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Research Article

Application of Statistical Tools-Mixture Optimal Designs on Optimization of Glipizide Controlled Release Tablets

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ABSTRACT

The principal aim of this paper is to apply the experimental design of experiments (mixture designs) to formulate a solid dosage form (glipizide controlled release tablets) using push pull osmotic drug delivery systems through the study of the excipients and their proportion in the formulation. The effect of different formulation variable namely, amount of Poly ethylene oxide in push and pull layers, amount of sodium chloride in push layer and effect of percentage weight gain of semi permeable membrane which influence the dissolution on 4 hrs, 8 hrs and 16 hrs was analysed. The design space obtained range between 156.943 mg-160.246 mg of Poly ethylene oxide (3 Lakh Molecular Weight (MW)), 84.5853 mg-84.8986 mg of Poly ethylene oxide (70 Lakh Molecular Weight) and 30.169 mg-32.1584 mg of Sodium chloride. All factors having significant effect on dissolution.

Keywords: Osmotic controlled drug delivery systems, Push pull drug delivery systems, Design of experiments, I-optimal mixture designs

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INTRODUCTION

Osmotic controlled drug delivery systems is one and only systems for zero order drug release (Release rate is independent on concentration of the drug). This is having following advantages:

- Maintenance of constant blood levels within the therapeutic window
- Enhanced bioavailability
- Reduced inter patient variability
- Decreased dosing frequency
- Improved patient compliance
- Reduced side effects

Glipizide is used along with diet and exercise, and sometimes with other medications, to treat type 2 diabetes (condition in which the body does not use insulin normally and, therefore, cannot control the amount of sugar in the blood). Glipizide is in a class of medications called sulfonylureas (Khavare NB, *et al.*, 2010). Glipizide lowers blood sugar by causing the pancreas to produce insulin (a natural substance that is needed to break down sugar in the body) and helping the body use insulin efficiently. This medication will only help lower blood sugar in people whose bodies produce insulin naturally. Glipizide is not used to treat type 1 diabetes (condition in which the body does not produce insulin and, therefore, cannot control the amount of sugar in the blood) or diabetic ketoacidosis (a serious condition that may occur if high blood sugar is not treated). Due to short biological half-life (2 hr-4 hr) of glipizide, it was easy to extend 24 hours in the body to maintain the glucose levels by using controlled release tablets (Gupta BP, *et al.*, 2010).

The mixture design is the most suitable method used in optimizing the tablet production process. For example, in four components of formulation:

$X_1+X_2+X_3+X_4$=Total sum of variables

There are many types of mixture design: Simplex-lattice design, simplex-centroid design, axial design, and D/I-optimal design. I-optimality minimizes the average prediction variance of model over a region of measurement parameters, so it is more naturally applied when know the form of the model and want "good" prediction over design space. For this reason, I-optimality finds more use in a response surface optimization context. As compared with other designs, I-optimal design has a smaller number of runs and thus needs low cost of experimentation. So, based on this strategy these design selected for this study (Wen H and Park K, 2011) *(Tables 1 and 2)*.

Table 1: Design studied in optimisation of glipizide controlled release tablets

Study type	Design type	Design model	Subtype	Runs	Blocks
Mixture	I-optimal, Coordinate Exchange	Quadratic	Randomized	12	No Blocks

Table 2: Parameters studied in optimisation of glipizide controlled release tablets

Component	Name	Units	Type	Minimum	Maximum
A	PEO (MW 3 lakh)	Mg	Mixture	145	175
B	PEO (MW 70 lakhs)	Mg	Mixture	80	90
C	NaCl (Push layer)	Mg	Mixture	20	40
				Total	275
Note: PEO: Polyethylene oxide, MW: Molecular Weight					

MATERIAL AND METHODS

Materials

Glipizide taken from Orchid Health care, Poly ethylene oxide (PEO) (Grades-3 lakhs Molecular Weight, 50 lakhs Molecular Weight, 70 lakhs Molecular Weight, Opadry cellulose acetate and Opadry Pink taken from Dow and Colorcon respectively (Keraliya RA, *et al.*, 2012). Microcrystalline cellulose (Avicel pH 101) used from Food Machinery and Chemical Corporation (FMC)/Signet Chemical Corporation Pvt Ltd. Magnesium stearate taken from Peter greven/S Zhaveri Pharmachem Pvt ltd. Iron oxide yellow taken from Sensient. NaCl, acetone and other analytical grades taken from Merk (Jamzad S and Fassihi R, 2006).

