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Formulation and Evaluation of Extended Release Dosage Form Using Principles of Quality By Design (QbD)

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Abstract

A QbD approach (DOE approach) was applied to obtain the targeted profile for Drug Ganciclovir (GCR), Lopinavir (LPR). The excipients used in the preparation process of liquisolid formulation has an enormous impact on dry free flowing powder, and this results in significant variation in flow properties, compressibility during preparation. To study the impact of those excipients on flow properties, compressibility and in vitro dissolution use of experimental design approach need to be implemented. Many statistical designs of experiment (DOE) are used. First, application of Plackett–Burman screening design helps to identify the most significant factors affecting flow properties. Next, a Factorial design achieves the exact relationship between the post compression parameters and two factors (that have been identified in the screening study). The factorial design is a technique that allows identification of interaction between factors which affects the post compression parameters. Hence to solve the problems associated with BCS Class II drugs there is a need to modify flow properties, particle size, solubility and finally dissolution rate using Quality by design (QbD) approach.

Key Words: Liquisolid, Ganciclovir, Lopinavir.

Introduction

Initially, the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the RLD product, and consideration of the RLD label and intended patient population. Example MR Tablets were designed to achieve all of the attributes in the QTPP. However, our investigation during pharmaceutical development focused on those critical quality attributes (CQAs) that could be impacted by a realistic change to the drug product formulation or manufacturing process.[1]

Over the years, pharmaceutical QbD has evolved with the issuance of ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System). In addition, the ICH Q1WG on Q8, Q9, and Q10 Questions and Answers; the ICH Q8/Q9/Q10 Points to Consider document; and ICH Q11 (Development and Manufacture of Drug Substance) have been issued, as have the conclusions of FDA-EMA's parallel assessment of Quality-By-Design elements of marketing applications. These documents provide high level directions with respect to the scope and definition of QbD as it applies to the pharmaceutical industry.[2]

Nonetheless, many implementation details are not discussed in these guidances or documents. There is confusion among industry scientists, academicians, and regulators despite recent publications. This paper is intended to describe the objectives of pharmaceutical QbD, detail its concept and elements, and explain implementation tools and studies.[2]

Experimental

Liqui solid Parameters for Liqui solid formulations of GCR and LPR:

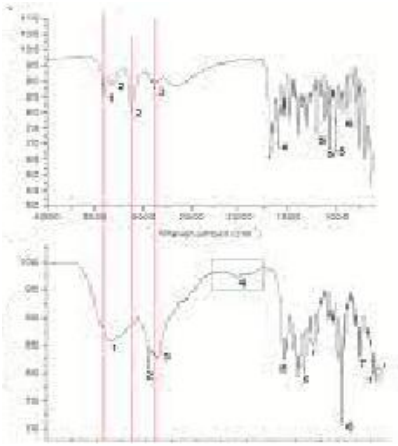
A) Angle of slide measurement (θ) [3]:

Angle of slide is used as a measure of flow properties of powders. Determination of angle of slide is done by weighing the required quantity of carrier material and placing it at one end of the metal plate having a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as the angle of slide. Angle of $33^{o}$is considered as optimum.

B) Flowable liquid retention potential determination (ϕ)[3]:

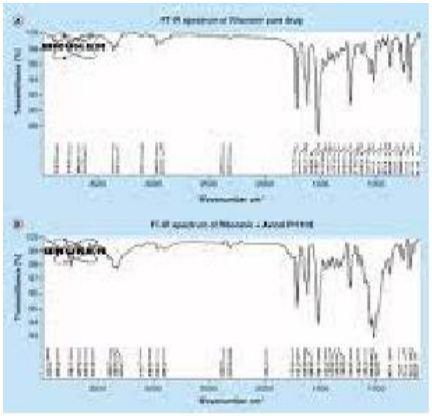
Increasing amount of selected solvent was added and mixed well with the 10gm of each of material (carrier and coating respectively). The corresponding Phi-value was calculated from the following equation after every addition ofthenon-volatileliquid.
Φ–value =Wt. of liquid/Wt. of solid

The Phi-value corresponding to an angle of slide of 33° was recorded as theflowable liquid retention potential of carrier and coating material. The Phi-values for carrier and coating material have been abbreviated asϕ_{CA} and ϕ_{CO} respectively. The carrier and coating material with maximum liquid retentionpotentialhavebeen selected as optimum.



