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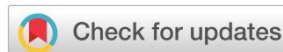
Journal of Drug Delivery and Therapeutics

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Review Article

Formulation and Evaluation of Floating Oral *In-Situ* Gel of Etodolac: A Comprehensive Review

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Article Info:



Article History:

Received 14 July 2026
Reviewed 03 Sep 2026
Accepted 26 Sep 2026
Published 15 Oct 2026

Cite this article as:

Sahu RK, Sahu N, Gupta R, Sahu D, Dev R, Bhardwaj SK, Formulation and Evaluation of Floating Oral *In-Situ* Gel of Etodolac: A Comprehensive Review, Journal of Drug Delivery and Therapeutics. 2026; 16(10):165-178 DOI: <https://doi.org/10.22270/jddt.v16i10.8039>

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Abstract

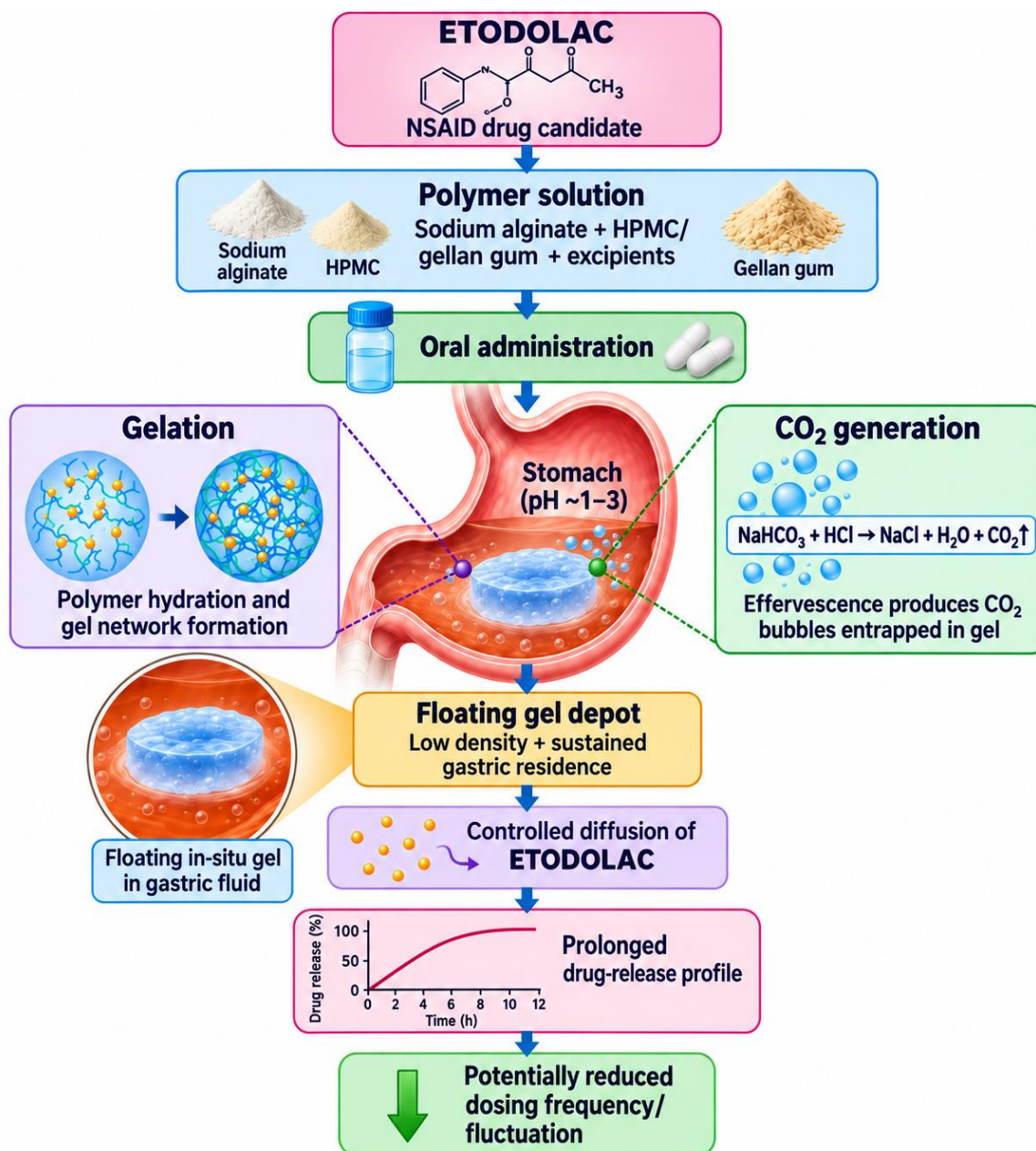
Etodolac is a non-steroidal anti-inflammatory drug (NSAID) used for the management of pain and inflammatory disorders. Although conventional oral administration provides effective systemic exposure, the relatively short terminal half-life and rapid gastrointestinal transit may necessitate repeated administration and may produce fluctuating drug concentrations. Gastroretentive drug delivery systems (GRDDS), particularly floating oral *in-situ* gels, provide an attractive approach for prolonging gastric residence and regulating drug release. This review and experimental framework focus on the development of a floating oral *in-situ* gel of etodolac using suitable hydrophilic and ion-responsive polymers. The formulation is designed to remain in the stomach by generating a low-density, gelled structure following contact with gastric fluid. Sodium alginate, gellan gum, hydroxypropyl methylcellulose (HPMC) and suitable gas-generating agents can be investigated to achieve rapid gelation, adequate floating ability, appropriate viscosity and sustained drug release. Important formulation and evaluation parameters include appearance, pH, viscosity, gelation characteristics, floating lag time, total floating duration, drug content, swelling, *in-vitro* dissolution, release kinetics and stability. Optimization of polymer concentration and polymer combinations is essential because viscosity, gel strength, buoyancy and drug diffusion are interdependent. A well-designed etodolac floating *in-situ* gel may provide prolonged gastric residence and controlled drug delivery, although *in-vivo* gastric-retention and pharmacokinetic studies are required to establish its clinical advantage.

Keywords: Etodolac; Floating *in-situ* gel; Gastroretentive drug delivery; Sodium alginate; Sustained release

Highlights

- ✓ Etodolac floating *in-situ* gel was proposed for gastroretentive delivery.
- ✓ Sodium alginate and HPMC support gel formation and sustained release.
- ✓ Effervescence-induced buoyancy enables prolonged gastric residence.
- ✓ Formulation optimization targets viscosity, gel strength and drug release.
- ✓ *In-vivo* studies are essential to confirm gastroretention and pharmacokinetic benefits.

Graphical Abstract



1. Introduction

The oral route remains one of the most convenient and widely accepted routes for drug administration because of its simplicity, patient acceptability, low cost and ease of administration.¹ However, conventional oral dosage forms may undergo rapid gastric emptying, resulting in relatively short residence at the upper gastrointestinal tract. This can be problematic when prolonged gastric residence, controlled release or improved dissolution under acidic conditions is desirable.² Gastroretentive drug delivery systems (GRDDS) have therefore been investigated to prolong the residence of dosage forms in the stomach and regulate drug release.³ GRDDS include floating, mucoadhesive, expandable, high-density, magnetic and raft-forming systems.⁴ Among these, floating systems are designed to possess a density lower than gastric contents, allowing them to remain buoyant for an extended period. Floating systems may be

broadly classified into effervescent and non-effervescent systems. Hydrophilic polymers such as HPMC and sodium alginate can hydrate and form gel barriers that contribute to buoyancy and sustained drug release.⁵ An *in-situ* gel is administered as a liquid or low-viscosity formulation and undergoes gel formation after exposure to physiological conditions. Gelation can be triggered by pH, temperature, ions or solvent exchange. In gastroretentive systems, ionic or pH-responsive gelation can be combined with gas generation to produce a buoyant gel depot in the stomach. Sodium alginate is particularly attractive because of its gel-forming ability, biocompatibility and suitability for gastroretentive formulations.⁶ Etodolac is an NSAID exhibiting analgesic and anti-inflammatory activity. It is well absorbed orally and does not undergo significant first-pass metabolism. The reported terminal half-life in healthy adults is approximately 6.4 h, while the mean time to peak concentration is approximately

1.4 h. Food does not substantially alter the extent of absorption but can reduce peak concentration and delay the time to peak concentration.⁷

Etodolac has a molecular formula of $C_{17}H_{21}NO_3$, reported pKa of approximately 4.65 and logP of approximately 2.5.⁸ These physicochemical characteristics make polymeric gastroretentive formulations worthy of investigation, particularly when the objective is to modify the release profile rather than simply provide immediate systemic exposure. The present review therefore focuses on the scientific rationale, formulation strategy, polymer selection, preparation, characterization, evaluation and future development of floating oral *in-situ* gel of etodolac.

