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REVIEW ARTICLE

REVIEW OF RECENT STUDIES ON STATISTICAL OPTIMIZATION IN DRUG DELIVERY TECHNOLOGIES

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ABSTRACT

Statistical modeling and experimental design are essential tools in field of drug delivery during product development and can be divided into formula and process optimization. Experimental design allows efficient experimentation in which all or a large subset of factors are together varied over a set of experiments, in contrast to the traditional approach of varying only one variable at time (OVAT). Good estimates for the required composition, geometry, dimensions and preparation procedure of various types of delivery systems will be available, taking into account the desired administration route, drug dose and release profile. Thus, the number of required experimental studies during product development can be significantly reduced, saving time and reducing costs. The present review discusses types of designs and methodologies used recently in academic as well as industrial research for optimization of novel drug delivery systems.

Keywords: Statistical modeling, Experimental design, Drug Delivery

INTRODUCTION

All product development and optimization involves experimentation. An interesting question is how to make this experimentation achieve the stated objective as accurately and efficiently as possible considering critical quality attributes of product in short time. The traditional approach of optimizing a formulation or process essentially entails studying the influence of the corresponding composition and process variables by changing single variable or factor at a Time, while keeping others as constant. This technique, known as OVAT i.e., One Variable at a Time [1, 2, 3]. This approach involves large number of experiments with little gain of information on considered factors. One more disadvantage of this approach is interactions between the factors cannot be studied which may lead to misinterpretation of results at the final stage of product development. This leads to application of 'Design of experiments'. Table 1 shows pros of using DoE approach in optimizing drug delivery systems.

Design of experiments (DoE) was invented by Ronald A. Fisher in the 1920s and 1930s at Rothamsted Experimental Station, an agricultural research station 25 miles north of London. In Fisher's first book on design of experiments [4, 5] he showed, how valid conclusions could be drawn efficiently from experimentss with natural fluctuations such as temperature, soil conditions, and rain fall, that is, in the presence of nuisance variables. The application of DoE optimization techniques invariably covers use of experimental tools and generation of mathematical equations and graphic outcomes, thus illustrating a complete effect of considered variables on responses [6, 7, 8]. Further in contrast to traditional approach, DoE approach reveals complete information with respect to factors and their interactions on considered responses with real mathematical correlation.

FUNDAMENTAL PRINCIPLES

The fundamental principles in design of experiments are solutions to the problems in experimentation which serve to improve the efficiency of experiments. Those fundamental principles are listed in Table No 2

Table 1: Pros of DoE approaches over OVAT

Formulation and process variables can be studied independently as well as in combination
Optimization can be done in short period of time with saving cost
Require fewer experiments
Large number of variables can be studied with fewer experiments
RSM designs gives detailed information about interactions between considered variables
Lead to comprehensive understanding of the formulation system.
Help to understand significant and insignificant factors
Yield the "best solution" in the presence of competing objectives.
Shows complete mathematical correlation for studied factors on responses
Establishing and maintaining quality control
Designing robust products

Table 2: Fundamental Principles for DoE

Principles	Description	Reference
Independent Variables /Factors	Affects system directly. The may be **Numeric** as concentration of polymer, milling speed, time etc. or **Categorical** as type of polymer, excipient etc.	[8,9,10]
Dependent Variables/ Responses	These are the measured properties of the system to estimate the outcome of the experiment e.g. drug release at 10 min, impurity level etc.	
Randomization	A method that protects against an unknown bias distorting the results of the experiment	[11,12]
Replication	Replication increases the sample size and is a method for increasing the precision of the experiment.	[13]
Blocking	Blocking is a method for increasing precision by removing the effect of known factors	[14]
Orthogonality	It is used if the estimated effects are due to the main factor of interest and are independent of interactions	[15]
Confounding	It is a bias that must be controlled by suitable selection of the design and data analysis.	[16]
Resolution	It is the ability to describe the degree to which the estimated main effects are aliased	[13]

EXPERIMENTAL DESIGNS

There are a number of types of experimental designs. Various commonly employed experimental designs for RSM, screening, and factor-influence studies in pharmaceutical product and process development are

- **Central composite designs**
- **Box–Behnken designs**
- **Factorial designs**
- **Plackett–Burman designs**

A . RESPONSE SURFACE METHODOLOGY

The impact of each variable can be assessed by varying each variable while keeping others constant. However, it fails to take into account the interactions between these factors. Response surface methodology (RSM) is a suitable experimental design strategy to overcome this problem. Using RSM, the influence of the selected variables on the subject responses in a defined experimental region can be predicted by constructing mathematical models. The goodness of fit of the obtained mathematical models can be checked by statistical analysis. Therefore, RSM is a combination of mathematical and statistical techniques to analyze models and achieve the goal of optimizing the responses.

