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Taming the Morning Surge: A QbD-Engineered Multiparticulate Capsule for Sequential RAAS and β_1-Blockade in Circadian Hypertension

Gokul Haribut
SRM College of Pharmacy, SRM Institute of Science and Technology
Suriya Prakaash Kannan
SRM College of Pharmacy, SRM Institute of Science and Technology
Damodharan Narayanasamy
damodhan@srmist.edu.in

SRM College of Pharmacy, SRM Institute of Science and Technology

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Taming the Morning Surge: A QbD-Engineered Multiparticulate Capsule for Sequential RAAS and β_1-Blockade in Circadian Hypertension

Gokul Haribut[1], Suriya Prakaash Kannan[2], Damodharan Narayanasamy[1*]

Department of Pharmaceutics, SRM College of Pharmacy, Faculty of Medicine and Health Sciences, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu-603203, India.

Orcid ids:

1.Gokul Haribut: http://orcid.org/0009-0002-0359-1937

2. Suriya Prakaash Kannan: http://orcid.org/0009-0006-9479-2935

3. Damodharan Narayanasamy: http://orcid.org/0000-0003-4246-5351

Corresponding Author:

Dr. Damodharan Narayanasamy

Department of Pharmaceutics,

SRM College of Pharmacy,

SRM Institute of Science and Technology,

Kattankulathur, Tamil Nadu-603203.

E-mail: damodhan@srmist.edu.in

Abstract

Purpose: Morning blood pressure surge increases cardiovascular risk due to circadian activation of the renin–angiotensin–aldosterone and sympathetic nervous systems. This study developed a Quality by Design (QbD)-based dual-release multiparticulate capsule providing immediate release of olmesartan medoxomil followed by pH-responsive delayed release of metoprolol succinate for chronotherapeutic management of circadian hypertension.

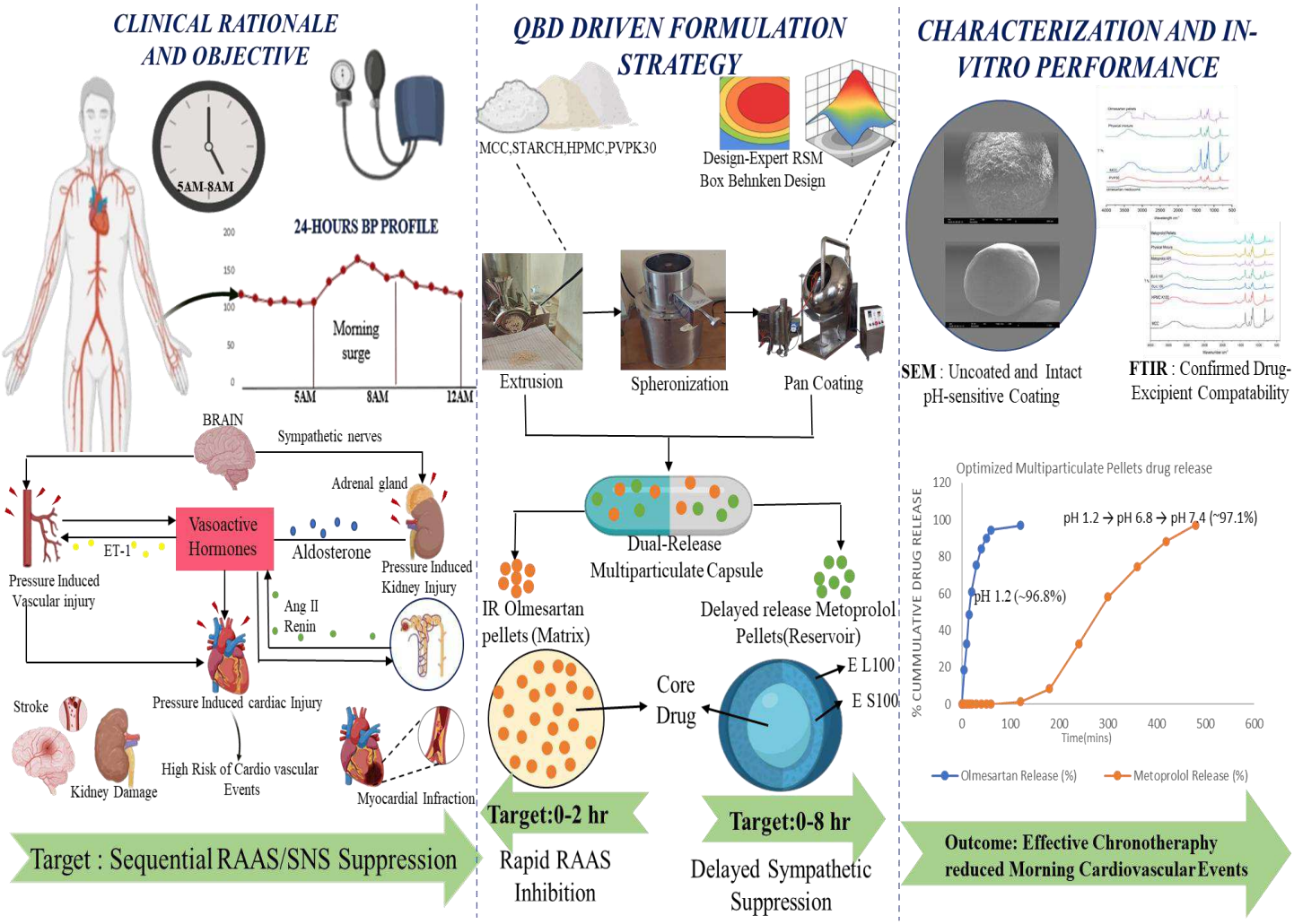
Methods: Immediate and delayed-release pellets were prepared by extrusion-spheronization and optimized using Response Surface Methodology with a Box-Behnken Design. Critical formulation variables were optimized to maximize entrapment efficiency, production yield, and drug release. Optimized formulations were evaluated by FTIR, SEM, dissolution studies, release kinetics, and accelerated stability testing.

