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ENHANCING SOLUBILITY AND DISSOLUTION OF RESERPINE THROUGH OPTIMIZED SOLID DISPERSION AND FAST- DISSOLVING FILM FORMULATION: A QUALITY BY DESIGN APPROACH

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Keywords:

Reserpine, Anti-hypertensive agent, Solubility enhancement, Dissolution characteristics and Quality by Design (QbD)

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ABSTRACT: This study aims to enhance the therapeutic effectiveness of reserpine, an essential anti-hypertensive agent, by addressing its poor solubility and dissolution properties. Employing a Quality by Design (QbD) methodology, the research systematically optimized the formulation using solid dispersion technology and fast-dissolving films. Characterization of reserpine included its physical properties, such as melting point and partition coefficient, along with the establishment of a validated UV method for accurate quantification. The optimized solid dispersion (DRPSD14) achieved a theoretical solubility of 14.94% and dissolution of 96.88% at 20 minutes. Subsequently, a fast-dissolving film was developed from the optimized solid dispersion. Among twelve formulations, DRPSD14FDF11 exhibited promising characteristics, with 98.977±0.253% reserpine content. *In-vitro* dissolution studies demonstrated rapid dissolution for all formulations, with DRPSD14FDF11 displaying the highest dissolution rate. Release kinetics modeling and Fourier-transform infrared spectroscopy (FTIR) confirmed uniform drug distribution in the film, which also exhibited stability under various storage conditions. Guided by QbD principles, this comprehensive approach successfully optimized reserpine's pharmaceutical properties, offering a promising formulation for hypertension treatment. The study provides valuable insights into formulation variables, enhancing therapeutic outcomes and extending reserpine's clinical applications.

INTRODUCTION: Blood pressure (BP) stands as a pivotal factor influencing cardiovascular and renal health within populations [1]. Hypertension remains a pervasive health concern globally, necessitating the continuous exploration of innovative formulations to enhance the therapeutic efficacy of anti-hypertensive drugs.

QUICK RESPONSE CODE

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Reserpine, derived from the roots of Rauwolfia serpentina, stands out as a significant agent in managing hypertension and certain neurological disorders [2, 3]. However, its clinical utility is impeded by poor aqueous solubility, leading to suboptimal bioavailability and unpredictable pharmacokinetics [4].

To overcome these challenges, researchers have undertaken formulation strategies, and one promising avenue involves the combination of solid dispersion technology and fast-dissolving films [5, 6]. Solid dispersion has been widely acknowledged for its potential in improving the solubility of poorly water-soluble drugs, while fast-dissolving films

offer a patient-friendly dosage form with enhanced drug dissolution and absorption [7]. This study builds upon these principles, seeking to optimize the solubility and dissolution characteristics of reserpine through the synergistic application of solid dispersion and fast-dissolving film formulation.

Quality by Design (QbD) principles guides the systematic development of pharmaceutical formulations, emphasizing a comprehensive understanding of formulation variables and their impact on the final product [8, 9]. QbD ensures a scientific and reproducible approach to product development, ultimately resulting in a robust formulation [10].

In the context of this research, QbD principles serve as a guiding framework to unravel the intricate interplay of formulation variables in the design of solid dispersions and fast-dissolving films for reserpine.

This introduction sets the stage for a comprehensive exploration of reserpine's pharmaceutical properties, emphasizing the need for improved solubility and dissolution characteristics. By employing a QbD approach and integrating solid dispersion technology with fast-dissolving films, this research aims to provide valuable insights that contribute to the advancement of reserpine-based pharmaceuticals. The subsequent sections will delve into the experimental methodology, results, and discussion, ultimately offering a promising avenue for addressing the challenges associated with reserpine's limited bioavailability and expanding its therapeutic potential.

MATERIAL & METHOD:

Preparation of Reserpine Poly Ethylene Glycol Containing Fast Dissolving Film: The solvent casting approach was employed to develop a fast-dissolving dissolving film that contains reserpine polyethylene glycol solid dispersion.

An accurately measure amount of the solid dispersion equivalent to the 4mg of reserpine, film-forming polymer HPMC of varying grade, citric acid and plasticizer, were added to the beaker containing water and under continuous stirring at 100 rpm until a clear solution was achieved. A glass Petri dish measuring 28.56 cm^2 in area was used to transfer the aqueous solution, which was then dried at room temperature. Depending on the temperature, the film takes between 5 and 12 hours to dry. Carefully removing the dried film and cutting it to the appropriate size for testing [11].

TABLE 1: COMPOSITION OF THE RESERPINE-POLY ETHYLENE GLYCOL SOLID DISPERSION AS PER THE CENTRAL COMPOSITE DESIGN

Formulationcode	Factor 1 X1: Amount of drug (mg)	Factor 2 X2: Amountof PEG (mg)	Response 1 Y1: Percentagesolubility (%)	Response 2 Y2:Percentage dissolution at 20min (%)
DRPSD1	4	120	15.11	97.664
DRPSD2	4	120	14.43	97.076
DRPSD3	2	80	8.24	88.304
DRPSD4	6	160	9.08	88.012
DRPSD5	4	120	13.74	96.199
DRPSD6	4	120	13.91	96.491
DRPSD7	6	80	3.09	81.287
DRPSD8	6.82	120	7.85	85.088
DRPSD9	4	63.43	2.17	84.211
DRPSD10	1.17	120	13.88	86.842
DRPSD11	2	160	11.6	83.626
DRPSD12	4	176.56	8.88	85.965
DRPSD13	4	120	15.05	97.661

Percentage Drug Content: A precisely measured Patch theoretically equivalent to 4mg reserpine was dissolved in 10ml of water and shaken for 10 minutes. To remove the undissolved particles, the resulting solution was centrifuged at 10,000 rpm for 15 minutes. Drug concentration in the supernatant solution was appropriately diluted with methanol before being spectrophotometrically measured at 268 nm with further dilutions against the suitable blank [12].

TABLE 2: PERCENTAGE DRUG CONTENT

Formulation code	Percentage drug content
DRPSD14FDF1	91.082±1.540
DRPSD14FDF2	92.398±0.913
DRPSD14FDF3	95.906±1.013
DRPSD14FDF4	94.737±0.760
DRPSD14FDF5	92.690±0.560
DRPSD14FDF6	95.322±0.670
DRPSD14FDF7	93.860±0.760
DRPSD14FDF8	94.006±1.104
DRPSD14FDF9	96.784±1.266
DRPSD14FDF10	91.520±0.506
DRPSD14FDF11	98.977±0.253
DRPSD14FDF12	96.053±0.877

Weight of Patch: The Weight of 2×2cm^2 film form all tested formulations was recorded employing an electronic balance.

TABLE 3: WEIGHT OF THE PREPARED FORMULATIONS

Formulation code	Weight (mg)
DRPSD14FDF1	434.120±0.125
DRPSD14FDF2	434.743±0.110
DRPSD14FDF3	434.463±0.105
DRPSD14FDF4	434.227±0.120
DRPSD14FDF5	335.310±0.555
DRPSD14FDF6	534.610±0.451
DRPSD14FDF7	834.967±0.734
DRPSD14FDF8	535.013±0.634
DRPSD14FDF9	535.177±1.025
DRPSD14FDF10	484.367±0.199
DRPSD14FDF11	634.497±0.125
DRPSD14FDF12	734.360±0.331

Thickness: A screw gauge was employed to measure the thickness of the 2×2 cm^2 fast-dissolving film. After ensuring that the pointer was set to zero, the anvil of the thickness gauge was cranked, and the film was then inserted. The film was supported by the anvil, and the dial reading was recorded [13].

