Nirma Univ J Pharm Sci; 2014, 1(1) 19-35

INVITED ARTICLE

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

Bhupinder Singh[1,2*], Sarwar Beg[1], Gajanand Sharma[1], Atul Jain[2] and Poonam Negi[1]

[1]University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Studies, Panjab University, Chandigarh-160014, India

[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)", 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.

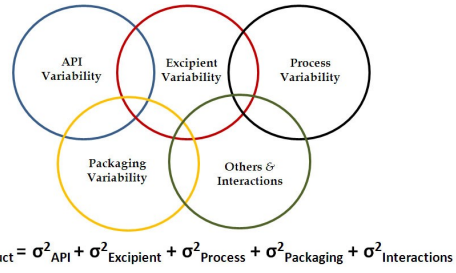

Figure 1: Sources of myriad variability during drug product development

With the consequent growing concern and criticisms, the ICH instituted a series of quality guidances like Q8, Q9, Q10 and Q11, all emphasizing the adoption of systematic principles of Quality by Design (QbD) and Process Analytical Techniques (PAT) as its 21st century quality initiatives. The principal endeavor of ICH has been to accentuate sound science and risk-based understanding of the pharma manufacturing by adopting rational and systematic approaches. Endorsement of such rational paradigms by key global regulatory agencies like USFDA, EMEA, MHRA, Health Canada, TGA and many others is unequivocal testimony to their immense significance for all the potential stake holders, *viz.* patients, industrial scientists and regulators [2-4].

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).

Figure 2: QbD leads to product and process understanding and continual improvement

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.

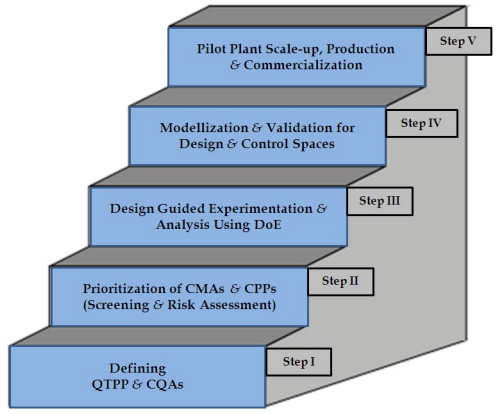

Figure 3: Five-step QbD methodology

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.

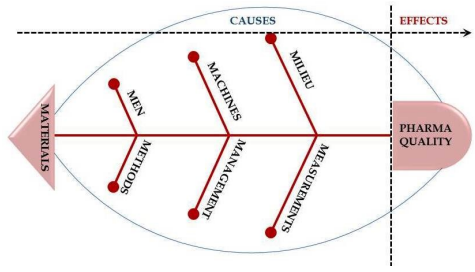

Figure 4: A typical Ishikawa-fish bone diagram depicting sources of variability

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.

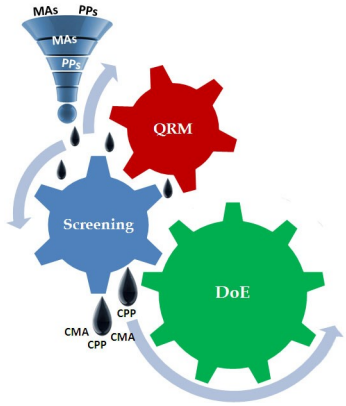

Figure 5: Prioritization using QRM and factor screening is necessary to identify CMAs and CPPs as a prelude to DoE optimization

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.

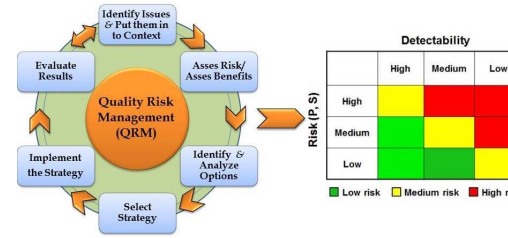

Figure 6: Layout of risk management strategy employing a typical risk estimation matrix

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.

