# Formulation And Evaluation Of Fast DissolvingFilm For The Treatment Of Hypertension

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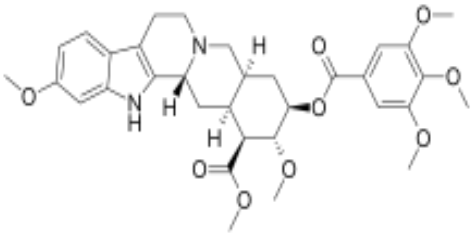
**Abstract**
The present study looked at ways to improve the drug's solubility and dissolution in order to treat hypertension. In this work, a fast-dissolving film comprising a solid dispersion of reserpine and polythene glycol was developed and optimised using a QBD strategy for the treatment of hypertension. The PEG 20000 carrier fusion technique was used to create the reserpine solid dispersion. Preliminary screening led to the selection of PEG 20000 concentration and reserpine concentration as the two parameters to be optimised. Thirteen different formulations of a reserpine-poly ethylene glycol solid dispersion were proposed using a central composite response surface design with three different levels of PEG 20000 (80mg and 160mg) and reserpine (2mg and 6mg). The % solubility of each batch was calculated after 20 minutes of reserpine dissolution from the solid dispersion. Using a numerical optimisation method based on desirability approaches, we were able to get the newly optimised solid dispersion (*DKFDF*14), which served as a benchmark. The best solid dispersion was formulated using 3.66 mg of reserpine (X1) and 124.88 mg of PEG 20000 (X2), producing theoretical values of 14.94% solubility and 96.88% dissolution after 20 minutes. A fast-dissolving film containing *DKFDF*14 was made via solvent casting. Variables such as HPMC concentration, plasticiser concentration, and plasticiser type were studied in relation to the fast-dissolving film's defining characteristics. There were 12 distinct formulations made and analysed. Customised formulations were found to have a surface pH range of 6.83 to 7.19, which is near to neutral and indicative of a lack of irritation to the sublingual mucosa and, therefore, greater patient acceptance. The medication was evenly distributed throughout the polymer film, with a percentage content ranging from 91.082±1.540% to 98.977±0.253% for all created formulations. The total amount of reserpine (98.977±0.253%) in formulation *DKFDF*14FDF11 is the highest of any of the formulations. In vitro dissolution investigations of the *DKFDF*14FDF11 formulation of reserpine-polyethylene glycol fast dissolving film revealed rapid disintegration of up to or more than 90% within 6 minutes.

## Introduction

The biopharmaceutical classification system (BCS) uses two strands to classify pharmaceuticals into four groups: aqueous solubility and permeability. Low solubility and high permeability characterise Class II medicines.
Bioavailability of orally taken BCS class II medicines is regulated by their release. This means that both bioavailability and negative effects may be improved by adjusting the release. The effectiveness of absorption of medicines in BCS class II is affected by their solubility and dissolution. Solutions and suspensions of drugs that aren't very water soluble can have their solubility improved through chemical means (prodrug) or through formulation techniques such as adjusting the pH, creating molecular complexes, using surfactants, and adding co-solvents.

## 1. Drug and excipient profile



**Reserpine**
**Physicochemical properties**

- Chemical Formula: $C_{33}H_{40}N_2O_9$
- Molecular weight: 608.688 $g \cdot mol^{-1}$
- Melting point: 264.5°C

- Solubility: It is a crystalline powder that is colourless, odourless, and insoluble in water, however it dissolves in chloroform and acetic acid and is just slightly soluble in alcohol. It is also destabilised in the presence of alkali, and its dissociation constant is 6.6.

