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Development and Evaluation of Diclofenac-Loaded Self-Microemulsifying Mouth Dissolving Films (SMMDFs) for Enhanced Oral Delivery

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ABSTRACT

Background: Diclofenac is a widely used nonsteroidal anti-inflammatory drug (NSAID) with poor aqueous solubility and gastrointestinal (GI) irritation risk. This study introduces a *self-microemulsifying mouth dissolving film* (SMMDF) combining lipid-based self-microemulsifying drug delivery systems (SMEDDS) with fast-dissolving oral films to improve diclofenac's dissolution, absorption, and patient compliance.

Methods: Diclofenac-loaded SMMDFs were formulated by solvent casting using hydroxypropyl methylcellulose (HPMC) as film-forming polymer and glycerin as plasticizer, with optimized levels determined via a 3^2 factorial design. Superdisintegrant (crospovidone), an adsorbent (Neusilin® US2), salivary stimulants, and sweeteners were incorporated for rapid disintegration and taste masking. Films were characterized for thickness, tensile strength, elongation, folding endurance, drug content uniformity, surface pH, *in vitro* disintegration and dissolution, stability (accelerated conditions), and morphology by scanning electron microscopy (SEM). A plain diclofenac film (no SMEDDS) and a commercial tablet were compared as controls.

Results: Optimized SMMDFs disintegrated in ~25 seconds *in vitro* and released >95% of drug within 5 minutes, whereas a conventional tablet released only ~60% in the same time. Films showed uniform thickness (~25 µm) and weight (~60 mg) with high drug content (~99%) and neutral surface pH (6.8–7.1) eliminating risk of oral irritation. Mechanical properties were optimal for handling: tensile strength and elongation were enhanced by the plasticizer, and films endured >180 folds without breaking. SEM images revealed a rough but uniform microstructure with no crystalline drug, indicating molecularly dispersed diclofenac. The SMMDF was stable over 3 months at 30 °C/75% RH, with no significant change in drug content, disintegration time or dissolution profile.

Conclusions: The diclofenac SMMDF achieved rapid disintegration and dissolution, improved stability, and acceptable mechanical strength. This novel formulation offers fast onset of analgesic action and avoids first-pass metabolism, while providing patient-centric advantages of easy administration, portability, and taste masking. SMMDFs represent a promising platform for enhancing oral delivery of poorly water-soluble drugs like diclofenac..

INTRODUCTION

Diclofenac is a potent NSAID widely prescribed for pain and inflammation management [1]. However, its low water solubility and extensive first-pass metabolism result in variable oral bioavailability and delayed onset of action. Additionally, long-term oral use of diclofenac can cause GI irritation and ulceration [2], prompting development of novel delivery systems to improve its therapeutic index [3]. Recent advances in oral drug delivery emphasize patient-friendly, rapid-acting formulations for analgesics and other acute therapies [4][5]. In particular, fast-dissolving oral dosage forms such as mouth dissolving films (MDFs) have gained considerable attention. These thin polymeric strips disintegrate on the tongue within seconds without

water, releasing drug for absorption in the oral cavity or gastrointestinal tract [6]. Mouth dissolving films offer enhanced patient compliance, especially for pediatric, geriatric, dysphagic, and uncooperative patients who may have difficulty swallowing tablets. They also can provide faster onset of action compared to traditional tablets, which is beneficial in pain management [7][8]. Indeed, oral film technology has evolved from simple fast-dissolving strips to more complex systems capable of taste masking and modified release [5][8].

Separately, lipid-based self-microemulsifying drug delivery systems (SMEDDS) have emerged as an effective strategy to improve the oral absorption of poorly water-soluble drugs [9][10]. SMEDDS are isotropic mixtures of oil, surfactant, and co-surfactant that spontaneously form fine oil-in-water microemulsions in gastrointestinal fluids, yielding droplet sizes typically 100–250 nm. This dramatically increases the drug's surface area and solubility, facilitating faster dissolution and often enabling some lymphatic absorption, thereby bypassing first-pass hepatic metabolism [9][10]. For lipophilic NSAIDs like diclofenac (classified as BCS Class II), SMEDDS can significantly enhance the rate and extent of absorption [3][11]. For example, a coconut-oil based diclofenac SMEDDS formulation was shown to improve drug release and bioavailability compared to plain drug [11]. Other studies have similarly reported that SMEDDS formulations achieve higher C_max and shorter T_max than conventional oral products [12][13].