Basically, the RSM can be classified into two categories:

- Box–Wilson central composite designs (CCD)
- Box–Behnken designs.

CCD is composed by the factorial experiment, axial points and center point. This structure makes it have a better prediction capability than the Box–Behnken design. These designs have been successfully used to optimize the technology and drug delivery systems such as sustained-release tablets, Liposomes, microspheres, nanoparticles in recent years.

Various examples of studies using response surface methodology are given in Table 3 along with details of study, design type and Inference of statistical optimization. Readers are advised to refer respective References for detailed study.

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Table 3. Examples of Studies using Response Surface Methodology

S. No.	Delivery System	Details of Study	Design Type	Inference	Ref.
1	Self micro-emulsion	A two-factor, five-level CCD was undertaken to investigate the main effects and the interactions of the two factors on the four responses. The formulation variables considered for optimization were oil percentage (10–50%) and Sur/Co-s ratio (1–4) to study effect on the response variables Droplet size, Polydispersity index, Equilibrium solubility and Intestinal absorption rate. Furthermore, the desirability function approach was used to simultaneously optimize the responses.	Central composite designs	It was observed that Polydispersity, Droplet size, Equilibrium Solubility and Intestinal absorption rate was significantly influenced by the oil percentage, whereas Sur/Co-surfactant ratio was of low significance for Polydispersity and Droplet size and Equilibrium solubility.	17
2	Oro-Dispersible Tablets	The author describe the application of a two factor, three level (3^2) face centered, central composite design to investigate in-process parameters for fast disintegrating orodispersible tablets. In process variables considered for optimization was tablet diameter and compression force (CF) to determine effect on Hardness, Disintegration Time (DT) and Porosity of Tablets.	Face centered central composite design	The study concludes that compression force and tablet diameter was observed to have profound and interactive effect on the characteristics of orodispersible tablets. The negative value of regression coefficient for tablet diameter showed an inverse relationship with hardness and DT. A positive value of regression coefficient for CF indicated an increase in Hardness and DT with increasing CF as a result of the decrease in tablet porosity.	18
3	Nano suspension for Tablet	Spray drying experiments of an itraconazole nanosuspension were conducted to generate a dry nanocrystal powder which was subsequently formulated into a tablet formulation for direct compression. Central Composite Design employed to identify the optimal drug-to-excipient ratio (Mannitol: Itraconazole ratio 3:1–5:1) and inlet temperature (110–130°C) on the particle size of spray-dried Itraconazole nanosuspension after redispersion. Further effect of talc (1–3%) and magnesium stearate (0.2–1%) mass ratio was investigated on the properties such as angle of repose and tablet hardness of the formulation.	Central composite design	From study it was observed that the spray drying of a nanosuspension with a mannitol-to-drug mass ratio of 1:1 and at an inlet temperature of 120°C resulted in a dry powder with the smallest increase in particle size. The angle of repose was not markedly affected by the change in the concentration of magnesium stearate but tablet hardness decreased significantly with increase in concentration. For talc an increase in talc concentration resulted in a gradual decrease of the angle of repose and with no effect on compressibility of tablets.	19
4	Effervescent Tablet	Strategy is to optimize and evaluate the effects of lubricants and compression force on the physical characteristics of effervescent tablets. Residual force, crushing strength and disintegration time are considered as response variables with factors as concentration of l-leucine, polyethylene glycol and the compression force.	A rotatable central composite design	Study concludes that increasing amounts of l-leucine, showing good lubricating properties, reduce the crushing strength and prolong tablet disintegration time.	20