**Pharmacokinetic data**

- Oral Bioavailability: 50%
- Location of Metabolism: Gut/liver
- Plasma Elimination half-life: phase 1 = 4.5h,

phase 2 = 271h,Average = 33h

- Excretion: 62% feces / 8% urine

**Poly ethylene glycol**

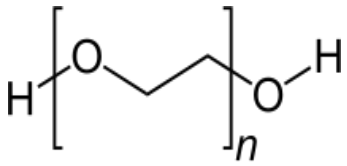
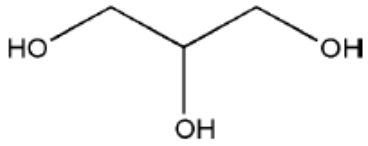



**Table 1 Specification of the PEG20000**

| Test Parameters | Standards | Actual Results |
|---|---|---|
| Physical texture (Colour) | White | White |
| State (Form) | Powder | Flakes |
| Solubility (Turbidity) 10% aq. solution | Clear | Clear |
| Solubility (Colour) 10% aq. solution | Colourless | Colourless |
| pH (5% aq. solution) | 6.5 - 8.0 | 6.5 |
| Melting Point | 63 - 65°C | 64°C |
| Viscosity (25%aq, 20°C) ~ | 100 cs | 97 cs |

**Glycerol**

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**Typical properties**

- Boiling point: 290°C (with decomposition)
- Density:

1.2656 g/cm$^3$ at 15°C;

1.2636 g/cm$^3$ at 20°C;

1.2620 g/cm$^3$ at 25°C.

- Flash point: 176°C (open cup)
- Hygroscopic
- Melting point: 17.8°C
- Osmolarity: a 2.6% v/v aqueous solution is isoosmotic with serum.
- Surface tension: 63.4mN/m (63.4 dynes/cm) at 20°C.
- Vapor density (relative): 3.17 (air = 1)

**Result and Discussion**

**Melting Point Determination**

The melting point of reserpine is stated to be in the range of 263±1°C to 265±33°C, which is quite close to the 264-265°C mentioned in the literature.

**Partition coefficient Determination**

Using the shake flask technique, the partition coefficient between water and n- octanol for reserpine was determined to be 8.416±0.548. The drug's lipophilic nature is shown by this number, which is quite close to the 8.0 mentioned in the literature.

**Determination of absorption maxima of reserpine in methanol**

Using a UV-VIS functionalized spectrophotometer, we scanned a working solution of 25 g/mL reserpine in methanol from 200 to 400 nm. Absorption maxima in methanol were found to be at 293nm and 268nm, as shown in figure 1

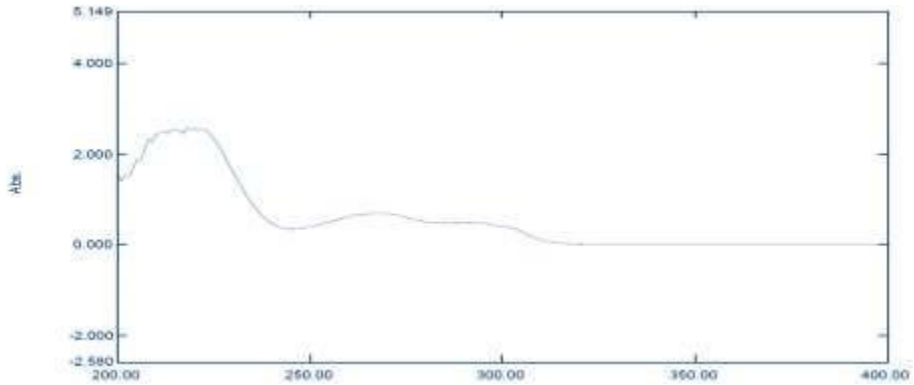


**Figure 1 :** UV absorption spectra of Reserpine in methanol (25µg/ml)

**Table 1:** Repeatability data of Reserpine in methanol at 293nm

| Concentration(µg/ml) | % Recovery | % MeanRecovery | STD | %RSD |
|---|---|---|---|---|
| 20 | 99.668 | 99.668 | 0.228 | 0.229 |
| | 99.923 | | | |
| | 99.668 | | | |
| | 99.413 | | | |
| | 99.413 | | | |
| | 99.923 | | | |

**Table 2:** Repeatability data of Reserpine in methanol at 268nm

| Concentration(µg/ml) | % Recovery | % MeanRecovery | STD | %RSD |
|---|---|---|---|---|
| 20 | 99.649 | 99.649 | 0.111 | 0.111 |
| | 99.825 | | | |
| | 99.649 | | | |
| | 99.649 | | | |
| | 99.474 | | | |
| | 99.649 | | | |

