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Research Article

# DESIGN AND OPTIMIZATION OF SUSTAINED RELEASE MATRIX TABLET OF OPIPRAMOL HCL BY USING QUALITY BY DESIGN APPROACH

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**ABSTRACT**

Quality by design (QbD) refers to an advanced approach toward drug development. QbD is a vital part of the modern approach to pharmaceutical quality. There is much confusion among pharmaceutical scientists in generic drug industry about the appropriate element and terminology of QbD. The purpose of this paper was to discuss 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.

**Keywords:** Quality by design, Sustain release, Opipramol HCl, Risk assessment.

## INTRODUCTION

"Quality by design (QbD)" concept was first outlined by well-known quality expert Joseph M. Juran on QbD (J.M.: "Juran on QbD,"). In the late 1990 Food and Drug Administration internal discussion began and in the year 2002 the concept paper on 21st century Good Manufacturing Practice was published. With the assistance of several biopharmaceutical companies, pilot programs were started to explore QbD application and understandings [1,2].

The traditional quality by testing (QbT) approach tests product quality by checking it against the approved regulatory specifications at the end of manufacturing stream at great effort and cost. There is a great deal of unpredictability in scaling up a product from research and development to production scale, and reasons for failure are generally not understood. QbD is a major shift from the traditional approach of QbT in ensuring quality control of products across the manufacturing stream. QbD principles promote innovation and continuous improvement of the product. Knowledge-based commercial manufacturing ensures enough regulatory flexibility for setting specifications and post-approval changes. Product and process are designed using innovative risk-based techniques to meet predefined quality objectives thereby satisfying the most critical patient needs and regulatory requirements at low cost [3].

Opipramol is an iminostilbene derivative belonging to the dibenzazepine group. Although belonging to tricyclic anti-depressant. Opipramol is freely soluble in water and alcohol also. The elimination half-life is approximately 11 hrs. The active ingredient is eliminated over 70% renaly and 10% in uncharged form. The, usually, recommended daily dose of opipramol in adults is 50 mg in the morning, in the afternoon and 100 mg in evening. The dosage of Opipramol can be increased up-to 100 mg thrice daily depending on its efficacy and tolerability [4].

Therefore dosage regime of conventional tablet of Opipramol of 50 mg and 100 mg are available in Indian market as twice and thrice a day, therefore there is need to formulate once daily sustained release (SR) tablet of Opipramol Hcl which is convenient from patient compliance point of view.

QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality target product profile (QTPP) provides initial quality of the product which is implemented in the first step of QbD. And then critical quality attributes (CQA) provides attributes that can affect the quality of the product. Then risk assessment for formulation attribute that was reduced in formulation development studies followed Optimization of the formulation by changing the concentration of the release retarding polymer has been carried out. SR matrix tablet of Opipramol HCl was prepared successfully from which, it has been observed that hydroxypropyl methycellulose (HPMC) K4M alone can be promising polymer for SR drug delivery systems. As the polymer concentration increases, there is retardation in amount of drug release from matrix system this is due to the formation of barrier layer gel. Design space was provided after formulation a study that gives the ranges of formulation and process attributes in which one can make a quality product. Design spaces followed by control strategy that provide optimize conditions for process and formulation attributes to impart quality product for Opipramol HCl SR tablets. *In vivo* study supported SR pattern of the matrix formulation. The formulation has the potential to liberate drug following diffusion mechanism having good degree of *in vitro-in vivo* correlation (IVIVC).

## MATERIALS

Opipramol was gifted from Sun Pharma (Mumbai, India). HPMC K4M, K15M was gifted from Colorcon. Talcum (Patel Industries, Ahmedabad, India), and magnesium stearate (Faci Asia Pacific Pte Ltd., Singapore) were USP grade. All other chemicals and solvents were of analytical grade. JMP® (SAS Campus Drive, Building T, Cary, NC, 27513).

## METHODS

### Analytical method development

A standard stock solution of Opipramol HCl was prepared by dissolving accurately weighed 10 mg of Opipramol HCl in 10 ml of water (1000 µg/ml). Appropriate dilutions were prepared to obtain 50 µg/ml solution. Spectrum was taken, and $\lambda_{max}$ was determined. Method development and validation were done as per ICH guidelines including parameters such as linearity and range, precision, accuracy, specificity, robustness, limit of detection, limit of quantitation and assay [5].

### Preformulation studies

Opipramol HCl received was studied for organoleptic characters such as color, odor, appearance and melting point [6].

### Study of QTPP for formulation

The QTPP is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." The QTPP is an essential element of a QbD approach and forms the basis of design of the generic product. The QTPP is a quantitative substitute for aspects of clinical safety and efficacy. QTPP includes, but not limited to dosage form, route of administration, strength, release or delivery of the drug, pharmacokinetic (PK) characteristics: e.g. dissolution [7].

### Study of CQA of formulation and process

It was stated that the ICH working definition of CQA was: "A CQA is a quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure that the product meets its intended safety, efficacy, stability and performance."

