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Invited Article

OPTIMIZATION OF PHARMACEUTICAL PRODUCT FORMULA-TION BY FACTORIAL DESIGNS: CASE STUDIES

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ABSTRACT

Optimization of a product or process is determination of best possible composition or operating conditions resulting in its optimal performance. Optimization techniques are relatively new to the practice of pharmacy. Optimization using factorial designs is an efficient technique used in formulation optimization. Factorial experiments with two level factors are used widely because they are easy to design, efficient to run, straight forward to analyze, and full of information. Five case studies, in which optimization was performed by factorial design are discussed.

Key words: *Optimization, Factorial Design, Recent Research, Case Studies.*

INTRODUCTION

The word "Optimize" means to make as perfect, effective or functional as possible. Optimization of product or process is determination of experimental conditions resulting in its optimal performance[1]. Optimization has been defined as the implementation of systemic approaches to achieve the best combination of product and/or process characteristics under a given set of conditions[2].

With respect to the drug formulations or pharmaceutical process, optimization is a phenomenon of finding "the best" possible composition or operating conditions. Although several optimization procedures are available to the pharmaceutical scientist, in general the procedure consists of preparing a series of formulations, varying the concentrations of formulation ingredients in some systemic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal[3].

Optimization of pharmaceutical formulations involve choosing and combining ingredients that will result in formulation whose attributes conform to certain pre requisite requirements. The choice of the nature and quantities of additives (or) excipients to be used in a formulation has to be based on some rational. The optimization techniques will help in fixing the quantities or levels of the excipients, Optimization techniques are relatively new to the practice of pharmacy. In general the traditional procedure consists of preparing a series of formulation, varying the concentrations of the formulation ingredients in some systemic manner. These formulations were then evaluated according to one or more attributes such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests a particular formulation or series of formulations may be predicted to be optimal the predicted optimal

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formulation has to be prepared and evaluated to confirm its quality .The formulation is generally optimized according to a single attribute.

Optimization by Factorial Design:

The modern approach for optimization is through the use of statistical techniques. Optimization using factorial designs is an efficient technique used in formulation optimization.

The optimization procedure is facilitated by construction of a mathematical equation that describes the experimental results as a function of the factor levels. A polynomial equation can be constructed in the case of a factorial design where the coefficients in the equation are related to effects and interactions of the factors.

The equation constructed from an 2^n factorial experiment is as follows:

$$y = ß_0 + ß_1x_{1+}ß_2x_2+ß_3x_3+\ldots\ldots\ldots$$
$$+ß_{12}x_1x_2+\ldots\ldots\ldots+ß_{123}x_1x_2x_3$$

Where y is the measured response, x_i is the level of the ith factor, $ß_1, ß_2, ß_{3\ldots\ldots}$ represent coefficients computed from the responses of the formulations in the design and $ß_0$ represent intercept.

Full Factorial Design (FFD)

Factorial experiments with two-level factors are used widely because they are easy to design, efficient to run, straightforward to analyze, and full of information. A full factorial design contains all possible combinations of a set of factors. This is the most fool proof design approach, but it is also the most costly in experimental resources. The full factorial designer supports both continuous factors and categorical factors with up to nine levels.

Factorial designs with only two-level factors have a sample size that is a power of two (specifically 2^f where f is the number of factors). When there are three factors have a sample size that is a power of three.

$$N = L^k$$

Where k = number of variables, L = number of variable levels, N = number of experimental trials, for example, in an experiment with three factors, each at two levels, we have eight formulations, a total of eight responses.

Case Studies of Optimization Using Factorial Design:

Case Study 1:

Formulation of Combined Drug Products

A 2^2 factorial experiment was designed to develop a combination drug product to obtain the dose of each drug which would result in an optimal response. For this purpose, the 2 levels selected for drug A(x_1) are5mg and10 mg and for drug B(x_2) the two levels are 50mg and 100 mg. This study is an example of a 2^2 factorial study and involves four formulations with selected combinations of the two levels of drug A and drug B. The four formulations as per 2^2 factorial design are prepared and the response (y) i.e. time to reach anaesthesia in minutes is measured with each formulation.

The formulations as per 2^2 factorial design, their responses(y) observed and potency transformations for developing the polynomial response equation are shown in Table 1

Table 1: Formulations as per 2^2 factorial design

Formulation Code	Potency (Mg)		Response Time (min) (Y)	Potency Transformed			Response Multiples for Determining Coefficients of Response Equation		
	A (X1)	B (X2)		A (X1)	B (X2)	sAB (X1X2)	X1Y	X2Y	X1X2Y
1	5	50	9.7	-1	-1	+1	-9.7	-9.7	+9.7
a	10	50	7.2	+1	-1	-1	+7.2	-7.2	-7.2
b	5	100	8.4	-1	+1	-1	-8.4	+8.4	-8.4
ab	10	100	4.1	+1	+1	+1	+4.1	+4.1	+4.1

