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DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS OF MIRTAZAPINE

Lavali Singh[1]†, Ashok Singh Baghel[2], Dinesh Kumar Sharma[3], Vishnu Kant Rai[4], Yogendra Singh[5]

[1-3, 5]Shri Ramnath Singh Mahavidyalaya (Pharmacy), Gormi, Bhind (M.P.) – 477660, India

[4]Azad College of Education (Pharmacy), Sakha Janwara, Ghatampur, Kanpur Nagar, U.P., India

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Corresponding Author:
† Lavali Singh,

† Shri Ramnath Singh Mahavidyalaya (Pharmacy), Gormi, Bhind (M.P.) – 477660, India

E-mail ID-
lavalisingh3003@gmail.com

ABSTRACT

Depressed mood, loss of interest or pleasure, guilt or low self-esteem, interrupted sleep or food, low energy, and difficulty concentrating are all symptoms of depression, a common mental illness. The antidepressant medication mirtazapine has a remarkable pharmacological profile. Additionally, its safety and tolerability profile is outstanding. In this study, a fast-dissolving tablet of mirtazapine (MTZ) was developed and evaluated utilizing co-processed excipients that contained mannitol and sodium starch glycolate. It is predicted that using a fast-dissolving dosage form will boost bioavailability and increase permeability across the blood-brain barrier due to its lipophilic nature. The formulation MFSC8 containing of sodium starch glycolate and croscarmellose sodium was found to have a higher percentage of dissolved in 5 minutes and to release the maximum amount within 1 to 2 hours, according to the physical characteristics of Mirtazepine fast dissolving tablets, in-vitro disintegration time, and in-vitro dissolution studies. As a result, MFSC8 is regarded as the best version of mirtazepine. We may conclude that the formulation of the tablet that contains mirtazepine can improve the drug's therapeutic efficacy.

Keywords: Mirtazapine, sodium starch glycolate and croscarmellose sodium, Microcrystalline Cellulose, fast-dissolving tablet, Bioavailability.

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INTRODUCTION

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities [1].

Excipients which are generally used in FDTs preparation should contain at least one superdisintegrant, a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweetening and flavoring agents as well. As most drugs are unpalatable, FDTs usually contain the medicament in a taste-masked form. FDTs after administration, it disintegrates or dissolves in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds. Hence, taste-masking of the drugs becomes critical to patient compliance. There are several biopharmaceutical advantages such as improved efficiency over conventional dosage forms for Fast disintegrating tablets. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. There are still many aspects to improve in the FDT formulations. The

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disintegration times of most FDTs on the market are acceptable i.e., less than 60 seconds but certainly there is a room for improvement. Because the disintegration time is related to other formulation variables, a balance has to be maintained between shortening the disintegration time and other tablet properties. The tablet hardness, friability, and stability can be further improved to such a level that multi-tablet packaging in conventional bottles becomes a norm. There may be no magic solution to this, but more effective use of existing taste masking technologies is expected to alleviate the problems associated with taste masking. The future of FDTs lies in the development of FDTs with controlled release properties. Despite advances in the FDT technologies, formulation of hydrophobic drugs is still a challenge, especially when the amount of drug is high [2,3-8]. Sharma R., et al., 2011, reported that the fast-dissolving tablets are those which disintegrate within 3 min. FDTs also do not require water because when it is placed in the mouth, it rapidly disintegrates and the drug is released in mouth itself. The FDTs are most useful for patients like paediatric, geriatric, dysphagia and those who are frequent travellers and who cannot carry water with them [11]. Rai RR, et al., 2012, published that FDTs has a wide range of application and can be used in formulating classes of drugs like anti-muscarinic, opioid analgesics, anthelmintic, antimalarial, antigout, antimigraine, NSAIDs, anti-arrhythmic and anti-angina, steroids, local anaesthetics, etc [12]. Bala R., et al., 2013, Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for the pediatric and geriatric patient. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds [13].

