Optimization of Lamivudine Solid Dispersions by Central Composite Design

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ABSTRACT

Lamivudine (LVD) is in BCS class II with the issue of minimal oral bioavailability. This issue can be improvised by complexing LVD with polyethylene glycol-4000 (PEG-4000) and Pluronic F-68 (PF-68) by formulation design. The attempt optimized LVD tablets through central composite design (CCD). LVD tablets will be with > 95% dissolution after 30 minitues by employing PEG-4000 and PF-68. Nine LVD tablets were formulated by design and assessed for physicochemical constraints, disintegration time, and drug dissolution. The separate and mutual consequences of PEG-4000 and PF-68 on the disintegration time of LVD tablets are highly significant (P< 0.01). Intermittent levels of PEG-4000 and more levels of PF-68 gave less time for disintegration and a greater amount of drug dissolved at the end of 30 minitues. The study concludes that PF-68 decreases the disintegration time with its concentration and PEG-4000 concentration ingresses the drug release from the formulation. The study also discovered that the optimized LVD tablet with > 97.5% dissolution in 30 minitues could be formulated by employing PEG-4000 at 30 mg and PF-68 at 44.8 mg (F-7).

Key Words: *Lamivudine, Solid dispersions, Optimization, Composite design, Disintegration*

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INTRODUCTION

The BCS class II drugs process issues related to their solubility systemically [1, 2]. It is a challenge to make an efficient formulation [3]. Lamivudine (LVD) is an approved drug for tackling Hepatitis B Virus infection and AIDS [4]. LVD is administered 150 mg twice daily, owing to its t½ of 5-7 h [5]. The conventional dosage forms of LVD are found to have issues like accumulation of drugs due to repetitive administration and poor patient compliance [6]. For resolving the issues related to poor aqueous solubility of LVD, numerous tactics were employed, including making solid dispersions by complexing with polyethylene glycol-4000 (PEG-4000) [7] and Pluronic F-68 (PF-68) [8] in the form of solid dispersions [9].

In this study, the authors made and succeeded in making LVD complexation with PEG-4000 and the addition of PF-68 for attaining diminished disintegration time (DT) and > 95% dissolution in 30 min by employing PEG-4000 and PF-68 that was optimized by central composite design (CCD).

Optimization of pharmaceutical parameters like picking and merging excipients will bring about some definite essential prerequisites. The utilization of plan optimization methods is generally new to the practice of pharmacy. Overall, the technique comprises setting up a progression of preparations, shifting the groupings of the detailing fixings efficiently. In this, the authors adopted a central composite design for optimization [10, 11].

These tablets were then appraised for other traits, such as uniformity in size/shape, hardness, friability, and dissolution.

MATERIALS AND METHODS

Materials

Lamivudine was gifted by Hetero, Hyderabad, India. PEG-4000, PF-68, colloidal silicon dioxide, and talc were from Qualigens. The rest of the materials are AR grade.

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Estimation of lamivudine

A UV Spectrophotometric method of measuring absorbance at 271.5 nm in 0.1N HCl was embraced for the guesstimate of LVD. The scheme was validated for linearity, accuracy, precision, and interference. The process pragmatic Beer's law at 1-10 µg/ ml [12, 13].

Formulation of lamivudine tablets

For optimization of LVD tablets as per CCD, PEG-4000 and PF-68 are considered as the two factors. The two levels of factor A (PEG-4000) were 15mg and 45mg and the two levels of factor B (PF-68) were 50 mg and 75 mg. Nine LVD tablets were made by employing PEG- 4000 and PF-68 as per CCD were made by direct compression method **(Table 1)**. The required quantities of LVD, PEG-4000, and PF-68 were blended thoroughly in a closed polythene bag. Colloidal silicon dioxide and Talc were included by passing through mesh # 80 and blended and compressed with a karnavati 24 station machine.

Table 1. Formulae of LVD tablets as per central composite design

Contents (mg)	Formulations								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**
Lamivudine	200	200	200	200	200	200	200	200	200
PEG-4000	15	45	15	45	8.78	51.21	30	30	30
Pluronic F-68	50	50	75	75	62.50	62.50	44.8	80.17	62.50
Micro Crystalline Cellulose	70	40	45	15	63.72	21.29	60.2	24.83	40
Colloidal silicon dioxide	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Wt. of the tablet	350	350	350	350	350	350	350	350	350

Evaluation of tablets

All the LVD tablets made were appraised for drug content, hardness, friability, DT, and DR as described [14-17].

