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Quality by Design (QbD) driven Formulation development and Optimization of Metoprolol Tartrate loaded Microspheres using Custom Design

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Abstract
Hypertension affects approximately 1.28 billion adults globally, with significant prevalence in low and middleincome countries. Metoprolol, a beta-blocker, effectively treats hypertension and other cardiovascular conditions but requires multiple daily doses due to its short half-life, leading to compliance issues. This study aimed to develop metoprolol-loaded sustained-release microspheres using a Quality by Design approach to provide consistent therapeutic effects over an extended period. The formulation utilized Eudragit RL 100, HPMC, PVP, and ethyl cellulose as polymers, optimized through a custom design in JMP® software, which simultaneously screened and optimized formulation parameters. The critical material attributes and critical process parameters included polymer type, drug-to-polymer ratio, solvent, stirring rate, and time. The critical quality attributes were selected as particle size, encapsulation efficiency, drug release profile, and % yield. The formulation trials were prepared and evaluated as per the design matrix of custom design and optimized numerically using the prediction profiler which showed 0.63 on a 0-1 scale. The optimized formulation achieved a controlled drug release, with an initial burst of less than 20% at 1 hour, followed by sustained release, ensuring patient compliance and therapeutic efficacy. Using Eudragit RL 100 resulted in the most favorable outcomes in terms of particle size, encapsulation efficiency, and % yield. The optimized formulation, validated through predictive modeling, promises a robust and efficient solution for hypertension management.
Keywords: Custom design, Metoprolol tartrate, Microspheres, Eudragit RL 100, Optimization

Introduction

An estimated 1.28 billion adults aged 30–79 years worldwide have hypertension, most (two-thirds) living in low- and middle-income countries. 46% of adults with hypertension are unaware that they have the condition. One of the global targets for non-communicable diseases is reducing hypertension prevalence by 33% between 2010 and 2030 [1].Metoprolol, a beta-blocker, is used to treat various cardiovascular conditions such as hypertension, angina, and heart failure. This is commonly prescribed for managing hypertension and other cardiovascular conditions [2,3]. Despite its efficacy, the conventional dosage forms of Metoprolol Tartrate (MPT) often require multiple daily administrations due to its short half-life of 3 to 7 hours. This necessitates variousdaily doses to maintain therapeutic blood levels, leading topotential issues with patient compliance and fluctuations in blood plasma levels [4]. To overcome the problems found in the conventional metoprolol formulation, the study was designed to formulate metoprolol microspheres sustained release formulation through a quality by design (QbD) approach. Sustained release formulations of metoprolol address these challenges by providing a consistent therapeutic effect over an extended period, improving patient adherence and clinical outcomes [5]. Microspheres are tiny spherical particles, typically ranging from 1 to 1000 micrometres in diameter, that can encapsulate the drug, providing a controlled release profile [6,7]. The novelty of sustained-release microspheres lies in enhanced bioavailability, reduced dosing frequency, minimized side effects, and improved therapeutic efficacy [8,9]. The formulation development through Quality by Design (QbD), ensures that the product meets predefined quality criteria [10]. This approach enhances the robustness and reliability of the final product [11,12]. Design of Experiment (DoE)mathematically identifies relationships between independent variables and dependent variables and helps in optimizing the respective variables. Additionally, DoE reduces the number of trials needed, saves time, and resources, and supports regulatory compliance [12].

In the present research, the modern DoE, custom design has been constructed simultaneouslyto screen and optimize metoprolol-loaded microspheres. This approach collects comprehensive data on multiple variables and their interactions in a single step, providing a thorough understanding of the selected variables. The improved predictive capability of custom designs creates accurate models, identifying and mitigating risks early in the development process.

Material and Methods

Materials

The gift sample of MPT was received from Zim Laboratories Mumbai, India, and Eudragit RL 100 was obtained from Sai Meera Pharma, Chennai. Hydroxy propyl methyl cellulose, Ethyl cellulose, and Polyvinyl pyrrolidone were received from S.D Fine Chemicals Ltd. Mumbai. Liquid paraffin heavy was obtained from Ponmani & Co Coimbatore, India. All the other chemicals, reagents, and solvents were of analytical grade.

Methods

Quality by DesignApproach

Identification of Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs)

As per ICH Q8 guidelines, the modern product development aspects start with identifying the QTPP. It defines the elements that are highly significant to product quality, safety, and efficacy. The QTPP is considered the key component of QbD, for the formulation of metoprolol microspheres, the QTTP was established based on the literature survey and functional attribute of the formulation. The QTPP elements and their justification are given in Table 1.Identifying and controlling CQAs is crucial for ensuring the product's performance meets the desired QTPP [13].Key CQAs for the microspheres may include particle size, drug loading, in vitro release profile, and surface morphology. The CQAs of metoprolol microspheres are given in Table 2.

