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Research Article

OPTIMIZATION AND QbD DEVELOPMENT OF AZATHIOPRINE LIQUISOLID COMPACTS USING 22 FACTORIAL DESIGN

S. Revathi[2], R. Natarajan[1] and R. Sambath kumar[3]
[1]Department of Pharmaceutics and Research, The Erode College of Pharmacy, Erode-638112, Tamil Nadu, India, E. Mail Id: natarajan.r@ecp.ac.in.

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ABSTRACT
Immunosuppressants which inhibit immune responses, and they are used for organ transplantation and autoimmune diseases. Azathioprine is a purine antimetabolite which has more marked immunosuppressant than antitumor action. Azathioprine comes under BCS class IV drugs. Azathioprine Liquisolid compacts was prepared by using different carriers and coating materials at various concentrations by using QbD approach. DESIGN-EXPERT® SOFTWARE Best in class design of experiments software makes R&D easy with user friendly interface. 22 factorial designs were used to optimize the formulation in which the carrier and coating material ratio were selected as independent variables. The optimized formulation F2 and F5 showed maximum drug release of 89.496% and 84.492% at the end of 10 hrs.

Key words: Liquisolid compacts, Azathioprine, QbD approach, optimization, 22 factorial design.

INTRODUCTION
The pharmaceutical industry is constantly looking for ways to ensure and improve the safety, quality and effectiveness of products. Recently, the concept of "Quality by Design" (QbD) has received a lot of attention to maintain quality in the pharmaceutical industry. It acts as a bridge between industry and pharmaceutical regulatory authorities, moving towards a scientific, risk-based holistic and proactive approach to pharmaceutical product development. It mainly involves the design and development of formulations and production processes to ensure a predefined product quality. However, drug recalls, manufacturing failure costs, scaling issues and recent regulatory burdens have presented enormous challenges to the industry. In traditional products, product quality and performance are largely ensured through end-product testing, where understanding of the process and critical process parameters is limited. Therefore, regulators are focusing on the implementation of quality design (QbD), a science-based approach that improves process understanding, reducing process variability and enabling process control strategies. The oral route is the best route for delivering drugs in single-dose systems and is easy to administer and cost-effective for the development of single-dose controlled or sustained-release or long-acting formulations. Extensive research has been conducted to improve patient compliance, and avoid repeated administration of a highly soluble drug under acidic pH conditions and lower solubility at pH above 7 resulted in a lower absorption window for the drug from the gut. The main advantages of Liquisolid concentrates are improving the bioavailability of poorly soluble drugs, especially BCS class II and IV drugs, the bioavailability of the drug increases, the frequency of dosing decreases [1, 2].
The release of the drug from the dosage form affects its bioavailability. Traditional solubility improvement methods are based on chemical or mechanical or physical modification of macromolecular properties of aggregated drug particles. In Liquisolid technology, the liquid can be made free-flowing, easily compressible

Address for Correspondence: R. Natarajan**,** Department of Pharmaceutics and Research, The Erode College of Pharmacy, Erode- 638112, Tamil Nadu, India, E. Mail Id: natarajan.r@ecp.ac.in.

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simply by mixing it with the carrier and coating material. The liquid system succeeded in improving dissolution. Recently, this has been investigated as a possible way to maintain drug release by properly choosing carrier excipients. Dosage forms are designed to release the drug at a predetermined rate to ensure efficacy, safety and patient compliance [3]

OPTIMIZATION

"Optimization methods are used in many fields of research to find solutions that maximize or minimize some research parameters, such as cost minimization in the production of a good service, profit maximization, raw material in product development or production maximization. In particular, they are described as used to maximize the use of thermal energy while minimizing production costs [4].

FACTORIAL DESIGN

"Factorial design is a type of research methodology that allows the study of key effects and environmental effects. interactions between two or more independent variables and one or more outcome variables. " Factorial experiments can be designed with one, two, three, or more factors. Experiments with only one factor are often called simple comparison experiments. In these cases, t-tests or ANOVA were used for analysis. Factorial experiments with two factors. (A and B) usually involve two-level factorial models to identify the factor effects of the response variable by examining all possible combinations of factor levels. A factor effect is defined as a change in the response variable by changing the factor level. For factorial experiments with multiple factors (A, B...K) and two levels ("low" and "high"), experimental complexity can be a problem.

