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Evaluation Of Hydrophilic And Polyacrylate Polymer-Enhanced Controlled Release Milnacipran Tablets For Antidepressant Activity

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Abstract

Milnacipran is a serotonin-norepinephrine reuptake inhibitor (SNRI) primarily used in the treatment of major depressive disorder and fibromyalgia. The aim of this study was to formulate and evaluate controlled-release Milnacipran tablets using hydrophilic polymers (HPMC K4M, HPMC K100M) and polyacrylate polymers (Eudragit RS100, Eudragit RL100) to enhance antidepressant activity. A total of 15 formulations (F1-F15) were developed using a direct compression method. "The micromeritic properties of the formulation blends were assessed." The compressed tablets were evaluated for various parameters such as hardness, friability, weight uniformity, and drug content, all of which met the required standards. The study concluded that both Eudragit and HPMC polymers effectively controlled the release of Milnacipran, making the formulations suitable for once-daily administration, potentially improving patient compliance and therapeutic outcomes.

1.1. **Keywords:** Milnacipran, Controlled Release, Eudragit, Antidepressant Activity, In Vitro Dissolution.

I. INTRODUCTION

Background of the study

The evaluation of hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and polyacrylate polymers like Eudragit in the formulation of controlled-release Milnacipran tablets aims to enhance their efficacy for antidepressant activity. Milnacipran, a serotonin-norepinephrine reuptake inhibitor (SNRI), is commonly used for the treatment of depression, but its effectiveness can be hindered by fluctuating plasma levels due to conventional immediate-release formulations. Controlled-release tablets, therefore, offer the advantage of maintaining steady drug concentrations over extended periods, reducing dosing frequency and minimizing side effects.

Hydrophilic polymers like HPMC are widely used in controlled-release formulations due to their ability to form a gel matrix in the presence of water, allowing for the gradual release of the drug. In this study, HPMC is evaluated for its role in modulating the release rate of Milnacipran, ensuring a sustained release over time. On the other hand, Eudragit, a class of polyacrylate polymers, is known for its versatility in drug delivery systems, offering protection against gastrointestinal degradation and controlling the release mechanism. By combining HPMC and

Eudragit, the study aims to achieve an optimal balance between drug release rate, tablet stability, and bioavailability.

The primary focus of the research is to assess the pharmacokinetics and pharmacodynamics of the controlled-release Milnacipran tablets. The evaluation involves determining the in-vitro drug release profile, which simulates the dissolution of the tablet in the gastrointestinal tract. Additionally, the in-vivo antidepressant activity is tested in animal models to measure the efficacy of the controlled-release formulation compared to conventional tablets. Key parameters such as drug release rate, peak plasma concentration, and duration of action are analyzed to demonstrate the benefits of this advanced formulation.

Milnacipran

Milnacipran is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) that was first designed for and remains licensed for the treatment of depression. In 2009, the US FDA approved milnacipran for the treatment of fibromyalgia; however, other regulatory bodies, such as the EMA, have not granted approval for this indication, citing insufficient evidence of efficacy, inadequate demonstration of sustained effect, and additional concerns. Milnacipran exhibits a distinctive trait among SNRIs, as it induces a relatively balanced reuptake inhibition of both serotonin and noradrenaline, with a slight inclination towards noradrenaline reuptake inhibition. This is noteworthy considering the plausible assertion that noradrenaline significantly contributes to the attenuation of pain signals within the descending inhibitory pain pathways of the brain and spinal cord.

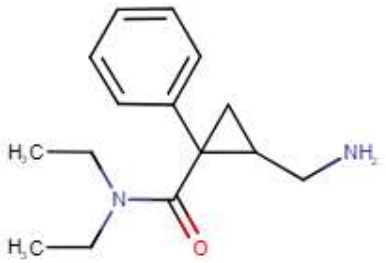

Figure 1: Structure of Milnacipran

Recent research indicates that the levorotatory enantiomer of milnacipran, levomilnacipran, may inhibit the activity of beta-site amyloid precursor protein cleaving enzyme-1 (BACE-1), which is investigationally linked to β-amyloid plaque formation, suggesting its potential as a treatment for Alzheimer's disease. Milnacipran is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) recommended for the treatment of fibromyalgia in individuals aged 18 and older. Milnacipran is indicated for the treatment of major depressive disorder (MDD) exclusively in adult patients aged 18 and older, owing to a heightened risk of suicidal ideation, thoughts, and behaviours in children, adolescents, and young adults prescribed antidepressants for MDD and other psychiatric conditions. Certain regional prescription information indicates that the medicine is intended just for the short-term symptomatic alleviation of Major Depressive Disorder (MDD). It is essential to acknowledge that the regulatory approval and/or indications for milnacipran may be inconsistent or significantly differ across various areas and countries.

