# Design, Formulation, and Evaluation of Sustained Release Delivery Systems for Diclofenac Sodium

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***Abstract*—Diclofenac Sodium, a potent non-steroidal anti-inflammatory drug (NSAID) widely used for rheumatoid arthritis and osteoarthritis, presents a therapeutic challenge due to its short biological half-life of 1-2 hours and potential for gastric irritation. This review consolidates findings from 11 key studies to evaluate the design, formulation, and evaluation of Sustained Release (SR) delivery systems aimed at maintaining therapeutic plasma levels for 12-24 hours. The primary focus is on matrix tablet technology, utilizing hydrophilic synthetic polymers like HPMC and natural gums such as Xanthan and Acacia to control drug release via hydration, swelling, and diffusion mechanisms. The review outlines pre-formulation studies, emphasizing the necessity of Wet Granulation to overcome the poor flow properties of the drug. Furthermore, it highlights the evolution of formulation optimization from traditional trial-and-error methods to advanced computational approaches using Artificial Neural Networks (ANN). Comparative in-vitro and in-vivo data demonstrate that SR formulations successfully delay $T_{max}$ and reduce gastrointestinal side effects compared to conventional dosage forms, confirming their clinical efficacy and improved patient adherence.**

***Index Terms*—Diclofenac Sodium, Sustained Release (SR), Matrix Tablet, HPMC (Hydroxypropyl-Methylcellulose), Natural Polymers (Xanthan Gum, Acacia), Wet Granulation, Artificial Neural Networks (ANN), Pharmacokinetics.**

## I. INTRODUCTION

### 1.1. Overview of the Therapeutic Challenge.

Diclofenac Sodium is a fundamental non-steroidal anti-inflammatory drug (NSAID) used for managing chronic inflammatory conditions like rheumatoid arthritis and osteoarthritis. Despite its high efficacy, its clinical utility is restricted by a short biological half-life of only 1–2 hours. This requires a regimen of multiple doses typically three to four times daily which often leads to missed doses and poor patient adherence [8]. Additionally, the rapid release of the drug from conventional forms can result in high local concentrations in the gastric mucosa, causing irritation, ulceration, or bleeding [2]. To address these issues, pharmaceutical research has heavily prioritized Sustained Release (SR) formulations [6]. These systems are designed to release the drug at a controlled, predetermined rate, maintaining therapeutic plasma levels for 12–24 hours while minimizing gastric exposure [1].

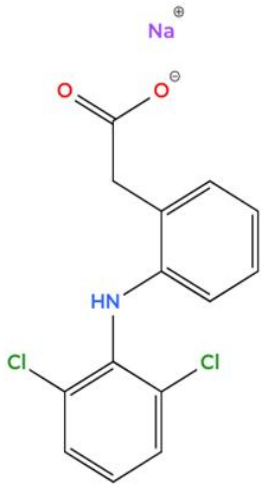


Figure 1: Chemical Structure of Diclofenac Sodium showing the dichlorophenyl amino group responsible for its anti-inflammatory activity.

### 1.2. Chemical Nature and Structure.

Chemically designated as Sodium 2-[(2,6-dichloroanilino)phenyl] acetate, Diclofenac Sodium falls under the hetero-aryl acetic acid derivative class of NSAIDs. Its structure includes a phenylacetic acid group, a secondary amino group, and a phenyl ring substituted with two chlorine atoms at the ortho

positions. These chlorine atoms induce significant torsion, preventing the two aromatic rings from becoming coplanar, which is essential for binding to the Cyclooxygenase (COX) enzyme. As the sodium salt of a weak acid, it dissociates readily in aqueous environments, although its solubility is heavily dictated by the pH of the medium [6].

1.3. Scope of this Review.

This review consolidates findings from 11 key studies, covering the progression from simple matrix tablets to advanced computational optimizations using Artificial Neural Networks and nanotechnology. It evaluates the effectiveness of synthetic polymers like HPMC versus natural gums such as Xanthan and Acacia, and examines the correlation between in-vitro dissolution and in-vivo performance.

