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Design, Optimization, and Characterization of NSAID-Based Fast-Dissolving Films Using HPMC–PVA Polymer Matrix

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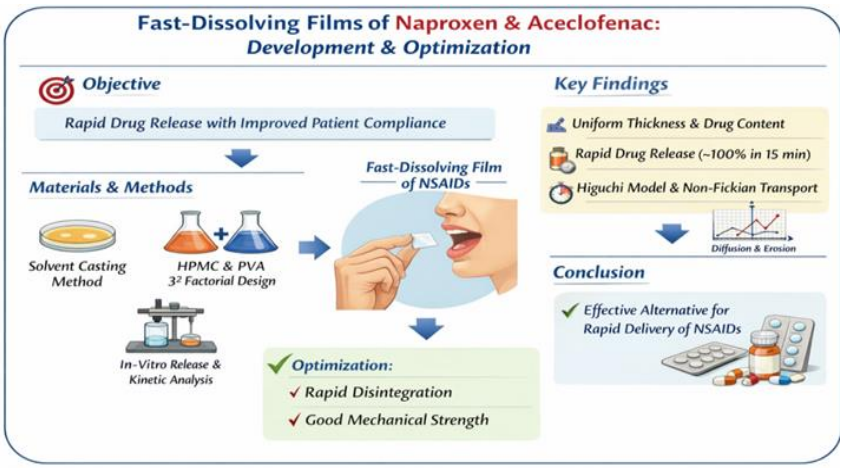
Abstract: Background: Overview- Fast-dissolving oral films (FDFs) are a cutting-edge drug delivery method intended to increase patient compliance and provide a speedy commencement of action, especially for medications that need a quick therapeutic effect. NSAIDs with conventional oral dosage forms, such naproxen and aceclofenac, are frequently linked to delayed onset and gastrointestinal adverse effects. Aim- In order to achieve quick drug release, sufficient mechanical strength, and increased patient acceptance, the current study set out to design and optimize fast-dissolving oral films of naproxen and aceclofenac.**Material and Methods-** The solvent casting method was used to create films that dissolved quickly. The impact of polyvinyl alcohol (PVA, X_2) and hydroxypropyl methylcellulose (HPMC, X_1) on formulation qualities was assessed using a 3^2 factorial design. Thickness, weight fluctuation, surface pH, consistency of drug content, mechanical characteristics, and folding endurance were all assessed. Phosphate buffer (pH 6.8) was used for in vitro drug release investigations, and different mathematical models were used to examine the release kinetics.**Result -** Every formulation showed consistent thickness, near-neutral surface pH, adequate mechanical strength, and drug content within permissible bounds. The medication was released quickly; almost full release was attained in 15 minutes. According to statistical analysis, PVA had a smaller impact on drug release than HPMC, which had a significant effect ($p < 0.05$). With non-Fickian transport behavior, release kinetics mostly adhered to the Higuchi model.**Conclusion-** The optimized fast-dissolving films showed good mechanical qualities, quick disintegration, and effective drug release, suggesting that they could be a useful substitute for traditional oral NSAID dosage forms.

Keywords: Fast-dissolving films, Naproxen, Aceclofenac, HPMC, PVA, Drug release kinetics



INTRODUCTION

The drug is ease of use, affordability, and high patient acceptance, oral medication delivery is still the most used method of administration. However, there are a number of drawbacks to traditional oral dose forms like tablets and capsules, such as inconsistent bioavailability, delayed onset of action, and trouble swallowing (dysphagia). These constraints have prompted the creation of innovative medication delivery methods that can improve patient compliance while offering quick therapeutic impact1. Among these, fast-dissolving oral films (FDFs) have drawn a lot of interest as a cutting-edge and effective drug administration method. When applied to the tongue, thin, flexible polymeric strips known as "fast-dissolving films" quickly dissolve, releasing the medication straight into the oral cavity2. This results in a quicker onset of action and better bioavailability by permitting pre-gastric absorption and partially avoiding first-pass metabolism. Furthermore, FDFs have a number of benefits, such as being simple to administer without the need for water, correct dose, enhanced stability, and suitability for certain groups, such as bedridden, elderly, and pediatric patients. Aceclofenac and Naproxen are two examples of non-steroidal anti-inflammatory medicines (NSAIDs) that are frequently recommended to treat rheumatoid arthritis, pain, and inflammation. Conventional formulations of these medications are frequently linked to poor patient compliance, delayed therapeutic response, and gastrointestinal irritation despite their efficacy3. By guaranteeing quick drug release, reducing stomach exposure, and improving patient convenience, the packaging of NSAIDs into fast-dissolving films offers a viable solution to these problems. The choice and concentration of polymers and excipients have a significant impact on the performance of fast-dissolving films. The hydrophilic polymer hydroxypropyl methylcellulose (HPMC E5) is well-known for its superior film-forming capacity, fast hydration, and swelling qualities that speed up drug release and disintegration. Another common polymer that greatly enhances the films' mechanical strength, flexibility, and structural integrity is polyvinyl alcohol (PVA)4. While additional excipients like sweeteners, flavoring agents, and saliva stimulants improve palatability and patient acceptance, plasticizers such polyethylene glycol (PEG 400) further improve film flexibility and avoid brittleness.

A 3^2 factorial design is an effective statistical tool for methodically examining the impact of formulation variables. This methodology makes it possible to assess how independent factors, specifically HPMC (X_1) and PVA (X_2), affect important quality characteristics such film thickness, mechanical strength, disintegration time, and drug release behavior both separately and in combination5,6. This method helps optimize the final dosage form while also offering a greater understanding of formulation dynamics. In the current study, the solvent casting process was used to create fast-dissolving films of naproxen and aceclofenac7. Physicochemical characterisation, mechanical property evaluation, surface pH measurement, drug content uniformity, in-vitro drug release investigations, and release kinetics modeling were all part of the thorough evaluation of the produced films. The importance of formulation factors was evaluated using statistical analysis utilizing ANOVA.

This study's main goal is to create and refine a fast-dissolving film formulation that offers good patient acceptability, sufficient mechanical strength, and quick drug release8. Additionally, the goal of this work is to demonstrate a strong relationship between formulation variables and film performance, which will aid in the logical development of efficient oral film drug delivery systems for NSAIDs.

Materials and Methods

Unless unless otherwise stated, all of the materials utilized in this inquiry were of pharmaceutical or analytical quality and were used exactly as received. For the purpose of developing fast-dissolving oral films, naproxen and aceclofenac were chosen as model non-steroidal anti-inflammatory medicines (NSAIDs)[9]. Because of their superior film-forming ability, quick hydration, and biocompatibility, polyvinyl alcohol (PVA) and hydroxypropyl methylcellulose (HPMC E5) were used as film-forming polymers. A plasticizer called polyethylene glycol 400 (PEG 400) was employed to add flexibility and keep the film from becoming brittle. To improve palatability, disintegration, and consistent drug distribution, additional excipients were added, such as flavoring agents, saliva-stimulating agents (citric acid), surfactants (Tween 80), and sweeteners (aspartame)[10]. All preparations were made with distilled or deionized water as the solvent.