Hardness and friability

The hardness of LVD tablets was resolute with a Pfizer hardness tester and a reading was obtained of kg/cm^2. The friability of the tablets was sedated in a Roche friabilator using the formula.

$$\text{Friability (\%)} \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (1)$$

Drug content

Five tablets were powdered in a glass mortar and pestle and the powder (≡200 mg of LVD) was grasped into a 100 ml volumetric flask, dissolved in 0.1N HCl and the solution was filtered through Whatman filter paper no.41. The filtrate was unruffled and suitably diluted with 0.1N HCl and assayed for LVD at 271.5 nm [18].

Disintegration time

The DT of the tablets was done using a single unit disintegration test apparatus (Electronics India-2901) employing water as the test fluid.

Drug release study

DR of LVD tablets so made was studied in 0.1N HCl (900 ml) employing a six-station dissolution apparatus (Electrolab- ED-2 SAPO) using a paddle maintained at 50 rpm and 37±0.5°C. A 5 ml of sample was withdrawn at different time intervals and assayed for LVD at 271.5nm (sink conditions were maintained for every sampling) [12].

Analysis of data

The DT and the dissolution data were analyzed as per Design-Expert software (11.0.5.0, Stat-Ease Inc.,). The design was operated to determine the key interface and quadratic possessions of independent variables on dependent variables with CCD [19, 20].

RESULTS AND DISCUSSION

Nine LVD tablet formulations were made using selected groupings of the two factors as per CCD. The tablets were made by the direct compression method **(Table 1)** and were evaluated for uniformity of size/shape, hardness, friability, DT, and DR features. The DT and dissolution in 30 min were analyzed as per ANOVA of CCD to find out the significance of the separate and joint consequences of the two factors involved on the DR. The physical strictures of the LVD tablets were as per **Table 2**. The hardness of the tablets was > 4.0 kg/cm^2. Weight loss in the friability test was <1 in all the cases. The DT was in the range of 12 to 46 sec. LVD tablets (F-5) formulated

employing PEG-4000 at 8.78mg and PF-68 at 62.5 mg disintegrated rapidly within 12 sec. All other tablets disintegrated rather slowly, up to 46 sec. The intermittent levels of PEG-4000 elevated the DT whereas an increase in PF-68 affected the confines were judged. However, all the LVD tablets fulfilled the official/non-official requirements concerning size/shape, hardness, friability, DT, and dissolution for an uncoated tablet.

Table 2. Physical Parameters evaluated as per central composite design with PEG- 4000 and PF-68

Formulations	Hardness (Kg/cm^2)	Friability (%)	Response 1 (Disintegration time) (sec)	Response 2 (Drug release at 30 min) (%)
F-1	6.91±0.2	0.55±0.01	23	78.5
F-2	7.62±0.5	0.54±0.01	45	95.8
F-3	4.28±0.6	0.52±0.02	13	70.1
F-4	8.98±0.7	0.47±0.03	33	87.6
F-5	4.28±0.8	0.58±0.01	12	75.0
F-6	6.64±0.5	0.38±0.02	38	93.6
F-7	6.84±0.9	0.39±0.05	46	97.5
F-8	5.85±0.5	0.46±0.03	29	81.4
F-9	7.80±0.3	0.59±0.02	34	90.0

Values in mean±S.D; trial (n)=3

DR of LVD tablets was studied in 0.1N HCl **(Figure 1)**.

