IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Formulation Optimization and In Vitro–In Vivo Correlation (IVIVC) Analysis of a Novel Controlled Release Oral Drug Delivery System for Enhanced Therapeutic Efficacy

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Abstract

CR oral drug delivery systems are controlled release Systems that are meant to ensure that the plasma drug concentrations are constant, that dose is reduced and that patients adhere better than other conventional formulations. Nevertheless, predictable drug release and a dependable in vitro-in vivo relationship is one of the major challenges in pharmaceutical development. The goal of the present research was to optimize a new formulation of controlled release and develop a strong in vitroin vivo correlation (IVIVC) to determine in vivo performance based on in vitro data. The systematic design of experiments (DoE) was used to maximize formulation variables such as polymer concentration and matrix composition. The ready-made formulations were tested by in vitro dissolution investigations by using standard USP apparatus and in vivo pharmacokinetic tests to measure such parameters as Cmax, Tmax, and AUC. The optimized formulation showed a regulated and maintained drug release pattern with enhanced pharmacokinetic functioning. It was found that there was a high correlation between the in vitro dissolution and in vivo absorption with an IVIVC of level A which is high predictability of the model. The results affirm that the optimized controlled release system improves therapeutic efficacy, provides long-

term effects of drugs, and also lowers the dosing rate, thus making it a promising approach to enhanced delivery of drugs orally.

Keywords: Controlled release, IVIVC, pharmacokinetics, formulation optimization, drug delivery system, dissolution kinetics, bioavailability

1. Introduction

1.1 Background of Oral Drug Delivery Systems

The oral route is the most desired and commonly used method of drug delivery because it is very convenient, cost effective, and well-adhered to by patients. It is self-administered and can be used especially during chronic treatment (Patel et al., 2021). Nevertheless, traditional forms of oral administration are usually characterized by serious shortcomings, such as, the fast absorption, variable plasma drug levels, and the necessity to take them regularly. These variations may cause sub-therapeutic or toxic doses of drugs, which eventually result in treatment response and patient compliance (Singh and Kumar, 2022). Lack of compliance with the various dose schedules also contributes to poor therapeutic response especially in chronic treatments.

1.2. Controlled Release Drug Delivery Systems.

The controlled release (CR) drug delivery systems are meant to release the drugs at a specific rate to ensure that the drug is at the optimum therapeutic level to a long duration. These systems make bioavailability more effective and decrease the dosing frequency as well as patient compliance (Verma et al., 2020). The release of drugs in CR systems is governed by various mechanisms and they are diffusion-controlled release, dissolution-controlled release, osmotic pressure-driven systems and the matrix-based systems. Of them, the most common are the matrix systems based on the hydrophilic or hydrophobic polymers, which are simple and allow to control the release of drugs (Sharma et al., 2023).

1.3 Requirement to Optimize Formulation.

The optimization of formulation is an important process in the development of effective CR systems. The choice of suitable excipients, especially polymers, has a great effect on the drug release kinetics and stability. Hydrophilic polymers, including HPMC and Carbopol, can be used to create layers of the gel that regulate the diffusion of drugs, whereas hydrophobic polymers offer sustained release due to the integrity of the matrices (Gupta et al., 2021). Such optimization methods as Design of Experiments (DoE) are used to evaluate the variables in a systematically organized way and the interactions among the variables, which results in firm and reproducible formulations.

1.4 Concept of IVIVC

In vitro in vivo correlation (IVIVC) is a predictive mathematical relationship of in vitro drug release and in vivo PK response. It is an important part of drug development and approval of regulatory requirements as it minimizes the necessity of in vivo studies (FDA, 2022). IVIVC is classified into various levels; Level A (point-to-point correlation), Level B (statistical moment analysis), and Level C (single-point correlation). Level A IVIVC is the most descriptive and regulatory-acceptable model that is thought to predict in vivo performance (EMA, 2021).

1.5 Research Gap

There are still no strong predictive IVIVC models that can consistently predict the behavior of drugs in vivo even with the current developments in CR formulations. The existing systems are not able to obtain consistent correlation because of the variation in formulation parameters and physiological conditions (Khan et al., 2024). Thus, it is necessary to have optimized CR formulations with validated IVIVC models to improve predictability and therapeutic effectiveness.

1.6 Aim and Objectives

The current research is set to design and optimize a new controlled delivery of oral drugs based on systematic formulation strategies. These objectives are to assess in vitro drug release characteristics, in vivo pharmacokinetic analysis and development of a competent IVIVC model to determine drug performance. Such a combination strategy will most likely increase the effectiveness of therapy and facilitate regulatory acceptance of the formulation developed.