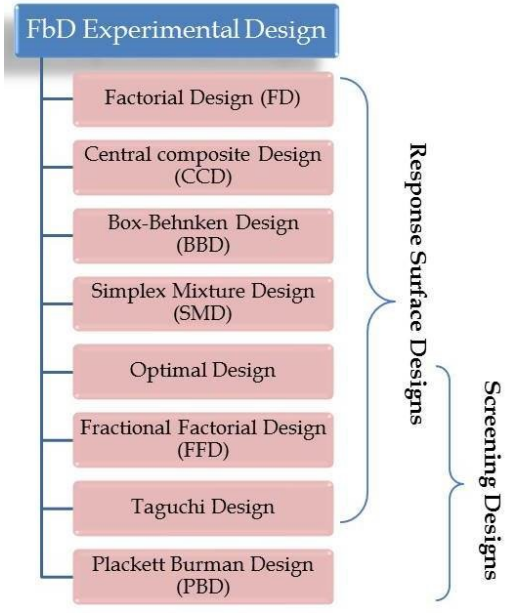

Figure 7: Key instances of experimental designs used during QbD optimization

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 out variable (i.e., CQAs) to discern the optimal solution with assurance of quality.

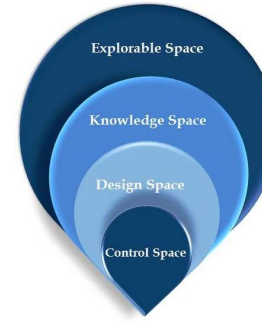

Figure 8: Interplay of knowledge, design and control spaces

Figure 8 illustrates the interrelationship among various spaces like, explorable, 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, iGrafx, etc., can be made use of.

Figure 9: Select computer software used during QbD implementation for product and process optimization

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.

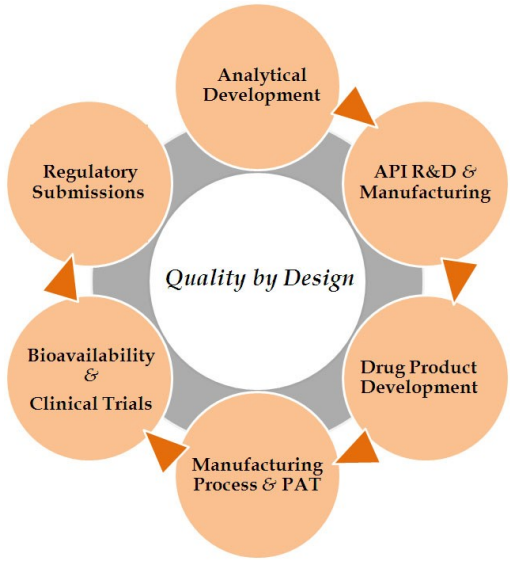

Figure 10: QbD is useful overall product development even after the product launch

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

Drug	QTPP	CFAs/CMAs/CPPs	CQAs	DoE	Ref. No.
Sumatriptan succinate	Mucoadhesive *in situ* gel	Amount of gellan gum, Lutrol F168	*In vitro* drug release, *ex vivo* permeation	FD	[11]
Iloperidone	Nanostructured lipid carriers	Concentration of lipid, drug and surfactant	Particle size, entrapment efficiency	BBD	[12]
Irbesartan	SNEDDS tablets	Amount of oil, surfactant and cosurfactant	Globule size	PCA	[13]
Tamoxifen Quercetin	SNEDDS	Amount of cremophor RH 40, Labrafil 1944 CS and Capmul MCM	Droplet size, PDI, drug content	D-OD	[14]
Curcumin	Nanoemulsion	Amount of oil, surfactant and co-surfactant	Globule size and zeta potential	BBD	[15]
Tamoxifen	Lecithin organogels	Amount of organic phase, water, Pluronic	Viscosity, gel strength, spreadability consistency	D-OD	[16]
Albendazole	Microspheres	Concentration of chitosan, pectin, carboxymethyl cellulose	Yield, encapsulation efficiency, drug release at 30 and 60 min	FD	[17]
Budesonide	Enteric-coated pellets	Amount of water soluble polymer, amount of water-permeable polymer	Drug release at 3 h, time required for 50% and 85% drug release	FFD	[18]
Carvedilol	Solid SNEDDS	Amount of Capmul MCM and Nikkol HCO-50	Globule size, MDT, dissolution efficiency emulsification time	CCD	[19]
Valsartan	Spray-dried microspheres	Inlet temperature, feed-flow rate and drug-polymer ratio	Yield, particle size, *in vitro* diffusion	FD	[20]
Lamivudine	Gastroretentive tablets	Concentration of Carbopol 971P and HPMC	Drug release in 16 h, buoyancy time, bioadhesion strength	CCD	[21]
Carvedilol	SNEDDS	Amount of Cremophor EL and Transcutol HP	Globule size, MDT, emulsification time	CCD	[22]
Quercetin	SLN	Amount of Compritol 888 and Tween 80	Particle size, drug release in 16 h, zeta potential	CCD	[23]
Tramadol	Controlled release bioadhesive tablets	Amount of Carbopol 971P and HPMC	Drug release in 16 h, bioadhesion strength, release exponent	CCD	[24]
Nimesulide	Liposomes	Amount of phospholipid, cholesterol	Percent entrapment, percent diffused, percent leakage	FD	[25]