## II. PHYSICOCHEMICAL PROPERTIES & PRE-FORMULATION

Table 1: Physicochemical Profile of Diclofenac Sodium

| Parameter | Description |
|---|---|
| IUPAC Name | Sodium 2-[2-(2,6-dichloroanilino)phenyl] acetate |
| Molecular Formula | $C_{14}H_{10}Cl_2NNaO_2$ |
| Molecular Weight | 318.13 g/mol |
| Solubility | Sparingly soluble in water; Soluble in Ethanol; Freely soluble in Methanol [6] [11] |
| pKa Value | 4.0 ± 0.2 (Weakly Acidic) [6] |
| Melting Point | 283°C – 285°C |
| Partition Coefficient | Log P approx 4.5 (Lipophilic) |

[6]

2.1. Solubility and pH Dependency.

The pH-dependent solubility of Diclofenac Sodium is a critical parameter. As a weak acid with a pKa around 4.0, it exhibits poor solubility in acidic environments like the stomach (pH 1.2), where it exists in its unionized form. Conversely, solubility increases significantly in the neutral to alkaline pH of the intestinal tract. This differential creates a challenge for SR formulations; without a robust matrix, the drug may release negligible amounts in the stomach and then "dump" the dose rapidly in the intestine [11]. Therefore, polymers like HPMC or Xanthan gum must be chosen to ensure consistent erosion or diffusion regardless of pH fluctuations [5].

2.2. Partition Coefficient and Absorption.

Diclofenac Sodium has a high partition coefficient (Log P approx 4.5), indicating strong lipophilic character. According to the Biopharmaceutics Classification System (BCS), it is classified as a Class II drug (Low Solubility, High Permeability). This implies that the rate-limiting step in its absorption is its dissolution rate rather than its permeation across the biological membrane. Consequently, the primary objective of the sustained-release formulation is to control this dissolution rate precisely over 12 to 24 hours.

2.3. Flow Properties and Compressibility.

In its pure crystalline form, Diclofenac Sodium powder often exhibits poor flow properties and compressibility due to irregular particle shape and cohesive forces. Preformulation studies typically evaluate the Angle of Repose, Carr's Index, and Hausner's Ratio. High values in these indices indicate poor flow, which necessitates the use of Wet Granulation rather than Direct Compression. As noted in the formulation methodologies (Savaser et al., 2005), the addition of binders like PVP K30 and glidants like Magnesium Stearate is essential to improve the flowability of the granules, ensuring uniform die filling and consistent tablet weight during the high-speed compression process [1] [3].

## III. MATRIX TABLET TECHNOLOGY: THE CORE STRATEGY

The most common method found in the literature for Diclofenac SR is the Matrix Tablet.

3.1. Mechanism of Release.

In a matrix system, the drug is embedded in a polymer network. Upon contact with gastrointestinal fluid, the polymer hydrates and swells.

- Swelling: A gel layer forms around the tablet.
- Diffusion: The drug dissolves and diffuses through this gel layer.
- Erosion: Eventually, the polymer matrix erodes [3].

