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Research Article

FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING FILM OF ROSUVASTATIN CALCIUM USING QBD APPROACH

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ABSTRACT

The aim of the present study was to design the mouth dissolving film of Rosuvastatin calcium (RC) by applying quality by design (QbD) approach. The mouth dissolving film was prepared using solvent casting method. The critical quality attributes (CQAs) and quality target product profiles (QTPP) of RC mouth dissolving films were defined based on previous studies. Plackett-Burman experimental design was used for initial screening of process and formulation variables. The screened variables were further optimized using 3^2 full factorial designs. The variables influencing formulation of film was HPMC E5 and PVP K30. The design space was determined using statistical tool and optimized formulations were prepared within the design space. The optimized films showed all the evaluation parameters within the QTPP. The results indicated that as long as formulation variables remain within the design space, mouth dissolving film of RC with desired characteristics and quality requirement could be formulated.

Keywords: Plackett-Burman; Rosuvastatin calcium; 3^2 full factorial design; quality by design; Mouth dissolving film.

INTRODUCTION

The oral route of drug administration is the most preferred route of drug delivery amongst all the routes of drug administration. Oral mouth dissolving film (MDF) is gaining popularity because of high patient compliance in treating paediatric and geriatric patients and provides immediate release as it offers quick onset of action[1,2]. The film dissolve or disintegrate quickly in the oral cavity and the fast dissolving action is due to quick wetting of the film in the moist oral cavity, leading to fast dissolving action. This also prevents choking or spitting out problems associated with solid oral dosage forms[3,4].

The MDF can be formulated using a variety of film formers and other excipients and the most common technique for its preparation is using solvent casting[4]. Variety of polymers and their different grades can be used in the formation of MDF depending upon the need of disintegration time, drug loading and mechanical properties[4]. Plasticizers added in MDF improve the flexibility and reduces the brittleness of the strip. They significantly enhance film forming properties through a reduction in the glass transition temperature of the polymers[5]. Variability in type and grade of polymer and plasticizer concentration may impact the MDF critical quality attributes (CQA) such as thickness, % elongation at break, yield stress, Young's modulus, folding endurance and dissolution rate of the film. The present study was carried out to investigate the impact of the formulation and process variables on the quality of mouth dissolving film using Quality by Design (QbD) approach.

Rosuvastatin is a synthetic, high potent third generation statin with cholesterol-lowering activity. Rosuvastatin competitively inhibits hydroxyl methyl glutaryl-coenzyme A (HMG-CoA) reductase which catalyses the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis, therefore, it is used for high cholesterol, blood lipid metabolic disorder and pure high triglyceride blood disease treatment[6,7]. Clinical studies have proven that fast disintegrating tablets can enhance patient compliance, provide an immediate onset time of action, and increase bioavailability[8]. Hence it was decided to use Rosuvastatin as a model candidate for oral dissolving film.

Quality by Design (QbD) is a scientific approach for product development. It ensures the quality of the product systematically by providing thorough understanding the compatibility of all the components and processes involved in manufacturing. QbD provides detailed insight on quality throughout the development process[8].

Typically, it involves identification of quality target product profile (QTTP) that are critical from the patient's perspective and helps in establishing the relationship between formulation/manufacturing variables and CQAs to consistently deliver a drug product to the patient[9]. In addition to the mechanical properties (yield stress, % elongation at the break and Young's modulus), a short disintegration time and fast drug dissolution constitute the desired QTPP of Rosuvastatin MDF product.[10] It is also important to identify critical material attributes (CMA) and critical process parameters (CPP) based on process and product understanding.

The aim of the present study was to design and optimize the Rosuvastatin calcium MDFs by using QbD. In the present study, Rosuvastatin calcium MDFs was developed, and a design space was established through a factorial design for optimization using Design Expert 9.0.3.1 software (Stat-Ease, Minneapolis, MN, USA). In our preliminary study, we investigated factors that could

affect CQAs by Placket Burman. Here, factors and their levels were determined and applied to the factorial design.

MATERIALS AND METHODS

Materials

Rosuvastatin calcium (RC) was obtained as gift sample from McCoy Pharma Pvt. Ltd, Boisar, HPMC E5 and PVP K30 were received as gift samples from Wockhardt Ltd., Aurangabad, Glycerine, and all other reagents used were of analytical grade.

Methods

Fundamental Design

The objective of fundamental design is to provide thorough understanding of the product and process. QbD tools were used for designing formulation which provides an effective and efficient model to build the quality into product[11].