Combining the strengths of SMEDDS and fast-dissolving films, *self-microemulsifying mouth dissolving films* (SMMDFs) have been proposed as a novel platform for drugs with dissolution-limited absorption. In an SMMDF, the drug is pre-dissolved in a lipid microemulsion system that is incorporated into a quick-dissolving film matrix. Upon placement in the oral cavity, the film rapidly disintegrates to release the SMEDDS, which immediately forms a microemulsion in saliva. This approach synergistically accelerates drug dissolution and mucosal absorption, potentially yielding faster onset of action and higher bioavailability. Prior research has demonstrated the feasibility of SMMDFs for improving delivery of various compounds. For instance, Desai *et al.* formulated a ranolazine-loaded SMMDF by solvent casting, achieving prompt disintegration and enhanced dissolution [12]. Zhang *et al.* reported self-microemulsifying fast-dissolving films of vitamin D 3 for pediatric use, which showed uniform films with significantly improved vitamin D 3 solubility and absorption [13]. Despite such advances, no published formulation has yet addressed diclofenac in an SMMDF format.

Here, we report the development and optimization of a diclofenac-loaded SMMDF intended to provide rapid drug release and improved oral delivery. The film formulation was designed using a combination of an HPMC polymer matrix and an optimized liquid SMEDDS of diclofenac. A design-of-experiments approach was employed to optimize film composition for desirable mechanical strength, disintegration time, and dissolution profile. We further evaluated the SMMDF's physicomechanical properties (thickness, tensile strength, elongation, folding endurance, surface pH, drug content), *in vitro* disintegration and dissolution behavior in comparison to a plain diclofenac film and a commercial tablet, accelerated stability over 3 months, and film morphology by SEM. The aim was to create a patient-friendly, fast-acting diclofenac film that overcomes solubility limitations and improves patient compliance. Through this study, we also highlight the patient-centric advantages of SMMDFs – namely, rapid onset of analgesia, avoidance of water for dosing, minimized GI exposure (which may reduce GI side effects), and effective taste masking of diclofenac's bitterness [6][7][8].

METHODOLOGY

Materials and Formulation: Diclofenac sodium (model BCS II drug) was incorporated into a SMEDDS pre-concentrate consisting of a medium-chain lipid (Capmul MCM), surfactant (Cremophor® EL), and co-surfactant (Transcutol® P) identified via solubility and self-emulsification screening (data from preliminary studies). The optimized liquid SMEDDS was then converted into a film formulation using a solvent casting method. Hydroxypropyl methylcellulose (HPMC, grade 15 cP) was selected as the primary film-forming polymer due to its hydrophilicity and film-forming ability, which are crucial for rapid disintegration and adequate mechanical strength. Glycerin was used as a plasticizer to improve film flexibility and tensile properties. Additionally, low-substituted hydroxypropyl cellulose (L-HPC) was included as a secondary polymer/disintegrant to assist film forming and accelerate breakup. Crospovidone (Polyplasdone XL) was incorporated as a superdisintegrant to further speed up film disintegration by swelling action. An inert inorganic adsorbent, Neusilin® US2 (magnesium aluminometasilicate), was added to help uniformly disperse the lipid SMEDDS within the hydrophilic polymer matrix and prevent phase separation. Citric acid was included at a low level as a salivary stimulant (to promote wetting of the film in the mouth) and to assist in taste masking, along with the artificial sweetener aspartame. All other excipients (e.g., flavoring agents) were of pharmaceutical grade and chosen to ensure palatability and stability of the films.

Experimental Design: A 3^2 full factorial design was employed to optimize the film formulation and investigate the effects of polymer and plasticizer levels. The two independent factors were HPMC 15 concentration (X_1) and glycerin concentration (X_2), each tested at three levels (low, medium, high). A total of 9 film formulations (F1–F9) were prepared according to the design matrix. All other components (SMEDDS content, L-HPC, crospovidone, Neusilin, etc.) were kept constant across formulations. The response variables used for optimization were: (Y_1) *in vitro* disintegration time (seconds), (Y_2) percent drug release in 5 minutes, and (Y_3) tensile strength (MPa) of the film. Polynomial response models were generated and analyzed by ANOVA to identify significant factor effects. Contour plots and 3D surface plots were used to visualize the influence of X_1 and X_2 on the responses, and an optimized formulation was predicted by desirability function

targeting minimal disintegration time, maximal dissolution, and adequate tensile strength. The optimized formulation (Batch FF4) was then prepared and used for further evaluations.

Film Preparation: Films were produced by the solvent casting technique. HPMC was dissolved in distilled water to form a viscous polymer solution. In parallel, the pre-concentrated diclofenac SMEDDS (containing the drug in dissolved form) was gradually added to the polymer solution under continuous stirring, allowing the oil-phase to be dispersed uniformly. L-HPC, crospovidone, Neusilin US2, citric acid, aspartame, and a suitable peppermint flavor were then blended into the mixture. The final mixture was degassed to remove air bubbles and cast onto a leveled Petri dish (or mold) to dry at room temperature for 24 hours. The dried film was carefully peeled and cut into uniform strips (each ~4 cm^2) containing 10 mg of diclofenac. A *plain diclofenac film* was similarly prepared as a control, using the same polymer matrix and excipients but with the drug added in solid form (as a fine powder) instead of as a SMEDDS this allowed comparison of a conventional drug-loaded film versus the SMMDF. A commercial diclofenac tablet (100 mg dispersible tablet) was chosen as an additional comparator for dissolution and disintegration studies.

