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(RESEARCH ARTICLE)

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QBD driven optimized approach for formulation of *ginkgo biloba* extract -fast dissolving oral films (FDOF'S)

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Abstract

As Alzheimer's disease (AD) advances, cholinergic dysfunction, β-amyloid plaques and neurofibrillary tangle development, oxidative damage, and neuroinflammation occur, making the major addressal setting the health care environment. Though less successful than a synthetic method, the therapy of AD has focused on cholinergic dysfunction, inflammation, and oxidative damage. Neurodegenerative diseases are treated commercially with gingko biloba extract. FDOFs are therefore effective in changing and enhancing the bioavailability of nutraceuticals. FDOFs of *Gingko biloba* extract were formulated using QbD 3^3 factorial designs in the current study, and the optimal formulations were examined for both in-vitro and in-vivo models of Alzheimer's disease. Twelve formulations have been prepared and described in compliance with ICH guidelines. The formulations F7 and F10 were chosen because of their optimal formulation properties.

Keywords: Alzheimer's disease; Gingko biloba; Formulation; FDOFs; QBD

1. Introduction

Alzheimer's disease (AD) is the main cause of cognitive decline; its defining features include agitation, sadness, mood swings, psychosis, and gradual memory loss[1].Major health problems associated with AD include the fact that 3.7 million senior adults in India suffer from dementia, a number that is expected to increase to three times by 2050 and twice by 2030 [2]. The following conditions are thought to be hallmarks of Alzheimer's disease (AD): cholinergic dysfunction, β-amyloid plaques and neurofibrillary tangle formation, other neurotransmitter dysfunction, higher levels of AGO, oxidative damage, neuroinflammation, genetic, and environmental factors [3,4].

The tau and amyloid beta proteins are the standard pharmacologic targets for disease-modifying therapies (DMTs) for Alzheimer's disease (AD). Regulators have not authorized the use of any tau-related drugs to treat AD[8].Due to this intricate etiopathology, a reaction to commonly given drugs such as galantamine, donepezil, rivastigmine, and memantine is, on the one hand, less predictable and usually unsatisfactory[5]. Nonetheless, it supports the use of herbal treatments due to their specific cholinesterase inhibitory activity as well as their general antioxidant and anti-inflammatory properties[6]. The increasing impression of the cost, safety, and effectiveness of herbal medications is driving up their appeal.Dementia is associated with neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease (AD), and epilepsy[7, 8]. Fast-dissolving films, or FDOFs, are a kind of stamp-sized, flexible, non-friable polymeric film that dissolves in the mouth to allow the active ingredient to cross oral mucosal membranes and enter the bloodstream[9]. The mobility, high stability, and convenience of handling of this dosage form are possible advantages. FDOF is intended to dissolve rapidly in saliva before being swallowed and entering the gastrointestinal tract by being inserted in the buccal region. Over the past few decades, FDOF research has drawn a lot of attention due to its

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distinct advantages over other rapid dissolving dosage forms[10]. Patients who are bedridden, old, or have swallowing difficulties can take their prescriptions since FDOF dissolves easily in saliva and doesn't require chewing or drinking [11, 12]. The buccal region's rich vasculature helps patients absorb pharmaceuticals more quickly, and FDOF, as a buccal drug delivery device, can also boost bioavailability by avoiding first-pass metabolism. The encapsulation of thermally liable chemicals is promoted by FDOFs produced using hot-melt extrusion and solvent casting[13]. Gingko biloba extract has been widely used in the management and prevention of peripheral vascular diseases, Alzheimer's disease (AD), Parkinson's disease (PD), and neurosensory problems (including tinnitus) as well as neurodegenerative dementias associated with aging[14].

In this work, the effects of a Gingko biloba extract loaded as FDOFs are examined. This extract may be used as an alternative to AD in neuropsychiatric treatment. According to the study, FDOFs combined with herbal nutraceuticals may be able to treat Alzheimer's disease instead of medication.

2. Materials and methods

2.1. Materials

All the materials and chemicals used for the study were of laboratory analytical g rade. The *Ginkgo biloba* leaf powder was obtained from Nutraherbs processing Pvt ltd India. for extraction and qualitative screening. Following two extractions of the extract with Pet-ether to defat it, Soxhletion was used to extract the extract using an aqueous solution which was then concentrated and dried (Figure 1). The yield percentage was computed and shown in Table 1.

2.2. Developing the Ginkgo biloba extract FODFs:

The FODFs were made via solvent casting, as shown by the listings in Table 2. The extract was mixed for 10 minutes with a precise volume of aqueous extract using an over-head stirrer, and then it was filtered. The polymer, plasticizer, super-disintegrants, preservative, saliva-stimulating agent, and sweetening component were added in precisely calibrated amounts, and the mixture was then stirred for 30 minutes. Air entraps were liberated from the viscous, thick fluid by means of ultrasonication. The solution was metered out and poured onto a glass plate that was 30 by 45 square centimeters. The plate was then heated to about 80°C for 15 minutes in a hot air oven to cast the film. Each film would offer a dosage of 50 mg (3 × 2 sqcm) when it was carefully removed.

2.3. Experimental Design

QbD Box Behnken design was applied to carry out the FDOF optimization. The design layout comprises three factors for evaluation: the kind of plasticizer (X2, which included PEG 400 and propylene glycol); the kind of super-disintegrant (X3, which included Cross Povidone and Croscarmellose sodium); and the type of polymer (X1, which included Pullulan gum, Maltodextrin, and HPMC 5 cps). These variables, which comprised folding endurance, disintegration time (sec), and in-vitro drug release (%), were selected as independent variables at one level above the dependent variables. A total of twelve alternative mouth-dissolving film formulations were produced by the QbD design arrangement, which includes several excipient levels [15].

