RESEARCH ARTICLE

Formulation Optimization and Evaluation of Herbal Films Containing Ethanol Leaves Extract of *Cassia auriculata* to Treat Chronic Constipation Disorder

Brahmaiah Bonthagarala[1], Seetha Devi Alla[2], Sudarshan Rao Nagineni[1], Rama Rao Vadapalli[1], Sri Rekha Malakapurapu[3*]

[1]*Department of Pharmaceutics, Shri Vishnu College of Pharmacy (Autonomous), Bhimavaram, Andhra Pradesh, India*
[2]*Department of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Nizampet, Hyderabad, India.*
[3]*Department of Pharmaceutics, Hindu College of Pharmacy, Guntur, Andhra Pradesh, India.*

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ABSTRACT

An intriguing trend in recent years has been the designing of oral films containing extracts from medicinal plants. Therefore, efforts were made in the current work to create fast-dissolving herbal films using *Cassia auriculata* ethanol leaf extract in order to create a dosage form that would be more convenient to administer and treat chronic constipation disorders in the elderly. Varying ratios of hydroxy propyl methyl cellulose as polymer, propylene glycol as film softener, and a solvent-casting approach were utilized to create the quickly dissolving herbal films of *C. auriculata* leaf extract. A number of quality control measures, including weight fluctuation, thickness variation, surface pH, percentage moisture uptake, percentage moisture loss, disintegration time and folding endurance, were assessed. According to the findings, every film had a decent appearance, a smooth texture, was free of particle matter, and had excellent folding endurance. According to a content uniformity analysis, the drug is dispersed evenly across the entire film, and each one dissolves in less than 95 seconds. *In-vitro* dissolving studies using Paddle type apparatus in pH 6.8 phosphate buffer pH 6.8, which is simulated saliva, were performed for each film composition. Out of all nine formulations, formulation F5, which is an herbal film with 10% propylene glycol and 40% HPMC, exhibited complete drug release (99.6%) in 30 minutes and had a strong folding endurance value. The release of medication from films was found to follow a first-order kinetics. Overall, studies indicate that the most feasible dose form that can be used in medical settings for the treatment of chronic constipation disorder is fast-dissolving herbal films containing *C. auriculata* leaves extract. This is especially true for patients who have difficulty swallowing.

Keywords: Herbal films, *Cassia auriculata*, Constipation, HPMC, Propylene glycol, Solvent casting method.

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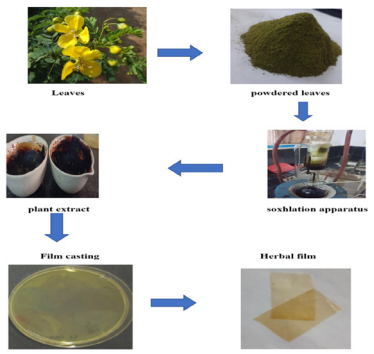

GRAPHICAL ABSTRACT

INTRODUCTION

One of the most prevalent gastrointestinal issues in the world is constipation. Over 4 million Americans experience constipation on a regular basis; women and individuals 65 years of age and older are the most likely demographics to report constipation. Constipation affects people of all ages, but as people become older, ailments tend to impact them more frequently. Most of the time, constipation is transient and not dangerous, and it affects almost everyone at some point in their lives. Anal fissures or hemorrhoids are two significant consequences that can arise from constipation. Hard stool brought on by constipation may result in rectal hemorrhage.