2. Rationale for developing etodolac floating *in-situ* gel

The development of a floating *in-situ* gel of etodolac is based on the need to combine gastroretention with controlled drug release.⁹ Following oral administration, the liquid formulation is expected to reach the stomach, where exposure to the acidic gastric environment promotes polymer hydration and *in-situ* gel formation. Incorporation of an effervescent agent can generate CO_2 , which becomes entrapped within the polymeric network and decreases the apparent density of the formed gel, thereby promoting buoyancy and prolonging gastric residence.¹⁰ The resulting floating gel depot can act as a sustained-release matrix from which etodolac is gradually released by diffusion, polymer relaxation, swelling and/or erosion. Etodolac → Oral administration → Gastric environment → Polymer hydration and *in-situ* gelation → CO_2 generation and entrapment → Floating gel depot → Prolonged gastric residence → Controlled etodolac release → Sustained drug exposure. The principal advantages expected from this approach include prolonged gastric residence, sustained drug release, reduced fluctuations in plasma drug concentrations, potential reduction in dosing frequency, and improved control over the drug-release profile.¹¹ The formulation also provides flexibility for optimizing polymer type, polymer concentration and polymer combinations to achieve an appropriate balance between viscosity, gel strength, buoyancy and drug diffusion. Thus, the floating *in-situ* gel approach may provide a useful platform for modifying the release characteristics of etodolac while maintaining the convenience of oral administration. However, prolonged gastric residence does not necessarily result in improved bioavailability or therapeutic efficacy. Gastric retention is influenced by several physiological and formulation-related factors, including the fed or fasted state, gastric motility, gastric emptying rate, dosage-form density, viscosity, gel strength and polymer characteristics.¹² Therefore, the proposed formulation should be evaluated systematically using *in-vitro* buoyancy, gelation, rheological, drug-release and stability studies, followed by appropriate *in-vivo* gastric-retention and pharmacokinetic investigations to establish whether the formulation provides a meaningful pharmaceutical advantage over conventional etodolac dosage forms.

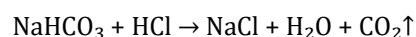
3. Drug profile of etodolac

Table 1: Comprehensive drug profile of etodolac¹³⁻¹⁶

Parameter	Description
Drug	Etodolac
Therapeutic class	NSAID
Primary actions	Analgesic and anti-inflammatory
Molecular formula	$C_{17}H_{21}NO_3$
Molecular weight	Approximately 287.36 g/mol
pKa	Approximately 4.65
LogP	Approximately 2.5
Oral absorption	Well absorbed
Tmax	Approximately 1.4 h in healthy adults
Terminal half-life	Approximately 6.4 h
Plasma protein binding	>99%
First-pass metabolism	Not significant
Major objective of formulation	Gastroretention and controlled release

4. Floating oral *in-situ* gel: concept and mechanism

Floating oral *in-situ* gels combine *in-situ* gelation with buoyancy to achieve prolonged gastric retention and sustained drug release.¹⁷ The formulation is administered as a liquid and, upon reaching the stomach, physiological conditions trigger polymer hydration, chain relaxation, and gel-network formation. When an effervescent component such as sodium bicarbonate reacts with gastric hydrochloric acid, carbon dioxide is generated:



The generated CO_2 becomes entrapped within the polymeric gel network, thereby reducing the apparent density of the gel and enabling it to float on the gastric fluid.¹⁸ Simultaneously, drug release occurs through diffusion from the hydrated and formed polymeric network, providing sustained drug delivery:

Polymer hydration → Chain relaxation → Gel-network formation → CO_2 entrapment → Reduced apparent density → Buoyancy → Drug diffusion → Sustained drug release

Thus, the overall mechanism involves two interconnected processes: (1) *in-situ* gel formation and (2) buoyancy generation which together enhance gastric residence time and support sustained drug release. Floating gastroretentive systems based on sodium alginate and other hydrocolloids have been extensively investigated, with alginate being particularly useful because of its excellent gel-forming ability, biocompatibility, and gastroretentive properties.^{19,20}

Figure 1 illustrates the proposed mechanism of the Etodolac *in-situ* gel following oral administration. After reaching the acidic gastric environment (pH ~1-3), polymer hydration and gel formation occur. Simultaneously, sodium bicarbonate reacts with gastric hydrochloric acid to generate CO₂, which becomes entrapped within the polymeric gel network. The

entrapped CO₂ reduces the apparent density of the formulation, resulting in the formation of a floating gel depot in the stomach. The retained gel gradually releases etodolac through controlled diffusion, thereby providing sustained drug release and prolonged gastric residence.

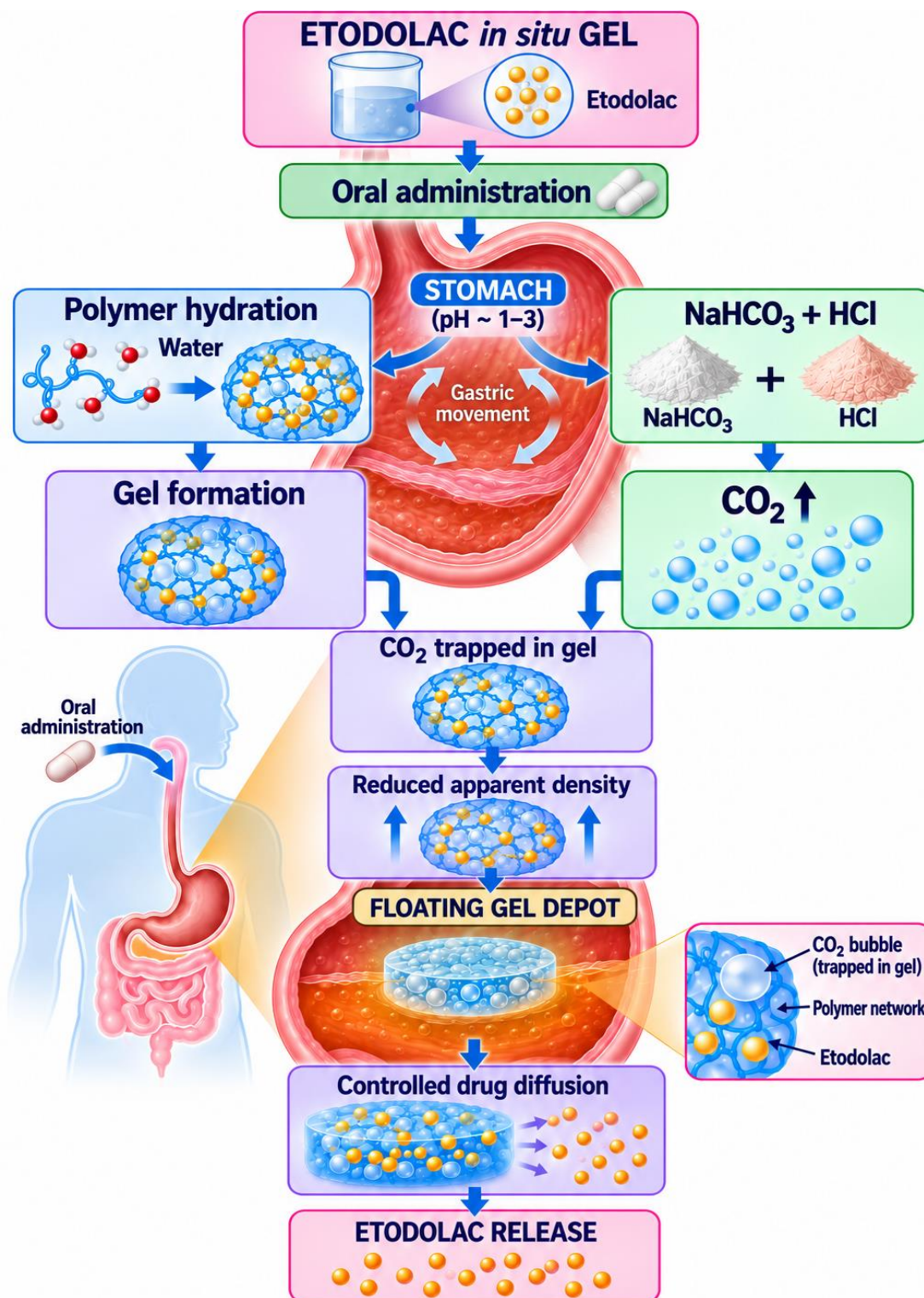


Figure 1. Mechanism of floating oral *in-situ* gel

[Schematic representation of gel formation, CO₂ entrapment, buoyancy and controlled release from an etodolac floating oral *in-situ* gel].