TABLE 4: THICKNESS OF THE PREPARED FORMULATIONS

Formulation code	Thickness (mm)
DRPSD14FDF1	1.365±0.023
DRPSD14FDF2	0.493±0.006
DRPSD14FDF3	0.560±0.025
DRPSD14FDF4	0.747±0.030
DRPSD14FDF5	0.512±0.010
DRPSD14FDF6	0.593±0.008
DRPSD14FDF7	0.627±0.004
DRPSD14FDF8	0.614±0.003
DRPSD14FDF9	0.494±0.001
DRPSD14FDF10	0.511±0.009
DRPSD14FDF11	0.522±0.007
DRPSD14FDF12	0.528±0.008

Solubility of the Reserpine in Solvents: Solubility of the reserpine shown in **Table 5.**

TABLE 5: SOLUBILITY OF THE RESERPINE IN DIFFERENT SOLVENTS

Solvent	Solubility (mg/ml)
Water	0.006±0.001
Simulated salivary fluid pH 6.8	0.009±0.001
Methanol	1.263±0.020
Ethanol	0.093±0.001
0.1NHcl	0.007±0.001

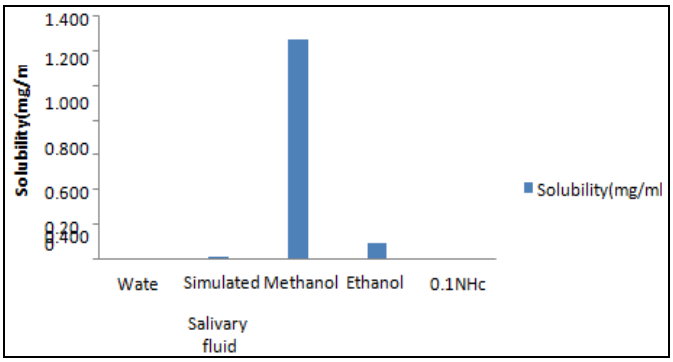

FIG. 1: SOLUBILITY PROFILE OF RESERPINE

Preparation of Reserpine Poly Ethylene Glycol Solid Dispersion (SDs): In order to expedite the drug's disintegration, reserpine solid dispersion was prepared. Drug and polymer particles had direct contact with one another in the solid dispersion's dry condition.

The high hydrophilic potency of polyethylene glycol in the mixture allowed the polymer particles to hydrate quickly into polymer solution when the mixture came into contact with water, which improved the drug particles' wettability. Therefore, higher solubility and dissolution of reserpine from solid dispersion may be connected to surface activity, the wetting effect, which may result in less agglomeration and consequently greater surface area, and the solubilizing impact of poly ethylene [14].

A number of process and formulation characteristics, such as a different technique, a different polyethylene glycol molecular weight, a different volume of polyethylene glycol, a different amount of reserpine, and a different cooling temperature. All of the prepared reserpine-loaded solid dispersions were tested using a variety of assessment criteria, including % yield, reserpine solubility, and percentage dissolution at 20 minutes.

The fusion process was used to develop solid dispersions of reserpine with PEG 20000 in an effort to increase the drug's solubility and behavior during dissolution. The percentage of reserpine dissolved from its solid dispersion formulations as a function of time. By creating solid dispersions with varied amounts of PEG 20000, the impact of changing the reserpine-to-PEG 20000 ratio in the solid dispersions was examined (4mg, 40mg, 80mg, 120mg, 160mg). It is apparent that when the PEG 000 content increased, the solubility and dissolution rate of reserpine increased as well. Increased wettability and dispersibility of a drug from the dispersion, drug dissolution in the hydrophilic carrier, drug conversion to an amorphous state, and finally the combination of the mentioned techniques are some of the potential mechanisms for increased solid dissolution rates. Thus, a number of mechanisms, including the solubilization impact, the change to an amorphous state, and greater wettability of reserpine, can contribute to the higher dissolving rate reported in this situation. Only this formulation was employed for the screening of additional parameters because the solid dispersions formulation with the higher amount of PEG 20000 (120 mg) displayed a higher dissolving profile (97.368±0.877%).

It is possible that the high viscosity of the molten poly ethylene glycol, which results in less uniform dispersion and low solubilization of the reserpine into the molten poly ethylene glycol dispersion, is the cause of the solubility and percentage dissolution both decreasing on further increase in concentration beyond 120mg. It was discovered that the percentage drug content ranged from 34.839±0.755% to 95.468±0.670% [15].

Effect of Different Amount of the Drug: As shown in table 6 different concentrations of reserpine (2 mg, 4 mg, and 6 mg) were studied during the preparation of the reserpine-loaded solid dispersion. The prepared solid dispersion was then evaluated through *in-vitro* characterization parameters like percentage yield, reserpine solubility, and percentage dissolution at 20min.

TABLE 6: *IN-VITRO* CHARACTERIZATION PARAMETERS

Formulation code	Visual appearance	Percentage yield (%)	Percentage drug content (%)	Percentag solubility (%)	Percentage dissolution at 20 min (%)
RPSD9	Off whitepowder	99.399±0.310	92.398±1.104	8.611±0.091	80.117±1.340
RPSD4	Off whitepowder	99.220±0.283	95.468±0.607	12.339±0.023	97.368±0.877
RPSD10	Off whitepowder	99.497±0.279	90.936±0.506	7.690±0.134	77.485±0.506

Solid dispersions containing varying amounts of the reserpine drug were made using the fusion method in an effort to increase the drug's solubility and behavior during dissolution. The percentage of reserpine dissolved over time from its solid dispersion formulations is shown in **Table 7**. By forming dispersions with variable amounts of reserpine, the effects of these variations in reserpine concentration were examined (2mg, 4mg, 6mg). It is evident that up to a concentration of 4 mg of reserpine (12.339±0.023% and 97.368±0.877%), the solubility and dissolution rate of reserpine improved with increasing concentration. However, at higher concentrations, the solubility and dissolution rate of reserpine decreases. Similar findings have been attributed to the creation of a polymer outer layer that regulates drug release, a continuous drug layer, or the discharge of intact particles from which disintegration spreads across a wide area. The percentage drug concentration was observed to range from 92.398±1.104% to 95.468±0.607% [16, 17]. At greater drug concentrations (6 mg), the drug, once freed from the dispersion, controls the dissolving rather than the polymer. According to the theory, dissolution begins quickly as the PEG 20000 on the disc's surface dissolves but then slows down due to the substantial amount of drug already present in the dissolution media. In order to further screen the process parameters, the drug concentration of 4 mg was used [18].

