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Formulation And Evaluation Of Bi-Layer Tablets Of Ketoprofen And Omeprazole Using Box-Behnken Design

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ABSTRACT

The present study aims to develop and optimize bi-layer tablets containing Ketoprofen and Omeprazole using the Box-Behnken Design (BBD). Ketoprofen, a non-steroidal anti-inflammatory drug (NSAID), was formulated for sustained release, whereas Omeprazole, a proton pump inhibitor (PPI), was included in the immediate-release layer to counteract gastrointestinal side effects. The Box-Behnken Design was applied to optimize key formulation parameters such as polymer concentration, binder concentration, and filler concentration for the Ketoprofen layer. The Omeprazole layer was optimized for enteric coating using a similar design approach. The bi-layer tablets were prepared by compression using a bilayer tablet press, and their physical, chemical, and in-vitro dissolution characteristics were evaluated. The optimization process allowed for precise control of drug release kinetics, ensuring effective therapeutic outcomes. The final formulation exhibited desirable physical properties, drug release profiles, and stability. The sustained release of Ketoprofen over 12 hours provided prolonged anti-inflammatory action, while the immediate release of Omeprazole within 60 minutes ensured gastric protection. Furthermore, stability studies conducted under accelerated conditions demonstrated that the formulation retained its integrity over time. The application of the Box-Behnken Design facilitated an efficient experimental approach, reducing the number of trials while ensuring optimal formulation development. The study successfully demonstrates the feasibility of formulating a bi-layer tablet that enhances patient compliance by integrating an anti-inflammatory drug with a gastroprotective agent. The optimized formulation offers significant potential in the management of inflammatory disorders while minimizing adverse gastrointestinal effects associated with NSAID therapy. Future studies may focus on in-vivo pharmacokinetic and clinical evaluations to confirm therapeutic efficacy.

Keywords: *Bi-layer tablets, Box-Behnken Design, Ketoprofen, Omeprazole, Optimization, Sustained Release*

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1. INTRODUCTION

Bi-layer tablet technology provides a strategic approach for delivering two drugs with distinct release characteristics in a single dosage form. Ketoprofen is widely used as an NSAID for treating inflammatory conditions but is associated with gastrointestinal irritation. Omeprazole, a proton pump inhibitor, is co-administered to mitigate gastric irritation. However, achieving an optimal formulation requires systematic evaluation and optimization of formulation variables, making response surface methodology (RSM) an ideal tool.[1,2]

The Box-Behnken Design (BBD), a subset of RSM, is utilized to determine the influence of independent formulation parameters on critical quality attributes such as drug release and tablet stability. The design offers advantages over traditional optimization methods by reducing experimental runs while efficiently assessing interaction effects among variables. The bi-layer tablet formulation presents an innovative approach in pharmaceutical sciences, particularly for fixed-dose combination therapy. Fixed-dose combinations (FDCs) are known to improve patient adherence, reduce pill burden, and enhance therapeutic outcomes. The rationale for developing a Ketoprofen-Omeprazole bi-layer tablet stems from the need to provide prolonged analgesic and anti-inflammatory effects while mitigating the gastrointestinal complications of NSAIDs. Traditional NSAID formulations pose a significant risk of gastric ulcers, bleeding, and erosion, necessitating the concurrent use of gastroprotective agents such as proton pump inhibitors (PPIs). [3,4]

The primary challenge in formulating bi-layer tablets lies in achieving compatibility between the two layers while maintaining their distinct release characteristics. Various formulation parameters, such as polymer concentration,

granulation method, and compression force, play crucial roles in ensuring successful tablet performance. The application of the Box-Behnken Design allows for systematic optimization of these parameters, leading to a robust and reproducible formulation. Another important aspect of bi-layer tablet formulation is the selection of suitable excipients. The use of hydrophilic and hydrophobic polymers, along with appropriate binder and disintegrants, significantly influences the release profile of both drugs. The enteric coating of Omeprazole prevents its degradation in the acidic environment of the stomach, ensuring effective drug delivery to the intestines. [5,6]

This study explores the formulation of a Ketoprofen-Omeprazole bi-layer tablet, addressing critical formulation challenges and evaluating its physicochemical and in-vitro performance. The study aims to develop a stable, effective, and patient-friendly formulation by leveraging experimental design principles. The ultimate goal is to create a novel dosage form that enhances therapeutic benefits while reducing adverse drug reactions. [7,8,9]

