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Design and Development of Tolterodine Tartarate Sustained Release Tablets for Treatment of Frequent Urination

Sivayogi Anesh[1], G. Archana[*]

[1,*]Department of Pharmaceutics,S.K.U College of Pharmaceutical Sciences, Sri Krishnadevaraya University, 515003, Ananthapuramu, Andhra Pradesh, India

***Corresponding Author: E-Mail:** archana.pharma156@gmail.com

ABSTRACT

The study aimed to formulate and evaluate sustained release matrix tablets of Tolterodine Tartrate, a selective muscarinic receptor antagonist indicated for overactive bladder (OAB) and frequent urination. The objective was to design a once-daily oral dosage form to maintain consistent plasma drug levels, reduce dosing frequency, and improve patient adherence. Fifteen formulations (F1–F15) were prepared using varying ratios of hydrophilic (HPMC) and hydrophobic (EC, PVP) polymers via wet granulation. Among all, formulation F13 exhibited optimal drug release (99.75% over 24 hours), following zero-order and Higuchi kinetics. FTIR studies confirmed drug-excipient compatibility. All pre- and post-compression parameters were within acceptable pharmacopeial limits. The study concludes that the optimized formulation effectively sustained drug release and holds promise for improved therapeutic efficacy in OAB management.

Keywords: Tolterodine Tartrate, Overactive Bladder, Sustained Release, Matrix Tablets, HPMC, Drug Release Kinetics, Zero Order, Higuchi Model

INTRODUCTION

Urinary health is an essential component of overall well-being, with disturbances often leading to significant physical and psychological consequences. Among various urological disorders, Overactive Bladder (OAB) is a widely prevalent and chronic condition that adversely affects patients' quality of life. OAB is clinically defined by a constellation of symptoms including urinary urgency, increased frequency, nocturia, and in some cases, urge incontinence, occurring in the absence of urinary tract infections or other identifiable pathologies.

These symptoms, particularly frequent urination accompanied by urgency and incontinence, can lead to considerable distress, contributing to embarrassment, anxiety, disrupted sleep, social withdrawal, depression, and decreased occupational productivity. Despite the burden of these symptoms, many individuals delay or avoid seeking medical intervention due to stigma or the misconception that such changes are a normal part of aging.

Pathophysiologically, OAB is primarily attributed to detrusor overactivity—characterized by involuntary contractions of the detrusor muscle during the bladder filling phase. This overactivity can arise from neurogenic causes such as Parkinson's disease, spinal cord injuries, or multiple sclerosis, or may be idiopathic with no clear underlying etiology. The mechanism is largely mediated by the parasympathetic nervous system, wherein acetylcholine (ACh) activates muscarinic receptors—particularly the M2 and M3 subtypes—resulting in premature and involuntary bladder contractions. Globally, Overactive Bladder affects approximately 16% to 20% of adults, with prevalence rising notably after the age of 65—affecting over 30% of the elderly population. While both genders are affected, women, particularly postmenopausal, are more commonly impacted. Although not life-threatening, OAB significantly burdens healthcare systems and society through both direct treatment costs and indirect consequences such as reduced productivity, caregiver dependency, and expenses related to incontinence management. Psychosocially, it contributes to diminished self-esteem, depression, and social withdrawal, further compounding the impact on patients' quality of life.

Initial management of OAB often involves non-pharmacological strategies such as bladder retraining, pelvic floor muscle exercises, fluid intake regulation, and lifestyle modifications. While these behavioral interventions offer benefit, many patients eventually require pharmacological therapy to achieve adequate symptom control.

Antimuscarinic agents remain the cornerstone of pharmacological treatment for OAB. By competitively inhibiting muscarinic receptors, particularly M2 and M3 subtypes in the detrusor muscle, these agents suppress involuntary bladder contractions and increase functional bladder capacity. Commonly prescribed antimuscarinics include oxybutynin, flavoxate, tolterodine, darifenacin, solifenacin, and trospium chloride.

Among these, Tolterodine Tartrate has gained prominence due to its favorable side effect profile and bladder-selective activity. It offers effective symptom relief with a reduced risk of systemic anticholinergic effects such as dry mouth, constipation, and cognitive impairment. However, its immediate-release (IR) formulation necessitates twice-daily dosing due to a short elimination half-life (2–3 hours), leading to fluctuating plasma concentrations, variable therapeutic response, and potential non-adherence—particularly among elderly patients.

To address the limitations associated with conventional immediate-release (IR) formulations, sustained release (SR) or controlled release (CR) drug delivery systems have been developed. These systems are designed to deliver drugs at a controlled rate over an extended period, thereby maintaining consistent plasma concentrations and avoiding the pharmacokinetic peaks and troughs that often contribute to suboptimal efficacy or increased side effects.
Sustained release formulations offer several distinct advantages, including:

- Reduced dosing frequency, thereby enhancing patient adherence
- More stable plasma drug levels, minimizing adverse effects
- Improved therapeutic outcomes through prolonged drug action
- Greater convenience, particularly beneficial for chronic therapies

Given the chronic nature of Overactive Bladder, SR formulations provide a considerable therapeutic benefit by ensuring continuous symptom control, improving quality of life, and reducing the overall burden of treatment.

