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RESEARCH ARTICLE

Innovative Approaches in Mirtazapine Delivery: Pharmacokinetic Simulations, Immediate Release to Controlled-Release Tablets, Formulation Optimization via D-optimal Mixture Design

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SUMMARY

This research study describes the formulation and evaluation of Mirtazapine Controlled-Release (CR) Tablets, intended to improve therapeutic efficacy and patient compliance. Utilizing pharmacokinetic data from the USFDA-approved Remeron Immediate-Release (IR) Tablets, we constructed a plasma profile curve and calculated the following pharmacokinetic parameters Cmax, T max, AUC, Vd, and Ke. The principle of superposition method was employed to simulate steady-state plasma concentrations (Css), establishing target Css max and Css min values. These targets guided the development of our controlled-release formulation, which was designed to achieve a zero-order release mechanism. The dose and release rate of the proposed controlled-release tablets were precisely adjusted to meet the targeted Css max and Css min concentrations. Our formulation strategy utilized different hydrophilic polymers such as HPMC, Carbopol, and Polyethylene oxide to create a robust ER matrix, we employed D Optimal Mixture Design to optimize the concentration of these three critical formulation variables. Dissolution studies were conducted in different media such as 0.01 N HCl, pH 4.5 Acetate buffer, and pH 6.8 Phosphate buffer for 14 hours to evaluate the rate, extent, and drug release kinetics. The successful simulation of plasma concentrations, followed by adjustments of dose, release rate, and subsequent optimization of formulation variables using the Design of experiments yielded a CR tablet that meets the pharmacokinetic endpoints set by the IR reference. This innovative approach to Mirtazapine CR tablet formulation could significantly enhance patient compliance by providing a more consistent and controlled drug delivery system.

Key Words: *Pharmacokinetic Simulations, Principle of superposition, Zero-Order release and absorption model. IR to CR conversions, Fluctuation index, Steady-state plasma concentration prediction.*

Mirtazapin Dağıtımında Yenilikçi Yaklaşımlar: Farmakokinetik Simülasyonlar, Hızlı Salımdan Kontrollü Salım Tabletlerine, D-Optimal Karışım Tasarımı Yoluyla Formülasyon Optimizasyonu

ÖZ

Bu çalışma, terapötik etkinliği ve hasta uyumunu iyileştirmeyi amaçlayan Mirtazapin Kontrollü Salım (CR) Tabletlerinin formülasyonunu ve değerlendirilmesini açıklamaktadır. USFDA onaylı Remeron Hızlı Salımlı (IR) Tabletlerden elde edilen farmakokinetik verileri kullanarak bir plazma profil eğrisi oluşturduk ve farmakokinetik parametreleri Cmax, Tmax, AUC, Vd ve Ke olarak hesapladık. Kararlı durum plazma konsantrasyonlarını (Css) simüle etmek için süperpozisyon yöntemi prensibi kullanıldı ve hedef Cssmax ve Cssmin değerleri belirlendi. Bu hedefler, sıfır-dereceli bir salım mekanizması elde etmek üzere tasarlanan kontrollü salım formülasyonunun geliştirilmesine rehberlik etmiştir. Önerilen kontrollü salım sağlayan tabletlerin dozu ve salım hızı, hedeflenen Css max ve Css min konsantrasyonlarını karşılayacak şekilde hassas bir şekilde ayarlanmıştır. Formülasyon stratejimiz doğrultusunda, sağlam bir ER matrisi oluşturmak için HPMC, Karbopol ve Polietilen oksit gibi farklı hidrofilik polimerleri kullandık; bu üç kritik formülasyon değişkeninin konsantrasyonunu optimize etmek için D Optimal Karışım Tasarımını kullandık. İlaç salım hızını, miktarını ve ilaç salım kinetiğini değerlendirmek amacıyla 0.01 N HCl, pH 4.5 Asetat tamponu ve pH 6.8 Fosfat tamponu gibi farklı ortamlarda 14 saat süreyle çözünme hızı çalışmaları yapıldı. Plazma konsantrasyonlarının başarılı bir şekilde simülasyonu, ardından doz ve salım hızının ayarlanması ve ardından deney tasarımı kullanılarak formülasyon değişkenlerinin optimizasyonu sonucunda IR referansı tarafından belirlenen farmakokinetik uç noktaları karşılayan bir CR tableti elde edilmiştir. Mirtazapin CR tablet formülasyonuna yönelik bu yenilikçi yaklaşım, daha tutarlı ve kontrollü bir ilaç iletim sistemi sağlayarak, hasta uyumunu önemli ölçüde artırabilir.

Anahtar Kelimeler: *Farmakokinetik Simülasyonlar, Süperpozisyon prensibi, Sıfır-dereceli salım ve absorpsiyon modeli, IR-CR dönüşümleri, Dalgalanma indeksi, Kararlı durum plazma konsantrasyonu tahmini.*

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INTRODUCTION

Mirtazapine (Jilani et al., 2023) is an atypical antidepressant, indicated for the treatment of a major depressive disorder. Mirtazapine belongs to the group of tetracyclic antidepressants. Mirtazapine exhibits an absolute bioavailability of approximately 50% due to extensive first-pass metabolism in the gut wall. It demonstrates linear pharmacokinetics within the 15-45 mg dose range. The time to reach maximum plasma concentration (T_{max}) is around 2 hours, and its plasma protein binding is approximately 85% (Timmer et al., 2000). The conventional immediate-release (IR) formulations of Mirtazapine, showed a wider fluctuation index (FI) due to a sharp rise and drop in plasma concentrations, to address these challenges, the development of a controlled-release (CR) formulation is a logical progression in the evolution of Mirtazapine's clinical application.

The objective of this study was to formulate Mirtazapine CR tablets that could maintain steady-state plasma concentrations within therapeutic windows over a prolonged period, and potentially enhance patient compliance. This was achieved by referencing pharmacokinetic (PK) data of the IR formulation from the US FDA's chemistry and pharmacokinetic review sections (U.S. Food and Drug Administration. Drugs@ FDA: FDA-Approved Drugs).

A plasma concentration profile curve was precisely plotted from the data of Remeron IR Tablets, and PK parameters were calculated to simulate the steady-state plasma concentrations. In this study, Microsoft Excel (Microsoft Corporation) was utilized to calculate the PK parameters, including steady-state plasma concentrations, as well as to analyze the zero-order release kinetics of the drug. The software's built-in functions and data analysis tools enabled precise and efficient data processing. The principle of superposition (Ritschel et al., 1989) served as an important step in this process, enabling the determination of target C_{ss}^{max} *and* C_{ss}^{min} values that would guide the formulation of the CR tablets (Geraili et al., 2021).

A zero-order absorption model (Shargel L. et al., 2012) was used to simulate the plasma concentrations of the CR tablets for both the single and multiple doses to meet the targeted C_{ss}^{max}, and C_{ss}^{min} concentrations set by the IR tablets of 15 and 45 mg. The dose and zero-order release rate of the proposed CR tablets were determined and adjusted further to meet the established C_{ss}^{max}, and C_{ss}^{min} concentrations, ensuring that the final formulation would meet the desired pharmacokinetic targets.

