fineness of dispersion. The results are shown in Table 7.

Table 7: Wetting time, water absorption ratio, in-vitro dispersion time and fineness of dispersion of Mirtazapine orally disintegrating tablets.

Formulation code	Wetting time (sec)	Water absorption ratio (%)	In-vitro dispersion time (sec)	Finess of dispersion
F1	110.26±0.42	85.22±0.21	112.1±0.18	Complies
F2	108.07±0.53	84.15±0.18	105.5±0.18	Complies
F3	112.14±0.45	84.76±0.15	101.7±0.15	Complies
F4	95.18±0.37	81.24±0.53	102.5±0.15	Complies
F5	94.45±0.35	81.49±0.43	92.17±0.12	Complies
F6	95.37±0.40	80.75±0.48	90.58±0.15	Complies
F7	88.25±0.52	85.25±0.14	68.17±0.10	Complies
F8	85.32±0.29	85.45±0.18	65.52±0.11	Complies
F9	86.44±0.26	85.48±0.17	62.25±0.15	Complies
F10	70.21±0.52	95.20±0.75	40.25±0.15	Complies
F11	70.15±0.51	95.25±0.62	42.18±0.12	Complies
F12	69.28±0.45	95.30±0.52	41.37±0.12	Complies
F13	72.39±0.74	90.12±0.82	65.31±0.17	Complies
F14	70.45±0.70	90.35±0.75	64.83±0.15	Complies
F15	71.18±0.72	90.20±0.69	62.95±0.13	Complies

Note: All values are expressed as mean ± SD, n=6.

The wetting time, water absorption ratio and in-vitro dispersion time of mirtazapine ODTs were found to be in the range between 112.14±0.45 to 69.28±0.45 seconds, 95.30±0.52 to 80.75±0.48% and 112.1±0.18 to 40.25±0.15 seconds, respectively. The water absorption ratio is directly proportional to the rate of dissolution, the higher the water absorption ratio faster the dissolution. Similarly wetting time and in-vitro dispersion time are indirectly proportional to the dissolution behavior, hence lower these values, the faster the dissolution. In the finess of dispersion test, the dispersion of all the formulations passed through sieve number 22 and complies with the test.

In vitro dissolution studies

The formulations having a disintegration time of fewer than 30 seconds, containing the disintegrants croscarmellose sodium, polacrilin potassium and crospovidone (F7 – F15) were selected and an in-vitro drug release study was performed. The drug release of mirtazapine orally disintegrating tablet was studied in 0.1 N HCL for up to 15 minutes. The dissolution results were given in Table 8 for the tablets along with one of the market-available samples.

Table 8: In-vitro drug release studies of Mirtazapine orally disintegrating tablets.

Formulation code	Percentage drug release (%)				
	3 minutes	6 minutes	9 minutes	12 minutes	15 minutes
F7 (CCS 1.5%)	56.1±0.6	60.3±0.2	66.8±0.2	71.3±0.3	80.2±0.6
F8 (CCS 3 %)	62.6±0.2	68.2±0.1	75.3±0.3	79.1±0.7	85.3±0.3
F9 (CCS 4.5%)	65.2±0.7	71.2±0.2	78.5±0.2	82.2±0.1	90.5±0.2
F10 (PP 1.5%)	70.6±0.2	79.6±0.2	92.8±0.2	100.1±0.2	100.3±0.1
F11 (PP 3%)	76.3±0.2	90.6±0.2	96.9±0.2	100.3±0.2	100.4±0.1
F12 (PP 4.5%)	82.7±0.2	92.9±0.3	100.4±0.2	100.6±0.2	100.7±0.3
F13 (CP 1.5%)	60.3±0.2	70.4±0.2	85.6±0.1	92.7±0.2	96.9±0.2
F14 (CP 3%)	65.6±0.2	78.9±0.2	90.6±0.4	98.1±0.6	100.1±0.2
F15 (CP 4.5%)	73.4±0.2	86.3±0.6	96.4±0.2	98.5±0.2	100.1±0.1
Market sample	63.2±0.1	74.4±0.2	85.2±0.2	92.2±0.2	99.5±0.2

Note: All values are expressed as mean ± SD, n=6. CCS – Croscarmellose sodium, PP – Polacrilin potassium, CP – Crospovidone.