CQA's are identified on the basis of the effect of quality attribute safety, efficacy of the formulation on patient. It is necessary to identify the quality attributes that are critical, i.e. those defining purity, potency and surrogate for bioavailability criticality etc. It is based on the impact of quality attribute/parameter on the safety, efficacy and quality (manufacturability) of the product [7].

#### *Excipient compatibility studies*

A compatibility study of drug with excipients is an early risk reduction strategy which precludes the use of excipients, which may interact with the drug substance.

Drug was triturated with individual excipients in 1:1 ratio with and without water (%). The samples were stored for 4 weeks at 40°C/75% RH and 30°C/65% RH, analyzed for drug content and impurities using stability indicating high-performance liquid chromatography (HPLC) method (U.S. Pharmacopeial Convention, 2007) [8].

### Risk assessment for drug substance attributes

According to ICH Q9 Quality Risk Management, it is important to note that "it is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures e.g. standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators." All formulation and process parameters are evaluated for risk by using failure mode and effects analysis (FMEA) method [9]. Based on the physicochemical and biological properties of the drug substance, the initial risk assessment of drug substance attributes on drug product CQAs classified into 3 classes low, medium, high.

#### *Initial risk assessment of formulation variable*

In this initial risk assessment for formulation development, the detailed manufacturing process has not been established. Thus, risks were rated assuming that for each formulation attribute that changed, an optimized manufacturing process would be established. For these studies, polymer level in the formulation as well as talc and magnesium stearate levels are considered as formulation variables while hardness is considered as process variable and risk assessment had been discussed [7].

### Formulation development

#### *Effect of polymer concentration*

In initial risk assessment of the formulation variables, risks were rated assuming that for each formulation attribute that changed, an optimized manufacturing process would be established. The goal of formulation development study #1 was to select the polymer level and dissolution level, to understand the interaction of these variables and evaluation of the impact of the polymer substance to the dissolution level. Selection of polymer was done after trials of various polymers like HPMC K4M, K15M and CPS in different ratios [4]. Finally, only single polymer K4M was used for formulation of SR tablet because it showed the release of drug from the formulation as stated in QTPP. Various materials selected for good tableting purpose include talc and magnesium stearate which is hydrophobic in nature was used as a lubricant. The dry blend has shown excellent flow and compression properties.

Direct compression method was used for tablet preparation to avoid problems observed in wet granulation technique like color change in granules after exposing to heat (as the drug is sensitive to temperature), very low hardness etc. (F1-F11). All the above trial batches were failing in hardness and dissolution studies with concern to QTPP. Only formulation containing HPMC K4M polymer was surviving in hardness and dissolution testing.

For determining levels of HPMC K4M, trial batches with different concentrations of HPMC K4M were prepared and evaluated for physiochemical properties and dissolution studies. In the trial runs, HPMC K4M concentration was varied from 25% to 75% of weight of active pharmaceutical ingredients (API) present in total formulation and then evaluated for hardness, friability, weight variation and finally for dissolution testing (F12, F13, F14). The formulated batches were evaluated for hardness, friability, weight variation and finally for dissolution testing.

*In-vitro* dissolution study

*In-vitro* drug release study of the samples was carried out using USP - Type II dissolution apparatus (peddle type). The dissolution medium, 900 ml of pH 7.4 phosphate buffer solution, was placed into the dissolution flask maintaining the temperature of 37±±0.5°C and rpm of 100. One Opipramol HCl matrix tablet was placed in each flask of the dissolution apparatus. The apparatus was allowed to run for 24 hrs. Samples measuring 5 ml were withdrawn after every 2 hrs up to 24 hrs manually, and samples were filtered. The fresh dissolution medium was replaced every time with the same quantity of the sample withdrawn. Collected samples were analyzed at 258 nm using pH 7.4 phosphate buffer solutions as blank. The cumulative percentage drug release was calculated using PCP Disso v3 software (Bharti Vidyapith, Pune) [4,10-13].

#### *Effect of talc and magnesium stearate level*

Formulation development focused on evaluation of the medium risk formulation variables as identified in the initial risk assessment. The goal of Formulation Development Study #2 was to select the magnesium stearate and talc level to friability, dissolution time and so to understand the interaction of these variables. Thus, the extra granular magnesium stearate level was studied between 0.5% and 1.5%. The talc level was adjusted accordingly to maintain a total of 3.5% extra granular glidant and lubricant with $3^2$ factorial designs of experiment (DOE) [3].

#### *Effect of hardness*

Formulation study was carried out to evaluate the impact of the hardness level to the dissolution time of product on the drug product CQAs. The goal of Formulation Development Study #3 was to select

the level of hardness, so to understand the interaction of this variable with dissolution period. The batches are carried out with different hardness level as 4, 5 and 6 kg/cm$^2$ and its impact on dissolution time was studied (F15, F16 and F17). A significant difference in dissolution period is observed with difference in hardness of tablet. After 16 hrs % release was recorded.

**Updated risk assessment of formulation variable**

Based on the results of the formulation development studies, the risk assessment of the formulation variables was updated [7].

**Defining design of space**

It consists of the established range of process parameters that have been demonstrated which provide assurance of quality. The change emphasizes the multidimensional interaction of input variables and closely binds the establishment of a design space to a conduct of a DOE that includes interactions among the input variables. A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process [7].

