Chapter

Applications of Statistical Tools for Optimization and Development of Smart Drug Delivery System

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Abstract

In the novel dosage form development, quality is the key criterion in pharmaceutical industry. The quality by design tools used for development of the quality products with tight specification and rigid process. The specifications of statistical tools are essentially based upon critical process parameters (CPPs), critical material attributes (CMAs), and critical quality attributes (CQAs) for the development of quality products. The application of quality by design in pharmaceutical dosage form development is systematic, requiring multivariate experiments employing process analytical technology (PAT) and other experiments to recognize critical quality attributes depend upon risk assessments (RAs). The quality by design is a modern technique to stabilize the quality of pharmaceutical dosage form. The elements of quality by design such as process analytical techniques, risk assessment, and design of experiment support for assurance of the strategy control for every dosage form with a choice of regular monitoring and enhancement for a quality dosage form. This chapter represents the concepts and applications of the most common screening of designs/experiments, comparative experiments, response surface methodology, and regression analysis. The data collected from the dosage form designing during laboratory experiments, provide the substructure for pivotal or pilot scale development. Statistical tools help not only in understanding and identifying CMAs and CPPs in product designing, but also in comprehension of the role and relationship between these in attaining a target quality. Although, the implementation of statistical approaches in the development of dosage form is strongly recommended.

Keywords: Quality by design, Critical quality attributes, Critical process attributes, Critical material attributes, Design of experiments, Smart drug delivery

1. Introduction

In an endeavour to fight various pathological manifestations, medicaments have been administered via various possible routes [1]. Experimental designs techniques have long been used for the optimization of various processes and the development of smart drug delivery system such as the factorial designs since 1926 [2], the designs for screening since 1946 [3], the central composite designs since 1951 [4], and the mixture designs since 1958 [5]. According to Joseph Juran, most of the quality problems are associated with the way by which a pharmaceutical smart drug delivery was designed. A poorly designed pharmaceutical dosage form will show poor efficacy and safety, no matter how many analyses or tests have been done to check its quality.

The quality by design (QbD) is a systemic approach for the development of pharmaceutical formulations that starts with predefined objectives and emphasizes process and product comprehension and process control, based on quality risk management and sound science [6]. The food and drug administration guidance, such as pharmaceutical product development (ICH Q8), quality risk evaluation (ICH Q9), pharmaceutical quality systems (ICH Q10), the briefly highlighted ICH approach to the achieve quality of product through QbD [7], and development and manufacture of drug substances (ICH Q11) [8]. The QbD based approach will provide scientific understanding and knowledge to support smart drug delivery system development [9]. The prime goals of QbD for pharmaceuticals may include: (a) to attain meaningful product and quality specification; (b) to enhance process ability and reduce product variability; (c) to enhance smart dosage form development and manufacturing efficiencies, and (d) to increase cause-effect investigation and regulatory flexibility [6]. The QbD is used to establish the relationship of product performance with the process and product attributes [7, 10]. The applications of QbD in pharmaceutical smart drug delivery system development is systematic, requiring multivariate experiments employing process analytical technology (PAT) and other experiments to recognize critical quality attributes (CQAs) depend upon risk assessments (RAs) [7].

The smart dosage form design and process development cannot be distinguished since dosage form cannot become a product unaccompanied by a defined process. The production process needs to produce a desired standard product typically requires multiple units operating conditions and operations [11]. The outline has to contain all the factors that require to be contemplated for the design of the process. The process factors which cause a vital impact on the quality of the product if changes are contemplated as the critical process attribute (CPAs). The process factor variability, which causes a vital impact on the critical quality of the ingredients should be controlled and monitored, at all times to make sure the process for the targeted quality [6, 11].

2. Basic elements of quality by design

2.1 Set the standard profile for the target smart dosage form

A target standard profile for smart dosage form describes how a smart dosage form will be utilized by the end-user. A systematically developed standard profile can ensure the arrangement of objectives across departments of the company, advance development of timelines, reduction of risks, and finally lead to an optimal smart dosage form. A targeted standard product profile is very important for smart drug delivery development due to the variety of administrations and the variety of possible end-user (patients, nurses, physicians, and pharmacists) [12].

2.2 Recognition of the critical quality attributes (CQAs)

The next step in QbD for smart dosage form development is recognition of the critical quality attributes (CQAs). CQAs are physical, chemical, biological, or microbiological characteristics or properties of the pharmaceutical smart drug delivery system (in-process or finished) that must be within specified standards to ensure quality. CQAs may include identification, content, assay, uniformity, solvents, degradation, products, dissolution or drug release, moisture content, moisture uptake, microbial limits, and other properties such as color, size, shape, etc. [9, 13].

