Original Research Article

Formulation Development and Characterization of Darunavir and Ritonavir Sustained Release Tablets using Quality by Design Approach

Abstract: *Darunavir is a nonpeptidic inhibitor of protease and is primarily metabolized by cytochrome P450 3A (CYP3A) isoenzymes. It is usually coadministered with low-dose ritonavir (Darunavir/r). Ritonavir is an inhibitor of CYP3A isoenzymes and pharmacologically enhances Darunavir which leads to increased plasma concentrations of darunavir and allows for daily lower dose. Here, we have developed combination SR formulation of Darunavir and Ritonavir and evaluated. In vitro drug release of all formulations was carried out in dissolution medium 900ml of pH 3.0, 0.05 M Sodium Phosphate Buffer + 2% Tween 20 for 75 RPM USP II apparatus (paddle). The results shown that, all the formulations of matrix tablets shown the good release of drug from trialed formulations however all formulations were not releasing the drug in enough amount. In matrix tablets F6, the release of drug shows NLT 80%. So, the formulation F6 have been considered as suitable for the SR tablet of Darunavir and Ritonavir. Tablets were also evaluated though Quality by Design (QbD) method.*

Keywords: **Darunavir, Ritonavir, Sustained release, Tablet, Dissolution, Quality by design**

1. INTRODUCTION

For each disease condition or the disorder of the patient, appropriate treatment is very important to maintain good health of the patient. For the same, the drug is administered conventionally by one or more of several well defined and popular routes of drug administration which include but not limited to oral, parenteral, rectal, alveolar, ocular and topical etc.[01,15] Nowadays, oral drug delivery system is the preferred way for the administration of drugs because of easy administration, better patient compliance and flexible design of the dosage forms.[02] In recently aura, much technical advancement have been done resulting in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue i.e. targeted drug delivery system. These advancements have led to the development of several "Novel Drug Delivery System".[03] There are several terms used interchangeably viz. controlled release, programmed release, sustained release, prolonged release, timed release, extended release etc. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance.[06-14]

Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. These system sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug.[04] Darunavir is a medicine used to decrease the amount of HIV virus in your body and make your immune system stronger. Darunavir is always used with other HIV medicines.[15] Darunavir inhibits and is primarily metabolized by cytochrome P450 3A (CYP3A) isoenzymes and is coadministered with low-dose ritonavir (Darunavir/r); ritonavir is an inhibitor of CYP3A isoenzymes and pharmacologically enhances Darunavir, resulting in increased plasma concentrations and allowing for a lower daily dose. The t1/2 (terminal elimination half-life) of Darunavir is 15 h in the presence of ritonavir. An extensive Darunavir/r drug-drug interaction programme has been undertaken, covering a wide range of therapeutic areas.[16,17,18,19,20,21]

It is known that Darunavir is rapidly absorbed from the intestine after oral administration, reaching peak plasma concentrations after 2.5–4.0 h. It is also known that P-glycoprotein expressed in intestinal epithelial cells is able to decrease the absorption of orally administered and low levels of intestinal absorption together with CYP450 activity are major factors in the reduced bioavailability of these drugs. Darunavir, co-administered with ritonavir (both medications are HIV-1 protease inhibitors), is indicated for use in the treatment of HIV-1 infection in combination with other antiretroviral medications.[17,18,21,22,23,24,25,26,27]

The objective of developing oral sustained drug delivery systems of Darunavir in current research study is to avoid other combination treatment to reduce frequency of drug administration, to improve patient compliance, to reduce blood level oscillation characteristic of multiple dosing of conventional dosage forms, to reduce amount of drug administered. The recommended maximum dose for the Darunavir is 800 mg and for ritonavir is 200 mg. Same dose has been selected and formulated for the combination drug. The objective of developing oral combination immediate drug delivery systems of Darunavir and Ritonavir is to facilitate patients with ease of combination treatment

and to evaluate the properties of both drugs which might lead to provide information about other new formulations of these drug.

2. DOSE CALCULATION

Ke = Elimination rate constant (Zero-order kinetic), T1/2 = Half-life, DI = Initial Dose,

DM = Maintenance Dose, DL = Loading Dose, Tmax = Time to achieve maximum plasma concentration

Ke = 0.693/T1/2

= 0.693/ 15

= 0.0462 R = Ke * DI

= 0.0462*400

= 18.48/H

DM = R*Tmax

= 18.48*20

= 369.6

≈ 375 mg DL = DI – R*Tmax

= 400 – 18.48*4

= 326.08

≈ 325 mg

Total Dose = DM + DL

= 375 + 325 = 700 mg

Summary: 325 mg of drug should be released in first 4 hrs. Of total 24 hrs. Remaining 375 mg drug should be released in remaining 20 hrs. Of total 24 hrs.

The SR tablet with different methods will be prepared in different batches. Outcome from the data analysis after dissolution test will be analyzed by statistical method comparing.

3. MATERIAL AND METHODS

Materials:

Darunavir, Ritonavir, Microcrystalline Cellulose (Avicel PH-101), Lactose monohydrate (Granulac 200), Hypromellose (METHOCELTM K100 Premium LVCR), Hypromellose (METHOCELTM K4M Premium CR), FD & C Green No.40, Magnesium stearate, Opadry White,Purified water.

Preparation of sustained release tablets:

The powder blends were prepared by taking required quantities of drug and polymer. They were mixed thoroughly. After that microcrystalline cellulose (MCC) was added as directly compressible filler, binder. Finally magnesium stearate was added as a lubricant. These powder blends were then passed through sieve to break any lumps or aggregates. The formulas are indicated in below Table.

Preparation of sustained release matrix tablets

The powder blends were compressed into tablets by direct compression technique on rotary tableting machine. The compression force was optimized by proper adjustment of upper and lower punches. The tablets formed did not show any defects like capping or chipping. These tablets of each formulation type (F-1 to F-6) were evaluated for various properties such as thickness, diameter, weight variation, uniformity of drug content, hardness, and friability.

The result of excipients compatibility study is presented in table below.

