Chemistry Research Journal, 2024, 9(3):42-62
Available online www.chemrj.org

Research Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Formulation Development and Optimization of Bi-layer Gastro retentive tablet of Ketorolac Tromethamine

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Abstract
Research indicates that pharmaceutical formulations exhibiting effective in vitro floating characteristics tend to endure longer periods in the stomach when tested. Ketorolac tromethamine, a potent NSAID, is administered orally at 10 mg three to four times daily for inflammation and pain relief by inhibiting prostaglandin synthesis. To enhance its gastric residence time and efficacy, a bi-layer gastro retentive tablet was formulated, offering sustained action for 24 hours with improved patient compliance and cost-effectiveness. This systematic approach aimed to optimize KET delivery, ensuring sustained therapeutic effects in the stomach**.** The methodology of formulating bilayer gastroretentive tablets of Ketorolac Tromethamine involves granulation, compression, and optimization techniques such as factorial design to ensure controlled release and gastric retention of the drug. It delves into its design, performance, and potential applications, offering insights into its drug profile, evaluation of physical parameters, preliminary trials (in-vitro dissolution), etc. Research Investigating bi-layer KET tablet: fast release layer for loading, slow release for 24hrs via HPMC. Addressing absorption and stability challenges.

Keywords: Ketorolac Tromethamine, Bi-layer Gastro retentive tablet

Introduction

Research indicates that pharmaceutical formulations exhibiting effective in vitro floating characteristics tend to endure longer periods in the stomach when tested in vivo. Significant determinants affecting their efficacy include the physical attributes of the device and the presence of food in the stomach. A lower density of the device compared to the gastric contents facilitates floating, but confirmation through in vivo studies is imperative to validate prolonged gastric retention.

For drugs necessitating local action or specific absorption requirements, extended-release formulations with prolonged stomach residence prove advantageous. Recent approaches encompass the utilization of bioadhesive and low-density devices.

For instance, floating tablets comprising drug-hydrocolloid blends or matrix tablets swell upon exposure to gastric fluid, thereby reducing density and facilitating floating. Diverse factors influencing floating properties have been explored through scientific inquiry.

Basic physiology of the gastrointestinal tract

As The stomach has three main parts: the fundus, body, and antrum (pylorus). The upper part, consisting of the fundus and body, serves as a storage area for undigested food, while the antrum facilitates mixing and acts as a pump to push food into the small intestine. Gastric emptying happens both during fasting and feeding. However, the motility patterns differ between these states. During fasting, there's a cyclic series of electrical events called the inter-digestive myoelectric cycle or migrating myoelectric complex (MMC), which occurs every 2 to 3 hours. This cycle has four phases:

- Phase I (basal phase) lasts 40 to 60 minutes with infrequent contractions.
- Phase II (preburst phase) lasts 40 to 60 minutes with sporadic action potential and contractions, intensifying gradually.
- Phase III (burst phase) lasts 4 to 6 minutes and involves strong, rhythmic contractions that push undigested material into the small intestine. This phase is known as the "housekeeper wave."
- Phase IV occurs for 0 to 5 minutes between phases III and I of two consecutive cycles.

Classification of Floating Drug Delivery Systems (FDDS)

Floating drug delivery systems are divided into (1) effervescent and (2) non-effervescent types.

Effervescent systems use swellable polymers and compounds like sodium bicarbonate to generate CO2, providing buoyancy. Ichikawa et al. developed a floating system with effervescent layers and swellable membranes for sustained drug release. Yang et al. created a triple-layer tablet with floating ability for prolonged gastric residence time of multiple drugs. Ozdemir et al. designed floating bilayer tablets for furosemide, controlling release through a solid dispersion and effervescent layer.

Non-effervescent systems utilize gel-forming hydrocolloids and polymers to create buoyancy. Thanoo et al. produced polycarbonate microspheres for floating drug delivery with increased drug loading and release rate. Nur and Zhang formulated floating tablets of captopril using hydrocolloids, observing buoyancy influenced by tablet hardness and porosity.

Factors affecting gastric retention

- Density, shape and size
- Fasting or fed state and nature of the meal
- Effect of liquid, volume of liquids, digestible solid and indigestible solid type food
- Frequency of feed
- Biological factors
- Gender
- Posture
- Effect of size of floating and non-floating dosage

Advantages of Floating Dosage Forms

- Versatility: Floating dosage forms are applicable to a wide range of medications, regardless of their type or class.
- Enhanced Absorption: They are effective for drugs absorbed from both the stomach and the intestine, providing equal efficacy.
- Gastric Protection: Floating formulations can prevent irritation caused by acidic substances like aspirin, making them suitable for administering such drugs.
- Targeted Delivery: Ideal for drugs absorbed through the stomach, such as ferrous salts and antacids, ensuring efficacy.
- Consistent Effectiveness: Medications administered using floating dosage forms exhibit sustained release, irrespective of the specific site of absorption, ensuring reliable performance.

Limitations/disadvantages of Floating Dosage Forms

- High stomach fluid levels are crucial for these systems to function optimally, but they may not work well for drugs with solubility or stability issues in the gastrointestinal tract (GIT).
- Drugs like nifedipine, which are absorbed throughout the GIT and undergo first-pass metabolism, may not be suitable for these systems.
- Irritant drugs for gastric mucosa and those unstable in acidic stomach environments aren't ideal candidates for these systems.
- Administering the dosage form requires a full glass of water (200-250 ml) and these systems don't provide significant advantages over conventional forms for drugs absorbed throughout the gastrointestinal tract.

Gastric retention by bioadhesion

It refers to a novel approach in drug delivery where pharmaceuticals are designed to adhere to the gastric mucosa, prolonging their residence time in the stomach. This technique offers several advantages, including enhanced absorption, controlled release, and improved therapeutic efficacy.

Introduction to Bi-Layer Tablet

Bi-layer tablets represent a distinctive pharmaceutical form comprising two distinct layers of active pharmaceutical ingredients (APIs) or drug combinations compacted into a single tablet. Each layer exhibits varying drug release profiles, facilitating controlled release, immediate action, or a blend of both. The key benefit of bi-layer tablets lies in their capacity to administer multiple medications or diverse dosages of a single medication concurrently, thereby enhancing therapeutic effectiveness, fostering patient adherence, and minimizing dosing intervals. Various types of bi-layer tablets exist, encompassing immediate release/extended release, delayed release/immediate release, and combinations tailored for synergistic therapeutic effects. These tablets are widely utilized across a spectrum of medical conditions, furnishing customized drug delivery solutions to optimize patient outcomes.

Aim & Objectives of Work

Ketorolac tromethamine, a potent NSAID, is administered orally at 10 mg three to four times daily for inflammation and pain relief by inhibiting prostaglandin synthesis. To enhance its gastric residence time and efficacy, a bi-layer gastro retentive tablet was formulated, offering sustained action for 24 hours with improved patient compliance and cost-effectiveness. Various methods such as floating systems, swelling polymers, and bioadhesive technologies were employed to achieve prolonged gastric retention. This systematic approach aimed to optimize KET delivery, ensuring sustained therapeutic effects in the stomach.