**Defining control strategy**

It consists of the planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to: Drug substance, drug-product materials and components, facility and equipment operating conditions, in-process controls, finished-product specifications, the associated methods [7].

***In-vivo* studies**

*In vivo* PKs studies were approved by Institutional Animal Ethics Committee and AISSMS College of Pharmacy, Pune. Male rabbits with weight of 1.5 kg and age of 12 months were selected. The 6 rabbits were divided into 3 groups. Each group consists of 2 rabbits. The animals were housed individually under environment conditions (25°, 12 hrs light and dark cycle). The rabbits were fasted overnight and allowed free accesses to water only. The optimum formulation was selected for *in vivo* studies. The formulations were administered orally by placing the tablet in a hollow polyethylene tube. A tube was inserted into the mouth of the rabbit and blown using rubber bulbs. The test formulations were administered to the rabbits by gastric intubation method [14]. 1 ml of blood samples were withdrawn from the marginal ear vein of the rabbit at various time intervals (2, 4, 8, 12 and 24 hrs). The plasma samples were separated by centrifugation; drug was extracted and then assayed by ultraviolet (UV)-HPLC studies.

Blood sample from marginal ear vein of the rabbit was collected in screw capped ethylenediaminetetraacetic acid (EDTA) tubes at predetermined time intervals. After collection, blood samples were immediately centrifuged for 10 minutes 10,000 rpm and separated plasma was stored in screw capped polypropylene tubes at −5°C till analysis. To each tube 0.5 ml of plasma was added, 1 ml of acetonitrile for protein precipitation, 0.5 ml of internal standard. The contents of the tube were vortex mixed for 3 minutes and then centrifuged for 5 minutes at 2500 rpm. The contents of the tubes were then injected into the HPLC system. Agilent HiQsil C18 column (250×4.6 mm, 5 µ) protected with guard column was used for analysis with 20 mM ammonium acetate: 20 mM acetic acid: acetonitrile (24:6:70) as mobile phase. Detection wavelength was 258 nm [15].

The $C_{max}$ (peak plasma concentration) and $T_{max}$ for test formulations were obtained directly from the plasma concentration time curves. Area under curve (AUC) area under the concentration-time curve ($AUC_{0-t}$) within a dosage interval was calculated by the linear trapezoidal rule. The terminal phase elimination rate constant ($K_{el}$) was estimated from the terminal phase of the plasma concentration-time curve using log linear regression. $AUC_{t-\infty}$ was calculated as $AUC_{t-\infty}$=Concentration of the drug obtained at last time interval/$K_{el.}$ Total AUC was calculated as Total AUC=$AUC_{0-t}$+$AUC_{t-\infty}$. Half-life of the drug ($t_{1/2}$) was calculated as $t_{1/2}$= 0.693/$K_{el}$. Individual concentrations of tramadol HCl in rabbit plasma for marketed and test formulation are listed. Concentration in µg/ml was plotted against time in hours [16].

**IVIVC Studies**

An IVIVC that correlates the entire *in vitro* and *in vivo* profiles has regulatory relevance and is called a level a correlation. This level of correlation is the highest category of correlation and represents a point-to-point relationship between *in vitro* dissolution rate and *in vivo* input rate of the drug from the dosage form [17] level a correlation is the most preferred to achieve; since it allows bio waiver for changes in manufacturing site, raw material suppliers, and minor changes in formulation. The purpose of level a correlations to define a direct relationship between *in vivo* data such that the measurement of *in vitro* dissolution rate alone is sufficient to determine the biopharmaceutical rate of the dosage form. Application of the de-convolution of *in-vivo* plasma profile by a model independent method such as the Wagner–Nelson method to estimate the *in vivo* percent drug absorbed from the cumulative AUC, followed by comparison if *in vivo* fraction of drug absorbed on Y-axis to *in vitro* fraction of drug dissolved on X-axis with three different batches of tablet having different dissolution profile Further linear correlation between concentration and absorbance were established for pooled mean data of formulations from Y=mX+c where Y is concentration; X is absorbance. For the model r was determined where r=1 indicates a linear relationship with good IVIVC.

## RESULT AND DISCUSSION

UV spectroscopy study, the maximum absorbance at wavelength ($\lambda_{max}$) of Opipramol HCl in water was found to be 258 nm. The reported $\lambda_{max}$ of Opipramol HCl in water is 258 nm. Table 1 shows a summary of validation studies.

**Preformulation studies**

Opipramol HCl received was studied for organoleptic characters such as color, odor, appearance and melting point. Table 2 shows results of organoleptic properties of received sample of Opipramol HCl were found to be similar as per RLD. Table 2 shows results of organoleptic properties.