The polynomial response equation to be developed is of the type

$$y = ß_0 + ß_1x_{1+}ß_2x_2+ß_3x_3+\ldots\ldots\ldots$$
$$+ß_{12}x_1x_2+\ldots\ldots\ldots+ß_{123}x_1x_2x_3$$

The polynomial equation describing that relationship between the response (y) and the variables x_1 and x_2 based on the observed data was found to be

$$y=7.35-1.7(x_1)-1.1(x_2)-0.45(x,_1x_2)$$

Based on the above relationship the optimized formulation with response (y) as 5 m shall contain +0.5 of A(8.75 mg)and +1 of B(100 mg) and hence this combination of drug A and B is the optimized formulation which would produce anesthesia in 5 m. Hence the optimized combined drug formulation should contain 8.75mg of drug A and 100mg of drug B.

Case Study 2:

Optimization of Diclofenac SRTablet Formulation by Factorial Design[4]

The study is to design diclofenac SR tablets employing a combination of HPMC K 100 M (hydrophilic polymer) and ethyl cellulose (lipophilic polymer) for better controlled release. Diclofenac SR tablet formulation was optimized by 2^2factorial design. Diclofenac SR tablets were formulated employing the selected combinations of HPMC (Factor A) and EC (Factor B) as per 2^2 factorial study and prepared by wet granulation method. The SR tablets were evaluated for drug release kinetics and mechanism. For optimization, time for 50 % release (T50) was taken as response (Y) and the percent of HPMC as X1 and percent of EC as X2. The polynomial equation describing the relationship between the response Y and the variables X1 and X2 based on the observed data was worked out.

The polynomial equation describing the relationship between the response Y (T_{50}) and the variables X_1 (% HPMC) and X_2 (% EC) based on the observed data was found to be

$$Y = 2.95 + 1.05\,X_1 - 0.25\,X_2 - 1.75\,(X_1X_2).$$

Based on the above polynomial equation the optimized diclofenac SR tablets with a T_{50} of 4 h could be formulated employing 50 % HPMC and 5.5 % ethyl cellulose as release retarding polymers. The optimized SR formulation prepared gave slow release of diclofenac over 12 h with a T_{50} of 4 h indicating validity of the optimization technique employed. Diclofenac release from the optimized SR formulation was diffusion controlled and release was by non-fickian (anomalous) diffusion mechanism. Based on pharmacokinetics, diclofenac SR tablets for b.i.d administration should contain a total dose of 100 mg of diclofenac and the desired release rate (K_0) is 8.66 mg/h. The drug release rate of optimized SR tablets formulated was found to be 8.54 mg/h, which is very close to the theoretical desired release rate. Hence the optimized formulation is considered as the best diclofenac SR formulation developed.

Case Study 3:

Optimization of Valsartan Tablet Formulation by 2^3 Factorial Design[5]

The objective of the study is to optimize valsartan tablet formulation by 2^3factorial design for selecting the best combinations of diluent, binder and disintegrant giving fast dissolution of valsartan, a BCS class II drug.

For formulation of valsartan tablets as per 2^3 factorial design the three factors involved arebinder, diluent and disintegrant. The two levels of the factor A (binder) are acacia and PVP at 2% concentration each and the two levels of the factor B (disintegrant) are potato starch (15%)and Primogel (5%). The two levels of the factor C (diluent) are lactose and DCP. Eight valsartan tablet formulations each containing 50 mg of valsartan were prepared employing selectedcombinations of the three factors i.e., binder, disintegrant and diluent as per 2^3 factorial design. The tablets were prepared by wetgranulation method.

Much variations were observed in the disintegration and dissolution characteristics of thevalsartan tablets prepared employing various combinations of binder (factor A),disintegrant (factor B) and diluent (factor C) as per 2^3 factorial design. Valsartan tablets formulated employing lactose as diluent (F1, Fa, Fb, Fab) disintegrated rapidly within 1 min whereas tablets formulated with DCP disintegrated relatively slowly in 3–5 m. Tablets formulated employing lactose as diluent gave higher dissolution rates (K1) and DE30 values when compared to the tablets formulated employing DCP. Formulation Fab (tablets prepared employing lactose, PVP and Primogel), F1 (tablets prepared employing lactose, acacia and potato starch) and Fabc (tablets prepared employing DCP, PVP and Primogel) gave higher dissolution rates and DE30 values and fulfilled the official (I.P 2010)dissolution rate test specification of valsartan tablets.Hence combinations of (i) lactose, PVP , Primogel, (ii) lactose, acacia, potato starch and(iii) DCP, PVP, Primogel are the best combinations of diluent, binder and disintegrant recommended for formulation of valsartan tablets giving rapid and higher dissolution of valsartan, a BCS class II drug.

