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Research Article

A RESEARCH ARTICLE ON AN INTEGRATED, QUALITY BY DESIGN (QBD) APPROACH FOR DESIGN, DEVELOPMENT AND OPTIMIZATION OF BILAYER TABLET FORMULATION OF CONTAINING SIMVASTATIN AS SUSTAINED RELEASE AND LABETALOL HCL AS IMMEDIATE RELEASE

Shubham Maruti Bhujbal *

** Vishal institute of Pharmaceutical Education and Research, ALE, Pune, Maharashtra, INDIA.*

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ABSTRACT

The objective of the present study was to design and develop a Bilayer tablet formulation of Containing Simvastatin as Sustained Release and Labetalol HCl as Immediate Release using quality by design principles. The target product profile (TPP) and quality target product profile (QTPP) was identified. Risk assessment was carried out by leveraging prior knowledge and experience to define the criticality of factors based on their impact by Ishikawa fishbone diagram and preliminary hazard analysis tool. The independent factors selected were compression pressure (X_1), concentration of super disintegrants (cross carmellose cellulose) (X_2), disintegrant concentration (X_3) and the responses were tablet crushing strength, tablet porosity, tablet friability. ANOVA and lack of fit test illustrated that selected independent variables had significant effect on the response variables, and excellent correlation was observed between actual and predicted values. Optimization by desirability function indicated that compression pressure, X_1 (1534 lbs), ammonium bicarbonate concentration, X_2 (7.68%) and Kollidon® CL-SF concentration, X_3 (6%) were optimum to prepare ODT formulation of carbamazepine of desired attributes complying with QTPP. Thus, in the present study, a high level of assurance was established for ODT product quality and performance.

KEYWORDS: *Quality By Design (QBD), Development and Optimization, Bilayer Tablet Formulation, Simvastatin, Sustained Release, Labetalol Hcl and Immediate Release.*

INTRODUCTION

Tablet is the convenient oral dosage form for patients and it is very popular. Bi-layer tablet is suitable for sequential release of two drugs in which one is immediate release and another is sustained release. Sustained release drug delivery is the important approaches to achieve the controlled release of drug to obtained sufficient bioavailability. Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatment [1, 2].

Simvastatin is the lipid lowering agent which is use to decrease the bad cholesterol level. It is potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme, [HMG-CoA] reductase which catalyzes the conversion of HMG-CoA to Mevalonate, an early rate determining step in cholesterol biosynthesis. Labetalol HCl. is a third generation selective alpha-1-aderenergic agonist and non-selective beta-adrenergic antagonist with vasodilatory and antihypertensive properties.

***Corresponding author:**
Shubham Maruti Bhujbal
Vishal institute of Pharmaceutical Education and Research, ALE, Pune, Maharashtra, INDIA.
** E-Mail: shubhambhujbal281997@gmail.com*

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Labetalol competitively bind to alpha-1-adrenergic receptor in vascular smooth muscle, thereby inhibiting the adrenergic stimulation of endothelial cell function and vasoconstriction and peripheral blood vessels. The result is a decrease in resting and exercise heart rate cardiac output and both systolic and diastolic blood pressure thereby resulting vasodilation and hence reduce the hypertension. The objective of development of dosage form using QbD- systematic approach is to ensure that industry has identified the critical material attributes and critical process parameters through prior knowledge, experimentation and risk assessment. It is FDA's expectation that sponsors will determine the functional relationships that link critical material attributes and critical process parameters to the product's critical quality attributes. The goal is for sponsors to envision commercialization of drug product at the start of development and continue to keep that objective in mind as they move through the development process. This is also referred to as Quality Target Product Profile (QTPP). The QTPP forms the basis of design for the development of the drug product. A sub-set of the QTPP is the Critical Quality Attributes (CQAs) which form the basis for the product specification.1113 After succinct amount of literature search of novel tablet form for type II diabetes, no report has been found in the area of MET sustained release core tablet and GLIMP immediate release active coating using stepwise systemic quality by designs (QbD) approach. The major aims of this study were: (i) step wise systemic formulation development and optimization Novel tablet of

Simvastatin as Sustained Release and Labetalol HCl as Immediate Release using QbD approach (ii) applying principles of risk assessment and Failure Mode and Effects Analysis (FMEA) for formulation and process development (iii) to implement full factorial design as optimization technique for establishment of mathematical equations and graphical results, thus depicting a complete picture of variation of the product/process response(s) as a function of the input variables and (iv) to perform capability analysis to investigate spread and control of process on reproducibility.