**Table 3 Interday Precision data of Reserpine in methanol at 293nm:**

| Conc.(µg/ml) | % Recovery | Mean % Recovery | STD | %RSD |
|---|---|---|---|---|
| 20 | 99.413 | 99.371 | 0.192 | 0.193 |
| 20 | 99.158 | | | |
| 20 | 99.668 | | | |
| 20 | 99.413 | | | |
| 20 | 99.158 | | | |
| 20 | 99.413 | | | |
| Day 2 | | | | |
| Conc.(µg/ml) | % Recovery | Mean %Recovery | STD | %RSD |
| 20 | 99.158 | 99.413 | 0.228 | 0.230 |
| 20 | 99.413 | | | |
| 20 | 99.668 | | | |
| 20 | 99.413 | | | |
| 20 | 99.158 | | | |
| 20 | 99.668 | | | |
| Day 3 | | | | |
| Conc.(µg/ml) | % Recovery | Mean %Recovery | STD | %RSD |
| 20 | 99.413 | 99.541 | 0.312 | 0.314 |
| 20 | 99.923 | | | |
| 20 | 99.923 | | | |
| 20 | 99.413 | | | |
| 20 | 99.158 | | | |

| | | | | |
|---|---|---|---|---|
| 20 | 99.413 | | | |
| Day 4 | | | | |
| Conc.(µg/ml) | % Recovery | Mean %Recovery | STD | %RSD |
| 20 | 99.158 | 99.626 | 0.442 | 0.444 |
| 20 | 99.158 | | | |
| 20 | 99.923 | | | |
| 20 | 99.668 | | | |
| 20 | 99.923 | | | |
| 20 | 99.923 | | | |
| Day 5 | | | | |
| Conc.(µg/ml) | % Recovery | Mean %Recovery | STD | %RSD |
| 20 | 99.158 | 99.626 | 0.390 | 0.391 |
| 20 | 99.413 | | | |
| 20 | 99.923 | | | |
| 20 | 99.923 | | | |
| 20 | 99.668 | | | |
| 20 | 99.668 | | | |
| Day 6 | | | | |
| Conc.(µg/ml) | % Recovery | Mean %Recovery | STD | %RSD |
| 20 | 99.668 | 99.668 | 0.147 | 0.148 |
| 20 | 99.923 | | | |
| 20 | 99.923 | | | |
| 20 | 99.923 | | | |
| 20 | 99.158 | | | |
| 20 | 99.413 | | | |

**Robustness**

The analysis's robustness was assessed by subjecting it to a shift of only 1 nm in wavelength. Six identical test sample solutions (20 µg/ml) were prepared, and tests were run at two different wavelengths (268 nm and 293 nm). The method was proven to be reliable, and the % RSD values were found to be well within the allowed range (2%; see Tables 4).

**Table 4:** Percentage recovery of reserpine in robustness parameter in methanol at 293nm

| Wavelength 292nm | | | | |
|---|---|---|---|---|
| Conc.(µg/ml) | % Recovery | % Mean Recovery | STD | %RSD |
| 20 | 99.158 | 99.541 | 0.268 | 0.269 |
| 20 | 99.413 | | | |
| 20 | 99.668 | | | |
| 20 | 99.923 | | | |
| 20 | 99.668 | | | |
| 20 | 99.413 | | | |
| Wavelength 293nm | | | | |
| Conc.(µg/ml) | % Recovery | % Mean Recovery | STD | %RSD |
| 20 | 99.923 | 99.456 | 0.298 | 0.300 |
| 20 | 99.413 | | | |
| 20 | 99.413 | | | |
| 20 | 99.158 | | | |
| 20 | 99.158 | | | |
| 20 | 99.668 | | | |
| Wavelength 294nm | | | | |
| Conc.(µg/ml) | % Recovery | % Mean Recovery | STD | %RSD |
| 20 | 99.413 | 99.741 | 0.289 | 0.290 |
| 20 | 99.923 | | | |
| 20 | 99.923 | | | |
| 20 | 100.102 | | | |
| 20 | 99.413 | | | |
| 20 | 99.668 | | | |