2.4. Evaluation

- The ability of an apolymer to form films that are separable from the surface on which they are cast is known as filmforming capacity. The movies were portrayed as excellent, better, ordinary, very poor, or poorest based on their abilities to make movies.
- Film appearance: A visual analysis based on observation will determine whether a film is clear or translucent.
- Tackiness: The film's tactility was determined by lightly rubbing it between the fingertips. Qualitatively, the results were classified as tacky or non-tacky[17].

2.5. Formulation attributes

2.5.1. Thickness

Using digital Vernier calipers that were calibrated, the thickness uniformity of each formulation was assessed. Random selections were made from various locations on the plate to select ten films, or fragments, from each formulation. The thickness's mean value was computed and measured [18].

2.5.2. Film disintegration in vitro

Visual analysis was used to quantify the in-vitro disintegration period of a fast-dissolving oral film in a petri dish containing 25 ml of phosphate buffer (pH6.8) at 37.0 ± 0.5°C. Disintegration time is the time that was recorded when the film began to break apart.

2.5.3. Surface pH study

It was decided to maintain the surface pH as close to neutral as feasible because an acidic or alkaline pH may irritate the oral mucosa. The film was left in contact with one milliliter of distilled water at room temperature for three minutes, allowing it to swell [21].

2.5.4. Morphological characteristics

A scanning electron microscope (Hitachi S-3400N type II model, Japan) was used to investigate the surface morphology of the optimized FDOFs of Gingkobiloba. At a 1000x magnification, images were captured with an excitation voltage of 1.0 KV. Air-sealed containers were used to preserve all of the developed formulations at a room temperature of 25 ± 30°C.

2.5.5. Folding endurance

This test, which was performed manually by firmly grasping and repeatedly folding the films through the middle, indicates a film's flexibility.The quantity of folds that must occur on the same crease in order for the film to break; this is the endurance value [22].

2.5.6. Weight Variation

An electronic scale was used to measure the weight of each 2 x 3 cm2 cut film that was cast at various locations for the experiment.The weight variation study used an average of three readings[19].

2.5.7. Percentage moisture loss

The percentage of moisture loss was calculated to verify the films' integrity when they were dry. 2-3 cm accurately weighed and cut films were stored in desiccators with fused anhydrous calcium chloride. After a whole day, the films were taken out and weighed once more. The quantity of moisture loss was shown by the weight of the films decreasing, which was measured. The formula below was used to determine the percentage loss in moisture:

$$\text{Percent moisture loss} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initialweight}} \text{x}100 \text{---------- (I)}$$

2.5.8. Moisture Absorption Percentage

Films were sliced into 2 x 3 cm2 patches to assess the moisture absorption. For a day, these films were placed in a desiccator filled with a saturated potassium sulfate solution at ambient temperature and 75% relative humidity. The sheets' increased weight indicated moisture absorption [16].The following formula was used to determine the percentage of moisture gained by the films:

$$\text{Percent moisture gain} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initialweight}} \text{x}100 \text{---------- (II)}$$

9. Swelling Index: A film that was first drug-loaded was placed on a 2% agar plate.Up until it achieved its steady weight, there was a noticeable increase in the film's weight. The formula below was used to calculate the degree of swelling[19].

$$\text{Swelling index} = \frac{W_t - W_o}{W_o} \text{x}100 \text{---------- (III)}$$

Wt is the weight of the film at time “t”; Wois theweight of film at t =0

9. *In vitro* release studies: Using the USP Dissolution Test Apparatus-II, the release rate of the gingkobiloba extract from the FDOFs was ascertained. The study was conducted at 37 ± 5 °C and 50 rpm speed in 900 ml of pH 6.8 phosphate buffer. To keep the sink conditions stable, a portion of the solution was collected and replaced every 30 seconds with fresh medium. To filter the aliquot, Whatman's filter paper was utilized[20]. The filtered solution's absorbance was

calculated at 268 nm previously calibrated. The sample ought to be removed at the location where the top surface of the rotating paddle and the surface of the dissolving medium meet, not less than one centimeter from the vessel wall. Using the calibration data, the cumulative amount of medication release was determined. There were three copies of the process completed.

Table 1 Calculation of percentage yield

Extract	Crude Powdertaken in gm	Yield after concentrationin gm	% yield
Aqueous extract	200	4.31	1.54

Table 2 Composition of *Ginko biloba* FODFs using different variables.

