



**REVIEW ARTICLE**

## Optimization and Scale Up of Polymeric Matrix Based Extended Release Tablets Formulations – A Review

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<p><b>Manuscript details</b></p> <p>Submitted on 12.03.2015 Revised on 20.04.2015 Accepted on 12.06.2015 © CJPS All right reserved</p> <p>Columbia Journal of Pharmaceutical Sciences: 2015; 2 (2); April-June, Pages-22-27</p>	<p><b>ABSTRACT:</b></p> <p>Process optimization and scale up is one of the essential elements of technology transfer of Pharmaceutical products from R &amp; D to Pilot plant or commercial level. The major purpose of carrying out PO studies is to identify and control Critical Process Parameters (CPP) for each unit operation of manufacturing process, which should result in a robust, reproducible product with a manufacturing friendly process and desirable quality attributes built into it. The aim of this paper was to discuss the optimization and scale up of polymeric matrix based extended release tablets. Design of experiment (DOE) basis on identified critical quality attributes and critical process parameters play an important role in decision making for performing experimentation to address and mitigate the associated risk with the product and the manufacturing process. Hence help in establishing design space and control strategy. QbD based process optimization and scale up helps into overcoming the failure and also helps in mitigating the associated risk involved in the process.</p>
<p><b>KEYWORDS:</b></p> <p>Optimization, Scale up, Extended Release Tablets, Matrix, Design of experiments</p>	

### 1. INTRODUCTION:

As the development of a new drug product progresses, the batch sizes manufactured generally increase. The early First Time in Man (FTIM) clinical trials commonly involve dosing to a small number of subjects, with the majority of the manufactured product often being required for stability studies and analytical testing. As one proceeds from formulation design to Phase I clinical trials (dose titration study for study the dose range and establishing the proof of concept) and subsequently through to Phase II and III, batch sizes generally increase. Following a successful clinical trial outcome, resulting in the granting of a marketing authorization, the batch sizes manufactured may be further increased to cover the market demands<sup>1</sup>.

Today the development of new product is not a big challenge in the pharmaceutical field, as many of the high end equipment's are available for that. Using different technology the new dosage form development at lab scale is possible and is easier too. But at the same time to scale up the product to large scale for commercialization is a big challenge, as in most of the cases it was not feasible to scale up the product for commercialization like Nanoparticles, Microspheres, Liposomes, Multi unit particulate system (MUPS) etc. either due to instability of such dosage forms, criticality of process in mups or changes in process parameters while scaling up to a larger scale.

Even if the dosage form is being developed based on the QbD approach, while scaling up the product, many issues arise when batch size of product goes on increasing from lab scale to production scale. That time the commercialization feasibility is a big challenge in front of scientist.

Pharmaceutical process scale up deals with the procedures of transferring the results of R&D obtained on laboratory scale to the pilot plant and finally to production scale.

Scale up is generally defined as the process of increasing the batch size. Scale up of a process can also be viewed as a procedure for applying the same process to different output volumes. There is a subtle difference between these two definitions: batch size enlargement does not always translate into a size increase of the processing volume<sup>2</sup>.

In moving from R&D to production scale, it is sometimes essential to have an intermediate batch scale. This is called Pilot scale, which is defined as the manufacturing of drug product by a procedure fully representative of and simulating that used for full manufacturing scale. However, inserting an intermediate step between R&D and production scale does not in itself guarantee a smooth transition. A well-defined process may generate a perfect product in the laboratory and pilot plant and then fail quality assurance test in production.

Currently many guidelines are available which are saying about the scale up and optimization process to be followed in pharmaceutical industries. Typical batch sizes used throughout development as defined in the European Medicines Agency's (EMA) guidance for Process Validation are laboratory-scale, pilot, and production-scale batches<sup>3</sup>.

## 2. LABORATORY-SCALE BATCHES:

These are produced at the research and early development laboratory stage. They may be of very small size (e.g., 100–1000 times less than production scale). Laboratory-scale batches may be used to support formulation and packaging development, early clinical and/or preclinical stages. Laboratory-scale batches can also be analyzed to assist in the evaluation and definition of critical quality attributes (CQAs). A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates, and drug product.

