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Optimizing Oral Controlled Release Drug Delivery Systems using Experimental Designs

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Abstract

The number of literature reports on the use of design of experiments optimization in development of drug delivery technology has been piling up steadily. This review article provides an updated bird's eye view survey account on the publications and optimization techniques of different novel controlled release delivery designs for use in oral applications. Such systematic techniques find their use in every type of conventional dosage form and novel drug delivery system. The drug delivery devices investigated for optimization using various designs include oral controlled release tablet. The present manuscript deal with various steps involved in design of experiments optimization methodology using diverse experimental designs. It also deals with a variety of showing literature findings as well as the potential application of such design of experiments procedures on optimization of assorted drug delivery systems. Such an explicit and updated review on drug delivery optimization has not been published anywhere else in the recent past.

Keywords: Controlled release; Tablet; Sustained release; Factors; Experimental designs

Abbreviations: HPMC: Hydroxypropylmethylcellulose; Na CMC: Sodium Carboxymethylcellulose; EC: Ethylcellulose; HEC: Hydroxyethylcellulose; DCP: Dicalciumphosphate; PVC: Polyvinylchloride; HPC: Hydroxypropylcellulose; MCC: Microcrystallinecellulose; PEG: Polyethylene Glycols; PVP: Polyvinylpyrrolidone

Introduction

The use of optimization techniques employing design of experiments (DoE), however, permeated the field of pharmaceutical product/process development around four decades ago. The first literature report on the rational use of optimization appeared in 1967, when a tablet of sodium salicylate was optimized using a factorial designs (FD). Since then, these systematic approaches have been put into practice in the development of drug formulations at steady pace. Despite tremendous advancements in diverse drug delivery approaches, the oral route remains the most "natural" route of drug administration. In addition, because of the low cost of oral therapy, ease of administration, and improved patient compliance associated with oral route, more than 50% of drug delivery systems available commercially are oral ones. In this context, oral controlled release drug delivery systems are quite popular, offering a number of advantages over conventional dosage forms [1,2]. Generally, the controlled release drug delivery systems for oral use are solid dosage forms, based upon the mechanism of diffusion, dissolution, or a blend of both to control the release rate of drug. These include reservoir devices wherein a polymeric membrane surrounds a drug core and matrix devices wherein the dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix. Most DoE literature reports in this category are focused on optimizing the levels of these release rate-controlling polymers. DoE optimization on oral controlled release matrix delivery devices started in the early 1980s. Such devices encompass the inert matrices such as hydrophilic, hydrocolloid, silicone elastomer, and lipid matrices. The common independent variables for all of these have been the quantities of the polymers or other ingredients, while the optimized responses invariably have been the parameters characterizing in vitro dissolution profile. The other response variables that have been optimized include disintegration time, bioavailability, and bioequivalence [3,4].

The literature reports on oral controlled release dosage forms have been compiled in various tables, categorized on the basis of various types of polymers (natural, semi-synthetic, synthetic) and the type of controlled release dosage form (matrices, dispersions, coated tablets). Table 1 depict the use of statistical experimental designs in optimization of oral sustained release (SR) matrices along with the selected drug candidate and various input variables (factors) studied.

Table 1 reports the work on DoE optimization of oral controlled release drug delivery systems, where natural, synthetic or semi-synthetic polymers have been taken as factors, invariably to control or modify the release rate of the drug. The natural polymers used comprise isapghula husk, guar gum, xanthan gum, pectin, carrageenan, and alginic acid. Optimization reports on sustained release tablets formulated using synthetic polymers such as acrylates, poly-methacrylates, silicone elastomers, and polyethylene glycols (PEG), are shown in Table 1. Apart from polymer level, various other factors that have been optimized include tablet size, compression force, and amount of granulation liquid, lubricant, and glidants. Although most studies focused on optimizing drug release parameters, some studies involved optimization of dissolution evaluation conditions as well. Semisynthetic polymers that frequently have been employed include mainly the cellulose derivatives i.e., hydroxyl-propyl-cellulose (HPC), hydroxyl-propyl-methyl-cellulose (HPMC), hydroxyethylcellulose (HEC), sodium carboxy-methylcellulose (Sodium CMC), and ethyl-cellulose (EC). Some studies on the gums involve treatment with acid

