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FORMULATE AND EVALUATE ORAL DISINTEGRATING TABLETS OF MIRTAZAPINE

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ABSTRACT

Mirtazapine is an antidepressant introduced by Organon International in 1996 used for the treatment of moderate to severe depression. It is extensively metabolized by liver and having oral bioavailabity of 50%. To improve the oral bioavailability of Mirtazapine oral disintegrating tablets were formulated using different natural and synthetic super disintegrants. In the present work, Oral disintegrating tablets of Mirtazapine were prepared by direct compression method using superdisintegrants such as crosspovidone, SSG and Ac-Di-Sol. The dispersion time of tablets were reduced with increase in the concentration of superdisintegrants. From the results obtained, it was concluded that Ac-Di-Sol was found to be the best among the superdisintegrants, the highest drug release was found to be 98.52% in F4 formulation at the end of 20 min.

KEYWORDS: Mirtazapine, FTIR, Crosspovidone SSG and Ac-Di-Sol.

INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water. Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients, psychiatric patients and patients with nausea, vomiting, and motion sickness complications

Mirtazapine is an antidepressant introduced by Organon International in 1996 used for the treatment of moderate to severe depression. Mirtazapine has a tetracyclic chemical structure and is classified as a noradrenergic and specific serotonergic antidepressant (NaSSA). It is the only tetracyclic antidepressant that has been approved by the Food and Drug Administration to treat depression.

Structure

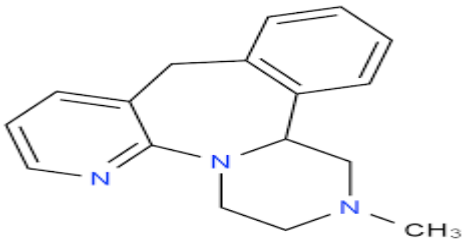


Fig 1: structure of Mirtazapine.

Experimental work

Materials

Mirtazapine sample was collected from Aurbindopharma Ltd., Hyd, Ac-Di-Sol Signet Chemical Corp., Mumbai, Cross povidone Signet Chemical Corp., Mumbai, SSG Signet Chemical Corp., Mumbai, Aspartame Signet Chemical Corp., Mumbai, Microcrystalline cellulose(Avicel) Rankem, Mumbai, Talc Rankem, Mumbai, Magnesium stearate S.D. Fine Chem. Ltd.

Methodology

Preformulationstudies:[35-39]

It is one of the important pre requisite in development of any drug delivery system. Reformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

Determination of Melting Point

Melting point of Mirtazapine was determined by

capillary method. Fine powder of Mirtazapine was filled in glass capillary tube (previously sealed at one end). The capillary tube wastied tothermometer andthe thermometer was placed in the Thais tube and this tube was placed on fire. Thepowderat what temperatureitmelted was noticed.

Solubility

Solubility of Mirtazapine was determined in pH1.2, pH6.8 and pH7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Mirtazapine in different beakers containing the solvents. The mixtures were shaken for 24hrs at regular intervals.The solutions were filtered by usingwhattmann's filter paper gradeno.41. The filtered solutions were analyzed spectrophotometrically at 311 nm.

Compatibility Studies

FTIR analysis

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of 2 cm–1 using Happ-Genzelapodization. The characteristic peaks were recorded.

Calibration Curve For Mirtazapine In Distilled Water

Procedure

Preparation of StandardStock Solution

10 mg of Mirtazapine was accurately weighed into 10 ml volumetric flask and volume was made up to 10 ml with the 6.8pH buffer to get a concentration of (1000µg/ml) SS-I. From this, 1 ml was withdrawn and diluted to 100 ml with 6.8pH buffer to get a concentration of (100 µg/ml) SS-II.

Scanning of Drug

From stock solution (SS-II), 1ml was with drawn and the volume was made upto 10ml with 6.8pH buffer to get a concentration of 10 µg/ml. UV scan range was taken between the wavelengths 200-400nm. It gave a peak at 311nm and the same was selected as λ_{max} for Mirtazapine.

CalibrationCurve in distilled water

From the standard stock solution (SS-II),0.2,0.4,0.6,0.8,1.0, and 1.2ml were with drawn and volume was made upto 10ml with 6.8pH buffer to give a concentration of 2,4,6,8,10,and 12µg/ml. Absorbance of these solutions was measured against a blank of 6.8pH buffer at 311 nm for Mirtazapine and the absorbance values are summarized in results section. Calibration curve was plotted, drug concentrations versus absorbance was given in the Fig in results section.

Disintegrantsandmechanismofaction[40-41]

A disintegrant is an excipient, which is added to aid in the break up of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of product is required.

The proposed mechanisms of action of disintegrants include

1. Water uptake through wicking
2. Swelling
3. Deformation (shape recovery)
4. Particlerepulsion
5. Heat of wetting

The later two mechanisms are not well supported by research.

Water penetration is an indispensable pre processing step for disintegration. Thesorption properties of various disintegrants are found to be essential for efficient disintegration and dissolution. If the wetting of the super disintegrants is slow, for example by coating the disintegrant with a hydrophobic substance, disintegration of the mass is also slowed. The extensive research on super disintegrants has not only implicated the extent of water uptake is important but also have conclusively demonstrated that the rate of water uptake is of critical importance for number of disintegrants.