Mirtazapine is an antidepressant drug with an exceptional pharmacological profile. It also has an excellent safety and tolerability profile. The present review provides a pharmacological update on mirtazapine and summarizes the research findings of mirtazapine's effects on different diseases. Mirtazapine is hypothesized to have antidepressant effects because of the synergy between noradrenergic and serotonergic actions and is effective in treating major depressive disorder and depression associated with epilepsy, Alzheimer's disease, stroke, cardiovascular disease, and respiratory disease. In cancer patients, mirtazapine significantly reduced sadness, nausea, sleep disruption, and pain and improved quality of life. Literature review has revealed that mirtazapine is practically insoluble in water and that no study on the enhancement of the drug's aqueous solubility by cosolvency and micellization has been reported. Therefore, we took to investigate the extent to which the aqueous solubility of mirtazapine could be enhanced by cosolvents (propylene glycol, polyethylene glycol 400) and surfactants (sodium lauryl sulfate, polysorbate 20, polysorbate 80) while envisaging that the aqueous solubility enhancement could potentially alleviate the drug problems that contribute to its withdrawal symptoms. Mirtazapine is practically insoluble in water and its logarithm partition coefficient (octanol-water) is 2.9, indicating high hydrophobicity. Due to potential withdrawal symptoms, such as diarrhea, nausea, anxiety, aggression, irritability, internal restlessness, hostility, deep depression etc., that occur during therapy with mirtazapine, the drug does not belong to the first line of antidepressants. These withdrawal symptoms could arise due to its very poor water solubility and high lipophilicity. The usual starting dose for mirtazapine is 15mg to 30mg a day. The pharmacokinetics of mirtazapine indicates that the drug has average bioavailability (50%), high protein binding (85%) and very high half-life (20 - 40 h)[14-16].

It was therefore envisaged that enhancement of aqueous solubility of mirtazapine could lead to improvement in its bioavailability, reduction in protein binding and half-life and invariably a decrease in its withdrawal symptoms. The present research involves the development and evaluation of Fast dissolving tablet of Mirtazapine (MTZ) by using co-processed excipients containing Sodium starch glycolate and mannitol was studied. It is hypothesized that utilizing fast dissolving dosage form will be able to increase bioavailability and its lipophilic nature increase permeability across the blood brain barrier.

MATERIAL AND METHODS

Mirtazapine was obtained as a gift sample from Sun Pharmaceutical Industries Ltd., Vadodara, India. Magnesium Stearate, and Talc were purchased from Loba Chemie, Mumbai, India. Sodium starch Glycolate, Croscarmellose Sodium and all others excipients were obtained from Merck Ltd, Ahmedabad, India. All other ingredients and reagents were of analytical grade.

PREPARATION OF FAST DISSOLVING MIRTAZEPINE TABLET BY USING DIRECT COMPRESSION METHOD [17-28]:

All formulations were prepared following direct compression method with single hand punching machine. Total nine formulations were prepared by varying in quantity of ingredients.

Powder blends of Mirtazepine, microcrystalline cellulose, mannitol and various superdisintegrants (Sodium starch Glycolate and or Croscarmellose Sodium) in various concentrations were mixed for 20-25 min. Magnesium stearate and talc were added to the above mixture. The Powder mixture was made to undergo direct compression using a tablet punching machine. For uniformity in particle size, each ingredient was passed through # 100 mesh sized screen before mixing. *S*odium starch glycolate, Croscarmellose Sodium, mannitol and microcrystalline cellulose were accurately weighed and mixed using mortar and pestle, and the added to mirtazepine. Finally, talc and magnesium stearate were added to the powder mixture. The various formulation trials were formulated using different superdisintegrants and they were given in **Table 1.**

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Table 1: Formulation of Mirtazepine FDTs.

Ingredients (mg/tablet)	MFS1	MFC2	MFS3	MFC4	MFSC5	MFSC6	MFSC7	MFSC8
Mirtazepine	15	15	15	15	15	15	15	15
Sodium starch Glycolate	15	---	30	--	15	15	30	30
Croscarmellose Sodium	----	15	--	30	15	30	15	30
Mannitol	100	100	85	85	85	70	70	55
MCC	250	250	250	250	250	250	250	250
Talc	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10
Total	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

EVALUATION OF MIRTAZEPINE FAST DISSOLVING TABLETS [18-28]

PRE-COMPRESSION PARAMETERS

For any drug, the pre-compression parameters have been studied in detail to know about the physical property (angle of repose, bulk density, tapped density, compressibility index /Carr's index, Hausner's ratio) of the drug.

Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by transferring the accurate weighed amount of sample in 50ml measuring cylinder, measured the volume of packing and tapped 50 times on a plane surface and tapped volume of packing recorded and LBD and TBD calculated by following formula.

$$LED = \frac{\text{Mass of powder}}{\text{Volume of packing}}$$

$$TBD = \frac{\text{Mass of powder}}{\text{Tapped volume of packing}}$$

Percentage compressibility index Percentage:

Compressibility of the powder mixed was determined by Carr's Compressibility Index calculated by the following formula-

% Carr's Index = (*TBD – LBD)*100/ TBD*

LBD = loose bulk density

TBD = Tapped bulk density

Angle of repose:

The frictional forces in loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a mass of powder or granules and the horizontal plane. The angle of repose is calculated-

$$\tan \theta = h/r \quad \theta = \tan^{-1} h/r$$

θ = Angle of repose : h = Hight of pile : r = Radius of pile

Hausner Ratio:

The ratio of the tapped density to the bulk density is Hausner's ratio. The formula calculates it as follows

Hausner's ratio= TBD/LBD

Where,

LBD = loose bulk density

TBD = Tapped bulk density

POST-COMPRESSION PARAMETERS

For any tablet the post-compression parameters were mandatory and these parameters have to be performed to alter the pharmacokinetic property of the drug.

