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Formulation and Evaluation of Mouth Dissolving Film of Artemether

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ABSTRACT

The fast-dissolving dosage form has emerged as an innovative drug delivery system offering enhanced therapeutic efficacy, improved bioavailability, and greater formulation stability while reducing the frequency of administration. By bypassing first-pass metabolism, it enables more efficient systemic absorption. This system facilitates rapid drug uptake through the pre-gastric region, leading to a quicker onset of action. The present study was designed to develop and evaluate mouth-dissolving films (MDF) of Artemether for the prevention and treatment of malaria. The films were formulated using the solvent casting method and evaluated for disintegration time, wetting time, percent drug release, and folding endurance. The optimized formulation exhibited a short disintegration time of 17.33±0.94 seconds, a high dissolution rate of 91±1.63%, and satisfactory physicochemical characteristics. These findings indicate that the developed MDF represents a promising and patient-friendly dosage form capable of enhancing drug delivery, accomplish faster therapeutic action, and improving treatment compliance.

KEYWORDS: Mouth dissolving films (MDFs), Artemether, Malaria, Bioavailability, and Formulation.

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INTRODUCTION

There has been growing interest in developing modified-release oral dosage forms, as oral drug delivery accounts for nearly 52% of the overall drug delivery market. However, several challenges are associated with oral administration, including the potential loss of active ingredients due to tablet or capsule crushing and inaccuracies in liquid dosing. These issues can result in imprecise dosing, leading to either drug overdosing or reduced therapeutic effectiveness [1-3]. To address these challenges, fast-dissolving drug delivery systems have gained significant attention. Among these, oral film strips have become increasingly popular in recent years, originally introduced as a novel method for breath freshening. These thin, gel-like films are placed on the tongue, where they rapidly dissolve, releasing their flavor [4-6]. Recent technological progress has prompted numerous pharmaceutical companies to investigate new possibilities in this field, aiming to achieve quick and precise dosing that can enhance patient compliance, especially in pediatric populations [7-9]. Significant advancements have recently been made in transmucosal drug delivery routes, as this method offers effective solutions to many challenges linked to traditional oral drug administration [9]. This dosage form eliminates the need for water or precise measurement, and once the film dissolves, the medication is easily swallowed. Drug absorption through the oral mucosa is particularly appealing because its rich vascularization ensures efficient permeability and rapid entry into systemic circulation. As a result, fast-dissolving films have gained popularity for delivering various medications, offering rapid disintegration due to their extensive surface area and ultimately enhancing patient compliance. Various hydrophilic polymers which provide rapid dissolution, acceptable mechanical properties and good mouth feel quality are used as a film forming agents.

Hydroxypropyl methylcellulose (HPMC) is a semi-synthetic, cellulose-derived polymer composed of a cellulose backbone with hydroxypropyl and methyl substitutions. It is available in food and pharmaceutical grades and is widely utilized in various industries due to its excellent film-forming, thickening, and stabilizing properties. In the pharmaceutical industry, HPMC is used as a binder, coating agent, and controlled-release matrix, while in the food sector, it functions as a thickener, emulsifier, and stabilizer. HPMC exhibits good water solubility, film-forming ability, and biocompatibility, making it suitable for a broad spectrum of applications. Its ability to form heat-sealable films with good oxygen barrier properties also makes it a popular choice for packaging and protective coatings in food and pharmaceutical formulations [10, 11]. Malaria is a severe mosquito-borne disease caused by the plasmodium parasite, which infects human blood cells. Artemether (ART) is an effective antimalarial drug that helps reduce the risk of infection and shortens the duration of the illness [12, 13]. Artemether, classified under Biopharmaceutics Classification System (BCS) class II [14] has a unique mechanism of action that lowers the likelihood of parasite resistance development [15]. However, as a poorly water-soluble drug, artemether exhibits low dissolution rates and slow absorption, resulting in inadequate and poor oral bioavailability. Predictions from dissolution tests and theoretical considerations indicated that on reducing the particle size of the drug leads to increased dissolution and increased oral bioavailability.

Hence, based on the rationale of the proposed research work, the aim of present investigation was to develop and formulate HPMC based mouth dissolving films of artemether by solvent casting method for the direct absorption of drug via transmucosal lining to the systemic circulation. The proposed formulation has the potential to improve compliance and presents multiple competitive advantages over its marketed oral dosage forms used in prevention and treatment of malaria.

MATERIALS AND METHODS

Materials

The drug component (Artemether) and excipients utilized for the preparation of mouth dissolving films of different compositions were obtained from authentic sources and authorized vendors while the drug artemether was received as gift sample from IPCA Laboratories, India. The ingredients used for formulations were of analytical grade and were utilized without any further purification.

Formulation development of fast dissolving films

Preliminary trials for screening of components

The development of a successful fast dissolving film heavily depends on the nature and concentration of the polymer used; various polymers were tested for their film-forming abilities. In the present study, hydroxy propyl methyl cellulose was selected as the film-forming polymer. Blank formulations were prepared by dissolving different polymers and plasticizer compositions in distilled water, as detailed in **Table 1 and** Table 2. The solutions were then cast and dried in an oven at 45 °C for 24 hours. The resulting films were evaluated for parameters such as surface appearance, stickiness, disintegration time, and folding endurance, with results summarized in **Table 4** to **Table 14**. HPMC is known for its excellent film-forming capacity, moisture retention, and oxygen barrier properties which contribute to the formation of uniform, flexible, and mechanically strong films suitable for mouth dissolving film applications.

Table 1. Composition of blank mouth dissolving films by using HPMC E15

Formulation ID#	HPMC (mg)	PEG400 (ml)	Water (ml)	Menthol (%)	Saccharin (%)	Ethanol (ml)
F1	100	5	15	1.0	0.3	3
F2	200	5	15	1.0	0.3	3
F3	300	5	15	1.0	0.3	3
F4	400	5	15	1.0	0.3	3
F5	500	5	15	1.0	0.3	3
F6	600	5	15	1.0	0.3	3
F7	700	5	15	1.0	0.3	3
F8	800	5	15	1.0	0.3	3
F9	900	5	15	1.0	0.3	3
# Formulations containing variable amount of polymer.						

Table 2. Composition of blank mouth dissolving films by using EUDRAGIT L-100

Formulation ID#	Eudragit L100 (mg)	PEG 400 (ml)	Dibutyl Phthalate (ml)	Triethyl Citrate (ml)	Acetone (ml)	Menthol (%)	Saccharin (%)
F1	300	5	-	-	5	1.0	0.3
F2	400	5	-	-	5	1.0	0.3
F3	500	5	-	-	5	1.0	0.3
F4	300	-	5	-	5	1.0	0.3
F5	400	-	5	-	5	1.0	0.3
F6	500	-	5	-	5	1.0	0.3
F7	300	-	-	5	5	1.0	0.3
F8	400	-	-	5	5	1.0	0.3
F9	500	-	-	5	5	1.0	0.3
# Formulations containing variable amount of polymer.							