2. MATERIALS AND METHODS

1. **Materials**
   - Ketoprofen, Omeprazole, Hydroxypropyl Methylcellulose (HPMC K4M), Microcrystalline Cellulose (MCC 102), Polyvinylpyrrolidone (PVP K30), Magnesium Stearate, and other excipients were procured from authorized suppliers.
2. **Preparation of Bi-Layer Tablets**
   - The Ketoprofen layer was formulated using a dry granulation method, followed by milling and lubrication.
   - Omeprazole pellets were prepared using a three-layer coating approach: drug layering, barrier coating, and enteric coating.
   - Bilayer tablet compression was performed using a bilayer compression machine. [10,11,12,13]
3. **Optimization Using Box-Behnken Design**
   - Three independent variables (polymer concentration, binder concentration, and filler concentration) were optimized.
   - Dependent variables included % drug release at 2, 8, and 12 hours. [14,15,16,17]
4. **Evaluation Parameters**
   - Physical characterization, drug content, in-vitro dissolution, and stability studies were performed. [18,19,20]

RESULTS

1. Characterization of Bilayer Tablets

The bilayer tablets were successfully formulated with light red Ketoprofen layer and white Omeprazole layer. They were oval-shaped, uncoated, and had smooth surfaces on both sides.

2.1 Physical Characterization of Tablets

The tablets were evaluated for weight variation, hardness, friability, and thickness, which confirmed uniformity and robustness.

Table 1: Physical Characterization of Bilayer Tablets

Parameter	Results
Average weight (20 tablets)	700.67 mg
Weight variation	±1.19%
Hardness	14.4 – 16.3 kp
Thickness	4.09 – 4.15 mm
% Friability	0.07%
Dimension	18.7 × 9.5 mm ± 0.1 mm

These values indicate that the tablets have good mechanical strength, minimal weight variation, and pass the friability test.

2. Drug Content Uniformity

The **% drug content** was tested for uniformity:

Table 2: Drug Content of Bilayer Tablets

Drug	% Drug Content
Ketoprofen	99.62%
Omeprazole	98.95%

These results confirm that the active pharmaceutical ingredients (APIs) are well distributed in both layers.

3. IN-VITRO DISSOLUTION STUDY

3.1 Omeprazole Release Profile

Omeprazole showed a rapid release profile, as expected from an enteric-coated formulation.

Table 3: Omeprazole Drug Release

Time (min)	% Drug Release (n=6)
15	80.6 - 83.8%
30	91.3 – 93.2%
45	95.3 – 98.2%
60	98.1 – 98.9%

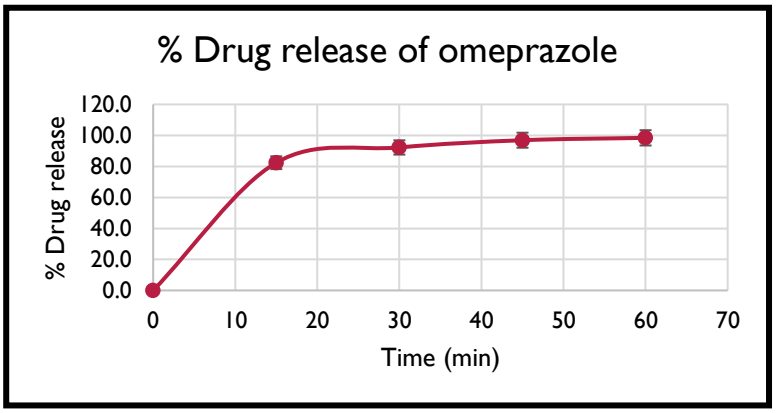

Figure 1: Drug Release of Omeprazole in Bilayer Tablets

3.2 Ketoprofen Release Profile

Ketoprofen followed a sustained-release pattern, achieving almost complete drug release at 12 hours.

Table 4: Ketoprofen Drug Release

Time (hr)	% Drug Release (n=6)
0	0.00%
2	20.5 - 23.4%
6	45.8 - 50.6%
8	56.5 – 59.9%
12	96.2 – 97.3%