*Author for Correspondence: rekhashankarsutari@gmail.com

Self-treatment of constipation using over-the-counter (OTC) laxatives is by far the most popular help, while treatment depends on the reason, severity, and length of constipation. In America, the annual cost of laxative products is estimated to be $725 million.[1]

Since oral delivery is the preferred method for administering most therapeutic agents because of its simplicity of usage, pain avoidance, and the inexpensive cost of treatment, some patient classes, particularly those with dysphasia, geriatric, and pediatric patients, feel it challenging to consume typical oral bulk dose forms such as capsules and tablets, because they are afraid of choking. However, the stability of the most practical liquid dosage forms, such as syrups and solutions, is restricted. In the late 1970s, oral fast dissolving films (OFDF) were a novel formulation designed as an option to adolescents and elderly people who struggle to swallow conventional oral dosage forms such as tablets and capsules.[2]

Oral fast-dissolving films (OFDFs) are thin strips with a tendency to break down and disintegrate swiftly in a matter of seconds, releasing the medication for intragastric or oral mucosal absorption. Because they prevent swallowing issues, they provide several benefits in comparison to conventional dosage forms like tablets and capsules. In the pharmaceutical industry, fast-dissolving films have gained significant prominence recently because of their special qualities and benefits, which include improved patient compliance, accurate dosing, quick onset of action, good mouthfeel, easy handling, portability, and an absence of the need for water for disintegration.[3]

Researchers are currently developing OFDFs that exhibit notable therapeutic activities that include antioxidant, anti-inflammatory, antibacterial, antiviral, antimigraine, antiarrhythmic, and immunomodulatory properties by combining active phytoconstituents such as flavonoids, polyphenols, glycosides, saponins, and so on alongside herbal extracts. Seeing these films may help manage dementia, cerebral insufficiency, and Alzheimer's disease.[4] As a result, the current study emphasizes the development and assessment of herbal extract-loaded OFDFs derived from the leaves of *Cassia auriculata* to treat chronic constipation conditions.

MATERIALS AND METHODS

Materials

In and around Guntur, Andhra Pradesh, India, *C. auriculata* leaves were harvested straight from the plant. Merck Laboratories in Mumbai provided HPMC. The suppliers of sodium starch glycolate and propylene glycol were Fishers Scientific in Mumbai. All of the remaining substances were pure and of analytical quality.

Methods

Extraction and characterization of leaves

collection, authentication and processing of plant material The leaves of the *C. auriculata* are distributed all over India. As a result, new leaves were gathered from the surrounding area of Guntur, and Dr. Ramaiah, Head of the Department of Pharmacognosy at the Hindu College of Pharmacy, University College of Acharya Nagarjuna, Guntur, Andhra Pradesh, India, verified that the plant is C. auriculata.

Leaves collected have been left to dry at ambient temperature in the shade. Before being used, the dried leaves were finely pulverized and kept in an airtight container. Next, ethanol was used to extract the Phytoconstituents from the coarse powder through the soxhlation process, and this procedure was carried out in eight cycles. After the solvent evaporated, the extract was dried was, gathered and stored using a desiccator until needed again.[5]

Phytochemical investigation

By using established procedures.[6], numerous active chemical components, including glycosides, alkaloids, phenolic compounds, flavonoids, tannins, steroids, diterpenoids, and triterpenoids, were examined in the resultant extract, and the findings of phytochemical screening are shown in Table 1.

Preformulation Studies

Compatibility studies by FTIR spectroscopy

Functional group identification is best accomplished *via* FTIR spectroscopy, which analyzes the infrared portion of electromagnetic spectra. The drug and polymer compatibility were examined using FTIR spectrum analysis.[7] The FTIR (Bruker) was used in the current investigation to record FTIR spectra of leave's extract of *C. auriculata* and the physical mixture of extracts and excipients, HPMC and propylene glycol. The resulting spectra are depicted in Figures 1-3.

Construction of standard Curve for C. auriculata leaves extract

The preparation of a stock solution involved dissolving 10 mg of precisely weighed *C. auriculata* leaf extract in 100 mL volumetric using pH 6.8 buffer. Subjected to sonication to get a clear stock solution (100 µg/mL). varying samples 1 to 5 mL were pipet out into 10 mL volumetric flask and volume made up to 10 mL to yield final concentrations of 10, 20, 30, 40, and 50 µg/mL. Then absorbances were measured using a UV-visible spectrophotometer at λ_{max} 274 nm and the results are shown in Table 2, Figure 4.