2.3 Preparation of drug loaded fast dissolving films

Polymeric solution (Solution A) was prepared by dissolving desired amount of hydroxy propyl methyl cellulose in sufficient quantity of distilled water (70%). Specific quantity of drug along with polyethylene glycol and other excipients were dissolved in remaining water (30%) with continuous stirring (Solution B). Solution B was slowly added in polymeric solution A with continuous stirring. Final solution obtained was kept aside for 30 mins for defoaming. After defoaming, solution was poured

in petri plate and dried at 45 °C in hot air oven for 24 h [16, 17]. Film casted in petri plate was then carefully peeled off and cut into pieces of desired shape and size. Different optimized combinations of film containing HPMC with PEG 400 were prepared as shown in **Table 3.** The prepared formulations were evaluated for the disintegration time, wetting time, folding endurance and drug release as shown in **Table 4** to **Table 14.**

Table 3. Composition of oral mouth dissolving film of Artemether

Formulation ID#	Artemether (mg)	HPMC (mg)	PEG 400 (ml)	Water (ml)	Saccharin (%)	Menthol (%)	Ethanol (ml)
F1	20	100	5	15	0.3	1.0	3
F2	20	200	5	15	0.3	1.0	3
F3	20	300	5	15	0.3	1.0	3
F4	20	400	5	15	0.3	1.0	3
F5	20	500	5	15	0.3	1.0	3
F6	20	600	5	15	0.3	1.0	3
F7	20	700	5	15	0.3	1.0	3
F8	20	800	5	15	0.3	1.0	3
F9	20	900	5	15	0.3	1.0	3
# Formulations containing variable amount of polymer.							

2.4 Evaluation of prepared aprepitant loaded MDF

2.4.1 Drug excipient interaction study

2.4.1.1 *Fourier transform infrared spectroscopy (FTIR)*

The Fourier Transform Infrared (FTIR) absorption spectra of the pure drug, hydroxypropyl methylcellulose (HPMC), and their physical mixture were obtained to analyze their molecular characteristics and interactions. The spectra were recorded in the terms of the wavenumber range of 4000 to 400 cm^{-1} using the potassium bromide (KBr) pressed pellet method. This method involved preparing samples by triturating a small amount of the substance (pure drug, HPMC, or their mixture) with KBr crystals, which is transparent to infrared radiation, and compressing the triturated mixture into a thin, transparent disc/pellet. The FTIR spectrophotometer (Spectrum GX, Perkin-Elmer, USA) was used to measure the infrared absorption, providing insights into the functional groups, chemical bonds, and potential interactions between the drug and HPMC in the mixture. The spectral range of 4000–400 cm^{-1} covers key vibrational modes, including O-H, C-H, C=O, and other molecular stretching and bending vibrations, enabling detailed characterization of the samples [18].

2.4.2 Thickness

The thickness of each oral film was measured at five distinct locations to ensure a comprehensive assessment of uniformity and consistency across the film's surface. Measurements were conducted using a screw gauge, a precision instrument capable of accurately determining the thickness of thin materials. The screw gauge was carefully calibrated to ensure reliable and reproducible results. For each oral film formulation, the thickness values obtained from the five different points were recorded, and the average thickness was calculated to provide a representative value for the film. Additionally, the standard deviation of these measurements was computed to quantify the variability in thickness, indicating the degree of uniformity or potential irregularities in the structure of film [19, 20].

2.4.3 Weight variation

To assess the weight uniformity of each oral film formulation, three film samples, each measuring 2 × 2 cm^2 (4 cm^2 in area), were randomly cut from different regions of the film to ensure representative sampling. The random selection of film sections helped account for potential variations in composition or thickness across the film surface. Each individual film sample was weighed using a high-precision electronic balance, which provided accurate and reliable measurements of mass. The weights of the three films from each formulation were recorded, and the mean weight for each formulation was calculated by averaging these values. This process allowed for the evaluation of weight consistency within and across formulations, which is critical for ensuring uniform drug content and quality in oral film formulations. The mean weight data served as an indicator of the films' physical uniformity, which is essential for their performance in applications in controlled drug delivery, as variations in weight could affect dosage accuracy and release profiles [16].

2.4.4 Surface pH

The surface pH of each oral film formulation was evaluated to assess its compatibility with the oral mucosa, as extreme pH values could cause irritation or discomfort during application. The test was conducted by placing an individual film sample in a clean Petri dish to provide a stable and controlled environment for measurement. The film was then moistened with 0.5 mL of phosphate buffer solution, which simulates the physiological conditions of the oral cavity and facilitates pH measurement. The buffer was allowed to interact with the film for 30 seconds to ensure adequate wetting of the surface. Subsequently, the electrode of a calibrated pH meter was brought into contact with the moistened surface of the film. To record accurate and stable readings, the pH meter was left in contact with the film for 1 minute, allowing sufficient time for equilibration of the electrode with the sample. To ensure reliability and account for potential variability, this procedure was repeated for three times for each film samples from individual formulation, and the average pH value was calculated from these values. This method provides a robust assessment of the surface pH, which is critical for confirming the safety and suitability of oral film formulations for mucosal administration [21].

2.4.5 Folding endurance

The folding endurance test was performed to evaluate the mechanical strength and flexibility of the oral film, specifically its ability to withstand repeated folding without breaking, which is an indicator of its tensile strength and durability. For this test, oral film samples with a uniform cross-sectional area and thickness were selected to ensure consistency and comparability of results. Each film was subjected to repeated folding at the same point, typically by bending it 180 degrees, until it either broke or developed visible cracks. The number of complete folds the film could endure before breaking was recorded as the folding endurance value. This value serves as a quantitative measure of the film's mechanical robustness, reflecting its ability to resist physical stress during handling, packaging, or application in the oral cavity. A higher folding endurance value indicates greater flexibility and tensile strength, which are critical for ensuring the film's integrity during manufacturing, storage, and use in drug delivery systems. This test is essential for confirming that the oral film can maintain its structural integrity under mechanical stress, thereby ensuring reliable performance in practical applications [22-24].

2.4.6 Uniformity of drug content

To determine the drug content uniformity across all oral film formulations, a random sampling approach was employed to ensure representative analysis. For each formulation, film samples measuring 2 × 2 cm^2 (4 cm^2 in area), referred to as the final dosage form (FDF), were randomly selected. Each selected film sample was dissolved in a phosphate buffer solution, chosen to mimic physiological conditions and facilitate complete dissolution of the drug and excipients. The resulting solution was filtered to remove any insoluble residues or particulates, ensuring a clear sample suitable for analysis. The filtered solution was then analyzed using a UV-Visible spectrophotometer to quantify the drug content. The UV-Visible spectrophotometer method enabled precise detection of the drug based on its characteristic absorbance at a specific wavelength, providing an accurate measurement of its concentration. To ensure reliability and account for potential variability, the drug content analysis was performed in triplicate for each formulation, and the mean drug content was calculated from these three determinations. This approach ensured robust and reproducible results, verifying the uniformity and accuracy of drug loading in the oral film formulations, which is critical for ensuring consistent therapeutic efficacy and quality control in pharmaceutical applications [25, 26].

2.4.7 Percentage moisture loss

To evaluate the integrity and physical stability of the oral film formulation, a percent moisture loss test was conducted to assess the film's ability to retain or lose moisture under controlled conditions, which is critical for its stability during storage and handling. A film sample measuring 2 × 2 cm^2 (4 cm^2 in area) was carefully cut from each formulation to ensure uniformity in size and consistency. The initial weight of the film was measured using a high-precision electronic balance. Subsequently, the film was placed in a desiccator containing fused anhydrous calcium chloride, a highly effective desiccant that absorbs moisture, creating a low-humidity environment. The film was left in the desiccator for three days to allow sufficient time for any moisture present in the film to be removed [27]. Further, the film patch was removed from the desiccator and weighed again using the same electronic balance to determine the final weight. The percentage moisture loss of the film was calculated using the following formula:

$$\text{Percentage Moisture Loss} = (\text{Initial Weight} - \text{final weight})/\text{Initial Weight} \times 100$$

2.4.8 In vitro wetting time

To assess the wetting time of the oral film formulation, which serves as an indicator of its hydrophilicity and ability to absorb moisture (an important factor for disintegration and drug release in the oral cavity), a standardized experimental procedure was employed. A circular piece of tissue paper, selected for its absorbent properties, was placed inside a clean Petri dish to create a uniform and controlled testing surface. A 6 mL solution of 0.1% w/v amaranth dye, a water-soluble red dye, was prepared and carefully added to the Petri dish, saturating the tissue paper. This dye solution was used to visually track the absorption process. A film strip, measuring 2 × 2 cm^2 (4 cm^2 in area), was then gently placed on the surface of the dye-soaked tissue paper, ensuring consistent contact. The time taken for the amaranth dye to penetrate through the film and become visible on its upper surface was recorded as the wetting time. This duration reflects the film's ability to absorb the aqueous solution, indicating its potential behavior in the moist environment of the oral cavity. The wetting time is a critical parameter for evaluating the film's disintegration and dissolution properties, as faster wetting typically correlates with rapid drug release, which is desirable for oral film formulations in pharmaceutical applications. The experiment was conducted with precision to ensure reproducibility, and the use of amaranth dye provided a clear visual endpoint for accurate timing [28].

