HOLISTIC APPLICATION OF QUALITY BY DESIGN (QbD) FOR PHARMA PRODUCT DEVELOPMENT EXCELLENCE AND REGULATORY COMPLIANCE

Bhupinder Singh\textsuperscript{1,2*}, Sarwar Beg\textsuperscript{1}, Gajanand Sharma\textsuperscript{1}, Atul Jain\textsuperscript{2} and Poonam Negi\textsuperscript{1}

\textsuperscript{1}University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Studies, Panjab University, Chandigarh-160014, India

\textsuperscript{2}UGC-Centre of Excellence in Nano Applications (Biomedical Sciences), Panjab University, Chandigarh-160014, India

Abstract

The realm of optimizing the drug formulations has gained significant momentum towards more systematic approach of “Quality by Design (QbD)” based strategies employing “Design of Experiments (DoE)” from the erstwhile traditional short-gun approach of changing “One Factor at a Time (OFAT)”. These traditional approaches are generally associated with multiple intricacies including utilization of greater magnitude of time, money and energy, inconduciveness to plug errors, unpredictability and inability to reveal interactions and only “just workable” solutions. In this regard, the new holistic QbD-based paradigm, i.e., “Formulation by Design (FbD)\textsuperscript{2}”, applicable especially in the development of drug delivery systems brings about complete understanding of the product and processes based on the sound knowledge of science and quality risk management. Further, the recent regulatory guidance’s issued by the key federal agencies to practice QbD has coerced the researchers in industrial milieu to employ these rational approaches during drug product development. Beyond the pharmaceutical formulation development, QbD has diverse applications in API synthesis, analytical method development, dissolution testing, manufacturing and stability testing. The present article describes the principles, methodology and applications of QbD in the entire product development life cycle for attaining product development excellence and regulatory compliance.

Keywords: Systematic Optimization, Design of Experiments (DoE), Quality by Design (QbD), Formulation by Design (FbD), Design Space

*Correspondent Author: Email: bsbhoop@yahoo.com, Phone: +91 172 2534103
Introduction

Since decades, the pharmaceutical products have been considered as the highly regulated products meant for human use for accomplishing desired therapeutic benefits for treatment of diverse ailments. Despite continuous innovations by the pharma industry, there has been a repeated set back owing their poor quality and manufacturing standards. The adoption of systematic approaches has been originated from a thought provoking article that appeared in The Wall Street Journal more than a decade back (i.e., September 2002) was an eye opener for the federal agencies. It stated that “although the pharmaceutical industry has a little secret even as it invents futuristic new drugs, yet its manufacturing standards lag far behind the potato chips and laundry soap makers” [1]. Figure 1 portrays multiple sources of variability during drug product development owing to variability in drug substance(s), excipient(s), process(es), packaging material(s), etc.

Based upon the Juran’s quality philosophy, pharmaceutical QbD embarks upon systematic development of product(s) and process(es) with desired quality. As a patient-centric approach, the QbD philosophy primarily focuses on the safety of patients by developing drug products with improved quality and reduced manufacturing cost by planning quality at first place to avoid quality crisis [5]. Beginning with pre-defined objectives, QbD reveals the pharmaceutical scientists with enhanced knowledge and understanding on the products and processes based on the sound science and quality risk management. Adoption of QbD principles, in particular, tends to unearth scientific minutiae during systematic product development and manufacturing process(es). For pharma industry in particular, QbD execution leads to improved time to market, enhanced knowledge sharing, limited product recalls and rejects, reduced consumer skepticism.
towards generics, decreased post-approval changes and efficient regulatory oversight.

