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DEVELOPMENT AND IN VITRO EVALUATION OF ACELOFENAC MOUTH DISSOLVING FILMS FOR REDUCED ANALGESIC ACTIVITY

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ABSTRACT
Background: The design of the current research work was to formulate mouth-dissolving films (MDFs) of aceclofenac (ACF) to improve patient compliance and convenience for older and younger patients, ultimately leading to improved therapeutic outcomes. ***Method:*** Evaluations were conducted on film formers such as HPMC and MC and film modifiers such as PEG and starch acting as solubilizing agents. ***Results:*** The physicomechanical qualities, in vitro disintegration time, and in vitro dissolving characteristics of the produced MDFs were assessed. Good mechanical qualities, including as tensile strength, folding durability, and percentage elongation, were demonstrated by every created MDF. FTIR, SEM, and X-RD analyses were used to assess MDFs. In contrast to other formulations, MDFs containing F8 provided superior dissolving properties. ***Conclusion:*** When pitted against other mixtures, the MDFs with sodium alginate (5%), methylcellulose (5%), and hydroxypropyl methylcellulose (HPMC)(5%) showed superior dissolving capabilities. In contrast to other mixtures, the F8 mixture, including HPMC, sodium alginate, and methylcellulose, demonstrated a complete and accelerated dissolution within 50 seconds. The mechanism behind this release is diffusion, as indicated by the release kinetics data.

INTRODUCTION

The mouth has long been thought to be the major frequent site for the administration of drugs. In 1847, Sobrero found that the oral cavity was the site of nitroglycerine absorption. Numerous active ingredients have since been researched for systemic or local application. New advancements in formulation technology have made oral dosing alternatives for pediatric, elderly, immobile, nauseated, or noncompliant patients feasible[1]. Research on creating new types of bioadhesive mucosal delivery systems, including adhesive tablets, gels, patches, and, more recently, flexible films for use in the mouth, has been the central area of study for MDFs. The mouth-dissolving films, a brand-novel and innovative drug administration method for oral medication administration, were created using the transdermal patch's technology. The delivery device is an extremely slit oral strip that is applied directly to the sufferers' tongue or any different oral mucosal layer. Saliva instantly hydrates the film, which then sticks to the utilization site [2]. After that, it melts

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and dissolves instantly, discharging the drug for immersion through the oral mucosa. Films have been produced using a variety of film formers, including chitosan, PA, PVP, maltodextrin, HPMC, hydroxy propyl cellulose (HPC), MC, and sodium carboxy methyl cellulose (NaCMC). Conversely, aceclofenac, a newer type of non-steroidal anti-inflammatory drug (NSAID) that effectively blocks cyclooxygenase-2 (COX-2), is an excellent choice for managing osteoarthritis, rheumatoid arthritis, toothache, and various other rheumatoid conditions. It also possesses strong anti-inflammatory, pain-relieving, and fever-reducing abilities. It is a highly permeable derivative of aryl acetic acid that is insoluble in water. It is classified as a class II drug under the BCS class. It has a short biological half-life of 4 to 4.3 hours and is heavily protein-bound. 100 mg of aceclofenac is often taken twice or three times a day. In addition to causing significant disruptions to therapy, the traditional dosage form of aceclofenac has specific unfavorable side effects, including peptic ulcers, gastrointestinal bleeding, and stomach upsets. Hence, developing sustained-release pharmaceuticals is an excellent way to decrease the frequency of doses, achieve a longer-lasting effect with better bioavailability, and enhance the medication's safety and effectiveness [3]. The quality of the polymers present in multiple batches of mucoadhesive aceclofenac tablets was assessed to formulate various in this research. This assessment covered carbopol 934, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose. [3].

One of the main benefits of oral films is the guarantee of a dose and treatment. This is caused, in part, by the decreased chances of spitting or choking. In contrast to conventional pharmaceuticals that might need to be chewed or swallowed with water, oral films offer a quick and secure way to take medicine. Patients using oral films must lay the thin strip on their cheek, beneath their tongue, or on top of it, and it will dissolve and administer the drug [4]. When aceclofenac is administered conventionally, side effects such as peptic ulcers, gastrointestinal bleeding, and disruptions in the gastrointestinal tract occur. This results in several inconveniences and fluctuations in therapy [4]. Hence, developing sustained-release pharmaceuticals is an excellent way to decrease the frequency of doses, achieve a longer-lasting effect with better bioavailability, and enhance the medication's safety and effectiveness [5].