5. Formulation Design

5.1 Selection of polymers

Polymer selection is one of the most critical factors in the development of an effective *in-situ* gel, as the polymer determines the formulation's rheological properties, gelation behavior, gastric retention and drug-release profile.²¹ An ideal polymer should provide appropriate viscosity before administration to facilitate easy swallowing and administration, followed by rapid and reproducible gelation under physiological gastric conditions.²² The formed gel should possess adequate mechanical strength and integrity to withstand gastric motility while maintaining good compatibility with the drug and other formulation components.²³ In addition, the polymer should promote prolonged gastric retention and controlled drug diffusion, thereby supporting sustained drug release. Finally, it should exhibit acceptable physical and chemical stability during storage and use. Ideal polymer requirements: **Appropriate pre-administration viscosity → Rapid & reproducible gelation → Adequate gel strength → Drug compatibility → Prolonged gastric retention → Controlled drug diffusion → Physical stability**

Sodium alginate

Sodium alginate is a natural polysaccharide widely investigated for gastroretentive systems. It can form hydrogels and can be combined with other polymers to modify gel strength and release characteristics.²⁴

HPMC

HPMC is a semisynthetic hydrophilic polymer commonly used as a viscosity enhancer and release-retarding polymer. Its hydration produces a viscous gel barrier, which can slow drug diffusion.²⁵

Gellan gum

Gellan gum is an ion-responsive polysaccharide capable of forming gels in the presence of suitable ions. It can therefore be investigated in combination with sodium alginate for improving gel structure.²⁶

Carbopol

Carbopol can increase viscosity and mucoadhesive characteristics. However, excessive polymer concentration can make the formulation difficult to administer and may adversely affect drug release.²⁷

Table 2. Major excipients and their functions

Excipient	Category	Primary function	ReF.
Sodium alginate	Natural polymer	Gel formation and controlled release	28
HPMC	Semisynthetic polymer	Viscosity enhancement and release retardation	29
Gellan gum	Natural/biopolymer	Ion-triggered gelation	30
Carbopol	Synthetic polymer	Viscosity and mucoadhesion	31
Sodium bicarbonate	Gas-generating agent	CO ₂ generation and buoyancy	32
Citric acid	Acidifying agent	Supports effervescence	33
Sodium citrate	Buffer/complexing agent	Modulation of ionic environment	34
Glycerin/propylene glycol	Vehicle/humectant	Formulation processing	35
Preservative	Preservative	Microbial protection where required	36
Purified water	Vehicle	Continuous phase	36

6. Proposed formulation development

The proposed formulation development of Etodolac floating *in-situ* gel involves the preparation of several experimental batches with varying concentrations and ratios of polymers, particularly sodium alginate and HPMC, while maintaining Etodolac and other excipients at suitable levels.³⁷ Gellan gum may be incorporated as a secondary gelling polymer, whereas sodium bicarbonate and citric acid are used to generate carbon dioxide and impart floating characteristics. The formulations are optimized based on viscosity, gelation capacity, floating lag time, total floating duration, drug content and *in-vitro* drug-release characteristics.³⁸ The final concentrations of the polymers and excipients are determined through preliminary formulation and optimization studies.

7. Preparation method³⁹⁻⁴¹

A suitable general preparation procedure is:

Step 1: Polymer dispersion

The required quantity of sodium alginate is dispersed gradually in purified water under continuous stirring to avoid lump formation.

Step 2: Secondary polymer incorporation

HPMC and/or gellan gum is separately hydrated and subsequently incorporated into the alginate dispersion.

Step 3: Drug incorporation

Etodolac is dispersed or solubilized using a suitable pharmaceutical vehicle/co-solvent system, depending on its concentration and formulation characteristics.

Step 4: Addition of excipients

Sodium bicarbonate and other formulation components are incorporated carefully under controlled stirring.

Step 5: Volume adjustment

The formulation is brought to the desired final volume using purified water.

Step 6: Deaeration

Entrapped air is removed because excessive air bubbles can alter viscosity, dose uniformity and apparent buoyancy.

Step 7: Final characterization

The formulation is evaluated for pH, viscosity, gelation, floating characteristics, drug content and dissolution. **Figure 2** illustrates the stepwise formulation development of Etodolac floating oral *in-situ* gel. Sodium alginate is initially hydrated in purified water under continuous stirring, followed by the incorporation of HPMC and/or gellan gum to obtain a uniform polymer dispersion. Etodolac is subsequently added, followed by suitable excipients and an effervescent agent. The formulation volume is adjusted with purified water and the preparation is deaerated to remove entrapped air. The resulting formulation is filled into a suitable container as an Etodolac floating oral *in-situ* gel and subjected to further physicochemical and performance evaluation.

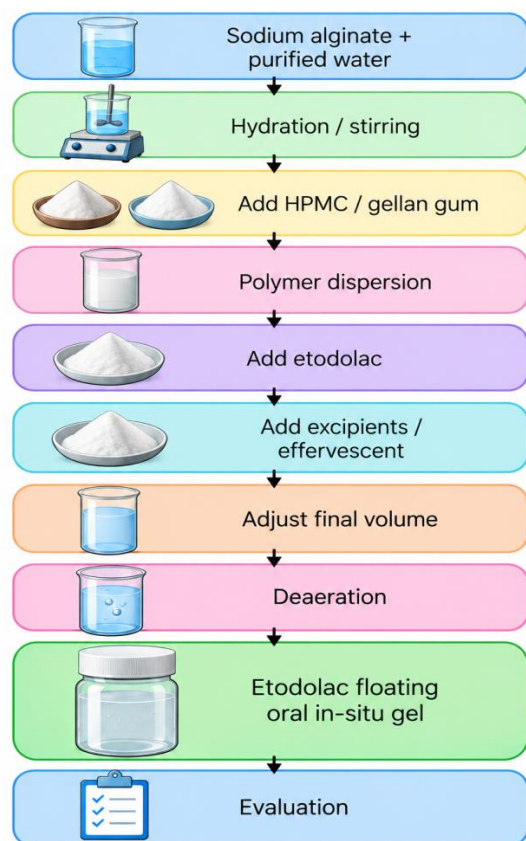


Figure 2: Formulation development process of etodolac floating oral *in-situ* gel

(Generalized manufacturing workflow for development of an etodolac floating oral *in-situ* gel).

8. Evaluation of floating oral *in-situ* gel

8.1 Appearance

The formulation should be visually examined for colour, clarity/opacity, homogeneity, phase separation, sedimentation and visible particulate matter.⁴²

8.2 pH

The pH should be determined using a calibrated digital pH meter. Measurements should be performed at room temperature, preferably in triplicate.^{42,43}

8.3 Viscosity

Viscosity is a critical parameter because it influences the pourability, syringe ability, ease of administration, gel formation, drug release and floating behavior of the formulation. Viscosity can be measured using a Brookfield-type viscometer with a suitable spindle and rotational speed.⁴³

8.4 Gelation study

A measured quantity of the formulation is introduced into simulated gastric fluid (SGF) or an acidic medium and the time required for gel formation, nature and integrity of the gel, gel duration and erosion behavior are observed and evaluated.^{44,45}

8.5 Floating lag time

Floating lag time is the time required for the formulation to begin floating after exposure to simulated gastric conditions. Lower floating lag time generally indicates faster establishment of buoyancy.⁴⁶

8.6 Total floating duration

The duration for which the formed gel remains buoyant should be recorded.^{47,48}

8.7 Drug-content uniformity

An accurately measured quantity of the formulation is appropriately diluted and analyzed using a validated UV-visible spectrophotometric or chromatographic method to determine the drug content.⁴⁹

The drug content is calculated as:

$$\text{Drug content (\%)} = \frac{\text{Actual drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

8.8 Swelling/gel strength

The increase in size or mass of the gel after exposure to simulated gastric medium can be investigated.^{50,51}

8.9 *In-vitro* drug-release study

Drug release can be investigated using a USP dissolution apparatus in an appropriate acidic medium at a controlled temperature. Samples are withdrawn at predetermined time intervals, analyzed for drug content and the withdrawn volume is replaced with an equal volume of fresh dissolution medium to maintain constant conditions.⁵²

Table 3. Evaluation parameters

Parameter	Method/Instrument	Importance	ReF.
Appearance	Visual inspection	Physical quality	53
pH	Digital pH meter	Stability and gastric compatibility	54
Viscosity	Brookfield viscometer	Administration and gel behavior	55
Gelation time	<i>In-vitro</i> gelation test	Rapid gel formation	56
Floating lag time	Visual observation	Initial buoyancy	57
Floating duration	<i>In-vitro</i> buoyancy test	Gastroretention potential	58
Drug content	UV/HPLC	Dose uniformity	59
Swelling index	Gravimetric method	Gel behavior	60
Gel strength	Texture/rheological method	Integrity	61
<i>In-vitro</i> release	USP dissolution apparatus	Release performance	62
Release kinetics	Mathematical models	Mechanism of release	63
Stability	Accelerated/long-term study	Product stability	63

9. Drug-release kinetic analysis⁶⁴⁻⁶⁸

The dissolution data should be fitted to different mathematical models.