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

Table 2: Select literature instances on QbD-based development of process(es) during drug product development

Drug	QTPP	CPPs	CQAs	DoE	Ref. No.
Polypeptide antibiotic	Fermentation process	Incubation time, temperature, pH, aeration rate, nitrogen and carbon concentration	Polypeptide concentration	TgD	[26]
Paclitaxel	Nanoparticles	PLGA amount, Surfactant conc., homogenization rate	Particle size, zeta potential, encapsulation	BBD	[27]
Ursodeoxy cholic acid	High-pressure homogenization technology	Pressure, concentration of ursodeoxycholic acid	Particle size	BBD	[28]
Solid dispersion	Spray drying process	Temperature, Concentration, flow rate, atomization	Yield, outlet temperature, particle size	BBD	[29]
Tinospora cordifolia extract	Extraction of alkaloid palmatine	Extraction temperature, time and cycles	Percent yield	CCD	[30]
Nanoparticles	Media milling process	Motor speed, pump speed, bead volume	time, particle size, yield	CCD	[31]
Matrix metallo proteinase-1	PLGA-PCL nanoparticles	Homogenization time, agitation speed and volume of organic to aqueous phase	Particle size, entrapment efficiency	CCD	[32]

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

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.

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.

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

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

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

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 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	MVA	[41]
Torcetrapib	Drug substance development	Concentration of reactants	Assay, % purity of drug & intermediates	CCD	[42]
DCBB	Improve reductive sulfonylation 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]

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_{max}, T_{max}, AUC, AUC_{0-t}, AUC_{∞}, 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

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

[1] New prescription for drug makers: Update the plants. *The Wall Street Journal.* 2003, CCXLII.

[2] Guidance for industry. Pharmaceutical development. FDA CDER. May 2006.

[3] Guidance for industry. Pharmaceutical quality system. FDA CDER. July 2007.

[4] FDA CDER. Guidance for industry. Quality risk management. FDA CDER. June 2006.

[5] Singh B. QbD in Pharma product development life cycle. *Chronicle PharmaBiz.,* 2013, November 28: 72-79.

[6] Singh B, Raza K, Beg S. Developing "Optimized" drug products employing "Designed" experiments. *Chem. Ind. Digest.,* 2013, June: 70-76.

[7] Singh B, Kumar R, Ahuja N. Optimizing drug delivery systems using systematic "design of experiments." Part I: fundamental aspects. *Crit. Rev. Ther. Drug Carrier Syst.,* 2005, 22: 27-105.

[8] Singh B, Kapil R, Nandi M, Ahuja N. Developing oral drug delivery systems using formulation by design: Vital precepts, retrospect and prospects. *Expert Opin. Drug Deliv.,* 2011, 8: 1341-60.

[9] Lionberger RA, Lee SL, Lee L, Raw A, Yu LX. Quality by design: concepts for ANDAs. *AAPS J.,* 2008, 10: 268-76.

[10] Singh B, Beg S, Kapil R, Raza K. Systematic development of carrier-based drug delivery systems employing Formulation by Design (FbD). In: Advancement in carrier based drug delivery, Jain, S.K. (ed.), Biohealthcare publishing Limited: Oxford, UK, In print 2013.

[11] Galgatte UC, Kumbhar AB, Chaudhari PD. Development of in situ gel for nasal delivery: Design,

optimization, *in vitro* and *in vivo* evaluation. *Drug Deliv.,* 2014, 21: 62-73.

[12] Mandpe L, Pokharkar V. Quality by design approach to understand the process of optimization of iloperidone nanostructured lipid carriers for oral bioavailability enhancement. *Pharm. Dev. Technol.,* 2013, [Epub ahead of print].

[13] Patel J, Dhingani A, Garala K, Raval M, Sheth N. Quality by design approach for oral bioavailability enhancement of Irbesartan by self-nanoemulsifying tablets. *Drug Deliv.,* 2013, [Epub ahead of print].