In this study, various batches of buccal aceclofenac films were to be formulated utilizing multiple polymers, such as methylcellulose, hydroxypropyl methylcellulose, starch, and sucrose, and their quality control was to be evaluated [6-10].

MATERIAL AND METHODS

Materials: Pine apple taste, aspartame, and aceclofenac were acquired from Darwin Laboratories in Vijayawada. Colorcon Asia Ltd., India, provided the HPMC, sodium alginate, and MC. We bought methanol, starch, Calcium chloride dihydrate, Dipotassium hydrogen phosphate, potassium chloride, sodium chloride, and sucrose from Loba Chemie in Bombay. Every other reagent utilized was of analytical quality.

Preparation of Artificial Saliva: The following method was used to manufacture artificial saliva: $CaCl_2 \cdot 2H_2O$: 0.193g, magnesium chloride hexahydrate: 0.111 g, KCl: 1.2g, NaCl: 0.844g, and K_2HPO_4: 0.342g. These components were added one by one to five hundred mL of $D.H_2O$, and more water was added to raise the volume to 1000 mL. Using 0.1 N hydrochloric acid, the pH was raised to 5.7 [11].

Preparation of ACF MDFs: The first step in the solvent casting method is dissolving the methanol-soluble polymers in methanol at 1,000 rpm. Every additional excipient color, flavoring, sweetener, etc., is dissolved in its way. After that, the two solutions are well combined while stirred at 1,000 rpm. The resulting solution is combined with the API dissolved in an appropriate solvent. By using a vacuum, the trapped air is released. After the resultant solution is dried and molded into a film, it is cut into pieces of the required size. Table No.1 provides the formulation codes [12].

Drug-Excipient Compatibility Studies (FTIR Studies): Attenuated total reflectance (ATR) method: In Germany, the Bruker ATR-FTIR spectrometer was employed to examine the samples. With a resolution of 1.0 cm−1, the ATR spectra were captured within the frequency range of 4000–500 cm−1. The sample spectrum was achieved by merely positioning the film sample or powder on the ATR crystal. This method is utilized, particularly for organic and inorganic substances, to research chemical composition, identify functional groups, and ascertain chemical structure [12].

X-RD Analysis

The Bruker D8 sophisticated diffractometer, located in Karlsruhe, Germany, was employed to analyze materials using

cu-kα X-ray radiation, with an energy of 1.54060A, under a power level of 45 kV and approximately 40 mA. With a scanning speed of 1 /min, the diffraction patterns of X-rays were captured over a 2θ range from 4 to 44°. The positions and strengths of the diffraction peaks were considered when identifying Aceclofenac in different samples. Used to quantify the amount that X-rays diffract through a material's crystal lattice, giving insight into the arrangement of molecules and atoms inside crystalline samples. Crystal structure, symmetry, lattice parameters, and crystallographic phases can all be found via XRD [12].

SEM Analysis

Scanning electron microscopy (SEM-JEOL, JSM-840A, Japan) analyzed the movie's form and outer texture. The specimens to be examined were positioned on the SEM sample holder with double-sided tape. An ion sputtering machine (JEOL, JFC-1100 E, Japan) was employed to apply a gold coating to the samples for five minutes at a low pressure of 0.001 torr to enhance their conductivity. Gold can be applied to materials' external surfaces to create binding or active sites, crucial for adsorption and catalytic processes [12].

Table No: 1 Formulae of Buccal Patch (%/film)

Ingredients(%/patch)	ACF1	ACF2	ACF3	ACF4	ACF5	ACF6	ACF7	ACF8
ACF	100	100	100	100	100	100	100	100
HPMC	--	5	--	5	--	5	--	5
Methyl Cellulose	--	--	5	5	--	--	5	5
Sodium alginate	--	--	--	--	5	5	5	5
Methanol	10	10	10	10	10	10	10	10
Starch	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PEG	1	1	1	1	1	1	1	1
Sucrose	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Pineapple flavor	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Aspartame	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Evaluation Parameters for ACF MDFs

Morphological Properties: The characteristics of uniformity, hue, clarity, and texture were all observed with the naked eye. Over six months, every mixture was evaluated monthly and stored at room temperature (25±3°C) and approximately 65±5% relative humidity. The moves came in packets made of aluminum foil [13].

