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ORIGINAL ARTICLE

Development and Validation of Critical Quality Attributes of a Novel Formulation of an Antihyperlipidemic Drug by Quality by Design Approach

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ABSTRACT

To formulate a novel Biopharmaceutics Classification System class II antihyperlipidemic drug and optimize its critical quality attributes using a quality-by-design approach. Atorvastatin was the drug of choice in this study. The material and critical quality attributes were identified by risk assessment, as per the International Conference of Harmonization Quality Guidelines. Material attributes were found to be the amounts of microcrystalline cellulose and croscarmellose sodium; the critical quality attribute selected for optimization was dissolution. A screening design with five experimental runs was performed for the amounts of croscarmellose sodium and microcrystalline cellulose in the ranges of 11–21 mg and 80–160 mg, respectively. The response surface methodology was used for optimization based on the results of the screening batches. A full factorial central composite design with 10 experimental runs was performed using microcrystalline cellulose and croscarmellose sodium in the range of 80–120 mg and 11–20 mg, respectively. Of these runs, batch R1 showed a drug release of 92.47% in 30 min with microcrystalline cellulose (120 mg) and croscarmellose sodium (16 mg). Quality by Design can be applied to optimize critical quality attributes and meet the desired Quality Target Product Profile.

Keywords: Quality by Design; Screening design; Full factorial design; Central composite design; Atorvastatin

INTRODUCTION

Drug delivery systems deliver drugs to desired tissues, organs, cells, and subcellular organs via various drug carriers for drug release and absorption[1]. In 2019, high plasma LDL-cholesterol levels were responsible for 4.40 million deaths and 98.62% of disability-adjusted life years (DALYs). Tablets, capsules, syrups, etc., are conventional drug delivery systems that are the first choice of scientists to deliver drugs to the body owing to various benefits such as self-administration, accurate dose, ease of administration, low cost, and patient compliance. However, these drug delivery systems suffer from various hurdles, such as frequent administration of drugs with low half-life, which increases the chances of missing the dose of the drug; fluctuations in steady-state drug plasma concentration; poor aqueous solubility; extensive first-pass metabolism leading to low bioavailability; lack of drug targeting; prolonged onset of action; and higher adverse effects, which enforced the modification of conventional drug delivery systems, resulting in innovative drug delivery systems which mainly include nanotechnology-based drug delivery systems[2,3]. Many drugs are used as enzyme inhibitors, which are responsible for the synthesis of cholesterol. Solubility is one of the main parameters for any drug to achieve the expected therapeutic effects[4].

Quality by Design (QbD) is the production of quality pharmaceutical products which is the major goal of the pharmaceutical industry[5]. The quality of pharmaceutical products includes all aspects that may have an impact on the prescribed products which will consequently affect the health of patients. Previously, the QbT (quality by testing method) was commonly used to ensure the quality of manufactured products. Quality by testing method relies on in-process testing of input materials, intermediates, and the final product[6]. On the other hand, the pharmaceutical industry requires a method to ensure quality before production and to adhere to the quality control testing procedures recommended by QbT. To achieve this,

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the current pharmaceutical industry and regulatory agencies are shifting towards a concept known as QbD. This approach ensures that pharmaceutical products are developed and manufactured in accordance with predefined quality attributes and is expected to significantly reduce the need for extensive testing during or after manufacturing. Additionally, QbD is expected to improve product efficacy, manufacturability, reproducibility, and safety[7]. As a result, Quality by Design (QbD) can be characterized as a forward-thinking strategy aimed at enhancing the quality of products[8]. Given the widespread use of potent liposomal-based drug products in clinical settings and their diverse applications in both clinical and pre-clinical scenarios, there is a pressing need for a strategic and systematic approach to the development of liposomes as highly effective drug delivery systems. Such an approach would enhance the therapeutic efficacy of loaded therapies and help to address the current gap in the market. Although numerous studies have documented the development of QbD liposomal drug delivery systems, there is a growing need to comprehend and convey the latest progress in employing QbD for liposomal formulation development. This endeavour aims to ensure that liposomal-based drug delivery systems deliver improved therapeutic outcomes and exhibit potential for industrial application[9].