Zero-order model

The zero-order kinetic model is expressed as:

$$Q_t = Q_0 + K_0 t$$

where Q_t is the amount of drug released at time t , Q_0 is the initial amount of drug and K_0 is the zero-order release constant. It is used to evaluate drug release at a constant rate, independent of the drug concentration remaining in the dosage form.

First-order model

The first-order kinetic model is expressed as:

$$\log Q_t = \log Q^0 - \frac{K_1 t}{2.303}$$

where Q_t is the amount of drug remaining at time t , Q_0 is the initial amount of drug and K_1 is the first-order release constant. It is used to evaluate concentration-dependent drug release, in which the release rate decreases as the drug concentration decreases.

Higuchi model

The Higuchi model is expressed as:

$$Q = K_h \sqrt{t}$$

where Q is the amount of drug released at time t , K_h is the Higuchi dissolution constant and t is the release time. It is used to evaluate diffusion-controlled drug release from a matrix system.

Korsmeyer-peppas model

Used to:

Evaluate drug-release kinetics and estimate the release mechanism. The exponent n provides information about whether release is predominantly diffusion-controlled, swelling-controlled, or governed by anomalous transport, depending on the dosage-form geometry and model assumptions.

$$\frac{M_t}{M_\infty} = K t^n$$

Hixson-Crowell Cube-Root Law - Theory

The Hixson-Crowell model describes drug release when the surface area and dimensions of a dosage form change continuously during dissolution.

Equation:

$$W_0^{1/3} - W_t^{1/3} = K t$$

Where:

W_0 = Initial amount of drug in the dosage form

W_t = Amount of drug remaining at time t

K = Hixson-crowell release constant

t = Time

Theory:

As the dosage form dissolves, its surface area and dimensions decrease. The Hixson-Crowell model accounts for this changing surface area and is commonly used for dissolution-controlled drug release from tablets and other solid dosage forms.

Table 4. Release models and interpretation

Model	Equation	Primary interpretation	Ref.
Zero-order	$Q = Q_0 + K_0t$	Constant drug-release rate	69
First-order	$\log Q = \log Q_0 - K_1t/2.303$	Concentration-dependent release	70
Higuchi	$Q = K^H\sqrt{t}$	Diffusion-controlled release	71
Korsmeyer-Peppas	$Mt/M_\infty = Kt^n$	Mechanistic assessment	72
Hixson-Crowell	$W_0^{1/3} - W_t^{1/3} = Kt$	Changes in surface area/dimensions	73

10. Stability studies

The optimized formulation should undergo stability testing in accordance with applicable ICH guidelines to evaluate its physical, chemical and performance stability during storage.⁷⁴ Key parameters should include appearance, pH, viscosity, drug content, gelation behavior, floating lag time, total floating duration and *in-vitro* drug-release profile. Comparative evaluation of the dissolution/drug-release profile before and after storage can help identify potential formulation changes and confirm the stability and performance of the optimized

formulation.⁷⁵ **Figure 3** presents the systematic formulation optimization and evaluation strategy for Etodolac floating oral *in-situ* gel. Preliminary trials are followed by a polymer concentration study to assess the effects on viscosity, gelation and buoyancy. The selected formulations are then evaluated for drug content and *in-vitro* drug release, followed by release-kinetic analysis. Based on the obtained results, the formulation is optimized and subjected to stability testing. The optimized formulation is subsequently considered for *in-vivo* gastric-retention and pharmacokinetic assessment.

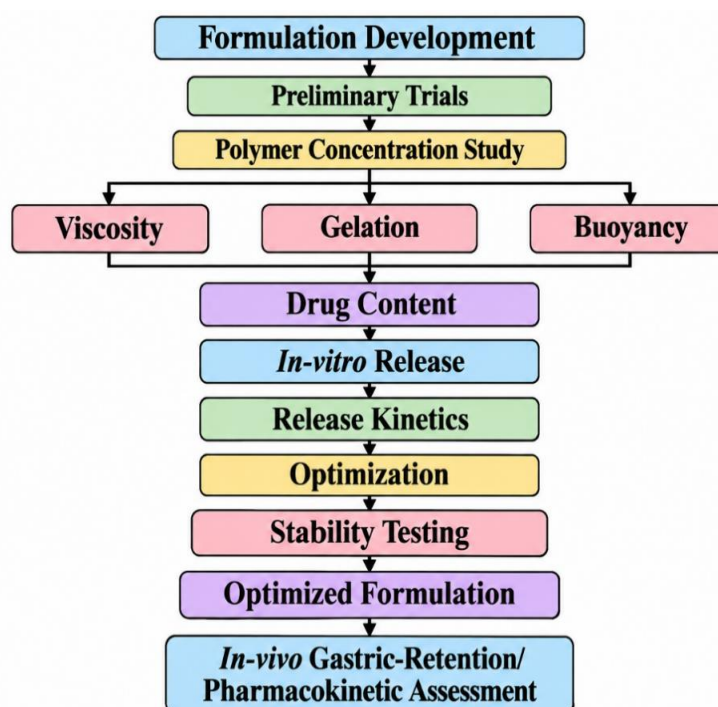


Figure 3. Flow diagram represents various steps involved in overall evaluation and optimization strategy (Integrated strategy for formulation optimization and evaluation of etodolac floating oral *in-situ* gel).

Table 5. Critical quality attributes and optimization targets

Critical attribute	Desired formulation characteristic	Major influencing factor	Ref.
Appearance	Uniform and physically stable	Polymer/vehicle compatibility	76
pH	Suitable for formulation stability	Buffer system	77
Viscosity	Pourable but sufficiently viscous	Polymer concentration	78
Gelation	Rapid and stable	Polymer type/concentration	79

Floating lag time	Short	Gas generation and polymer network	80
Floating duration	Prolonged	Density and gel integrity	81
Drug content	Uniform	Drug dispersion	82
Drug release	Controlled and reproducible	Polymer concentration	83
Gel strength	Adequate	Polymer type and crosslinking	84
Stability	Minimal change during storage	Formulation composition/storage	85

11. Advantages of the proposed system⁸⁶⁻⁸⁸

A floating oral *in-situ* gel of etodolac may provide:

- 1. Prolonged gastric residence:** Buoyancy may delay gastric emptying of the dosage form.
- 2. Controlled drug release:** Hydrated polymer networks can act as diffusion barriers.
- 3. Reduced dosing frequency:** Sustained release may potentially reduce repeated administration.
- 4. Liquid administration:** The formulation can be administered as a liquid before *in-situ* gel formation.
- 5. Formulation flexibility:** Polymer concentration and polymer combinations can be optimized.
- 6. Potential improvement in therapeutic consistency:** Controlled release may reduce rapid concentration fluctuations.

12. Safety considerations for etodolac

Etodolac belongs to the NSAID class. Gastroretentive delivery should therefore not be interpreted as eliminating the established systemic or gastrointestinal risks associated with NSAIDs. The formulation should be developed with appropriate attention to dose, excipient safety and the approved prescribing information.⁸⁹ Etodolac is highly protein bound (>99%), and its reported terminal half-life in healthy adults is approximately 6.4 h. For an experimental formulation, dose selection should be based on the intended research protocol and applicable ethical and regulatory requirements rather than simply increasing the dose to achieve prolonged release.⁹⁰⁻⁹³

13. Limitations and challenges

Despite the potential advantages, several challenges must be considered.

13.1 Gastric physiological variability

Gastric emptying varies substantially with fed or fasted state, food composition, gastric motility, age, disease state and individual physiology. Consequently, excellent *in-vitro* floating performance does not necessarily guarantee prolonged gastric retention in humans, highlighting the importance of appropriate *in-vivo* evaluation.

13.2 Viscosity-buoyancy relationship

Increasing polymer concentration may improve gel strength and sustained release but can make the formulation excessively viscous.

13.3 Dose loading

The amount of drug that can be incorporated while maintaining acceptable rheological and floating characteristics must be determined experimentally.