FULL FACTORIAL DESIGN

A full factorial design is convenient for small numbers of factors if resources are available. Generally, 2k factorial design, k represents multiple factors, while the number 2 represents multiple levels. Each factor has two levels low (-) and high (+). The number of combinations for 22 is four, for 23 eight, and so on. Each combination is called a treatment. The number of smaller units in each treatment is called the number of replicates. For example, if three units/samples were tested for each treatment, the number of replicates is three.

Types

Generalized 2k Factorial Design Design of Experiments (DOE) - Full Factorial Design method was used to conduct the experimental data analysis. This study presents and implements a case of Generalized 2k Factorial Design with k multiple factors at two levels.

Statistically, the model contains k main effect, (2) two-factor interaction, (k 3) three-factor interaction,..., (k,k) one k-factor interaction.

2k-factor construction procedure was as follows:

1. Estimated factor effects were estimated and their sizes examined to identify significant factors;
2. Original model formula - a complete model is included that accounts for all main effects and interactions.
3. Statistical Testing - ANOVA is used to test the significance of main effects and interactions.
4. Model refinement - irrelevant factors in the original model are removed.
5. Residual analysis - to check the adequacy of the model and assumptions.
6. Interpretation of results - graphical analysis of results such as main effects, interactions, etc.,

FRACTIONAL FACTORIAL DESIGN

If the number of factors increases, then the number of test units and treatment combinations (runs) increases. Because a small number of main effects and lower-order interactions are significant for the response variable, and higher-order interactions are generally not significant for the response variable, fractional factor models are adopted. Therefore, fractional factor models capture only a small number of main effects and lower-order interactions. Higher order interactions are ignored because their effect on the response variable is small. For example, $2^3 = 8$, i.e 8 treatment combinations and 8 test units are required. For some reason, he could not afford all eight combinations, but decided to use the half-factor model of $2^{3-1}=4$. Therefore, instead of 8 test units, we only test 4[5].

RESPONSE SURFACE METHODOLOGY

Important steps in the response surface methodology

1. After the necessary examination, the different factors of the experiment and the subsequent interactions were identified.
2. The priority was given to the different levels of the confirmed characteristics.
3. After optimization, the most suitable model was chosen.
4. An appropriate model can also be selected, which is perfect for experimental design.

5. To conduct experimental studies, specific factors and values that are necessary for system analysis must be considered.
6. The selected model can be validated. The rule is that if the data are not satisfactory, another model of the experimental equation and experimental design is better.
7. As the investigation continues, this point must therefore be repeated until a suitable model is obtained which is an acceptable representation of the data.

CENTRAL COMPOSITE DESIGN

Box-Wilson model or CCD model consisting of factor 1, 2 and 3 models.

1. The star points outside the domain and the center representing the experimental dominance help to define the response surface plot.

2. Evaluating the accuracy based on the surface responses, the value of a can be determined; where the letter design is α.

3. There are three types of CCD; α can be determined according to the computer capabilities and the required accuracy obtained from the surface responses. The location of the value determines the quality of the project or assessment. The planned speed is determined by locating the points.

4. The accuracy of the estimate is influenced by the number of tests performed in the center of the Dome. A quality-based approach is needed to estimate the coefficient of variation and responses.

5. One important consideration is invertibility, or isovariance by revolution, which means that the forecast error is identical from all points to the equicenters.

Eventually, the centre composite design was classified into three types:

Circumscribed design (CCC)

The CCD model is always large with corner points. These models have circular, spherical or hyper spherical symmetry and require 5 levels for each factor. By supplementing an already existing factor or factor model with a star point, a model is obtained.

Inscribed design (CCI)

If the factor configurations are constrained, the CCI design uses the factor configuration as star points and creates a factor model within these constraints.