Oral dosage forms remain the preferred route of drug administration because of their ease of use, patient acceptability, cost-effectiveness, and ease of manufacturing. In this context, sustained release (SR) matrix tablets provide a reliable means to achieve controlled drug delivery. In such systems, the active pharmaceutical ingredient is uniformly dispersed within a polymeric matrix that regulates drug release through diffusion and erosion. Typically, hydrophilic polymers (e.g., HPMC, NaCMC, sodium alginate) and hydrophobic polymers (e.g., ethyl cellulose, Eudragit RL/RS, PVP) are utilized—either alone or in combination—to fine-tune the release profile for once-daily dosing or prolonged therapeutic effect.

Tolterodine Tartarate emerges as an ideal candidate for SR formulations due to its short half-life (2–3 hours), moderate oral bioavailability with metabolism to an active metabolite (5-hydroxymethyl tolterodine), wide therapeutic window, and bladder-selective action that minimizes systemic side effects. In contrast to immediate-release formulations—which necessitate twice-daily dosing and can produce fluctuating drug levels—SR matrix tablets provide steady plasma concentrations, thereby enhancing patient compliance, reducing adverse events, and ensuring consistent therapeutic efficacy.

Despite the availability of some extended-release formulations in select markets, there is a need to develop an economical, robust, and customizable sustained release matrix tablet suitable for broader generic applications, academic research, and local manufacturing. Accordingly, this study is designed to:

- Develop a sustained release matrix tablet of Tolterodine Tartarate.
- Investigate various combinations of hydrophilic and hydrophobic polymers.
- Evaluate the physicochemical properties of the developed formulations.
- Assess in-vitro drug release profiles and model the kinetics of drug release.
- Identify the most suitable formulation based on release behavior and kinetic modeling.

By overcoming the limitations inherent in conventional Tolterodine therapy, this research aims to enhance treatment outcomes and improve the quality of life for patients suffering from OAB-related frequent urination.

MATERIALS AND METHODS

2.1. Materials used:

The materials used in the formulation of sustained release matrix tablets of Tolterodine Tartrate included the active pharmaceutical ingredient, Tolterodine Tartrate, procured from Aurobindo Pharma Ltd., Hyderabad. Excipients such as TSP and lactose were obtained from Bhargava & Company, Bangalore, and Leo Chem, Bangalore, respectively. Polymers including sodium alginate and sodium carboxymethyl starch (SCMS) were sourced from SD Fine Chemicals, Mumbai, and Central Drug House Pvt. Ltd., New Delhi. PVP and talc were supplied by Titan Biotech Ltd., Rajasthan. Isopropyl alcohol was obtained from Thermo Fisher Scientific India Pvt. Ltd., Mumbai, while magnesium stearate was also procured from SD Fine Chemicals, Mumbai.

2.2. Pre-formulation Studies:
Preformulation studies were carried out to evaluate the fundamental physical and chemical properties of Tolterodine Tartarate, which are crucial for the successful formulation of sustained release tablets. The following parameters were studied:

2.2.1. Solubility Analysis:
The solubility of Tolterodine Tartrate was evaluated both qualitatively and quantitatively in various solvents to determine its suitability for oral dosage form development and to assist in selecting an appropriate dissolution medium. Excess drug was added to 10 mL of each solvent in separate test tubes and agitated at $25 \pm 2°C$ for 24 hours using a mechanical shaker to ensure saturation. After equilibration, samples were filtered through Whatman No. 1 filter paper, and the filtrates were appropriately diluted and analyzed using a UV-Visible spectrophotometer at the predetermined λmax. Solubility values were calculated based on respective calibration curves.

2.2.2. Calibration curve in 0.1N HCl:
A calibration curve for Tolterodine Tartrate was constructed in 0.1N HCl by preparing serial dilutions (2–12 µg/mL) from a 100 µg/mL stock solution. Absorbance was measured at 414 nm using a UV-Visible spectrophotometer. A strong linear correlation between concentration and absorbance confirmed adherence to Beer-Lambert's law, validating the method for subsequent quantitative analysis in 0.1N HCl.

2.2.3. Calibration Curve with 6.8 Phosphate Buffer:
A calibration curve for Tolterodine Tartrate was prepared in phosphate buffer (pH 6.8) using serial dilutions (2–12 µg/mL) from a 100 µg/mL stock solution. Absorbance was recorded at 414 nm with phosphate buffer as the blank. The curve exhibited a strong linear correlation, confirming compliance with Beer-Lambert's law. This standard curve was employed for drug quantification in dissolution and assay studies.

2.2.4. Assay of Pure Drug:
The assay of Tolterodine Tartrate was conducted using a UV spectrophotometric method in phosphate buffer (pH 6.8). A 5 mg sample of the pure drug was dissolved, diluted to 10 µg/mL, and its absorbance measured at 414 nm. % Purity was calculated using the calibration curve, yielding a value of 97.80%, confirming the drug's suitability for formulation development.