Analytical and Instrumentation requirements

For spectrophotometric analysis, all analytical-grade reagents, solvents, and buffer solutions were utilized. The tools were used are UV-visible spectrophotometer for determining λmax and drug content, Film thickness using a micrometer screw gauge, Universal testing apparatus/texture analyzer (mechanical characteristics), Test equipment for disintegration (in-vitro disintegration study)[11,12]. Prior to experimentation, every instrument was calibrated to

guarantee precision and repeatability.

Preformulation study

Organoleptic evaluation

To determine identification and purity, naproxen and aceclofenac were assessed for color, odor, and physical appearance. Both medications showed up as white to off-white crystalline powders that were suitable for formulation and had no obvious contaminants.

Solubility studies

The shake-flask method was used to conduct solubility testing at 25 ± 2°C. Five milliliters of different solvents (distilled water, phosphate buffer pH 6.8, methanol, ethanol, acetone, and isopropyl alcohol) were mixed with an excess of each medication[13]. To reach equilibrium, the mixtures were agitated for a whole day and vortexed for two to three minutes. Samples were filtered using Whatman filter paper No. 1 and visually examined upon equilibration.

Determination of λmax

A UV-visible spectrophotometer was used to find the maximum absorption wavelength (λmax) of naproxen and aceclofenac. Each medication was diluted appropriately using a suitable solvent, and the absorption spectra of the solutions were obtained by scanning them over the ultraviolet spectrum[14]. Aceclofenac displayed a clear absorption maximum in the region of 276–278 nm, while naproxen displayed a distinctive absorption peak in the range of 230–232 nm. Throughout the investigation, these λmax values were employed for various analytical assessments and quantitative drug content estimation[15].

Drug excipient compatibity study

The determination possibility of any physical or chemical interactions between Naproxen, Aceclofenac, and the chosen formulation excipients, such as HPMC E5, PVA, and PEG 400, drug–excipient compatibility studies were conducted. In order to achieve equal blending, physical mixes of each medicine with specific excipients were made in a 1:1 ratio by precisely weighing and thoroughly combining the components with a mortar and pestle[16]. The prepared concoctions were put into glass vials that were dry, clean, and appropriately labeled. The vials were then carefully sealed to keep moisture out. For two weeks, these samples were kept in a stability chamber with accelerated stability conditions at 40 ± 2°C and 75 ± 5% relative humidity (RH).

Method of preparation of fast dissolving film

The solvent casting method, which was chosen for its capacity to create homogeneous, thin films with quick disintegration, was used to create fast-dissolving films. To create a uniform polymeric solution, HPMC E5 and PVA were precisely weighed and dissolved in distilled water while being constantly stirred. A plasticizer of PEG 400 (0.5% w/v) was applied. The medication (Aceclofenac or Naproxen) was added to the polymer solution[17]. A tiny amount of ethanol was added to aceclofenac to aid in dispersion. After adding citric acid, sweeteners, and flavorings, the mixture was continuously stirred. After removing trapped air bubbles using sonication, the solution was cast onto a glass or Teflon-coated surface[18]. Films were carefully peeled, cut into equal dimensions, dried at 40–45°C, and then kept in airtight containers.

Experimental design and formulation development

Application of factorial design

To methodically assess the impact of formulation variables on the characteristics of the fast-dissolving films, a 3^2 factorial design was utilized. Two independent variables were used for this design: the concentrations of PVA (X_2) and HPMC (X_1). These factors were examined at three distinct levels (low, medium, and high) to look into their individual and combined effects on the films' important quality characteristics, including thickness, mechanical strength, disintegration time, and drug release behavior. This statistical method made it possible to fully comprehend how the polymers interacted and made formulation optimization easier.

Table 1: Formulation Design of Naproxen and Aceclofenac Films (3^2 Factorial Design)

Variable	Low (−1)	Medium (0)	High (+1)
HPMC E5 - X1	2% w/v	3.5% w/v	5% w/v
PVA - X2	1% w/v	2% w/v	3% w/v

Table 2: Naproxen Films (F1–F9)

Code	HPMC (%)	PVA (%)	Drug (mg)	PEG 400 (%)	Sweetener (%)	Flavor (%)
F1	2	1	10	0.5	0.5	0.2
F2	2	2	10	0.5	0.5	0.2
F3	2	3	10	0.5	0.5	0.2
F4	3.5	1	10	0.5	0.5	0.2
F5	3.5	2	10	0.5	0.5	0.2
F6	3.5	3	10	0.5	0.5	0.2
F7	5	1	10	0.5	0.5	0.2
F8	5	2	10	0.5	0.5	0.2
F9	5	3	10	0.5	0.5	0.2

Table 3 : Aceclofenac Films (A1–A9)

Code	HPMC (%)	PVA (%)	Drug (mg)	PEG 400 (%)	Sweetener (%)	Flavor (%)
A1	2	1	10	0.5	0.5	0.2
A2	2	2	10	0.5	0.5	0.2
A3	2	3	10	0.5	0.5	0.2
A4	3.5	1	10	0.5	0.5	0.2
A5	3.5	2	10	0.5	0.5	0.2
A6	3.5	3	10	0.5	0.5	0.2
A7	5	1	10	0.5	0.5	0.2
A8	5	2	10	0.5	0.5	0.2
A9	5	3	10	0.5	0.5	0.2

Formulation composition

To guarantee consistent dosing and allow for a direct comparison of the impact of polymer concentrations on film properties, the drug dosage was kept constant in all formulations at 10 mg per film. In order to provide the films sufficient flexibility, lessen brittleness, and improve their folding endurance without negatively impacting their mechanical integrity, the plasticizer PEG 400 was added to all batches at a consistent concentration of 0.5% w/v[19]. The harsh taste of the medications was lessened by adding a sweetening ingredient at a concentration of 0.5% w/w to increase patient acceptability. In order to improve palatability and offer a pleasing mouthfeel during administration, a flavoring agent was also added at a rate of 0.2% w/w. To encourage quick wetting and disintegration of the film upon contact with saliva, a tiny but set quantity of citric acid (about 0.1–0.2% w/w) was added as a saliva-stimulating agent To ensure that any observed variations in film properties, such as mechanical strength, disintegration time, and drug release behavior, could only be attributed to changes in the concentrations of the independent variables, namely HPMC (X_1) and PVA (X_2), all of these excipients were kept constant across all formulations. This strategy guaranteed the factorial design study's validity and dependability.

Optimization strategy

In order to determine the best polymer combination that could offer sufficient mechanical strength, quick disintegration (within 60 seconds), consistent thickness, and full drug release, the produced formulations were methodically assessed. In order to verify reproducibility and guarantee consistency of the formulation process, the optimum formulation was chosen based on these parameters and further prepared in triplicate[20].

