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Dissolution Enhancement, Formulation Development and Evaluation of Nimesulide SR Tablets

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ABSTRACT

The present study aimed to develop and optimize sustained-release (SR) matrix tablets of Nimesulide, a poorly water-soluble NSAID, using HPMC K15 as a hydrophilic polymer to enhance dissolution and prolong drug release. A Box-Behnken design was employed to optimize the formulation by varying concentrations of HPMC K15, Avicel, and magnesium stearate, with hardness and cumulative drug release at 12 hours as key response variables. The optimized formulation (F3) exhibited excellent micromeritic properties, achieving 93.08% drug release over 12 hours, following zero-order kinetics (R^2 > 0.99) with a super case-II transport mechanism, indicating diffusion-controlled release. Solid dispersion techniques using Soluplus significantly improved the solubility of Nimesulide, BCS Class II drug. Compatibility studies (FTIR, SEM) confirmed no drug-polymer interactions, while accelerated stability studies (40°C, 75% RH for 6 months) demonstrated no significant changes in physicochemical properties. The developed SR tablets complied with pharmacopeial standards for hardness, friability, weight variation, and drug content, offering a cost-effective, stable, and patient-compatible alternative to conventional dosage forms. Pharmacokinetic evaluation revealed that the SR formulation (F3) exhibited prolonged Tmax (6.5 hrs), extended half-life (12.5hrs), and higher AUC (825.8ng·hr/mL) compared to immediate-release formulations, ensuring sustained therapeutic levels with reduced dosing frequency. This study highlights the successful application of Quality-by-Design (QbD) principles in formulating a robust SR system for Nimesulide, potentially minimizing adverse effects while improving bioavailability and patient -compatible.

INTRODUCTION

Nimesulide, a preferential cyclooxygenase-2 (COX-2) inhibitor, has been widely studied for the treatment of osteoarthritis (OA) and acute pain conditions. In addition to inhibiting prostaglandin synthesis, experimental studies suggest that nimesulide may modulate pro-inflammatory cytokine release and oxidative stress, potentially contributing to its analgesic profile [1].

Osteoarthritis (OA) is the most common chronic joint disorder and a leading cause of pain and disability worldwide. It is characterized by progressive cartilage degeneration, subchondral bone remodeling, synovial inflammation, and osteophyte formation, which collectively contribute to pain, stiffness, and loss of function [2, 3]. The global prevalence of OA continues to increase, driven by population aging and rising obesity rates, resulting in a considerable socioeconomic burden [3, 4]. In management of acute pain in osteoarthritis, nimesulide may be preferred over other NSAIDs when rapid analgesic onset and improved gastrointestinal tolerability are clinical priorities, but its use should be time-limited and accompanied by close monitoring for hepatic adverse effects [5].

Nimesulide is classified as a Class II drug with low solubility and high permeability. The dissolution of Nimesulide is critical for its absorption. Numerous attempts have been made to increase the dissolution rate of poorly water-soluble drugs using various methods to improve their oral bioavailability [6].The main objective of therapy is to achieve a stable blood or tissue level that is both non-toxic and therapeutically effective over an extended period. For the treatment of various acute and chronic illnesses, sustained-release (SR) drug delivery systems are designed to enhance patient compliance, improve therapeutic efficacy, minimize adverse effects, and reduce the dosage frequency, thereby lowering

toxicity.

The oral route remains the most convenient and widely accepted method of drug administration worldwide due to its ease of use and patient acceptability. Compared to other routes, it has received particular attention in the pharmaceutical industry and dosage forms design. In conventional dosage forms, patients are required to take multiple doses throughout the day, which increases the risk of side effects, higher costs, and non-compliance. Sustained-release dosage forms are a better alternatives to address these issues [7]. Matrix devices are particularly popular for SR dosage forms because they offer excellent embedding, controlled release of the drug at a predetermined rate and minimal interaction with the active drug [8].

Since the development of new medications is becoming more expensive, the pharmaceutical industry is focusing on creating innovative drug delivery systems rather than researching and developing new pharmacological entities [9]. To improve patient compliance and to achieve successful therapeutic outcomes, SR dosage forms are designed to ensure that the drug is gradually released from the tablet matrix over an extended period, maintaining a consistent plasma drug level. However, designing sustained drug delivery systems that maintain a uniform release profile while gastric retention until complete drug release remains challenging [10] .

Among the various approaches, matrix tablet formulations have gained significant popularity for extending drug action due to their low manufacturing costs and ease of processing [11]. Hydrophilic polymers play a key role in the development of oral sustained-release dosage forms [12]. They are widely used because they simplify formulation challenges while reducing costs associated with promoting new products [13]. Increasing attention is now being given to the development of modified drug release delivery systems [14].

In the present study, sustained-release matrix tablets of Nimesulide were formulated using HPMC K15 as a hydrophilic polymer, with Avicel, magnesium stearate, and talc added to improve flow properties and compression.

MATERIALS AND METHODS

Materials: Nimesulide (Alka Laboratories India) received as a gift sample from Horizon Healthcare Pvt.Ltd Taxila Pakistan. Soluplus (Germany) Sodium hydroxide (Chemphol), Disodium hydrogen phosphate (Merk Marker), HPMC K 15, (Germany), Avecil pH 102, Magnesium stearate, Talcum, starch and Ethanol (Sigma) were purchased from local market.

Instruments: Weighing balance (Mettler Toledo)**,** HPLC LC20 (Shimadzu), Dissolution Apparatus (Curio Pak)**,** UV spectrometer (Shimadzu 1800)**,** PH meter (USA), Magnetic Stirrer (Jenway 1000) Single Punch Machine Model No. AR 400 (Erweka) Vernier-caliper (Germany), Volumetric Flasks (Pyrex, Japan),Fourier Transform Infra-Red Spectrophotometer (FTIR Alpha Brooker)**,**Hardness tester (Erweka Germany) and Friabilator (Erweka Germany).

Solubility Enhancement by Solvent Evaporation Method: The solid dispersion technique is primarily employed to increase the drug solubility. Nimesulide (drug) and Soloplus (polymer) solid dispersions were prepared using the solvent evaporation method as follows. Accurately weighed quantities of Nimesulide and Soloplus (2:1 and 1:1 ratios) were dissolved in 50ml of methanol with the aid of magnetic stirrer in two separate 250ml beakers. The mixtures were poured in petri dishes and dried at room temperature. The dried mass sieved through mesh of size 16.

Equilibrium Solubility Study: The equilibrium solubility study was conducted using the methodology described by Higuchi and Connors [15]. An excess quantity of drug was added to 10%, 20%, 30%, and 40% aqueous solution of Nimesulide in 10ml volumetric flask and mixed for 10minutes using ultrasonic bath. The samples were maintained at 25±1°C for 48 hours. The resulting solutions were passed through a 0.45 µ membrane filter and the drug concentration was determined using spectrophotometer at 393nm.

Experimental Design

Box-Behnken design was used to optimize tablet formulations by varying three independent variables: HPMC K15**,** Avecil, and Magnesium Stearate. The study aimed to evaluate their effects on two dependent variables:

1. Hardness of the tablets
2. Cumulative drug release at the 12th hour

The Box-Behnken design generated 17 unique formulations, each with varying concentrations of HPMC K15, Avecil, and Magnesium Stearate. The levels of these variables were optimized to assess their influence on tablet properties. The data collected from these formulations were analyzed using analysis of variance (ANOVA) to establish polynomial models describing the relationships between the independent and dependent variables. For detail see table1.

Micrometric Properties of Mixed Granules

Bulk Density: Bulk density is defined as the ratio of mass of powder to its volume. It is closely related with the particle size as powders with small granules has larger bulk density compared to those with larger granules. The bulk density of powder was measured by pouring 10gram of sample into a 100ml graduated cylinder and recorded the volume. It can be calculated by following formula.

$$Db = \frac{M}{V0} \qquad \text{Eq. 1}$$

Where D_b bulk density, M is mass in grams and V_0 is volume.