MATERIAL AND METHOD

Materials:

Simvastatin and Labetalol HCl. gifted sample (Flamingo pharmaceutical), HPMCK4M, Cross Carmellose Cellulose, Carbapol, Talc (Thermosil fine chem.) Microcrystalline Cellulose, Sodium Saccharine, PVPk30 (research lab) Lactose, (Sahyadri scientific supply) Magnesium Stearate (Hilab chemicals) were sample is analytical grade.

Methods:

Quality by design approach for development of novel formulation:

QbD is a holistic approach where product specifications, manufacturing process and critical parameters are included in order to ease the final approval and ongoing quality control of new drug. In this research work, novel formulation (Chart 1) containing sustained release metformin.

Table No. 1: QTPP of MET extended release core tablet

QTPP Element	Target	Justification
Dosage form	Bi-Layer Tablet	Tablet because commonly accepted unit solid oral dosage form. Bilayer tablet formulation of Containing Simvastatin as Sustained Release and Labetalol HCl as Immediate Release. Possible therapeutic benefits of a properly designed Bi-Laye4r dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance.
Dosage design	Bilayer tablet	Bilayer tablet design needed to meet label claims
Route of administration	Oral	Pharmaceutical equivalence requirement: Same administration route
Weight of tablet	400 mg of tablet	Pharmaceutical equivalence requirement:Same administration route
Dose strength	Simvastatin- 20 mg Labetelol- 50 mg	As per batches taken.
Appearance	Round shaped tablet Divided in 2 layers.	Color- white Pharmaceutical equivalence requirement: Same appearance
Assay	For labetalol HCL- 99.8% For simvastatin- 99.60%	Pharmaceutical equivalence requirement: Same assay
Resistance to crushing (Hardness)	5.2 kg/cm2	Pharmaceutical equivalence requirement: Same Hardness
Stability	Short term stability of 3 months on accelerated condition 40 0C/ 75 % RH and 3 months long term conditions 250C/60 % RH	Minimum time period (at least 3 months initially) decided to study stability of final formulation
Drug product quality attributes	Physical Attributes identification	No physical defects in core tablet Pharmaceutical equivalence requirement: Meeting the same or compendia or other applicable (quality) standards (i.e., identity, assay, purity, and quality

Optimization of MET core tablet using Design of Experiment (DOE) approach:

Quality Target Product Profile (QTPP) of MET core tablet:

The quality target product profile (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.14 For Abbreviated new drug approval (ANDAs), the target should be defined early in development based on the properties of the drug substance (DS), characterization of the Reference listed drug (RLD) product and consideration of the RLD label and intended patient population. The International conference of

harmonization (ICH) Q8 (R2) recapitulates them as QTPP.15 The QTPP includes all product attributes that are needed to ensure equivalent safety and efficacy to the RLD. By beginning with the end in mind, the result of development is a robust formulation and manufacturing process with a control strategy that ensures the performance of the drug product. QTPP for Simvastatin as Sustained Release and Labetalol HCl as Immediate Release Bi- Layer tablet is depicted in Table 1.

Preparation and optimization of Simvastatin as Sustained Release and Labetalol HCl as Immediate Release Bi- Layer tablet:

Tablets containing 400 mg of Simvastatin as Sustained Release and Labetalol HCl as Immediate Release Bi- Layer tablet were prepared by direct compression method. The ingredients Labetalol HCl, lactose, Crosscarmellose cellulose, Sodium saccharine Microcrystalline cellulose, Magnesium Stearate, Carbapol, HPMCk4M were passed through sieve 40# and co-ground properly to mix together in motor pestle for 5 mins. Talc and magnesium stearate were passed through sieve # 80, mixed, and blended with initial mixture in a poly-bag upto 3 min.