Effect of Cooling Temperature: The preparation of the reserpine-loaded solid dispersion was investigated at different cooling temperatures (25°C, 10°C, and 2°C), and the prepared solid dispersion was assessed using *in-vitro* characterization parameters like percentage yield, solubility of the reserpine, and percentage dissolution at 20 min as shown in **Table 8.**

TABLE 7: *IN-VITRO* CHARACTERIZATION PARAMETERS

Formulation code	Visual appearance	Percentage yield (%)	Percentage drug content (%)	Percentage solubility(%)	Percentage dissolution at 20 min (%)
RPSD4	Off whitepowder	99.220±0.242	95.468±0.670	12.339±0.023	97.368±0.877
RPSD11	Off whitepowder	99.220±0.242	96.491±1.3016	13.713±0.135	97.661±1.826
RPSD12	Off whitepowder	99.140±0.168	99.269±0.508	15.965±0.191	98.830±0.506

The fusion approach was used to create solid dispersions with various cooling temperatures, with the goal of enhancing the solubility and dissolution behavior of reserpine. According to Table 7, reserpine's solubility and dissolution both increase with lowering cooling temperature, though not significantly. A higher energy state for drug particles at low temperatures, leading to a more amorphous shape, maybe the cause of the observed relationship between temperature and amount of drug dissolved. The produced solid dispersion has the highest solubility and dissolution (15.965±0.191% and 98.830±0.506%) when it is cooled to 2°C. As a result, 2°C was chosen as the cooling temperature for the formulation's subsequent development. The percentage drug concentration was revealed to be between 95.468 ± 0.670% to 99.269±0.508% [19].

Optimization of Reserpine-poly Ethylene Glycol Solid Dispersion using the Central Composite Design: The central composite response surface design was used to suggest a total of 13 trial formulations of the sreserpine-poly ethylene glycol solid dispersion for the following independent variables: PEG 20000 and reserpine amount were adjusted to three different levels. The amount of solid dispersion dissolved in 20 minutes (Q 20) and the percentage solubility of each batch was measured. Multiple regression was used to produce an interactive and polynomial equation from the dependent variables that were collected at three levels of the two independent variables (X1 and X2). The primary impacts (X1 and X2) show what happens when you gradually increase each element from a low value to a high value. The answer alters when two factors are simultaneously altered, as shown by the interaction term (X1X2). The polynomial terms (X1 and X2) are including investigating nonlinearity.

For the 13 trial batches (DRPSD1 to DRPSD13), the percentages of solubility and dissolution at 20 minutes indicated a significant range of 2.17% to 15.11% and 81.28 to 97.66%, respectively **Table 8.**

TABLE 8: SUMMARY OF THE CENTRAL COMPOSITE DESIGN

Factor	Name	Units	Low actual	High actual	Mean
X1	Amount of drug	Mg	2	6	4
X2	Amount of PEG	Mg	80	160	120
Response	Name	Units	Analysis	Minimum	Maximum
Y1	Percentage solubility	%	Polynomial	2.17	15.110
Y2	Percentage dissolution at 20 min	%	Polynomial	81.28	97.66

The observation demonstrates a substantial relationship between the chosen independent variables and the % solubility and dissolution at 20 minutes. **Table 10** displays the model (full and reduced), which links the responses, % solubility, and percentage dissolution at 20 minutes to the transformed factor.

TABLE 9: COMPOSITION OF THE RESERPINE-POLY ETHYLENE GLYCOL SOLID DISPERSION AS PER THE CENTRAL COMPOSITE DESIGN

Formulation code	Factor 1 X1: Amount of drug (gm)	Factor 2 X2: Amount of PEG (mg)	Response 1Y1: Percentage solubility (%)	Response 2Y2: Percentage dissolution at 20 min (%)
DRPSD1	4	120	15.11	97.664

DRPSD2	4	120	14.43	97.076
DRPSD3	2	80	8.24	88.304
DRPSD4	6	160	9.08	88.012
DRPSD5	4	120	13.74	96.199
DRPSD6	4	120	13.91	96.491
DRPSD7	6	80	3.09	81.287
DRPSD8	6.828427125	120	7.85	85.088
DRPSD9	4	63.43145751	2.17	84.211
DRPSD10	1.171572875	120	13.88	86.842
DRPSD11	2	160	11.6	83.626
DRPSD12	4	176.5685425	8.88	85.965
DRPSD13	4	120	15.05	97.661

Percentage Solubility ANOVA: The result of the analysis of variance (ANOVA) for the model simplification by eliminating on significant terms ($P > 0.05$) was shown in **Table 11.**

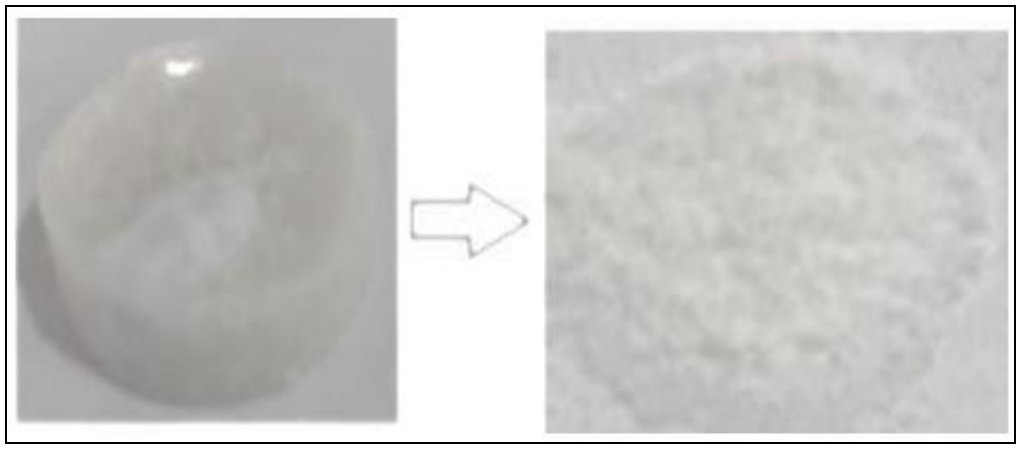

FIG. 4: IMAGE OF OPTIMIZED FORMULATION DRPSD14

TABLE 10: ANOVA FOR THE RESPONSE PERCENTAGE SOLUBILITY

Source	Sum of Squares	df	Mean Square	F Value	p- value Prob >F	
Model	231.4457	5	46.28914	184.0859	<0.0001	Significant
X1- Amount of drug	32.79572	1	32.79572	130.4243	<0.0001	
X2- Amount of PEG	44.36525	1	44.36525	176.4348	< 0.0001	
X1X2	1.729225	1	1.729225	6.87690	0.0343	
X12	23.5424	1	23.5424	93.62506	<0.0001	
X22	141.4728	1	141.4728	562.6189	<0.0001	
Residua l	1.760178	7	0.251454			
Lack of Fit	0.168498	3	0.056166	0.141149	0.9302	Not significant
Pure Error	1.59168	4	0.39792			
Cor	233.2059	1				
Total		2				
Std. Dev.	0.501452		R-Squared	0.992452		
Mean	10.54077		Adj R-Squared	0.987061		
C.V. %	4.757261		Pred R-Squared	0.984198		
PRESS	3.685211		Adeq Precision	36.251		

TABLE 11: DIAGNOSTICS CASE STATISTICS ACTUAL VALUE AND PREDICATED VALUE

Standard Order	Actual Value	Predicted Value	Residual
1	8.24	8.426	-0.186
2	3.09	3.061	0.028
3	11.6	11.820	-0.220

4	9.08	9.086	-0.006
5	13.88	13.632	0.247
6	7.85	7.905	-0.055
7	2.17	2.098	0.071
8	8.88	8.759	0.120
9	15.05	14.448	0.602
10	13.74	14.448	-0.708
11	15.11	14.448	0.662
12	13.91	14.448	-0.538
13	14.43	14.448	-0.018

Preparation of the Reserpine-polyethylene Glycol Complex Fast Dissolving Film: Fast dissolving films are widely used in the pharmaceutical sector thanks to their many benefits, including precision dose, easy administration, and quick bioavailability. According to several studies, notably in paediatric and geriatric patients, 80% of patients prefer fast-dissolving dosage forms over traditional solid oral dosage forms. Because of this, many drugs, including donepezil, rotavirus vaccine and dextromethorphan, have been developed and sold as FDFs. The restriction of the dose size is a crucial factor to take into account while manufacturing medicine into FDF.