Characterization of Fast dissolving film

Thickness, weight variation and content uniformity

To guarantee consistency throughout the film surface, the thickness of the film was tested at several locations using a micrometer. To verify uniformity in medication and polymer distribution, weight variation was assessed by weighing specific films on an individual basis. Surface morphology was assessed visually for homogeneity, smoothness, and the lack of flaws like cracks or air bubbles. Together, these factors guaranteed the prepared films' quality, repeatability, and consistent performance.

Mechanical Properties

Tensile strength and percentage elongation were used to assess the prepared films' mechanical characteristics. A modified balancing method was used to assess film samples that were cut into uniform strips of 2 x 5 cm. The force needed to break the film was measured, and the tensile strength was computed by dividing the force at break by the cross-sectional area (width × thickness). Using the initial length (L_0) and final length (L^f), the increase in length of the film at the point of breaking was measured, and the result was expressed as a percentage. To guarantee accuracy and repeatability, all measurements were performed in triplicate (n = 3) and the findings were reported as mean ± standard deviation.

Folding Endurance

The produced films' flexibility and mechanical durability were evaluated by measuring their folding endurance. From each formulation, uniform-sized (2 × 2 cm) film samples were chosen. Every film was physically folded repeatedly at the same location until it broke or showed obvious breaks. The folding endurance value was determined by counting how many times the film could be folded without breaking. For every formulation, the test was run in triplicate, and the average result was determined. The films' appropriateness for handling, packaging, and administration was confirmed by a higher folding endurance, which showed improved flexibility and resilience to mechanical stress[21].

Surface pH

A pH electrode was placed on the moistened film surface to test the surface pH. In order to replicate the conditions of the oral cavity, a little amount of distilled water was added to gently hydrate the film before measurement. Measurements were made in duplicate and the readings were obtained after giving enough time for stabilization. In order to prevent oral mucosal irritation, a surface pH that was almost neutral was thought to be ideal.

Drug Content Uniformity

For complete drug extraction, individual film samples were precisely weighed and dissolved in a suitable volume of phosphate buffer (pH 6.8). The resulting solutions were filtered to remove any undissolved polymeric residues and appropriately diluted. A UV-Visible spectrophotometer was used to measure the drug content at the corresponding λmax values of each

drug, and the results were expressed as mean ± standard deviation to confirm uniform distribution of the drug within the films. The analysis was done in triplicate.

In-Vitro drug release study

The USP dissolution apparatus Type II (paddle method) was used to assess the in-vitro drug release of naproxen and aceclofenac from the manufactured fast-dissolving films. Phosphate buffer (pH 6.8) was used as the dissolving media in the study to mimic salivary circumstances. A steady stirring speed of 50 rpm was used to keep a total volume of 300 mL of dissolving medium at 37 ± 0.5°C. The dissolution medium was carefully filled with a film strip containing 10 mg of medication[22]. To maintain sink conditions, 5 mL samples were removed at predefined intervals (3, 6, 9, 12, and 15 minutes) and replaced with an equivalent volume of new dissolution medium.

Whatman filter paper was used to filter the samples, and a UV-Visible spectrophotometer was used to examine them at each drug's corresponding λmax values. Each experiment was carried out in triplicate (n = 3), and the mean ± standard deviation was used to compute the cumulative % drug release.

Analysis of release kinetic

The in-vitro dissolution data were fitted to a number of kinetic models, including zero-order (cumulative percentage drug release versus time), first-order (log cumulative percentage drug remaining versus time), Higuchi (cumulative percentage drug release versus square root of time), Hixson–Crowell (cube root of drug remaining versus time), and Korsmeyer–Peppas (log fraction of drug released versus log time), in order to comprehend the mechanism of drug release from the prepared fast-dissolving films[23]. The best-fitting release kinetics were determined by calculating the correlation coefficient (R^2) values for each model. Additionally, the drug release mechanism in the Korsmeyer–Peppas model was described by determining the release exponent (n) and release rate constant (k). Fickian diffusion ($n \leq 0.5$), non-Fickian or anomalous transport ($0.5 < n < 1$), Case II transport ($n = 1$), and super Case II transport ($n > 1$) were the interpretations of the release mechanism based on the value of n.

Statistical analysis

One-way ANOVA was used to statistically assess how formulation factors affected drug release. To ascertain statistical significance, the computed F-values were compared with critical F-values, with the significance level set at $p < 0.05$[24].

Result and Discussion

Preformulation Studies

Organoleptic properties

The organoleptic characteristics of naproxen and aceclofenac, such as color, odor, and appearance, were assessed. Naproxen was found to be a white to off-white crystalline powder, whereas Aceclofenac was found to be a white crystalline powder with a distinctive odor. Both medications were free of visible impurities and discoloration, indicating their acceptable quality and suitability for formulation development.

Solubility studies

The shake-flask method was used to evaluate the solubility behavior of both medications in various solvents. Naproxen showed limited solubility in aqueous solutions but moderate solubility in organic solvents like ethanol and methanol. Although aceclofenac was still poorly soluble in water, it showed relatively greater solubility in organic solvents. In order to improve medication dispersion and homogeneity inside the polymeric matrix, appropriate formulation strategies are required, as suggested by the observed solubility pattern.

Table 4 : Solubility Profile of Drugs

Solvent / Medium	Naproxen	Aceclofenac
Distilled water	Practically insoluble	Practically insoluble
Phosphate buffer (pH 6.8–7.4)	Slightly soluble	Slightly soluble
Methanol	Soluble	Soluble
Ethanol	Soluble	Soluble
Acetone	Soluble	Soluble
Chloroform	Soluble	Soluble

Determination of λmax

UV-visible spectrophotometry was used to calculate the λmax of naproxen and aceclofenac. Aceclofenac displayed a maximum absorption peak at 276–278 nm, while naproxen displayed a peak at 230–232 nm. Additional quantitative analysis, such as drug content estimation and in vitro investigations, was conducted using these values.

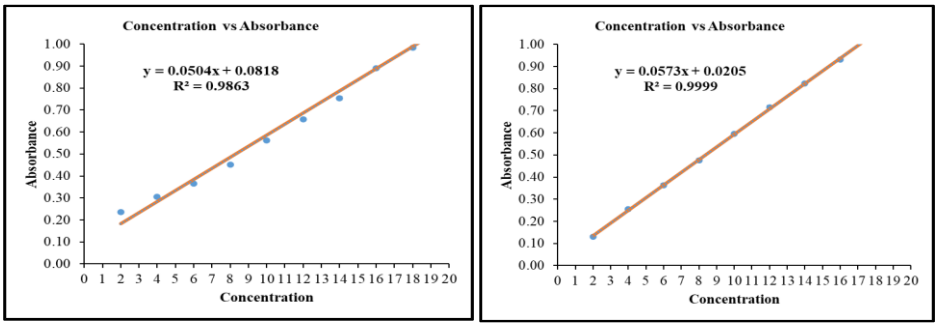


Fig No 1 – Calibration Curve of Naproxen at 271nm and Aceclofenac at 276 nm

Overall, the developed UV–Visible spectrophotometric method is accurate, precise, and suitable for routine quantitative analysis of both drugs in subsequent formulation and evaluation studies.