Face Centered design (CCF)

In this model, the star points are the midpoints of each side of the factor space. Therefore, α=1. This variable requires 3 levels of each factor. Face-centered models (CCFs) are irreversible[6].

COMPOSITION OF DIFFERENT FORMULATION FOR LIQUIOLID COMPCTS

A total number of nine formulations (F1-F9) were prepared by using liquisolid technology. Tablets of Azathioprine were prepared by using drug, and various concentrations of non-volatile solvents, carriers such as Ethyl cellulose, Eudragit RSPO, HPMC K100 and coating material as Aerosil 200, while lactose monohydrate used as filler; Magnesium stearate was incorporated as lubricant and talc as anti-adherent.

Table: 1- Composition of different formulation

S. No	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Drug	50	50	50	50	50	50	50	50	50
2	Ethyl cellulose	50	100	150	-	-	-	-	-	-
3	Eudragit RSPO	-	-	-	50	100	150	-	-	-
4	HPMC K100	-	-	-	-	-	-	50	100	150
5	Aerosil 200	25	50	75	25	50	75	25	50	75
6	Magnesium stearate	5	5	5	5	5	5	5	5	5
7	Talc	2	2	2	2	2	2	2	2	2
8	Lactose Monohydrate	168	93	18	168	93	18	168	93	18
9	Total weight	300	300	300	300	300	300	300	300	300

METHODOLOGY

CALCULATION OF LOADING FACTOR

In a liquid system, the ratio of the masses of the carrier (Q) to the coating material (q), which is called the powder-to-filler ratio R (R=Q/q) in the formulation, if the maximum amount of liquid retained is the carrier, then a liquid system with an acceptable flow rate is produced, and that characteristic liquid volume is called the liquid to the load factor The mass ratio of the liquid drug (W) to the carrier powder (Q) in the system is called the liquid fill factor (i.e Lf = W/Q). To calculate the loading factor, 10 g of polyethylene glycol 600 (a drug-free liquid) was added to the carrier material and mixed for 1 minute. The procedure is repeated until the flow rate is reached 7,8.

Therefore,

$$R = Q/q, \quad Lf = W/Q$$

OPTIMIZATION

STAT-EASE DOE SOFTWARE

DESIGN-EXPERT® SOFTWARE Best in class design of experiments software makes R&D easy with user friendly interface and amazing graphics

Table: 2 CONSTRAINTS

S.NO	FACTORS	GOAL	LOWER LIMIT	UPPER LIMIT
1	Carrier	Is in range	50	150
2	Coating	Is in range	25	75

Table: 3 TYPES OF RESPONSE

S.NO	RESPONSE	GOAL	LOWER LIMIT	UPPER LIMIT
1	IVD	Is in range	92	99
2	Drug content	Is in range	92	99

SELECTION OF APPROPRIATE CONSTRAINTS[118]

Constraints

	Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
	A:Carrier	is in range	50	150	1	1	3
	B:Coating	is in range	25	75	1	1	3
	IVD	is target = 95.5	92	99	1	1	3
	StdErr(IVD)	none	0.531442	0.920484	1	1	3
	DC	is target = 95.5	92	99	1	1	3
	StdErr(DC)	minimize	0.531442	0.920484	1	1	3

Fig: 1-Constraints

ANOVA

Analysis of variance (ANOVA) is an analytical tool used in statistics that divides the aggregated variation observed in a data set into two parts: systematic factors and random factors. Fisher's statistical test using ANOVA was performed to evaluate the significance of the reduced linear model. ANOVA results show that 1.47 for lack of fit means that it is not significantly related to the pure experimental error, indicating that the model correlates well with the experimental values. A non-significant lack of fit is also good because the main goal was to fit the model to the experimental data. The R2 value of 0.47 showed that the resulting model was able to give a good estimate of the system response in the area

CONTOUR PLOT

Contour plot is a graphic technique to represent a three-dimensional surface by drawing constant z-sections, so -called. contours, in 2-dimensional format. In other words, given a z-value, lines are drawn to connect the (x,y) coordinate where that z-value occurs. Contour compiler is an alternative to three-dimensional surface plotting. The actual methods for determining the correct iso-response values are quite complex and are always computer generated. An additional variable may be needed to set the z-values for drawing the iso-lines. If the data (or function) does not form a regular grid, we usually have to do 2-D interpolation to form a regular grid.