Size, Shape, Thickness and colour of tablets

The uncoated tablets are analyzed for shape and colour under a microscope. The **size and shape** of tablet can be dimensionally described, covered and controlled. **Tablet thickness** is an important parameter in reproducing appearance and also in counting by using filling outfit. Some filling outfit utilizes the even consistence of the tablets as a counting procedure. Ten tablets were taken and their thickness was recorded using micrometer. [22-26]

Hardness test

The hardness of the tablet shows the capability of the tablet to resist mechanical strength while handling it. The hardness of the tablets was found using the Monsanto hardness tester. It was denoted in kg/cm^2. Randomly 5 tablets were taken from every formulation and the average and SD (standard deviation) were found.

Weight variation test

Randomly from each formulation 20 tablets were picked weighed individually the mean and the standard deviation were evaluated.

Friability test

The friability of tablets was measured using a Roche fribilator. Friabilator possesses a chamber made of plastic that is usually made to revolve at Revolutions per minute (RPM) of 25, during the revolution it drops those tablets from a distance of six inches during every revolution. The tablets were placed in the friabilator for a minimum of four minutes. After the end of the process, processed tablets were dusted and reweighed, the weight of the tablet loss gives the friability and is expressed in percentage as-

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$$F = \frac{100 \times W(\text{initial}) - w(\text{final})}{W(\text{initial})}$$

The tablets whose weight loss was more than 1% weight were specified to be non-compliant.

Wetting time of tablets:

A piece of tissue paper was folded twice in a tiny Petri dish with 10 ml of water (internal diameter-6.5), a tablet was positioned on paper and the total wetting time was evaluated.

Disintegration time:

It is the time taken by the tablet to split into the small, specified size of granules under pre-set test parameters. The tablet disintegration time was found by the Indian Pharmacopeia specified disintegration test apparatus. One tablet is kept in each of the six tubes of the basket. Then the disc is added to all 6 tubes and the apparatus was made to run at 37±2°C using phosphate buffer pH 6.8 (simulated saliva fluid) as immersion fluid. The apparatus assembly was made to raise and low for about 30 cycles per minute. The time taken by the apparatus to completely disintegrate the tablet without any palpable mass was recorded in seconds.

Drug Content:

The content of mirtazepine in the formulated tablet was measured by randomly picking 10 tablets from the batch and then powdered by using a mortar and pestle. Then the powder of weight equivalent to 5mg of mirtazepine was dissolved in methanol and then diluted up to 100mL using the same. The drug content of mirtazepine tablets was estimated by taking 10 tablets which were crushed using a mortar and pestle. The weight of powder equivalent to 5 mg of the drug was dissolved in methanol and diluted up to 100mL with the same. From this solution, 1 mL was further diluted to make up 10 mL using the methanol. Then the absorbance of this resulting solution was determined at 233nm spectro-photometrically. The content of the drug in the tablet was found using the calibration curve.

In vitro dissolution study:

In vitro dissolution study was performed using USP XXII rotation basket method, which is made to revolve at 75 rpm. One tablet was positioned in each of 6 dissolution baskets having 900mL of 0.1 N HCl (pH 1.2) as a medium which was studied at 37°C ± 0.5°C previously. After each time intervals of 5, 10, 20, 30, 50, 60, and 120 min, 5ml of the aliquot was withdrawn from midway of the zone between the top of the rotating blade and surface of the dissolution medium, not less than 1 cm from the sides of the vessel wall and filtered by using 0.45µm membrane filter and same amount of fresh dissolution medium was transferred after withdrawing each samples. The samples collected at predestined time intervals were diluted to the needed volume with help of a medium. The samples were measured by UV-spectrometry at 232nm. Then the percentage of drug release was measured using an equation from a standard calibration curve.

Conditions

Dissolution apparatus method	: USP XXII rotation basket
Dissolution medium	: 900 ml
R.P.M.	: 75
Temperature	: 37 ± 0.5ºC
Dissolution media	: 0.1 N HCl (pH 1.2)
Tablet mg of mirtazepine	: Equivalent weight to 15
Sampling time and 120 min	: 5, 10, 20, 30, 50, 60,
Sampling quantity replacement	: 5ml aliquots with

Stability study (Temperature dependent):

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation (dosage form or drug product) in a specific container and closer system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its self life" [21-24].