Drug Excipient Compatibity study

Fourier Transform Infrared (FTIR) spectroscopy was used in drug–excipient compatibility studies to assess possible interactions between naproxen, aceclofenac, and particular formulation excipients. We examined and contrasted the FTIR spectra of pure medications and the corresponding physical combinations. Naproxen's FTIR spectrum showed distinctive peaks that corresponded to aromatic C=C stretching vibrations, C=O stretching of the carboxyl group about 1725 cm^{-1}, and O–H stretching of the carboxylic acid group at about 3180 cm^{-1}. Aceclofenac also displayed clear peaks for aromatic ring vibrations, C=O stretching of ester and carboxylic groups about 1717 cm^{-1}, and N–H stretching at about 3319 cm^{-1}.

Table 5 : Summary of Drug–Excipient Compatibility (FTIR Analysis)

Drug	Characteristic Functional Group	Pure Drug Peak (cm^{-1})	Peak in Physical Mixture (cm^{-1})	Observation
Naproxen	O–H stretching	~3180	~3180	No significant shift
Naproxen	C=O stretching	~1725	~1725	No interaction observed
Aceclofenac	N–H stretching	~3319	~3319	No significant change
Aceclofenac	C=O stretching	~1717	~1717	No interaction observed

There were slight fluctuations in peak strength, which are more likely to be caused by physical mixing and dilution effects than by chemical interactions. These results unequivocally show that there is no incompatibility between the medications and the chosen excipients. Both naproxen and aceclofenac are chemically stable and compatible with the formulation excipients, according to the FTIR compatibility research. As a result, there is no chance of interaction or degradation when using the chosen polymers and plasticizer to create oral films that dissolve quickly.

Evaluation of Fast Dissolving Film

Thickness, Weight variation and Surface Uniformity

The evaluation of the physical quality and consistency of all prepared fast-dissolving films of Naproxen (F1–F9) and Aceclofenac (A1–A9), thickness, weight variation, and surface uniformity were assessed. Naproxen films ranged in thickness from 0.138 to 0.191 mm, but Aceclofenac films showed a small rise with greater polymer concentration, ranging from 0.140 to 0.195 mm. The weight variation, which ranged from 40.8 to 59.4 mg for Naproxen films and 41.5 to 61.0 mg for Aceclofenac films, was found to be within acceptable bounds. The low standard deviation indicated that the drug and excipients were distributed uniformly. Effective film formation and good component compatibility were confirmed by the smooth, uniform surfaces of all formulations, which were free of air bubbles, cracks, and drug crystallization.

Mechanical Properties: Tensile Strength and Percent Elongation

Tensile strength and percent elongation were used to assess the mechanical characteristics of fast-dissolving Naproxen (F1–F9) and Aceclofenac (A1–A9) films. Naproxen and Aceclofenac films had tensile strengths ranging from 1.82 to 4.15 MPa and 1.90 to 4.36 MPa, respectively, with a steady upward trend from lower to higher formulation batches. This suggests that the films' mechanical strength was improved by a higher polymer content.

Comparably, the percent elongation values for Naproxen and Aceclofenac films showed enhanced flexibility with increasing polymer content, ranging from 18.5% to 36.8% and 19.2% to 38.5%, respectively. In comparison to Naproxen films, aceclofenac films showed marginally greater elongation and tensile strength, indicating improved interaction within the polymer matrix. While lower polymer formulations displayed relatively lower values, formulations with higher polymer concentrations (F7–F9 and A7–A9) generally demonstrated improved mechanical strength and flexibility. PEG 400's efficacy as a plasticizer was confirmed by the fact that none of the films displayed brittleness or cracking. Every formulation showed mechanical qualities that were appropriate for handling and administration.

Folding Endurance

The prepared fast-dissolving films' folding endurance was assessed to determine how flexible and resistant they were to mechanical stress during handling (Table 6). Naproxen films had folding endurance values between 72 and 125, but Aceclofenac films had values between 75 and 132, showing high mechanical durability. From F1 to F9 and A1 to A9, folding endurance gradually increased, indicating that increased polymer concentrations improved the flexibility and strength of the film. Compared to Naproxen films, aceclofenac films showed somewhat greater folding endurance, suggesting superior mechanical performance.

All formulations showed good folding durability overall, with no indications of cracking or breaking at lower folds, demonstrating sufficient flexibility and the usefulness of PEG 400 as a plasticizer. These findings show that the films may be handled, packaged, and administered.

Table 6 : Folding Endurance of Aceclofenac Films (A1–A9) and Naproxen Films (F1-F9)

Code	Folding Endurance (Mean ± SD, n=3) for Aceclofenac	Folding Endurance (Mean ± SD, n=3) for Naproxen
A1/F1	75 ± 3	72 ± 3
A2/F2	82 ± 4	78 ± 4
A3/F3	88 ± 5	84 ± 5
A4/F4	96 ± 4	92 ± 4
A5/F5	103 ± 5	98 ± 5
A6/F6	110 ± 6	105 ± 6
A7/F7	118 ± 5	112 ± 5
A8/F8	124 ± 6	118 ± 6
A9/F9	132 ± 7	125 ± 7

All formulations showed good folding durability overall, with no indications of cracking or breaking at lower folds, demonstrating sufficient flexibility and the usefulness of PEG 400 as a plasticizer. These findings show that the films may be handled, packaged, and administered.

Surface pH and Drug Content Uniformity

The verification of oral compatibility and uniform medication distribution, the produced fast-dissolving films of naproxen (F1–F9) and aceclofenac (A1–A9) were assessed for surface pH and drug content uniformity (Table 7). Aceclofenac films had surface pH values between 6.48 and 6.85, whereas Naproxen films had values between 6.52 and 6.86. The pH values of all the formulations were near neutral, which is ideal for oral mucosal administration since it reduces irritation and increases patient acceptability. There was no discernible difference in surface pH between the various formulations, suggesting that the excipients did not negatively impact the films' pH.