GCR

GCR +Excipient



LPR

LPR + Excipients

Calculation of loading factor (Lf), amount of carrier (Q) and coating material (q):
On the basis of Phi-value of optimized carrier and coating; the liquid load factor (L_f) and quantities of carrier and coating materials were calculated using following formula.

$$L_f = \phi_{CA} + \phi_{CQ}(1/R)$$

$$L_f = W/QR = Q/q$$

Where,

L_f= Liquid load factor;

ϕ_{CA} = Flowable retention potential for carrier material;ϕ_{CQ} = Flowable retention potential for coating material;R=Excipientratio (Q/q);
W=Weight of liquid vehicle;Q=Weight of carrier material;q=Weight of coating material

C) Drug excipient compatibility study for Liquisolid formulationsof GCR and LPR[3]:
Drug and excipient were mixed in 1:1 ratio and placed in sealed vials for 4weeks at 40°C/75% RH as per ICH guidelines. Drug excipient compatibilitywasevaluated by;
i) Physical Observation: By the physical examination by naked eye no changes were observed.
ii) FTIR: No significant Changes were observed by comparative study of FTIR chromatograph.

Plackett Burman (PB) Screening Design for Liquisolid powder of GCR and LPR:
PB screening designs are fractional factorial designs that are used to identify the effects of a large number of factors that are likely to affect critical qualities of aparticular formulation. Because PB designs are fractional factorial designs, the number of runs needed to investigate main effects is equal to 2n or multiples of 4andsothey can be used to identify critical factors with the least number of experimental runs, with very good degree of accuracy.

PB design screens large number of input factors and at the same time reduces thenumber of runs**.** They are therefore very useful when the aim is to identify factors or variables that can befixed or eliminated in further investigations. A set of experiments using the PBscreening design was adopted to prepare Liquisolid powder of GCR and LPR.Independent variables were considered at

two levels for the study. Levels of each independent variable were selected on the basis of drug concentration, Liquid load factor (Lf) and R value (carrier/coating ratio). This design investigates every input factor and arLPRges them on the Pareto chart based on the magnitude of itsinfluence with positive or negative sign respectively (blue or grey colour). The factor with bar extending beyond the vertical line on the Pareto chart shows significant influence at 95% confidence level. The factors show positive or negative sign on the pare to chart reflecting increased or decreased effect respectively when moving from lowest to the highest level for the specific factor.

ForGCR:

Total twelve experimental trials involving four independent and four dummy variables were generated using STATGRAPHICS XVI. Four factors that may affect the experimental responses and four dummy factors were selected as independent variables at two levels for the study. The amountof PEG 400 (A), Neusilin US2 (B), Aerosil 200 (C), Primojel (D) were selected as independent variables and Dummy 1(E), Dummy 2(F), Dummy 3(G) and Dummy 4 (H) were selected as dummy variables. Angle of repose, Carr's index and Hauser's ratio were set as response variables. **Table 1** depicts composition of GCR Liquisolid formulations F1 to F12.

Independent variables	Low	High	Units
PEG 400 (A)	80	180	mg
Neusilin US2 (B)	157.109	172.935	mg
Aerosil 200 (C)	8.647	15.711	mg
Primojel (D)	20.77	21.17	mg
Dummy 1 (E)	-1	+1	-
Dummy 2 (F)	-1	+1	-
Dummy 3 (G)	-1	+1	-
Dummy 4 (H)	-1	+1	-

Table1: Composition of GCR Liquisolid powder formulations

Batch	Drug (mg)	R	Lf	PEG400 (mg)	Neusilin US2 (mg)	Aerosil200 (mg)	Primojel (mg)	Lactose (mg)	Total (mg)
F1	20	10	1.273	180	157.109	15.711	20.77	60	453.59
F2	20	20	1.156	180	172.935	8.647	21.17	60	462.752
F3	20	20	0.578	80	172.935	8.647	20.77	60	362.352
F4	20	20	0.637	80	157.109	8.647	21.17	60	346.926
F5	20	20	1.156	180	172.935	8.647	21.17	60	462.752
F6	20	20	0.578	80	172.935	15.711	20.77	60	369.416
F7	20	10	0.637	80	157.109	8.647	20.77	60	346.526
F8	20	20	1.156	180	172.935	15.711	20.77	60	469.416
F9	20	10	1.273	180	157.109	8.647	20.77	60	446.526
F10	20	20	1.273	180	157.109	15.711	21.17	60	453.99
F11	20	10	0.637	80	157.109	15.711	21.17	60	353.99
F12	20	10	0.578	80	172.935	15.711	21.17	60	369.816

