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AURUM MÜHENDİSLİK SİSTEMLERİ VE MİMARLIK DERGİSİ
AURUM JOURNAL OF ENGINEERING SYSTEMS AND ARCHITECTURE

Cilt 7, Sayı 2 | Kış 2023
Volume 7, No 2 | Winter 2023

APPLICATIONS OF MATHEMATICAL MODELLING IN PHARMACEUTICAL FORMULATION AND PROCESS DEVELOPMENT

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Received: 27.10.2023
Accepted: 08.11.2023
Published: 31.12.2023
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Review Article
pp.303-313
DOI: 10.53600/ajesa.1382037

Abstract

Pharmaceutical development and authorization stages have high requirements that increase labour and costs. Risks for product quality and process robustness also increase in parallel with complex practices existing in the pharmaceutical industry and emerging as a result of developments. Although it is challenging to eliminate parameters leading to increased risks, there is a need to appropriately manage the risks likewise set up procedures for decision-making. Designing and optimizing formulation and production processes to deliver the predetermined product quality is known as Quality by Design (QbD) in pharmaceutical development. In terms of data and knowledge, QbD can be carried out using a variety of technologies in this process. Mathematical modelling is one of these tools allows for the quick formation of subject knowledge, which may subsequently be used in an independent or integrated manner and to produce Design of Experiments (DOE). Artificial Neural Network (ANN), Genetic Algorithm (GA) and Response surface method (RSM) are some of the assistive technologies used in mathematical modelling that enables to enlighten the effect of formulation and process and formulation variables on product quality attributes. The use of advanced mathematical modelling techniques in product and process development has become widespread and it appears to be beneficial in different areas of pharmaceutical development.

Keywords: Quality by Design, Design of Experiments, Mathematical Modelling, Pharmaceutical Development

FARMASÖTİK FORMÜLASYON VE SÜREÇ GELİŞTİRMEDE MATEMATİKSEL MODELLEME UYGULAMALARI

Özet

İlaç geliştirme ve ruhsatlandırma süreci, iş gücü ve maliyetleri artıran yüksek gereksinimlere sahiptir. İlaç endüstrisinde var olan ve gelişmeler sonucu yeni ortaya çıkan kompleks uygulamalara paralel olarak ürün kalitesi ve süreç sağlamlığına ilişkin riskler de artmaktadır. Risklerin artmasına neden olan parametreleri ortadan kaldırmak zor olsa da risklerin doğru yönetilmesi ve aynı şekilde karar alma süreçlerinin düzenlenmesi gerekmektedir. Önceden belirlenmiş ürün kalitesini sunmak için formülasyon ve üretim süreçlerinin tasarlanması ve optimize edilmesi, farmasötik geliştirmede Tasarımla Kalite (QbD) olarak bilinir. Veri ve bilgi açısından QbD uygulanması için birçok araçtan yararlanılabilir. Bu araçlardan biri de konu bilgisinin kolaylıkla oluşturulmasını ve daha sonra bağımsız ya da bütünleşik biçimde kullanılması sağlayacak matematiksel modellerin ve Deney Tasarımının (DOE) oluşturulmasıdır. Yapay Sinir Ağı (YSA), Genetik Algoritma (GA) ve Yanıt yüzeyi yöntemi (RSM), proses ve formülasyon değişkenlerinin ürün kalite özellikleri üzerindeki etkisini aydınlatmak üzere gerçekleştirilen matematiksel modellemede kullanılan yardımcı teknolojilerden bazılarıdır. Gelişmiş matematiksel modelleme tekniklerinin ürün ve proses geliştirmede kullanımı oldukça yaygınlaşmış olup; ayrıca farklı farmasötik geliştirme alanlarında fayda sağladığı görülmektedir.