Mechanism of action

Milnacipran's combined capacity to block the reuptake of serotonin (5HT) and norepinephrine (NE) enhances its efficacy in treating fibromyalgia and major depressive disorder (MDD).
It is well accepted that serotonin (5HT) and norepinephrine (NE) contribute to the control of endogenous analgesic

mechanisms via the descending inhibitory pain pathways in the brain and spinal cord. While the precise mechanism of action is not fully understood, certain studies suggest that diminished levels of 5HT may correlate with heightened pain sensitivity, a condition potentially ameliorated by milnacipran's ability to elevate 5HT levels through the inhibition of its reuptake via serotonin transporters at synaptic clefts. Moreover, it is widely accepted that norepinephrine released from descending pathways can alleviate pain sensations by exerting inhibitory effects on alpha-2A-adrenoceptors located on the central terminals of primary afferent nociceptors, through direct alpha-2-adrenergic action on pain-relay neurones, and via alpha-1-adrenoceptor-mediated activation of inhibitory interneurons. The alleviation of NE pain is thus augmented by milnacipran's capacity to increase NE levels by preventing its absorption via norepinephrine transporters at synaptic clefts. Simultaneously, milnacipran's ability to block the reuptake of both serotonin and norepinephrine enhances its efficacy in treating major depressive disorder. The monoamine hypothesis posits that reduced serotonin (5HT) levels are linked to anxiety, obsessions, and compulsions, while diminished norepinephrine (NE) levels lead to decreased alertness, energy, attention, and overall interest in life. Consequently, it is suggested that milnacipran, functioning as a serotonin and norepinephrine reuptake inhibitor, may alleviate symptoms of major depressive disorder (MDD) by enhancing the availability of both 5HT and NE through the inhibition of their reuptake.

II. REVIEW OF RELATED STUDIES

Khamkat, Piyali et al. (2023). To create and produce sustained-release tablet formulations of propranolol hydrochloride using various grades of HPMC and MCC, followed by in vitro assessments. The impact of different polymer grades on medication release from tablets and other attributes was examined and compared. Materials and Methods: Propranolol hydrochloride, microcrystalline cellulose (PH-101), microcrystalline cellulose (PH-102), HPMC (K15 M), HPMC (K100 M), HPMC (K4 M), HPC LF, isopropyl alcohol, povidone (K-30), and magnesium stearate were used in various formulations. "Tablets were prepared using direct compression, dry granulation, and wet granulation procedures." Results: Among several formulations, SR008 including HPMC K100M exhibited superior sustained release properties, with percentages of 69.1%, 76.6%, and 82.3% at 8, 10, and 12 hours, respectively, in comparison to other formulations, which had a moisture content of 71% and a hardness of 71N. The matrix embedding approach using HPMC K100M has effectively prolonged the release of propranolol hydrochloride. It is very effective for producing directly compressed sustained-release matrix tablets that meet required criteria and exhibit well-reproducible drug release characteristics. Unlike the typical formulation recommended three times daily, the developed formulations allow for a once-day dosage, resulting in decreased dosing frequency and daily medication dosage. It is determined that HPMC K100M, in acceptable quantities, is effective for manufacturing sustained-release tablets that demonstrate diffusion-controlled Higuchi kinetics for propranolol hydrochloride.

Kaur, Navdeep and Kumar, Mohit. (2022). This work included the preparation of once-daily sustained-release bilayered matrix tablets of valsartan, using various viscosity grades of HPMC (K4M, K15M, and K100M) by direct compression, followed by evaluation of physicochemical characteristics and in vitro drug release tests. All physical characteristics of bilayered matrix tablets containing valsartan (F1 to F6) were within acceptable limits, and all matrix formulations facilitated drug release over 24 hours in a regulated way without compromising their physical integrity in the dissolving media. "The findings from in vitro drug release tests, when analysed using dissolution kinetics, indicated that valsartan release from all formulations (F1 to F6) adhered to first-order kinetics via a Fickian diffusion mechanism." Among all formulations, F2 (HPMC K4M), F4 (HPMC K15M), and F6 (HPMC K100M) are superior as they achieved sustained release of valsartan for 24 hours, with $f2$ values over 50, suggesting that their drug release profiles closely resemble the theoretical release profile. The stability experiments indicated that valsartan bilayered matrix formulations remained stable throughout the storage duration. FTIR and DSC analyses unequivocally demonstrated the absence of drug-polymer interaction.