Table 1: QTPP elements with their justification

QTPP elements	Target	Justification
Dosage type	Microsphere	To ensure the sustained release of the product.
Dosage strength	100 mg	Reduced dose
Route of administration	oral	Patient compliance
Pharmacokinetic properties	To maintain a Steady-statecondition of metoprolol	To avoid multiple administrations
Product quality attributes	Drug release rate, Particle size distribution, Encapsulation efficiency	To ensure the final quality of the product
Drug Release	Sustained release profile over 24	To achieve a sustained release to

	hours	maintain therapeutic levels.
Shelf-life	Minimum shelf-life of 2 years	To assess the degradation pattern of the formulation by monitoring product quality.

Table 2: CQAs with their justification

Product Quality attributes		**Target**	**CQA**	**Justification**
Surface Morphology	Appearance	Smooth and spherical particles	No	Impacts on drug release mechanism and stability
Drug loading		20% w/w	Yes	Determines the amount of active ingredient in each microsphere and ensures dose uniformity
Encapsulation Efficiency (%)		≥ 90%	Yes	Indicates the efficiency of the drug encapsulation process, impacting the overall yield.
Particle size Distribution (nm)		50-200 µm	Yes	Affects drug release rate, bioavailability, and stability.
Invitro drug release (24 hrs)		Initial burst < 20%, 90-110% of QTPP	Yes	To achieve a sustained release to maintain therapeutic levels.
Stability		2 years at recommended conditions	Yes	Ensures that the microspheres maintain their quality attributes over the intended shelf-life.

Risk identification and assessment

Risk assessment is a systematic process of identifying, evaluating, and prioritizing potential risks to product quality and determining strategies to mitigate these risks. Identification of potential risks related to raw materials, and process parameters are utilized techniques like Ishikawa diagram and risk estimation matrix [14,16]. Effective risk assessment ensures proactive identification and control of factors that could impact product quality. Ishikawa diagram is known as the fishbone diagram structured to identify the possible causes and sub-causes affecting the CQAs of the product. The potential factors affecting the product CQAs are identified in Figure 1.Which represents potential factors affecting the quality of the

formulation process, helping to identify root causes of variations or issues.Risk Estimation Matrix Table can be used to assess potential risks in the formulation of metoprolol sustained-release microspheres. This table helps evaluateeach risk factor's grade of low, medium, and highproviding a measure of overall riskas shown in Table 3.