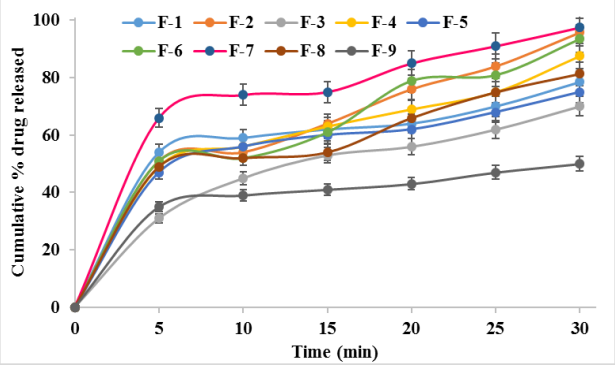


Figure 1. Drug release at different intervals till 30 min

The fit summary suggested linear with P-value 0.0038 for response 1 and 0.0019 for response 2 **(Table 3)** and ANOVA for the DT and drug release at 30 min **(Table 4)** indicated that the separate and collective upshot of the two factors, PEG-4000, and PF-68, in influencing the DR of LVD tablets is highly significant ($P < 0.01$). The Model F-value of 38.17 (for response1) and 9.72 (for response 2) suggests the model is significant.

Table 3. Fit Summary for response 1 and 2

Source	Sequential p-value	Adjusted R^2	Predicted R^2
Fit Summary for response 1			
Linear	**0.0038**	**0.7928**	**0.6322**
2FI	0.8776	0.7527	0.5821
Quadratic	**0.0317**	**0.9587**	
Cubic	0.8907	0.9018	
Fit Summary for response 2			
Linear	**0.0019**	**0.8352**	**0.7291**
2FI	0.9824	0.8023	0.5530
Quadratic	0.3227	0.8450	
Cubic	0.8279	0.6812	

Table 4. ANOVA for response 1 and 2

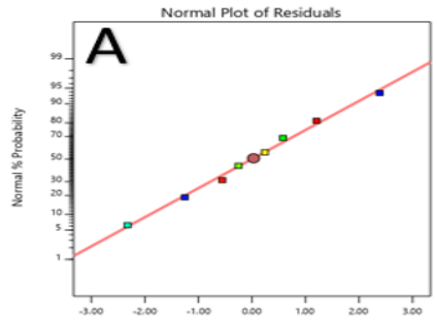
Source	Sum of Squares	df	Mean Square	F-value	p-value
ANOVA for response 1 i.e., Disintegration time (R_1)					
Model	1212.93	5	242.59	38.17	0.0064
A-PEG-4000	775.58	1	775.58	122.04	0.0016
B-Pluronic F-68	264.98	1	264.98	41.69	0.0075
Residual	19.07	3	6.36		
Cor Total	1232.00	8			
ANOVA for response 2 i.e., LVD release at the end of 30 min (R_2)					
Model	709.77	5	141.95	9.72	0.0451
A-PEG-4000	466.72	1	466.72	31.96	0.0110
B-Pluronic F-68	193.74	1	193.74	13.27	0.0357
AB	0.0100	1	0.0100	0.0007	0.9808
A^2	42.42	1	42.42	2.91	0.1869
B^2	4.50	1	4.50	0.3082	0.6175
Residual	43.81	3	14.60		
Cor Total	753.58	8			

The DT and drug release at the end of 30 min were investigated by diagnostic plots to observe the golly of fit **(Figures 2a–2h)**. The normal likelihood plot of outwardly studentized residuals designated that the maximum of the colored points demonstrating the DT and drug release at the end of 30 min were seen around the normal probability line. The normal plot of residuals was pleased since the residuals are maneuvered near the straight line

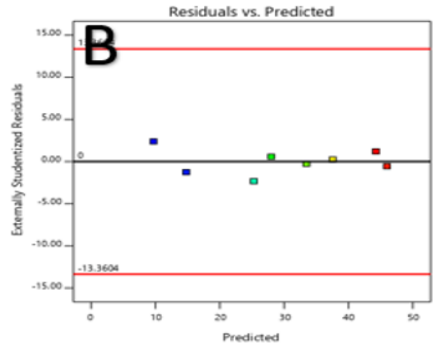
(Figures 2a and 2e). The superficially studentized residuals vs. predicted tenets plot signifies that the colored points of DT and drug release at the end of 30 min were privileged the limits **(Figures 2b and 2f)**. The Box-cox plot for power exposed a linear relationship **(Figures 2c and 2g)**. The Cook's distance was maintained, and no points were crossed. The red line represents DT and drug release at the end of 30 min was in close contact with the predicted values **(Figures 2d and 2h)**.

The Model F-value of 9.72 denotes the model is significant. There is only a 4.51% chance that more F-values are due to noise.