2.3 Smart dosage form design and development

The physic-chemical and pharmacological properties of the medicaments determine the critical attributes for novel dosage form development. The objectives of the novel dosage form development by using QbD for identification of attributes and to achieve desired patient requirements that the resultant product should possess to exhibit intended therapeutic response. The smart dosage form development must invariably be scientific, systemic, and with basic risk management facilitation to achieve these predefined objectives. The CQAs identification is strongly and thoroughly based on the understanding of product and manufacturing process. These CQAs must be controlled to get reproducible and desired results. **Table 1** summarizes the different CQAs for medicaments, additives, in-process

Attribute (CMAs, CQAs & CPAs)	Comments
Drug-related	
Indication	Note if target patients may have limitations (e.g., sodium hydrochloride and hypertension)
Types of the route of administration	May impact the acceptability of drug product (e.g., the tablet is more preferred than parenteral)
Range of dose, frequency of dosing, duration of therapy	The concentration, duration of therapy, and frequency of dosing may affect the use of some additives (are these outside the statutory use levels?)
Pharmacokinetic properties (in-vitro/in-vivo)	Is activity associated or toleration with total exposure or the plasma concentration? For novel drug delivery formulations, what is the required profile?
Drug combination which may be designed or mixed for the formulation	Are there possible incompatibilities?
Dosage form-related	
pH, tonicity, site of application etc. Administration ante/post cibum (oral), need to reconstitute/dilute and with what? Packaging types (single/multi-dose packaging)	If more than a single, will be available at the initial stage? Does existing machinery work for packaging? Will the packaging be a kit (with a device, diluent, etc.)? Are there any considerations for disposal (may differ for various regions)? Is functional labelling required (e.g., anti-counterfeiting measures, freeze indicators, etc.)?
Storage conditions	Include in-use constraints and stability requirements (e.g., requirement of secondary packaging to protect from light, "do not freeze")
Requirements for shipping	Are there any limitations (susceptibility to shaking, temperature excursion, etc.)?
Legitimate-related	
Liberty to operate	Does the process or product contravene any patents, copyright, and applications?
Manufacturing-related	
Cost of the product	It should cover any royalties as appropriate
The machinery required for manufacture	Will the process according to existing machinery?
Processing time for the dosage form	Required to consider sterility. Also, may be a matter for some processes (e.g., freeze-drying).

Table 1.
Different critical attributes to formulate a novel dosage form [12].

materials, and dosage form [14, 15]. On the basis of suitable statistical methods such as DoE (design of experiments), proper risk assessment, and management tools can escort to a good and knowledge-based smart dosage form development. Further, understanding of CQAs helps to set up flexible and meaningful regulatory product specifications. Knowledge of smart drug delivery development can facilitates QbD and increase the manufacturing capability (**Figure 1**) [16].

2.4 Critical process attributes (CPAs)

To develop an optimal manufacturing procedure, all the critical process attributes including facilities, equipment, manufacturing variables, and material transfer