Drug Content: In a 10 mL volumetric flask, one cm2 film was collected and dissolved in five milliliters of methanol, with methanol accounting for the remaining volume. After properly diluting the samples, synthetic saliva's absorbance at 273 nm was determined. Three separate estimations were made[13].

Variation of Mass: A digital scale was utilized to document the weight of a 1 cm^2 film across various lots of the mixtures. Three distinct approximations were calculated.

Thickness: A screw gauge with a precision of 0.001 mm and a range from 0 to 10 mm was employed to determine the thickness of the film. Once the pointer was aligned with zero on the gauge, the film was inserted, and the anvil of the thickness gauge was rotated. The film was positioned on the anvil, and the measurement on the dial was noted down. Three separate measurements were taken [13].

In Vitro Disintegration Studies: The disintegration time provides information on the film's dissolution and disintegration characteristics. Regarding MDFs, it is difficult to discern between the dissolution and disintegration processes. It is challenging to replicate these natural settings and measurements using a suitable approach if the MDF disintegrates when it dissolves in a tiny quantity of saliva simultaneously. Nonetheless, two disintegration techniques were used in the current study [13].

Drop Method: During the initial method, a pipette was used to add a single drop of distilled water to the oral films. Once the films were positioned on the glass slide, it was gently pressed onto a Petridis. The duration required for the film to deteriorate and form a hole was measured. Three separate predictions were recorded [13].

Petridish Method: Using this procedure, two milliliters of distilled water were put in a Petridis, one film was placed on the water's surface, and the amount of time needed for the oral film to dissolve entirely was calculated. Both approaches were used to study drug-loaded films, and three different estimations were made [13].

Tensile Strength: The maximum force exerted on the point where the film sample fractures is referred to as its tensile strength. This value is calculated as follows: the force required to break the film divided by the area of the film's cross-section.

$$Tensile\ strength = \frac{load\ at\ failure}{film\ thickness\ \times\ film\ width} \times 100$$

This was determined through the Shimadzu AG-100kNG (Winsoft tensile and compression testing) device. The film, measuring 3x2 cm^2 and in flawless condition, was positioned between two clamps, with a gap of 10 mm. The film was stretched at a rate of 5 mm per minute using a clamp. The entire experiment was repeated thrice [13].

Percent Elongation (% E): Strain is the term used to describe the stretching of a film sample under stress. Strain is essentially the distortion of the film divided by its original dimension. In general, the film elongation rises with the concentration of the plasticizer. After determining the tensile strength, the film's length increase was calculated using the formula provided to find the percentage elongation[13].

$$\%\ Elongation = \frac{L - L_0}{L_0} \times 100$$

where L = final length and L_0 = initial length. The estimations were carried out in triplicate.

Young's Modulus: The rigidity of a film is gauged by its Young's modulus, sometimes referred to as elastic modulus. In the area of elastic deformation it is represented by the following fraction of the force applied to the material divided by the resulting change in length:

$$Young's\ modulus = \frac{Slope}{film\ thickness \times cross\ head\ speed} \times 100$$

A tough, rigid coating with minimal stretching has a high tensile strength and Young's modulus. Three distinct calculations were conducted [13].

Folding Endurance: To measure folding endurance, the film was repeatedly folded at the same spot until it broke. This provides a hint as to how fragile the film is. The folding endurance value was calculated as the number of times the film could be folded without breaking. Three different estimations were made [14].

In Vitro Dissolution Studies: In the in vitro dissolution tests, 500 milliliters of synthetic saliva served as the liquid to dissolve the substances, in addition to a specialized type 5 dissolution apparatus. The experiment was conducted at a speed of 50 revolutions per minute and a temperature of 37 degrees Celsius. As shown in Figure 1, each film was positioned on a watch glass with a nylon wire mesh covering it. With dimensions suitable for 100 mg of ACF. Then, a dissolving flask was filled with the watch glass. Five milliliter samples were removed and swapped out with five milliliters of brand-new dissolving media at intervals of 10, 20, 30, 40, 50, 60, 80, 100, and 120 seconds. The absorbance of the samples was measured at 273 nm for analysis. Three separate dissolving experiments were carried out [14].