The formulation strategy was centered around the use of HPMC, Carbopol, and Polyethylene oxide polymers (Draganoiu et al., 2005, Ganesh et al., 2008, Sunil et al., 2008) to prepare a matrix-type controlled-release system. These polymers were chosen for their proven ability to control drug release rate and maintain tablet matrix for a prolonged period. D Optimal Mixture Design (Anderson et al., 2023, Sagiraju et al., 2024) was employed to optimize the concentration of these three formulation variables to get the desired drug release. Dissolution studies were performed to determine the rate, extent, and release kinetics of the proposed CR formulation. D-Optimal Mixture Design is a statistical approach used to optimize the formulation of mixtures; this design is particularly useful for determining the ideal proportions of different components to achieve a desired outcome. In the current research study, D-Optimal Mixture Design was applied to optimize the composition of three polymers HPMC, Carbopol, and Polyethylene Oxide in the formulation of Mirtazapine-CR tablets. This design helps in efficiently exploring the combination of these components to achieve a tablet with the desired release profile, ensuring the drug is released at a controlled and sustained rate.

MATERIALS AND METHODS

1. Pharmacokinetic data collection: PK data from Remeron® 15 and 45 mg IR Tablets available on the US FDA website has been collected and used as the starting point for this study.

2. Plotting plasma concentration curve of IR tablets: Application of PK parameters to plot plasma

concentration-time curves of IR tablets of 15 and 45 mg doses.

3. Simulation of steady-state plasma concentrations: Employing the principle of superposition method to simulate the multiple dose plasma profile and determining the steady-state plasma concentrations C_{ss}^{max}, and C_{ss}^{min} for IR tablets 15, and 45 mg.

4. Simulation of Zero-Order *in vivo* absorption model: Simulation of zero-order absorption model for single dose and multiple doses. Adjusting the dose size and zero-order release rate of the proposed CR formulation to meet the desired steady-state concentrations which are finalized from the IR 15 mg and 45 mg tablets simulated profiles.

5. *In vitro* Zero-Order release rate calculation: Calculation of zero-order *in vitro* release rate as a target dissolution profile for the proposed CR formulation to meet the desired *in vivo* absorption of single dose and subsequent multiple doses for attaining the steady-state plasma concentrations.

6. Formulation optimization: The concentration of critical formulation variables a) HPMC K100 MCR, b) Carbopol 974P, and c) Polyethylene oxide WSR 303, have been optimized using D Optimal Mixture Design.

Mirtazapine (API) is supplied by Zhiyu Biotechnology, Avicel is supplied by Dow Chemicals, Polyethylene oxide WSR 303 is supplied by Dow Chemicals, Methocel K100 MCR, is supplied by Colorcon, and Carbopol 974P, is supplied by Lubrizol.

7. Dissolution testing: Conducting dissolution profile of the Mirtazapine CR tablets in 900 mL of multimedia, (0.01 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) using USP II (paddle) apparatus at a rotation speed of 50 rpm.

Research Methodology

The research methodology involves a step-by-step approach such as simulation of the pharmacokinetic (PK) profile of Mirtazapine CR tablets with a thorough analysis of the PK data of the IR tablets for establishing the dose size and release rate for the CR formulation followed by formulation optimization using design of experiments. PK simulations were performed to adjust the dose and release rate, ensuring that the target C_{ss}^{max} and C_{ss}^{min} concentrations were achieved. The formulation development involves the selection and optimization of suitable hydrophilic polymers to achieve the desired release profile. These experiments were planned using a D-Optimal Mixture Design to optimize these formulation variables and to achieve the desired release profile. The CR formulation was designed to reduce the FI and incidence of side effects commonly associated with peak plasma levels.

Step 1. Pharmacokinetic data of Remeron® IR Tablets available on the USFDA website has been collected from the below path.

Drugs@FDA > FDA Approved Drugs > Mirtazapine > Teva> Review

The collection of pharmacokinetic data for Remeron® IR Tablets from the USFDA website is a critical step in understanding the drug's absorption, distribution, metabolism, and excretion characteristics. This activity involves navigating through the Drugs@FDA portal to access the FDA Approved Drugs section, where Mirtazpine's approval history is available. By reviewing the drug approval package, specifically the chemistry review and clinical pharmacology and biopharmaceutical review sections, we collected this data. This data includes detailed analyses and evaluations conducted by the FDA, providing insights into the drug's behavior in the body and its interaction with biological systems. Such information is crucial for developing new formulations like the CR tablet, as it lays the groundwork for simulation studies and informs decisions regarding dosing regimens and release mechanisms. The thorough examination of this data ensures that the new formulation adheres to established safety and efficacy standards while aiming to enhance patient compliance and therapeutic outcomes.

Step 2. Construction of plasma profile curve Mirtazapine IR tablets

Utilizing the pharmacokinetic data from the US FDA Website, a detailed construction of the plasma

profiles for both 15 mg and 45 mg doses of Remeron® IR Tablets was undertaken as shown in **Figure 1**. This step is pivotal in the development of the CR formulation as it provides a clear picture of the drug's concentration in the bloodstream over time. By plotting the concentration of the drug against time, the plasma profiles for the two doses were meticulously mapped out. This allowed for the observation of the peak plasma concentrations (C_{max}), the time to reach these peaks (T_{max}), and the overall exposure to the drug (area under the curve, AUC). These profiles are instrumental in predicting the onset, duration, and intensity of the drug's therapeutic effect, as well as its safety margin. The construction of these profiles is not only a technical task requiring precision and attention to detail but also a foundational one, as it directly informs the dosing strategy and release kinetics of the new CR formulation, ensuring that it delivers the desired therapeutic effect while minimizing potential side effects.

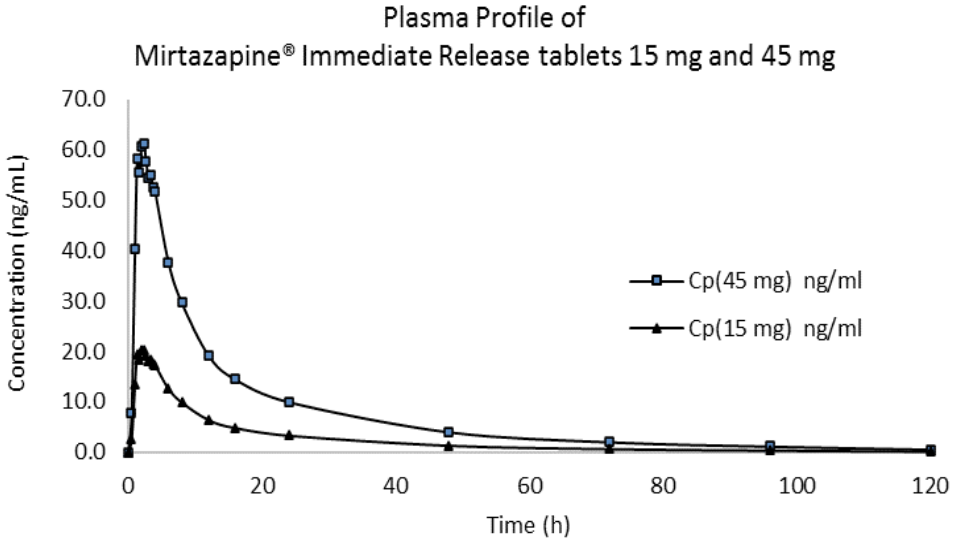

Figure 1. PK Profile of Mirtazapine 15 and 45 mg tablets plotted from the data of FDA Database