Formulation development

using a solvent casting technique, nine distinct formulations (F1–F9) with compositions listed in Table 3 were created. The ingredients included sucrose (Sweetener), citric acid (Salivary stimulating agent), sodium starch glycolate (Superdisintegrant), propylene glycol (Plasticizer), and HPMC (Film-forming agent). The herbal films are made by solvent casting procedure, which involves dissolving weighed quantities of medicine and excipients in the needed volume of water, then casting the solution to a glass plate and allowing it to evaporate the solvent. Finally, all films were carefully retrieved, and a 6 cm^2 portion was punched out, rolled in wax paper and kept in a desiccator until analysis.[8]

The following formula can be used to determine how many films are made for each batch.

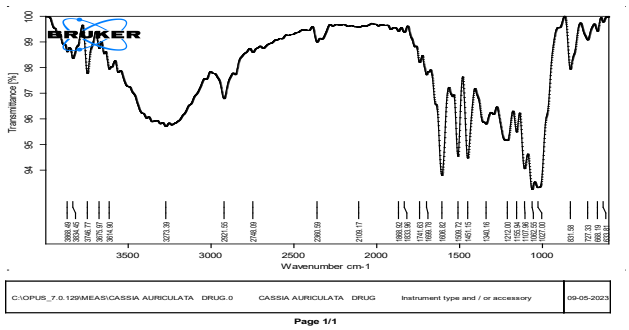

Figure 1: FTIR Spectrum of ethanol extract of *C. auriculata* leaves

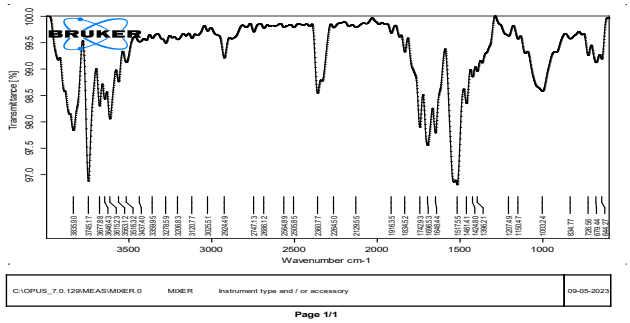

Figure 2: FTIR spectra of physical mixture (*C. auriculata* leaves extract+ HPMC+ Propylene glycol)

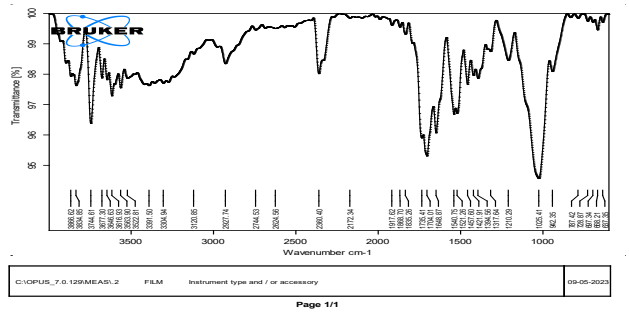

Figure 3: FTIR spectrum of optimized herbal film

Total an area of petri dish = 63.64 cm^2
Area of single film = 3×2 = 6 cm^2

Total number of films made in a batch = 63.64/6 = 10.6
There were about eleven films produced.

Evaluation of Fast-Dissolving Herbal Films

Morphological properties

Visual observations were made to identify morphological characteristics, such as color, transparency, surface roughness, and the homogeneous nature of the film.[9]

Uniformity of weight

About 20 films were individually weighed in order to determine the average weight and determine the weight variance of the herbal film. The weight of two films can vary from a mean to a maximum of 7.5% in order for the film to be approved; no film may depart by more than 15%.[10]

Table 1: Data from a phytoconstituents screening

S. No	*Test for phytoconstituents*	*Result*
	Carbohydrates and glycosides	+
	Alkaloids	-
	Steroids	+
	Saponins	+
	Proteins and free amino acids	+
	Tannins	-
	Flavonoids	+