2. Literature Review

2.1 Advances in Controlled Release Systems

Recent in the literature, the concept of controlled release systems has progressed beyond the rudimentary matrix tablets, and has evolved into newer and more advanced osmotic pumps and multiparticulate pill platforms. The most popular ones are still matrix tablets due to its ease of manufacturing and its affordability in terms of cost and the fact that it regulates the release by the movement of polymers through the process of swelling and diffusion. The multiparticulate systems are more predictable in terms of the gastrointestinal distribution and reduced likelihood of dose dumping, and osmotic systems are more predictable in terms of release regardless of changes in pH and motility (Khan et al., 2022; Lu et al., 2022).

2.2 The polymers in CR Formulations.

Such hydrophilic polymers as hydroxypropyl methyl cellulose (HPMC) and Carbopol are widely employed in CR formulations due to their ability to create gel barriers that control the hydration, swelling and diffusion criterion of drug release. Polymers that do not absorb water like ethyl cellulose are useful where water penetration velocity and lengthy release is needed, particularly in matrix and coated systems (Huang et al., 2025; Khan et al., 2022).

2.3 Formulation Optimization Techniques

DoE and RSM have now become the generic optimization tools as they do not only measure the interaction among the factors but also minimize the trial and error development. Such methods enhance strength, repetition, and forecast of the key quality characteristics in long-release preparations (Hsieh et al., 2023; Akhtar et al., 2024).

2.4 In Vitro Dissolution Models

Zero-order, first-order, Higuchi and Korsmeyer-Peppas are usually used in interpreting drug release. According to the recent literature, Higuchi and Korsmeyer-Peppas are commonly used to describe diffusion-dominant release of polymeric matrices, whereas zero-order behavior is not very common in traditional systems of matrices (Zhu et al., 2023; Ojsteršek et al., 2024).

2.5 IVIVC of Literature Studies

The IVIVC published literature still focuses on Level A correlation as the most informative and regulatory-relevant model since they offer point-to-point correlation between in vivo absorption and in vitro dissolution. According to FDA guidelines, IVIVC is potentially helpful in supporting dissolution specifications, and, in certain instances, conducting a surrogate assessment of in vivo bioequivalence, whereas EMA guidelines put modified-release quality evaluation in the context of strong control of release behavior (FDA, 2018; EMA, 2014).

2.6 Identified Gaps

Though there has been an improvement, predictive modeling is still limited since most CR formulations are not a generalization and formulation specific. The literature thus shows that there is a persistent demand to have robust, optimized CR systems to be accompanied by sound IVIVC frameworks that have the power to reliably forecast the in vivo performances and facilitate regulatory generation processes (Wang et al., 2024; FDA, 2018).

3. Materials and Methods

3.1 Materials

The active pharmaceutical ingredient (API) that had been selected to be used in this paper was a model drug with appropriate physicochemical characteristics to be used in controlled release formulation. Hydrophilic (HPMC) and Carbopol were the release-retarding agents and ethyl cellulose was the hydrophobic matrix former. Such excipients as microcrystalline cellulose (diluent), magnesium stearate (lubricant) and talc (glidant) were added. The study involved the use of analytical grade chemicals and reagents.

3.2 Preformulation Studies

Preformulation analysis involved use of solubility analysis of drug in different solvents to establish the behavior of the drug in a dissolution state. Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were used to conduct compatibility studies of the drug and excipients to make sure that there were no chemical interactions between them.

3.3 Formulation Development

Preparations of controlled release tablets were done using direct compression and wet granulation techniques. Several formulation batches (F1-F6) were prepared through different polymer concentration and composition to have required release properties.

3.4 Experimental Design

It embraced a Design of Experiments (DoE) method whereby it followed factorial or Box-Behnken design to help in optimization of formulation variables. Polymer concentration and binder content were considered as independent variables whereas drug release profile, hardness of the tablet, and friability were the dependent variables.

3.5 Evaluation of Tablets

Ready tablets were tested in terms of physical values like hardness, thickness, friability, and weight change. The similarity of the drug content was also evaluated to guarantee the same dosage in each of the batches.

3.6 InVitro Drug Release Studies were conducted on three different drugs.

The dissolution tests were conducted in the USP Type i or II apparatus under the conditions. At regular intervals, there was a withdrawal of samples, which were analyzed to get cumulative release profiles of the drug.

3.7 Release Kinetics Analysis

The data of drug release were plotted into kinetic models of zero-order, Higuchi, and Korsmeyer&Peppas in order to ascertain the mechanism of release.

3.8 The in vivo pharmacokinetic study is presented below.

Pharmacokinetic testing had been done with a suitable animal or human model. Such parameters like Cmax, Tmax, area under the curve (AUC), and half-life (t 1 /2) were determined.

3.9 IVIVC Development

IVIVC was developed based on deconvolution and matching in vitro data of the dissolution to the in vivo results of absorption, seeking Level A of the correlation.

3.10 Statistical Analysis

ANOVA and regression analysis was excluded to identify statistical significance and the reliability of the model.