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APIs	Investigated Factors	Experimental Designs	Ref.
Paracetamol	Carbopol 971P, Carbopol 71G, Tablet size	Factorial Design	[8]
Fluoride	HPMC K4M, HPMC K100 LV, Eudragit RL PO	Simplex Lattice Design	[9]
Metformin HCl	Various viscosity grades HPMC, Adhesive type, Lubricant	Response Surface Methodology	[10]
Verapamil HCl	HPMC, Na CMC	Central Composite Design	[11]
Metoprolol tartrate	HPMC, HEC, DCP	Factorial Design	[12]
Ketorolac Tromethamine	HPMC: Na CMC Ratio, EC	Factorial Design	[13]
Diltiazem HCl	Various Grades Carrageenan and Cellulose Acetate Propionate, Ionic strength, Buffer concentration	Factorial Design	[14]
Diltiazem HCl	Succinic Acid-treated Ispaghula Husk, DCP	Factorial Design	[15]
Diltiazem HCl	Guar Gum, Ispaghula Husk	Factorial Design	[16]
Diltiazem HCl	Guar Gum (Modified and Unmodified), DCP	Simplex Lattice Design	[17]
Diltiazem HCl	Modified Guar Gum, Succinic Acid, Drug content	Rotatable Central Composite Design	[18]
Diltiazem HCl	Ispaghula Husk, Water, Heating Time	Factorial Design	[19]
Ropivacaine	Pectin, EC, Binder	D-Optimal Design	[20]
Metoprolol tartrate	HPMC, Lactose: DCP ratio, magnesium Stearate, lubricant blend time, compression force	Face Centered Composite Design	[21]
Diclofenac sodium	Ispaghula husk, Lactose, MCC	Simplex Centroid Design	[22]
Diclofenac sodium	HPMC of Different Grades	Factorial Design	[23]
Diclofenac sodium	Spray-dried Rice Starch, Croscarmellose sodium, magnesium Stearate, compression force	Central Composite Design	[24]
Diclofenac sodium	EC, PVC, Talc	Factorial Design	[25]
Chlorpheniramine maleate	ψ Carrageenan, HPMC	Simplex Lattice Design	[26]
Chlorpheniramine maleate	γ-Carrageenan:cross-linked Na CMC, α-Lactose monohydrate, DCP	Simplex Mixture Design	[27]
Chlorpheniramine maleate	Na CMC, HPMC, HPC, HEC	Artificial Neural Networks, Simplex Centroid Design	[28]
Calcium phosphate	HPMC K4M, HPMC K10 M,	Simplex Mixture Design	[29]
Propranolol HCl	HPMC, Na CMC	Simplex Lattice Design, D-Optimal Design	[30]
Verapamil HCl	HPMC, Sodium Alginate	Sequential Simplex Design	[31]
Trapidil	HPMC, MCC	Central Composite Design, Artificial Neural Networks	[32]
Caffeine, ibuprofen	PEG 6000 and Acacia amount in Core	Factorial Design	[33]
Theophylline	HPC, MC, compression force	Central Composite Design	[34]
Theophylline	HPMC, HPC, MCC	Simplex Lattice Design	[35]
Theophylline	HPMC of Different Grades	Response Surface Methodology	[36]
Naftidrofuryl	Guar Gum, Xanthan Gum, MCC, Calcium Phosphate Dihydrate	Simplex Centroid Design	[37]
Naftidrofuryl	Xanthan Gum, Guar Gum	Central Composite Design	[38]
Misoprostol	HPMC, Na CMC, Lactose	Factorial Design	[39]
Alprazolam	Na CMC: Lactose ratio, HPMC 4000: HPMC 100 ratio,	Rotatable Central Composite Design	[40]
Atenolol	Various grades Carbopol	Factorial Design	[41]
Theophylline	Gelucires, Melting point, HLB, paddle rotation Speed	Factorial Design	[42]
Dextromethorphan Hydrobromide	Polydimethylsiloxane, Silicone to Silica ratio	Full Factorial Design	[43]
Potassium chloride	Silicone Elastomer Latex, PEG of Various Grades	Extreme Vertices Design	[44]
Phenyl propanolamine	Eudragit NE-40D, MCC, milling of granules before compression	Factorial Design	[45]
Ibuprofen	Eudragit (L100, RS, RSPM, RLPM), EC, HPMC, HPMC phthalate	Principal Component Analysis, Response Surface Methodology	[46]
d-Chlorpheniramine maleate	EC, Eudragit, Magnesium Stearate, Talc	Factorial Design	[47]
Theophylline, Etophylline, Proxyphylline	Gelucire 50/02 & 50/13	Response Surface Methodology	[48]
Captopril	Glyceryl Monostearate, Groundnut oil	Factorial Design	[49]
Ibuprofen	Eudragit S-100, Lubricant to Glidant Ratio, Diluents, compression force	Latin Square Design	[50]
Ketoprofen	Eudragit S 100, Lactose	Box Behnken Design	[51]
Chlorpheniramine maleate	Carbopol, PVP, MCC	Extreme Vertices Design	[52]
Lobenzarit disodium	Eudragit RS-PO, MCC	Central Composite Design	[53]
Aspirin	Eudragit L100, compression force	Central Composite Design	[54]
Bumetanide	Polymer, pH Modifiers, Solubility Modifiers	Central Composite Design, D-Optimal Design	[55]
Nifedipine, Nimpodipine	Carbopol 934P, Carbopol 971P, Carbopol 974P	Artificial Neural Networks	[56]
Naproxen	De-aggregating Agent, Compression Pressure	Box Behnken Design	[57]
Didanosine	Eudragit RS-PM: Ethocel 100 Ratio	Doehlert Design	[58]
Aspirin	Eudragit RS-PO, compression force	Central Composite Design	[59]
Theophylline	PEG 6000, Lactose, Stearic Acid	Response Surface Methodology	[60]

