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INNOVATIVE APPROACHES IN DESIGNING A PREGABALIN ORODISPERSIBLE FILM FOR EPILEPSY TREATMENT

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ABSTRACT

The study aimed to develop a fast-disintegrating Pregabalin film, targeting API bitterness suppression, reduced disintegration time, and improved drug release. With Pregabalin bioavailability range affected by first-pass metabolism, a mouth dissolving film was chosen to circumvent this issue, particularly beneficial for pediatric epilepsy treatment. The buccal route was preferred due to enhanced absorption resulting from drug ionization at gastric pH. The process involved preparing a solid dispersion using the kneading method, followed by solvent casting, and evaluating it for API bitterness, solubility, drug content, and release rate. In vitro drug release analysis demonstrated that the solid dispersion effectively suppressed API bitterness, increased solubility, and achieved faster drug release compared to the pure drug. Various parameters such as physical appearance, surface pH, thickness uniformity, disintegration duration, drug content uniformity, folding durability, and tensile strength were assessed. A 3^2 full factorial design, utilizing Design-Expert® software Version 13, optimized the mouth dissolving film (MDF). The optimized MDF underwent evaluation for palatability, in vitro dissolution, ex vivo permeation, and stability. It exhibited a disintegration time of 25 seconds and released 90% of the drug within 6 minutes for Pregabalin, confirming its efficacy. Rapid stability studies indicated stability across all formulations under extreme conditions.

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Introduction

Oral dispersing medicines were created to benefit patients, particularly kids, who have difficulty swallowing traditional oral solid dosage formulations [1]. These products include dissolving tablets and oral lyophilized preparations [2]. These drugs offer an alternative dosage form that is very helpful for patients who are young, uncooperative, or elderly [3, 4]. Oral disintegrating films (ODFs) offer promise for administering water-soluble drugs since they disintegrate fast and don't require water [5, 6]. ODFs' small size, precise dosing, and fast breakdown make them very helpful for pediatric formulations. Compared to liquid formulations, they have better stability and convenience of administration [7-9]. In developed countries, there are 3.2 to 5.5 incidences of epilepsy for every 1000 children, and 12–39% of these cases also have attention deficit hyperactivity disorder [10, 11].

Pregabalin, commonly marketed as LYRICA, is a second-generation antiepileptic drug used to treat focal onset seizures and neuropathic pain in both adults and children [12, 13]. Its formulation as a mouth-dissolving film aims to maximize absorption by its buccal route, raise patient compliance, and avoid first-pass metabolism to increase bioavailability [14-16]. Among the characteristics of Pregabalin include its significant permeability, high solubility, and bitter taste [17, 18]. The study aimed to use a design of experiments (DoE) to create and evaluate pediatric oral disintegrating film formulations containing 25 mg of Pregabalin per film.

Materials and Methods

Materials

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Pregabalin, β Cyclodextrin, Glycerol anhydrous, Propylene Glycol, PVA, Hydroxypropyl methylcellulose E3, E5, E15, Sucralose, Eco cool, citric acid, chocolate flavor, Mannitol, ethanol (absolute HPLC grade) were purchased from SCION PHARMA PVT. LTD. Every experiment utilized distilled water. As supplied, all chemicals were utilized.

Methods

Formulation of Solid Dispersion

By using a conventional mixing procedure, several ratios of βCyclodextrin and Pregabalin (1:0.5, 1:1, 1:1.5, 1:2, 1:3, 1:4, 1:5, and 1:6) were used to generate solid dispersion (SD) [19]. A thick paste was produced by combining ethanol and water (in a 1:1 ratio) in a mortar and grinding with a porcelain pestle for 30-40 minutes until it dissolved [20]. The SD was sieved through a 250μ screen and kept for further examination after oven-drying [19].