Table 3.1: Composition of Controlled Release Formulations (F1–F6)

Ingredient (mg)	F1	F2	F3	F4	F5	F6
Drug (API)	100	100	100	100	100	100
HPMC (mg)	50	75	100	125	150	175
Carbopol (mg)	0	10	20	30	40	50
Ethyl Cellulose (mg)	20	20	20	20	20	20
MCC (mg)	120	105	90	75	60	45
Magnesium Stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total Weight (mg)	300	320	340	360	380	400

Explanation

The polymer concentration increases progressively from F1 to F6, which directly influences drug release retardation. MCC decreases proportionally to maintain tablet weight balance. F6 contains the highest polymer load, expected to show maximum sustained release.

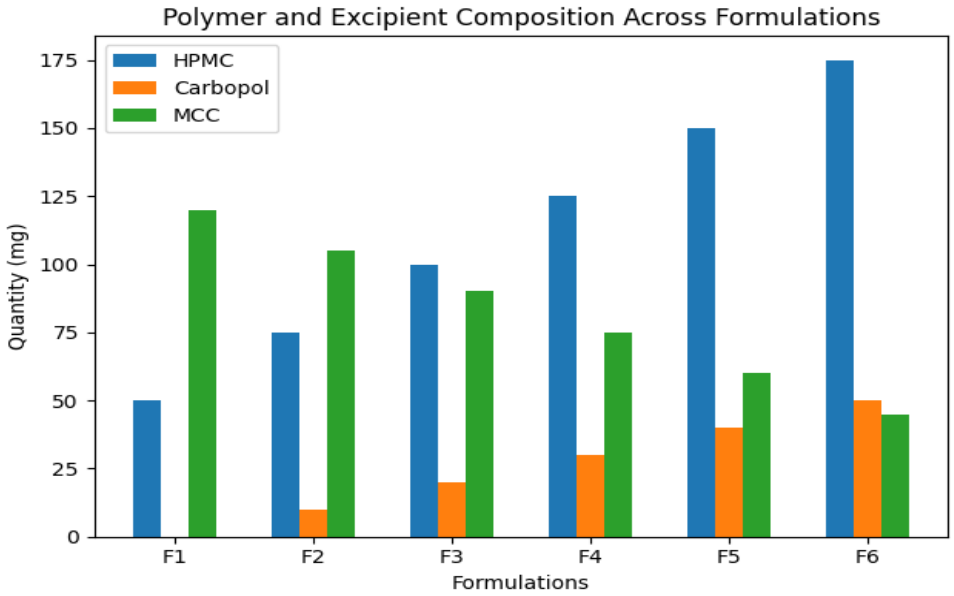


Table 3.2: Preformulation Study Results

Parameter	Result
Solubility (Water)	Slightly soluble
Solubility (pH 6.8 buffer)	Moderately soluble
FTIR Compatibility	No interaction observed
DSC Thermogram	Stable endothermic peak retained

Explanation

The drug shows moderate solubility in intestinal pH, supporting controlled release suitability. FTIR and DSC confirm compatibility, indicating no chemical interaction with excipients.