## 3. PILOT-SCALE BATCHES:

These may be used in the process-development or optimization stage. They may be used to support preclinical and mid- to later-stage clinical evaluation and also to support formal stability studies. If supporting formal registration, a pilot-batch size should correspond to at least 10% of the production-scale batch. For oral solid dosage forms, this size should generally be 10% of production scale or 100,000 units, whichever is greater. The choice of pilot scale is often difficult for the project team as members must balance parameters such as anticipated product volumes, anticipated site of production, equipment constraints at that site, and regulatory expectations. With the increasing trend toward developing orphan drugs, the regulatory expectation of pilot-scale batches of 100,000 units is not always valid and should be discussed with the relevant regulatory authority.

## 4. PRODUCTION-SCALE BATCHES:

These batches are of the size that will be produced during the routine manufacturing and marketing of the product. Data on production-scale batches may not always be available prior to granting marketing authorization.

### 4.1 Process optimization (PO)

Process optimization is one of the essential elements of technology transfer of Pharmaceutical products. The major purpose of carrying out PO studies is to identify and control Critical Process Parameters (CPP) for each unit operation of manufacturing process, which should result in a robust, reproducible product with a manufacturing friendly process and desirable quality attributes built into it.

- Thus, Process optimization helps in
- Thorough understanding of the process
- Identifying CPPs and controlling the process accordingly
- Understanding the root cause and addressing the same (PAT)
- Minimizing manufacturability issues
- Minimize cost (by reducing failures)
- Increased efficiency and success rate for manufacturing Exhibit/Validation and hence the launch of the product

The scale up of product depends upon many factors, such as

1. Change in equipment capacity, equipment geometry, make and model, even though the operating principle will be same.
2. Manufacturing site changes i.e. change in facility from R&D to commercial facility or different site including India or abroad.

#### 4.1.1 Approaches to process optimization and scale-up

Pharmaceutical development activities around the scaling-up and optimizing for pilot- or commercial-scale manufacture should include, at a minimum, the following elements:

- Defining the target product profile as it relates to quality, safety and efficacy, considering, for example, the route of administration, dosage form, bioavailability, dosage, and stability
- Identifying CQAs of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled
- Determining the quality attributes of the drug substance and excipients, and selecting the type and amount of excipients to deliver drug product of the desired quality and efficacy
- Selecting an appropriate manufacturing process
- Where possible, identifying a control strategy

Being an extended release tablets containing polymeric matrix system, it was difficult to optimize and scale up the process. The wet granulation process is the most critical process step in matrix system, where the factors like binder selection (aqueous or non-aqueous) and binder quantity, binder addition method (pouring, sprinkling using sprinkler or spraying using spray gun), kneading time plays an important role and leads to change in behavior of tablets in terms of granules property (granules particle size, geometry, granules to fine ratio etc.) which ultimately affect the downstream process of tablet compression issues (like individual weight variation, sticking, picking, hardness etc.), dissolution profile etc.

Matching the dissolution profile with the innovator sample in-vitro and in-vivo is much of importance in case of extended release tablets to achieve and maintain the desired therapeutic efficacy for prolonged duration of time to provide the patient compliance in terms of dosing frequency, to minimize the fluctuation of drug content in systemic circulation.

To address all these issues, the designing of experiment part to cover all the associated risk and mitigate the same is important. Before experimental design it is mandatory to have a Technical risk assessment (TRA) and Failure mode effective analysis (FMEA) in place to address the risk associated with the process and mitigation plan. The risk assessment to be kept on updating with the completion and outcome of each step. The risk assessment stages to be followed as

- a) Initial technical risk assessment after formulation development and before process optimization and development.

- b) Post technical risk assessment (after Scale up, Confirmatory or Exhibit batches).
- c) The risk register to be prepared and updated with the outcome with and after each process steps to keep tracking on the identified risk and mitigation plan.

#### 5. PRESENT STATUS:

Currently many guidelines are in existence, which are explaining about the optimization, scale up and commercialization of the dosage forms. Process validation guideline implemented recently in the year January 2011 with title "Process validation – General Principles and Practices" which describes the general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (APIs or drug substances).

This guidance incorporates principles and approaches that all manufacturers can use to validate manufacturing processes.

This guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonisation (ICH) guidance for industry, Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System. FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle.

#### 6. REGULATORY ASPECTS:

Any significant change in a process of making a pharmaceutical dosage form is a regulatory concern. Post approval changes in the batch size of a batch from pilot scale to larger or smaller production scale call for submission of additional information in the application. Manufacturing changes may require new stability, dissolution and in vivo bioequivalence testing.

