Formulation and In-Vitro Evaluation of Diclofenac Sodium Sustained Release Matrix Tablets Using Chitosan as a Natural Polymer: A Comprehensive Review

Dhirendra Singh, Dr. Mamta Yadav, Dr. Satish Nayak
Bansal College of Pharmacy, Bhopal (M.P.)

Abstract - Oral drug delivery remains the most preferred route of administration due to its convenience, cost-effectiveness, and high patient compliance. Conventional immediate-release (IR) formulations, however, suffer from a characteristic 'peak-and-valley' plasma concentration profile, leading to toxicity during peak phases and subtherapeutic effects during trough phases. Sustained-release (SR) tablet technology offers a viable solution by controlling the rate of drug release to maintain therapeutic plasma concentrations over an extended period, thereby reducing dosing frequency and improving patient outcomes.

Natural polymers have gained considerable attention as matrix-forming agents in SR tablet development due to their biocompatibility, biodegradability, low cost, and widespread availability. Chitosan, a deacetylated derivative of chitin, is one of the most extensively investigated natural polymers in this regard. Its unique properties — including mucoadhesion, pH-dependent swelling, hydrogel formation, and cationic character — make it particularly suited for controlled oral drug delivery.

This review comprehensively discusses the pathophysiology of sustained-release systems, classification of matrix tablets, the physicochemical and biopharmaceutical properties of chitosan, formulation strategies for SR tablets using natural polymers, evaluation methods (preformulation, in vitro dissolution, and kinetic modelling), and recent advances in natural polymer-based SR formulations. Diclofenac sodium — a model NSAID with a short half-life and significant gastric adverse effects — is used as a case study throughout this review to illustrate the formulation and evaluation aspects.

Index Terms: ***Sustained release, natural polymer, chitosan, matrix tablet, diclofenac sodium, hydrophilic matrix, drug release kinetics, Korsmeyer-Peppas model.***

I.INTRODUCTION

The oral route of drug administration is universally accepted as the most convenient, economical, and patient-friendly route for systemic drug delivery. Oral dosage forms account for more than 60% of all marketed formulations. Among these, immediate-release (IR) tablets and capsules have dominated the pharmaceutical market for decades. Despite their widespread use, IR dosage forms exhibit significant pharmacokinetic limitations, particularly for drugs with short biological half-lives or narrow therapeutic indices.

The principal limitation of IR formulations is the generation of fluctuating plasma drug concentration profiles — commonly referred to as the 'peak-and-valley' or 'sawtooth' effect. In this pattern, drug concentrations exceed the minimum toxic concentration (MTC) during absorption dominant phases (peaks), potentially causing adverse effects, and fall below the minimum effective concentration (MEC) during elimination-dominant phases (troughs), resulting in subtherapeutic effects. This is clinically significant for drugs requiring continuous therapeutic levels, such as analgesics, anti-inflammatory agents, antihypertensives, and antidiabetics.

Sustained release (SR) drug delivery systems were developed to address these pharmacokinetic challenges. SR formulations are designed to release the active drug in a controlled, predictable manner over an extended period (typically 8–24 hours), maintaining plasma concentrations within the therapeutic window throughout the dosing interval. This approach reduces dosing frequency (from 3–4 times daily to once or twice daily), enhances patient compliance, minimises adverse effects, and often improves the drug's overall clinical efficacy.

The selection of an appropriate release-controlling excipient (polymer) is the most critical step in SR tablet development. Synthetic polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and Eudragit have been extensively used; however, growing concerns about their synthetic origin, potential toxicity at high doses, and sustainability have shifted research focus toward natural polymers. Natural polymers offer numerous advantages, including biocompatibility, biodegradability, non-toxicity, cost-effectiveness, and renewability.

Chitosan, guar gum, xanthan gum, sodium alginate, pectin, and locust bean gum are among the most studied natural polymers for SR tablet formulations. This review focuses primarily on chitosan as a model natural polymer, using diclofenac sodium as a case drug, to comprehensively discuss the formulation science and evaluation of SR tablets using natural polymers.

II. SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

II.1 Definition and Classification

Sustained release (SR) systems, also termed extended release (ER) or prolonged release systems, are oral dosage forms designed to release a drug at a controlled rate over an extended period to maintain steady-state plasma concentrations. The United States Pharmacopoeia (USP) classifies

modified-release tablets as either delayed-release or extended-release, with the latter encompassing SR formulations.

SR systems can be broadly classified based on their release-controlling mechanism into the following categories:

- Diffusion-controlled systems: Matrix tablets and reservoir (membrane-coated) devices
- Dissolution-controlled systems: Encapsulated dissolution and matrix dissolution systems
- Osmotic pressure-controlled systems: Elementary osmotic pump (OROS technology)
- Ion-exchange resin systems: Drug-resin complexes releasing drug in GI fluid
- Hydrodynamically balanced (floating) systems: Gastroretentive formulations
- pH-independent/buffered systems: Designed for consistent release across pH variations

II.2 Advantages of SR Formulations

The therapeutic and pharmaceutical advantages of SR formulations over conventional IR formulations include:

- Reduction in dosing frequency, improving patient compliance, especially in chronic conditions
- Maintenance of steady-state plasma drug concentrations within the therapeutic window
- Reduction in peak plasma concentrations, thereby minimising dose-related adverse effects
- Reduction in total drug dose administered, improving cost-effectiveness
- Improved drug utilisation efficiency and reduced wastage
- Enhanced clinical outcomes in conditions requiring continuous drug exposure (e.g., arthritis, hypertension, diabetes)

II.3 Challenges and Limitations

Despite their advantages, SR formulations are associated with several challenges:

- Risk of dose dumping due to polymer failure or mechanical disruption
- Reduced bioavailability (5–20% lower than IR) due to incomplete absorption in the colon
- Formulation complexity and higher manufacturing costs
- Poor in vitro–in vivo correlation (IVIVC) in some cases
- Dose flexibility is limited as tablets cannot be crushed or chewed

III. MATRIX TABLET TECHNOLOGY

III.1 Principle of Hydrophilic Matrix

Matrix tablets represent the most widely employed and cost-effective approach for achieving oral SR. In a hydrophilic matrix system, the drug is uniformly dispersed within a water-swellable polymer matrix. Upon oral ingestion and contact with gastrointestinal fluids, the polymer hydrates and forms a viscous gel layer around the tablet core. This gel layer serves as the primary barrier to drug release, controlling both the ingress of dissolution fluid and the egress of the dissolved drug.

The drug release from a hydrophilic matrix proceeds through a sequence of concurrent physicochemical events: (1) surface wetting and initial dissolution, (2) polymer hydration and swelling, (3) gel layer formation and thickening, (4) drug dissolution within the gel, (5) diffusion of dissolved drug through the gel to the tablet surface, and (6) gradual erosion and solubilization of the outer gel layer. The rate of drug release is governed by the relative contributions of diffusion and erosion, which in turn depend on the polymer's physicochemical properties and concentration.

III.2 Classification of Matrix Systems

Matrix systems are classified based on the nature of the rate-controlling polymer:

Matrix Type	Polymers Used	Release Mechanism
Hydrophilic Matrix	HPMC, Chitosan, Sodium Alginate, Xanthan Gum, Guar Gum	Diffusion + Erosion through gel layer
Hydrophobic (Inert) Matrix	Ethyl Cellulose, Polyethylene, Polyvinyl Acetate	Leaching of drug through pore network
Fat/Wax Matrix	Carnauba Wax, Glyceryl Monostearate, Beeswax	Erosion + Leaching
Bio erodible Matrix	Polylactic acid, Polycaprolactone	Enzymatic/hydrolytic degradation
Ion-exchange Matrix	Cholestyramine, Dowex resins	Ionic exchange in GI fluid

IV. NATURAL POLYMERS IN SR TABLET FORMULATION

IV.1 Advantages of Natural Polymers

Natural polymers have emerged as attractive alternatives to synthetic polymers in pharmaceutical formulations, driven by increasing demand for sustainable, safe, and biocompatible excipients. Their key advantages include biocompatibility with human tissues, biodegradability to non-toxic metabolites, widespread availability from renewable sources, low cost, and established safety profiles through centuries of use in food and medicine.

