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Research Article

Formulation and Evaluation of Sustained Release Matrix Tablets of Apremilast Using Different Polymers

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ABSTRACT

The present study was aimed at the formulation and evaluation of sustained release matrix tablets of Apremilast using hydrophilic polymers to improve therapeutic efficacy and patient compliance. Apremilast is a phosphodiesterase-4 (PDE4) inhibitor used in the treatment of psoriasis and psoriatic arthritis, but its short half-life requires frequent administration. To overcome this limitation, sustained release matrix tablets were prepared by the direct compression method using polymers such as HPMC K4M and HPMC K15M. Preformulation studies including organoleptic properties, solubility study, melting point determination, UV spectrophotometric analysis, and drug–excipient compatibility studies were performed. The prepared formulations were evaluated for pre-compression and post-compression parameters such as angle of repose, bulk density, hardness, friability, drug content, and in vitro dissolution studies. All formulations showed satisfactory pharmaceutical properties within acceptable limits. Dissolution studies demonstrated that polymer concentration significantly affected drug release behavior. Among all formulations, batch F5 showed optimized sustained drug release up to 12 hours with acceptable hardness, friability, and drug content. Drug release kinetics followed Higuchi and Korsmeyer–Peppas models, indicating diffusion-controlled release. Stability studies conducted according to ICH guidelines confirmed the stability of the optimized formulation under accelerated conditions. The study concluded that sustained release matrix tablets of Apremilast can be successfully developed using hydrophilic polymers for prolonged drug delivery.

INTRODUCTION

Introduction to Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by abnormal proliferation and differentiation of keratinocytes, leading to the formation of thick, erythematous, and scaly plaques on the skin. It is a multifactorial disease influenced by genetic, immunological, and environmental factors. The

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disease commonly affects the scalp, elbows, knees, lower back, and nails, and in severe conditions it may also involve joints, resulting in psoriatic arthritis. Psoriasis affects approximately 2–3% of the global population and significantly impacts the physical, psychological, and social well-being of patients [1].

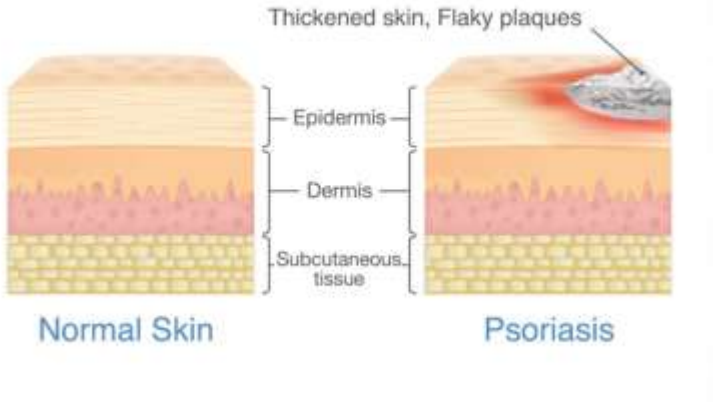

Figure 1: Comparison between normal skin and psoriatic skin

The exact pathogenesis of psoriasis is complex and involves dysregulation of the immune system. Activated T-lymphocytes release inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-17 (IL-17), and Interleukin-23 (IL-23), which stimulate rapid multiplication of skin cells. This accelerated cell turnover results in accumulation of immature keratinocytes on the skin surface, producing characteristic psoriatic lesions.

Among the modern therapeutic agents used in psoriasis treatment, Apremilast has gained considerable attention due to its targeted mechanism of action and favorable safety profile. Apremilast is an orally active selective phosphodiesterase-4 (PDE4) inhibitor that regulates intracellular cyclic adenosine monophosphate (cAMP) levels and suppresses inflammatory mediators responsible for psoriasis progression [3].