3D SURFACE INTERPRETATION

1. 3D response surface and contour plots were made to investigate the relationship between different variables and response, to obtain the optimal formulation conditions that would maximize the yield.

2. Three-dimensional 3D response surface and contour plot showing the effect of Polymers9.

RESULTS

OPTIMIZATION BY CENTRAL COMPOSITE DESIGN (CCD):

The desirability of the total design was found. The two responses in the study should be evaluated in the optimization of IR tablet. However, it was almost impossible to optimize all the objectives simultaneously because they do not coincide with each other and conflict may occur. The optimum condition reached in one response may have an opposite influence on another response. Thus, the multi-criteria problem can be treated as single criterion problem using the desirability function approach.

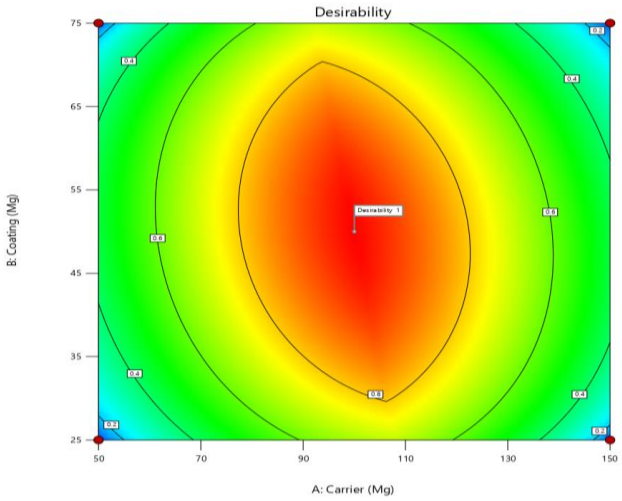

Fig: 2 Contour plot - Desirability

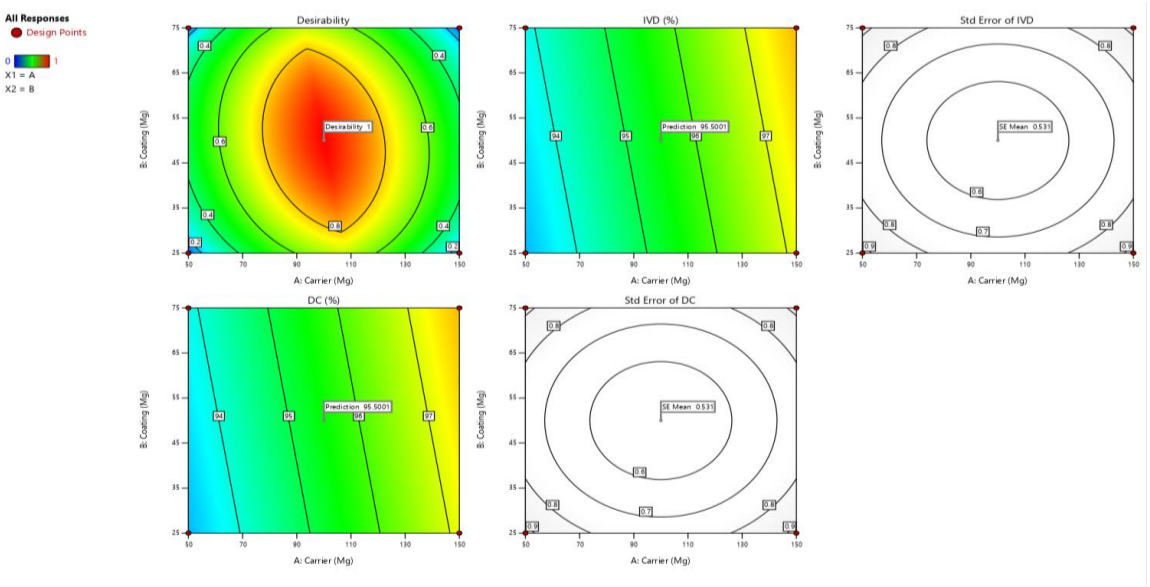

Fig: 3 Desirability and standard error of responses (IVD and DC)