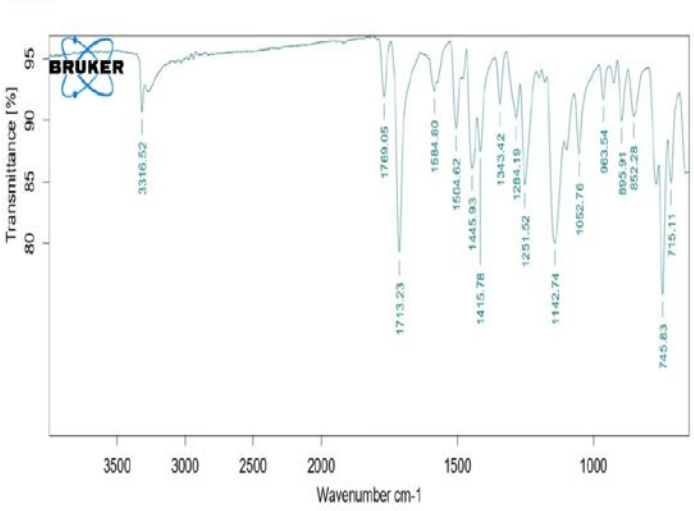

Figure 1: FTIR Spectrum of Aceclofenac pure drug

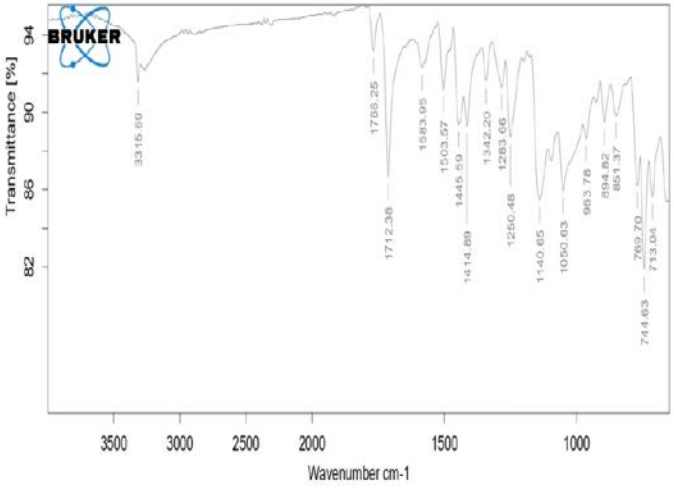

Figure 2: FTIR Spectrum of optimum formula

RESULTS AND DISCUSSION

Preparation and Physical Characterization of ACF MDFs.

Initially, different polymers were used to make the placebo MDFs. These included sodium alginate, starch, and methanol as minor excipients and significant polymers like HPMC and MCC. Ultimately, a subset of the trials' outcomes was chosen for additional research and development. The formulation was supplemented with an appropriate amount of ACF (equal to 100 mg of Aceclofenac base), and MDFs were created. The drug's crystallization was seen with polymers HPMC MCC over time. Hence, these two polymers were not included in the research. Various ACF MDFs were made using sodium alginate C, HPMC, and MCC according to the formulas listed in Table 1.

FTIR Studies: The ethyl ester's infrared absorption band in pure ACF was seen at 1297 cm^{-1}, sulfonic acid salts at 1196 cm^{-1}, aliphatic ethers at 1115 cm^{-1}, and the dihydropyridine ring's stretching vibration of the N–H bond at 2890 cm^{-1}. The MDFs retained each of these unique ACF infrared absorption bands. These results demonstrate that there is no interaction between the excipients of the MDFs and ACF. There were spectra visible in Figures 1 and 2.

X-RD Studies: To explore the structural characteristics of ACF within MDFs, these research efforts were conducted on a selected group of ACF MDFs. ACF exhibited distinct peaks at 6.5°, 22.6°, 23.6°, and 25.93° 3θ. The X-ray diffraction patterns of the ACF MDFs displayed minimal to no signal compared to the expected peaks of pure ACF. This could be attributed to the spread-out arrangement of ACF within the MDFs. The SEM images and X-ray diffraction tests show that the ACF in MDFs was not arranged in a crystalline form.

SEM Analysis: The created ACF MDFs were transparent and colorless on a macroscopic level. The selected MDFs' 2500x magnification SEMs and pure ACF are shown in Figures Nos. 3 and 4. The uniform distribution of ACF is suggested by the smooth surfaces of the MDFs, which were free of transverse striations and scratches, as seen in the SEM pictures. No ACF crystals were seen in the MDFs.