One of the integral tools in the QbD armamentarium while developing optimized products and processes has been “Design of Experiments (DoE)” employing apt usage of experimental designs [6]. Amidst a multitude of plausible interactions of the drug substance with a plethora of functional and non-functional excipients and processes, adoption of systematic approaches lead to evolution of the breakthrough systems with minimal expenditure of time, developmental effort and cost. With the objective of developing an impeccable products or processes, earlier this task has been attempted through trial and error, supplemented with the previous knowledge, wisdom and experience of the formulator, termed as the short-gun approach or one factor at a time (OFAT) approach [7, 8]. Using this methodology, the solution of a specific problematic product or process characteristic cannot be achieved and attainment of the true optimal solution was never guaranteed. However, the QbD-based approach usually provides systematic drug product development yielding the best solutions. Such approaches are far more advantageous, because they require fewer experiments to achieve an optimum formulation, reveal interaction among the drug-excipient-process, simulates the product performance and subsequent scale-up. Figure 2 illustrates the QbD-oriented development of drug product embarking upon the comprehensive understanding of the quality traits associated with a product(s) and process(es).

With the percolation of such systematized approaches, the domain of pharmaceutical product development has endowed a newer look towards drug formulation development and subsequent patient therapy. Owing to the immense benefits, the applications of QbD are galore such as in drug substance manufacturing, formulation development, analytical development, stability testing, bioequivalence trials, etc.

The holistic QbD-based philosophy of product development revolves around five fundamental elements viz. defining the quality target product profile (QTPP), identification of critical quality attributes (CQAs), critical formulation attributes (CFAs) and critical process parameters (CPPs), selection of apt experimental designs for DoE-guided, precise definition of design and control spaces to embark
upon the optimum formulation, postulation of control strategy for continuous improvement [9, 10]. Figure 3 illustrates the five step methodology for drug product development employing QbD-based approach.

Figure 3: Five-step QbD methodology

**Step I: Ascertaining Drug Product Objective(s)**

The target product quality profile (QTPP) is a prospective summary of quality characteristics of the drug delivery product ideally achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product. During drug product development, QTPP is embarked upon through brain storming among the team members cutting across multiple disciplines in the industry. Critical quality attributes (CQAs) are the physical, chemical, biological or microbiological characteristic of the product that should be within an appropriate limit, range or distribution to ensure the desired product quality. The identification of CQAs from the QTPP is based on the severity of harm a patient may get plausibly owing to the product failure. Thus after defining the QTPP, the CQAs which pragmatically epitomize the objective(s), are earmarked for the purpose.

**Step II: Prioritizing Input Variables for Optimization**

Material attributes (MAs) and process parameters (PPs) are considered as the independent input variables associated with a product and/or process, which directly influence the CQAs of the drug product. Ishikawa-Fish bone diagram are used for establishment of cause-effect relationship among the input variables affecting the quality traits of the drug product. Figure 4 illustrates a typical cause-effect diagram highlighting the plausible causes of product variability and their impact on drug product CQAs.

Figure 4: A typical Ishikawa-fish bone diagram depicting sources of variability

Prioritization exercise is carried out employing initial risk assessment and quality risk management (QRM) techniques for identifying the “prominent few” input variables, termed as critical material attributes (CMAs) and critical process parameters (CPPs) from the “plausible so many”. This process is
popularly termed as factor screening. Comparison matrix (CM), risk estimation matrix (REM), failure mode effect analysis (FMEA) and hazard operability analysis (HAZOP) are the examples of commonly employed risk assessment techniques. Using these techniques, various MAs and PPs are assigned with different risk levels viz. low, medium and high risk based on their severity and likelihood of occurrence. The moderate to high risk factors are chosen from patient perspectives through brainstorming among the team members for judicious selection of CMAs.

Comparison matrix (CM), risk estimation matrix (REM), failure mode effect analysis (FMEA) and hazard operability analysis (HAZOP) are the examples of commonly employed risk assessment techniques. Using these techniques, various MAs and PPs are assigned with different risk levels viz. low, medium and high risk based on their severity and likelihood of occurrence. The moderate to high risk factors are chosen from patient perspectives through brainstorming among the team members for judicious selection of CMAs.

The moderate to high risk factors are chosen from patient perspectives through brainstorming among the team members for judicious selection of CMAs.