Formulation entry	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
G. biloba extract	50	50	50	50	50	50	50	50	50	100	100	100
Pullulan gum	100	-	-	100	-	-	100	-	-	100	-	-
Maltodextrin	-	100	-	-	100	-	-	100	-	-	100	-
HPMC	-	-	100	-	-	100	-	-	100	-	-	100
Propylene glycol	100	100	100	100	100	100	-	-	-	-	-	-
PEG 400	-	-	-	-	-	-	100	100	100	50	50	50
Cross Povidone	50	50	50	-	-	-	50	50	50	-	-	-
Croscarmellose sodium	-	-	-	50	50	50	-	-	-	50	50	50
Citric acid	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Polysorbate 80	25	25	25	25	25	25	25	25	25	25	25	25
Carbopol	5	5	5	5	5	5	5	5	5	5	5	5
Sucralose	25	25	25	25	25	25	25	25	25	25	25	25
Distilled water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Q.S = Quantity sufficient

Table 3 Characteristic formulation features of *G.biloba* FODFs

F. Code	Film forming capacity	Appearance of films	Tackiness	thickness (mm)	Surface pH	% moisture loss	% moisture gain
F1	Very good	Transparent	Non-tacky	0.29 ± 0.02	5.18 ± 0.21	17.21 ±0.23	10.82 ± 0.14
F2	Good	Transparent	Non-tacky	0.32 ± 0.04	5.28 ± 0.36	16.73 ± 0.07	12.51 ± 0.23
F3	Good	Transparent	Slightly-tacky	0.42 ± 0.03	5.39 ± 0.58	12.27 ± 0.32	11.23 ± 0.18
F4	Very good	Transparent	Non-tacky	0.24 ± 0.04	5.48 ± 0.41	11.42 ± 0.07	8.43 ± 0.17
F5	Good	Transparent	Non-tacky	0.56 ± 0.07	5.41 ± 0.64	19.36 ± 0.69	11.27 ± .45
F6	Good	Transparent	Slightly tacky	0.78 ± 0.05	5.53 ± 0.41	13.19 ± 0.58	11.32 ± 0.17

F7	Very good	Transparent	Non-tacky	0.55 ± 0.04	6.15 ± 0.38	9.27 ± 0.29	11.35 ± 0.45
F8	Good	Transparent	Non-tacky	0.23 ± 0.03	6.13 ± 0.23	8.73 ± .0.68	7.43 ± .64
F9	Very good	Transparent	Non-tacky	0.45 ± 0.07	6.36 ± 0.34	8.51 ± 0.57	11.51 ± 0.33
F10	Very good	Transparent	Non-tacky	0.62 ± 0.05	6.28 ± 0.24	6.90 ± 0.86	5.32 ± 0.07
F11	Good	Transparent	Slightly tacky	0.63 ± 0.06	6.22 ± 0.18	6.91 ± 0.14	6.31 ± 0.21
F12	Very good	Transparent	Non-tacky	0.56± 0.07	6.58 ± 0.16	11.51 ± 0.66	10.45 ± 0.38

All the experiments are performed in triplicate and results are represented as Mean±SD

Table 4 Formulation characteristics of Gingko biloba extract loaded FDOFs- QbD based approach

Formulation code	**Weight variation**	**Folding Endurance**	**Disintegration Time**	**Swelling index**	**Content Uniformity**
F1	52.4 ± 051	101 ± 0.63	59 ± 0.23	29.1 ±0.11	65.36 ± 0.23
F2	59.7 ± 0.46	162 ± 0.52	61 ± 0.24	17.2 ± 0.14	63.55 ± 0.24
F3	71.5 ± 0.54	139 ± 0.59	69 ± 0.26	16.2 ± 0.13	71.33 ± 0.15
F4	72.5 ± 0.12	155 ± 0.63	55 ± 0.25	21.4 ± 0.21	66.41 ± 0.65
F5	69.6 ± 0.39	163 ± 0.58	59 ± 0.18	19.5 ± 0.15	75.35 ± 0.23
F6	65.4 ± 0.52	164 ± 0.54	73 ± 0.24	21.3 ± 0.22	81.23 ± 0.25
F7	65.7 ± 0.46	183 ± 0.56	49 ± 0.25	32.6 ± 0.21	85.35 ± 0.24
F8	61.8 ± 0.48	206 ± 0.54	55 ± 0.17	26.6 ± 0.13	75.23 ± 0.78
F9	52.9 ± 0.49	198 ± 0.45	61 ± 0.26	31.9 ± 0.24	88.33 ± 0.65
F10	43.2 ± 0.63	215 ± 0.68	45 ± 0.22	29.5 ± 0.16	92.24 ± 0.78
F11	52.3 ± 0.52	201 ± 0.45	49 ± 0.21	35.1 ± 0.24	91.74 ± 0.84
F12	61.5 ± 0.47	211 ± 0.74	51 ± 0.32	20.6 ± 0.25	81.31 ± 0.85

All the experiments are performed in triplicate and results are represented as Mean±SD

Table 5 Optimization of FDOFs of G. biloba based on 3^3 factorial design

F. Code	**Independent variable**			**Dependant variable**	
	X1 (Polymer)	X2 (Plasticizer)	X3 (Superdisintigrant)	Y1 (Folding endurance)	Y2 (Disintegrationtime in sec)
F1	Pullulan gum	Propylene glycol	Cross Povidone	101 ± 0.63	59 ± 0.23

F2	Maltodextrin	Propylene glycol	Cross Povidone	162 ± 0.52	61 ± 0.24
F3	HPMC	Propylene glycol	Cross Povidone	139 ± 0.59	69 ± 0.26
F4	Pullulan gum	Propylene glycol	Croscarmellose sodium	155 ± 0.63	55 ± 0.25
F5	Maltodextrin	Propylene glycol	Croscarmellose sodium	163 ± 0.58	59 ± 0.18
F6	HPMC	Propylene glycol	Croscarmellose sodium	164 ± 0.54	73 ± 0.24
F7	Pullulan gum	PEG 400	Cross Povidone	183 ± 0.56	49 ± 0.25
F8	Maltodextrin	PEG 400	Cross Povidone	206 ± 0.54	55 ± 0.17
F9	HPMC	PEG 400	Cross Povidone	198 ± 0.45	61 ± 0.26
F10	Pullulan gum	PEG 400	Croscarmellose sodium	215 ± 0.68	45 ± 0.22
F11	Maltodextrin	PEG 400	Croscarmellose sodium	201 ± 0.45	49 ± 0.21
F12	HPMC	PEG 400	Croscarmellose sodium	211 ± 0.74	51 ± 0.32