The self-nanoemulsifying drug delivery system (SNEDDS) of statins could be a novel formulation for enhancing the drug profile. SNEDDS of statins improved the drug dissolution rate[10], increased the oral bioavailability by approximately 2.4-fold[10,11], and increased the drug release 4-fold[12] compared to that of pure statins. The statin-loaded SNEDDS system exerts remarkable antihyperlipidemic properties by normalizing serum lipid levels[13]. Overall, it has the potential to improve oral absorption and pharmacodynamic efficacy compared with pure drugs[14]. Statin nano-therapy involving diverse nanotechnology systems could potentially contribute to a decrease or removal of typical adverse side effects associated with statin treatment, while also facilitating statin delivery and enhancing their beneficial pleiotropic effects, according to recent studies[15]. Various formulations are currently being prepared to enhance drug solubility which may in turn improve the bioavailability of the drug. Studies have revealed that different methodologies have been used to overcome the bioavailability issue which is the key limiting factor[16,17]. The present study focused on antihyperlipidaemic lipophilic drugs and different types of novel formulation approaches for lipid-soluble drugs.

METHODOLOGY

Materials used

The materials utilized in the formulation included atorvastatin calcium, obtained from Microlabs (P) Ltd., serving as the drug component. For dilution purposes, calcium carbonate from Thermo Fischer Scientific India Pvt. Ltd and lactose monohydrate from S D Fine Chem Limited, Mumbai, were used. Microcrystalline cellulose, which acts as a disintegrant, was procured from S D Fine Chem Limited. Polyvinylpyrrolidone from Thomas Baker Chemicals, Mumbai, was used as a binder. Croscarmellose sodium, another disintegrant, was obtained from Shreeji Chemicals Pvt. Ltd. (Mumbai, Japan). Polysorbate-80, which served as a surfactant, was purchased from Merck Pvt. Ltd. Magnesium stearate, sourced from Loba Chemie Pvt. Ltd., was utilised as a lubricating agent. The reagents used in the formulation process included sodium hydroxide and methanol from S D Fine Chem Limited, Mumbai, and potassium dihydrogen orthophosphate from Medilise Chemicals.

Equipment used

The equipment utilized in the laboratory included a Shimadzu Digital Balance ATY224 for precise weighing measurements, a Digisun Digital Ph Meter2001 for pH level analysis, and a hardness tester from Lab-Hosp for assessing material hardness. Additionally, an Electrolab EF-1W Friability apparatus was used to test the durability of the tablets. For pharmaceutical analysis, a Lab India DS8000 Dissolution apparatus and a Rimek Mini Press Compression machine were utilized. The laboratory also features a UV/visible spectrophotometer, with models including the Tech Comp-UV/Vis Double Beam 2301 and Shimadzu Pharma Spec-UV/Vis Double Beam 1700, for conducting various spectroscopic analyses. The Vernier calipers and Tray dryer models are unspecified in the provided list. Finally, the disintegration apparatus from Lab-Hosp was used to analyze the disintegration time of the tablets.

Defining QTTP and CQA of the product

QTTP was defined for atorvastatin calcium according to International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q8 (R2). It is defined based on the quality target product profile (QTTP) of a reference drug (RLD) (Lipitor®). To meet the QTTP criteria, CQAs were identified by risk assessment according to the ICHQ9 guidelines.

Preliminary methods

Solubility of the drug

Atorvastatin calcium (50 mg) was weighed and the solubility of this sample was checked in water, methanol, and phosphate buffer. The drug was found to be soluble in methanol.