R:Carrier:coating ratio,Lf: Liquidload factor

ForLPR:

Total twelve experimental trials involving five independent and three dummy variables were generated using STATGRAPHICS XVI. Four factors that may affectthe experimental responses and four dummy factors were selected as independentvariables at two levels for the study as shown in **Table 2**. The amount of PEG 400(A), Neusilin US2 (B), Aerosil 200 (C), PVP K30 (D), Eudragit L100 55 (E) were selected as independent variables and Dummy1 (F), Dummy2 (G) and Dummy3 (H) were selected as dummy variables. Angle of repose, Carr's index and Hausners ratio were set as response variables.

Independent variables	**Low (-1)**	**High (+1)**	**Units**
PEG 400 (A)	41.667	66.176	mg
Neusilin US2 (B)	308.30	430.44	mg
Aerosil 200 (C)	71.74	102.77	mg
PVP K30 (D)	18	20	mg
Eudragit L100 55 (E)	55	60	mg
Dummy 1 (F)	-1	+1	-
Dummy 2 (G)	-1	+1	-
Dummy 3 (H)	-1	+1	-

Batch	**Drug**	**R value**	**Lf**	**PEG400 (mg)**	**Neusilin US2 (mg)**	**Aerosil200 (mg)**	**PVPK30 (mg)**	**Eudragit L10055 (mg)**	**Total (mg)**
F1	375	6	1.025	66.176	430.44	71.74	20	60	1031.23
F2	375	3	1.431	66.176	308.3	102.77	18	55	930.527
F3	375	6	1.025	66.176	430.44	102.77	18	60	1060.26
F4	375	6	0.969	41.667	430.44	102.77	20	55	1032.74
F5	375	6	0.969	41.667	430.44	102.77	18	60	1035.74
F6	375	3	1.351	41.667	308.3	71.74	18	55	874.958
F7	375	3	1.431	66.176	308.3	102.77	20	55	932.527
F8	375	3	1.351	41.667	308.3	102.77	20	60	912.988
F9	375	6	1.025	66.176	430.44	71.74	20	55	1026.23
F10	375	3	1.351	41.667	308.3	71.74	20	60	881.958
F11	375	6	0.969	41.667	430.44	71.74	18	55	999.716
F12	375	3	1.431	66.176	308.3	71.74	18	60	904.497

Table3: Composition of LPR Liquisolid powder formulations

R: carrier:coating ratio, Lf: Liquid load factor

Formulation of Liquisolid powders of GCR and LPR: For GCR[5]:
GCR was dispersed in PEG 400. Neusilin US2 and Aerosil 200 were added tothe above mixture under continuous mixing in a mortar. Finally, Primojel as super disintegrant and Lactose as filler were mixed and mixture was blended for a period of 10 minutes.
ForLPR:

LPR was dispersed in PEG 400. PVP K30 was added in the mixture. NeusilinUS2 and Aerosil200 were added to the above mixture under continuous mixing in a mortar. Finally, Eudragit L100 55 was mixed and mixture wasblendedfor aperiod 10minutes.

Evaluation of Plackett Burman design batches of Liquisolid powder of GCR and LPR[6]:

a. Pre-compression parameters and application of Plackett Burman design[6]:

i. Angle of repose: Accurately weighed samples were passed separately in a glass funnel of 25ml capacity with diameter 0.5cm. Funnel was adjusted in such a way that the stem of the funnel lies 2.5cm above the horizontal surface. The sample was allowed to flow from the funnel, so the height of the pile h just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters.