Morphological Properties: The consistency, clarity, hue, and silkiness of ACF MDFs were examined visually; the results are shown in Table 2. When contrasted with the initial characteristics, all the properties of the formulations remained unchanged over the 6 months, and no ACF crystals formed.

Drug Content: 1 cm^2 films were cut from various locations throughout the picture, and the amount of ACF was approximated. The outcomes are displayed in Table 2. These findings showed that ACF was well-uniformed within the films and generally well-soluble in the formulations.

Variation of Mass: 1 cm^2 films were cut and weighed from various batches. The outcomes are displayed in Table No. 2. Three batches of films yielded the same mass, demonstrating the consistency of the formulation and processing process.

Thickness: To evaluate how consistent the preparation method is, the thickness of the MDFs was measured at various points with a screw gauge. Approximately 90% of the film's initial thickness was eliminated throughout the drying stage. The results are shown in Table 2. It was observed that the thickness was uniform throughout. Compared to cinema lacking sodium alginate and sucrose, MDFs containing HPMC and MC it displayed a more significant mass variation and a greater film thickness, indicating a greater drug concentration Table 2.

Disintegration Time: Table 2 displays the disintegration time results. According to these findings, the F8 formulations decomposed more quickly than the MC and HPMC formulations. Compared to MDFs with other compositions, the ACF MDFs, including HPMC, MC, and SA, disintegrated more quickly. The F2 and F8 formulations dissolved/disintegrated more rapidly than the other formulations when using the petri dish method.

Elastic modulus, percent elongation, and tensile strength: MDFs ought to have a high percentage of drug release, low EM, a high percentage of elongation (% E), and a moderate tensile strength. According to the results, all films had modest tensile strength values. Compared to other formulas, films of formula F8 displayed the highest percentage E, while films of formula F2 had the lowest EM. The outcomes are displayed in Table 3.

Folding Endurance: Every MDF has been prepared with respectable folding endurance. F4's folding endurance is higher compared to other MDFs. The outcomes are displayed in Table 3.

Table 2: Physicomechanical properties of different ACF MDFs

Code	Drug content (mg/cm^2) (n=3)	Mass variation (mg)	Thickness (μm) (n=6)	Disintegration time (sec)					
				Drop method (n=3)	Petri dish method (n=3)	Tensile strength (N/cm^2)	Elasticity modulus (N/cm^2)	Folding endurance	% Elongation (cm %)
ACF1	0.82±0.21	2.98±0.75	48.3±0.62	20.58±0.85	35.62±0.95	2.65±0.24	3.51±0.52	98±0.11	85.32±0.84
ACF2	1.52±0.62	2.57±0.35	52±0.75	20.62±0.14	31.57±0.41	3.12±0.62	2.96±0.75	92±0.66	81.62±0.11
ACF3	1.62±0.84	3.24±0.24	38.35±0.62	26.52±0.32	22.68±0.63	2.47±0.24	2.48±0.53	111±0.51	96.35±0.62
ACF4	0.985±0.62	3.25±0.62	58.95±0.24	23.54±0.95	35.14±0.57	1.86±0.25	3.52±0.15	117±0.49	72.96±0.52
ACF5	1.24±0.48	3.85±0.85	59.54±0.35	20.48±0.75	25.95±0.96	2.55±0.85	1.67±0.59	102±0.82	82.51±0.63
ACF6	1.51±0.95	3.42±0.96	60.42±0.28	21.62±0.14	45.85±0.25	2.95±0.95	2.57±0.86	106±0.95	88.42±0.85
ACF7	1.27±0.74	3.14±0.24	58.47±0.95	22.95±0.62	41.24±0.15	3.62±0.75	2.94±0.84	98±0.27	70.59±0.97
ACF8	1.92±0.62	3.57±0.12	60.47±0.84	19.47±0.58	19.15±0.11	3.59±0.32	6.25±0.52	94±0.48	91.55±0.45

