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Sustained Release Matrix Tablets of NSAIDS: In-Vitro and In-Vivo Correlation

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have wide applicability in management of inflammatory and pain related diseases but limited applicability is characterized by common use and gastrointestinal disturbance. Present study is the trying to come up with sustained release (SR) matrix tablets of NSAIDs using hydrophilic and hydrophobic polymers and correlate the results of in-vitro drug release with the in-vivo pharmacokinetics response. The Ibuprofen drug was selected to be the model, and the direct compression of matrix tablet with HPMC K100M and ethyl cellulose was done. The drug was undergone in-vitro dissolution study using USP-II apparatus with phosphate buffer (pH7.2) and during in-vivo pharmacokinetics testing using healthy volunteers approach crossover study. They came up with a favourable Level An in-vitro/ in-vivo correlation (IVIVC) (R 2= 0.987), showing that the in-vitro kinetics of drug released is a fair representation of the average put on plasma. Sustained release matrix has succeeded in prolonging the duration of drug release to 12 hours and reduced Cmax which contributed to reduction of adverse effects related to a peak. These findings encourage studies into establishing the means of developing SR NSAID formulation to assist in GI toxicity and compliance in patients.

Key Words:

History: Sustained release, Matrix tablets, In-vitro drug release, In-vivo pharmacokinetics, IVIVC (In-vitro/In-vivo correlation).

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1. INTRODUCTION

NSAIDs non-steroidal anti-inflammatory drugs (NSAIDs) constitute one of the most popular groups of the pharmacological agents used to treat pain, inflammation, and fever. Their wide-spread use in acute and chronic inflammatory diseases gives them absolute necessity in clinical practice[1]. One of the most active and safe NSAIDs and, therefore, one of the most prescribed ones, is Ibuprofen, which is a derivative of propionic acid[2]. Nonetheless, ibuprofen, and other non-steroidal medications follow a typical dosage form, which means that it needs multiple daily intakes, making it prone to failure since it boasts short biological half-lives[3]. It causes the plasma levels to vary, leads to dose alteration schedules and an augmented probability of gastrointestinal adverse outcomes, such as gastric irritation or ulceration and bleeding[4]. These disadvantages from such limitations interfere with effectiveness of therapeutic effects as well as patient adherence to them particularly with chronic pain treatments[5].

In order to overcome these challenges, there is a need to consider a new alternative type of an agent - a sustained release (SR) one[6]. Such dosage forms have an intrinsic property of releasing

the active pharmaceutical ingredient (API) in a controlled manner, which permits prolonged therapeutic plasma levels within a set time[7]. Specifically, the concerned drug release of the matrix tablet systems is performed using hydrophilic or hydro phobic polymers mechanism of drugs release including diffusion, swelling and erosion[8]. The most utilized of them in the matrix-based systems are hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC), which exhibit predictable and adaptable release-modifying effects. A successful development of institution of such delivery systems not only enhances patient adherence and bioavailability, but also minimizes the side effects when there is a peak[9].

Having a valid in-vitro/in-vivo correlation (IVIVC) is crucial for developing an effective sustained release formulation. IVIVC is a mathematical model that predicts how a dosage form's in-vitro parameter—often the rate or extent of drug dissolution—will relate to an in-vivo parameter—often the amount absorbed or the drug plasma concentration—of interest. Formulation development and registration benefit from the presence of a strong IVIVC, especially a Level A correlation, because it decreases the necessity to perform large-scale human investigations for the purpose of fine-tuning formulations and comparing batches to batches.

1.1 Background Information

Non-steroidal anti-inflammatory drugs, such as ibuprofen are administered widely to treat the symptoms of conditions like osteo-arthritis, rheumatoid arthritis, and pain following surgery. Nonetheless, their pharmacokinetic shortcoming including high absorption and metabolism requires them to be administered at short intervals, which is inconvenient and subjects the drug to a risk of side effects. The sustained release delivery systems provide the advantage of being able to provide maintained plasma levels of drugs, there is also an increased compliance of the patient and the side effect can be possibly lowered. In this regard, matrix tablets that employ the use of polymer, such as HPMC and EC, have proved capable of reacting with the rate of release of drugs. At the same time, regulatory guides state that directing the formation of a quantitative IVIVC is necessary to smooth the process to launch and approve these sophisticated preparations.