Results: Optimized formulations showed excellent agreement with the quadratic models (R^2 = 0.9915–0.9988; $p < 0.0001$). Immediate-release olmesartan pellets provided rapid drug release, while Eudragit-coated metoprolol pellets minimized gastric release and achieved controlled intestinal release. The optimized capsule exhibited satisfactory physicochemical properties, high content uniformity, low friability, reproducible sequential drug release, and acceptable accelerated stability.

Conclusion: The QbD-based multiparticulate system successfully combined immediate and delayed drug release in a single chronotherapeutic dosage form. The optimized formulation established a robust design space and demonstrated the potential of sequential multiparticulate delivery for improving management of the early morning hypertension surge.

Keywords: Chronotherapeutics; Quality by Design; Multiparticulate Pellets; Circadian Hypertension; Sequential Drug Release; Response Surface Methodology; Cardiovascular Risk Reduction.

Graphical abstract



1. Introduction

Hypertension is among the most common chronic cardiovascular diseases and the leading cause of morbidity and mortality worldwide [1]. Consistent high blood pressure can lead to many cardiovascular diseases such as myocardial infarction, stroke, heart failure, chronic kidney disease, and others. Despite the availability of many anti-hypertensive medications, it is hard to control blood pressure due to its circadian fluctuations[2]. Blood pressure is known to decrease when people are asleep and to increase suddenly after waking up, which is called morning blood pressure surge (MBPS)[3, 4]. The main mechanism that leads to MBPS is the activation of renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system, increasing the risk of cardiovascular diseases at early morning times[5]. Chronotherapy-based drug delivery systems synchronize drug delivery with disease biological rhythms instead of the time of administration. These types of drug delivery systems increase the efficacy of the therapy

and reduce the unnecessary side effects[6]. Multiparticulate pellets are considered among different kinds of chronotherapeutic strategies that offer gastrointestinal homogeneity in drug delivery, minimal absorption variations, less possibility of dose dumping, better gastric emptying rate, and formulation versatility (Fig. 1)[7, 8] .

Olmesartan medoxomil, which is an AT1 blocker, can quickly block RAAS through inhibition of AT1 receptors. On the other hand, metoprolol succinate, which is a selective β1-adrenoceptor blocker, can reduce the heart rate, cardiac output, and renin secretion through inhibition of sympathetic activity [9, 10]. Considering that RAAS and sympathetic activation are factors in MBPS, a combination of the two should be more effective than using either drug alone. Conventional fixed dose combination, which releases the two drugs at once without considering their different pharmacokinetics, cannot be considered a better alternative [11, 12].Extrusion–spheronization is a widely used technique for producing multiparticulate pellets with excellent sphericity, uniform size distribution, flow properties, mechanical strength, and drug loading[13]. Immediate-release pellets can be prepared using suitable binders and disintegrants, whereas delayed-release pellets are achieved by coating with pH-sensitive polymers such as Eudragit L100 and Eudragit S100. Combining immediate-release olmesartan pellets with delayed-release metoprolol pellets in a single capsule enables sequential drug delivery to suppress RAAS and sympathetic activity at appropriate times [14].

The concept of QbD allows one to take a more structured approach to developing pharmaceutical products by introducing quality into the drug formulation process itself, as opposed to quality being introduced only at the later stages of manufacturing through testing the final product[15] . The quality-by-design approach includes QTPP, CQAs, CMAs, CPPs, risk assessment, DoE, among others to create a solid design space [16]. Using Response Surface Methodology with Box-Behnken Design can help optimize pellet parameters such as entrapment efficiency, yield, size, sphericity, and drug release.

Whereas the use of chronotherapeutic and multiparticulate drug delivery systems has received much attention in recent years, research that combines a systematic quality-by-design approach with sequential dual-drug delivery for control of early morning rise in blood pressure is still very few. For this reason, this current study reports on the preparation of a quality-by-design dual delivery multiparticulate capsule containing immediate-release olmesartan medoxomil pellets and pH-sensitive delayed-release metoprolol succinate pellets by extrusion-spheronization and Box-Behnken optimization.

2.Materials and Methods:

2.1 Materials:

Microcrystalline Cellulose (MCC-Avicel PH-101) – Procured from Indian Fine Chemicals, Mumbai. Hydroxypropyl Methylcellulose (HPMC K100M) was purchased from HiMedia Laboratories, mumbai. Polyvinyl pyrrolidine k 30,Talc Obtained from SD Fine Chemicals Ltd, Chennai. Corn Starch – Procured from SD Fine Chemicals Ltd, Chennai. Eudragit S 100 and L 100 -procured from Yarrow chem, Mumbai. Olmesartan medoxomil and Metoprolol succinate is an active pharmaceutical drug, was received as a gift sample. The remaining chemicals and reagents used in this experiment were all of analytical grade.

2.2 Methods

2.2.1 Application of the Quality by Design (QbD)

The Quality by Design (QbD) approach is a science- and risk-based strategy that uses knowledge about material attributes and process parameters to develop quality during the process, instead of relying on tests performed on the end-product alone. It involves determining the formulation and process variables that impact the CQA in order to obtain consistent product quality. In this research, the QbD approach has been employed to develop optimal IR olmesartan medoxomil pellets and pH dependent DR metoprolol succinate pellets. The RSM with BBD method has been employed to optimize formulation variables and determine their impact on entrapment efficiency, production yield, and in vitro drug release[17].