Siraj et al. (2021). The controlled release matrix tablets of Itopride hydrochloride (ITP) were created using the direct compression method. The influence of several polymers (HPM, EC, Kollidon ® SR), concentrations (20-40%), and viscosity grades (HPMC-4000 cps, HPMC-100000 cps, EC-10 cps, and Kollidon SR) on drug release was assessed using distinct polymers. Twelve pill formulations were developed, each carrying a uniform dosage of ITP (150 mg). The dissolution studies of controlled-release matrix formulations were performed in an acidic

buffer at pH 1.2 and a phosphate buffer at pH 6.8. The kinetics of drug release were studied using the first-order, zero-order, Higuchi, Korsmeyer-Peppas, and Weibull models, utilising DD Solver, an add-in for MS Excel. The formulations ECF7, ECF8, and ECF9, including EC at concentrations between 20% and 40%, proficiently controlled the release rate of the medication over a period of 12 hours. The drug release from tablet formulations K4F3, K100F5, and ECF8 demonstrated zero-order kinetics, with regression values between 0.966 to 0.999. The tablet formulations K4F2, KK4F3, K4F4, ECF7, KSRF10, KSRF11, and KSRF12 demonstrated non-Fickian diffusion as its release mechanism. The release mechanism of formulations K4F1, K100F5, K100F6, ECF8, and ECF9 was determined to be a super case-II transport mechanism. HPMC and ethylcellulose (EC-10cps) at concentrations of 20-30% were identified as very effective polymers for modulating the release of itopride HCl.

Wadher, Kamlesh, et al. (2021). This work aimed to create oral controlled-release metoclopramide hydrochloride matrix tablets using Eudragit RSPO and natural gums such as guar copal as rate-controlling polymers, and to assess drug release characteristics according to several kinetic models. The sustained-release matrix tablets of Metoclopramide HCl were formulated using the wet granulation method. All tablets were assessed for their physical properties both pre-compression and post-compression. FTIR and DSC analyses demonstrated the absence of chemical interactions between the medication and polymers. The use of synthetic Eudragit RSPO and gum copal did not effectively prolong medication release beyond 10 hours. The amalgamation of both polymers was seen to delay medication release for 12 hours. All batches exhibited a Mixed Matrix and Peppas model as the optimal fit for release kinetics, indicating that drug release from the formulated tablets is maintained by swelling, followed by drug diffusion and gradual polymer degradation. A similarity test was conducted between the marketed and optimised formulations, revealing an equal release profile.

Krosuri, Pavankumar et al. (2021). Minocycline HCl, an antiulcer agent, has little systemic absorption and is swiftly excreted from the organism. These attributes make it an appropriate choice for a medication delivery system capable of floating in the stomach and facilitating prolonged release. The objective of formulating the minocycline floating tablets was to improve the drug's bioavailability and prolong its retention in the stomach. The floating tablets were formulated using HPMC K15M, Ethyl Cellulose, and Eudragit E100 as the polymers. The utilised excipients are lauric acid, sodium bicarbonate, magnesium stearate, talc, and microcrystalline cellulose (MCC). The tablets were produced with the wet granulation method. The manufactured tablets were subjected to quality control assessments, which included weight variation, hardness, friability, swelling index, floating lag time, and total floating duration. The drug release of the tablets was evaluated in 0.1N HCl using an in vitro approach. The drug release from the improved formulation F9, as assessed by curve fitting analysis, demonstrated a robust adherence to zero-order kinetics. This indicates that the drug's release is independent of its concentration. The 'n' value in the Korsmeyer-Peppas model exceeded 0.5, indicating a non-Fickian diffusion process.

Mounika, Dhulipalla, et al. (2020). The objective of the current study was to develop sustained-release tablets of Venlafaxine HCl (VHL) through direct compression utilising the natural polymer xanthan gum and semi-synthetic polymers, including hydroxypropyl methylcellulose (HPMC) K4M, HPMC K15M, HPMC K100M, and Carbopol, either individually or in combination. The medication and all excipients were assessed for compatibility and flow characteristics. The formulated tablets were assessed for dimensions, weight fluctuation, friability, drug content, and in vitro drug release analysis. The FTIR analysis of the drug in conjunction with the excipients indicated the absence of any interaction between the drug and the excipients. The pre-compression analysis of the powder mix demonstrated favourable flow characteristics. All the tablets exhibited size and hardness within the specified limits. The friability and weight variation tests were deemed good. The drug content ranged from 94.24% to 101.02%, and all formulations exhibited prolonged drug release. A formulation with equal quantities of carbopol and xanthan gum demonstrated a 90.02% drug release after 12 hours. The aforementioned findings indicate that VHL tablets formulated with carbopol and xanthan gum by direct compression exhibit prolonged drug release, potentially beneficial for the treatment of depressive disorders.