Table 7 : Surface pH and Drug Content of Naproxen(F1–F9) and Aceclofenac(A1-A9) Films

Code	Surface pH (Mean ± SD, n=3)	Drug Content (%) (Mean ± SD, n=3)	Code	Surface pH (Mean ± SD, n=3)	Drug Content (%) (Mean ± SD, n=3)
F1	6.52 ± 0.05	96.8 ± 1.2	A1	6.48 ± 0.05	96.2 ± 1.3
F2	6.58 ± 0.04	97.5 ± 1.1	A2	6.54 ± 0.04	97.0 ± 1.2
F3	6.61 ± 0.06	98.2 ± 1.3	A3	6.59 ± 0.05	97.8 ± 1.1
F4	6.65 ± 0.05	98.9 ± 1.0	A4	6.63 ± 0.06	98.5 ± 1.0
F5	6.70 ± 0.04	99.4 ± 0.9	A5	6.68 ± 0.05	99.1 ± 0.9
F6	6.74 ± 0.05	99.8 ± 1.1	A6	6.72 ± 0.04	99.6 ± 1.0
F7	6.78 ± 0.06	100.2 ± 1.0	A7	6.76 ± 0.05	100.0 ± 0.8
F8	6.82 ± 0.05	100.6 ± 0.8	A8	6.80 ± 0.06	100.5 ± 0.9

F9	6.86 ± 0.04	101.1 ± 0.9	A9	6.85 ± 0.05	101.0 ± 1.0

Values for Naproxen and Aceclofenac films ranged from 96.8% to 101.1% and 96.2% to 101.0%, respectively, according to drug content analysis. The uniform distribution of the drug inside the film matrix and the effectiveness of the solvent casting process were confirmed by the fact that all formulations fell within acceptable bounds. Improved drug trapping within the denser polymer network may account for a small increase in drug content in higher formulations.

Overall, all formulations showed acceptable drug content uniformity and surface pH, suggesting that they are suitable for oral administration with dependable and consistent drug delivery.

Effect of Formulation Variables

A 3^2 factorial design was used to comprehensively assess the impact of formulation factors on the performance of fast-dissolving films, with PVA (X_2) and HPMC (X_1) chosen as independent variables. The findings showed that both polymers significantly affected the films' important quality parameters, such as thickness, tensile strength, disintegration time, and overall mechanical behavior. The films disintegrated more quickly when the HPMC concentration (X_1) increased. The very hydrophilic property of HPMC, which encourages quick water absorption, swelling, and subsequent film dissolution upon contact with saliva, is responsible for this behavior. Higher HPMC formulations showed faster disintegration times, which made them better suited for quick drug release.

On the other hand, higher tensile strength results showed that an increase in PVA concentration (X_2) significantly improved mechanical strength. This results from PVA's greater film density and improved polymer chain entanglement. Higher PVA concentration did, however, also cause a minor increase in disintegration time. This is probably because water penetration is slowed down by the creation of a more compact and less permeable film matrix. The overall performance of the films was found to be significantly influenced by the interaction between HPMC and PVA. To produce films with enough mechanical strength and quick disintegration, an ideal ratio between the two polymers was required. While higher PVA concentrations improve strength and postpone breakdown, excessive HPMC resulted in unduly soft films.

Finding an ideal polymer combination was thus made easier by the factorial design approach, guaranteeing the creation of quick-dissolving films with advantageous mechanical qualities and excellent drug release features.

Optimization and Validation of Formulation

Based on the evaluation of critical quality parameters such as tensile strength, disintegration time (<60 seconds), uniform thickness, and drug content, an optimized formulation was selected from the prepared batches. The chosen formulation showed quick disintegration, consistent drug distribution, and a good balance between mechanical strength and flexibility. The improved batch also demonstrated acceptable physicochemical characteristics, suggesting that it is suitable for efficient oral drug administration.

Table No : 8 Comparison of Optimized Formulation with Other Batches

Parameter	**Lower Formulations (F1–F3 / A1–A3)**	**Mid Formulations (F4–F6 / A4–A6)**	**Optimized Formulation (F8 / A8)***	**Higher Formulations (F9 / A9)**
Tensile Strength (MPa)	Low (1.82–2.39)	Moderate (2.64–3.32)	High (3.84–4.02)	Very High (4.15–4.36)
Percent Elongation (%)	Low flexibility (18–23%)	Moderate (25–31%)	High flexibility (34–36%)	Very High (36–38%)
Folding Endurance	72–88 (less durable)	92–110	118–124 (excellent)	125–132 (maximum)
Surface pH	6.48–6.61	6.63–6.72	~6.80 (near neutral)	6.85–6.86
Drug Content (%)	96–98%	98–99.6%	~100–100.5% (optimal)	~101%
Disintegration Time	Very fast but weaker films	Balanced	< 60 sec (ideal)	Slightly increased
Mechanical Integrity	Less strong	Good	Optimal balance	Very rigid
Overall Performance	Not ideal	Acceptable	⭐ Optimized	Slightly over-rigid

For further confirm the reliability of the optimized formulation, it was prepared in triplicate and evaluated for the same parameters. The results showed minimal variation among the batches, demonstrating high reproducibility and consistency of the formulation process. These findings validate the robustness of the solvent casting method and confirm that the optimized formulation is stable, reliable, and suitable for further development.

In vitro drug release kinetic

The solvent casting approach is appropriate for immediate-release oral films, as evidenced by the in-vitro drug release profiles of naproxen and aceclofenac fast-dissolving films, which showed a quick and steady increase in cumulative drug release over time.

In-Vitro drug release of Naproxen Films

Naproxen formulations (F1–F9) showed a consistent rise in cumulative drug release from approximately 11–13% at 3 minutes to 88.06–103.94% at 15 minutes (Table 9). A diffusion-controlled release from the polymer matrix follows the initial fast release, which shows instantaneous hydration and drug dissolution on the surface (Fig no 2).

Drug release rose to 44.68–60.55% at 9 minutes, indicating effective swelling and erosion of the films, from 24.11% (F1) to 39.98% (F9) at 6 minutes. Near-complete release was demonstrated by the majority of formulations, which released 69.61–85.48% of the medication by 12 minutes.

Table No 9 : *In-vitro* Drug Release Profile of Naproxen FDFs

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	TP
3	11.274 ± 0.091	11.651 ± 0.091	11.829 ± 0.091	11.968 ± 0.091	12.087 ± 0.091	12.306 ± 0.091	12.524 ± 0.091	12.683 ± 0.091	12.861 ± 0.091	**12.5**
6	24.114 ± 0.303	27.884 ± 0.303	29.669 ± 0.303	31.058 ± 0.303	32.249 ± 0.303	34.431 ± 0.303	36.614 ± 0.303	38.201 ± 0.303	39.987 ± 0.303	**25**
9	44.683 ± 0.397	48.452 ± 0.397	50.238 ± 0.397	51.627 ± 0.397	52.817 ± 0.397	55 ± 0.397	57.183 ± 0.397	58.77 ± 0.397	60.556 ± 0.397	**50**
12	69.616 ± 0.303	73.386 ± 0.303	75.172 ± 0.303	76.561 ± 0.303	77.751 ± 0.303	79.934 ± 0.303	82.116 ± 0.303	83.704 ± 0.303	85.489 ± 0.303	**75**
15	88.069 ± 0.999	91.839 ± 0.999	93.624 ± 0.999	95.013 ± 0.999	96.204 ± 0.999	98.386 ± 0.999	100.569 ± 0.999	102.156 ± 0.999	103.942 ± 0.999	**100**
f_2 factor	**59.581**	**69.157**	**71.663**	**71.051**	**68.908**	**63.371**	**57.859**	**54.296**	**50.748**	

Formulation F9 displayed the highest release (103.94%) at the last time point (15 minutes), followed by F8 and F7, while F1 displayed a relatively lower release (88.06%). For every formulation, the similarity factor (f_2) values were found (Fig no 3-5) to be greater than 50, indicating a satisfactory degree of similarity with the predicted release profile. The two that most closely matched the ideal release profile were F3 (f_2 = 71.66) and F4 (f_2 = 71.05).