2.2.1.1 Defining QTPP and CQAs

QTPP (Quality Target Product Profile) provided the desired quality, safety, and performance characteristics of the chronotherapeutic dual release multiparticulate capsule, which include oral delivery system, sequential release of drugs, dose strength, distribution of pellet sizes, drug loading capacity, friability, flowability, content uniformity, and stability.On the basis of the QTPP, Critical Quality Attributes (CQAs) of the drug product included distribution of pellet sizes, sphericity, friability, entrapment efficiency, yield of preparation, immediate release of olmesartan, delayed release of metoprolol, assay, content uniformity, and stability.[18].

2.2.1.2 Risk Assessment

A risk assessment was done through the use of fish bone diagram and qualitative risk matrix on the factors that influence CQAs on the formulation and process. The variables such as MCC,

PVP K30, HPMC, binder, Eudragit L100/S100, extrusion speed, spheronization speed, and temperature of drying among others were used, and those of high risk were chosen as CMAs and CPPs. FMEA was done and the RPN value was calculated as follows:

RPN = Severity (S) × Occurrence (O) × Detectability (D)

Those variables having high RPN values especially MCC, PVP K30, HPMC, and starch binder were optimized through Box Behnken design [19].

2.2.1.3 Formulation Optimization

Formulation optimization of chronotherapeutic multiparticulate pellets system was carried out employing three factors, three levels Box-Behnken Design (BBD) with 17 runs via Design-Expert® software (Version 13, Stat-Ease Inc., USA). Formulations were optimized independently for Immediate release (IR) olmesartan medoxomil and Delayed Release (DR) metoprolol succinate pellets. After preliminary experiments and risk evaluation, MCC, starch, and PVP K30 were chosen as independent variables for IR pellets; whereas, MCC, HPMC, and starch binder concentration for DR pellets were chosen. Entrapment efficiency, production yield, and in vitro drug release were chosen as the responses. For the Delayed Release pellets, optimization was carried out with minimum drug release at acidic condition and maximum release at intestinal pH conditions.

2.2.3 Evaluation of Core Olmesartan and Metoprolol Pellets

2.2.3.1 Entrapment efficiency:

The entrapment efficiency of the pellets was evaluated through UV spectrophotometry. Extraction of the drug was done in 0.1 N HCl for olmesartan and phosphate buffer (pH 6.8) for metoprolol through sonication. The absorbance was determined at 256 nm for olmesartan and 223 nm for metoprolol[20].

2.2.3.2 In Vitro Drug Release of Core Pellets:

The in vitro drug release was assessed using USP Dissolution Apparatus I (Basket, Labholic, India) having 900 mL dissolution medium at 37 ± 0.5 °C and 50 rpm. In the case of olmesartan, the pellets were subjected to 0.1 N HCl (pH 1.2)[21, 22], while in the case of metoprolol, the pellets were evaluated in 0.1 N HCl (pH 1.2) followed by phosphate buffer (pH 6.8). Samples of 5 mL were taken out at regular intervals and replaced with fresh dissolution medium [23].

2.2.3.3 Percentage Yield:

The production yield was obtained as a ratio of the weight of dried pellets to the total weight of formulation ingredients employed for pellet formation and represented as percentage. High yield denotes higher process efficiency and less material wastage in the process of extrusion-spheronization[24].

$$\text{Percentage Yield} = \frac{\text{Weight of dried pellets obtained}}{Total\ weight\ of\ initial\ Materials} \times 100$$

2.2.4 Coating of Core Metoprolol pellets:

The core pellets of Metoprolol were coated with Eudragit L100 and Eudragit S100 with an aim of obtaining a drug delivery system with pH-dependent delay. The coating dispersion was prepared by the use of acetone (70 mL) and distilled water (10 mL). Plasticizing agents and anti-tacking agents were then added to the coating dispersion in the form of triethyl citrate (10% w/w of total polymer) and talc (10% w/w of total polymer) respectively. Coating was done in a pan coater at a speed of 25 rpm and temperature of 45°C with a spray rate of 1 mL/min. Layers were repeatedly coated for 3 minutes. Drying and storage of the pellets in a desiccator followed the process.[24, 25] .

2.2.5 Characterization of Optimized Olmesartan and Metoprolol Pellets:

2.2.5.1 Pellet Size Analysis:

Pellet size distribution was established through sieve analysis using standard sieves (1700, 1180, 1000, and 710 μm) that were placed in a descending order. Weighing of the pellets retained in each sieve after 5 min of sieving, along with the determination of their weight fractions, were made. The pellets with sizes ranging from 710 to 1000 μm were used for further analysis [26, 27].

2.2.5.2 Fourier Transform Infrared Spectroscopy:

Compatibility and chemical stability of drug and excipients were investigated using Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR, Bruker). Infrared spectra of pure drug and excipients, as well as of the optimized pellets, were taken in the range

of 4000-600 cm^{-1} for detecting any shifts or loss of the characteristic peaks of functional groups[28].

2.2.5.3 Scanning Electron Microscopy:

Surface morphology of both uncoated and coated pellets was analyzed using Scanning Electron Microscope (ALFATECH). Pellets were fixed on aluminum stubs using double-sided carbon tape and then sputtered with gold in vacuum for examining the shape and surface properties of pellets and coating [29].

2.2.6 Evaluation of Optimized Formulation Pellets:

2.2.6.1 Production Yield, Entrapment Efficiency:

The same procedure mentioned above was followed to obtain the production yield and entrapment efficiency measurement.