Another layer was also prepared by direct compression, drug and polymer (HPMCk4M, carbapol) were pass through the 40# sieve transfer into poly bag and mixed properly up to 3 min. Other excipients were mixed well and finally added Magnesium Stearate in above blend and were mixed for 2 min.

Finally above blends were compressed by rotary tablet compression machine (Make-CREATE INDUSTRIES, MODEL-LP-8GMP) [1, 2, 7].

The formulated tablets were stored in a tightly closed glass container and evaluated for various characteristics. A 32 factorial design with two factors, three levels, and nine runs was selected for the optimization study independent and dependent variables with their constraints are listed in Table 2. The data of 9 experimental runs were interpreted using Design-Expert ® Software Version 9 Trial Version and the final batch was optimized on the basis of above result.

Table No. 2: Formulation variables and their levels for 32 full factorial design

Factors	Coded levels	Actual levels
X1 : Amount of HPMC K4M in 40mg.	**-1**	45
	0	90
	1	120
X2 : Amount of cross carmellose cellulose in 50mg	-1	45
	0	50
	1	110

Identification of critical quality attributes (CQA):

It is 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." CQAs are generally associated with the drug substance, drug product, intermediates. Potential drug product CQAs derived from the QTPP and prior knowledge was used to guide the product and process development. 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.

Case 1 - Influence of blending speed and blending time on content uniformity:

Critical process parameters are identified with their levels and those are discussed with different case study. CQA that affect the final quality of tablet is content uniformity. Blending speed was varied from 10 to 30 rpm and blending time is from 10 to 20 min. different batches were prepared using design space approach and response was observed. Assessment was done on result and ranking were given as per the results obtained. The relative impact of blend time and blending speed on content uniformity is obtained. A screening design was not employed because prior experience with this type of formulation gave a reasonable likelihood that all three factors would be significant to some extent.

Likely to pose the greatest risk to the quality of the product and be associated with a drug product CQA. In compression unit operation, compression speed and compression force were identified as critical parameters those affect CQAs like dissolution and hardness. Different levels were taken and DOE was used to get experimental runs.

Risk assessment by failure mode effect analysis (FMEA):

The concept and spurts of quality risk management was introduced in ICH Q9, 2005 guidance.21 The CQAs depend on dosage form designed; type of formulation, manufacturing method, etc. employed and is selected amongst many possible options. Thus based upon feasibility studies, we defined the formulation and manufacturing method as described in table 3.

Table No. 3: Risk assessment by FMEA analysis to identify criticality of failure modes

Formulation/process parameter component	Failure Mode	Failure Effects	S	Potential causes of root failure	O	Detectability method or control	D	RPN
Hardness	Inadequate hardness and its range	Drug release and friability	5	Machine failure, operator's error, excipient selection	4	Hardness tester, friability testing, dissolution	2	40

Amount of HPMCK4M	Improper concentration	Drug release	5	Improper concentration and improper mixing	5	Dissolution	2	40
Amount of Talc	Improper concentration	Friability	5	Improper concentration	6	friability	2	30
Amount of Binder Microcrystalline cellulose	Improper concentration	Drug release and friability	5	Improper concentration and improper mixing	2	Dissolution	3	50

Evaluation of pre-compression parameters and preformulation studies:

1. Identification by UV visible spectrophotometer:

A] For Labetelol Hcl: 50 mg of Labetalol Hcl was weighed accurately and transferred it to 50 ml volumetric flask. Dissolved it in 0.1N Hcl and make the volume up to 50 ml with respective solvent. This was considered as stock solution (1000 mcg/ml). further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer.

B] For Simvastatin: 50 mg of Simvastatin was weighed accurately and transferred it to 50 ml volumetric flask. Dissolved it in Phosphate buffer (6.8pH) and make the volume up to 50 ml with respective solvent. This was considered as stock solution (1000 mcg/ml). Further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer.