Angle of repose was calculated by formula: $\theta = \tan -1 (h/r)$

ii. Hausner ratio: HR was obtained by using formula; HR = TD/BD

iii. Carr's index: Carr's index (CI) which is calculated as follows:

$$CI\ (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ X } 100$$

The above results of the responses were added into Plackett Burman Screening design and effects of independent variables were evaluated. The ANOVA results were used to determine the most influencing effect. The variables which were significant at 5% level ($P<0.05$) from the regression analysis wereconsidered to have greater impact on responses. The variables were correlatedusingthe followingpolynomial equation with PBdesign.

$Y=A0+A1X1+A2X2+A3X3+A4X4+$ .....$+AnXn$ (1)

where,Y is the response, A0 is the arithmetic mean response, and A1, A2

……AnarethecoefficientsofthefactorsX1,X2……Xn.

b. Evaluation of Liquisolid powder of GCR and LPR[7]:

Liquisolid powder was evaluated by following techniques:

i. Solubility studies of Liquisolid powder:

Solubility of liquisolid powder was carried out in distilled water, 0.1N HCl and pH6.8 buffer using. Solubility of drugs and liquisolid powder was compared in respective media.

ii. FTIR: The FTIR spectrums of drug samples were recorded on a Shimadzu FTIR8400. The spectra's were recorded after appropriate background subtraction using FTIR spectrometer equipped with a

diffuse reflectance accessory (DRS8000, Shimadzu Corporation, Japan) and a data station. About 2-3 mg of the sample was mixed with 100 mg of dry potassium bromide and the samples were scanned from 4000-400 cm-1 wave numbers at a resolution of 2 cm-1. The characteristic peaks were recorded.

iii. DSC: Differential Scanning Calorimetry (DSC): The thermal behaviour of drug samples was examined by DSC (Mettler Toledo India Pvt. Ltd, DSC Star 1). The system was calibrated with a high purity sample of Indium. Scanning was done at the heating rate of 10ºC/min over a temperature range of 0 to 200 ºC. Melting endotherms of the drug and optimized formulation were determined in the same way.

iv. PXRD: Powder X-ray Diffraction (PXRD): Powder X-ray diffraction patterns of drug samples were recorded by X-ray diffractometer (x-Pert, Philips, UK) using Cu-Ka radiation (1.542A) with a voltage of 40 kV and a current of 35 mA. Samples were scanned from 2° to 50° 2θ.

v. SEM: Scanning Electron Microscopy (SEM): The external morphology of drugs was determined by scanning electron microscopy (Oxford Instruments, INCA X Sight, UK). Samples were mounted on double faced adhesive tape and coated with a thin gold–palladium layer by sputter-coated unit and surface topography was analyzed

vi. Particlesize: Determination of particle size: The mean particle size was determined by laser diffraction technique using Malvern 2000 SM (Malvern Instruments, Malvern, UK). Analysis was carried out at room temperature keeping angle of detection 90º. The mean particle size was expressed in terms of D (0.9), that is, size of the 90% of the particle.

c. Comparison of Physico-chemical properties of pure drug and liquisolid powder of respective drug:

Physicochemical properties of pure drug and its liquisolid powder were compared to check them for identifications of drug after the liquisolid formulation.

Table 4: Five Factor Analyses with Two Levels

A	B	C	D	E	*Y*
-1	-1	-1	-1	-1	75.87
1	-1	-1	-1	-1	76.14
-1	1	-1	-1	-1	109.95
1	1	-1	-1	-1	109.55
-1	-1	1	-1	-1	80.17
1	-1	1	-1	-1	80.3
-1	1	1	-1	-1	114.07
1	1	1	-1	-1	114.05
-1	-1	-1	1	-1	68.77
1	-1	-1	1	-1	68.63
-1	1	-1	1	-1	102.41
1	1	-1	1	-1	102.27
-1	-1	1	1	-1	72.95
1	-1	1	1	-1	72.68

-1	1	1	1	-1	106.98
1	1	1	1	-1	106.65
-1	-1	-1	-1	1	75.79
1	-1	-1	-1	1	75.71
-1	1	-1	-1	1	110.08
1	1	-1	-1	1	110.04
-1	-1	1	-1	1	80.49
1	-1	1	-1	1	80.86
-1	1	1	-1	1	113.49
1	1	1	-1	1	114.06
-1	-1	-1	1	1	68.22
1	-1	-1	1	1	68.6
-1	1	-1	1	1	102.5
1	1	-1	1	1	102.3
-1	-1	1	1	1	73.03
1	-1	1	1	1	73.3
-1	1	1	1	1	106.08
1	1	1	1	1	106.7

Normal Plot

The primary goal of screening designs is to identify the vital few factors or key variables that influence the response. A normal plot is one of the graphs that help identify these influential factors.

