DEVELOPMENT AND CHARACTERIZATION OF MIRTAZAPINE FAST DISSOLVING TABLETS

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Abstract:

Despite significant innovation in the area of formulation, the oral route remains the most favored and recognized method for administration of therapeutic agents because it provides precise dosage, cheap production costs, self-medication, a non-invasive approach, and simplicity of administration.

Geriatric individuals have a variety of physiological and neurological changes as they age, including difficulties swallowing/dysphagia, memory loss, vision loss, hand tremors, hearing loss, choking risk, and changes in taste and smell. Dysphagia has been linked to a variety of medical illnesses, including stroke, Parkinson's disease, AIDS, thyroid surgery, head and neck radiation treatment, and other neurological disorders such as cerebral palsy. Furthermore, individuals who have little or no access to water find it challenging to use orally given traditional pills or capsules.

Introduction

Fast disintegrating tablets, fast dispersion tablets, rapid dissolving tablets, rapid melt tablets, quick disintegrating tablets, and orally disintegrating tablets are all terms used to describe the technology. Patients may easily take the pills since they dissolve into tiny granules or melt in their tongue from a hard solid structure to a gel-like shape. The time it takes for those pills to disintegrate ranges from a few seconds to more than a minute. Direct compression, wet granulation, compression molding, volatilization, vacuum drying, and freeze-drying are some of the methods that may be used to deliver fast-dissolving drugs. These tablets include chemicals that speed up the pace of tablet disintegration in the oral cavity and are more accurately referred to as fast-disintegrating tablets since it takes no more than 60 seconds for the tablet to fully dissolve.

Drawbacks of Conventional Tablets (Habib et al. 61)

Patients who are elderly, pediatric, bedridden, traveling, or who do not have simple access to water have poor patient compliance. Bioavailability is hampered by poor solubility.

The need for growth

Patients' low acceptance and compliance with current dose forms, drug firms' restricted market size and medication applications, and the high cost of illness treatment all contribute to the need for non-invasive delivery methods.

Patient-related factors

Patients who have trouble swallowing conventional tablets and capsules with an 8-ounce glass of water should use orally disintegrating dose forms.

The following are some of them:

- Patients of all ages, including children and the elderly
- Patients who have a choking fear

Factor of efficiency

These formulations claim to have increased bioavailability and a quicker start of the effect. Pre gastric absorption from certain formulations is caused by dispersion in the

saliva of theoral cavity in situations when the medication dissolves rapidly.

Factors affecting manufacturing and marketing

When a drug's patent life is coming to an end, it's usual for pharmaceutical companies to createa new and better dosage form.

Significance

FDTs have the benefits of both solid and liquid dosage forms, such as: Patient cooperation:
Dosing precision:

Rapid response:

Bioavailability is enhanced since the drug is absorbed via the mouth, throat, and esophagus.Easy to administer
Simple packing:

Free of obstructions:
Enhanced palatabilityBudget-friendly:
Ideal properties

- They shouldn't need water to swallow, but they should melt or disintegrate in seconds in themouth.
- Be tolerant to flavor masking.

AIM AND OBJECTIVES

Aim:

Development and characterize of mirtazapine fast dissolving tablets

Objectives:

- Patient compliance,
- Rapid onset of action,
- Increased bioavailability and good stability make these tablets popular as a dosageForm of choice in the current market.
- For rapid dissolution of drug and absorption which may produce rapid onset of action
- To avoid the first-pass metabolism
- It can be designed to leave minimal or no residue in the mouth
- To improved biopharmaceutical properties and better safety compared with conventional oral dosage forms.

DRUG PROFILE[30,31]

Name: Mirtazapine.