Table 4: Drug release kinetics data

Formulations	DP10 (mean ± SD)	$R2$ (first order plot)	Mean "k" (sec−1) (0–50 sec)	Higuchi constant KH (sec−1/2)	$R2$ (Higuchi plot)
ACF1	9.57±0.25	0.977	0.051	8.63	0.938
ACF2	15.69±0.84	0.962	0.063	11.52	0.977
ACF3	21.85±0.62	0.978	0.051	9.78	0.986
ACF4	24.68±0.15	0.991	0.031	10.63	0.967
ACF5	18.42±0.59	0.956	0.085	11.85	0.986
ACF6	20.58±0.84	0.976	0.014	10.89	0.971
ACF7	24.68±0.75	0.987	0.065	8.63	0.981
ACF8	28.18±0.35	0.998	0.096	14.25	0.963

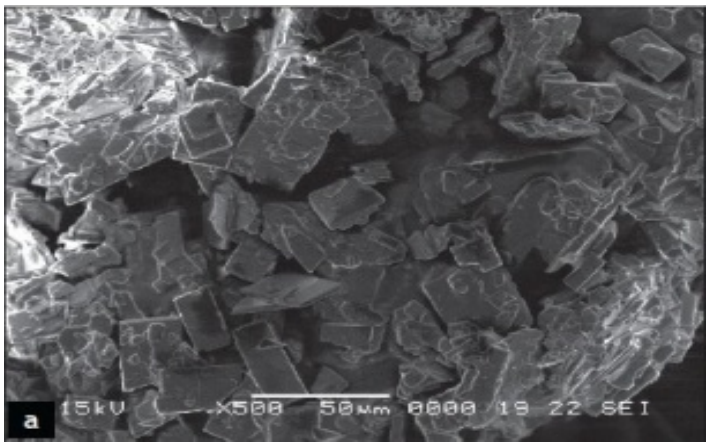

Figure 3: SEM photographs of pure Aceclofenac

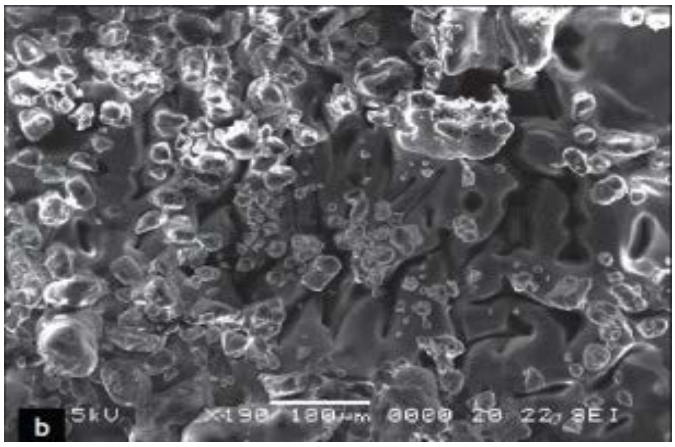

Figure 4: SEM photographs of optimized formula (F8)

***In Vitro* Dissolution Studies:** Figures 5 and 6 show the in vitro dissolution patterns of the ACF MDFs. Eight distinct formulations of ACF were created using sodium alginate, starch, and sucrose as film-forming polymers, along with HPMC, MC, and other ingredients. After 10 seconds, the cumulative percent ACF released for F1 through F4 is 26.85±0.23, 99.61±1.47, 98.68±1.32, and 99.63±0.40, respectively. For F1 through F4, the complete ACF release was achieved at 350, 150, 200, and

150 seconds, respectively. Figures 5 and 6 display the comparative release profile. After 10 seconds, the cumulative percent ACF released for F5 to F8 is 99.98±0.23, 98.34±1.47, 96.68±1.32, and 101.63±0.40, respectively. For F5 through F8, the ACF release was obtained at 350, 200, 200, and 50 seconds, respectively. Figures 5 and 6 display the comparable release profile. Overall, F1>F5>F7>F6>F3>F4>F2>F8 is the order of %ACF dissolution from MDFs. Additionally, the impact of solubilizing and/or wetting agents on the dispersion of ACF was examined. Compared to the other mixtures, the total percentage of F8 demonstrated superior dissolving characteristics.