Anahtar Kelimeler: Tasarımla Kalite, Deney Tasarımı, Matematiksel Modelleme, Farmasötik Geliştirme

1. Introduction

The pharmaceutical industry has seen significant advancements in production information, risk management and quality management systems over the past few years as it attempts to keep up with innovations by leaps and bounds. It has also created cutting-edge production tools that can help ensure production quality. Risks on product quality and process control also increase in parallel with complex practices which get evolve each day in the pharmaceutical industry. Although it can be challenging to remove complications that increase hazards, it is necessary to properly manage risks and organize decision-making processes. Additionally, efforts to launch new pharmaceutical products on the market are genuinely hampered by "stalemates" in the development of pharmaceutical products and the necessity of restarting a development cycle for any variations even after the pharmaceutical product and its manufacturing process have received licenses. Due to these obstacles, there was a new approach Quality by Design (QbD) to the pharmaceutical development embrace building the quality from the beginning and to continuing throughout the lifecycle of the product.

2. Quality by Design (QbD)

QbD is a concept that pioneered by Dr. Joseph Moses Juran, an American Engineer, in the early nineteen seventies through his recognised book "Juran on Quality by Design," which was later accepted by many technology driven areas such as the automobile, robotics, telecommunications and aviation industries engaged in the progress of high quality services and products. The approach was eventually accepted by the health care industry, particularly by producers of medical devices in the 1990s (Beg, Hasnain, Rahman, & Swain, 2019). Dr. Juran thinks that quality should be built into a product, and this is the majority of quality problems and crises arise from the way a product was created at first (Yu et al., 2014; Bastogne, 2017).

ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) is a forum that gathers the authorities and experts of the pharmaceutical industry. The forum mainly aim to unify the technical standards for pharmaceutical products, and one of its tasks it to publish updated guidelines. ICH published the Q8 guide in 2005, and with this guide, the concept of "quality by design" (QbD) entered the pharmaceutical industry. Pharmaceutical QbD is a systematic development strategy that emphasizes product and process understanding and control based on solid science and quality risk management (Yu et al., 2014; Jiwa, Ozalp, Yegen, & Aksu, 2021).

Pharmaceutical QbD objectives may include achieving purposeful product quality requirements based on clinical performance; expanding process capability and reducing product variability and defects through improved product and process understanding, design and their control; boosting product development and manufacturing effectiveness; and enhancing post-approval change management and root cause analysis (Yu et al., 2014).

QbD philosophy is mainly made up of a collection of fundamental aspects and phases for gaining a deep knowledge of a process or product. These include declaring the quality target product profile (QTPP), critical quality attributes (CQAs), critical process parameters (CPPs) and critical material attributes (CMAs); choosing screening/optimization designs and proposing a continuous improvement control strategy (Beg, Hasnain, Rahman,

& Swain, 2019; Grangeia, Silva, Simões & Reis, 2020). In QbD, experiments are first carried out in a structured manner with variations in CPPs utilizing the Design of Experiments (DoE). Then, using the experimental data produced by DoE, multivariate data analysis (MVDA) techniques are employed to model the multivariate and multi-collinear relationships among the CQAs and CPPs and/or CMAs.

3. Design of Experiment (DoE)

DoE is a QbD tool that is essential for achieving Target Quality Product Profile (QTPP). It helps in the analysis of received replies and the achievement of the study's aim in an acceptable manner. DoE proven to be the most successful and efficient instrument across various phases of the formulation process while assisting in making informed judgments and generating a product of high performance, stability and design (Dhoot, Fernandes, Naha, Rathnanand, & Kumar, 2019).

DoE significantly reduces the number of experiments required to generate model design space. Optimized parameters can be resorted to in order to establish a design space with clearly visible outcomes within relevant ranges in multi-factorial form, for using in model predictions and planned tests. It is also feasible to separate parameter sets into logical groupings in order to decrease the experiment number required for experimental design or model verification. In product development, small groups can be formed by focusing on factors linked to single unit processes.

Screening: Determining the levels of critical factors

Optimization: Identifying the appropriate input factors (variables) and values of them to yield the best reply.

Robustness: Determining the sensitivity of the reaction to slight differences in the components of Design of Experiment may be used for a variety of purposes, including comparing the count of suppliers and materials, screening factors/variables, robustness, optimization of the system, and the relationship between input factors/variables and responses of the output.