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S. No.	Delivery System	Details of Study	Design Type	Inference	Ref.
5	Orally disintegrating tablets	CCF design was applied to study the influence of formulation variables (gelatin, carrageenan and alanine concentrations) on the crucial responses of the formulation (disintegration time, hardness, viscosity and pH).	Face centered central composite design	The disintegration time and viscosity were controlled by the associative interaction between gelatin and carrageenan upon hydration which forms a strong complex that increases the viscosity of the stock solution and forms tablet with higher resistance to disintegration in aqueous medium. Therefore, the levels of carrageenan, gelatin and their interaction in the formulation were observed to be the significant factors.	21
6	Delayed Release Multi Particulates System	Studies were performed to elucidate the effect of formulation variables i.e. amount of eudragit polymer, surfactant concentration and agitation speed on in-vitro release profiles, drug entrapment efficiency and particle size of multi-particulates system of indomethacin.	Face centered central composite design	It was found that in-vitro release was decreased significantly with increase in amount of eudragit polymer but increased significantly with increase in surfactant concentration and stirring speed. Finally, the results of response surface linear model were evaluated by Design Matrix analysis techniques. Further FDS graph was considered to check the linearity of model.	22
7	Extended release matrix tablets	A face-centered central composite design (26 runs 13 center points) was selected and the variables studied were filler ratio (lactose: dicalcium phosphate (50:50), polymer level (15/32.5/50%), magnesium stearate level (1/1.5/2%), lubricant blend time (2/6/10 min) and compression force (400/600/800 kg). Responses studied included percent drug released at 1,4, 6 and 12hr	Face centered central composite design	Analysis of variance indicated that percent metoprolol release was found to be significantly reduced by an increase in polymer level from 10 to 50%. Increase in lactose level was found to increase release at 4, 6 and 12 h. Magnesium stearate and lubricant blend time main effects were not found to be statistically significant. Interactions between magnesium stearate and lubricant blend time, filler ratio and polymer level were found to be statistically significant.	23
8	Solid lipid nanoparticles	A two-factor, five-level CCD was applied to explore the optimum levels of independent variables such as Amount of lipid (% w/v) and drug/lipid ratio (%nw/w). Physicochemical properties of the Solid lipid nanoparticles, i.e. entrapment efficiency, particle size and Polydispersity index were selected as dependent variables.	Central composite design	Quantitative estimation of the significant models showed that lipid concentration and ratio of drug to lipid had the influence on the entrapment efficiency and particle size suggesting that increasing the amount of lipid and ratio in the formulation increased the entrapment efficiency and particle size of solid lipid nanoparticles. However for polydispersity index there is no impact of drug/polymer ratio.	24
9	Nanoparticles	The independent variables considered for the optimization of camptothecin nanoparticles were percentage of camptothecin in raw material, concentration of camptothecin in working liquid, cycles numbers and homogenizer pressure for responses as drug loading efficiency, particle size and polydispersity index.	Central composite design	The effect of percentages of camptothecin and concentration of camptothecin on drug loading efficiency showed the linear relationship. At smaller concentration of camptothecin, particle size increase with the increase in percentages of camptothecin. However, particle size slightly decreases with the increase in percentages of camptothecin when concentration of camptothecin is higher. However, numbers	25

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				of cycles and pressure of the homogenizer on particle size shows opposite effect. polydispersity index decrease at first with the increase of camptothecin percentages and increase at the end.	
S. No.	**Delivery System**	**Details of Study**	**Design Type**	**Inference**	**Ref.**
10	Self-emulsifying drug delivery system	A three level Box Behnken design applied to investigate effect of independent variables as ratio surfactants/oil, cosurfactant / surfactant and percentage of cosolvent. The responses chosen were droplet size and cumulative percentage drug released in 20 min	Box Behnken design	It was concluded that droplet size was significantly affected by the antagonistic effect of ratio of cosurfactant/surfactant, the interaction between the amount of cosolvent and the ratio cosurfactant/surfactant. Further drug release at 20min increases by low levels of ratio of co surfactant/ surfactant.	26
11	Extended-release matrix tablets	3-factor, 3-level Box–Behnken statistical design studied considering independent variables as the amount of hydroxypropyl methylcellulose (K4M), sodium alginate and microcrystalline Responses studied included percent drug released at 2,4, 8,14 and 24hr.	Box Behnken design	IT was concluded that the effect of combination of hydroxypropyl methylcellulose (K4M) and sodium alginate was the most influencing factors on the drug release from extended release matrix tablets. The mechanism of drug release from ER tablets was dependent on the added amount of Sodium alginate.	27
12	Solid Lipid Nano-particles	Independent variables (factors) studied were drug to lipid ratio, surfactant concentration and stirring speed on dependent variables (responses) i.e. particles size, entrapment efficiency, and drug loading.	Box Behnken design	An increase in particle size was observed on increasing the drug to lipid ratio and vice versa for surfactant concentration (up to certain limit) and stirring speed. An increase in % entrapment efficiency was observed on increasing the drug lipid ratio and opposite effect observed for surfactant concentration and stirring speed. The effect of drug to lipid ratio on % drug loading is concentration dependent. A decrease in % drug loading was observed on increasing the drug to lipid ratio while stirring speed also showed positive effect on % drug loading.	28
13	Controlled release tablets	Studies were performed to evaluate the main and interaction effects of de-aggregating agent concentration, compression pressure and amount of precipitating water on naproxen release, thickness and hardness of tablets and yield and angle of repose of microspheres.	Box Behnken design	All three factors showed antagonistic effect on drug release i.e. increase in compression pressure affects the integrity of the resultant microspheres from which the tablets are prepared, resulting in increasing hardness of the tablets and, hence, the amount of drug dissolved was found to be decreased.	29