The graphical representation of the dissolution profile comparison between the prepared formulations was shown in Figures 3, 4 and 5.

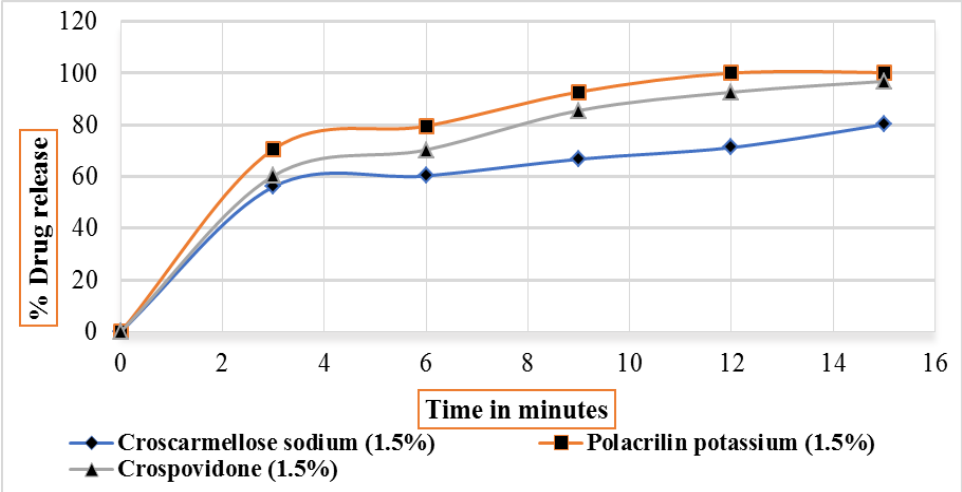

Figure 3: Dissolution profile for orally disintegrating tablets of Mirtazapine containing different super disintegrants at 1.5% concentration.

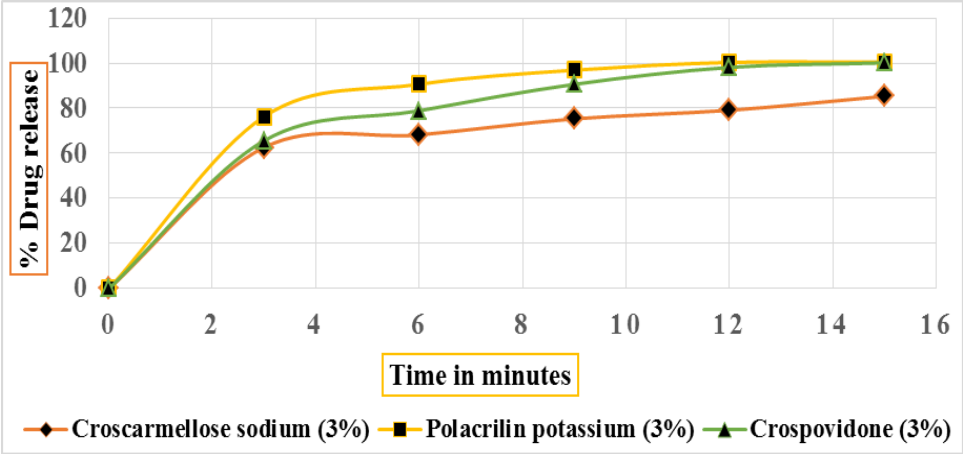

Figure 4: Dissolution profile for orally disintegrating tablets of Mirtazapine containing different super disintegrants at 3% concentration.