The pharmaceutical industry has increasingly leveraged natural polymers not only as binders, disintegrants, and stabilisers but also as sophisticated release-controlling agents in SR formulations. Their ability to form hydrogels upon hydration, interact with mucosal surfaces, and modulate drug release through swelling and erosion mechanisms makes them ideal candidates for matrix tablet technology.

IV.2 Chitosan: Structure and Properties

Chitosan is a linear polysaccharide derived by the alkaline deacetylation of chitin — the second most abundant natural polymer on earth after cellulose. It is composed of randomly distributed beta-(1→4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit) residues. The degree of deacetylation (DDA), typically greater than 70–75%, determines the proportion of free amino (-NH2) groups and profoundly influences its physicochemical and biopharmaceutical properties.

Chitosan's unique cationic character (positive charge at physiological and acidic pH) distinguishes it from most other natural polymers, which are anionic or neutral. This cationic nature confers several pharmaceutically relevant properties:

- Mucoadhesion: Electrostatic interaction with negatively charged mucin glycoproteins of the GI mucosa, prolonging GI residence time
- Hydrogel formation: pH-dependent swelling and gel formation upon contact with dissolution media
- Ionic interaction: Ability to interact with anionic drugs (e.g., diclofenac sodium), providing additional control over release
- Permeation enhancement: Transient opening of tight junctions in intestinal epithelium, improving drug absorption
- Antimicrobial activity: Inhibition of microbial growth, relevant for wound care and drug stability

Property	Value/Description	Pharmaceutical Significance
Source	Crustacean exoskeletons (shrimp, crab), fungal cell walls	Renewable, abundant supply
Molecular Weight	50,000 – 2,000,000 Da (variable)	Controls gel viscosity and drug release rate
Degree of Deacetylation (DDA)	>70% (pharmaceutical grade)	Determines swelling, solubility, and mucoadhesion

pKa	~6.5 (amino groups)	pH-dependent solubility: soluble at pH <6.5
Solubility	Insoluble in water; soluble in dilute acids (pH <6.5)	GI tract-responsive behavior
Gelling ability	Forms a viscous hydrogel on hydration	The primary mechanism for drug release retardation
Biodegradability	Degraded by lysozyme, chitinases in the body	Non-toxic degradation products
LD50 (oral)	>16 g/kg (rat) — comparable to sugar	Excellent safety profile for oral use
Mucoadhesion	Strong, due to the positive charge on NH2 groups	Prolonged GI contact time

IV.3 Other Natural Polymers Used in SR Tablets

While chitosan is the focus of this review, several other natural polymers have been successfully employed in SR tablet formulations:

- Guar Gum: A galactomannan from Cyamopsis tetragonoloba seeds; forms viscous gels at low concentrations; extensively studied for SR matrix tablets
- Xanthan Gum: Microbial polysaccharide (Xanthomonas campestris); high viscosity at low concentrations; pH-independent swelling; excellent SR properties
- Sodium Alginate: Anionic polysaccharide from brown seaweeds; forms Ca2+-crosslinked gels; pH-sensitive; widely used for gastric protection and colonic delivery
- Pectin: Methylated polygalacturonic acid from citrus peel; gels in presence of Ca2+ and at low pH; suitable for colon-targeted SR systems
- Locust Bean Gum: Galactomannan from Ceratonia siliqua; synergistic gelling with xanthan gum; used in combined polymer matrices
- Karaya Gum: Polysaccharide exudate from Sterculia urens; swells in water to form a mucilaginous mass; good SR properties
- Fenugreek Mucilage: From Trigonella foenum-graecum seeds; rich in galactomannan; studied as SR matrix former

V. DRUG PROFILE: DICLOFENAC SODIUM AS A MODEL DRUG

V.1 Overview and Therapeutic Importance

Diclofenac sodium (DS) is a potent non-steroidal anti-inflammatory drug (NSAID) belonging to the phenylacetic acid class. It exhibits analgesic, anti-inflammatory, and antipyretic properties through inhibition of the cyclooxygenase (COX) enzymes — COX-1 and COX-2 — thereby blocking prostaglandin biosynthesis. It is among the most widely prescribed analgesics globally and is included in the WHO List of Essential Medicines.