Synonyms : Mirtazapine ,Remeron ,Mepirzepine
Description: Mirtazapine is a benzazepine and a tetracyclic antidepressant.

the drug, an H1-receptor antagonist, and nitrogen.
IUPAC name :5-methyl-2,5,19-triazatetracyclo[13.4.0.$0^{2,7}$.$0^{8,13}$]nonadeca-1(15),8,10,12,16,18-hexaene

Structure:

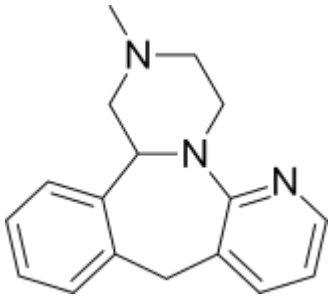


Fig-: Molecular structure of Mirtazapine
Chemical Formula: $C_{17}H_{19}N_3$
Molecular weight: 265.36 g/mol

CLINICAL PHARMACOLOGY:

Mechanism of Action: The novel antidepressant mirtazapine has a dual mode of action. **Pharmacodynamics:** The novel antidepressant mirtazapine has a dual mode of action**Pharmacokinetics**
Bioavailability: 50%

Protein binding: 85%

Metabolism: Hepatic

Route of elimination: Renal, Faecal

Elimination half-life: 20 to 40 hours

Uses: Mirtazapine is an antidepressant medicine.

1. EXCIPIENT PROFILE

CROSCARAMELLOSE SODIUM

Non-proprietary Names BP: Croscarmellose Sodium JP: Croscarmellose Sodium PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

Descriptions

Croscarmellose sodium occurs as an odorless, white, or grayish-white powder.

Synonyms

Ac-Di-Sol; carmellose natricum conexum; cross-linked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Prime lose; Solutab; Vivasol.

Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, cross-linked [74811-65-7]

Empirical Formula and Molecular Weight

Croscarmellose sodium is a cross-linked polymer of carboxymethylcellulose sodium

Structural Formula

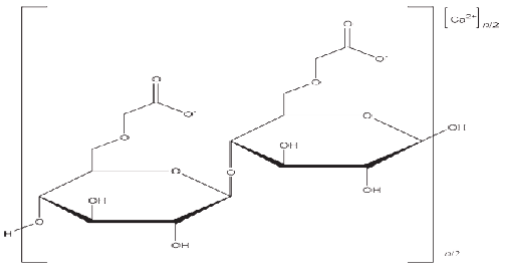


Fig-: Molecular structure of Croscaramellose

Functional Category: Tablet and capsule disintegrant

SODIUM STARCH GLYCOLATE

Synonyms: Carboxymethyl starch; sodium salt, Explosol; Explotab, Glycolys; primojel; starch carboxymethyl ether; Tablo; Vivastar P.

Functional Category: Tablet and capsule disintegrant

Structure:

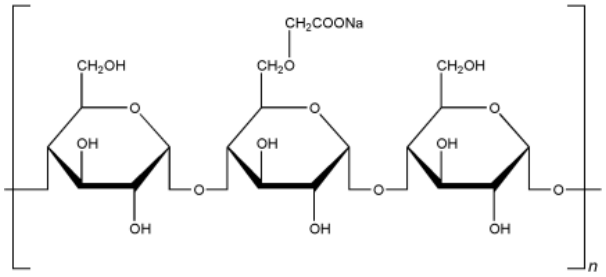


Fig-: Molecular structure of Sodium starch glycolate

Applications in Pharmaceutical Technology:

- Sodium starch glycolate has also been investigated for use as a suspending vehicle.

TALC

Empirical Formula:
$Mg_6 (Si_2O_5)_4 (OH)_4$

Structure:

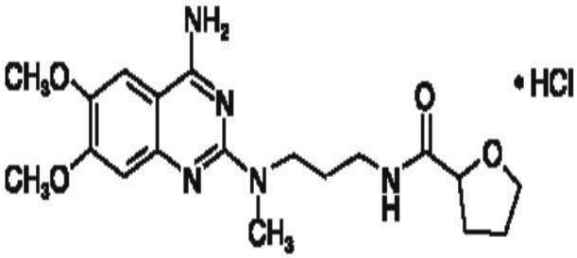


Fig-: Molecular structure of Talc

Solubility:
Insoluble in water, organic solvents, cold acids and dilute alkalis. Stability & Storage **conditions**:
Stable, preserve in a well-closed container.
Uses:Lubricant or glidant in tablets and capsules manufacture (1-4%), filler for tablets and capsules(5-30),

2. ATERIAL AND EQUIPMENT

Table-: List of excipients

S.no	Drug/excipients	Name of supplier
1	mirtazapine	Hetero Labs, Hyd
2	Croscarmellose Sodium	A. R Chemicals, Hyd.