The suitable instruments for generating design space can be chosen based on a variety of aspects, including the complexity of the assessed system, precision, relevant scientific knowledge, and corporate choice. There is no single instrument or method that is perfect for every situation. All of them can provide very significant information; nevertheless, there are several factors to consider when deciding which tool to utilize.

Procedure of conducting DoE can be summarized in the stages that follow as determination of problem or defining target quality attributes, selection of CQAs, factor selection and defining the levels of the factors, forming experimental design, conducting the experiments then data or response analysis which lead to a conclusion like optimised responses and finally to create a Design Space (DS) (Dhoot, Fernandes, Naha, Rathnanand, & Kumar, 2019; Politi, Colombo, Colombo & Rekkas, 2017; Beg, Swain, Rahman, Hasnain & Imam, 2019).

3.1. Determination of problem

For optimal experimental design selection, components or levels, variables and responses, the experiment should have a defined purpose. The objectives of the experimental approach must be articulated. It is always beneficial to establish a list of concerns that the experiment will solve (Beg, Hasnain, Rahman, & Swain, 2019).

3.2. Selection of (CQAs)

A critical quality attribute is a biological, physical, microbiological or chemical feature of a material output, such as completed pharmaceutical goods, that must be in an accepted range, distribution, or limit to provide quality of the product. Quality features of a drug product include assay, residual solvents, content uniformity, dissolution or drug release, microbiological limitations, degradation products, moisture content, and physical properties like shape, color, friability, size, odor and score configuration. These characteristics might be critical or non-critical (Yu et al., 2014). Critical quality attributes are the results or reactions of experiments, which can differ depending on the aims and aid in meeting study objectives.

3.3. Factor selection and factor levels

Factors are investigated to assess the magnitude of their impact on responses. Material qualities and/or processing parameters are two sorts of factors. The levels are the range that must be chosen for a certain factor. Typically, more than two values from the range may be chosen.

3.4. Experimental design selection

According to the objectives, factors and their levels; appropriate experimental design can be chosen. Experimental design used during QbD-approach can be of two types such as screening designs and optimization design (or also called as response surface designs). The use of customized optimization designs (also known as response surface designs) is extremely beneficial in producing the best factor values. A screening experiment is frequently followed by an optimization experiment. Taguchi design, Fractional factorial design and Plackett-Burman design are often used for screening investigations, whereas factorial design, Box-Behnken design, central composite design, optimum design and mixture design are extremely useful for response surface design. Through the monitoring of CMA levels at low, medium and high levels, using these designs aids in mapping the responses and CQAs based on the studied objective(s) (Beg, Hasnain, Rahman, & Swain, 2019).

A thorough evaluation of the independent variables and effects of their interactions is made possible by the full factorial design, which makes efficient utilization of the data. On the other hand, with full factorial design the number of independent variables and their levels rises, the amount of experimental runs also rises exponentially. When there are more parameters, fractional factorial designs are frequently used to estimate the main and interaction effects by only running a specific subgroup of full factorial experiments.

It is common practice to estimate the primary factors that contribute to product variability using the Plackett-Burman design. With only a small number of experiments, this design enables the screening of numerous factors. However, The Plackett-Burman design has the drawback that main effects are frequently mistaken for interactions between variables.

However, the Taguchi design, also called orthogonal arrays, allows one to analyze the interactions and effects between the noise variables which are factors that can only be controlled in laboratory experiments and controlled variables.

The Box-Behnken design is beneficial for product optimization because it facilitates experimentation with an increasing number of independent variables. Furthermore, response surfaces are constructed using Central composite designs are favored due to their increased model robustness and capacity to incorporate multiple points (e.g., center and corner points).

Response-surface-oriented methods, such as I-optimal design and D-optimal design, are types of optimal designs that define the design space where the quality attributes of final product meet the target product profile. But, the primary drawback of these designs is the length of time required to complete them.