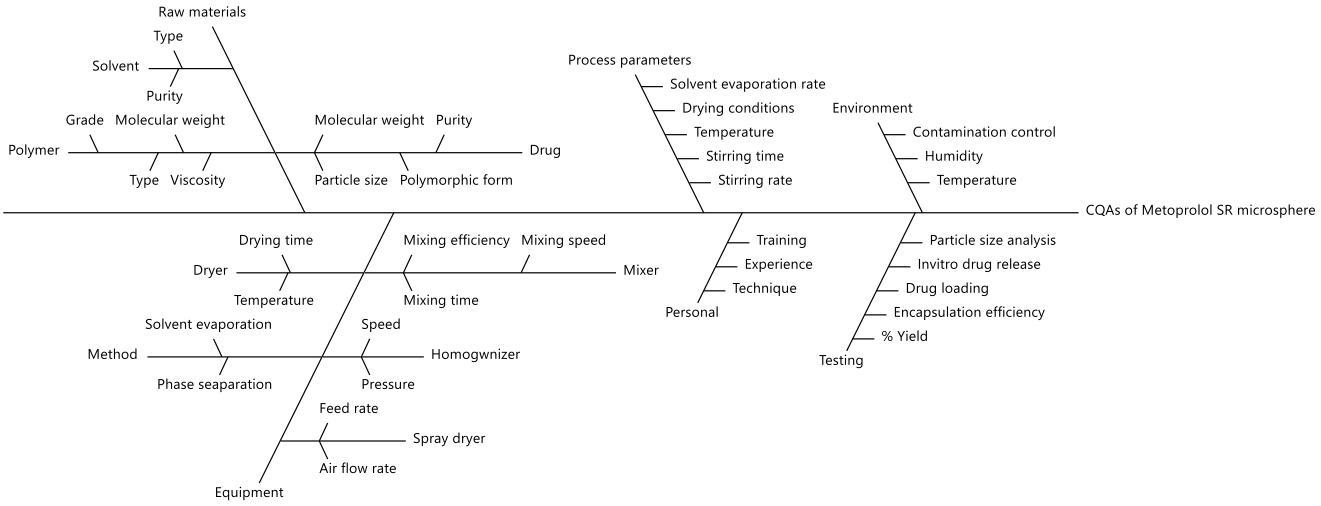


Figure1. Cause and Effect Diagram for metoprolol microspheres

Table 3: Risk Assessment Matrix

CMA/ CPP / CQA	% yield of microspheres	Drug load	Particle size distribution	Encapsulation efficiency	Drug release profile
Polymer	Low	High	Medium	High	High
Solvent	High	Low	High	High	Medium
Drug: Polymer ratio	Low	Medium	Medium	High	High
Polymorphic form	Low	Medium	Low	Medium	High
Homogenization	Low	High	Medium	Low	High
Stirring rate	Medium	Low	High	High	High

Stirring time	Low	Medium	High	Low	Low

Design of Experiment- Custom Design (CD)

In the present study, simultaneous screening and optimization were performed by employing the modern DoE- the CD, which was constructed using the JMP® 17.0.0 software (Trial version). The CD is particularly advantageous for pharmaceutical formulations because it can accommodate a mixture of factor types (continuous and categorical) and allows for the screening and optimization of process conditions in a relatively smaller number of trials compared to traditional designs. Also, offers the flexibility needed to adapt to various experimental constraints such as limited resources, time, or material availability.The Custom Designer always makes the best use of your experimental budget [18]. Using its computer-generated designs allows you to tackle a wide range of challenges, all within a unified framework. It also includes the continuous, multilevel categorical, and mixture factors within the same design, and specifies hard- and very hard-to-change factors for automatic creation of the appropriate split-plot, split-split, and strip-strip designs [19,20]. In the present study of formulation development of metoprolol-loaded SR microspheres, the CMAs are as categorial factors like polymer, solvent, drug and polymer ratio, and non-solvent medium and CPPs were selected as continuous factors such as stirring time and stirring rate. The CQAs identified were Particle size, Encapsulation efficiency, drug release, and % yield of microspheres. Both the independent and dependent factors that were chosen are mentioned in the table 4, 4a & 5.

Table 4: Categorical factors of CMAs

Factors	Raw materials
Polymers (Categorical)	Eudragit RL100
	HPMC
	PVP
	Ethylcellulose
Solvents (Categorical)	Dichloromethane
	Ethanol
	Acetone
Drug: polymer ratio (Categorical)	1:1.4
	1:1

Non-solvent medium (Categorical)	Liquid Paraffin Heavy
	Sodium Chloride

Table 4a. CPPs and their limits

Factors	Process Parameters	Lower limit	Upper limit
Continuous	Stirring Rate (rpm)	800	1200
Continuous	Stirring time (min)	200	250

Table 5: Responses and limits set in Custom Design

Responses	Goal	Lower limit	Upper limit
Entrapment Efficiency (%)	Maximize	90	100
Vesicle Size (nm)	Minimize	100	200
Invitro drug release (%)	Maximize	90	100

Preparation of Metoprolol loaded microspheres.

Metoprolol SR microspheres were prepared by solvent evaporation technique. The polymers ethyl cellulose, Eudragit RL100, PVP, and HPMC were dissolved in a solvent such as Ethanol, Acetone, and Dichloromethane. Then the drug was added to the polymer solution. The resulting mixture was then added drop by drop into a Liquid Paraffin Heavy or Sodium Chloride solution while stirring continuously. The stirring rate was maintained at 800 or 1200 rpm and continued for four hours until the organic solvent evaporated completely.The dispersed drug and polymer were transferred into fine droplets, which subsequently solidified into rigid microspheres due to solvent evaporation. The microspheres formed were collected by filtration, washed 4 to 5 times with distilled water, and dried at room temperature for 24 hours [21,22]. There was a total of 24 runs of the experiment. All the runs of experiments were formulated and responses were recorded. The formulation development of Metoprolol microsphere JMP-assisted runs of the experiment is shown in Table. 6.

Design Evaluation:Design Diagnostics

The efficiency of CD was evaluated using design evaluation parameters, such as a colour map on correlations and design diagnostics. The Colour Map on Correlations Shows the absolute correlations between effects on a plot using an intensity scale and design diagnostics were estimated by % efficiency of design.

Model fit

The various responses obtained for all 24 formulations of metoprolol microspheres were incorporated into the design to check the model fit. The data was statistically analyzed by fitting a multiple regression model with zero intercepts. The effects summary obtained for the whole model and the actual Vs predicted plots were analyzed for the model fit.