Objectives:

- Developing a dual-layer tablet containing Ketorolac, employing a high-viscosity floating polymer along with a bioadhesive polymer to ensure retention in the stomach.
- The immediate-release layer is designed to release Ketorolac within 30 minutes through rapid disintegration facilitated by super disintegrating agents.
- Examination of formulation and procedural factors affecting drug release is conducted.
- Optimization involves adjusting polymer concentration, selecting suitable fillers, and incorporating gas-generating agents to enhance tablet properties, drug release kinetics, buoyancy, and bioadhesive properties.

Material & Method

Material used in the present investigation

Table 1: Material used in the present investigation

Ketorolac Tromethamine	Sun Pharmaceuticals., Vadodara, India.
Hydroxypropyl methyl cellulose K4M	Colorcon Asia pvt. Limited, Goa.
Hydroxypropyl methyl cellulose K100M	Colorons Asia pvt. Limited, Goa.
Ac- di-sol	S. D. Fine Chemicals Ltd., Mumbai, India.
SSG	S. D. Fine Chemicals Ltd., Mumbai, India.
Cross- providon	S. D. Fine Chemicals Ltd., Mumbai, India.
Sodium bicarbonate	S. D. Fine Chemicals Ltd., Mumbai, India.
Micro crystalline cellulose	S. D. Fine Chemicals Ltd.
Barium sulphate (X-ray grade)	Ashirvad Chemicals Ahmedabad.
Hydrochloride Acid	S. D. Fine Chemicals Ltd.
Dibasic calcium phosphate	S. D. Fine Chemicals Ltd.
Lactose	S. D. Fine Chemicals Ltd.
Talc	S. D. Fine Chemicals Ltd.
Magnesium stearate	S. D. Fine Chemicals Ltd.

Instrument used in present investigation

Table 2: Instrument used in present investigation

UV Spectrophotometer	Systronic 1601 UV/Vis double beam Spectrophotometer (Japan).
Tablet compression machine	Multipunch tablet compression machine, Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India.
Dissolution test apparatus	Dissolution test apparatus-TDT-06T, Electrolab, Mumbai, India.
pH meter	Systronic, 361-micro pH meter.
Balance	Modified analytical balance.
Sartorious electronic balance	Model CP- 224 S, Labtronic.
Roche Friabilator	Camp-bell Electronics, Mumbai, India
Hardness Tester	Validated dial type, Model:1101, Shivani Scientific Industries Pvt. Ltd., Mumbai.
Brookfield digital viscometer	Model No: LVDV-2P230
Optical microscope	AVC CXRIII 561, Digital Color CCD Camera, Labomed
Digital Camera	Model-Fuji s9500 dslr
Hydraulic Pellet Press	Type:KP-587, PCI services, Mumbai.

(I) Formulation, evaluation & optimization of immediate release layer of Ketorolac tromethamine

Ketorolac tromethamine (KET) is a commonly used non-steroidal anti-inflammatory drug for pain and inflammation. Bi-layer gastro retentive tablets were developed to decrease dosing frequency and enhance patient compliance. One layer ensures immediate release using various super disintegrating agents, with the optimal agent selected based on concentration.

Material and method: Received KET from Sun Pharmaceuticals Ltd, Baroda, India. Croscarmellose, sodium starch glycolate, cross providone sourced from S. D. Fine chemicals, Mumbai. Remaining ingredients were laboratory-grade.

Preparation of Standard Calibration curve of Ketorolac tromethamine: Dissolve 10 mg of KET in 0.1 N HCl (pH=1.2) to make 100 ml solution in a volumetric flask. Dilute to obtain 0-18 µg/ml. Measure absorbance at 322 nm

with Shimadzu UV-1601 UV/V spectrophotometer using 0.1 N HCl as reference. Create standard curve (0-18 µg/ml) shown in Table 3.

Table 3: Standard calibration curve of ketorolac tromethamine in 0.1 N HCl

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	0	0	0	0	0
2	03	0.165	0.164	0.165	0.165
3	05	0.258	0.258	0.258	0.258
4	10	0.502	0.502	0.501	0.502
5	15	0.737	0.736	0.736	0.737
6	18	0.853	0.853	0.853	0.853

Pharmacokinetic parameters of Ketorolac Tromethamine:

Table 4: Pharmacokinetic parameters of Ketorolac Tromethamine

Bio-availability	Steady State concentration (µg/ml)	Volume of distribution (lit/kg)	Half-life (hour)	Clearance (ml/min)
100%	0.1 – 0.3	0.21	5.3	1.2

Preliminary Trials (Immediate Release Formulation): Composition of preliminary trials for immediate release formulation is shown in Table no 5. Different immediate release tablets formulations were prepared by direct compression technique. All the powders were passed through 80 mesh sieve. Each tablet contained 5 mg of KET and other pharmaceutical ingredients as listed in table in each section.

Table 5: Preliminary trials of immediate release formulation

	A1	A2	A3	A4	A5	A6	A7	A8	A9
Drug	5	5	5	5	5	5	5	5	5
Cross-pvp	2	3	5	-	-	-	-	-	-
Ac-di-sol	-	-	-	2	3	5	-	-	-
SSG	-	-	-	-	-	-	2	4	6
DCP	90	89	87	90	89	87	90	88	86
Mg-sterate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Total Wt.	100	100	100	100	100	100	100	100	100

*All the ingredients are in mg

Optimization of immediate release formulation: Initial trials showed croscarmellose sodium and sodium starch glycolate yielded satisfactory results. Hence, varied concentrations were used with the drug. Table no 6 displays batch compositions.

Table 6: Optimization of immediate release formulation

	A10	A11	A12	A13	A14	A15
Drug	5	5	5	5	5	5
Ac-di-sol	-	-	-	5	5.5	6
SSG	2.5	3	3.5	-	-	-
DCP	89.5	89	88.5	87	86.5	86
Mg-sterate	1	1	1	1	1	1
Talc	2	2	2	2	2	2
Total Wt.	100	100	100	100	100	100

***In-vitro* dissolution profile:** Immediate release tablet dissolution testing utilized USP XXIV apparatus II (paddle method) with 900 ml 0.1 N HCl (pH=1.2) at 37±0.5°C, 50 rpm. Samples withdrawn at 2, 5, 10, 15, 20, 25, 30 min intervals, replaced with fresh medium. Absorbance measured at 322 nm.