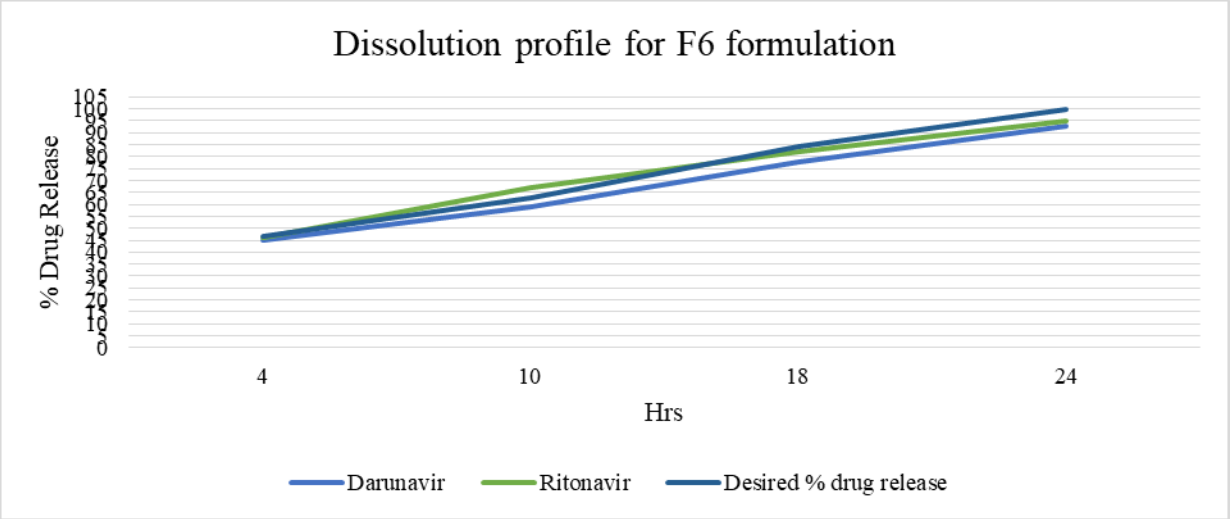
Table 1: Formulations and dissolution profile for sustained release Darunavir and Ritonavir tablet

	F1	F2	F3	F4	F5	F6
Ingredients	**Quantity Required (mg/Tablet)**	**Quantity Required (mg/Tablet)**	**Quantity Required (mg/Tablet)**	**Quantity Required (mg/Tablet)**	**Quantity Required (mg/Tablet)**	**Quantity Required (mg/Tablet)**
Darunavir	375.00	375.00	375.00	375.00	375.00	375.00
Ritonavir	110.00	110.00	110.00	110.00	110.00	110.00
Microcrystalline Cellulose (Avicel PH-112)	52.00	42.00	36.00	31.00	27.50	22.00
Lactose monohydrate (Granulac 200)	52.00	42.00	36.00	31.00	27.50	22.00
Hypromellose (METHOCELTM K100 Premium LVCR)	100.00	120.00	130.00	138.00	142.00	150.00
Hypromellose (METHOCELTM K4M Premium CR)	25.00	25.00	27.00	29.00	32.00	35.00
FD & C Green No.40	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium Stearate	5.00	5.00	5.00	5.00	5.00	5.00
Opadry White (03B28796)	20.00	20.00	20.00	20.00	20.00	20.00
Purified Water	**q. s.**	**q. s.**	**q. s.**	**q. s.**	**q. s.**	**q. s.**
Total Weight	740.00	740.00	740.00	740.00	740.00	740.00

Dissolution profile												
%Drug Release												
Time Points	**F1**		**F2**		**F3**		**F4**		**F5**		**F6**	
	D	R	D	R	D	R	D	R	D	R	D	R
4 hr (NMT 50 %)	75	78	68	75	64	69	60	63	50	56	45	46
10 hr (55-75)	85	88	79	83	74	79	70	74	68	72	59	67

Ingredients	F1		F2		F3		F4		F5		F6	
	Quantity Required (mg/Tablet)		Quantity Required (mg/Tablet)		Quantity Required (mg/Tablet)		Quantity Required (mg/Tablet)		Quantity Required (mg/Tablet)		Quantity Required (mg/Tablet)	
18 hr (70-90)	92	97	89	90	86	87	84	85	82	86	78	82
24 hr (NLT 90)	99	99	97	98	95	97	94	96	94	96	93	95

D = Darunavir; R = Ritonavir



Graph 1: Dissolution profile for F6 formulation

Quality Target Product Profile for the Antiretroviral Sustained Release Tablets

The Quality Target Product Profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." The QTPP is an essential element of a QbD approach and forms the basis of design for the development of the product. For SR Tablets, the target should be defined early in development based on the properties of the drug substance (DS), characterization of the product. By beginning with the end in mind, the result of development is a robust formulation and manufacturing process with an acceptable control strategy that ensures the performance of the drug product.

A critical quality attribute (CQA) is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."1 The identification of a CQA from the QTPP is based on the severity of harm to a patient should the product fall outside the acceptable range for that attribute.

All quality attributes are target elements of the drug product and should be achieved through a good quality management system, appropriate formulation/process design and development. From the perspective of pharmaceutical development, we only investigate the subset of CQAs of the drug product that also have a high potential to be impacted by the formulation or process variables. Our investigation culminates in an appropriate control strategy.

4. QUALITY BY DESIGN

Study Plan: A 2^3 full Factorial design was used and three center points was included to evaluate any curvature effects exist. Batch size of 700 units was executed at lab scale as per different combination of factor as per DOE plan. All Processing parameter like granulation, wet milling, drying, milling, blending and compression are kept constant to reduce additional noise. All factors are numeric factor and the drug product CQA to be evaluated is ***% Drug released at 24 hrs. For both API.*** Study design is given in **Table.** Formulation composition and experimental results for drug release profile for all designed experiments are given.

Power Calculation for design: For selected design power also found to be above 80% for all three factors.

Data of signal/Noise ratio and power obtained for the selected design at. 5% alpha level to detect specified signal to noise ratio are presented in below Table.

Table 2: Design of the Regular 2^3 Factorial DOE with 1 Centre Points to Study Impact of Critical Excipients

Factors : Formulation Variables		**Levels**		
		-1	**+1**	**Center point level**
A	Hypromellose (METHOCELTM K100 Premium LVCR)	142.50 mg/tab	157.50 mg/tab	150 mg/tab
B	Hypromellose (METHOCELTM K4M Premium CR)	33.25 mg/ tab	36.55 mg/ tab	35 mg/ tab
C	Magnesium Stearate	4.0 mg/tab	5.13 mg/tab	5 mg/tab
Response		**Goal**	**Acceptance Range**	
Y1	Dissolution of Darunavir at 4 Hrs. (%)	Minimum	NMT 50%	
Y2	Dissolution of Darunavir at 18Hrs. (%)	Minimum	70- 90%	
Y3	Dissolution of Ritonavir at 4 Hrs. (%)	Minimum	NMT 50%	
Y4	Dissolution of Ritonavir at 18Hrs. (%)	Minimum	70- 90%	

Power Calculation for design: For selected design power also found to be above 90 % for all three factors. Data of signal/Noise ratio and power obtained for the selected design at. 5% alpha level to detect specified signal to noise ratio are presented in below Table.