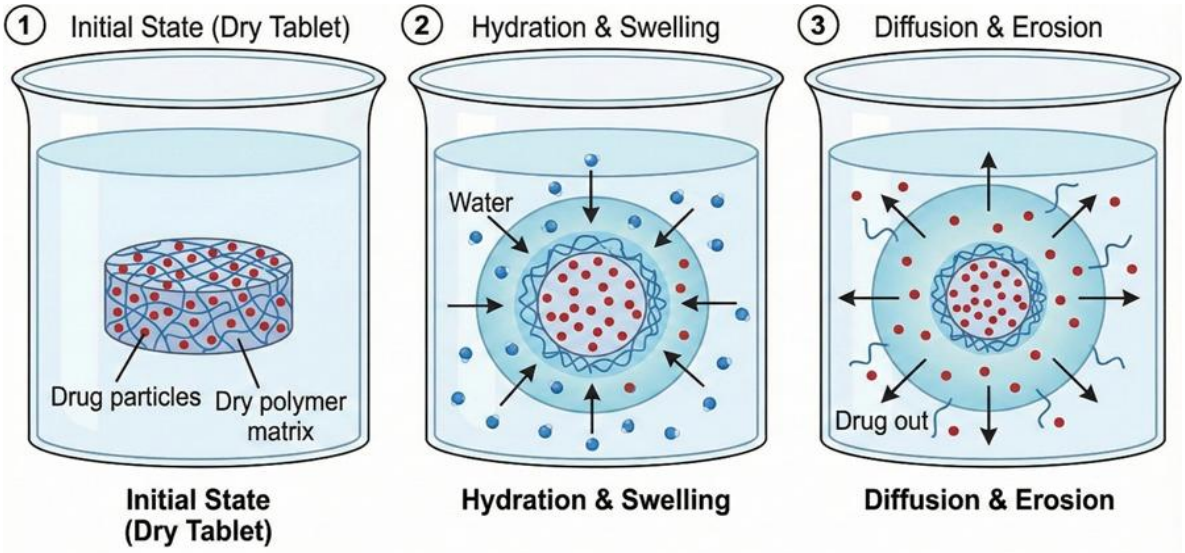


**Figure 2:** Mechanism of drug release from a Hydrophilic Matrix Tablet involving hydration, swelling (gel formation), and diffusion.

3.2. Synthetic Polymers: The Role of HPMC.
Hydroxypropyl Methylcellulose (HPMC) is the industry standard.
Savaser et al. (2005) [Ref 1]: Investigated the interaction between HPMC and Chitosan. They demonstrated that while HPMC alone provides sustained release, the addition of Chitosan modifies the matrix permeability. The study found that specific ratios of Drug:Polymer were critical for achieving Zero-Order release (constant release over time) [1].
Liu et al. (2003) [Ref 2]: Compared a generic HPMC-based formulation with the innovator product, Voltaren SR. They utilized dissolution testing to prove that properly formulated HPMC matrices could match the release profile of commercial standards ($f_2$ similarity factor > 50) [2].

3.3. Natural Polymers: "Green" Excipients.
Natural Polymers.
There is a growing trend toward using natural gums due to their low cost and non-toxicity.
Xanthan Gum: Galgatte et al. identified Xanthan Gum as a potent retardant that swells significantly more than HPMC, sustaining release for 12 hours via Higuchi diffusion kinetics [7].
Acacia Gum: Bharti et al. combined Acacia gum with HPMC K4M to achieve a robust matrix. Acacia acted synergistically with HPMC, improving mechanical strength and reducing the need for expensive synthetic polymers [9].

General Findings: Natural polymers often result in a "tighter" gel structure, which is beneficial for highly soluble drugs.

Table 2: List of Polymers Reviewed in Literature.

| Polymer | Type | Key Finding in Literature | Reference |
|---|---|---|---|
| HPMC | Synthetic | Gold standard; consistent release; improved by Chitosan. | [1], [2] |
| Xanthan Gum | Natural | High swelling index; dominates release via diffusion. | [7] |
| Acacia | Natural | Cost-effective; synergistic effect when mixed with HPMC. | [9] |
| Chitosan | Natural (Marine) | Modulates permeability; pH sensitive. | [1] |

## IV. ADVANCED FORMULATION & OPTIMIZATION

Modern pharmaceutics moves beyond "trial and error."

4.1. Artificial Neural Networks (ANN).

Bozič et al. (1997) introduced a computational approach to formulation. They used an Artificial Neural Network to model dissolution data using inputs like PVP, Cetyl alcohol, and Magnesium Stearate concentrations. The ANN accurately predicted drug release profiles, allowing for optimization without extensive physical batch testing, representing a significant efficiency leap for research [4].