Determination of lambda max

Fifty milligrams of the drug was dissolved in 50 ml of methanol (1 mg/ml). Ten milliliters of this solution were

withdrawn, and the volume was made up to 100 ml. Appropriate dilutions were made with methanol to obtain a concentration of 10 μg/ml, scanned in the UV range from 200 to 400 nm, which could be utilized for analysis, and the spectrum was recorded.

Construction of the calibration curve

Preparation of standard stock solution. A calibration curve was obtained at a concentration range of 5 – 25 μg/ml of the pure atorvastatin calcium drug. The spectra were recorded, absorbance was measured at 246 nm, and a calibration curve was plotted [18].

Formulation

Screening batches

To identify vital factors affecting the desired response, a screening design was followed. The screening batches were formulated based on the definitive screening design performed using the statistical software JMP®11 by SAS for two factors: the amount of microcrystalline cellulose (MCC) and amount of croscarmellose sodium (CCS) (Table 1). The design was performed for five experimental runs with the amounts of MCC and CCS ranging from 80 mg to 160 mg and 11 mg to 21 mg, respectively. These ranges were determined based on a prior literature survey on the formulation of atorvastatin immediate-release tablets. The batches were evaluated, and the dissolution profiles of the batches were investigated.

Procedure for preparing atorvastatin tablets

Weighed amounts of atorvastatin calcium, calcium carbonate, lactose monohydrate, and microcrystalline cellulose were added. Polyvinylpyrrolidone and polysorbate 80 were dissolved in purified water (50 °C) by slow stirring until a clear solution was obtained. The granulating solution was cooled to 30°C. The powder mix was kneaded with the granulating solution and passed through #22 mesh to obtain the desired granules. The granules were then dried at 60 °C. The dried granules were passed through #16 mesh. CCS and magnesium stearate were sifted and mixed with the granules. These granules were compressed to the target weight and hardness [19].

Response surface methodology batches

Based on the results of the screening batches, a response surface methodology (RSM) design was designed (Table 1) using the statistical software JMP® 11 by SAS for MCC and CCS amounts ranging from 80 mg to 120 mg and 11 mg to 20 mg, respectively. This design was used for the quantitative optimization of MCC and CCS. A factorial design with 10 experimental runs for two levels was performed for the batches developed. Evaluation tests were performed, and the dissolution profiles were investigated.

Evaluation studies [20]

Weight variation test

Twenty tablets were randomly selected from each batch and weighed individually. The average weight of 20 tablets was calculated, and no more than two of the individual weights deviated from the average weight by more than $\pm$ 5% (Table 1).

Thickness test

The thickness of five randomly selected tablets from each batch was measured using Vernier callipers.

Hardness test

The hardness of five tablets randomly selected from each batch was measured using a Monsanto hardness tester.

Friability test

Friability of the tablets was determined using a Roche friabilator. The results were expressed as a percentage (%). Twenty tablets were weighed (Wi) and transferred to a friabilator. The friabilator was operated at 25 rpm for 4 min or up to 100 rpm. The tablets were then weighed again (Wf). The % friability was then calculated by

$$\%F = \frac{W\ initial - W\ final}{W\ initial} X\ 100$$

Disintegration test

The disintegration time of six randomly selected tablets was determined using a disintegration apparatus. One tablet was placed in each of six tubes in a beaker containing 1000 ml of purified water maintained at 37 $\pm$ 2 °C, and the apparatus was operated. The time taken for tablets to disintegrate and pass through the mesh was recorded.

Dissolution test

The dissolution test was performed based on the FDA dissolution profile. The solution was dissolved in phosphate buffer (pH 6.8). Atorvastatin release was measured in a USP dissolution apparatus II at an operating temperature of 37$\pm$0.5 °C. The stirring rate of the paddle was 75 rpm. The dissolution of the six tablets was measured for 30 min at an interval of 5 mins. Aliquots were diluted to obtain the required concentration and the absorbance was measured using a UV spectrophotometer at 246 nm.