Factorial Design in Experiment

Experimental factorial design was conducted using Design-Expert® software (Version 13), employing a statistical analysis approach. While response surface modeling was utilized to explore and optimize the non-linear multidimensional connection between components and response, a D-optimal design for the Design of Experiments (DoE) with a quadratic model was chosen. In an in-vitro drug release study, weight consistency (mg), crumbling time (sec), thickness (mm), collapsing persistence, and the effects of autonomous variables X1 Glycerol anhydrous (ml) and X2 (HPMC E15) (gm) were investigated using a 3^2 complete factorial design. This involved generating nine feasible trial bunches with two variables tested at three levels (1, 0, +1).

$$Y = \beta 0 + \beta 1A + \beta 2B + \beta 3AB + \beta 4A2 + \beta 5B2 \quad (1)$$

Eq. 1 represents the model used for analysis, where Y is the dependent variable, and $\beta 0$, $\beta 1$, $\beta 2$, $\beta 3$, $\beta 4$, and $\beta 5$ are regression coefficients.

Formulation of Oral Fast-Dissolving Film

We used a solvent-casting method for the formulation of fast-dissolving films. First, we took a fixed quantity of water and heated it in a glass beaker at 80-90°C, and film-forming polymers such as PVA or Hydroxypropyl methylcellulose (E3, E5, and E15) were added into the water while continuously stirring. To ensure a smooth dispersion of various percentage (w/v) solutions, the polymer solution was left overnight. Subsequently, plasticizers like Glycerol anhydrous or Propylene Glycol were added to the solution, with care taken to avoid bubble entrapment. If necessary, the solution was sonicated. In a separate vessel, a specified quantity of water was taken to dissolve the resulting solid dispersion of Pregabalin Super disintegrate, followed by the addition of a salivary agent, cooling agent, flavoring agent, and sweetening agent. The drug solution was then combined with the polymer solution using a magnetic stirrer for an hour to ensure homogeneity. Any trapped air bubbles were eliminated by setting the resultant solution aside and rinsing the vessel with the remaining specified quantity of water, which was then added to the solution and mixed well for 30 minutes. The film was cast onto polyester plastic film and dried at 90°C for 40-45 minutes. To determine the equivalent dose per strip, the film was carefully removed from the polyester plastic film, inspected for flaws, and cut to the necessary size (3 × 2 cm). Finally, the samples were stored in aluminum foil until further analysis.

Evaluation of Solid Dispersion

Practical Yield %

Calculating the percentage practical yield allowed for the selection of the most suitable production technique by providing information on the efficiency or percent yield of each given process. The equation below was used to compute practical yield once the final weights of the produced solid dispersions were determined.

$$\text{Yield} = [p/q + r] \times 100 \quad (2)$$

Where,
P is the weight of the solid dispersion sifted through a number 60 sieve
Q is the weight of Pregabalin taken for solid dispersion preparation,
R is the weight of β-Cyclodextrin taken for solid dispersion preparation.

Solubility

An excess of Solid Dispersion was added to the solvent (water, 7.4 pH phosphate buffer) at room temperature to determine the solubility. The solution combination was then filtered and examined using a Shimadzu UV 1800 double-beam spectrophotometer. If necessary, dilute the sample.

UV–VIS Spectrophotometric Assay Method for Pregabalin

To create a standard stock solution with a concentration of 1000 µg/mL, 25 mg of Pregabalin was weighed, transferred, and then volumetrically put into a 10 ml flask. Ten-milliliter volumetric flasks were filled with standard PGB (Pregabalin) solutions diluted with water, with final concentrations ranging from 5 to 50 µg/ml. 1 ml of 0.01N sodium hydroxide and 1 ml of 0.5% NQS (1, 2-Naphthoquinone-4-sulphonate) are added to these solutions [10]. Once the orange color started to emerge, the mixture was gently shaken. We used distilled water to dilute the contents up to 10 ml. In comparison to the reagent blank, each solution's absorbance was measured at 485 nm. The three-day sequence of experiments was carried out in triplicate. The regression coefficient was derived from the straight-line equation and shown against concentration on the data. Between five and forty-five mg/ml, there was linearity.