In the pharmacokinetic analysis of our study, we precisely calculated a comprehensive set of parameters from the plasma concentration profiles. These parameters are pivotal in understanding the drug's behavior within the body. The formulas used to derive each PK parameter and calculated values for each parameter were systematically presented in **Table 1** to ensure clarity and reproducibility of our methods, providing a clear and quantifiable overview of the drug's kinetics (Ducharme et al., 2022)

Table 1. The formula used for calculating the PK parameters from plasma profile (n=39)

Parameter		Formula in PK Simulations	45 mg	15 mg	units
Kel [1]	=	-slope {(ln(C2:C1)),(t2:t1)}	*0.0272*	*0.0272*	*/h*
$AUC_{0\text{-}t}$ [2]	=	$\frac{1}{2}\sum_{o}^{n}[(c_1 + c_2)(t_2 - t_1)]$	*899.71*	*299.90*	*ng.h/mL*
$AUC_{t\text{-}\infty}$	=	c_∞ / k_{el}	*20.15*	*6.72*	*ng.h/mL*
$AUC_{0\text{-}\infty}$	=	$AUC_{0\text{-}t}+AUC_{t\text{-}\infty}$	*919.86*	*306.62*	*ng.h/mL*
v_Z [3]	=	$dose/(AUC_{0\text{-}\infty})(k_{el})$	*1798.52*	*1798.52*	*L*
C_t [4]	=	$Co.e^{-kel.t}$	*Showed in Figure 2*		
$t_{½}$ [5]	=	$0.639/K_{el}$	*25.48*	*25.48*	*h*
FI [6]	=	$(C^{ss}_{max} - C^{ss}_{min})/(C^{ss}_{Avg})$	*Refer Table 2*		
C^{ss}_{Avg} [7]	=	F.D/Vz. Kel. τ [8]	*Refer Table 2*		
C max [9]	=	Max {plasma concentration}	*61.13*	*20.38*	*ng/mL*
t max [10]	=	Time corresponding to C max	*2.33*	*2.33*	*h*

1. Elimination Rate Constant; 2. Area under the curve; 3. Volume of Distribution;
4. Concentration at time t 5. Elimination Half-life; 6. Fluctuation Index;
7. Steady-state Concentration 8. F: Fraction absorbed, D: Dose, τ: Dosing Frequency 9. Peak plasma concentration
10. Time for achieving C max

Step 3. The steady-state plasma concentrations of IR tablets with dosages of 15 mg and 45 mg were determined using the principle of superposition. This principle postulates that the concentration-time profile of multiple doses can be predicted by summing the profiles of individual doses. To achieve this, we first established the elimination curve for a single dose administered on Day -1. We employed a first-order elimination rate, which assumes that the rate of drug elimination is directly proportional to the drug concentration in the plasma.

The concentration remaining at any time (t) after administration was calculated using the formula:

$Ct = Co.e^{-kel.t}$

Where:

Ct is the plasma concentration at time (t); C_0 is the initial concentration

(e) is the base of the natural logarithm; K_{el} is the first-order elimination rate constant

(t) is the time elapsed since the drug administration

By extrapolating the elimination curve until the plasma concentration approached nearly baseline, we could determine the residual concentration after the effect of the single dose diminished. For subsequent doses, we added the calculated concentrations at corresponding times to the baseline profile as shown in **Figure 2**, thus constructing a composite curve that represents the cumulative effect of multiple doses. This approach allowed us to accurately model the pharmacokinetics of the IR tablets at steady-state, providing valuable insights into the dosing regimen and its potential therapeutic outcomes. The extrapolated elimination curve serves as a crucial component in predicting the drug's behavior over extended dosing periods and is instrumental in optimizing dosage for maximum efficacy with minimal side effects.

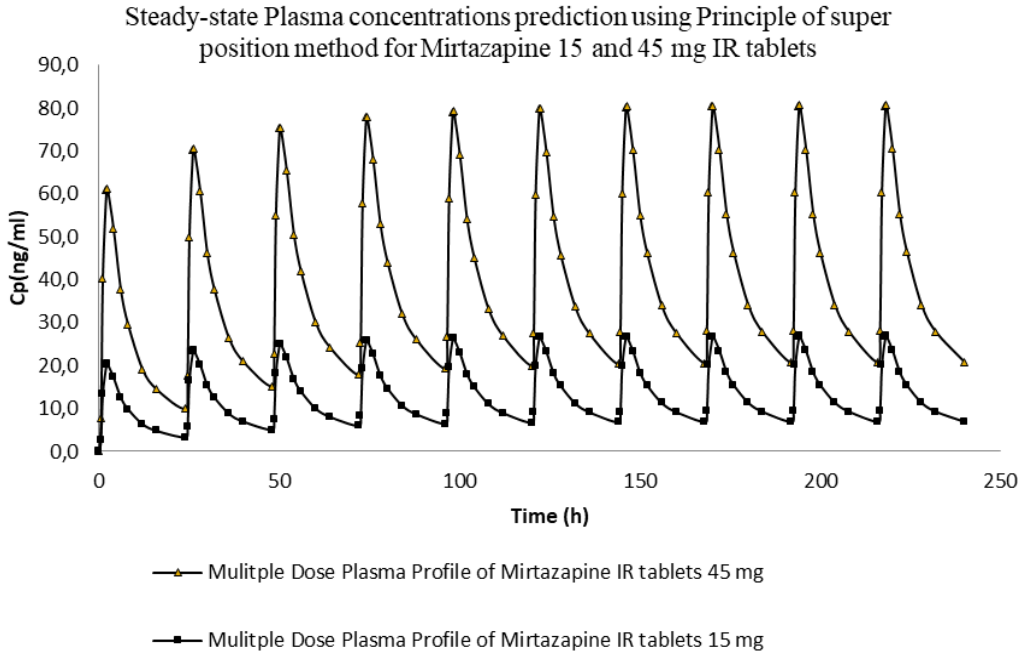

Figure 2. Simulated Steady-State Plasma Profile of Mirtazapine 15 and 45 mg IR Tablets using multiple doses with the Principle of Superposition

The FI was calculated from the steady-state plasma concentrations in **Table 2**. The FI, a measure of the extent to which plasma drug levels oscillate over a dosing interval at steady-state, was determined to be 1.56. This index is derived by dividing the range of concentration fluctuations specifically, the difference between the peak (C_{max}) and trough (C_{min}) concentrations by the mean concentration (C_{avg}) within the dosing period. The resulting value is indicative of the relative variability in drug exposure between doses. A FI of 1.56 suggests that there is a 156% fluctuation in the mean plasma concentration, which has critical implications for both the therapeutic efficacy and safety profile of the pharmacological intervention (Wakamatsu et al., 2013). Such a substantial fluctuation could potentially lead to periods of subtherapeutic exposure, as well as peaks that may approach toxic levels. Therefore, the FI (Sheehan et al., 2012) is an essential parameter for optimizing dosage regimens to balance efficacy and minimize adverse effects, ensuring a therapeutic window that maximizes patient outcomes.