+ Presence of phytoconstituents
- Absence of phytoconstituents

Table 2: Data for plotting standard curve for ethanol leaf extract of *C. auriculata*

Concentration (µg)	*Absorbance (nm)*
0	0
10	0.049
20	0.094
30	0.122
40	0.172
50	0.225

Uniformity of film thickness

At five key locations, the films' thickness was tested with a screw gauge. Thus, aids in ascertaining the homogeneity of fast-dissolving herbal film thickness, which is directly related to dosage accuracy.[11]

Folding endurance

Folding endurance validated the facts about the films' physical capabilities and flexibility. Films were repeatedly folded hard in the middle to measure it. The folding endurance value was computed by counting the number of folds needed to fracture the film.[12]

Surface pH

To ascertain any potential *in-vivo* adverse effects, the fast-dissolving film's surface pH was measured. For this, pH strips that are sold commercially were employed. A petri dish containing the film to be tested was briefly moistened with water. A pH strip that was in touch with the oral film's surface was used to measure the pH. For every formulation, the mean from three estimations is calculated.[13]

Swelling index

Stimulated salivary fluid is used to compute the film's swelling index. After the film sample has been weighed, it is put onto a calibrated wire mesh, which is submerged in the mortar containing 50 mL of the stimulated salivary medium. The mass of the film was measured at regular time intervals until consistent weight was obtained.

Following formula was used to compute extent of swelling.[14]

Swelling Index (SI)= $w_t - w_o / w_o$

Where, w_t is final weight and w_o is film initial weight

Table 3: Formulation composition of fast dissolving herbal films

Components	*Formula code*								
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
C. auriculata leaves extract (%)	30	30	30	30	30	30	30	30	30
HPMC (%)	30	30	30	40	40	40	50	50	50
Propylene glycol (%)	5	10	15	5	10	15	5	10	15
Citric acid (%)	3	3	3	3	3	3	3	3	3
Sodium starch glycolate (%)	4	4	4	4	4	4	4	4	4
Sucrose (%)	4	4	4	4	4	4	4	4	4

Table 4: Physical-chemical characteristics of prepared herbal films

S. No	*Formula code*	*Weight (mg)*	*Thickness (mm)*	*Folding endurance*	*Surface pH*
1	F1	62.6 ± 1.34	0.2 ± 0.01	360 ± 8.16	6.6 ± 0.15
2	F2	67.3 ± 2.33	0.2 ± 0.00	537 ± 4.52	6.4 ± 0.15
3	F3	69.6 ± 2.34	0.2 ± 0.02	642 ± 2.47	6.3 ± 0.1
4	F4	73.3 ± 2.33	0.3 ± 0.00	436 ± 6.57	6.5 ± 0.2
5	F5	78.3 ± 2.33	0.3 ± 0.02	687 ± 4.4	6.2 ± 0.1
6	F6	83.6 ± 1.24	0.3 ± 0.01	545 ± 4.58	6.3 ± .0.15
7	F7	84.5 ± 0.5	0.4 ± 0.01	454 ± 5.3	6.3 ± 0.4
8	F8	88.6 ± 1.14	0.4 ± 0.03	363 ± 5.6	6.5 ± 0.5
9	F9	92.6 ± 1.59	0.4 ± 0.01	470 ± 5.36	6.4 ± 0.15

Percent loss of moisture

Loss of moisture was investigated to assess the film's physical durability. For three days, pre-weighed films (3x2 cm^2) were placed in a desiccator comprising anhydrous calcium dichloride. At the end of the study, films were collected and the percentage loss of moisture was calculated using the below formula.[15]

%Loss of moisture = ((Initial film weight − Final film weight)/ Initial film weight) × 100