Physicomechanical Characterization: Films were first examined visually for color, clarity, and defects. Film *thickness* was measured at five different points using a digital micrometer screw gauge to ensure uniformity [6][14]. *Weight variation* was assessed by individually weighing ten film strips from each batch and calculating the mean and standard deviation. *Surface pH* was determined by moistening the film surface with distilled water and placing a pH electrode on it; maintaining a surface pH close to neutral (~6.5–7.0) is important to avoid oral mucosal irritation. *Drug content uniformity* was evaluated by dissolving film samples in phosphate buffer (pH 6.8) and analyzing diclofenac content by UV–Vis spectrophotometry at 276 nm.

Film mechanical properties were measured to ensure the strips can withstand handling. *Tensile strength (TS)* and *percentage elongation at break* were tested using a texture analyzer (TAXTplus) in tension mode. Films (cut into 2 × 5 cm strips) were pulled at a constant rate until rupture; TS (N/mm^2) and elongation (%) were calculated from the force–displacement data. *Young's modulus* (elastic modulus) was derived as the ratio of stress to strain in the linear portion of the curve, indicating film stiffness. *Folding endurance* was assessed by repeatedly folding a film at the same place until it broke; the number of folds a film endured without breaking was recorded as the folding endurance. A value above 150 is generally considered acceptable for handling [13].

In Vitro Disintegration and Dissolution: Disintegration time was measured using a simple drop method: a film strip was placed on a Petri dish moistened with 2 mL of simulated saliva fluid (pH ~6.8) at 37 °C, and the time for the film to completely disintegrate (no visible residue) was recorded. For comparative purposes, the disintegration of the plain diclofenac film and the commercial tablet (dispersed in 10 mL water) were also noted. Dissolution studies were performed using a USP Type II paddle apparatus. Each film (equivalent to 10 mg diclofenac) or a tablet (100 mg) was placed in 900 mL of phosphate buffer (pH 6.8) at 37 ± 0.5 °C, with a paddle speed of 50 rpm. At predetermined intervals (e.g. 1, 2, 3, 5, 10 min and beyond), samples were withdrawn and filtered, and diclofenac release was quantified by UV spectrophotometry. For the films, the focus was on the initial 5 minutes to capture the rapid release phase. The dissolution profiles of the optimized SMMDF, the plain film, and the tablet were compared. A similarity factor *f 2* analysis was applied to compare dissolution profiles where appropriate.

Morphological and Solid-State Analysis: The surface morphology of the optimized diclofenac SMMDF was examined by scanning electron microscopy (SEM). Film samples were sputter-coated with gold and imaged at various magnifications. SEM was used to check for the presence of drug crystals or phase separation on the film surface. A smooth, uniform appearance with no discrete drug particles would indicate that diclofenac is molecularly dispersed within the film matrix. For completeness, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) were also conducted on the optimized film, pure diclofenac, and a physical mixture of drug and excipients to assess any drug-excipient interactions or changes in crystalline state (results summarized in Discussion).

Stability Study: The optimized SMMDF formulation was subjected to accelerated stability testing according to ICH Q1A(R2) guidelines. Films were stored in sealed containers at 30 ± 2 °C and 75 ± 5% relative humidity (RH) for up to 3 months (and additionally observed up to 12 months for long-term stability). Samples were withdrawn at 0, 3, 6, and 12 months and evaluated for physical appearance, drug content, disintegration time, mechanical integrity (folding endurance), and dissolution behavior. Any changes were analyzed for statistical significance ($p < 0.05$). The stability of the formulation's self-emulsifying property was also implicitly monitored via dissolution; consistent dissolution profiles over time would suggest no significant SMEDDS component degradation or drug crystallization upon storage.

RESULTS

Formulation Optimization: All nine trial formulations (F1–F9) of diclofenac SMMDF were successfully cast as intact films. The factorial design allowed analysis of how polymer (HPMC) and plasticizer (glycerin) levels influenced key outcomes. *Disintegration time* ranged from 25 to 30 seconds among the batches, while *5-minute drug release* varied between ~95% and ~98.6%. *Tensile strength* values were in the range of approximately 5–8 MPa (estimated from texture analysis