**Study of QTPP for formulation**

The QTPP is contains a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

QTPP was performed on diclofenac sodium, based on the clinical and PK characteristics as well as the *in vitro* dissolution and physicochemical

**Table 1: Summary of validation studies**

| Validation parameter | Opipramol HCl |
|---|---|
| ($r^2$) | $r^2$=0.998 |
| Range | 10-35 µg/ml |
| Precision (% RSD) | 0.18% |
| Accuracy (% recovery) | Within limits (100±2%) |
| Limit of detection | 0.14 µg/ml |
| Limit of quantitation | 0.56 µg/ml |
| Specificity | Specific |
| Robustness | Robust |

RSD: Relative standard deviation

**Table 2: Results of organoleptic properties**

| Appearance | Bulk powder |
|---|---|
| Color | Yellow |
| Odor | Odorless |
| Melting point | 290-292°C |
| Solubility | Freely soluble in water and organic solvents like methanol |
| Assay | 99.55% |

characteristics of the formulation that we needed, in final quality product. Table 3 shows QTPP for Opipramol HCl sustains release tablet.

**Study of CQA of formulation and process**

Identification of CQAs was done through risk assessment as per the ICH guidance Q9. Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments. Such knowledge may also include relevant data from similar molecules and data from literature references. This information provides a rationale for relating the CQA to product safety and efficacy. The use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm. CQA's are identified on the basis of the effect of quality attribute safety, efficacy of the formulation on patient. Table 4 shows the CQA's for Opipramol HCl SR tablet.

*Excipient compatibility studies*

Comparison between Opipramol HCl, combination of Opipramol HCl-excipients was done by using infrared (IR) spectrophotometry. It was observed that there was no interference of excipients with pure Opipramol HCl, as there is no variation was observed in IR spectrum of Opipramol HCl, combination with HPMC-talc with magnesium stearate. Hence, the excipient was compatible with drug.

**Risk assessment for formulation attributes**

The assessment of factors including particle size distribution, polymer, talc and magnesium stearate which could affect quality and efficacy of drug formulation was done by studying parameters like assay, content uniformity and dissolution, by using FMEA method. Tables 5 and 6 show risk assessment for formulation variables and justification for risk assessment respectively.

**Formulation development**

*Effect of polymer concentration*

The first formulation study evaluated the impact of the polymer substance to the dissolution level on the drug product CQAs. The goal of Formulation Development Study #1 was to select the polymer level and dissolution level and to understand interaction of these variables. This study also sought to establish the robustness of the proposed formulation.

Due to low flow properties of pure drug, batches F1-F6 were carried out by using wet granulation technique by using different polymers and their but there were problems in hardness of tablet and there was color change in granules after exposing to heat as the drug is sensitive to temperature and photo stability. F1-F11 trial batches were failing in hardness and dissolution studies with concern to QTPP. Only formulation containing HPMC K4M polymer was surviving in hardness and dissolution testing. So, for determining levels of HPMC K4M trial batches with different concentrations of HPMC K4M were prepared and evaluated for physicochemical properties and dissolution studies. In the trial runs, HPMC K4M concentration was varied from 25, 50 and 75% of weight of API present in total formulation F12, F13 and F14 (Table 7), then evaluated for hardness, friability, weight variation, thickness, assay and dissolution testing.

Evaluation of formulated batches F12-F14

All batches were passed in evaluation parameters.

In-vitro studies

After 24 hrs formulated batch F12 shows 95% release while F13 and F14 batches are shows total release of drug within 18 hrs from which we can conclude that as there is increase in polymer concentration, the release of drug sustains from formulation. Fig. 1 shows graphical representation of drug release from F12 to F14 formulation batches.

*Effect of talc and magnesium stearate level*

Two important factors which can affect tablet quality is level of glidant and lubricant with respect to friability and dissolution profile. The level of these variables was varied based on $3^2$ factorial design by keeping hardness, level of polymer constant and varying level of magnesium stearate as well as talcum level in tablet. Fig. 2 shows a counter plot for effect of talc and magnesium stearate on friability.

It was found that both variable level (i.e. of magnesium stearate as well as talcum level) affects friability losses but these losses observed within limit i.e. <1% for all formulations.

And with respect to dissolution profile % release after 16 hrs, it was found that there is no significant effect of levels of talc and magnesium stearate on dissolution profile % release of drug after 16 hrs, as all batches formulated under $3^2$ formulation design shows nearby %

**Table 3: QTPP for Opipramol HCl sustain release tablet**

| QTPP | Target | Requirement |
|---|---|---|
| Dosage form | Tablet | Pharmaceutical equivalence requirement: Same dosage form |
| Dosage design | Sustained release matrix tablet | Sustained release design needed to meet label claims |
| Route of administration | Oral | Pharmaceutical equivalence requirement: Same route of administration |
| Dosage strength | 178.8 mg | Pharmaceutical equivalence requirement: Same strength |
| Pharmacokinetics | Absorbed throughout GIT | Bioequivalence requirement needed to ensure rapid onset and efficacy |
| Stability | At least 24-month shelf-life at room temperature | Equivalent to or better than RLD shelf-life |
| Drug product quality attributes | Physical attributes | Pharmaceutical equivalence requirement: Must meet the same compendia or other applicable (quality) standards (i.e., identity, assay, purity, and quality) |
| | Identification | IR |
| | Assay | 100% w/w of label claim |
| | CU | More than 90% |
| | Dissolution | Sustained but complete drug release can be displayed in phosphate buffer. (pH 7.4) |
| Container closure system | Container closure system qualified as suitable for this drug product | Needed to achieve the target shelf-life and to ensure tablet integrity during shipping |
| Administration/ concurrence with labeling | Similar food effect as RLD | RLD labeling indicates that a high fat meal increases the AUC and Cmax by 8-12%. The product can be taken without regard to food |
| Alternative methods of administration | None | None are listed in the RLD label |