The stability of a product can be evaluated if its degradation impurities, it's assay, its dissolution and disintegration time does not generate/alter considerably after 6 months of accelerated stability testing at 40°C and 75% RH as per the ICH guidelines [22].

The best selected fast dissolving tablet formulations are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines at 40 ± 1 °C and RH 75% ± 5% .

The tablets were withdrawn after a period of 30, 60 and 90 days and analyzed for friability, hardness, thickness and drug content and cross checked the dissolution profile.

Data analysis:

Results are expressed as mean values and standard deviation (±S.D.) and the significance of the difference observed was analyzed by the Student's t-test. In all tests, a probability value of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSIONS:

Drug excipients interaction study:

This study was carried out to check for any possible interaction between the drug and excipients. Drug and various excipients (Microcrystalline cellulose, mannitol, Sodium starch Glycolate and or Croscarmellose Sodium) were mixed separately in a ratio of 1:1 and were stored at room temperature and checked visually after one month interval for 3 months. If any coulor changes are there, then it may be due to interaction of drug with excipients **(table 2).** Finally it was analysed for quantification of pure drug through UV-visible spectrphotometric methods. Later on it was further confirmed by FTIR & DSC studies.

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Table 2: Changes of physio-chemical behaviour of drug with excipients

Sl. No.	Drug: Excipients (1:1)	Color of physical mixtures			Analysed by UV-visible spectrophotometer
		After 1 month	After 2 months	After 3 months	% of drug in physical mixures
1	Drug: Sodium starch Glycolate	No change	No change	No change	98.65
2	Drug: Croscarmellose Sodium	No change	No change	No change	98.79
3	Drug: Microcrystalline cellulose	No change	No change	No change	98.92
4	Drug: mannitol	No change	No change	No change	98.77

IR Spectroscopy:

Excipient compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish or rules out any possible interaction of Microcrystalline cellulose, mannitol, Sodium starch Glycolate and or Croscarmellose Sodium.

The FT-IR spectra of the coprocessed excipient were compared with the FT-IR spectra of pure compound. The results are shown in below figures, indicating that there is no significant shift in the IR values; hence it may conclude that there is no chemical interaction between Microcrystalline cellulose, mannitol, Sodium starch Glycolate and or Croscarmellose Sodium.

The FTIR spectrum of drug sample showed sharp peaks at 3439.42 cm^{-1} (N-H stretching), a band at 2932.23 cm^{-1} arising from a methyl group connected to N_2 atom, and bands for C–C stretching of the phenyl group at 1584.24 cm^{-1} and 1447.31 cm^{-1}. The bands at 1336–1253 cm^{-1} were produced by primary aromatic amines with N directly linked to the ring. The benzene ring C–H arises in the 1359–1074 cm^{-1} range **(Fig. 1 and 2).**

The absorption peaks of the sample were found to be identical to the FTIR spectra **(Fig. 1)** of mirtazepine as reported in the literature which confirmed the gift sample was mirtazepine [4-7].