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B. FACTORIAL DESIGNS

Optimization with factorial designs is a powerful, efficient and systemic tool that shortens the time required for the development of pharmaceutical dosage forms and improves research and development work.

Various examples of studies using factorial designs are given in Table 4 along with details of study, design type and Inference of statistical optimization.

C. D- OPTIMAL DESIGNS

The most popular criterion in custom designs is d-optimality. D-optimal designs are based on principle minimization of variance and covariance of parameters. Unlike traditional designs, D-optimal designs do not require orthogonal design matrices, and as a result, parameter estimates may be correlated.

Various examples of studies using D-optimal designs are given in Table 5 along with details of study, design type and Inference of statistical optimization.

D. PLACKETT–BURMAN EXPERIMENTAL DESIGN

Plackett–Burman experimental design (PB), which, a widely used and efficient screening design for the identification of "main factors" that cause variability in product quality. These designs commonly used in order to isolate the most important factors, to be used at their optimal level and the best responses to be achieved; a lot of experiments must be performed, including all the possible combinations between the different factors. The advantage of the PB design is that many factors can be screened with a relatively few number of trials. The disadvantage of these designs is that interactions between variables are generally confounded and cannot be easily determined, as there are not enough degrees of freedom. Also, unless treatments are replicated, variability cannot be evaluated. While these are significant limitations, when a large number of studies would be needed to implement higher-resolution factorial designs, the Plackett–Burman can be a pragmatic solution [42, 43].

Various examples of studies using Plackett–Burman experimental designs are given in Table 6 along with details of study, design type and Inference of statistical optimization.

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Table 4. Examples of Studies using Factorial Design

