BIRLA INSTITUTE OF TECNOLOGY AND SCIENCE – PILANI

First Semester 2023– 2024

Course No.: **PHA G547**

Course Title: **Quality by Design in Pharmaceutical Product Development**

Max. Marks: **35** Duration: **3 hr** Date: **09/12/2023**

Write clear and legible answers. Avoid overwriting. Write the answers in the sequence only. Write appropriate equation or formula in calculation wherever applicable.

Q1. A formulation scientist aimed to study the effect of 'polymers' on drug release using material X_1 and X_2 in the modified release tablet dosage form. Formulations were prepared with 2^2 Factorial Design where polymer X_1 was used at 50 and 100 mg/tablet; polymer X_2 was used at 25 and 50 mg/tablet. The experiments were conducted in replicate (n=3). Formulator achieved the below liner polynomial equation for the response mean dissolution time $T_{50\%}$ (min). [6+2 M]

$$\mathbf{y = 40.83 + 20.5X_1 + 10.165X_2 + 4.835X_1X_2}$$

(i) With help of above equation, determine the significant and insignificant factors based on their F-Ratio. Assume the Total Sum of Squares in ANOVA was found to be 6583.67.

(ii) Calculate the T50% when polymer X_2 at 40 mg/Tablet and X_1 at 80 mg/Tablet

Q2. A solid oral formulation was devloped with simplex lattice design. A total of 100 mg of three components , (A), (B) and (C) were added to a tablet formulation. In-vitro Dissolution time of tablets was measured in a simplex design with the following results:

Batch Number	Component and its %	Dissolution time (T80%)
F-1	100% A	292 min
F-2	100% B	5.6 min
F-3	50%A, 50%B	25.6 min
F-4	100% C	50.4 min
F-5	50%B, 50%C	15.6 min
F-6	50%A, 50%C	124.5 min
F-7	1/3A,1/3B and 1/3C	37 min

Compute the simplex equation. What will be the predicted dissolution time when component A and B are at 20% and 40% respectively. [3+2 M]

Q3. (a) In what situation centre composite design is preffered? Write its advantages and limitations. How will you determine the 'α' (local axial point) in Central Composite Designs. [2M]

(b) What are the information required and how will you draw the half normal plot. What information one can get from half normal plot. [2M]

Q4. (a) Assume you have implemented various QbD elements such as QTPP, CQAs, Risk assement, and DOE for sustained release pellets product development. After implementing DOE in this product, what will be your control strategies to 'minimize the risk' associated in product for 'pateint saftey' and 'product efficacy'. [2M]

(b) Explain why 'Pareto' Charts used in DoE results display 't' values of the factorial effects (in the form of bars) rather than the magnitude of estimates of the factorial effects. [2M]

Q5. (a) Discuss the significance of 'design space' in QbD based product development? How is it different from control space? What will be your preference between design space and control space to run a controlled release coating process? Justify your answer. [2M]

(b) How Process Analyzers is different from Process Sensors. Diffrenciate the 'At line' and 'In-line' Process Analyzers. Give any two examples of PAT. [2M]

Q6. (a) Write CQAs (related to formulation attributes only) for a injectable liposomal product of anticancer drug. Justify your selection. [2M]

(b) Write advantages of developing and validating a HPLC method using the concepts of of analytical QbD? [2M]

Q4. Based on following tabulated data obtained, Construct the DoE main effect plots for Factor A and Factor B. Using the plot, draw some inference on how the Factor A and Factor B, individually, affects the response. Construct the DoE Interaction plot for Factorial Effect AB. Using the plot draw some inference on how the interaction between Factor A and Factor B affects the response. [6M]

Batch No.	**Factor A (polymer) %**	**Factor B (PVA) %**	**Factor C (drug/polymer ratio)**	**% Drug loading**
1	1	0.25	0.05	49
2	2	0.25	0.05	64
3	1	0.5	0.05	51
4	2	0.5	0.05	63
5	1	0.25	0.1	69
6	2	0.25	0.1	42
7	1	0.5	0.1	68
8	2	0.5	0.1	76

TABLE G (*continued*)

$F_{.95}$

Denominator Degrees of Freedom	Numerator Degrees of Freedom								
	1	2	3	4	5	6	7	8	9
1	161.4	199.5	215.7	224.6	230.2	234.0	236.8	238.9	240.5
2	18.51	19.00	19.16	19.25	19.30	19.33	19.35	19.37	19.38
3	10.13	9.55	9.28	9.12	9.01	8.94	8.89	8.85	8.81
4	7.71	6.94	6.59	6.39	6.26	6.16	6.09	6.04	6.00
5	6.61	5.79	5.41	5.19	5.05	4.95	4.88	4.82	4.77
6	5.99	5.14	4.76	4.53	4.39	4.28	4.21	4.15	4.10
7	5.59	4.74	4.35	4.12	3.97	3.87	3.79	3.73	3.68
8	5.32	4.46	4.07	3.84	3.69	3.58	3.50	3.44	3.39
9	5.12	4.26	3.86	3.63	3.48	3.37	3.29	3.23	3.18
10	4.96	4.10	3.71	3.48	3.33	3.22	3.14	3.07	3.02
11	4.84	3.98	3.59	3.36	3.20	3.09	3.01	2.95	2.90
12	4.75	3.89	3.49	3.26	3.11	3.00	2.91	2.85	2.80
13	4.67	3.81	3.41	3.18	3.03	2.92	2.83	2.77	2.71
14	4.60	3.74	3.34	3.11	2.96	2.85	2.76	2.70	2.65
15	4.54	3.68	3.29	3.06	2.90	2.79	2.71	2.64	2.59
16	4.49	3.63	3.24	3.01	2.85	2.74	2.66	2.59	2.54
17	4.45	3.59	3.20	2.96	2.81	2.70	2.61	2.55	2.49
18	4.41	3.55	3.16	2.93	2.77	2.66	2.58	2.51	2.46
19	4.38	3.52	3.13	2.90	2.74	2.63	2.54	2.48	2.42
20	4.35	3.49	3.10	2.87	2.71	2.60	2.51	2.45	2.39
21	4.32	3.47	3.07	2.84	2.68	2.57	2.49	2.42	2.37
22	4.30	3.44	3.05	2.82	2.66	2.55	2.46	2.40	2.34
23	4.28	3.42	3.03	2.80	2.64	2.53	2.44	2.37	2.32
24	4.26	3.40	3.01	2.78	2.62	2.51	2.42	2.36	2.30
25	4.24	3.39	2.99	2.76	2.60	2.49	2.40	2.34	2.28
26	4.23	3.37	2.98	2.74	2.59	2.47	2.39	2.32	2.27
27	4.21	3.35	2.96	2.73	2.57	2.46	2.37	2.31	2.25
28	4.20	3.34	2.95	2.71	2.56	2.45	2.36	2.29	2.24
29	4.18	3.33	2.93	2.70	2.55	2.43	2.35	2.28	2.22
30	4.17	3.32	2.92	2.69	2.53	2.42	2.33	2.27	2.21
40	4.08	3.23	2.84	2.61	2.45	2.34	2.25	2.18	2.12
60	4.00	3.15	2.76	2.53	2.37	2.25	2.17	2.10	2.04
120	3.92	3.07	2.68	2.45	2.29	2.17	2.09	2.02	1.96
∞	3.84	3.00	2.60	2.37	2.21	2.10	2.01	1.94	1.88