Modde, Design Expert, Statistica, Minitab, and SigmaXL are some software tools includes these designs and may be used to implement Design of Experiment. These programs assist in obtaining solutions more affordably, quickly, and easily (Dhoot, Fernandes, Naha, Rathnanand, & Kumar, 2019; Beg, Hasnain, Rahman, & Swain, 2019). These statistical programs used by scientists, engineers and statisticians were created to ease the development stage of a pharmaceutical product or process with an experimental design capability.

In a QbD strategy, the value of the information obtained, and the suitability of the studies are more significant than the number of optimization studies conducted in order to create a quality pharmaceutical product. As a result, QbD and DoE are not equal, but DoE can be an essential part of QbD (Yu et al., 2014; Politi, Colombo, Colombo, & Rekkas, 2017)

Formulation optimization studies are critical and substantial for generating a stable formulation and final product. A formulation is probably in high risk without optimization studies since it is uncertain if differences in the raw material or formulation qualities would have a substantial influence on the quality and performance of the medicinal product. Formulation optimization studies ensure significant information about factors below (Yu, et al., 2014):

- Formulation robustness, including the establishment of functional linkages between critical quality attributes and critical material attributes,
- CMA recognition of excipients, drug substance, in-process materials,
- Drug substance development and excipient control techniques.

3.5. Modelling - Data or response analysis

The acquired data is statistically investigated using procedures like, student's t-test, regression analysis and analysis of variance (ANOVA).

In accordance with ANOVA, a model is considered to be relatively less significant if its R2 (coefficient of determination) is equal 0.5. Q2 (predictive power of the model) which is accepted as the best and most sensitive indicator should be above 0.1 for a significant model and above 0.5 for a good model. And also, for a good model, the difference between R2 and Q2 should also be less than 0.3.

Figure 1 shows the coefficient plot taken from Modde Pro 12 (Umetrics, Sartorius Stedim Biotech, Sweden) software which is a graphic representation of terms in the model on account of determining their significance and indicates the scale of the effects of variables on the responses, while their sign indicates whether these effects are positive or negative (Jiwa, Ozalp, Yegen & Aksu 2021).

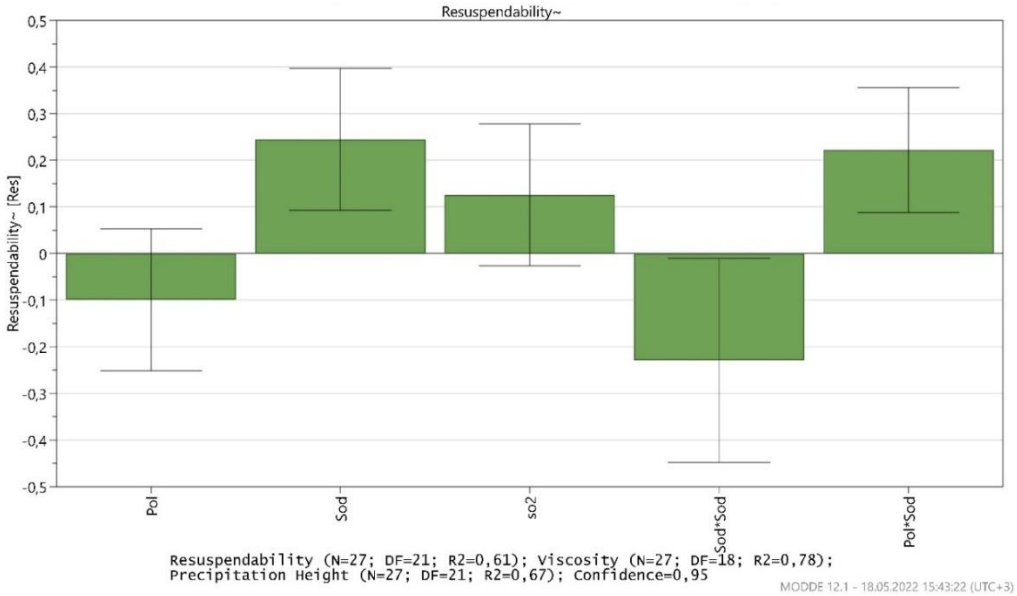

Figure 1. An example of the coefficient plot from Modde Pro 12.1 software

3.6. Design space (DS)

After the data has been examined, an appropriate conclusion is reached upon which suggestions are founded. To control well-understood variables, the DS—a multidimensional combination and interaction of CPPs and CMAs—should be formed. It has been shown to provide assurance of quality. Software-suggested compositions are carried out practically based on criteria and attractiveness factors. Additional confirmatory tests are carried out to validate the conclusions and suggestions.