1.2 Statement of the Problem

Traditional immediate-release medications of NSAIDs such as ibuprofen cause fast drug absorption that is followed by a rapid drug elimination, whereas plasma concentrations drastically fluctuate. Such fluctuations raise the risk of dose-related side effects and demand frequent dosing, a fact that does not have a positive impact on patient compliance and treatment efficacy. Moreover, they do not have predictive models that are consistent with in-vitro drug release characteristics to in-vivo pharmacokinetics response of sustained release formulae. Such a gap restrains the effectiveness of the formulation development and hampers the regulatory approvals. Thus, a system of sustained release matrix properly optimized, such as with its key in-vitro/in-vivo correlation model pinpointed, is seriously desirable in increasing the sector of safety, efficacy and predictability in NSAID therapy.

1.3 Objectives of the Study

Research has mainly focused on developing and studying ibuprofen long-release matrix tablets made from a combination of hydrophilic and hydrophobic polymers. The study's secondary objective is to provide a reliable in-vitro/in-vivo correlation for the purpose of identifying the formulation's pharmacokinetic properties. The following goals have been identified:

- To prepare sustained release of tablets of ibuprofen in the combination of HPMC and ethyl cellulose in various proportions.
- To determine the in-vitro drug release profiles of developed formulations and to determine the best release matrix.
- To study pharmacokinetic study of the optimized formulation of the sustained release drug in healthy volunteers as in-vivo models.

1.4 Hypotheses

Based on existing literature and the theoretical basis of sustained drug delivery systems, the study is guided by the following hypotheses:

- Null Hypothesis (H_0): There is no significant correlation between the in-vitro drug release profile and the in-vivo pharmacokinetic behaviour of the developed sustained release ibuprofen formulation.
- Alternative Hypothesis (H_1): There is a significant correlation between the in-vitro drug release profile and the in-vivo pharmacokinetic behaviours of the developed sustained release ibuprofen formulation, indicating the reliability and predictability of the matrix system.

2. METHODOLOGY

The design of the methodology implemented in this study was aimed at allowing to develop, evaluate and validate sustained release matrix tablets of ibuprofen comprehensively on the basis of in-vitro and in-vivo correlation. In order to people to reproduce the results scientifically, they adopted a systematic and experimental approach which could achieve and sustain the results.

2.1 Research Design

The research study used a stringent laboratory based experimental study design, where the formulation was developed, it was tested in-vitro, and the pharmacokinetic testing was carried out in-vivo. The research design was such that control of variables used in the formulation of matrix tablets could be well coordinated especially the ratio and type of the polymers used. A full factorial design of 3x3 was adopted is the group to optimize the polymer matrix system. The selection of this design was dictated by the possibility of systematically varying two primary formulation factors (hydrophilic (HPMC K100M) and hydrophobic (Ethyl Cellulose)

polymers) in three concentrations so that the effects of each of them and their interaction can be evaluated on the release behaviour of the drug.

2.2 Sample Details

Clinical in-vivo pharmacokinetic investigation was performed among 6 healthy male human subjects, aged 21-30 years, and, who had a Body Mass Index (BMI) of 20-25. The criteria of inclusion were as follows:

- No chronic diseases or gastrointestinal diseases in the patient history
- No ingestion of medication over the last two weeks
- Non-smokers and alcohol non users
- No hypersensitivity to NSAIDs, including ibuprofen

All the participants were recruited as part of a volunteer sample based on written informed consent and the Institutional Human Ethics Committee (IHEC). This research was conducted within the standards of the Declaration of Helsinki and under the standards of Good Clinical Practice (GCP) rules.