Tiwari, Rajesh. (2016). The objective of the research was to manufacture gastro-retentive floating tablets of

venlafaxine HCl, an antidepressant, aimed at enhancing stomach residence duration and hence extending drug release in the current investigation. The tablets were created using direct compression utilising several polymers, including HPMC K4M, Carbopol 940, and sodium bicarbonate as a gas-generating agent. The formulated tablets were assessed for several criteria, including hardness, friability, weight uniformity, in vitro buoyancy, and in vitro dissolution. The FTIR analysis indicated an absence of interaction between the medication and the excipients. The tablets exhibited a weight variation of 0.17mg±0.15mg to 0.62mg±0.36mg, hardness ranging from 4.2kg/cm²±0.34kg/cm² to 5.2kg/cm²±0.63kg/cm², a percentage friability of less than one, and a thickness between 3mm±0.27mm and 4.6mm±0.025mm. Venlafaxine HCl released 92.25±2.9% to 93.35±2.1% of the drug by the conclusion of the 10th hour in the in vitro release study. Formulation F9 was chosen as the optimised formula due to its superior performance in the in vitro buoyancy assay, excellent floating integrity, prolonged drug release, and its adherence to zero-order release kinetics, shown by a r^2 value of 0.94.

III. MATERIAL AND METHOD

Materials used:

Milnacipran Hydrochloride was procured from Torrent Pharmaceutical limited, Ahmedabad, Gujarat, India.

Polymers:

- Eudragit RL100 and Eudragit RS100: Procured from Yarrow Chem. Products, Mumbai (India).
- HPMC K4M and HPMC K100M: Procured from Yarrow Chem. Products, Mumbai (India).

Excipients:

- Lactose Monohydrate: Procured from Finer Chemicals Ltd., Mumbai (India).
- Talc: Purchased from Loba Chemie Pvt. Ltd., Mumbai (India).
- Magnesium Stearate: Purchased from Moly Chem, Mumbai (India).

Methods:

Formulation of Sustained Release Milnacipran Tablets:

Preparation of Tablets: Different tablet batches (F1-F15) were prepared using the direct compression method. The active ingredient (Milnacipran) was blended with hydrophilic polymers (HPMC K4M, HPMC K100M) and polyacrylate polymers (Eudragit RL100, Eudragit RS100) in varying ratios to achieve controlled release formulations.

Table 1: Formulation of different batches of tablets

Batch No.	Milnacipran (mg)	Eudragit RS100 (mg)	Eudragit RL100 (mg)	HPMC K4M (mg)	HPMC K100M (mg)	Lactose Monohydrate (mg)	Talc (mg)	Magnesium Stearate (mg)	Total Tablet Weight (mg)
F1	100	30	-	-	-	240	5	5	380

F2	100	40	-	-	-	230	5	5	380
F3	100	50	-	-	-	220	5	5	380
F4	100	60	-	-	-	210	5	5	380
F5	100	-	30	-	-	240	5	5	380
F6	100	-	40	-	-	230	5	5	380
F7	100	-	50	-	-	220	5	5	380
F8	100	-	60	-	-	210	5	5	380
F9	100	-	-	30	-	240	5	5	380
F10	100	-	-	40	-	230	5	5	380
F11	100	-	-	50	-	220	5	5	380
F12	100	-	-	60	-	210	5	5	380
F13	100	-	-	-	30	240	5	5	380
F14	100	-	-	-	40	230	5	5	380
F15	100	-	-	-	50	220	5	5	380

The required quantities of Milnacipran, polymers, lactose monohydrate, talc, and magnesium stearate were weighed and mixed uniformly. This blend was directly compressed into tablets using a rotary tablet press machine with suitable punches.

Micromeritic Properties of Formulation Blends:

The prepared powder blends for all batches (F1–F15) were evaluated for micromeritic properties:

Angle of Repose: Measured to determine the flow properties of the powder blend using a fixed funnel method.

Bulk Density: Determined by pouring a known weight of the powder blend into a graduated cylinder and measuring the volume.

Tapped Density: The cylinder containing the sample was tapped until a constant volume was achieved. Tapped density was calculated as the ratio of the weight of the sample to the final tapped volume.