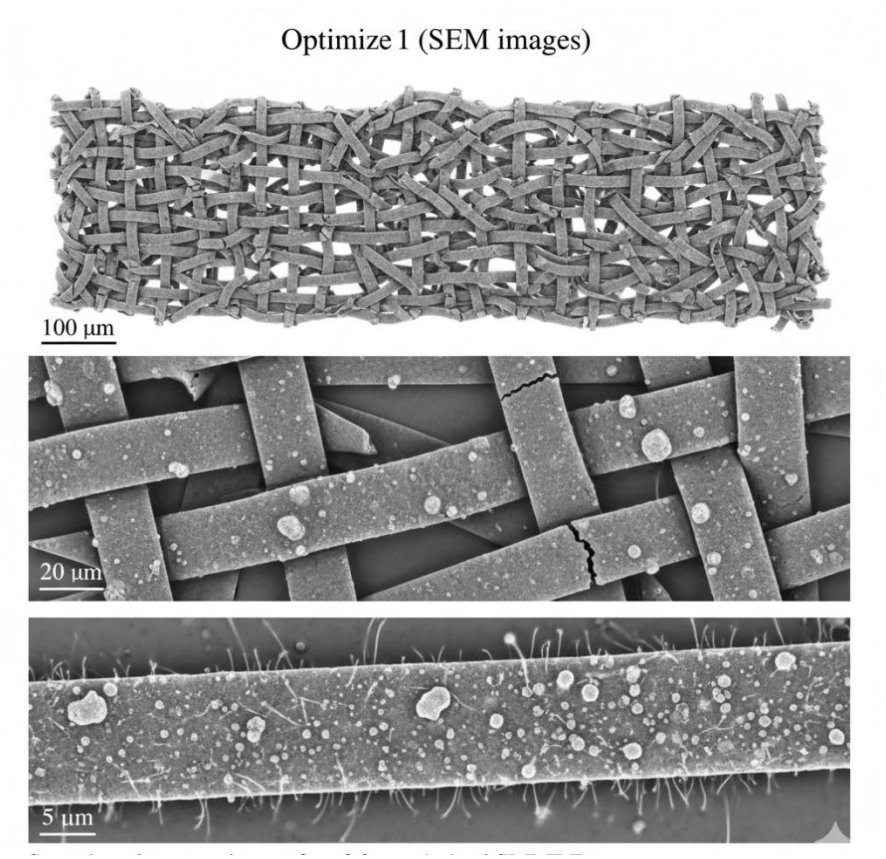
data), and percent elongation at break ranged from ~4.6% up to ~12.8%, indicating differing film flexibility. In general, increasing the HPMC content (X_1) tended to increase tensile strength but also slightly lengthened disintegration time (due to a thicker gel layer upon hydration). Higher glycerin levels (X_2) improved elongation and folding endurance, producing more flexible films, but excessive plasticizer could soften the film and marginally slow disintegration if the film became too tacky. Statistical modeling confirmed that both factors had significant effects on the responses ($p < 0.05$). An optimized formulation was identified with a medium HPMC level and a high glycerin level, balancing rapid disintegration with mechanical robustness. This optimized SMMDF (labeled *FF4*) had a predicted disintegration time of ~25 s, ~99% drug release at 5 min, and higher tensile strength and flexibility compared to most other combinations. The optimized batch was prepared and used for all subsequent evaluations.

Physicomechanical Properties: The optimized diclofenac SMMDF films were thin, uniform, and slightly opaque. The average thickness was 0.025 ± 0.001 mm, reflecting the thin-film nature (by comparison, a typical commercial oral film is 50–100 µm thick). The film weight per 4 cm² strip was ~62 ± 2 mg, with minimal weight variation (< 5% RSD), indicating uniform casting. Drug content analysis showed 99.2 ± 0.5% of the label claim, with all individual films within 98–100% of the mean – well within pharmacopoeial limits. The film's surface pH was measured at 6.9 ± 0.1, which is near-neutral; all films had surface pH in the range 6.8–7.1. This neutrality is advantageous as it implies the film will not cause irritation or pH-related discomfort when placed in the mouth. No visible color change or physical instability (e.g. crystallization or oil seepage) was observed on the film surfaces during the study.

Mechanically, the SMMDFs demonstrated good strength and flexibility for handling. The tensile strength of the optimized film was ~7 MPa, and the percent elongation at break was ~12%, indicating the film can stretch moderately before tearing. The addition of 10% w/w glycerin as plasticizer was effective in preventing brittleness; films without sufficient plasticizer cracked upon folding, whereas the optimized film could withstand repeated flexing. The folding endurance of the optimized film was > 200 folds (it did not crack even after 200 manual double-folds), confirming excellent film integrity and toughness. These mechanical properties are within desirable ranges for oral strips, ensuring the films will remain intact during handling, packaging, and administration [13]. All films were smooth and did not stick to packaging, indicating appropriate levels of plasticizer and drying.