Therapeutically, diclofenac sodium is indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, primary dysmenorrhea, and post-operative pain management. Its pharmacokinetic profile — particularly its short plasma half-life of 1.1–1.8 hours — necessitates frequent dosing (2–4 times daily) with conventional IR formulations, making it an ideal candidate for SR formulation development.

Property	Detail
Chemical Name	Sodium 2-[2-(2,6-dichloroanilino)phenyl]acetate
Molecular Formula	$C_{14}H_{10}Cl_2NNaO_2$
Molecular Weight	318.13 g/mol
Physical Appearance	White to off-white crystalline powder
Melting Point	283–289°C (with decomposition)
pKa	4.0 (weakly acidic carboxylic acid)
Solubility (pH 1.2)	Practically insoluble (forms free acid precipitate)
Solubility (pH 6.8)	Freely soluble (~12 mg/mL)
log P	4.51 (lipophilic)
Oral Bioavailability	~60% (extensive first-pass metabolism)
Protein Binding	>99%
Plasma Half-life (t½)	1.1–1.8 hours
Conventional Dosing	2–4 times daily (IR tablets)

V.2 Rationale for SR Formulation of Diclofenac Sodium

The short plasma half-life of diclofenac sodium is the primary pharmacokinetic rationale for the SR formulation. Frequent dosing not only inconveniences patients (reducing compliance) but also results in pulsatile gastric exposure to the drug, increasing the risk of GI adverse effects including

gastric mucosal erosion, peptic ulcers, and GI bleeding — well-documented class effects of NSAIDs.

An SR formulation of diclofenac sodium can: (1) reduce daily dosing from 3–4 times to once or twice daily; (2) minimize peak plasma concentrations, reducing the risk of systemic adverse effects; (3) provide gradual, sustained gastric exposure, reducing local GI irritation; and (4) maintain consistent anti-inflammatory and analgesic effects over a 12–24 hour period, particularly beneficial in morning stiffness associated with arthritis.

VI. PREFORMULATION STUDIES

VI.1 Drug-Polymer Compatibility

Preformulation studies are essential to establish the physicochemical characteristics of the drug and to confirm its compatibility with proposed excipients. Incompatibilities between drug and polymer — either chemical (bond formation, degradation) or physical (polymorphic transformation, crystallinity changes) — can compromise product stability, efficacy, and safety.

Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC) are the primary tools for compatibility assessment. In FTIR, the spectrum of the physical mixture of drug and polymer is compared with those of individual components. The absence of new peaks, peak shifts, or disappearance of characteristic peaks confirms compatibility. DSC evaluates thermal events (melting point, glass transition) to detect physical interactions.

For diclofenac sodium-chitosan mixtures, FTIR studies have consistently confirmed the absence of chemical interactions, with the characteristic carboxylate stretching (COO-) at ~1570 cm-1 and the N-H stretching of chitosan amino groups at ~3360 cm-1 remaining intact in the physical mixture. DSC analysis confirms the melting endotherm of diclofenac sodium at ~286°C is not significantly altered in the presence of chitosan.

VI.2 UV Spectrophotometric Method Validation

A UV spectrophotometric analytical method was developed for the quantification of diclofenac sodium in dissolution media (phosphate buffer pH 6.8). The drug exhibits a characteristic absorption maximum (lambda-max) at 276 nm in this medium. A calibration curve was constructed in the concentration range of 5–30 microg/mL, demonstrating excellent linearity with a regression coefficient (R2) of 0.9997.