Compressibility Index (Carr's Index): This was determined using the bulk density and tapped density with the following equation:

$$\boldsymbol{Carr's Index}\ (\%) = \frac{\boldsymbol{Tapped\ Density - Bulk\ Density}}{\boldsymbol{Tapped\ density}} \times \mathbf{100}$$

Hausner's Ratio: Calculated as the ratio of tapped density to bulk density to evaluate powder flow properties:

$$\boldsymbol{Hausner's\ Ratio} = \frac{\boldsymbol{Tapped\ Density}}{\boldsymbol{Bulk\ Density}}$$

Evaluation of Compressed Tablets:

After the tablets were compressed, they were evaluated for various physical properties, including:

- Thickness: Measured using a digital vernier caliper to ensure uniformity across batches.
- Hardness: Measured using a hardness tester to assess the mechanical strength of the tablets.
- Friability: Tablets were subjected to a friability test using a friabilator to determine their resistance to abrasion. A sample of pre-weighed tablets was rotated in the friabilator for a set number of revolutions, and the weight loss was calculated as a percentage.
- Weight Variation: 20 tablets from each batch were weighed individually, and the average weight was calculated. The weight variation was compared against the prescribed limits.
- Drug Content Uniformity: The content of Milnacipran in the tablets was evaluated. Tablets were crushed, dissolved in a suitable solvent, and the drug content was determined spectrophotometrically at a specific wavelength to ensure uniform distribution of the active ingredient.

In Vitro Dissolution Studies:

- Dissolution Testing: The in vitro drug release of the tablets was performed using a USP Dissolution Apparatus II (paddle method). The dissolution medium was phosphate buffer (pH 6.8) maintained at 37°C ± 0.5°C.
    - ❖ Tablets were placed in the dissolution apparatus, and samples were withdrawn at predetermined time intervals.
    - ❖ The collected samples were filtered and analyzed using UV spectrophotometry to determine the amount of Milnacipran released at each time point.
- Drug Release Kinetics: The dissolution data were fitted into various mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas to study the release kinetics and mechanism of drug release.

Stability Studies:

- The formulated tablets were subjected to accelerated stability testing under conditions of 40°C ± 2°C and 75% RH ± 5% for a period of three months.
- Tablets were analyzed at regular intervals for physical changes, drug content, and dissolution profile.

IV. EXPERIMENTAL RESULTS

In this section, the experimental results for the development and evaluation of controlled-release Milnacipran tablets using hydrophilic polymers such as HPMC and polyacrylate polymers like Eudragit are presented.

Table 1: Evaluation results of Micromeritic properties of formulation blends

Batch No.	Angle of Repose (°)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio
F1	30.2	0.42	0.48	12.50	1.14
F2	28.5	0.45	0.52	13.46	1.16
F3	31.0	0.40	0.46	13.04	1.15
F4	29.8	0.43	0.49	12.24	1.14
F5	30.5	0.44	0.50	12.00	1.13
F6	32.1	0.41	0.48	14.58	1.17
F7	29.0	0.43	0.50	14.00	1.16
F8	31.3	0.40	0.46	13.04	1.15
F9	28.7	0.42	0.48	12.50	1.14
F10	30.8	0.45	0.51	11.76	1.13
F11	29.5	0.44	0.50	12.00	1.13
F12	32.2	0.41	0.48	14.58	1.17
F13	30.0	0.42	0.48	12.50	1.14
F14	29.2	0.43	0.49	12.24	1.14
F15	31.6	0.40	0.46	13.04	1.15

1.1. he evaluation of the micromeritic properties of the formulation blends in Table 2 reveals important characteristics such as the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio, which collectively provide insights into the flowability, compressibility, and packing behavior of the formulation powders.

1.1. Angle of Repose:

1.1. The angle of repose, which indicates the flowability of the powder, varies across the batches. Most formulations exhibit an angle between 28.5° and 32.2°, suggesting acceptable flow properties. The lower values, such as 28.5° (F2) and 28.7° (F9), indicate better flowability, while higher values like 32.2° (F12) may suggest slightly poorer flow behavior.

1.1. Bulk and Tapped Density:

1.1. The bulk density values range from 0.40 to 0.45 g/cm³, and the tapped density values range from 0.46 to 0.52 g/cm³. These values reflect the powder's ability to pack under gravitational force. Batches such as F2 and F10, which have the highest bulk and tapped densities (0.45 g/cm³ and 0.52 g/cm³, respectively), may have more tightly packed particles, while batches with lower densities (e.g., F3, F8) demonstrate looser packing.

1.1. Carr's Index:

1.1. Carr's index, a measure of compressibility, ranges between 11.76% and 14.58% across the batches, indicating good to fair flowability. Lower values, such as 11.76% (F10), reflect better compressibility and packing efficiency, while higher values, such as 14.58% (F6, F12), suggest slightly less favorable compressibility.

1.1. Hausner's Ratio:

1.1. The Hausner's ratio, which further assesses flowability based on the ratio of tapped to bulk density, is consistently between 1.13 and 1.17 for all batches. Values close to 1.13, such as in F5, F10, and F11, indicate good flow properties, while values approaching 1.17, such as in F6 and F12, suggest poorer flow characteristics. Overall, the micromeritic evaluation demonstrates that most formulation blends possess acceptable flow and compressibility characteristics suitable for further processing, with slight variations in packing efficiency and flowability across the batches.