Table 3: Design Power Evaluation

Name	**Unit**	**Difference to detect delta (Signal)**	**Est. Std. Deviation Sigma (Noise)**	**Delta/Sigma (Signal/Noise ratio)**	**Power**
Dissolution of Darunavir at 4 Hrs. (%)	%	2	0.5	4	99.8
Dissolution of Darunavir at 18Hrs. (%)	%	2	0.5	4	99.8
Dissolution of Ritonavir at 4 Hrs. (%)	%	2	0.5	4	99.8

Dissolution of Ritonavir at 18Hrs. (%)	%	2	0.5	4	99.8

Table 4: Formulation Details for 2^3 Factorial Design

Sr. No.	Run Number	1	2	3	4	5	6	7	8	9	10	11
	Batch Number	**DOE-1**	**DOE-2**	**DOE-3**	**DOE-4**	**DOE-5**	**DOE-6**	**DOE-7**	**DOE-8**	**DOE-9**	**DOE-10**	**DOE-11**
	Ingredients	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**
Dry Mixing												
1	Darunavir	375.00	375.00	375.00	375.00	375.00	375.00	375.00	375.00	375.00	375.00	375.00
2	Ritonavir	110.00	110.00	110.00	110.00	110.00	110.00	110.00	110.00	110.00	110.00	110.00
3	Microcrystalline Cellulose (Avicel PH 101)	12.80	22.00	13.05	27.87	31.37	22.00	31.12	27.62	16.37	22.00	16.12
4	Lactose monohydrate (Granulac 200)	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00
5	Hypromellose (METHOCELTM K100 Premium LVCR)	157.50	150.00	157.50	142.50	142.50	150.00	142.50	142.50	157.50	150.00	157.50
6	Hypromellose (METHOCELTM K4M Premium CR)	36.57	35.00	36.57	36.75	33.25	35.00	33.25	36.75	33.25	35.00	33.25
7	FD & C Green No.40	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Binder												
8	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Lubrication												
9	Magnesium Stearate	5.13	5.00	4.88	4.88	4.88	5.00	5.13	5.13	4.88	5.00	5.13
Film Coating												
10	Opadry White (03B28796)	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
Tablets Weight		**740.00**	**740.00**	**740.00**	**740.00**	**740.00**	**740.00**	**740.00**	**740.00**	**740.00**	**740.00**	**740.00**

Table 5: Experimental Results of the DOE to study Drug release

Batch No.	Factors : Formulation Variables			Response			
				Dissolution (%)			
				4 Hrs. NMT 50%		18Hrs. 70- 90%	
	Factor 1 **A**: Controlled Release Polymer Hypromellose (METHOCELTM K100 Premium LVCR)	**Factor 2** **B:** Controlled Release Polymer Hypromellose (METHOCELTM K4M Premium CR)	**Factor 3** **C:** Level of Lubrication Magnesium Stearate	**Darunavir R1**	**Ritonavir R2**	**Darunavir R1**	**Ritonavir R2**
DOE-1	157.50	36.57	5.13	42	46	72	78
DOE-2	150.00	35.00	5.00	43	48	79	82
DOE-3	157.50	36.57	4.88	43	46	73	78
DOE-4	142.50	36.57	4.88	46	48	81	87
DOE-5	142.50	33.25	4.88	46	49	82	88
DOE-6	150.00	35.00	5.00	44	48	77	81
DOE-7	142.50	33.25	5.13	45	48	81	86
DOE-8	142.50	36.75	5.13	44	48	79	84
DOE-9	157.50	33.25	4.88	42	47	77	80
DOE-10	150.00	35.00	5.00	42	47	78	83
DOE-11	157.50	33.25	5.13	42	46	78	80

ANOVA for selected factorial model

Response 1: Darunavir-Dissolution 4 hr (NMT 50%)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	18.88	7	2.70	2.20	0.2771	not significant
A-Hypromellose(Methocel K 100)	3.12	1	3.12	2.55	0.2083	
B-Hypromellose(Methocel K4M)	0.1250	1	0.1250	0.1022	0.7702	
C-Magnesium Stearate	1.12	1	1.12	0.9195	0.4083	
AB	1.13	1	1.13	0.9195	0.4083	
AC	10.12	1	10.12	8.28	0.0637	
BC	0.1250	1	0.1250	0.1022	0.7702	
ABC	3.12	1	3.12	2.55	0.2083	
Residual	3.67	3	1.22			
Lack of Fit	1.67	1	1.67	1.67	0.3254	not significant
Pure Error	2.00	2	1.0000			
Cor Total	22.55	10				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 2.20 implies the model is not significant relative to the noise. There is a 27.71% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case there are no significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

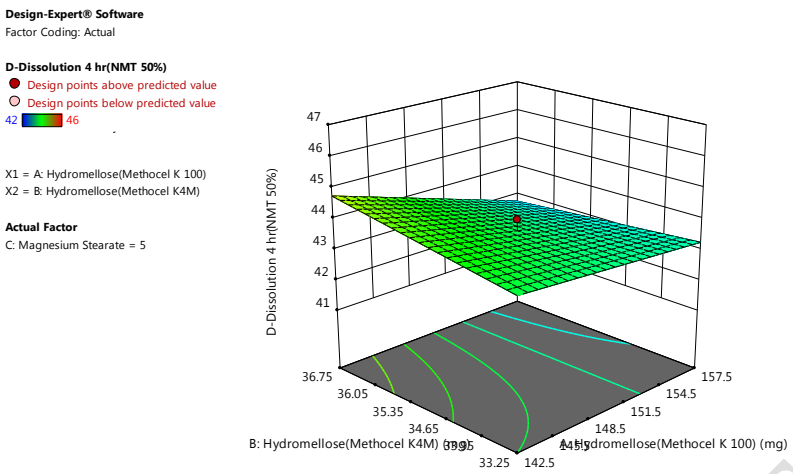
The **Lack of Fit F-value** of 1.67 implies the Lack of Fit is not significant relative to the pure error. There is a 32.54% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	1.11	**R^2**	0.8372
Mean	43.64	**Adjusted R^2**	0.4573
C.V. %	2.53	**Predicted R^2**	-16.5596
		Adeq Precision	4.2405

A negative **Predicted R^2** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 4.240 indicates an adequate signal. This model can be used to navigate the design space.



Graph 2: Dissolution 4 hrs (factorial design)

Response 2: Darunavir-Dissolution 18 hr (70-90 %)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	57.88	7	8.27	8.70	0.0515	not significant
A-Hypromellose(Methocel K 100)	15.12	1	15.12	15.91	0.0282	
B-Hypromellose(Methocel K4M)	6.12	1	6.12	6.44	0.0848	
C-Magnesium Stearate	1.13	1	1.13	1.18	0.3563	
AB	6.13	1	6.13	6.44	0.0848	
AC	28.12	1	28.12	29.58	0.0122	
BC	1.12	1	1.12	1.18	0.3563	
ABC	0.1250	1	0.1250	0.1315	0.7409	
Residual	2.85	3	0.9508			
Lack of Fit	0.8523	1	0.8523	0.8523	0.4534	not significant
Pure Error	2.00	2	1.0000			
Cor Total	60.73	10				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 8.70 implies there is a 5.15% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, AC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