Evaluation of Oral Fast-Dissolving Films

Weight

Using an analytical balance, the average weight of each oral fast-dissolving film was calculated. Consistency in the film weight should be maintained. By verifying that a film has the appropriate quantity of excipients and API.

Thicknesses

Measuring the film's thickness with a micrometer screw gauge and calculating the average is essential for maintaining consistency, which directly impacts dosing accuracy. It is an important parameter to monitor as it can affect the Dosing frequency and efficacy of the film.

pH

Ensuring uniformity in the pH of the film is crucial. This was achieved by dissolving it in 10 ml of distilled water and performing the measurement in three separate sets to obtain the pH of the solution.

Folding Endurance

Studying the film's folding durability is crucial to understanding its flexibility during handling and storage. One film at a time, at the same location, was folded repeatedly until it broke to assess the film's folding durability. It is believed that this reveals good film qualities. An equal-sized film (3×2 cm^2) was cut, then folded at the same spot repeatedly until it broke. Every calculation was done three times.

Tensile Strength

The maximum load placed on a film at which it breaks is called its tensile strength. Eq. 3 below gives the calculation, which is based on dividing the applied load at rupture by the strip's cross-sectional area.

Tensile strength= maximum force at break/ initial cross-sectional area of film (3)

Uniformity

By dissolving one oral dissolving film containing 10 mg of medication in 100 ml of water, the drug content was ascertained. To guarantee the full solubility of the active component, the solution was sonicated for ten minutes without the use of heat. A 1 ml sample aliquot was taken out and mixed with 10 ml of water. Subsequently, the mixture was passed through Whatman filter paper and subjected to UV spectrophotometer analysis at the drug's 485 nm. For every batch of the film, three separate content uniformity studies were conducted.

Dispersion Test

The modified dispersion approach was carried out in accordance with the 2015 Vidyadhara *et al*. [7] protocol. To sum up, a Petri dish holding 10 ml of distilled water was filled with the necessary size of film (3 cm × 2 cm), and the dish was swirled every 10 seconds. The point at which the film began to fracture or crumble was measured as the dispersion time. Every study was carried out in triplicate for every batch.

In vitro Dissolution Studies

Using the USP type II (paddle) dissolving device, the release profile of a chosen ODF formulation was investigated. The pregabalin-containing film was submerged in 900 milliliters of pH 7.4 phosphate buffer. The trial was conducted with the paddle speed set at 100 rpm and the buffer temperature kept at 37 ± 0.5 ◦C. At the designated times, such as1,2,3,5,6,7,8,9, or 10 minutes, a sample of around 5.0 mL was taken out and the same volume was added back in right away to keep the sink condition. At 485 nm, absorbance was measured after the withdrawal samples were filtered through a 0.45 µm membrane. The entire procedure was carried out three times [21].

Taste Masked Pregabalin Film

With a score of 1 representing very disliked and a score of 9 representing highly liked, 25 panellists assessed the composition shown in **Table 1** using several sensory assessment criteria for flavours, mouthfeel, and taste. The Evaluation criteria are listed in **Table 2**.

Table 1. Evaluation of Parameters and score of palatability test.

Score	No. of Panellists	%	Parameters		
			Flavor	Mouth feel	Taste
3	2	9	Ok	Gritty and irritating	Bitter
4	1	5	Ok	gritty	Slight Bitter after 10 sec
5	1	5	Ok	ok	Increase sweetener Slightly
6	4	18	Ok	Good/Increase Slightly	After taste Slightly Bitter
7	9	41	Good/Increase Slightly	-	Good
8	4	18	Good/Appropriate/ should be less	Good/Appropriate/ should be less	Very Good
9	1	5	Very good	Very good	Excellent
Total Panellists	22	100			

Table 2. Evaluation criteria

9 Liked extremely	6 Liked slightly	3 Disliked moderately
8 Liked very much	5 Neither liked nor disliked	2 Disliked very much
7 Liked moderately	4 Disliked Slightly	1 Disliked extremely

Stability Study

The improved rapid-dissolving film formula underwent an accelerated stability investigation to determine its physical and chemical stability. Each film sample, measuring 3 cm by 2 cm, was wrapped in aluminum foil and kept at 40° C ± 02° C / 75% ± 5% RH) for three months. Pregabalin tensile strength, disintegration time, and cumulative drug release percentage at 6 minutes were measured for every fast-dissolving film sample at the predetermined time intervals of 1, 2, and 3 months.