Formulation of Oraldisintegrating Tablets of Mirtazapine

Oral disintegrating tablets of Mirtazapine were prepared by direct compression according to the formulae given in the table 4.

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.

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 F12 (100mg).

Table: Formulation table of Mirtazapine Oral Disintegrating Tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Mirtazapine	15	15	15	15	15	15	15	15	15	15	15	15
Ac-Di-Sol	2	4	6	8	-	-	-	-	-	-	-	-
Crosspovidone	-	-	-		2	4	6	8	-	-	-	-
SSG	-	-	-	-	-	-	-	-	2	4	6	8
Mannitol	15	15	15	15	15	15	15	15	15	15	15	15
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
Magnesium stearate	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
Total weight	100	100	100	100	100	100	100	100	100	100	100	100

Evaluationof Oral Disintegrating Tablets[44-52]

Evaluationwas performed to assess the physicochemical properties and release characteristics of the developed formulations.

I) Preformulation studies

a) 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. It is expressed in g/cc and is given by:

Where,

M = mass of the powder

Vo = bulk volume of powder.

b) 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 (the difference between these two volumes should be less than 2%). It is expressed in g/cc and is given by:

$D_t = M/V_t$

Where,

M = mass of the powder

V_t= tapped volume of powder.

c) 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.

$\tan \theta = h/r$

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

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

d) 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. Compressibility index is calculated by –

$$\text{Compressibility index (\%)} = \frac{D_t - D_b}{D_t} \times 100$$

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

e) Hausner's Ratio

It is the ratio of tapped density tothe bulk density. It is given by- Hausner's ratio = D_t / D_b

Where, D_t= Tapped density

D_b= Bulk density.

II) Post-compression parameters

a) Shape of Tablets

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

b) 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.

c) Hardness

Hardness indicates the ability of a tablet to withstand mechanicalshocks 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.

d) 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.The friabilator 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.

e) 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.

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

f) Test for Content Uniformity

Tablet containing 15mg 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 311nm. 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.

i) In vitro Dispersion Time

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

k) 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 311nm. 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.

***l*) Drug Kinetics**

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Qv/st), firstorder [Log(Q_0-Q)v/st], Higuchi's square root of time (Qv/$st^{1/2}$) and Korsemeyer Peppas double logplot (logQ v/slogt) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t. 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 (Peppasexponential equation)

RESULTS AND DISCUSSION

In the present study, an attempt has been made to formulate and evaluate Oral disintegrating tablets of Mirtazapine by direct compression method using Cross povidone, Sodium starch glycolate, Ac-Di-Sol as super disintegrants. 12 formulations were prepared and complete composition of all batches shown in Table No.. The tablets were then characterized for various physico-chemical parameters.

Preformulation Studies

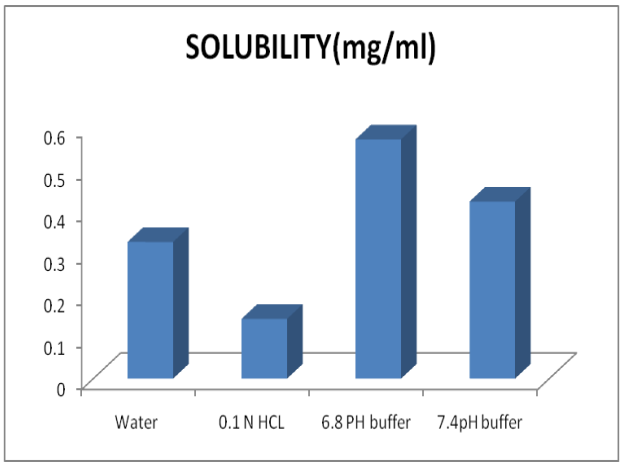
Determination of melting point

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 25^0C using 0.1 N HCL, 6.8 phosphate buffer, 7.4pH bufferand purified water.

Medium	Solubility(mg/ml)
Water	0.325
0.1 N HCL	0.142
6.8 PH buffer	0.569
7.4pH buffer	0.421



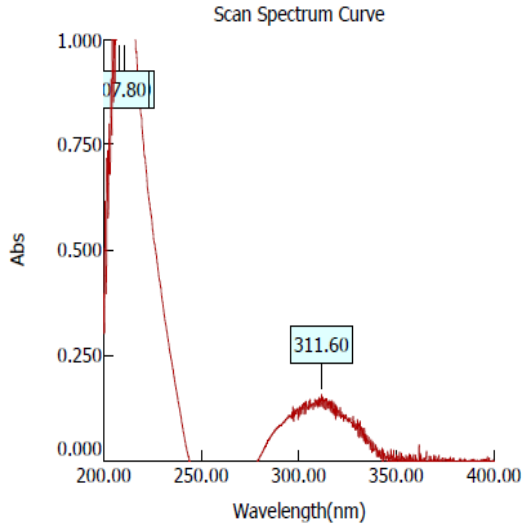
Solubility studies of Mirtazapine

DISCUSSION

From the above conducted solubility studies in various buffers we can say that 6.8pH buffer solution has more solubility when compared to other buffer solutions.

7.1 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.



I) Standard Calibration Curve of Mirtazapinein6.8pH 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 311 nm as shown in Fig. 1. The absorbance values are tabulated in Table 4. Standard calibration curve of Mirtazapine in the Beer's range between 5-30µg/ml is shown in Fig.2.