Table 1: Optimization reports on oral sustained release tablet formulations.

or alkali to modify the swelling properties of the naturally existing gum and subsequent optimization of their proportion, to be used in SR matrices. Experimental designs have also successfully been employed in the case of the core-in-cup type of compressed SR matrices, studying role of non-swell-able polymers and the other process variables in retarding the release of soluble (caffeine) and insoluble (ibuprofen) drugs employing factorial designs [5-7].

Design of experiments and optimization techniques in pharmaceutical research

The design of experiments (*DOE*) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions. Experimental designs can be defined as the strategy for setting up experiments in such a manner that the information required is obtained as efficiently and precisely as possible. Well-chosen experimental designs maximize the amount of information that can be obtained for a given amount of experimental effort. Optimization of a formulation or process is finding the best possible composition or operating conditions. Determining such a composition or set of conditions is an enormous task, probably impossible and certainly unnecessary. Hence in practice, optimization may be considered as the search for a result that is satisfactory and at the same time the best possible within a limited field of search.

The purpose of optimization is to determine quantitatively the influence of the different factors together on the response variables. The number of levels is usually limited to two, but sufficient experiments are carried out to allow for interaction between factors (Figure 1) [7].

Experimental designs have long been employed to optimize various industrial products and/or processes such as;

- Completely randomized designs (CRD)
- Randomized block designs (RBD)
- Screening Designs since 1946
- Simplex Lattice Design
- Latin squares designs (LSDs)
    - o Graeco-Latin squares designs
    - o Hyper-Graeco-Latin squares designs
- Factorial Designs (FDs) since 1926
    - o Full factorial designs
    - o Fractional factorial designs
- Plackett-Burman designs (PBDs)
- Central composite designs (CCDs) since 1951
    - o Face Centered Composite Design
    - o Rotatable Central Composite Design
- Box-Behnken designs (BBD)
- Response Surface Methodology (RSM)
- D-Optimal Design (D-OD)
- Simplex Centroid Design (SCD)
- Simplex Mixture Design (SMD) since 1958
- Sequential Simplex Design (SSDs)
- Artificial Neural Networks (ANN)
- Extreme Vertices Design (EVD)
- Doehlert Design
- Principal Component Analysis (PCA)

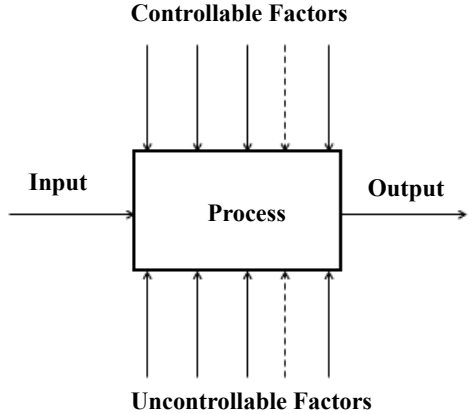
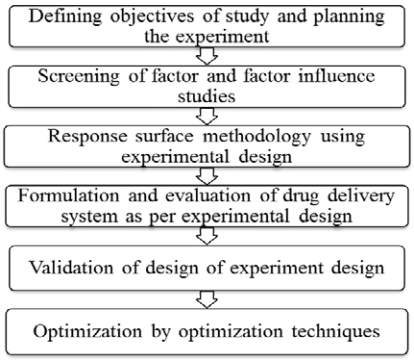


Figure 1: Process Models for DOE.