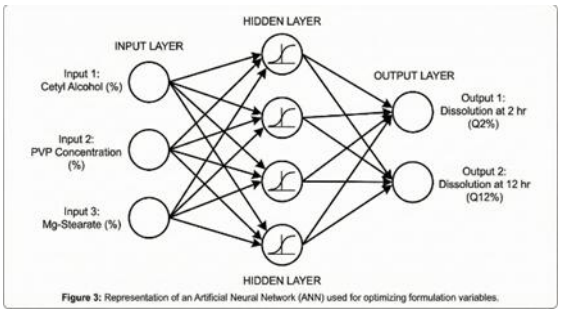

**Figure 3:** Representation of an Artificial Neural Network (ANN) used for optimizing formulation variables.

4.2. Nanotechnology Approaches.

Recent research discusses Nanoemulsion Drug Delivery, where Diclofenac is encapsulated in nano-sized oil droplets. This method significantly enhances bioavailability and offers a route for transdermal delivery, bypassing the stomach to eliminate gastric irritation [10].

## V. METHODS OF PREPARATION

To replicate these studies in a lab (a requirement for B.Pharm projects), the following methods are detailed in the literature:

5.1. Wet Granulation.

1. Blending: Diclofenac Sodium + Polymer (HPMC/Xanthan) + Diluent (Lactose/MCC).
2. Binder Addition: PVP K-30 dissolved in Isopropyl Alcohol is added to the powder mix.
3. Granulation: Mass is passed through a #20 mesh screen.
4. Drying: Granules dried at 50-60°C.
5. Compression: Lubricated with Mg-Stearate and compressed into tablets.

[1,7,9].

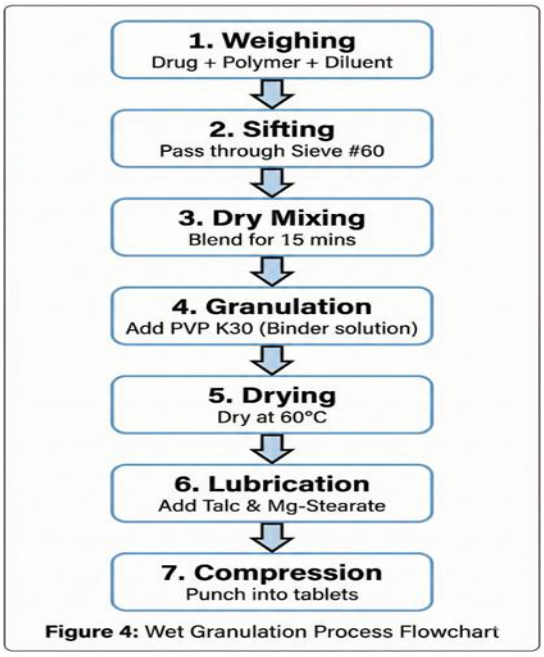

**Figure 4:** Wet Granulation Process Flowchart

5.2. Direct Compression.

Nishihata et al. mention this as a "Simple Formulation". It involves directly mixing the drug with a compressible vehicle, though it requires excipients with excellent flow properties [8].

5.3. Formulation Design.

Prototype development involves varying polymer concentrations to identify the optimal ratio for the target dissolution profile (e.g., >80% release at 12 hours). A typical master formula based on Galgatte et al. uses a combination of HPMC K100M and Xanthan Gum. Three batches (F1, F2, F3) are typically proposed with increasing polymer concentrations to vary the release rate, while keeping drug load and tablet weight constant [7].

In this experimental design, formulation F1 represents the lowest polymer concentration, which is expected to show the fastest drug release. Conversely, F3, with the highest total polymer content (80 mg total of HPMC and Xanthan Gum), is expected to form the strongest gel barrier, resulting in the slowest release rate. Microcrystalline Cellulose (MCC) or Lactose is adjusted

(q.s.) to maintain a constant tablet weight of 300 mg across all batches, ensuring that any difference in dissolution is due to polymer variation and not tablet size [7].