Optimization by Prediction Profiler

The most popular numerical approach used for simultaneous optimization of the formulation is the desirability function approach. The desirability function approach utilizes a prediction profiler, whereas the optimization is performed by attaining individual desirability functions for the respective responses. The global desirability function value generated is assigned a value ranging from 0 to 1. A value close to one indicates the maximization of desirability.

Table 6, Custom Design Matrix for Formulation of Metoprolol Microspheres

Number of Runs	Polymer	Solvent	Drug:polymer ratio (w/w)	Stirring rate (RPM)	Non- solvent medium	Stirring Duration (min)	Particle Size (µm)	Encapsulation Efficiency (%)	Drug Release Rate at 1 hour (%)	Yield of Microspheres (%)
1	Ethylcellulose	Acetone	01:01.4	800	Sodium Chloride	250	130.31	80.21	29.64	67.87
2	Eudragit RL100	Acetone	01:00.0	800	Liquid Paraffin Heavy	200	67.11	83.14	45.65	72.47
3	HPMC	Acetone	01:01	1200	Sodium Chloride	200	129.72	73.94	23.8	93.73
4	Ethylcellulose	Ethanol	01:01	800	Sodium Chloride	200	108.45	73.04	38.22	84.93
5	Ethylcellulose	Ethanol	00:01	1200	Liquid Paraffin Heavy	200	99.69	93.13	30.87	72.05
6	PVP	Ethanol	01:00.0	800	Liquid Paraffin Heavy	250	138.35	98.56	27.01	87.7
7	PVP	Ethanol	00:01	800	Sodium Chloride	200	150.93	84.28	30.92	81.46
8	Eudragit RL100	Ethanol	01:00.0	1200	Sodium Chloride	250	147.94	95.04	10.12	94.53
9	PVP	Dichloromethane	00:01	1200	Sodium Chloride	200	94.82	88.62	27.8	69.47
10	HPMC	Dichloromethane	01:01.4	800	Sodium Chloride	250	110.72	78.55	33.57	75.09
11	PVP	Acetone	01:00.0	800	Liquid Paraffin Heavy	250	129.94	88.61	44.78	74.12
12	Ethylcellulose	Dichloromethane	01:01	1200	Liquid Paraffin Heavy	250	149.27	100.38	24.82	58.05
13	HPMC	Dichloromethane	01:01	800	Liquid Paraffin Heavy	200	109.93	77.67	25.34	64.42
14	HPMC	Acetone	01:01	1200	Sodium Chloride	200	97.23	81.21	17.88	83.23
15	PVP	Acetone	00:01	1200	Liquid Paraffin Heavy	250	112.95	70.43	22.28	62.79
16	PVP	Dichloromethane	01:00.0	1200	Sodium Chloride	200	130.46	71.38	25.55	77.09
17	Ethylcellulose	Dichloromethane	01:01	1000	Liquid Paraffin Heavy	225	95.32	77.19	19.25	55.4
18	HPMC	Ethanol	00:01	1200	Liquid Paraffin Heavy	250	95.32	74.94	26.88	61.72
19	Ethylcellulose	Acetone	01:01.4	800	Sodium Chloride	250	131.58	81.57	25.6	76.97
20	Eudragit RL100	Ethanol	01:00.0	1200	Sodium Chloride	250	115.35	75.46	23.54	82.38
21	Eudragit RL100	Dichloromethane	00:01	800	Liquid Paraffin Heavy	200	90.61	72.94	21.99	76.71
22	HPMC	Ethanol	01:01.4	1000	Liquid Paraffin Heavy	225	110.85	87.33	34.26	73.84
23	Eudragit RL100	Acetone	01:01.4	1200	Liquid Paraffin Heavy	200	90.73	78.87	24.93	71.99

24	Eudragit RL100	Dichloromethane	01:01.4	800	Sodium Chloride	250	70.43	76.4	22.7	85.57

Characterization of microspheres

Percentage(%) yield

The prepared and dried microspheres were weighed and percentage yield was calculated using the following formula.

$$Percentage\ yield = \frac{weight\ of\ microsphere}{Total\ expected\ weight\ of\ drug\ and\ polymer} \times 100$$

Particle Size Distribution

Metoprolol-loaded microspheres were suspended in water and the particle size was analyzed utilizing a Mastersizer 3000 instrument paired with a Hydro 3000S dispersion unit [22]. The mean particle size was recorded.