Due to the thickness requirement of the film a good film should be thin, tiny, and not impede the tongue's movement drugs with higher doses are challenging to formulate into FDF.

Films have been made using a variety of methods, including solvent casting, hot melt extrusion, solid dispersion extrusion, semisolid casting, and gel rolling. Solvent casting, however, is the type most frequently used in industry. Reserpine film was created in this study using the solvent casting technique. This method has been employed in numerous experiments that have demonstrated its ability to produce high- quality films with consistent thickness, excellent clarity, and desirable physical qualities.

A typical FDF consists of a medicine, a water-soluble polymer, a plasticizer, a saliva-stimulating ingredient, and various fillers, such as sweeteners and flavours in the case of drugs and colours with bitter tastes. The composition of the film should be given careful study because it has a significant impact on both its mechanical qualities and, consequently, its delivery profile. In this work, twelve distinct formulations with modified polymer and plasticizer percentages have been developed. For a film to be nonsticky and useful, the choice of the ideal polymer dosage is essential. The ideal film-forming polymer should be safe and non-irritating and should have excellent wetting properties, great spreadability, and nice mouth feel. Numerous studies have demonstrated the necessity of a polymer content of at least 10% to 15% in order to create a film that will dry properly and be thick enough to peel off from the release line.

According to the manufacturer's instructions, sodium alginate and various grades of the polymers employed in this investigation. HPMC, on the other hand, is regarded as a water-soluble polymer and has been utilised in numerous FDF investigations that have demonstrated its effectiveness in producing high-quality films. The benefits of water- soluble polymers include good mechanical qualities, rapid disintegration, and a pleasing mouth feel [265].

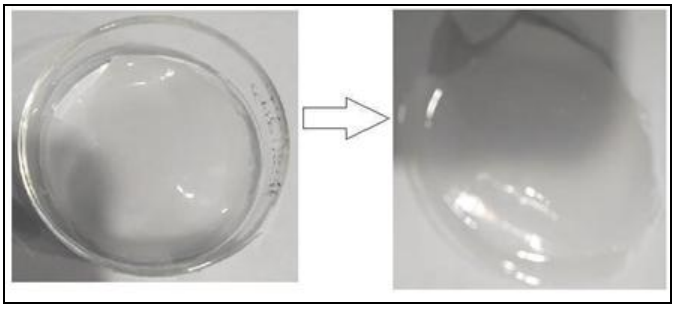

FIG. 5: IMAGE OF THE PREPARED RESERPINE-POLYETHYLENE GLYCOL LOADED FAST DISSOLVING PATCH DRPSD14FDF11

***In-vitro* Characterization of the Reserpine-polyethylene Glycol Loaded Fast Dissolving Patch:**

Physical Appearance and Film Forming Capacity: The physical characteristics and ability to form films of the polymer depicted in **Table 13** were examined for each prepared formulation.

TABLE 12: PHYSICAL APPEARANCE AND FILM FORMING CAPACITY

Formulation code	Visual Observation	Film forming Capacity
DRPSD14FDF1	Homogeneous, Uniform, Flexible, Smooth little brittle and break down during peeling	Less
DRPSD14FDF2	Homogeneous, Uniform, Nonstick and Easily peel out	Good
DRPSD14FDF3	Homogeneous, Uniform, Nonstick and Easily peel out	Good
DRPSD14FDF4	Homogeneous, Uniform, Nonstick and Easily peel out	Good
DRPSD14FDF5	Homogeneous, Uniform, little brittle and break down during peeling	Less
DRPSD14FDF6	Homogeneous, Uniform, Nonstick and Easily peel out	Good
DRPSD14FDF7	Homogeneous, Uniform, Nonstick and Easily peel out	Good
DRPSD14FDF8	Homogeneous, Uniform, Nonstick and Easily peel out	Good
DRPSD14FDF9	Homogeneous, Uniform, Nonstick and Easily peel out	Good
DRPSD14FDF10	Homogeneous, Uniform, little brittle and break down during peeling	Less
DRPSD14FDF11	Homogeneous, Uniform, Nonstick and Easily peel out	Good
DRPSD14FDF12	Homogeneous, Uniform, sticky and difficulty to peel out	Less

The physical characteristics and ability to form films of the polymer depicted in **Table 13** were examined for each prepared formulation. Except for the formulations DRPSD14FDF1, DRPSD14FDF10, and DRPSD14FDF12, which were either challenging to peel out or broke down during the peeling out from the petri dish, all prepared reserpine loaded fast dissolving formulations were homogeneous, uniform, nonstick, and easily peel out [20].

pH: The most often used metrics to evaluate how irritating a produced product is to oral mucosa are pH levels. Investigating the possibility of adverse effects requires measuring the pH of the oral film's surface. Maintaining the pH near to neutral pH is crucial because acidic or basic pH can disrupt the oral mucosa and affect how quickly the polymers hydrate. The pH of all created formulations was examined and is displayed in **Table 14.** The surface pH was discovered to be between 6.83 and 7.19, which is close to neutral pH, indicating that films may have less potential to irritate the sublingual mucosa and, thus, be more accepted by the patients [20].

TABLE 13: PH OF ALL PREPARED FORMULATIONS

S. no.	Formulation Code	pH
1	DRPSD14FDF1	6.873±0.031
2	DRPSD14FDF2	6.987±0.057
3	DRPSD14FDF3	6.837±0.038
4	DRPSD14FDF4	7.153±0.135
5	DRPSD14FDF5	7.147±0.059
6	DRPSD14FDF6	6.947±0.025
7	DRPSD14FDF7	6.857±0.042
8	DRPSD14FDF8	6.923±0.023
9	DRPSD14FDF9	7.050±0.010
10	DRPSD14FDF10	7.197±0.038
11	DRPSD14FDF11	7.140±0.046
12	DRPSD14FDF12	6.967±0.015

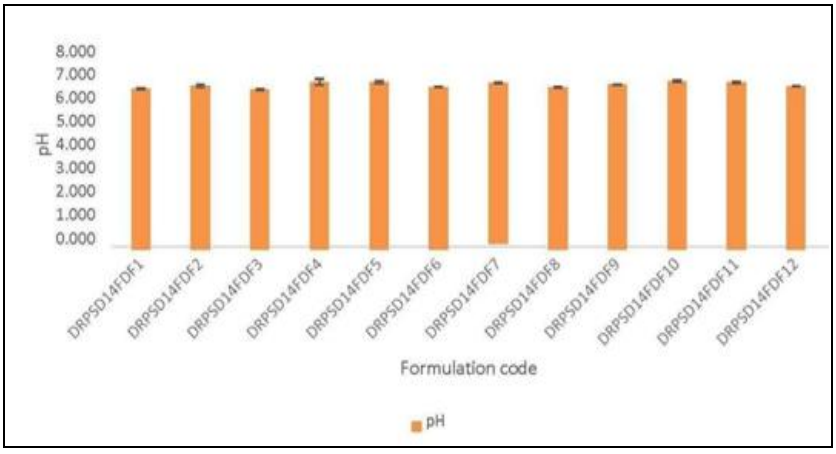

FIG. 5: PH OF ALL PREPARED FORMULATIONS

Percentage Drug Content: In order to make sure that all films have the desired amount of drug, a test for drug content in percentage was conducted. As stated in **Table 14**, the amount of reserpine in each film is estimated to yield the percentage drug content.