Evaluation Physical parameters of tablets:

i. Tablet disintegration time: Tablet disintegration time (DT) was tested in 0.1 N HCl (pH=1.2) at 37 ± 0.5oC using Electro lab ED-2 Bowl USP apparatus. Six tablets were tested simultaneously, aiming for disintegration within 15 minutes, with triplicate determinations.

ii. Weight variation test: Twenty tablets of each formulation weighed on Sartorius balance, tested per official method, triplicate determinations made.

iii. Hardness: Tablet hardness assessed via diametral compression using dial hardness tester (Model 1101, Shivani Scientific Ind). Ideal stability at 4-5 kg. Triplicate determinations.

(II) Formulation, evaluation & optimization of sustained release layer of Ketorolac tromethamine

Ketorolac tromethamine (KET) is a commonly prescribed nonsteroidal anti-inflammatory drug for pain and inflammation. Bi-layer Gastro retentive tablets of KET were developed to enhance patient compliance by reducing administration frequency. One layer provides sustained release using HPMC, floating, and bio-adhesive mechanisms, aided by sodium bicarbonate as a gas generator.

Materials and methods: Received Ketorolac tromethamine from Sun Pharma, Vadodara. HPMC from Colorcon Asia. Sodium bicarbonate from S.D.Fine Chemicals, Mumbai. The rest were lab-grade.

Preliminary trials and optimization of gas generating agents: Table no 7 displays preliminary batch compositions. The gastro retentive layer contains 15mg drug maintenance dose, varying grades of HPMC (K4M, K100M, K15M), NaHCO3, microcrystalline cellulose, lactose, talc, and magnesium stearate. Ingredients were blended, compressed using a Hydraulic Pellet Press, Mumbai. Tablets underwent in vitro dissolution and physical parameter evaluations, with varying sodium bicarbonate concentrations for optimization.

Table 7: Preliminary trials formulation

	R1	R2	R3	R4	R5	R6	R7
Drug	15	15	15	15	15	15	15
HPMC K100M	80	40	0	60	0	90	30
HPMC K4M	0	40	80	0	0	0	30
HPMC K15M	-	-	-	-	80	-	20
$NaHCO_3$	35	25	35	35	20	25	35
Citric acid	15	0	0	15	20	15	15
Lactose	9	24	24	29	14	09	09
MCC	40	40	40	40	40	40	40
Mg-stearate	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200

* All the ingredients in mg

Measurement of viscosity of polymer blend: The viscosity of polymer mixture was computed by using the empirical equation provided by Dow chemical company.

$$\{\ \eta_B^{1/8} = F_1\eta_1^{1/8} + F_2\eta_2\ \}$$

Where,

η_B = desired combined viscosity,

F_1 and F_2 = fraction of HPMC K4M and HPMC K100M respectively.

η_1 = viscosity of HPMC K4M

η_2 = viscosity of HPMC K100M.

Optimization of tablet formulation using 3^2 full factorial designs: By conducting multiple regression analysis, statistically significant terms are determined, and counter plots visualize variable impacts. Optimal points can be pinpointed and verified through replicate trials. In this study, a 3x2 randomized full factorial design was used, evaluating two factors at three levels each. Nine combinations were tested, guided by preliminary studies on HPMC polymer blend content and viscosity. Dependent variables included drug release time, release at 24 hours, and similarity factor f2. The design layout and coded value of independent factor is shown in Table no 8 and Table no respectively. Batch formulations are detailed in Table no 8.

Table 8: Full Factorial Design Layout

Batch code	X_1	X_2
F1	-1	-1
F1	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

*X1 code for content of polymer blend and X2 code for Viscosity of HPMC blend

Table 9: Coded values for content of polymer blend & viscosity of polymer blend

Coded value	Content of polymer blend (mg) X_1	Viscosity of HPMC blend (cps) X_2
-1	50	5600(HPMC K4M)
0	65	26325(HPMC K4M+HPMC K100M)
1	80	10096328(HPMC K100M)

Table 10: Formulation using 3^2 full factorial design

Formulations Code→	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	15	15	15	15	15	15	15	15	15
HPMC K100M	-	25	50	-	32.5	65	-	40	80
HPMC K4M	50	25	-	65	32.5	-	80	40	-
$NaHCO_3$	35	35	35	35	35	35	35	35	35
Lactose	54	54	54	39	39	39	24	24	24
MCC	40	40	40	40	40	40	40	40	40
Mg-stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total wt.	200	200	200	200	200	200	200	200	200

* All the ingredients in mg.

In-vitro dissolution profile: KET release from tablets tested with USP XXIV paddle method in 0.1 N HCl (pH=1.2) at 37°C, 50 rpm. Samples withdrawn at intervals, filtered, and analyzed spectrophotometrically at 322 nm for drug release calculation.

Comparison of dissolution profiles: SUPAC guidelines use similarity factor (f2) to compare dissolution profiles of modified release dosage forms. Profiles are similar when f2 ranges from 50 to 1009, calculated using a specific formula.

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5} \times 100\right\}$$

where,
n = number of dissolution time,
Rj and Tj = reference and test dissolution values at time t.

In vitro buoyancy studies: Tablets floated in 0.1 N HCl. Time to surface measured for buoyancy determination.

Evaluation of physical parameters of prepared tablets:

i. Uniformity of weight: Weights determined within ±1mg using Sartorious balance (Model CP-224S), based on triplicate determinations from 20 tablets.

ii. Hardness: Tablet hardness tested with dial type tester (Model no 1101) to ensure mechanical stability (4-5 kg). Triplicate determinations.

iii. Friability: Tablet friability tested in Roche friabilator. Tablets weighed (W0), dedusted, weighed (W) after 100 revolutions. % friability calculated. Limit: 1%. Triplicate tests.

$$\%Friability = \frac{W_0 - W}{W_0} \times 100$$

iv. Swelling index: Tablet swelling tested in pH 1.2 HCl at room temp. Swollen weight measured over time. Swelling index calculated. Triplicate tests.

$$SwellingIndex = \frac{W_t - W_0}{W_t}$$

Where,
W_0 = initial weight of tablet,
W_t = weight of the tablet at time t.
The tablet was lowered onto the mucosa under a constant weight of 5 g for a total contact period of 1min.

v. Kinetic modeling and mechanism of drug release: Drug release data analyzed using various kinetic models. Korsmeyer-Peppas equation used to investigate release mechanisms, comparing different formulations.

$$\frac{M_t}{M_\infty} = kt^n$$

Where, M/Mt∞ is the fraction of drug released at time t, k the kinetic constant, and n the release exponent that characterizes the mechanism of drug release.

(III) Formulation Development and optimization of Bi-Layer Gastro retensive tablet of Ketorolac Tromethamine

Bi-layer tablet of ketorolac tromethamine developed to reduce dosing frequency. Immediate release layer for loading dose, super disintegrating agents aid release. Gastro retentive layer ensures sustained release with HPMC polymer. Tested for physicochemical properties.