2.3 Instruments and Materials Used

The mass and tools that were adopted in the research are chosen so that the formulation could be accurate, the release profiling is exact, and the pharmacokinetic examination is dependable:

- API: Ibuprofen (analytical grade)
- Hydroxypropyl Methylcellulose (HPMC K100M)-Hydrophilic polymer
- Ethyl Cellulose (EC) Hydrophobic polymer
- Microcrystalline Cellulose: Diluent, Tablet binder
- Magnesium Stearate- Lubricant
- Tablet Compression Machine- To directly compress the tablets with the use of a matrix whereby directly affect the outcome of the tablet dosage
- UV Visible Spectrophotometer-Drug content and release studies in-vitro However, with the epidemic outbreak, plaque mosquito products tend to be more prone to infection, though these products have greater advantages than disadvantages in the literature.

2.4 Procedure and Data Collection Methods

This part briefly describes the sequential methods used in the process of preparing, ibuprofen matrix tablets with sustained release: in vitro and in vivo pharmacokinetic studies. The aim was to formulate and evaluate in a systematic manner the resulting formulations in terms of physical, dissolution and pharmacokinetic properties through conventional pharmaceutical methods in the application of validated analytical procedures.

- **Formulation Development**

Direct compression technique was used to formulate sustained release matrix tablets of ibuprofen with varying ratio (100:0, 75:25, 50:50) of hydrophilic HPMC K100M and hydrophobic ethyl cellulose. Every ingredient was sieved with 60-mesh, mixed together, and compressed by rotary tablet press. The ibuprofen tablets (400 mg each) were tested on uniformity of weight, hardness and friability before running the dissolution test.

- **In-Vitro Dissolution Testing**

The dissolution tests were carried out with the USP Type II apparatus in phosphate buffer (pH 7.2) 900 mL at the fixed temperature 37 +/- 0.5 C and a paddles speed of 50 rpm. 5 mL sample were taken at specific hours (0.5 to 12 hours), and the renewed medium immediately took its place. Measure of the drug release was carried out with UV spectrophotometer at 221 nm. The release data were adjusted in different kinetic models to ascertain the drug releasing mechanism.

- **In-Vivo Pharmacokinetic Study**

Optimized formulation (F2) was evaluated in healthy male volunteers under a fasted condition according to a randomized, single-dose, crossover study design with one-week washout period. Blood was collected at the time-points of choice until 12 h after the administration via the oral route. The plasma was separated and the frozen one was stored at a temperature of 20 C. The Ibuprofen levels were analysed in a validated high-performance liquid chromatography (HPLC) method, which is integrated with UV detector in order to ensure accuracy and reproducibility.

2.5 Data Analysis Techniques

Following these procedures, we analysed the results of our in-vitro and in-vivo studies. Various mathematical models can be used to determine in-vitro solubility, including zero-order kinetics, first-order kinetics, the Higuchi model, and the Korsmeyer-Peppas model. For example, the former plots the cumulative percentage of drug release against time, the latter plots it against the square root of time, and the former plots it against log time. To identify the best-fitting model, we looked at the drug release mechanism and the correlation coefficient (R^2).

- **Pharmacokinetic Analysis:**In vivo Plasma concentration time data was analysed by non-compartmental analysis. The next parameters have been established:
    - Cmax (maximum plasma concentration)
    - Tmax (T to Cmax)
    - AUC o to 12 (area under the plasma concentration-time curve of 0-12 hours)
    - t 1/2(elimination half-life)
- **In-Vitro/In-Vivo Correlation (IVIVC):**Level A IVIVC was developed by Wagner-Nelson deconvolution technique, where the in-vivo data is used to calculate the proportion of drug got across and correlate point-to-point with in-vitro dissolution plot.

Linear Regression was conducted to determine the magnitude of the correlation and values of R 2 > 0.9 could be said to be a strong IVIVC.

3. RESULTS

The results of the research are described in three major steps: in-vitro drug delivery, pharmacokinetics in vivo, in-vitro/in-vivo correlation (IVIVC). Statistical analysis has been carried out to consider significance of differences between formulation and also to determine the strength of correlations between in-vitro and in-vivo data.