Figure 5: Prioritization using QRM and factor screening is necessary to identify CMAs and CPPs as a prelude to DoE optimization

QRM is rational approach which not only provides holistic understanding of the risks associated with each stages of product development, but also facilitates mitigation of risks too. Experimental designs and risk assessment techniques are used during QRM exercise for factor screening, respectively (Figure 5). Figure 6 portrays the flow layout of overall risk assessment plan employing risk assessment and risk management for identifying the potential CMAs employing a prototype REM model.

Figure 6: Layout of risk management strategy employing a typical risk estimation matrix

The low-resolution first-order experimental designs (e.g., fractional factorial, Plackett-Burman and Taguchi designs) are highly helpful for screening and factor influence studies. Before venturing into product or process optimization, prioritization of CMAs/CPPs using such QRM and/or screening is obligatory.

Step III: Design-guided Experimentation & Analysis

Response surface methodology is considered as a pivotal part of the entire QbD exercise for optimization of product and/or process variables discerned from the risk assessment and screening studies. The experimental designs help in mapping the responses on the basis of the studied objective(s), CQAs being explored, at high, medium or low levels of CMAs.
Figure 7 provides bird’s eye view of key experimental designs employed during QbD-based product development. Factorial, Box-Behnken, composite, optimal and mixture designs are the commonly used high resolution second-order designs employed for drug product optimization.

**Design matrix** is a layout of experimental runs in matrix form generated by the chosen experimental design, to guide the drug delivery scientists. The drug formulations are experimentally prepared according to the design matrix and the chosen response variables are evaluated meticulously.

**Step IV: Modelization & Validation of QbD Methodology**

Modelization is carried out by selection of apt mathematical models like linear, quadratic and cubic models to generate the 2D and 3D-response surface to relate the response variables or CQAs with the input variables or CMAs/CPPs for identifying underlying interaction(s) among them. Multiple linear regression analysis (MLRA), partial least squares (PLS) analysis and principal component analysis (PCA) are some of the key multivariate chemometric techniques employed for modelization to discern the factor-response relationship. Besides, the model diagnostic plots like perturbation charts, outlier plot, leverage plot, Cook’s distance plot and Box-Cox plot are also helpful in unearthing the pertinent scientific minutiae and interactions among the CMAs too. The search for optimum solution is accomplished through numerical and graphical optimization techniques like desirability function, canonical analysis, artificial neural network, brute-force methodology and overlay plot. Subsequent to the optimum search, the optimized formulation is located in the design and control spaces. Design space is a multidimensional combination of input variables (i.e., CMAs/CPPs) and output variable (i.e., CQAs) to discern the optimal solution with assurance of quality.
Figure 8 illustrates the interrelationship among various spaces like, exploratory, knowledge, design and control spaces. Usually in industrial milieu, a narrower domain of control space is construed from the design space for further implicit and explicit studies.

**Step V: QbD Validation, Scale-up and Production**

Validation of the QbD methodology is a crucial step that forecasts about the prognostic ability of the polynomial models studied. Various product and process parameters are selected from the experimental domain and evaluated as per the standard operating conditions laid down for the desired product and process related conditions carried out earlier, commonly termed as checkpoints or confirmatory runs. The results obtained from these checkpoints are then compared with the predicted ones through linear correlation plots and the residual plots to check any typical pattern like ascending or descending lines, cycles, etc. To corroborate QbD performance, the product or process is scaled-up through pilot-plant, exhibit and production scale, in an industrial milieu to ensure the reproducibility and robustness. A holistic and versatile “control strategy” is meticulously postulated for “continuous improvement” in accomplishing better quality of the finished product.

**Software Usage during QbD**

The merits of QbD techniques are galore and their acceptability upbeat. Putting such rational approaches into practice, however, usually involves a great deal of mathematical and statistical intricacies. Today, with the availability of powerful and economical hardware and that of the comprehensive QbD software, the erstwhile computational hiccups have been greatly simplified and streamlined. Figure 9 enlist the select computer softwares available commercially for carrying out QbD studies in industrial milieu. Pertinent computer softwares available for DoE optimization include Design-Expert®, MODDE®, Unscrambler®, JMP®, Statistica®, Minitab®, etc., are at the rescue, which usually provide interface guide at every step during the entire product development cycle. Softwares providing support for chemometric analysis through multivariate techniques like MNLRA, PCA, PLS, etc. encompass, MODDE®, Unscrambler®, SIMCA®, CODDESA®. For QRM execution using Fish-bone diagrams, REM and FMEA matrices during risk assessment studies, etc., softwares like, Minitab®, Risk®, Statgraphics, FMEA-Pro, iGrafxf, etc., can be made use of.