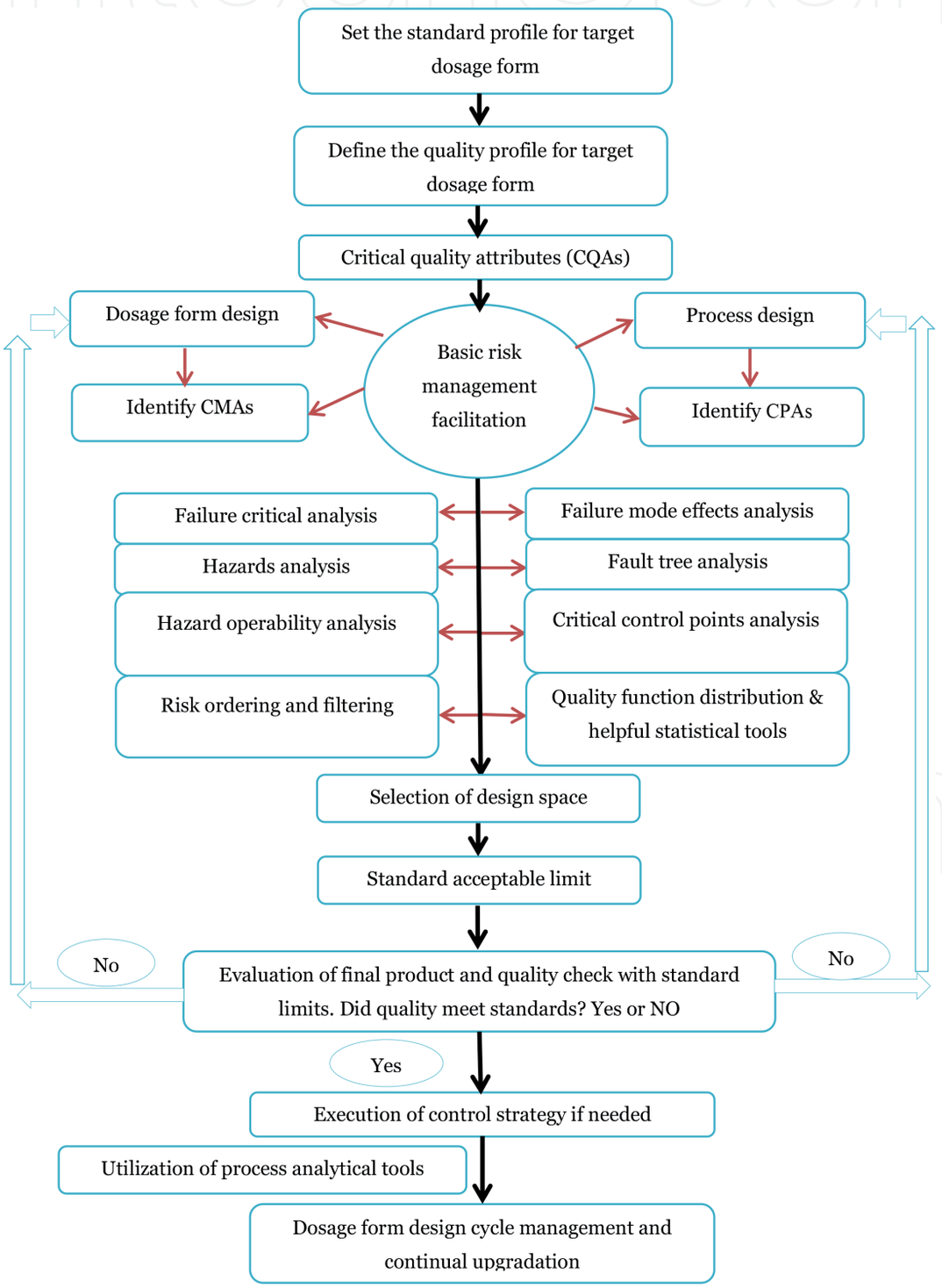

Figure 1.
The fundamental approach of QbD for designing of a pharmaceutical dosage form.

should be considered. Pulverization, homogenization time/mixing, type of mixer, and energy input are the major critical attributes in the manufacturing of novel dosage form. The process attributes using these associated factors require be identifying and carefully controlling to formulate batches with reproducible quality [17].

Size reduction of the material may be affected by the types of mill used. Different types of material need a special type of mill for pulverization such as lignocellulosic biomass material (like wood) required 'fine grinding' (less than 100 μm) [18] but in other studies, the 'fine grinding' has been used for particle sizes up to 1 mm [19–21]. The excess temperature during processing can increase the degradation of ingredients [22, 23], while less temperature can cause the failure of the process due to drug solubility issues [24]. Mixing speed and time is a critical attribute to develop a smart dosage form. For optimizing the mixing speed and time, the minimum needed time to dissolve the components and the maximum time of mixing can affect the viscosity of the product (causing product failure) and it should be identified [22, 25, 26].

2.5 Critical material attributes (CMAs)

The quantitative and qualitative information of active pharmaceutical ingredients (API) is prime attributes as material attributes [11]. Although an API is mostly incorporated at low concentrations and occupies a negligible part in the final formulation, the additives (inactive ingredients) usually elucidate the physical properties of a formulation [11, 27]. A number of researches have shown that additive(s) can influence the fate of an API in dosage form [28, 29]. Different grades of additives show a substantial effect on quality attributes of the final product as well as the API stability in the product [30]. Impurities in a raw material may show a detrimental impact on the stability of API/additives. Another prime challenge during the design and development of a novel dosage form is the compatibility of additives and API.

2.6 Design of experiments (DOEs)

The DOEs is not a replacement for experience, intelligence, or expertise; it is a precious element for choosing experiments systematically and efficiently to give dependable and coherent information [31]. DOEs are defined as "an organized, structured technique for deciding the relationship between attributes influencing a process and the output of the process" [32]. The DOEs can be applied for the screening of designs/experiments, comparative experiments, response surface methodology, and regression analysis [33].