3	Sodium starch glycolate	A. R Chemicals, Hyd.
4	Mannitol	A. R Chemicals, Hyd.
5	Microcrystallin ecellulose	A. R Chemicals, Hyd.
6	Magnesium stearate	A. R Chemicals, Hyd.
7	Talc	A. R Chemicals, Hyd.

EQUIPMENT

Table-: List of equipment used

	Equipment and Supplier Company Name
Equipment	**Company name**
UV/VISDouble Spectrophotometer	Lab India Double beam UV/VIS Spectrophotometer, Hyderabad
Tap Density Tester	Electro Lab
Tablet dissolution tester USP	Lab India
Weighing balance	Afcoset ER-120A
Hardness tester	Pfizer hardness tester
Friability tester	Roche friability tester
Disintegration tester	Scientific

3. METHODOLOGY[41,42]

Preformulation study:

Preformulation stability studies are usually the first quantitative assessment of the chemicalstability of a drug as well as stability in presence of other excipients.

a) Determination of melting point: melting point of Mirtazapine was determined by thecapillary method.

b) Solubility: solubility of the Mirtazapine was determined in 6.8 pH buffer, ethanol, methanol, and chloroform.

Preparation of standard curve of Mirtazapine

Mirtazapine was analyzed using a UV/visible spectrophotometer, using a solution prepared in Preparation of standard curve of Mirtazapine in 6.8 pH. Mirtazapine 10 mg was properly weighed and dissolved in 10ml of 6.8 phosphate buffer forthe standard graph. Different concentrations of Mirtazapine, namely 10, 20, 30, 40, and 50 mcg/ml, were produced from the stock solution (1 mg/ml) and brought up to volume with 6.8 phosphate buffer.

Drug excipient compatability[43]

Fourier transform infrared spectra of the samples were obtained in the range of 4000 to 450 cm-1 using an FTIR by the KBr disc method

Formulation table: [44]

Mirtazapine fast dissolving tablets with varying doses of super disintegrants were produced using the direct compression technique. To begin, the powders of natural super disintegrants were individually filtered through mesh no.60 and set aside. The medication, super disintegrants, diluents, binder, talc, and magnesium stearate were blended in a mortar and pestle to achieve a homogeneous blend and then passed through mesh no. 60. The powder produced in this manner was crushed into tablets using a single punch rotary tablet compression machinewith eight stations.

Table-: Formulation table

S. No	Ingredient	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	Mirtazapine	5	5	5	5	5	5	5	5

2	Sodium starch glycolate	10	15	20	25	-	-	-	-
3	Crospovidone	-	-	-	-	10	15	20	25
4	Mannitol	80	75	70	65	80	75	70	65
5	Magnesium stearate	3	3	3	3	3	3	3	3
6	Talc	2	2	2	2	2	2	2	2
7	Total. wt	100	100	100	100	100	100	100	100

Pre compression parameters[45,46,47]

Bulk density = weight of sample taken /volume notedTapped density = weight of sample taken/tapped volume

Carr index-Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner ratio

Angle of repose

Hausner's ratio = Tapped density / Bulk density

tan□ = h/r

□= $\tan^{-1}$ h/r

Pre compression parameters Uniformity of weight

The 20 randomly selected tablets were weighed individually; the average weight and the standard deviation were calculated. 10 Drug content Weighed tablets (5) were powdered usinga glass mortar and pestle.

Friability test

Friability = (W1 – W2)/W1 × 100

Wetting time

A simple method was used to determine the wetting time of the tablets. Five circular tissue sheets with a diameter of ten centimeters were put in a Petri dish with a diameter of ten centimeters. The wetting time was defined as the time needed for water to reach the tablets' top surface.

Wetting times were determined.

In-vitro disintegration test

The in-vitro disintegration studies were carried out using a digital tablet disintegration test apparatus.

Dissolution study

The release rate of Mirtazapine from fast disintegrating tablets was determined by using USP(Lab India, DS 8000) dissolution testing apparatus II (paddle method).

Stability study

The stability also includes the study of product-related factors that influence its quality.

4. RESULTS AND DISCUSSION

In the present study, 8 formulations with variable concentrations of polymer were prepared and evaluated for physic-chemical parameters, in-vitro release studies, and stability studies.