In the normal probability plot of the effects, points that do not fall near the line have measured values that are significantly beyond the observed variation, and usually signal important effects. Important effects are larger and generally further from the fitted line than unimportant effects. Unimportant effects tend to be smaller and centered around zero.

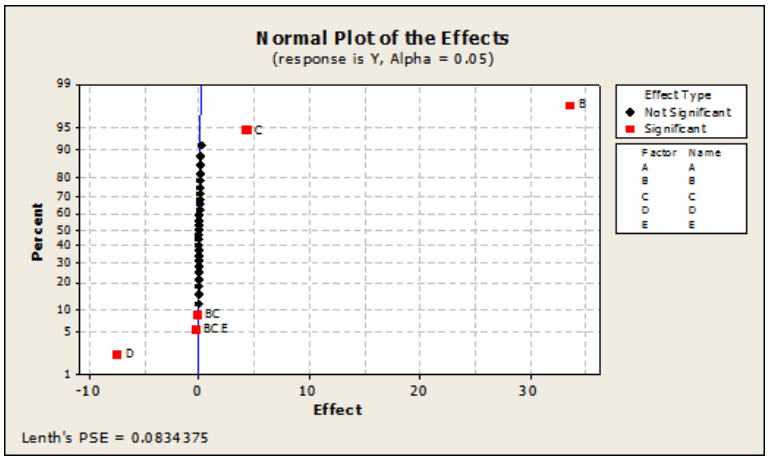


Figure 3: Normal Plot of the Effects

As shown in the normal plot (Figure 4) and the analysis of variance (ANOVA, Figure 3), the factors B, C and D are significant to the response. Additionally, there are two-way interactions between factors B and C and three-way interactions among B, C and E.

Main Effects Plot: In experimental design, a main effects plot is used in conjunction with ANOVA to examine differences among level means for one or more factors. It graphs the response mean for each factor level connected by a line. A main effect is present when different levels of a factor affect the response differently (shown as a slope on a two-level plot).

Some general patterns to look for with main effects plots include the following:

- When the line is horizontal (parallel to the x-axis), then there is no main effect present. Each level of the factor affects the response in the same way, and the response mean is the same across all factor levels.
- When the line is not horizontal, then a significant main effect may be present. Different levels of the factor affect the response differently. The greater the slope, the greater the likelihood that a main effect is statistically significant.

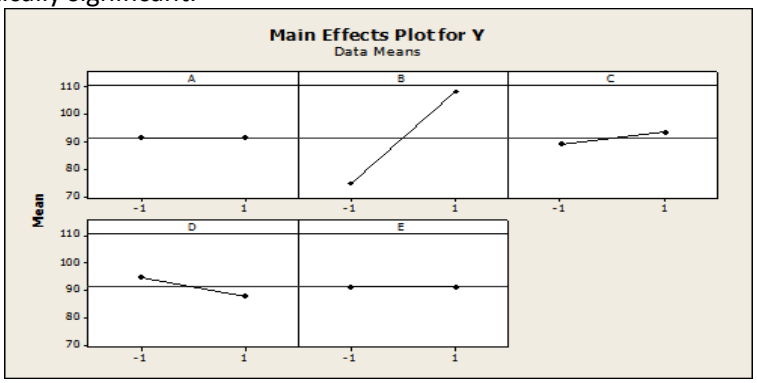


Figure 6: Main Effects Plot for Y

The factors B, C and D are shown to be significant to the response Y as shown in Figure 6

The Response Optimizer function in Minitab helps to identify the combination of input variable settings that jointly optimize a single response or a set of responses. (Note: Minitab requires the user create a starting point for the optimization and will find the first best solution based on the requested optimization objective.) This function provides an optimal solution for the input variable combinations and an optimization plot. The optimization plot is interactive – input variable settings on the plot can be adjusted to search for more desirable solutions.