2.2.6.2 Friability:

Evaluation of friability was done by placing 10 g of pellets in a friabilator run at 25 rpm for 4 minutes. The pellets were then dedusted and weighed again to get the percentage weight loss which determines the mechanical strength of the pellets [30].

2.2.6.3 Micromeritic Properties:

For flow properties, angle of repose, bulk density, tapped density, Carr's Index, and Hausner's ratio were obtained. These parameters were used in determining the flow ability of the pellets for capsule filling [31].

2.2.6.4 Weight Variations Test

The weight variation was determined by weighing 20 capsules each and determining the average weight of the capsules. Acceptable weight variation according to pharmacopoeial specifications is ±7.5% [32].

2.2.6.5 Content Uniformity:

The drug content was evaluated by taking out pellets from capsules and sonicated in methanol (10 mL) containing 25 mg metoprolol and 20 mg olmesartan for 15 minutes, diluted to 50 mL with distilled water and diluted further to obtain the concentration of approximately 10 µg/mL metoprolol and 8 µg/mL olmesartan. The absorbance at 223 nm and 256 nm were recorded using simultaneous equations [33].

2.2.6.6 In-vitro Drug Release Study:

For assessment of the pH-responsive extended-release profile, the coated metoprolol succinate pellets were tested for dissolution in three media sequentially: 0.1 N HCl (pH 1.2) for 2 hours, then in phosphate buffer (pH 6.8) for 4 hours, and phosphate buffer (pH 7.4) till end of the experiment [34]. In case of multiparticulate capsule, the immediate-release profile of olmesartan medoxomil was tested in 0.1 N HCl (pH 1.2) using 256 nm wavelength. For metoprolol, sequential testing at pH 1.2, 6.8 and 7.4 was carried out. The samples were withdrawn at preset time intervals, measured using 223 nm and replenished with equivalent volume of dissolution medium[35, 36].

2.2.6.7 Release Kinetic Modeling:

Data from in vitro drug release rate was analyzed using DD-Solver software in accordance with Zero Order Kinetic Model, First Order Kinetic Model, Higuchi Equation, Hixon-Crowell Equation, and Korsmeyer-Peppas Equation. The best model chosen had the highest R2 value.[37].

2.2.6.8 Stability Studies:

Stability studies were conducted in order to establish physical and chemical stability of the optimized multiparticulate capsules with IR olmesartan medoxomil and pH-dependent DR metoprolol succinate pellets according to ICH Q1A(R2) guidelines [38]. The capsules packaged in aluminum-PVDC blister packs were kept in accelerated conditions of 40 ± 2°C/75 ± 5% RH for 3 months. Physical appearance, drug content and dissolution were tested at 0, 1, 2 and 3 months.Drug content was analyzed by UV-visible spectrophotometry at 256 nm for olmesartan and 223 nm for metoprolol. Dissolution tests were carried out using USP Apparatus I at 37 ± 0.5°C and 75 rpm in 900 mL of dissolution media. Olmesartan dissolution test was performed in 0.1 N HCl (pH 1.2), whereas metoprolol dissolution was performed sequentially in phosphate buffers pH 6.8 and 7.4 up to 8 hours. Dissolution profiles were compared before and after storage by using similarity factors f_1 and f_2 [41].

2.2.6.9 Mixing of Pellets

The final multiparticulate capsule with dual release was produced using empirical optimization of the ratio of immediate release and delayed release pellets of olmesartan and metoprolol respectively. The formulation consisted of a total amount of 75 mg olmesartan pellets (equivalent to 20 mg of olmesartan) and four metoprolol pellet formulations: M1, M2, M3, and

M4 (50%, 12%, 16%, and 22% respectively). 384.10 mg of metoprolol pellets was used in order to get 50 mg of metoprolol.

3. Results and discussion

3.1. Application of the Quality by Design (QbD)

3.1.1. Defining the QTPP and CQAs

The Quality Target Product Profile (QTPP) was developed to help in developing a chronotherapeutic dual release multiparticulate capsule for the treatment of circadian hypertension and early morning BP spike. The drug delivery system was intended to release olmesartan medoxomil immediately for rapid suppression of renin–angiotensin–aldosterone system (RAAS) and pH-dependent delayed release of metoprolol succinate for suppressing sympathetic activities in early morning. This QTPP was helpful in setting up certain critical product characteristics, which include dosage form, route of administration, dosage strength, pharmacokinetic attributes, stability and container-closure system of the products to maintain their quality and effectiveness (Table 1) [40].

As per the QTPP, the CQAs that have been determined are pellet size distribution, sphericity, friability, entrapment efficiency, production yield, immediate release of olmesartan, pH-dependent delayed release of metoprolol, assay, content uniformity, and stability. The target specifications of these CQAs are listed in Table 2.

3.1.2. Risk assessment

Ishikawa (fishbone) diagram and Failure Mode and Effects Analysis (FMEA) were applied to study the factors contributing to the formulation and process which affect dual-release multiparticulate pellet system (Fig 2). Qualitative risk assessment revealed that microcrystalline cellulose (MCC), PVP K30, starch binder solution and HPMC are the critical material attributes that affect the CQAs of pellets. FMEA revealed that for the formulation of immediate-release olmesartan pellets, the highest Risk Priority Number (RPN) is 64 for MCC and PVP K30; while, for delayed-release metoprolol pellets, the RPN is 48 for MCC, HPMC and starch binder solution (Tables 3 and 4). The identified high-risk factors have been chosen for optimization with the help of Box–Behnken Design (BBD). ANOVA results indicate significant interaction and quadratic effects which confirm the inclusion of formulation variable interactions during optimization process.