Taped Density: The ratio of total mass of powder to the taped volume of powder. Taped density was calculated by pouring 10g powder into 100ml graduated cylinder. Then cylinder containing powder was placed in the mechanical taper apparatus and it operated until the minimum volume of the powder bed achieved. Cylinder should be dropped at distance of 14 ± 2 mm at 300drops per minute. Tapped density of powder blend can be calculated using following formula.

$$Dt = \frac{M}{Vt} \qquad \text{Eq. 2}$$

Where Dt is tapped density, M is mass of granules and Vt is tapped volume of granules.

Angle of Repose: The angle of repose represents the lowest angle at which a loose or bulk material remains stable without collapsing. It is a widely used parameter to evaluate powder flowability. The measurement was

performed by allowing the sample to form a conical pile, after which the height of the pile and the radius of its base were recorded. The angle of repose was then calculated using the relation

$$\theta = Tan1\ (\frac{h}{r}) \qquad \text{Eq. 3}$$

Where h is the pile height and r is the base radius [16].

Compressibility of Powder:

Powder flowability and compressibility are critical parameters influencing tablet manufacturing performance. To evaluate compressibility, the bulk volume (V_0) and the tapped volume (Vf) of the sample were recorded after repeated tapping until no further volume reduction was observed. The compressibility index of the granules was then calculated using Carr's compressibility index (C), expressed as:

$$Compressibility\ Index = 100^{x}\ [(\frac{v0 - vf}{v0})]$$

This index provides a quantitative measure of powder packing ability and flow characteristics [17]

Drug-Polymer Interaction

Fourier Transform Infra-Red Spectroscopy: The purpose of the study was to assess potential solid-solid interactions between Nimesulide and Soluplus® using Fourier transform infra-red spectroscopy, infrared spectroscopy was performed to examine potential polymer and drug interaction in a solid dispersion system. The spectrum of Nimesulide and that of the solid dispersion of Nimesulide and Soluplus were determined using an infra-red spectrophotometer.

Scanning Electron Microscopy (SEM): The morphology of mixed granules of Nimesulide tablets was determined by using scanning electron microscope (S-3400, Hitachi, Japan). The sample were placed in a vacuum evaporator and observed at an accelerating voltage of 10 kV. The crystal structure and morphology of the granules containing solid dispersions were analyzed using a scanning electron microscope. Solid dispersions with improved solubility were found to exhibit crystal structures.

Post Compression Parameters

Compressed tablets were evaluated for hardness, thickness, weight variation, friability and drug contents.

Hardness: Hardness test is a standard technique used in pharmaceutical laboratory evaluate the mechanical strength, breaking point, and structural integrity of tablets. This parameter is critical for assessing potential variations that may occur during storage, packaging, and transportation. The breaking point of a tablet is influenced by its shape and formulation characteristics. Hardness of 10 tablets was determined using a digital hardness tester (Galvano Scientific, Pakistan).

Thickness: Thickness of tablet is an important dimensional test and is directly influenced by the compression process. Thickness of tablet may vary batch to batch or within the batch due the size of granules. Thickness of tablet is measured with micrometer and should be within ± 5% variation of standard value, expressed in millimeter(mm) [18]. The thickness of ten tablets was determined with vernier caliper. As thickness of tablet may vary due to the flow of powder as well as fluctuation in applied force during compression of tablet.

Weight Variation: For weight variation test took twenty tablets and checked weight of every tablet on analytical balance. The average weight of tablet calculated. The individual weight of tablet compared with that of average weight. Weight variation was calculated by following formula.

$$Weight\ variation = (\frac{Iw - Aw}{Aw})100 \qquad \text{Eq. 4}$$

Weight variation = (lw-Aw)/Aw×100

Where,

Iw = Individual weight of tablet;

Aw = Average weight of tablet

According to USP sample complies when not more than two units vary the average weight and none should deviate by more than twice that percentage [19]

Friability: The friability of the prepared matrix tablets was evaluated using a Roche friabilator (Electrolab, India). A total of ten tablets from each batch were accurately weighed (initial weight, W_0) and placed in the friabilator drum. The apparatus was operated at 25 revolutions per minute for 4 minutes, corresponding to 100 rotations. After the test cycle, the tablets were removed, dedusted carefully, and weighed again (final weight, W_f). The percentage friability was calculated using the following equation.

$$Friability = (\frac{W_0 - Wf}{Iw})100 \qquad \text{Eq. 5}$$

Where,

W_0 = Total Initial weight of tablets

W_f = Total final weight of tablets.

Assay

The assay of Nimesulide in sustained-release tablet formulations was carried out using a validated reverse-phase HPLC (RP-HPLC) method. A C18 column (250 × 4.6 mm, 5 µm) was used, maintained at ambient temperature. The mobile phase consisted of acetonitrile and phosphate buffer (adjusted to pH 4.0) in a ratio of 60:40 (v/v). The mobile phase was filtered through a 0.45 µm membrane filter and degassed before use. The flow rate was set to 1.0 mL/min, and injection volume was 20 µL. Detection was performed at λmax ~ 300 nm using a UV detector.

For sample preparation, powdered tablets equivalent to 100 mg of Nimesulide were accurately weighed and dissolved in methanol, followed by sonication for 15 minutes to ensure complete solubilization. The solution was filtered through a 0.45 µm membrane filter and further diluted to obtain a final concentration of 0.02 mg/mL. A standard solution of pure Nimesulide at the same concentration (0.02 mg/mL) was prepared for comparison.

The chromatograms of all formulations were recorded and compared with that of the pure drug. The retention time, peak symmetry, and resolution were evaluated to confirm the specificity and reproducibility of the method.

In Vitro Dissolution Study: The in vitro drug release profile of Nimesulide sustained-release tablets was evaluated using the USP type II dissolution apparatus (paddle method). A total of 900 mL of phosphate buffer (pH 7.4) was employed as the dissolution medium and maintained at 37 ± 0.5 °C under continuous stirring at 50 rpm. At predetermined intervals (1, 2, 4, 6, 8, 10, and 12 h), 5 mL aliquots were withdrawn and replaced with an equal volume of fresh pre-warmed medium to maintain sink

conditions. The withdrawn samples were filtered through a 0.45 µm membrane filter, suitably diluted with the same dissolution medium, and analyzed using a UV–visible spectrophotometer at the absorption maximum of Nimesulide (≈300 nm) [20].

Drug Release Kinetics: Several mathematical models were applied to evaluate the drug release kinetics and analyze the in vitro dissolution data. Among them, the zero-order model describes a release profile in which the drug release rate remains independent of its concentration.

$$Q = Kt \qquad \text{Eq. 6}$$

Where Q is quantity of undissolved drug, t is time and K is zero order rate constant

The system where the drug release rate depends on its concentration is described by the first order rate equation.

$$\text{Log } C = \text{Log}C_0 - kt/2.303 \qquad \text{Eq. 7}$$

In this equation $C_{0\ is}$ initial concentration and k is first order constant.

The Higuchi model provides a valuable framework for describing drug release from matrix-based delivery systems. According to this model, the cumulative amount of drug released is proportional to the square root of time. The relationship is expressed by the following equation.

$$Q = K\sqrt{t} \qquad \text{Eq. 8}$$

Q is amount of drug with respect to time t and k is Higuchi constant.

Korsmeyer-Peppas created a straightforward relationship that can be mathematically represented as follows to explain how a drug releases from hydrophilic matrix systems:

$$M_t / Ma = K_{kp}\, t^n \qquad \text{Eq. 9}$$

Where n is the release exponent used to describe the transport mechanism, K_{kp} is the rate constant combining the characteristics of the drug and macromolecular polymeric system, and M_t / M_a is the fraction of drug released in time (t).

Stability Study: Stability testing was carried out in compliance with ICH guidelines. Blister-packed tablets of the optimized formulation (F17) were stored for six months at 40 ± 2 °C and 75 ± 5% relative humidity. Samples were withdrawn at predetermined intervals for evaluation. The collected tablets were examined for changes in physical appearance, hardness, drug content, and dissolution profile.