1.1. Table 2: Evaluation of Compressed Milnacipran Tablets (F1-F15)

Batch No.	Weight Variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	100 ± 1.2	4.8	4.5	0.72	98.4
F2	100 ± 1.0	5.0	4.6	0.68	99.1
F3	100 ± 1.1	5.3	4.7	0.65	98.9
F4	100 ± 1.2	5.5	4.8	0.70	98.5
F5	100 ± 1.3	5.1	4.6	0.74	99.3
F6	100 ± 1.4	5.2	4.7	0.69	98.8
F7	100 ± 1.2	5.0	4.6	0.75	99.0

F8	100 ± 1.3	4.9	4.6	0.73	98.7
F9	100 ± 1.1	5.2	4.7	0.65	99.2
F10	100 ± 1.2	5.3	4.8	0.70	98.6
F11	100 ± 1.1	5.5	4.9	0.68	98.5
F12	100 ± 1.3	5.4	4.7	0.72	98.9
F13	100 ± 1.0	5.6	4.8	0.66	99.0
F14	100 ± 1.1	5.7	4.9	0.65	98.7
F15	100 ± 1.0	5.9	5.0	0.70	99.1

1.1. The evaluation of compressed Milnacipran tablets (F1-F15) in Table 2 provides crucial data on various parameters, including weight variation, hardness, thickness, friability, and drug content, which together assess the quality and consistency of the tablet formulations. All batches maintain a consistent weight of 100 mg with minimal variation, ranging from ±1.0 to ±1.4 mg. This reflects good manufacturing precision, ensuring that each tablet contains a uniform amount of the active ingredient. The hardness of the tablets, which is a measure of their mechanical strength, ranges from 4.8 to 5.9 kg/cm². Batches such as F15 (5.9 kg/cm²) and F14 (5.7 kg/cm²) exhibit the highest hardness, indicating strong tablet integrity, while F1 (4.8 kg/cm²) has the lowest hardness, which may suggest slightly softer tablets.

1.1. The thickness of the tablets across the batches varies slightly from 4.5 mm to 5.0 mm. F1 has the thinnest tablets (4.5 mm), while F15 is the thickest (5.0 mm), which corresponds with the variations in tablet hardness and compression force applied during manufacturing. Friability, which measures the tablet's ability to resist breaking or crumbling, remains well below the acceptable limit of 1% for all batches, with values ranging from 0.65% to 0.75%. This indicates that the tablets exhibit excellent resistance to abrasion, with F9, F3, and F14 showing the lowest friability (0.65%), while F7 has the highest (0.75%). The drug content across all batches is consistent, ranging between 98.4% and 99.3%, ensuring that each tablet delivers the correct dosage of Milnacipran. F5 (99.3%) and F9 (99.2%) have the highest drug content, while F1 (98.4%) and F11 (98.5%) are slightly lower but still within the acceptable range.

1.1. Result of In-Vitro Dissolution Study

1.1. Table 3: In Vitro Dissolution Profile of Controlled Release Milnacipran Tablets with Various Concentrations of Eudragit Polymer (F1 to F8)

Time (hours)	F1 (% drug release)	F2 (% drug release)	F3 (% drug release)	F4 (% drug release)	F5 (% drug release)	F6 (% drug release)	F7 (% drug release)	F8 (% drug release)
1	18.5	16.3	15.2	14.1	19.3	17.6	16.4	15.1
2	29.7	27.4	25.6	23.9	30.4	28.1	26.3	24.7
4	45.2	42.9	40.8	38.7	47.3	44.5	42.2	40.1
6	58.6	55.7	52.8	50.0	60.7	57.8	55.1	52.4

8	71.3	68.2	65.0	61.9	73.5	70.1	66.7	63.4
10	82.4	78.7	74.6	70.8	83.7	80.0	76.3	72.5
12	91.0	87.2	82.6	78.0	92.3	88.9	84.5	80.2
16	99.8	96.4	91.9	87.6	100.0	97.5	92.8	88.7