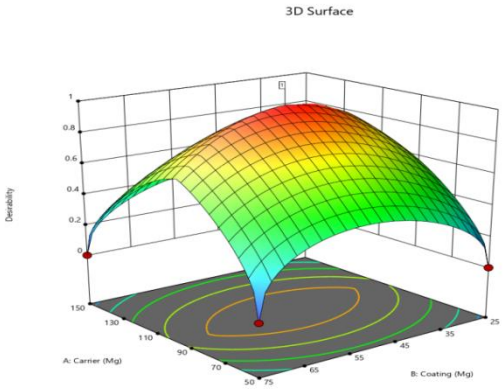

Fig-4 3D Response curve

INTERPRETATION

The below mentioned factors will give the response

Carrier- 99.9 → Dissolution 95.5%

Coating- 50 → Drug content 95.5%

Table-4 Optimized Formulation

S. No	Ingredients (mg)	Quantity (mg)
1	Drug	50
2	Carrier	100
3	Coating material	50
4	Magnesium stearate	5
5	Talc	2
6	Lactose Monohydrate	93
7	Total	300

IN-VITRO DRUG RELEASE STUDIES:

Table-5 **PERCENTAGE RELEASE OF AZATHIOPRINE IN LIQUISOLID TECHNIQUE**

Time (Hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	**0**	0	0	**0**	0	0	0	0
0.5	7.488	**9.486**	11.484	8.496	**13.5**	6.984	0	5.49	0
1	16.488	**17.496**	19.494	17.496	**20.484**	11.484	3.996	9.486	6.498
2	22.986	**26.496**	24.984	23.994	**27.486**	18.486	7.488	16.488	10.998
3	29.484	**39.492**	31.5	29.484	**36.486**	24.984	11.484	23.994	14.49
4	36.486	**47.484**	37.494	35.496	**47.484**	32.49	16.488	28.998	19.494
5	43.488	**56.988**	46.998	42.984	**55.494**	38.988	19.494	31.5	22.986
6	51.498	**65.484**	53.496	49.5	**62.496**	47.484	23.49	34.488	26.496
7	57.996	**73.998**	59.49	54.486	**69.498**	56.484	27.486	39.492	29.484
8	62.496	**79.992**	65.988	59.494	**73.998**	64.998	29.484	42.984	31.986
9	65.484	**85.5**	71.496	64.494	**79.488**	70.992	31.5	45.486	34.488
10	68.994	**89.496**	73.494	67.5	**84.492**	75.996	33.498	47.484	37.494