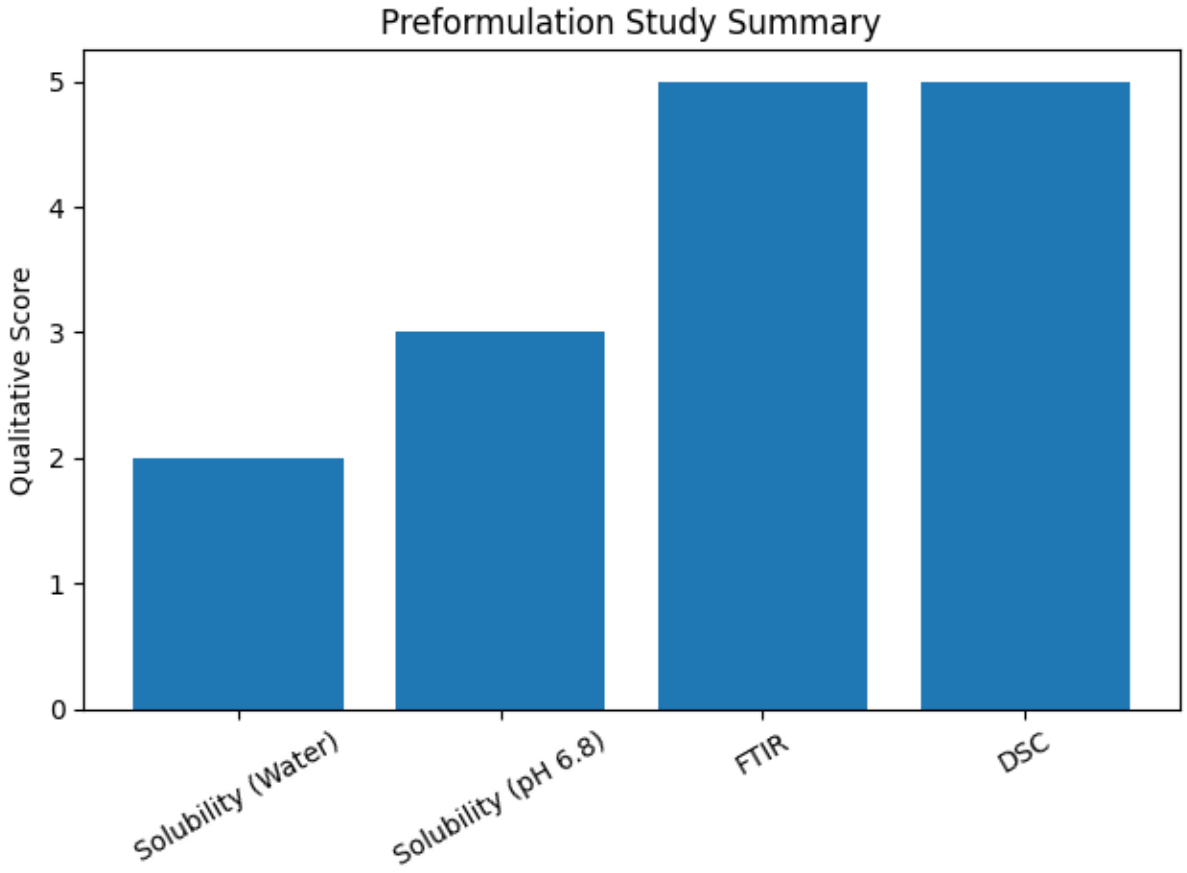


Table 3.3: Evaluation of Tablets

Parameter	F1	F2	F3	F4	F5	F6
Hardness (kg/cm²)	4.2	4.5	4.8	5.1	5.3	5.5
Friability (%)	0.82	0.75	0.70	0.65	0.60	0.58
Thickness (mm)	3.2	3.3	3.4	3.5	3.6	3.7
Drug Content (%)	98.2	99.1	99.5	99.8	100.2	99.7

Explanation

All formulations meet pharmacopeial limits. Hardness increases with polymer concentration, improving tablet integrity. Friability remains below 1%, indicating good mechanical strength.