Methods

Preliminary study of screening the variables: From the literature the viscosity of the polyethylene oxide of low and high Molecular Weight was used in pull and push layer respectively (Verma RK and Garg S, 2004).

Initially, trails are started with low Molecular Weight polyethylene oxide (6 lakhs Molecular Weight) in pull layer and polyethylene oxide (70 lakhs Molecular Weight) for F1 Trail (Zhang Y, *et al.*, 2003).

High Molecular Weight polyethylene oxide (3 lakhs Molecular Weight) in pull layer and polyethylene oxide (70 lakhs Molecular Weight) used for trial F2 *(Tables 3 and 4)*.

Preparation of glipizide control release tablets using I-optimal mixture designs: Based on above trails Poly ethylene oxide (PEO) in both layers play a critical role along with Sodium chloride. So, these factors considered as Critical quality attributes (Thombre AG, *et al.*, 2004).

Further, Polyethylene oxide (3 lakhs Molecular Weight) in pull layer, Polyethylene oxide (70 lakhs Molecular Weight) and Sodium chloride in Push layer was optimised using Mixture designs (Trails from F3-F14) *(Table 5)*.

I-optimal mixture design was used to determine the optimum amount of ingredients used in the formulation toward the responses, which is dissolution at 4 hours, 8 hours and 16 hours of the tablet. The statistical parameters used in evaluating and selecting the best-fitted model are coefficient of determination, adjusted coefficient of determination (adjusted), predicted coefficient of determination (predicted), Coefficient of Variation (CV), Standard Deviation (SD), Predicted Residual Sum of Squares (PRESS), lack-of-fit, and regression data (value and value) (Mangukia D, *et al.*, 2012). The statistical analysis also constructs an equation from the best-fitted model. From the equation, the positivity of the coefficient presents the positive contribution toward the response, and vice versa. Also, a contour plot and three-dimensional response surface graph for each response were generated by Design-Expert Software *(Tables 6 and 7)*.

Table 3: Formulation trails of Glipizide controlled release tablets

Pull layer (drug layer)																
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
Glipizide	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
PEO (3L MW)	160.00 (6L MW)	160	160.00	150.525	156.944	154.059	154.059	168.43	145.00	168.43	162.503	171.381	171.381	156.944	156.944	160.00
NaCl	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Micro Crystalline Cellulose	30.00	30.00	30.00	39.47	33.06	35.95	35.95	21.57	45.00	21.57	27.5	18.62	18.62	33.06	33.06	30.00
Magnesium stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00	211.00
Push layer																
PEO (70L MW)	85.00	90.00	85.00	90.00	85.8945	80.9407	80.9407	80.00	90.00	80.00	90.00	83.6188	83.6188	85.8945	85.8945	85.00
NaCl	30.00	34.475	30.00	34.475	32.1616	40.00	40.00	26.5702	40.00	26.5702	22.497	20.00	20.00	32.1616	32.1616	30.00
Micro crystalline cellulose	15.00	9.53	15.00	9.53	11.95	9.06	9.06	23.43	0.00	23.43	17.51	26.39	26.39	11.95	11.95	15.00
Iron oxide Yellow	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Magnesium stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00	132.00
Semi permeable membrane (12%)																
Opadry CA	41	41	41	41	41	41	41	41	41	41	41	41	41	41	27 (8%)	34 (10%)
Total	384.00	384.00	384.00	384.00	384.00	384.00	384.00	384.00	384.00	384.00	384.00	384.00	384.00	384.00	370.00	377.00
Colour coat (3.11%)																
Opadry pink	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Total	396.00	396.00	396.00	396.00	396.00	396.00	396.00	396.00	396.00	396.00	396.00	396.00	396.00	396.00	382.00	389.00
Note: NaCl in pull layer, Magnesium stearate and iron oxide are constant and Micro Crystalline Cellulose (MCC) adjusted as per total weight																