13.4 Effervescent stability

Gas-generating agents can be sensitive to moisture. Therefore, manufacturing and packaging conditions are important.

13.5 *In-vitro/in-vivo* correlation

Dissolution and floating studies alone cannot establish therapeutic superiority. Pharmacokinetic and gastric-retention studies are needed.

14. Future perspectives

The future development of etodolac floating oral *in-situ* gel can move beyond conventional polymer screening toward systematic formulation optimization.

14.1 Quality-by-Design approach

A Quality by Design (QbD) strategy can be employed to identify critical material attributes (CMAs) and critical process parameters (CPPs) that influence formulation performance. Potential CMAs include polymer concentration, polymer ratio, drug concentration, gas-generating agent concentration and polymer molecular weight, while potential CPPs include mixing speed, hydration time, addition sequence, temperature and homogenization conditions. Identifying and controlling these factors can improve formulation robustness, reproducibility, and overall product quality.

14.2 Design of experiments

Factorial designs, central composite designs and Box-Behnken designs can be used to identify interactions among formulation variables and optimize multiple responses simultaneously.

14.3 Advanced rheological characterization

Oscillatory rheology can provide detailed information on gel strength, elastic modulus (G'), viscous modulus (G''), gel-network development and structural recovery, thereby helping to characterize the viscoelastic behavior, structural integrity and stability of the gel system.

14.4 *In-vivo* gastric-retention studies

Future studies should investigate actual gastric residence using appropriate imaging techniques or validated pharmacokinetic approaches. Gastroretention

is highly dependent on physiological variables, so *in-vivo* confirmation is important.

14.5 Pharmacokinetic evaluation

Important pharmacokinetic parameters include C_{max}, T_{max}, AUC, t_{1/2} and mean residence time (MRT). The objective is to determine whether controlled gastroretentive delivery provides a meaningful pharmacokinetic advantage, such as improved drug exposure, prolonged residence, or sustained systemic availability, rather than merely demonstrating prolonged *in-vitro* drug release.

14.6 Advanced manufacturing

Emerging manufacturing technologies, including 3D printing and other controlled fabrication approaches, may eventually enable personalized gastroretentive dosage forms with programmable drug-release profiles. Recent research has explored advanced manufacturing strategies for gastroretentive systems.

14.7 Mucoadhesive-floating hybrid systems

Combining buoyancy with controlled mucoadhesion could potentially provide an additional mechanism for gastric retention. However, excessive adhesion must be avoided because the system should not interfere with normal gastric physiology.

14.8 Patient-centric formulations

Future formulations may focus on improving palatability, providing greater dose flexibility, facilitating easy administration, enhancing physical stability and reducing administration frequency to improve patient convenience, adherence and therapeutic outcomes.

15. Conclusion

Floating oral *in-situ* gel represents a promising gastroretentive platform for controlled delivery of etodolac. The approach combines liquid administration with rapid *in-situ* gel formation and buoyancy, potentially prolonging gastric residence and regulating drug release. Sodium alginate, HPMC and other hydrophilic polymers can be systematically investigated to obtain an appropriate balance among viscosity, gel strength, floating ability and drug-release control. Sodium bicarbonate or another suitable gas-generating component can provide buoyancy through CO₂ generation in the acidic gastric environment. Existing literature supports the broader suitability of alginate-based and polymeric gastroretentive systems, but formulation-specific performance must be demonstrated experimentally. For etodolac specifically, the development should emphasize controlled release rather than simply maximizing gastric residence, because conventional etodolac is already well absorbed orally and has measurable systemic bioavailability. The optimized formulation should therefore be selected using a combination of physicochemical characterization, floating performance, dissolution kinetics, stability testing and, ideally, *in-vivo* gastric-retention and pharmacokinetic studies. Such an integrated strategy can establish whether the floating

in-situ gel provides a genuine pharmaceutical advantage over conventional etodolac dosage forms.

Abbreviations

AUC : Area Under the Curve

API : Active Pharmaceutical Ingredient

C_{max} : Maximum Plasma Concentration

CO₂ : Carbon Dioxide

CMA : Critical Material Attribute

CMAs : Critical Material Attributes

CPP : Critical Process Parameter

CPPs : Critical Process Parameters

DoE : Design of Experiments

FDDS : Floating Drug Delivery System

GRDDS : Gastroretentive Drug Delivery System

GI/GIT : Gastrointestinal/Gastrointestinal Tract

HPLC : High-Performance Liquid Chromatography

HPMC : Hydroxypropyl Methylcellulose

HCl : Hydrochloric Acid

ICH : International Council for Harmonisation

MRT : Mean Residence Time

NaHCO₃ : Sodium Bicarbonate

NaCl : Sodium Chloride

NSAID : Non-Steroidal Anti-Inflammatory Drug

pH : Potential of Hydrogen

QbD : Quality by Design

R² : Coefficient of Determination

T_{max} : Time to Maximum Plasma Concentration

t_{1/2} : Half-Life

UV : Ultraviolet

USP : United States Pharmacopeia

Declaration:

Ethics approval and consent to participate: Ethical approval and informed consent were not applicable to this study because it was a literature-based narrative review and did not involve any original research involving human participants or experimental animals.

Clinical Trial No: Clinical trial registration was not applicable to this manuscript, as it presents a narrative review based exclusively on previously published literature and does not involve any clinical trials.

Consent for publication: Clinical trial registration was not required for this study because the manuscript is a narrative review based entirely on previously published literature and does not include any clinical trial or prospective human intervention.

Availability of data and material: Data availability was not applicable to this study, as the manuscript is a narrative review based solely on previously published literature and does not involve the generation, collection, or analysis of original datasets.

Funding: The authors declare that no specific financial support was received from any government agency, commercial entity, or non-profit organization for the preparation of this review.

Declaration of competing interest: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Acknowledgements: The authors sincerely acknowledge the Principals of Columbia Institute of Pharmacy, Columbia Professional University, Raipur, Chhattisgarh, India and Gracious College of Pharmacy, Village Belbhata, Abhanpur, Raipur, Chhattisgarh, India, for their valuable encouragement, support and provision of the necessary infrastructure and library facilities that contributed to the successful

completion of this review.

Authorship contribution statement:

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References:

- Kumar A, Kumar A. Smart Pharmaceutical Formulations of Biopolymeric Materials in Buccal Drug Delivery. *Biomedical Materials & Devices*. 2025;3(2):741-749. <https://doi.org/10.1007/s44174-024-00223-y>
- Qu W, Wu P, Yang S, Liu T, Qi S, Chen XD. Mechanistic prediction of food-induced variability in drug release and pharmacokinetics using a dynamic gastrointestinal system and convolution-based modeling. *Int J Pharm*. 2026;701:127107. <https://doi.org/10.1016/j.ijpharm.2026.127107> PMID:42320737
- Singh A, Mandal RK, Sahoo S, Shah TM, Pal R. Gastro-Retentive Drug Delivery Systems (GRDDs) as a Promising Strategy for Disease Targeting: A Comprehensive Review. *Drug Deliv Lett*. 2026;16. <https://doi.org/10.2174/0122103031410778251206145139>
- Shah K, Singh D, Agrawal R, Garg A. Current Developments in the Delivery of Gastro-Retentive Drugs. *AAPS PharmSciTech*. 2025;26(2):57. <https://doi.org/10.1208/s12249-025-03052-4> PMID:39920556
- Ashraf F, Shah KU, Saeed MD, et al. Non-effervescent Polymeric Floating Tablets of Clarithromycin and Pantoprazole: Preparation and In-Vitro Evaluation for Improved Gastric Drug Retention. *J Pharm Innov*. 2025;20(1):6. <https://doi.org/10.1007/s12247-024-09917-8>
- Mathews MM. Alginate-Based Composites in Drug Delivery. In: *Natural Biopolymeric Composites for Biomedical Research*. Springer Nature Singapore; 2026:333-350. https://doi.org/10.1007/978-981-95-9909-7_14
- Toth SH, Stoica AD, Sevcencu C. Redesigning Ibuprofen for Improved Oral Delivery and Reduced Side Effects. *Bioconj Chem*. 2025;36(5):893-913. <https://doi.org/10.1021/acs.bioconjchem.4c00558> PMID:40292773
- Sebaa R, AlMalki RH, Sukkarieh H, et al. Systemic Metabolic Alterations Induced by Etodolac in Healthy Individuals. *Pharmaceuticals*. 2025;18(8):1155. <https://doi.org/10.3390/ph18081155> PMID:40872546 PMCID:PMC1238885
- Dutta P, Dhar A, Dhang P, Mukherjee K, Giri TK. In Situ Gellable Hydrogels for Gastroretentive Drug Delivery Systems. In: *In Situ Gellable Hydrogels for Drug Delivery and Tissue Engineering*. Springer Nature Singapore; 2026:87-115. https://doi.org/10.1007/978-981-95-6619-8_4
- Liu G, Jin X, Yang R, Chen N, Sharafat A, Zhang W. Gastric fluid-triggered echogenic hydrogel for long-term ultrasound imaging and drug release. *Chemical Engineering Journal*. 2025;526:170837. <https://doi.org/10.1016/j.cej.2025.170837>
- Gupta S, Agrawal N, Siddiqui MA, Sharma AK, Jain SK, Lanjhiyana SK. Current trends in colon-targeted delivery using microbeads system: approaches, methodologies and therapeutic aspects. Published online August 6, 2026. <https://doi.org/10.1007/s43538-026-00859-y>
- Wang C, Chen J, Chen N, et al. Sodium alginate/gelatin/guar gum oral delivery ternary composite hydrogel beads loaded with Anzhong decoction: Gastric floating retention and controlled release. *Int J Biol Macromol*. 2026;344:150390. <https://doi.org/10.1016/j.ijbiomac.2026.150390> PMID:41571133
- Singh JK, Kaur S, Chandrasekaran B, et al. A QbD-Navigated Approach to the Development and Evaluation of Etodolac-Phospholipid Complex Containing Polymeric Films for Improved Anti-Inflammatory Effect. *Polymers (Basel)*. 2024;16(17):2517. <https://doi.org/10.3390/polym16172517> PMID:39274149 PMCID:PMC11398249
- Bhamble S, Dighe S, Katari O, Yadav V, Ansari MdM, Jain S. Ionic liquid-based Ionogel: A novel strategy to improve dermal delivery and in vivo efficacy of etodolac in rheumatoid arthritis management. *J Mol Liq*. 2024;412:125841. <https://doi.org/10.1016/j.jmolliq.2024.125841>
- Sánchez-Luquez K, Reis Silveira AM, Sánchez-Vinces S, et al. Etodolac Single Dose Metabolic Profile Elucidation: Pharmacokinetics and Adverse Events in Healthy Volunteers. *Pharmaceuticals*. 2025;18(1):82. <https://doi.org/10.3390/ph18010082> PMID:39861145 PMCID:PMC11768370
- Basu S, Varghese R, Debroy R, Ramaiah S, Veeraraghavan B, Anbarasu A. Non-steroidal anti-inflammatory drugs ketorolac and etodolac can augment the treatment against pneumococcal meningitis by targeting penicillin-binding proteins. *Microb Pathog*. 2022;170:105694. <https://doi.org/10.1016/j.micpath.2022.105694> PMID:35921951
- Bachhar A, Barman S, Sarkar A, Bose A, Biswas P, Mandal S. Advances in biopolymer-based floating raft drug delivery systems for gastroretentive therapy. *J Biomater Sci Polym Ed*. Published online March 5, 2026:1-39. <https://doi.org/10.1080/09205063.2026.2636795> PMID:41784228
- Siripruekpong W, Wiwattanapatapee R, Chabbin O, Assifaoui A. Structural and mechanistic exploration in the development of floating drug delivery systems using calcium-pectinate gels with sodium bicarbonate as CO₂ gas-forming agent. *J Drug Deliv Sci Technol*. 2025;107:106729. <https://doi.org/10.1016/j.jddst.2025.106729>
- Puyathorn N, Senarat S, Lertsuphotvanit N, Phaechamud T. Physicochemical and Bioactivity Characteristics of Doxycycline Hyclate-Loaded Solvent Removal-Induced Ibuprofen-Based In Situ Forming Gel. *Gels*. 2023;9(2):128.

- <https://doi.org/10.3390/gels9020128> PMID:36826298
PMCID:PMC9956372
20. Lee CS, Hwang HS. Starch-Based Hydrogels as a Drug Delivery System in Biomedical Applications. *Gels*. 2023;9(12):951. <https://doi.org/10.3390/gels9120951> PMID:38131937
PMCID:PMC10743264
 21. Mishra MK, Shukla D, Sharma S, Sharma JN, Singh TP. From Liquid to Gel: Multifunctional Stimuli-responsive Polymers for Targeted Oral Drug Delivery. *AAPS PharmSciTech*. 2026;27(7):285. <https://doi.org/10.1208/s12249-026-03519-y> PMID:42717126
 22. Kolawole OM, Cook MT. In situ gelling drug delivery systems for topical drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*. 2023;184:36-49. <https://doi.org/10.1016/j.ejpb.2023.01.007> PMID:36642283
 23. Basak A, Ghosh S, Pattanayak D, Das S. Floating-Mucoadhesive Gastro-Retentive Tablets for Enhanced Oral Delivery of Glimepiride: Formulation, Optimization, and Controlled Release. *AAPS PharmSciTech*. 2026;27(3):142. <https://doi.org/10.1208/s12249-026-03395-6> PMID:41840294
 24. A Gellan Gum/Sodium Alginate-based gastric-protective hydrogel loaded with a combined herbal extract consisting of Panax notoginseng, Bletilla striata and Dendrobium officinale.
 25. Afrose N, Chakraborty R, Kuotsu K. A strategic design improvement in patient-centric sustained delivery of metoprolol succinate using natural gum blend matrix: design, development and in-vitro comparative evaluation. *Journal of Polymer Research*. 2023;30(9):367. <https://doi.org/10.1007/s10965-023-03757-9>
 26. Bhowmik A, Dey C, Giri TK, Mukherjee K. Properties of Polymers Enabling In Situ Gel Formation. In: *In Situ Gellable Hydrogels for Drug Delivery and Tissue Engineering*. Springer Nature Singapore; 2026:33-61. https://doi.org/10.1007/978-981-95-6619-8_2
 27. Rahbar N, Darvish S, Farrahi F, Kouchak M. Chitosan/carbomer nanoparticles- laden in situ gel for improved ocular delivery of timolol: in vitro, in vivo, and ex vivo study. *Drug Deliv Transl Res*. 2025;15(4):1210-1220. <https://doi.org/10.1007/s13346-024-01663-1> PMID:38976207
 28. Lv Q, Xiao T, Dong G, et al. Preparation and characterization of starch carbamate modified natural sodium alginate composite hydrogel blend formulation and its application for slow-release fertilizer. *Int J Biol Macromol*. 2024;278:134713. <https://doi.org/10.1016/j.ijbiomac.2024.134713> PMID:39154686
 29. Mori D, Dudhat K, Soniwal A, et al. Polymers used in pharmaceutical industry for oral delivery: insight to synthesis, structure-activity relationship, and recent applications. *Polymer Bulletin*. 2024;81(18):16373-16413. <https://doi.org/10.1007/s00289-024-05509-1>
 30. Dong W, Ji J, Wang X, et al. The biomedical applications of flavonoid-containing hydrogels. *Phytochemistry Reviews*. Published online August 10, 2026. <https://doi.org/10.1007/s11101-026-10294-y>
 31. Golshani S, Vatanara A, Balalaie S, Kadkhoda Z, Abdollahi M, Amin M. Development of a Novel Histatin-5 Mucoadhesive Gel for the Treatment of Oral Mucositis: In Vitro Characterization and In Vivo Evaluation. *AAPS PharmSciTech*. 2023;24(7):177. <https://doi.org/10.1208/s12249-023-02632-6> PMID:37639072
 32. Liu G, Mei D, Wu H, Zhang W. Core-shell floating hydrogel assembly for sustained dual-drug delivery and ultrasound imaging in rheumatoid arthritis. *Appl Mater Today*. 2026;52:103369. <https://doi.org/10.1016/j.apmt.2026.103369>
 33. He S, Nielsen CU, Mu H, Jacobsen J. In vitro and ex vivo evaluation of bilayered effervescent microenvironmental pH modifying buccal films with saquinavir. *J Drug Deliv Sci Technol*. 2022;78:103954. <https://doi.org/10.1016/j.jddst.2022.103954>
 34. Ferreira CMH, Pinto ISS, Soares E V., Soares HMVM. (Un)suitability of the use of pH buffers in biological, biochemical and environmental studies and their interaction with metal ions - a review. *RSC Adv*. 2015;5(39):30989-31003. <https://doi.org/10.1039/C4RA15453C>
 35. de Saldanha Simon E, Wingert NR, Gobetti C, et al. Development, Quality by Design-Based Optimization, and Stability Assessment of Oral Liquid Formulations Containing Baclofen for Hospital Use. *AAPS PharmSciTech*. 2022;23(8):301. <https://doi.org/10.1208/s12249-022-02447-x> PMID:36385217
 36. Okoye CO, Okeke ES, Ezeorba TPC, Chukwudozie KI, Chiejina CO, Fomena Temgoua NS. Microbial and Bio-based Preservatives: Recent Advances in Antimicrobial Compounds. In: 2022:53-74. https://doi.org/10.1007/978-981-19-5711-6_4
 37. Okeke OC, Boateng JS. Composite HPMC and sodium alginate based buccal formulations for nicotine replacement therapy. *Int J Biol Macromol*. 2016;91:31-44. <https://doi.org/10.1016/j.ijbiomac.2016.05.079> PMID:27222284
 38. Song Z, Hou J, Liu X, Wei Q, Hao H, Zhang L. Conformance control for CO₂-EOR in naturally fractured low permeability oil reservoirs. *J Pet Sci Eng*. 2018;166:225-234. <https://doi.org/10.1016/j.petrol.2018.03.030>
 39. Khan I, Khan I, Saeed K, et al. Polymer nanocomposites: an overview. In: *Smart Polymer Nanocomposites*. Elsevier; 2023:167-184. <https://doi.org/10.1016/B978-0-323-91611-0.00017-7>
 40. Tarhini A, Tehrani-Bagha AR. Advances in Preparation Methods and Conductivity Properties of Graphene-based Polymer Composites. *Applied Composite Materials*. 2023;30(6):1737-1762. <https://doi.org/10.1007/s10443-023-10145-5>
 41. Rusdin A, Mohd Gazzali A, Ain Thomas N, et al. Advancing Drug Delivery Paradigms: Polyvinyl Pyrrolidone (PVP)-Based Amorphous Solid Dispersion for Enhanced Physicochemical Properties and Therapeutic Efficacy. *Polymers (Basel)*. 2024;16(2):286. <https://doi.org/10.3390/polym16020286> PMID:38276694 PMCID:PMC10820039
 42. Moaaz EM, Abdel-Moety EM, Rezk MR, Fayed AS. Smartphone based TLC approach versus conventional densitometric measurement for the simultaneous determination of donepezil and memantine, content uniformity testing along with greenness and whiteness assessment. *Sustain Chem Pharm*. 2024;42:101789. <https://doi.org/10.1016/j.scp.2024.101789>
 43. Hao J, Yang M, Mintah BK, et al. Chemometric monitoring of critical parameters in rice wine fermentation using near-infrared spectroscopy with ultrasound-assisted *S. cerevisiae* cultivation. *Microchemical Journal*. 2026;223:117397. <https://doi.org/10.1016/j.microc.2026.117397>
 44. Nasal administration of a temozolomide-loaded thermoresponsive nanoemulsion reduces tumor growth in a preclinical glioblastoma model.
 45. Shen Y, Tan X, Zhou L, et al. An injectable in situ gel formed by ropivacaine with small lipid molecules to achieve long-term postoperative analgesia. *Acta Biomater*. 2025;198:151-160. <https://doi.org/10.1016/j.actbio.2025.04.033> PMID:40246260
 46. Kam LY, Wong JW, Yuen KH. HPMC Substitution Influences the Buoyancy and Release in Gastroretentive Floating Tablets. *AAPS PharmSciTech*. 2026;27(1):77. <https://doi.org/10.1208/s12249-025-03306-1> PMID:41540294
 47. Zhang J, Yan Y, Jia W, Yang W, Wang Q, Zhao S. Design and application of gel coagulation-spontaneous flotation integrated process in water treatment: "Clouds in water." *Water Res*. 2023;243:120407. <https://doi.org/10.1016/j.watres.2023.120407> PMID:37516081
 48. Kwang GD, Sampathkumar K, Loo SCJ. Ultralong floating hydrogel raft for prolonged gastric retention. *MRS Bull*. 2023;48(4):342-350. <https://doi.org/10.1557/s43577-022-00406-2>
 49. Chiani E, Beaucamp A, Hamzeh Y, Azadfallah M, Thanusha AV, Collins MN. Synthesis and characterization of gelatin/lignin hydrogels as quick release drug carriers for Ribavirin. *Int J Biol Macromol*. 2023;224:1196-1205. <https://doi.org/10.1016/j.ijbiomac.2022.10.205> PMID:36309240
 50. Akalin GO. Alginate/carboxymethylcellulose-based hydrogels as pH-sensitive drug delivery systems: facile production with enhanced degradation, thermal and mechanical properties.