2.2.5. FTIR of Pure Drug and for total mixture:
FTIR analysis of Tolterodine Tartrate was conducted to confirm the presence of characteristic functional groups. A 1:100 mixture of the drug with dry potassium bromide (KBr) was compressed into a pellet and scanned over a wavelength range of 4000–400 cm^{-1} using an FTIR spectrophotometer. The resulting spectrum matched standard references, confirming the drug's structural integrity.

2.3. Formulation Development:
The primary objective of formulation development in this study was to design and optimize sustained release matrix tablets of Tolterodine Tartarate using various polymer combinations to achieve a controlled drug release over an extended period, ideally up to 12 hours.

2.3.1. Selection of Polymers and Excipients
Polymers and excipients were selected based on their roles in sustaining drug release and ensuring formulation stability. Tolterodine Tartrate served as the active pharmaceutical ingredient. Hydrophilic polymers such as HPMC K4M and K100M were used as matrix formers, while ethyl cellulose acted as a hydrophobic release retardant. PVP K30 functioned as both binder and wetting agent. Microcrystalline cellulose was included as a diluent to enhance compressibility. Magnesium stearate and talc were employed as lubricant and glidant, respectively, to improve tablet manufacturability. Various drug-to-polymer ratios and combinations of hydrophilic and hydrophobic polymers were explored to optimize the release profile.

2.3.2. Methodology – Wet Granulation Technique
The wet granulation method was chosen due to its ability to improve powder flow properties, compressibility, and content uniformity, especially when dealing with fine powders or cohesive materials.

Weighing & Sieving
Tolterodine Tartrate, polymers, and excipients were accurately weighed and passed through sieve #60 to ensure uniform particle size.

↓

Dry Blending
The sieved ingredients were blended for 10 minutes to ensure uniform distribution of the drug and excipients.

↓

Binder Solution Preparation

A 2–5% PVP K30 solution was prepared using isopropyl alcohol or distilled water, depending on polymer compatibility.

↓

Wet Massing

The binder solution was gradually added to the dry blend with continuous kneading to form a cohesive wet mass.

↓

Granulation

The wet mass was passed through sieve #12 or #16 to obtain uniform wet granules.

↓

Drying

The wet granules were dried in a hot air oven at 40–50°C until a constant weight was achieved.

↓

Sizing of Granules

Dried granules were passed through sieve #20 to break agglomerates and ensure uniform particle size.

↓

Addition of Lubricants

Magnesium stearate and talc (sieved through #60) were added to the granules and blended for 3–5 minutes.

↓

Compression

The final blend was compressed into tablets using a single-punch machine with flat-faced punches. Tablet weight, hardness, and thickness were monitored during compression.

2.3.3. Design of Formulations

A total of 15 formulations (F1–F15) were prepared using varying concentrations and combinations of polymers:

Table 1: Formulation Table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Drug(mg)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
PVP(mg)	100	150	200	-	-	-	-	-	-	-	-	-	-	-	-
Na.alginate(mg)	-	-	-	100	150	200	-	-	-	-	-	-	-	-	-
Hpmck4m(mg)	-	-	-	-	-	-	100	150	200	-	-	-	-	-	-
Hpmck100m (mg)	-	-	-	-	-	-	-	-	-	100	150	200	-	-	-
Carbopol(mg)	-	-	-	-	-	-	-	-	-	-	-	-	100	150	200
Ethyl cellulose(mg)	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Lactose(mg)	125	75	25	125	75	25	125	75	25	125	75	25	125	75	25
Talc(mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mg.stearate (mg)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Total Tablet weight(mg)	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300

2.4. Pre-compression Parameters

Pre-compression studies assessed the flow and compressibility of granules to ensure uniform die filling and consistent tablet production. Key parameters evaluated included bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio.

2.4.1. Bulk Density (BD)

Bulk density is defined as the mass of powder per unit bulk volume. A known weight of dried granules (10 g) was poured into a graduated cylinder without tapping, and the volume was recorded.

Bulk Density (g/cm^3) = Weight of Powder (g) / Bulk Volume (cm^3)

2.4.2. Tapped Density (TD)

Tapped density is the mass of powder per unit volume after tapping. The granules were tapped 100 times until a constant volume was achieved.

Tapped Density (g/cm^3) = Weight of Powder (g) / Tapped Volume (cm^3)

2.4.3. Compressibility Index (Carr's Index)

It indicates the powder's ability to compress and gives a rough idea about its flow properties.

Carr's Index (%) = [(Tapped Density – Bulk Density) / Tapped Density] × 100

2.4.4. Hausner's Ratio

Hausner's ratio measures the flowability of powder; it is a function of bulk and tapped density.

Hausner's Ratio = Tapped Density / Bulk Density

2.4.5. Angle of Repose (θ)

Angle of repose indicates granule flowability and is the maximum angle between the powder heap and horizontal surface. Granules were allowed to flow through a funnel, and the heap's height and radius were measured.