Table 4: Percentage cumulative drug release of trails F1 and F2

Time (hrs)	F1	F2
0	0	0
1	0	0
2	2	1
4	13	10
8	30	32
16	48	70
20	58	77
24	62	80

Table 5: Percentage cumulative drug release of trails F3-F14

Run	Component 1	Component 2	Component 3	Response 1	Response 2	Response 3
	A:PEO (MW 3 lakh)	B:PEO (MW 70 lakhs)	C:NaCl (Push layer)	Dissolution 4 hrs	Dissolution 8 hrs	Dissolution 16 hrs
	Mg	Mg	Mg	%	%	%
F3	160	85	30	10	32	73
F4	150.525	90	34.475	12	30	71
F5	156.944	85.8945	32.1616	10	30	70
F6	154.059	80.9407	40	18	30	68
F7	154.059	80.9407	40	19	31	66
F8	168.43	80	26.5702	7	28	78
F9	145	90	40	16	27	67
F10	168.43	80	26.5702	8	29	76
F11	162.503	90	22.4971	8	26	78
F12	171.381	83.6188	20	6	20	95
F13	171.381	83.6188	20	7	22	96
F14	156.944	85.8945	32.1616	11	29	71

Table 6: Response of formulation trails F3-F14

Response	Name	Units	Observations	Analysis	Minimum	Maximum	Mean	SD	Ratio	Transform	Model
R1	Dissolution 4 hrs	%	12	Polyno-mial	6	19	11.00	4.43	3.17	None	Quadratic
R2	Dissolution 8 hrs	%	12	Polyno-mial	20	32	27.83	3.61	1.60	None	Quadratic
R3	Dissolution 16 hrs	%	12	Polyno-mial	66	96	75.75	10.04	1.45	None	Special Cubic

Table 7: Coefficients table

Variables	A	B	C	AB	AC	BC	ABC
Dissolution 4 hr	5.46759	13.233	33.1018	0.718639	-23.2663	-46.9172	
p-values	<0.0001	<0.0001	<0.0001	0.9645	0.0009	0.0348	
Dissolution 8 hrs	20.5752	41.9614	20.8186	-19.755	46.4674	-4.71225	
p-values	0.0014	0.0014	0.0014	0.5394	0.0008	0.8938	
Dissolution 16 hrs	109.423	101.408	101.661	-122.345	-179.161	-155.348	543.964
p-values	<0.0001	< 0.0001	<0.0001	0.1131	0.0007	0.0745	0.0073

Formulation and development: Formulation development trails conducted based on the values of mixture design observing the product characteristics and performance parameters like dissolution profile (Lu EX, *et al.*, 2003) *(Table 3)*.

Manufacturing procedure: Based on drug substance flow properties (Poor) wet granulation technique adopted (Aulton ME and Taylor K, 2013) (*Figure 1)*.

Based on design space, optimised trials of F5 and F14 was further selected for checking the effect of coating weight gain on drug release (Optimization of semi permeable membrane), F15, F16 trails performed for 8% and 10% weight gain respectively *(Table 6)*.

Evaluation of Osmotic Tablets: These compression parameters are tested for uncoated and coated tablets: Assay, weight variation, hardness, friability, thickness, coating uniformity (for coated tablets), *in vitro* drug release studies (for coated tablets) (Jain NK, 2008).

These Pre-compression parameters are testes for optimised trails: Bulk density, tapped density, Carr's index, Hausner's Ratio, angle of repose and particle size distribution *(Figures 2 and 3)*.