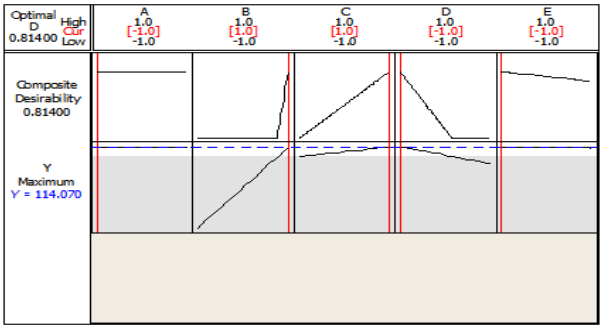


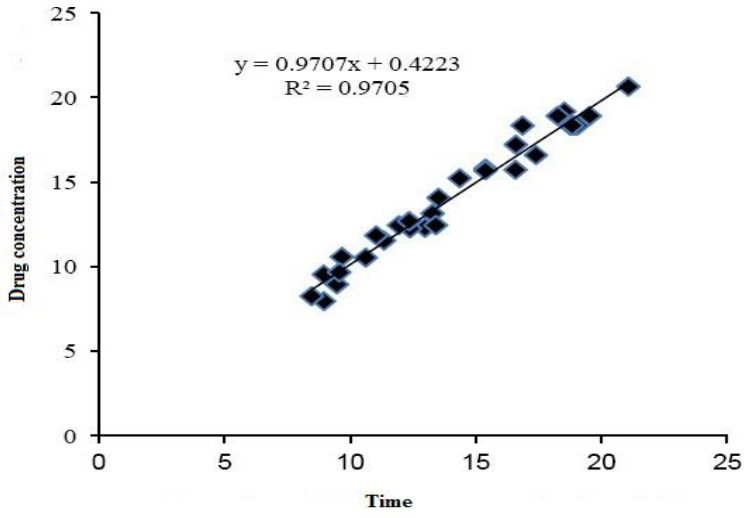
Figure 7: Optimal Solution Using Response Optimizer (where D = optimal response)

The nature of the response, Y, is "the larger the better" – and the maximum value that can be achieved in this experiment is 114.07, as shown in Figure 7.

That means to achieve the maximum value of Y, the process variables should be set as shown in Table 5

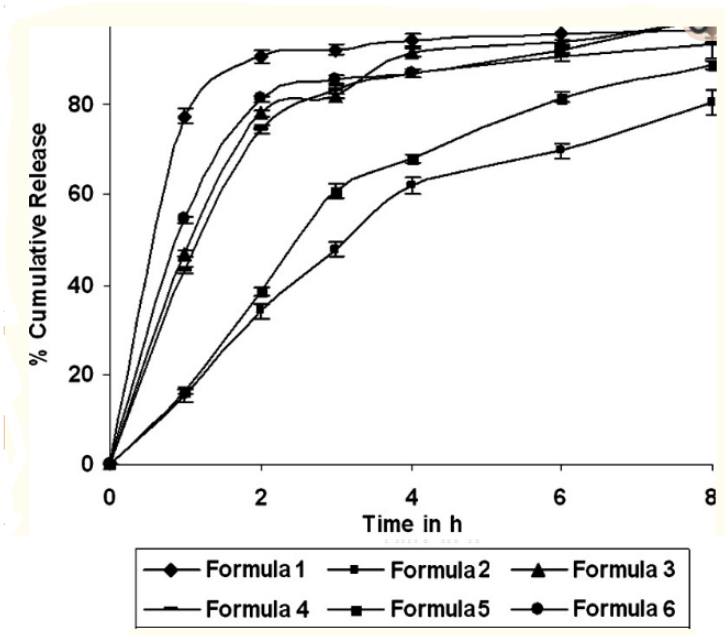
Table 5: Levels of Process Variables

Variable	Optimal Level	Notes
A	-1	A is insignificant and might not create high impact if it is changed to +1
B	1	
C	1	
D	-1	
E	-1	E is insignificant and might not create high impact if it is changed to +1



Regression model for PEG concentration

The ANOVA for the PEG regression model presented in Table 6 indicated that the model was highly significant (F=371.07; P=0.000). All the linear predictor terms and only the square terms of nickel, iron, and boron were significant. Six of the interactive predictor terms were also significant; however, Aerosil*PVP interaction, although included in the model, was not significant (P=0.051). The magnitude and direction of significant effect of model predictors are given by the T values of the coefficient estimates of the predictors (data not shown) and reveal that the linear.