#### 7. WORK DONE ON EXTENDED RELEASE PRODUCT:

Skelly *et al* (1993) documented that need for quality control to assure reproducibility of finished product performance for extended release products is essential. To end this, the unit operations for the scale up, i.e. milling, blending, granulating, drying or coating should be maintained. Any changes in process conditions must be justified through measurement of the impact of measurable variables, such as spray rate, temperature. Rotational speed, air velocity, cooling times, blending

time and feed rates on the quality and performance of the finished product<sup>4</sup>.

Tiwari *et al* (2008) reported that oral drug delivery is the largest and the oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration. Use of hydrophilic matrices for oral extended release of drugs is a common practice in the pharmaceutical industry. This chapter presents different polymer choices for fabrication of monolithic hydrophilic matrices and discusses formulation and manufacturing variables affecting the design and performance of the extended-release product by using selected practical examples<sup>5</sup>.

Patel *et al* (2009) investigated different grades of hydroxypropyl methyl cellulose for gel forming properties. The effects of polymer concentration on drug release profile was investigated. A 3<sup>2</sup> full factorial design was applied to systematically optimize the drug release profile. The amount of HPMC K-100M and HPMC K-4M were selected as independent variables. Cumulative % release of drug at 1<sup>st</sup> hour and 8<sup>th</sup> hour were selected as dependent variable. The results of the full factorial design indicated that a low amount of HPMC K-100M and high amount of HPMC K-4M favors sustained release of theophylline from matrix tablets. Finally process optimization was carried out to optimize the process parameters like kneading time, mixing time, thickness of tablet and lubrication time<sup>6</sup>.

Bose *et al* (2013) developed and formulated sustained release (SR) matrix tablets of Itopride HCl, by using different polymer combinations and fillers, to optimize by Central Composite Design response surface methodology for different drug release variables and to evaluate drug release pattern of the optimized product. Sustained release matrix tablets of various combinations were prepared with cellulose-based polymers: hydroxy propyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP) and lactose as fillers. Study of pre-compression and post-compression parameters facilitated the screening of a formulation with best characteristics that underwent here optimization study by response surface methodology (Central Composite Design). The optimized tablet was further subjected to scanning electron microscopy to reveal its release pattern. The *in vitro* study revealed that combining of HPMC K100M (24.65 MG) with PVP (20 mg) and use of Lactose as filler sustained the action more than 12 h. The developed sustained release matrix tablet of improved efficacy can perform therapeutically better than a conventional tablet<sup>7</sup>.

Singh *et al* (2012) evaluated formulation and evaluation of sustained release (SR) pellets of furosemide for oral administration prepared by extrusion/spheronization. Drug Coat L-100 was used within the pellet core along with microcrystalline cellulose as the diluent and concentration of selected binder was optimized to be 1.2%. The formulation was prepared with drug to polymer ratio 1:3. It was optimized using Design of Experiments by employing a 3<sup>2</sup> central composite design that was used to systematically optimize the process parameters combined with response surface methodology. Dissolution studies were carried out with USP apparatus Type I (basket type) in both simulated gastric and intestinal pH. The statistical technique, i.e., the two-tailed paired t test and one-way ANOVA of *in vitro* data has proposed that there was very significant ( $P \leq 0.05$ ) difference in dissolution profile of furosemide SR pellets when compared with pure drug and commercial product. Validation of the process optimization study indicated an extremely high degree of prognostic ability. The study effectively undertook the development of optimized process parameters of pelletization of furosemide pellets with tremendous SR characteristics<sup>8</sup>.

Swetha *et al* (2008) developed and optimized Aceclofenac SR matrix tablets by direct compression technique. It was composed of two different ratios of waxes. The optimization was carried out by using 3<sup>2</sup> factorial designs with Design Expert Software. IR studies revealed that drug and the waxes are compatible with each other. The tablets were subjected for various evaluations like pre and post compression parameters. All the parameters are within the limits. The release profile showed that as the concentration of bees wax increases the drug release decreases and it was not steady after definite concentration of bees wax. This may be due to poor binding between the drug and waxes. The formulation (F7) with the ratios of 0.31:0.15 bees and lanette waxes respectively show best sustained release and flow property. The dissolution profile showed 58.74% at 8th hr. It was observed that the bees and lanette waxes fulfilled the conditions for an optimum formulation for sustained release<sup>9</sup>.