Table: Calibration data of Mirtazapine in 6.8pH buffer at λ_{max} 311nm.

Concentration(µg/ml)	Absorbance
0	0
5	0.101
10	0.182
15	0.285
20	0.395
25	0.495
30	0.587

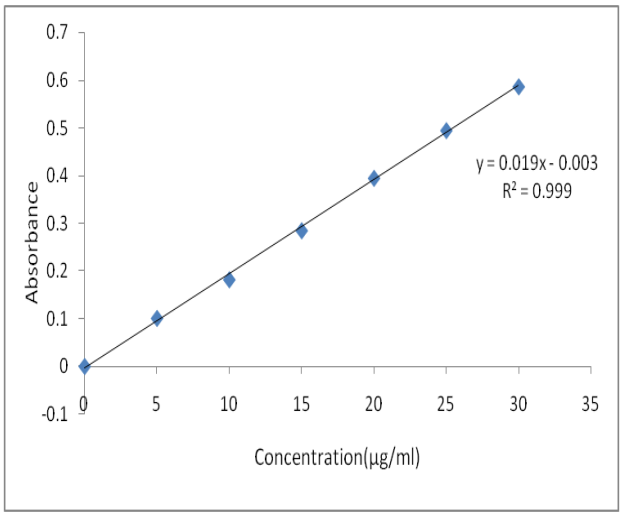


Fig. 2: Standard calibration curve for Mirtazapine in 6.8pH buffer at λmax 311 nm.

II) Compatibility Study

Compatibilitystudieswereperformedusing FT-IR spectro photometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristicabsorptionpeaks of Mirtazapinewereobtainedatdifferentwave numbers in different samples. Thepeaksobtainedin the spectrao feach for mulation correlateswith the peaks of drugspectrum. This indica testhat the drugiscompatiblewiththe for mulationcomponents.

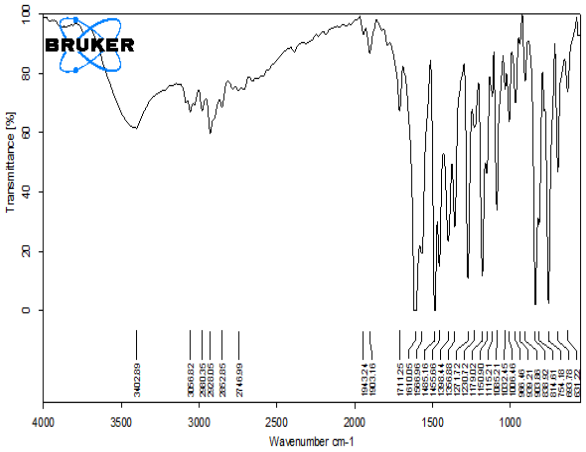


Fig: Ftir Graph of mirtazapine.

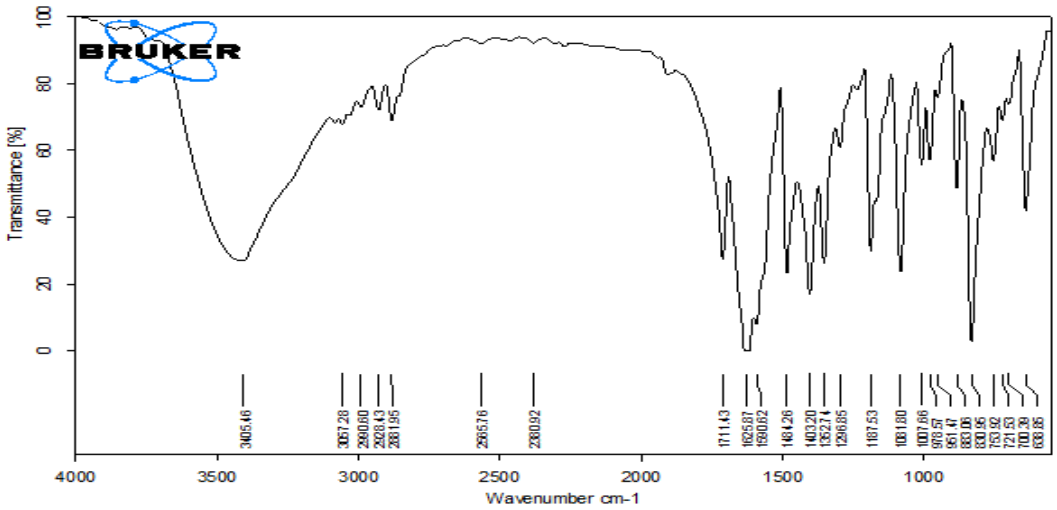


Fig: Ftir Graph of mirtazapine and excipients.

Table: Micromeretic properties.
Table: Pre Compression parameters.

Table: Post compression parameters of Mirtazapine ODT.