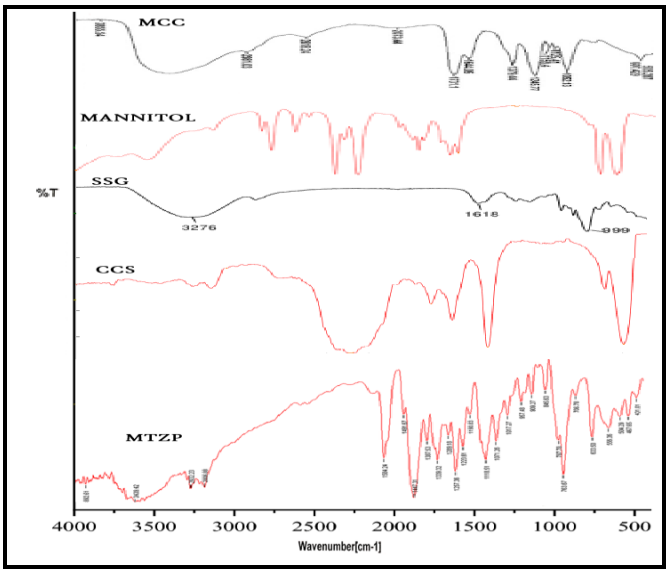

Figure 1: IR Spectra of drug and different excipients

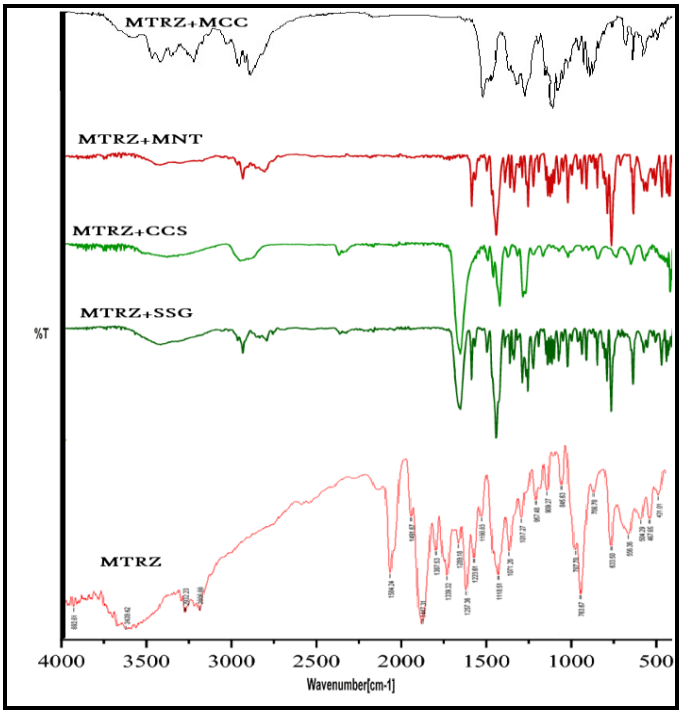

Figure 2: IR Spectra of drug with different excipients

PREPARATION OF FAST DISSOLVING MIRTAZEPINE TABLET BY USING DIRECT COMPRESSION METHOD:

Total 8 nos. of formulation of Mirtazepine FDTs (F1-F8) were prepared with two different superdisintegrants mainly with sodium starch glycolate and or Croscarmellose Sodium, and other additives likes mannitol and microcrystalline cellulose (disintegrant) were mixed using mortar and pestle, and finally all were lubricated with small amount of talc and Magnesium Stearate. MFS1 and MFS3 were prepared with only Sodium starch Glycolate without addition of any Croscarmellose Sodium whereas MFC2 and MFC4 were prepared with Croscarmellose Sodium only without addition of any Sodium starch Glycolate. But other 4 formulations like MFSC5, MFSC6, MFSC7 and MFSC8 were prepared with both the combinations of Sodium starch Glycolate and Croscarmellose Sodium by using different amounts.

PRECOMPRESSION EVALUATIONS

Micrometric properties of Mirtazepine Fast dissolving tablets were summarized and given in **Table 3.** The micrometric study of Mirtazepine FDTs signifies that there was no conclusive change in all formulations. The result was found to be within the acceptable range and passed the test.

The precompression evaluation like tapped density, bulk density, Carr's index, Hausner's ratio and angle of repose was calculated for all formulation and all the results were tabulated in **table 3.**

The bulk density was found in the range of 0.42 to 0.57 gm/cm^3, tapped density was found in the range of 0.56 to 0.76 gm/cm^3. Compressibility index was observed in the range of 15.10 to 34.10 which indicate good flowability and compressibility of the powder blend. Hausner's ratio results in the range of 1.16 to 1.53, which showed different pattern of flow properties of formulated batches. On the basis of all the data of precompression it may be concluded that the flow properties of all the mixing powders are within the good to passable limit.

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Table 3: Results of Pre-compression parameters-

Formulation code	Bulk Density (gm/cm³)	Tapped Density (gm/cm³)	Carr' s index (CI) %	Hausner' s Ratio	Angle of Repose (⁰)
MFS1	0.50	0.62	19.35	1.24	26.20±0.60
MFC2	0.51	0.74	31.00	1.45	23.22±0.44
MFS3	0.48	0.73	34.10	1.53	24.72±0.88
MFC4	0.52	0.63	17.46	1.21	28.26±0.67
MFSC5	0.54	0.76	28.00	1.38	23.52±0.18
MFSC6	0.50	0.59	16.25	1.18	28.22±0.69
MFSC7	0.57	0.66	15.10	1.16	29.22±0.38
MFSC8	0.42	0.56	24.56	1.33	28.35±0.67

POST COMPRESSION PARAMETERS

The post compression parameter of formulated tablets showed promising results which comply the pharmacopeial limits also and all the results were tabulated in **table 4.**

The tablets weight variation was in the range of 0.75 to 1.15% which reveals good control of weight of tablets by the powder blend. The tablets hardness was found in the range of 2.94±0.5 to 3.37±0.45 kg/cm². This revealed that, good mechanical properties were maintained among all the formulated tablets. The thickness of tablets was in the range of 2.53±0.11to 2.82±0.12 nm. Post-compression results of Mirtazepine fast dissolving tablets showed there were no dominant differences in the thickness of the tablet, and weight variation in all the formulations (MFS1-MFSC8).