Table 2. PK parameters calculated from the steady-state plasma profile

PK Parameter	*45 mg*	*15 mg*	*units*
$^{11}C_{ss}{}^{max}$	*80.7*	***26.9***	*ng/mL*
$^{12}C_{ss}{}^{min}$	***20.8***	*6.9*	*ng/mL*
$C_{ss}{}^{avg}$	*38.32*	*12.78*	*ng/mL*
Fluctuation Index	*1.56*	*1.56*	--

11. steady-state maximum concentration

12. steady-state minimum concentration

Desired steady-state plasma concentrations for the proposed CR tablets of Mirtazapine tablets have been fixed based on the steady-state concentration of IR tablets as 26.9 ng/ml and 20.8 ng/ml. The $C_{ss}^{\ max}$ of 15 mg and $C_{ss}^{\ min}$ of 45 mg observed in IR tablets were selected as target plasma concentrations for the proposed CR dosage forms. These targets ensure that the plasma concentrations remain consistently within the therapeutic window, thereby delivering the desired therapeutic effect to the patient throughout the treatment duration.

Step 4. In the pharmacokinetic simulation for the CR formulation of Mirtazapine tablets, we employed a zero-order absorption model to predict the drug release and absorption kinetics. This model assumes that the drug is released at a constant rate, regardless of the concentration, which is characteristic of many CR formulations. The simulation involved calculating key PK parameters, as mentioned in **Table 4**. These parameters are crucial for designing a CR tablet that can maintain therapeutic drug levels over an extended period without the peaks and troughs associated with IR formulations. The T_{elm} and $T_{\text{zero-order delivery}}$ are particularly important for ensuring that the drug is released not only at a constant rate but also for a duration that aligns with the drug's elimination half-life, thereby maintaining steady-state conditions. The $D^{CR}_{\text{Preliminary}}$ and $R^{0}_{\text{preliminary}}$ are used to fine-tune the dosage form to ensure that the desired drug release profile is achieved, which is essential for optimizing the therapeutic efficacy and minimizing side effects. This detailed simulation approach allows for the precise tailoring of the CR tablet's pharmacokinetic profile to meet specific clinical needs.

Table 3. Formula for simulating the plasma profile of proposed Mirtazapine CR tablets (preliminary)

Parameter		*Formula in PK CR Simulations*	*Results*
[13] T_{elm}	=	$\frac{(ln(C_{max}^{SSDesired}) - ln(C_{Min}^{SSDesired}))}{K_{el}}$	*9.45 h*
[14] T_{del}	=	$\tau. - T_{elm}$	*14.55 h*
[15] D_{IR}	=	*45 mg*	
[16] $D_{CR\ Preliminary}$	=	$D_{IR} \times 0.693 \times \tau) / t_{½}$	*29.38 mg*
[17] R^{0}_{prelim}	=	$D_{ER\ Prelim} \times F \times p / T_{del}$	*2.02 mg/h*
[18] $C^{Prelim\ Zero\ Sim}_{0\text{-}tmax}$	=	$\frac{(R^{0}_{prelim} \times (1 - (e^{-k_e \times t}))}{(V_Z \times K_{el})}$	
[19] $C^{Prelim\ Zero\ Sim}_{tmax\text{-}t\ inf}$	=	$Cmax.e^{-kel.(t\text{-}t\ del)}$	

13. T for elimination T_{elm}: The time required for the drug to be eliminated from the body after it has been completely absorbed.
14. T for delivery of dose in zero-order T_{del}: The duration over which the drug is released from the CR tablet at a constant rate.
15. Immediate - release tablets dose
16. CR preliminary dose ($D_{CR\ Preliminary}$): The initial dose of the CR formulation to achieve the desired plasma concentration profile.
17. CR preliminary release rate ($R^{0}_{preliminary}$): The rate at which the drug is released from the CR tablet into the systemic circulation.
18. Simulated plasma concentrations for the CR tablets from 0-t_{max}
19. Simulated plasma concentrations for the CR tablets from t_{max}-t_{inf}

Using the above formulae the calculations have been done for the determination of essential parameters needed for the simulations i.e. T elm, T delivery of the dose (for determining the dissolution time point for the CR dosage form), Dose for the proposed CR dosage form (preliminary dose) $D_{CR\ Prelim}$ and Preliminary release rate $R_{0\ Prelim}$ of the proposed CR dosage form , and presented in Table 3. Plasma concentrations for a single dose have been calculated using the above formula of $C^{\ prelim\ zero\text{-}order}_{0\text{-}t\ max}$ until t max and the elimination curve is constructed post tmax by calculating the decay concentrations using the formula $C^{\ prelim\ zero\text{-}order}_{t\ max\text{-}t\ inf}$. Plasma concentrations of multiple dosing of the proposed CR formulation have been calculated using the principle of superposition which is similar to the one used for IR formulations.

In the graphical representation of PK data shown below, the delineation of plasma concentration profiles following both single and multiple dosing regimens provides critical insights into the drug's absorption, distribution, metabolism, and excretion characteristics. The multiple dose profile, in particular, elucidates the time course to reach steady-state concentrations, a pivotal milestone in therapeutic drug monitoring.

The graph shown in Figure 3, indicates that steady-state conditions are attained after approximately 10 days of repeated dosing. This temporal aspect is reflective of the drug's PK properties, such as its half-life and accumulation factor. Achieving steady-state concentrations depends on both the drug's elimination rate constant and the dosing interval. At this point the input (dose rate) and output (clearance rate) of the drug reach an equilibrium, resulting in consistent plasma levels that are conducive to sustained therapeutic effect.

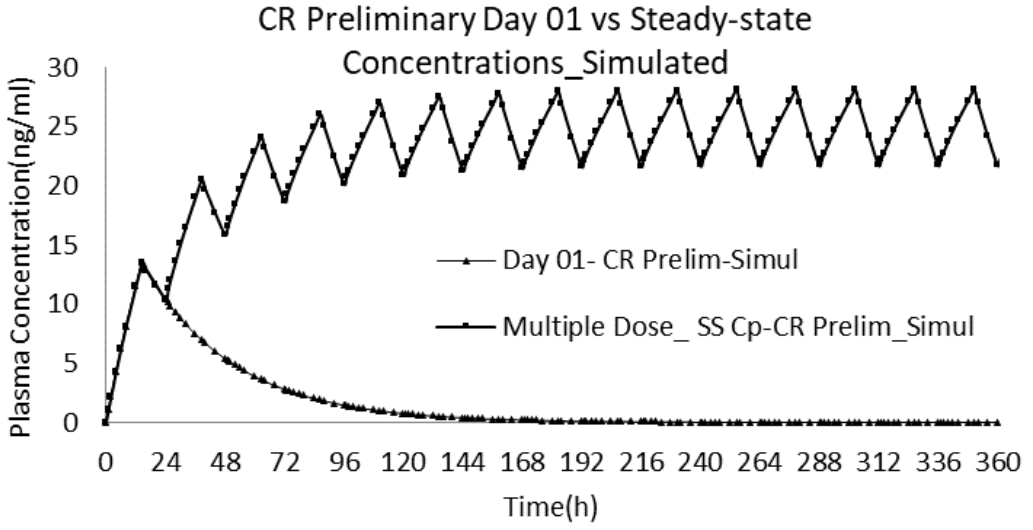

Figure 3. Simulated Steady-State plasma profile of Mirtazapine 29.38 mg CR tablets with R_0 - 2.02 mg/h (preliminary) using multiple doses with the principle of superposition

According to the simulated plasma profile provided, it is determined that the maximum steady-state plasma concentration ($C_{ss}^{\ max}$) is 28.15 ng/ml, while the minimum steady-state plasma concentration ($C_{ss}^{\ min}$) is 21.77 ng/ml. However, the steady-state plasma concentrations indicated in Table 4 are slightly lower than the observed values, indicating the need for further reduction in both dose and release rate to meet the desired targets for the proposed CR dosage form.