2.4.9 Disintegration time

The disintegration time of the oral film formulation was determined to evaluate its ability to break down rapidly in a simulated physiological environment, a critical parameter for ensuring effective drug release in the oral cavity. A film strip measuring 2 × 2 cm² (4 cm² in area) was selected for its uniform size and consistency, ensuring reliable and comparable results. The film was placed in a Petri dish with a diameter of 6 cm, which provided a controlled and standardized testing environment. The Petri dish was filled with 6 mL of phosphate buffer solution maintained at a pH of 6.8, mimicking the pH of saliva in the oral cavity to simulate *in vivo* conditions. The time required for the film to completely disintegrate, defined as the point at which no solid residue of the film remained visible in the buffer, was carefully recorded using a stopwatch or timer. To ensure accuracy and account for potential variability, the disintegration test was performed in triplicate for each film formulation, with three separate film samples tested under identical conditions. The disintegration times from these three measurements were averaged to obtain a representative value, and the mean disintegration time was reported. This triplicate testing approach enhanced the reliability and reproducibility of the results, providing a robust assessment of the film's disintegration behavior, which is essential for optimizing its performance in oral drug delivery applications [29, 30].

2.4.10 In vitro release study

To evaluate the dissolution profile of the oral film formulations, an *in vitro* dissolution study was carried out to determine the rate and extent of drug release under conditions simulating the oral cavity environment. The study was performed using a beaker containing 30 mL of phosphate buffer (pH 6.8), which mimics the pH of human saliva and ensures physiological relevance. To enhance drug solubility and simulate the natural surfactants present in the oral cavity, 1% w/v sodium lauryl sulfate (SLS) was incorporated into the dissolution medium. The temperature of the medium was maintained at 37±0.5 °C to replicate human body temperature. The entire setup, including the film and dissolution medium, was placed on a mechanical shaker to provide gentle agitation and ensure uniform drug release.

At predetermined time intervals, a 1.0 mL aliquot of the dissolution medium was withdrawn to monitor the progressive drug release. To maintain constant volume and sink conditions, each withdrawn sample was immediately replaced with an equal volume of fresh phosphate buffer (pH 6.8) containing 1% w/v SLS, pre-warmed to 37±0.5 °C. The samples were filtered to remove any undissolved film residues, ensuring clarity for spectrophotometric analysis. The filtered samples were suitably diluted with phosphate buffer (pH 6.8) to bring the concentration within the linearity range of the calibration curve.

Finally, the diluted samples were analyzed using a UV–Visible spectrophotometer at the drug's predetermined λmax (260 nm), and the absorbance values were used to calculate the cumulative percentage drug release at each time point.

The *in vitro* release data obtained from the dissolution study were analyzed by fitting the data to three mathematical kinetic models—zero-order, first order, Higuchi, and Korsmeyer-Peppas models—to elucidate the drug release profile and underlying release mechanism. The zero-order model assumes a constant drug release rate independent of the drug concentration, which is typical for controlled-release systems where the release rate remains steady over time. The Higuchi model describes drug release as a diffusion-controlled process, where the amount of drug released is proportional to the square root of time, commonly applicable to matrix-based systems like oral films. The Korsmeyer-Peppas model, a semi-empirical model, was used to further characterize the release mechanism by analyzing the release exponent (n), which indicates whether the release is governed by Fickian diffusion ($n \leq 0.45$), non-Fickian (anomalous) transport ($0.45 < n < 0.89$), or case-II transport ($n \geq 0.89$), such as polymer swelling or erosion. By fitting the dissolution data to these models, the release kinetics and mechanisms were determined, providing critical insights into whether the drug release was driven by diffusion, matrix erosion, or a combination of these processes. This comprehensive analysis was essential for understanding the performance of the oral film formulation, optimizing its design, and ensuring its suitability for effective and controlled drug delivery in oral applications [31, 32].

RESULTS

3.1 Characterization of artemether loaded fast dissolving films

3.1.1 Organoleptic properties

The organoleptic features of the drug were observed, and the observations were recorded in **Table 4.**

Table 4. Organoleptic properties of artemether

Sr. No	Property	Inferences
1.	Color	White colored buff powder
2.	Taste	Bitter
3.	Odor	Odorless
4.	Melting point	86 to 88°c
5.	Solubility	Sparingly soluble in water Soluble in, acetone, methanol, and ethanol.Insoluble in methylene chloride

6.	Physical form	Crystalline

3.1.2 Identification of drug

3.1.2.1 Determination of absorption maxima

Determination of absorption maxima of the prepared solution (10, 20, 30, 40, 50, 6, 70, 80, 90, 100,110, 120 µg/mL) of Artemether in methanol was scanned individually on a double beam UV spectrophotometer, and the absorption maxima were observed at 260 nm.

Table 5. Determination of absorption

Con.(µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Mean Abs[a]
10	0.065	0.052	0.074	0.064±0.011
20	0.095	0.1	0.109	0.101±0.007
30	0.135	0.142	0.154	0.144±0.010
40	0.171	0.187	0.199	0.186±0.014
50	0.234	0.24	0.257	0.244±0.012
60	0.274	0.28	0.297	0.284±0.012
70	0.323	0.329	0.346	0.333±0.012
80	0.374	0.38	0.397	0.384±0.012
90	0.427	0.423	0.433	0.424±0.008
100	0.457	0.466	0.483	0.469±0.013
110	0.5	0.502	0.519	0.507±0.010
120	0.539	0.545	0.562	0.549±0.012
[a] Mean±SD of absorbance of three different experiments.				

3.1.2.2 Development of calibration curve

In the range of 10-120 µg/mL, the calibration curveof the drug was found linear with coefficient of regression (R^2) 0.995. The data is given in **Table 5**.