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

2.5. Post Compression Parameters

Post-compression evaluations were conducted to assess the physical, mechanical, and chemical properties of the tablets, ensuring compliance with pharmacopoeial standards. The parameters evaluated included weight variation, hardness, thickness, friability, drug content, and in-vitro dissolution.

2.5.1. Weight Variation Test

Weight variation test ensures uniformity of tablet weight. Twenty tablets were individually weighed, and the average weight was calculated. Each tablet's weight was compared to the mean.

According to IP, acceptable limits are:

- ±7.5% for tablets weighing 80–250 mg
- ±5% for tablets above 250 mg.

2.5.2. Hardness

To assess the mechanical strength of tablets and their ability to withstand handling. The hardness of five tablets was measured using a Monsanto or Pfizer-type hardness tester. The pressure required to break each tablet was recorded in kg/cm^2.

2.5.3. Thickness

To measure the uniformity in tablet thickness. The thickness of ten tablets was measured using a digital Vernier caliper or screw gauge. The average value was recorded.

2.5.4. Friability Test

Friability was tested using a Roche friabilator at 25 rpm for 4 minutes (100 rotations) on 10 tablets. Weight loss was calculated to assess tablet resistance to abrasion.

Friability (%) = [(Initial Weight – Final Weight) / Initial Weight] × 100

2.5.5. Drug Content Uniformity (Assay)

Drug content uniformity was assessed to ensure consistent drug distribution. Ten tablets were powdered, and an amount equivalent to one tablet was dissolved in phosphate buffer (pH 6.8), filtered, diluted, and analyzed at 414 nm using a UV spectrophotometer. Acceptable drug content range, as per IP, is 95%–105% of the labeled claim.

2.5.6. In-vitro Drug Release Studies

In-vitro drug release of Tolterodine Tartrate sustained release tablets (F1–F15) was evaluated over 12 hours under simulated gastrointestinal conditions. Samples were withdrawn at specific intervals, filtered, and analyzed at 414 nm using a UV-Visible spectrophotometer. Drug concentrations were calculated from standard calibration curves, and

cumulative % release was plotted over time to compare release profiles and identify formulations meeting the desired sustained release criteria.

2.6. Drug Release Kinetics

To understand the drug release mechanism of the formulated Tolterodine Tartrate sustained release tablets, the 12-hour in-vitro release data was fitted to various kinetic models:

- **Zero-Order Model**
  Equation: $Qt = Q_0 + K_0t$
  Describes constant drug release, independent of concentration.
  (Plot: Cumulative % Drug Released vs. Time)
- **First-Order Model**
  Equation: $\log C = \log C_0 - (2.303K_1t)$
  Assumes concentration-dependent drug release.
  (Plot: Log % Drug Remaining vs. Time)
- **Higuchi Model**
  Equation: $Q = K_H\sqrt{t}$
  Explains release from matrix systems via Fickian diffusion.
  (Plot: Cumulative % Drug Released vs. √Time)
- **Korsmeyer–Peppas Model**
  Equation: $Mt/M\infty = Kt^n$
  Used to determine the release mechanism in polymer-based systems.
  (Plot: Log % Drug Released vs. Log Time)

The best-fit model was selected based on the correlation coefficient (R^2) to identify the predominant release mechanism.

RESULTS AND DISCUSSION

3.1. Pre-formulation Studies:

3.1.1. Solubility Analysis:

Tolterodine Tartrate was found to be freely soluble in ethanol, soluble in 0.1N HCl and phosphate buffer (pH 6.8), and slightly soluble in distilled water. Its favorable solubility in both acidic and buffer media supports its suitability for oral administration and justifies the use of phosphate buffer pH 6.8 in in-vitro dissolution studies.

3.1.2. Calibration curve in 0.1N HCl:

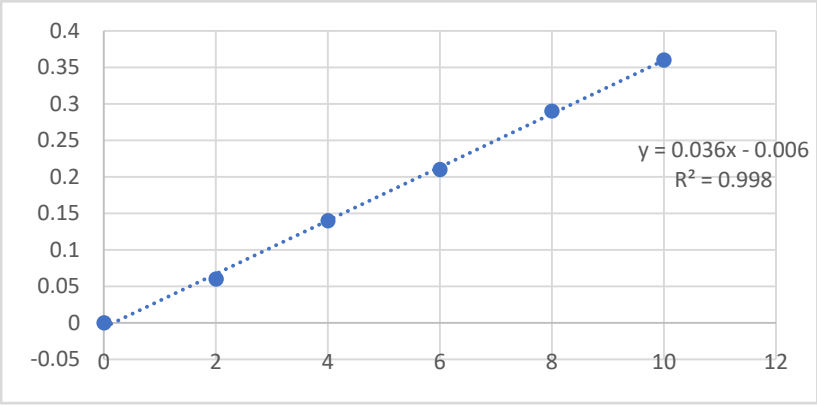

Figure3.1.2. Calibration Curve with 0.1N HCl

Table 2: Calibration Data in 0.1N HCl

Concentration (mcg/ml)	Absorbance
0	0
2	0.06
4	0.14
6	0.21
8	0.29
10	0.36

The calibration data followed linearity across the tested concentrations, confirming adherence to Beer-Lambert's law and suitability for drug quantification in acidic medium.