Preformulation studies

a) Organoleptic evaluation

Table-: Organoleptic properties of Mirtazapine

Properties	Results
Description	crystalline powder
Taste	tasteless
Odor	odorless
Color	white to creamy white

b) Determination of melting point

The melting point of Mirtazapine was found

in the range of 115 ^{0}c,

c) Solubility-Very soluble in acid solutions, Sparingly soluble in water, soluble in methanol and chloroform

Preparation of standard curve of Mirtazapine

The R^{2} value is 0.999

Table-: Calibration curve of Mirtazapine

S. no	Concentration (µg/mol)	Absorbance
1	0	0
2	10	0.115
3	20	0.245
4	30	0.333
5	40	0.438
6	50	0.543

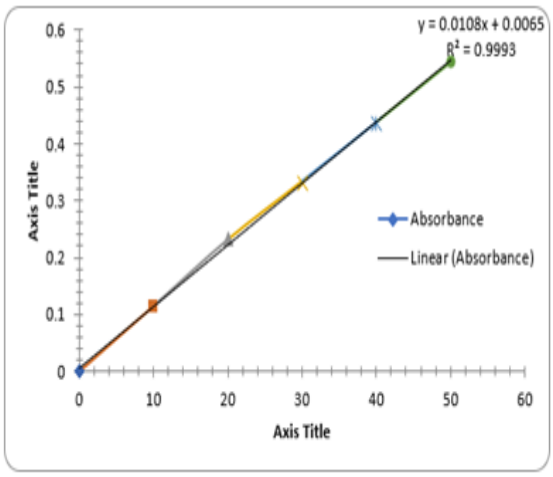


Fig-: Calibration curve of MirtazapineFT-IR Spectrum of Mirtazapine

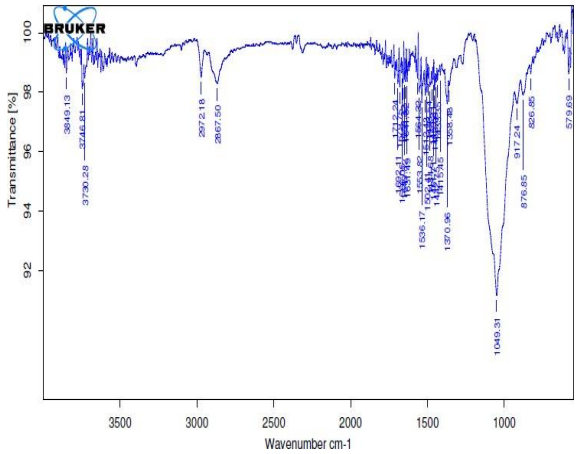


Fig-: FTIR Studies of Mirtazapine

Table-: Characteristic Peaks for Mirtazapine

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3500-3000	2972.18
2	OH Bending	1000-1500	1049.31
3	C-H stretching	3000-2500	2867.50
4	C=O stretching	2000-1500	1692.11

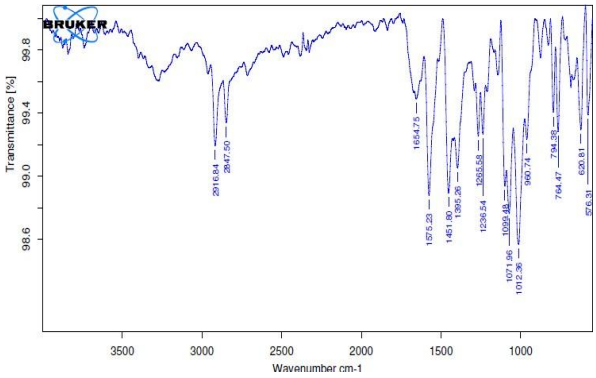


Fig-: FTIR Studies of physical mixture of drug and sodium starch glycolate

Table-: Characteristic Peaks for drug and sodium starch glycolate

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3000-2500	2916.84 cm-1
2	OH Bending	2000-1500	1575.23 cm-1
3	C=O stretching	1500-1000	1575.23 cm-1