Apremilast and Its Therapeutic Importance

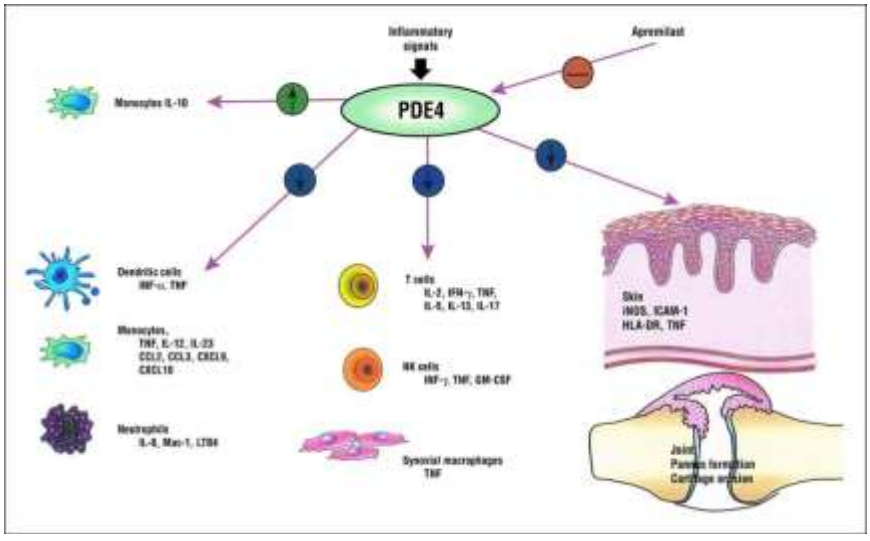

Figure 2: Mechanism of Action of Apremilas

By inhibiting PDE4 enzyme activity, Apremilast decreases the production of pro-inflammatory cytokines such as TNF-α, IL-17, IL-23, and interferon-gamma while increasing anti-inflammatory cytokines like IL-10. Due to this mechanism, Apremilast effectively reduces inflammation and improves clinical symptoms in patients with moderate to severe plaque psoriasis and psoriatic arthritis [4].

Despite its therapeutic advantages, Apremilast possesses certain limitations such as:

- Short biological half-life (6–9 hours)
- Requirement of twice-daily administration
- Fluctuation in plasma drug concentration
- Reduced patient compliance during long-term therapy

These limitations necessitate the development of a sustained release dosage form capable of maintaining prolonged therapeutic drug levels and reducing dosing frequency [5].

Sustained Release Drug Delivery System

Sustained release (SR) drug delivery systems are designed to release the drug slowly and continuously over an extended period of time, thereby maintaining constant plasma drug concentration within the therapeutic range. These systems improve therapeutic efficacy, minimize side effects, reduce dosing frequency, and enhance patient compliance [6].

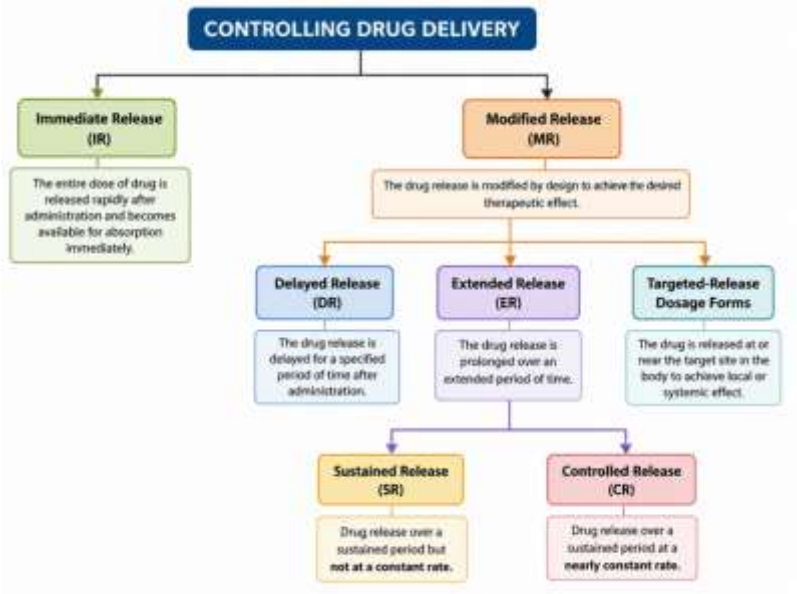

Figure 3: Classification of Controlled and Modified Drug Delivery Systems

Among various controlled release approaches, matrix tablet systems are widely preferred because of:

- Simple manufacturing process
- Cost-effectiveness
- Better reproducibility
- Ease of scale-up
- Ability to accommodate various drugs and polymers [7]

In matrix tablets, the drug is dispersed uniformly within a polymer matrix. Upon contact with gastrointestinal fluids, the polymer hydrates and forms a gel barrier around the tablet. Drug release

occurs through diffusion, swelling, and erosion mechanisms [8].

Role of Polymers in Sustained Release Formulation

Polymers play a crucial role in controlling the release behavior of drugs from sustained release systems. Hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC) swell upon hydration and form a viscous gel layer that regulates drug diffusion. Hydrophobic polymers such as Ethyl Cellulose retard penetration of dissolution media and prolong drug release [9].

The present study utilizes polymers such as:

- HPMC K4M
- HPMC K15M
- HPMC K100M
- Carbopol 934
- Xanthan Gum
- Ethyl Cellulose

These polymers were selected based on their swelling behavior, gel-forming capacity, viscosity, and ability to sustain drug release over an extended duration [10].

Need for the Present Study

Although Apremilast is clinically effective in psoriasis management, frequent administration decreases patient adherence and may produce fluctuations in therapeutic response. Development of sustained release matrix tablets can overcome these limitations by:

- Extending drug release up to 12 hours
- Reducing dosing frequency
- Improving patient compliance
- Minimizing side effects
- Maintaining consistent plasma drug concentration [11]

Therefore, the present investigation focuses on the formulation and evaluation of sustained release matrix tablets of Apremilast using different polymer combinations.

Goals of the Research

The major goals of the present research work are:

1. To formulate sustained release matrix tablets of Apremilast using suitable polymers.
2. To evaluate physicochemical and pre-compression properties of the drug and excipients.
3. To study the effect of polymer concentration on drug release behavior.
4. To evaluate prepared tablets for hardness, friability, drug content, and dissolution profile.
5. To optimize the formulation based on sustained drug release characteristics.
6. To study release kinetics and mechanism of drug release.
7. To perform stability studies as per ICH guidelines.

Research Objectives

- To enhance patient compliance by reducing dosing frequency.

- To maintain prolonged therapeutic drug concentration.
- To achieve controlled and sustained drug release for up to 12 hours.
- To develop a stable and effective oral sustained release formulation of Apremilast.

The development of sustained release matrix tablets of Apremilast represents an important approach for improving therapeutic effectiveness and patient adherence in the management of psoriasis. By employing suitable hydrophilic and hydrophobic polymers, controlled drug release can be achieved effectively. The present study aims to formulate and evaluate an optimized sustained release matrix tablet capable of providing prolonged drug release with acceptable pharmaceutical characteristics [12].

