



PHARMACEUTICAL FORMULATION DEVELOPMENT PROCESS BY FACTORIAL DESIGN, OPTIMIZATION AND ANOVA TECHNIQUES: AN REVIEW

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Article Received on 25/07/2016

Article Revised on 15/08/2016

Article Accepted on 05/09/2016

ABSTRACT

Experimental design and optimization are tools that are used to systematically examinedifferent types of problems that arise within research, development and production. It is obvious that experiments are performed randomly the result obtained will also be random. Therefore, it is a necessity to plan the experiments in such a way that the interesting information will be obtained. In a factorial design the influences of all experimental variables, factors, and interaction effects on the response or responses are investigated. Experiments are conceived to compare, estimate and test such effects are drug treatment, formulation difference and analytical methods can be design to yield an optimal return for effort expended. ANOVA separates the total variance in the data into parts. Final variance would separate the effect these factors by computing that part of total variance attributed that variation due to experimental error. Screening methods are used to identify manufacturing process. Factorial studies are quantitative studies of the effects of changing potentially critical process and for systematic screening and factor influence studies are closely related to optimization, being often sequential stages.

KEY WORDS: Factorial Design, Optimization, ANOVA, Experimental Design, Process variables.

INTRODUCTION

1. Optimization

Optimization is finding the best possible composition conditions, determining that type of composition is an enormous task. Optimization be considered as the search for a result that is satisfactory and at the same time the best possible with in a limited field of search. The relative and total proportions of the excipients are varied to obtain the best end point (or) a process is chosen, and a study is carried out to determine the best operating conditions to obtain the desired formulation properties. Screening methods are used to identify manufacturing process. Factorial studies are quantitative studies of the effects of changing potentially critical process and for systematic screening and factor influence studies are closely related to optimization, being often sequential stages in the development process and involving statistical experimental design methods that are^[1,2,3]

a) Statistically designed experiment b) Direct optimization method c) One-factor-at-a time method d) Non-systematic approach.

1.1 Statistically Designed Experiment: In this experiment are set up in a matrix to estimate the coefficients in a mathematical model that predicts responses within the limits of operating Conditions are studied.

1.2 Direct Optimization Method: The best known being the sequential simplex is a rapid and powerful method for determining an experimental domain, optimization is best experimental design.

1.3 One-Factor-at-a-time method: In this method the experiment varies first one factor to find the best value, and then another disadvantage is it can be used for multiple responses and that it will not work when there are strong interactions between factors.

1.4 Non- Systematic Approach: It is allowed to improve results changing a number of factors at the same time is often surprisingly successful.

2. FACTORIAL DESIGNS

Factorial designs are used in experiments where the effects of different factors/conditions, on experimental results are to be elucidated^[4,5,6]. The experiments to determine the effect of compression pressure and lubricant on the hardness of a tablet formulation to determine the efficacy of a combination of two active ingredients in an over the counter cough preparation. Factorial designs are the designs of choice for simultaneous determination of the effects of several factors and their interactions.

2.1 Factors

A factor is an assigned variable such as glident, binder, lubricating agent in formulation development. Factor can be qualitative or quantitative. A quantitative factor has a numerical value assigned to it. The factor glident may be given the values 1%, 2%, and 3%. A qualitative factor is treatment, diets, batches of material, laboratory, analysts and tablet diluents. Qualitative factors are assigned names rather than numbers.

2.2 Levels

The levels of a factor are the values assigned to the factor. Examples: 5% and 10% for the factor binder, glident, drug and placebo for the factor in formulation development. The runs or trails that comprise factorial experiments consist of all combinations of all levels of all factors. Example showing in table.1

Table.1

Symbol	Formulation
(1)	Low drug and low lubricant concentration.
A	Low drug and high lubricant concentration
B	High drug and low lubricant concentration.
AB	High drug and high lubricant concentration.

Low and high refer to the low and high concentrations pre-selected for the drug and lubricant. (1), a, b, ab is standard when, factor A is at its high level and factor B is at its low level, the combination is called a. factor B is at the high level, the combination is called b. The both A and B are their high levels called ab.

2.3 Effects

The effect of a factor is the change in response caused by varying the levels of the factor. The main effect is the effect of a factor averaged over all levels of the other factors.

2.4 Interaction

Interaction may be thought of as a lack of additivity of factor effects. If the effect is greater than 15 when both factors are at their high levels, the result is

synergistic with respect to the two factors. In statistical terminology, the lack of additivity is known as interaction. When the lubricant is at the low level [a-(1)] is different from the drug effect measured when the lubricant is at the high level (ab-b). If the drug effects are the same in the presence of both high and low levels of lubricant.