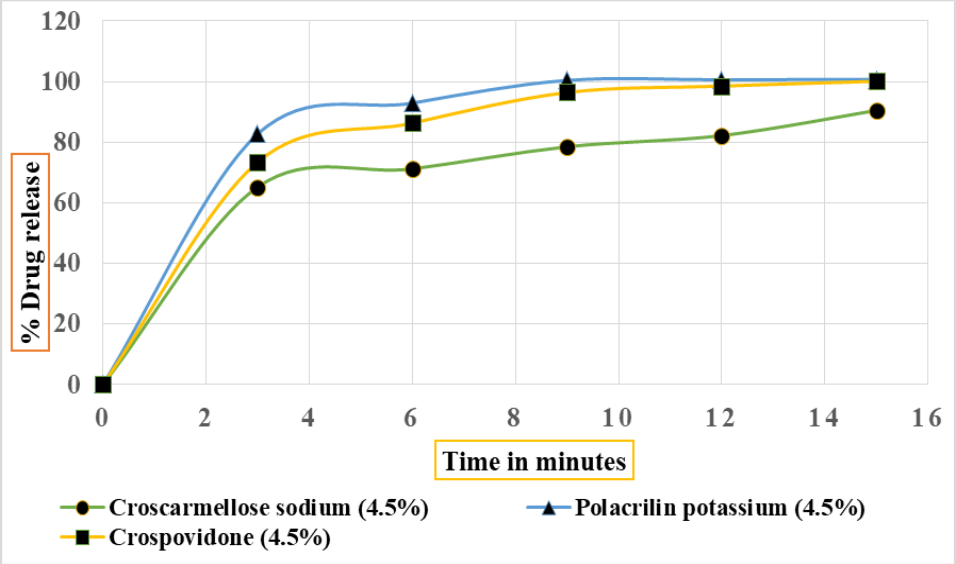

Figure 5: Dissolution profile for orally disintegrating tablets of Mirtazapine containing different super disintegrants at 4.5% concentration.

The drug release of formulations F7, F8 and F9, which contain croscarmellose sodium at a concentration of 1.5%, 3% and 4.5% were found to be 80.16±0.62%, 85.25±0.28% and 90.50±0.18% respectively at 15 minutes. The formulation F10 and F11 which contains polacrillin potassium at 1.5% and 3% showed drug release of 92.75±0.15% and 96.95±0.21% respectively at 9 minutes. Formulation F12 containing polacrillin at 4.5% concentration releases 92.95±0.22% at 6 minutes. In further trials F13 containing crospovidone at a concentration of 1.5%, the drug release was found to be 92.73±0.18% at 12 minutes, whereas F14 and F15 contained 3% and 4.5% concentration of crospovidone showing drug release of 90.56±0.40% and 96.35±0.15% respectively at 9 minutes. Polacrilin potassium (PP) is a monofunctional minimally crosslinked carboxylic acid-exchange resin prepared by the copolymerization of methacrylic acid with divinylbenzene and subsequently neutralized with potassium hydroxide. PP is an efficient disintegrant in low concentration. The functionality of PP as a super disintegrant is related to its fluid uptake by wicking which is capillary action and swelling characteristics. PP has a very high swelling tendency on hydration and fast disintegration without the formation of lumps. In comparison to other disintegrants both the properties of wicking and swelling characteristics of PP in the formulation F10-F12 attribute an increased quantity of solvent uptake and better disintegration followed by dissolution. The order of enhancement of the dissolution rate with various super disintegrants at various concentrations was found to be:
Polacrillin potassium (F10-F12) > Crospovidone (F13-F15) > Croscarmellose sodium (F7-F9).

In Figure 6, the comparison is established between the prepared trial tablets and with market sample. Formulations F8, F11 and F14 having 3% medium concentration of croscarmellose sodium, polacrilin potassium and crospovidone respectively as disintegrants were compared to the marketed sample.

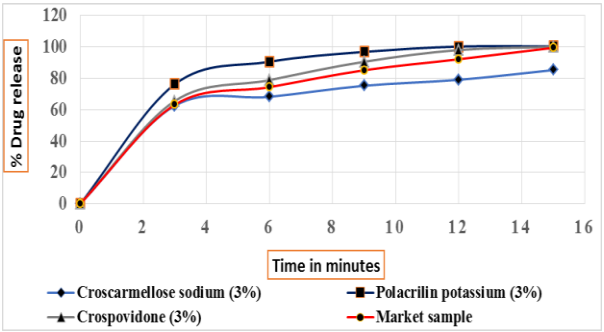

Figure 6: Comparative dissolution profile of Mirtazapine tablets prepared using different disintegrants with market sample.