All the experiments are performed in triplicate and results are represented as Mean±SD

Table 6 In-vitro dissolution of FDOFs

F.code	Y3 (% release of extract) Amount released in minutes							
	0	3	7	12	17	22	27	30
F1	0	11.6 ± 0.1	21.6 ± 1.3	37.2 ± 3.1	61.4 ± 4.2	68.1 ± 5.3	74.6 ± 5.6	78.2 ± 5.3
F2	0	12.3 ± 0.9	16.4 ± 1.2	29.5 ± 2.4	62.9 ± 3.6	74.5 ± 4.8	78.4 ± 5.3	81.6 ± 6.9
F3	0	8.6 ± 0.6	13.9 ± 0.8	26.6 ± 2.1	35.7 ± 3.9	46.9 ± 2.1	58.8 ± 6.3	72.4 ± 4.8
F4	0	17.8 ± 0.8	33.7 ± 2.1	44.5 ± 0.6	56.2 ± 4.1	7260 ± 3.6	81.1 ± 6.1	87.2 ± 4.3
F5	0	16.6 ± 1.2	31.7 ± 2.5	41.9 ± 2.2	57.9 ± 3.8	72.4 ± 6.1	76.6 ± 4.8	86.3 ± 4.9
F6	0	13.6 ± 1.1	24.4 ± 2.3	32.9 ± 2.4	43.6 ± 3.2	89.8 ± 4.6	64.8 ± 5.3	75.9 ± 5.1
F7	0	30.5 ± 1.9	66.8 ± 3.2	78.6 ± 3.7	85.9 ± 4.6	94.9 ± 5.1	98.6 ± 5.8	98.8 ± 5.3
F8	0	22.7 ± 1.5	37.5 ± 3.4	51.3 ± 3.3	80.6 ± 4.9	84.9 ± 3.9	87.7 ± 6.3	91.6 ± 5.9
F9	0	21.6 ± 1.7	33.1 ± 2.8	49.7 ± 0.26	63.9 ± 5.3	75.9 ± 5.1	83.3 ± 5.1	88.9 ± 6.3
F10	0	33.6 ± 2.3	64.8 ± 3.9	82.7 ± 0.25	93.6 ± 6.1	95.6 ± 4.8	98.8 ± 5.3	98.9 ± 6.5
F11	0	29.7 ± 2.1	59.4 ± 3.4	74.4 ± 0.21	85.9 ± 5.4	91.8 ± 6.6	96.6 ± 4.1	98.5 ± 6.7
F12	0	21.8 ± 1.6	33.04 ± 2.9	42.3 ± 0.22	51.1 ± 6.2	63.3 ± 5.8	77.1 ± 6.3	81.3 ± 5.2

All the experiments are performed in triplicate and results are represented as Mean±SD

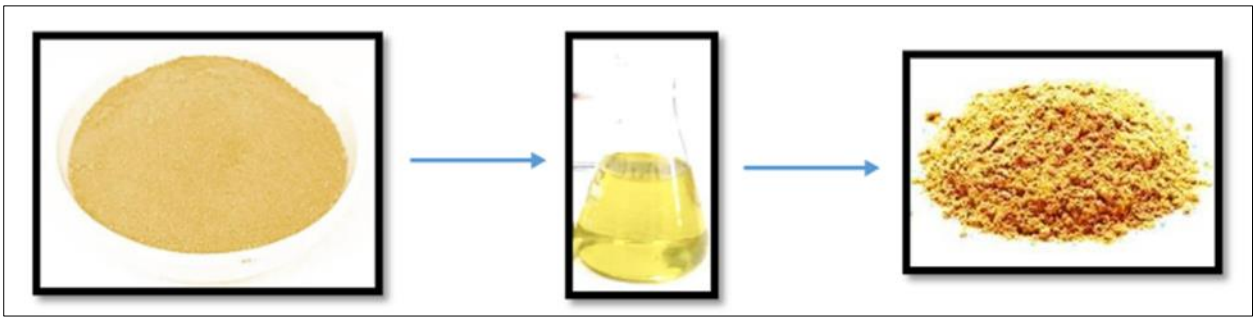
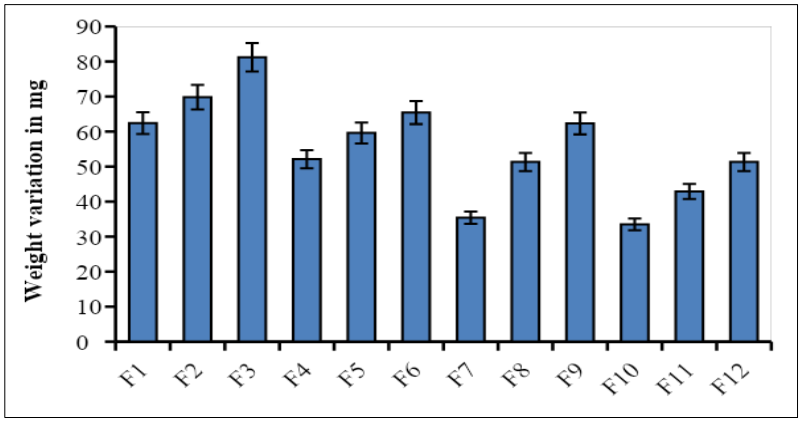