Comparison of Optimized Pregabalin MDF with Marketed Pregabalin Formulation

The optimized formulation of Pregabalin MDF will be compared with the Marketed product Pregabalin. The results are shown in **Figure 1**.

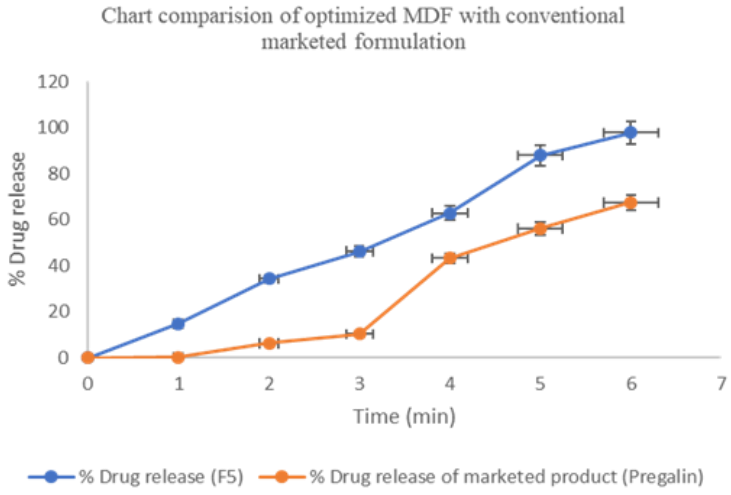


Figure 1. Chart comparison of optimized MDF with conventional marketed formulation
*All results are shown in mean ± S.D. (n=3)

Results and Discussion

Primary Screening of Drug: Carrier Ratio for Solid Dispersion

Practical % Yield

For further investigation, the ideal solid dispersion formulation of 1:2 weight ratio Pregabalin:β-Cyclodextrin was chosen. **Table 3** illustrates the percentage practical yield of Pregabalin solid dispersions, which ranged from 88.33 to 94.5. Low solid dispersion values in the percent practical yields assured that there was no major drug loss during the preparation of solid dispersions. The solvent employed does not influence the outcomes when kneading mixes are prepared. The percentage yield was low for 1:3 and high for 1:2.

Table 3. % Practical Yield and Solubility data of Solid Dispersions Containing Pregabalin (mean ±S.D.) (n=3)

% Practical Yield			Solubility data		
Sr. No.	**Drug: polymer**	**% yield**	**Solvent**	**Absorbance (mean± S.D.)**	**Solubility (mg/ml)**
1	1:0.5	88.33	Distilled water & planned drug	0.265	11.32
2	1:1	87.1			
3	1:1.5	92.5			
4	1:2	94.3			
5	1:3	81.2	Distilled water & Drug:β-CD (1:2)	0.416	19.29
6	1:4	90.2			
7	1:5	93.3			
8	1:6	92.1			

Solubility

Using kneading mixes, the drug:β -cyclodextrin inclusion complex was produced in various ratios. The inclusion complex of β-cyclodextrins enhances the drug's solubility and dissolving properties at the ideal concentration (1:2).

Refinement of Formulation

Design experts' statistical methods were utilized to improve the oral fast-dissolving films. A clear solution was rapidly generated by the plasticizer polymer and film forming. Compared to other polymers, the combination produced more transparent, flexible sheets. Ranges for formulation and processing variables may be explored, and optimization approaches offer a deep understanding of these ranges. Quantitatively selecting a formulation involves using a logical approach to choosing the various excipients and manufacturing processes for a particular product [8, 9].