GIT: Gastrointestinal tract, IR: Infrared, AUC: Area under curve

**Table 4: The CQA's for Opipramol HCl SR tablet**

| Drug product | Target | Is this a CQA? | Justification |
|---|---|---|---|
| Physical attributes | Appearance<br>Color and shape acceptable to the patient. No visual tablet defects observed | No | Color, shape and appearance are not directly linked to safety. And efficacy. Therefore, they are not critical. The target is set. To ensure patient acceptability |
| | Odor<br>No unpleasant odor | No | In general, a noticeable odor is not directly linked to safety and efficacy, butodor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process |
| | Size<br>Similar to RLD | No | For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD |
| | Weight variation<br>NMT 2 tablets should out of the range of ±10% of 178 mg | Yes | It is carried out when the tablet has 90-95% of active ingredient. This test need not to be done for potent drug because this test is not sufficient to assure uniform potency of tablet of moderate/low drug dose in excipients make up bulk of tablet weight |
| | Hardness<br>NLT 5 kg/cm$^2$ | Yes | It is the valuable parameter which might influence tablet disintegration |
| | Friability<br>NMT 1.0% w/w | No | Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints |
| Identification | Positive for Opipramol HCl | Yes | Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development |
| Assay | ≥98% w/w of label claim | Yes | Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development |
| CU | More than 90% | Yes | Variability in CU will affect safety and efficacy. Both formulation and process variables impact CU, so this CQA will be evaluated throughout product and process development |
| Dissolution | Sustained but complete drug release can be displayed in phosphate buffer. (pH 7.5) | Yes | Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development |

**Table 5: Risk assessment for formulation variables**

| Drug product CQA | Polymer (HPMC) | Talc level | Magnesium stearate level |
|---|---|---|---|
| Assay | Low | Low | Low |
| CU | Medium | Low | Low |
| Dissolution | High | Low | Low |

HPMC: Hydroxypropyl methycellulose, CQA: Critical quality attributes

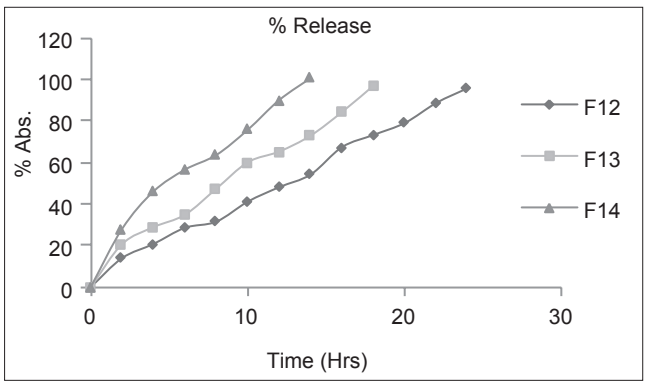


**Fig. 1: Graphical representation of drug release from F12-F14 formulation batches**

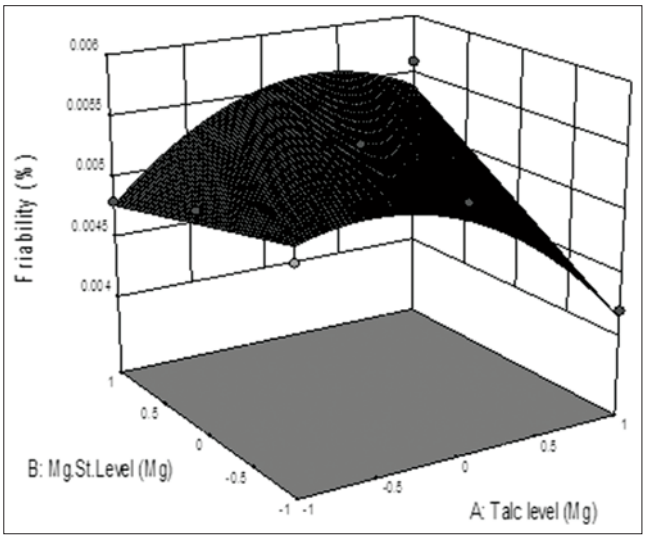


**Fig. 2: A counter plot for effect of talc and magnesium stearate on friability**

release within 24 hrs. Fig. 3 shows % release for 1-9 batches by using $3^2$ factorial design while Fig. 4 shows a counter plot for effect of talc and magnesium stearate on dissolution profile.