Drug Content

About 10 mg of metoprolol microspheres were accurately weighed and placed into 5 mL volumetric flasks. Approximately 3 ml of phosphate buffer solutions (pH 7.4), was then added, and the mixture was sonicated until the microspheres were fully dissolved. The solution was then diluted to a final volume with phosphate buffer solutions (pH 7.4). The resulting clear solution was filtered through a 0.2-micron syringe filter and the drug content was subsequently determined using a UV spectrophotometer. The UV detector was set to operate at a wavelength of 274 nm for the measurement of absorbance. The loading percentage and entrapment efficiency (EE) were determined using the following formulas [22,23].

$$Drug\ loading\ (\%) = \frac{Drug\ content\ in\ microspheres}{Total\ weight\ of\ microspheres} \times 100$$

$$Entrapment\ efficiency\ (EE) = \frac{Drug\ loading\ content\ in\ microspheres}{Total\ weight\ of intial\ drug\ content} \times 100$$

***In-vitro* Drug Release Study of Metoprolol Tartrate Microspheres**

In vitro drug release from MT,microspheres were studied using the rotating basket method.

Microspheres equivalent to 100 mg of MT were carefully placed in a basket, which was secured using a muslin cloth. The basket was then immersed in 900 mL of phosphate buffer with a pH of 7.4, serving as the dissolution medium. The system was set to rotate at 100rpm, and the temperature was maintained at 37°C ± 0.5°C to ensure consistent conditions.Samples of 5 mL were withdrawn at predetermined hourly intervals for up to 2 hours. An equal volume of fresh dissolution medium was added each time a sample was taken to maintain sink conditions. After the initial 2-hour period, the dissolution medium was replaced with 900 mL of fresh phosphate buffer with a pH of 7.4. The study then continued under these new conditions for up to 12 hours. The collected samples were analyzed using aUV spectrometer at a wavelength of 274 nm to determine the cumulative % drug release [22,23].

Results and Discussion

Quality by Design Approach

The development of a quality-by-design (QbD) approach for the preparation of metoprolol tartrate-loaded sustained-release microspheres was investigated in this study. The critical quality attributes of the microspheres, including particle size, drug loading, % yield, and *in-vitro* drug release were identified, and the critical formulation and process variables that influence these attributes were systematically evaluated. Pharmaceutical companies often focus more on the development process rather than the manufacturing, which can lead to an inability to meet pre-specified quality standards or predict the effects of scale-up on the final product [25].

The quality target product profile was defined, and the critical quality attributes were identified. Risk assessment was studied usingthe Ishikawa diagram, risk estimation matrix was performed to recognize the critical formulation, process, and delivery device variables.

Ishikawa diagram was constructed to identify the potential causes of variation for each CQA. It visualizes the relationship between CMAs and CPPs or deviations in CQAs. The risk estimation matrix was analyzed to prioritize potential risks based on their overall risk using the scoring system used (e.g., low, medium, high) for both probability and severity.

Design of Experiment- Custom Design (CD)

The Design of Experiments (DOE) is a crucial statistical tool used in engineering and science to plan, conduct, analyze, and interpret controlled tests to evaluate the factors that control the value of a parameter or group of parameters. In pharmaceutical manufacturing, particularly in

microsphere formulation, understanding these factors is vital to ensure the efficacy and safety of the final product. JMP software's custom design DOE was employed to formulate and optimize the MT microspheres, a method well-suited for managing the complex interactions among formulation variables. The selection of a custom design in JMP was driven by its robustness in handling complex experiments where interactions between multiple factors are expected. This design type is particularly advantageous for pharmaceutical formulations because it can accommodate a mixture of factor types (continuous and categorical) and allows for the optimization of process conditions in a relatively smaller number of trials compared to traditional factorial designs.

Preparation of Metoprolol loaded microspheres

In the formulation of metoprolol sustained-release microspheres, various factors were meticulously optimized to ensure effective drug delivery. Ethylcellulose, Eudragit RL100, PVP, and HPMC were selected as polymers for their unique properties influencing drug release and structural integrity. Ethanol, acetone, and dichloromethane were chosen as solvents for their effectiveness in dissolving polymers and controlling particle uniformity. Drug:polymer ratios of 1:1 and 1:1.4 were tested, and stirring rates of 800 to 1200 rpm were explored to impact mixture homogenization and microsphere size. Non-solvent mediums, such as liquid paraffin heavy and sodium chloride, were examined for their effects on solvent removal and particle stability. Stirring durations of 200 to 250 minutes were set to assess mechanical agitation's impact on microsphere properties. Key responses included particle size, enhancing drug dissolution; encapsulation efficiency, indicating process efficiency; drug release rate at 1 hour, crucial for therapeutic effectiveness; and microsphere yield, essential for commercial viability.