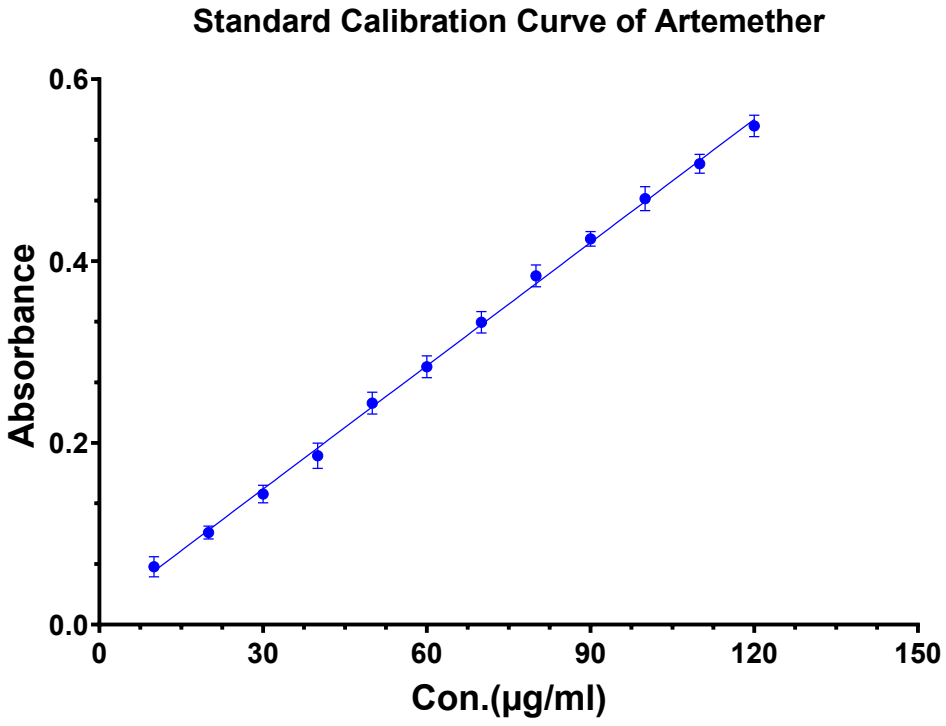

Figure 1. Calibration curve of artemether

3.2 FTIR spectral analysis

The FTIR spectra of procured sample show comparable principal absorption bands with that ofFTIR spectra obtained from Artemether which compliance between the values of characteristicpeaks indicates the drug purity.

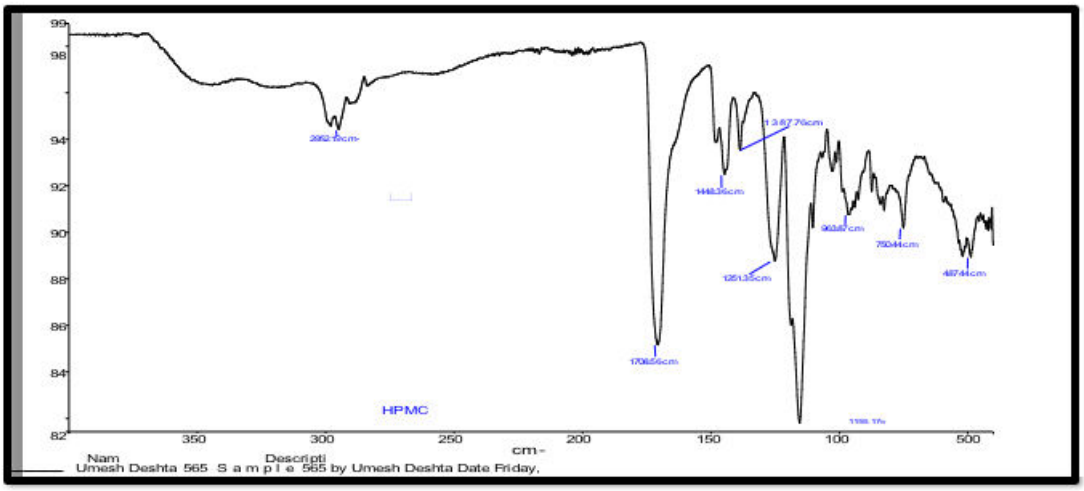

Figure 2. FTIR Spectroscopy graph of artemether

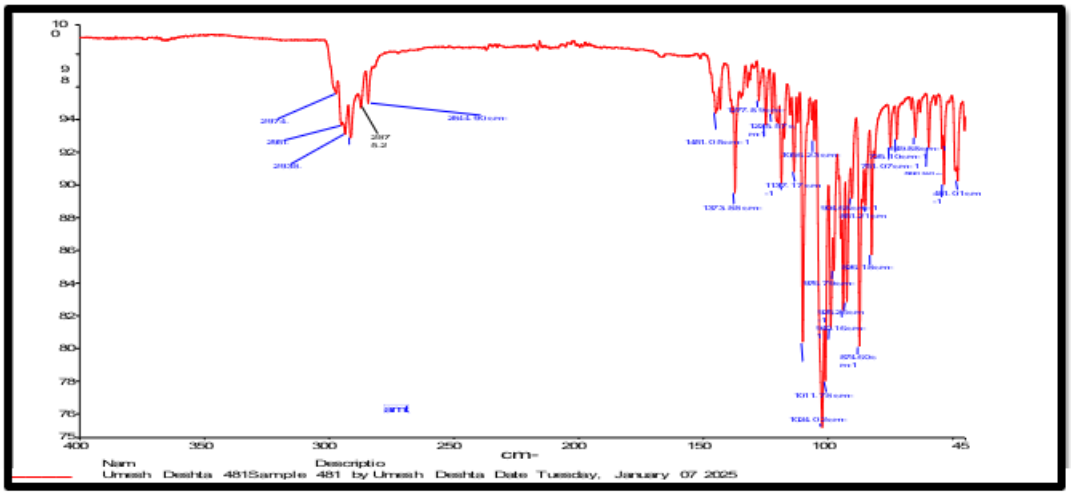

Figure 3. FTIR Spectroscopy graph of HPMC

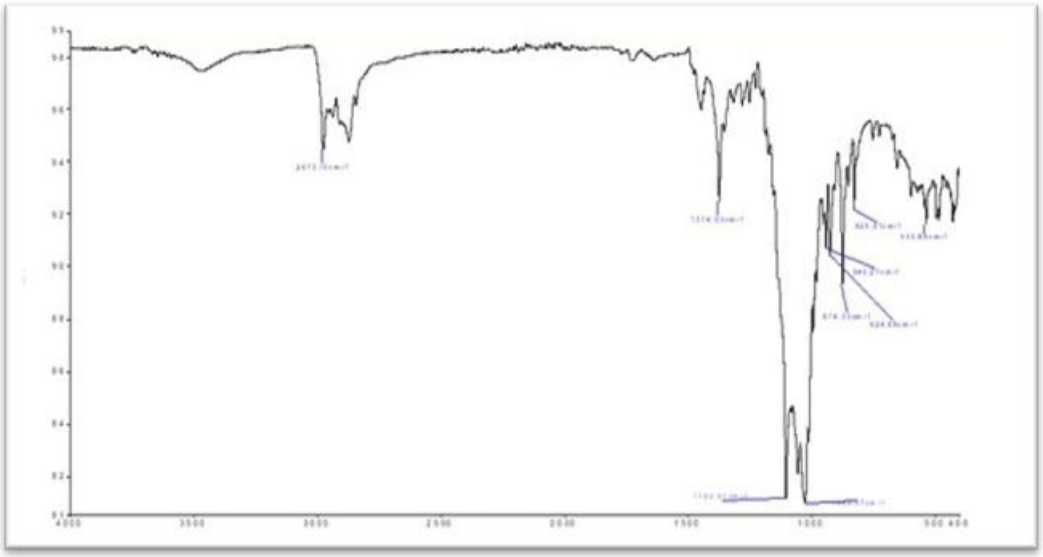

Figure 4. FTIR Spectroscopy graph of artemether and HPMC

These FTIR peaks characterize the individual chemical groups in artemether and HPMC. In the combined formulation, shifts or changes in peak intensities, especially in O–H or C–H stretching regions, could indicate physical interactions like hydrogen bonding between HPMC and artemether. Such interactions play a vital role in stabilizing the drug within the polymer matrix and improving dissolution or bioavailability.

This detailed peak assignment supports the understanding of molecular compatibility and is crucial for designing stable and effective artemether-HPMC formulations.