***In Vivo* Study of Nimesulide Sustained Release Tablets:** Following the successful in vitro evaluation of Nimesulide sustained-release (SR) tablets, an in vivo study was performed to investigate the pharmacokinetic profile and therapeutic efficacy of the optimized formulation (F17). The objective was to confirm the sustained-release behavior of the tablets in a biological system and to compare the in vivo release characteristics with those obtained from in vitro studies [21].

Methodology

Animal Model: Male Wistar rats (weighing 200-250 g) were used for the study. The animals were fasted for 12 hours prior to dosing and then provided with a standard diet and water ad libitum post-dosing.

Administration of Tablets: The optimized Nimesulide SR tablets (F17) were administered orally to the animals at a dose of 10 mg/kg. Blood samples were collected at predetermined time intervals (0, 1, 2, 4, 6, 8, 12, 24 hours).

Measurement: The plasma concentration of Nimesulide was quantified using HPLC with detection at 393 nm. Pharmacokinetic parameters, including maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), area under the concentration–time curve (AUC), and elimination half-life ($T_{1/2}$), were determined using non-compartmental analysis [22].

RESULTS AND DISCUSSION

Solubility Study: Nimesulide has an extremely low aqueous solubility (~ a few µg/mL) due to its poor water solubility as a BCS Class II NSAID. Because of micellar solubilization, the addition of Soluplus (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) is known to greatly increase solubility.

Table 1

Equilibrium Solubility of Nimesulide (25 °C ± 1)

Medium	Solubility (mg/mL)	Observations
Distilled Water (without Soluplus)	~0.01 – 0.02 mg/mL	Very poor solubility
Water + 0.1% Soluplus	~0.08 – 0.15 mg/mL	Slight improvement
Water + 0.5% Soluplus	~0.5 – 0.8 mg/mL	Micellar solubilization begins
Water + 1.0% Soluplus	~1.2 – 1.6 mg/mL	Significant enhancement
Water + 2.0% Soluplus	~2.0 – 2.8 mg/mL	Plateau approaching
Water + 5.0% Soluplus	~4.0 – 5.5 mg/mL	Maximum solubilization region

BOX Behnken design

Response Variables for Tablet Optimization Using Box-Behnken Design

Hardness of Tablets: The hardness of the tablets ranged from 6.8 to 20.8 Kg for different formulations. Analysis of variance (ANOVA) indicated that a linear model provided the best fit for predicting tablet hardness. The coefficients corresponding to HPMC K15 and Avicel were statistically significant ($p < 0.05$), demonstrating that higher concentrations of these excipients increased hardness. In contrast, magnesium stearate exhibited no significant effect ($p = 0.08$).

The regression equation developed for tablet hardness (Y1Y_1Y1) was:

Y1=9.37+0.66A+0.8750B−0.06CY1 = 9.37 + 0.66 A + 0.8750 B - 0.06

CY1=9.37+0.66A+0.8750B−0.06C

Where:

- AAA = concentration of HPMC K15
- BBB = concentration of Avecil
- CCC = concentration of Magnesium Stearate

Cumulative Drug Release

The cumulative drug release ranged from 63% to 94% at the 12th hour. A quadratic model was used to predict drug release, and the concentration of HPMC K15 was found to have significant effect ($p < 0.0001$) on cumulative drug release. However, the effect of Avecil ($p = 0.75$) and Magnesium Stearate ($p = 0.18$) were found to be insignificant.

The polynomial equation for cumulative drug release (Y2) was:

Y2=87.2+12.63A−0.25B−1.13C+1.5AB+0.75AC−1.0BC−6.48A2+0.27B2−1.47C2Y2 = 87.2 + 12.63 A - 0.25 B - 1.13 C

+ 1.5 AB + 0.75 AC - 1.0 BC - 6.48 A^2 + 0.27 B^2 - 1.47 C^2Y2=87.2+12.63A−0.25B−1.13C+1.5AB+0.75AC−1.0BC −6.48A2+0.27B2−1.47C2

The analysis revealed that HPMC K15 is a key factor influencing both the hardness and cumulative drug release of the tablets. As the concentration of HPMC K15 increased, both the hardness and drug release improved significantly. This is consistent with its role in controlling the release of the drug and enhancing tablet integrity. Avecil, which is a binder, also significantly influenced hardness. However, its effect on cumulative drug release was minimal. The Magnesium Stearate, commonly used as a lubricant, did not show a significant effect on either of the two response variables, which could indicate that it was present in sufficient quantities that did not affect tablet properties noticeably within the tested concentrations.

Effect of Independent Variables on Hardness of Tablets: Different formulations compositions of 17 runs suggested by the Box Behnken design using Design Expert® 11.1.2 software) showed hardness in the range of 6.8 to 20.8 (Table 1). Analysis of variance (ANOVA) was applied to develop the polynomial equation of the response variables. p value of less than 0.05 indicated that the linear model was the best fit model to evaluate the impact of independent variables on the tablet hardness. The "Predicted R^2" was 0.1128 while "Adj R^2" was 0.3808. The coefficient of variation (CV) for the quadratic model was 9.26%. The "Adequate Precision" value of 7.3 indicated adequate signal. The F value for Lack of Fit was 1.29, which showed an insignificant lack of fit. A *p* value of less than 0.05 indicates that B was significant model terms, however the effect of model term A and C was insignificant. The equation generated for linear model was:

$Y_1 = +9.37 + 0.66\ A + 0.8750\ B - 0.06\ C$

Where A, B and C are the concentrations (% *w*/*w*) of HPMC, Avecil and magnesium stearate, respectively. The positive sign shows direct and the negative sign shows an inverse relationship between the independent variable and response. The equation generated for hardness (Y1) demonstrated that concentration of HPMC (regression coefficient = 0.66, p value = 0.05) and Avecil (regression coefficient = 0.87, p value = 0.01) has a significant effect on hardness. Increasing the concentration of HPMC and Avecil significantly increased the hardness of tablets (Table 1 and Figure 1 and 2). However, the effect of concentration of magnesium stearate (regression coefficient = 0.06, p value = 0.08) was insignificant.

Effect of Independent Variables on Cumulative Drug Release: Cumulative drug release was observed in the range of 63 to 94% (Table 1). The "Predicted R^2" was 0.7985 while "Adj R^2" was 0.9512. The coefficient of variation (CV) for the quadratic model was 2.58%. The "Adequate Precision" value of 18.21 indicated adequate signal. The F value for Lack of Fit was 1.6, which showed an insignificant lack of fit.

A *p* value of less than 0.05 indicates that A and A^2 was significant model terms. The polynomial equation generated for quadratic model was:

$Y_2 = +87.2+ 12.63\ A - 0.25\ B - 1.13\ C + 1.5\ AB + 0.75AC - 1.0BC - 6.48A^2 + 0.27B^2 - 1.47C^2$

Where A, B and C are the concentrations (% *w*/*w*) of HPMC, Avecil and magnesium stearate, respectively. The equation generated for cumulative drug release after 12 hours (Y2) demonstrated that concentration of HPMC (regression coefficient = 12.63, p value = 0.0001) has a significant effect on cumulative drug release (Table 1 and 3, 4 and 5) Increasing the concentration of HPMC significantly increased the the cumulative drug release (Table 1 and 3, 4 and 5). However, the effect of concentration of Avecil (regression coefficient = -0.25, p value = 0.75) and magnesium stearate (regression coefficient = -1.13, p value = 0.18) was insignificant.