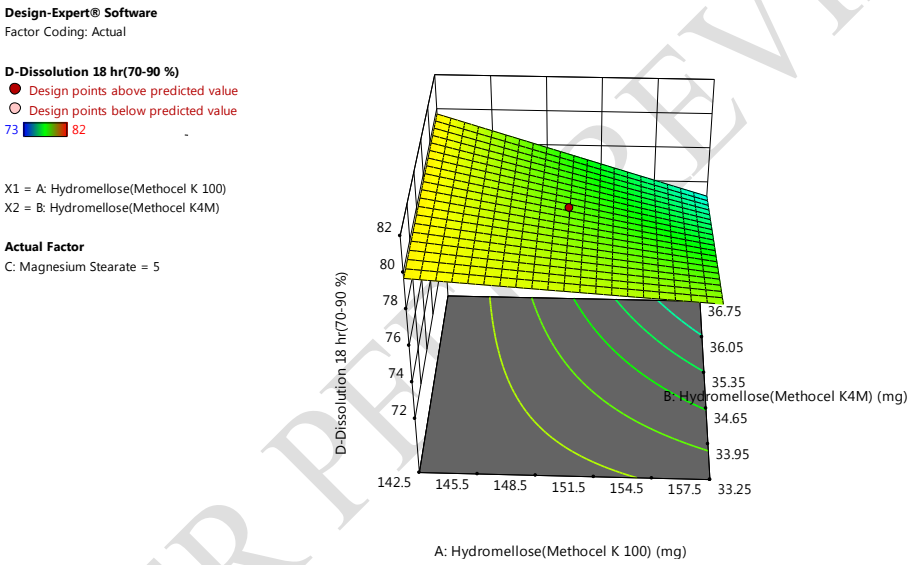
The **Lack of Fit F-value** of 0.85 implies the Lack of Fit is not significant relative to the pure error. There is a 45.34% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	0.9751	**R^2**	0.9530
Mean	78.45	**Adjusted R^2**	0.8434
C.V. %	1.24	**Predicted R^2**	-2.3456
		Adeq Precision	10.8233

A negative **Predicted R^2** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 10.823 indicates an adequate signal. This model can be used to navigate the design space.



Graph 3: Dissolution 18 hrs (factorial design)

ANOVA for selected factorial model

Response 3: Ritonavir -Dissolution 4 hr(NMT 50%)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	7.88	7	1.13	3.96	0.1428	not significant
A-Hypromellose(Methocel K 100)	1.13	1	1.13	3.96	0.1407	
B-Hypromellose(Methocel K4M)	0.1250	1	0.1250	0.4400	0.5545	
C-Magnesium Stearate	0.1250	1	0.1250	0.4400	0.5545	
AB	1.12	1	1.12	3.96	0.1407	
AC	3.13	1	3.13	11.00	0.0452	
BC	1.13	1	1.13	3.96	0.1407	
ABC	1.13	1	1.13	3.96	0.1407	
Residual	0.8523	3	0.2841			
Lack of Fit	0.1856	1	0.1856	0.5568	0.5333	not

						significant
Pure Error		0.6667	2	0.3333		
Cor Total		8.73	10			

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 3.96 implies the model is not significant relative to the noise. There is a 14.28% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case AC is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

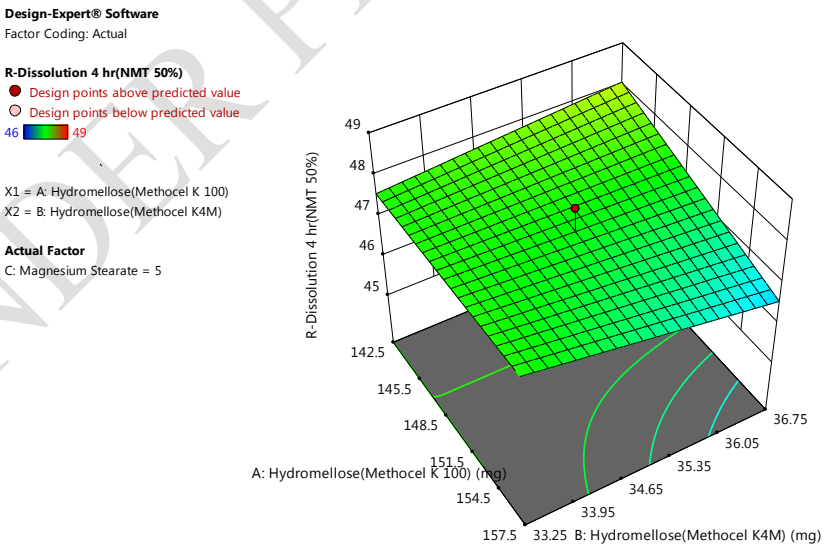
The **Lack of Fit F-value** of 0.56 implies the Lack of Fit is not significant relative to the pure error. There is a 53.33% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	0.5330	**R^2**	0.9023
Mean	47.45	**Adjusted R^2**	0.6745
C.V. %	1.12	**Predicted R^2**	-4.1019
		Adeq Precision	6.6000

A negative **Predicted R^2** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 6.600 indicates an adequate signal. This model can be used to navigate the design space.



Graph 4: Dissolution 4 hrs (factorial design)

ANOVA for selected factorial model

**Response 4: Ritonavir -Dissolution 18 hr (70-90 %) **

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	94.87	7	13.55	8.54	0.0528	not

						significant
A-Hypromellose(Methocel K 100)	21.13	1	21.13	13.31	0.0355	
B-Hypromellose(Methocel K4M)	1.13	1	1.13	0.7088	0.4617	
C-Magnesium Stearate	0.1250	1	0.1250	0.0788	0.7972	
AB	10.12	1	10.12	6.38	0.0857	
AC	55.13	1	55.13	34.73	0.0098	
BC	1.13	1	1.13	0.7088	0.4617	
ABC	6.13	1	6.13	3.86	0.1442	
Residual	4.76	3	1.59			
Lack of Fit	2.76	1	2.76	2.76	0.2385	not significant
Pure Error	2.00	2	1.0000			
Cor Total	99.64	10				

Factor coding is **coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 8.54 implies there is a 5.28% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, AC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

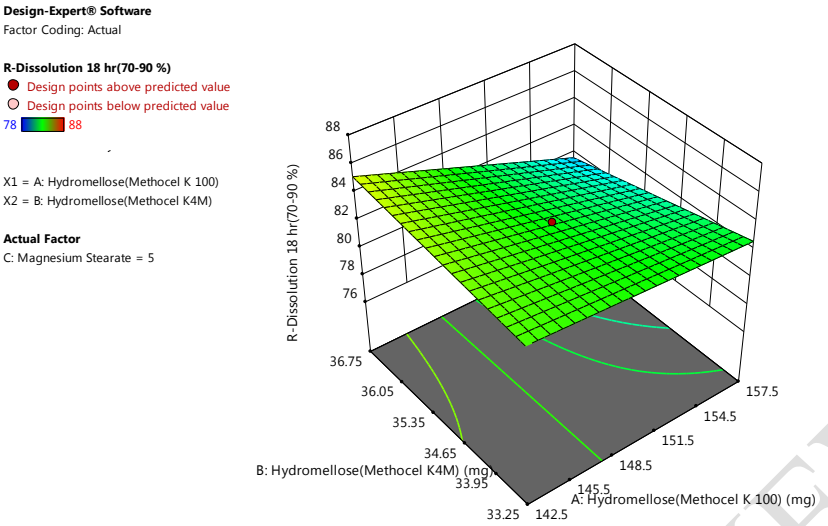
The **Lack of Fit F-value** of 2.76 implies the Lack of Fit is not significant relative to the pure error. There is a 23.85% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	1.26	**R^2**	0.9522
Mean	82.82	**Adjusted R^2**	0.8407
C.V. %	1.52	**Predicted R^2**	-5.5523
		Adeq Precision	9.3078

A negative **Predicted R^2** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 9.308 indicates an adequate signal. This model can be used to navigate the design space.