Materials and methods: KET from Sun Pharma Vadodara, HPMC from Colorcon Asia, and Sodium bicarbonate from S.D.Fine Mumbai were gifted samples used in the study.

Preparation of Standard Calibration curve of Ketorolac tromethamine: Calibrated KET curve made as in chapter (I) procedure for standardization.

Calculation of theoretical release profile of Bi-layer floating tablet of ketorolac tromethamine: Theoretical release profile of bi-layer tablet of KET prepared as per the data and procedure given in chapter (I).

Preparation of Bi-layer gastro retentive tablet of ketorolac tromethmine:

Table 11 lists bi-layer tablet composition.

Table 11: Composition of bi-layer gastro retentive table

Composition	Immediate release formulation Batch (A10)	Sustained release formulation Batch (F7)	Bi-layer floating tablet
Drug	5	15	20
Ac-Di-sol	5	-	5
DCP	87	-	87
HPMC K4M	-	80	80
$NAHCO_3$	-	35	35
MCC	-	40	40
Lactose	-	24	24
Mg-stearate	1	2	3
Talc	2	4	6
Total wt.	100	200	300

* All the ingredients in mg.

Optimization of bi-layer gastro retentive table of Ketorolac tromethamine: Table no 12 shows the composition of KET Bi-layer tablets. First, immediate release layer was pressed at 10kg/cm^2 for 30s, followed by sustained release layer. Pressures of 20kg/cm^2 to 50kg/cm^2 were applied. Tablets were evaluated for physical parameters, dissolution, in-vivo, and stability.

Table 12: Composition of different batches of bi-layer gastro retentive tablet formulation

Formulation Code →	**BGT1**	**BGT2**	**BGT3**	**BGT4**
Compression Force (kg/cm^2)	20	30	40	50
Drug	20	20	20	20
Ac-Di-sol	5	5	5	5
DCP	87	87	87	87
HPMC K4M	80	80	80	80
NAHCO3	35	35	35	35
MCC	40	40	40	40
Lactose	24	24	24	24
Mg-stearate	3	3	3	3
Talc	6	6	6	6
Total wt.	300	300	300	300

In-vitro dissolution profile: In vitro dissolution study of different bi-layer gastro retentive tablets was carried out as per the procedure given in chapter (II).

Comparison of dissolution profiles: Comparison of dissolution profiles of different bi-layer tablets was carried out as per the procedure given chapter (II).

In vitro buoyancy studies: In vitro buoyancy studies of bi-layer gastro retentive tablet of ketorolac was carried out as per the procedure given in chapter (II).

Evaluation of physical parameters of Bi-layer tablet: Prepared bi-layer tablet was evaluated for various parameters like, disintegration time (immediate release layer), weight variation test, hardness, friability, diameter etc, as per procedure given the chapter (I).

Kinetic modeling and Mechanism of drug release: Kinetic modeling and mechanism of drug release was determined as per the procedure given in chapter (II).

Accelerated stability study of the optimized batch: Bi-layer gastro retentive KET tablets underwent accelerated stability tests in aluminum foil pouches. Despite aluminum's protective reputation, foil was used. The goal: maintain floating time and drug release profile. Dosage form designed for stomach delivery must avoid dose dumping and buoyancy failure. Best batch tablets tested at 40°C, 75% RH for 3 months in aluminum pouches. X-ray opaque formulation administered with 250ml water, subjects upright. Light meal given after 2 hours to assess gastro retention. X-ray screening monitored tablet position in gastrointestinal tract at 1, 12, and 24 hours.

Results & Discussion

(I) Formulation, evaluation & optimization of immediate release layer of Ketorolac tromethamine

Preparation of Standard Calibration curve of Ketorolac tromethamine: Standard calibration curve of KET was obtained which shown in Figure no 1. Correlation Co-efficient: **0.9985**. Equation of Absorbance = **0.0474 x Conc. + 0.0159.**

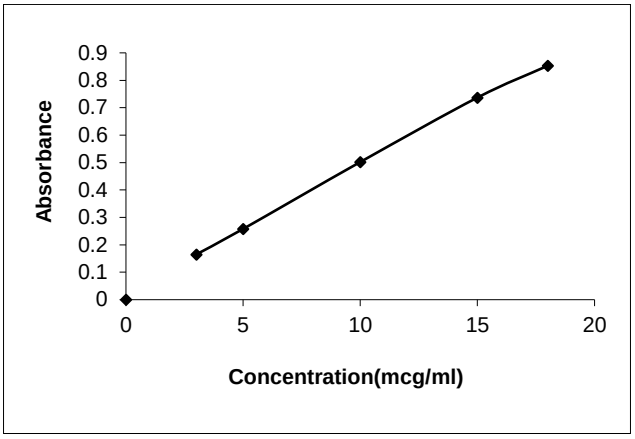

Figure 1: Calibration curve of KET

Calculation of total dose and theoretical drug release profile: KET's pharmacokinetics informed a 24-hour release profile. Immediate release for a bi-layer tablet was 5 mg (25%) in 30 minutes, and 15 mg (4.25% hourly) thereafter.

- Calculation of the Immediate Release Dose:

$$\textbf{IRD} = \frac{\textbf{Css x } V_d}{\textbf{F}}$$

= 4.41 mg

≅ 5.00 mg

- Calculation of Maintenance Dose (MD):

$$\textbf{Maintenance Dose} = \frac{C_l \times T_c \times \tau}{\textbf{F}}$$

= 15 mg

Where, C_l **= clearance**

$$= \frac{0.693 \times V_d}{t_{1/2}}$$

Theoretical release profile is shown in Table 13.

Table 13: Theoretical release profile of Sustained release layer of KET

Time (hrs)	Theoretical release profile %
0	0
1	4.25
2	8.5
4	17.01
6	25.52

8	34
10	42.53
12	51.04
14	59.54
16	68
18	76.53
20	85
22	93.53
23.5	99.92

In-vitro dissolution profile (preliminary trials): In the preliminary trial, various super disintegrating agents were tested at different concentrations. Croscarmellose at 3% (Batch A5) and 5% (Batch A6) achieved 95% and 100% release in 25 minutes. SSG at 4% (Batch A8) achieved 100% release in 5 minutes. Cross PVP batches A1, A2, and A3 achieved 68%, 83%, and 84% release respectively, not suitable for immediate release. Hence, croscarmellose at 5%, 5.5%, 6% and SSG at 2.5%, 3%, 3.5% were chosen for further optimization.

Optimization of immediate release formulation: Graphs in Figure no 2 depict drug release for batches A10 to A15. Batch A13 achieved 99.56% release within 20 mins (5% croscarmellose), making it the best choice.