Formula	Post compression parameters					
	Avg.Wt (mg)	Hardness (kg/cm^2)	Thickness(mm)	Friability (%)	Disintegration time(secs)	Drug content (%)
F1	98.15±0.26	3.15±0.15	2.15±0.15	0.05±0.04	49±0.15	96.15±0.43
F2	99.15±0.22	3.15±0.26	2.52±0.26	0.62±0.05	52±0.42	86.52±0.05
F3	97.01±0.36	3.47±0.36	2.41±0.42	0.15±0.69	61±0.36	82.63±0.14
F4	100.2±0.15	3.63±0.10	2.52±0.36	0.52±0.85	79±0.14	98.14±0.96
F5	99.2±0.32	3.47±0.01	2.63±0.47	0.63±0.36	45±0.52	81.85±0.85
F6	97.8±0.63	3.72±0.16	2.41±0.88	0.18±0.24	49±0.63	89.69±0.46
F7	100.9±0.15	3.15±0.26	2.85±0.69	0.46±0.16	50±0.48	90.75±0.49
F8	97.5±0.36	3.42±0.30	2.52±0.15	0.18±0.19	59±0.96	92.49±0.36
F9	99.4±0.14	4.20±0.96	2.36±0.52	0.52±0.05	29±0.05	94.52±0.52
F10	97.2±0.35	3.15±0.10	2.04±0.31	0.63±0.26	35±0.46	93.06±0.18
F11	98.8±0.26	3.26±0.01	2.15±0.24	0.15±0.14	41±0.17	88.34±042
F12	96.7±0.14	3.14±0.16	2.20±0.26	0.52±0.16	56±0.85	96.05±0.15

Table: Cumulativepercent drug release of ODT of different formulations of Mirtazapine (F1toF6).

TIME	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	35.19	39.75	42.51	49.63	25.46	29.84
10	46.81	46.52	59.24	62.48	42.61	45.18
15	56.94	59.43	69.75	80.75	53.8	59.63
20	78.52	72.49	82.63	98.52	68.43	70.54
25	82.63	82.64	96.75		75.49	82.49
30	89.42	93.62			85.63	90.75

Table: Cumulativepercent drug release of ODT tablets ofdifferent formulations of Mirtazapine (F7toF12)

TIME	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	32.89	40.61	25.64	36.19	39.05	45.21
10	42.51	52.05	40.63	42.61	49.63	59.62
15	53.28	69.42	53.49	53.94	62.53	76.52
20	69.48	82.64	60.54	62.49	71.54	85.64
25	85.64	96.42	69.35	75.06	85.63	98.63
30	98.26		78.52	89.62	99.34	

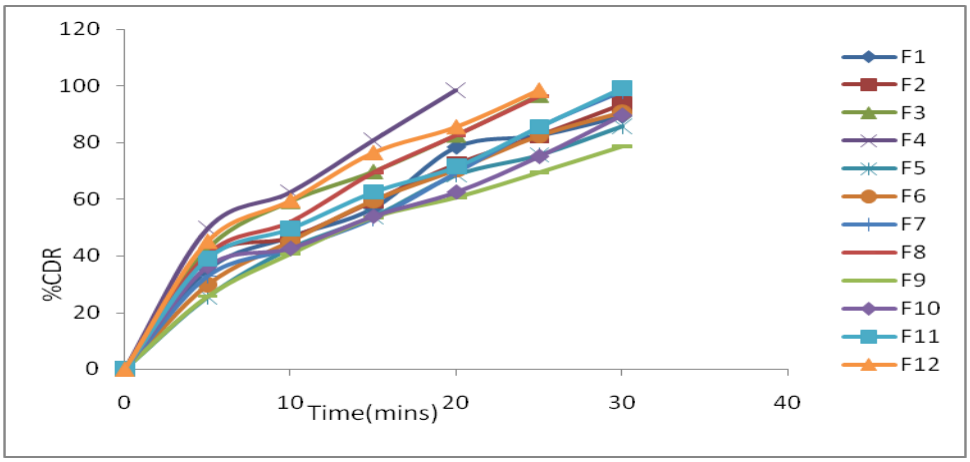


Fig: Cumulativepercentagedrugreleaseofcoreformulation F1 –F12.

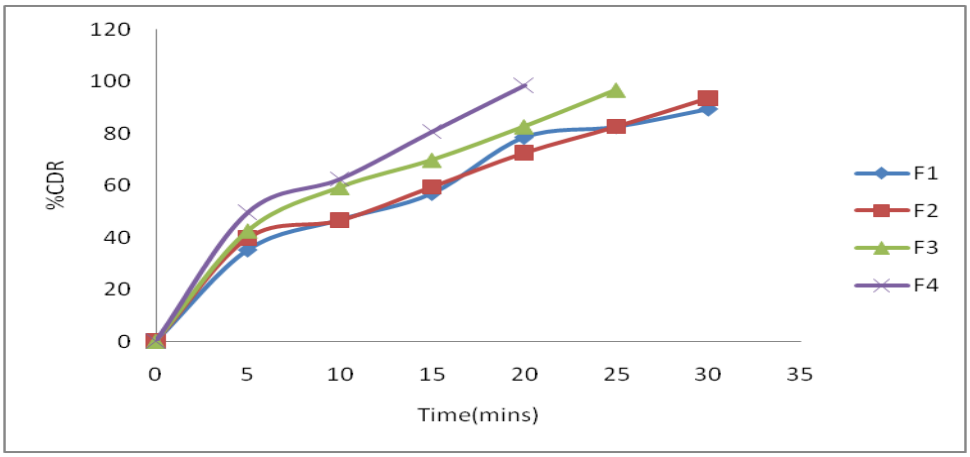


Fig: Cumulativepercentagedrugreleaseofcoreformulation F1 –F4.