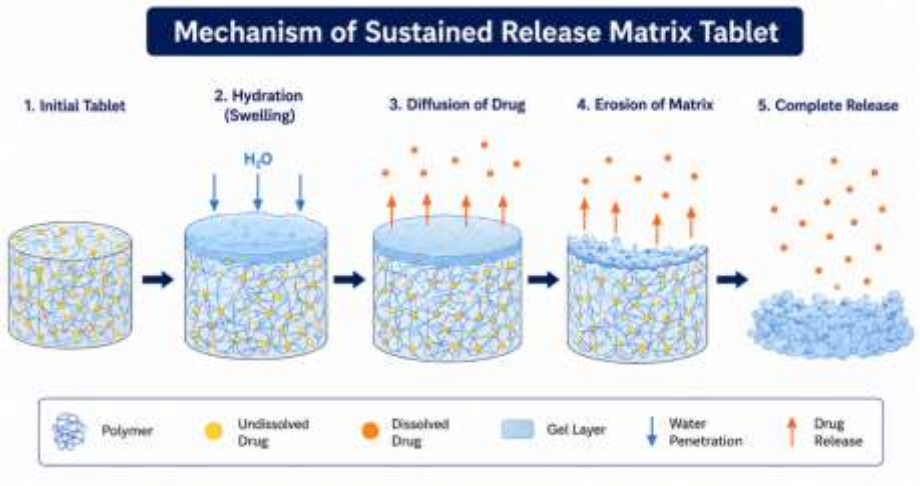

Figure 4: Classification of Controlled and Modified Drug Delivery Systems

MATERIALS AND METHODS

Materials

Apremilast was obtained as a gift sample and used as the active pharmaceutical ingredient (API) for the preparation of sustained release matrix tablets. Hydroxypropyl methylcellulose polymers such as HPMC K4M and HPMC K15M were used as release-retarding agents. Microcrystalline cellulose (MCC) and lactose were used as diluents, while magnesium stearate and talc were used as lubricant and glidant respectively. All chemicals and reagents used in the study were of analytical grade.

Methods

Preformulation Studies

Preformulation studies of Apremilast were carried out to evaluate its physicochemical properties and compatibility with excipients. The following studies were performed:

- Organoleptic evaluation (color, odor, appearance)
- Solubility study in various solvents
- Melting point determination by capillary method
- Determination of λmax using UV–Visible spectrophotometry
- Drug–excipient compatibility study using FTIR spectroscopy

- Evaluation of powder flow properties including angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio

Formulation of Sustained Release Matrix Tablets

Sustained release matrix tablets of Apremilast were prepared by the direct compression method. Accurately weighed quantities of drug, polymers, and excipients were passed through sieve no. 60 and blended uniformly. Magnesium stearate and talc were added at the final stage as lubricant and glidant. The prepared blend was compressed into tablets using a rotary tablet compression machine.

Evaluation of Powder Blend

The prepared powder blends were evaluated for pre-compression parameters including:

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner ratio

Evaluation of Tablets

The compressed tablets were evaluated for post-compression parameters such as:

- Thickness
- Hardness
- Friability
- Weight variation
- Drug content uniformity

In-vitro Dissolution Study

In-vitro drug release studies were carried out using USP Type II dissolution apparatus (paddle method). The dissolution medium consisted of 900 mL phosphate buffer pH 6.8 maintained at 37 ± 0.5°C with a paddle speed of 50 rpm. Samples were withdrawn at predetermined intervals up to 12 hours and analyzed spectrophotometrically at 268 nm.

Stability Studies

The optimized formulation was subjected to accelerated stability studies according to ICH guidelines at 40°C ± 2°C and 75% ± 5% RH for a period of three months. Samples were evaluated periodically for physical appearance, hardness, friability, drug content, and dissolution profile.

RESULTS & DISCUSSIONS

The present study was aimed at the formulation and evaluation of sustained release matrix tablets of Apremilast using different polymers. The results obtained from preformulation studies, formulation development, evaluation parameters, dissolution studies, kinetic modeling, and stability studies are discussed in detail.

Preformulation Studies

Preformulation studies were carried out to evaluate the physicochemical properties of Apremilast and its suitability for sustained release matrix tablet formulation.

Organoleptic Properties

The organoleptic properties of Apremilast were examined visually for color, odor, and appearance.

Table1: Organoleptic Properties of Apremilast

Parameter	Observation
Color	White to pale yellow
Odor	Odorless
Appearance	Crystalline powder

The drug appeared as a white to pale yellow crystalline powder with no characteristic odor. These observations complied with the standard characteristics reported for Apremilast, indicating purity and suitability for formulation development.

Solubility Study

Table 2: Solubility Study

Solvent	Solubility
Water	Slightly soluble
Methanol	Soluble
Ethanol	Freely soluble
pH 6.8 Buffer	Moderately soluble

The poor aqueous solubility suggests that dissolution may be a limiting step in drug absorption. However, moderate solubility in intestinal pH indicates that drug release can be effectively controlled in the gastrointestinal tract.