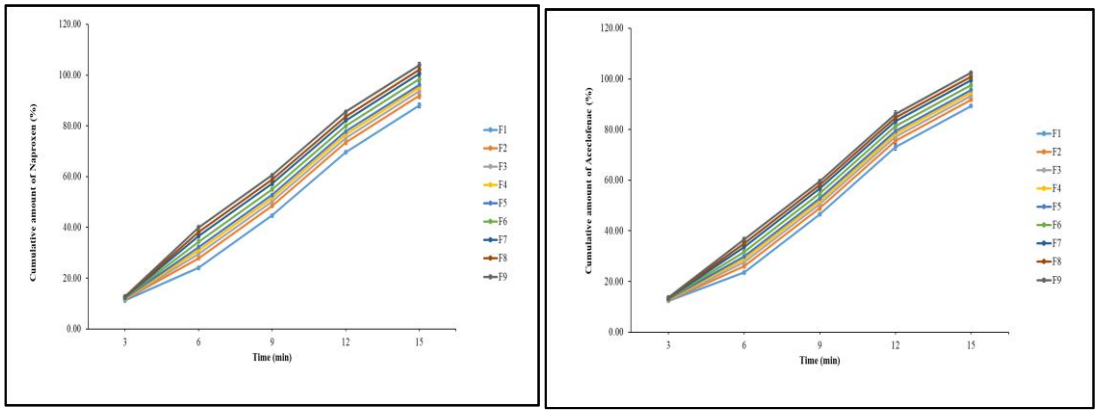


Figure 2: In-vitro release of Naproxen and Aceclofenac from different formulations

Effect of Formulation Variables

ANOVA was used to statistically assess the impact of formulation factors on drug release. The findings showed that HPMC (X_1) significantly affected drug release at 12 and 15 minutes ($p < 0.05$). Drug release was significantly improved by an increase in HPMC concentration, rising from 91.17% to 102.22% at 15 minutes and from 72.72% to 83.76% at 12 minutes. This behavior is explained by HPMC's hydrophilic properties, which encourage quick film matrix degradation, swelling, and hydration and speed up drug diffusion. On the other hand, although a minor increasing tendency was noted with increasing concentration, PVA (X_2) did not have a statistically significant influence ($p > 0.05$) on drug release. PVA contributes somewhat to the overall release behavior, whereas HPMC is the primary factor regulating drug release, according to the main effect and interaction plots. It was discovered that the interaction between HPMC and PVA was low to moderate, suggesting that their combined impact on drug release is more additive than substantially synergistic.

In-Vitro drug release of Aceclofenac Films

With cumulative release ranging from 12.36–13.67% at 3 minutes to 89.32–102.41% at 15 minutes, the Aceclofenac fast-dissolving film formulations demonstrated a quick and progressive drug release profile (Table 10).

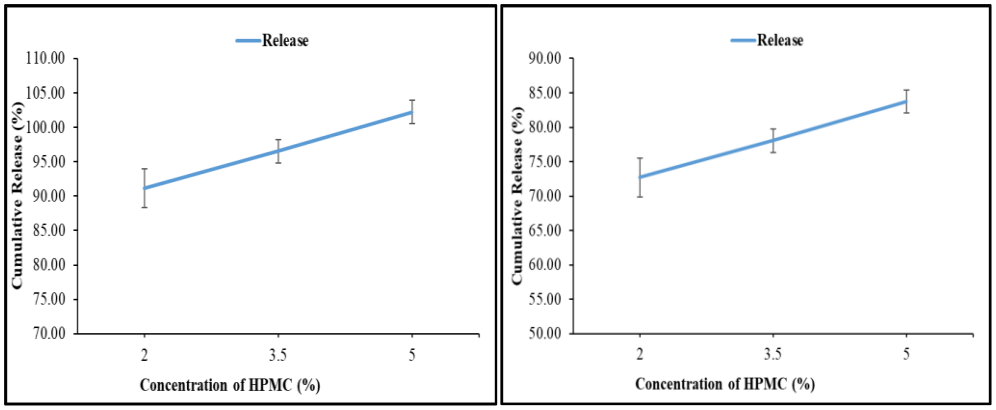


Fig no 3 -- Average effect of concentration of HPMC on *In-vitro* release of Naproxen from different formulations at 15 min. and 12 min

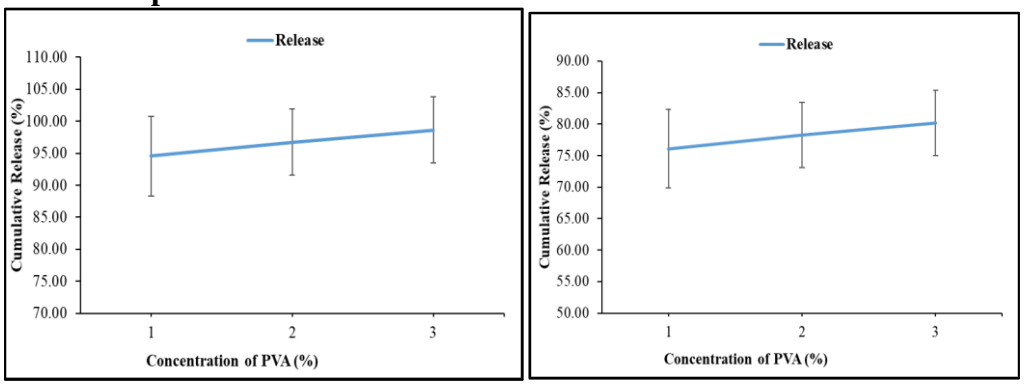


Figure No 4 : Average effect of concentration of PVA on In-vitro release of Naproxen from different formulations at 15 min. and 12 min