The friability of all batches was found less than 1%. The drug content of different batches was found in the range of 98.0±0.14to 99.9±0.05. The wetting time was found in the range of 16.2±2.42 to 46.3±2.22 second. The disintegration time was found in the range of 22.0±1.62 to 42.2±2.43 second.

Table 4: Result of the post-compression parameter-

Formulation code	Weight variation %	Hardness (Kg/cm²)	Thickness (mm)	Friability (%)	Drug content (%)	Wetting time (sec)	Disintegration time (Sec)
MFS1	0.85	3.37±0.04	2.62±0.40	0.69±0.01	99.8±0.37	32.2±2.08	39.3±3.05
MFC2	0.86	3.32±0.04	2.62±0.02	0.65±0.01	99.9±0.02	46.3±2.22	42.2±2.43
MFS3	1.18	3.35±0.07	2.72±0.13	0.58±0.01	98.9±0.01	26.2±3.51	30.2±1.63
MFC4	0.80	3.09±0.06	2.56±0.25	0.69±0.05	99.9±0.05	34.3±1.52	38.3±2.08
MFSC5	0.75	3.37±0.45	2.72±0.09	0.55±0.01	99.4±0.16	22.3±1.52	28.3±1.52
MFSC6	0.58	2.94±0.50	2.53±0.11	0.59±0.01	98.9±0.37	19.3±2.52	26.3±2.32
MFSC7	1.15	3.20±0.015	2.53±0.57	0.59±0.03	99.1±0.08	17.3±1.15	25.1±3.23
MFSC8	0.96	3.19±0.005	2.82±0.12	0.66±0.01	98.0±0.14	16.2±2.42	22.0±1.62

Evaluation of tablets [table 4]:

Hardness:

The tablets hardness was found in the range of 2.94±0.5 to 3.37±0.45 kg/cm². All tablets were found hard enough so they could undoubtedly endure the taking care of and capacity conditions without becoming broken.

Weight variation:

The tablets weight variation was in the range of 0.75 to 1.15% which reveals good control of weight of tablets by the powder blend.

Friability:

All the tablets exhibited acceptable friability as none of the tested batches showed percentage friability that exceeded 1%. Thus, it was proved that tablets could withstand the pressure, mechanical shocks during handling, transportation, storage and manufacturing processes.

Drug content:

The drug content of different batches was found in the range of 98.0±0.14to 99.9±0.05. Hence, it can be concluded that all the formulations are having an accurate amount of drug distributed uniformly in powder mass and followed acceptable limits as per IP . i.e. 85 to 115 % of average content **table 4.**

Disintegration studies:

The disintegration time was found in the range of 22.0±1.62 to 42.2±2.43 second. *In vitro* disintegration time was done by the USP disintegration apparatus. The disintegration rate has a correlation with water absorption capacity of disintegrate. The outcomes were tabulated and data demonstrated in **table 4.**

All the formulation showed disintegration time of less than 42s. It was found that the formulation MFSC8 will show least disintegration time 22s as compare to other formulation.

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The order for a disintegration time in the fast dissolving tablet was found to be MFSC8 <MFSC7<MFSC6 <MFSC5 <MFS3<MFC4 <MFS1 <MFC2. The order of disintegration time may be due to the interaction and main effects of the super disintegrants used in the fast dissolving tablets **(Fig. 3).**

Wetting time:

The wetting time was found in the range of 16.2±2.42 to 46.3±2.22 second. This increased behavior due to the water taking the ability of super disintegrants. The wetting time found was tabulated and data demonstrated in **table 4**.