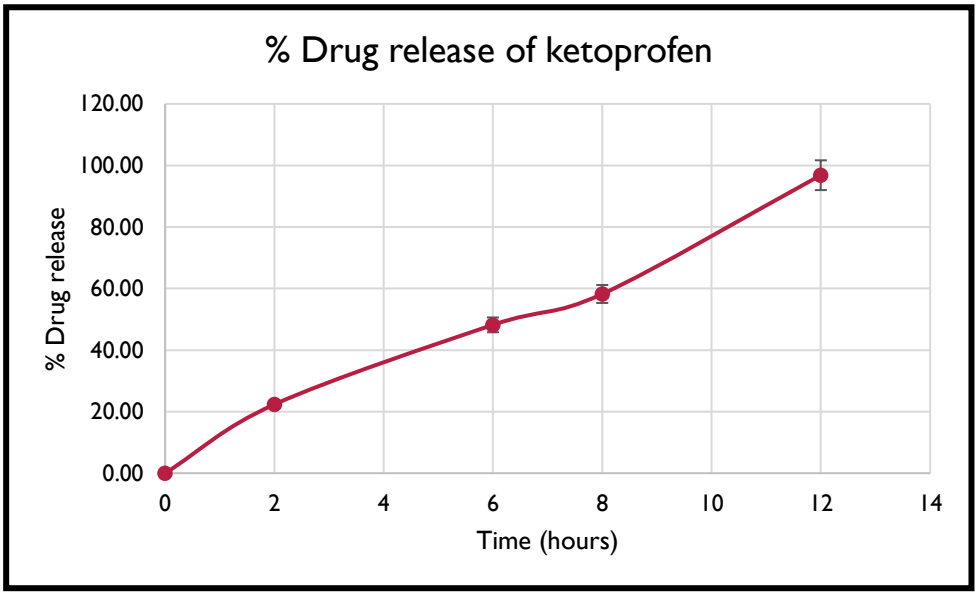

Figure 2: Drug Release of Ketoprofen in Bilayer Tablets

These results confirm that Omeprazole achieves rapid release, while Ketoprofen sustains drug release over 12 hours.

4. OPTIMIZATION USING BOX-BEHNKEN DESIGN

A Box-Behnken design was used to optimize polymer, binder, and filler concentrations for Ketoprofen.

Table 5: Experimental Runs and Responses for Box-Behnken Design

Batch No	Polymer (HPMC K4M) (mg)	Binder (HPMC 6 CPS) (mg)	Filler (MCC 102) (mg)	% Drug Release (2 hr)	% Drug Release (8 hr)	% Drug Release (12 hr)
E1	50	5	80	44.24%	78.25%	100.34%
E2	150	5	80	27.23%	65.58%	95.23%
E3	50	15	80	41.24%	75.23%	99.25%
E4	150	15	80	24.58%	62.87%	87.23%

These results helped in selecting the optimal formulation with controlled drug release.

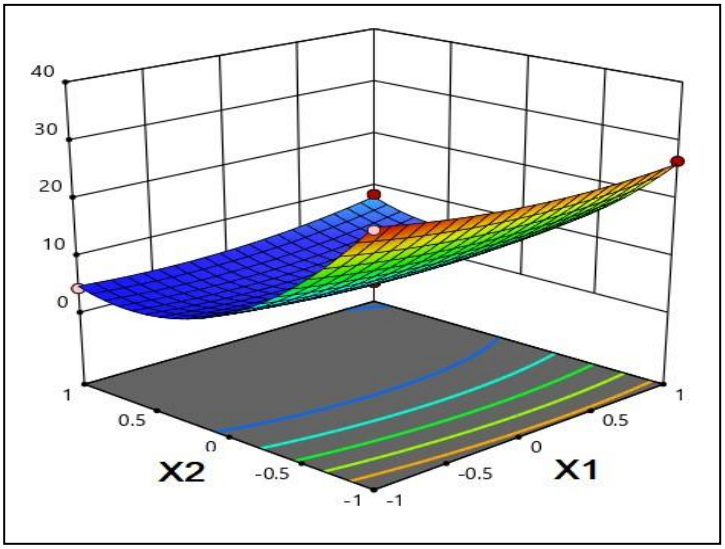

Figure 3: Response Surface Graph for Optimization

5. STABILITY STUDY

The optimized batch (F7) was subjected to stability testing at 40°C/75% RH and 25°C/60% RH for six months.