**Table 5 In-vitro characterization parameters**

| S. No. | Formulation code | Visual appearance | Percentage yield (%) | Percentage drug content (%) | Percentage solubility (%) | Percentage dissolution at 20min (%) |
|---|---|---|---|---|---|---|
| 1 | FDF9 | Off white powder | 99.399±0.310 | 92.398±1.104 | 8.611±0.091 | 80.117±1.340 |
| 3 | FDF4 | Off white powder | 99.220±0.283 | 95.468±0.607 | 12.339±0.023 | 97.368±0.877 |
| 4 | FDF10 | Off white powder | 99.497±0.279 | 90.936±0.506 | 7.690±0.134 | 77.485±0.506 |

The fusion technique was used to develop solid dispersions containing different concentrations of reserpine medication in an attempt to improve the solubilization of active pharmaceutical ingredients and their behaviour throughout the unique dissolving process. Table 5 displays the dissolution rate of reserpine from its solid dispersion formulations as a function of time. The effects of different reserpine concentrations (2mg, 4mg, and 6mg) were investigated by preparing dispersions containing varying levels of reserpine. It is clear that the solubilization and dissolution of reserpine increase with increasing concentration up to a concentration of 4 mg (12.339±0.023% and 97.368±0.877%). However, the rate of solubilization and dissolution of reserpine reduces at greater concentrations. It has been shown that a polymer coating controls the release of active ingredients in a substances, a uniform coating of drugs, or the release of unbroken particles that cause a domino effect of breakdown. Drug concentrations were measured to be between 92.398±1.104% and 95.468±0.607%.

Once the medication is released from the dispersion at higher concentrations (6 mg), it takes over dissolution from the polymer. The PEG 20000 coating on the disc's surface dissolves fast, so the idea goes, but the rest of the dissolving process is sluggish since there's already so much medication in the dissolution medium. Drug concentrations of 4 mg were employed in the screening procedure for the various process parameters.

**Effect of different amount of poly ethylene glycol**

The amount of polythene glycol 20000 used to make the reserpine-loaded solid dispersions range from 4 mg to 160 mg, as indicated in table 6. In vitro characteriszation measures including percentage yield, solubility of the reserpine, and percentage dissolution at 20 minutes were used to evaluate the generated solid dispersions.

**Table 6 :** In-vitro characterization

| S.No. | Formulation code | Visual appearance | Percentage yield (%) | Percentage drug content (%) | Percentage solubility (%) | Percentage dissolutionat 20min (%) |
|---|---|---|---|---|---|---|
| 1 | *FDF*5 | Off white powder with drug crystal | 74.394±0.473 | 34.839±0.755 | 3.874±0.141 | 44.737±1.754 |
| 2 | *FDF*6 | Off white powder | 97.738±0.315 | 91.082±1.104 | 9.576±0.091 | 72.515±1.340 |
| 3 | *FDF*7 | Off white powder | 98.902±0.460 | 93.567±1.104 | 10.278±0.067 | 88.889±1.826 |
| 4 | *FDF*4 | Off white powder | 99.220±0.242 | 95.468±0.670 | 12.339±0.024 | 97.368±0.877 |
| 5 | *FDF*8 | Off white powder | 99.330±0.279 | 90.205±0.913 | 8.319±0.134 | 85.673±0.506 |


**Figure 2 :** Solid dispersion under presence of different amount of poly ethylene glycol

**Percentage dissolution at 20min.ANOVA**

Table 7 displays the results of ANOVA

**Table 7:** ANOVA for the response percentage dissolution at 20min.

| Source | Sum ofSquares | df | Mean Square | F Value | p-valueProb >F | |
|---|---|---|---|---|---|---|
| Model | 453.371 | 5 | 90.67421 | 331.6419 | < 0.0001 | Significant |
| X1-Amount of drug | 3.27554 | 1 | 3.27554 | 11.98032 | 0.0105 | |
| X2-Amount of PEG | 2.55931 | 1 | 2.55931 | 9.360704 | 0.0183 | |
| X1X2 | 32.54703 | 1 | 32.54703 | 119.0411 | < 0.0001 | |
| $X1^2$ | 216.8029 | 1 | 216.8029 | 792.959 | < 0.0001 | |
| $X2^2$ | 252.1155 | 1 | 252.1155 | 922.1151 | < 0.0001 | |
| Residual | 1.91387 | 7 | 0.27341 | | | |
| Lack of Fit | 0.121849 | 3 | 0.040616 | 0.090661 | 0.9614 | Not significant |
| Pure Error | 1.792021 | 4 | 0.448005 | | | |
| Cor Total | 455.2849 | 12 | | | | |
| Std. Dev. | 0.522886 | | R-Squared | 0.995796 | | |
| Mean | 89.87508 | | Adj R-Squared | 0.992794 | | |
| C.V. % | 0.581792 | | Pred R-Squared | 0.991947 | | |
| PRESS | 3.666516 | | Adeq Precision | 44.08589 | | |