Formulation containing polacrilin potassium shows an increased rate of drug release compared to all other formulations and market samples due to its mechanism as discussed earlier under in-vitro dissolution studies.

5.3 Accelerated stability studies for the formulation of orally disintegrating tablets

The formulations F8, F11and F14 having a medium level of disintegrants concentration of 3% including croscarmellose sodium, polacrilin potassium and crospovidone were selected for the stability study and stored at 40°C ± 2°C & 75% ± 5% RH for 3 months. Samples were withdrawn at a specified period and analyzed the stability indicating parameters such as hardness, disintegration time, in-vitro dispersion time and dissolution at every one-month interval. For in-vitro drug release testing samples were analyzed at 6 and 15-minute time points. The stability results were compiled and the results were shown in Table 9.

The stability study revealed that there were no significant changes observed between the initial analysis results and

with end of the stability analysis for 3 months of storage at accelerated storage conditions.

Table 9: Stability data for Mirtazapine orally disintegrating tablets.

Formulation details and sampling period		Stability indicating parameters				
		Hardness (Kg/cm^2)	Disintegration time (sec)	Invitro dispersion time (sec)	In-vitro drug release (%)	
					6 mins	15 mins
F8 - contains Croscarmellose sodium 3%	Initial	4.4±0.49	26.18±0.12	65.52±0.11	68.2±0.1	85.3±0.3
	1 M	4.5±0.45	25.78±0.20	63.88±0.09	67.8±0.5	86.4±0.2
	2 M	4.6±0.77	27.97±0.17	65.01±0.22	68.9±0.3	84.7±0.6
	3 M	4.2±0.95	26.17±0.22	65.78±0.30	68.0±0.4	84.1±0.3
F11 - contains Polacrilin potassium 3%	Initial	5.6±0.45	14.15±0.21	42.18±0.12	90.6±0.2	100.4±0.1
	1 M	4.9±0.20	13.66±0.37	44.08±0.37	91.7±0.8	98.4±0.7
	2 M	5.2±0.25	15.08±0.27	42.44±0.27	88.6±0.4	100.4±0.3
	3 M	5.2±0.25	14.74±0.13	43.17±0.52	89.6±0.2	99.2±0.6
F14 - contains Crospovidone 3%	Initial	4.9±0.25	20.10±0.12	64.83±0.15	78.9±0.6	100.1±0.2
	1 M	5.2±0.30	21.44±0.29	65.24±0.28	79.9±0.3	100.4±0.4
	2 M	5.1±0.15	21.79±0.21	63.55±0.70	78.0±0.9	99.7±0.5
	3 M	5.0±0.40	20.91±0.19	65.02±0.85	78.0±0.4	99.4±0.8

CONCLUSION

In this present research work, the taste-masked mirtazapine drug granules were formulated into solid dosage forms of orally disintegrating tablets by direct compression method which is an easy process and cost-effective. FT-IR studies revealed that there was no chemical interaction between mirtazapine and the excipients used for the preparation of tablets. The type of disintegrants and their concentration; other excipients like mannitol, microcrystalline cellulose, flavours and sweeteners used in the formula played a vital role in the quality parameters of compressed tablets. Formulations having less wetting and dispersion time show fast disintegration and quick release of the drug in the medium. A higher rate of drug release was observed in tablets prepared using polacrilin potassium which improves the dissolution behaviour and hence it imparts better oral bioavailability of the drug. Among all the formulations, F12 containing polacrilin potassium of 4.5% concentration showed the least disintegration time of 10.75±0.18 seconds, wetting time of 69.28±0.45 seconds and more than 90% drug release within 6 minutes. The addition of super disintegrants and selected excipients of optimum concentration is a promising approach to preparing orally disintegrating tablets of mirtazapine. Hence, using this efficient formulation method, the bitter drug mirtazapine can be formulated into a dosage form of orally disintegrating tablets with all improved quality characteristics. Further, the systemic absorption of prepared formulations will be established by conducting bioequivalence or clinical study for its therapeutic effect and scale-up to be done for commercial manufacturing.

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