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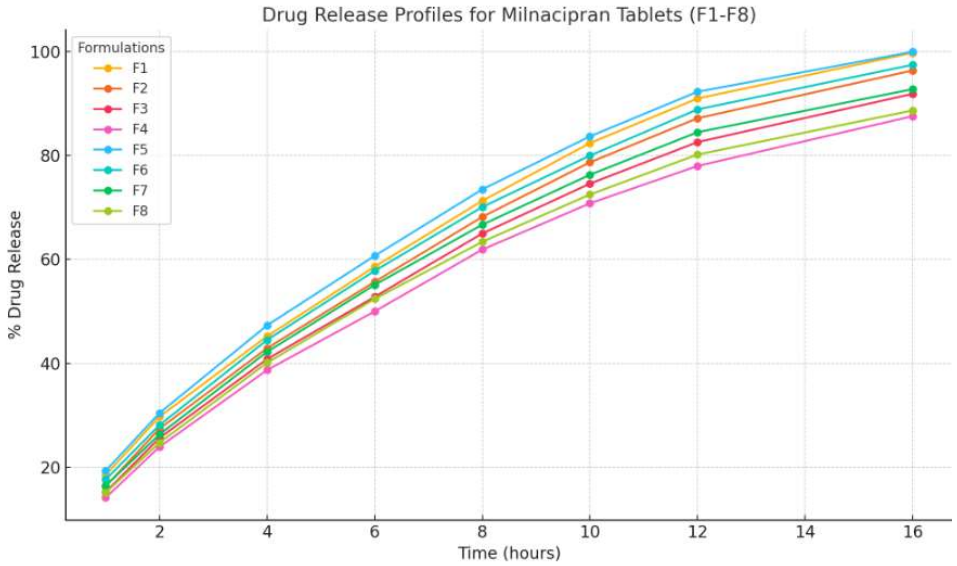

Figure 2: Graph showing In-Vitro Dissolution Profile of Controlled Release Milnacipran Tablets with Various Concentrations of HPMC Polymer (F9 to F15)

The in vitro dissolution profile of controlled release Milnacipran tablets with varying concentrations of Eudragit polymer (F1 to F8) demonstrates a gradual release of the drug over a period of 16 hours. At the 1-hour mark, the percentage of drug release ranged from 14.1% (F4) to 19.3% (F5). Formulation F5 exhibited the highest initial release, while F4 showed the slowest release at this early stage. By the 2-hour point, drug release increased across all formulations, ranging from 23.9% (F4) to 30.4% (F5). F5 consistently displayed the highest release rate, while F4 continued to exhibit the slowest release. This pattern persisted throughout the 4-hour period, with F5 showing a release of 47.3%, while F4 reached 38.7%.

At the 6-hour mark, drug release continued to rise, with formulations ranging from 50.0% (F4) to 60.7% (F5). As time progressed to 8 hours, F5 maintained the highest release percentage at 73.5%, while F4 trailed at 61.9%. By the 10-hour time point, the formulations demonstrated further release, with percentages ranging from 70.8% (F4) to 83.7% (F5). At 12 hours, F5 reached 92.3%, showing near-complete drug release, while F4 had released 78.0%. Finally, by the 16-hour mark, F5 exhibited 100% drug release, while F4 reached 87.6%.

Overall, formulation F5 consistently showed the highest percentage of drug release across all time intervals, while F4 demonstrated the slowest release. The other formulations (F1, F2, F3, F6, F7, F8) exhibited intermediate release profiles, with gradual increases in drug release over time. "This data suggests that the concentration of Eudragit polymer in the formulations plays a significant role in controlling the release rate of Milnacipran over an extended period."

Table 4: In Vitro Dissolution Profile of Controlled Release Milnacipran Tablets with Various Concentrations of HPMC Polymer (F9 to F15)

Time (hours)	F9 (% drug release)	F10 (% drug release)	F11 (% drug release)	F12 (% drug release)	F13 (% drug release)	F14 (% drug release)	F15 (% drug release)
1	14.7	13.5	12.9	12.1	11.2	10.7	10.1
2	26.8	24.3	22.9	21.5	19.7	18.5	17.3
4	40.6	38.2	35.7	33.9	31.0	29.6	28.2
6	55.2	52.4	49.6	46.8	42.7	40.2	38.0
8	68.7	65.0	61.5	58.0	53.7	50.3	47.0
10	80.6	76.8	73.1	69.5	64.0	60.4	57.0
12	90.1	85.9	81.7	77.8	72.5	68.3	64.0
16	99.5	95.3	91.2	87.4	81.5	77.0	72.7