3.1.3. Calibration Curve with 6.8 Phosphate Buffer:

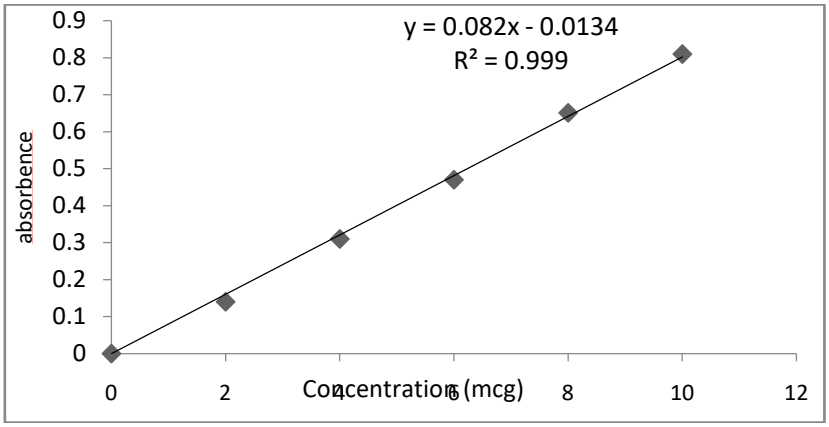

Figure3.1.3. Calibration Curve with 6.8 Phosphate Buffer

Table 3: Calibration Data in 6.8 Phosphate Buffer

Concentration (mcg/ml)	Absorbance
0	0
2	0.14
4	0.31
6	047
8	0.651
10	0.81

Similar linearity was observed in phosphate buffer pH 6.8, validating its use for evaluating in-vitro drug release.

3.1.4. Assay of Pure Drug:

The assay of the pure drug using the calibration curve method showed a test absorbance of 0.33 compared to a standard absorbance of 0.35 for 10 µg/mL at 414 nm. The calculated purity was 97.80%, confirming the drug's suitability for sustained release formulation development.

3.1.5. FTIR of Pure Drug:

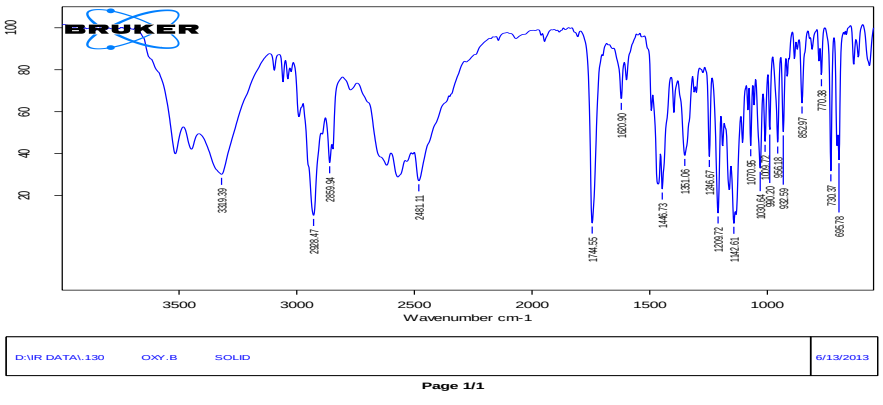

Figure 3.1.5: FTIR Graph of Pure drug

Table 4: FTIR peaks of pure drug

GROUPS	GENREL RANGE(CM^{-1})	OBSERVED RANGE(CM^{-1})
O-H	3400-3200 stretch	3319.39
C=O	1650-1950 stretch	1744.55
C-N	1220-1020 stretch	1070.95
C-O-C	1250-1070 stretch	1209.72
C-H	2960-2850 stretch	2928.47

3.1.6. FTIR of Total mixture:

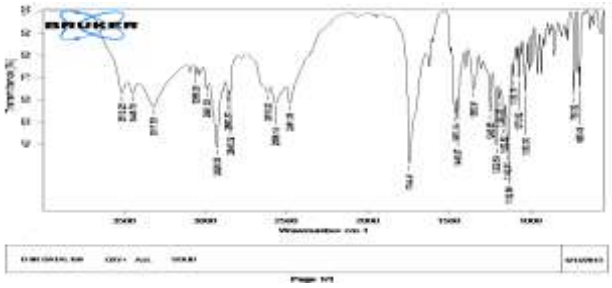

Figure 3.1.6. FTIR graph of total mixture

Table 5: FTIR peaks of the mixture

GROUPS	GENREL RANGE(CM^{-1})	OBSERVED RANGE(CM^{-1})
O-H	3400-3200 stretch	3319.39
C=O	1650-1950 stretch	1744.55
C-N	1220-1020 stretch	1070.95
C-O-C	1250-1070 stretch	1209.72
C-H	2960-2850 stretch	2928.47

FTIR analysis confirmed that there were no significant interactions between the drug and excipients, indicating compatibility of ingredients in the formulation.