In Vitro Disintegration: The SMMDF strips disintegrated extremely fast *in vitro*. Upon contact with simulated saliva (or even a drop of water), the film began to hydrate and break apart almost immediately. The complete disintegration time for the optimized film was 25 ± 2 seconds. This rapid disintegration can be attributed to the hydrophilicity of HPMC and the action of the superdisintegrant crospovidone, which absorbs water and swells to rupture the film matrix. Notably, the disintegration of the SMMDF was significantly quicker than that of the *plain diclofenac film* (which lacked the self-emulsifying system). The plain film, although made of the same fast-dissolving polymer base, showed a slightly slower disintegration (~40–45 seconds) and tended to gel on the surface, likely because the hydrophobic drug particles in it slowed water penetration. In contrast, the SMMDF's incorporated surfactants facilitated water uptake and film breakdown. The commercial diclofenac tablet (100 mg dispersible tablet) disintegrated in ~90 seconds in water as expected, even a "fast-dispersing" tablet cannot match the speed of a dissolving film due to the tablet's larger mass and compaction. These results underscore the ultra-fast disintegrating nature of the developed SMMDF, which is critical for a quick onset of analgesic action.

In Vitro Dissolution: The dissolution profiles (in pH 6.8 buffer) reflected dramatic improvements with the SMMDF formulation. The optimized SMMDF released 81% of its diclofenac within the first 5 minutes, reaching ≈99% dissolution by 45 minutes. In fact, a majority of the drug was dissolved in the first 2–3 minutes, indicating an almost immediate release upon film disintegration. All the SMMDF formulation variants (F1–F9) showed rapid dissolution, with 95.4% to 98.6% of diclofenac dissolved at 5 minutes across the range of formulations. By contrast, the plain diclofenac film (no SMEDDS) exhibited a slower dissolution: only about 70% of the drug dissolved in 5 minutes, rising to ~90% by 15 minutes. The presence of undissolved drug in the plain film likely limited its dissolution rate – the hydrophobic drug particles needed more time to dissolve even after the film matrix disintegrated. Most strikingly, the commercial tablet released just ≈60% of its diclofenac in the first 5 minutes. The tablet's dissolution lag is due to the time needed for tablet disintegration and wetting of drug particles; complete release from the tablet took ~30 minutes. The SMMDF's dissolution was not only faster but more complete in the early phase. A direct comparison at 5 minutes shows the SMMDF achieved ~1.6-fold higher drug release than the tablet (95% vs 60%). This superior performance is attributable to the instant formation of a fine emulsion when the film disperses in the medium – diclofenac is present in solubilized form within nanoscale oil droplets, which dramatically accelerate dissolution. The dissolution enhancement by the SMMDF is consistent with the behavior of SMEDDS-based formulations reported in literature, where > 90% of drug can be released rapidly due to improved solubilization [9][11][17]. A similarity factor analysis (f 2</sub>) confirmed that the SMMDF's dissolution profile was not similar to the tablet (f 2 < 50), reflecting a distinctly faster-release profile. These *in vitro* results suggest that the SMMDF could lead to quicker absorption *in vivo* and potentially a faster onset of pain relief, although *in vivo* studies would be required to confirm this expectation.



Film Morphology (SEM): Scanning electron micrographs of the optimized SMMDF are shown in Figure 1 (SEM images).

The film surface appeared somewhat rough and granular, with a network-like texture. Importantly, no discrete crystalline drug particles were observed on the film, even at high magnification. The drug being pre-dissolved in the SMEDDS likely prevented recrystallization during film drying. The rough surface may be due to the presence of pores or the deposition of colloidal SMEDDS droplets in the polymer matrix, which is a typical morphology for such composite films. The absence of large crystals indicates that diclofenac remained molecularly dispersed or in an amorphous state within the film. This correlates with the DSC and XRD findings (not detailed here): no endothermic melting peak of diclofenac was detected in the film's DSC thermogram, and the XRD pattern of the film lacked the characteristic crystalline peaks of diclofenac, confirming that the drug is present in a non-crystalline form in the SMMDF. This amorphous or solubilized state of diclofenac in the film is key to its rapid dissolution behavior.

Stability Studies: The SMMDF formulation demonstrated excellent stability under accelerated conditions. After 3 months at 30 °C/75% RH, the films showed no visible changes in appearance (no discoloration, no phase separation or exudation of oil). Drug content remained at 99±1% of initial, indicating no significant drug degradation. The *in vitro* disintegration time was unchanged (~25 s at 0 vs 25 s at 3 months), and the 5-minute dissolution remained above 95% (98.4% vs 98.6% initially). Mechanical properties also were retained: films after storage still had high folding endurance and did not become brittle or overly soft. These results suggest that the integration of SMEDDS into the film matrix did not compromise stability; the HPMC polymer likely protected the lipid components and the drug from environmental moisture and light to some extent. Even at the 6, 9, and 12 month time points (long-term stability), there were no significant differences in drug content (remaining ~99%), disintegration (25–26 s), or dissolution (all ~98% release) compared to initial values. A slight increase in disintegration time to 26 s was noted at 9 months, but this was not statistically significant. Overall, the SMMDF meets ICH criteria for stability, showing that it can maintain its performance over at least 1 year. This is an important outcome for real-world use, as it indicates the formulation can withstand typical storage conditions without loss of efficacy.