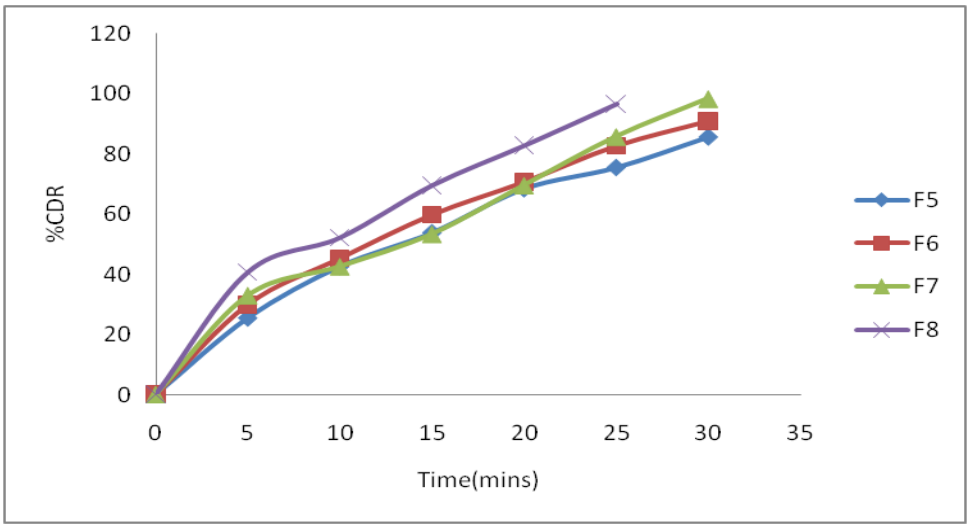


Fig: Cumulativepercentage drugrelease of core formulation F5.

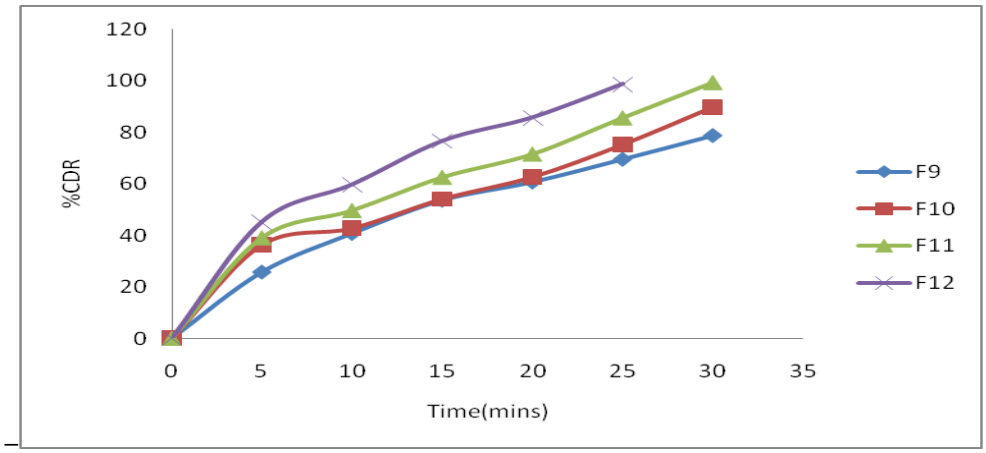


Fig: Cumulativepercentagedrugreleaseofcoreformulation F9 –F12.

Drug release kinetics mechanisms

Zero order release kinetics

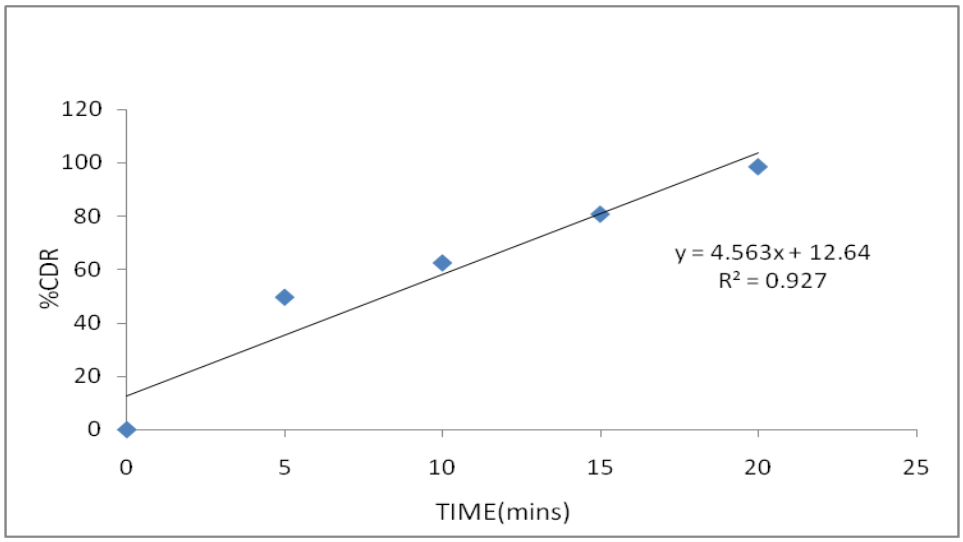


Figure: zero order release kinetics for best formulation (F4).