Optimization can now be a helpful technique to quantify a formulation that has been determined qualitatively. ANOVA was used to do a statistical analysis of the acquired data using Design-Expert (Version.13) software. To investigate the interaction between HPMC E15 (gm) (X2) and glycerol anhydrous (ml) (X1), the results were further submitted to the 3-D response surface approach **(Figure 2a)**. **Table 4** displays the real Pregabalin fast-dissolving film formulation design based on the complete factorial design (3^2) arrangement.

Table 4. Batches concentrations of fast disintegrating films of Pregabalin

Ingredients	**PGB F1**	**PGB F2**	**PGB F3**	**PGB F4**	**PGB F5**	**PGB F6**	**PGB F7**	**PGB F8**	**PGB F9**
PGB+βCyclodextrin(mg)					25				
Glycerol anhydrous (ml)	1	1.5	2.0	1	1.5	2.0	1	1.5	2.0
HPMC E15 (gm)		0.25			0.30			0.35	
SSG (gm)					0.075				
Eco cool (gm)					0.040				
Citric acid (gm)					0.070				
Mango flavor (gm)					0.050				
Sucralose (gm)					0.050				
Distilled water (ml)					10				

The parameter Tensile strength can be described by the model equation, TS= 2.24 – 0.0300 X1 – 0.5100 X2 - 0.0550 X1 X2 + 0.3067 X1 X1 + 0.3867 X2 X2. The formulation's tensile strength was negatively impacted by a reduced concentration of glycerol anhydrous and HPMC E15, as shown by the negative signs for coefficients X1 (– 0.0300 X1) and X2 (– 0.5100 X2). A good correlation between the independent and dependent variables is indicated by the tensile strength's R-value of

0.8918. Model significance is implied by the expression "Prob value with 0.0001". Model terms are important if the value of "Prob > P" is less than 0.0500. Values higher than 0.1000 signify that the model terms lack significance.

The formula for the parameter Disintegration time is DT= 72.80 + 2.75 X1 – 40.88 X2 – 3.39 X1 X2 + 14.04 X1 X1 – 3.85 X2 X2. The formulation's disintegration time is positively impacted by a larger concentration of glycerol anhydrous, as indicated by the positive sign for coefficient X1 (+ 2.75 X1). Significantly affecting the formulation's disintegration time is the concentration of HPMC E15, as indicated by the negative sign for coefficient X2 (-40.88 X2). The disintegration time's R-value of 0.987733 shows a strong association between the independent and dependent variables. The model is deemed significant by the term value of 0.0011. Model terms are significant if the value of "Prob> P" is less than 0.0500. Values higher than 0.1000 signify that the model terms lack significance.

The parameter %Cumulative drug release can be described by the model % CDR= 92.88 – 1.25 X1 + 5.11 X2+ 0.12 X1 X2 – 2.50 X1 X1 – 2.84 X2 X2 The Negative sign for coefficient X1 (-1.25 X1) is that higher concentration of Glycerol anhydrous in the formulation hurts the %Cumulative drug release of the formulation. A considerable positive influence of HPMC E15 concentration on the formulation's cumulative drug release was shown by the positive sign for coefficient X2 (+ 5.11X2). An R-value of 0.935438 for cumulative medication release shows that the independent and dependent variables have a strong association. A substantial model is implied by the term value of 0.0002. (Model terms are significant if the value of "Prob> P" is less than 0.0500. Values higher than 0.1000 signify that the model terms lack significance.)

Tensile strength, Disintegration time, %Cumulative drug release optimized formulation (F5) were found to be 2.85± 0.06Kg/cm2, 60.25 ± 2.01Sec and 91.10±1.25 %. The mouth-dissolving oral film of Pregabalin (F5) demonstrated good tensile strength, rapid disintegration, and a percentage of cumulative drug release, according to the data **(Table 5)**.