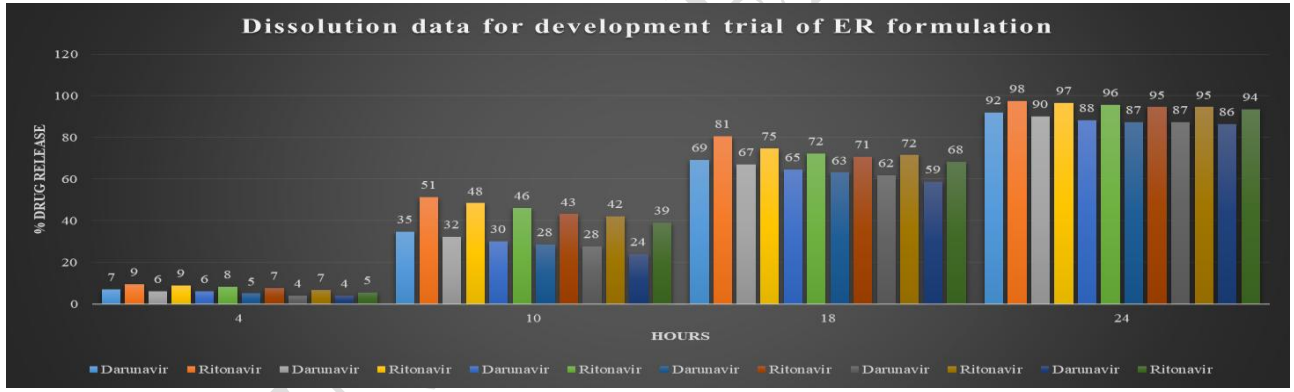
Graph 5: Dissolution 18 hrs (factorial design)

Table 6: Development Trial of Darunavir and Ritonavir Extended release tablet

Ingredients		D1		D2		D3		D4		D5		D6	
DRY MIXING		**Qty mg/Tab**	**%W/W**	**Qty mg/Tab**	**%W/W**	**Qty mg/Tab**	**%W/W**	**Qty mg/Tab**	**%W/W**	**Qty mg/Tab**	**%W/W**	**Qty mg/Tab**	**%W/W**
1	Darunavir	375.00	50.68	375.00	50.68	375.00	50.68	375.00	50.68	375.00	50.68	375.00	50.68
2	Ritonavir	110.00	14.86	110.00	14.86	110.00	14.86	110.00	14.86	110.00	14.86	110.00	14.86
3	Microcrystalline Cellulose (Avicel PH 101)	52.00	7.03	42.00	5.68	36.00	4.86	31.00	4.19	27.50	3.72	22.00	2.97
4	Lactose monohydrate (Granulac 200)	52.00	7.03	42.00	5.68	36.00	4.86	31.00	4.19	27.50	3.72	22.00	2.97
5	Hypromellose (METHOCELTM K100 Premium LVCR)	100.00	13.51	120.00	16.22	130.00	17.57	138.00	18.65	142.00	19.19	150.00	20.27
6	Hypromellose (METHOCELTM K4M Premium CR)	25.00	3.38	25.00	3.38	27.00	3.65	29.00	3.92	32.00	4.32	35.00	4.73
7	FD & C Green No.40	1.00	0.14	1.00	0.14	1.00	0.14	1.00	0.14	1.00	0.14	1.00	0.14
GRANULATION:													
8	Purified Water	q.s	---	q.s	---	q.s	---	q.s	---	q.s	---	q.s	---
LUBRICATION:													
10	Magnesium Stearate	5.00	0.68	5.00	0.68	5.00	0.68	5.00	0.68	5.00	0.68	5.00	0.68
Total		**720.00**		**720.00**	**-**	**720.00**		**-**	**720.00**	**-**	**720.00**	**-**	**720.00**
FILM COATING:													
11	Opadry White (03B28796)	20.00	2.70	20.00	2.70	20.00	2.70	20.00	2.70	20.00	2.70	20.00	2.70
12	Purified Water[#]	q.s		q.s	--	q.s	--	q.s	--	q.s	--	q.s	--
Total		**740.00**		**740.00**	100.00	**740.00**	100.00	**740.00**	100.00	**740.00**	100.00	**740.00**	100.00
D = Development trial													

Table 7: Extended Release Dissolution profile in matrix formulation

900mL pH 3.0 0.05 M Sodium Phosphate Buffer + 2% Tween 20 , 75 RPM												
Batch No.	**D1**		**D2**		**D3**		**D4**		**D5**		**D6**	
	% Release		**% Release**		**% Release**		**% Release**		**% Release**		**% Release**	
Time (hr)	**Darunavir**	**Ritonavir**	**Darunavir**	**Ritonavir**	**Darunavir**	**Darunavir**	**Darunavir**	**Ritonavir**	**Darunavir**	**Ritonavir**	**Darunavir**	**Ritonavir**
4 (NMT 10%)	7	9	6	9	6	8	5	7	4	7	4	5
10 (20 -45 %)	35	51	32	48	30	46	28	43	28	42	24	39
18 (55-75 %)	69	81	67	75	65	72	63	71	62	72	59	68
24 (NLT 80 %)	92	98	90	97	88	96	87	95	87	95	86	94
D = Development trial												