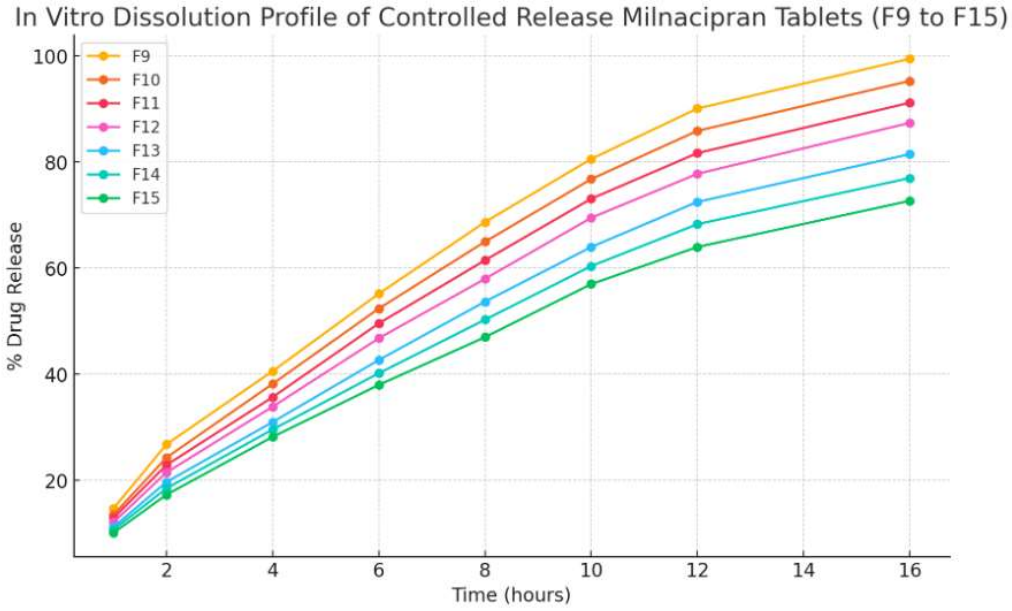

Figure 3: Graph showing In-Vitro Dissolution Profile of Controlled Release Milnacipran Tablets with Various Concentrations of HPMC Polymer (F9 to F15)

The in vitro dissolution profile of controlled-release Milnacipran tablets formulated with various concentrations of HPMC polymer (F9 to F15) reveals a controlled and gradual drug release over a 16-hour period. At the 1-hour mark, the percentage of drug release ranged from 10.1% (F15) to 14.7% (F9). Formulation F9 exhibited the fastest initial release, while F15 showed the slowest. As the release progressed to 2 hours, F9 continued to release the highest percentage (26.8%), whereas F15 remained the slowest (17.3%). This trend remained consistent over the 4-hour period, with F9 releasing 40.6%, and F15 releasing 28.2%.

At the 6-hour point, F9 showed a release of 55.2%, and F15 released 38.0%. This pattern of F9 having the highest release rate and F15 the lowest continued across all time intervals, highlighting the strong control over release exerted by the HPMC polymer concentration. By 8 hours, F9 released 68.7% of the drug, while F15 released 47.0%. As time progressed to 10 hours, the formulations exhibited further release, ranging from 57.0% (F15) to 80.6% (F9). At the 12-hour mark, F9 approached near-complete drug release at 90.1%, while F15 had released 64.0%.

Finally, by 16 hours, formulation F9 reached a maximum release of 99.5%, indicating almost complete dissolution, while F15 showed 72.7% release. Other formulations (F10 to F14) displayed intermediate release profiles, with percentages increasing as time progressed. The data suggests that higher concentrations of HPMC in the formulations (such as in F15) result in a slower drug release, providing more sustained control, while lower concentrations (such as in F9) lead to a faster release rate. "This highlights the role of HPMC polymer concentration in modulating the dissolution rate of Milnacipran tablets."

V. CONCLUSION

The present study aimed to develop and evaluate controlled-release Milnacipran tablets using hydrophilic (HPMC K4M, HPMC K100M) and polyacrylate (Eudragit RS100, Eudragit RL100) polymers for enhanced antidepressant activity. The formulations were designed to provide a sustained release of Milnacipran over a prolonged period, which would improve patient compliance by reducing dosing frequency and maintaining stable drug levels.

Polyacrylate-based formulations (F1-F8) containing Eudragit RS100 and RL100 demonstrated an extended drug release up to 16 hours. Eudragit RL100-based formulations exhibited a slightly faster release profile due to its higher permeability, whereas Eudragit RS100-based formulations showed more controlled release. HPMC-based formulations (F9-F15) using HPMC K4M and HPMC K100M showed a more gradual and consistent drug release, with HPMC K100M formulations providing the slowest and most prolonged release, extending up to 16 hours. All formulations met the necessary pharmaceutical parameters for controlled-release tablets, including acceptable hardness, friability, thickness, and uniformity in drug content. Additionally, micromeritic properties of the formulation blends were within acceptable ranges, ensuring good compressibility and flow characteristics.

In vitro dissolution studies confirmed that the selected polymers effectively modulated the release rate of Milnacipran, making the formulations suitable for once-daily administration. The use of HPMC K100M is particularly recommended for achieving the most extended release, while Eudragit RL100 may be preferred where a faster initial release is desired.

In conclusion, both Eudragit and HPMC polymers can be successfully used to formulate controlled-release Milnacipran tablets, offering potential for improved therapeutic outcomes in treating depression. Further in vivo studies are recommended to confirm the antidepressant efficacy and pharmacokinetic performance of the optimized formulations.

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