3.1.3. Formulation Optimization Using Experimental Design

Box-Behnken Design (BBD) with three factors and three levels was employed to develop optimal conditions for immediate-release olmesartan pellets containing MCC, starch, and PVP K30, and delayed-release metoprolol pellets containing MCC, HPMC, and starch binder concentration. The impact of these factors on entrapment efficiency, production yield, and drug release rate was studied using 17 experiments per formulation.Olmesartan pellets had entrapment efficiency, production yield, and drug release rate of 78.5-96.5%, 79.4-95.8%, and 78.5-96.5%, respectively, while metoprolol pellets had entrapment efficiency, production yield, and drug release rate of 75.3-94.5%, 72.9-93.8%, and 74.8-94.5%, respectively. Predictive capability of the developed quadratic models was high (R^2 = 0.9915-0.9988) with extremely significant F-values ($p < 0.0001$), confirming adequacy of the experimental design (Tables 5 and 6).Even though the selected responses appropriately reflect formulation quality, such important parameters like pellet hardness, coating uniformity, and long-term mechanical strength have been neglected. Moreover, wet mass homogeneity, extrusion, spheronization, and drying.

I. Effect of Independent Variables on Entrapment Efficiency

The entrapment efficiency quadratic model was found to be statistically highly significant ($p < 0.0001$), which proved its validity in prediction of entrapment efficiency of IR olmesartan and DR metoprolol pellets. The response surfaces and contour plots (Fig 3) represented the effect of different formulation factors on entrapment efficiency. The experimental results of entrapment efficiencies were between 78.5% and 96.5% for olmesartan pellets and between 75.3% and 94.5% for metoprolol pellets, respectively, thus proving efficient drug entrapment [41] (Table 5). The insignificant lack of fit further confirmed the predictive ability of the quadratic models (Table 6).

Olmesartan pellets

$$\text{Entrapment Efficiency} = 86.00 + 7.06A - 0.1250B - 1.79C - 0.1500AB - 1.33AC - 0.0500BC + 2.11A^2 - 2.16B^2 - 1.94C^2$$

Metoprolol pellets

$$\text{Entrapment Efficiency} = 86.68 - 0.2750A + 0.1750B + 1.10C + 0.2500AB - 0.5000AC - 0.9500BC + 4.66A^2 + 2.56B^2 - 11.54C^2$$

The regression analysis revealed that the entrapment efficiency of olmesartan pellets was mainly dependent on microcrystalline cellulose (A), but the increase in PVP K30 concentration (C) decreased the drug entrapment, thereby pointing to the optimal concentration of binder. Starch (B) exhibited marginal effect [42]. However, the concentration of starch binder (C) was the main variable affecting the formation of metoprolol pellets; whereas, microcrystalline cellulose (A) and HPMC (B) had linear as well as interaction effect on the entrapment efficiency of metoprolol pellets[43, 44].

II. Effect of Independent Variables on Production Yield

The yield of production was between 79.4 to 95.8 percent for olmesartan pellets and 72.9 to 93.8 % for metoprolol pellets, signifying an effective process of extrusion-spheronization (Table 5). Statistical significance of the quadratic model and graphs plotted showed the impact of formulation factors on the yield of production (Fig 3). The lack of fit test was not significant (Table 6).[45, 46].

Olmesartan pellets

Production Yield = 86.80 + 6.24A −0.2250B – 1.69C – 0.2000AB – 1.33 AC + 0.3500BC + $1.51A^2$ – $2.26B^2$ – $2.04C^2$

Metoprolol pellets

Production Yield = 83.20 – 0.2000A + 0.0250B + 1.05C + 0.2750AB – 0.6750AC – 0.6750BC – $6.09A^2$+ $3.79B^2$ – $12.31C^2$

The results of regression analysis indicated that Microcrystalline Cellulose (A) had a positive effect on the yield of olmesartan pellets, while increased concentrations of Polyvinylpyrrolidone K30 (C) had negative effects on their yield. The effect of starch (B) was rather weak. In the case of metoprolol pellets, the highest positive effect was exerted by the concentration of starch binder (C), while Microcrystalline Cellulose (A) and HPMC (B) had lesser effects.[47].

III. Effect of Independent Variables on In Vitro Drug Release

The drug release in vitro was between 78.5% to 96.5% in the case of immediate-release olmesartan pellets and 74.8% to 94.5% in delayed-release metoprolol pellets indicating good release behavior (Table 5). The models developed were statistically significant, and the contour plots and response surface plots (Fig 3) demonstrated the influence of various factors on drug release. Lack of fit being insignificant validated the models (Table 6)[48].

Olmesartan pellets

Invitro release = 86.88 + 6.40A – 0.4250B −2.05C – 0.5000AB – 1.10AC + 0.0000BC + $0.9850A^2 – 1.56B^2 – 1.47C^2$

Metoprolol pellets

Invitro release = 86.26 – 0.1875A + 0.0875B + 0.9000C + 0.2500AB – 0.4750AC – 0.7250BC + $5.07A^2 + 2.57B^2 – 12.15C^2$

Regression analysis showed that microcrystalline cellulose (A) and PVP K30 concentration (C) had a significant effect on the release rate of drug from olmesartan pellets, but not the starch (B). In metoprolol pellets, starch binder concentration (C) was found to be the most influential variable, while the microcrystalline cellulose (A) and hydroxylpropyl methylcellulose (B) were found to have an influence on the drug release via quadratic interactions[46, 49].