RESULTS

Determination of solubility

The drug was found to be soluble in methanol

Determination of lambda max of the drug

The drug was scanned from 200 to 400 nm in methanol. Maximum absorbance (λ max) was observed at 246 nm.

Table 1: Definitive screening design and response surface methodology batches

Definitive screening design batches					
Ingredients	**S1 Mg**	**S2 Mg**	**S3 Mg**	**S4 Mg**	**S5 Mg**
Atorvastatin	40	40	40	40	40
Calcium carbonate	144	144	144	144	144
Lactose monohydrate	260	260	260	260	260
Microcrystalline cellulose	120	120	120	80	160
Polyvinylpyrrolidone	12	12	12	12	12
Croscarmellose sodium	11	21	16	16	16
Polysorbate -80	1.6	1.6	1.6	1.6	1.6
Magnesium stearate	2.4	2.4	2.4	2.4	2.4
Purified water	Q.S	Q.S	Q.S	Q. S	Q.S
Total weight of each tablet	591	589	584	544	624

Response surface methodology batches										
Ingredients	**RSM Design**									
	R1 Mg	**R2 Mg**	**R3 Mg**	**R4 Mg**	**R5 Mg**	**R6 Mg**	**R7 Mg**	**R8 Mg**	**R9 Mg**	**R10 Mg**
Atorvastatin calcium	40	40	40	40	40	40	40	40	40	40
Calcium carbonate	144	144	144	144	144	144	144	144	144	144
Lactose	260	260	260	260	260	260	260	260	260	260
Microcrystalline Cellulose	120	80	100	100	100	80	100	120	80	120
Polyvinyl pyrrolidone	12	12	12	12	12	12	12	12	12	12
Croscarmellose Sodium	15.5	15.5	11	15.5	15.5	20	20	11	11	20
Tween-80	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight of the tablet (mg)	593.5	553.5	569	573.5	573.5	558	578	589	549	598

Weight variation test		
Dosage form	**Average weight**	**Percentage deviation**
Uncoated and film or coated tablets	80 mg or less	10
	More than 80 mg but less than 250 mg	7.5
	250 mg or more	5

Construction of the calibration curve of atorvastatin in methanol

A standard calibration curve of atorvastatin in methanol was constructed, and the Beer's range was found to be between 5-25 μg/ml with an R^2 value of 0.9957.

Defining QTPP and CQA of the drug

The QTPP of the drug was defined based on the QTPP of an RLD (Lipitor®). This is defined in Table 2.

Experimental runs and evaluation of screening batches

Screening batches of 5 experimental runs were performed using the amounts of MCC and CCS, out of these runs Batch S3 showed significant % drug release of 93% within 30 mins. with MCC and CCS amounts of 120 mg and 16 mg, respectively (Table 3). Out of all the batches, S3 showed a drug release of 93.94% which meets the target requirement.

Experimental runs of RSM batches

From the results obtained from the screening batches, 10 RSM runs were performed using MCC and CCS in the amounts, out of which batch R1 showed a % drug release of 92.47% with the amounts of MCC and CCS of 120 mg and 15.5 mg respectively (Table 3).

Cumulative drug release of RSM batches and Similarity index

This design space shows a dissolution of 84.76% with the amounts of CCS and MCC in the range of 16 mg and 120 mg, respectively (Figure 1). The prediction profiler, surface plot, and contour profile are shown in Figure 2.

Table 2: QTPP and CQA of the drug

Quality Attributes	**Target**		
Dosage form	Tablet		
Dosage type	Immediate release		
Dosage strength	40mg		
Route of administration	Oral		
Pharmacokinetics	Immediate release, t max is 1-2 hrs, c max is 85-90%, and elimination half-life is 14 hrs		
Packing	Alu-Alu blister		
Quality attributes of the drug product	**Target**	**CQA conformance**	**Justification**
Physical attributes	Color odor appearance	No	It does not affect the targeted response directly
	Weight of the tablet	Yes	It affects the drug content of the product
	Thickness	Yes	It affects the flow properties of the granules
	Hardness	Yes	It affects the disintegration which indirectly affects the response
	Friability	No	It does not affect the targeted response directly
Disintegration	5-10 mins	Yes	Disintegration affects the drug release.
Dissolution	90-100% drug release	Yes	As the dosage form is immediate release it was identified as CQA