S. No.	Delivery System	Details of Study	Design Type	Inference	Ref.
14	Multiparticulate system	The studied factors (independent variables) were Eudragit S100: Eudragit L100 ratio and coating level. The dependent variables were lag time (the time required for drug release up to 2%) at pH 6.8 and percent of drug release at pH 6.8 in 5 h.	3^2 full Factorial designs	The results of study revealed that factorial design is a suitable tool for optimization of coating formulations to achieve colon delivery. It was shown that coating formulation consisted of Eudragit S100: Eudragit L 100 in 4:1 ratio at 20% coating level has potential for colonic delivery of indomethacin loaded pellets.	30
15	Controlled release microspheres	Influence of three variables were studied as the stirring speed, concentration of CaCl and % of heavy liquid paraffin in a blend of heavy and light liquid paraffin in the dispersion medium on the response as time for 80% drug dissolution.	3^3 full factorial design	The results of multiple linear regression analysis and F-statistics revealed that for obtaining controlled drug release, the microspheres should be prepared using relatively lower stirring speed, higher concentration of CaCl and higher percentage of heavy liquid paraffin in the dispersion medium.	31
16	Mouth dissolving tablets	The two independent factors, concentration of Indion-234 and concentration of camphor were selected with three different levels to evaluate response variables as disintegration time, friability, and percent drug release.	3^2 full Factorial designs	Study reveled that the use of superdisintegrant in higher concentration and camphor in lower concentration results in faster disintegration of the tablets, faster release with low friability.	32
17	Controlled release tablets	The three level factor corresponds to the three HPMC viscosity grades of 100, 4000 and 15,000 mPa s respectively. The two level factor corresponds to either water and fasted state dissolution media at same dip speed (10 dpm) or water and fed state dissolution media at same dip speed (15 dpm) The dependant variable for the statistical analysis of tablet erosion was derived as the erosion rate (Ker) (%/h).	3^2 full Factorial designs	Dip speed has negligible effect on release and erosion rates. Using fasted media instead of water slightly decreases caffeine release from 100 and 4000 mPa HPMC viscosity tablets as well as erosion rates, while 15,000mPa tablets remain unaffected. Fed compared to fasted media decreases caffeine release rate, and the food effect is greater for the 100mPa viscosity tablets compared to the 4000and 15,000mPa viscosity tablets. The investigation using texture analysis indicates that Ensure Plus® becomes rate-limiting for caffeine release from HPMC tablets by forming hydrophobic barrier around the tablets. The barrier decreases tablet water permeation, which decreases erosion rate in 100mPa viscosity tablets, swelling in 15,000 mPa viscosity tablets and caffeine release from both tablets.	33
18	Gastric floating drug delivery system	Independent variables evaluated included different ratios of HPMC K4M and K100LV, and absence or presence of CP934. Dependent variables studied included release parameters, i.e. calcium release at 6 h, time for the release of 50% of calcium (T50%) and floating properties, i.e. area under floating kinetics curve, and residual floating force.	3^2 full Factorial designs	The decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with lower viscosity (HPMC K100LV) was shown to be beneficial than higher viscosity polymer (K4M) in improving the floating properties of delivery system. Incorporation of Carbopol, however, was found to compromise the floating capacity of delivery system and release rate of calcium.	34
19	Buccal tablet	The four compactor parameters that were to be optimized for the tablet properties were the compaction force, the gap between the rolls, the roll surface and the sieve aperture.	2^4 full Factorial designs	From the tablet strength results, low compaction force, smooth rolls and large gap was preferred. From the dissolution profile and the bio-adhesive characteristic results, high compression pressure, ribbed rolls and small sieve aperture was preferred. Smooth roll was optimal for tablet strength, but ribbed roll was optimal for the dissolution profile. As the dissolution profile was considered more important than tablet strength, ribbed rolls was chosen as optimal for the buccal tablet characteristics.	35

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Table 5. Examples of Studies using D-optimal design

S. No.	Delivery System	Details of Study	Design Type	Inference	Ref.
21	Controlled release Matrix tablet	Influence of three formulation variables were studied as fraction of hydroxypropyl methylcellulose, fraction of sodium carboxymethylcellulose and Fraction of propranolol HCl and dependent variables were cumulative percents of drug released after 1, 6 and 12 h sampling intervals	D-optimal design	The results enabled the formulation of tablets with the desired dissolution characteristics together with a fairly complete characterization of the system. Optimization of release rate was performed applying constraints on the cumulative amounts of drug released after 1, 6 and 12 h release time intervals. Optimized formulations presented release rates that were close to the predicted values.	36
22	Controlled release Matrix tablet	The effects of the type of pectin as an amidated pectin and calcium salt of a high methoxylated pectin, the addition of ethylcellulose, the use of ethanol were evaluated with respect to responses such as hardness, Cumulative percentage of the drug released after 60 min (in SGF), 240 min (total amount released prior to the exposure to the enzymes) and 330 min (a point on the release curve in SCF where the whole dose has not yet been released).	D-optimal design	Amidated pectin produced harder tablets than the calcium salt of pectin and was more susceptible to enzymatic degradation. Addition of ethylcellulose increased the tablet strength and the dissolution rate. Furthermore, directly compressed Amidated pectin tablets were produced by addition of coarse or micronised qualities of ethylcellulose.	37
23	Solid dispersion	The factors considered from D-optimal mixture design were itraconazole fraction (20% - 50% w/w) HPMC and HP-β-CD fractions (10% w/w and 60% w/w). The responses chosen were clear extrudates, the torque, glass transition temperature and the apparent itraconazole solubility in 0.1 N HCl.	D-optimal design mixture	The results of study revealed that High itraconazole fraction in the mixture promoted a better melt processing (minimizes torque). High HPMC fraction (>33% w/w) resulted in clear extrudates, indicating a solid dispersion and resulted in high glass transition temperature of the melt. High HP-beta-CD fraction resulted in increased apparent itraconazole solubility in 0.1 N HCl. The optimal itraconazole formulation consisted of 45% w/w HPMC and 15% HP-beta-CD w/w.	38
24	Extended-release matrix tablets	The formulation variables investigated were applied compression force, granulometric fraction of Eudragit and Ethocel, drug content (%) and Eudragit–Ethocel ratio (%). Response variables variables considered were concentration of didanosine released after 60, 180, 360 min (% w/w), Dissolution efficiency at 360 min (%) and time to dissolve 10% of drug.	D-optimal design	From study it was observed that, the drug content and the polymers ratio had the most important effect on drug release, moreover, was favored by greater polymers particle size; on the contrary the compression force did not have a significant effect.	39
25	Gene Delivery	Formulation independent variables considered were pH, ionic strength, temperature, viscosity of the aqueous solutions, polymer/plasmid ratio and the presence of stabilizers for colloidal systems which affect the size of polymer/plasmid complexes	D-optimal design	From screening design, it was observed that at a fixed concentration of plasmid (40 μg/ml) after incubation with polymer, the size of the resulting polyplexes was highly dependent on the polymer/plasmid ratio as well as on the pH, viscosity (i.e. sucrose concentration) and ionic strength of the aqueous solution. However, the temperature, PEG 600 (up to 5% (v/v)) and Tween 80 (up to 0.2%) had a marginal effect on the size of the polyplexes.	40