2. Melting Point determination:

The melting points of Simvastatin and Labetalol were determined by Melting point apparatus. The melting point was determined by introducing small amount of substance in the capillary attached to graduated thermometer.

3. Determination of solubility:

Qualitative solubility analysis of drugs were done by dissolving 5 mg of drug in 5 ml solvent such as distilled water, methanol, ethanol, chloroform, phosphate buffer (7.4), ether.

4. Compatibility study, by FT-IR spectroscopy:

The powdered substance of the tablet were mix, dried potassium bromide (IR grade) ratio of sample is should be 1:100 mg, i.e 1mg sample:100mg KBr. are compressed to form transparent pellets. The sample was scanned from 4000 to 400 cm^{-1} at ambient temperature.

5. Pre-compression Evaluation:

Bulk density was determined by placing the power blend into measuring cylinder and total volume was measured and also total powder weight was measured. The bulk density was calculated by using formula.

Bulk density (BD) = weight of powder /bulk volume.

5.1. Tapped density: Tapped density was obtained by tapping the cylinder by using tapped density apparatus. Tapped the cylinder up to 100 times and then measure the tapped volume and calculate the tapped density by using formula.

Tapped Density (TD) = weight of powder /tapped volume

5.2. Hausner's ratio: Hausner's ratio is the number that is correlated to the flowability of a powder or powder blend. it is calculated using formula,

Hausner's ratio = tapped density / bulk density

5.3. Compressibility index: Compressibility index was calculated by formula,

Carr's index (%) = Tapped density – bulk density/ tapped density* 100

5.4. Angle of repose: The angle of repose of powder blend of each layer of each formulation was determined by fix funnel method. The blend was poured through funnel separately until apex of pile so formed just touch the tip of the funnel. The angle of repose was calculated by using formula

$$\theta = \tan^{-1} h/r$$

h is height of pile; r is radius of pile

6. Post compression evaluation:

6.1. Uniformity weight: Average weight of the tablet was determined by selecting 20tablet randomly. This selected tablet weighing individually and the weight of individual tablet was compared with average weight.

Table No. 4: Limits for Tablet Weight variation test:

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5%

6.2. Thickness: Thickness of the tablet was measured by using vernier calliper. 5 tablets were selected and thickness was measured in (mm).

6.3. Hardness: Hardness is important parameter of evaluation of tablet. The resistance of the tablet to break under condition of handling, transportation and storage depend upon hardness. The hardness of tablet was measured by using Monsanto hardness tester. The unit of hardness is expressed in term of kg/cm^2.

6.4. Friability: Friction and shock are the forces that most often cause tablets to chip, cap or break. 20 tablets are weighed and placed in the roche friabilator apparatus they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any

broken or smashed tablets are not picked. The percentage friability was determined by the formula [7];

% friability = [initial weight – final weight/initial weight]*100

6.5. Content Uniformity:

6.5.1. For Labetalol HCl: Tablets were taken and crushed into morter to form powder. From that, sample equivalent to 50 mg of drug was taken and transferred to 100ml volumetric flask. Methanol (20ml) was added and gently heated on water bath to dissolve the drug, cool to room temperature and volume was made up to mark with methanol, this was filtered. From the filterate 1ml was taken and diluted with pH 6.8 phosphate buffer and absorbance of this solution was measured by using U.V-spectrophotometer at 302nm (SHIMADZU; U.V1800).

6.5.2. For Simvastatin: In this test, 5 tablets were randomly selected and crushed into morter to form powder; sample equivalent to 20 mg was dissolved in 100ml of phosphate buffer pH 6.8, followed by stirring. The solution was filtered through a whattman filter paper, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 247 nm using phosphate buffer pH 6.8 as blank. Then absorbance of this solution was measured by using U.V-spectrophotometer (SHIMADZU; U.V1800).