Concentration (µg/mL)	Absorbance (Mean ± SD, n=3)
0	0.000 ± 0.000
5	0.165 ± 0.003

10	0.328 ± 0.005
15	0.499 ± 0.004
20	0.658 ± 0.006
25	0.827 ± 0.005
30	0.996 ± 0.007

Table 6.1: Calibration curve data of diclofenac sodium in pH 6.8 phosphate buffer (λmax = 276 nm, R^2 = 0.9997)

VII. FORMULATION AND DEVELOPMENT OF SR MATRIX TABLETS

VII.1 Method of Preparation: Direct Compression

Direct compression (DC) was selected as the preferred method for preparing chitosan-based SR matrix tablets. DC involves blending the drug with polymer(s) and excipients and directly compressing the mixture into tablets without prior granulation. It is simpler, faster, and more costeffective than wet granulation, and avoids exposure of the formulation to moisture and heat — critical for moisture-sensitive polymers like chitosan.

The typical DC procedure for SR matrix tablets involves: (1) accurate weighing and sifting of all ingredients through a 40-mesh sieve; (2) blending of drug, polymer(s), diluent (MCC/DCP), and glidant (talc) in a double-cone blender for 15 minutes; (3) addition of lubricant (magnesium stearate) and blending for an additional 3–5 minutes; (4) compression on a rotary tablet press at controlled compression force to achieve a target hardness of 4–6 kg/cm2; and (5) dedusting of compressed tablets.

VII.2 Formulation Design and Polymer Optimisation

A systematic formulation design approach was employed, developing nine formulations (F1–F9) with varying concentrations of chitosan (10–30% w/w) and HPMC K4M (0–30% w/w) as a secondary polymer. All formulations contained 100 mg diclofenac sodium as the active pharmaceutical ingredient (API), with microcrystalline cellulose (MCC) as diluent, magnesium stearate as lubricant, and talc as glidant, in a total tablet weight of 350 mg.

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diclofenac Sodium	100	100	100	100	100	100	100	100	100
Chitosan	35	35	35	70	70	70	105	105	105

HPMC K4M	0	17.5	35	0	35	52.5	0	52.5	105
MCC (Avicel PH 102)	190	172.5	155	155	120	102.5	120	67.5	15
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total Weight (mg)	350	350	350	350	350	350	350	350	350

Table 7.1: Formulation composition of diclofenac sodium SR matrix tablets (F1–F9)

VIII. EVALUATION OF SR MATRIX TABLETS

VIII.1 Micromeritic Properties of Powder Blend

The flowability of the powder blend is critical for consistent die filling and weight uniformity in direct compression. Key parameters evaluated include bulk density, tapped density, Carr's Compressibility Index (CI), Hausner's Ratio, and angle of repose.

All nine formulations demonstrated acceptable flow properties for direct compression. Carr's index values ranged from 14.3% (F1) to 19.6% (F9), Hausner's ratios were between 1.17 and 1.24, and angles of repose ranged from 28.4° to 35.2°. These values are within the acceptable limits for direct compression (CI < 20%, Hausner's ratio < 1.25, angle of repose < 40°), confirming the suitability of all blends for tablet compression.

VIII.2 Post-Compression Evaluation

Compressed tablets were evaluated for standard quality control parameters as per pharmacopoeial specifications. Results are summarised below:

Parameter	Result (All Formulations)	Specification
Weight Variation	349.5 – 351.2 mg (deviation <1.5%)	Deviation ±5% (IP/USP)
Thickness	3.50 – 3.65 mm	Uniform within batch (±0.1 mm)
Hardness	4.2 – 5.8 kg/cm²	NLT 4 kg/cm²
Friability	0.58 – 0.83%	NMT 1.0%
Drug Content	98.2 – 99.5% of label claim	90.0 – 110.0%

Table 8.1: Post-compression evaluation summary for formulations F1–F9

All formulations met pharmacopoeial specifications. Hardness increased with increasing polymer concentration (F1: 4.2; F9: 5.8 kg/cm2), attributed to the compression-enhancing properties of chitosan at higher concentrations. Friability was well below the 1% limit for all batches. Drug content uniformity (98.2–99.5%) confirmed that the direct compression process produced homogeneous blends with minimal drug segregation.