3.1.4. Validation of the Design to Select the Optimized Formulation

Optimization studies using desirability function were carried out for determining the optimal formulations of olmesartan medoxomil immediate-release and metoprolol succinate delayed-release pellets. The optimization process involved maximizing the entrapment efficiency, manufacturing yield and in vitro release rate of the drugs while keeping the variables within the predetermined experimental range [50]. The optimization parameters and desirability functions are provided in Tables 7 and 8. Predicted response values, experimental response values, percentage prediction errors and desirability functions are shown in Table 9. Experimental results agreed well with the predicted values which validated the quadratic models used in the optimization process. All prediction errors were within acceptable levels indicating that the optimization process and design space are robust. Small changes in the manufacturing process such as wet massing, extrusion, spheronization and drying had no significant effect on the quality of the pellets. Thus, the optimal formulations met the predetermined quality criteria.

3.1.5 Influence of Coating Variables on pH-Dependent Drug Release and Chronotherapeutic Performance of Metoprolol Pellets:

Metoprolol pellets (M1-M4) were coated with Eudragit L100 and Eudragit S100 in order to examine the effect of coating conditions on drug release. The selected formulations (M1C, M2C, M3D, and M4B) exhibited pH-sensitive release pattern at 12%, 16%, 20%, and 24% (w/w) coating weight gains. The order of drug release was M2C > M3D > M1C > M4B, meaning that the drug release was faster when coating weight gain was lower and vice versa due to the formation of a thicker polymer film.Drug release was slower when using Eudragit S100 than Eudragit L100 due to pH-sensitivity of both polymers. All formulations revealed slow drug release under acidic conditions (gastric juice) and rapid drug release at alkaline pH (intestines, pH 6.8-7.4). However, no pulsatile drug release was observed; the sequential drug release from M2C, M3D, M1C, and M4B in one capsule indicated the possibility of timed multiparticulate systems for the treatment of cardiovascular diseases [52]. The components used in coating of metoprolol formulations are shown in (Table 10).

3.2 Characterization of Pellets

3.2.1 Pellet Size Analysis

Sieve analysis of optimized olmesartan (O) and coated metoprolol (M1C, M2C, M3D, and M4B) pellets was carried out and the results of the size distribution of pellets have been provided in Table 11. The size distribution of optimized olmesartan pellets was found to be uniform, where 96.23 ± 0.31% pellets were obtained on passing through the 1000 µm sieve, showing good efficiency of pellet formation using extrusion-spheronization process. Likewise, percentages of pellets passing through the 1000 µm sieve were 93.23 ± 0.34%, 95.43 ± 0.27%, 94.80 ± 0.29% and 91.53 ± 0.39% for M1C, M2C, M3D, and M4B, respectively. Higher percentage of larger pellets (1180 and 1700 µm) was observed for M4B due to high coating weight gain (24%), making the diameter of the pellets slightly larger.

3.2.2 ATR-Fourier Transform Infrared Spectroscopy:

The optimized immediate-released olmesartan medoxomil and delayed-released metoprolol succinate pellets showed the characteristic functional groups of both drugs and formulation excipients, which showed that there was chemical compatibility and stability between the drugs and excipients (Fig 4). Characteristic peaks of starch were observed at 3400 cm^{-1} (O–H), 2925

cm^{-1} (C–H), and 1150–1000 cm^{-1} (C–O–C/C–O). MCC showed peaks at 3340 cm^{-1} (O–H), 2900 cm^{-1} (C–H), and 1430–1058 cm^{-1}, while PVP K30 exhibited a characteristic C=O stretching peak at ~1655 cm^{-1}. HPMC showed characteristic peaks at ~3400 cm^{-1} (O–H), ~2920 cm^{-1} (C–H), and 1150–1050 cm^{-1} (C–O–C). The ester C=O stretching band was observed at 1720-1730 cm-1 and the ester C–O stretching band was observed at 1260-1140 cm-1 in the FTIR spectrum of Eudragit® polymers. The optimized olmesartan pellets exhibited characteristic peaks at 1730–1705 cm^{-1} (C=O), 1600–1500 cm^{-1} (aromatic C–C), 1250–1050 cm^{-1} (C–O/C–N), 2950–2850 cm^{-1} (aliphatic C–H), and 3400–3300 cm^{-1} (O–H). Similarly, optimized metoprolol pellets showed characteristic peaks at 3450–3300 cm^{-1} (O–H), 2950–2850 cm^{-1} (aliphatic C–H), 1610–1510 cm^{-1} (aromatic C=C/N–H), and 1250–1030 cm^{-1} (C–O–C/C–N). The peak shifting, disappearance and formation of new peak were not observed after extrusion–spheronization and coating, which proves there were no drug–excipient interactions. Hydrogen bonding and overlapping polymer absorption bands were suggested as the causes for the minor peak broadening and lower peak intensity. Overall, FTIR results have confirmed that the optimized pellet formulations with combinations of starch, MCC, HPMC, PVP K30, Eudragit® L100 and Eudragit® S100 are chemically stable with olmesartan medoxomil and metoprolol succinate.

3.2.3 Scanning Electron Microscopy (SEM)

SEM (ALFATECH) was employed for studying the surface morphology of coated and uncoated pellets. Optimal uncoated olmesartan pellets and an exemplary coated metoprolol formulation were studied using this technique. The surface morphology of uncoated olmesartan pellets appeared to be rough and irregular. On the other hand, the coated metoprolol pellets had a smooth and regular surface, which indicated the efficacy of the coating process. A uniform film of Eudragit® L100/S100 coating was obtained which could deliver drugs in a pH-dependent manner (Fig 5).