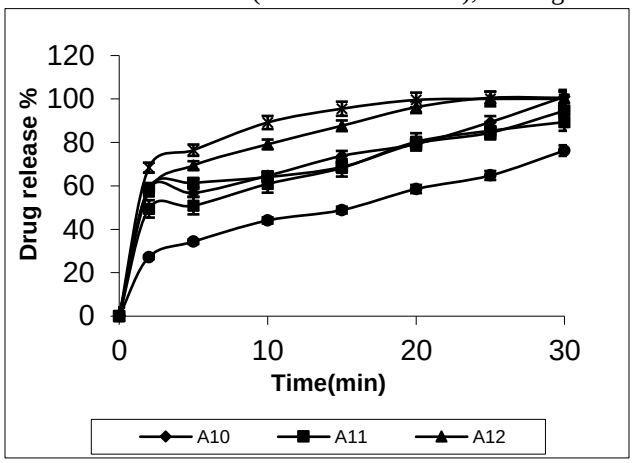

Figure 2: Drug release profile immediate release formulation of KET

Evaluation Physical parameters of tablets: Tablet formulations met specs for weight, hardness, friability. Results detailed in Table 14.

Table 14: Physical Properties of tablets containing KET

Formulation	Disintegration Time (sec)	Hardness (kg/cm^2) Mean (n=20)	Weight variation (mg) (n=20)	% Friability (n=20)
A10	6 ± 0.076	3.5 ± 0.032	98 ± 0.264	0.12 ± 0.001
A11	7 ± 0.0146	4.0 ± 0.01	100 ± 0.004	0.32 ± 0.013
A12	6 ± 0.076	4.5 ± 0.032	99 ± 0.152	0.30 ± 0.013
A13	5 ± 0.1527	4.0 ± 0.012	98 ± 0.264	0.58 ± 0.011
A14	5 ± 0.1527	4.0 ± 0.012	101 ± 0.152	0.50 ± 0.015
A15	6 ± 0.076	4.5 ± 0.032	102 ± 0.264	0.22 ± 0.012

Discussion: Batch A13 of ketorolac tromethamine exhibited rapid release with a loading dose within 20 minutes, attributed to its 5-second disintegration time.

(II) Formulation, evaluation & optimization of sustained release layer of Ketorolac tromethamine

Preliminary trials: Batch R3 showed 97% release over 23.5 hrs, meeting sustained effect criteria. Tablet hardness was 4.5 kg/Cm2, leading to selection for further work.

Optimization of gas generating agents: Table no 15 shows Floating lag time and Floating time of different formulation. Preliminary trials varied gas-generating agent concentrations to optimize floating time and lag. In batch R3, 35mg sodium bicarbonate yielded >24hr floating time, 1.5min lag, ideal for immediate release. Thus, 35mg bicarbonate was chosen for further study, all batches exhibiting >24hr floating time.

Table 15: Floating lag time & Floating Time of preliminary formulation

Formulation code	R1	R2	R3	R4	R5	R6	R7
Floating lag Time (Second)	35	120	90	60	70	50	55
Floating Time (hrs)	>24	>24	>24	>24	>24	>24	>24

Measurement of viscosity of polymer blend: Viscosity of HPMC K4M & K100M blend calculated using equation 1: 26325. Table 16 displays viscosities of various polymers and blends.

Table 16: Viscosity of different polymer and blend of polymer

Polymer	HPMC K 4M	HPMC K4M + HPMC K100M	HPMC K100M
Viscosity	5600cps	26325cps	10096328cps

In-vitro dissolutions profile of factorial batches: The in vitro drug release profile of factorial batches are shown in Figure 3.

Statistical analysis used multiple linear regression in Excel 2003. Results in Table 17 showed strong dependency of Q24, t50, and f2 on independent variables.

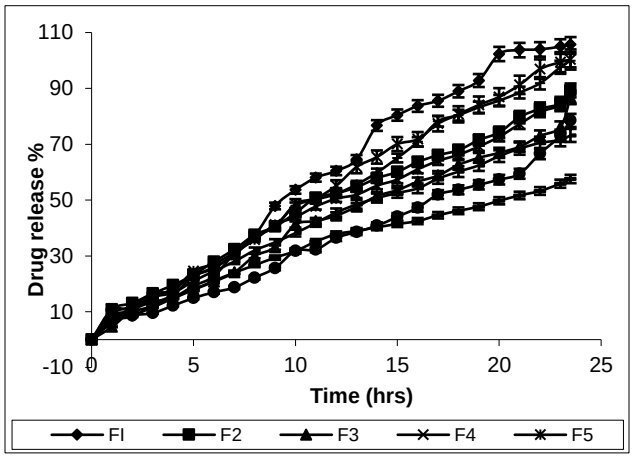

Figure 3: Drug release profile of factorial batches

Table 17: Effect of dependent variables

Formulation code	Dependent variables		
	Q_{24}	$t_{50\%}$	f_2
F1	105.73	10.21	49.27
F2	89.25	12.32	59.34
F3	86.83	14.25	47.58
F4	100.34	11.07	71.21
F5	86.35	12.77	56.18

F6	78.51	16.62	37.42
F7	99.92	11.46	79.79
F8	73.14	14.66	44.09
F9	57.53	19.5	31.54

- $\mathbf{Q_{24Hrs}} = 84.99 - 8.53\ X_1 - 13.8X_2 - 5.8X_1X_2 - 3.12X_1^2 + 5.23X_2^2$
  ($R^2 = 0.9843$)
- $\mathbf{t_{50}} = 13.08 + 2.9X_1 + 2.93X_1 + 1.0X_1X_2 + 0.24X_1^2 + 0.60X_2^2$
  ($R^2 = 0.806$)
- $\mathbf{f_2} = 55.20 - 0.1X_1 - 13.9X_2 - 11.64X_1X_2 - 3X_1^2 - 0.40X_2^2$
  ($R^2 = 0.947$)

Correlation coefficient reflects fit. Polynomial Equation informs conclusions based on coefficient magnitude and sign. X1 and X2 impact Q24hrs significantly ($P < 0.005$).

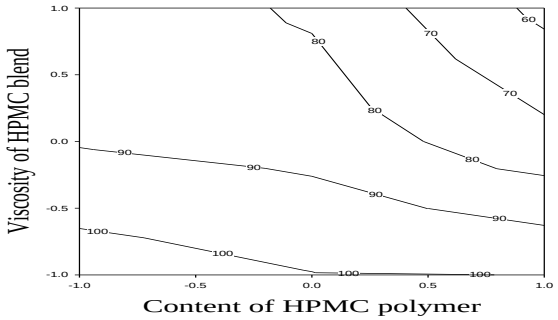

Figure 4: Counter plot of content of HPMC polymer (X_1) and viscosity of HPMC blend (X_2) versus Q_{24hrs}