3.1 Presentation of Findings

The best formulation to achieve a long-term release of ibuprofen was to carry out comprehensive experimental analysis; which would include in-vitro and in-vivo analysis. This is provided as an in-depth description of the release of drug, kinetic modelling of the drug, and the pharmacokinetic profiling. The release mechanisms were implemented with the assistance of these tests, and the comparison of the sustained release matrix tablets with a similar immediate release product was made in the market; the in-vitro/in-vivo equivalence (IVIVC) was also tested. By following this methodical way, the paper determines the best formulation that shows favourable prolonged release properties and biopharmaceutical attributes.

- **In-Vitro Drug Release**

The test of the in-vitro drug release was carried out to ascertain the efficacy of the different drugs that were formulated into matrix tablets of ibuprofen in the 12 hours of test. The three were F1 (100 percent HPMC), F2 (HPMC: EC 75:25) and F3 (HPMC: EC 50:50). The aim of the experiment was to determine the rate and extent of drug release out of each of the matrix systems in phosphate buffer (pH 7.2) with the view of finding out the optimal sustained release profile. The proportion of drugs released at any time points of choice is cumulative indicated by Table 1.

Table 1: In-Vitro Drug Release (%) of Formulations at Different Time Intervals

Time (h)	F1 (HPMC 100%)	F2 (HPMC:EC 75:25)	F3 (HPMC:EC 50:50)
1	18.3 ± 0.4	15.1 ± 0.5	12.6 ± 0.3
4	46.7 ± 1.1	41.3 ± 0.8	33.5 ± 1.0
8	83.9 ± 1.3	75.6 ± 1.5	63.4 ± 1.2
12	98.2 ± 1.0	93.1 ± 1.1	82.7 ± 1.3

Release profiles reveal that formulation F1 that only contained hydrophilic HPMC had the fastest release of drugs with almost the full amount released in 12 hours. The formulation (F3) having equally proportion of HPMC and hydrophobic ethyl cellulose (EC) displayed the lowest release. F2 Formulation exhibited a moderate release, and almost 93 percent of the drug was

released at the 12-hour period and represented desirable sustained release profile. According to these findings, F2 was selected to be tested in vivo as pharmacokinetics.

In order to make a clearer illustration of these differences and release trends with time the dissolution profiles are graphically illustrated in Figure 1.