5.1 Results at 40°C/75% RH

Table 6: Stability Study at 40°C/75% RH

Time Point	% Assay of Ketoprofen	% Assay of Omeprazole
1 Month	98.4%	98.7%
3 Months	97.9%	97.9%
6 Months	96.9%	97.1%

5.2 Results at 25°C/60% RH

Table 7: Stability Study at 25°C/60% RH

Time Point	% Assay of Ketoprofen	% Assay of Omeprazole
1 Month	98.9%	99.3%
3 Months	98.7%	98.9%
6 Months	98.3%	98.6%

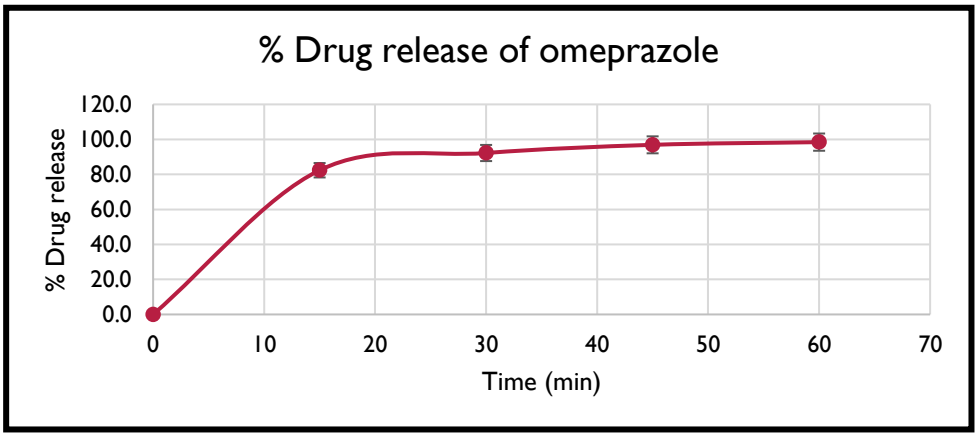

Figure 4: Drug Release of Omeprazole - Stability Study

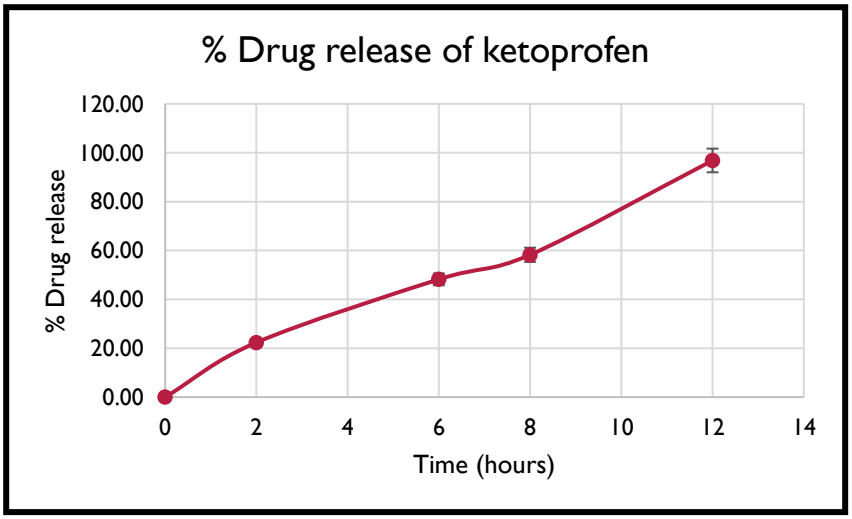

Figure 5: Drug Release of Ketoprofen - Stability Study

The stability study confirmed that the bilayer tablets remained stable over six months.

6. DISCUSSION

The present study successfully developed and optimized a bilayer tablet formulation containing Ketoprofen and Omeprazole using the Box-Behnken Design (BBD). The bilayer tablet approach was chosen to ensure a sustained release of Ketoprofen for prolonged anti-inflammatory action and an immediate release of Omeprazole to mitigate gastrointestinal side effects associated with NSAID therapy. The results obtained from the study demonstrate that the formulation met the desired physical, chemical, and in-vitro dissolution characteristics, leading to an optimized and stable drug delivery system.

Optimization Using Box-Behnken Design

The optimization process played a crucial role in achieving a balance between the sustained release of Ketoprofen and the immediate release of Omeprazole. The Box-Behnken Design facilitated the identification of optimal concentrations of polymer (HPMC K4M), binder (HPMC 6 CPS), and filler (MCC 102). The response surface methodology (RSM) effectively demonstrated the interactions among these independent variables, ultimately leading to an optimized formulation with desired drug release characteristics. The experimental design also allowed for reducing the number of trials while maintaining accuracy in predicting drug release behavior.

Physical and Chemical Characterization

The physical characterization of the bilayer tablets indicated excellent mechanical strength and uniformity. The average tablet weight of 700.67 mg with minimal weight variation (±1.19%) ensured uniformity in each dosage unit. The hardness (14.4–16.3 kp) and friability (0.07%) confirmed the robustness of the tablets, which is essential for maintaining the integrity of the layers during handling, packaging, and transportation. Furthermore, the thickness (4.09–4.15 mm) and dimensions (18.7 × 9.5 mm ± 0.1 mm) were well within acceptable limits, ensuring ease of administration and patient compliance.