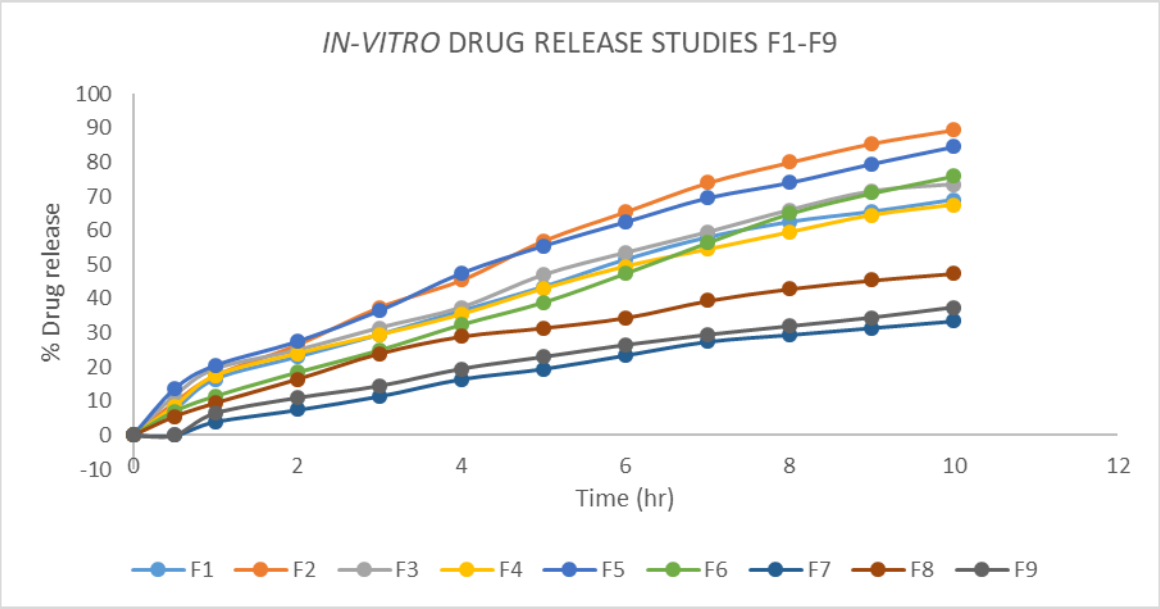

Fig: 5 In vitro drug release studies

CONCLUSION

Azathioprine Liquisolid compacts were prepared by using different carriers and coating materials at various concentrations by using QbD approach and Optimization was carried out using Stat Ease software. A randomized 22 full factorial design was selected. Based on Central composite design the carriers and coating concentration should be optimized. The optimized formula should select on the basis of ANOVA for reduced linear model, Desirability and lack of fit value The Solubility study of drug was carried out to select the non volatile solvent. To select the amount of non volatile solvent, Liquid Loading factor is calculated. In-Vitro drug release characteristics were studied in 0.1 N HCl (2hr) and Phosphate Buffer pH6.8 (8hr) for up to 10 hrs; using USP dissolution apparatus type II (paddle type). The results of optimized formulation F2 and F5 shows the higher drug release of 89.496 %and 84.492% at the end of 10 hrs.

REFERENCES

1. E. Bhavya, M.D. Dhere. Liquisolid Compacts Technique of poorly water soluble Drugs: An Overview. Research Journal of Pharmacy and Technology 2021; 14(10): 5569-2. doi: 10.52711/0974-360X.2021.00970.

2. Patil H, Tiwari RV, Repka MA. Advancements in bioadhesive floating drug delivery systems: JDDST.2016; 31:65-71.

3. Amal Ali Elkordy et al. Liquisolid technique to enhance and to sustain griseofulvin dissolution: Effect of choice of non-volatile liquid vehicles. International Journal of Pharmaceutics 434 (2012) 122-132. http://dx.doi.org/10.1016/j.ijpharm.2012.05.072.

4. Mee R. A comprehensive guide to factorial two-level experimentation. Springer Science &Business Media; 2009.

5. Montgomery DC. Introduction to statistical quality control. New York: John Wiley & Sons; 2007.

6. https://www.jmp.com/en_in/statistics-knowledge-portal/what-is-design-of- experiments/html

7. Spireas S et al. Effect of powder substrate on the dissolution properties of methyclothiazide liquisolid compacts. Drug Dev Ind Pharm 1999;25:163–8

8. Chella Naveen et al. Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. Acta Pharmaceutica Sinica B 2012; 2(5):502–508.

9. https://www.statisticshowto.com/contour-plots

10. Asija Rajesh et al. the Liquisolid technique for Enhancement of Drug Dissolution. Research J. Pharm. And Tech. 5(10): October 2012; Page 1270-1274.

11. Sanjeev Gubbi, Ravindra Jarag. Liquisolid Technique for Enhancement of Drug Dissolution Properties of Bromhexine Hydrochloride. Research J. Pharm and Tech.2 (2): April- June.2009; Page 382-386