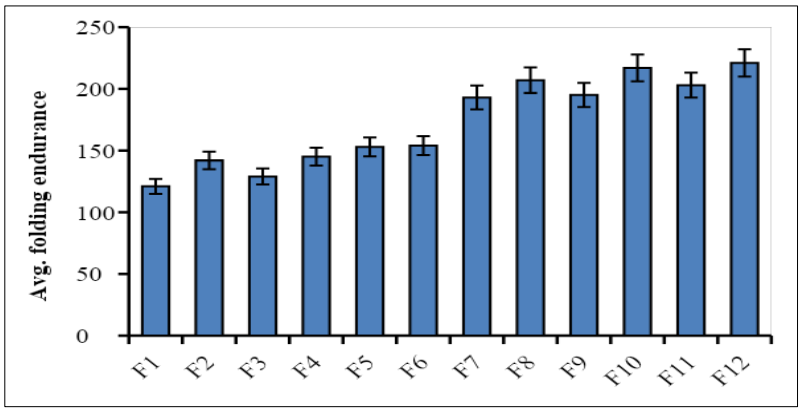
Figure 1 Extraction of Ginko biloba powder

Other characteristic features of G.biloba FODFs:

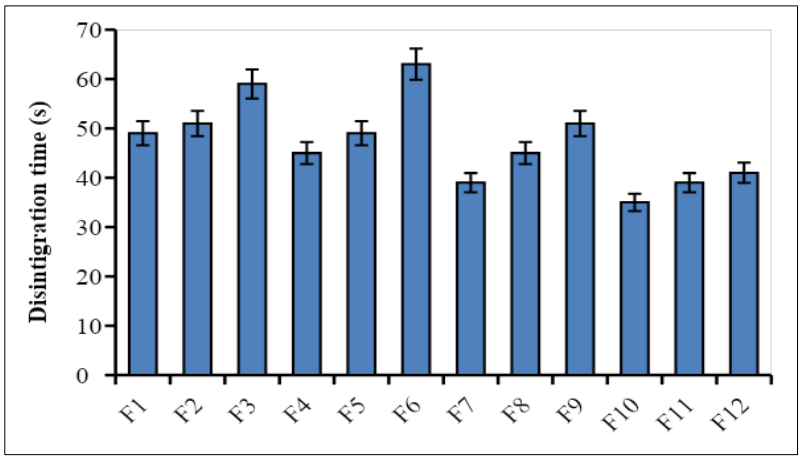
Weight Variation



Folding endurance



Disintegration Time (s)



Swelling Index

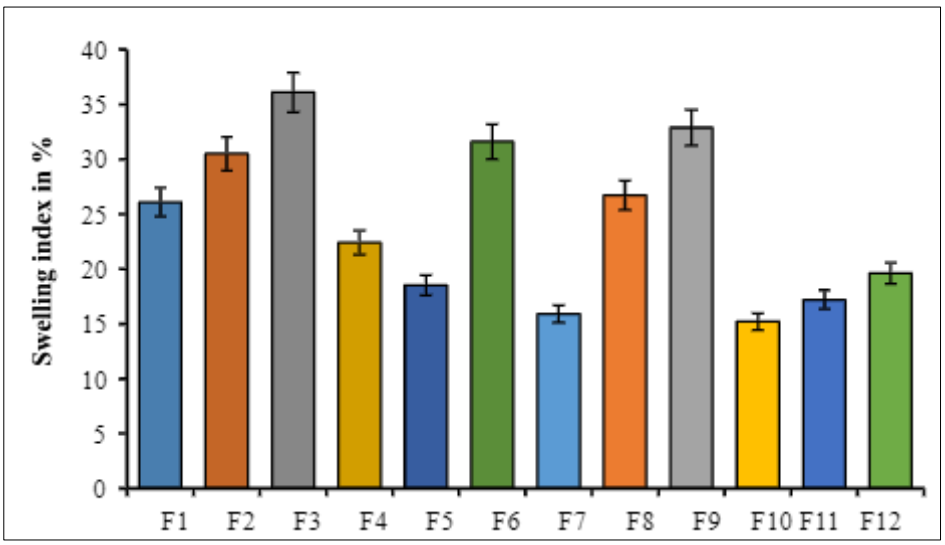
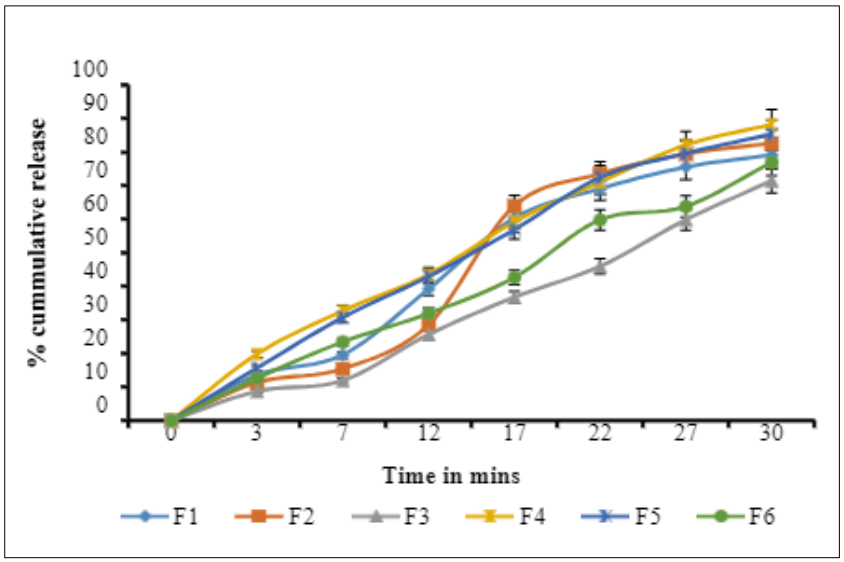