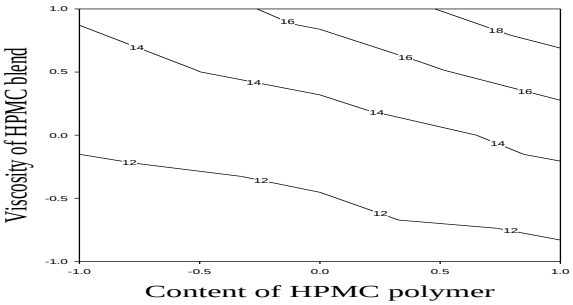

Figure 5: Counter plot of content of HPMC polymer (X_1) and viscosity of HPMC blend (X_2) versus $t_{50\%}$

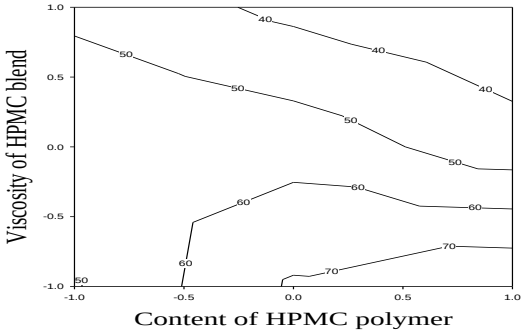

Figure 6: Counter plot of content of HPMC polymer (X_1) and viscosity of HPMC blend (X_2) versus f_2

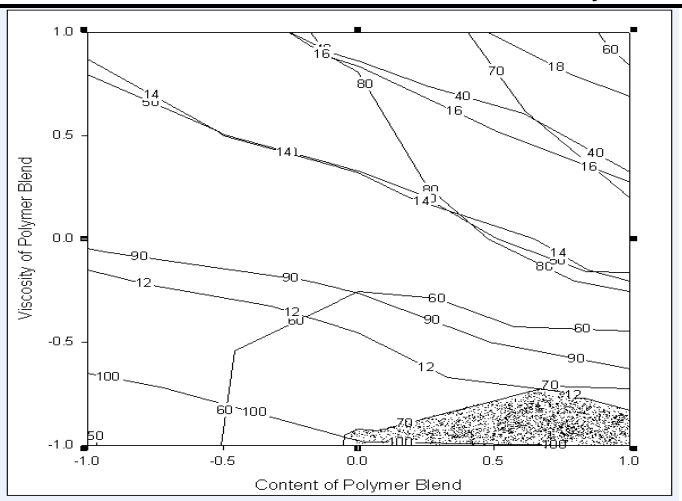

Figure 7: Overlapping counter plot of content of polymer blend (X_1) and viscosity of polymer blend (X_2) versus Q_{24}, t_{50},f_2

Figures 4, 5 and 6 display HPMC content (X_1) and viscosity (X_2) vs. Q_{24hrs} $t_{50\%}$ and f_2. Sigma Plot used. X_1, X_2 affect drug release. Figure 7 shows optimized area.

Comparison of dissolution profiles: Dissolution profiles compared using similarity factor (f2) per SUPAC guidelines. Profiles are similar if f2 is 50-100. Results in Table no 18 show all batches are like theoretical profile; F7 scored highest f2 at 79.79.

Table 18: Similarity factor amongst the factorial batches

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Similarity factor (f_2)	49.27	59.34	47.58	71.21	56.18	37.42	79.79	44.09	31.54
MDT (hrs)	5.15	5.32	5.39	5.43	5.29	6.57	6.12	4.87	4.79

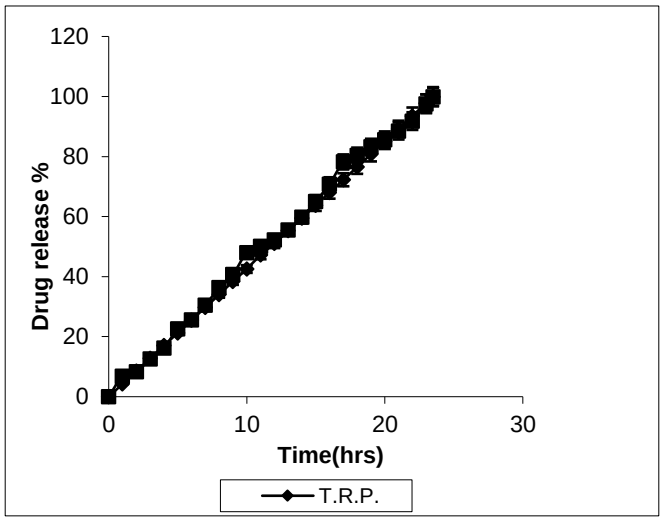

Figure 8: Comparison of theoretical drug release profile and batch F_7

In vitro buoyancy studies: Formulations exhibit floating lag time <2 minutes. Figure no 9 depicts buoyancy, swelling, and stability of the best batch in vitro.

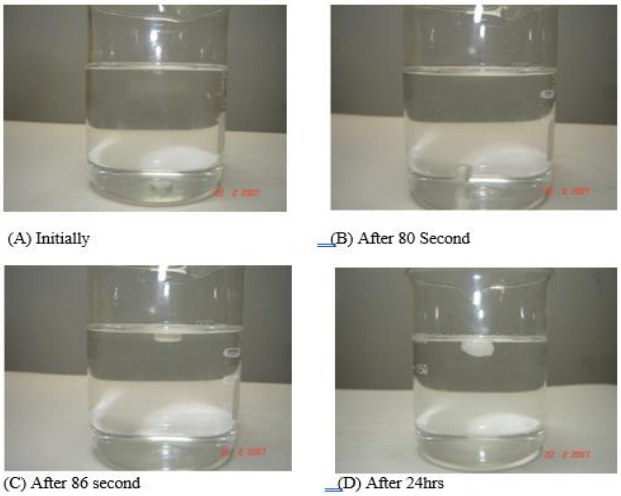

Figure 9: In vitro buoyancy studies

Swelling index study: Table 19 lists swelling index of top batch, attributed to HPMC's high viscosity and water retention.

Table 19: Swelling index study of best batch F7

Time (hrs)	Swelling index
6 hrs	1.831
12 hrs	2.184
18 hrs	3.157
24 hrs	3.31

Bioadhesion Study: Bioadhesion study results, detailed in Table 20, show increasing bioadhesive strength with higher HPMC polymer amounts and viscosity. Maximum strength occurs at peak polymer levels due to enhanced swelling and polymer chain mobility, facilitating mucin interaction.

Table 20: Bio-adhesion study

Batch Code	Force required (gms)
F1	6
F2	6
F3	7
F4	7
F5	7
F6	9
F7	10
F8	10
F9	12

Evaluation of physical parameters of prepared tablets: All tablet formulations met specifications for weight, hardness, and friability. Hardness above 3-5 kg/cm^2 prevents breakage; friability below 1% prevents material loss.