Formulation of Liquisolid tablets of GCR and LPR[7-10]:

ForGCR:

Liquisolid tablets of GCR were prepared each containing 20 mg drug, usingthe single punch tablet press. GCR was dispersed in PEG 400. Neusilin US2 and Aerosil200 were added to the above mixture under continuous mixing in a mortar. Finally, Primojel as superdisint eg LPRt and Lactose as filler were mixed and mixture was blended for a period of 10 minutes. The blend was compressed in to tablets using the single punch tablet press.

For LPR:

Liquisolid tablets of LPR were prepared each containing 375 mg drug, usingthe single punch tablet press. LPR was dispersed in PEG 400. PVP K30 was added in the mixture. Neusilin US2 and Aerosil 200 were added to the above mixture under continuous mixing namortar. Finally, Eudragit L10055 was mixed and mixture was blended for a period of 10 minutes. The blend was compressed in to tablets using the single punch tablet press.

Evaluation of Liquisolid tablets of GCR and LPR[10-14]:

a. Post compression parameters:

Thickness:

The thickness was measured using vernier caliper. Five tablets from eachbatch were used and average values were calculated.

Hardness:

The hardness of the tablets was determined using Monsanto hardnesstester. It is expressed in kg/cm^2. Six tablets from each formulation weretestedforhardness.

i. Friability:

The test was performed using Roche friabilator (Electrolab).Twenty tablets were weighed and placed in the drum of the friabilator. The tabletswere allowed to revolve, fall from height of six inches for 4 min. Then tablets were de-dustedand re-weighed.
The% friability was then calculated using formula,

$$\%\text{Friability} = \frac{\text{Weight of tablets before test} - \text{Weight of tablets after test}}{\text{Weight of tablets after test}} \times 100$$

ii. Disintegration time:

The disintegration time of the tablets was measured in distilled water (37 ±2°C) using disintegration test apparatus (Electrolab, India) with disk. Five tablets from each formulation were tested for the disintegration time.

V. Drugcontent:

The GCR content in different liquisolid tablet formulations was determined by accurately weighing 20 tablets of each formula individually. Each tablet was then crushed and a quantity of powder equivalent to 10 mgof GCR was dissolved in 100 mL methanol. 1 mL of this solution wasdiluted to 10 mL with methanol and measured spectrophotometrically at λ max of 257nm.

VI. *In vitro* drug release: For GCR[15-16]:

The *in vitro* drug release study of the GCR tablets was performed using USP Type II dissolution apparatus (LABINDIADS8000). Liquisolid tablets and pure drug (20 mg) separately, were put into each of 900 mL phosphate buffer pH6.8, at 37±0.5°C with a 50 rpm rotating speed. Samples (10 ml) were withdrawn at regular time intervals (2, 4, 6, 8, 10, 15, 20 and 25min) and filtered using a 0.45μm filter. An equal volume ofthe dissolution medium was added to maintain the volume constant.
The drug content of the samples was assayed using UV-visible spectrophotometric method at 257 nm. All measurements were done intriplicate.

ForLPR:

The *in vitro* drug release study of the LPR tablets was performed using USP Type II dissolution apparatus (LABINDIADS8000). Liquisolid tablets were put into each of 900 mL 0.1 HCl, at 37±0.5°C with a 100 rpmrotating speed. Samples (10 ml) were withdrawn at regular time intervals(1, 4, 8 and 12 hr) and filtered using a 0.45μm filter. An equal volume ofthe dissolution medium was added to maintain the volume constant. The drug content of the samples was assayed using UV visible spectrophotometric method at 272 nm. All measurements were done intriplicate.

b. Polynomial fitting, ANOVA and Optimization[17-19]:

Design Expert trial version 8.0.7.1 (Stat-ease Inc., Minneapolis, MN, USA) was used for polynomial fitting and ANOVA results. Appropriate models were selected by comparing lack of fit, p values and R^2 values. Graphs were plotted for statistically significant models within significant lack of fitat desired confidence levels. The formulations were optimized using desirability approach to select optimum combination of formulation variables (X1andX2).