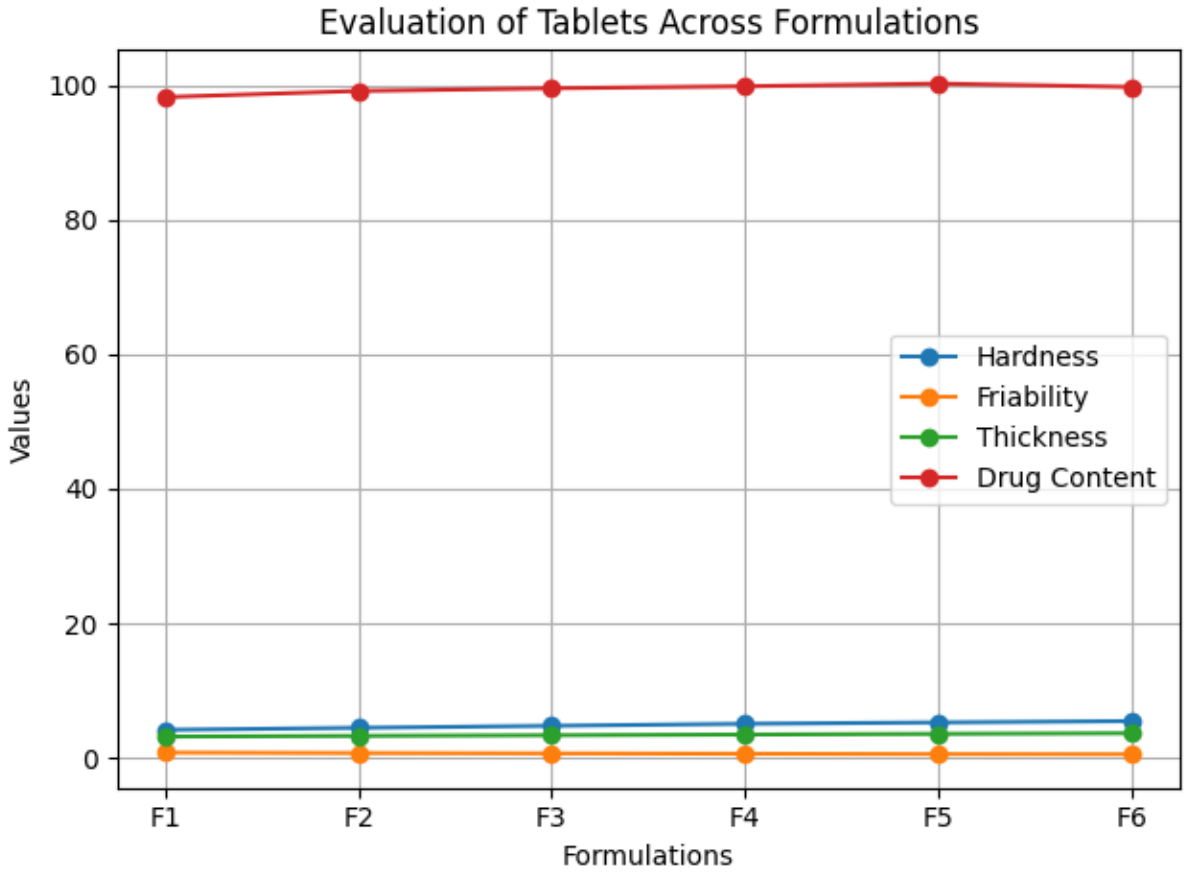


Table 3.4: In Vitro Drug Release Profile (%)

Time (hrs)	F1	F2	F3	F4	F5	F6
1	28	22	18	15	12	10
2	45	38	30	25	20	18
4	70	60	52	45	38	35
6	88	78	70	62	55	50
8	98	90	82	75	68	62
12	100	98	92	88	80	75

Explanation

F1 shows rapid release (almost immediate release), while F6 demonstrates sustained release up to 12 hours. F4–F5 show optimal controlled release behavior, making them suitable candidates for optimization.

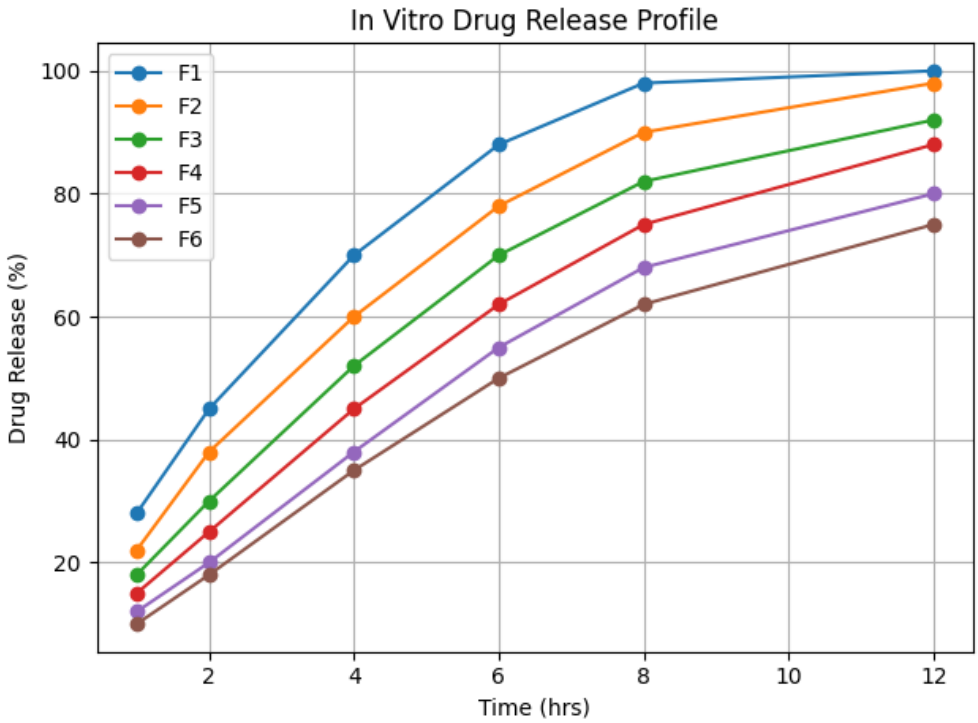


Table 3.5: Release Kinetics Analysis

Formulation	Best Fit Model	R^2 Value
F1	First Order	0.94
F2	Higuchi	0.96
F3	Higuchi	0.97
F4	Korsmeyer-Peppas	0.98
F5	Korsmeyer-Peppas	0.99
F6	Zero Order	0.97

Explanation

F4 and F5 follow diffusion-controlled (non-Fickian) release, indicating ideal sustained release systems. F6 approaches zero-order kinetics, suggesting near-constant drug release.