Figure 2 Weight variation (a), Folding endurance (b), Disintegration time (c), Swelling index (d) of FDOFs of *G. biloba* (F1 to F12).



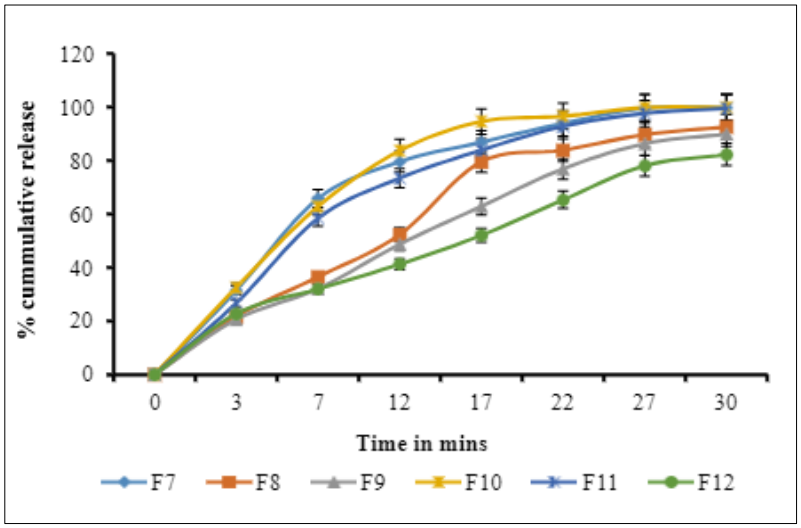


Figure 3 Cumulative % release of *G.biloba* extract from FDOFs F1-F12; (a) F1 to F6; (b) F7 to F12.