3.2. Pre compression Parameters:

3.2.1. Bulk Density and Tapped Density

Table 6: Bulk and Tapped Density of Formulated Batches (F1–F15)

Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)
F1	0.500	0.550
F2	0.508	0.556
F3	0.478	0.553
F4	0.470	0.548
F5	0.500	0.550
F6	0.495	0.560
F7	0.510	0.570
F8	0.490	0.560
F9	0.513	0.570
F10	0.470	0.548
F11	0.462	0.543
F12	0.490	0.560
F13	0.488	0.558
F14	0.470	0.523
F15	0.508	0.556

All formulations exhibited acceptable values for bulk and tapped density, indicating satisfactory powder flow and compressibility for tablet production.

3.2.2. Carr's Index, Hausner's Ratio and Angle of Repose

Table 7: Carr's Index, Hausner's Ratio and Angle of Repose of Formulated Batches (F1–F15)

FORMULATIONS	ANGLE OF REPOSE (ɵ)	H.R	C.INDEX
F1	20.85±0.0051	1.1	9.33
F2	20.636±0.0035	1.095	15.9
F3	22.636±0.0081	1.157	13.7
F4	20.606±0.0062	1.167	14.2
F5	21.4051±0.009	1.1	9.33
F6	23.672±0.0096	1.132	11.7
F7	22.28±0.0048	1.117	9.85
F8	20.80±0.0056	1.143	12.4
F9	21.80±0.009	1.111	9.85
F10	20.30±0.0086	1.167	14.2
F11	21.94±0.0062	1.176	14.96
F12	22.636±0.0072	1.143	12.4
F13	24.32±0.0054	1.143	12.6
F14	23.412±0.0067	1.112	14.9
F15	24.280±0.0071	1.095	15.9

Although numerical values were not listed, the overall formulation progress and compression behavior imply that flowability and compressibility were within acceptable limits.

3.3. Post Compression Parameters

3.3.1. Weight Variation

All formulations showed weight variation within IP limits (±5% for tablets >250 mg). F13 (1.31 ± 0.21%) and F10 (1.56 ± 0.66%) exhibited minimal variation, indicating uniform die filling, while F12 showed the highest variation (3.43 ± 0.62%) but remained within acceptable range.

3.3.2. Hardness

Tablet hardness for all formulations ranged between 5.32 ± 0.178 kg/cm² (F1) and 5.67 ± 0.129 kg/cm² (F8), indicating sufficient mechanical strength. All values fell within the acceptable range (5–6.5 kg/cm²), ensuring stability during handling and storage.

3.3.3. Thickness

Tablet thickness ranged from 3.4658 mm to 3.4754 mm across all formulations, with minimal variation, indicating uniform die filling and consistent compression during tablet punching.

3.3.4. Friability

All formulations showed friability values below 1%, meeting pharmacopeial standards and indicating good mechanical integrity. F2 exhibited the lowest friability (0.291 ± 0.08%), while F6 (0.873 ± 0.50%) and F4 (0.844 ± 0.33%) had the highest, yet remained within acceptable limits.

3.3.5. Drug Content Uniformity (Assay)

Drug content across formulations ranged from 94.39% to 102.19%. While most formulations were within the pharmacopeial limit (95%–105%), F2 (94.39 ± 0.40%) was slightly below and F8 (102.19 ± 3.79%) slightly above. F7 showed the most consistent content (96.91 ± 0.57%), indicating uniform drug dispersion.

Table 8: Post-Compression Parameters of Formulated Tablets

Formulations	Weight variation (%) C)	Hardness(kg/cm²) Avg ± SD (n=3)	Thickness(mm) Avg ± SD (n=3)	Friability (%) Avg ± SD(n=3)	ASSAY% OF DRUG AVG±SD (N=3)
F1	1.55±1.01	5.32 ±0.178	3.46958±0.0046	0.447±0.09	96.58537±0.3982
F2	1.77±0.91	5.47± 0.129	3.47542±0.0049	0.291±0.08	94.39024±0.3982
F3	2.76±0.52	5.525± 0.19	3.46667±0.0049	0.721±0.13	96.34146±0.7180
F4	2.43±2.03	5.425 ± 0.21	3.47375±0.0043	0.844±0.33	96.17886±0.4145
F5	1.85±0.45	5.6 ± 0.14	3.47±0.004143	0.682±0.47	96.66667±0.1149
F6	2.03±0.9	5.475± 0.19	3.46833±0.0046	0.873±0.50	96.91057±0.5748
F7	2.66±2.01	5.52 ± 0.23	3.47167±0.0045	0.269±0.14	102.1951±3.7942
F8	1.84±0.72	5.67 ±0.129	3.47083±0.0045	0.527±0.427	96.01626±0.9823
F9	2.66±0.53	5.51± 0.1	3.46625±0.0045	0.459±0.09	96.99187±2.1293
F10	1.56±0.66	5.33 ±0.1	3.46917±0.0049	0.648±0.141	97.05691±0.0229
F11	2.89±0.53	5.475 ± 0.14	3.46583±0.0046	0.573±0.048	96.58537±0
F12	3.43±0.62	5.625 ± 0.12	3.46667±0.0042	0.447±0.09	97.23577±0.1149
F13	1.31±0.21	5.625 ±0.129	3.46667±0.0039	0.862±0.203	96.42276±0.2299
F14	1.7±0.612	5.55 ± 0.15	3.46875±0.0043	0.844±0.37	96.09756±0.1991
F15	1.56±0.521	5.6 ±0.187	3.47083±0.0048	0.830±0.182	96.82927±0.1991