This supports the development of a sustained release system, where controlled dissolution enhances therapeutic effectiveness.

Melting Point

The melting point was found to be 156–158°C. The observed melting point is within the reported range, confirming the purity and identity of the drug.

λmax Determination

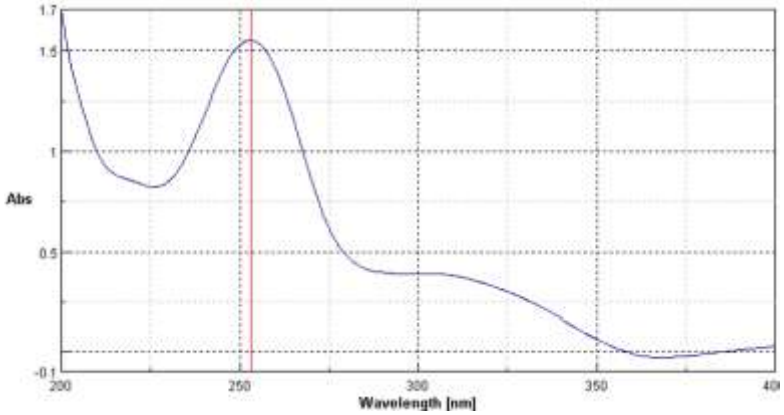

Figure 5: λmax Determination

Apremilast showed maximum absorbance at 268 nm. This wavelength was selected for further analytical studies including drug content estimation and dissolution analysis. The sharp peak confirmed good absorbance behavior and analytical suitability.

Drug–Excipient Compatibility Study

FTIR studies were performed to evaluate compatibility between Apremilast and excipients.

Table 3: FTIR Compatibility Study

Functional Group	Pure Drug Peak (cm^{-1})	Drug-Excipient Mixture (cm^{-1})
C=O Stretching	1760	1758
N-H Stretching	3360	3358
S=O Stretching	1145	1143

No significant shifting or disappearance of characteristic peaks was observed in drug-excipient mixtures. This confirmed compatibility between Apremilast and selected polymers/ excipients.

Evaluation of Tablets

Post-Compression Evaluation

Table 4: Post-Compression Evaluation

Formulation	Hardness (kg/cm²)	Friability (%)	Drug Content (%)
F1	5.2	0.6	98
F2	5.5	0.5	99
F3	5.8	0.5	99
F4	5.3	0.6	98
F5	5.6	0.5	99
F6	5.9	0.5	99

The hardness values ranged from 5.2–5.9 kg/cm², indicating sufficient mechanical strength of tablets. Friability values were below 1%, demonstrating good resistance to abrasion during handling. Drug content ranged from 98–99%, confirming uniform drug distribution within the formulations.

In-Vitro Dissolution Study

The dissolution study was carried out using USP Type II dissolution apparatus in phosphate buffer pH 6.8.

Table 5: In-Vitro Drug Release Data of Formulations F1–F6

Formulation	Hardness (kg/cm²)	Friability (%)	Drug Content (%)
F1	5.2	0.6	98
F2	5.5	0.5	99
F3	5.8	0.5	99
F4	5.3	0.6	98
F5	5.6	0.5	99
F6	5.9	0.5	99