Table 4. Steady-State plasma concentrations of CR preliminary dose and release rate - Mirtazapine CR tablets (Preliminary)

Parameter	*value*	*units*
C_{ss}^{max} *desired*	*26.9*	*ng/ml*
C_{ss}^{min} *desired*	*20.8*	*ng/ml*
C_{ss}^{max} *achieved*	*28.15*	*ng/ml*
C_{ss}^{min} *achieved*	*21.77*	*ng/ml*
Fluctuation Index	*0.255*	--

The proposed adjustment needs a precise approach for reducing the dose, based on the difference between the existing and targeted plasma concentrations. Additionally, a careful modulation of the release rate is advocated as shown in **Table 5** to reduce the peak plasma levels and improve consistency between doses.

This strategic optimization is anticipated to improve the therapeutic index of the CR formulation, ensuring efficacious drug delivery within the optimal therapeutic window, while avoiding the potential for adverse drug reactions.

Table 5. Formula for simulating the plasma profile of proposed Mirtazapine CR tablets (Final)

Parameter		*Formula in PK CR Simulations*	*Results*
[20] $D_{CR\,final}$	=	$\frac{c_{max\ desired}^{ss}(ng/ml)}{c_{max\ achievend}^{ss}(ng/ml)} \times D_{CR\ Preliminanary}$	*28 mg*
[21] R_{final}^{0}	=	$D_{CR\,final}/t_{del}$	*1.93 mg/hr*

20. CR Final dose ($D_{CR\,final}$): The final dose of the CR formulation to achieve the desired plasma concentration profile.

21. CR preliminary release rate (R^{0}_{final}): The final rate at which the drug is released from the CR tablet into the systemic circulation.

The initial dose was set at 29.38 mg with a zero-order release rate of 2.02 mg/h. Subsequent adjustments entailed a reduction in both the dose and the release rate to achieve correspondence with the desired steady-state concentrations. The revised dosing parameters presented in **Table 5**, now set at 28 mg for the dose and 1.93 mg/h for the release rate, have successfully yielded steady-state concentrations that align precisely with the target values of 26.9 ng/ml C_{ss}^{max} and 20.8 *ng/ml* C_{ss}^{min}.

These findings underscore the significance of dose optimization in CR formulations to ensure therapeutic efficacy and minimize the potential for adverse effects.

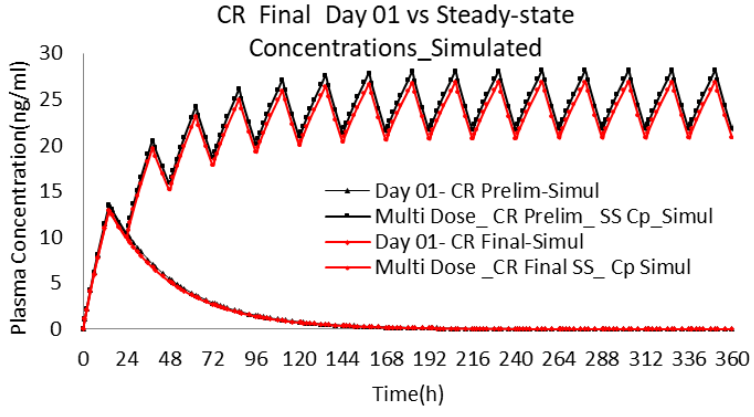

Figure 4. Simulated Steady-State plasma profile of Mirtazapine 28 mg CR tablets with R_0 - 1.93 mg/h (Final) using multiple doses with the principle of superposition

In **Figure 4**, the anticipated steady-state plasma concentrations, C_{ss}^{max}, and C_{ss}^{min} resulting from the simulations mentioned above were determined to be 26.9 and 20.8 ng/mL, respectively, aligning with the desired concentrations for the suggested CR dosage forms. As a result, the dosage for the proposed CR formulation and the *in-vivo* absorption rate constant in zero-order have been finalized at 28 mg and 1.93 mg/h, respectively, and are detailed in **Table 6**.

Table 6. Steady-State plasma concentrations of CR final dose and release rate - Mirtazapine CR tablets (final)

Parameter	*value*	*units*
Css max desired	*26.9*	*ng/ml*
Css min desired	*20.8*	*ng/ml*
Css max achieved	*26.9*	*ng/ml*
Css min achieved	*20.8*	*ng/ml*
Fluctuation Index	*0.255*	--

Step 5. Based on the above two parameters, the in-vitro release rate was determined using the below formula

$$\%drugrelase = \frac{t \times 100 \times R^{0}_{final}}{dose} = 6.88\ \%/h$$

RESULTS AND DISCUSSION

Step 6. In this study, D-optimal Mixture Design (Bodea et al., 1997, Jin et al., 2008, Habib et al., 2022) **Table 7** was employed to optimize the formulation variables of Hydroxypropyl Methylcellulose (HPMC) K100 MCR, Polyethylene Oxide (Polyox) WSR 303, and Carbopol 974P for achieving Zero-Order Controlled-Release. Dissolution at 6 hours (h) and 12 hours (h) in pH 6.8 buffer were selected as responses to assess the rate and extent of formulations and 14 h is the last time point as per the T Del determined in **Table 3**. Design-Expert software (version 13) from State Ease® was employed to design the experiments, analyze the data, and optimize the formulation components. This software facilitated the systematic exploration and identification of optimal conditions, ensuring efficient and reliable formulation development.

Factor A, B, and C are selected as HPMC K100 MCR at 0-60 mg/tablet, PEO WSR 303 at 0-60 mg/tablet, and Carbopol 974 P at 0-60 mg/tablet respectively, the mixture total (A+B+C) was fixed as 80 mg/tablet.

Two models, namely the linear model and the Special cubic model, were evaluated for their suitability in predicting dissolution profiles at 6 hours and 12 hours. While both models demonstrated alias-free behavior and statistically significant p-values (< 0.05), the Special cubic model exhibited a negative Predicted R square. Consequently, the linear model was chosen for its superior predictive performance, offering valuable insights into optimizing formulation variables for controlled-release applications.