Table 5. Batch-wise results of oral fast-dissolving film

Formulations	X_1	X_2	Tensile strength *(Y1)	Disintegration Time *(Y2)	CDR* in 6 min (Y3)
	Glycerol anhydrous	HPMC E15	Kg/cm^2	Seconds	%
F1	-1	-1	2.54 ±0.07	75.33± 1.52	86.86± 1.72
F2	0	-1	2.28 ± 0.26	68.66± 6.11	85.76 ± 0.83
F3	+1	-1	2.15 ±0.39	62.33 ±4.93	82.82±0.81
F4	-1	0	2.48 ± 0.04	78.33 ± 4.72	83.39± 0.44
F5	0	0	2.85± 0.06	60.25 ± 2.01	91.10±1.25
F6	+1	0	2.36± 0.08	90.03 ±3.14	90.21± 0.32
F7	-1	+1	2.50 ± 0.06	98.14 ± 4.58	90.03±0.52
F8	0	+1	3.61±0.07	133.24 ±10.81	82.15± 4.30
F9	+1	+1	3.57± 0.38	164.12±7.21	76.54± 0.50

*All results are shown in mean ± S.D. (n=3)

Evaluation of Factorial Design Batches

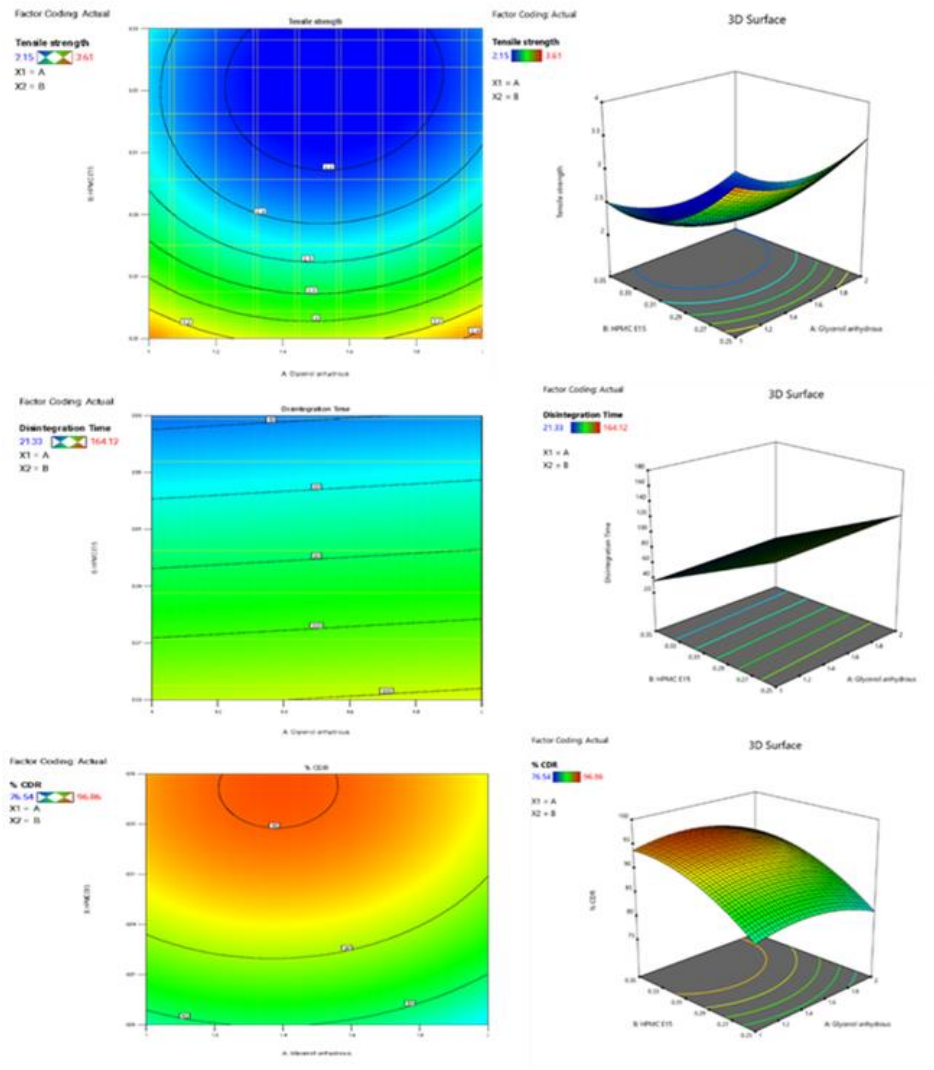
The 1.74 ml glycerol anhydrous plasticizer and 0.362 gm HPMC E15 polymer are employed, per the appealing research and overlay investigation. Based on the assessment of factorial plan clumps perception, overlay study, tensile strength, disintegration time, and percent drug discharge, the detailing F5, comprising 0.30 gm HPMC E15 polymer and 1.5 ml glycerol anhydrous plasticizer, was selected as the improved cluster.

