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# Formulation, Evaluation & Development of Extended-Release Tablet of Class I Anti–Depressant Drug

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**A B S T R A C T**

This study aimed to develop and assess extended-release tablets of Mirtazapine using various release-retarding polymers to achieve sustained therapeutic effects and enhance patient compliance. A UV-Visible spectrophotometric method was validated for drug quantification in 0.1N HCl and pH 6.8 phosphate buffer, showing excellent linearity over a 2–10 µg/ml range. Pre-compression analysis revealed favorable flow and compressibility characteristics of powder blends. Tablets prepared by direct compression exhibited uniform thickness, suitable hardness, low friability, and consistent drug content within pharmacopeia limits. In vitro dissolution studies demonstrated that drug release was influenced by polymer concentration, with formulation F3 showing the most promising controlled-release profile. FTIR spectroscopy confirmed no significant interactions between Mirtazapine and excipients, ensuring formulation stability. Kinetic modeling indicated that drug release from the optimized formulation followed the Higuchi model, reflecting a diffusion-controlled mechanism, with non-Fickian anomalous transport confirmed by the Peppas model. Carbopol was identified as the most effective release-retarding polymer. The optimized formulation provided sustained Mirtazapine release up to 24 hours, positioning it as a potential once-daily oral dosage form to improve therapeutic outcomes and adherence in depression management.

**Keywords:** Mirtazapine, extended-release tablets, UV-Visible spectrophotometry, Carbopol, drug release kinetics, Higuchi model, controlled release.

**A R T I C L E I N F O**

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**C O N T E N T S**



## 1. Introduction

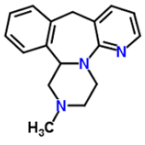

**Fig.1:** Mirtazapine

**Molecular Formula**: $C_{17}H_{19}N_3$
**Molecular Weight**: 265.35 g/mol

**IUPAC Name**:1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1a]pyrido [2,3-c] benzazepine
**Chem Spider ID**: 4039
**Density**: ~1.22 g/cm³ (predicted)
**Boiling Point**: ~432.4 °C (predicted)
**Vapour Pressure**: Not readily available
**Flash Point**: 9 °C
**Refractive Index**: Not specified
**Polar Surface Area**: Not specified

**LogP (Octanol/Water)**: ~3.5 (estimated)
**Generic Name**: Mirtazapine
**Brand Names**: Remeron, Avanza, Zispin, Mirtaz, and many others globally
**Drug Category**: Tetracyclic antidepressant (NaSSA – Noradrenergic and Specific Serotonergic Antidepressant)
**Indications**: Major depressive disorder, anxiety, insomnia, appetite stimulation
**Pharmacology**: Blocks $\alpha_2$-adrenergic receptors and 5-$HT_2$/5-$HT_3$ receptors, enhancing noradrenergic and serotonergic activity
**Potency**: High affinity for histamine $H_1$ and serotonin receptors (pKi ~9.3 for $H_1$)
**Tolerability**: Generally well-tolerated; sedation and weight gain are common
**Contraindications**: Hypersensitivity to mirtazapine; caution in hepatic/renal impairment
**Adverse Effects**: Sedation, increased appetite, weight gain, dry mouth, dizziness
**Availability**: Widely available in oral tablet and orodispersible forms across many countries
**Mechanism of Action:**
Mirtazapine acts as a NaSSA (Noradrenergic and Specific Serotonergic Antidepressant)**.** It blocks α2-adrenergic autoreceptors, heteroreceptors**,** increasing norepinephrine and serotonin release. It antagonizes 5-HT2 and 5-HT3 receptors**,** enhancing mood via 5-HT1A pathway**.** Strong H1 receptor blockade produces sedation and appetite stimulation. Overall, it improves mood, reduces anxiety, and aids sleep in depression.