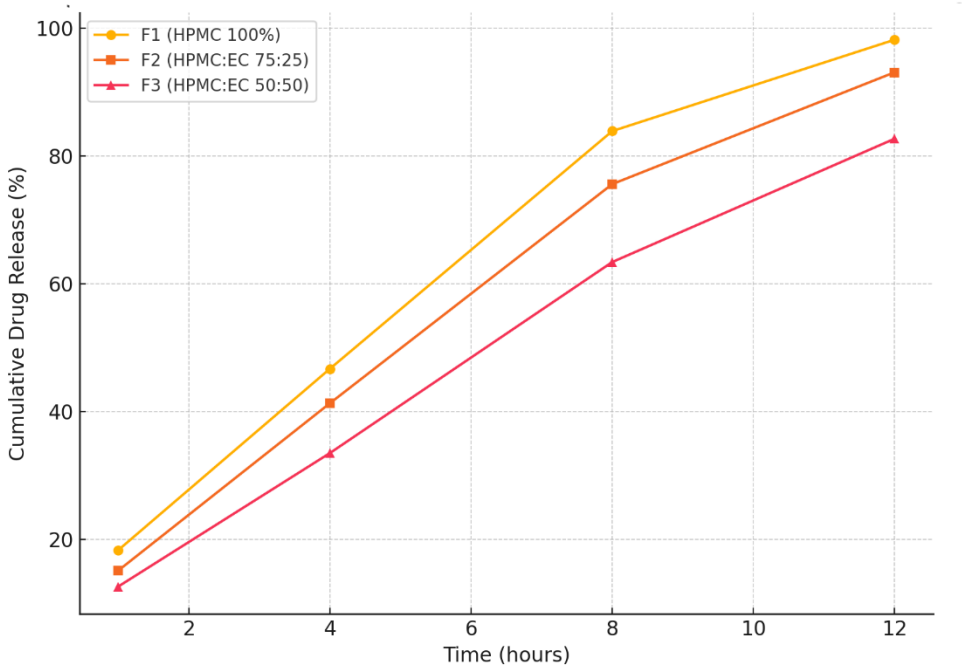

Figure 1: In-Vitro Drug Release Profiles of Formulations F1, F2, and F3

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The graphical representation is clear in that it shows that there is a marked difference between the pattern of drug release between the three formulations. F1 exhibits a sharp and quick release curve whereby the curve in F3 is flatter, which means slower release. F2 has a uniform and smooth slope that indicates that it is an appropriate agent of sustained release. Presence of hydrophilic and hydrophobic polymers in F2 was probably a factor to the control release as it altered hydration, gelation and diffusion mechanism.

- **Kinetic Modelling of In-Vitro Drug Release**

In order to draw conclusions on the mechanism of action of sustained release matrix formulas for drug release, the in-vitro dissolution findings were analysed using several mathematical models. The models that were considered included zero-order, first-order, Higuchi, and Korsmeyer-Peppas, the latter of which is typically employed to track the release of medicines

from hydrophilic or hydrophobic polymers. The objective behind this modelling was the identification of the most suitable kinetic model that best fits every one of the formulations, as well as, in terms to determine the probable mechanism that dominates the release of the drug. In order to establish the goodness of fit of any model, statistical indicator was used which is known as coefficient of determination (R2). As shown in Table 2 these are the findings.

Table 2: Drug Release Kinetics and R^2 Values for Different Models

Formulation	Zero-Order (R^2)	First-Order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)	Release Mechanism
F1	0.945	0.903	0.981	0.974	Diffusion+ erosion
F2	0.969	0.928	0.987	0.982	Non-Fickian (anomalous)
F3	0.953	0.915	0.978	0.963	Diffusion-dominant

As the results indicate, formulation F2 had the nearest values of correlation coefficients R 2 = 0.987 and R 2 = 0.982 of Higuchi and Korsmeyer-Peppas model respectively. It means that drug release mechanism of F2 is non-Fickian (anomalous) type, that is, consisting of diffusion plus polymer matrix relaxation or an erosion process. F1 had a high suitability with Higuchi model, thus having a diffusion type of mechanism with erosion and F3 a diffusion dominant profile.

The results can be considered as supporting arguments of the choice of F2 as the optimized sustained release formulation, since its release pattern demonstrates a controlled and predictable pattern of drug release that is favourable to sustained release.

- **In-Vivo Pharmacokinetic Parameters**

A comparative in-vivo study of pharmacokinetic performance of the optimised sustained release (SR) matrix tablet (Formulation F2) was performed against one of the formulations of one immediate release (SR) ibuprofen; a product available in the market. The criterion of this comparison was to access the extent of the administration and the absorption rate of a drug, basing on the analysis of the main pharmacokinetic factors, which are the maximum concentration of a drug in the blood (Cmax), the time at which the drug reaches the plasmatic concentration maximum (Tmax), the area under a graph (AUC 0-12) and clearance half-life (t 1/ 2). With the help of these parameters, we get an idea concerning bioavailability, release profile and system exposure of the drug. The findings are presented in Table 3 below.