Design Evaluation

The design evaluation was done to evaluate the constructed CD. Color Map Correlations from Figure 1 shows the absolute correlation between effects on a plot using an intensity scale which was used to estimate the effect of each factor alone or in combination with other factors on the required responses. The deep red colouring indicates absolute correlations representing the most effective combination. Either deep blue or light blue corresponds to

correlations between quadratic terms in descending order of effectiveness in attaining the required responses. Design Diagnostics in Table 6 indicates the optimality criterion used to construct and gives efficiency measures of D, G, and A with the design creation time of 0.01 seconds for CD.

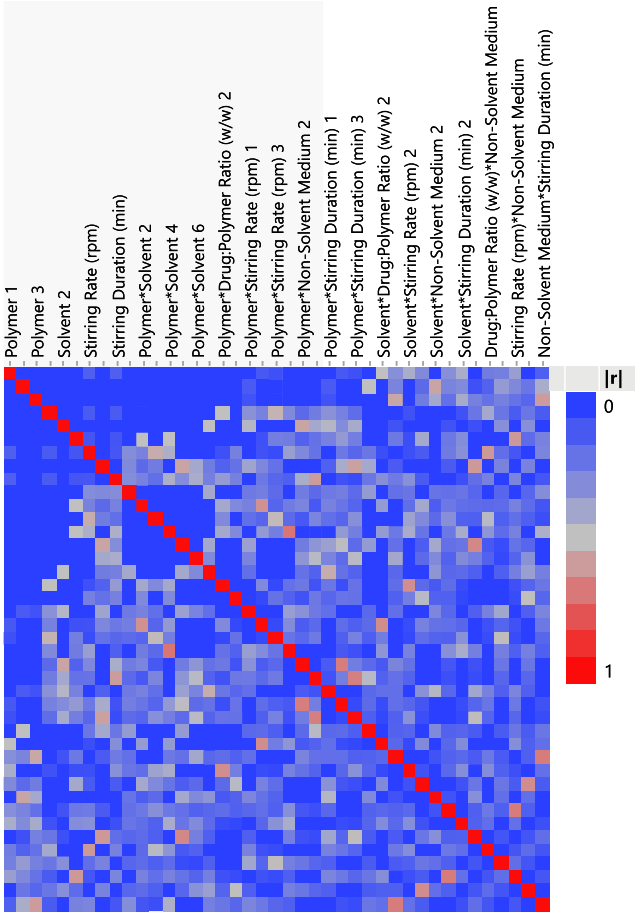


Figure1. **Color Map on Correlations**

Table 6. **Design Diagnostics**

D Efficiency	97.52905
G Efficiency	88.50081
An Efficiency	96.68032
Average Variance of Prediction	0.3678
Design Creation Time (seconds)	0.016667

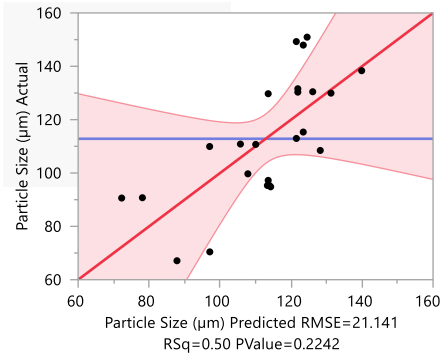
Model fit

After all the responses were evaluated, the results were incorporated into the selected CD. The model was studied by analyzing the effect summary and actual Vs predicted the plot of all responses. The non-solvent medium has shown highly significant (*P*=0.00107) in the responses. The stirring rate and solvent showed a significant effect, Polymer, drug: polymer ratio, and stirring duration were insignificant. The effect summary of model fit statistics is summarized in Table 7.

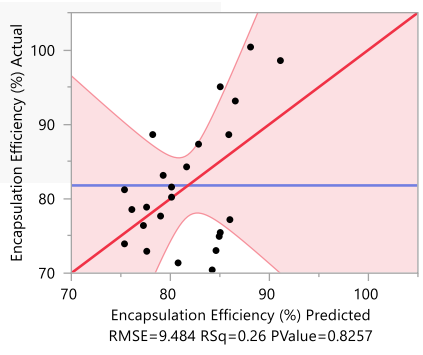
Table 7 Effect Summary of CMAs and CPPs

Source	LogWorth		PValue
Non-Solvent Medium	2.971		0.00107
Stirring Rate (rpm)(800,1200)	1.643		0.02274
Solvent	1.449		0.03553
Polymer	1.069		0.08534
Drug:Polymer Ratio (w/w)	0.858		0.13881
Stirring Duration (min)(200,250)	0.836		0.14580

The actual Vs predicted plot was analyzed, The R2 and p values obtained from all the responses like particle size (R^2=0.50, *P*=0.2242), Encapsulation efficiency (R^2=0.26, *P*= 0.8257), in-*vitro* drug release (R2=0.43, *P*=0.3728), and % yield of microsphere (R^2=0.72, *P*=0.0094) (Figure 2a,2b,2c,2d) were shown the correlation between actual Vs predicted responses and the correlation is significant.