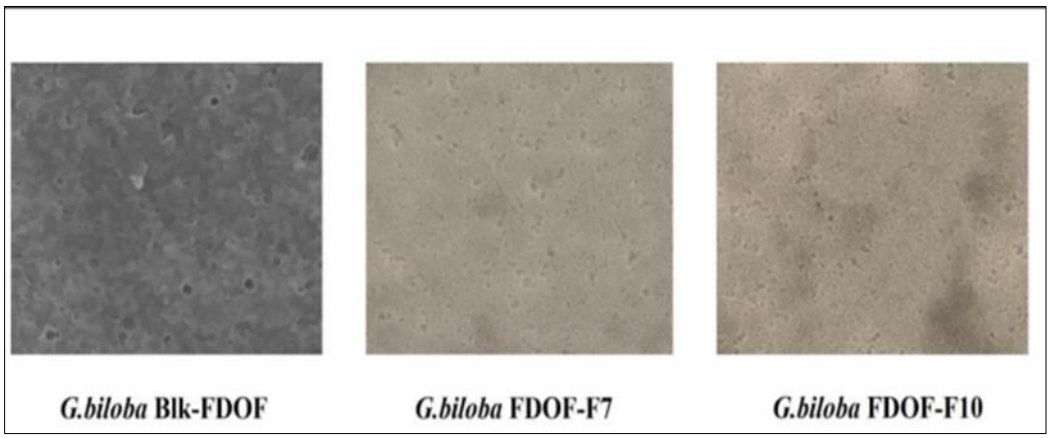


Figure 4 SEM Images of Selected FDOFs of *G.biloba*

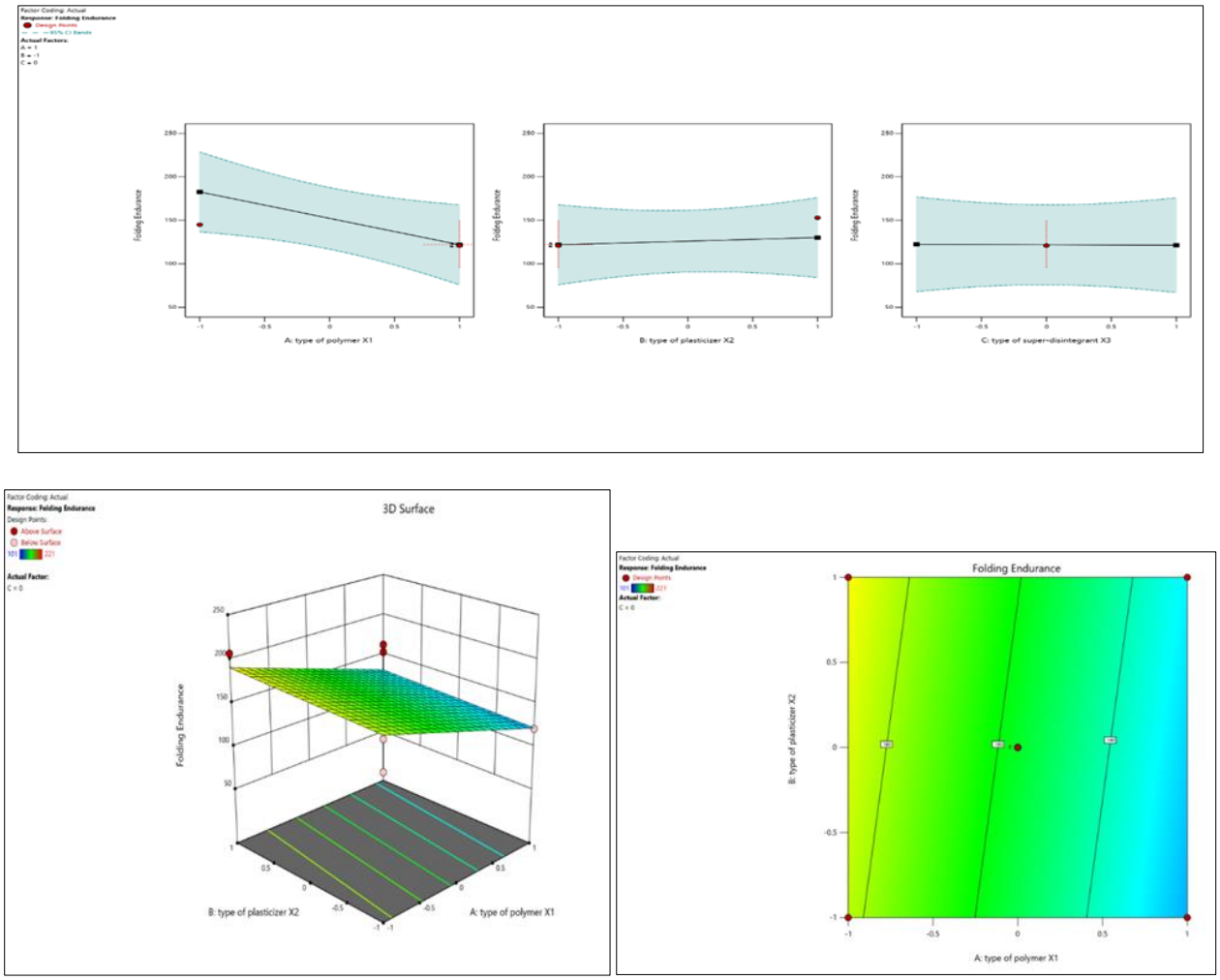


Figure 5.1 3^3 fractional factorial design analysis of independent variables X_1, X_2, and X_3 on Folding Endurance (Y_1); Visual representation of the folding endurance profile through a schematic illustration (a); Contour plot depicting the relationship between X1, X2, and Folding Endurance (b); Three-dimensional surface plot providing a comprehensive depiction of the Folding Endurance in response to variations in X1 and X2 (c).