First Order Release Kinetics

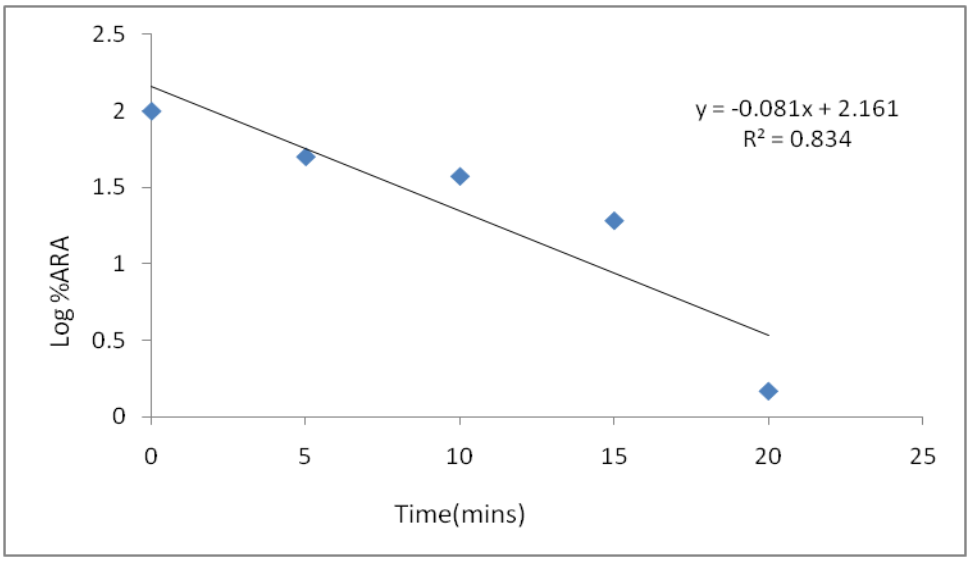


Fig: First Order Release Kinetics For Best Formulation (F4).

Higuchi Plot

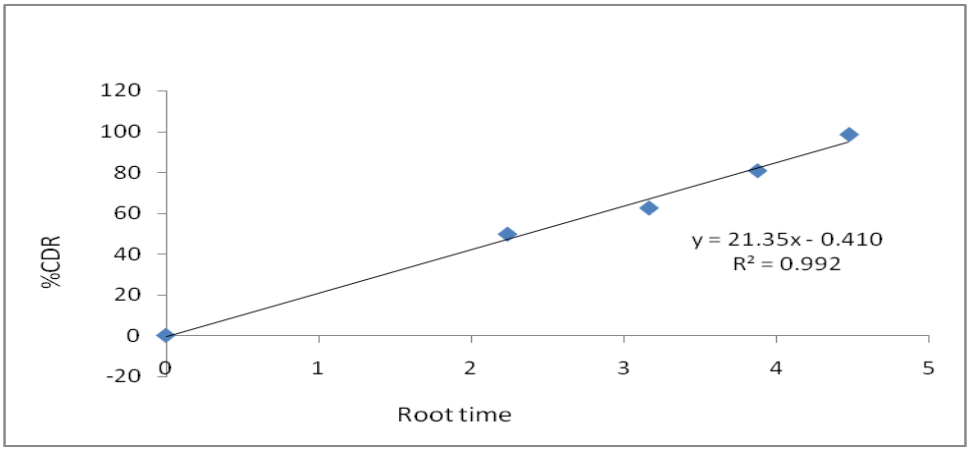


Fig: Higuchi Plotrelease Kinetics For Best Formulation (F4).

Peppas Plot

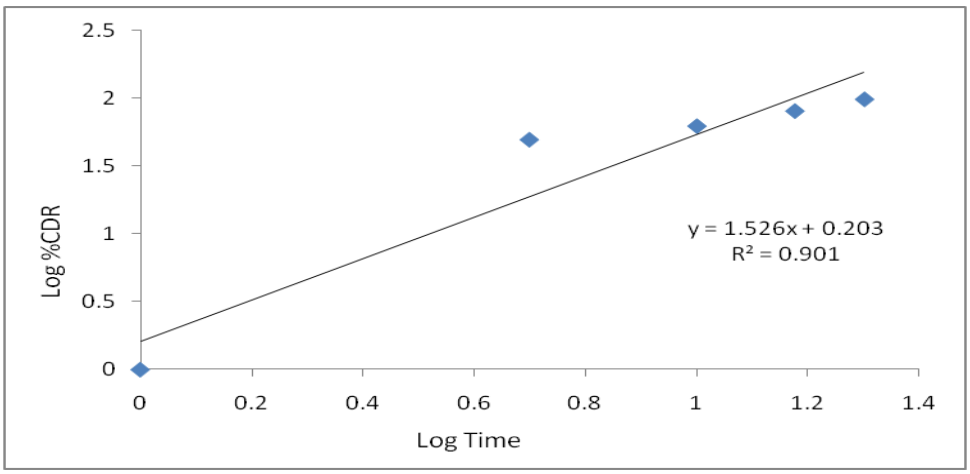


Fig: Peppas Plotrelease Kinetics For Best Formulation (F4).

Table: *In-Vitro*drugreleasemechanism of best formulation.