Table 21: Physical parameters of prepared tablet

Bathes	Weight variation (mg) (n=20)	Hardness (kg/cm^2) (n=10)	Friability (%) (n=10)
F1	205 ± 2.88	4.8 ± 0.124	0.92 ± 0.0028
F2	200 ± 2.51	4.5 ± 0.057	0.87± 0.0018
F3	200 ± 2.51	4.5 ± 0.057	0.95 ± 0.0023
F4	200 ± 2.51	5 ± 0.15	0.83 ± 0.0018
F5	195 ± 2.88	5 ± 0.15	0.79 ± 0.0015

F6	190 ± 2.88	5.5 ± 0.057	0.68 ± 0.00149
F7	200 ± 2.51	5 ± 0.15	0.826 ± 0.0018
F8	205 ± 2.88	6 ± 0.137	0.93 ± 0.0028
F9	200 ± 2.51	5 ± 0.15	0.856 ± 0.0018

Kinetic modeling and mechanism of drug release: The dissolution profile of the best batch was analyzed using various models to determine drug release kinetics and mechanisms.

Table 22: Kinetic modeling data of batch F7

Model	Zero order	First-order	Higuchi plot	Hixon Crowell	Weibull	Kors-meyer
F-value	4.07	1139.38	58.21	98.84	33.60	4.12
R^2	0.9980	-0.7869	0.9710	0.8960	0.9181	0.9938
Slope	4.23	-0.1631	23.51	0.1382	1.35	0.9398
Inter-cept	1.35	5.33	-23.65	-0.3728	-1.483	-1.4839

F-statistics determined model selection. Bamba's test analyzed drug kinetics. Batch F7 data (Table 6.12) fit Zero-order (F=4.07), indicating optimal drug release.

Discussion: This study found that polymer blend content and viscosity influence in vitro drug release. Using HPMC K4M & K100M is beneficial for gastro retentive tablets. Gas generating agent concentration was optimized at 35mg. All factorial batches had floating lag time under two minutes and good bioadhesion. Full factorial design optimized drug release, showing significant effects of HPMC blend content and viscosity. Batch F7 had the highest similarity factor (f2 = 79.79) with desired release profile. A zero-order drug release mechanism was observed.

(III) Formulation Development and optimization of Bi- Layer Gastro retensive tablet of Ketorolac Tromethamine

Theoretical release profile of Bi-layer gastro retentive tablet of ketorolac tromethamine:

Table 23: Theoretical release profile of Bi-layer gastro retentive tablet of KET

Time (Min)	Drug release %
2	1.66
5	4.15
10	8.3
15	12.45
20	16.6
25	20.75
30	24.9
60	26.45
120	29.65
240	36.05
360	42.4
480	48.8
600	55.2
720	61.55
840	68
960	74.35
1080	80.7
1200	87.1
1320	93.45
1440	99.85

Preparation of Bi-layer gastro retentive tablet of ketorolac tromethamine: Figure no 10 Bi-layer tablet of ketorolac tromethamine. Bottom layer: maintenance dose, floating. Upper layer: immediate release, loading dose.

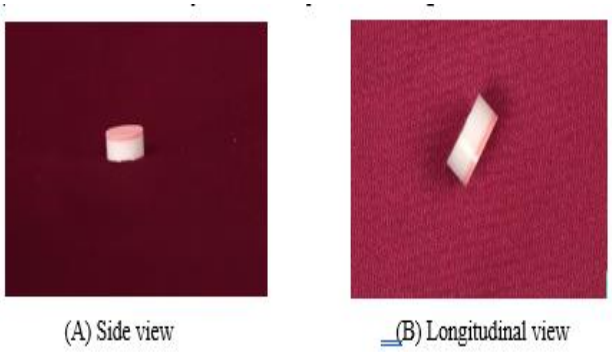

Figure 10: Bi-layer tablets of ketorolac tromethamine

Optimization of Bi-layer gastro retentive tablet of Ketorolac tromethamine: Bi-layer KET gastro retentive tablet optimized via varied compression force (20-50kg/cm2) using Hydraulic Pellet Press for desired release profile.

In vitro dissolution study: In vitro dissolution behavior of bi-layer tablets is shown in figure 11.

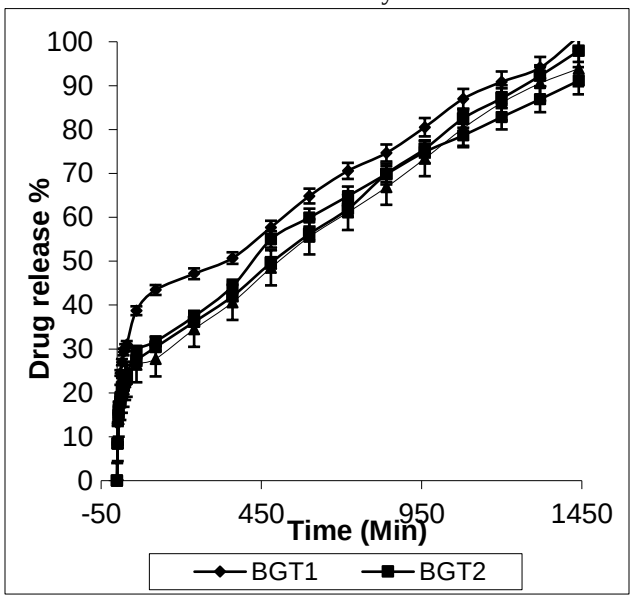

Figure 11: Release pattern of bi-layer tablets of KET

Comparison of dissolution profiles: Modified release dosage forms were compared using a similarity factor (f2) between 50 and 100. In vitro drug release profiles of bi-layer tablets were compared, with batch BGT2 showing the highest f2 at 71.48.

Table 24: Similarity factor of different Bi-layer formulation of KET

Formulation code	BGT1	BGT2	BGT3	BGT4
Similarity factor (f_2)	51.67	71.48	71.58	63.84
MDT (Min)	210	250	242	206

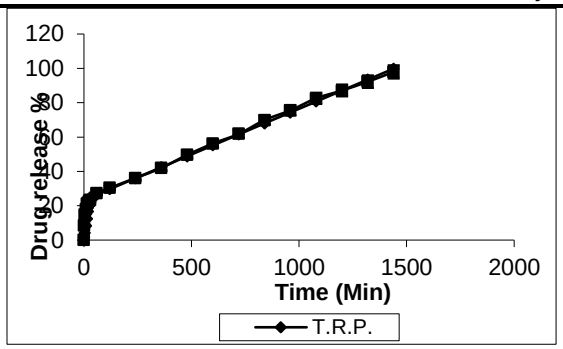

Figure 12: Comparison of theoretical release profile and best batch (BGT2) of Bi-layer tablet of ketorolac tromethamine

In vitro buoyancy studies: Various formulations exhibited floating lag time < 2 minutes. Figure no 13 illustrates in vitro buoyancy study results, indicating stable tablet buoyancy and swelling.