**Table 6: Justification for risk assessment for formulation development respectively**

| Formulation variables | CQA's | Justification |
|---|---|---|
| Polymer (HPMC) level | Assay | Polymer can impact the flow properties of the blend. This, in turn, can impact tablet CU. The risk is high. Occasionally, poor CU can also adversely impact assay. The risk is medium |
| | CU | |
| | Dissolution | Release of drug from tab depends on the amount of polymer in formulation so the risk is high |
| | Degradation | Polymers are compatible with the drug substance and will not impact drug product degradation, the risk is low |
| Talc level | Assay | Generally, talc enhances blend flowability. A low level of talc is not likely to impact assay and CU. The risk is low |
| | CU | |
| | Dissolution | Compared to magnesium stearate, talc has less impact on disintegration and dissolution. The low level of talc used in the formulation is not expected to impact dissolution. The risk is low |
| Magnesium stearate level | Assay | Since the level of magnesium stearate used is low and its impact on flow is minimal, it is unlikely to impact assay and CU. The risk is low |
| | CU | |
| | Dissolution | The risk is low |

CU: Content uniformity, CQA: Critical quality attributes, HPMC: Hydroxypropyl methycellulose

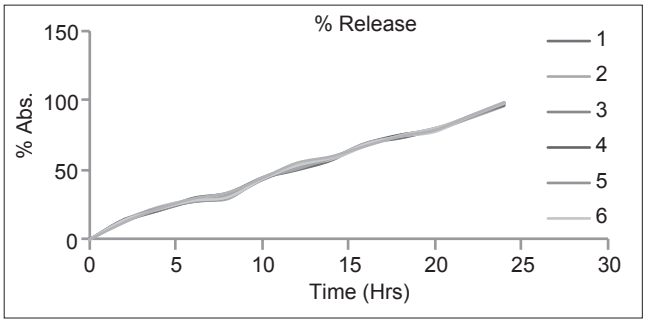


**Fig. 3: Percentage of release for 1-9 batches by using 32 factorial design**

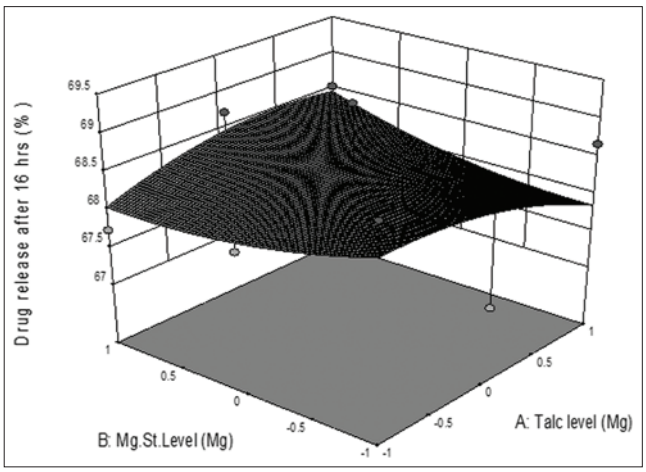


**Fig. 4: A counter plot for effect of talc and magnesium stearate on dissolution profile**

*Effect of hardness*

The objective of this study was to optimize the hardness of tablet which influences one of the CQA which affect the dissolution profile and ultimately the *in-vivo* performance of formulation. It was found that increase in hardness can cause decrease in the % release of the formulation at the end of 24 hrs.

Dissolution of the compacts was difficult, because of its brittle nature and lack of self-disintegration ability, still attempt was made to check the release behavior, the erosion of the formulation was directly proportional to the compressed pressure, hence the disintegration ability was poor dissolution profile also get affected by this. Increment of release of drug from higher hardness to lower hardness signifies surface erosion is responsible for the release, as there is an overall significant drop of the release which clearly indicates that there is effect of hardness on release behavior [18].

**Table 7: Formulation batches carried out using HPMC K4M polymer**

| Content | F12 | F13 | F14 |
|---|---|---|---|
| OPI | | 178.8 | |
| HPMC K4M | 134.1 | 89.4 | 44.7 |

HPMC: Hydroxypropyl methycellulose, OPI: Ocular protection index

The third formulation study evaluated the impact of the hardness level to the dissolution time of product on the drug product CQAs. The effect of hardness level in formulation was studied on three batches which are carried out at 4, 5 and 6 kg/cm$^2$ hardness.A significant difference in dissolution period is observed with difference in hardness of tablet. Fig. 5 shows graphical representation of drug release profile with different hardness level.

**Updated risk assessment of formulation variables**

During process development, the identified high risks for each process step were addressed. Experimental studies were defined and executed in order to establish additional scientific knowledge and understanding, to allow appropriate controls to be developed and implemented, and to reduce the risk to an acceptable level. After detailed experimentation, the initial manufacturing process risk assessment was updated in line with the current process understanding.

Hence that the hardness of the final formulation was optimized at 5 kg/cm$^2$, also polymer and its level has been selected, optimized to give dissolution profile as per QTPP and level of talc, magnesium stearate was optimized with respect to friability. Based on the results of the formulation development studies, the risk assessment of the formulation variables was updated. Table 8 shows updated risks assessment for formulation development.

**Defining design space**

CQAs were identified by the risk assessment and their relationship to critical material attributes/unit operations was established by multivariate experimental design (Rathore *et al.,* 2007). This relationship known as "design space" is the space within which the quality of the product can be built. The wider the design space, the more robust and flexible the process is to accommodate variations. Risk assessment, multivariate experimental design, literature and prior experience/knowledge contribute in defining the design space. Table 9 shows design space for Opipramol HCl SR tablet.