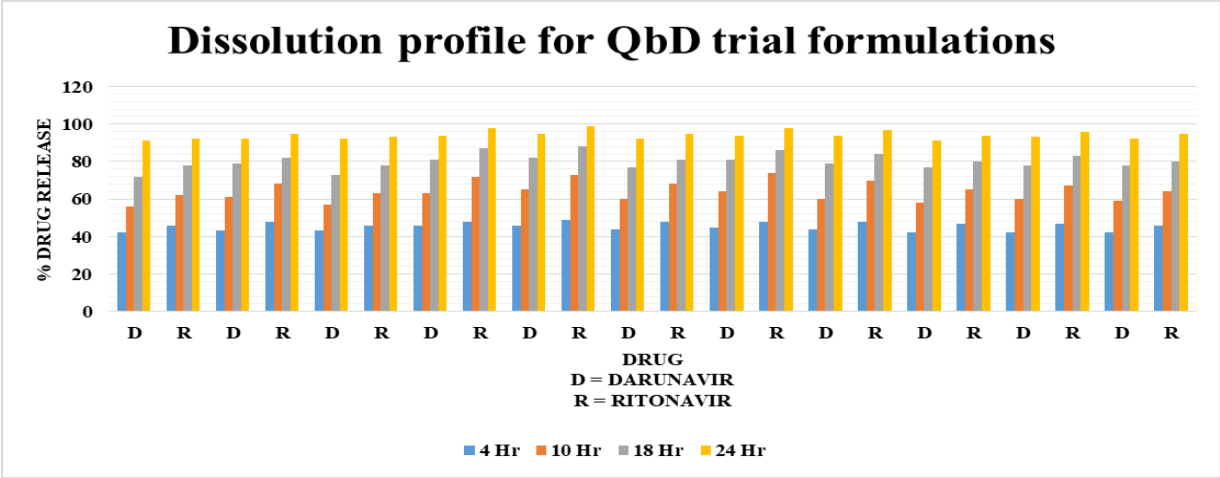


Graph 6: Dissolution data for development trial of ER formulation

Table 8: QbD data for Extended Release profile in matrix formulation

		F1		F2		F3		F4		F5		F6		F7		F8		F9		F10		F11	
Time point	**Acceptable range**	**% Drug Release**		**% Drug Release**		**% Drug Release**		**% Drug Release**		**% Drug Release**		**% Drug Release**		**% Drug Release**		**% Drug Release**		**% Drug Release**		**% Drug Release**		**% Drug Release**	
		D	**R**	**D**	**R**	**D**	**R**	**D**	**R**	**D**	**R**	**D**	**R**	**D**	**R**	**D**	**R**	**D**	**R**	**D**	**R**	**D**	**R**
4 hrs	NMT 50 %	42	46	43	48	43	46	46	48	46	49	44	48	45	48	44	48	42	47	42	47	42	46
10 hrs	55 – 75 %	56	62	61	68	57	63	63	72	65	73	60	68	64	74	60	70	58	65	60	67	59	64
18 hrs	70 – 90 %	72	78	79	82	73	78	81	87	82	88	77	81	81	86	79	84	77	80	78	83	78	80
24 hrs	NLT 90 %	91	92	92	95	92	93	94	98	95	99	92	95	94	98	94	97	91	94	93	96	92	95

D = Darunavir, R = Ritonavir



Graph 7: Dissolution profile for QbD trial formulation

ANOVA for selected factorial model

Response 1: D-Dissolution 4 hr(NMT 50%)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	18.88	7	2.70	2.20	0.2771	not significant
A-Hydromellose(Methocel K 100)	3.12	1	3.12	2.55	0.2083	
B-Hydromellose(Methocel K4M)	0.1250	1	0.1250	0.1022	0.7702	
C-Magnesium Stearate	1.12	1	1.12	0.9195	0.4083	
AB	1.13	1	1.13	0.9195	0.4083	
AC	10.12	1	10.12	8.28	0.0637	
BC	0.1250	1	0.1250	0.1022	0.7702	
ABC	3.12	1	3.12	2.55	0.2083	
Residual	3.67	3	1.22			
Lack of Fit	1.67	1	1.67	1.67	0.3254	not significant
Pure Error	2.00	2	1.0000			
Cor Total	22.55	10				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 2.20 implies the model is not significant relative to the noise. There is a 27.71% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case there are no significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

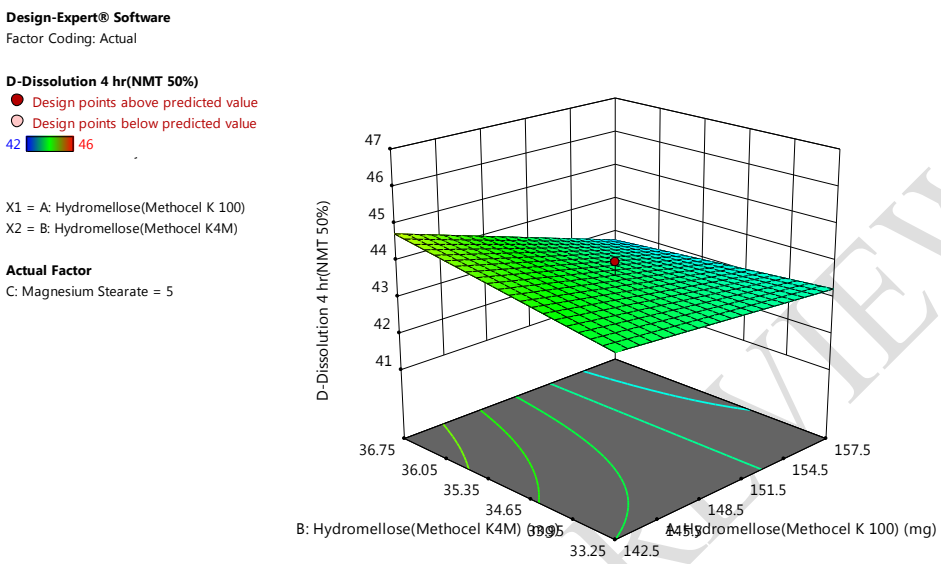
The **Lack of Fit F-value** of 1.67 implies the Lack of Fit is not significant relative to the pure error. There is a 32.54% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	1.11	**R^2**	0.8372
Mean	43.64	**Adjusted R^2**	0.4573
C.V. %	2.53	**Predicted R^2**	-16.5596
		Adeq Precision	4.2405

A negative **Predicted R²** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 4.240 indicates an adequate signal. This model can be used to navigate the design space.



Graph 8: Dissolution 4 hrs (factorial design)

ANOVA for selected factorial model

Response 2: D-Dissolution 18 hr(70-90 %)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	57.88	7	8.27	8.70	0.0515	not significant
A-Hydromellose(Methocel K 100)	15.12	1	15.12	15.91	0.0282	
B-Hydromellose(Methocel K4M)	6.12	1	6.12	6.44	0.0848	
C-Magnesium Stearate	1.13	1	1.13	1.18	0.3563	
AB	6.13	1	6.13	6.44	0.0848	
AC	28.12	1	28.12	29.58	0.0122	
BC	1.12	1	1.12	1.18	0.3563	
ABC	0.1250	1	0.1250	0.1315	0.7409	
Residual	2.85	3	0.9508			
Lack of Fit	0.8523	1	0.8523	0.8523	0.4534	not significant
Pure Error	2.00	2	1.0000			
Cor Total	60.73	10				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 8.70 implies there is a 5.15% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, AC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