TABLE 14: PERCENTAGE DRUG CONTENT

Formulation code	Percentage drug content
DRPSD14FDF1	91.082±1.540
DRPSD14FDF2	92.398±0.913
DRPSD14FDF3	95.906±1.013
DRPSD14FDF4	94.737±0.760
DRPSD14FDF5	92.690±0.560
DRPSD14FDF6	95.322±0.670
DRPSD14FDF7	93.860±0.760
DRPSD14FDF8	94.006±1.104
DRPSD14FDF9	96.784±1.266
DRPSD14FDF10	91.520±0.506
DRPSD14FDF11	98.977±0.253
DRPSD14FDF12	96.053±0.877

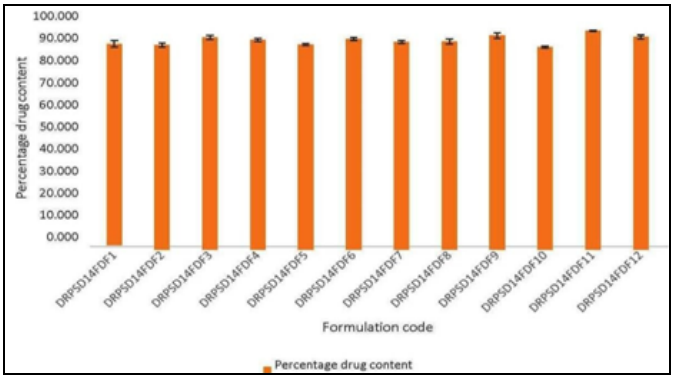

FIG. 6: BAR DIAGRAM OF THE PERCENTAGE DRUG CONTENT

Fig. 6 shows the percentage drug content of all manufactured formulations, which ranged from 91.082±1.540% to 98.977±0.253%, demonstrating the drug's uniform distribution within the polymer film. Formulation DRPSD14FDF11, which includes all formulations, contains the most reserpine (98.977±0.253%) of any of them 281.

***In-vitro* Ddissolution Study:** *In-vitro* dissolution properties of control patch containing pure drug reserpine, DRPSD14FDF9, and DRPSD14FDF11 were assessed in simulated salivary fluid pH 6.8 without enzyme. Based on the hypothesis that drug release and subsequent oral absorption in the oral cavity may increase the bioavailability of reserpine, dissolution at salivary pH was conducted to evaluate the release of drug from the film at pH 6.8.

Table 15 [21] compares the *in-vitro* drug release profiles of the reserpine-poly ethylene glycol fast dissolving film formulations DRPSD14FDF9 and DRPSD14FDF11 with the control patch containing pure drug reserpine.

TABLE 15: COMPARISON OF THE *IN-VITRO* DISSOLUTION PROFILE OF THE RESERPINE-POLY ETHYLENE GLYCOL FAST DISSOLVING FILM FORMULATIONS DRPSD14FDF9, DRPSD14FDF11 AND CONTROL PATCH CONTAINING PURE DRUG RESERPINE

Time (min)	Percentage drugrelease of control Patch	Percentage drugrelease of DRPSD14FDF9	Percentage drugrelease of DRPSD14FDF11
0	0.000±0.00	0.000±0.00	0.000±0.00
0.25	18.13±1.01	20.18±0.88	21.64±1.34
0.5	22.22±1.83	24.59±0.05	40.64±0.51
1	34.21±0.88	32.46±0.99	48.83±1.83
2	38.01±1.34	40.06±1.34	64.91±1.52
3	39.18±1.01	56.14±1.75	84.21±0.88
4	40.35±0.67	69.01±1.48	93.57±1.44
5	42.69±1.10	78.95±1.75	96.49±0.75
6	43.86±0.96	81.58±0.60	97.95±0.48

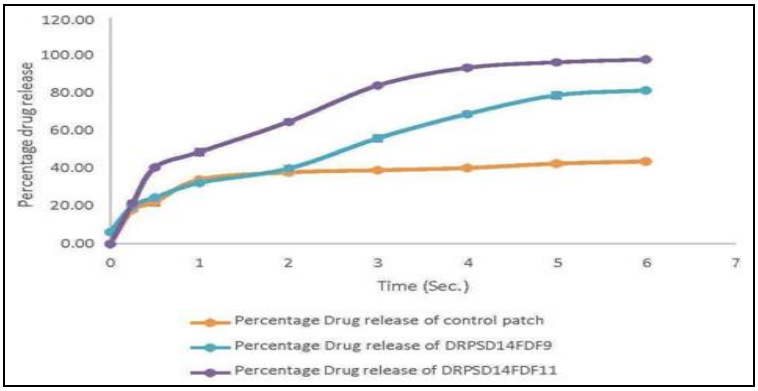

FIG. 7: LINEAR GRAPH OF THE COMPARISON OF THE *IN-VITRO* DISSOLUTION PROFILE OF THERESERPINE-POLY ETHYLENE GLYCOL FAST DISSOLVING FILM FORMULATIONS DRPSD14FDF9, DRPSD14FDF11 AND CONTROL PATCH CONTAINING PURE DRUG RESERPINE

Reserpine polyethylene glycol fast dissolving film formulations DRPSD14FDF9 and DRPSD14-FDF11 *in-vitro* dissolution studies showed faster drug dissolution with up to or more than 90% of drug dissolved within 6 minutes **Fig. 7**. According to published research, a fast-dissolving buccal film should be given 10 to 40 minutes to completely dissolve its drug. The amount of plasticizer and film-forming polymer present affects the dissolving process. However, the impact of the plasticizer was significantly greater since drug dissolution increased as plasticizer concentration increased [22].

The hydrophilic polymers' capacity to absorb water may be the cause of the increased rate of drug release by facilitating the dissolution and subsequent release of the highly water-soluble drug. Additionally, when the hydrophilic polymers expand, new pores and channels will be created for the medicine to diffuse out of the patches [23].

Glycerol, a plasticizer, has played a crucial part in dissolution. It was discovered that the content of glycerol increased the rate of dissolution. As a result, glycerol served as a plasticizer as well as a dissolution-facilitating agent. In simulated salivary fluid with a pH of 6.8, the formulation DRPSD14FDF11 demonstrated the maximum dissolve 97.95±0.48%, within 6 minutes, as opposed to the DRPSD14FDF9's 81.58±0.60% solubility. These findings showed that the polyethylene glycol solid dispersion utilized to make the films significantly increased the amount and rate of reserpine's dissolution from the made DRPSD14FDF. It is common knowledge that drugs in their amorphous forms dissolve more quickly than those in their corresponding crystalline forms.

Due to the drug's low mobility in the film formulation, the driving force for crystallization is decreased, increasing the physical stability of the amorphous medicines. Polymers are predicted to reduce the drug's molecular mobility within film. As a result of the HPMC E15 polymer's presence, the film's surface developed pores and a network-like structure. Through the network's pores, the dissolving media can quickly disintegrate and dissolve this porous surface [148].

***In-vitro* Drug Release Kinetic Study:** Various models were used to estimate the DRPSD14FDF11 formulation's *in-vitro* drug release profile.

Zero Order: Fig. 8 depicts the zero order model of the DRPSD14FDF11 formulation's *in-vitro* drug release profile.