Percentage moisture uptake

Using a saturated potassium chloride solution in desiccator, the weighted films were subjected to 84% relative humidity till consistent weight reached. Percentage uptake of moisture computed from below formula.[16]

$$\%\text{Uptake of Moisture} = (w_0 - w_f)/w_0 \times 100$$

Disintegration studies

The modified disintegration method was used to measure the disintegration time. To achieve this, 10 mL of water were added to the watch glass and the film was carefully positioned at the middle. Table 5 shows how long it took for the film to fully break down into tiny particles.[17]

Content uniformity

Every film's drug content was ascertained using the UV spectrophotometric method. This involved dissolving a 2 × 3 cm^2 area film in 100 mL of pH 6.8 buffer medium and then stirring the resulting solution for an hour with a magnetic stirrer. After filtering the mixture, the absorbance of the sample was recorded at 274 nm, and the drug content was calculated using the drug's standard curve.[18]

Drug release studies

Using Paddle apparatus, it was determined how quickly the *C. auriculata* leaf extract evolved from herbal film. Release investigations were carried out in 300 mL of simulated salivary medium (pH 6.8 buffer) at 50 rpm, 37 ± 5°C to replicate the *in-vivo* circumstances. Fresh medium was substituted for an aliquot of the solution at various intervals of 1, 3, 5, 7, 10, 15, 20, 25, 30, 45, and 60 minutes. After filtering each sample, absorbance was observed at 274 nm. Compute percent cumulative drug release using the calibration data.[19]

Stability testing

Optimized formulation was assessed for stability testing. For that, cover the films in laminated aluminum foil and store them under 37 ± 3°C, 75% RH for three three-month stability period. Following the stability period, all samples were removed and examined for physical characteristics, disintegration time, and percent drug content.[20]

RESULTS AND DISCUSSION

After being dried, the extract underwent screening for Phytoconstituents and the resulting data was displayed in Table 1.

Chemical interaction between herbal extract and selected additives was examined by FTIR spectral analysis and the resultant spectrums are shown in Figures 1, 2, and 3. Regarding the pure *C. auriculata* infrared spectrum, there was no appreciable shift in the peak's location or intensity, suggesting that the medication and the polymers employed did not interact. This was demonstrated by contrasting the FTIR spectra of pure *C. auriculata* leaf extract with the physical combination of medications, including excipients.

C. auriculata's standard plot, as seen in Figure 4, demonstrated high linearity with an R^2 of 0.994, indicating that it obeys Beers-Lambert's statement at a level of concentration from 0 to 50 µg/mL.

Using a solvent casting technique, the extract was combined with varied amounts of polymer, such as HPMC and propylene glycol, to create nine distinct herbal film formulations. The super disintegrant utilized was sodium starch glycolate, while the sweetener was sucrose. Table 3 depicts formulas used in the design of herbal films.

The produced films were further assessed for various morphological and physicochemical properties. It was found that every film that was made was transparent, yellow in color, smooth, flexible, non-sticky, and free of particles.

Table 4 shows the observed findings of the Weight variation test. The total mass of films differs with polymer content, ranging from 62.6 ± 1.34 to 92.6 ± 1.59. Film weight increased with an increasing polymer concentration, which decreased its flexibility and durability.

Thickness of each herbal film estimated with micrometre. It was determined that the thickness fluctuated with a relatively