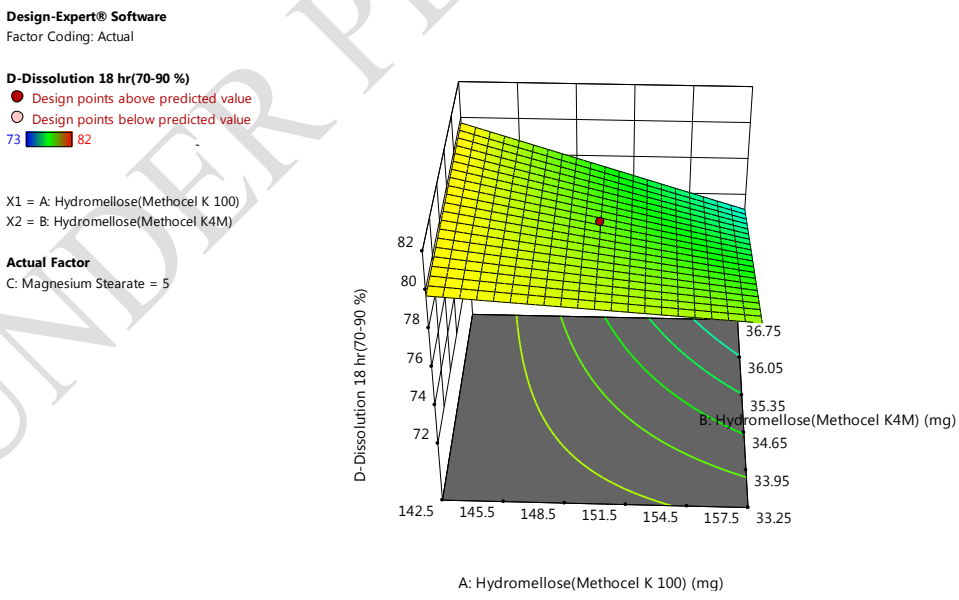
The **Lack of Fit F-value** of 0.85 implies the Lack of Fit is not significant relative to the pure error. There is a 45.34% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	0.9751	**R^2**	0.9530
Mean	78.45	**Adjusted R^2**	0.8434
C.V. %	1.24	**Predicted R^2**	-2.3456
		Adeq Precision	10.8233

A negative **Predicted R^2** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 10.823 indicates an adequate signal. This model can be used to navigate the design space.



Graph 9: Dissolution 18 hrs (factorial design)

ANOVA for selected factorial model

Response 3: R-Dissolution 4 hr(NMT 50%)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	7.88	7	1.13	3.96	0.1428	not significant
A-Hydromellose(Methocel K 100)	1.13	1	1.13	3.96	0.1407	
B-Hydromellose(Methocel K4M)	0.1250	1	0.1250	0.4400	0.5545	
C-Magnesium Stearate	0.1250	1	0.1250	0.4400	0.5545	
AB	1.12	1	1.12	3.96	0.1407	
AC	3.13	1	3.13	11.00	0.0452	
BC	1.13	1	1.13	3.96	0.1407	
ABC	1.13	1	1.13	3.96	0.1407	
Residual	0.8523	3	0.2841			
Lack of Fit	0.1856	1	0.1856	0.5568	0.5333	not significant
Pure Error	0.6667	2	0.3333			
Cor Total	8.73	10				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 3.96 implies the model is not significant relative to the noise. There is a 14.28% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case AC is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

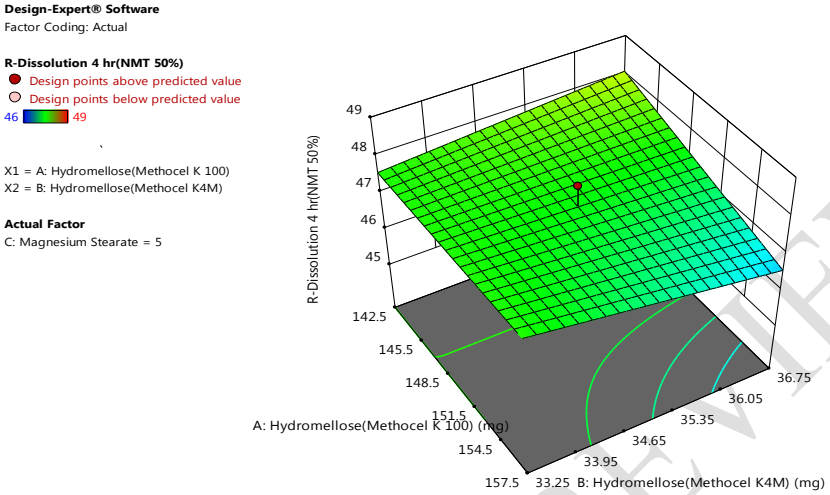
The **Lack of Fit F-value** of 0.56 implies the Lack of Fit is not significant relative to the pure error. There is a 53.33% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	0.5330	**R^2**	0.9023
Mean	47.45	**Adjusted R^2**	0.6745
C.V. %	1.12	**Predicted R^2**	-4.1019
		Adeq Precision	6.6000

A negative **Predicted R²** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 6.600 indicates an adequate signal. This model can be used to navigate the design space.



Graph 10: Dissolution 4 hrs (factorial design)

ANOVA for selected factorial model

**Response 4: R-Dissolution 18 hr(70-90 %) **

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	94.87	7	13.55	8.54	0.0528	not significant
A-Hydromellose(Methocel K 100)	21.13	1	21.13	13.31	0.0355	
B-Hydromellose(Methocel K4M)	1.13	1	1.13	0.7088	0.4617	
C-Magnesium Stearate	0.1250	1	0.1250	0.0788	0.7972	
AB	10.12	1	10.12	6.38	0.0857	
AC	55.13	1	55.13	34.73	0.0098	
BC	1.13	1	1.13	0.7088	0.4617	
ABC	6.13	1	6.13	3.86	0.1442	
Residual	4.76	3	1.59			
Lack of Fit	2.76	1	2.76	2.76	0.2385	not significant
Pure Error	2.00	2	1.0000			
Cor Total	99.64	10				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 8.54 implies there is a 5.28% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, AC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

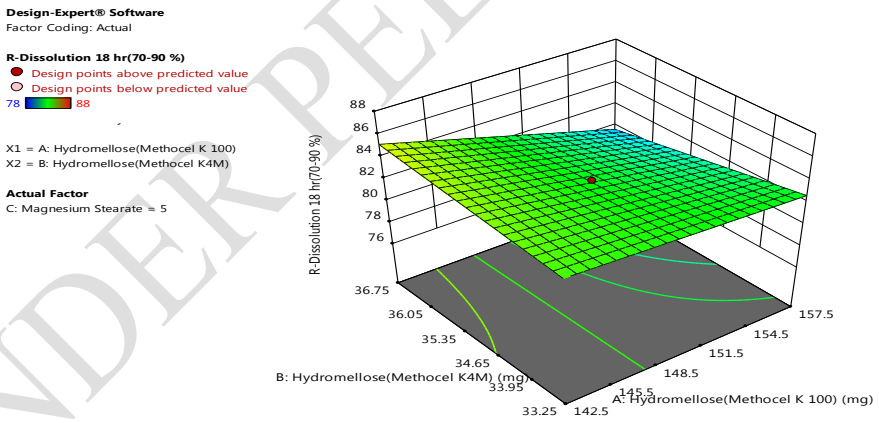
The **Lack of Fit F-value** of 2.76 implies the Lack of Fit is not significant relative to the pure error. There is a 23.85% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	1.26	**R^2**	0.9522
Mean	82.82	**Adjusted R^2**	0.8407
C.V. %	1.52	**Predicted R^2**	-5.5523
		Adeq Precision	9.3078

A negative **Predicted R^2** implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 9.308 indicates an adequate signal. This model can be used to navigate the design space.