- Iranian Polymer Journal. 2023;32(8):1013-1032. <https://doi.org/10.1007/s13726-023-01182-9>
51. Barman S, Sarkar A, Das U, Mandal S. Double Target Strategy of Novel Floating Raft System Containing Metronidazole. *J Pharm Innov.* 2025;20(6):230. <https://doi.org/10.1007/s12247-025-10187-1>
 52. Khan BA, Ahmad N, Alqahtani A, Baloch R, Rehman AU, Khan MK. Formulation development of pharmaceutical nanoemulgel for transdermal delivery of feboxostat: Physical characterization and in vivo evaluation. *European Journal of Pharmaceutical Sciences.* 2024;195:106665. <https://doi.org/10.1016/j.ejps.2023.106665> PMID:38056779
 53. Gururaj N, Vinod V, Vijayakumar K. Deep grading of mangoes using Convolutional Neural Network and Computer Vision. *Multimed Tools Appl.* 2023;82(25):39525-39550. <https://doi.org/10.1007/s11042-021-11616-2>
 54. Chaikham P, Yutsapremanon S, Baipong S, et al. High pressure processing of sweet corn milk yogurt: A plant-based probiotic carrier with enhanced stability. *Food Chemistry Advances.* 2025;9:101174. <https://doi.org/10.1016/j.focha.2025.101174>
 55. Abd Allah NH, Helmy AM, Tammam OY, El-Sherif MW, Abouelmagd SA. Dual-responsive in situ gelling polymer matrix for tunable ketamine general anesthesia in experimental animals. *Int J Pharm.* 2024;652:123820. <https://doi.org/10.1016/j.ijpharm.2024.123820> PMID:38242258
 56. Liu A, Cui S, Song L, et al. Ultrafast self-gelling, superabsorbent, and adhesive chitosan-based hemostatic powders for rapid hemostasis and wound healing. *Carbohydr Polym.* 2025;355:123362. <https://doi.org/10.1016/j.carbpol.2025.123362> PMID:40037735
 57. Bendaouia A, Ismaili T, Najib I, et al. Intelligent real-time flotation froth stability monitoring using embedded computer vision: lead (Pb) processing case study. *The International Journal of Advanced Manufacturing Technology.* 2025;141(3-4):1313-1328. <https://doi.org/10.1007/s00170-025-16740-z>
 58. Rodrigues GS, Buranello LP, Barboza JM, et al. Pharmacomagnetography of floating gastroretentive systems in vivo in different prandial states evaluated by AC biosusceptometry. *European Journal of Pharmaceutics and Biopharmaceutics.* 2026;218:114907. <https://doi.org/10.1016/j.ejpb.2025.114907> PMID:41207573
 59. Salah El-Din SH, Mahmoud AM, Morsi A. Eco-friendly RP-HPLC method for simultaneous determination of water-soluble and fat-soluble vitamins in nano-formula and pharmaceutical dosage forms. *BMC Chem.* 2025;19(1):76. <https://doi.org/10.1186/s13065-025-01441-1> PMID:40114284 PMCid:PMC11927356
 60. Ali A, Hussain MA, Haseeb MT, et al. Synthesis, characterization, and acute toxicity of pH-responsive *Salvia spinosa* mucilage-co-acrylic acid hydrogel: A smart excipient for drug release applications. *React Funct Polym.* 2023;182:105466. <https://doi.org/10.1016/j.reactfunctpolym.2022.105466>
 61. Qin Z, Yang Y, Zhang Z, et al. A Critical Review: Gel-Based Edible Inks for 3D Food Printing: Materials, Rheology-Geometry Mapping, and Control. *Gels.* 2025;11(10):780. <https://doi.org/10.3390/gels11100780> PMID:41149385 PMCid:PMC12563521
 62. Kubinski AM, Sosa RD, Shivkumar G, et al. Predictive dissolution modeling across USP apparatuses I, II, and III. *J Pharm Sci.* 2025;114(6):103765. <https://doi.org/10.1016/j.xphs.2025.103765> PMID:40107419
 63. Santadkha T, Skolpap W, Thitapakorn V. Diffusion Modeling and In Vitro Release Kinetics Studies of Curcumin-Loaded Superparamagnetic Nanomicelles in Cancer Drug Delivery System. *J Pharm Sci.* 2022;111(6):1690-1699. <https://doi.org/10.1016/j.xphs.2021.11.015> PMID:34838781
 64. Chen YC, Shishikura S, Moseson DE, et al. Control of drug release kinetics from hot-melt extruded drug-loaded polycaprolactone matrices. *Journal of Controlled Release.* 2023;359:373-383. <https://doi.org/10.1016/j.jconrel.2023.05.049> PMID:37295729
 65. Neolaka YAB, Lawa Y, Riwu M, et al. Synthesis of Zinc(II)-natural zeolite mordenite type as a drug carrier for ibuprofen: Drug release kinetic modeling and cytotoxicity study. *Results Chem.* 2022;4:100578. <https://doi.org/10.1016/j.rechem.2022.100578>
 66. Wang M, Li N, Guo X, et al. Development of microemulsions-filled sodium alginate-chitosan composite hydrogels: Preparation, characterization and release kinetics analysis. *Food Hydrocoll.* 2025;163:111059. <https://doi.org/10.1016/j.foodhyd.2025.111059>
 67. Kalyani P, Khandelwal M. Drug release kinetics from in-situ modulated agar/chitosan-bacterial cellulose patches for differently soluble drugs. *Int J Biol Macromol.* 2024;283:137602. <https://doi.org/10.1016/j.ijbiomac.2024.137602> PMID:39549810
 68. Development, Optimization and Evaluation of Naproxen Amorphous ASDs Tablets for Enhanced Solubility and Dissolution Using Hydrophilic Polymers.
 69. Kumar G, Verma V. Formulation and simultaneous estimation of sustained release bilayer tablet containing polythiazide and reserpine. *Curr Pharm Anal.* 2026;22(2):169-180. <https://doi.org/10.1016/j.cpan.2026.01.002>
 70. Potent Therapeutic Efficacy of 9-Bromo-Noscapine Against Breast Cancer Cells Via Enhanced Bioavailability of the Noscapine-Cyclodextrin Inclusion Complex.
 71. Shariful Juhari MH, Luthfi AAI, Saleh NM, et al. Pineapple peel cellulose based eco-friendly fertilizer nanocomposites for improved nutrient delivery. *Sci Rep.* 2026;16(1):8971. <https://doi.org/10.1038/s41598-025-32774-5> PMID:41708668 PMCid:PMC12987989
 72. Mathew D, Thomas B, NM S, George J, EK R. Trimethyl Chitosan-Based Amphotericin B Nanoparticles: Improved Gastrointestinal Stability, Hemocompatibility, Monomeric Stabilization, and Controlled Drug Release. *Bionanoscience.* 2025;15(3):520. <https://doi.org/10.1007/s12668-025-02117-9>
 73. Rehman Q, Akash MSH, Rasool MF, Rehman K. Role of Kinetic Models in Drug Stability. In: *Drug Stability and Chemical Kinetics.* Springer Singapore; 2020:155-165. https://doi.org/10.1007/978-981-15-6426-0_11 PMCid:PMC7174708
 74. Patel M, Parikh D, Parihar A, et al. Protein and Peptide Therapeutics: Stability Challenges, Regulatory Demands, and Innovative Formulation Solutions for Enhanced Clinical Effectiveness. *Protein Pept Lett.* 2025;32. <https://doi.org/10.2174/0109298665375151250626124048> PMID:40660448
 75. EMERGING FRONTIERS IN THE DRUG FORMULATION DESIGN. INTECHOPEN; 2025.
 76. Alexeeva O V., Konstantinova ML, Siracusa V, et al. Characterization and Evaluation of Zero-Order Release System Comprising Glycero-(9,10-trioxolane)-trialeate and PLA: Opportunity for Packaging and Biomedicine Applications. *Polymers (Basel).* 2024;16(24):3554. <https://doi.org/10.3390/polym16243554> PMID:39771406 PMCid:PMC11679401
 77. Khan MFH, Baudin F, Sudalaiyadum Perumal A, Kamen AA. Freeze-Drying of mRNA-LNPs Vaccines: A Review. *Vaccines (Basel).* 2025;13(8):853. <https://doi.org/10.3390/vaccines13080853> PMID:40872937 PMCid:PMC12389932
 78. Zhang B, Bai Y, Li X, Wang Y, Dong J, Jin Z. Effects of molecular entanglements in amylopectin on the anti-thixotropy, gel properties and viscosity properties. *Food Hydrocoll.* 2024;154:110115. <https://doi.org/10.1016/j.foodhyd.2024.110115>
 79. Wang R, Chang Y, Hartel RW, Zhang Y, Wang S. Soluble dietary fibers as structuring agents in gelatin gelation: Effects on phase behavior, network formation, water mobility, and colorant stability in low- and high-solid matrices. *Food Hydrocoll.* 2026;174:112410. <https://doi.org/10.1016/j.foodhyd.2025.112410>