Table 5: Physical-chemical characteristics of prepared herbal films

S. No	*Formula code*	*Swelling index (%)*	*%Loss of moisture*	*%Uptake of moisture*	*Disintegration time (Seconds)*	*Content uniformity (%)*
1	F1	33 ± 00	0.91 ± 0.06	2.30 ± 0.01	44.4 ± 3.14	98 ± 1.10
2	F2	45 ± 0.4	1.02 ± 0.04	2.56 ± 0.06	73.0 ± 4.0	99 ± 1.13
3	F3	53 ± 0.01	1.14 ± 0.01	4.42 ± 0.01	58.0 ± 1.00	100 ± 1.15
4	F4	34 ± 0.54	1.06 ± 0.05	2.05 ± 0.06	51.0 ± 1.00	100.3 ± 1.15
5	F5	44 ± 0.4	1.27 ± 0.05	3.12 ± 0.04	67.3 ± 2.33	97.6 ± 0.57
6	F6	51.5 ± 0.0	1.56 ± 0.04	3.34 ± 0.06	95.0 ± 1.33	98.3 ± 1.14
7	F7	42 ± 0.01	1.62 ± 0.01	4.51 ± 0.04	68.3 ± 1.55	98.35 ± 1.52
8	F8	45 ± 0.4	1.57 ± 0.01	4.32 ± 0.05	87.3 ± 2.33	98.3 ± 1.15
9	F9	55 ± 002	1.92 ± 0.02	4.94 ± 0.04	95.3 ± 1.33	100.6 ± 1.52

Table 6: Drug release kinetics

Formulation code	*Correlation coefficient (R^{2}) values of various release kinetics*	
	Zero-order	*First-order*
F1	0.852	0.987
F2	0.847	0.9147
F3	0.821	0.9401
F4	0.765	0.9568
F5	0.658	0.9658
F6	0.744	0.9748
F7	0.852	0.9852
F8	0.835	0.9865
F9	0.775	0.9975

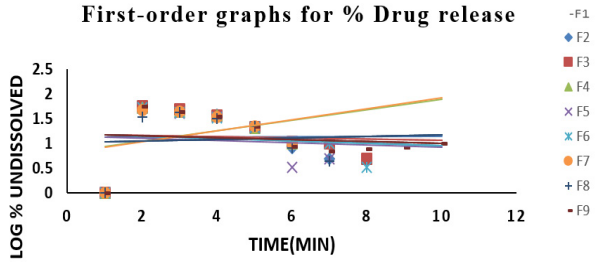

Figure 6: First-order graphs for %drug release from herbal films loaded with *C. auriculata* leaves extract

small standard deviation, ranging from 0.3 to 0.4 mm. As such, each film's dosage accuracy is assured. The findings show that the thickness of the rapidly dissolving herbal film rises with increasing polymer content, while the increase is quite slight. Folding endurance provides a measure of the film's brittleness. The prepared films were found to have folding endurance ranging from 360 to 687. F5 formulation, which has a 40% polymer concentration and 10% plasticizer, has the

Table 7: Stability studies for the optimized herbal film (F5)

Parameter	*Initial*	*After 45 days on 40 c,75% RH*
Physical texture	Transparent yellow	Slight yellow transparent
Mean weight (mg)	83.6 ± 1.24	80.1 ± 0.31
Folding endurance	563 ± 2.30	547 ± 1.90
pH	6.69 ± 0.03	6.56 ± 0.01
Rupture time (sec)	47.0 ± 4.0	50.2 ± 0.03
Content uniformity (%)	99.71 ± 1.36	98.67 ± 0.54

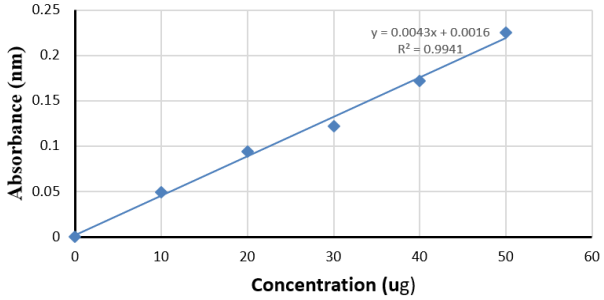

Figure 4: Calibration curve for ethanol extract of *C. auriculata* using pH 6.8 buffer

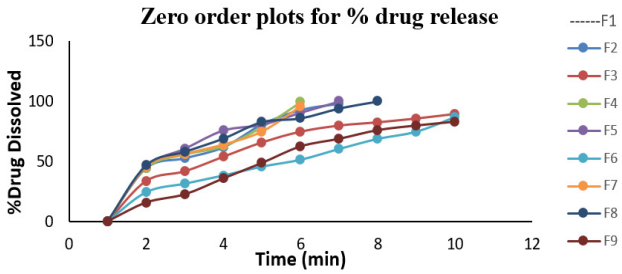

Figure 5: Zero order plots for % loaded with *C. auriculata* leaves extract

highest folding endurance (687) of all the formulations. The concentrations of hydrophilic polymer and plasticizer determine the brittleness of the film. In accordance with the findings, the folding endurance of herbal films increases as polymer concentration rises and the folding endurance value falls as plasticizer concentration decreases.