2a



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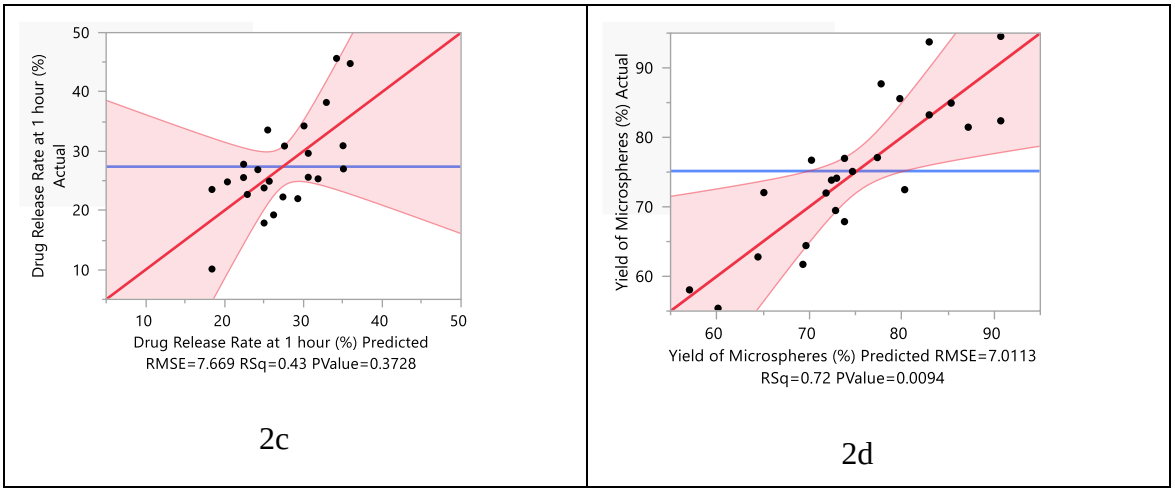

Figure 2a,2b,2c,2d, Actual vs predicted plot of particle size, Encapsulation efficiency, % drug release, and % yield of microspheres

Particle Size

The particle size directly influences the drug release. The lesser the particle size, the higher the surface area and more the bioavailability. The average particle size for microspheres was found to be less than 200 µm. The particle sizes of metoprolol-loaded microspheres were polymer type, drug-to-polymer ratio, and solvent and non-solvent ratio. Among the selected polymers ethyl cellulose, Eudragit RL 100, Polyvinyl pyrrolidone, and hydroxy propyl methyl cellulose, Eudragit RL 100 has shown the lesser particle size. This may be attributed to properties like solubility, solution's viscosity, surface activity, and film-forming ability prominently affecting the efficient emulsification which helps produce the smaller microspheres.

Also, Eudragit has formed a robust matrix around the drug particles and ensures the drug release. The drug-to-polymer ratio influences the particle size. The higher the drug-to-polymer ratio, the lower the particle size imparting to the viscosity of the formulation. The higher viscosity of the formulation leads to higher particle size. The results agree with Xu, J *et*., al.

Process parameters like stirring time and stirring rate significant parameters thataffect the solvent evaporation rate. A faster evaporation rate leads to smaller particle size and ensures uniform particle size in the metoprolol SR microspheres.

Encapsulation Efficiency (EE)

EE of the drug into the microspheres depends on the proportion of metoprolol loaded in

the formulation. The polymer concentration and drug-to-polymer ratio influence the EE. The higher the polymer concentration increases the EE. The formulation trials have shown the EE range from 70.43% to 100.88%. It was clearly understood higher drug concentration and equal ratio of drug and polymer have shown higher EE. The formulation coded 12, with a 1:1 ratio of drug and polymer with a stirring time of 1200 mins for 250 mins has shown the EE.

Precentage(%) Drug release at 1 h

Drug release from microspheres depends on multiple factors. The most significant material attribute that influenced the drug release was identified as polymer type. In the metoprolol, SR microspheres have followed the pattern of initial burst release followed by sustained release. The eudragit polymer was controlled to balance the initial burst and provided a sustained release. The polymer-to-drug ratio plays a vital role in the burst release and controls the release rate. The results agreed with Arefin, P *et*., al.

Based on the formulation trial responses, all the formulations of eudragit RL 100 met the standard limit of 20% initial release at 1h.