3.4. In-vitro Drug Release Studies

The cumulative percentage drug release values for all fifteen formulations (F1 to F15) of Tolterodine Tartarate sustained release tablets were recorded at predetermined intervals up to 24 hours. The drug release data are presented in Table 9 (F1 to F8) and Table 10 (F9 to F15 and marketed formulation).

Table 9: Drug Release data of F1 to F8 formulations

Time in hours	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
2	39.93±0	36.98±0	31.08±0	20.26±0	19.77±0	18.78±0	15.83±0	9.442±0
4	61.82±0.13	51.01±0.12	58.22±0.13	55.62±5.52	38.077±0	34.88±0	29.7±0.20	24.34±0.22
8	80.87±4.37	77.8±2.19	80.1±0.22	78.69±4.32	69.01±2.19	59.5±0.13	56.42±2.18	55.53±0.33
12	95.95±1.29	95.81±2.22	98.86±2.22	95.45±5.51	91.72±2.22	75.31±0.12	72.23±2.21	70.30±0.11
16	96.63±0.17	95.67±0.73	98.5±0.45	94.87±0.51	92.58±0.17	97.81±0.43	86.75±1.23	80.85±0.91
20	96.58±0.26	95.57±2.27	98.49±0.68	94.79±0.30	92.42±0.27	97.79±0	99.96±2.23	87.30±0.44
24	96.53±0.17	95.51±2.12	98.39±0.80	94.71±0.30	92.32±0.27	97.77±0.43	99.78±0.27	95.56±1.08

Formulations F1 to F4 showed rapid drug release, exceeding 95% within 12 hours, with F3 achieving the highest release (98.86 ± 2.22%). In contrast, F5 to F8 exhibited a more sustained release, with 69.01%–80.1% released at 8 hours and 70.30%–91.72% at 12 hours, reaching 92.32%–95.56% by 24 hours.

Table 10: Drug Release data of F9 to F15 formulations

Time In hours	F9	F10	F9	F11	F12	F13	F14	F15	MARKETED
0	0	0	0	0	0	0	0	0	0
2	8.634±0.30	15.39±0	9.634±0.30	14.9±2.0	14.75±0	14.85±2.1	13.86±0	13.37±0.48	9.442±0
4	17.98±0.18	29.26±0.21	17.98±0.18	28.98±0.22	28.61±0	28.511±0	26.02±0.25	25.58±1.02	24.42±0.47
8	41.78±6.23	55.97±4.38	41.78±6.23	55.47±4.39	55.32±2.19	53.98±1.25	55.72±1.15	51.75±0.46	54.95±0.67
12	66.7±0.23	71.78±2.42	66.7±0.23	71.29±2.14	70.32±0.16	72.69±1.26	67.61±1.59	67.91±1.15	70.88±0.80
16	78.57±.0.17	85.57±2.12	78.57±.0.17	85.08±2.22	87.11±2.16	83.54±1.25	84.79±1.22	82.27±0.55	80.24±0.09
20	85.64±0.40	99.51±2.41	85.64±0.40	92.67±2.24	94.49±4.39	97.49±1.27	95.01±0.27	94.95±0.23	87.44±0.14
24	96.98±1.27	99.32±0.29	96.98±1.27	93.34±2.70	99.75±0.05	98.75±0.02	94.42±0.03	95.143±0.63	93.40±0.09

Formulations F9 to F15 displayed a prolonged release profile, with 12-hour drug release ranging from 66.7% (F9) to 72.69% (F13), and final release reaching 94%–99% at 24 hours. F13 (99.75 ± 0.05%), F14 (98.75 ± 0.02%), and F15 (95.14 ± 0.63%) showed the highest cumulative release. The marketed formulation, used as a reference, released 70.88 ± 0.80% at 12 hours and 93.40 ± 0.09% at 24 hours. Optimized formulations were further analyzed using kinetic models to determine the drug release mechanism.