Batch Code	Zero Order r2	First Order r2	Higuchi plot r2	Peppas plot r2	N Value n
F4	0.927	0.834	0.992	0.906	1.526

SUMMARY AND CONCLUSION

In the present work, Oral disintegrating tablets of Mirtazapine were prepared by direct compression method using superdisintegrants such as Cross povidone, Sodium starch glycolate, Ac-Di-Sol. From the results obtained, it can be concluded that:-

- The flow properties of polymer and drug were good.
- FT-IR studies revealed that there is no chemical interaction between Mirtazapine and the excipients used in the study.
- The tablets prepared were found to be good without any chipping, capping and sticking.
- Formulated tablets gives satisfactory result for various physico-chemical evaluation of tablets like tablet dimension, hardness, friability, weight variation, *in vitro* dispersion time, and drug content.
- The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
- The in-vitro dissolution study of Mirtazapine tablet is tested in phosphate buffer 6.8(simulated fluid).

From the *invitro* dissolution data, among all formulations it was observed that, formulations containing Ac-Di-Sol as super disintegrant showed maximum dissolution rate 98.52%of drug release in F3 in 20minutes.

From the present study, it may be concluded that the Oral disintegrating tablets of Mirtazapine can be prepared by direct compression method using superdisintegrants. Among Cross povidone, Sodium starch glycolate, Ac-Di-Sol was found to be the best among the superdisintegrants. the highest drug release of F3 is 98.52% of the drug in 20 min.

BIBLIOGRAPHY

1. Seager H. Drug delivery products and the zydis fast dissolving dosage forms. J. Pharm. Pharmacol, 1998; 50: 375-382.
2. Chang RK, Guo X, Burnside BA, Couch RA. Fast dissolving tablets. Pharm. Tech., 2000; 24(6): 52-58.
3. Dobetti L. Fast melting tablets: Developments & Technologies. Pharm. Tech., 2001; (Suppl): 44.
4. Kuchekar BS, Aruagam V. Fast dissolving tablets. Indian J. Pharm. Edu, 2001; 35: 150-152.
5. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets: A novel drug delivery system. Pharma. Times, 2003; 35: 7-9.
6. Bradoo R, Shahani S, Poojary S, Deewan B, Sudarshan S. An observer blind, randomized controlled clinical trial to compare the onset of action, efficacy and safety of cetrizine flash tablets with oral Loratidine and cetrizine conventional tablets in allergic rhinitis. JAMA India, 2001; 4(10): 27-31.
7. European Directorate for quality of medicines (www.pheur.org) Pharmeuropa, 1998; 10(4): 547.
8. Udupa N, Venkatesh, Srinivas M, Venugopal K. Nimesulide dispersible tablets from 'Direct compression' method. 2001; 38(4): 208-10.
9. Luca Dobetti. Fast melting tablets: Developments & Technologies. Pharmaceutical Technology, 2001; 11.
10. Reddy LH, Ghosh B, Rajneesh. Fast dissolving drug delivery systems: A review of the literature. Indian J. Pharm. Sci, 2002; 7: 331-336.
11. Lindgreen S, Janzon L. Dysphagia: Prevalence of swallowing complaints and clinical findings. Med. Clin. North Am. 1993; 77: 3-5.
12. Bhushan SY, Sambhaji SP, Anant RP, Kaka Saheb RM. New drug delivery system for elderly. Ind. Drugs, 2000; 37: 312-18.
13. Wilson CG, Washington N, Peach J, Murray GR, Kennerley J. The behaviour of a fast-dissolving dosage form (expidet) followed by g-scintigraphy. Int. J. Pharm., 1987; 40: 119-23.
14. Ainley W, Paul JW. Handbook of Pharmaceutical excipients. 2nd Edition. The Pharmaceutical Press, London 1994: 483-86.
15. Chowdary KPR, Hymavathi R. Formulation and dissolution rate studies on dispersible tablets of ibuprofen. Indian J Pharm. Sci., 2000; 213-16.
16. Gupta GD, Gaud RS. Formulation and evaluation of nimesulide dispersible tablets using natural disintegrants. Indian J Pharm. Sci., 2000; 62(5): 339-42.
17. Chandra sekhara Rao G, Nagoji KEV, Bhanoji rao ME. Formulation and evaluation of nimesulide dispersible tablets. Indian J Pharm. Sci., 2002; 598-99.
18. Scheirmeier S, Peter CS. Fast dispersible ibuprofen tablets. Eur J Pharm Sci., 2002; 15: 295-305.
19. Hisakadsu Suanada,Yunxia Bi. Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technology, 2002; 122: 188-198.
20. Yıldız S1, Aytekin E1, Yavuz B1, Bozdağ Pehlivan S, Ünlü N. Formulation studies for mirtazapine orally disintegrating tablets. Drug Dev Ind Pharm, 2016; 42(6): 1008-17.
21. Manidipa Debnath, Ashutosh Kumar S. and Madugula Dharmaraju, Formulation, Development And In-Vitro Release Kinetics Of Linagliptin Tablet Using Different Super.
22. Disintegrating Agents, CIBTech Journal of Pharmaceutical Sciences, 2015; 4(3): 12-25.
23. mita Kolhe, Apurva Deshpande , Dhananjay "Formulation and Evaluation of Taste Masked Cetrizine Dihydrochloride Orally Disintegrating Tablets: A Research" Int. J. Drug Dev. & Res., January-March 2013; 5(1): 357-365.
24. Anirudha V. Munde et.al., Formulation and in-vitro Evaluation of orodispersible Tablets of Lansoprazole, JIPBS, Vol 2 (4), 469-477, 2015.
25. Gawande Shilpa et.al., Formulation and evaluation of orodispersible tablet of Risperidone, Der Pharmacia Lettre, 2011; 3 (6): 151-156.
26. Yourong Fu et.al., Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies Therapeutic Drug Carrier Systems, 2004; 21(6): 433–475.
27. G.Sahitya et. al., Formulation And Evaluation Of Fast Dissolving Tablets Using Solid Dispersion Of Clopidogrel Bisulphate Int J Adv Pharm Gen Res., 2014; 2(1): 15- 23.
28. Navel Kishore Singh A et.al., Formulation and Evaluavation of Clopidogrel Bisulfate Immediate Release Tablets International Journal of Life Sciences Research (IJLSR), 2013; 1(1): (11-18).
29. Nawar M.Toma et.al., Formulation and Evaluation of Bilayer Tablets Containing Immediate Release Aspirin Layer and Floating Clopidogrel Layer Iraqi J Pharm Sci, 2013; 22(1).
30. Bhanu Prasad S et.al., Controlled Release Floating Matrix Tablets for Clopidogrel Bisulfate Based on Gas Generating System: Development, Optimization and In-Vitro Evaluation Am. J. PharmTech Res., 2014; 4(6).
31. Md. Shafayat Hossain et.al., Formulation Development and Evaluation of Ticagrelor Tablet for Regulatory Market Journal of Applied Pharmaceutical Science, 2013; 3(10): 114-118.
32. N Narasimha Rao et.al., Design and Development of Press Coated Prasugrel Hydrochloride Tablets for Pulsatile Drug Delivery System. January – February, 2014; 5(1): 1056-1064.
33. Indurwade NH, Rajyaguru TH, Nakhat PD.Novel Approach – Fast Dissolving Tablets. Indian Drugs, 2002; 39(8): 405-9.
34. Watanae Y, Koizumi K, Zama Y, Kiriyama M, Matsumoto M.New Compressed Tablet Rapidly Disintegrating in Saliva in the Mouth using Crystalline Cellulose and a Disintegrant. Bio Pharmaceutical Bulletein, 1995; 8: 1308-10.
35. Bi Y, Yonezawa Y, Sunanda H.Rapidly