| Ingredients | Function | F1 (mg) | F2 (mg) | F3 (mg) |
|---|---|---|---|---|
| Diclofenac Sodium | Active Pharmaceutical Ingredient (API) | 100 | 100 | 100 |
| HPMC K100M | Polymer (Release Retardant) | 30 | 40 | 50 |
| Xanthan Gum | Polymer (Release Retardant) | 10 | 20 | 30 |
| MCC / Lactose | Diluent (Bulking Agent) | q.s. | q.s. | q.s. |
| PVP K30 | Binder | 10 | 10 | 10 |
| Mg-Stearate | Lubricant / Glidant | 5 | 5 | 5 |
| Total Weight | - | 300 | 300 | 300 |

## VI. EVALUATION AND CLINICAL CORELATION

### 6.1. In-Vitro Dissolution.

Matrix studies utilize USP Type I (Basket) or Type II (Paddle) apparatuses. The standard test uses a pH change method: 2 hours in pH 1.2 (simulated stomach) followed by 10–12 hours in pH 6.8 buffer (simulated intestine). The target is less than 20% release in the first 2 hours and greater than 80% release by 12 hours [2].

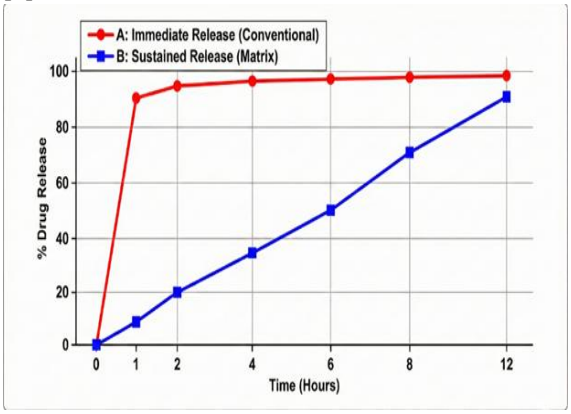


Figure 4: Comparative in-vitro dissolution profile of conventional vs sustained release diclofenac sodium tablets.

### 6.2. In-Vivo and Clinical Performance.

Clinical studies confirm the efficacy of SR formulations.

- Pharmacokinetics: SR formulations successfully delay the $T_{max}$ (time to peak concentration).
- Bioequivalence: Liu et al. confirmed that if in-vitro dissolution curves match ($f_2 > 50$), the in-vivo bioavailability is likely equivalent to the market leader [2].
- Safety: Patients switched to SR formulations reported a reduction in gastrointestinal complaints [6] [8].

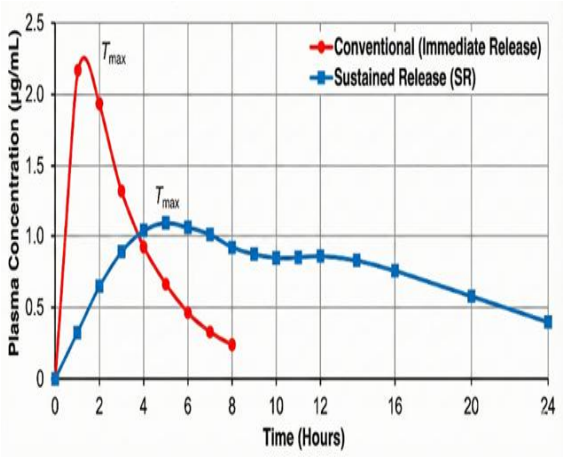


Figure 5: Plasma concentration-time profile demonstrating the extended half-life and delayed t-max of the sustained-release formulation.

## VII. CONCLUSION

The literature from 1987 to the present highlights a distinct evolution in the delivery of Diclofenac Sodium. Foundational research established the viability of simple matrix systems [8]. Subsequent innovation in polymers demonstrated that blending HPMC with Chitosan or utilizing natural gums like Xanthan and Acacia offers stable, cost-effective release profiles. Optimization techniques using AI and ANN have proven capable of predicting formulation outcomes [4]. Clinically, these SR formulations effectively maintain therapeutic efficacy while reducing side effects. Future developments are likely to focus on nanotechnology, offering faster onset, sustained duration, and minimal toxicity [10] [11].

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