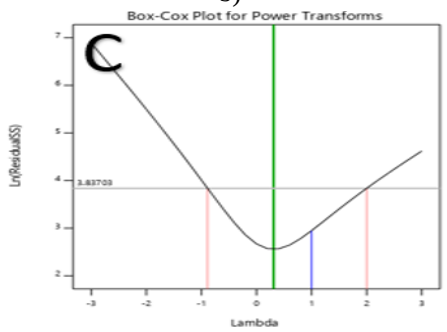
The normal plots, residual plots, Box-cox plots, and cooks' distance for DT and DR at 30 min were shown in **Figure 2**. The 3D surface plots for DT and DR at 30 min were shown in **Figure 3**.



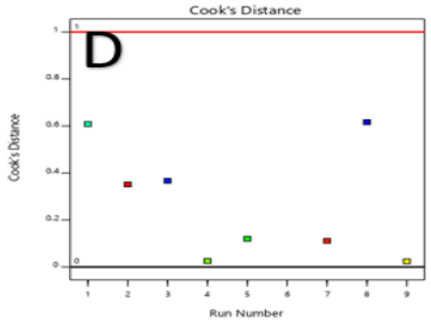
a)



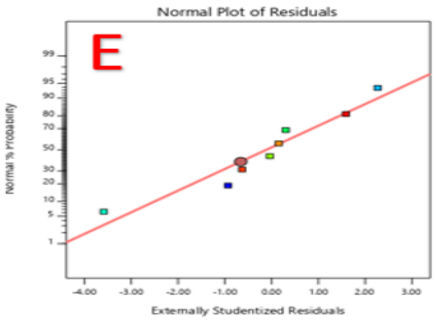
b)



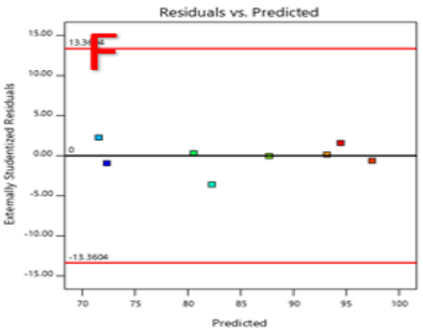
c)



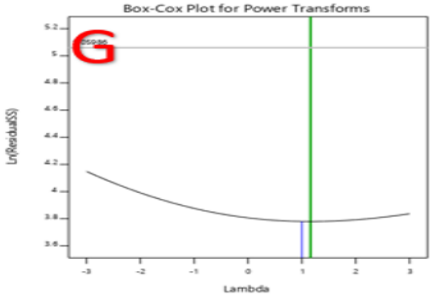
d)



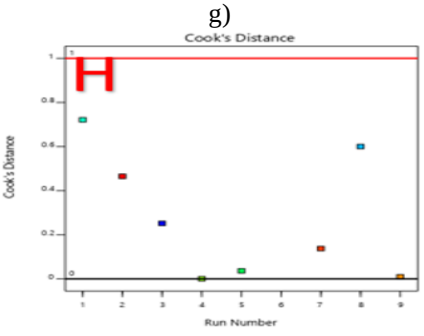
e)



f)



g)



h)

Figure 2. Plots showing the interaction impact of PEG- 4000 and PF-68 on disintegration (a-d) and drug released at the end of 30 min (e-h)