Evaluation of Optimized batch of Liquisolid tablets of GCR and LPR[20]:

i. FTIR: The FTIR spectrums of drug samples were recorded on a Shimadzu FTIR8400. The spectra's were recorded after appropriate background subtraction using FTIR spectrometer equipped with a diffuse reflectance accessory (DRS8000, Shimadzu Corporation, Japan) and a data station. About 2-3 mg of the sample was mixed with 100 mg of dry potassium bromide and the samples were scanned from 4000-400 cm-1 wave numbers at a resolution of 2 cm-1. The characteristic peaks were recorded.

ii. DSC: Differential Scanning Calorimetry (DSC): The thermal behavior of drug samples was examined by DSC (Mettler Toledo India Pvt. Ltd, DSC Star 1). The system was calibrated with a high purity sample of Indium. Scanning was done at the heating rate of 10ºC/min over a temperature range of 0 to 200 ºC. Melting endotherms of the drug and optimized formulation were determined in the same way.

iii. PXRD: Powder X-ray Diffraction (PXRD): Powder X-ray diffraction patterns of drug samples were recorded by X-ray diffractometer (x-Pert, Philips, UK) using Cu-Ka radiation (1.542A) with a voltage of 40 kV and a current of 35 mA. Samples were scanned from 2° to 50° 2θ.

c. Release Kinetics of Optimized batch[21]:

Release kinetics of optimized batch, were studied using kinetic models: Zero order, First order, Korsemayer-Peppasand Higuchi's model.

d. Comparison with Reference product tablet[21]:

In vitro drug release profile of optimized batch was compared with the reference product tablet. (For GCR; Natclovir Tablet, Manufactured by NATCO, and for LPR; Titomune Tablets, Manufactured By CIPLA were used.

Stability studies of Liquisolid tablets of GCR and LPR[22]:

Stability studies were carried out for 6 months for the optimized batches of GCR and LPR liquisolid tablets at a temperature 40±2°C/ RH 75±5%. The physical observation and drug content were checked at 1st, 3rd and 6th month.

	For GCR			**For LPR**		
	1st month	3rd month	6th month	1st month	3rd month	6th month
Drug Contain observed	98.96±0.25	99.14±0.30	98.58±0.41	99.23±0.17	99.19±0.24	98.76±0.22

Summary and Conclusion: To study the impact of those excipients on flow properties, compressibility and in vitro dissolution use of experimental design approach need to be implemented. Many statistical designs of experiment (DOE) are used. First, application of Plackett–Burman screening design helps to identify the most significant factors affecting flow properties. Next, a Factorial design achieves the exact relationship between the post compression parameters and two factors (that have been identified in the screening study). The factorial design is a technique that allows identification of interaction between factors which affects the post compression parameters. Hence to solve the

problems associated with BCS Class II drugs there is a need to modify flow properties, particle size, solubility and finally dissolution rate using Quality by design (QbD) approach.

First, application of Plackett–Burman screening design helps to identify the most significant factors affecting flow properties. a 32 Factorial design achieves the exact relationship between the post compression parameters and two factors (that have been identified in the screening study). The factorial design is a technique that allows identification of interaction between factors which affects the post compression parameters.

Hence to solve the problems associated with BCS Class II drugs there is a need to modify flow properties, particle size, solubility and finally dissolution rate using Quality by design (QbD) approach.\

Formulation of Liquisolid powders and parameters for Liquisolid formulations of GCR and LPR were tested using various independent vaiables, Drug excipient compatibility study for Liquisolid formulations of GCR and LPR were tested, and the liquisolid powder were evaluated by Plackett burmn design, Stability studies were also performed for Liquisolid powder, tablets were formulated for Liquisolid tablets of GCR and LPR, then the liquisolid tablet dosage form were evaluated under various parameters like Thickness, Hardness, friability, Disintegration time, Drug content and results were found to be satisfactory. In vitro evaluation Studies were also carried out and results obtained were found very gratifying.

Drug excipint studies show no signs of interaction for both the drugs. Stability studies were carried out for 6 months for the optimized batches of GCR and LPR liquisolid tablets at a temperature 40±2°C/ RH 75±5%. The physical observation and drug content were checked at 1st, 3rd and 6th month, and both the drug were found stable

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Conflict of Interest: The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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