[14] Jain AK, Thanki K, Jain S. Solidified self-nanoemulsifying formulation for oral delivery of combinatorial therapeutic regimen: Part I. Formulation development, statistical optimization and *in vitro* characterization. *Pharm. Res.,* 2013, [Epub ahead of print].

[15] Sood S, Jain K, Gowthamarajan K. Optimization of curcumin nanoemulsion for intranasal delivery using design of experiment and its toxicity assessment. *Colloids Surf. B Biointerfaces.,* 2013, 113: 330-37.

[16] Bhatia A, Singh B, Raza K, Wadhwa S, Katare OP. Tamoxifen-loaded lecithin organogel (LO) for topical application: Development, optimization and characterization. *Int. J. Pharm.,* 2013, 444: 47-59.

[17] Garcia A, Leonardi D, Piccirilli GN, Mamprin ME, Olivieri AC, Lamas MC. Spray drying formulation of albendazole microspheres by experimental design. *In vitro-in vivo* studies. *Drug Dev. Ind. Pharm.,* 2013, [Epub ahead of print].

[18] Raval MK, Ramani RV, Sheth NR. Formulation and evaluation of sustained release enteric-coated pellets of budesonide for intestinal delivery. *Int. J. Pharm. Investig.,* 2013, 3: 203-11.

[19] Singh B, Singh R, Bandyopadhyay S, Kapil R, Garg B. Optimized nanoemulsifying systems with enhanced bioavailability of carvedilol. *Colloids Surf. B Biointerfaces.,* 2013, 101C: 465-474.

[20] Pardeshi CV, Rajput PV, Belgamwar VS, Tekade AR. Formulation, optimization and evaluation of spray-dried mucoadhesive microspheres as intranasal carriers for Valsartan. *J. Microencapsul.,* 2012, 29: 103-14.

[21] Singh B, Garg B, Chaturvedi SC, Arora S, Mandsaurwale R, Kapil R. Formulation development of gastroretentive tablets of lamivudine using the floating-bioadhesive potential of optimized polymer blends. *J. Pharm. Pharmacol.,* 2012, 64: 654-69.

[22] Singh B, Khurana L, Bandyopadhyay S, Kapil R, Katare OO. Development of optimized self-nano-emulsifying drug delivery

systems (SNEDDS) of carvedilol with enhanced bioavailability potential. *Drug Deliv.,* 2011, 18: 599-612.

[23] Dhawan S, Kapil R, Singh B. Formulation development and systematic optimization of solid lipid nanoparticles of quercetin for improved brain delivery. *J. Pharm. Pharmacol.,* 2011, 63: 342–351.

[24] Singh B, Rani A, Babita, Ahuja N, Kapil R. Formulation optimization of hydrodynamically balanced oral controlled release bioadhesive tablets of tramadol hydrochloride. *Sci. Pharm.,* 2010, 78: 303-23.

[25] Singh B, Mehta G, Kumar R, Bhatia A, Ahuja N, Katare OP. Design, development and optimization of nimesulide-loaded liposomal systems for topical application. *Curr. Drug Deliv.,* 2005, 2: 143-153.

[26] Muhammad SA, Ahmed S, Ismail T, Hameed A. Taguchi's experimental design for optimizing the production of novel thermostable polypeptide antibiotic from Geobacillus pallidus SAT4. *Pak. J. Pharm. Sci.,* 2014, 27: 11-23.

[27] Yerlikaya F, Ozgen A, Vural I, Guven O, Karaagaoglu E, Khan MA, Capan Y. Development and evaluation of paclitaxel nanoparticles using a quality-by-design approach. *J. Pharm. Sci.,* 2013, 102: 3748-61.

[28] Li Y, Wang Y, Yue PF, Hu PY, Wu ZF, Yang M, Yuan HL. A novel high-pressure precipitation tandem homogenization technology for drug nanocrystals production - A case study with ursodeoxycholic acid. *Pharm. Dev. Technol.,* 2013, 19: 662-70.

[29] Patel AD, Agrawal A, Dave RH. Investigation of the effects of process variables on derived properties of spray dried solid-dispersions using polymer based response surface model and ensemble artificial neural network models. *Eur. J. Pharm. Biopharm.,* 2013, S0939-6411: 340-48.

[30] Ali H,Dixit S. Extraction optimization of Tinospora cordifolia and assessment of the anticancer activity of its alkaloid palmatine. *Sci. World J.,* 2013, 376216.