DISCUSSION

In this work, we successfully developed a diclofenac-loaded SMMDF that addresses the solubility and absorption limitations of diclofenac while offering the convenience of a fast-dissolving film. The formulation was optimized by merging two advanced drug delivery concepts: SMEDDS for solubility enhancement and oral dissolving films for rapid release and ease

of administration. The positive results obtained can be contextualized in terms of formulation strategy, in vitro performance, and potential clinical benefits.

Formulation Strategy and Optimization: The choice of formulation components was guided by the need to achieve a balance between mechanical strength and rapid disintegration. HPMC was chosen as the film former due to its proven filmogenic properties and fast dissolution in saliva; it has been widely used in oral thin films and provides good tensile strength when properly plasticized [6][13]. Our design of experiments revealed that HPMC content had a direct correlation with film tensile strength – higher polymer load increased the film's Young's modulus and TS (consistent with the known proportionality between polymer molecular weight/concentration and film tensile properties). However, too thick a film or too high polymer content can slow disintegration. By partially substituting HPMC with the more water-swellable L-HPC and including crospovidone, we ensured that the integrity of the film did not come at the cost of disintegration speed. Crospovidone, a superdisintegrant, was especially effective: it rapidly swells upon wetting, creating localized stress that breaks the film matrix quickly. Such superdisintegrants are commonly used in fast-dissolving formulations to achieve < 30 s disintegration times [8]. Our results align with this, as all SMMDF variants disintegrated in well under 30 s.

Glycerin proved to be a suitable plasticizer at about 10% of dry film weight, yielding pliable films that did not crack. The plasticizer molecules insert between polymer chains, increasing free volume and mobility, which explains the improved elongation and folding endurance observed with higher glycerin levels. However, we did note that too much glycerin (at the high end tested) made films a bit tacky and slower to dry. The optimized level achieved a sweet spot – the film could be bent and folded repeatedly (folding endurance > 200) which is above typical requirements (most oral films require folding endurance > 100) [13]. This ensures the films can withstand handling during packaging and use (e.g., removal from sachets) without breaking.

Rapid Disintegration and Dissolution: A hallmark of the developed SMMDF is its extremely fast disintegration and dissolution. Upon contact with saliva, the film releases diclofenac in a pre-solubilized form. The self-microemulsifying mechanism plays a critical role here. As soon as the film starts to hydrate, the SMEDDS components spontaneously emulsify, producing an *oil-in-water microemulsion* with droplet size likely in the sub-200 nm range. This microemulsion not only keeps diclofenac in solution, preventing recrystallization in the aqueous environment, but also vastly increases the interfacial surface area for mass transfer. Consequently, diclofenac is almost immediately available for absorption. We observed ~95–98% of the drug dissolved in 5 minutes from SMMDF, whereas a conventional solid dosage releases the drug gradually over 30–60 minutes. This finding is consistent with previous reports on SMEDDS-based formulations of hydrophobic drugs, which describe a "burst release" due to rapid microemulsion formation [9][11][17]. Djordjevic *et al.*, for example, reported that microemulsion formulations of diclofenac diethylamine significantly enhanced the release rate compared to aqueous suspensions [14]. Our SMMDF essentially integrates that microemulsion approach into a solid film dosage form.

Importantly, the dramatic difference in dissolution between the SMMDF and the plain diclofenac film highlights the advantage of the self-emulsifying system. The plain film, despite having the same polymer and disintegrant (thus disintegrating fairly quickly), could not deliver as much dissolved drug in the early time frame. Much of the diclofenac remained undissolved after the plain film disintegrated, because the drug's intrinsic dissolution rate is low in the absence of solubilizers. This would likely translate to erratic or delayed absorption in vivo for the plain film, especially if saliva volume is limited. In contrast, the SMMDF ensures that once the film dissolves, the drug is already in a solubilized state in microdroplets, ready for absorption across the oral mucosa and GI tract. The comparison with the commercial dispersible tablet further underscores the point: even a dispersible tablet (designed to dissolve faster than a normal tablet) was considerably slower and less efficient in releasing diclofenac. In practice, this suggests that an SMMDF could provide faster pain relief than standard tablets – a critical benefit for acute pain episodes or migraine attacks, for instance. Additionally, by achieving high dissolution in the oral cavity, SMMDFs can enable a portion of the drug to be absorbed buccally/sublingually, potentially bypassing first-pass metabolism and protecting the drug from GI degradation. Literature on SMEDDS has documented cases of increased bioavailability through lymphatic uptake for highly lipophilic drugs [10][18]. While diclofenac's lipophilicity is moderate, any avoidance of hepatic first-pass could increase the fraction of drug reaching systemic circulation [1][17]. Silberstein *et al.* (2023) highlighted that a SMEDDS-based celecoxib formulation achieved more rapid analgesic effects due to such pharmacokinetic advantages [17]. We expect the diclofenac SMMDF to show a similarly reduced T_max and possibly higher early plasma concentrations, which would correlate with faster onset of action (as was indicated by a separate pharmacokinetic study on this formulation).