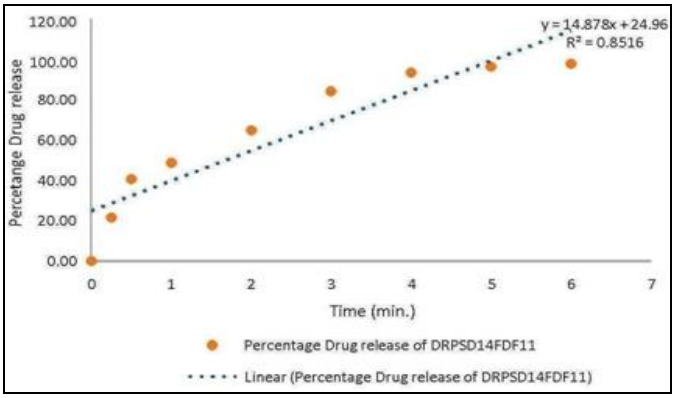

FIG. 8: ZERO ORDER OF RELEASE PROFILE OF FORMULATION DRPSD14FDF11

First Order:

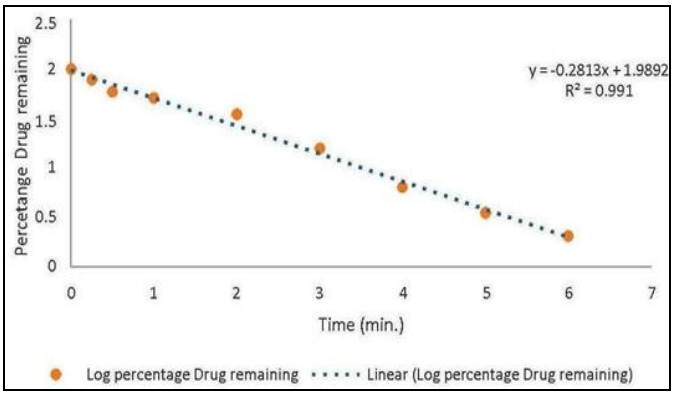

FIG. 9: DEPICTS THE FIRST ORDER MODEL OF THE DRPSD14FDF11 FORMULATION'S *IN-VITRO* DRUG RELEASE PROFILE

Higuchi Order: In **Fig. 10,** the Higuchi order model of the *in-vitro* drug release profile of formulation DRPSD14FDF11 is displayed.

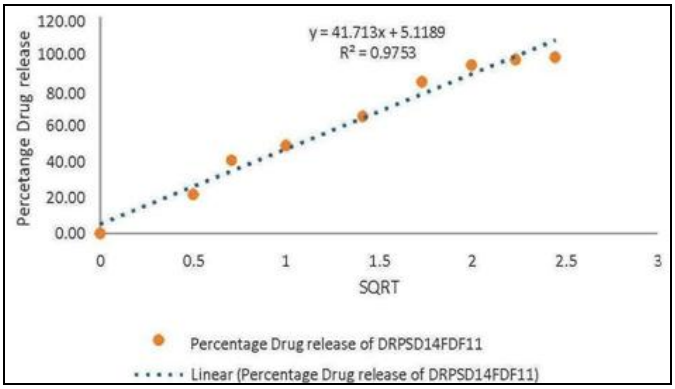

FIG. 10: HIGUCHI ORDER OF RELEASE PROFILE OF FORMULATION DRPSD14FDF11

The *in-vitro* drug release after using the release model for formulation DRPSD14FDF11 was best

explained by first order, as the plots exhibited the maximum linearity (R^2 = 0.991), followed by zero order (R^2 = 0.851), Higuchi order, and finally Higuchi.

FTIR Spectroscopy: The incompatibility between the drug and excipients was identified using the FTIR spectrum of reserpine, poly ethylene glycol 20000, a physical mixture of reserpine and poly ethylene glycol, optimal formulation DRPSD14, and optimized fast dissolving film DRPSD14FDF11.