**Defining control strategy**

For SR tablets, the control strategy was developed after the estimation of residual risk and an assessment for its acceptability. The control strategy is to detect and mitigate the risk. Thus, success of the overall product and process performance would depend on the execution of an operating plan, including an appropriate control strategy and appropriate process monitoring, model for control strategy which links QTPP to the manufacturing controls needed to deliver the objectives (Davis *et al.*, 2008). Table 10 shows control strategy for the SR tablets of Opipramol HCl.

***In-vivo* studies**

Blood sample from marginal ear vein of the rabbit was collected in screw capped EDTA tubes at predetermined time intervals. After collection, blood samples were immediately centrifuged for 10 minutes 10,000 rpm and separated plasma was stored in screw capped polypropylene tubes at −5°C till analysis. To each tube was added 0.5 ml of plasma, 1 ml of acetonitrile for protein precipitation, 0.5 ml of internal standard. The contents of the tube were vortex mixed for 3 minutes and then centrifuged for 5 minutes at 2500 rpm. The contents of the tubes were then injected into HPLC system.

For optimum formulation F12, peak plasma concentration was found were shown with respect to time in graphical representation which has shown in Fig. 6.

For optimum formulation F12, peak plasma concentration was found to be 0.8497 µg/ml at 10 hrs ($T_{max}$). AUC of $AUC_{0-t}$ and $AUC_{t-\infty}$ was found to be 13 µg h/ml and 16.29 µg hr/ml. Total AUC was calculated as 29.40 µg hr/ml. This data supports the entire SR profile of drug.

**IVIVC studies**

Out of four modeling methods, level A is mostly used and the typical mathematical process of developing a level a IVIVC involves assessment of cumulative percent drug released from *in vitro* dissolution studies then obtained AUC using the trapezoidal rule. Application of the de-convolution of *in-vivo* plasma profile by a model independent method such as the Wagner–Nelson method to estimate the *in vivo* percent drug absorbed from the cumulative AUC shown in Table 11, followed by comparison if *in vivo* fraction of drug absorbed on Y-axis to *in vitro* fraction of drug dissolved on X-axis with three different batches of tablet having different dissolution profile shown in Table 12. Further linear correlation between concentration and absorbance were established for pooled mean data of formulations from Y=mX+c. For the model r was determined where r=1 indicates a linear relationship with good IVIVC.

**Table 8: Updated risks assessment for formulation development**

| CQA | Drug substance PSD | Polymer (HPMC) | Talc level | Magnesium stearate level |
|---|---|---|---|---|
| Assay | Low | Low* | Low* | Low* |
| CU | Low | Low | Low* | Low* |
| Dissolution | Low | Low | Low | Low |

*The level of risk was not reduced from the initial risk assessment.
HPMC: Hydroxypropyl methylcellulose, CU: Content uniformity, CQA: Critical quality attributes, PSD: Particle size distribution