RESULTS AND DISCUSSION

The following pre-compression parameters are obtained for trials F5 and F14:

1. Bulk density (g/mL): 0.42 for pull layer and 0.48 for push layer

2. Tapped density (g/mL): 0.54 for pull layer and 0.58 for push layer

3. Carr's index (%): 22.2 for pull layer and 17.2 for push layer

4. Hausner's ratio: 1.28 for pull layer and 1.20 for push layer

5. Flow character: Passable for pull layer and Fair for push layer

6. Angle of Repose: 32 for pull layer and 34 for push layer (Flow property is good)

7. Particle size distribution: #60 retention 22% for pull layer and 34% for push layer and base plate/fines 34% for push and pull layers.

The following Compression parameters are obtained for trials F1-F16:

1. Assay (95%-105%): All are trails are under mentioned range (97%-103%)

2. Average Weight (for 10 Tablets) of Uncoated bilayer tablet (3.43 g ± 3 g): All are trails are under mentioned range (3.41 g-3.46 g).

3. Individual Weight of Uncoated bilayer tablet (343 mg ± 5 mg): All are trails are under mentioned range (340 mg-348 mg).

Contour diagram and 3D diagram of relationship between three variables, A: Poly ethylene oxide (PEO) (3 Lakh Molecular Weight), B: Poly ethylene oxide (PEO) (70 Lakhs Molecular Weight), C: NaCl on Response: Dissolution in 4 hours, 8 hours and 16 hours are mentioned in graphical way *(Figures 4-9) (Table 8)*.

Optimisation of factors and response using overlay plot and design space obtained range between 156.943 mg-160.246 mg of Poly ethylene oxide (3 Lakh Molecular Weight), 84.5853 mg-84.8986 mg of Poly ethylene oxide (70 Lakh Molecular Weight) and 30.169 mg-32.1584 mg of Sodium chloride *(Figure 10)*.

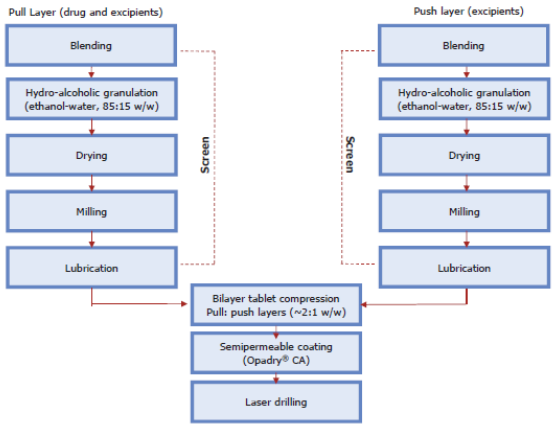

Figure 1: Manufacturing procedure for push-pull osmotic tablet

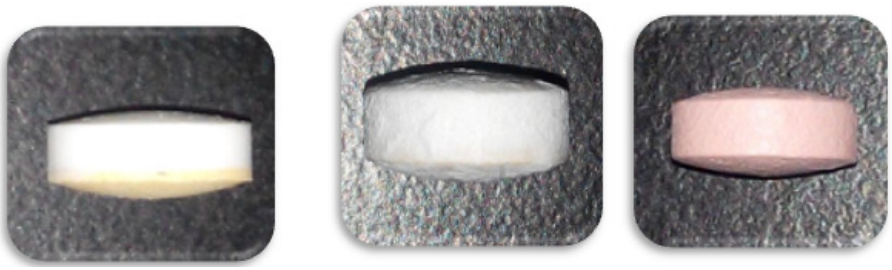

Figure 2: Side view of uncoated bi layered, Semi-permeable membrane coated, Top coated osmotic tablets

Figure 3: Top view of coated osmotic tablet with surface laser drilling

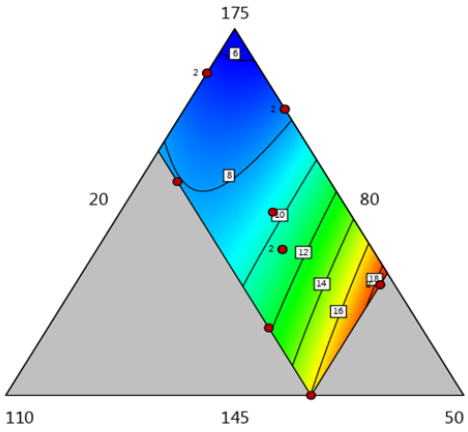

Figure 4: Contour diagram of relationship between three variables by using Design-Expert® Software Trail Version (Component Coding: Actual), A: Poly ethylene oxide (PEO) (MW 3 Lakh) (mg), B: PEO (MW 70 Lakhs) (mg), C: NaCl (Push layer) (mg) on response 1: dissolution in 4 hours (%)