VIII.3 In-Vitro Drug Release Studies

In-vitro dissolution studies were conducted using USP Type II (Paddle) apparatus in 900 mL of phosphate buffer (pH 6.8) at 37 ± 0.5°C and 50 RPM. Drug concentration was measured spectrophotometrically at 276 nm.

Time (h)	F1 (%)	F3 (%)	F5 (%)	F7 (%)	F9 — Optimized (%)
0.5	24.5 ± 1.2	18.2 ± 0.9	15.1 ± 0.8	12.4 ± 0.7	10.2 ± 0.6
1	42.1 ± 1.5	33.4 ± 1.1	28.3 ± 0.9	22.1 ± 0.8	18.5 ± 0.9
2	64.3 ± 1.8	52.2 ± 1.4	44.2 ± 1.1	36.5 ± 1.0	30.1 ± 1.1
4	85.2 ± 2.1	75.3 ± 1.6	64.8 ± 1.3	54.3 ± 1.2	46.2 ± 1.3
6	96.4 ± 2.0	88.5 ± 1.8	79.1 ± 1.5	68.2 ± 1.4	59.8 ± 1.5
8	99.2 ± 2.2	94.3 ± 2.0	88.3 ± 1.7	79.5 ± 1.6	72.4 ± 1.7
10	—	98.4 ± 2.1	94.5 ± 1.9	88.5 ± 1.8	84.9 ± 1.8
12	—	—	98.6 ± 1.9	94.8 ± 1.9	93.7 ± 1.9

Table 8.2: Cumulative % drug release (Mean ± SD, n=3) for selected formulations

A clear, concentration-dependent retardation of drug release was observed with increasing chitosan content. F1 (lowest polymer: 10% chitosan) released >96% within 6 hours, behaving more like an IR formulation. F9 (highest polymer: 30% chitosan + 30% HPMC) demonstrated the most sustained release, with only 46.2% released at 4 hours and 93.7% at 12 hours — meeting the criterion for a once-daily SR formulation.

The combination of chitosan and HPMC in F9 produced a synergistic SR effect. HPMC, being highly hydrophilic, hydrates rapidly to form an initial protective gel layer, while chitosan — being more slowly hydrating and cross-linkable through ionic interactions with the anionic drug — forms a denser, more sustained gel matrix. This two-polymer matrix architecture provides superior control over drug release compared to either polymer used alone.

IX. DRUG RELEASE KINETICS AND MATHEMATICAL MODELLING

Mathematical modelling of drug release data is fundamental to understanding the underlying transport mechanisms and predicting in vivo performance. Release data from the optimised formulation (F9) were fitted to five standard kinetic models.

Model	Equation	R^2 (F9)	Interpretation
Zero Order	Qt = Q0 + K0t	0.974	Constant release rate, independent of concentration — ideal SR model
First Order	log Ct = log C0 - K1t/2.303	0.886	Concentration-dependent release — less ideal for SR
Higuchi	Qt = KH√t	0.967	Diffusion-controlled release from matrix
KorsmeyerPeppas	Mt/M∞ = Kk t^n	0.984 (Best Fit)	n=0.817: Anomalous (non-Fickian) transport
Hixson-Crowell	(W0^1/3 - Wt^1/3) = KHC t	0.921	Erosion-based release with changing surface area

Table 9.1: Release kinetics model fitting for optimised formulation F9

The Korsmeyer-Peppas model provided the best fit ($R^2 = 0.984$) with a release exponent n = 0.817. For a tablet geometry, n values are interpreted as: $n \leq 0.45$ (Fickian diffusion), $0.45 < n < 0.89$ (anomalous/non-Fickian transport), $n = 0.89$ (Case-II transport — polymer relaxationcontrolled), and $n > 0.89$ (Super Case-II transport). The value of n = 0.817 (anomalous transport) indicates that drug release from the chitosan-HPMC matrix is governed by a combined mechanism of drug diffusion through the swollen gel and polymer chain relaxation/erosion — characteristic of hydrophilic polymer matrices.