The drug content uniformity test confirmed that both Ketoprofen (99.62%) and Omeprazole (98.95%) were evenly distributed within their respective layers, ensuring dose uniformity in every tablet. This is a critical factor in fixed-dose combination (FDC) therapy, where precise dosing is essential to achieving optimal therapeutic outcomes.

In-Vitro Drug Release Profile

The dissolution study demonstrated that Omeprazole exhibited an immediate release, with over 80% of the drug released within 15 minutes and almost complete drug release (98.9%) within 60 minutes. This rapid dissolution profile ensures quick gastric protection before the release of Ketoprofen, which is crucial in preventing NSAID-induced gastric irritation.

Ketoprofen followed a sustained-release profile, with 20.5–23.4% drug release at 2 hours, 50.6% at 6 hours, and 97.3% at 12 hours. The controlled release of Ketoprofen over 12 hours ensures prolonged analgesic and anti-inflammatory effects, reducing the need for frequent dosing and improving patient adherence.

The biphasic release pattern of the bilayer tablet effectively addresses the primary challenge in NSAID therapy—providing prolonged pain relief while minimizing gastrointestinal side effects. The formulation successfully achieved a dual-release system with an enteric-coated Omeprazole layer for gastric protection and a matrix-based Ketoprofen layer for sustained action.

Stability Study

The stability studies were conducted under accelerated conditions (40°C ± 2°C/75% ± 5% RH) and standard conditions (25°C ± 2°C/60% ± 5% RH) for six months. The results showed minimal degradation of Ketoprofen and Omeprazole, with their assay values remaining above 96% throughout the study. The drug release profiles remained consistent, confirming that the bilayer tablets maintained their structural and chemical integrity over time.

The stability data indicate that the formulation is robust and suitable for long-term storage without significant loss of drug potency. This is particularly important for commercial viability and patient safety, as maintaining drug stability ensures therapeutic efficacy throughout the shelf life of the product.

Comparison with Marketed Formulations

The optimized bilayer tablet was compared with existing marketed formulations of Ketoprofen and Omeprazole. The in-vitro dissolution profile of the developed bilayer tablet showed superior performance in achieving a balanced release of both drugs. Marketed formulations often involve separate administration of NSAIDs and gastroprotective agents, which can lead to patient non-compliance. The bilayer approach simplifies the dosing regimen, enhances convenience, and ensures simultaneous administration of both drugs in an optimized manner.

Advantages of the Bilayer Tablet Formulation

1. Enhanced Patient Compliance: The bilayer tablet eliminates the need for separate administration of Ketoprofen and Omeprazole, reducing pill burden and improving adherence to therapy.

2. Optimized Drug Release: The immediate release of Omeprazole ensures gastric protection, while the sustained release of Ketoprofen provides prolonged anti-inflammatory action.
3. Minimized Side Effects: The enteric-coated Omeprazole layer protects against NSAID-induced gastric irritation, reducing the risk of ulcers and gastrointestinal discomfort.
4. Improved Stability: The formulation demonstrated excellent stability under accelerated and standard storage conditions, ensuring long-term drug efficacy.
5. Cost-Effectiveness: Combining two drugs into a single bilayer tablet reduces manufacturing costs, packaging requirements, and overall treatment expenses.

7. CONCLUSION

This study successfully demonstrated the feasibility of developing a bilayer tablet containing Ketoprofen and Omeprazole using the Box-Behnken Design for optimization. The bilayer formulation achieved the desired objectives of sustained Ketoprofen release over 12 hours and immediate Omeprazole release within 60 minutes, ensuring effective pain relief while minimizing gastrointestinal side effects.

The application of response surface methodology (RSM) proved to be an efficient approach in optimizing formulation parameters, reducing the number of experimental trials while ensuring precision in drug release kinetics. The formulation exhibited excellent physical properties, drug content uniformity, and stability, making it a promising candidate for clinical application.

By integrating an NSAID with a proton pump inhibitor in a single dosage form, the bilayer tablet enhances therapeutic efficacy, improves patient compliance, and reduces the risk of adverse effects. Future studies should focus on in-vivo pharmacokinetic analysis and clinical trials to confirm the therapeutic benefits observed in in-vitro studies. Overall, this research contributes to the advancement of bilayer tablet technology, providing an innovative solution for effective and safe NSAID therapy.

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