![Select computer software used during QbD implementation for product and process optimization](image-url)
QbD is an inimitable quality-targeted approach for developing efficacious, cost- efficacious, safe and robust drug products, generics as well as innovator’s. On industrial fronts, a formulation scientist can derive its stellar benefits at each stage of product development lifecycle and beyond, even after commercial launch and post-marketing surveillance. Figure 10 pictorially illustrates the application of strategic principles of QbD during various stages of drug product development.

**Figure 10: QbD is useful overall product development even after the product launch**

**Formulation by Design (FbD)**

Formulation by Design (FbD) is a recent QbD-based paradigm, applicable exclusively for development of pharmaceutical dosage forms. Product and process understanding are the twin keystones of FbD. It also requires holistic envisioning of the formulation development, including how CMAs and CPPs tend to impact CQAs during laboratory scale, production and exhibit scale leading to a robust and stable drug product [8]. Defining such relationships between these formulation or process variables and quality traits of the formulation is almost an impossible task without the application of FbD model. More the formulator knows about the system, the better he can define it, the higher precision he can monitor it with. Such approach has been widely employed in the development of drug formulations of diverse kinds. Table 1 and Table 2 illustrates the select literature instances on the product and process optimization of drug delivery products employing FbD approach enlisting their QTPP, CMAs, CPPs, CQAs and type of experimental design employed, respectively.

**Analytical QbD (AQbD)**

AQbD, on the heels of QbD, endeavors for understanding the predefined analytical objectives. These comprise, quality target method profile (QTMP) of an analytical method and identifying the critical method variables (CMVs) affecting the critical analytical attributes (CAAs) for attaining enhanced method performance, like high robustness, ruggedness and flexibility for continual improvement within the ambit of analytical design space [33, 34]. Besides, AQbD helps in reducing and controlling the source of variability to gain in-process information for taking control decisions in a timely manner. This facilitates attaining flexibility in analysis of API and impurities in dosage forms, stability samples and biological samples and to go beyond
Table 1: Select literature instances on QbD-based development of various drug delivery products

<table>
<thead>
<tr>
<th>Drug</th>
<th>QTPP</th>
<th>CFAs/CMA/CPs</th>
<th>CQAs</th>
<th>DoE</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iloperidone</td>
<td>Nanostructured lipid carriers SNEDDS tablets</td>
<td>Amount of oil, surfactant and cosurfactant</td>
<td>Globule size</td>
<td>BBD</td>
<td>[12]</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>SNEDDS</td>
<td>Amount of cremophor RH 40, Labrafil 1944 CS and Capmul MCM</td>
<td>Droplet size, PDI, drug content</td>
<td>D-OD</td>
<td>[14]</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>SNEDDS</td>
<td>Amount of oil, surfactant and co-surfactant</td>
<td>Globule size and zeta potential</td>
<td>BBD</td>
<td>[15]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Nanoemulsion</td>
<td>Amount of organic phase, water, Pluronic</td>
<td>Viscosity, gel strength, spreadability, consistency</td>
<td>D-OD</td>
<td>[16]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Microspheres</td>
<td>Concentration of chitosan, pectin, carboxymethyl cellulose</td>
<td>Yield, encapsulation efficiency, drug release at 30 and 60 min</td>
<td>FD</td>
<td>[17]</td>
</tr>
<tr>
<td>Albendazole</td>
<td>Enteric-coated pellets</td>
<td>Amount of water soluble polymer, amount of water-permeable polymer</td>
<td>Drug release at 3 h, time required for 50% and 85% drug release</td>
<td>FFD</td>
<td>[18]</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Solid SNEDDS</td>
<td>Amount of Capmul MCM and Nikkol HCO-50</td>
<td>Globule size, MDT, dissolution efficiency, emulsification time</td>
<td>CCD</td>
<td>[19]</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Spray-dried microspheres</td>
<td>Inlet temperature, feed flow rate and drug polymer ratio</td>
<td>Yield, particle size, in vitro diffusion</td>
<td>FD</td>
<td>[20]</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Gastroretentive tablets</td>
<td>Concentration of Carbopol 971P and HPMC</td>
<td>Drug release in 16 h, buoyancy time, bioadhesion strength</td>
<td>CCD</td>
<td>[21]</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>SNEDDS</td>
<td>Amount of Cremophor EL and Transcutol HP</td>
<td>Globule size, MDT, emulsification time, Particle size, drug release in 16 h, zeta potential</td>
<td>CCD</td>
<td>[22]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>SLN</td>
<td>Amount of Compritol 888 and Tween 80</td>
<td>Percent entrapment, percent diffused, percent leakage</td>
<td>FD</td>
<td>[23]</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Controlled release bioadhesive tablets</td>
<td>Amount of Carbopol 971P and HPMC</td>
<td>Drug release in 16 h, bioadhesion strength, release exponent</td>
<td>CCD</td>
<td>[24]</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>Liposomes</td>
<td>Amount of phospholipid, cholesterol</td>
<td>Percent entrapment, percent diffused, percent leakage</td>
<td>FD</td>
<td>[25]</td>
</tr>
</tbody>
</table>