3.3 Evaluation parameters for placebo MDF

Evaluation parameters of placebo oral dispersible film were observed and the observation wererecorded in Table 6.

Table 6. Evaluation parameter of Blank MDF

Formulation ID[#]	Wt. Variation[a]	Thickness[b]	Folding endurance[c]	Disintegration Time[d]	Surface pH[c]
F1	20.18±0.11	0.21±0.10	52±2	42±2	6.69±0.04
F2	19.23±0.12	0.15±0.08	55±2	46±1	6.72±0.02
F3	17.16±0.15	0.18±0.07	64±1	41±3	6.75±0.01
F4	19.23±0.21	0.12±0.04	80±3	39±2	6.77±0.02
F5	20.29±0.31	0.13±0.05	92±2	37±3	6.78±0.03
F6	17.24±0.19	0.12±0.02	54±3	40±2	6.73±0.02
F7	20.21±0.16	0.14±0.01	56±3	42±1	6.74±0.03
F8	19.23±0.23	0.15±0.07	65±1	39±3	6.77±0.01
F9	18.23±0.13	0.13±0.05	67±4	45±3	6.76±0.03
[a] = percent weight; [b] = millimeter; [c] = unitless; [d] = Time in seconds; data are shown as mean±SD of 3 different experiments; # Blank formulations containing variable amount of polymer.					

3.4 Formulation of mouth dissolving film

Mouth dissolving film of Artemether was prepared by Solvent Casting Method. The mouth dissolving film of Artemether was shown in **Figure 5**.

Figure 5. Final optimized MDF of artemether by solvent casting method

3.5 Evaluation parameters for MDF of artemether

Evaluation parameters of oral dispersible film of Artemether were observed and the observations presented into following sections**.**

3.5.1 Evaluation of weight variation of MDF of artemether

The % weight variation data for nine polymer-containing formulations (F1–F9) showed mean values ranging from 21.28% (F7) to 24.37% (F9), reflecting the influence of variable polymer content on weight dynamics. F4 exhibited the highest reproducibility (SD = 0.59%), while F5 and F6 showed higher variability (SD = 1.62% and 1.60%, respectively), suggesting formulation-specific instabilities. Mid-range formulations (F3–F4) generally had lower variability, indicating a potential optimal polymer range.

Table 7. Weight variation evaluation of MDF of artemether

Formulation ID[#]	% wt. variation			Mean[a]
	Experiment 1	Experiment 2	Experiment 3	
F1	22.16	24.16	25.28	23.87±1.58
F2	20.8	21.71	22.23	21.58±0.72
F3	21.49	20.09	22.3	21.29±1.12
F4	21.67	22.07	22.83	22.19±0.59
F5	21.16	23.16	24.36	22.89±1.62
F6	23.19	20.19	22.64	22.01±1.60
F7	21.19	20.19	22.46	21.28±1.14
F8	23.63	22.32	21.38	22.44±1.13
F9	23.59	24.29	25.22	24.37±0.82

[a] Mean±SD of three different experiments; # formulations containing variable amount of polymer.

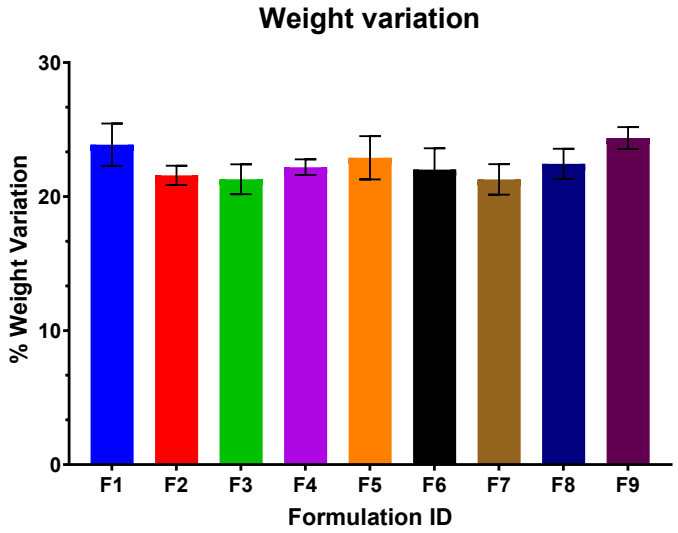

Figure 6. Graphical presentation of weight variation of all formulations (F1–F9).

3.5.2 Thickness evaluation of MDF of artemether

The thickness data for nine polymer-containing formulations (F1–F9) showed mean values ranging from 0.15 mm (F8) to 0.21 mm (F3, F6), indicating subtle variations likely due to polymer content. Most formulations (F1, F3, F4, F5, F6, F7, F9) exhibited high reproducibility with an SD of 0.01 mm, reflecting robust processing control. F2 and F8 showed slightly higher variability (SD = 0.02 mm), suggesting potential instability in polymer distribution or processing. No clear trend links polymer content to thickness without further data, but F3, F4, F5, F6, and F7 are promising for uniform thickness applications. Further optimization of F2 and F8 could enhance consistency.

Table 8. Thickness evaluation of MDF of artemether

Formulation ID[#]	Thickness[a]			Mean[b]
	Experiment 1	Experiment 2	Experiment 3	
F1	0.18	0.17	0.19	0.18±0.01
F2	0.18	0.19	0.16	0.18±0.02
F3	0.20	0.21	0.22	0.21±0.01
F4	0.17	0.18	0.18	0.18±0.01
F5	0.16	0.17	0.15	0.16±0.01

F6	0.21	0.20	0.22	0.21±0.01
F7	0.16	0.18	0.17	0.17±0.01
F8	0.14	0.15	0.17	0.15±0.02
F9	0.17	0.19	0.18	0.18±0.01
# formulations containing variable amount of polymer; [a] = thickness in millimeter; [b] = mean±SD of 3 different experiments.				

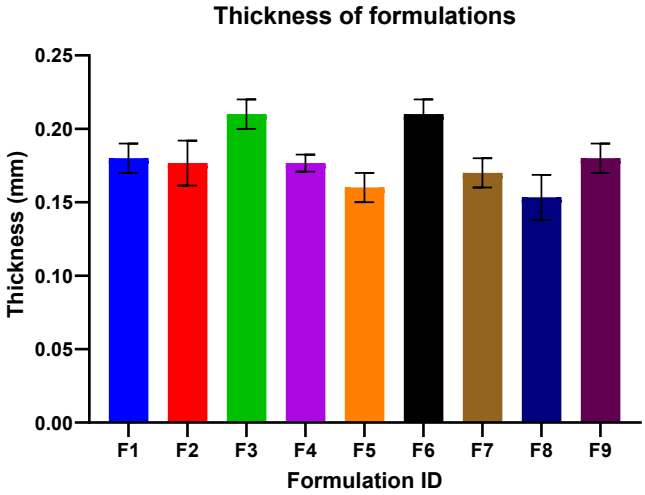

Figure 7. Comparative analysis of thickness of mouth dissolving films formulations (F1-F9)

3.5.3 Percent moisture loss evaluation of MDF of artemether

The % moisture loss across nine formulations ranged from 3.77% (F4) to 5.47% (F3), highlighting polymer content's role in moisture retention. Lowest loss in F4 (3.77 ± 0.12%) and F1 (3.87 ± 0.05%) indicates superior barrier properties, while highest in F3 (5.47 ± 0.05%) and F8 (5.37 ± 0.12%) suggests poorer retention. Reproducibility was excellent for F1 and F3 (SD = 0.05%), but F6 showed highest variability (SD = 0.16%). F1 and F4 emerge as optimal for stability-focused applications, with F6 needing refinement. Overall, lower-loss formulations likely benefit from denser or more hydrophilic polymers.