## 2. Materials and Methods

**Table 1:** List of Materials and Suppliers

| S.No | Ingredients | Suppliers |
|---|---|---|
| 1 | Mirtazapine | Supplied By Qulaychrome research labs |
| 2 | Carbopol | SD Fine Chemicals, Mumbai |
| 3 | HPMC K4M | SD Fine Chemicals, Mumbai |
| 4 | HPMC K15M | SD Fine Chemicals, Mumbai |
| 5 | PVP K30 | SD Fine Chemicals, Mumbai |
| 6 | MCC | SD Fine Chemicals, Mumbai |
| 7 | Talc | SD Fine Chemicals, Mumbai |
| 8 | Magnesium stearate | SD Fine Chemicals, Mumbai |

**Table 2:** List of equipment's and Companies

| S.No | Name of the Equipment | Model |
|---|---|---|
| 1 | Electronic weighing balance | Scale-tec |
| 2 | Friabilator | Roche Friabilator Electrolab,Mumbai |
| 3 | Laboratory oven | Dtc-00r |
| 4 | Compression machine | Cmd(Cadmach) |
| 5 | Tablet hardness tester | Pfizer Hardness Tester, Mumbai |
| 6 | UV | Labindia Uv 3000+ |
| 7 | Dissolution apparatus | Electrolab TDT-08L |
| 8 | Vernier calipers | Cd-6"Cs |

**I. Analytical Method Development in 0.1N HCL:**
**Preparation of 0.1 N Hydrochloric Acid (pH 1.2)**
8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml.
**Determination of $\lambda_{max}$ of Mirtazapine in 0.1N HCL:**
**Procedure:**
**Working standard**: 100mg of Mirtazapine was weighed and dissolved in 10ml methanol and then make up to the volume of 100ml with 0.1N HCL it give 1000µg/ml concentrated stock solution.
**Dilution 1**: From the working standard, 10ml solution was diluted to 100ml with 0.1NHcl it will give 100 µg/ml concentrated solution.
**Dilution 2**: From the dilution1, 10ml solution was diluted to 100ml with 0.1NHcl it will give 10 µg/ml concentrated solution. This solutions was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as $\lambda_{max}$
**Construction of calibration curve of Mirtazapine in 0.1N HCL:**
**Working standard**:
100mg of Mirtazapine was weighed and dissolved in 10ml methanol and then make up to the volume of 100ml with 0.1N HCL it give 1000µg/ml concentrated stock solution.
**Dilution 1**:
From the working standard, 10ml solution was diluted to 100ml with 0.1NHcl it will give 100 µg/ml concentrated solution.
From dilution 1, take 0.2, 0.4, 0.6, 0.8, and 1ml of solution was diluted up to mark in 10ml volumetric flask to obtain 2, 4, 6, 8 and 10µg/ml concentrated solutions. This solutions absorbance was noted at 280nm.
**III. Analytical Method Development in 6.8 phosphate buffer: Preparation of 6.8 phosphate buffer:**
6.8gms of potassium di hydrogen ortho phosphate was taken in a 1000ml volumetric flask and dissolved with distilled water and make up to 1000 ml with distilled water and adjust pH up to 6.8 with Sodium hydroxide solution.
**Determination of $\lambda_{max}$ of Mirtazapine in 6.8 phosphate buffer::**
**Working standard**: 100mg of Mirtazapine was weighed and dissolved in 10ml methanol and then make up to the volume of 100ml with 6.8 phosphate buffer it give 1000µg/ml concentrated stock solution.
**Dilution 1**: From the working standard, 10ml solution was diluted to 100ml with 6.8 phosphate buffer it will give 100µg/ml concentrated solution.
**Dilution 2**: From the dilution-1, 10ml solution was diluted to 100ml with 6.8 phosphate buffer it will give 10µg/ml concentrated solution. This solution was scanned at range of 200-400nm wavelength light corresponding scan

spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as $\lambda_{max.}$

**Construction of calibration curve of Mirtazapine 6.8 phosphate buffer:**

**Working standard**: 100mg of Mirtazapine was weighed and dissolved in 10ml methanol and then make up to the volume of 100ml with 6.8 phosphate buffer it give 1000µg/ml concentrated stock solution.