3.3 Evaluation of Optimized Formulation Pellets:

3.3.1 Production Yield and Entrapment Efficiency

Production yield and entrapment efficiency of the optimized systems (O and M1-M4) are listed in Table 9. Optimal olmesartan formulation (O) gave the best entrapment efficiency (96.18 ± 0.42%) and production yield (95.32 ± 0.51%), very close to the estimated values, proving thus that the predictions of the RSM model are reliable. For the metoprolol formulations, M1

showed the highest entrapment efficiency and production yield, while the formulations with higher MCC content had lower responses because of the denser matrix. Formulation M4, which included medium amount of MCC and high amount of HPMC, had average response with good process efficiency. Prediction errors for production yield (Table 12) were less than 10% for all formulations. After coating, the error decreased down to 1%. M1C demonstrated the highest production yield, while M4B was characterized by low production yield because of the high amount of coating gained.

3.3.2 Friability

Friability of the optimized formulations was done to find out the pellet's mechanical strength (see Table 13). For the optimized formulation of olmesartan (O), the friability value was 0.40 ± 0.10%, whereas for coated metoprolol pellets (M1C, M2C, M3D, and M4B), the friability value was between 0.40 ± 0.10% and 0.60 ± 0.10%. The value was less than 1%, which means that the pellets have good mechanical strength.

3.3.3 Micromeritic Properties

The micromeritic characteristics of optimized olmesartan (O) and coated metoprolol (M1C, M2C, M3D and M4B) pellets are provided in Table 14. The angle of repose was in the range of 24.3 ± 0.5° to 27.1 ± 0.9° which is considered good flowability. The bulk densities were found to be in the range of 0.44–0.48 g/cm³ and tapped densities were 0.51–0.55 g/cm³. The flow properties were acceptable with Carr's Index (12.73-13.72%) and Hausner ratio (1.14-1.16) as it would allow for uniform capsule filling.

3.3.4 Weight Variation Test

The weight variation of capsules containing olmesartan and metoprolol pellets was assessed (Table 15). The mean weight of the capsules was 644.8 ± 0.35 mg (n = 20) with the range of variation being within the pharmacopoeial limit of ±7.5%.

3.3.5 Content Uniformity

UV spectrophotometric simultaneous equation method was used to determine the drug content uniformity (Table 16). The contents of olmesartan was found to be 96.1 to 97.8% and for metoprolol was 96.5 to 98.3%. The mean drug contents were 96.87 ± 0.55% for olmesartan and 97.33 ± 0.60% for metoprolol, and the %RSD values were below 1%, which means that the drug was homogeneously distributed and met the pharmacopoeial specifications.

3.3.6 In Vitro Drug Release Study

In vitro drug release profile of the optimized olmesartan pellets, coated metoprolol pellets, and the optimized multiparticulate capsule is depicted in figu(6-8). The optimized olmesartan pellets displayed quick drug release in 0.1 N HCl (pH 1.2), where 18.5% and 96.8% were released within 5 min and 120 min, respectively, indicating the immediate release property of the pellets (fig 6).However, coated metoprolol pellets released no drug in an acidic medium, thus showing the protective action of the Eudragit coating. The M1C displayed the minimum lag time, while M2C, M3D, and M4B showed delayed release within 6, 8, and 10 hours, respectively, dependent on the thickness of the coating and Eudragit L100/S100 ratio (fig 7).The final multiparticulate capsule showed a biphasic release profile, consisting of immediate release of olmesartan (96.8%) within 120 min and delayed release of metoprolol in a pH-dependent manner within 480 min (fig 8). Thus, it could be concluded that the design of both immediate- and delayed-release pellets was successfully accomplished in a multiparticulate formulation.

3.3.7 Drug Release Kinetics Study

Various kinetic models were used to characterize the release rate of drug from the optimized pellets of olmesartan and coated metoprolol, and the value of R^2 is shown in Table 17. For olmesartan pellets, R^2 (0.9972) was highest for first-order kinetics, which suggests that the drug was released in a concentration-dependent manner, whereas the release exponent (n = 0.380) suggested Fickian diffusion mechanism. On the other hand, Korsmeyer-Peppas model was found to be the best fit model (R^2 = 0.9727) for coated metoprolol pellets, having release exponent of 1.680.

3.3.8 Stability Studies

The improved multiparticulate capsules consisting of immediate-release olmesartan and delayed-release metoprolol pellets were examined during 3 months of accelerated stability testing at 40 ± 2 °C and 75 ± 5% RH according to ICH Q1A(R2) criteria. There were no changes detected in appearance, content, and in vitro drug release of the formulation proving its physical and chemical stability (Tables 18, 19). The f_1 (difference factor) and f_2 (similarity factor) were calculated to establish comparison between dissolution curves before and after storage. All f_1 values were <15 and f_2 values were >50 (Table 20).

3.4 Key Findings

The chronotherapeutic dual-release multiparticulate pellet system was successfully developed for the management of circadian hypertension by the application of QbD. Box–Behnken Design (BBD) was used to optimize formulation variables and led to the immediate-release olmesartan medoxomil pellets and the pH-dependent delayed-release metoprolol succinate pellets with high entrapment efficiency and desired drug release properties. The optimization process was found to have excellent predictive ability, as close agreement was obtained between the predicted and experimental results, which confirmed the robustness of the optimization process and quadratic models. Concentration of microcrystalline cellulose and concentration of binder significantly affected the characteristics of the pellets, and the optimized formulation showed a good physicochemical property, good reproducibility, and good sequential drug release. The design space established further reflects the applicability of the QbD approach for formulation development which is reproducible and can be scaled up.