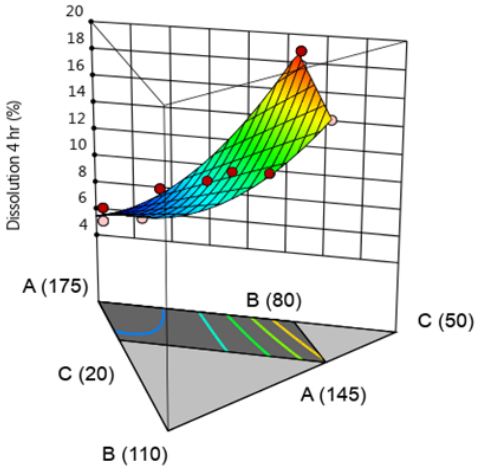

Figure 5: 3D diagram of relationship between three variables by using Design-Expert® Software Trail Version (Component Coding: Actual), A: PEO (MW 3 Lakh) (mg), B: PEO (MW 70 Lakhs) (mg), C: NaCl (Push layer) (mg) on response 1: dissolution in 4 hours (%)

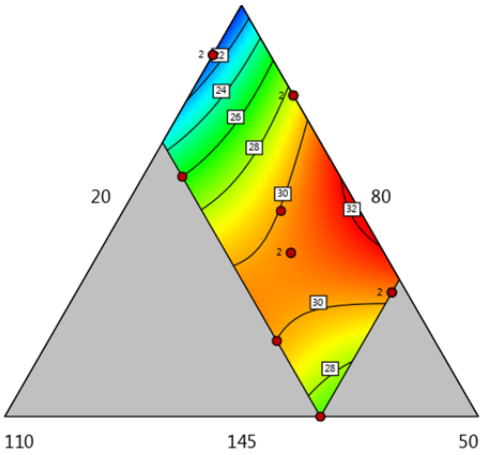

Figure 6: Contour diagram of relationship between three variables by using Design-Expert® Software Trail Version (Component Coding: Actual), A: PEO (MW 3 Lakh) (mg), B: PEO (MW 70 Lakhs) (mg), C: NaCl (Push layer) (mg) on response 1: dissolution in 8 hours (%)

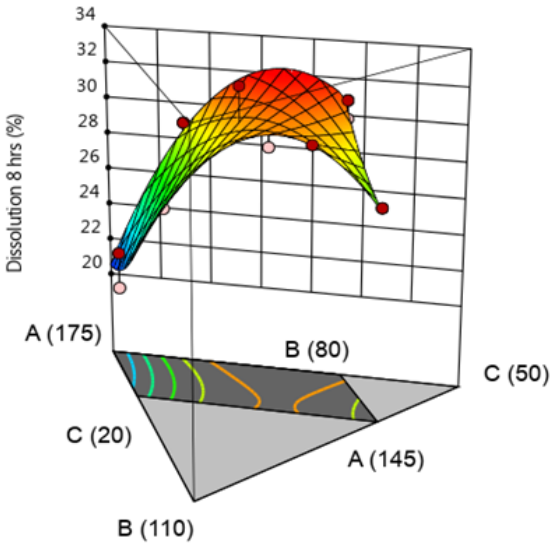

Figure 7: 3D diagram of relationship between three variables by using Design-Expert® Software Trail Version (Component Coding: Actual), A: PEO (MW 3 Lakh) (mg), B: PEO (MW 70 Lakhs) (mg), C: NaCl (Push layer) (mg) on response 1: dissolution in 8 hours (%)