QTPP: Quality target product profile; CQA: Critical quality attributes; CMA: Critical material attributes; FD: Factorial design; FFD: Fractional factorial design; CCD: Central composite design; BBD: Box-Behnken design; D-OD: D-optimal mixture design; PCA: Principal component analysis
traditional ICH procedure of method validation. Like FbD, the AQbD also embarks upon risk-assessment studies through REM/FMEA and DoE-guided factor screening and optimization studies for improving the method performance. Instances of CMVs during AQbD optimization include mobile phase composition, flow rate, gradient time, column oven temperature, pH, while CAAs include peak area, retention time, theoretical plates, asymmetry factor and capacity factor. Literature reports on QbD-based analytical method development are enlisted in Table 3.

<table>
<thead>
<tr>
<th>Drug</th>
<th>QTPP</th>
<th>CPPs</th>
<th>CQAs</th>
<th>DoE</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypeptide antibiotic fermentation process</td>
<td>Incubation time, temperature, pH, aeration rate, nitrogen and carbon concentration PLGA amount, Surfactant conc., homogenization rate</td>
<td>Polypeptide concentration</td>
<td>TgD</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel nanoparticles</td>
<td>Pressure, concentration of ursodeoxycholic acid</td>
<td>Particle size</td>
<td>BBD</td>
<td>[27]</td>
<td></td>
</tr>
<tr>
<td>Ursodeoxycholic acid high-pressure homogenization technology</td>
<td>Temperature, Concentration, flow rate, atomization</td>
<td>Particle size</td>
<td>BBD</td>
<td>[28]</td>
<td></td>
</tr>
<tr>
<td>Solid dispersion spray drying process</td>
<td>Extraction temperature, time and cycles</td>
<td>Yield, outlet temperature, particle size</td>
<td>BBD</td>
<td>[29]</td>
<td></td>
</tr>
<tr>
<td>Ursodeoxycholic acid high-pressure homogenization technology</td>
<td>Extraction temperature, time and cycles</td>
<td>Yield, outlet temperature, particle size</td>
<td>BBD</td>
<td>[28]</td>
<td></td>
</tr>
<tr>
<td>Tinospora cordifolia extract nanoparticles</td>
<td>Extraction temperature, time and cycles</td>
<td>Yield, outlet temperature, particle size</td>
<td>BBD</td>
<td>[29]</td>
<td></td>
</tr>
<tr>
<td>Ursodeoxycholic acid high-pressure homogenization technology</td>
<td>Extraction temperature, time and cycles</td>
<td>Yield, outlet temperature, particle size</td>
<td>BBD</td>
<td>[28]</td>
<td></td>
</tr>
<tr>
<td>Ursodeoxycholic acid high-pressure homogenization technology</td>
<td>Extraction temperature, time and cycles</td>
<td>Yield, outlet temperature, particle size</td>
<td>BBD</td>
<td>[28]</td>
<td></td>
</tr>
<tr>
<td>Matrix metalloproteinase-1 plga-pcl nanoparticles</td>
<td>Homogenization time, agitation speed and volume of organic to aqueous phase</td>
<td>Percent yield</td>
<td>CCD</td>
<td>[30]</td>
<td></td>
</tr>
<tr>
<td>Ursodeoxycholic acid high-pressure homogenization technology</td>
<td>Extraction temperature, time and cycles</td>
<td>Yield, outlet temperature, particle size</td>
<td>BBD</td>
<td>[28]</td>
<td></td>
</tr>
<tr>
<td>Ursodeoxycholic acid high-pressure homogenization technology</td>
<td>Extraction temperature, time and cycles</td>
<td>Yield, outlet temperature, particle size</td>
<td>BBD</td>
<td>[28]</td>
<td></td>
</tr>
</tbody>
</table>