It was found that the formulation MFC2 containing 15mg croscarmellose sodium showed highest wetting time i.e. 46.3±2.22 s compared to other formulations. Whereas it was found that the formulation MFSC8 containing 30 mg Sodium starch Glycolate and 30 mg croscarmellose sodium showed less wetting time i.e. 16.2±2.42s The order for a wetting time in the fast dissolving tablet was found to be MFSC8 <MFSC7<MFSC6 <MFSC5 <MFS3<MFC4 <MFS1 <MFC2 **(Fig. 3).**

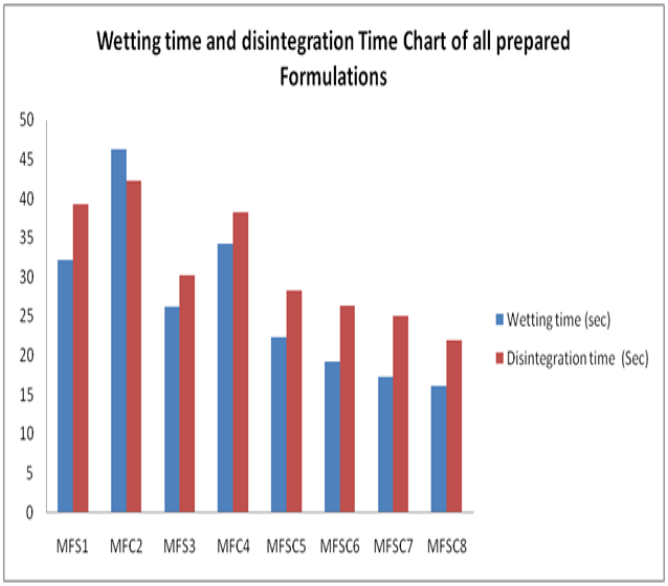

Figure 3: Comparative study of wetting time and disintegration time of all prepared Formulations

***In vitro Dissolution* studies:**

Table 5: Result of cumulative % drug release of FDT of Mirtazepine formulations

Formulations code	Time (min)						
	5	10	20	30	50	60	120
MFS1	18.5±0.45	31.16±1.05	43.03±1.68	51.56±0.83	61.56±1.51	68.36±1.38	76.9±1.90
MFC2	14.03±0.86	22.7±1.21	30.96±1.70	42.43±1.20	51.5±0.88	62.46±0.90	72.03±1.07
MFS3	24.83±0.95	41.7±1.5	55.23±1.05	68.43±1.07	81.76±1.07	87.33±0.8	91.36±1.2
MFC4	20.33±0.68	34.86±1.497	45.8±1.053	57.86±1.46	65.43±0.70	73.5±0.70	82.4±0.80
MFSC5	20.96±1.68	36.43±1.07	52.36±2.08	62.73±1.35	75.3±1.37	81.23±1.00	88.3±0.80
MFSC6	28.46±1.22	45.6±1.07	61.63±0.8	72.6±0.7	85.43±1.00	91.66±0.75	91.66±0.25
MFSC7	23.36±0.51	35.9±0.95	47.43±0.05	61.8±0.6	73.26±0.80	82.5±1.1	93.53±1.2
MFSC8	32.73±0.70	48.8±0.87	65.5±0.98	76±0.2	92.06±1.05	97.0±1.02	98.76±0.51

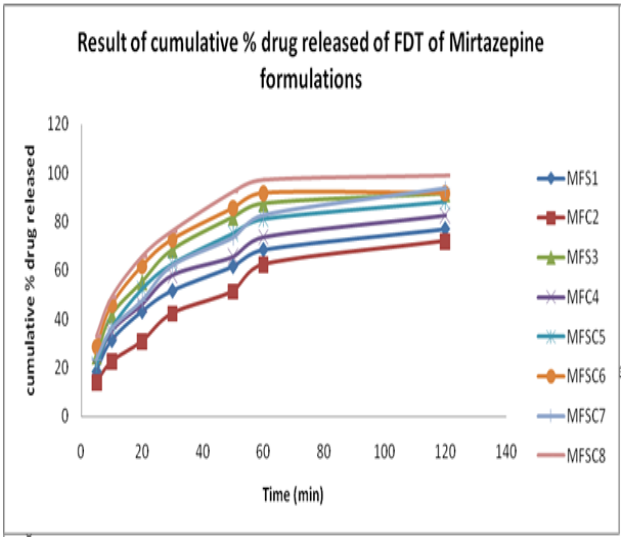

Figure 4: Cumulative % Drug Release of FDT of Mirtazepine

The comparative *in vitro* release data of all tablets formulations are presented in **Table 5** and **Fig. 4.** The *in vitro* release profiles of all the Mirtazepine tablet formulations are shown in **Figure 4.** From the release data it was revealed that the MFSC8 tablet formulations were released Mirtazepine within 60 minutes. The release profile of MFSC8 portrait that the faster release of Mirtazepine was occurred as compared to other formulations.