This layout successfully captured the area that matched the perfect details. To create this overlay plot, a structural plot was overlapped with the essential reaction forms. In the variable space, the zone of enticing response is visually shown **(Figure 2b)**.

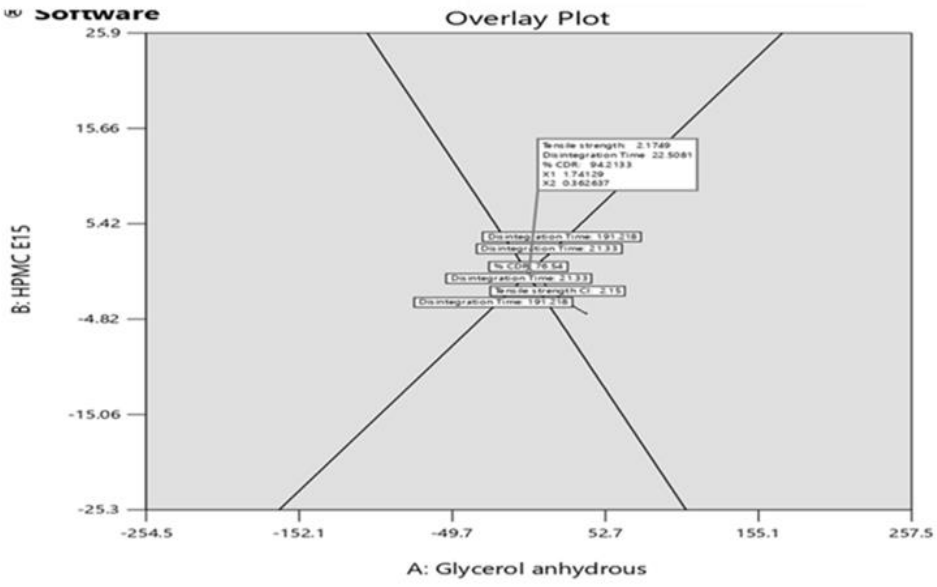
Because of the developed spot group, a projected value and discovered worth are practically the same. Tensile strength (2.03±0.58), % drug release (92.25±3.18), and disintegration time (25.26±0.58). As a result, it is perceived as a clump that has been improved and chosen to create a mouth-dissolving film.

The results of the film-forming process, using selected polymer and plasticizer concentration is gave by lowest disintegration 0.15±0.02 minutes, 299.25±1.15 a good mechanical qualities (folding endurance more than 200/tensile strength), and a surface pH of 6.7±0.04, which is within the normal physiological pH range of the oral cavity.