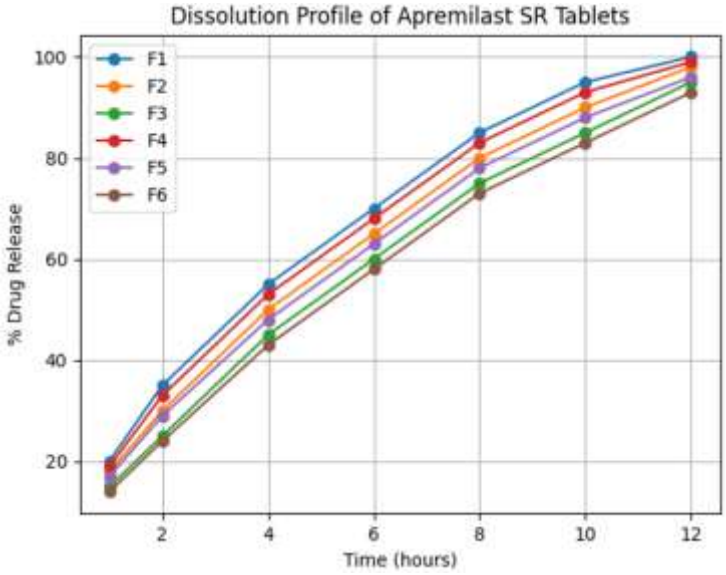

Figure 5: Comparative Dissolution Profiles of F1–F6

The dissolution study demonstrated that polymer concentration significantly influenced drug release behavior.

Formulations F1–F3

These formulations contained HPMC K4M, a lower viscosity polymer. Drug release was comparatively faster due to rapid hydration and quicker diffusion of dissolution medium through the matrix. F1 released almost complete drug within 10 hours.

Formulations F4–F6

These formulations contained HPMC K15M, which has higher viscosity. Increased viscosity resulted in stronger gel layer formation and slower drug diffusion. Drug release was sustained for up to 12 hours.

Effect of Polymer Concentration

Increasing polymer concentration decreased the rate of drug release because:

- Matrix integrity increased
- Water penetration reduced
- Diffusion path length increased
- Gel barrier became stronger

Optimized Formulation (F5)

Formulation F5 showed optimum sustained release characteristics with:

- Controlled release up to 12 hours
- Uniform release pattern
- Good matrix integrity
- Acceptable physical parameters

The release profile of F5 indicated an ideal balance between polymer concentration and drug diffusion characteristics.

Drug Release Kinetics

The dissolution data were fitted into different kinetic models.

Table 6: Drug Release Kinetic Model Analysis

Model	Observation
Zero Order	Moderate fit
First Order	Drug release concentration dependent
Higuchi Model	Best fit
Korsmeyer–Peppas	Non-Fickian diffusion

The optimized formulation followed Higuchi kinetics, indicating diffusion-controlled drug release. Korsmeyer–Peppas analysis suggested anomalous transport involving both diffusion and erosion mechanisms. The hydrophilic polymer formed a gel barrier around the tablet, controlling the penetration of dissolution medium and drug diffusion.

Stability Studies

The optimized formulation F5 was subjected to accelerated stability studies.

Table 7: Stability Study Data

Time (Months)	Hardness (kg/cm²)	Friability (%)	Drug Content (%)	Drug Release at 12 hr (%)
0	5.2	0.45	99.5	98.2
1	5.1	0.48	99.0	97.8
2	5.0	0.50	98.7	97.2
3	5.0	0.52	98.5	96.9

No major changes were observed during the stability study period. Hardness and friability remained within acceptable limits. Drug content showed minimal variation, indicating chemical stability of the formulation. The dissolution profile remained nearly unchanged after storage, demonstrating that the polymer matrix maintained sustained release behavior throughout the study period. The results confirmed that formulation F5 possessed satisfactory stability under accelerated conditions.

CONCLUSION:

The present study successfully developed sustained release matrix tablets of Apremilast using hydrophilic polymers by the direct compression method. Preformulation studies confirmed the suitability and compatibility of the

drug with selected excipients. All prepared formulations showed acceptable pre- and post-compression characteristics, including good flow properties, hardness, friability, and uniform drug content. In-vitro dissolution studies demonstrated that polymer concentration significantly influenced drug release behaviour. Among all formulations, batch F5 showed the best sustained release profile with controlled drug release up to 12 hours and satisfactory tablet properties. Drug release followed Higuchi and Korsmeyer–Peppas kinetics, indicating diffusion-controlled release mechanism. Stability studies confirmed that the optimized formulation remained stable under accelerated conditions without significant changes in physicochemical properties or drug release pattern. Overall, the study concluded that sustained release matrix tablets of Apremilast can be successfully formulated to improve therapeutic efficacy, maintain prolonged drug release, and enhance patient compliance in the treatment of psoriasis and psoriatic arthritis.

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