Model F-value, at 331.64, controls model significance. The F-Values for the model terms X1, X2, X1X2, X12, and X22 are all less than 0.1000, making them significant. A lack of fit that is not statistically significant is OK since we want the model to work. There is a high degree of concordance between the "Pred R- Squared" value of 0.9919 and the "Adj R-Squared" value of 0.9928. "Adeq Precision" employs a signal-to-noise ratio threshold of 4. The significance of this procedure was shown by the value of 44.086 in the present situation. Use this model to navigate the design space. Here is the equation for multiple regression:

**Percentage dissolution at 20min.** = $97.015-0.63X1+0.56X2+2.85X1X2-5.58X1^2-6.02X2^2$

Findings of the analysis of multiple regression models show that coefficient β1 bears a negative sign, indicating the antagonistic impact of variables towards the response proportion dissolution, while coefficient β2 bears a positive sign, suggesting a combined effect of variables towards the percentage solubility. The interaction plot and three-dimensional response surface plots in Figure 3 show that increasing the amount of the drug increases the percentage solubility up to a certain point, but beyond that point, the percentage solubility decreases. This is because increasing the amount of either PEG is expected to increase the percentage dissolution up to a certain amount; furthermore, improvement would not affect reserpine's ability to dissolve. Figure 4 is a set of three-dimensional response surface plots used to examine the influence of each element and their interaction on the response.

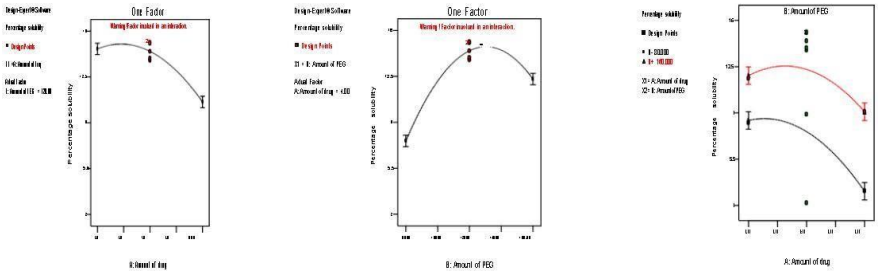


**Figure 3: Effect of the single variables and combination of variables over thepercentage dissolution at 20min.**

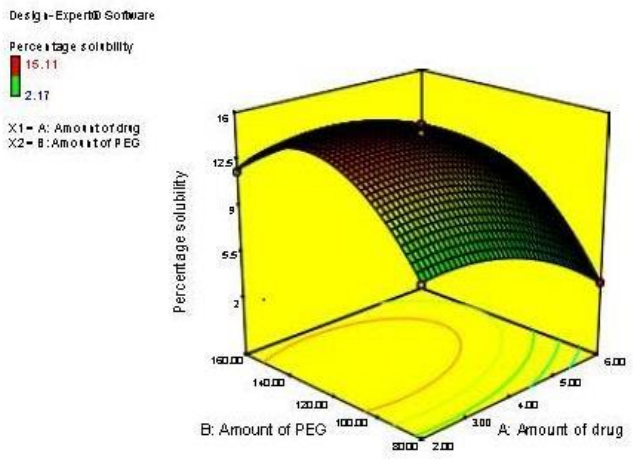


**Figure 4: 3D response graph**

## 4. Conclusion:

Reserpine is a single-crystal alkaloid with no impurities.Reserpine's hypotensive effect may be achieved with far lower dosages. The present study looked at ways to improve the drug's solubility and dissolution in order to treat hypertension. In this work, a fast-dissolving film comprising a solid dispersion of reserpine and polythene glycol was developed and optimised using a QBD strategy for the treatment of hypertension.

## 5. References

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