Table 3: Experimental runs of screening batches, evaluation of the screening batches and RSM batches

Screening batches					
Batches	**Microcrystalline cellulose (MCC)in mg**		**Croscarmellose sodium (CCS) in mg**		
S1	120		11		
S2	120		21		
S3	120		16		
S4	80		16		
S5	160		16		
Evaluation of screening batches					
Formulation	**Weight variation(g)± SD**	**Thickness (mm) ± SD**	**Hardness (kg/cm^2)± SD**	**Friability (%) ± SD**	**Disintegration time(min) ± SD**
S1	0.589±0.029	3±0.047	6±0.081	0.74±0.008	5±0.081
S2	0.587±0.029	3.1±0.046	5.9±0.08	0.80±0.008	6±0.072
S3	0.582±0.029	3±0.047	6.4±0.082	0.76±0.007	5.5±0.023
S4	0.542±0.027	3.2±0.047	6.2±0.08	0.810.006	6±0.054
S5	0.622±0.031	3±0.047	5.8±0.081	0.90±0.007	8±0.083
RSM batches					
R1		120		15.5	
R2		80		15.5	
R3		100		11	
R4		100		15.5	
R5		100		15.5	
R6		80		20	
R7		100		20	
R8		120		11	
R9		80		11	
R10		120		20	