Evaluation studies

Precompression parameters

Table-: Precompression parameters of Mirtazapine Mouth dissolving tablets

S. no	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
F1	0.225	0.319	29.46	1.41	29^0c
F2	0.215	0.308	30.19	1.43	31^0c
F3	0.23	0.321	28.34	1.39	26^0c
F4	0.227	0.319	28.84	1.4	28^0c
F5	0.27	0.32	11.36	1.17	29^0c
F6	0.29	0.34	15.31	1.18	30^0c
F7	0.33	0.416	19.68	1.24	27^0c
F8	0.29	0.34	15.31	1.18	29^0c

Post compression parameters

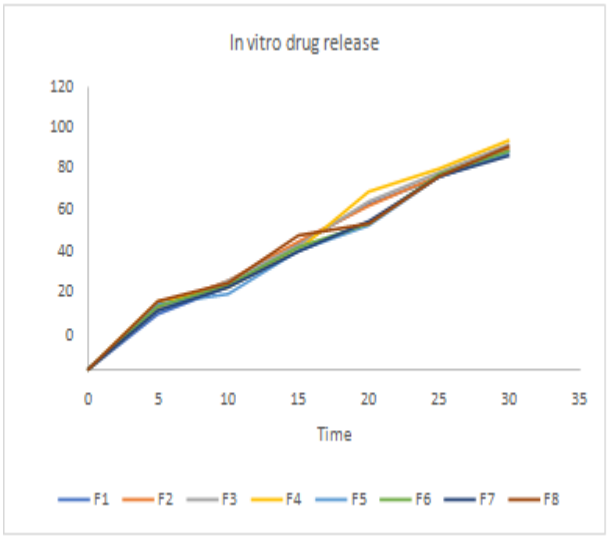
Table-: Evaluation parameters of Mirtazapine mouth dissolving tablets

F. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)	Disintegration time(sec)	Wetting time (sec)
F1	99	2.2	3.45	0.42	89.96	22	158
F2	101	2.3	3.32	0.4	93.5	25	161
F3	100	2.4	3.3	0.35	95.58	28	148
F4	99	2.1	3.86	0.41	91.39	26	150
F5	99	2.5	3.74	0.48	86.21	27	149
F6	100	2.6	3.68	0.37	84.62	25	152
F7	101	2.4	3.12	0.41	90.32	21	146
F8	98	2.2	3.68	0.36	92.27	29	153

Dissolution studies

Table-: Drug release studies of all formulations

Time	F1	F2	F3	F4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
5	23.72	26.36	25.18	28.98	27.89	26.94	25.19	29.18
10	35.42	37.89	37.82	35.16	32.28	36.15	35.14	36.95
15	53.56	54.59	52.95	50.92	50.71	52.18	50.31	57.16
20	70.42	69.86	71.53	75.88	61.46	62.17	63.18	62.18
25	81.93	82.63	83.91	85.52	82.19	83.14	82.15	82.28
30	93.52	94.28	95.86	97.69	92.17	93.18	91.18	95.12



Dissolution Profile of F1 to F8 formulationsTable: Kinetic studies for optimized formulation:

S.NO	TIME (Hrs)	LOG T	SQUARE ROOT OF TIME	%CR	%DRUG REMAINING	LOG %CR	LOG% DRUG RETAINED	(% retained)[13]
1	0	0	0	0	100	0	2	4.64159
2	5	0	1	15.56	78.12	1.33025	1.8524	4.26467
3	10	0.31123	1.21321	23.67	65.19	1.54413	1.71438	4.02426
4	15	0.61216	2	56.95	46.54	1.72919	1.62764	3.5165
5	20	0.72915	2.44845	79.92	17.72	1.91177	1.21091	2.61298
6	25	1	3.16328	86.14	7.05	1.9652	0.82881	1.91738
7	30	1.07816	3.4741	96.92	2.72	1.98507	0.41297	1.38419

DRUG RELEASE KINETICS

Zero-order kinetics:

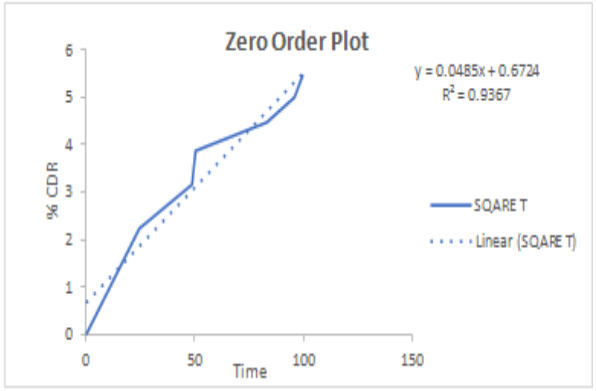


Fig no: Zero Order Plot For best preparation:

First-order kinetics

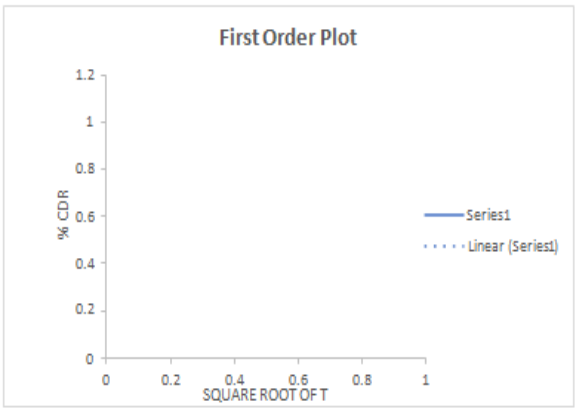


Fig no: First Order Plot for best preparation

Higuchi Model:

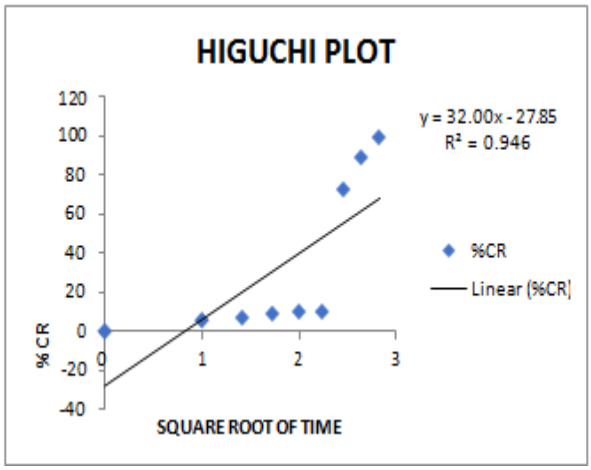


Fig no: Higuchi Plot for best preparation

Korsmeyer Peppas equations:

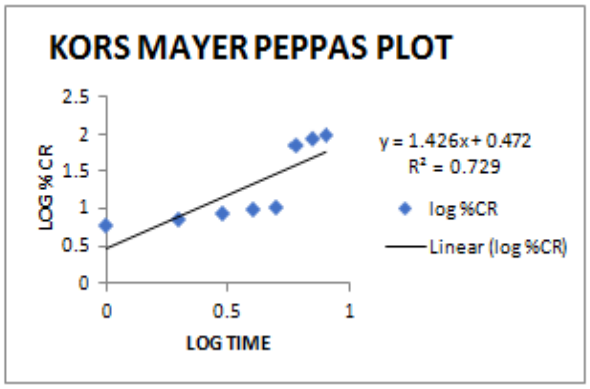


Fig no: Kores Mayer Peppas Plot For best preparation

Stability Study

Table-: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	25^{0}C/60%RH % Release	97.69	96.98	95.99	94.15	Not less than 85 %
F-4	30^{0}C/75% RH % Release	97.69	96.85	95.84	93.98	Not less than 85 %
F-4	40^{0}C/75% RH % Release	97.69	96.78	94.98	93.56	Not less than 85 %

5. CONCLUSION

The purpose of this research was to produce a custom-designed, Mirtazapine-containing Mouth dissolving tablet. Mirtazapine is a medication used to treat depression. The drug is usedin the treatment of depression, as well as obsessive-compulsive disorder and certain anxiety disorders. Because of its ability to dissolve quickly, fast-dissolving tablets were developed using the direct compression technique during pre-formulation tests. Sodium starch glycolate and crospovidone were used as super disintegrants in the formulation. The granules were assessed for the angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio before compression. Following dissolution research, disintegration time, and wetting time, the most suitable batch of Mouth dissolving tablets was selected. The data collected indicates that Formulation F4's drug release rate was at 97.69% with a disintegration time of 19 seconds after 30 minutes. Because of this, the F4 formulation is the best formulationfor optimization.

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