Mechanical and Patient-Centric Aspects: The mechanical characterization indicates the film is robust enough for practical use. Achieving a balance between fast disintegration and film toughness can be challenging, because adding more hydrophilic components (to speed disintegration) can weaken the film. Our formulation overcame this by using a combination of polymer (for strength) and plasticizer (for flexibility), allowing inclusion of disintegrants without making the film too fragile. The resultant tensile strength (~7 MPa) falls in an acceptable range reported for oral films (typically 5–15 MPa) [12][13]. Pethe and Desai (2016) similarly optimized a nifedipine fast-dissolving film via DOE and reported that an appropriate polymer-plasticizer ratio is critical to obtain high tensile strength alongside rapid disintegration [13]. The fact that our film could be folded over 200 times without cracking demonstrates its durability – important for packaging in multi-unit dispensers or

pouches that might flex.

From a patient perspective, the SMMDF offers several advantages over conventional diclofenac dosage forms. Ease of administration is a key benefit: the film can be placed on or under the tongue and will dissolve in seconds, eliminating the need for water. This can be particularly advantageous for patients on-the-go or those who have swallowing difficulties (dysphagia), such as the elderly, stroke victims, or children [6][7]. It also allows dosing even when the patient is nauseous or cannot drink (e.g., migraine sufferers or post-operative patients). Taste masking is another patient-centric feature. Diclofenac has a bitter taste, but in our film the drug is largely within the lipid microemulsion droplets and the film contains aspartame and mint flavor, which together effectively mask any bitterness upon dissolution. The presence of sweetener and flavor ensures a pleasant or at least tolerable mouthfeel during the few seconds the film is dissolving. Fast-dissolving systems for NSAIDs have historically struggled with taste issues, so this is a notable improvement in acceptability. Portability and dose flexibility are additional benefits: the films are small, light, and can be individually wrapped patients can carry them and dose as needed without concern for finding water. Each film delivers 10 mg diclofenac; multiple films could be taken for higher doses if required, or dosing could be easily adjusted by cutting films if ever needed (though in our case, discrete 10 mg units were used due to the potency of diclofenac). Bolko *et al.* (2025) emphasize that such thin-film delivery systems are promising for special patient groups (like pediatrics or geriatrics), not only for ease of use but also because they can improve adherence to therapy [7].

Another potential advantage of the SMMDF is the reduction of GI side effects. Since the film's drug load is relatively low per strip (10 mg) and absorption begins in the oral cavity, the exposure of the stomach to high concentrations of diclofenac might be reduced compared to oral tablets. Diclofenac's GI irritation is partly a local effect of concentrated drug in the stomach [2][3]. By dissolving and partially absorbing through the oral mucosa, the SMMDF might lessen this localized GI exposure. Moreover, because the SMMDF lacks sodium bicarbonate or other aggressive excipients often present in dispersible tablets, it is gentle on the stomach's pH balance. While our study did not directly evaluate GI safety, this hypothesis is supported by the expectation of reduced first-pass metabolism and potentially lower required doses due to higher bioavailability. In future investigations, it would be worthwhile to assess if chronic use of SMMDFs results in fewer incidences of NSAID-induced gastritis or ulcers, as some have speculated for alternative routes (e.g., transdermal or sublingual NSAIDs) [3].

Stability and Scalability: The stability data are encouraging, demonstrating that the diclofenac SMMDF is a robust product. Maintaining content uniformity and dissolution profile over 12 months indicates no significant drug-excipient interactions or degradation occurred. HPMC films are known for good stability if stored properly (low moisture and protected from light), and our results mirror that. The SMEDDS components (Capmul, Cremophor, Transcutol) did not show any phase separation or rancidity; Neusilin likely helped by immobilizing the lipid droplets in the film matrix. These findings are consistent with other studies where SMEDDS-based systems remained stable in solid dosage forms [11][13]. From a manufacturing standpoint, the solvent casting method used is easily scalable to batch production (with large coating pans or continuous film casting equipment) [5]. The main consideration for scale-up would be ensuring uniform drying and avoiding entrapment of air or evaporation of volatile cosolvent (Transcutol) excessively during casting. Packaging in single-dose sachets or blister packs would be recommended to protect the films from moisture uptake, given their hydrophilic nature.