Quality Target Product Profile

Quality target product profile (QTPP), a knowledge-based system, was utilized to identify drug product characteristics so as to accomplish the targeted quality product (Table 1). Identification of critical quality attributes such as dosage form, dose, disintegration time, *in vitro* drug release, elongation and young's modulus is furnished in QTPP.

Formulation and optimization of MDFs using DOE

The solvent casting method was used for preparation of MDFs. HPMC E5 and PVP K30 was dissolved in 6 ml of hot water in one beaker and RC and glycerine were dissolved in 14 ml of 95% ethanol in another beaker, stirred continuously in magnetic stirrer about 30 minutes. The drug solution was then added to the polymeric solution was stirred for 30 min using magnetic stirrer and was kept for sonication till the entrapped air bubbles were removed. The aqueous solution was casted in a Petri-dish and was dried in hot air oven. The dried film was carefully removed from the petri-dish and was cut into size required for testing[12].

Choice of design and experimental layout

Initially a set of experiments using the Plackett Burman screening design was adopted to prepare MDF of RC. PB design screens are useful in screening large numbers of variables with the minimum number of runs. A nine-factor 12-run Plackett–Burman screening design was generated using Design-Expert 6.0.10 (Version 2.05, Stat-Ease Inc., Minneapolis, USA; Table 1). The CPP and CQAs were defined based on the literature review. Each variable was represented at two levels, namely, "high" and "low". These levels define the upper and lower limits of the range covered by each variable. The responses obtained in the study were compared to QTPP obtained after defining CQAs (critical quality attributes) for the final product (Table 2). The variables showing significant effect were selected from Pareto chart. The Design-Expert Software assigned the best fitted model and the model was selected based on their significance using an analysis of variance (ANOVA) F-test[13].

Table 1: Factors in Plackett- Burman Screening Design

CPPs	Unit	Low	High
HPMC E5	%	2	4
PVP K30	%	0.25	1
Glycerine	%	1	2
Drying time	Hours	3	4
Drying temperature	Celsius	40	60
Dummy1		-1.00	+1.00
Dummy 2		-1.00	+1.00
Dummy 3		-1.00	+1.00
Dummy 4		-1.00	+1.00
Dummy 5		-1.00	+1.00
Dummy 6		-1.00	+1.00
Dummy 7		-1.00	+1.00

Table 2: The QTPP of CQAs

CQAs	Limit
Disintegration time	< 50 s
In-vitro Drug release	NLT 80% in 30 min
Elongation	> 10%
Tensile strength	2 N/mm^2
Young's modulus	< 550 N/mm^2

Optimization of MDF of RC by using 3^2 Factorial designs

The factors identified in the PB design having the influence on the formulation of MDF were further optimized using 3^2 full factorial designs. The coded value and the design layout for the factorial batches are shown in Table 3 and 4.

Table 3: Coded Value for the Factorial batches

Coded value		-1	0	+1
X_1	HPMC E5	2.2 %	2.5 %	2.8 %
X_2	PVP K30	0.3 %	0.5 %	0.7 %

To each run different variables were assigned by the program resulting in different plots, e.g. contour or 3D surface plot. For each run, a different percentage of HPMC (X1) and different percentage of PVP K30 (X2) was applied. In order to check the data for normality a normal probability plot of residuals was used.

Characterization of MDF

The formulated MDF using DoE were characterized for thickness, weight, appearance and mechanical properties i.e. tensile strength, % elongation at the break, Young's modulus and folding endurance. The optimized films were also tested for drug assay, disintegration, and dissolution rate.

Film weight and Thickness

The weight of films (n = 6) was recorded using a sensitive weighing balance (Shimadzu). The film thickness of the MDFs (n = 6) was measured by means of a micrometre screw gauge from five different locations.

% Elongation at break, yield stress and Young's modulus

Mechanical properties of MDF was analysed using an in-house fabricated mechanical analyser. A 2 × 2 cm^2 film was cut and tension was applied on the film and the load needed to break the film was calculated the % elongation at break, yield stress and Young's modulus were calculated using the following equations.

$$\textbf{Tensile strength (N/mm}^2\textbf{)} = \frac{\text{Load at failure} \times 100}{\text{stripthickness} \times \text{stripwidth}}$$

% Elongation at break = Increase in length of strip × 100/Initial length of strip

$$\textbf{Young's modulus (N/mm}^2\textbf{)} = \frac{\text{Tensile strength}}{t \times b}$$

Determination of drug content

A film was cut into three pieces of equal dimension (4 cm^2). Each film was dissolved in 100 mL of pH 6.8 phosphate buffer and stirred for 10 min. The solutions were filtered and diluted accordingly with the phosphate buffer. The RC content was determined using the validated UV Spectrophotometric method at 240 nm wavelength.