Table 7. D-optimal Mixture Design for composition optimization of formulation variables of Mirtazapine CR tablets (n=10 runs)

Run	Components			Response: % Drug Release	
	A: HPMC K100 MCR (mg)	B: PEO WSR 303 (mg)	C: Carbopol 974P (mg)	6 h	12 h
1	25.2	29.8	25.0	12	25
2	60.0	10.8	9.2	25	49
3	0.0	60.0	20.0	15	36
4	43.8	6.4	29.8	30	58
5	0.0	20.0	60.0	42	87
6	28.9	0.0	51.1	38	78
7	60.0	10.8	9.2	23	45
8	20.0	60.0	0.0	15	37
9	20.0	60.0	0.0	12	28
10	2.5	38.5	39.0	37	68

The above experimental design layout consisted of a systematic arrangement to investigate the effects of three formulation factors on two responses, dissolution at 6 hours and 12 hours. With a total of 10 experiments conducted, the design aimed to comprehensively explore the influence of Hydroxypropyl Methylcellulose (HPMC) K100 MCR, Polyethylene Oxide (Polyox) WSR 303, and Carbopol 974P on the controlled-release kinetics of the formulation. Each experiment represented a unique combination of factor levels, facilitating the assessment of their individual and combined effects on the desired dissolution profiles.

In the Design of Experiments (DoE) for tablet formulation, the above three critical factors were selected for investigation. The formulation process utilized a wet granulation method, with the following excipients kept constant across all DoE runs, 2% PVP K30 as a binder, dissolved in ethanol, Avicel PH101 as a diluent to ensure the proper tablet weight and consistency, 1% colloidal silicon dioxide as an anti-adherent to prevent sticking during processing, 1% magnesium stearate as a lubricant to facilitate tablet ejection from the dies.

The total weight of each tablet was maintained at 300 mg. The process began with the precise weighing of all excipients, followed by sifting through a screen to ensure uniform particle size. Subsequently, the PVP ethanol solution was added to the mix. After thorough blending, the wet mass was dried and milled to achieve the desired granule size. The granules were then blended with colloidal silicon dioxide to enhance flow properties. Finally, magnesium stearate was incorporated as a lubricant. The resulting blend was compressed into tablets using 9.5 mm standard punches to ensure uniformity in size and weight.

Table 8. ANOVA Table for Response 1-dissolution at 6 h time point in pH 6.8 phosphate buffer

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Remarks
Model	888.71	2	444.36	11.10	0.0067	significant
Linear Mixture	888.71	2	444.36	11.10	0.0067	
Residual	280.19	7	40.03			
Lack of Fit	273.69	5	54.74	16.84	0.0570	not significant
Pure Error	6.5	2	3.25			
Cor Total	1168.9	9				

The ANOVA **Table 8** for the first response reveals the significance of the model, with an F value of 11.10 and a corresponding p-value of 0.0067, indicating statistical significance. There is only a 0.67% chance that a "Model F Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. Moreover, the lack of fit is not deemed significant, affirming the adequacy of the suggested model. The "Lack of Fit F-value" of 16.84 implies there is a 5.70% chance that a "Lack of Fit F-value" this large could occur due to noise.

In this case, Linear Mixture Components are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

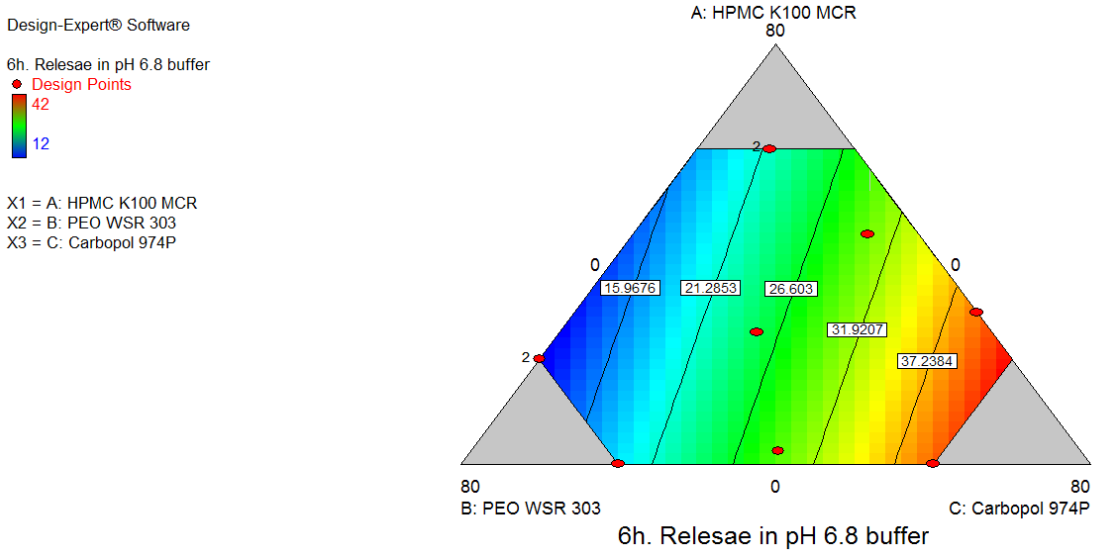

Figure 5. Model graph of dissolution in pH 6.8 phosphate buffer at 6 hours

Table 9. ANOVA Table for Response 2-dissolution at 12 h time point in pH 6.8 phosphate buffer

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Remarks
Model	3036.04	2	1518.02	10.70	0.0074	Significant
Linear Mixture	3036.04	2	1518.02	10.70	0.0074	
Residual	992.86	7	141.84			
Lack of Fit	944.36	5	188.87	7.79	0.1177	Not significant
Pure Error	48.50	2	24.25			
Cor Total	4028.90	9				

The ANOVA **Table 9** for the second response reveals the significance of the model, with an F value of 10.70 and a corresponding p-value of 0.0074, indicating statistical significance. There is only a 0.74% chance that a "Model F Value" this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. Moreover, the lack of fit is not deemed significant, affirming the adequacy of the suggested model. The "Lack of Fit F-value" of 7.79 implies there is a 11.77% chance that a "Lack of Fit F- value" this large could occur due to noise.

In this case, Linear Mixture Components are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