DOE steps:

- Problem statement
- Choice of factors, levels, and ranges
- Choice of response variable(s)
- Choice of experimental design
- Performing the experiment
- Statistical analysis
- Conclusions and recommendations

STEPS:



DOE applications in process development:

- Improve process yield
- Reduce variability
- Reduce development time
- Reduce overall costs

DOE objectives:

- Determine influential variables (factors)

- Determine where to set influential factors to optimize response
- Determine where to set influential factors to minimize response variability
- Determine where to set influential factors to minimize the effect of the uncontrollable factors.

DOE applications in design:

- Evaluate and compare alternatives
- Evaluate material alternatives
- Product robustness
- Determine key design parameter.

Optimizing Oral Controlled Release Tablet Fomulations

An exhaustive literature search carried out by the authors in pharmaceutical journals and texts reveals that the DoE optimization techniques have been employed for almost all of these dosage forms, ranging from the simple conventional ones to that of the most intricate novel DDS. The updated literature reports unequivocally point out the increasing application of DoE techniques, with a significant shift in the focus of the formulator from optimization of the conventional formulations to that of the modern drug delivery devices [7].

Current and Future Developments

With the advent of newer, sophisticated technologies, the task of drug delivery has become more intricate, involving a greater number of resources in terms of cost, time, and energy. To circumvent these developmental hiccups, adoption of DoE analytical tools is prudently called for. Particularly, when finding the correct compromise is not straight forward, a pharmaceutical scientist should mandatorily consider the use of optimization studies.

DoE techniques have been applied with fruition on almost all kinds of drug delivery systems, not only for optimizing the formulations but their processes too. Nevertheless, there are many new drug delivery applications awaiting demonstrations. The pivotal benefits of DoE have not been thoroughly investigated in some newer drug delivery areas such as gene delivery, peptide delivery, reverse micellar systems, dendrimer based delivery systems and the like. Understanding the formulation or process variables rationally using experimental designs will help in achieving the desired goals with phenomenal ease. Experimental designs can prove to be useful, even if the primary aim is not the selection of the optimum formulation, because it tends to reveal the degree of improvement in the product characteristics as a function of the change in any excipient or process parameter(s). The major impediment in using DoE has been to envision the entire exercise as a whole. The more the formulator knows about the system, the better it can be defined, and the higher the precision with which it can be modified. The difficulties in optimizing a pharmaceutical formulation are due to the difficulty in understanding the real relationship between casual and individual responses. DoE studies can come to the rescue of the formulator, yielding much better prognostic abilities. Once the empirical relationship between the cause and the effect is unraveled, the developmental or post-developmental thoughts can be realized quite rapidly as well as rationally. Defining the relationship between the formulation or process variables and quality traits of the formulation is almost an impossible task without the application of an apt design model. Trial and error methods, in this regard, can never allow the formulator to know how close any particular formulation is to optimal drug delivery solution. This would provide the desired impetus to the product development scientist, facilitating further evolution of research on oral controlled release drug delivery innovations and next-generation product launches.

Conclusions

The literature search indubitably ratifies the steadily increasing popularity of DoE in drug delivery optimization. Verily, the number of optimization studies would be much higher in the drug industry, where DoE methods are applied much more frequently. Because only a miniscule fraction of industrial studies is reported, most investigations remain as only in-house information. Nevertheless, the DoE usage is far from being adopted as a standard practice. Many more endeavors have to be undertaken to highlight the enormous benefits of these techniques before this can happen as a global trend. With the easy availability and affordability of DoE software, these powerful tools can be implemented with the simple click of a mouse. However, there are some key issues that depend upon the experimenter but not upon the software. These include 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. If the experimenter has not endeavored DoE as yet or if a significant jump in information and impact in production capability has not yet been obtained, it is the most opportune time to get started. Eventually, the day will come when the benefits of DoE would be harvested by drug industry and research to their fullest advantage. Providing a relatively pithy overview, this article thus endeavors to act as a disambiguation of knowledge, and knows how to guide and provide ideas to the product development scientists in formulating varied oral controlled release drug delivery systems. I hope that my effort is going to find new application or new idea in nearer future.

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