2.6.1 Common experimental designs

In order to provide a logical relationship among the dependent variables and independent variables, experimental designs may be classified into four classes: a) screening designs, b) optimization designs [34–36] c) comparative experiments, and d) regression modelling.

2.6.1.1 Screening of designs/experiments

Screening of designs involves the selection of prime factors affecting a response. For the selection of experiments; fractionate factorial designs, the full factorial designs, and Placket-Burman designs are mostly used for screening because these designs have cost-effective advantages. These screening designs permit one to study various input factors with minimum numbers of experiments. However, these

designs also show some limitations that should be contemplated in order to impart a better interpretation of the effects of input elements on output responses [34–36]. Only the linear responses are supported by screening designs. Thus, if a nonlinear response is observed, or a more accurate phenomenon of the response surface is required or more complex design may be applied [37].

2.6.1.2 The factorial approach

The full factorial and fractional factorial designs are generally used by the most of the researchers as an alternative methodological technique to standard relative randomized controlled trials (RCTs) and module designs, which has supremacy over both for determining the active elements of formulations. The factorial designs are employed to explore the prime impacts of critical factors and interactions among factors [38–42].

The common and simple full factorial design is the 2^2 factorial designs, where 2^2 is indicating two factors at two levels means the total run of experiments is four, which are located in 2-dimensional factor space at the rectangle's corners. If there are 2^3 factorial designs is applied then total eight experiments are mandatory which are located at the corners of an orthogonal hexahedron on a 3-dimensional space. If large numbers of factors are used at large numbers of levels then the number of runs needed to finish the task. To minimize the number of runs, the fractional factorial design should be used (i.e., ½ or ¼ of the real number of runs of full factorial design) [43–45].

Table 2 shows the three factors at two coded levels 0 and 1, where 0 represents a low level and 1 represents a high level. In **Table 2**, the last column shows the response values of random variables. The main effect of any factor (A, B, C) or interaction (AB, AC, BC, ABC) is the difference of two means, the means of the responses corresponding to high levels and the means of responses corresponding to low levels.

When we compare the suggestions of **Table 2** with the suggestions of fractionate factorial design shown in **Table 3**. In **Table 3**, every-even numbered test experiment eliminated from **Table 2**. Again, factor effects are differences in mean responses. Even though, the prime effect for factor A is absolutely similar and opposite in sign from the interaction AB; i.e., A is aliased with -AB. Each result in **Table 3** is aliased with another result, having the prime result for B which is aliased with the evaluation of the overall average response. Therefore, every difference in means measures the difference of two results; e.g., A-AB. Had the half-fraction accompanied the odd-numbered test experiments been removed, every difference of means for a result would be evaluating the sum of two results; e.g., A + AB.

Experiment	A	B	C	AB	AC	BC	ABC	Response
1	0	0	0	1	1	1	0	R_1
2	0	0	1	1	0	0	1	R_2
3	0	1	0	0	1	0	1	R_3
4	0	1	1	0	0	1	0	R_4
5	1	0	0	0	0	1	1	R_5
6	1	0	1	0	1	0	0	R_6
7	1	1	0	1	0	0	0	R_7
8	1	1	1	1	1	1	1	R_8

Table 2.
Full factorial design with three factors at two levels.

Experiment	A	B	C	AB	AC	BC	ABC	Response
1	0	0	0	1	1	1	0	R_1
3	0	1	0	0	1	0	1	R_3
5	1	0	0	0	0	1	1	R_5
7	1	1	0	1	0	0	0	R_7

Table 3.
Fractional factorial design of a full factorial design with three factors.

Every fractional factorial design needs the aliasing of all or some of the factor effects. Many times the selection of fractional factorial designs is the unscientific that can lead to ambiguity, even wrong, conclusions about factor effects. Inversely, it is precisely the attentive selection of which fraction is applied that can increase the experimentation efficiently without the aliasing of main effects. **Table 4** shows another half-fraction of the full factorial design.

2.6.1.3 Plackett-Burman designs or Hadamard designs

This design is special two-level full factorial design and generally employed for the screening of factors. Plackett-Burman designs are mainly applicable for screening a large number of factors if we want to test the effect of 7 factors then we have to put some dummy factors. The results of full factorial designs, Plackett-Burman design, and Taguchi design are interpreted by using a half-normal plot and Pareto chart. By using these designs we can detect all prime effects economically and all other interactions assumed as negligible when compared with few prime effects [46–48].