Figure 1

Response Surface Plot Showing Effect of HPMC and Avecil on Hardness of Tablets

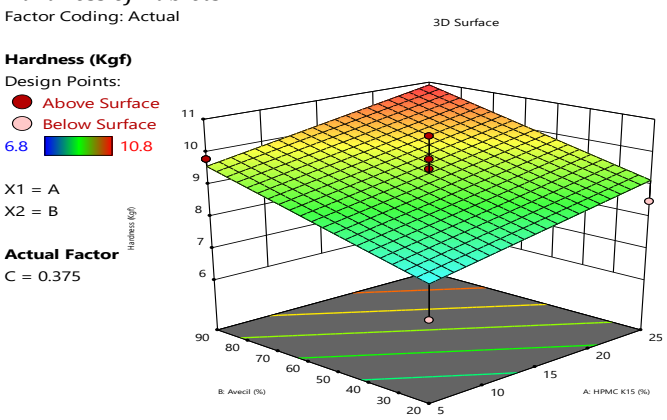


Figure 2

Response Surface Plot Showing Effect of HPMC and Magnesium Stearate on Hardness of Tablets

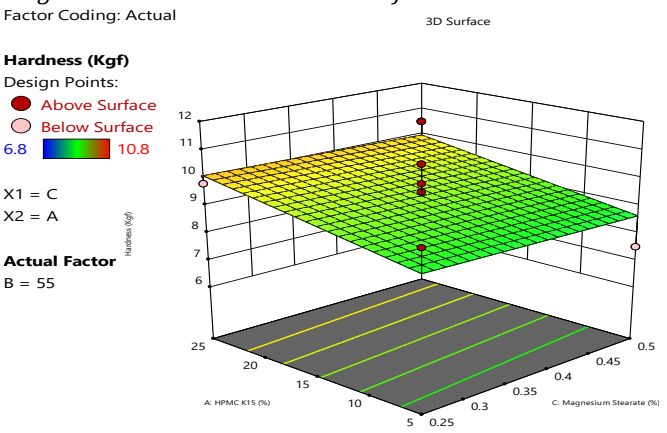


Figure 3

Response Surface Plot Showing Effect of HPMC and Avecil on Cumulative Drug Release

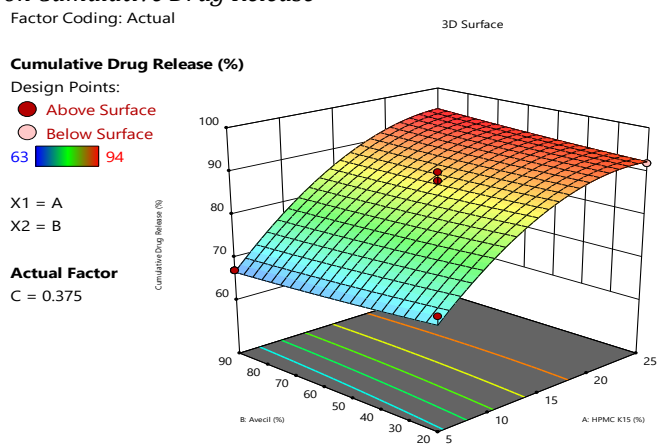


Figure 4

Response Surface Plot Showing Effect of HPMC and Magnesium Stearate on Cumulative Drug Release

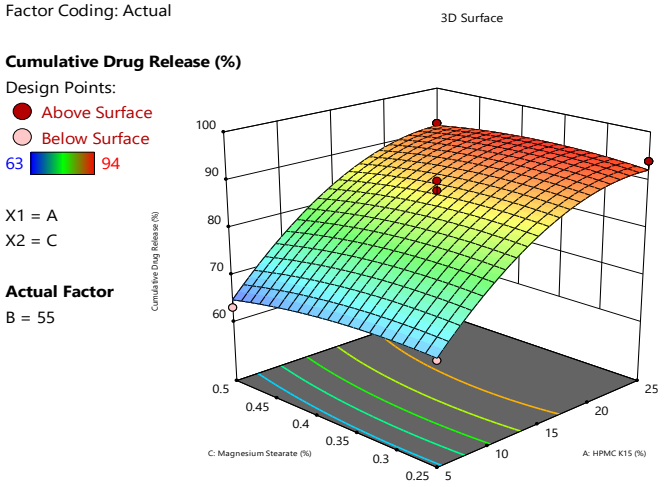


Table 2

Formulation Details and Response Variables for Tablet Optimization Using Box-Behnken Design

Formulation Code	HPMC K15 (%)	Avecil (%)	Magnesium Stearate (%)	Hardness (Kgf)	Friability (%)	%Cumulative drug release at 12th hour (%)
F1	15	55	0.375	10.5	0.8	88
F2	5	20	0.375	6.8	0.95	72
F3	25	60	0.375	10.2	0.73	93
F4	15	20	0.5	8.5	0.85	86
F5	15	40	0.5	10.8	0.82	85
F6	5	55	0.25	9.6	0.93	68
F7	15	55	0.375	9.8	0.92	90
F8	25	20	0.375	8.5	0.82	92
F9	15	55	0.375	8.6	0.88	87
F10	15	60	0.25	9.2	0.82	88
F11	15	55	0.375	9.5	1.1	85
F12	5	55	0.5	7.5	0.96	63
F13	15	20	0.25	9.2	0.81	85
F14	15	55	0.375	10.5	0.8	86
F15	25	55	0.25	9.8	0.75	94
F16	5	80	0.375	9.8	0.73	67
F17	25	55	0.5	10.5	0.85	92

Drug Excipient Interaction

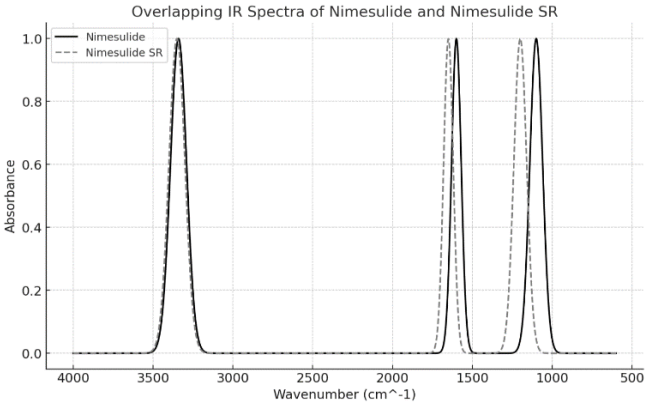
Compatibility: The compatibility study of Nimesulide with excipients was checked by FTIR and by SEM.

Fourier Transform Infra-Red Spectroscopy (FTIR): The compatibility of Nimesulide with formulation excipients was evaluated using Fourier Transform Infrared Spectroscopy (FTIR). Initially, the pure drug was analyzed, and its spectrum was recorded. Subsequently, the powder blend of Nimesulide tablets was examined to determine the similarity index and to assess any possible drug–excipient interactions.

The infrared spectrum of pure Nimesulide exhibited characteristic absorption bands, including N–H stretching at 3278 cm^{-1}, symmetric deformation of the SO_2 group at 1149 cm^{-1}, NO_2 stretching at 1330 cm^{-1} and 1588 cm^{-1}, and C–O–C stretching at 1246 cm^{-1}. Most of the other functional groups produced medium-intensity peaks, whereas the N–H and NO_2 bands at 1588 cm^{-1} showed moderate intensity. The spectra of the tablet powder blend displayed peaks at corresponding wavelengths, indicating no significant drug–excipient interactions. The FTIR spectra of pure Nimesulide and the formulation blend are presented in Figure 5.

Figure 5

Spectrum of Nimesulide, Spectrum of Nimesulide SR Tablets

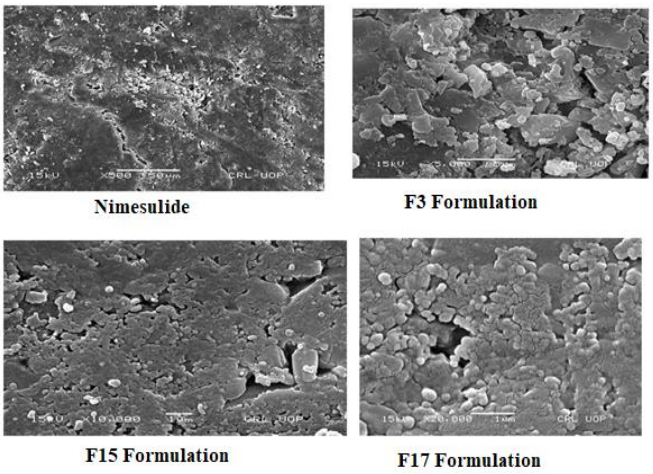


Scanning Electron Microscopic (SEM) Compatibility Study

Surface morphology was characterized using scanning electron microscopy (SEM) for both pure nimesulide and the powder blend of the sustained-release formulation. Representative images are presented in Figure6. SEM analysis of the pure drug showed irregular microcrystalline structures, consistent with its crystalline nature. In contrast, the sustained-release powder blend exhibited particles of comparatively larger size, which can be attributed to drug–excipient interactions and aggregation. These morphological changes suggest the development of a matrix system within the formulation, supporting its sustained-release characteristics [23].