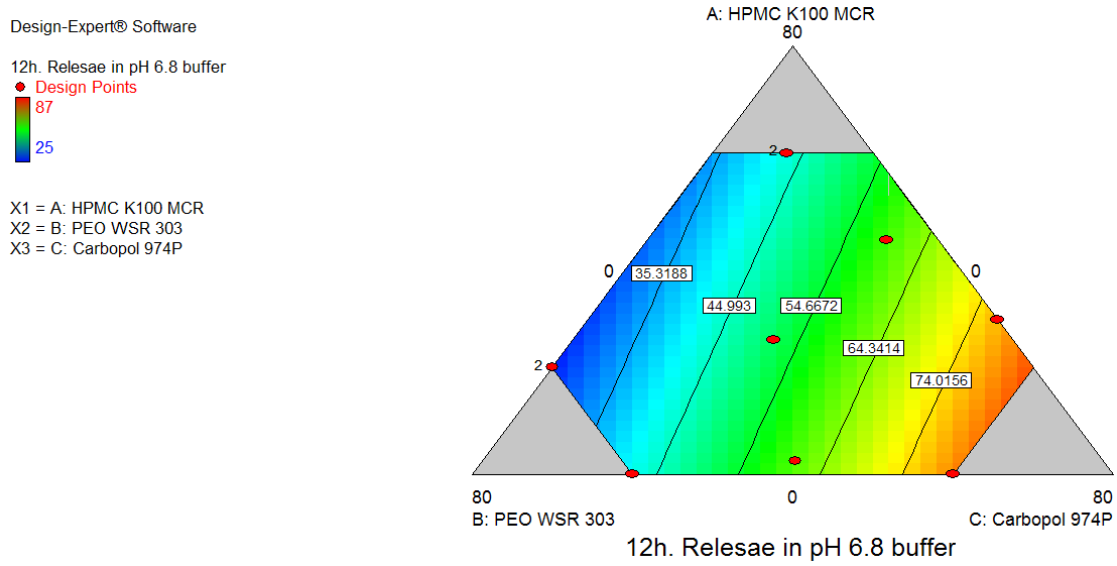

Figure 6. Model graph of dissolution in pH 6.8 phosphate buffer at 12 hours

Based on the findings of ANOVA and model graphs **Figure 5**, and **Figure 6** the recommended model for the first and second responses is the linear mixture model, which effectively captures the relationship between the formulation factors and the dissolution profiles at 6 and 12 hours. This analysis underscores the robustness of the experimental design and the reliability of the statistical model in elucidating the factors influencing the controlled-release kinetics of the formulation.

Table 10. Regression table for response 1, 2-dissolution at 6h, 12h time point in pH 6.8 phosphate buffer

Regression Analysis	Response 1- Dissolution at 6 h	Response 2- Dissolution at 12 h
R-Squared	0.7536	0.7603
Adj R-Squared	0.6832	0.6918
Pred R-Squared	0.6198	0.6361
Adeq Precision	8.128	8.183

The regression **Table 10** indicates a strong relationship between the independent variables and the dependent variable, as evidenced by an R-squared (R^2) value of about 0.75-0.76 This suggests that 75%-76% of the variability in the dependent variable can be explained by the model. The Adjusted R-squared, which is 0.68-0.69, adjusts for the number of predictors in the model and indicates a good fit as well. The Predicted R-squared of 0.62-0.63 is in reasonable agreement with the Adjusted R-squared, which implies that the model should predict future observations with a similar level of accuracy. Furthermore, an Adequate Precision ratio of around 8 indicates that the model has a desirable signal-to-noise ratio and that the model's predictions can be considered reliable. Overall, these metrics suggest that the regression model is statistically significant and can be used for making predictions with confidence.

The results indicated that a linear mixture model significantly influenced both dissolution responses. Among the formulation variables, Carbopol 974P emerged as the most significant factor, followed by HPMC and Polyox. Diagnostic plots revealed satisfactory results with no outliers detected.

Table 11. Numerical optimization- constraints

Name	Goal	Lower limit	Upper limit
HPMC K100 MCR	Minimize	0	60
PEO WSR 303	Minimize	0	60
Carbopol 974P	in range	0	60
6 h. Release in pH 6.8 buffer	Maximize	12	42
12 h. Release in pH 6.8 buffer	Maximize	25	87

Constraints were given for factors and responses using numerical optimization **Table 11**. Five solutions with desirability values greater than 0.8 were found based on the provided constraints in **Table 12**. The Design of Experiment (DoE) suggested specific factor combinations to achieve desired dissolution targets, specifically, Factor A (HPMC) and Factor B (Polyox) were recommended within the range of 0-20 mg, while Factor C (Carbopol) at 50-60 mg per tablet was identified as optimal for achieving the desired controlled-release profile as shown in **Figure 7**.

Table 12. Solutions of numerical optimization with desirability

Solutions	HPMC K100 MCR	PEO WSR 303	Carbopol 974P	6h. Release	12h. Release	Desirability
1	15.96	4.03	60	42.0	82.9	0.894
2	20	0	60	42.6	83.7	0.891
3	0	20	60	39.8	80.0	0.860
4	13.3	13.3	53.3	38.2	76.2	0.812

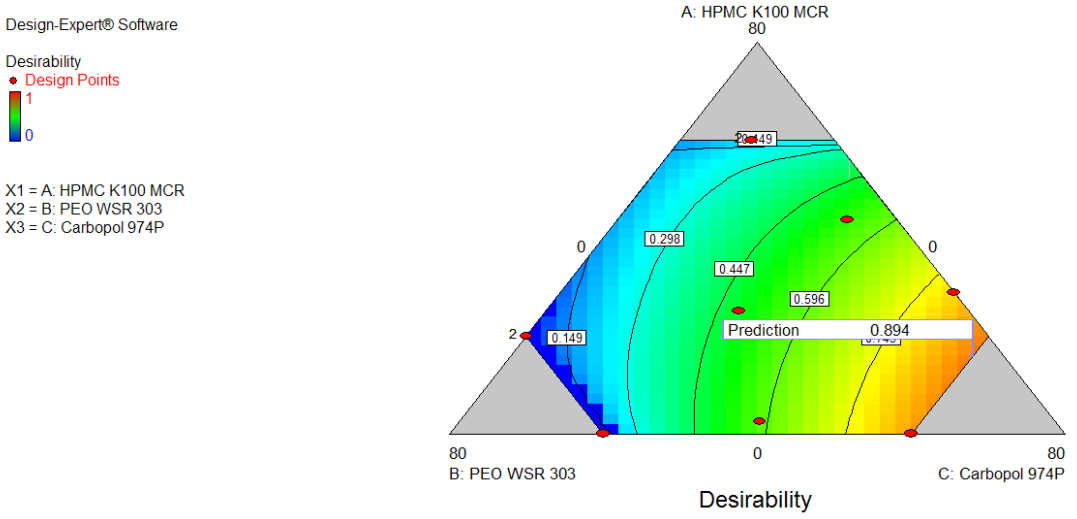

Figure 7. Desirability plot of overlay plot

Step 7. The conclusion of the design of experiments (DoE) was the execution of a final trial, which was selected based on a desirability index exceeding 0.8. This trial underwent dissolution testing in various media, including 0.01 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, The dissolution profile obtained as presented in **Table 13**, was compared against a predetermined zero-order target dissolution profile in **Figure 8**. The results were promising, demonstrating a dissolution behavior that was comparable to the target profile. This indicates a successful optimization of the formulation parameters, aligning with the desired release characteristics of the tablets.

Typically, formulation development begins with *in vitro* evaluations to predict the *in vivo* performance of the dosage form. However, in this study, to design controlled-release (CR) dosage forms based on immediate-release (IR) formulations, we initiated the process with pharmacokinetic (PK) simulations. This involved conducting simulations of IR multiple dosing to establish steady-state plasma concentration targets. Using these targets, CR dosing plasma concentrations were simulated for both single and multiple dosing regimens, which allowed us to set precise *in vitro* release targets before commencing the dosage form design.

As part of the CR formulation development, the Design of Experiments (DoE) was implemented to systematically optimize the formulation components. The optimized formulation was subsequently evaluated through multi-media dissolution studies to ensure that the dissolution profiles aligned with the predefined *in vitro* release targets. This step was critical in verifying that the *in vitro* release behavior would match the desired zero-order release profile, thereby providing confidence in the anticipated *in vivo* performance.