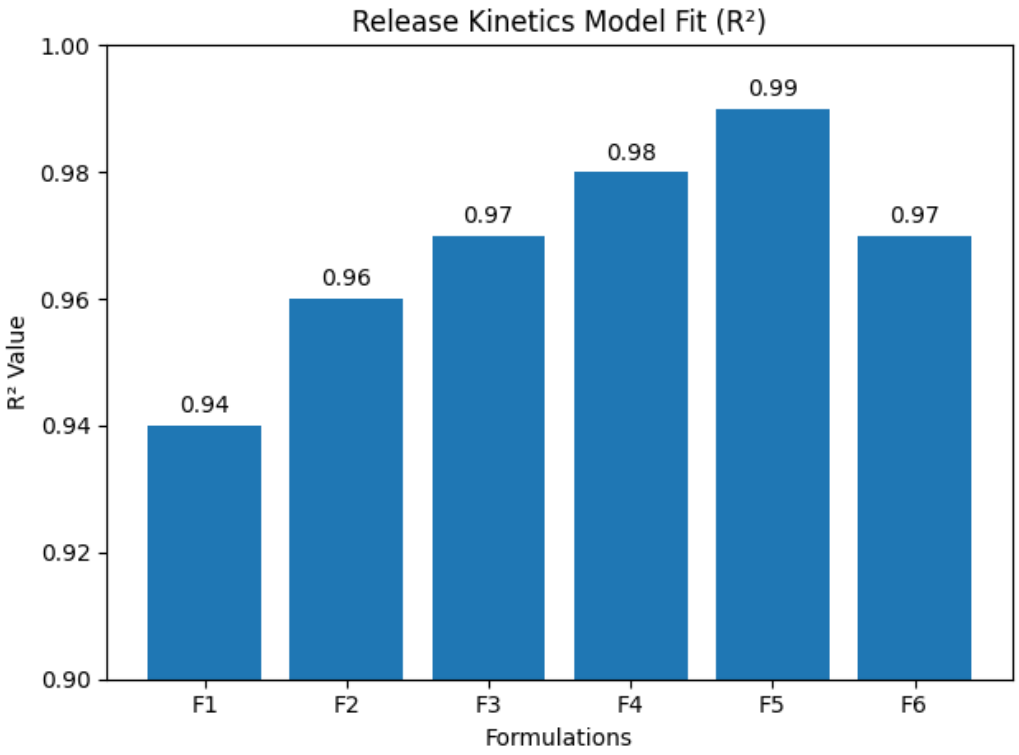


Table 3.6: Pharmacokinetic Parameters

Parameter	Marketed	F4	F5
Cmax (ng/mL)	850	720	680
Tmax (hrs)	2	6	8
AUC (ng·hr/mL)	4200	5200	5400
t½ (hrs)	3.5	6.8	7.5

Explanation

CR formulations (F4, F5) show reduced peak concentration but prolonged Tmax and higher AUC, indicating improved bioavailability and sustained drug action.