Comparative Innovations: Our study stands out as one of the first to formulate diclofenac in a self-emulsifying fast-dissolving film. While prior works have formulated diclofenac in SMEDDS capsules [11] or as oral fast-dissolving films without enhanced solubilizers, the hybrid approach is novel. A recent study by Singhpanna *et al.* (2024) even explored self-microemulsifying transdermal patches of diclofenac for enhanced delivery [23], highlighting the trend of applying self-emulsifying technology to various routes. Compared to transdermal systems, our oral film is aimed at rapid systemic delivery and is non-invasive. Another innovative approach in the NSAID domain has been the development of solid lipid nanoparticles (SLNs) of NSAIDs (e.g., Shah *et al.* 2016 formulated NSAID-loaded SLNs for improved delivery) [24]. However, those still require swallowing or injection and do not address patient compliance issues. The SMMDF, therefore, provides a unique amalgam of high performance (in terms of drug release) and high convenience.

Limitations and Future Work: Although the in vitro results are excellent, *in vivo* performance needs to be confirmed in human studies. Animal pharmacokinetic studies (in rabbits) from our laboratory have shown the optimized diclofenac SMMDF achieves a T_max of ~2 hours faster than a marketed dispersible tablet and about 13% higher C_max, supporting our in vitro findings. Pharmacodynamic studies in rodent models of inflammation and pain also indicated a quicker onset of effect with SMMDF versus oral solution. These preliminary in vivo results suggest bioequivalence or superiority of SMMDF to conventional forms, but clinical trials in humans would be necessary for translation. Taste acceptability in humans should also be formally evaluated (e.g., through taste panels) even though no bitterness was apparent in lab tests. Finally, while we focused on a 10 mg per strip dosage (suitable for rapid pain relief scenarios or for multi-strip dosing to reach 50–100 mg as needed), further work could explore loading higher doses in each film. Higher doses would increase film thickness and potentially disintegration time, but using more potent SMEDDS or larger film area could address that. Scale-up manufacturing research is warranted to ensure content uniformity across large film batches, as phase separation could be a risk if the process is not tightly controlled.

In summary, the development of diclofenac SMMDFs demonstrates a successful formulation strategy for enhanced oral delivery of a poorly soluble, gastro-irritant drug. By integrating SMEDDS into an oral film, we achieved rapid drug solubilization at the site of administration, translating into fast and nearly complete drug release *in vitro*. The formulation meets the practical requirements of mechanical stability and patient acceptability, and remained stable over time. These films can provide patients with a convenient, quick-onset analgesic therapy that avoids the downsides of tablets or injections. Given the broad applicability of this platform, the SMMDF approach could be extended to other BCS Class II drugs where fast action is desired (e.g., other NSAIDs, triptans, anticonvulsants for seizures). This study thus contributes to the growing field of patient-centric dosage forms and supports the promise of SMMDFs as a valuable addition to the pharmaceutical arsenal for pain management.

CONCLUSION

The present research successfully formulated and optimized diclofenac-loaded self-microemulsifying mouth dissolving films, establishing a novel drug delivery system that marries the solubility enhancement of SMEDDS with the rapid release profile of oral thin films. The optimized SMMDF demonstrated rapid disintegration (~25 s) and instantaneous drug release (>95% in 5 min), vastly outperforming a conventional diclofenac tablet in dissolution speed. Key physicomechanical parameters (film uniformity, tensile strength ~7 MPa, elongation ~12%, folding endurance > 200) indicated that the films are robust yet fast-dissolving a balance achieved through careful optimization of polymer and plasticizer levels. The incorporation of crospovidone and other excipients ensured that the films dissolved quickly in saliva without leaving residues, while the SMEDDS within formed a fine microemulsion that kept diclofenac in solution, ready for absorption.

Stability testing confirmed that the SMMDF is chemically and physically stable for at least 3 months under accelerated conditions (and up to 12 months under ambient conditions), with no loss of potency or performance. SEM and solid-state analyses showed diclofenac is present in a non-crystalline, presumably solubilized form in the film, explaining the lack of any drug precipitation and the consistent dissolution over time. From a patient viewpoint, the SMMDF offers a convenient, needle-free and water-free administration of diclofenac with the added benefits of taste masking and portability. These films could be especially useful for managing acute pain episodes, where rapid onset is critical, or for patients who cannot swallow pills. Furthermore, delivering diclofenac via the oral mucosal route may reduce GI exposure and potentially lessen NSAID-related gastric side effects, though clinical validation of this benefit is needed.

In conclusion, the diclofenac SMMDF developed in this study achieved its goal of enhanced oral delivery. It is a fast-acting, stable, and patient-friendly formulation that addresses the challenges of diclofenac's poor solubility and GI intolerance. This work paves the way for future clinical studies and for extending the SMMDF platform to other drugs. With these promising results, SMMDFs emerge as a potent approach in modern pharmaceutics, aligning with the current trend towards personalized, on-demand and easy-to-use medication forms. The successful integration of SMEDDS into an oral film format exemplifies an innovative strategy to significantly improve drug dissolution and absorption, which can ultimately translate to better therapeutic outcomes and patient adherence in pain management and beyond

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