QTPP: Quality target product profile; CQA: Critical quality attributes; CPP: Critical process parameters; FD: Factorial design; FFD: Fractional factorial design; CCD: Central composite design; BBD: Box-Behnken design; TgD: Taguchi design

Other QbD applications in product lifecycle

QbD not only facilitates comprehension of products or processes, but also helps in attaining excellence in federal compliance with phenomenal ease and economy. Hence, besides the drug formulation development and analytical method development, the concept of QbD has slowly been percolating into other diverse interdisciplinary areas like API development, dissolution testing, manufacturing, bioequivalence studies and stability testing.
Developing drug substances employing the systematic QbD-based paradigm has been recently popularized to accomplish the desired objective of producing drug substance with reduced variability, high purity and yield. ICH Q11 guidance, in this regard, provides detailed understanding of the key principles of manufacturing drug substance employing rational paradigms. As per the QbD approach, the quality target profile for drug substance are defined, which includes molecular, physiochemical and biological properties, pharmacokinetics, storage and packaging conditions, etc [40]. The concentration of reactants, solvents, initiators, stabilizers employed during synthesis of drug substance are mainly used as the CMAs, which are subsequently optimized for their impact on CQAs like, API particle size and size distribution, polymorphism, hygroscopicity, density, flow property, aqueous solubility, etc. Table 4 illustrates the select literature reports on development of drug substances employing QbD approach.

## QbD in dissolution testing

As dissolution testing is primarily considered as one of the most important quality control test for preparing the release specification for any pharmaceutical dosage form, the QbD approach helps in optimizing the drug product composition for accomplishing analogous drug release profile to that of the reference listed product. Important examples of CQAs which determines the

### Table 3: Select literature instances on analytical method development using QbD

<table>
<thead>
<tr>
<th>Drug</th>
<th>QTMP</th>
<th>CMVs/CMPs</th>
<th>CAAs</th>
<th>DoE</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-artemether and lumefantrine</td>
<td>Stability-indicating HPLC method</td>
<td>Mobile phase ratio, flow rate</td>
<td>Retention factor, peak symmetry</td>
<td>PBD</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>Degradation product characterization</td>
<td>Buffer strength, pH</td>
<td>Peak resolution</td>
<td>FD</td>
<td>[36]</td>
</tr>
<tr>
<td>Ebastine</td>
<td>Stability-indicating UPLC method</td>
<td>Mobile phase ratio, pH, column oven temperature</td>
<td>Peak resolution and retention time of degradation products</td>
<td>CCD</td>
<td>[37]</td>
</tr>
<tr>
<td>Darifenacin hydrochloride</td>
<td>Stability-indicating UPLC method</td>
<td>Mobile phase ratio, buffer strength, pH</td>
<td>Peak resolution, peak asymmetry</td>
<td>RCCD</td>
<td>[38]</td>
</tr>
<tr>
<td>Rosuvastatin, Telmisartan, Ezetimibe, Atorvastatin</td>
<td>Simultaneous estimation using HPLC method</td>
<td>Mobile phase ratio, buffer strength, flow rate</td>
<td>Peak resolution, peak asymmetry</td>
<td>CCD</td>
<td>[39]</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>Simple HPLC method development</td>
<td>Flow rate, temperature, pH</td>
<td>Peak resolution, tailing factor</td>
<td>CCD</td>
<td>[39]</td>
</tr>
</tbody>
</table>