80. Pandey P, Sil D, Komal KM, Kumar M. Innovative approaches in *HELICOBACTER pylori* therapy: Clinical trials and advancements in Gastro-Retentive drug delivery systems. *Arab Journal of Gastroenterology*. 2025;26(4):473-484. <https://doi.org/10.1016/j.ajg.2025.09.010> PMID:41206255
81. Takbirgou H, Salami M, Askari G, Emam-Djomeh Z, Kennedy JF. Characterization of novel alginate-Aloe Vera raft systems for treatment of gastroesophageal reflux disease. *Int J Biol Macromol*. 2024;257:128686. <https://doi.org/10.1016/j.ijbiomac.2023.128686> PMID:38092117
82. Jacob S, Kather FS, Satyam SM, et al. Injectable In Situ Thermoreversible Gel Depot System of Lidocaine Nanoemulsion for Prolonged Anesthetic Activity in Dental and Operative Procedures. *Pharmaceutics*. 2025;17(10):1355. <https://doi.org/10.3390/pharmaceutics17101355> PMID:41155990 PMCID:PMC12567530
83. Bhalala K, Jadeja D, Dudhat K. Microspheres: Preparation Methods, Advances, Applications, and Challenges in Drug Delivery. *Biomedical Materials & Devices*. 2026;4(1):221-260. <https://doi.org/10.1007/s44174-025-00281-w>
84. Synthesis and performance evaluation of multi-crosslinked preformed particle gels with ultra-high strength and high-temperature and high-salinity resistance for conformance control.
85. Formulation optimization of emulsifier-based hydrated gel cake improver for α -crystal stabilization using D-optimal mixture design.
86. Nayak C, Swain RP, Mohapatra R, Panigrahi KC. Next-Generation Nanostructured Lipid Carriers: A Review of Latest Trends and Innovations. *Biomedical Materials & Devices*. Published online December 4, 2025. <https://doi.org/10.1007/s44174-025-00605-w>
87. Real JP, Frenquelli E, Barrientos BA, Palma SD, Real DA. The use of hydrogels in oral drug delivery. In: *Hydrogels in Drug Delivery*. Elsevier; 2025:351-378. <https://doi.org/10.1016/B978-0-443-22017-3.00007-X>
88. Srinatha N, Battu S, Vishwanath BA. Microsponges: a promising frontier for prolonged release-current perspectives and patents. *Beni Suef Univ J Basic Appl Sci*. 2024;13(1):60. <https://doi.org/10.1186/s43088-024-00519-4>
89. Wirth T, Lafforgue P, Pham T. NSAID: Current limits to prescription. *Joint Bone Spine*. 2024;91(4):105685. <https://doi.org/10.1016/j.jbspin.2023.105685> PMID:38159794
90. Sebaa R, AlMalki RH, Sukkarieh H, et al. Systemic Metabolic Alterations Induced by Etodolac in Healthy Individuals. *Pharmaceutics*. 2025;18(8):1155. <https://doi.org/10.3390/ph18081155> PMID:40872546 PMCID:PMC12388885
91. Drăgoi CM, Nicolae AC, Dumitrescu IB. The Indole Scaffold in Biochemistry and Therapeutics: A Privileged Structure with Diverse Chemical, Biological, and Clinical Significance. *Targets*. 2026;4(1):4. <https://doi.org/10.3390/targets4010004>
92. Zou Y, Zhang J, Chen L, Xu Q, Yao S, Chen H. Targeting Neuroinflammation in Central Nervous System Diseases by Oral Delivery of Lipid Nanoparticles. *Pharmaceutics*. 2025;17(3):388. <https://doi.org/10.3390/pharmaceutics17030388> PMID:40143051 PMCID:PMC11944764
93. Allegaert K, Mitra S, Smits A, Turner MA. Advocating for drug development in newborn infants. *Early Hum Dev*. 2024;199:106136. <https://doi.org/10.1016/j.earlhumdev.2024.106136> PMID:39488008