Graph 11: Dissolution 18 hrs (factorial design)

5. CONCLUSION

The present work was carried out to formulate and evaluate Darunavir and Ritonavir SR tablets. The drug excipient compatibility studies were carried out. Based on the results, it was confirmed that there is no interaction between drug and excipient at different conditions. Six formulation trials of Darunavir and Ritonavir tablets were conducted using different polymers at different concentrations.

In vitro drug release of all formulations was carried out in dissolution medium 900ml of pH 3.0, 0.05 M Sodium Phosphate Buffer + 2% Tween 20 for 75 RPM USP II apparatus (paddle). The

results shown that the all the formulations matrix tablets shown the good release of the drug from the formulations. In F6, the release of drug shows NLT 80% i.e. near to the desired target release. So, the formulation F6 is suited for the SR table of Darunavir and Ritonavir. Tablets were also evaluated for dissolution studies by QbD method.

6. REFERENCES

1. Asha Gandhi, SL Hari Kumar, Recent Trends in Immediate Release Drug Delivery System; International Journal of Interdisciplinary and Multidisciplinary Studies (IJIMS), 2014;1(6):122-134.
2. Ojha Kumar Abhishek* and Verma Sushma, A Review - Immediate Release Drug Delivery Technology; World Journal of Pharmacy And Pharmaceutical Sciences, Mar 2018;7(5):250-260.
3. Rahul P Gaikwad, Formulation and Evaluation Immediate Release Floating Multi-Particulate Oral Drug Delivery System; ACTA Scientific Pharmaceutical Sciences, 2019;3(5):128-141.
4. Kube Rahul S. *et al.*, Immediate release drug delivery system: A review; Indian Journal of Research in Pharmacy and Biotechnology, 2015;3(3):2320-3471.
5. Gaurav Agarwal, Shilpi Agarwal, PK Karar and Shagun Goyal, Oral Immediate Release Tablets: An Overview with a Special Emphasis on Matrix Tablet; American Journal of Advanced Drug Delivery, May 2017;5(2):64-76.
6. Ali J, Khar RK, Ahuja A. A Textbook of Biopharmaceutics& Pharmacokinetics. Birla Publications Pvt. Ltd. Delhi, 2008;252-72.
7. Agarwal G, Kaushik A. Pharmaceutical Technology-II. 1stEd. CBS Publishers, New Delhi, 2012;123-34:174-89.
8. Brahmankar DM, Jaiswal SB. Controlled release medication. Biopharmaceutics and Pharmacokinetics- A treatise. 2ndEd. VallabhPrakashan. Delhi, 2009;397-400.
9. Zalte HD, Saudagar RB. Review on immediate release matrix tablet. Int J Pharm Biol Sci., 2013;3(4):17-29.
10. Ratnaparkhi MP,Gupta JP. Immediate release drug delivery system- An overview. Int J Pharma Res Rev., 2013;2(3):11-21.
11. Tapaswi RD, Verma P. Matrix tablets: An approach towards oral extended release drug delivery. Int J Pharma Res Rev. 2013;2(2):12-24.
12. Patel H, Panchal DR, Patel U. *et al.* Matrix type drug delivery system: A Review: J Pharm Sci Bio-Sci Res. 2011;1(3):143-51.
13. Jamini M, Kothari A. Immediate release matrix type drug delivery system: A review. JDDT. 2012;2(6):142-8.
14. Pooja R. Alli, Pratima B. Bargaje, Nilesh S. Mhaske, Immediate Release Drug Delivery System: A Modern Formulation Approach; Asian journal of pharmaceutical technology and innovation, 2016;4(17):108-118.
15. Sandhya Mishra, Immediate Release Oral Drug Delivery System: A Concise Review; Int. J. Pharm. Sci. Rev. Res., 2019;54(1), 2: 5-15.

16. M.M. Gupta, Ray Brijesh, A Review On: Immediate Release Technology; nternational Journal of Therapeutic Applications, 2012;8:18–23.
17. NM Bhopale, PB Aswar, NB Banarase, SS Khadabadi. Design, Development and In-vitro Evaluation of Immediate Release Rubia cordifolia Matrix Tablet. Research J. Pharm. and Tech. 1(4): 2008;475-477.
18. Das S, Bhuyan NR, Chanda R, Bahadur S, Saha S, Choudhury A. Preparation and Evaluation of Sustained Release Enteric Coated Mucoadhesive tablets of Omeprazole for Local Action. Research J. Pharm. and Tech. 1(3): July-Sept. 2008; Page 166-170.
19. Mridanga Raj Ray, Sekhar Kumar Bose, Koushik Sengupta. Design, Development and In Vitro Evaluation of Directly Compressed Sustained Release Matrix Tablet of Famotidine. Research J. Pharm. and Tech. 1(3): July-Sept. 2008; Page 175-178.
20. Sourabh Jain, SK Yadav, UK Patil. Preparation and Evaluation of Sustained Release Matrix Tablet of Furosemide using Natural Polymers. Research J. Pharm. and Tech. 1(4): Oct.-Dec. 2008;Page 374-376.
21. Mridanga Raj Ray, Sekhar Kumar Bose, Koushik Sengupta. Design, Development and In Vitro Evaluation of Directly Compressed Sustained Release Matrix Tablet of Famotidine. Research J. Pharm. and Tech. 1(3): July-Sept. 2008; Page 175-178.
22. LP Hingmire, VN Deshmukh, DM Sakarkar. LP Hingmire, VN Deshmukh, DM Sakarkar. Development and Evaluation of Sustained Release Matrix Tablets Using Natural Polymer as Release Modifier. Research J. Pharm. and Tech. 1(3): July-Sept. 2008; Page 193-196.
23. SH Lakade, MR Bhalekar. Formulation and Evaluation of Sustained Release Matrix Tablet of Anti-Anginal Drug, Influence of Combination of Hydrophobic and Hydrophlic Matrix Former. Research J. Pharm. and Tech. 1(4): Oct.-Dec. 2008;Page 410-413.
24. Prabhakara P, Harish NM, Gulzar Ahmed M, Narayana Charyulu R, Santhosh P, Satyanarayana D, Subrahmanyam EVS. Formulation and In Vitro Evaluation of Sustained Release Tablets of Domperidone. Research J. Pharm. and Tech.2 (2): April.-June.2009,; Page 358-362.
25. Pankaj P. Ostwal, Yogesh L. Jadhav, Mayur S. Jain, Sumit P. Jain. Dissolution Profiling of Bilayered Conventional Release Paracetamol and Sustained Release Ibuprofen (By Simultaneous Estimation Method UV). Research J. Pharm. and Tech. 5(4): April 2012; Page 490-493.
26. Shinde Sunita S., Amol S. Shete, Patil Manisha V., J.I. Disouza. Formulation and Evaluation of Sustained Release Tablets using Direct Compression Method. Research J. Pharm. and Tech 6(6): June 2013; Page 637-640.
27. Mukesh P. Ratnaparkhi, Pravin K. Garje, Shilpa P. Chaudhari. Formulation and Evaluation of Sustained Release Floating Drug Delivery System of Metoprolol Succinate. Research J. Pharm. and Tech. 6(9): September 2013; Page 1058-1063.