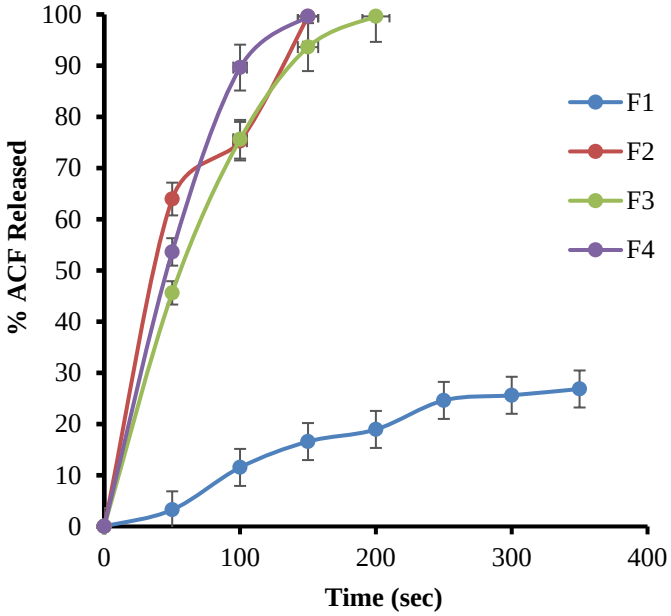

Figure 5: Drug release characteristics of (F1-F4)

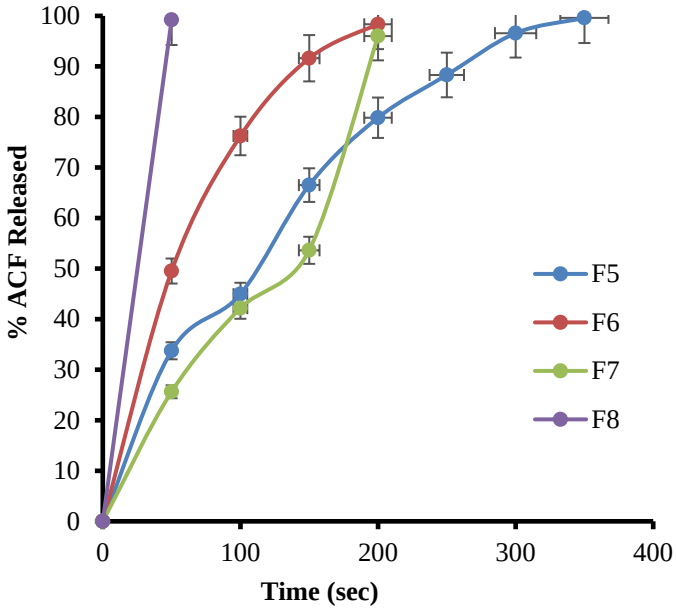

Figure 6: Drug release characteristics of (F5-F8)

Drug Release Kinetics: To gain a deeper insight into the patterns of drug release from ACF MDFs formulations, the information on drug release collected over different time intervals was adjusted into kinetic equations, including zero order, first order, and Higuchi models. The correlation coefficient (*R*2) and the rate constant for release (RRC) of ACF MDFs, as derived from the dissolution data from 0 to 50 seconds, are presented in Table 4. The "k" values were distributed as follows overall: F6>F8>F3>F1>F5>F4>F7>F2. Values for F2 and F5, which contained three excipients, were considerably higher when compared to "k." The "k" value for Formulation 8 was noticeably higher than the other seven formulations. The Higuchi square root model was pinpointed as the release method, showing increased correlation coefficient values (0.968) across all formulations. The outcomes are displayed in Table No. 4. According to the results above, the F8 had the greatest rate of dissolution and the shortest in vitro disintegration times, which were suitable for MDFs.

CONCLUSION

It is clear from this study that ACFs can be effectively formed into MDFs. The MDFs made using sodium alginate, MC, and HPMC formers all had excellent physicomechanical and dissolving qualities. Out of the eight formulations made, the F8 formulation produced the highest in vitro ACF release (101.92 ± 1.15% after 50 seconds). By the conclusion of the six-month trial (at a temperature of 25°C and a humidity of 65%), the characteristics of the MDFs, including their uniformity, clarity, hue, and smoothness, remained unchanged compared to their starting condition, precisely, there was no formation of ACF crystals observed. These findings demonstrate the stability of ACF in MDFs. Compared to the currently available formulations, such as IR and ODTs, the proposed ACF MDFs may offer a quicker onset of action, increased oral bioavailability, improved patient compliance, and therapeutic efficacy.

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FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Bharathi Arigela was responsible for designing the study and planning it, including its objectives. Chandra Sekhar Naik D reviewed the manuscript and edited the article. Venkata Suresh Babu Agala and Cherukuri Vidyulatha Chowdary conducted the work, gathered data, and authored the manuscript.

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