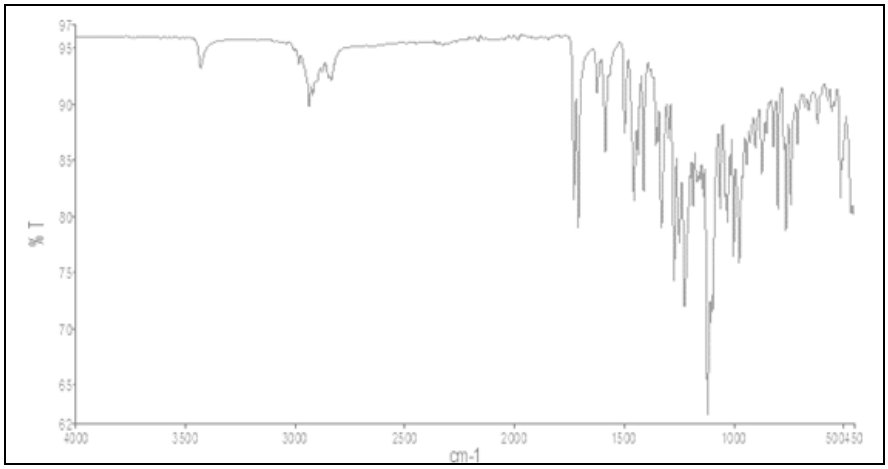

FIG. 11: FTIR SPECTRUM OF THE DRUG RESERPINE

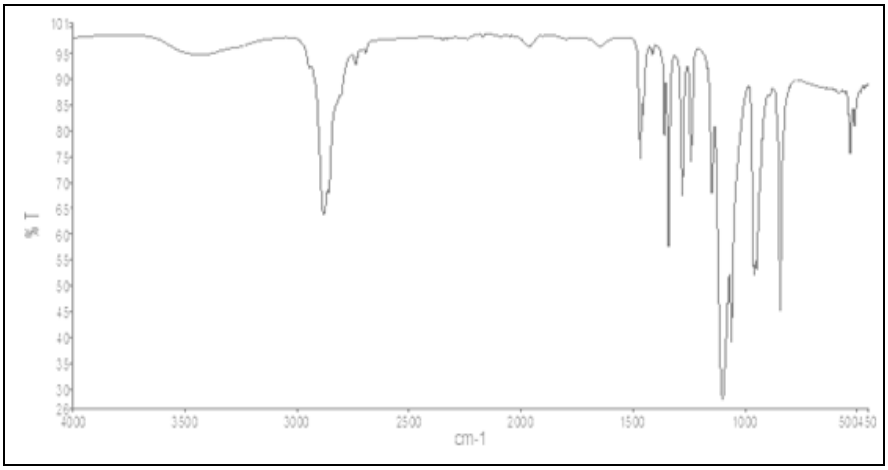

FIG. 12: FTIR SPECTRUM OF THE POLY ETHYLENE GLYCOL 20000

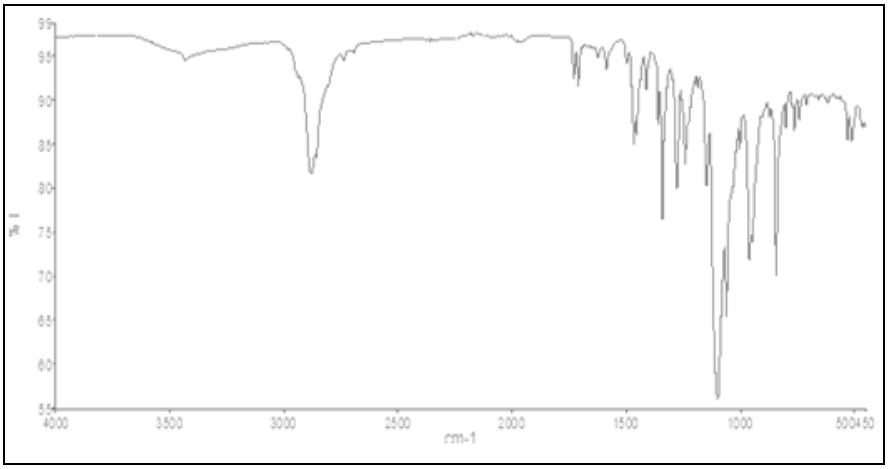

FIG. 13: FTIR SPECTRUM OF THE PHYSICAL MIXTURE OF DRUG RESERPINE AND POLYETHYLENEGLYCOL

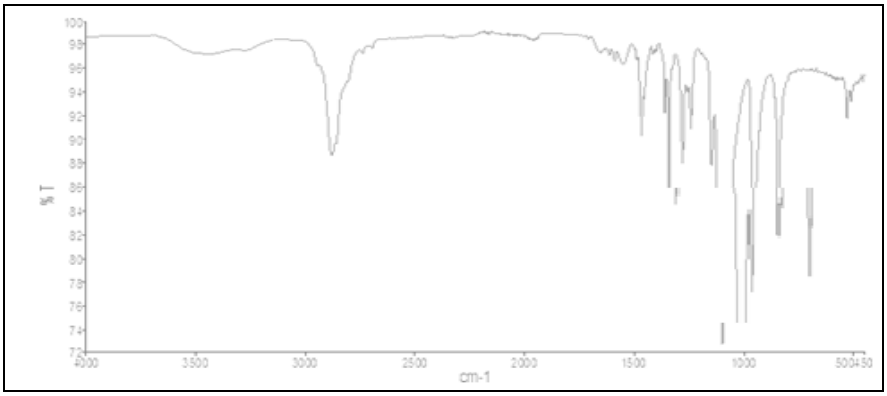

FIG. 14: FTIR SPECTRUM OF THE OPTIMIZED FORMULATION DRPSD14

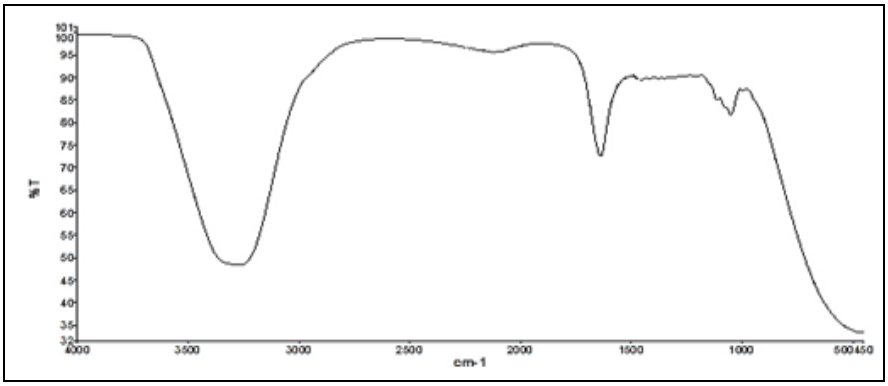

FIG. 15: FTIR SPECTRUM OF THE OPTIMIZED FORMULATION FAST DISSOLVING FILM DRPSD14FDF11

The reserpine drug's FTIR spectra showed the typical peaks at 3432.7 cm^{-1}, 2937.58 cm^{-1}, 1729.20 cm^{-1}, and 1709.65 cm^{-1}, which are associated with the N-H stretching, C-H stretching, C=O stretching of the acetyl group, and C-H stretching trimethoxybenzoate group, respectively [24]. In contrast, the PEG 20000 displayed a typical broad spectrum with O-H stretching vibrations starting at 3418.850 cm^{-1}, C-H stretching of OC2H5 groups starting at 2883.38 cm^{-1}, and C-O stretching starting at 1059.77 cm^{-1}. The characteristic peak C=O stretching of reserpine is visible in the physical mixture's FTIR spectra at a wavelength of 1729.39 cm^{-1}, while other results also show that reserpine and PEG 20000 are compatible. The characteristic peak of the drug reserpine in this solid dispersion DRPSD14 indicates that the drug is miscible with the poly ethylene glycol, either by being absent or by being present but with very little intensity. Furthermore, FTIR spectra of the fast dissolving film containing drug solid dispersion DRPSD14FDF11 indicate the peak of the HPMC 15 but did not demonstrate the peak of drug indicates the uniform dispersion of the solid dispersion contain reserpine into the fast dissolving film with enhance solubility [25].

Differential Scanning Calorimetry: DSC thermogram of the drug reserpine, solid dispersion formulation DRPSD14 and fast dissolving film DRPSD14FDF11 was shown in **Fig. 16-17.**