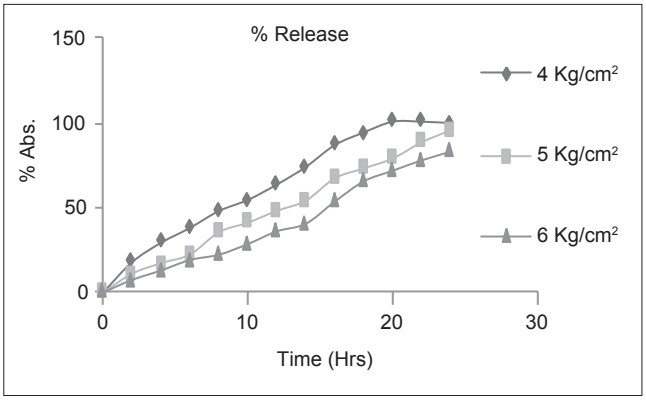


**Fig. 5: Graphical representation of drug release profile with different hardness level**

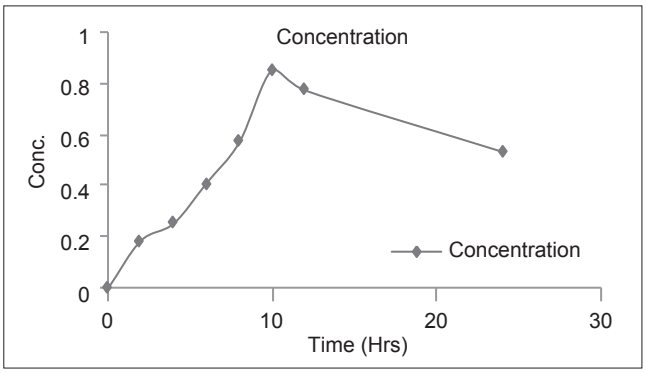


**Fig. 6: Graphical representation of peak plasma concentrations with respect to time**

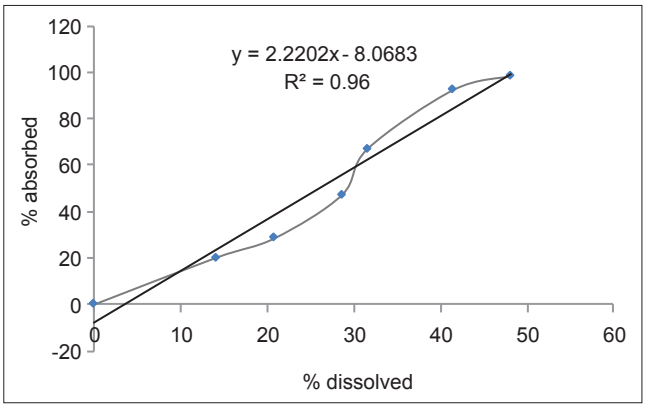


**Fig. 7: Correlation of % absorbance to % dissolved for formulation having slow release**

**Table 9: Design space for Opipramol HCl SR tablet**

| Formulation attributes | Design space | Response |
|---|---|---|
| Drug | Fine powder having good flow properties and no impurities.<br>Assay - 98-102 %<br>Volume - 178.8 mg±0.5 mg | CU |
| Polymer level | 75%±2% of total volume of API present in formulation | Real time release |
| Talcum level | 0.50-1.50% of total volume of formulation | Physical characteristic |
| Magnesium stearate level | 0.50-1.0% of total volume of formulation | Physical characteristic |
| Mixing | Mixing time and speed so that assay must be 98-102% w/w | CU |
| Compression parameters | Weight of tablet - 150 mg±5%<br>Hardness - 5 kg/cm²±0.55 kg/cm² | Assay, CU, dissolution time |

CU: Content uniformity, SR: Sustained release, API: Active pharmaceutical ingredients

**Table 10: Control strategy for the SR tablets of Opipramol HCl**

| Attributes | Control strategy |
|---|---|
| Drug | Pass through #44 mesh size<br>Assay 98-102%<br>Should have good flow properties |
| Polymer | HPMC polymer<br>Grade K4M<br>Volume used 75% of total weight of API in formulation<br>Pass through #44 mesh size |
| Magnesium stearate and talc | Pass through #44 mesh size<br>Volume added talc 0.50-1.50% of total volume of formulation<br>And 0.50-1.0% of total volume of formulation |
| Mixing | Throughout mixing of ingredients<br>Assay 97-100% of drug |
| Compression | Punch - 8 mm<br>Compression force –5 kg/cm$^2$<br>Single punch used |
| Dissolution | Apparatus - USP Apparatus II paddle type<br>Dissolution medium - 900 ml of phosphate buffer pH 7.5<br>Temp - 37±0.5 C<br>Speed - 100 rpm. 5 ml<br>Samples withdrawn at predetermined time intervals and replaced with fresh medium<br>Analysis on UV spectrophotometer - @ 258 nm |

SR: Sustained release, HPMC: Hydroxypropyl methylcellulose, UV: Ultraviolet

**Table 11: *In vivo* percent drug absorbed from the cumulative area under curve**

| Time (Hrs) | % Absorbance | Cumulative area under curve |
|---|---|---|
| 0 | 0 | 0 |
| 2 | 20.4 | 0.1861 |
| 4 | 28.52 | 0.6253 |
| 6 | 47.14 | 1.2884 |
| 8 | 67.07 | 2.2674 |
| 10 | 92.43 | 3.6861 |
| 12 | 98.29 | 5.3048 |
| 24 | 56.96 | 13.106 |

**Table 12: Summery of comparison of % absorbance of drug and % release dissolution profile with different consecutive batches**

| Time | % abs of F12 | % release (slow) | % release (medium) | % release (fast) |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 2 | 20.4 | 28.06 | 20.11 | 36.8 |
| 4 | 28.52 | 46.09 | 33.59 | 49.01 |
| 6 | 47.14 | 56.56 | 48.36 | 68.1 |
| 8 | 67.07 | 63.61 | 58.69 | 78.31 |
| 10 | 92.43 | 75.76 | 65.16 | 100 |
| 12 | 98.29 | 87.01 | 100 | 100 |
| 24 | 56.96 | 100.01 | 100 | 100 |
| $R^2$ | - | 0.960 | 0.917 | 0.926 |

The graphical representation of IVIVC with respect to three different batches of tablets were having different dissolution profile i.e. slow, medium and fast % release of drug shown in following graphical representations. Fig. 7 shows correlation of % absorbance to % dissolved for formulation having slow release.

From above data we can conclude that the optimized formulation i.e. F12 (slow release dissolution profile) has a good linear relationship with respect to IVIVC.

## CONCLUSION

QbD is an essential part of the modern approach to pharmaceutical quality. This study clarifies the use of QbD including emphasis on the importance of the target product quality profile in articulating a quantitative performance target for QbD. Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process. Clarification that critical process parameters are operating parameters and should be combined with critical material attributes to describe the relation between unit operation inputs and outputs. A definition of non-critical, unclassified, and critical that provides a way to classify process parameters and in-process material attributes. The role of the control strategy as the mechanism for incremental implementation of QbD elements into practice. An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs. Thus, this study shown the application of QbD in formulation development of model drugs Opipramol Hcl, which release drug for extended period of time thus reducing dosing frequency and improving patient compliance.

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