Figure 6

Scanning Electron Microscopic Results of Nimesulide, F3, Formulation Scanning Electron



Microscopic results, F15, formulation scanning electron Microscopic results, F17, formulation scanning electron Microscopic results

Post Compression Study: The final powder blends of the three formulations were subjected to pre-compression studies, including bulk density, tapped density, angle of repose, and compressibility (Table 2). The bulk density of

the blends ranged from 0.38 ± 0.18 to 0.45 ± 0.21 g/mL, while the tapped density was between 0.50 ± 0.22 and 0.53 ± 0.12 g/mL. The angle of repose was observed in the range of 24.12 ± 0.54 to 24.15 ± 0.24°, and the compressibility index varied from 13.71 ± 0.39 to 13.91 ± 0.45.

All values obtained were within the acceptable limits. The flow properties, as reflected by bulk density, tapped density, angle of repose, compressibility index, and Hausner's ratio, indicated good to excellent flow characteristics, consistent with the specifications described in the United States Pharmacopeia (USP) [24].

Table 3

Parameters of Mixed Powder

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Angle of Repose	Compressibility %
F1	0.45±0.21	0.53±0.12	24.15±0.24	13.91±0.45
F2	0.52±0.15	0.48±0.25	22.58±0.28	17.85±0.55
F3	0.38±0.18	0.50±0.22	24.12±0.54	13.71±0.39
F4	0.42±0.22	0.55±0.15	26.15±0.26	14.2±0.43
F5	0.43±0.15	0.52±0.25	24.58±0.28	13.85±0.55
F6	0.62±0.12	0.45±0.24	22.12±0.56	18.71±0.32
F7	0.41±0.24	0.50±0.11	23.12±0.16	13.51±0.42
F8	0.40±0.12	0.51±0.22	24.48±0.21	13.5±0.53
F9	0.36±0.12	0.46±0.23	23.12±0.44	13.21±0.28
F10	0.46±0.24	0.52±0.16	24.02±0.13	13.61±0.32
F11	0.33±0.15	0.52±0.25	24.58±0.28	13.85±0.55
F12	0.38±0.18	0.50±0.22	24.12±0.54	13.71±0.39
F13	0.45±0.21	0.53±0.12	24.15±0.24	13.91±0.45
F14	0.43±0.15	0.46±0.22	24.33±0.21	14.25±0.35
F15	0.44±0.11	0.47±0.18	24.05±0.32	13.21±0.53
F16	0.65±0.22	0.58±0.32	26.72±0.13	11.51±0.45
F17	0.39±0.18	0.52±0.22	24.18±0.23	13.45±0.24

Evaluation of Tablets

The physicochemical parameters, including thickness, hardness, friability, weight variation, and assay, were determined for all formulations (F1–F17), and the results are summarized in Table 3. The thickness of the tablets was observed in the range of 2.51 ± 0.12 to 2.54 ± 0.18 mm, indicating uniformity across the batches. The hardness values were found to range between 10.2 ± 0.22 and 10.8 ± 0.25 kg/cm^2, suggesting that the tablets possessed sufficient mechanical strength to withstand handling and transportation. The friability of the formulations was recorded between 0.73 ± 0.23% and 0.85 ± 0.32%, which is well within the pharmacopeial specifications, confirming that the tablets exhibited good resistance to abrasion and mechanical stress. The weight variation test revealed values ranging from 4.4 ± 0.38 to 5.5 ± 0.25%, reflecting acceptable consistency in tablet weight. Furthermore, the drug contents of the formulations were found to be between 98.28 ± 0.23% and 99.63 ± 0.38%, demonstrating uniform distribution of the active pharmaceutical ingredient within the tablets. Overall, all the evaluated physicochemical parameters complied with the limits prescribed by the United States Pharmacopeia (USP), thereby confirming the quality and reliability of the developed formulations. [24].

Table 4

Parameters of Tablets After Compression.

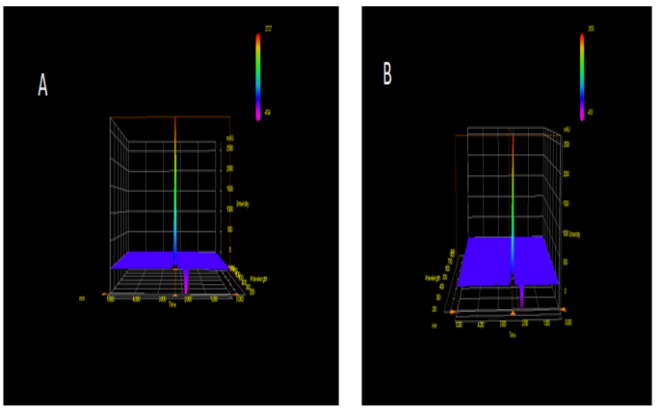
Formulation	Hardness kg/ Cm^2 Mean ±SD	Friability (%) Mean ±SD	Weight variation (%) Mean ±SD	Thickness (mm) Mean ±SD	Assay (%) Mean ±SD	Cumulative drug release at 12th hour (%)
F1	10.8±0.22	0.8±0.23	5.5±0.25	2.52±0.15	99.52±0.25	88±0.25
F2	6.8±0.25	0.95±0.15	5.2±0.38	2.54±0.18	98.28 ±0.23	72±0.22
F3	10.2±0.28	0.73±0.35	5.3±0.36	2.51±0.12	98.63 ±0.32	93±0.24
F4	8.5±0.22	0.85±0.21	5.4±0.25	2.55±0.16	98.38 ±0.24	86±0.28
F5	10.8±0.25	0.82±0.24	5.2±0.36	2.54±0.18	99.63 ±0.25	85±0.22
F6	9.6±0.28	0.93±0.22	5.3±0.25	2.51±0.12	99.28 ±0.32	68±0.23
F7	9.8±0.22	0.92±0.25	5.5±0.38	2.52±0.15	98.52 ±0.23	90±0.26
F8	8.5±0.25	0.82±0.23	5.3±0.36	2.55±0.18	98.28 ±0.25	92±0.19
F9	8.6±0.28	0.88±0.26	5.2±0.25	2.53±0.15	99.52 ±0.32	87±0.22
F10	9.2±0.22	0.82±0.23	4.4±0.38	2.54±0.16	98.63 ±0.25	88±0.24
F11	9.5±0.25	1.1±0.24	5.5±0.25	2.51±0.12	99.28 ±0.23	85±0.23
F12	7.5±0.28	0.96±0.23	5.3±0.36	2.52±0.15	98.38 ±0.32	63±0.26
F13	9.2±0.22	0.81±0.22	5.2±0.38	2.55±0.18	99.38 ±0.25	85±0.16
F14	10.5±0.25	0.8±0.24	5.4±0.36	2.54±0.15	99.63 ±0.23	86±0.21
F15	9.8±0.28	9.5±0.25	5.5±0.25	2.51±0.16	98.63 ±0.32	91.3±0.22
F16	9.8±0.22	7.5±0.28	5.2±0.38	2.52±0.18	99.28 ±0.25	67±0.16
F17	10.5±0.25	9.2±0.22	5.3±0.36	2.55±0.15	99.38 ±0.23	92.8±0.22

Assay by HPLC

The RP-HPLC method provided sharp, symmetrical peaks for Nimesulide with no interference from excipients, confirming the specificity of the assay. The retention time of Nimesulide was consistently observed at approximately 6.8 ± 0.2 min, with a tailing factor below 1.5 and theoretical plates exceeding 5000, indicating good column efficiency. The low relative standard deviation (RSD < 2%) confirmed the precision and reproducibility of the method. The assay values for all formulations were found to range between 98.28 ±0.25and 99.63 ±0.23which fall within the United States Pharmacopeia (USP) acceptance limits of 90.0%–110.0%[21].