Table 13. *In vitro* dissolution conditions and dissolution profile in multi-media

In vitro Evaluation conditions	
Apparatus	Lab India Dissolution apparatus with autosampler
The volume of the medium	900 ml.
Temperature	37^0 ±0.5^0 C
Apparatus	USP Type II (paddle)
RPM	50
Sample collection intervals	1, 2 4, 6, 8, 10, 12 and 14 h.

Dissolution Profile in Multi-media				
Time	0.01 M HCl	pH 4.5 Acetate buffer	pH 6.8 phosphate buffer	Target Zero-Order
0	0	0	0	**0**
1	15	4.49	7.86	**6.88**
2	25.4	12.12	12.9	**13.76**
4	42.2	22.37	26.24	**27.52**
6	60.7	37	42.36	**41.28**
8	75.9	52.44	58.12	**55.04**
10	85.4	67	72.12	**68.8**
12	91.9	77.38	87.43	**82.56**
14	96.4	90	99.02	**96.32**
Slope				
Zero-order release rate	*6.95*	*6.60*	*7.21*	***6.88***
Slope (Actual/Target)	*101.07*	*95.93*	*104.80*	--
F2 Similarity factor	*43*	*70*	*76*	--
R^2				
Regression coefficient	*0.95*	*1.00*	*1.00*	***1.00***

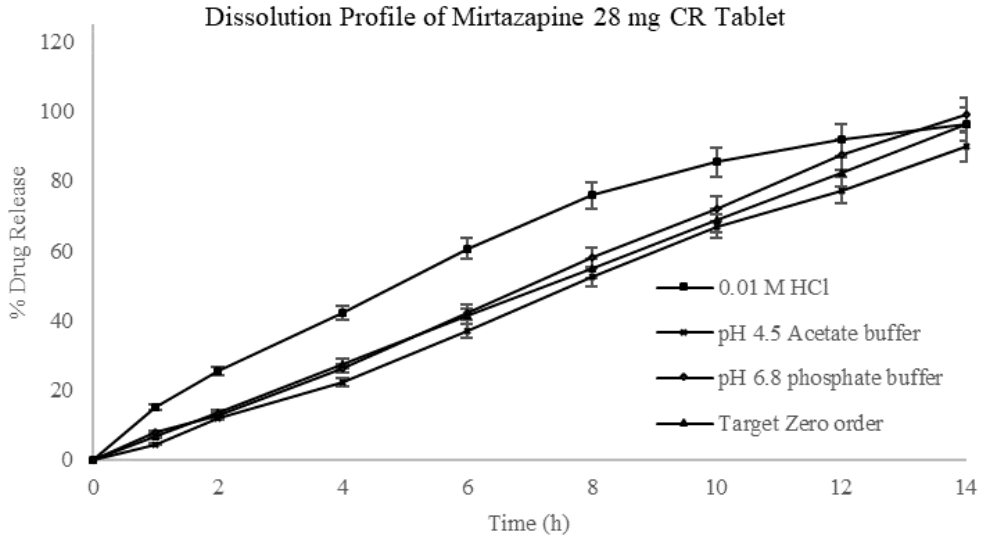

Figure 8. Dissolution profile of Mirtazapine 28 mg CR tablets in multi-media

The similarity factor (F_2) was calculated for the target zero-order release profile compared to *in vitro* dissolution in 0.01 N HCl (pH 2), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, yielding values of 43, 70, and 76, respectively. Although the F_2 value at pH 2.0 was lower than the generally accepted threshold of 50, this is not considered problematic due to the total dissolution time and the anticipated T_max exceeding 12 hours. The lower F_2 at acidic pH is not relevant to the overall performance of the CR formulation, as the release behavior in the higher pH media (pH 4.5 and pH 6.8), with F_2 values of 70 and 76, respectively, is more pertinent to the intended therapeutic effect. These values indicate satisfactory release profiles at these pH levels, which are more reflective of the physiological conditions post-gastric transit.

Although the formulation was designed for pH-independent drug release due to the high solubility of Mirtazapine at lower pH, a slightly faster release rate was observed in acidic conditions compared to the target zero-order release. However, the overall release slope across all pH conditions remained close to the target zero-order kinetics, nearly 100% in all three media. This suggests that the proposed CR formulation is adequate for achieving the desired *in vivo* targets, even with slight variations in release at lower pH.

(Ranjan et al., 2011) developed CR chitosan microspheres of Mirtazapine, demonstrating improved bioavailability and altered PK parameters, with increased AUC, prolonged half-life, and reduced clearance. The CR formulation achieved sustained drug release up to 48 hours (Ranjan et al., 2011). *In vivo* studies conducted in rats further confirmed the enhanced pharmacokinetic profile, highlighting the potential of CR microspheres in optimizing Mirtazapine's therapeutic effect.

(Koradia et al., 2018) developed unidirectional buccoadhesive CR tablets of Mirtazapine using Carbopol 934P and HPMC K4M, achieving controlled drug release over 6 hours with enhanced permeability through the buccal mucosa (Koradia et al., 2018). The formulation showed optimal swelling, good bioadhesive strength, and stability, offering a potential alternative delivery system for Mirtazapine.

A study by Vysloužil et al. developed PLGA micro-particles for the CR of Mirtazapine using the o/w solvent evaporation method (Vysloužil et al., 2014). The micro-particles, prepared with dichloromethane and stabilized with PVA, showed high encapsulation efficiency (64.2%) and released the drug over 5 days. The release followed near zero-order kinetics (R^2 0.95–0.98), with drug release driven by a combination of diffusion and surface erosion, enhanced by polymer swelling and chain relaxation.

CONCLUSION

The study successfully formulated Mirtazapine controlled-release (CR) tablets that met the pharmacokinetic targets derived from the IR reference product. The optimized formulation, achieved through a D-optimal mixture design, demonstrated a CR profile consistent with the zero-order kinetics model. Dissolution studies further confirmed the formulation's consistency and robustness, ensuring a reliable and predictable release of the drug. "The obtained *in vitro* dissolution results demonstrated an almost zero-order release profile, with an R-squared value close to one, across pH conditions ranging from 2.0 to 6.8. The release rate, observed was between 6.6%/h to 7.2%/h, which approximates the target zero-order release rate of 6.8%/h, suggesting zero-order absorption of Mirtazapine in vivo conditions. However, a bioavailability study may be necessary to confirm these findings."

This research provides a novel methodology for the development of CR tablets aligning with zero-order kinetics, potentially improving patient adherence and therapeutic outcomes for Mirtazapine, underscoring the application of the D-optimal mixture design in achieving a consistent and robust formulation. This approach has potential applications for other medications requiring controlled-release mechanisms, representing a significant advancement in pharmaceutical formulation.

AUTHOR CONTRIBUTIONS

SRK Raju Sagiraju was responsible for conducting developing the hypothesis, literature research, performing pharmacokinetic simulations, conducting experiments using DoE, statistical analysis, interpretation of the data, preparing and reviewing the study text. Pankaj Kumar Sharma and Jaya Sharma reviewed the data, manuscript, and approved the final version.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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