4. Results and Discussion

Some studies carried out using mathematical modelling for optimizing the pharmaceutical process and formulation was given in this section to emphasize the role of the concept.

In a study by Jiwa, Ozalp, Yegen and Aksu (2021), it was aimed to enrich the understanding of the effect of excipients in formulation (filler and lubricant; mainly used in tablet dosage forms); also to create and optimise the formulation using experimental design and mathematical modelling methods in the frame of the QbD approach. An experimental design study was conducted using the Modde Pro 12.1 statistical computer program that enables optimization by modelling complex relationships. According to the results of the ideal formulation, MicroceLac® 100 was chosen as filler and magnesium stearate (1%) was the ideal lubricant. Additionally, a design space was created that shows the safety operation limits for the formulation and process variables.

In a study by Garg et al. (2017), nanostructured lipid carriers (NLCs) including Aceclofenac was designed to prepare and characterize employing QbD approach. NLCs and Aceclofenac loaded NLCs were prepared & characterized and further evaluated for stability and transdermal penetration potential. Various surfactants and lipids were selected to produce NLCs as CMAs using the microemulsion method. For NLCs, the critical formulation attributes (CFAs) were screened using a Taguchi orthogonal array design that makes use of seven factors at two levels. A total of 8 formulations were examined for CQAs including drug entrapment percentage (PDE), particle size and PDI. CFAs were decided, running experimental data in the Design Expert1 v 10.0 (StatEase, USA) software and analysing the results. For optimization of NLCs, a 3^3 factorial design was used to evaluating them for different critical CQAs (particle size, drug entrapment efficiency). The optimized NLC-based gel formulation outperformed the commercial formulation in terms of rheological profile, texture properties and cell uptake efficiency, as well as ex vivo skin permeability efficiency.

In other study on radiopharmaceuticals, an optimised Technetium-99m-imatinib mesylate ([99mTc]TcIMT) was developed as a new radiopharmaceutical to be used in breast cancer diagnosis. Using Modde Pro 12 as a platform for experimental design and process optimization, the quality by design concept was used to examine the impact of critical process parameters on the stability and product quality. The results demonstrate that the method proposed for the preparation of [99mTc]TcIMT is within established acceptable limits, and radiochemical purity, stability, and in vitro cell binding assessment of the agent suggested that it can be used for imaging breast cancer cells (Gündogdu, Demir, Özgenç, Yegen, & Aksu, 2020).

A study by Yegen, Aksu and Cevher (2021) aimed to develop an Orally Disintegrating Tablet ODT, a solid dosage form rapidly disintegrates or dissolves to release the drug upon contact with saliva in the mouth, formulation contains Metoprolol tartrate with appropriate attributes via QbD approach with the assistance of AI modelling programs. The experimental data was evaluated with FormRules V3.32 (Intelligensys, UK) to comprehend the relation between the CQAs and the independent input variables; subsequently, with INForm V5.1 (Intelligensys, UK) for optimization. According to test results, the optimized formula was prepared, and tablets showed compliance with pharmacopoeia limits.

In a research study by Bulbul et al. (2022) patches for transdermal delivery of acemetacin, to be used in treatment of rheumatic diseases were developed using Modde Pro 12 to use different statistical design and response surface methodology for optimisation process and the potential use of the patches were further investigated with in-vivo studies. It was observed that optimised patch was employed more efficiently for rheumatic disease.