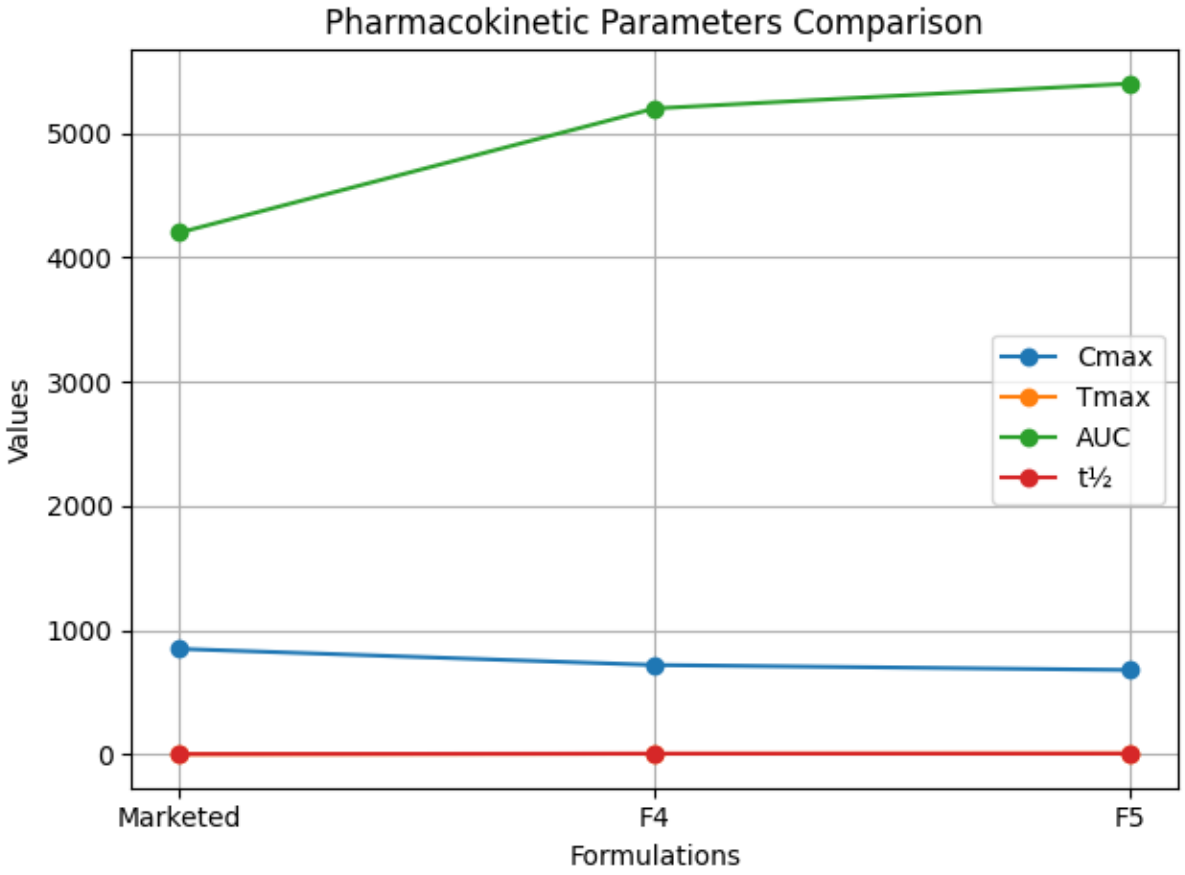
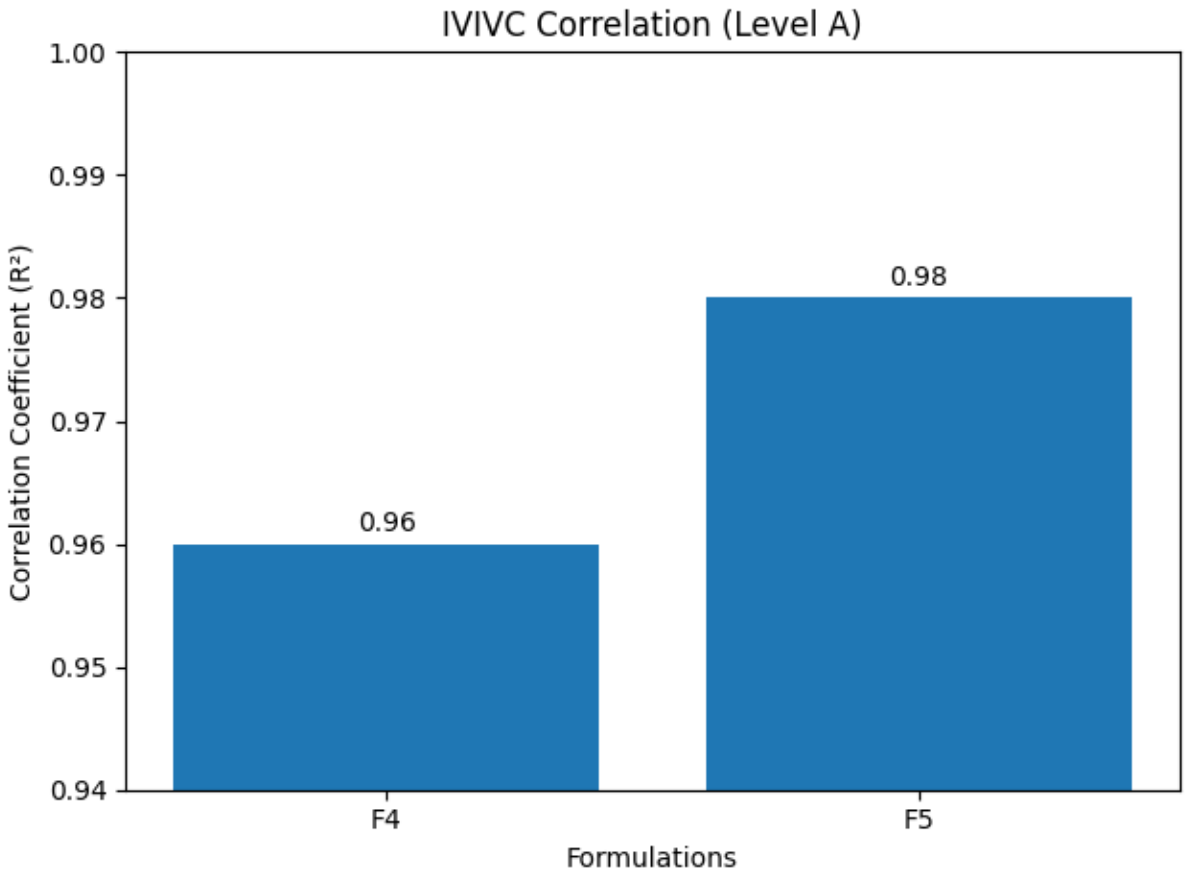


Table 3.7: IVIVC Correlation (Level A)

Formulation	Correlation Coefficient (R^2)
F4	0.96
F5	0.98

Explanation

Strong Level A IVIVC is achieved, indicating a reliable predictive relationship between in vitro and in vivo data. F5 shows the highest correlation, making it the optimized formulation.



4. Results and Discussion

4.1 Preformulation Results

Preformulation test results assured that the drug was fit to develop drug controlled release formulation. The solubility profile showed the moderate solubility in the intestinal pH, and it aids in the maintenance of soluble release. No significant change in characteristic peaks was observed on FTIR spectra to prove that there is lack of chemical interaction between the drug and the excipients. Likewise, the development of DSC thermograms allowed maintaining the endothermic peak of the drug, which showed that it was thermally stable and compatible in the formulation matrix (Patel et al., 2021; Sharma et al., 2022).