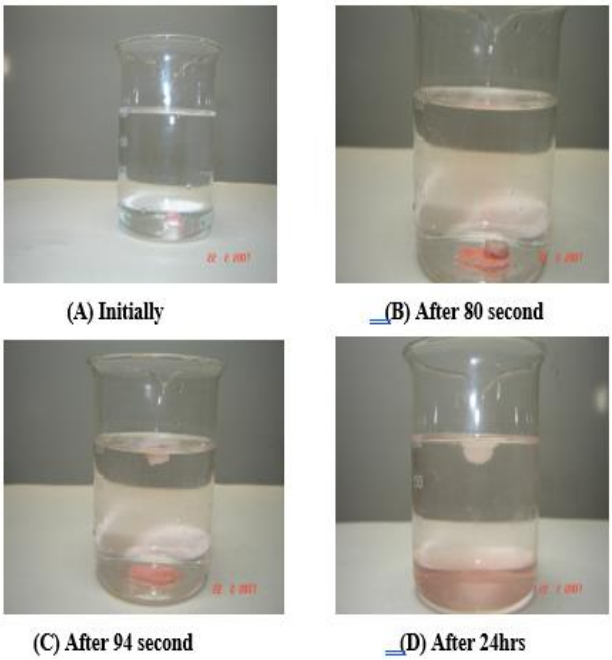

Figure 13: In vitro buoyancy studies of best batch (BGT2)

Physical parameters of bi-layer tablet of KET: Batch BGT2 selected for further studies due to its superior physical properties among all four batches.

Table 25: Physical Properties of Tablets Containing KET

Formulation	Dia-meter (mm) (n=20)	Dis-integration Time (Min)	Hardness (kg/cm^2) Mean (n=20)	Weight variation (mg) (n=20)	% Friability (n=20)
BGT1	8 ± 0.215	1.2 ± 0.11	4 ± 0.076	300 ± 0.76	0.12 ± 0.0025
BGT2	8 ± 0.219	1.4 ± 0.15	5 ± 0.076	300 ± 0.76	0.32 ± 0.0028
BGT3	8 ± 0.216	1.8 ± 0.20	5.5 ± 0.15	305 ± 0.516	0.30 ± 0.0026
BGT4	8 ± 0.285	2.0 ± 0.18	6.7 ± 0.133	305 ± 0.516	0.58 ± 0.0021

Kinetic modeling and mechanism of drug release: The dissolution profile of the best batch was analyzed using various models to determine drug release kinetics. Bamba et al's method was utilized for model selection.

Table 26: Kinetic modeling data of batch BGT2

Model	Zero-order	First-order	Higuchi plot	Hixon Crowell	Wei-bull	Kors-meyer
F-value	65.87	278.77	71.74	86.34	100.22	85.26
R^2	0.9169	0.8205	0.9095	0.9269	0.6010	0.4749
Slope	3.58	-0.1300	20.37	0.1213	0.9065	0.5557
Inter-cept	16.66	4.89	-6.02	-0.015	-0.925	-0.817

F-statistics guided model selection. Bamba's test determined drug dissolution kinetics. Batch BGT2, with highest f2, followed Zero-order (F=65.87). Least F-value suggests preferred model, indicating Zero-order drug release.

Accelerated stability study of the optimized batch: Ethical drug makers ensure safe, effective products. Stability studies determine storage and expiry conditions, vital for global markets and regulatory compliance. The results of accelerated stability studies are shown in Figure 14.

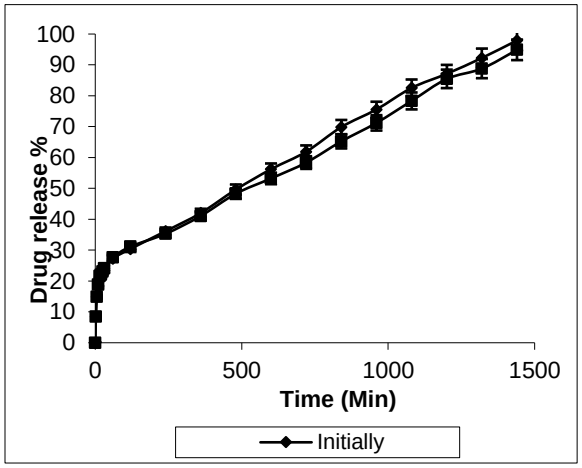

Figure 14: Comparison of dissolution profile after stability study

Stability studies show good similarity in dissolution profiles (f2 > 50, ~74.87) and no significant change in floating lag time.

In vivo study: Various studies suggest that pharmaceutical dosage forms with good in vitro floating behavior exhibit prolonged gastric residence in vivo. Density, size, and food presence in the stomach are key factors affecting performance. In vivo studies on healthy volunteers corroborated these findings. Photographs at various intervals are shown in figure no 15.

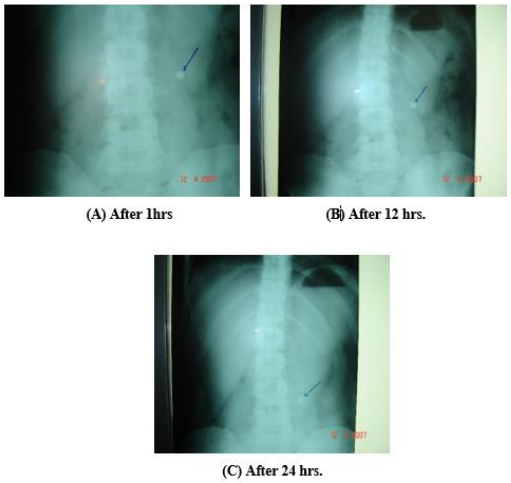

Figure 15: In vivo X-ray study of bi-layer gastro retentive tablet of ketorolac tromethamine

X-Ray shows tablet remains in stomach after 6 hrs, unaffected by food. Likely due to bioadhesiveness and HPMC's floating property. Confirmed after 24 hrs.

Discussion: In this study, a bi-layer gastro retentive tablet of ketorolac was developed, comprising an immediate release layer and a sustained release layer. The loading dose released within 30 minutes, providing quick pain relief, followed by a maintenance dose lasting 24 hours. The tablet demonstrated good floating and bioadhesive properties, ensuring sustained release via diffusion mechanism.

Summary and Conclusion

The investigation aimed to develop a bi-layer gastro retentive tablet of ketorolac tromethamine (KET). One layer provides an immediate release for a loading dose within 30 minutes using super disintegrating agents. The second layer, for sustained release, maintains the dose for 24 hours through floating and bioadhesive mechanisms of HPMC polymer. Ketorolac, an NSAID, requires frequent dosing due to stomach absorption. Formulation challenges led to the bi-layer tablet approach. Optimization involved croscarmellose for fast disintegration and sodium bicarbonate for floating. HPMC K4M showed the best sustained release and floating ability. Kinetic modeling revealed zero-order release via diffusion. In vivo studies confirmed gastro retention for 12 hours, with stable formulation.

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