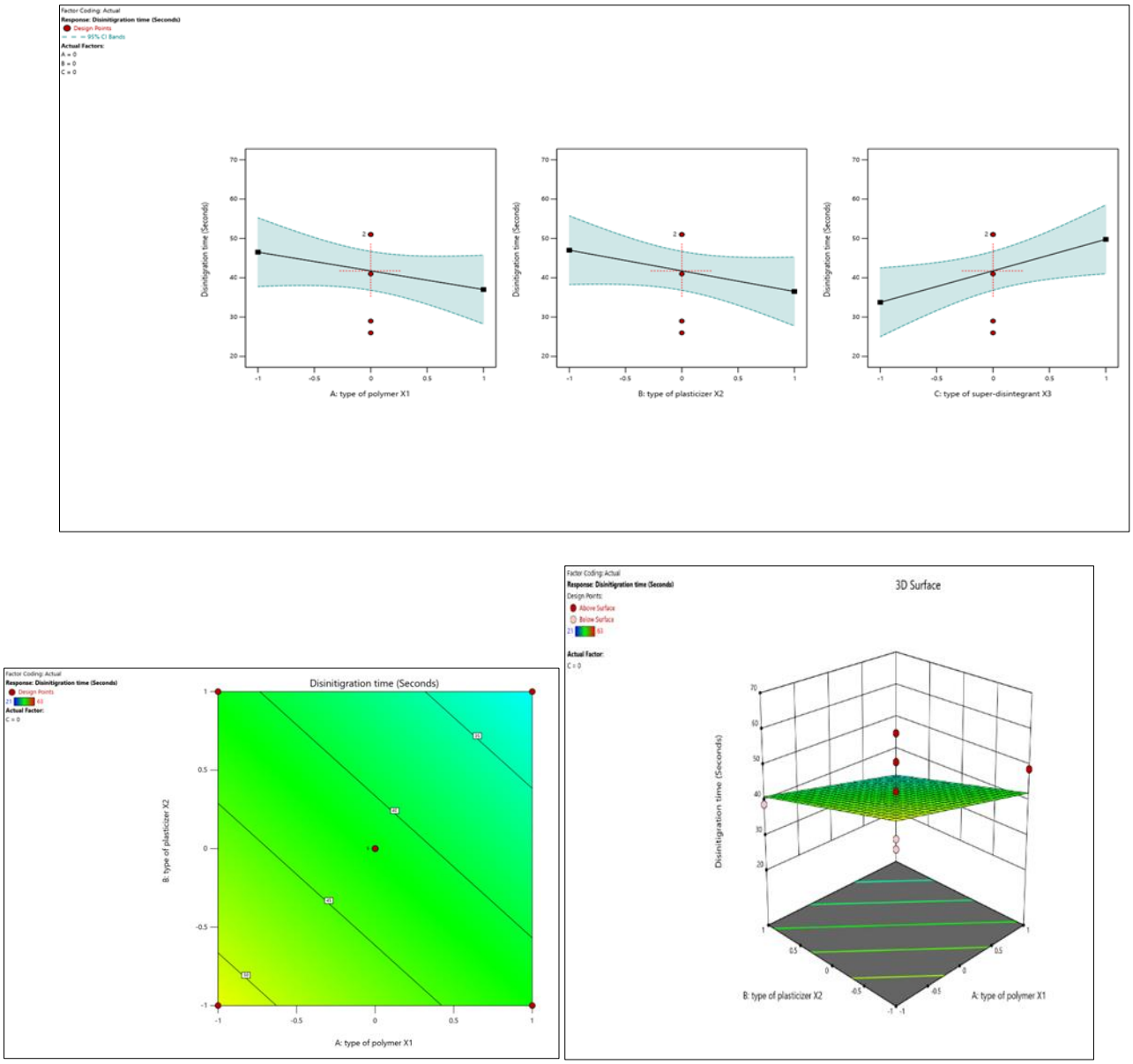


Figure 5.2 3^3 fractional factorial design analysis of independent variables X_1, X_2, and X_3 on Disintegration time (Y_2); Visual representation of the disintegration time profile through a schematic illustration (a); Contour plot depicting the relationship between X_1, X_2, and disintegration time (b); Three-dimensional surface plot providing a comprehensive depiction of the disintegration time in response to variations in X_1 Table 2.7 presents a comparative analysis of R^2 values, standard deviations (SD), and observed responses.

3. Results and discussion

Extract yield percentage and qualitative analysis: the aqueous extract Gingko biloba extract yield percentage was determined to be 1.77%, indicating the presence of significant polar components in the mixture (Table 1). Additionally, the extract's qualitative screening revealed the presence of phytoconstituents such as alkaloids, flavonoids, anthraquinones, glycosides, saponins, terpenoids, and tannins.

Formulation characteristics: Twelve formulations were created as a result of the design, and these formulations were tested in 3^3 factorial designs using folding endurance and disintegration time as the dependent factors and plasticizer, surfactant, and thickness concentrations as the independent variables (Table 2). Upon visual inspection, the formulations were found to be uniformly colored and light brown in appearance. Not changing in color till the study is over. The average thickness ranged from 0.33 to 0.62 mm, while the pH was found to be neutral and suitable for skin pH, ranging from 6.28 to 7.68. 6–12% of the moisture was lost, while 7–16% of the moisture was gained. F7 and F10

have the best formulation qualities. F7 and F10 disintegrated more quickly because the disintegration time was determined to be between 35 and 49. The F7 formulation swelling was confirmed by the swelling index, which was found to be between 15.2 and 36.1. to lessen the excipient's leaching at the location. The weight variance was determined to be in the range of 33.2-69.8, with the best formulations, F7 and F10, having the lowest weights that are ideal for the films to dissolve at the site. There was minimal variation in weight. Figure 4 of the SEM images showed the distinct morphology devoid of aggregates. The folding endurance of the F7 was found to be as low as 183, while the F10 had the highest value at 215. For the F7 and F10 formulations, the in vitro dissolution experiments showed a 99% release in 30 minutes. Therefore, based on the formulation characteristics (Figure 2, 3, 4, and Table 3, 4, 5, 6), F7 and F10 were determined to be the best match models for the investigation.

3.1. Optimization

Three independent variables—folding endurance (Y1), disintegration duration (Y2), and super-disintegrant (X3)—were found to have an impact on the design of oral films. The two dependent variables were shown to be influenced by these three independent variables. Twelve different formulas (F1 through F12) were created based on the provided factors; the accompanying table displays the outcomes of the experiments. For statistical analysis, the folding endurance (Y1) and disintegration duration (Y2) data were fitted into several polynomial models using the QbD 3^3 fractional factorial design (Table 5,6).

The combination of PEG 400 and Croscarmellose sodium showed better disintegration times than the other formulations, indicating higher efficacy in promoting the breakdown of the oral films (F7 to F12), as shown in Figures 5.1 and 5.2. The standard deviations (SD), R2 values, and observed responses are compared for each of the 3^3 fractional factorial designs in Tables 6 and 7. Furthermore, for each response variable for each of its corresponding variables, a proportionate rise was shown in the regression equations. Based on the provided data, it is evident that the three independent variables—X1, X2, and X3—have an impact on the two responses, Y1 and Y2. The intricate link between several variables and the desired response can be effectively illustrated using surface plots.

4. Conclusion

Traditional medicine has long recognized gingko biloba for its powerful anti-Alzheimer's effects. Therefore, the oral fast-dissolving films are specifically designed to solve and ensure the target delivery and bioavailability concerns through formulator adjustments. In order to create 12 formulations of the gingko biloba extract, the current study used a QbD 3^3 factorial design. Studies were conducted on all the usual methods for formulation and evaluation to ensure that the consistency of weight variation, moisture gain and loss, and appearance was maintained. PEG 400 and croscarmellose sodium together shortened the disintegration times and were more effective at promoting the breakdown of the oral films. Additionally, a quadratic model was followed by the linear model for suited for disintegration time and folding endurance. F7 and F10, the optimized formulations, were thus chosen as the best fit models.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

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