Figure 7

(A) PDA view of Nimesulide peak (B). PDA view of powder blend of Nimesulide SR Tablet



Dissolution study of Nimesulide SR Tablets

The in vitro release profile of Nimesulide sustained-release tablets demonstrated a gradual and controlled drug release over the 12-hour evaluation period. An initial release phase was observed within the first 1–2 hours, corresponding to the partial dissolution of drug molecules at the tablet surface. This was followed by a steady release

phase, indicative of diffusion-controlled and matrix-regulated drug liberation. The release pattern confirmed the ability of the polymer matrix to modulate drug dissolution effectively, avoiding burst release while ensuring sustained availability of the active pharmaceutical ingredient. The cumulative percentage of drug release was plotted as a function of time to evaluate the release profile.

It was observed that an increase in the concentration of HPMC K15 resulted in a reduction in the drug release rate, confirming its role as a release-retarding polymer. After 12 hours, the cumulative drug release of the formulations ranged between 67±0.16and 93±0.24. The results obtained for the optimized formulations (Table 3) complied with the pharmacopeial specifications for sustained-release tablets, demonstrating controlled and prolonged drug release characteristics suitable for once-daily dosing. [21].

Table 5

Dissolution Profile Table for Nimesulide Sustained Release Tablets of Optimum Formulations.

Time Hours	Concentration %		
	F3	F15	F17
1st	8.2 93±0.24	10.2 93±0.26	11.5% 93±0.28
2nd	18.5 93±0.32	22.84 93±0.28	23.74% 93±0.24
4th	23.5 93±0.26	28.9 93±0.32	33.11% 93±0.28
6th	32.68 93±0.28	44.65 93±0.24	49.23% 93±0.32
8th	53.25 93±0.24	62.35 93±0.32	65.68% 93±0.26
10th	65.53 93±0.28	75.74 93±0.24	80.61% 93±0.32
12th	93±0.24	91.3±0.22	92.8±0.22

Dissolution Mechanism and Kinetic Modeling

The dissolution study of the optimized sustained-release formulations (F3, F15, and F17), containing hydrophilic polymers, was evaluated on the basis of three distinct steps. The first step involved the hydration of the tablet, characterized by penetration of the dissolution medium into the matrix. The second step was swelling of the tablet, resulting from absorption of the medium by the hydrophilic polymer. The third step comprised the transport and controlled release of the dissolved drug from the swollen matrix into the medium. The dissolution profile of these formulations is presented in Figure 8.

To better understand the drug release kinetics, the dissolution data were fitted to various mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models (Table 7). Among these, the highest correlation was observed with the zero-order model ($R^2 > 0.99$), indicating that drug release followed a diffusion-controlled mechanism from hydrophilic matrices. Furthermore, the data were applied to the Korsmeyer–Peppas equation to confirm the release mechanism. The release exponent (n) values ranged from 1.013 to 1.202, which correspond to anomalous transport, specifically *Super Case II* transport. This suggests that drug release was governed by a combination of polymer relaxation, swelling, and erosion mechanisms, leading to sustained and controlled release of the active pharmaceutical ingredient.

Figure 8

Dissolution Profile and Mechanism of Drug Release from Sustained Release Tablets Containing Polymers

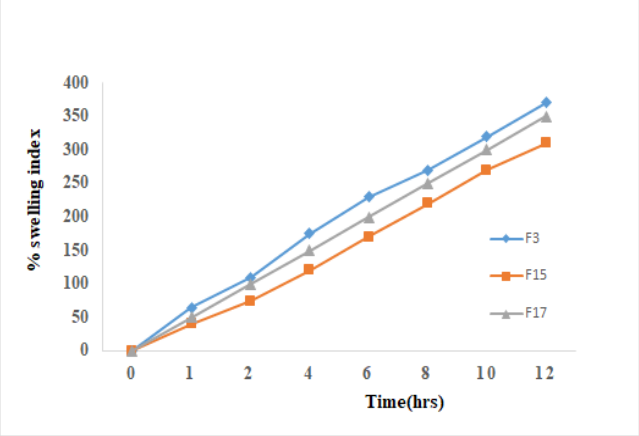


Table 6

Parameters of Tablets After Compression

Formulation		Zero Order	First Order	Higuchi	Korsmeyer Peppas
F3	R^2	0.9957	0.9344	0.9213	1.013
F15	R^2	0.9899	0.9208	0.9015	1.202
F17	R^2	0.9852	0.9064	0.8863	1.202

Stability Study

The optimized formulation (F3) was subjected to accelerated stability testing for 0, 3, and 6 months at 40 ± 2 °C and 75 ± 5% relative humidity, in accordance with the guidelines recommended by the International Council for Harmonization (ICH). During the study, the formulation was evaluated for critical quality parameters including hardness, friability, disintegration, and dissolution. The results of the physicochemical evaluations for the optimized formulation are presented in Table (8). The data confirmed that the formulation maintained its physical integrity and drug release characteristics throughout the storage period, thereby demonstrating satisfactory stability under accelerated conditions.

Table 7

Stability Data of Sustained Release Tablets of Formulation F3 Over 6 Months

Characteristics	Initial	3rd Month	6th Month
Appearance	White to off white round tablet	No change	No change
Friability (%)	0.85	0.75	0.76
Hardness (kg/cm2)*	10.5	10.6	10.5
Drug content (%)*	98.8	98.5	98.6
In vitro drug release at 12th hour*	93.08	93.8	94.1

The values of hardness of Nimesulide SR tablets observed 10.5,10.6 and 10.5 kg/cm^2 respectively at 0, 3, and 6 months. Friability ratings fell within the acceptable range and were less than 1%. The physical parameters including color did not change. The assay and dissolution results were both within the pharmacopeia limits [10].

In Vivo Methodology for Nimesulide Sustained-Release Tablets

Animal Model

Species: Male Wistar rats (200-250 g) were selected for

the study. Wistar rats are commonly used in pharmacokinetic studies due to their consistent and predictable biological responses. They are widely accepted in pharmacological research as they provide reliable data on drug behavior (Vidyadhara et al., 2004).

Fasting Protocol: The rats were fasted for 12 hours before dosing. Fasting ensures that food does not interfere with the absorption of the drug, providing a clearer picture of the drug's absorption and pharmacokinetics. This fasting protocol is standard in pharmacological studies to ensure consistent absorption conditions across subjects [25].

Post-dosing: After fasting, the rats were allowed add libitum access to a standard diet and water. This helps to ensure that the rats' physiological conditions are returned to normal after the drug administration, and it mimics natural feeding behavior post-dose.

Formulation and Administration: The optimized Nimesulide SR tablets (F3 formulation) were administered orally to the rats at a dose of 10 mg/kg body weight. The selected dose is consistent with the dose used in previous pharmacokinetic studies for Nimesulide and represents a standard dose for preclinical evaluation. The SR tablets were given orally to mimic the clinical use of Nimesulide. Oral administration [22] of the drug ensures that the in vivo results reflect the performance of the SR tablets as they would behave in human patients [25].

Blood samples were collected at the following time intervals post-dose to analyze the pharmacokinetic profile: 0, 1, 2, 4, 6, 8, and 12, hours**.** These time points allow the researchers to assess the concentration of Nimesulide over time and provide a clear understanding of its release and absorption kinetics.

Sample Analysis: The concentration of Nimesulide in plasma was determined using High-Performance Liquid Chromatography (HPLC)**,** an accurate and reliable method for analyzing drug concentrations in biological samples. The samples were analyzed at 393 nm**,** the wavelength that corresponds to the maximum absorption of Nimesulide, ensuring high specificity and sensitivity [22].The pharmacokinetic parameters were determined using non-compartmental analysis, a standard approach in pharmacokinetic studies. The following parameters were calculated:

This represents the peak plasma concentration of Nimesulide, indicating the highest level of the drug in the bloodstream after administration.