Disintegrating Tablets prepared by the wet compression method- mechanism and optimization. Journal of pharmaceutical sciences, 1999; 88(10): 1004-1010.
36. Rakesh KR.Orally Disintegrating Tablets- Novel Approach to Drug Delivery. The Pharma Review, 2004; 2(12): 34-6.
37. Pfister WR, Ghosh TK.Orally Disintegrating Tablets: Products, Technologies, and Development Issues. Pharm Tech, 2005; 25(9): 44-50.
38. Robin H, Bogner: Fast Dissolving tablets. www.US.Pharmacist, Jobson Publication, 2007.
39. Gerard J. Tortora and Bryan Derrickson : Principles of Anatomy and Physiology, John Wiley & Sons, edition 13th vol 1, 2000; 482.
40. Reddy.L.H et al., "Fast dissolving drug delivery systems: A review of the literature, IJPS, 2002; 331-336.
41. Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. J Pharm Pharmacol, 1998; 50: 375-82.
42. Behnke K, Sogaard J, Martin S, Bauml J, Ravindran AV, Agren H, et al. Mirtazapine orally disintegrating tablet versus sertraline: A prospective onset of action study. J Clin Psychopharmacol, 2003; 23: 358-64.
43. Jaccard TT, Leyder J. Une nouvelle forme galenique le lyoc. Ann Pharm Fr., 1985; 43: 123-31.
44. Dobetti L. Fast-melting tablets: Developments and technologies. Pharm Technol N Am, 2001; 44-50.
45. Van Scoik KG. Solid Pharmaceutical dosage in tablet triturates form and method of producing the same. US Patent, 5,082,667.
46. Allen LV, Wang B, Davis LD. Rapidly dissolving tablet. US Patent, 1998; 5: 807-576.
47. Bhaskaran S, Narmada GV. Rapid Dissolving tablet A Novel dosage form Indian Pharmacist, 2002; 1: 9-12.
48. Abdelbary G,Prinderre P,Eouani C,Joachim J, Reynier JP, Piccerelle P.The preparation of orally disintegrating tablets using a hydrophilic waxy binder.Int J Pharm, 2004; 278: 423-33.
49. Kuno Y, Kojima M, Ando S, Nakagami H. Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols. J Control Release, 2005; 105: 16-22.
50. Koizumi K, Watanabe Y, Morita K, Utoguchi N, Matsumoto M. New method of preparing highporosity rapidly saliva soluble compressed tablets using mannitol with camphor: A subliming material. Int J Pharm, 1997; 152: 127- 31.
51. Bonadeo D, Ciccarello F, Pagano A. Process for the preparation of a granulate suitable to the preparation of rapidly disintegratable mouthsoluble tablets and compositions obtained thereby. US Patent 6,316,029; 1998.
52. Bandari S, Mittapalli RK, Gannu R, Rao YM. Orodispersible tablets: An overview. Asian journal of pharmaceutics. 2008; 2(1): 2.