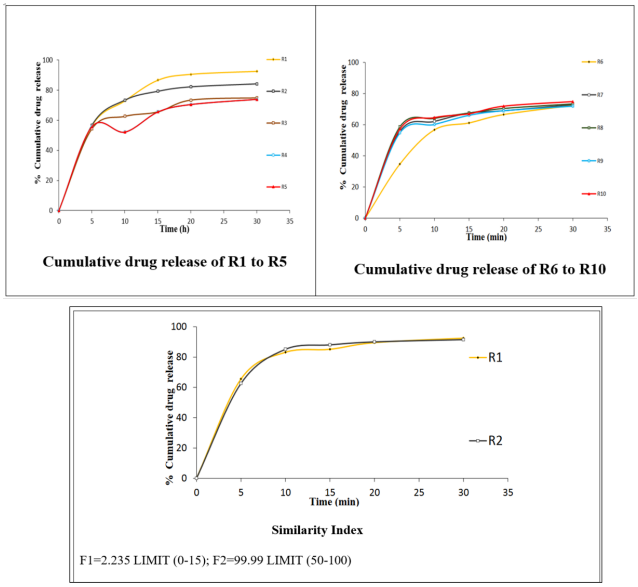

Fig. 1: Cumulative drug release and similarity index

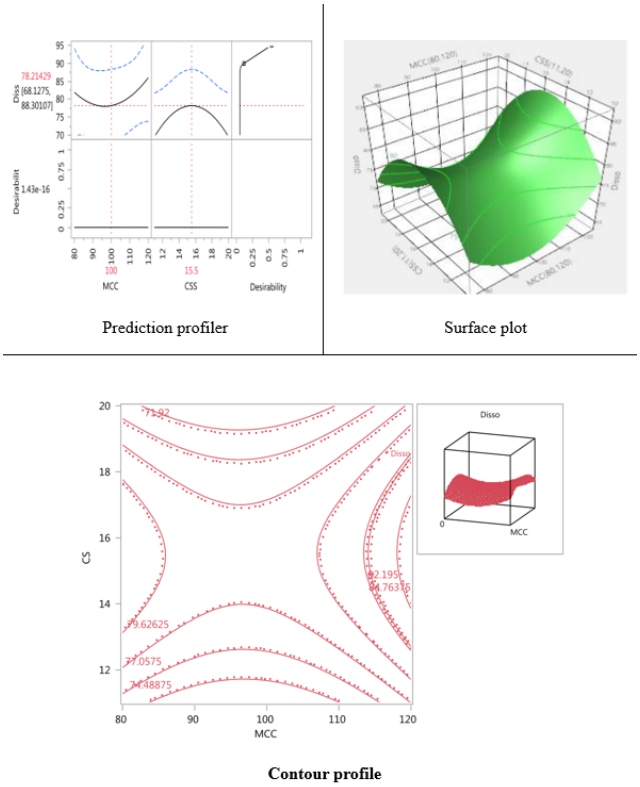

Fig. 2: Prediction profiler, surface plot and contour

DISCUSSION

Formulating a novel Antihyperlipidemic BCS class II drug product and optimizing CQAs using QbD was demonstrated. The QTPP was defined based on the QTPP of an RLD (Lipitor®), and CQAs were identified according to the ICHQ 9 guidelines. The drug product was formulated as a tablet by the wet granulation method.

The drug was soluble in methanol and showed maximum absorbance at 246 nm. A linear plot was obtained with an R^2 value of 0.9957. A definitive Screening Design with five experimental runs was performed out of these batches, and S3 was found to provide a drug release of 93.94% and was selected for further optimization. After the screening design, RSM design was performed with 10 experimental runs. Of these batches, R1 showed a drug release of 92.47% which met the target requirements. The weight of all tablets was within the limit, and the hardness of the randomly selected tablets was within this range. The disintegration of the selected tablets occurred within the specified time. The similarity factor of the optimized formulation was tested against that of a marketed formulation. (Lipitor®). The similarity factor was set to 99.99. Thus, QbD was successfully applied for screening the critical factors and optimizing them.

In conventional drug delivery systems used for hyperlipidemia, a non-invasive peroral route of administration, where the dosage form is consumed through the mouth, is the most conventional method for delivering anti-hyperlipidemic drugs[21]. This route has certain limitations; for example, drugs with short half-lives require frequent administration, which increases the chance of missing drug doses, leading to poor patient compliance. It is difficult to obtain a steady-state condition because of unavoidable fluctuations in drug concentration. The first-pass metabolic effect on drugs is another major limitation of this route which reduces the bioavailability of several important drugs[22]. Moreover, variability is also observed due to the presence of food, physiological parameters of the body, and diseased conditions. In summary, the shortcomings of conventional dosage forms can be summarized as favourable biodistribution, low bioavailability, lack of water solubility, poor site specificity, low therapeutic response despite high doses, and elevated side effects and toxicity. To overcome these limitations, the development of novel drug delivery systems (NDDS) which include drug modification (chemically or physically), drug entrapment within lipid copolymeric small vesicles, and particle size reduction of drugs, is necessary[23]. The FbD methodology involves defining the quality target product profile (QTPP), identification of critical quality attributes (CQAs), critical material attributes (CMAs), critical process parameters (CPPs) using screening and risk assessment, optimization data analysis using DoE, modelization, and optimum search through response surface methodology (RSM) to embark on the design space, and postulation of the control strategy for continuous improvement.

At the onset, systematic FbD-based product development embarked upon defining the patient-centric QTPP and CQAs to achieve maximum therapeutic benefits in terms of efficacy and safety. Initial risk assessment studies, carried out with the help of a fish-bone diagram, helped establish the cause-and-effect relationship among the possible material attributes and/or process parameters affecting the CQAs.

CONCLUSION

In this study, a BCS class II Antihyperlipidemic formulation was developed. The critical range of MCC and CCS amounts was obtained following a definitive screening design. The optimal amounts of MCC and CCS were found by RSM design which showed a targeted dissolution of 90%-100%. The optimal formulation showed dissolution similar to that of RLD(Lipitor®). Thus, QbD was successfully used to optimize the formulation.

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