Here is the comparision of all the dissolution graphs-

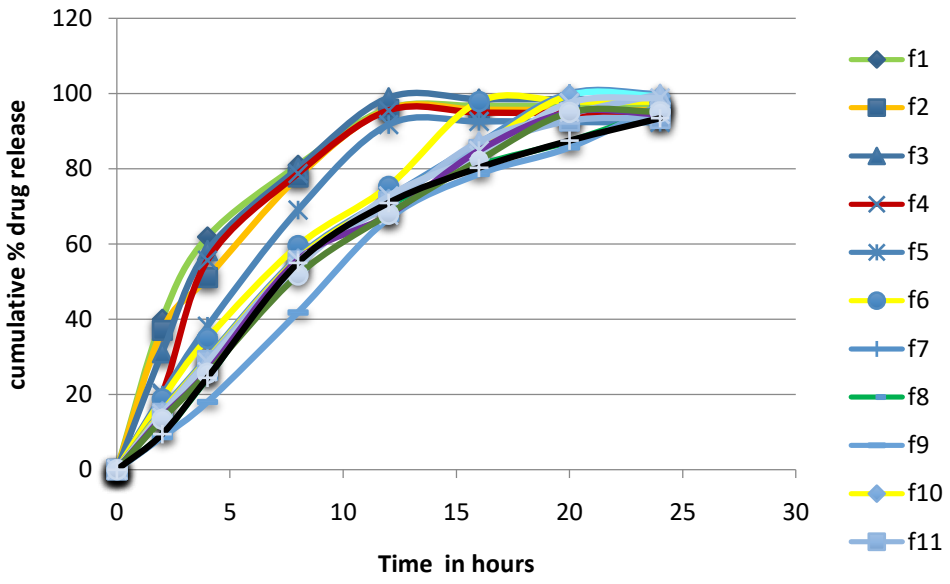

Figure 3.4: Comparative In-vitro Drug Release Profile of All Formulations

3.5. Drug Release Kinetics

The First Order model showed lower correlation for most batches compared to Zero Order and Higuchi models, except in F8 and F11, where R^2 values were 0.973 and 0.985, respectively.

Table 11: Kinetic modelling data for formulation F1-F15

Formulation codes	ZERO ORDER		HIGUCHI		FIRST ORDER		KORSMEYER		Drug release mechanism
	R^2	slope	R^2	Slope	R^2	slope	R^2	(n)	
F1	0.295	5.42	0.873	23.63	0.825	-0.061	0.911	0.455	fickian
F2	0.738	3.52	0.923	20.71	0.839	-0.062	0.928	0.407	fickian
F3	0.731	3.67	0.915	21.61	0.814	-0.087	0.890	0.453	fickian
F4	0.727	3.69	0.897	21.56	0.829	-0.06	0.829	0.577	Non fickian
F5	0.798	3.84	0.926	21.74	0.94	-0.053	0.919	0.638	Non fickian
F6	0.900	4.19	0.967	22.80	0.766	-0.081	0.972	0.688	Non fickian
F7	0.941	4.29	0.975	22.93	0.909	-0.129	0.983	0.762	Non fickian
F8	0.933	4.02	0.961	21.59	0.973	-0.056	0.953	0.819	Non fickian
F9	0.966	4.22	0.948	21.96	0.918	-0.056	0.983	1.000	Case II
F10	0.942	4.27	0.974	22.82	0.859	-0.098	0.982	0.771	Non fickian
F11	0.922	4.01	0.972	21.65	0.985	-0.053	0.974	0.758	Non fickian
F12	0.944	4.23	0.975	22.58	0.841	-0.091	0.982	0.782	Non fickian
F13	0.944	4.23	0.974	22.59	0.927	-0.079	0.983	0.781	Non fickian
F14	0.934	4.12	0.967	22.04	0.958	-0.058	0.976	0.802	Non fickian
F15	0.947	4.15	0.969	22.04	0.957	-0.059	0.983	0.817	Non fickian

Higuchi model showed the highest correlation for most formulations, indicating diffusion as the dominant mechanism. Korsmeyer-Peppas model revealed Fickian diffusion in F1–F3, non-Fickian transport in F4–F15 (excluding F9), and Case II transport in F9. Zero-order kinetics was observed in formulations F6 to F15, suggesting near-constant drug release. First-order kinetics was less significant overall but fitted well for F8 and F11.

The overall results suggest that sustained drug release from Tolterodine Tartrate matrix tablets was achieved through a combination of diffusion and erosion mechanisms, with polymer concentration playing a critical role in modulating the release profile.

CONCLUSION

The present study effectively formulated and evaluated sustained release matrix tablets of Tolterodine Tartrate to improve therapeutic management of overactive bladder. The use of both hydrophilic and hydrophobic polymers enabled controlled drug release, with all formulations meeting pharmacopeial standards for quality and performance. Among them, formulation F13 exhibited a consistent and extended-release profile, achieving nearly complete drug release over 24 hours and demonstrating superior performance compared to the marketed product. Drug release kinetics confirmed a diffusion-controlled mechanism, primarily following Higuchi and Zero-order models. These findings suggest that the optimised formulation has strong potential to educe dosing frequency, enhance patient adherence, and improve clinical outcomes in long-term OAB therapy.

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