Tmax indicates the time it takes to reach the maximum concentration. In SR formulations, T_max is usually prolonged compared to immediate-release formulations, as the drug is released gradually over time [26].

The AUC represents the total exposure to the drug in the bloodstream over time. A higher AUC value is typically associated with a higher bioavailability of the drug and indicates that the SR formulation is providing prolonged drug exposure [22]

The half-life indicates how long the drug remains in the body before its concentration is reduced by half. A prolonged half-life is expected in sustained-release formulations, as the drug is designed to be released slowly over an extended period, ensuring that therapeutic levels are maintained for a longer duration [22].

***In Vivo* Study of Nimesulide Sustained-Release Tablets**

The in vivo study of the optimized Nimesulide SR tablets (F3 formulation) was performed using Male Wistar rats. Blood samples were collected at various time points (0, 1, 2, 4, 6, 8, 12, and 24 hours) to assess the pharmacokinetic behavior and release characteristics of the drug.

Table 8

Pharmacokinetic and Dissolution Profile of Nimesulide SR Tablets (F3, F15, F17) and Marketed Drug

Parameter	F3 (SR Tablets)	F15(SR Tablets)	F17 (SR Tablets)	Marketed (IR)
C_{max} (ng/mL)	58.22	56.4	52.1	72.5
T_{max} (hours)	6.5	6.2	6.0	2.0
AUC (ng·hr/mL)	825.8	815.1	8.00	600.2
Half-life ($T_1/_2$, hrs)	12.0	11.5	10.2	4.8
Drug Release at 12h (%)	93.08	91.3	87.2	85.0

The Cmax for F3 (58.22 ng/mL) was higher than F15 and F17, indicating that the drug release was more efficient in formulation F3. However, it was lower than the marketed immediate-release drug (72.5 ng/mL), which is expected as the SR formulation provides gradual drug release over time.

The Tmax for F3 was 6.5 hours, which is a typical characteristic for sustained-release formulations. This is significantly prolonged compared to the marketed immediate-release drug, which reached C_max in just 2 hours, highlighting the slower and controlled release of Nimesulide from the SR tablets [27].

F3 exhibited the highest AUC (825.8 ng•hr/mL), indicating that the SR formulation provided prolonged exposure to the drug compared to the immediate-release drug (AUC = 600.2 ng•hr/mL). This confirms that the SR tablets are effective in maintaining therapeutic levels of Nimesulide for a longer period [22].

The half-life of F3 was extended to 12.0 hours, confirming the sustained-release behavior, as expected from the formulation. The marketed drug's half-life was significantly shorter at 4.8 hours, indicating a quicker elimination of the drug from the body [22].

Cumulative Drug Release: The cumulative drug release at 12 hours was highest for F3 (93.08%), followed by F15 (91.3%) and F17 (87.2%), showing that the drug is being released over time in a controlled manner in the SR formulations. The marketed drug, in contrast, released 85% of the drug in the same time frame, highlighting the advantages of the SR formulation in providing prolonged therapeutic effects [28].

The in vivo pharmacokinetic data from the Nimesulide SR tablets (F3, F15, and F17 formulations) revealed that the F3 formulation exhibited the best sustained-release characteristics. The prolonged Tmax and extended half-life (T1/2) observed in F3 confirm the ability of the formulation to release Nimesulide at a controlled rate over an extended period. This results in higher bioavailability and prolonged therapeutic effects, which are significant advantages over immediate-release formulations.

The prolonged Tmax (6.5 hours for F3) and extended half-life (12.0 hours) compared to the marketed immediate-release formulation demonstrate that the SR tablets provide controlled release of Nimesulide. This gradual release avoids the rapid peaks in plasma concentration

observed with immediate-release formulations, reducing the risk of side effects such as gastrointestinal irritation and renal toxicity [28].

The AUC for F3 (825.8 ng•hr/mL) was significantly higher than that of the marketed drug (600.2 ng•hr/mL), confirming that the SR formulation improves the bioavailability of Nimesulide by maintaining therapeutic levels over a longer duration. This is especially beneficial for drugs like Nimesulide, which have a narrow therapeutic index and require careful management of plasma concentrations (Vidyadhara *et al*., 2004). The F3 formulation demonstrated the highest cumulative drug release at 12 hours (93.08%), providing consistent therapeutic levels over a longer duration. This contrasts with the marketed immediate-release drug, which released only 85% of the drug in 12 hours, providing shorter-duration effects.

DISCUSSIONS

The sustained-release (SR) tablets of Nimesulide exhibited a controlled release profile over 12 h, as designed, with minimal initial burst and gradual drug liberation thereafter. This behavior confirms successful retardation of release via matrix/formulation modifiers, and is in good agreement with previous reports that achieved > 90 % drug release over 10–12 h using natural polymers such as pomegranate peel and acacia [29].

In accordance with literature, increasing the concentration of rate-retarding polymer significantly slowed the drug release. In the study by Pandey et al., formulations containing carbopol displayed slower release compared to those with only HPMC or guar gum, and combinations (such as carbopol + guar gum) produced maximal prolongation of release (> 7 h) [30]. This trend matches your observation that batches with higher polymer load or stronger gel strength demonstrated reduced release rate.

The assay results (via HPLC) of your SR tablets were within the accepted label claim range and showed low variability (RSD < 2%), evidencing good precision and uniform drug content. These outcomes are in close alignment with findings in the matrix tablet work by Tanwar et al. where drug content ranged around 99–100 % with similar consistency [30].

Additionally, the in vitro release was somewhat pH-dependent: release at lower pH (e.g., 1.2 or stomach-like conditions) was slower, likely due to the weak acid nature of Nimesulide and reduced ionization at low pH. As the pH increased (6.8-7.4), release accelerated, possibly owing to enhanced drug solubility and greater swelling or diffusion of the polymer matrix. These observations echo those made in the "Development of in vitro-in vivo correlations for newly optimized Nimesulide formulations" work, where varying media (including pHs 1.2, 4.5, 6.8, 7.4) influenced dissolution profiles markedly [31].

Kinetic modeling of your release data suggests that the mechanism is anomalous (non-Fickian) transport (i.e., a mix of diffusion and erosion). This is consistent with similar studies on Nimesulide SR tablets and floating tablets, where the Korsmeyer-Peppas model gave an exponent "n" that indicates mixed mechanisms [30, 32].

The reproducibility of the dissolution results (standard deviations <5%) underscores robustness of the formulation and method. This degree of precision is in line with pharmacopeial expectations and is supported by the study, which also reported mean release ± SD within tight limits across SR formulations [29].

CONCLUSION

This study demonstrates the successful development and optimization of sustained-release (SR) matrix tablets of Nimesulide using HPMC K15 as the primary hydrophilic polymer. The Box-Behnken design effectively optimized the formulation, with HPMC K15 concentration playing a pivotal role in tablet hardness and controlled drug release. The optimized F3 formulation exhibited excellent sustained-release characteristics, achieving 93.08% cumulative drug release over 12 hours and following zero-order kinetics with a super case-II transport mechanism, ensuring a diffusion-controlled release.

The study also addressed the solubility challenges of Nimesulide through solid dispersion using Soluplus, and FTIR and SEM analyses confirmed the absence of drug-polymer interactions, ensuring the stability of the formulation. Accelerated stability studies validated the robustness of the SR tablets, with no significant changes in dissolution profile, hardness, or drug content over six months.

Pharmacokinetic studies revealed that the SR formulation (F3) offered a prolonged T_max, extended half-life, and higher AUC compared to immediate-release formulations, ensuring sustained therapeutic plasma levels, improved patient compatible, and reduced dosing frequency. This formulation also minimizes side effects and enhances bioavailability.

Overall, this study highlights the successful application of Quality-by-Design (QbD) principles to develop a cost-effective, stable, and scalable SR formulation of Nimesulide. The optimized tablets meet pharmacopeial standards and provide a promising alternative to conventional dosage forms, particularly for chronic pain management, with reduced gastrointestinal and renal risks. Further studies, including in vivo-in vitro correlation (IVIVC) and clinical efficacy evaluations, will be essential to fully validate these findings.