Table 9. Percent moisture loss evaluation of MDF of artemether

Formulation ID[#]	% Moisture loss[a]			Mean[b]
	Experiment 1	Experiment 2	Experiment 3	
F1	3.8	3.9	3.9	3.87±0.05
F2	5.1	5	5.2	5.10±0.08
F3	5.4	5.5	5.5	5.47±0.05
F4	3.6	3.8	3.9	3.77±0.12
F5	4	4.3	4.2	4.17±0.12
F6	4.9	4.7	4.5	4.70±0.16
F7	5.4	5.2	5.1	5.23±0.12
F8	5.5	5.4	5.2	5.37±0.12
F9	4.5	4.3	4.2	4.33±0.12
# formulations containing variable amount of polymer; [a] = percent moisture loss; [b] = mean±SD of 3 different experiments.				

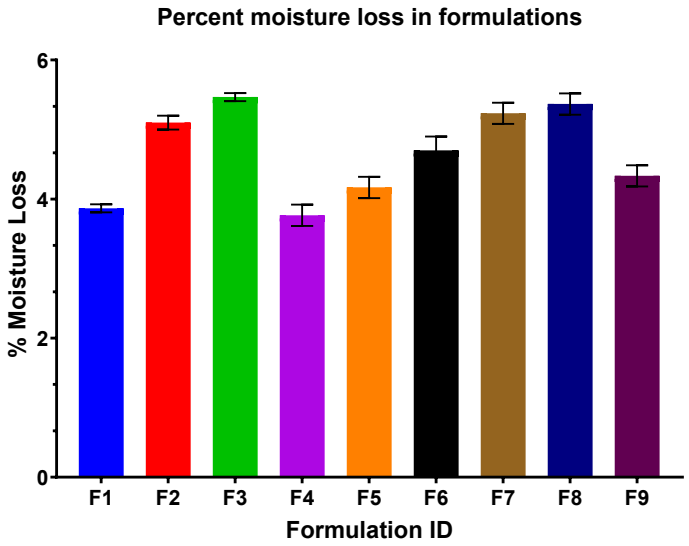

Figure 8. Comparative analysis of % moisture loss of mouth dissolving films formulations (F1-F9)

3.5.4 Folding endurance evaluation of MDF of artemether

The folding endurance of nine formulations (F1–F9) ranged from 82.33 (F2) to 91.33 (F1), indicating varied mechanical durability influenced by polymer content. F1 showed the highest flexibility, while F2 was the least durable, suggesting differences in polymer elasticity or concentration. Most formulations (F3–F9) had similar endurance (84.33–85.33), with F4 and F8 exhibiting the highest reproducibility (SD = 0.85 and 0.82). Higher SDs in F1, F2, F3, F5, and F7 (1.25–1.26) indicate minor variability. F1 is optimal for flexible applications, while F2 needs further optimization. Further studies on polymer properties could enhance formulation durability.

Table 10. Folding endurance evaluation of MDF of artemether

Formulation ID[#]	Folding endurance[a]			Mean[b]
	Experiment 1	Experiment 2	Experiment 3	
F1	93	90	91	91.33±1.25
F2	81	84	82	82.33±1.25
F3	86	85	83	84.67±1.25
F4	86	84	85	85.00±0.85
F5	86	85	83	84.67±1.25
F6	86	84	84	84.67±0.94
F7	86	84	83	84.33±1.26
F8	86	85	84	85.00±0.82
F9	86	84	86	85.33±0.94
# formulations containing variable amount of polymer; [a] = thickness in millimeter; [b] = mean±SD of 3 different experiments.				

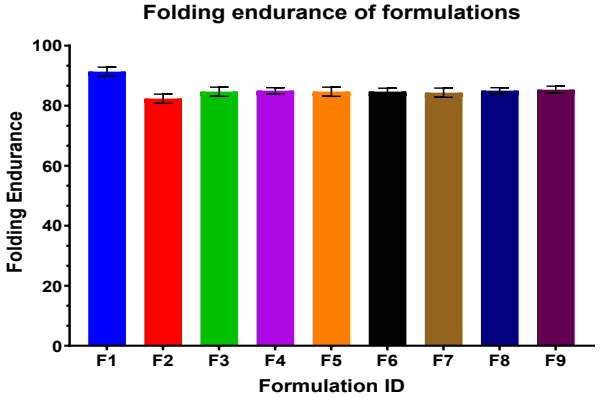

Figure 9. Comparative analysis of folding endurance of mouth dissolving films formulations (F1-F9)

3.5.5 Wetting time evaluation of MDF of artemether

The wetting time for nine formulations (F1–F9) ranged from 13.00 seconds (F4) to 26.33 seconds (F2), reflecting varied hydrophilicity due to polymer content. F4 showed the fastest wetting and highest consistency (SD = 0.82), ideal for rapid-absorption applications, while F2 was the slowest. F3 and F5 also exhibited fast wetting, whereas F7, F8, and F9 had slower times and higher variability (SD = 1.63–2.05). Higher SDs in F8, F7, and F9 suggest potential formulation or processing inconsistencies. F4 is optimal for quick wetting, while F2, F7, and F9 may need reformulation to enhance performance. Further studies on polymer properties could improve formulation design.

Table 11. Wetting time evaluation of MDF of artemether

Formulation ID[#]	Wetting Time[a]			Mean[b]
	Experiment 1	Experiment 2	Experiment 3	
F1	16	15	18	16.33±1.25
F2	26	25	28	26.33±1.24
F3	15	14	17	15.33±1.25
F4	14	12	13	13.00±0.82
F5	13	15	17	15.00±1.63
F6	17	18	20	18.33±1.25
F7	23	24	20	22.33±1.70
F8	16	18	21	18.33±2.05
F9	23	25	21	23.00±1.63
# formulations containing variable amount of polymer; [a] = wetting time in seconds; [b] = mean±SD of 3 different experiments.				

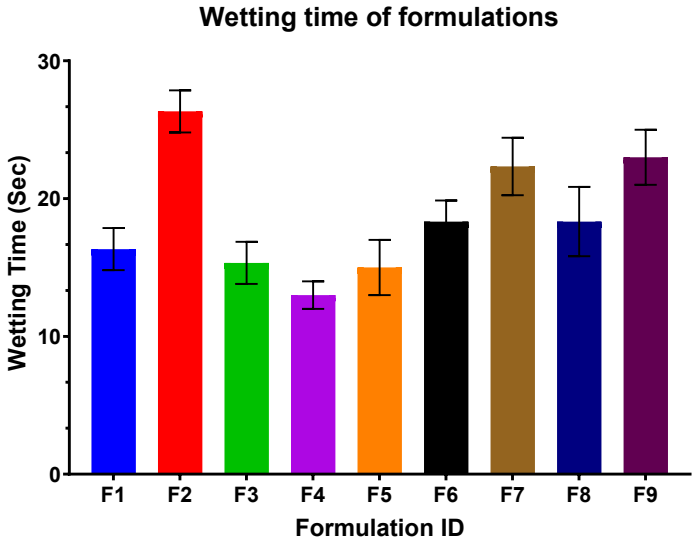

Figure 10. Comparative analysis of wetting time of mouth dissolving films formulations (F1-F9)

3.5.6 Disintegration time evaluation of MDF of artemether

The disintegration time for nine formulations (F1–F9) ranged from 17.33 seconds (F4) to 31.67 seconds (F2), reflecting varied polymer-driven breakdown rates. F4 and F8 showed the fastest disintegration (17.33 ± 0.94 and 19.00 ± 0.82 seconds), ideal for rapid-release applications, while F2, F7, and F9 were slowest (30.00–31.67 seconds). F1 and F3 exhibited the highest reproducibility (SD = 0.47), whereas F2, F5, F6, and F7 had higher variability (SD = 1.25). Faster disintegration likely stems from porous or less cohesive matrices, while slower times suggest denser structures. F4 and F8 are optimal, but F2, F7, and F9 may need reformulation. Further polymer studies could enhance disintegration performance.