The application of a DoE driven QbD strategy for the anti-solvent crystallization of dexlansoprazole is presented in the study by Garg and Rathore (2021). Crystallization of Active Pharmaceutical Ingredients (APIs) have been investigated in recent years to produce crystals with desired physical properties. It is crucial to implement QbD in this process because many issues in downstream processes can be led to poor particle characteristics occurred during the crystallization. Software for statistical analysis, Minitab19 (Minitab Inc.), was used to design and conduct the experiment. Thusly developed, the empirical model was statistically significant. As suggested by the QbD paradigm, the model has also been used to design a control strategy that enables in-process control of the crystal size

distribution during crystallization. As a result, they stated an empirical model that could be applied to real-time crystallization process control.

In another study, chitosan-coated nanoemulsions that shows mucoadhesive characteristic were optimized for for rosmarinic acid (RA)'s nasal delivery. Using Box-Behnken design (BBD) via Minitab 17.0.1 (Minitab Inc.), the optimal ratio between the formulation components that resulted in maximal ζ-potential and RA content and minimum droplet size and PDI was found. Higher RA penetration/retention through the porcine nasal mucosa and long-lasting permeation times was demonstrated by optimized chitosan-coated RA nanoemulsions, which also exhibited suitable physicochemical properties, prolonged drug release, high mucoadhesion. Overall finding shows that optimized formula was a suitable carrier for nasal delivery of RA that aims neuroprotective therapies (Nathiely et al., 2018).

A study on twin screw wet granulation, a continuous manufacturing technique is swiftly gaining importance in pharmaceutical manufacturing, conducted by Portier et al. (2020) evaluated the effect of screw configuration and process settings on eight model formulations varying in filler type (Lactose, MCC: Microcrystalline Cellulose, HPMC: Hydroxypropylmethylcellulose), active pharmaceutical ingredient (API) characteristics and drug load. Five factors were assessed in a D-optimal design as part of the study: the fraction of kneading elements (KE) in the initial kneading zone; the thickness of KE; throughput; screw speed and the ratio of liquid to solid (L/S). The experimental design was set up and analysed using MODDE Pro 12.0. Response surface models were built using multiple linear regression (MLR) with a reproducibility and predictive power (Q2) higher than 0.5 and a model fit (R2) > 0.5 and validity > 0.25 for most responses. After modelling studies, a viable platform formulation was proposed since formulations with lactose/MCC as filler were less affected by various screw configurations, process parameters, and API features.

An article published by Tome, Časar and Obreza (2020) presented successful application and optimization of a selective and robust analytical method for determining process-related impurities of celecoxib with least analysis run time following Analytical Quality by Design (AQbD). This would make it possible to test for all seven process-related impurities of celecoxib in an effective and straightforward manner using a single HPLC method, thus avoiding separate testing with the EP and USP methods. After choosing appropriate column for HPLC method, a central composite face response-surface design was used to further investigate the critical method parameters: flow rate, column temperature, and the ratio of acetonitrile in the mobile phase. To ascertain the factor–response relationships, a MLR method was applied to fit the mathematical models on the experimental data. The developed models exhibit good predictive ability and an adequate fit. The Monte Carlo simulation method was used to establish the design space. The developed method was suitable for determination of seven process-related impurities of celecoxib verifying in terms of precision, sensitivity, accuracy, and linearity.

5. Conclusion

Product development is a recognized process as time-consuming, highly complex, and requires extensive knowledge. The effectiveness of pharmaceutical products depends critically on the choice of excipients with the appropriate functionality and levels. Throughout the study using DoE methodology including mathematical

modelling in the frame of QbD was shown as beneficial in terms of evaluating critical parameters and gaining enhanced product and process knowledge. DoE is a science and statistical based approach, and it chooses appropriate ranges/points for formulation variations. It was also helpful to reach a robust formulation development stage. It appears to be useful in optimizing the formulation and preparation processes of many different dosage forms, drug molecule synthesis, analytical methods etc. and in examining the effects of parameter variables on output properties. Artificial intelligence-based modelling programs will also be useful if developed.

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