Disintegration test

A simple test was used to evaluate the disintegration time of the film. A beaker containing 25 mL of water maintained at a temperature of 37 ± 1° C was taken and the film was placed in it. The solution was swirled every 10 sec and the time for the disintegration of the film was noted.

In vitro Drug Release

The drug release studies were performed using USP dissolution test apparatus Type II. The USP dissolution apparatus was thermostat at the temperature of 37 ± 1° C and stirred at a rate of 50 rpm in a 900 mL dissolution medium of pH 6.8 phosphate buffer. The aliquots of 5 mL were withdrawn at the time interval of every 5 min and replaced with equal volume of dissolution medium. The sink condition was maintained throughout the study. The samples were analyzed at 240 nm in a UV Spectrometer and cumulative amount of drug release at various time intervals was calculated.

RESULTS AND DISCUSSION

An attempt was made in this research to formulate the mouth dissolving film of rosuvastatin by using a QbD approach. Before carrying out the experiments the CQAs and CQPs were identified, this was based on the literature review of the similar research work. All the formulations were evaluated based on QTPPs. Thus, based on literature review the CQAs of the MDF were mechanical strength, disintegration time and *In vitro* drug dissolution. The disintegration time and dissolution have a direct influence on the performance and safety of the MDF and the mechanical properties play a significant importance in handling, easy administration, and stability.

The Plackett–Burman screening design was used to evaluate the effect of the five independent variables the mechanical properties, disintegration time and *In vitro* drug release. Each factor was screened at high and low values which were based on preliminary trials. The effect of the factors on the responses was determined based on the magnitude and direction of the factor coefficient in the polynomial equations and the Pareto chart generated for all the responses. Form the analysis of data it was interpreted that the concentration of HPMC E5 and PVP K30 has a significant influence on the mechanical properties, disintegration and *in vitro* drug release. Factors such as the concentration of citric acid and glycerine, drying temperature and drying have insignificant influence on the responses. The Pareto chart for the responses are shown in Figure 1.

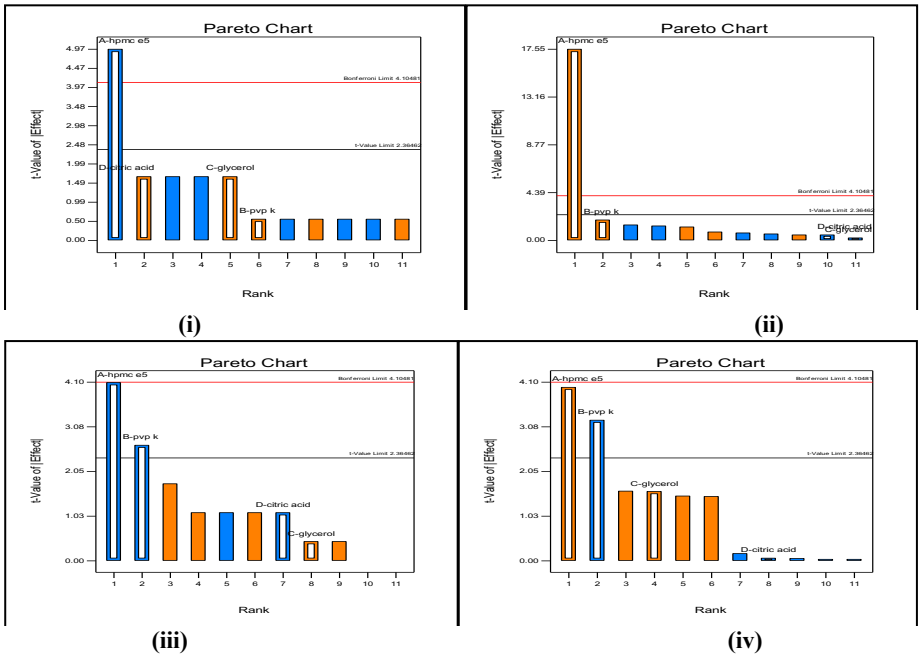

Figure 1: Pareto chart for i) %Drug release ii) Disintegration time iii) % Elongation and iv) Tensile strength

Optimization of Film

Based on the PB screening study, the two factors which could influence the performance of RC MDF was determined to be the concentration of HPMC E5 and PVP. Thus, it was decided to further optimize the concentration of these two factors using 3^2 full factorial design, Nine MDF films were prepared and evaluated for various evaluation parameters (Table 4) and were statistically optimized using Stat-Ease Design Expert 7.0.0 software.