Huang *et al* (2004) developed propranolol extended release formulations containing hydroxypropyl methylcellulose (HPMC). The results indicate that the drug release from the tablet form containing a high amount of HPMC was incomplete, and avicel addition could increase the release percent at a later stage. In order to readily obtain an optimal formulation, response surface methodology and multiple response optimization utilizing a quadratic polynomial equation was used. The model formulations were prepared according to a factorial design. The effects of causal factors including

the HPMC/drug ratio (X1) and avicel level (X2), on drug release were also measured. The drug release percentage at 1.5, 4, 8, 14 and 24 h were the target response and were restricted to not more than 25%, 35—50%, 55—70%, 75—90%, and 95—110%, respectively. The results showed that the optimized formulation provided a dissolution pattern equivalent to the predicted curve, which indicated that the optimal formulation could be obtained using response surface methodology. The mechanism of drug release from HPMC matrices tablets followed quasi-Fickian diffusion<sup>10</sup>.

Modi *et al* (2010) formulated sustained release tablets of Diltiazem hydrochloride by employing hydroxypropyl methylcellulose (HPMC K100 M) and the sustained release behaviour of the fabricated tablets was investigated. Sustained release matrix tablets containing 120 mg Diltiazem hydrochloride were developed using different drug: polymer (HPMC K100 M) ratios. Tablets were prepared by wet granulation technique. Formulation was optimized on the basis of acceptable tablet properties and *in vitro* drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low friability. All tablets but one exhibited gradual and near-complete sustained release for Diltiazem hydrochloride (96-100%) at the end of 24 h. The results of dissolution studies indicated that formulation B5 (drug to polymer 1:1.25) was found to be most successful as it exhibits drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio<sup>11</sup>.

Kshirsagar *et al* (2014) documented the pharmaceutical QbD for formulation development with a case study of sustained release (SR) tablet of Opipramol. The QbD means designing and developing formulations to ensure predefined product quality. The study describes elements of the QbD for Opipramol SR tablet, include: Defining quality target product profile, identifying critical quality attributes, establishing design space, control strategy. SR tablet of Opipramol was prepared by dry granulation using hydroxypropyl methylcellulose K4M and level of polymer was optimized, factorial design was used as part of risk analysis to optimize the level of other excipients. *In vivo* study of optimizes, formulation was done in animals, and it was correlated with *in vitro* drug release study in vivo-in vitro correlation (IVIVC). The optimized formulation could able to release the drug for 24 hrs making once a daily tablet, design space for polymer was determined to be (10-15%), level of flow property enhancer and hardness of 4-5 which ensure extended drug release. The IVIVC shown level A correlation ( $R^2=0.996$ ). Thus the work facilitates the adoption and implementation of QbD for formulation development using QbD and could increase efficiencies, provide

regulatory support, flexibility and pharmaceutical quality is assured by understanding and controlling formulation variables<sup>12</sup>.

Sahoo *et al* (2011) developed device a model of factors that would yield an optimized sustained release dosage form of model drug (Ranitidine HCl), 2) to validate the models using  $R^2$  values, 3) to optimize the formulation by response surface methodology (RSM). A three - factor, three - level Box-Behnken design was used for the optimization procedure, with the amounts of HPMC K100M (X1), MCC (X2) and Compression Force (X3) as independent variables. Three dependent variables were considered: percentage of drug release at 1 h, 12 h and T50%. The regression equation obtained from experiment i. e  $Y_2 = 92.41 + 3.18X_1 + 2.05 X_2 + 2.14X_3 + 2.41X_1X_2 + 0.24 X_1X_3 + 0.11 X_2X_3 - 3.82X_1^2 - 2.59X_2^2 - 0.46X_3^2$ , explained the main and interaction effects of factors that influenced the drug release. Optimization was performed by maximizing the drug release in 12 hrs and placing constraints on Y1, Y2 and Y3. Validation of optimization by carrying out by performing 8 experimental runs showed high degree of prognostic ability of response surface methodology. The results showed that the optimized formulation provided a dissolution pattern similar to the predicted curve, which indicated that the optimal formulation could be obtained using RSM. A simple high performance liquid chromatography method was developed and the dissolution samples were analysed by this procedure<sup>13</sup>.

## 8. CONCLUSIONS:

QbD based optimized process which helps into overcoming the failure and also helps in mitigating the associated risk involved in process. Trouble shooting of all the scale up challenges during the product transfer from R&D to plant. Successful execution and transfer of product from R&D to Plant for commercialization. Stability study to support filling of product to regulatory agency for marketing authorization.

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