Case Study 4:

Optimization of Valsartan Tablet Formulation by 2^3Factorial Design[6]

Valsartan, a widely prescribed anti-hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bio availability due to its poor aqueous solubility. It needs enhancement in the

dissolution rate in its formulation development. Complexation with ß-cyclodextrin (ßCD), use of Primojel and PVP K 30 are tried for enhancing the dissolution rate of valsartan in its formulation development. The objective of the present study is optimization of valsartan tablet formulation employing Primojel, ßCD and PVP K 30 by 2^3 factorial design. Formulation of valsartan tablets with NLT 85% dissolution in 10 min employing Primojel, ßCD and PVP K 30 was optimized by 2^3 factorial design. Eight valsartan tablet formulations were prepared using selected combinations of the three factors as per 2^3 factorial design. Valsartan tablets were prepared by direct compression method and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K_1) values were analysed as per ANOVA of 2^3 factorial design to find the significance of the individual and combined effects of the three factors (ßCD, Primojel and PVP K 30) involved on the dissolution rate of valsartan tablets formulated. ANOVA of K_1 values indicated that the individual and combined effects of the three factors, ßCD, Primojel and PVP K 30 in influencing the dissolution rate of valsartan tablets are highly significant ($P < 0.01$).

Valsartan tablet formulations PF_a and PF_{ac} disintegrated rapidly within 1 m and gave very rapid dissolution of valsartan, 100% in 10 m. Higher levels of ßCD and lower levels of Primojel gave low dissolution rates of valsartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was$PF_a = PF_{ac} > PF_{ab} > PF_{abc} > PF_{bc} > PF_b > PF_c > Pf_1$. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10min (Y) and the levels of Primojel (X_1) , ßCD (X_2) and PVP K 30 (X_3) based on the observed results is $Y = 56.146 + 37.478(X_1) + 1.676(X_2) – 5.288(X_1 X_2) + 1.563(X_3) - 2.942(X_1 X_3) – 1.123(X_2 X_3) -0258(X_1 X_2 X_3)$. Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing Primojel at 26.77% of drug content, ßCD at 1:3ratio of drug: ßCD and PVP K 30 at 1% of drug content. The optimized valsartan tablet formulation gave 87.23% dissolution in 10 m fulfilling the target dissolution set. The dissolution profile of the optimized valsartan tablet formulation was similar to that of a commercial brand (Valent 40). Hence formulation of valsartan tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 factorial design.

Case Study 5:

Optimization of Efavirenz Tablet Formulation Employing CD and Soluplus by 2^2 Factorial Design[7]

Efavirenz, a widely prescribed antiretroviral drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It needs enhancement in the dissolution rate in its formulation development. Complexation with ß-cyclodextrin (ßCD) and use of surfactant (Soluplus) are tried for enhancing the dissolution rate of efavirenz in its formulation development. The objective of the present study is optimization of efavirenz tablet formulation employing ßCD and Soluplus by 2^2 factorial design. Formulation of efavirenz tablets with NLT 85% dissolution in 15 min employing ßCD and Soluplus was optimized by 2^2 factorial design. Four efavirenz (50 mg) tablet formulations were prepared using selected combinations of the two factors as per 2^2 factorial design. Efavirenz tablets were prepared by direct compression method and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. All the efavirenz tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets. Much variations were observed in the disintegration and dissolution characteristics of the efavirenz tablets prepared due to formulation variables. The disintegration times were in the range 25 sec to 6 min 30 sec with various tablets. Efavirenz tablets (Eb) which are prepared employing ßCD in 1:0.5 ratio of drug : ßCD and Soluplus at 2 % of drug content gave very rapid dissolution of efavirenz than others. These tablets (Eb) gave 99.65 % dissolution in 15 min. The increasing order of dissolution rate (K1) observed with various formulations was Eb> Eab > Ea > E1. For optimization, percent drug dissolved in 15 min was

taken as response (Y) and level of ßCD as (X1) and level of Soluplus as (X2). The polynomial equation describing the relationship between the response, Y and the variables, X1 and X2 based on the observed data was found to be $Y = 69.88 + 8.68 (X1) + 24.9 (X2) – 13.56 (X1 X2)$. Based on the above

polynomial equation, the optimized efavirenz tablet formulation with NLT 85% dissolution in 15 m could be formulated employing ßCD at 1:2.75 ratio of drug: ßCD and Soluplus at 1.64 % of drug content. The optimized efavirenz (50 mg) tablet formulation prepared employing ßCD (137.5 mg / tablet) and Soluplus (0.82 mg/ tablet) gave 85.69% dissolution in 15 m fulfilling the target dissolution set. Thus optimization by 2^2factorial design could be successfully used for the development of efavirenz tablets with NLT 85 % dissolution in 15 min.

Conclusion

Optimization by factorial designs is a promising technique in formulation development of dosage forms and drug delivery systems. It is the central component of Quality by Design (QbD), which emphasizes the systematic development of pharmaceutical products based on sound scientific principles.

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