2.6.1.4 Response surface methodology (RSM)

Response surface methodology is used after the identification of the critical variables affecting a response. Response surface methods such as central composite design, Box–Behnken design, and three-level factorial designs can recognize the optimum/suitable processing parameters or conditions [49, 50]. The primary advantages of response surface methodology are as hitting a target, minimizing or maximizing a response, minimizing variations, setting a robust process, and finding multiple objectives.

2.6.1.5 Central composite designs or Box-Wilson design

This is one of the most commonly employed optimization design because this is used for 5 levels of each loaded factor with a less number of runs required when compared with 3 levels full factorial designs. Central composite designs are

Experiment	A	B	C	AB	AC	BC	ABC	Response
2	0	0	1	1	0	0	1	R_2
4	0	1	1	0	0	1	0	R_4
6	1	0	0	0	0	1	1	R_6
8	1	1	1	1	1	1	1	R_8

Table 4.
Fractional factorial design of a full factorial design, prime results can be estimated.

generally used for nonlinear responses. In this model, a two-factor central composite design is similar to a 32 factorial design by using the experimental domain at $\alpha = \pm 1$. Dash RN et al. successfully developed a glipizide-loaded formulation by using central composite designs [51].

2.6.1.6 Box–Behnken design

This is a specially made design, which needs only three levels for each factor and it is widely employed in response surface methodology for fitting second-order models for all responses. In this method, 15 experiments are run three levels for each factor. Box–Behnken designs are a combination of incomplete block designs with two-level factorial designs and these are almost rotatable. This design has the benefits that there are no runs where three levels for each factor and that there are no corner points run. Runs at the corner points may be expensive or inconvenient [52].

2.6.1.7 Three level factorial designs

This design is mainly used only for two-three factors because the large numbers of runs are needed. The required number of runs may be calculated as 3 K, where K is selected factor for study.

2.6.1.8 Comparative experiments

Comparative studies are performed for selecting a suitable one between two/more alternatives. From a sample of data, the mean results are generated and compared for suitable selection from each alternative. For example, the selection of a vendor for a medicament from two/more vendors can be a relative experiment. The narrow scoped comparative designs are good for an initial comparison and broad scope design is appropriate for a confirmatory comparison [53].

2.6.1.9 Regression modelling

Regression modelling is an essential statistical component for the analysis of the data. It is employed for the identification and depiction of relationships among various factors. It is also used for the identification of prognostically pertinent risk elements and the determination of risk results for each prognostication [54]. The most commonly used regression techniques are the following: Linear regression, Cox regression, and Logistics regression. Regression modelling is used for the statistical evaluation of the data by enabling three things: (a) Description analysis shows the relationship among the independent variables and the dependent variables and it can be statistically defined. (b) Estimation of the data for the dependent variables can be estimated from defined data of the independent variables. (c) Prediction of risk elements that influence the results can be identified, and individual prediction can be determined [55].

3. Conclusion

The ever-rising cost of novel dosage form development projects have not provided assurance of increased efficiency for delivering new drugs. In recent times, quality by design has shown great attention and is being spotlighted more than previously among pharmaceutical producers. Although consideration about its nomenclature and concepts remains indistinct, that may result in a lack of confidence

in applying the smart dosage form development. Knowing the disadvantages of quality by design on the one hand and in the other hand, getting a comprehensive understanding of quality by design can enable pharmaceutical manufacturers for employing the concepts of quality by design in utilization.

Robust manufacturing of smart pharmaceutical dosage forms, with their numerous complex formulations and the necessity for rigid similarity with the commercial formulations, essential for the understanding of CPPs and CMAs. The details collected from the development of novel dosage form overtime at laboratory scale provide the substructure for pivotal or pilot scale development. Statistical tools help not only in understanding and identifying CMAs and CPPs in dosage form development, but also in comprehension of the role and relationship between these in attaining a target quality. Although, the implementation of statistical approaches in the development of dosage form is strongly recommended. From a commercial point of view, at all stages of product development, the implementation of quality by design reduces the costs and accelerates the process of product commercialization.

Authors' contributions

I declare that this work was done by the author named in this article. PS conceived, designed the study, carried out the literature collection of the data, writing, and corrected the manuscript. The author read and approved the final manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interest.

Availability of data and materials

All the information in the manuscript has been referred from the included references and is available upon request from the corresponding author.

Abbreviations

QbD	Quality by design
ICH	International conference on harmonization
PAT	Process analytical technology
CQAs	Critical quality attributes
RAs	Risk assessments
CPAs	Critical process attributes
CMAs	Critical material attributes
API	Active pharmaceutical ingredients
DOEs	Design of experiments
RCTs	Randomized controlled trials
RSM	Response surface methodology

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