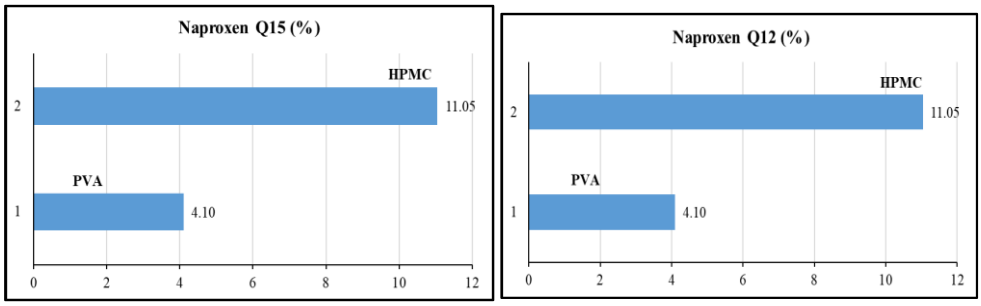


Figure No 5 : Main Effect of Concentration of HPMC and PVAon In-vitro release of Naproxen at 15 min. and 12 min

Table 10: *In-vitro* Drug Release Profile of Aceclofenac FDFs

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	TP
3	12.365 ± 0.087	12.609 ± 0.087	12.766 ± 0.087	12.888 ± 0.087	12.993 ± 0.087	13.185 ± 0.087	13.377 ± 0.087	13.517 ± 0.087	13.674 ± 0.087	**12.5**
6	23.589 ± 0.504	26.033 ± 0.504	27.603 ± 0.504	28.825 ± 0.504	29.872 ± 0.504	31.792 ± 0.504	33.711 ± 0.504	35.108 ± 0.504	36.678 ± 0.504	**25**
9	46.51 ± 0.349	48.953 ± 0.349	50.524 ± 0.349	51.745 ± 0.349	52.792 ± 0.349	54.712 ± 0.349	56.632 ± 0.349	58.028 ± 0.349	59.599 ± 0.349	**50**
12	73.095 ± 1.263	75.538 ± 1.263	77.109 ± 1.263	78.33 ± 1.263	79.378 ± 1.263	81.297 ± 1.263	83.217 ± 1.263	84.613 ± 1.263	86.184 ± 1.263	**75**
15	89.325 ± 0.403	91.768 ± 0.403	93.339 ± 0.403	94.561 ± 0.403	95.608 ± 0.403	97.528 ± 0.403	99.447 ± 0.403	100.844 ± 0.403	102.414 ± 0.403	**100**
f_2 factor	**64.074**	**70.564**	**72.852**	**72.405**	**70.564**	**65.534**	**60.310**	**56.861**	**53.393**	

Drug release was found to be between 23.58% and 36.67% at 6 minutes, and it increased to 46.51–59.59% at 9 minutes, showing effective drug dissolution and dispersion from the film matrix. The cumulative release reached 73.09–86.18% by 12 minutes, indicating quick drug availability appropriate for prompt release action. Formulation F9 had the maximum drug release (102.41%) at the 15-minute mark, while F1 had a relatively lesser release (89.32%). All formulations were found to have similarity factor (f_2) values more than 50, indicating that they were similar to the predicted release profile. The formulations that most nearly matched the intended drug release pattern were F3 (72.85), followed by F4 (72.40) and F2 (70.56).

Effect of Formulation Variables

Statistical analysis was used to assess the impact of formulation variables on the in-vitro drug release of Aceclofenac films. The findings showed that drug release at 12 and 15 minutes was significantly impacted ($p < 0.05$) by HPMC concentration. Drug release rose from 91.47% to 100.90% at 15 minutes and from 75.25% to 84.67% at 12 minutes in response to an increase in HPMC concentration. This is explained by HPMC's hydrophilic properties and quick swelling behavior, which promote quicker drug diffusion and matrix hydration. PVA concentration, on the other hand, contributed somewhat to the overall release profile but did not exhibit a statistically significant effect ($p > 0.05$) on drug release (Fig No 2).

Overall, the results show that while PVA plays a supporting role by boosting film integrity and somewhat increasing drug release, HPMC is the primary contributor to drug release. It was discovered that the interaction between PVA and HPMC was additive rather than highly synergistic.

Release Kinetic Study

Naproxen Film Release Kinettics

Along with correlation coefficient (R^2) values ranging from 0.9887 to 0.9984, the Higuchi model offered the best fit for most formulations in the release kinetics data of Naproxen fast-dissolving films. This suggests that the drug release primarily followed a diffusion-controlled mechanism through the hydrated polymeric matrix. Formulation F1, on the other hand, fit the zero-order

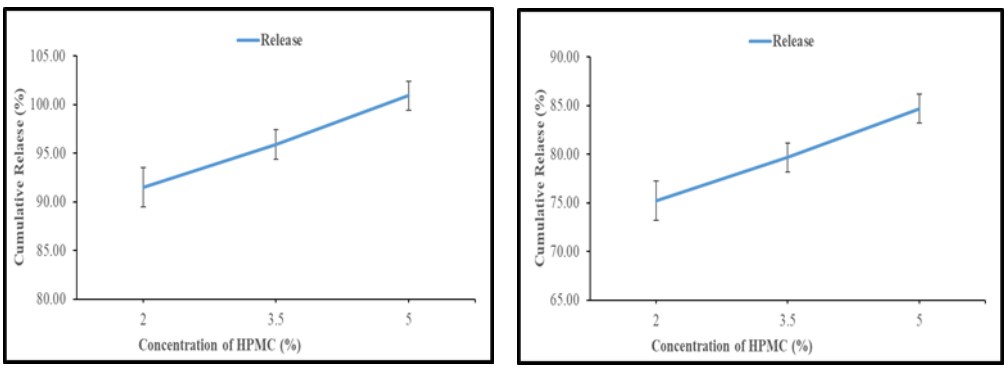


Fig no 6 -- Average effect of concentration of HPMC on In-vitro release of Aceclofenac from different

formulations at 15 min. and 12 min

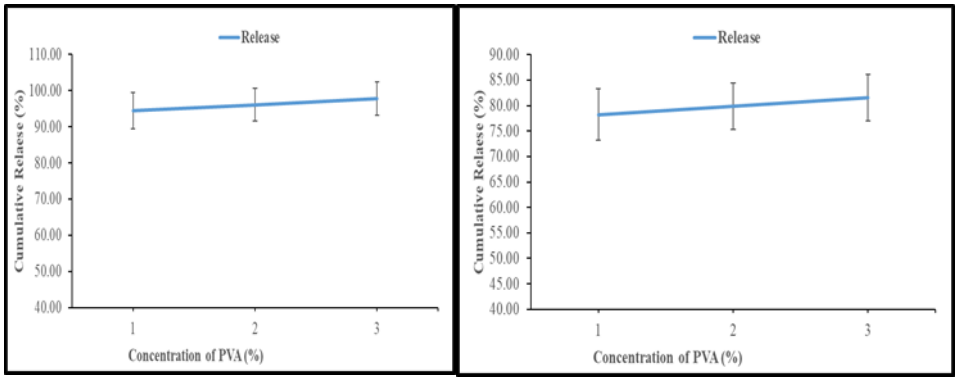


Figure No 7 : Average effect of concentration of PVA on In-vitro release of Aceclofenac from different formulations at 15 min. and 12 min