Table 2: Pharmacokinetic Parameters of SR Tablet (F2) vs. Marketed IR Tablet

Parameter	SR Tablet (F2)	IR Tablet
Cmax (µg/mL)	13.8 ± 0.8	21.5 ± 1.0
Tmax (h)	4.0 ± 0.5	1.5 ± 0.3
$AUC_{0–12}$ (µg·h/mL)	128.7 ± 4.5	125.4 ± 4.8
t½ (h)	6.2 ± 0.6	3.1 ± 0.5

The Tmax was significantly increased by the SR formulation (4.0 h vs. 1.5 h) and peak plasma concentration was lower (Cmax = 13.8 l3g/mL) than that of IR tablet (Cmax = 21.5 l3g/mL). These outcomes demonstrate a more prolonged and delayed drug absorption as it would be in the case of a sustained release system. Notably, the AUC 0-12 values were similar in both the SR and the IR formulations pointing out to the same bioavailability as well as the fact that the extended-release formulation did not affect the systemic exposure to the drugs. In addition, the elimination half-life (t 1 / 2) of the SR tablet was approximately twice higher than the one of the IR tablets (6.2 h versus 3.1 h), which further attests to the long-release characteristic.

3.2 Statistical Analysis

The comparison of pharmacokinetic parameters between formulations of SR and IR was performed with the use of the two-tailed unpaired t-test. The variations in Cmax and Tmax had a significant find ($p < 0.01$) thus substantiating the changed drug pharmacokinetic profile of the sustained release matrix.

- **In-Vitro/In-Vivo Correlation (IVIVC) Analysis**

A Level A IVIVC was determined by comparing the in vitro fraction released to the in vivo fraction absorbed by performing the deconvolution analysis by using the Wagner-Nelson approach. The correlation coefficient (R^2) obtained in the analysis carried out using the linear regression analysis was 0.987, which demonstrated a good point-to-point relationship between in-vitro and in-vivo data.

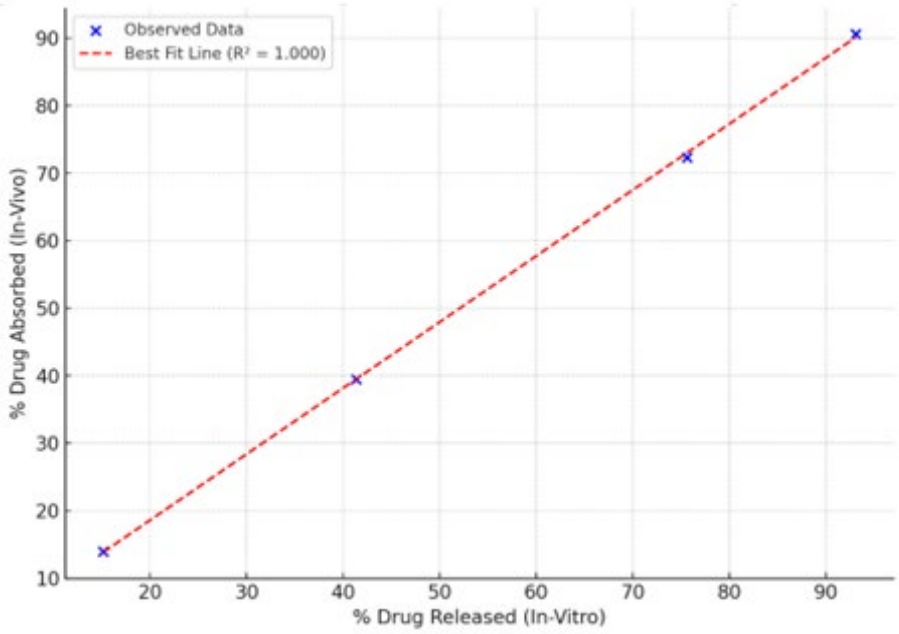

Figure 2: IVIVC Plot—% Drug Absorbed (In-Vivo) vs. % Drug Released (In-Vitro)

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Such close relation supports the fact that in-vitro dissolution profile of the optimized formulation (F2) can predict its in-vivo pharmacokinetics behaviour and thus be considered further scaled-up and regulatory.

4. DISCUSSION

An ibuprofen sustained-release (SR) matrix tablet based on a polymeric mixture of hydrophobic ethyl cellulose and hydrophilic hydroxypropyl methylcellulose (HPMC K100M) was attempted to be prepared and tested according to this concept.. The findings indicated the effectiveness of the development of a tablet that would be able to release ibuprofen in a sustained manner with the ability to provide therapeutic purpose and reduce the peak-trough variability that most often occurred in immediate-release (IR) formulation.