Release kinetics

Table 6: Dissolution parameters of Mirtazepine of best fast dissolving tablet formulation

FORMULATION CODE	KINETIC PARAMETERS			
	$t_{1/2}$ (Min)	$t_{80\%}$ (Min)	WT (Sec)	DT (Sec)
MFSC8	11	32	16.2±2.42	22.0±1.62

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The *in vitro* release data of all the tablet formulation were subjected to evaluation of release kinetics and release mechanism **(Fig. 4).** The release kinetics and release mechanism of Mirtazepine of all the tablet formulations are presented in **Tables 6-8.** The release of Mirtazepine from all the tablet formulations followed first order kinetic. This was indicated the release of Mirtazepine dependent on the concentration of Mirtazepine present in the tablets. The low value of R^2 in Higuchi model revealed that the release of Mirtazepine from all the formulations not followed diffusion controlled. The release data when fitted to the Korsmeyer-Peppas model it was found that formulations MFSC8 followed this model and diffusion exponent was found less than 0.501 indicating the release of Mirtazepine from the tablet followed non-Fickian transport.

Table 7: Result of cumulative % drug release and other parameters of FDT of Mirtazepine formulation of MFSC8

Time (Min)	% Cumulative release	% Cumulative unreleased
5	32.73	67.27
10	48.8	51.2
20	65.5	34.5
30	76	24
50	92.06	7.94
60	97	3
120	98.76	1.24

Table 8: Release kinetics and release mechanism of Mirtazepine from MFSC8.

Formulation Code	Release kinetics and release mechanism of MFSC8			
	Zero Order	First Order	Higuchi	Korsmeyer Peppas
Equation	y = 0.525x + 50.83	y = -0.015x + 1.801	y = 7.857x + 26.82	y = 0.364x + 1.313 n=0.364
(R^2)	R^2 = 0.676	R^2 = 0.919	R^2 = 0.851	R^2 = 0.936

Stability study:

Table 9: Quality control test parameters of tablets at time different time intervals during stability study [MFSC8]

Parameters	Initial	After 30 days	After 60 days	After 90 days
Physical appearance	White to off white	No change	No change	No change
Weight variation (mg)	0.96	0.98	0.99	0.98
Thickness (mm)	2.82±0.12	2.84±0.10	2.83±0.15	2.84±0.16
Hardness (kg/cm²)	3.19±0.005	3.18±0.005	3.2±0.006	3.21±0.006
Friability (%)	0.66±0.01	0.68±0.04	0.69±0.03	0.65±0.03
% Drug content Uniformity	98.0±0.14	98.11±0.25	98.43±0.24	98.33±0.16
Wetting time (sec)	16.2±2.42	16.42±2.49	16.55±2.48	16.26±2.45
Disintegration Time (Sec)	22.0±1.62	22.11±1.64	22.24±1.68	22.44±1.65
***In vitro* drug release studies**				
Time (Hrs)	**% Cumulative drug release**			
	Initial	After 30 days*	After 60 days*	After 90 days*
5	32.73±0.70	30.55±0.76	33.33±0.89	32.74±1.54
10	48.8±0.87	46.44±0.86	44.667±0.87	47.55±0.88
20	65.5±0.98	66.33±0.94	63.15±0.96	65.35±0.99
30	76±0.2	75.85±1.21	76.32±1.33	76.65±1.2
50	92.06±1.05	91.44±1.44	93.04±1.45	92.99±1.05
60	97.0±1.02	98.77±1.22	98.02±1.33	97.66±1.02
120	98.76±0.51	98.88±2.26	98.86±1.52	98.33±2.51

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In vitro release study at different time intervals were carried out on six tablets and the mean value is presented. The evaluated quality control test parameters of MFSC8 for stability studies at different time intervals and there were no significant changes in the test parameters like: physical appearance, weight variation, diameter, thickness, hardness, friability, drug content uniformity and disintegration time observed in tablets after 3 months of storage at accelerated stability conditions **(table 9).** The *in vitro* release data of tablet formulation at initial stage was considered as the reference for release study. The *in vitro* release profile revealed that the release profile after 3 months of storage at accelerated condition was found to be similar to that of reference one. Based on the results it was opined that the tablet was stable after 3 months of storage at accelerated stability conditions.

CONCLUSION

The results of physical properties of Mirtazepine fast dissolving tablets, *in-vitro* disintegration time and *in-vitro* dissolution studies, it was known that the formulation MFSC8 employing 30mg of sodium starch glycolate and 30mg croscarmellose sodium exhibited more percent dissolved in 5 minutes as well as released maximum amount with in 1h to 2hrs. Hence, MFSC8 is considered as an ideal formulation of Mirtazepine. It can be concluded that the tablet can be formulated using Mirtazepine formulation is able to enhance the therapeutic efficacy of drug. However, extensive preclinical studies and clinical trials of the presently developed Mirtazepine tablet needs to be conducted to determine and document the safety profiles of the Mirtazepine.

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