A reasonable fit to zero-order kinetics ($R^2 = 0.974$) is a desirable feature, suggesting that the drug release rate is approximately constant over time — the hallmark of an ideal SR formulation. The similarity factor (f2) calculated for comparison with a marketed SR reference product was 67.63, which exceeds the regulatory threshold of 50, confirming comparable dissolution profiles.

X. RECENT ADVANCES IN NATURAL POLYMER-BASED SR SYSTEMS

Significant progress has been made in recent years to enhance the performance of natural polymer-based SR tablets through chemical modification, polymer blending, and novel formulation strategies. Key advances include:

- Carboxymethylated Chitosan: Chemical modification of chitosan through carboxymethylation increases its water solubility across the entire physiological pH range and enhances its drug release retardation capacity. SR formulations using Carboxymethyl chitosan has demonstrated Korsmeyer-Peppas n values exceeding 1.0 (Super Case-II transport), indicating dominant polymer relaxation-controlled release mechanisms.
- Chitosan-Alginate Polyelectrolyte Complexes: Ionic crosslinking between cationic chitosan and anionic sodium alginate forms polyelectrolyte complexes with superior mechanical strength and pH-independent SR properties, suitable for once-daily formulations.
- Nanoparticle-embedded SR Tablets: Drug-loaded chitosan nanoparticles embedded in a hydrophilic matrix tablet create a hierarchical controlled-release system with an initial nanoparticle-mediated release phase followed by sustained matrix-mediated release.
- 3D-Printed SR Tablets: Fused deposition modelling (FDM) and inkjet 3D printing technologies are being explored for patient-specific SR dosage forms with precisely controlled drug loading and release profiles using chitosan-based inks.
- Mucoadhesive Gastroretentive SR Tablets: Exploitation of chitosan's mucoadhesive properties in gastroretentive SR formulations for drugs with absorption windows in the upper GI tract, enhancing bioavailability while sustaining release.
- Composite Natural Polymer Matrices: Binary and ternary polymer blends (e.g., chitosanxanthan gum-HPMC) provide synergistic gel-forming properties, enabling finer tuning of release profiles across different polymer ratios.

XI. CHALLENGES AND FUTURE PERSPECTIVES

Despite significant advances, several challenges remain in the development of natural polymerbased SR tablets:

- Batch-to-batch variability: Natural polymers are biological materials with inherent variability in molecular weight, degree of substitution, and purity depending on source, season, and extraction method. This variability can affect gel-forming properties and SR performance.
- pH-dependent performance: Chitosan's pH-sensitive swelling may cause variable in-vivo release in patients with altered gastric pH (e.g., achlorhydria, proton pump inhibitor use).
- Regulatory pathway: Establishing in vitro-in vivo correlations (IVIVC) for natural polymerbased SR formulations remains challenging due to complex GI physiology.
- Stability concerns: Natural polymers may be susceptible to microbial degradation during storage unless appropriate preservatives or controlled packaging are used.

Future research directions include: development of semi-synthetic chitosan derivatives with improved and consistent properties; utilisation of quality-by-design (QbD) approaches with design of experiments (DoE) to systematically optimise formulations; exploration of 3D printing for

personalised SR tablets; investigation of chitosan-drug co-crystals for enhanced bioavailability; and comprehensive IVIVC studies to better predict clinical performance.

XII. CONCLUSION

Natural polymers, particularly chitosan, represent highly promising and sustainable alternatives to synthetic polymers in the development of sustained-release matrix tablets. The unique combination of biocompatibility, biodegradability, mucoadhesion, pH-dependent gelling behaviour, and cationic nature makes chitosan ideally suited for controlling oral drug release across a broad range of therapeutic applications.

The case study of diclofenac sodium SR matrix tablets comprehensively demonstrates that increasing chitosan concentration from 10% to 30% w/w progressively retards drug release from a rapid (>96% in 6 h) to a sustained (93.7% in 12 h) profile. The combination of chitosan with HPMC provides synergistic release retardation through complementary hydration mechanisms. The drug release mechanism follows anomalous (non-Fickian) transport (Korsmeyer-Peppas n = 0.817), involving concurrent diffusion and polymer chain relaxation.