Table 12. Disintegration time evaluation of MDF of artemether

Formulation ID[#]	Disintegration Time[a]			Mean[b]
	Experiment 1	Experiment 2	Experiment 3	
F1	22	21	22	21.67±0.47

F2	32	30	33	31.67±1.25
F3	21	22	21	21.33±0.47
F4	18	18	16	17.33±0.94
F5	24	21	22	22.33±1.25
F6	19	21	22	20.67±1.25
F7	32	31	29	30.67±1.25
F8	18	19	20	19.00±0.82
F9	31	30	29	30.00±0.82
# formulations containing variable amount of polymer; [a] = disintegration time in seconds; [b] = mean±SD of 3 different experiments.				

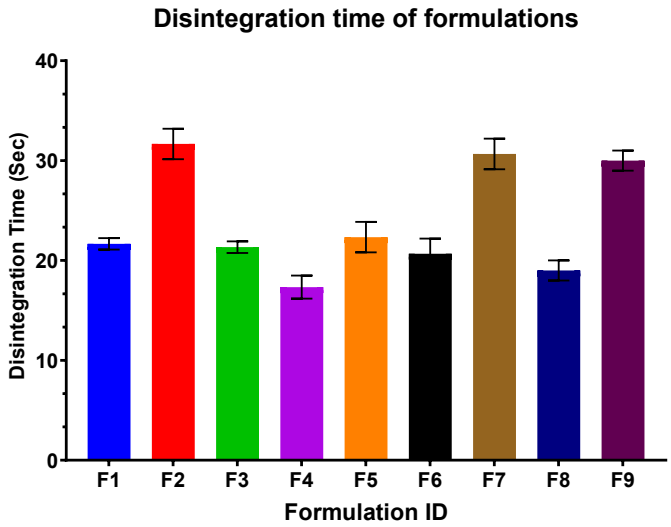

Figure 11. Comparative analysis of disintegration time of mouth dissolving films formulations (F1-F9)

3.5.7 Surface pH evaluation of MDF of artemether

The surface pH of nine formulations (F1–F9) ranged from 6.66 (F4) to 6.78 (F5), all near-neutral, suggesting suitability for biocompatible applications like pharmaceutical films. F1, F2, F6, and F7 showed high consistency (SD = 0.01), while F4 and F9 had slightly higher variability (SD = 0.02). The narrow pH range indicates limited impact of polymer variations, possibly due to buffering effects. F5 and F8's slightly higher pH may reflect basic components, while F4's lower pH suggests a more acidic matrix. All formulations are promising, but F4 and F9 could benefit from processing optimization. Further studies on polymer-pH relationships could enhance formulation design.

Table 13. Surface pH evaluation of MDF of artemether

Formulation ID[#]	Surface pH			Mean[a]
	Experiment 1	Experiment 2	Experiment 3	
F1	6.69	6.66	6.68	6.68±0.01
F2	6.72	6.7	6.73	6.72±0.01
F3	6.75	6.72	6.74	6.74±0.01
F4	6.65	6.64	6.68	6.66±0.02
F5	6.78	6.76	6.79	6.78±0.01
F6	6.73	6.71	6.7	6.71±0.01
F7	6.74	6.72	6.71	6.72±0.01
F8	6.77	6.75	6.74	6.75±0.01
F9	6.76	6.74	6.72	6.74±0.02

formulations containing variable amount of polymer; [a] = mean±SD of 3 different experiments.

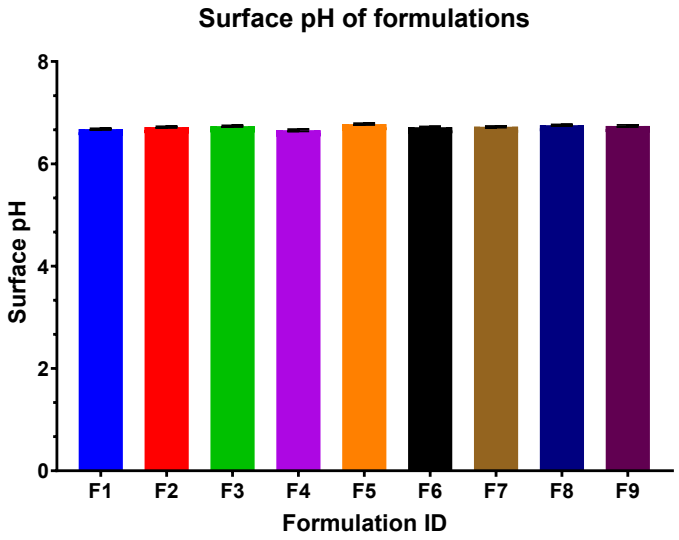

Figure 12. Comparative analysis of surface pH of mouth dissolving films formulations (F1-F9)

3.5.8 Percent drug release evaluation of MDF of artemether

The percent drug release for formulations F1–F9 ranged from 80% (F7) to 91% (F4), with F4 showing the highest release and good consistency (SD = 1.63%). % weight variation ranged from 21.28% (F7) to 24.37% (F9), with F4 exhibiting the lowest variability (SD = 0.59%). F4's high release and uniformity make it ideal for efficient drug delivery, while F7's low release suggests suitability for controlled release. F2 and F5 showed higher variability in both parameters, indicating potential instability. F1 and F5 offer strong release but need improved uniformity. Further polymer studies could optimize performance and consistency.

Table 14. Percent drug release evaluation of MDF of artemether

Formulation ID[#]	Percent drug release			Mean[a]
	Experiment 1	Experiment 2	Experiment 3	
F1	86	88	90	88±1.63
F2	82	85	88	85±2.45
F3	86	89	85	87±1.70
F4	91	93	89	91±1.63
F5	88	85	90	88±2.05
F6	86	84	83	84±1.25
F7	79	82	80	80±1.25
F8	85	83	86	85±1.25
F9	84	85	82	84±1.25
# formulations containing variable amount of polymer; [a] = mean±SD of 3 different experiments.				

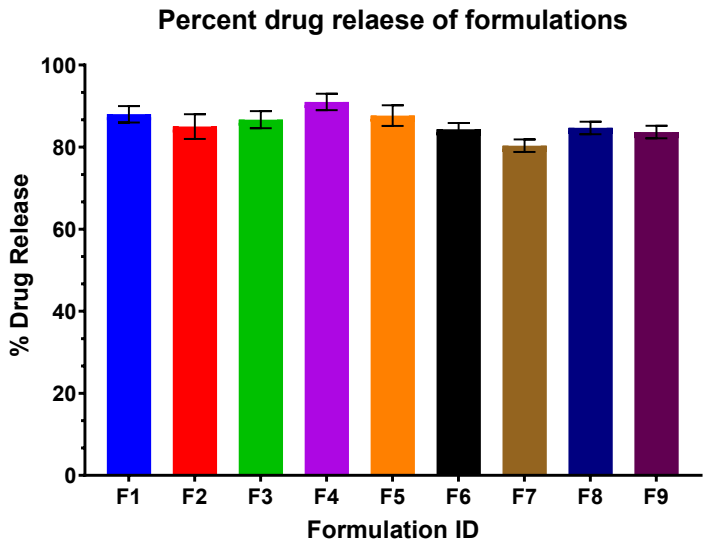

Figure 13. Comparative analysis of % drug release of mouth dissolving films formulations (F1-F9)

Table 15. Percent drug release of formulation F4 with respect to time

Time (min)	Formulation (F4)			MEAN[a]
	Experiment 1	Experiment 2	Experiment 3	
0.5	28	30	35	31.0±2.94
1	35	40	38	37.7±2.05
2	51	59	54	54.7±3.30
3	60	65	57	60.7±3.30
4	81	84	76	80.3±3.30
5	79	87	80	82.0±3.56
6	87	83	85	85.0±1.63
7	91	93	89	91.0±1.63
[a] Mean±SD of three different experiments				

The highest release was found to be 91±1.63% of the formulation. The F4 formulation showed better drug release as compare to other formulation.