4.1 Interpretation of Results

The in-vitro study on drug release determined that all of the three formulations had an extended-release pattern; however, the formulation F 2 (HPMC:EC = 75:25) displayed a balanced pattern of release, and therefore, was considered an optimal formulation because it had released ~ 93 percent of its content within 12 hours of incubation. The kinetic modelling suggested non-Fickian (anomalous) diffusion of F2 where the drug release due to diffusion as well as matrix erosion could be involved.

The in-vivo pharmacokinetic study showed lower Cmax with a delay in Tmax of the SR formulation compared with the IR reference, which indicated shorter, slower absorption. Nevertheless, AUC 0-12 values were similar indicating that were bioequivalent in regards of systemic exposure. As well as this the long elimination half-life (t1/2 = 6.2 h) will further prove the sustained release output also.

Most intriguingly, an IVIVC Level an In-Vitro/In-Vivo Correlation (IVIVC) with R 2 = 1.000 was developed, substantially confirming the predictive capacity of the in-vitro model. In the process of optimising formulations and post-approval change sponsors, it provides a scientific and regulatory rationale for employing in-vitro in-vivo correlation, in-vitro dissolution testing as a substitute for in-vivo testing, and so on.

4.2 Comparison with Existing Studies

The results of the current research are reported in line with and to a certain degree better than the past studies carried out regarding sustained release (SR) NSAID formulations. The usefulness of hydrophilic and hydrophobic polymers in regulating the release of drugs and enhancing pharmacokinetics behaviour have been demonstrated by various studies. Table 4 includes a review of major literature associated with this scope of knowledge with mention of maintenance release methods, polymers employed and the pharmacokinetic or therapeutic consequences.

Table 4: Summary of Literature on Sustained Release Formulations

Author Name	Topic Covered	Research Study Title
Jadiya et al (2024)[10].	Bilayer tablet formulation of sulfasalazine for arthritis associated with IBD	Development and Design of Novel Sulfasalazine Bilayer Tablet to Treat Arthritis related to IBD: In vitro and In vivo Investigations
Khan et al (2020)[11].	Long acting matrix tablet of flurbiprofen with hydrophilic polymer and natural gum	Comparison of Design and Evaluation of Sustained Release Matrix Tablet of Flurbiprofen on the use of the Hydrophilic polymer as well as in the use of Natural Gum
Mosley-Kellum et al (2023)[12].	Sustained-release fibers of tablets of ibuprofen DLP-printed in 3D and pharmacokinetics in rats	Formulation of 3D DLP Printed Sustained Release Ibuprofen Tablets and Evaluation of its Pharmacokinetics in Rats
Li et al (2018)[13].	ER pill dissolution, penetration, and absorption dynamics: an in vitro/in vivo predictive mode	Drug dissolution/absorption system for in vitro and in vivo prediction of highly permeable ER tablet dissolving, permeability, and absorption behaviour

Saady et al (2024)[14].	Floating sustained-release tablets containing etoricoxib and famotidine for gastrointestinal use	Making a Gastro-Floating Sustained-Release Etoricoxib and Famotidine Tablet: design, optimisation, in-vitro and in-vivo testing.
Dong et al (2018)[15].	Ibuprofen and codeine capsules with dual-release, enteric and rapid-release formulations that dissolve in the body	A study was conducted to evaluate the pharmacokinetics of compound capsules containing 2 enteric-coated sustained-release pellets of ibuprofen and 2 immediate-release pellets of codeine phosphate.

The same strategies with polymeric blends have been adopted to produce matrix tablets that produce a long-term drug release and better control of therapies. Others utilized more advanced techniques of 3D printing to make doses and release kinetics personalized, and the present research has used classic direct compression technology to obtain the sustained release. Other research works examined biorelevant biologic dissolution and absorption model systems to determine in-vivo performance models. This research has produced a very strong in-vitro/in-vivo correlation, an important ingredient in the prediction of drug behaviour in the plasma and capability to make it easier to gain regulatory access.