**Dilution 1**: From the working standard, 10ml solution was diluted to 100ml with 6.8 phosphate buffer it will give 100 µg/ml concentrated solution. From dilution 1, take 0.2, 0.4, 0.6, 0.8 and 1ml of solution and was diluted up to mark in 10ml volumetric flask to obtain 2, 4, 6, 8 and 10µg/ml concentrated solutions. This solutions absorbance was noted at $\lambda_{max=270}$

**II. Formulation of Extended release tablets of Mirtazapine by direct compression method**

**Processing steps involved in direct compression method:** The matrix tablets were prepared by following the General Methodology as given below:

1. All ingredients (Mirtazapine + MCC + polymer + PVP K30) were weighed accurately and co sifted by passing through #22 sieve, blended in a Poly Bag for 5 min.
2. The above blend were lubricated with # 40 Sieves passed Talc and Magnesium stearate.
3. The final blend was then compressed into tablets using 16 station tablet compression machine with an average hardness of 5.0 - 7.0Kg/cm$^2$, by using 8-12mm die.

**Table 3:** Formulation of mirtazapine SR tablets by direct compression method

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Mirtazapine | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Carbopol | 30 | 60 | 90 | - | - | - | - | - | - |
| HPMC K4M | - | - | - | 30 | 60 | 90 | - | - | - |
| HPMC K15M | - | - | - | - | - | - | 30 | 60 | 90 |
| PVP K30 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| MCC | 126 | 96 | 66 | 126 | 96 | 66 | 126 | 96 | 66 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Mg.stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total Weight(mg) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

## 3. Results and Discussion

**Construction of Standard calibration curve of Mirtazapine in 0.1N HCL:** The absorbance of the solution was measured at 280nm, using UV spectrometer with 0.1N HCL as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml

**Table 4:** Standard Calibration graph values of Mirtazapine in 0.1N HCL

| Con. (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.218 |
| 4 | 0.413 |
| 6 | 0.621 |
| 8 | 0.81 |
| 10 | 0.988 |

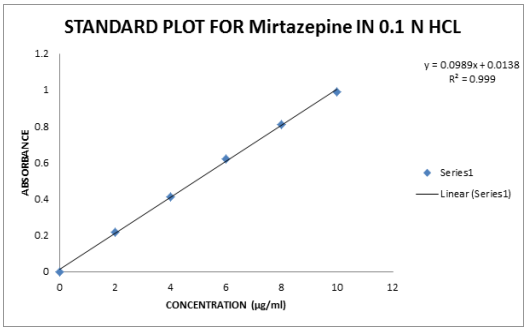


**Fig.2:** Standard calibration curve of Mirtazapine in 0.1N HCL

**Construction of Standard calibration curve of Mirtazapine in 6.8 phosphate buffer:** The absorbance of the solution was measured at 270nm, using UV spectrometer with 6.8 phosphate buffer as blank. The values shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml

**Table 5:** Standard Calibration graph values of Mirtazapine in 6.8 phosphate buffer

| Con.(µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.191 |
| 4 | 0.372 |
| 6 | 0.558 |
| 8 | 0.744 |
| 10 | 0.948 |