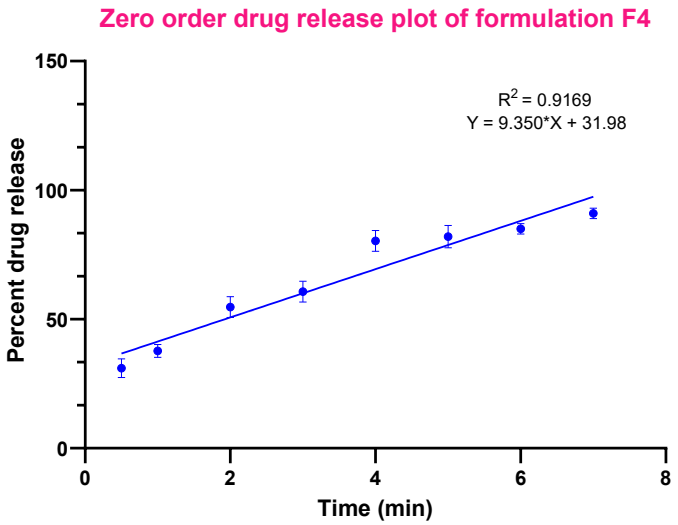

Figure 14. Graphical representation of Zero Order plot of formulation F4

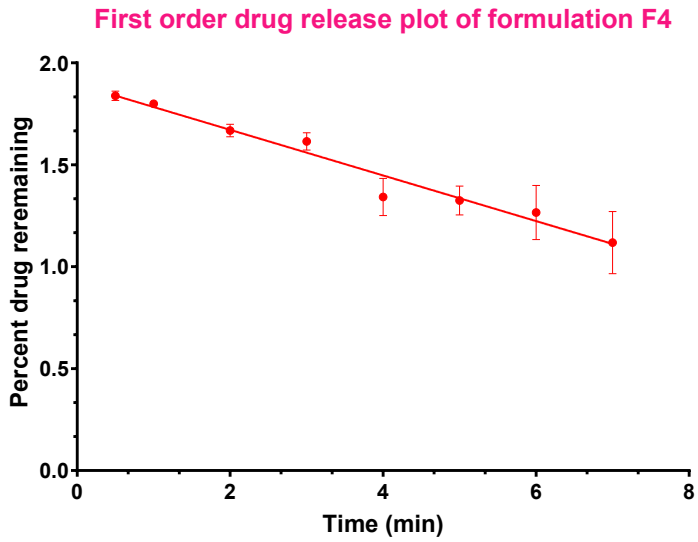

Figure 15. Graphical representation of first order plot of formulation F4

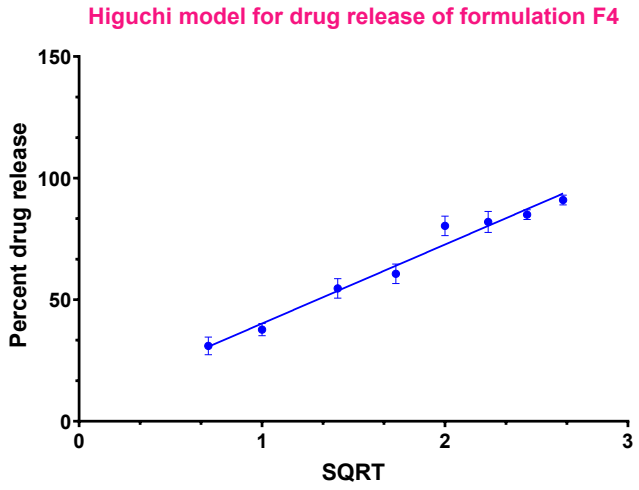

Figure 16. Graphical representation of Higuchi plot of formulation F4

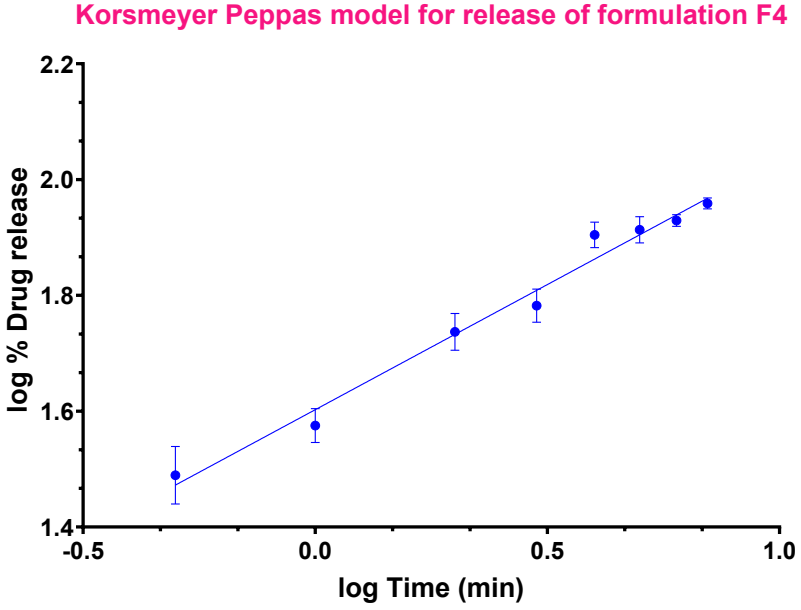

Figure 17. Graphical presentation of Korsmeyer-Peppas plot of formulation F4

CONCLUSION

The present research has demonstrated the successful development and comprehensive evaluation of mouth-dissolving films (MDF) of Artemether for the prevention and treatment of malaria. Employing the solvent casting method, a series of formulations were systematically optimized and subjected to rigorous assessment of key pharmaceutical parameters, including disintegration time, wetting time, percentage drug release, and folding endurance. Among the evaluated batches, the optimized film displayed a remarkably short disintegration time of 17.33 ± 0.94 seconds and achieved a high dissolution rate of 91 ± 1.63%, indicating its capacity for rapid drug release in the oral cavity and swift therapeutic onset.

The mechanical and physicochemical characteristics of the films, such as uniform thickness, satisfactory folding endurance, and good handling properties, further reinforce their suitability for practical use and patient acceptability. The buccal delivery approach enables bypassing of first-pass hepatic metabolism, thereby improving systemic bioavailability of Artemether, and addressing the limitations associated with conventional solid dosage forms—especially in populations with swallowing difficulties or poor access to water.

Taken together, these findings highlight the potential of Artemether MDF as an advanced, patient-friendly alternative for malaria management, offering rapid onset of action, improved efficacy, and better treatment adherence. The developed formulation can not only enhance therapeutic outcomes but also contribute to the broader public health goal of malaria control by providing a robust, easy-to-administer delivery system for use in diverse healthcare settings.

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