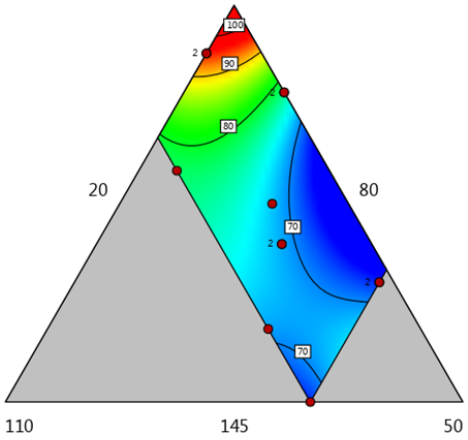

Figure 8: Contour diagram of relationship between three variables by using Design-Expert® Software Trail Version (Component Coding: Actual), A: PEO (MW 3 Lakh) (mg), B: PEO (MW 70 Lakhs) (mg), C: NaCl (Push layer) (mg) on response 1: dissolution in 16 hours (%)

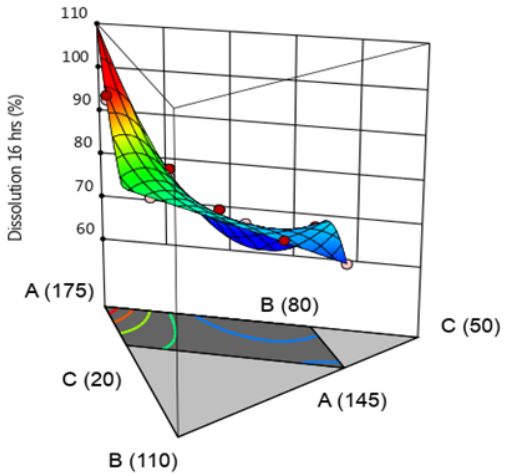

Figure 9: 3D diagram of relationship between three variables by using Design-Expert® Software Trail Version (Component Coding: Actual), A: PEO (MW 3 Lakh) (mg), B: PEO (MW 70 Lakhs) (mg), C: NaCl (Push layer) (mg) on response 1: dissolution in 16 hours (%)

Table 8: Percentage cumulative drug release of trails F15 and F16

Time (hrs)	F15	F16
0	0	0
1	6	2
2	9	4
4	30	22
8	62	56
16	100	100
20	100	100
24	100	100

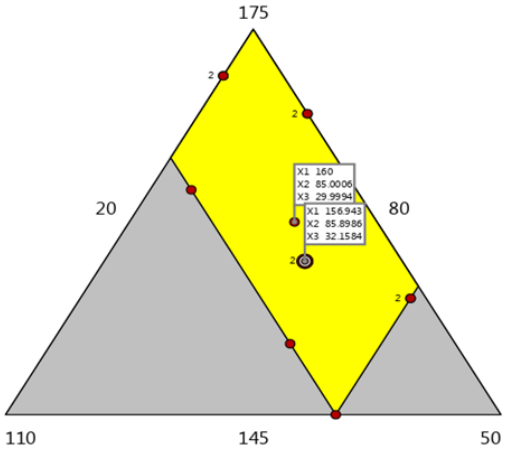

Figure 10: Overlay plot for relationship between three variables by using Design-Expert® Software Trail Version (Component Coding: Actual), A: PEO (MW 3 Lakh) (mg), B: PEO (MW 70 Lakhs) (mg), C: NaCl (Push layer) (mg)

F15 and F16 clearly indicated that the effect of % weight gain of semi permeable membrane on dissolution (Zen NIM, *et al.*, 2015).

CONCLUSION

Dissolution at 4 hrs, 8 hrs and 16 hrs of Glipizide control release tablets evaluated by using different factors namely Poly ethylene oxide (PEO) 3 lakhs in pull layer and Poly ethylene oxide (PEO) 70 lakhs and NaCl using mixure designs. All factors shows significant effect on dissolution clearly mentioned in contour diagram and 3D diagrams as well as percentage weight gain of semi permeable membrane having significant effect on dissolution.

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