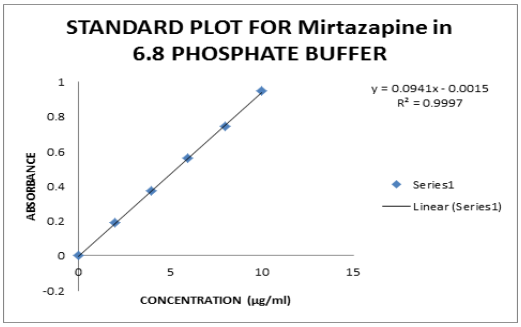


**Fig.3:** Standard calibration curve of Mirtazapine in 6.8 phosphate buffer

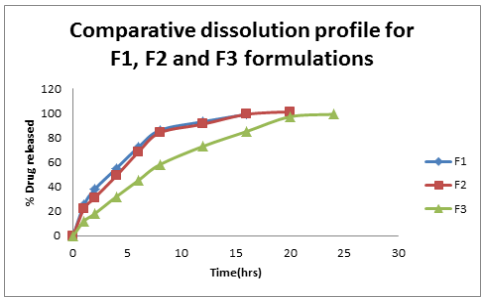


**Fig.4:** Comparative dissolution profile for F1, F2 and F3 formulations

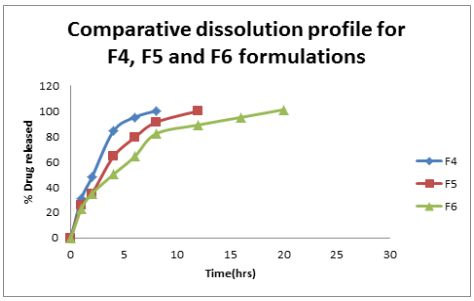


**Fig.5:** Comparative dissolution profile for F4, F5 and F6 formulations

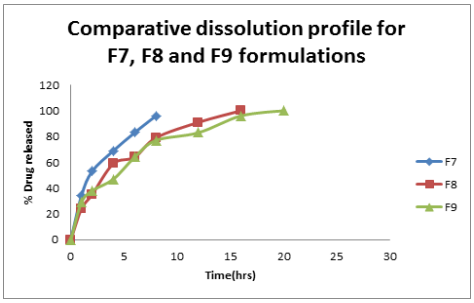


**Fig.6:** Comparative dissolution profile for F7, F8 and F9 formulations

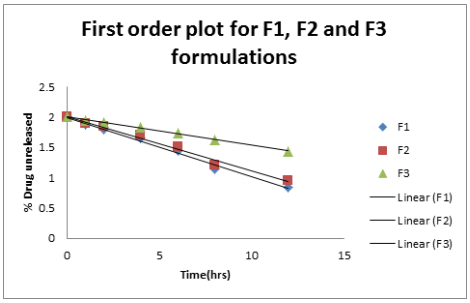


**Fig.7:** First order plot for F1, F2 and F3 formulations

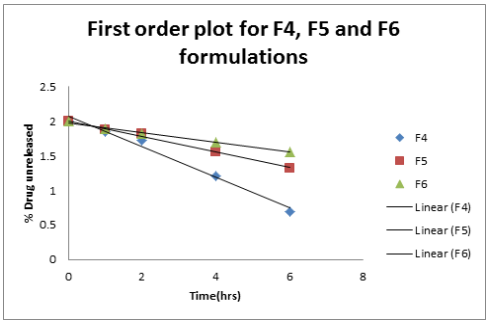


**Fig.8:** First order plot for F4, F5 and F6 formulations

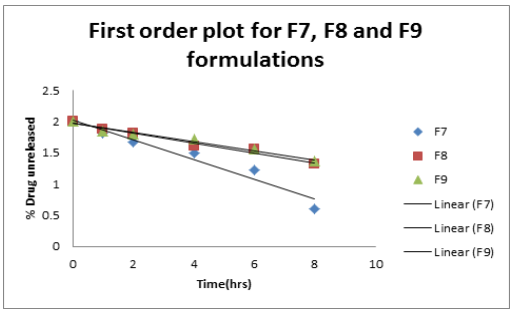


**Fig.9:** Higuchi plot for F7, F8 and F9 formulations

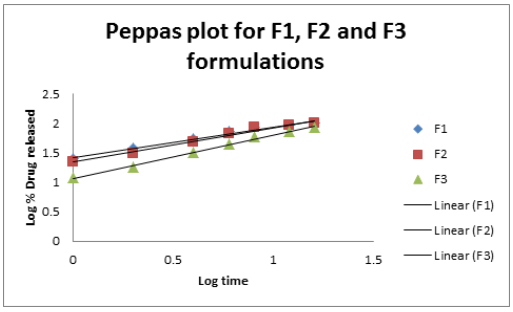


**Fig.10:** Peppas plot for F1, F2 and F3 formulations

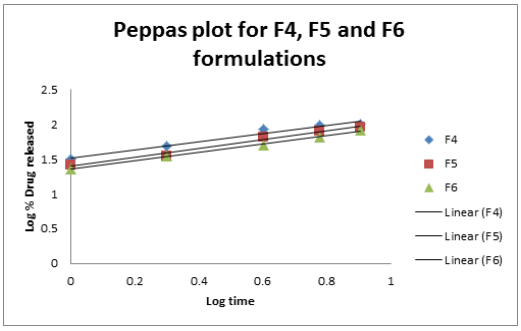


**Fig.11:** Peppas plot profile F4, F5 and F6 formulations

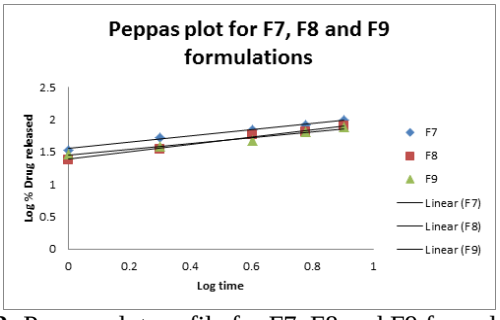


**Fig.12:** Peppas plot profile for F7, F8 and F9 formulations

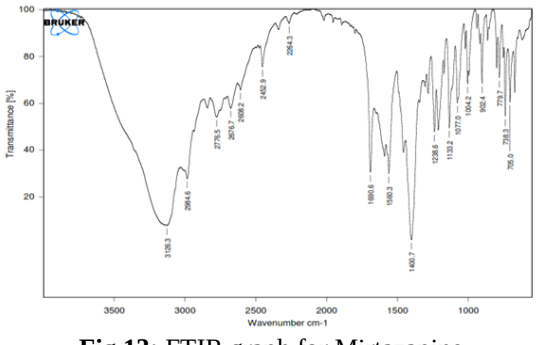