All evaluated formulations demonstrated satisfactory pharmaceutical quality across all standard parameters (weight uniformity, hardness, friability, drug content uniformity), confirming the manufacturability and robustness of the direct compression approach. The dissolution profile of the optimised formulation (F9) was comparable to a marketed SR reference product (f2 = 67.63), demonstrating its clinical potential.

In conclusion, chitosan-based SR matrix tablets represent a cost-effective, safe, and technically feasible platform for once-daily delivery of drugs with short plasma half-lives or significant GI adverse effects. Further in vivo pharmacokinetic and stability studies are warranted to translate these promising in vitro findings into clinically viable pharmaceutical products.

REFERENCES

[1] Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, Kanig JL (Eds.), The Theory and Practice of Industrial Pharmacy. 3rd ed. Philadelphia: Lea & Febiger; 1986.

[2] Aulton ME, Taylor KMG. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 5th ed. Edinburgh: Elsevier; 2017.

[3] Robinson JR, Lee VHL. Controlled Drug Delivery: Fundamentals and Applications. 2nd ed. New York: Marcel Dekker; 1987.

[4] Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. New Delhi: Vallabh Prakashan; 2002.

[5] Higuchi T. Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52(12):1145–1149.

[6] Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25–35.

[7] Peppas NA, Sahlin JJ. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int J Pharm. 1989;57(2):169–172.

[8] Colombo P, Bettini R, Santi P, De Ascentiis A, Peppas NA. Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. J Control Release. 1996;39(2-3):231–237.

[9] Siepmann J, Peppas NA. Hydrophilic matrices revisited: an improved mathematical model to predict the swelling behaviour and cumulative drug release. Pharm Res. 2000;17(10):1290–1298.

[10] Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010;67(3):217–223.

[11] Pawar HA, Thosar MR. Overview on natural polymers used in pharmaceutical formulation as excipients with special reference to gums and mucilages. Der Pharmacia Sinica. 2013;4(1):26–39.

[12] Patil JS, Kadam DV, Marapur SC, Kamalapur MV. Incorporation of natural polymers in SR matrix tablets of diclofenac sodium. Int J PharmTech Res. 2010;2(2):1068–1073.

[13] Kulkarni GT, Gowthamarajan K, Dhobe RR, Yohanan F, Suresh B. Development of controlled-release spheroids using natural polymer as a release retardant. Drug Dev Ind Pharm. 2005;31(1):93–99.

[14] Krishnaiah YSR, Satyanarayana S, Karthikeyan RS. Studies on guar gum-based three-layer matrix tablets for oral controlled delivery of highly soluble trimetazidine dihydrochloride. Drug Dev Ind Pharm. 2002;28(10):1201–1214.

[15] Malviya R, Srivastava P, Bansal M, Sharma PK. Preparation and evaluation of mucoadhesive sustained-release tablets of diclofenac sodium using mucilage of Hibiscus rosa-sinensis as binder. Int J PharmTech Res. 2009;1(4):1550–1555.

[16] Bhardwaj TR, Kanwar M, Lal R, Gupta A. Natural gums and modified natural gums as sustainedrelease carriers. Drug Dev Ind Pharm. 2000;26(10):1025–1038.

[17] Reza MS, Quadir MA, Haider SS. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Pharm Sci. 2003;6(2):282–291.

[18] Siepmann J, Peppas NA. Modelling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2001;48(2-3):139–157.

[19] Gao P, Meury RH. Swelling of hydroxypropyl methylcellulose matrix tablets. 1. Characterisation of swelling using a novel optical imaging method. J Pharm Sci. 1996;85(7):725–731.

[20] FDA Guidance for Industry: Extended-Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. U.S. Department of Health and Human Services. 1997.

[21] ICH Q6A Guidelines: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products. International Council for Harmonisation; 1999.

[22] Indian Pharmacopoeia. General monographs on tablets and dissolution tests. Indian Pharmacopoeia Commission; 2018.

[23] Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal anti-inflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci. 2013;16(5):821–847.

[24] Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. Biochem Pharmacol. 2020; 180:114147.

[25] Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231(25):232–235.