All of the films' surface pHs were discovered to be between 6.2 and 6.6; the findings are displayed in Table 4. Every formulation's surface pH was nearly equal to that of saliva, suggesting that films would be less likely to irritate patients' oral mucosa and, therefore, more tolerable.

The prepared films' swelling percentage was tested in pH 6.8 buffer, and the findings are displayed in Table 5. The formulation F9, which has the highest swelling index of 55% among all formulations, has a high polymer concentration of (50% of HPMC). The findings led to the conclusion that the swelling index of the fast-dissolving film rises with polymer content.

A study on percentage moisture loss, which alters the stability of the films, was used to ascertain the amount of moisture that remained in the films after they had fully dried out. The results demonstrated that the samples were not inherently fragile and that the moisture loss was less than 2%.

The percentage of moisture absorbed by the films provides insight into their stability. Every formulation had a moisture uptake value of less than 5%, indicating its stability. It is expected that the polymers included in the films' compositions would have an impact on the film's moisture uptake capacities. The proportion of moisture uptake varied from around 2 to 5.3%, generally showing an increase in moisture uptake as both the polymer and plasticizer levels increased.

Table 5 displays the findings of a disintegration test. According to the results, all the films broke up in less than one minute (with a range of 44–95 seconds). It showed that all of the prepared herbal films quickly fell apart.

The films' drug content was determined to range from 97 to 100%; the findings are displayed in Table 5. The films were determined to fulfil 85 to 115% of the label claim standards for content homogeneity in accordance with USP regulations. There was no discernible variation in the drug content of any film, indicating that the active principle was evenly distributed across each film's fixed 6 cm^2 area.

Using type-II (Paddle) dissolution testing device, a drug release analysis of the films was conducted. The film's release statistics confirmed that the release occurred immediately. Figures 5 and 6 shows the dissolving profiles of each formulation. Based on the findings; it found, the medication release remains delayed with subsequent increases in polymer concentration.

The release mechanism is explained by comparing the correlation coefficient data for each formulation's zero and first-order kinetics. Correlation coefficient (R2) values for first-order plots were higher than those for zero-order, as shown in Table 6. Thus, the *C. auriculata* leaf extract-loaded herbal films proved to follow first-order release characteristics.

Table 7 displays the stability study's findings. During the course of a 45-day stability period, storage at 40°C and 75% RH was not found to appreciably alter drug content, folding endurance, surface pH, or disintegration time. Despite this, the film's physical appearance changed from yellow to a somewhat yellow color. The findings show that the herbal films loaded with drugs remained stable for the course of the stability period.

CONCLUSION

An attempt has been made in the current work to create herbal films that dissolve quickly and include an extract from the leaves of *C. auriculata*. The solvent-casting approach was used to create fast-dissolving herbal films. Qualitative properties of formulated herbal films, including folding endurance, mean weight, thickness, pH, disintegration time, content uniformity, and drug release, were assessed. All of the prepared films disintegrated in 95 seconds and were clear, uniform, and free of particle matter. They also demonstrated good folding endurance. Out of all nine formulations, formulation F5, which is an herbal film with 10% propylene glycol, and 40% HPMC, exhibited complete drug release (99.6%) in 30 minutes and had a strong folding endurance value. Films were found to follow first-order kinetics. Overall, this study's findings imply that the most convenient form of medication for clinical management of chronic constipation disorder was fast-dissolving herbal films using extract from *C. auriculata* leaves.

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