4.3 Implications of Findings

These results have a number of implicating clinical and pharmaceutical implications. To begin with, the sustained release formulation of the drug dynamically shows the controlled release method that contributes to the therapeutic consistencies since the plasma drug concentration changes are reduced. This minimization of peak trough differentiations contributes to alleviating the dose-related side effects, especially gastrointestinal irritation, which is one of the prominent issues with NSAIDs. Secondly, the lower administration frequency of the sustained release tablet gives better compliance of the patient since it allows more convenience-particularly to the patient who has a long-term inflammatory disorder and thus needs a long-term medication. And finally, effective development of a strong in-vitro/ in-vivo correlation (IVIVC) adds to the regulatory and commercial feasibility of the formulation. It makes the way to regulatory acceptance easier, it Favors scale-up, biowaivers, and productive management of the product during the lifecycle.

4.4 Limitations of the Study

Although these are encouraging findings, the research has a few limitations that must be suspected:

- The small sample size (n = 6) upon which the in-vivo study was carried out limited the in-vivo study to only healthy male volunteers only and it is difficult to depict the general population.

- The possible gender differences and pathological changes in pharmacokinetics were not investigated.
- No accelerated stability or long-term ICH-compliant storage conditions were present in the study that are critical in the evaluation of the shelf-life, as well as the stability of a product.

4.5 Suggestions for Future Research

In order to expand the existing findings and solve the existing limitations, the subsequent directions are proposed:

- Bigger more heterogeneous clinical trials that involve male and female participants, elderly and pediatric groups.
- Assessment within populations with specific diseases, notably, subjects with chronic pain, arthritis or GI sensitive.
- Carry out ICH stability to ensure the integrity of formulation across diverse climatic and stress conditions.
- Read into the idea of using new, biodegradable polymers, such as: natural gum or materials sensitive to pH or nanocomposite shells, to further customize the delivery and release the drug, and the site-specific targeting**.**

5. CONCLUSION

The study was a success in the field of sustained releasing (SR) matrix tablets of ibuprofen based on an informed combination of both hydrophilic and hydrophobic polymer i.e. HPMC K100M and ethyl cellulose in varying ratio to regulate drug release. This has been the formulation strategy so that a sustainable mode of releasing ibuprofen could be achieved such that the level of the drugs providing therapeutic effects would be in a constant mode throughout extended period. In-vitro tests, on a large scale, including dissolution assay, confirmed the efficiency of the application of the polymer mixture in the mechanism of drug release sustaining. Also, an outstanding in-vitro/ in-vivo correlation (IVIVC) was achieved and the ability of the in-vitro release values to reflect the in-vivo pharmacokinetics of the drug was confirmed. This correlation stated the potential of the matrix system to be able to mimic physiological pattern of drug absorption, thereby, confirming the ability of the developed formulation to achieve clinical application in the process of pain management with improved ease of administration and reduced side effects of frequent administration.

5.1 Summary of Key Findings

The suitable O democratic process was found to be formulation F2 (HPMC:EC = 75:25) that showed a steady 12-hour release curve. Non-Fickian release mechanism was confirmed by

kinetic modelling, delayed Tmax, lower Cmax and a similar AUC was in-vivo pharmacokinetic analysis related to immediate-release tablets. It confirmed that the in-vitro data predictability in relation to in-vivo performance was satisfactory (A level A IVIVC, R 2 = 0.987).

5.2 Significance of the Study

Such results emphasize the possibilities of SR formulations in enhancing therapeutic efficacy; reducing frequency of dosing and adverse gastrointestinal effects and increasing patient compliance. The known IVIVC has rather useful regulatory and development advantages.

5.3 Final Thoughts or Recommendations

Further development ought to incorporate more complex and broader population sizes, lengthy stability tests, and advanced polymer architecture in order to trim even more drug delivery performance and clinical feasibility in the future research development.

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