**Fig.13:** FTIR graph for Mirtazapine

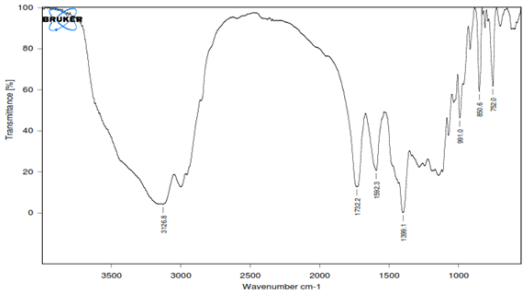


**Fig.14:** FTIR graph for Carbopol

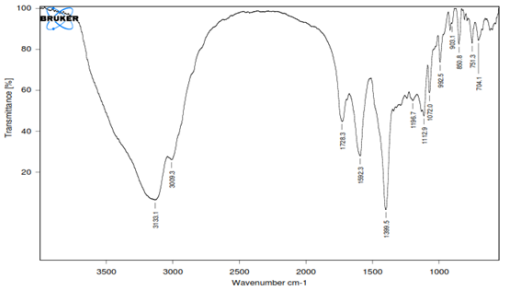


**Fig.15:** FTIR graph for Best formulation (F3)

**Table 6:** Pre compression studies of Mirtazapine ER tablets

| Formulation Code | Pre compression studies*,*n=3 | | | | |
|---|---|---|---|---|---|
| | Angle of repose ( $^{o}$) | Bulk density (g/cc) | Tapped density (g/cc) | Carr's Index (%) | Hausner's Ratio |
| **F1** | 22.17±0.15 | 0.515±0.015 | 0.522±0.008 | 13.15±1.04 | 1.10±0.07 |
| **F2** | 31.11±0.11 | 0.471±0.011 | 0.476±0.012 | 16.23±0.23 | 1.21±0.11 |
| **F3** | 25.71±0.13 | 0.505±0.005 | 0.527±0.015 | 14.26±0.65 | 1.15±0.31 |
| **F4** | 23.31±0.13 | 0.522±0.023 | 0.519±0.022 | 12.36±0.26 | 1.09±0.23 |
| **F5** | 31.11±0.11 | 0.471±0.011 | 0.476±0.012 | 16.23±0.23 | 1.21±0.11 |
| **F6** | 25.71±0.13 | 0.505±0.005 | 0.527±0.015 | 14.26±0.65 | 1.15±0.31 |
| **F7** | 23.31±0.13 | 0.522±0.023 | 0.519±0.022 | 12.36±0.26 | 1.09±0.23 |
| **F8** | 31.11±0.11 | 0.471±0.011 | 0.476±0.012 | 16.23±0.23 | 1.21±0.11 |
| **F9** | 31.11±0.11 | 0.471±0.011 | 0.476±0.012 | 16.23±0.23 | 1.21±0.11 |