Table 4: Evaluation parameters for factorial batches

	Thickness (µm)	D.T (sec)	Elongation (%)	Tensile strength (N/mm^2)	Young's modulus (N/mm^2)	Drug content (%)	Drug release (30 min) (%)
F1	63.3 ± 5.77	39 ± 1	8.33 ± 2.8	2.88 ± 0.04	19.3 ± 8.73	94.2 ± 2	99 ± 1
F2	66.6 ± 5.77	31.6 ± 0.5	14.3 ± 1.1	3.10 ± 0.005	10.9 ± 1.30	99.6 ± 1.06	100 ± 2.64
F3	63.3 ± 5.77	31.3 ± 3.2	9.8 ± 5.2	2.862 ± 0.005	18.5 ± 11.72	99.3 ± 1.1	96 ± 4
F4	60	32 ± 2.6	5.3 ± 0.57	2.861 ± 0.005	27.04 ± 2.71	99.14 ± 1.2	99.3 ± 3.21
F5	63.3 ± 5.77	32.3 ± 2.5	10.16 ± 0.28	2.863 ± 0.005	14.08 ± 0.36	98.5 ± 1.7	99.3 ± 0.57
F6	66.6 ± 5.77	30.3 ± 1.5	14.3 ± 1.6	2.04 ± 0.005	7.18 ± 0.85	99.4 ± 1.2	96.3 ± 4.0
F7	60	35 ± 4	5.3 ± 0.5	3.37 ± 0.09	31.79 ± 4.08	96 ± 4	100.6 ± 5.03
F8	63.3 ± 5.77	38 ± 2	10 ± 4.3	3.43 ± 0.005	32.42 ± 3.30	97.5 ± 1.3	101.3 ± 1.5
F9	70	28.3 ± 0.5	15.16 ± 0.28	2.94 ± 0.14	9.69 ± 0.28	98.3 ± 1.5	102 ± 6.24

Regression analysis

Results of regression polynomial equation for the individual dependent variable (DT, % elongation, % drug release and Young's modulus) and it uses to approximate the surface response plot and contour plots. The polynomial equations are given in terms of Eq. 1, 2, 3 and 4 and response plots for various responses that is disintegration time, % drug release and % elongation are shown in Figure 2 to 4. The various responses studied were

Disintegration time

DT = -3.19444+14.44444 * HPMC E5+4.16667* PVP K30 ..... (1)

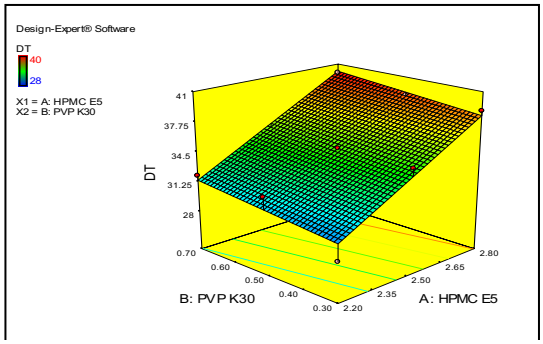

Figure 2: Response surface plot of DT

The polynomial Eq. (1) for disintegration time indicated that as the amount of HPMC increases there is a decrease in disintegration time and with increasing the amount of PVP there is an increase in the disintegration time. Amount of PVP K30 had a positive effect and HPMC E5 had a negative effect over disintegration time. The plot between the predicted and actual value represents the linear relationship with the R2 value of 0.9422 indicating excellent fit of surface response model. The Model F-value of 48.91 implies the model is significant.