Percentage(%) yield of microspheres

The % yield of microspheres was arguably affected by the polymer type and its properties like viscosity and stability of the polymer. Higher viscosity forming polymers show higher % yield. Eudragit RL100 contains formulation coded as8, followed by HPMC (formulation code 3) have shown the highest yield, due to its viscosity and process factors stirring speed, drying method, and phase volume ratio were imparting to the % yield of microspheres.

Optimization

The prediction profiler was adjusted with maximized desirability to optimize the selected factors and responses. The prediction profiler reveals the desirability of individual responses on the desirability scale. The particle size and encapsulation efficiency have shown a desirability of 0.5, whereas % drug release and % yield of microsphere have shown 1 and 0.75 respectively. The global desirability function value of the overall prediction profiler is 0.63 shown in Figure 3. Hence, all responses were predicted to be within the desired limit (0-1).Hence the optimized formulation of SR microspores was predicted by JMP Table 8 and was further considered for the validation and analysis.

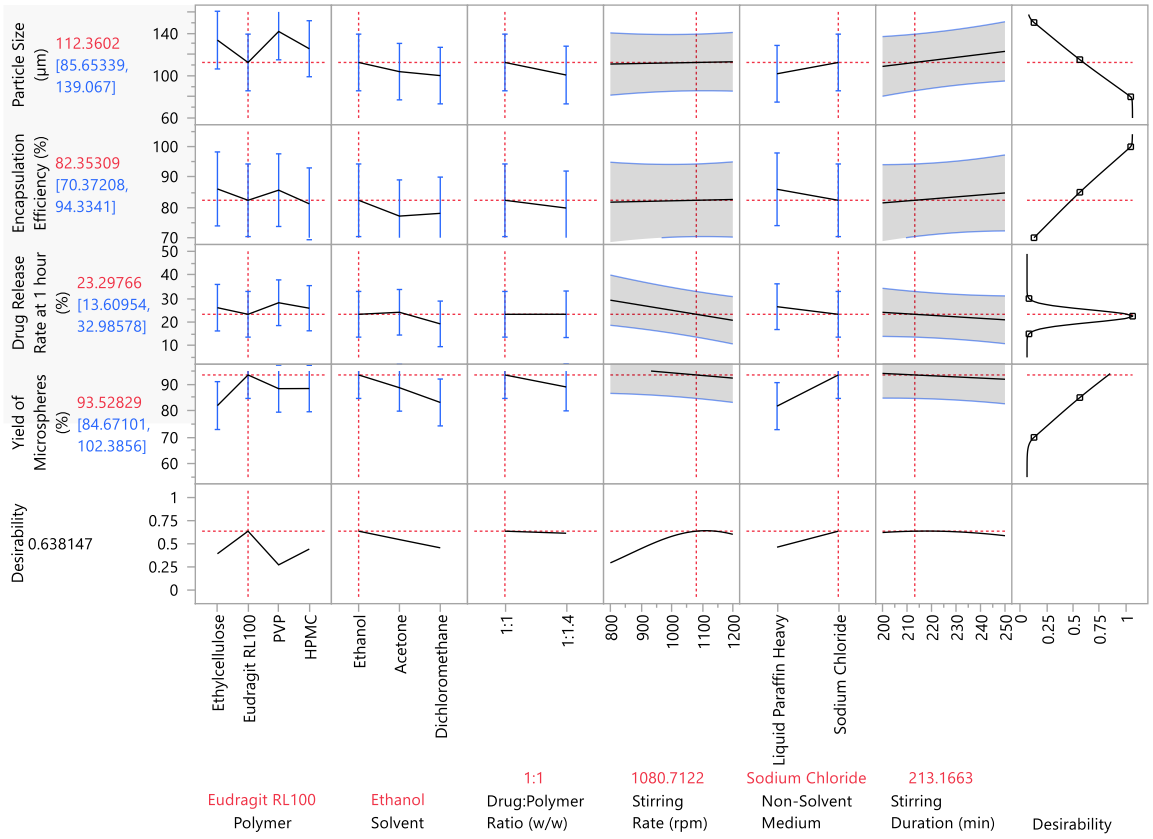

Figure 3. Prediction Profiler with maximized desirability

Conclusion

The Modern DoE custom design was devised to perform the simultaneous screening and optimization of metoprolol tartrate-loaded microspheres. Eudragit RL 100 showed a good response on particle size, encapsulation efficiency, and % yield of microspheres. The formulations were optimized using the prediction profiler of JMP, which predicts the optimum set of factors to optimal desired responses. The responses optimized by were met predetermined QTPP. The optimized factors further to be validated and could be used for pilot studies. This sound scientific approach has laid a promising basis for the successful development and commercialization of metoprolol-loaded microspheres. The optimized formulation would meet patient compliance rightly by producing a consistent drug release for the management of hypertension.

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