**Table 7:** Post compression studies of Mirtazapine ER tablets

| Formulation Code | Post compression studies | | | | |
|---|---|---|---|---|---|
| | Weight variation | Thickness (mm)(n=3) | Hardness (kp)(n=3) | *%Friability | %Drug content (n=3) |
| **F1** | Pass | 5.82±0.34 | 5.9±0.26 | 0.59 | 99.98±0.18 |
| **F2** | Pass | 5.91±0.23 | 6.2±0.25 | 0.68 | 100.21±0.20 |
| **F3** | Pass | 5.84±0.1 | 6.3±0.21 | 0.58 | 99.67±0.12 |
| **F4** | Pass | 5.88±0.1 | 5.9±0.23 | 0.59 | 100.32±0.14 |
| **F5** | Pass | 5.84±0.1 | 6.3±0.21 | 0.58 | 99.67±0.12 |
| **F6** | Pass | 5.91±0.23 | 6.2±0.25 | 0.68 | 100.21±0.20 |
| **F7** | Pass | 5.82±0.34 | 5.9±0.26 | 0.59 | 99.98±0.18 |
| **F8** | Pass | 5.91±0.23 | 6.2±0.25 | 0.68 | 100.21±0.20 |
| **F9** | Pass | 5.84±0.1 | 6.3±0.21 | 0.58 | 99.67±0.12 |

**Table 8:** In-vitro Dissolution results for Mirtazapine ER tablets

| Time (hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 25 | 22 | **12** | 31 | 26 | 23 | 34 | 24 | 29 |
| 2 | 38 | 31 | **18** | 48 | 35 | 35 | 53 | 35 | 38 |
| 4 | 55 | 49 | **32** | 84 | 64 | 50 | 69 | 59 | 47 |
| 6 | 72 | 68 | **45** | 95 | 79 | 64 | 83 | 64 | 64 |
| 8 | 86 | 84 | **58** | 100 | 91 | 82 | 96 | 79 | 77 |
| 12 | 93 | 91 | **73** | - | 100 | 89 | - | 91 | 83 |
| 16 | 99 | 99 | **85** | - | - | 95 | - | 100 | 96 |
| 20 | - | 101 | **97** | - | - | 101 | - | - | 100 |
| 24 | - | - | **99** | - | - | - | - | - | - |

**Table 9:** $R^2$ value and n result table

| FORMULATION CODE | $R^2$ VALUES | | | | "N" VALUES |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi | PEPPAS | |
| F1 | 0.840 | 0.991 | 0.976 | 0.978 | 0.515 |
| F2 | 0.832 | 0.985 | 0.964 | 0.979 | 0.579 |
| F3 | 0.938 | 0.996 | 0.984 | 0.995 | 0.737 |

| | | | | | |
|---|---|---|---|---|---|
| F4 | 0.886 | 0.986 | 0.976 | 0.970 | 0.593 |
| F5 | 0.883 | 0.994 | 0.980 | 0.985 | 0.634 |
| F6 | 0.839 | 0.987 | 0.973 | 0.995 | 0.592 |
| F7 | 0.892 | 0.950 | 0.996 | 0.990 | 0.482 |
| F8 | 0.872 | 0.978 | 0.988 | 0.986 | 0.574 |
| F9 | 0.855 | 0.971 | 0.982 | 0.970 | 0.457 |

## 4. Conclusion

The present study was undertaken to develop and evaluate extended-release tablets of Mirtazapine using different release-retarding polymers. Calibration curve studies in 0.1N HCl (280 nm) and pH 6.8 phosphate buffer (270 nm) confirmed linearity in the range of 2–10 µg/ml with excellent correlation ($R^2$ = 0.999). Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio revealed good flow and compressibility of the powder blends, while post-compression evaluations demonstrated uniform thickness, acceptable hardness, low friability (<1%), and satisfactory drug content (98–102%). In-vitro dissolution studies indicated that release patterns varied with polymer concentration, with formulation F3 showing the most desirable controlled-release profile. FTIR spectra further confirmed drug-excipient compatibility, as the characteristic peaks of Mirtazapine were retained in the optimized formulation. Kinetic modeling revealed that the drug release from F3 followed the Higuchi model, suggesting a diffusion-controlled mechanism, while the Peppas model indicated a non-Fickian anomalous diffusion (n = 0.737), involving both diffusion and polymer relaxation. Overall, the results demonstrated that Carbopol had the highest drug release-retarding effect, and F3 provided a sustained release of Mirtazapine up to 24 hours. Thus, the optimized formulation can be considered a potential candidate for once-daily extended-release Mirtazapine tablets, offering consistent therapeutic action, improved patient compliance, and better clinical outcomes in the management of depression.

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