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Table 6. Examples of Studies using Plackett Burnam design

S. No.	Delivery System	Details of Study	Design Type	Inference	Ref.
26	Liposomes	The author describes the application of Plackett burrnan design cosidering 11 important factors that are effective for stabilization of liposomal systems. Factors taken into consideration were 1) Free-complex 2) Oil red, 3) Oxybenzone, 4) Deoxybenzone, 5) Sulisobenzone, 6) Carotene, 7) DRV or MLV, 8) Cholesterol, 9) DSPC 10) Sonication time, 11) Sonication type. Stabilization ration was measured as dependent variable.	Plackett Burnam design	Results from studies showed that the most significant effect is the presence of the light absorber oil red O and the second most important factor is the complex with the cyclodextrin form of the vitamin. The third most important factor is the preparation method and indicates that the DRV is superior to that of MLV preparation method. The molar ratios of cholesterol as well as the presence of the rest light absorbers do not play an important role in the stabilization of vitamin.	43
27	Osmotically controlled Gastrointestinal Therapeutic System	The variables studied were orifice size, % coating weight gain, amounts of sodium chloride, Polyox N80 and 303, and Carbopol 934P and 974P on drug release. The response variable considered is Cumulative percent of drug released in 24 hours	Plackett Burnam design	The design has revealed that orifice size, % coating weight gain and amount of Carbopolw 934P have prominent influence on in-vitro atenolol release. The results indicated that the drug release was influenced by the factors with decreasing order of importance as % coating weight gain) Carbopol 934P) olyox N80) Carbopol 974P) Polyox 303) amount of sodium chloride) orifice size.	44
28	Immediate-Release Tablets	During study, different categoric and numeric factors were selected as 1)Disintegrant gelatinization 2)Tablet compression force 3) Speed of granulator after roller compaction 4)API particle size 5) Source/supplier of lubricant 6) Filler particle size 7) Binder grade (hydroxypropyl cellulose) 8) Ratio of roll speed to feed screw speed 9) Blending time 10) Glidant level 11) Roller pressure. The quality attributes of the tablet that were measured included: weight variation, tablet breaking force, disintegration time, and dissolution time .	Plackett Burnam design	It was observed that compression force and roller pressure were the most important parameters affecting tablet breaking force. Klucel® grade and Pmax were the most critical factors governing cipro release, *i.e.*, disintegration and Q30 dissolution. In terms of granule properties (particle size, bulk density, and Carr index), roller pressure is critically affecting both particle size and the Carr Index. Mg stearate type and glidant level also affected particle size and the Carr index, respectively.	45

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CONCLUSION

It is important for a pharmaceutical scientist to use effective methodology to develop products in a timely manner without sacrificing quality. The use of DoE is a leading edge approach to optimization and screening of experimental parameters. Currently, it has gained acceptance as a pivotal developmental tool in diverse industrial processes. Current review is done considering the studies reported employing different types of statistical optimization. Key points while designing statistical optimization are choosing suitable responses (output variables) and factors (input variables), setting appropriate factor ranges or levels, managing the experimentation, interpreting numeric outcomes and graphic manifestations of the findings, presenting the results, and finally deciding whether to continue further with process optimization or just run confirmatory experiment(s) to validate DoE. Design of experiments will ultimately lead to scientific understanding about the product and resultant product will be robust with minimum processing issues and market withdrawals.

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