% Drug release

Drug release = +97.25000+0.00000* HPMC E5+7.50000* PVP K30 .....(2)

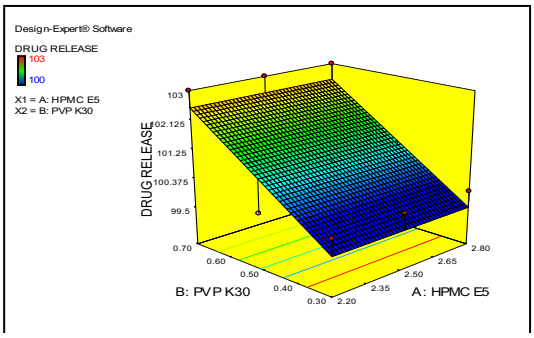

Figure 3: Response Surface plot for drug release

The polynomial Eq. (2) for the % drug release indicated that the amount of HPMC E5 had positive effect on the % drug release and the amount of PVP K30 had a positive effect on % drug release. Plot between the prideicted and actual value represent the linear relation ship with R^2 value of 0.7500 indicating good fit of surface response model. The Model F-value of 9.00 implies the model is significant.

% Elongation

Elongation = +48.88889-13.88888 * HPMC E5-8.33333* PVP K30 .....(3)

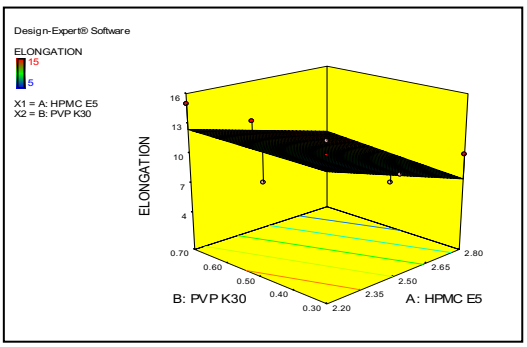

Figure 41: Response surface for Elongation

The polynomial Eq. (3) for % elongation indicated that amount of film-forming polymer (PVP K30) and HPMC E5 had a negative effect on the elongation. There is a significant interaction between the two variables as indicated by the diagnostic graph for interaction. The response surface plot demonstrated the effect of the amount of PVP K30 and HPMC E5 on the elongation of the film. The plot between the predicted and actual value represents the linear relationship with the R2 value of 0.8056 indicating excellent fit of surface response model. The Model F-value of 12.43 implies the model is significant.

Young's modulus

Young's modulus = -74.25239+31.26056* HPMC E5+29.28667 * PVP K30 .....(4)

The polynomial Eq. (4) for tensile strength indicated that amount of film-forming polymer (PVP K30) and HPMC E5 had a positive effect on Young's modulus. There is a significant interaction between the two variables as indicated by the diagnostic graph for interaction. The response surface plot demonstrated the effect of the amount of PVP K30 and HPMC E5 on Young's modulus of the film. The plot between the predicted and actual value represents the linear relationship with the R2 value of 0.7807 indicating excellent fit of surface response model. The Model F-value of 10.68 implies the model is significant.

Model justification

The normal probability plot of residuals showed for all test that residuals fell approximately along a straight line indicating that the data was normally distributed. To statistically analyse the CQAs DT, %DR, % elongation and Young's modulus a linear model was used. The ANOVA F- test indicated a high degree of significance ($p < 0.01$) for all chosen models.

Design space

The design space was determined from surface response plot and contour plot and the values are reported in Table 5.

Table 5: Design space

	Low	High
HPMC E5	2.53 %	2.8 %
PVP K30	0.32 %	0.49 %

The final optimized batches of RC MDF were formulated within design space and evaluated for various parameters and the results obtained are reported in Table 6.

Table 4: Evaluation of Optimized batches

Batch	HPMC (%)	PVP K30 (%)	D.T (sec)	Elongation (%)	Tensile strength (N/mm^2)	Young's modulus (N/mm^2)	Drug release (in 30 min) (%)
Dsb 1	2.53	0.32	38	10	2.861	14.305	100
Dsb 2	2.66	0.40	37	5	2.861	28.61	103
Dsb 3	2.80	0.49	33	5	3.024	30.24	100

Dsb- design space batch

The result indicated that batches of RC MDF prepared within the design space showed the value within QTPP indicating the success of application QbD in formulation of mouth dissolving film.

CONCLUSION

The mouth dissolving films was formed by solvent casting technique. Applying PB design various polymers and different concentration of polymers, drying time, and drying temperature was screened for the preparation of fast dissolving films. Based on PB trials two variables were found to have critical impact on formulation of films. These variables that are concentration of HPMC E 5 and PVP K 30 was further optimized using 3^2 full factorial design. The design space was determined and the final optimized MDF prepared within design space showed the results as per QTPP.

Thus it can be concluded that the successful formation and optimization of fast dissolving films of RC using HPMC E5 as film-forming polymer and glycerol as a plasticizer Hence, RC can be conveniently administered orally in the form of films.

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