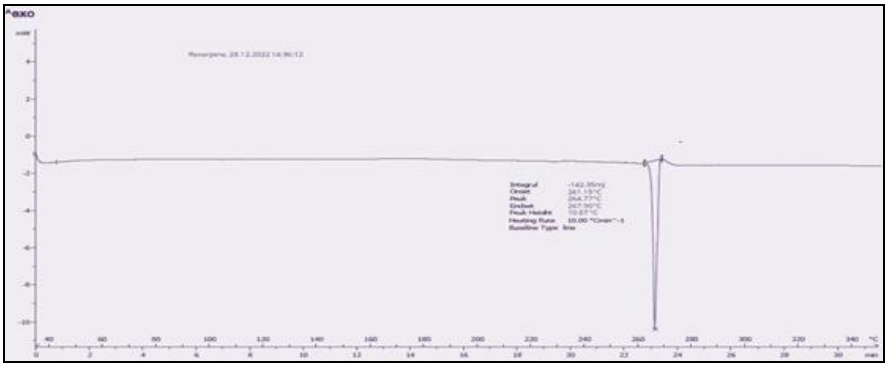

FIG. 16: DSC THERMOGRAM OF THE DRUG RESERPINE

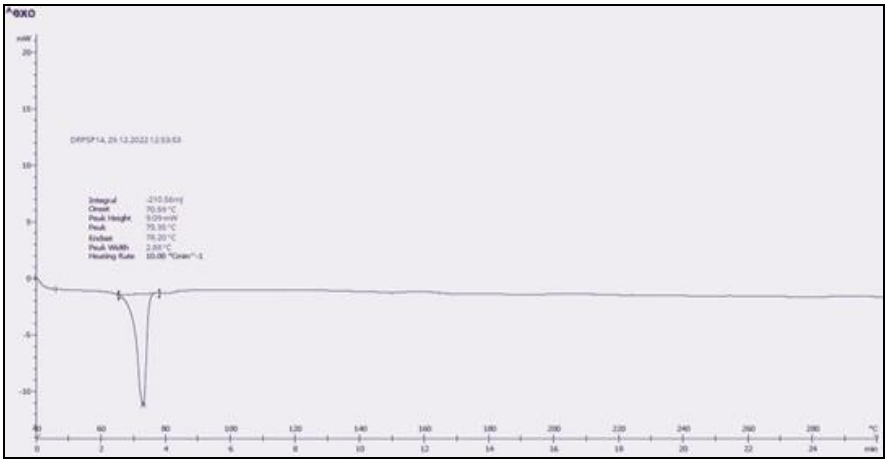

FIG. 17: DSC THERMOGRAM OF THE OPTIMIZED FORMULATION DRPSD14

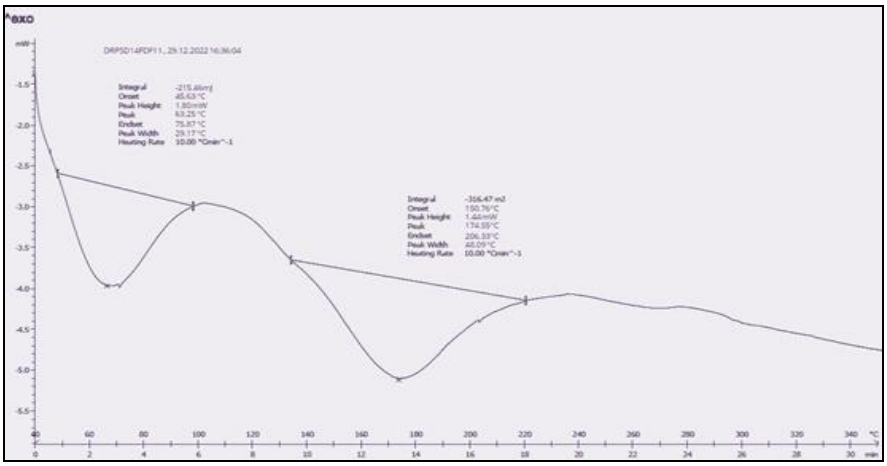

FIG. 18: DSC THERMOGRAM OF THE OPTIMIZED FORMULATION FAST DISSOLVING FILM DRPSD14FDF11

Solid dispersion was analyzed by DSC and FTIR to better understand the potential processes of enhanced dissolving. The DSC thermograms of reserpine **Fig. 16** revealed an apparent endothermic peak at 264.77°C respectively [25]. The absence of a reserpine signal in the SDs DRPSD14 thermograms indicates that PEG 20000 entirely solubilizes reserpine in the liquid phase. Other research teams have also shown that endothermic peaks of drug in SDs do not exist [26]. Furthermore the absence of the peak of drug into the fast dissolving film indicates reserpine is uniformly distributed and caged in linear chain of film-forming polymer [22].

Scanning Electron Microscopy: Scanning electron microscopic pictures of the formulation DRPSD14.

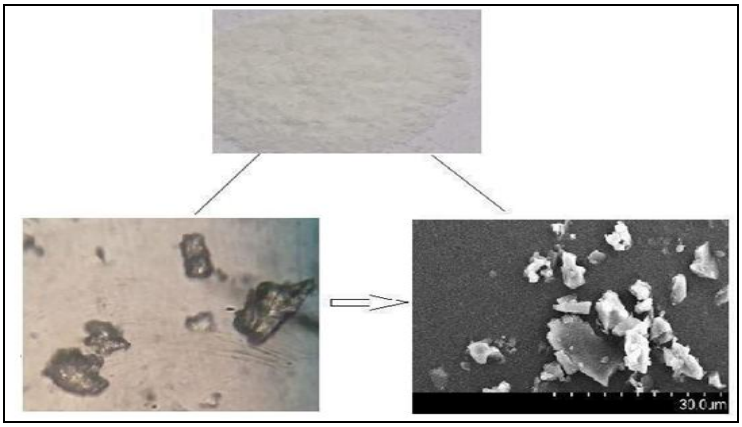

FIG. 19: SEM IMAGES OF THE FORMULATION DRPSD14

Images showed that the solid dispersion particles were uniformly and thoroughly blended, with a smooth surface that contained tiny flakes. According to SEM images, effective SD systems were formed since the surface characteristics of PEG 20000 and reserpine were lost during melting and solidification. Reserpine was homogeneously diffused throughout the polymer, as evidenced by the surface morphology of SDs [25]. SEM analysis of the surface morphology of the formulation DRPSD14FDF11 revealed that the drug was distributed uniformly throughout the film. Additionally, there is no accumulation of particles. The overall SEM image reveals no striations or fractures in the film, indicating that the produced film will not have any mechanical property issues and won't cause any striations [27].

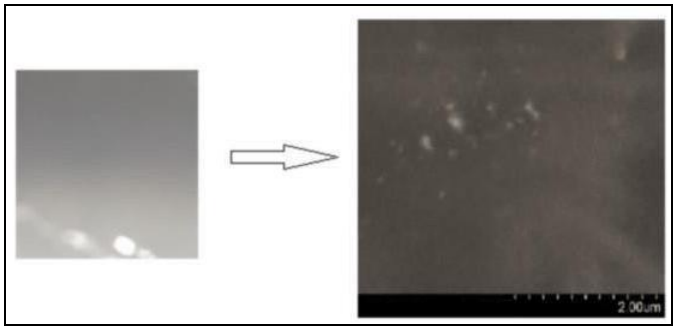

FIG. 20: SEM IMAGES OF THE FORMULATION DRPSD14FDF11

Stability Study: Investigations were made into the formulation DRPSD14FDF11 stability under various storage settings, including 2-8℃, 25o/60% RH, and 40oC/75%RH. Through the use of several *in-vitro* characterization parameters, such as physical appearance and % drug content, the impact of storage conditions on the customized formulation was examined.

CONCLUSION: The primary objective of this study was to improve the solubility and dissolution characteristics of reserpine, an anti-hypertensive drug. This was achieved through the development of a solid dispersion in combination with polyethylene glycol (PEG) and the formulation of a fast-dissolving film, guided by the principles of Quality by Design (QBD). The physical properties of reserpine, including its melting point (263±1.00°C to 265.33±1.15°C) and partition coefficient (8.416±0.548), were determined. A UV method at 268nm was validated for quantification, demonstrating a limit of detection (LOD) of 0.21µg/ml and a limit of quantification (LOQ) of 0.665µg/ml. The method exhibited high accuracy, with percentage recovery ranging from 99.498±0.390% to 99.803±0.312% at 293nm and 99.357±0.268% to 99.727±0.135% at 268nm. The precision of the method was confirmed by low percentage relative standard deviation (% RSD) values below 2%. The optimized reserpine solid dispersion (DRPSD14) was formulated using a central composite response surface design, resulting in a formulation with a theoretical solubility of 14.94% and dissolution of 96.88% at 20 minutes. This optimized formulation served as the basis for the creation of a fast-dissolving film through solvent casting. Twelve formulations were prepared, and except for DRPSD14FDF1, DRPSD14FDF10, and DRPSD14FDF12, which exhibited challenges during peeling or breakdown, all formulations were homogeneous, uniform, and easily peelable. The surface pH of the formulations ranged from 6.83 to 7.19, indicating compatibility with sublingual mucosa. The percentage drug content of the formulations ranged from 91.082±1.540% to 98.977±0.253%, confirming uniform drug distribution. Formulation DRPSD14FDF11, containing 98.977±0.253% reserpine, was identified as particularly promising. In vitro dissolution studies demonstrated rapid dissolution, with DRPSD14FDF11 exhibiting the highest dissolution rate. The release kinetics of this formulation were modeled successfully, and FTIR spectra indicated uniform drug distribution in the fast-dissolving film. Furthermore, the customized formulation exhibited stability under various storage conditions. Overall, the study successfully enhanced the pharmaceutical properties of reserpine, offering a promising formulation for hypertension treatment.

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