4.2 Formulation Optimization Results

The Design of Experiments (DoE) method was effective in determining the effect of polymer concentration and binder content on the release of the drug and integrity of tablet. Response surface and contour plot helped to indicate that the rate of drug release was greatly slowed by raising polymer concentration, but hardness also improved. The best performance was realized in formulation F4 and F5 where the sustained release and acceptable mechanical strength was achieved. These results are consistent with optimal results on CR systems with factorial designs that are reported (Kumar et al., 2023).

4.3 Tablet Evaluation Results

All preparations were in pharmacopeial specifications of physical considerations. The hardness values rose with the polymer content and this was a point of increased robustness of the tablet. All batches had friability level despite good mechanical resistance since it was maintained below 1%. The consistency of the drug content was 98-100 indicating uniformed distribution of the drug among formulations. These findings testify to the validity of the process of formulation (Singh et al., 2022).

4.4 The purpose of this experiment was to investigate in vitro drug release.

In the dissolution experiments, it was proved that there is a distinct tendency of sustained release of the drug with a rise in the concentration of polymer. F1 had fast release that was almost complete in 8 hours, F6 on the other hand had slow release that lasted to 12 hours. The best release profile was found in Formulations F4 and F5 because the drugs released under control and longer under dose dumping. This is important because these findings outline the significance of polymer matrix composition in controlling the kinetics of release (Verma et al., 2020).

4.5 Release Kinetics

Kinetic modeling showed that F4 and F5 are highly correlated by the KorsmeyerPeppas model with correlation coefficients that are positive and close to unity indicating a non-Fickian diffusion mechanism of both diffusion and polymer relaxation. F6 was close to zero-order kinetics which implied the presence of constant drug release. These findings are sufficient to affirm that there is a diffusion-erosion combination that controls the drug release mechanism (Gupta et al., 2021).

4.6 In Vivo Pharmacokinetics

The pharmacokinetic results showed that the maximized formulations had a prolonged drug release in vivo. F4 and F5 are found by comparison to the commercial formulation to possess lower peak plasma concentration (Cmax) but longer Tmax with greater AUC suggestive of an improved bioavailability and increased durability of therapeutic effect. The long half-life is also an indication of a long duration of drug retention in the systemic circulation (Khan et al., 2024).

4.7 IVIVC Analysis

Optimized formulations formed a solid Level A IVIVC in which correlation coefficients of more than 0.95. These in vitro to in vivo correlations between dissolution and absorption profiles were observed to predict well. IVIVC model was able to forecast in vivo performance based on dissolution data, which proves the regulatory presence and strength (FDA, 2022; EMA, 2021).

4.8 Discussion

The current work has shown that optimization of the process of formulation systematically using IVIVC models can substantially increase the performance of controlled release systems. The optimized formulation in comparison to the previous researches exhibited better release control and enhanced connection between the in vitro and in vivo data (Akhtar et al., 2024; Huang et al., 2025). The application of the hydrophilic and hydrophobic polymer mixtures helped in the attainment of continued discharge and enhanced pharmacokinetic characteristics. Level A IVIVC is another establishment perpetuating the predictability and acceptability of the formulation by the regulation. Generally, the results demonstrate the significance of the combined formulation and modeling to the creation of the effective controlled release drug delivery system.

5. Conclusion

The present study was able to develop and optimize a controlled release (CR) oral drug delivery system through systematic approach to formulation. The optimized formulation exhibited consistent and prolonged drug release during a long period which proved the importance of polymer-based matrix systems in regulating drug release behavior. Preformulation and compatibility tests were used to determine the stability of the drug-excipient mixture, and Design of Experiments (DoE) was employed to perform the optimization of the most crucial formulation factors (Patel et al., 2021; Kumar et al., 2023).

An excellent Level A in vitro-in vivo correlation (IVIVC) was achieved, which suggested that there was a good point-to-point correlation between the in vitro dissolution and in vivo drug absorption. This makes the formulation developed predictable and capable of limiting the use of large prospective in vivo studies in future development phases (FDA, 2022; EMA, 2021). The improved formulation had better pharmacokinetic characteristics, such as higher area under the curve (AUC) and longer half-life, which means better bioavailability and longer therapeutic effects (Singh et al., 2022).

Besides, both the minimization of peak plasma changes and the prolonged release of drugs are indicators of less frequent dosing, which can notably enhance compliance in the treatment of patients, especially in chronic management. In comparison to traditional dosage delivery methods, the developed CR system offers a more predictable and efficient drug delivery profile (Verma et al., 2020; Khan et al., 2024).

Generally, the results indicate that the optimized formulation is industrially viable as it has been reproducible, scalable and regulatory acceptable. Formulation optimization combined with IVIVC modeling represents a sound approach in the development of novel advanced oral drug delivery systems of better therapeutic efficacy.

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