[31] Nekkanti V, Marwah A, Pillai R. Media milling process optimization for manufacture of drug nanoparticles using design of experiments (DoE). *Pharm. Dev. Technol.,* 2013, [Epub ahead of print].

[32] Sun P, Song H, Cui D, Qi J, Xu M, Geng H. Preparation and optimization of matrix metalloproteinase - 1 - loaded poly (lactide - co - glycolide - co-caprolactone) nanoparticles with rotatable central composite design and response surface methodology. *Nanoscale Res. Lett.,* 2012, 7: 359.

[33] Reid GL, Morgado J, Barnett K, Harrington B, Wang J, Harwood J, Fortin D. Analytical Quality by Design (AQbD) in pharmaceutical development. *Amr. Pharma. Rev.* 2013, Available online at: http://www.americanpharmaceuticalreview.com/

[34] Orlandini S, Pinzauti S, Furlanetto S. Application of quality by design to the development of analytical separation methods. *Anal. Bioanal. Chem.,* 2012, 405: 443-50.

[35] Suleman S, Vandercruyssen K, Wynendaele E, D'Hondt M, Bracke N, Duchateau L, Burvenich C, Peremans K, De Spiegeleer B. A rapid stability-indicating, fused-core HPLC method for simultaneous determination of beta-artemether and lumefantrine in anti-malarial fixed dose combination products. *Malar. J.,* 2013, 12: 23-31.

[36] Schmidt AH, Molnar I. Using an innovative Quality-by-Design approach for development of a stability indicating UHPLC method for ebastine in the API and pharmaceutical formulations. *J. Pharm. Biomed. Anal.,* 2013, 78-79: 65-74.

[37] Murthy MV, Krishnaiah C, Srinivas K, Rao KS, Kumar NR, Mukkanti K. Development and validation of RP-UPLC method for the determination of darifenacin hydrobromide, its related compounds and its degradation products using design of experiments. *J. Pharm. Biomed. Anal.,* 2012, 72: 40-50.

[38] Janardhanan VS, Manavalan R, Valliappan K. Chemometric technique for the optimization of chromatographic system: Simultaneous HPLC determination of Rosuvastatin, Telmisartan, Ezetimibe and Atorvastatin used in combined cardiovascular therapy. *Arab. J. Chem.,* 2012, [Epub ahead of print].

[39] Awotwe-Otoo D, Agarabi C, Faustino PJ, Habib MJ, Lee S, Khan MA, Shah RB. Application of quality by design elements for the development and optimization of an analytical method for protamine sulfate. *J. Pharm. Biomed. Anal.,* 2012, 62: 61-67.

[40] Grewal NK,Leadbeater NE. The central role of chemistry in 'quality by design' approaches to drug development. *Future Med. Chem.,* 2012, 4: 1799-810.

[41] Eon-duval A, Valax P, Solacroup T, Broly H, Gleixner R, Strat CL, Sutter J. Application of the quality by design approach to the drug substance manufacturing process of an Fc fusion protein: towards a global multi-step design space. *J. Pharm. Sci.,* 2012, 101: 3604-18.

[42] Ende D, Bronk KS, Mustakis J, O'Connor G, Santa Maria CL, Nosal R, Watson TJN. API Quality by Design xxample from the torcetrapib manufacturing process. *J. Pharm. Innov.,* 2007, 2: 71-86.

[43] Chen JJ, Nugent TC, Lu CV, Kondapally S, Giannousis P, Wang Y, Wilmot JT. Rapid improvement of a reductive sulfonylation using Design of Experiment methods. *Org. Process Res. Dev.,* 2003, 7: 313 317.

[44] Larkin JP, Wehrey C, Boffelli P, Lagraulet H, Lemaitre G, Nedelec A, Prat D. The synthesis of 17r-Methyl-11â-arylestradiol: Large-scale application of the Cerium (III)-mediated alkylation of a ketone. *Org. Process Res. Dev.,* 2002, 6: 20 27.

[45] Zhang J, Kirchhoff EW, Zembower DE, Jimenez N, Sen P, Xu ZQ, Flavin MT. Automated Process Research. An Example of Accelerated Optimization of the Friedel-Crafts Acylation Reaction, a Key Step for the Synthesis of Anti-HIV (+)-Calanolide A. *Org. Process Res. Dev.,* 2000, 4: 577 580.