2.5 Advantages: Factorial Design

- In the absence of interaction, factorial designs have maximum efficiency in estimating main effects.
- If interactions exist, factorial designs are necessary to reveal and identify the interactions.
- Maximum use is made of the data since all main effects and interactions are calculated from all of the data^[7].
- The purpose of the factorial design described is to find at an early stage in the development of a drug formulation the best suitable excipients from the point of view of drug stability. For this purpose the active substance is mixed with different excipients in powder form and stored at different temperatures for a given period of time. The drug substance is subsequently analyzed for degradation products. It is well known that the chemical stability of a drug substance in a binary drug substance excipients mixture may differ completely from a multi component drug substance-excipients mixture. The interactions between the drug substance and the excipients and also to interactions between the excipients. The statistical planning of experiments can reveal easily such effects and interactions.^[8-15]

3. ANOVA^[16-32]

Analysis of variance (ANOVA) is a statistical technique to analyze variation in a response variable measured under conditions defined by discrete factors. ANOVA is connected to experimental design. Experiments are conceived to compare, estimate and test such effects are drug treatment, formulation difference and analytical methods can be design to yield an optimal return for effort expended. ANOVA separates the total variance in the data into parts. Final variance would separate the effect these factors by computing that part of total variance attributed that variation due to experimental error.

RESEARCH WORK DONE BY FACTORIAL DESIGN WITH FORMULATION DEVELOPMENT

S.no	Drug/Material	Technique	Objective	Discussion
1.	Microcel MC ^[33]	Spheronization/extrusion technique	The objective of the investigation the effect of certain variables friability of micro pellets by the extrusion/spheronization technique	The selected process variables such as water content, extruder screen size, spheronizer speed As well as their influences on the properties of Particle size distribution, density was determined. The results observed that high levels of the three Factors increased sphere size, and low levels decreased

				it.
2.	Salbutamol sulphate ^[34]	Solvent evaporation technique	In the preparation of formulation used as 2 ³ factorial design based on 3 independent variables: i) drug loading ii) amount of gelatin iii) concentration	Extended release was observed for 96 hours with F ₈ formulation.
3.	Naproxen ^[35]	integrated Process analytical technology	Objective of work to develop integrated process analytical technology approach for a dynamic progress coprecipitation, characterisation and design space	In this work, a dynamic pharmaceutical coprecipitation process of gradually introducing water (non-solvent) to the ternary system of naproxen (drug) Eudragit L100 (polymer)–alcohol (solvent) was monitored in real-time and in situ by using Lasentec F BRM and PVM technology.
4.	Diclofenac sodium ^[36]	Tablets	To optimize three physicochemical parameters: i) rotation speeds of the stirring elements ii) pH and ionic strengths of the dissolution medium affecting the release of diclofenac sodium from the tablets. The chosen dependent variables were accumulative percentage of dissolved diclofenac sodium in 2, 6, 12 and 24 h.	Our study proved that experimental design methodology could efficiently be applied for characterization and optimization of analytical parameters affecting the drug release maximum amount of information in a short period of time and with the few number of experiments
5.	Vitamin-E acetate ^[37]	liposomal technique	The vitamin-E acetate was encapsulated into liposome for improving its topical delivery	Liposome dispersion and gel formulation were found to be stable for 3 months. Factorial design was found to be well suited to identify the key variables affecting drug deposition. Improved drug deposition from liposomal preparations demonstrates it.
6.	Ibuprofen gel ^[38]	Experimental design technique	This study was to develop a transdermal gel formulation for ibuprofen using experimental design techniques and to evaluate its pharmacokinetic properties.	Transdermal ibuprofen gel was formulated successfully using the technique of experimental design and these results helped in finding the optimum for formulation for transdermal drug release.
7.	Mannitol hemihydrate ^[39]	Response surface modeling technology	The objective of formulation study of Mannitol has been potentially negative with stability. The formulation parameters are: i) Composite face centered design were the overall solid content, ii) Protein concentration, protein type and the ratio between Mannitol and	This study shows that the application of DOE can lead to a systematic overview of the influence of formulation and processing factors on the formulation of MHH during freeze drying

			sucrose.	
8.	Venlafaxine hydrochloride ^[40]	Sublimation technique	The objective of present study is to develop novel method of preparing compressed tablets for Venlafaxine hydrochloride with high porosity which dissolves rapidly in mouth, using camphor as sublimating agent	It may be concluded that developed novel method of preparing compressed tablets for venlafaxine hydrochloride with high porosity which dissolves rapidly in mouth, could be industrially feasible
9.	Telmisartan ^[41]	Extrusion–spheronization technique	The objective incorporation of camphor, cross carmellose sodium (CCS) and spray dried lactose (SDL) into MCC pellets to enhance the dissolution rate of telmisartan	This study shows that the dissolution of telmisartan from MCC pellets can be successfully enhanced by incorporating water soluble excipient, disintegrant and pore formers.
10.	Zidovudine ^[42]	Nanoprecipitation technique	To determine the interaction between excipients used and to find out nature of drug in the formulation it evaluates the effect of process and formulation variables.	This study shows that there was no degradation of drug in the formulation after 90 days of preparation.
11.	Tinidazole ^[43]	Emulsion solvent evaporation method	The objective of the present study was to formulate and optimize colon targeted tinidazole microspheres.	Physicochemical characterization and in vitro drug release studies all the physicochemical characters and drug release upto 8 h released 92% of the tinidazole
12.	Curcumin loaded PLGA ^[44]	Emulsion solvent evaporation technique	The objective of the work Curcumin loaded nanoparticles revealed that the mean particle sizes of nanoparticles ranged from 181.5nm-206.9nm	Pharmacokinetics and pharmacodynamics of drug effect
13.	Aceclofenac ^[45]	Wet granulation technique	To prepared independent variables are tween 80, Eudragit RL100, RS100 and dependent variables are particle size, entrapment efficiency, percent drug release	Formulations for the poorly water soluble drugs, which are having low bioavailability by oral administration
14.	Alginate Microspheres ^[46]	Sublimation technique	To evaluate the effects of different variables: i) Percentage yield ii) percentage encapsulation efficiency iii) in vitro release characteristics	i) Hardness and ii) friability of all formulations was less iii) Weight variation iv) drug content were within USP limits no drug excipients interaction.
15.	Captopril ^[47]	Wet granulation technique	The objective of the study was to develop a zero order sustained release floating formulation and optimized drug release for enhanced oral bio-availability with F ₉ formulations	Concentration of HPMCK100M, Xanthan gum were chosen as control variables