The cumulative percentage of Pregabalin release between prepared formula F5 and marketed Pregabalin oral dispersible tablet (Pregalin), as illustrated in **Figure 1**, by comparing the dissolution release profile of the chosen fast-release layer formulation F5 gave 90% drug release in 6 min with the 60% drug release profile of the marketed product Pregalin oral dispersible tablet release in 6 min.



a)



b)

Figure 2. a) Influence of independent variables on responses. The information shown was produced utilizing programming, and the surface plot and reaction surface plot were made utilizing a factorial plan. Fig show the Surface plot of the variable's effect on responses Y1, Y2, and Y3, as well as the Reaction surface plot of the variable's effect on responses Y1, Y2, and Y3. b) Overlay plot for optimized batch. According to the attractiveness research and overlay study, the 1.74 ml Glycerol anhydrous plasticizer and 0.362 gm HPMC E15 polymer are used

Taste Masking Evaluation

Human panel participants assessed taste masking. Taste masked pharmaceutical composition of inclusion complexes PREGABALIN with β- CYCLODEXTRINS in selected ratio 1:2 by using SOLID DISPERSION (Kneading) Technique. The complex-forming ability of CD is suppression of the API bitterness. Due to their highly hydrated exterior, these complex molecules do not adhere to the T2R (taste buds) in the oral cavity of the tongue. The results are depicted in **Table 1**.

Stability Study

The sample was stored at (400 C ± 020 C / 75 % ± 5% RH) and the initial condition did not reveal any changes in Tensile strength, Disintegration Time (Sec), or % CDR. Instability studies results show in **Table 6**, that the increased lag time suggests the potential for drug and polymer moisturizing reactions during the study period. However, the Tensile strength, Disintegration Time, and Dissolution profile of the film-forming product have had very little effect. No significant change was observed in all Parameters of drugs before and after 3-month stability studies.

Table 6. Stability study

Parameter	**Initial***	**After 3 months***
	(40^0 C ± 02^0 C / 75 % ± 5% RH) Storage condition	
Appearance	Very good	Very good
Tensile strength(kg/cm^2)	2.03 ± 0.58	2.37±0.63
Disintegration Time(Sec)	25.26±0.58	25.59 ± 4.34
% CDR	92.25 ± 3.18	92.05±1.47

*All results are shown in mean ± S.D. (n=3)

Conclusion

This work aimed to create an oral dissolving film with enhanced solubility and bitterness of Pregabalin. Pregabalin solid dispersion was formulated using β- Cyclodextrins in ratio 1:0.5,1:1,1:1.5,1:2,1:3,1:4,1:5 and 1:6 by Kneading Technique. Pregabalin:β-Cyclodextrin solid dispersions with an ideal weight ratio of 1:2 were chosen. Additionally, the films were created using the solvent casting technique. For quick film hydration, the film-forming polymer HPMC E15 was employed. For quick disintegration, sodium starch glycolate was employed as a super disintegrant. Several factors were investigated for the films, including thickness, folding endurance, in-vitro disintegration duration, in-vitro dispersion research, taste masking, and stability testing. Mixing sugars, flavors, and citric acid allowed for the successful masking of taste. When creating a mouth-dissolving film, the type of flavoring ingredient used was crucial. HPMC E-15 and glycerol anhydrous independent variable, where tensile strength, disintegration time, and cumulative drug release percentage were measured using a 32-factorial design. The optimal formulation was determined to be 1.5 ml glycerol anhydrous plasticizer and 0.30 gm HPMC E15 polymer based on the findings. Characterization and in-vitro experiments revealed that β-cyclodextrins, in particular HPMC E-15 as a film-forming polymer and glycerol anhydrous as a plasticizer, may dissolve the oral dissolving film of Pregabalin, In contrast to the commercial product Pregalin oral tablet, the Pregabalin mouth dissolving film formulation was thought to have a superior approach that improved the dissolve rate. During three months at 400 C ± 020 C / 75% ± 5% RH, the optimized batch F5 was found to be stable, indicating that an optimum dosage form of Pregabalin for treating epilepsy might be developed.

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Conflict of interest: None

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Ethics statement: None

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