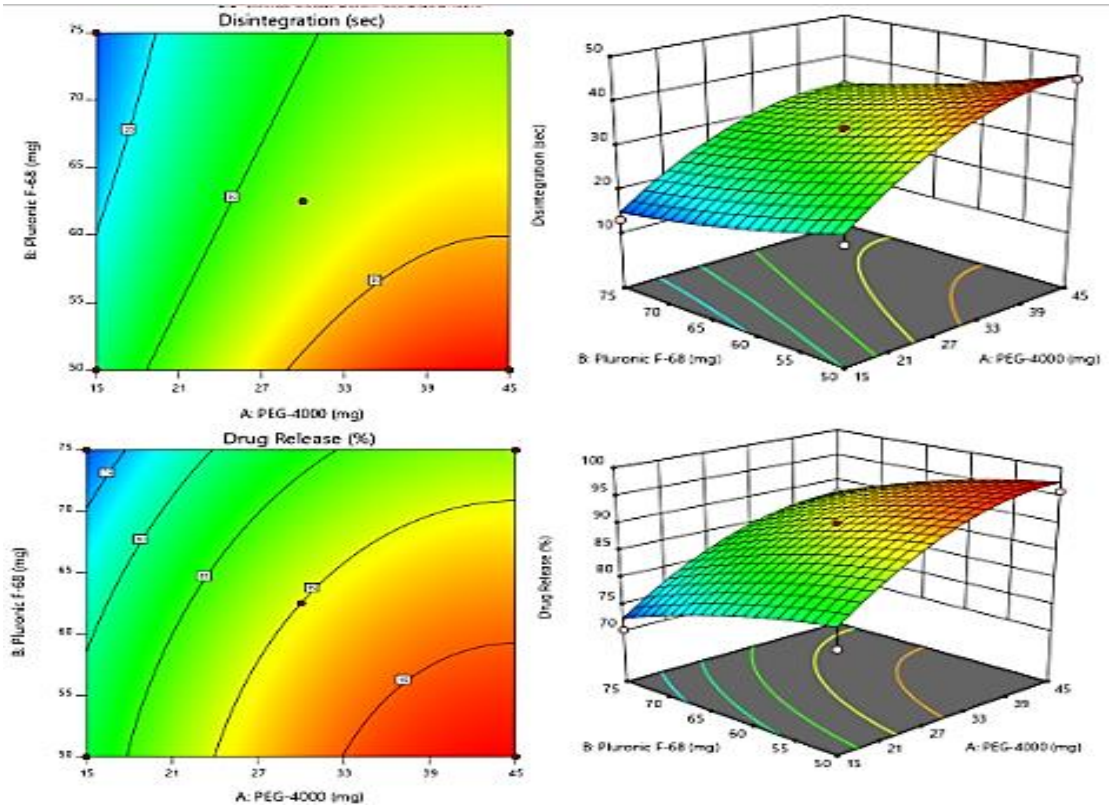


Figure 3. Contour plot and 3D response plot for disintegration time and drug dissolved at the end of 30 min

LVD tablets (F-5) which are made by employing PEG-4000 (0.78mg) and PF-68 at 62.5, gave a very rapid DT than others. The decreasing order of DT was F-5 > F-3 > F-1 > F-8 > F-4 > F-9 > F-6 > F-2 > F-7. The multinomial equation narrates the interconnection between the response (Y_1) and the variables A and B based on the perceived data was formed to be Y_1= +34.00+9.85A-5.76B-0.50AB-5.19A_2 +1.06B_2.

LVD tablets (F-7) gave 97.5% dissolution after 30min. Intermittent levels of PEG-4000 and higher levels of PF-68 gave good dissolution of LVD tablets. The decreasing order of drugs dissolved after 30 min was F-7 > F-2 > F-6 > F-9 > F-4 > F-8 > F-1 > F-5 > F-3.

The polynomial equation relating the link between the response (Y_2) and the variables A and B based on the detected data was formed to be Y_2=+90.00+7.64A-4.92B+0.05AB-3.82A_2-1.24B_2.

CONCLUSION

The individual and collective consequences of PEG-4000 and Pluronic F-68 on the Lamivudine discharge are highly significant (P<0.01). Intermittent levels of PEG-4000 and higher levels of PF-68 gave low disintegration time of the tablets. The multinomial equation relating to the correlation between the disintegration time in sec (Y_1) and the levels of PEG-4000 (A) and PF-68 (B) based on the detected results is Y_1= +34.00+9.85A-5.76B-0.50AB-5.19A_2+1.06B_2. The multinomial equation unfolding the link between the response, i.e., drug dissolved in 30 min (Y_2), and the levels of PEG-4000 (A) and PF-68 (B) based on the perceived results is Y_2=+90.00+7.64A-4.92B+0.05AB-3.82A_2-1.24B_2. Based on the above polynomial equation, the optimized LVD tablet with > 97.5% dissolution in 30 min could be formulated by employing PEG-4000 at 30 mg and PF-68 at 44.8 mg (F-7). Hence, tablets with more dissolution in 30 min could be optimized by central composite design.

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Conflict of interest: None

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Ethics statement: None

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