16.	Nateglinide ^[48]	Wet granulation method	The objective of this study to develop floating tablet of Nateglinide to enhance its bioavailability and sustained action.	Two factors evaluated
17	Pioglitazone ^[49]	Wet granulation technique	The objective of the present study was to formulate Pioglitazone tablets for controlled release as developed for better control of blood glucose level by prolonging its duration of action	The drug release was 68 to 71.23% in 24 hrs within 24 hrs. Eight formulations and it was improved and gave 99.04% release in 24 hrs.
18.	Valsartan ^[50]	Wet granulation method	Optimize valsartan tablet formulation by 2 ³ factorial design for selecting the best combinations of diluents, binder, disintegrant for fast dissolving of the drug	The drug shows combinations of 3 factors that is binder, disintegrant, diluent rapid higher dissolution rate of valsartan
19.	Lamotrigine ^[51]	Wet granulation technique	Lamotrigine using 3 ² factorial design having high permeability and poor solubility	This study shows that the tablets were evaluated for different compression parameters i) drug content ii) hardness iii) friability iv) mean diameter
20.	Diazepam ^[52]	Experimental design method	Evaluate by using droplet size, size distribution, surface charge	Full factorial design factors oil type, oil content, drug presence affecting nanoemulsion
21.	Lornoxicam ^[53]	Freeze drying/ direct compression method	Prepared by direct compression method by using crosspovidone as Superdisintegrating agent and optimized by 3 ² factorial design.	Independent variables were concentration of crosspovidone and hydroxypropyl cellulose while dependent variables were disintegration time and percent drug released.
22.	Cephalexin ^[54]	Direct compression method	To study investigate by direct compression method to identify the pharmacokinetics and mechanism of drug release	Shows that the effect of concentration of polymers on drug is HPMC
23.	Ibuprofen ^[55]	Solvent evaporation technique	Objective of the present study to formulate nanoemulsion for topical delivery of ibuprofen by solvent evaporation technique.	Shows that the tablets having parameters are i) drug content ii) mean hardness iii) friability
24.	Tizanidine hydrochloride ^[56]	Emulsification phase separation technique	Microspheres were prepared by using different volumes.	Percentage mucoadhesion/ drug entrapment efficiency
25.	Loratidine ^[57]	Direct compression method	Prepare stable formulation no interaction between drug and excipients	Shows the parameters like: i) hardness ii) thickness iii) friability
26.	Cefpodoxime proxetil ^[58]	Direct compression method	Objective of this study was to formulate Cefpodoxime Proxetil compression-coated tablets for gastro retentive drug delivery.	In this study 2 ² full factorial design was studied revealed that the concentration of HPMC and Xanthan gums significantly affect the dependent variable

27.	Ofloxacin ^[59]	Direct compression method	Objective of the present work was to develop gastro retentive formulation	3 ² randomized full factorial design was applied in the present study 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all the 9 possible combinations
28.	Metoprolol succinate ^[60]	Wet granulation technique	Study was designed and evaluation of controlled release matrix tablet optimization of formulation of matrix tablet was done by 2 ³ factorial design.	Concluded that the developed controlled release matrix tablet using HPMC, K4M, guar gum Shows satisfactory release retarding.
29.	Atenolol ^[61]	Direct compression technique	Floating tablets of atenolol using 3 ² factorial design by using direct compression method	Show that the different parameter like: i) drug content ii) mean hardness iii) friability
30.	Paraffin oil ^[62]	Phase inversion Technique.	Work is to apply factorial design methods to reduce the number and time of the various steps required to formulate and evaluate stable emulsions.	Determine the required HLB with good approximation in five runs for the average diameter and viscosity studies while the conductivity study.

CONCLUSION

Optimization have been taken as being equal/ closer to what is considered most desirable with respect to the mean responses. It is also necessary that all units of all batches manufactured fall within those specifications. Apart from variation in the measurement method, all variation is attributed to the manufacturing process and the manufacturing and storage environment. Taking the traditional quality control approach, any product that is within the specifications will pass and is considered equally good. However, one might still normally consider that the nearer the response to the target, the better the product.

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