6.6. In Vitro Drug Dissolution Studies:

6.6.1. In vitro drug release was study for immediate release tablet (Labetalol HCl): In vitro drug release was studied using USP II (paddle) apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 15 h, at 50 rpm. 0.1 N HCl (pH 1.2). 5ml of sample was withdrawn in 10 min time intervals. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. Collected samples were analyzed by U.V spectrophotometrically at 302 nm, and cumulative percent drug release was calculate

6.6.2. In vitro drug release was study for sustained release tablet (Simvastatin): The In-vitro dissolution study for the Simvastatin sustained release tablets were carried out in USP type-II dissolution test apparatus (Paddle type) using 900 ml of phosphate buffer pH 6.8 at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed by measuring the absorbance at 247 nm using UV Visible spectrophotometer and calculate the percentage drug release.

6.6.3. In vitro drug release was study for bilayer tablet: The release of bilayer tablets was determined using USP Type II (Paddle) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a 0.1N HCl solution (pH=1.2), at 370c±0.20c for 1hour. Then dissolution media replace by phosphate buffer (6.8pH). The stirring speed was 50 rpm. Aliquot of the solution was collected at specific interval were replaced with fresh dissolution medium. The Labetalol and Simvastatin were analyzed spectrophotometrically at 302 nm and 247 nm respectively using simultaneous equation method.

Quality target product profile (QTPP) of Bi-Layer tablet:

Laying down QTPP depends upon formulation type and process chosen.23, 24 Based on preliminary trials undertaken, the parameters that will be focused in our study were selected and enlisted as QTPP for Bi-Layer (Table 1). Thus, except recitation of our QTPP, the further steps to describe the QTPP are not discussed. The said QTPP will lay down the foundation for determining CQA.

RESULTS AND DISCUSSION

Quality target product profile (QTPP):

Laying down QTPP depends upon formulation type and process chosen.Based on preliminary trials undertaken, the parameters that will be focused in our study were selected and enlisted as QTPP for Bi-Layer tablet (Table 1). Thus, except recitation of our QTPP, the further steps to describe the QTPP are not discussed. The said QTPP will lay down the foundation for determining CQA.

Evaluation of pre-compression parameters of HPMC powder blends:

The micrometrics properties of all powder blends were evaluated. Bulk density and tapped density were in the range of 38 to 41 mg/ml and 0.47 to 0.51 mg/ml respectively. The angle of repose value was in the range of 30-39° which indicates fair flow properties. The result of Carr's index shows that good compressibility of powder blend for direct compression. All the results were found to be within the desired criteria.

Risk assessment by FMEA:

The factors that were embarked and assessed by FMEA in development of MET sustained delivery are highlighted in Table 3. In the current approach for development, the factors that exhibited RPN ≥40 was considered as high risk, ≥20 to <40 was considered as medium risk and <20 was considered as low risk.25 It is clearly stipulated that amount of HPMC K4M and croscarmellose cellulose have RPN 50 and require through investigation and optimization. Thus, the optimization of this two main factors that affect the core tablet formulation i.e. amount of polymers was done statistically using 32 full factorial design for establishing design space. Hardness and Granule sizes RPN fall under moderate risk category.

Risk analysis by FMEA:

32 full factorial design was employed to examine the multidimensional interaction of input variables of the core tablet which were ranked as h risk in the initial risk assessment for establishment of a design space. The acceptable region within which a quality of the product can be constructed is called as design space. The risk mitigation and control strategy is fused outline of how quality is established based on current process and existing product knowledge. Blending speed has risk priority number (RPN) of 4, which shows low risk with containing particle size of drug and excipients. Blending time has RPN of 2, which shows low risk with certain controls. Both the critical parameters have RPN less than 9, which represent low risk level for content uniformity.

Risk reduction by implementation of control strategy:

Innovative approaches such as quality risk management together with design space, continuous improvement programs can be adopted to improve the quality of Bi-Layer tablet. Understanding the relationship between critical material and critical process attributes culminates in process control. After overall risk assessment was done, different control strategies have been found that have minimum impact on CQAs. In order to optimize compression process with lower risk, compression speed was found to be 20 rpm and

compression force was found to be 22.4 KN for best finished product quality.

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