QTMP: Quality target method profile; CMVs: Critical method variables; CMPs: Critical method parameters; CAAs: Critical analytical attributes; FD: Factorial design; CCD: Central composite design; RCCD: Rotatable CCD; PBD: Plackett-Burman design
product quality include amount of drug release at specified time intervals, mean dissolution time, dissolution efficiency, release exponent, etc., whereas the concentration of polymers, disintergrants, type of medium are used as CMAs which tend to affect the dissolution profile of drug products.

**QbD in bioequivalence testing**

Implementation of QbD during bioequivalence study helps in optimizing the drug products (i.e., generics) in obtaining desired pharmacokinetic profile matched with that of the reference listed product. Important pharmacokinetic metric like, $C_{\text{max}}$, $T_{\text{max}}$, AUC, AUC$_{0-\infty}$, AUC$_{0-t}$, are considered as the critical quality traits for optimizing the formulation variables like, concentration of release controlling polymer, coating composition, coating percentage, etc.

**QbD in stability testing**

QbD approach in stability testing furnishes better understanding of the product stability and shelf-life, information on degradation products, compatibility of container(s)/closure(s) with packaging materials. This helps in preparing the specifications related to safety, efficacy of finished product(s) with respect to the concentration of degradants and final qualifications of them for marketing approval.

**Conclusion**

Today, the federal agencies look for assurance of patient-centric quality “built-in” into the system, rather than through end-product testing. Notwithstanding the enormous utility of QbD-based philosophy in developing optimal drug products, it leads research mindsets to evolve “out-of-box” strategies too. As variability tends to exist at each and every stages of product development life cycle, QbD application needs to be omnipresent. Apt implementation of QbD paradigms, accordingly, would be pivotal in achieving a “win-win situation” for patients, drug industry and regulators. The practice of systematic QbD implementation for

| Table 4: Select literature instances on API development employing QbD approach |
|---------------------------------|-----------------|-----------------|--------------------|-----------------|-----------------|
| Drug                            | QTPP            | CMAs/CPPs       | CQAs               | DoE              | Ref.            |
| Fc fusion protein               | Overall yield of protein synthesis | Aggregate level of reactant in load, elution buffer pH | Yield of host cell protein, residual protein, DNA Assay, % purity of drug & intermediates | MVA | [41] |
| Torcetrapib                     | Drug substance development | Concentration of reactants | | CCD | [42] |
| DCBB                            | Improve reductive sulfonation process | Sulfite amount, time and temperature | Percent yield | FD | [43] |
| 17 α-methyl-11β-arylestradiol    | Optimization of target product yield | Reactant concentration, Reaction temperature | Yield and percent purity | FD | [44] |
| Calanolide A                    | Optimization for improving yield | Amount of AlCl$_3$ and reaction temperature | % yield of intermediate | FD | [45] |

Singh B. et al : Holistic Applications of QbD for Product Development
products has undoubtedly spiced up over the past a few decades, yet it is far from being adopted as a standard practice. Federal regulations for generic drug products are already in place. Several initiatives still need to be undertaken to inculcate mundane use of diverse QbD paradigms in the holistic domain. Apart from these, the synergistic use of in-process PAT and RTRT tools in tandem with process engineering approaches like extensometry and chemometry, can also be helpful in ameliorating product and process understanding and enhancing the process capability for efficient manufacturing. With the growing acceptance of QbD paradigms, in a nutshell, it is rationally prophesized that soon these QbD philosophies will be required to be implemented to innovators, biosimilars, analytical development, API development and even beyond.

References