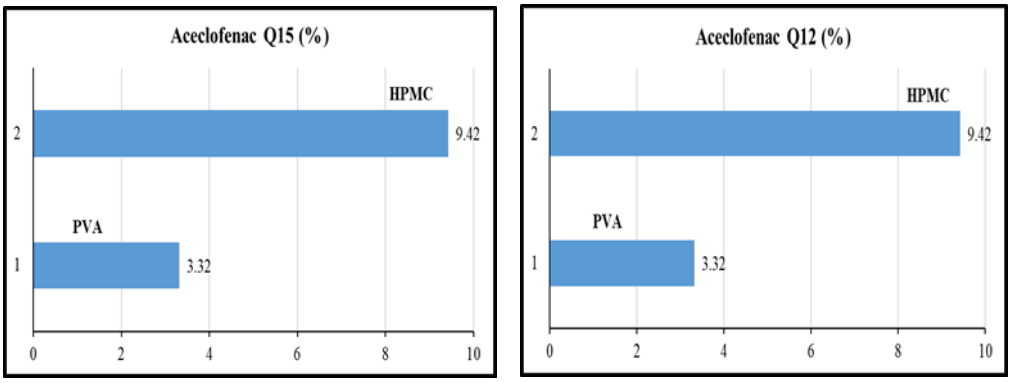


Figure No 8 : Main Effect of Concentration of HPMC and PVAon In-vitro release of Aceclofenac at 15 min. and 12 min

model better (R^2 = 0.9952), indicating a consistent and concentration-independent drug release pattern.

Table No 11 :Release Kinetics and Model Fitting of Naproxen Formulations

Release kinetics-Model Fitting							
Formultion Code	**Co-relation Coefficient for the model**					**Korsemeyer-Peppas**	
	0 - order R% vs T	**1 - order log R% vs T**	**Highuchi R% vs $T^{1/2}$**	**Hixon-Crowell ($100^{1/3}$ - $R\%^{1/3}$) vs T**	**Korsemeyer-Peppas M_t/M_∞ vs T**	**k**	**n**
F1	0.9952	0.9805	0.9800	-0.9934	0.9952	0.0255	1.3086
F2	0.9796	0.8896	0.9984	-0.9287	0.9796	0.0088	0.8092
F3	0.9770	0.8817	0.9975	-0.9227	0.9770	0.0092	0.8050
F4	0.9748	0.8756	0.9967	-0.9180	0.9748	0.0096	0.8019
F5	0.9729	0.8704	0.9959	-0.9139	0.9729	0.0099	0.7995
F6	0.9692	0.8612	0.9942	-0.9065	0.9692	0.0104	0.7955
F7	0.9654	0.8522	0.9922	-0.8991	0.9654	0.0110	0.7919

F8	0.9624	0.8458	0.9906	-0.8937	0.9624	0.0114	0.7870
F9	0.9591	0.8389	0.9887	-0.8878	0.9591	0.0118	0.0787

The release was not primarily dependent on the residual drug concentration, as evidenced by the first-order model's somewhat lower R2 values (Table 11) . In a similar vein, the Hixson–Crowell model demonstrated weak correlation, indicating that variations in particle size and surface area had little effect on the drug release mechanism.

Formulation F1 showed a n value of 1.3086, indicating super Case II transport, where drug release is mostly controlled by polymer relaxation and erosion, according to additional study using the Korsmeyer–Peppas model. Formulations F2 through F8, on the other hand, displayed n values between 0.78 and 0.81, indicating non-Fickian (anomalous) transport in which the release mechanism is influenced by both polymer relaxation and diffusion. Overall, the findings imply that a combination of polymer relaxation and diffusion processes controls drug release from Naproxen films.

Aceclofenac Film Release Kinetics

Aceclofenac fast-dissolving film formulations showed a release pattern similar to Naproxen films, according to the kinetic analysis. With strong correlation coefficient (R^2) values ranging from 0.9918 to 0.9977, the Higuchi model outperformed the other models assessed for the majority of formulations, suggesting that drug release is primarily controlled by diffusion through the hydrated polymeric matrix. Formulation F1, on the other hand, showed a stronger connection with the zero-order model (R^2 = 0.9925), indicating a more consistent and concentration-independent drug release pattern.

Table No 12 : Release Kinetics and Model Fitting of Aceclofenac Formulations

Release kinetics-Model Fitting							
Formultion Code	**Co-relation Coefficient for the model**					**Korsemeyer-Peppas**	
	0 - order R% vs T	**1 - order log R% vs T**	**Highuchi R% vs $T^{1/2}$**	**Hixon-Crowell ($100^{1/3}$ - $R\%^{1/3}$) vs T**	**Korsemeyer-Peppas M_t/M_∞ vs T**	**k**	**n**
F1	0.9925	0.9816	0.9776	-0.9914	0.9925	0.0280	1.2797
F2	0.9782	0.9018	0.9977	-0.9346	0.9782	0.0093	0.7994
F3	0.9763	0.8954	0.9973	-0.9300	0.9763	0.0097	0.7953
F4	0.9747	0.8904	0.9969	-0.9263	0.9747	0.0101	0.7923
F5	0.9733	0.8861	0.9964	-0.9231	0.9733	0.0104	0.7900
F6	0.9705	0.8783	0.9954	-0.9172	0.9705	0.0109	0.7860
F7	0.9676	0.8705	0.9941	-0.9111	0.9676	0.0114	0.7825
F8	0.9654	0.8649	0.9931	-0.9067	0.9654	0.0118	0.7801
F9	0.9628	0.8587	0.9918	-0.9017	0.9628	0.0122	0.7777

Formulation F1 exhibited a n value of 1.2797, indicating a Super Case II transport mechanism where drug release is primarily regulated by polymer relaxation and erosion, according to further interpretation using the Korsmeyer–Peppas model. Formulations F2 through F9, on the other hand, displayed n values in the range of 0.77 to 0.79, which corresponds to Non-Fickian (anomalous) transport, indicating that the drug release mechanism is influenced by both diffusion and polymer relaxation.

Overall, the findings demonstrate that polymer swelling and erosion mechanisms play a major role in the diffusion-controlled drug release from Aceclofenac fast-dissolving films, guaranteeing effective and regulated drug delivery.

CONCLUSION

The solvent casting approach was effectively used to create fast-dissolving oral films of naproxen and aceclofenac, which were then optimized using a 3^2 factorial design. The formulations demonstrated appropriate mechanical strength, quick disintegration, consistent drug content, and satisfactory physicochemical qualities. Studies on in vitro drug release showed effective and quick drug release, with PVA mainly contributing to film integrity and HPMC having a major impact on release behavior. Drug release mostly followed Higuchi diffusion with non-Fickian transport pathways, according to kinetic studies. The optimized formulations demonstrated desired performance and reproducibility, indicating that fast-dissolving films offer a viable substitute for quick and efficient NSAID delivery with increased patient compliance.

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