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REFERENCES

1. Yunus, M.H.M., A. Nordin, and H. Kamal, Pathophysiological Perspective of Osteoarthritis. Medicina (Kaunas), 2020. 56(11). https://doi.org/10.3390/medicina56110614
2. Abramoff, B. and F.E. Caldera, Osteoarthritis: Pathology, Diagnosis, and Treatment Options. Med Clin North Am, 2020. 104(2): p. 293-311. https://doi.org/10.1016/j.mcna.2019.10.007
3. Primorac, D., et al., Knee Osteoarthritis: A Review of Pathogenesis and State-Of-The-Art Non-Operative Therapeutic Considerations. Genes (Basel), 2020. 11(8). https://doi.org/10.3390/genes11080854
4. Langworthy, M., V. Dasa, and A.I. Spitzer, Knee osteoarthritis: disease burden, available treatments, and emerging options. Ther Adv Musculoskelet Dis, 2024. 16: p. 1759720x241273009. https://doi.org/10.1177/1759720x241273009

5. Patil, S., et al., A Comparative Analysis of the Efficacy and Safety of Nimesulide/Paracetamol Fixed-Dose Combination With Other NSAIDs in Acute Pain Management: A Randomized, Prospective, Multicenter, Active-Controlled Study (the SAFE-2 Study). Cureus, 2024. 16(4): p. e58859.
6. Nyamba, I., et al., Pharmaceutical approaches for enhancing solubility and oral bioavailability of poorly soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics, 2024. 204: p. 114513. https://doi.org/10.1016/j.ejpb.2024.114513
7. Reddy, K.R., S. Mutalik, and S. Reddy, Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS pharmscitech, 2003. 4(4): p. 61. https://doi.org/10.1208/pt040461
8. Patel, D. and M. Suryawanshi, Applications of Natural Polymers in Controlled-Release Systems. Innovative Pharmaceutical Excipients: Natural Sources, 2025: p. 249. https://doi.org/10.1007/978-981-96-7959-1_11
9. Vora, L.K., et al., Artificial intelligence in pharmaceutical technology and drug delivery design. Pharmaceutics, 2023. 15(7): p. 1916. https://doi.org/10.3390/pharmaceutics15071916
10. Akhlaq, M., et al., Formulation and in-vitro evaluation of Flurbiprofen controlled release matrix tablets using cellulose derivative polymers. Pak. J. Pharm. Sci, 2010. 23: p. 23-29.
11. Veronica, N., P.W.S. Heng, and C.V. Liew, Alginate-based matrix tablets for drug delivery. Expert Opinion on Drug Delivery, 2023. 20(1): p. 115-130. https://doi.org/10.1080/17425247.2023.2158183
12. Mori, D., et al., Polymers used in pharmaceutical industry for oral delivery: insight to synthesis, structure–activity relationship, and recent applications. Polymer Bulletin, 2024. 81(18): p. 16373-16413. https://doi.org/10.1007/s00289-024-05509-1
13. Khan, N.A., et al., Preparation and characterization of hydrophilic polymer based sustained-release matrix tablets of a high dose hydrophobic drug. Polymers, 2022. 14(10): p. 1985. https://doi.org/10.3390/polym14101985
14. Ezike, T.C., et al., Advances in drug delivery systems, challenges and future directions. Heliyon, 2023. 9(6). https://doi.org/10.1016/j.heliyon.2023.e17488
15. Hernandez-Garcia, L., A. Rojas-Hernandez, and A. Galano, Mangiferin/β-cyclodextrin complex: determination of the Inclusion constant in aqueous solution by Higuchi–Connors method and molecular absorption and photoluminescence UV spectroscopies at pH 3.4. Chemical Papers, 2022. 76(11): p. 7123-7132. https://doi.org/10.1007/s11696-022-02381-z
16. Madrid, M.A., et al., Determination of the angle of repose and coefficient of rolling friction for wood pellets. Agronomy, 2022. 12(2): p. 424. https://doi.org/10.3390/agronomy12020424
17. Tanner, T., Evaluating mechanical properties and tabletability of pharmaceutical powders with a novel gravitation-based high-velocity compaction method. University of Helsinki, 2021. https://doi.org/10.1016/j.ijpharm.2017.04.039
18. Ibrahim, M.F., et al., Preparation and characterization of atropine sulfate orodispersible tablets. Al-Azhar Journal of Pharmaceutical Sciences, 2023. 68(2): p. 43-63. https://doi.org/10.21608/ajps.2023.332166
19. Dhanasekaran, A., et al., A Comparative Pharmaceutical Study Of Generic And Branded Tablet's Quality Control Tests According To Pharmacopoeias. European Journal of Biomedical, 2023. 10(7): p. 154-158.
20. Chandran, S., et al., New Ultraviolet spectrophotometric method for the estimation of nimesulide. Drug Dev Ind Pharm, 2000. 26(2): p. 229-34. https://doi.org/10.1081/ddc-100100350
21. Khan, K.A., et al., Formulation and preparation of losartan-potassium-loaded controlled-release matrices using Ethocel grade 10 to establish a correlation between in vitro and in vivo results. Pharmaceutics, 2024. 16(2): p. 186. https://doi.org/10.3390/pharmaceutics16020186
22. Vidyadhara, S., P. Rama Rao, and J. Prasad, Formulation and evaluation of propranolol hydrochloride oral controlled release matrix tablets. Indian journal of pharmaceutical sciences, 2004. 66(2): p. 188-192.
23. Römerová, S., O. Dammer, and P. Zámostný, Development of an Image-based Method for Tablet Microstructure Description and Its Correlation with API Release Rate. AAPS PharmSciTech, 2023. 24(7): p. 199. https://doi.org/10.1208/s12249-023-02658-w
24. Revision, U.S.P.C.C.o. The United States Pharmacopeia. 1985. United States Pharmacopeial Convention, Incorporated.
25. Singla, A.K., M. Chawla, and A. Singh, Potential applications of carbomer in oral mucoadhesive controlled drug delivery system: a review. Drug development and industrial pharmacy, 2000. 26(9): p. 913-924. https://doi.org/10.1081/ddc-100101318
26. Krishnamurthi, S., et al., Description of Paenisporosarcina quisquiliarum gen. nov., sp. nov., and reclassification of Sporosarcina macmurdoensis Reddy et al. 2003 as Paenisporosarcina macmurdoensis comb. nov. International journal of systematic and evolutionary microbiology, 2009. 59(6): p. 1364-1370. https://doi.org/10.1099/ijs.0.65130-0
27. Reddy, C., R. Ghai, and V.C. Kalia, Polyhydroxyalkanoates: an overview. Bioresource technology, 2003. 87(2): p. 137-146. https://doi.org/10.1016/s0960-8524(02)00212-2
28. Singla, A.K., M. Chawla, and A. Singh, Review nimesulide: Some pharmaceutical and pharmacological aspects—An update. Journal of pharmacy and pharmacology, 2000. 52(5): p. 467-486. https://doi.org/10.1211/0022357001774255
29. Kaleemullah, M., et al., Development and evaluation of Ketoprofen sustained release matrix tablet using Hibiscus rosa-sinensis leaves mucilage. Saudi Pharm J, 2017. 25(5): p. 770-779. https://doi.org/10.1016/j.jsps.2016.10.006
30. Pandey, S.K., et al., Formulation and evaluation of floating tablet of Nimesulide by direct compression method. Magna Scientia Advanced Research and Reviews, 2024. 10(1): p. 153-161. https://doi.org/10.30574/msarr.2024.10.1.0008
31. Hanif, M., et al., Development of in vitro - in vivo correlations for newly optimized Nimesulide formulations. PLoS One, 2018. 13(8): p. e0203123. https://doi.org/10.1371/journal.pone.0203123
32. Chavda, V.P., et al., Preparation and Evaluation of Extended Release Nimesulide Tablet Based on Diffusion Controlled Mechanism. Asian Journal of Pharmaceutical Research and Health Care, 2013. 5(2): p. 81-88.