3.5 Current and Future Development

Chronotherapeutic multiparticulate drug delivery methods are effective strategies for providing a synchronized release of drug with the circadian rhythm of hypertension. The dual-release developed system using the QbD approach provided sequential delivery via immediate-release olmesartan medoxomil pellets and pH-dependent delayed-release metoprolol succinate pellets, providing better control of the blood pressure "morning surge. The optimized formulation showed good physicochemical characteristics and sustained in vitro drug release, but more studies are needed to determine the efficacy of the formulation in the clinical environment. Future investigations should address the following points: in vitro–in vivo correlation (IVIVC), pharmacokinetic and pharmacodynamic investigations, antihypertensive efficacy in appropriate animal models, long-term stability studies, scale-up validation, and process verification. Pellet microstructure, coating integrity and drug distribution could be further explained by applying the advanced characterization techniques such as micro-computed tomography (micro-CT), terahertz pulsed imaging (TPI) and near-infrared chemical imaging (NIR-CI). Furthermore, process validation, regulatory evaluation and technology transfer will support the translation of this chronic therapeutic multiparticulate system to clinical application and commercialization.

3.6 Conclusion

This study was successful in creating a Quality by Design (QbD) guided dual release multiparticulate capsule to treat a circadian hypertension profile and early morning blood

pressure surge. Immediate release olmesartan medoxomil pellets and pH-dependent delayed-release metoprolol succinate pellets were optimized by extrusion–spheronization using Box–Behnken Design. The quadratic models had an excellent predictive capability (R2: 0.9915–0.9988), with good agreement between the model and the experimental results, which is indicative of good design space.The optimized olmesartan pellets showed rapid drug release (96.8% within 120 min) while the metoprolol pellets coated with Eudragit® L100/S100 exhibited negligible gastric release and sustained intestinal release (97.1% within 480 min). The final multiparticulate capsule exhibited high entrapment efficiency (>93%), production yield (>92%), excellent micromeritic properties and low friability (<1%) and %RSD drug content (<1%). Drug–excipient compatibility was confirmed by ATR-FTIR, uniform coating integrity was confirmed by SEM, and accelerated stability studies (40 ± 2 °C/75 ± 5% RH for 3 months) confirmed formulation stability with no changes in dissolution profile ($f_2 > 50$).In summary, the optimized dual-release multiparticulate system was able to achieve sequential drug delivery, which was in line with the circadian rhythm of the action of antihypertensive drugs, resulting in an effective chronotherapeutic drug delivery system. In vitro – In vivo correlation (IVIVC), Pharmacokinetics, Pharmacodynamics and scale-up validation studies are warranted for clinical translation.

Credit authorship contribution statement

Gokul H: Writing - review & editing, Writing - original draft, Software, Methodology, Investigation.

Suriya Prakaash Kannan: Writing -review & editing ,Validation, Resources, Investigation.

Damodharan Narayanasamy: Writing - review & editing, Visualization, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

Research ethics

Not applicable.

Informed consent

Not applicable.

Consent for publication

The authors confirm that this manuscript has not been published previously and is not currently under review for publication elsewhere.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors used artificial intelligence (AI)-assisted tools solely for the creation and enhancement of figures included in this manuscript. No AI or generative AI tools were used in the writing, interpretation, analysis, or preparation of the scientific content of the manuscript. The authors take full responsibility for the accuracy, integrity, and originality of all content presented in this work.

Not applicable.

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Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

All data are available in the manuscript.

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Figures

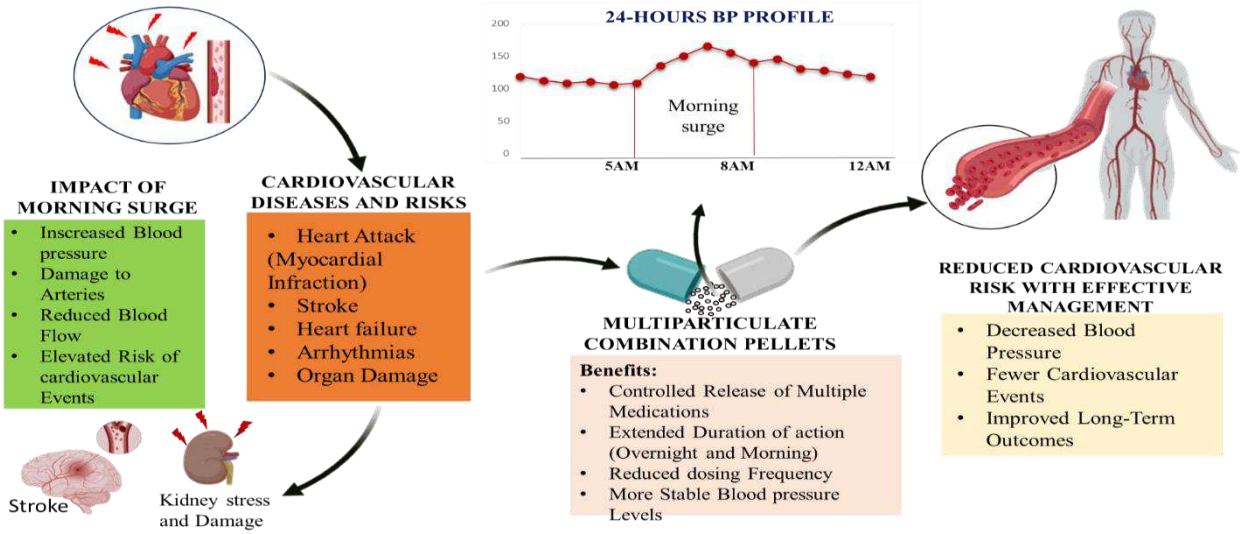


Fig.1: Pathophysiological basis of circadian hypertension and therapeutic rationale for a dual-release multiparticulate chronotherapeutic drug delivery

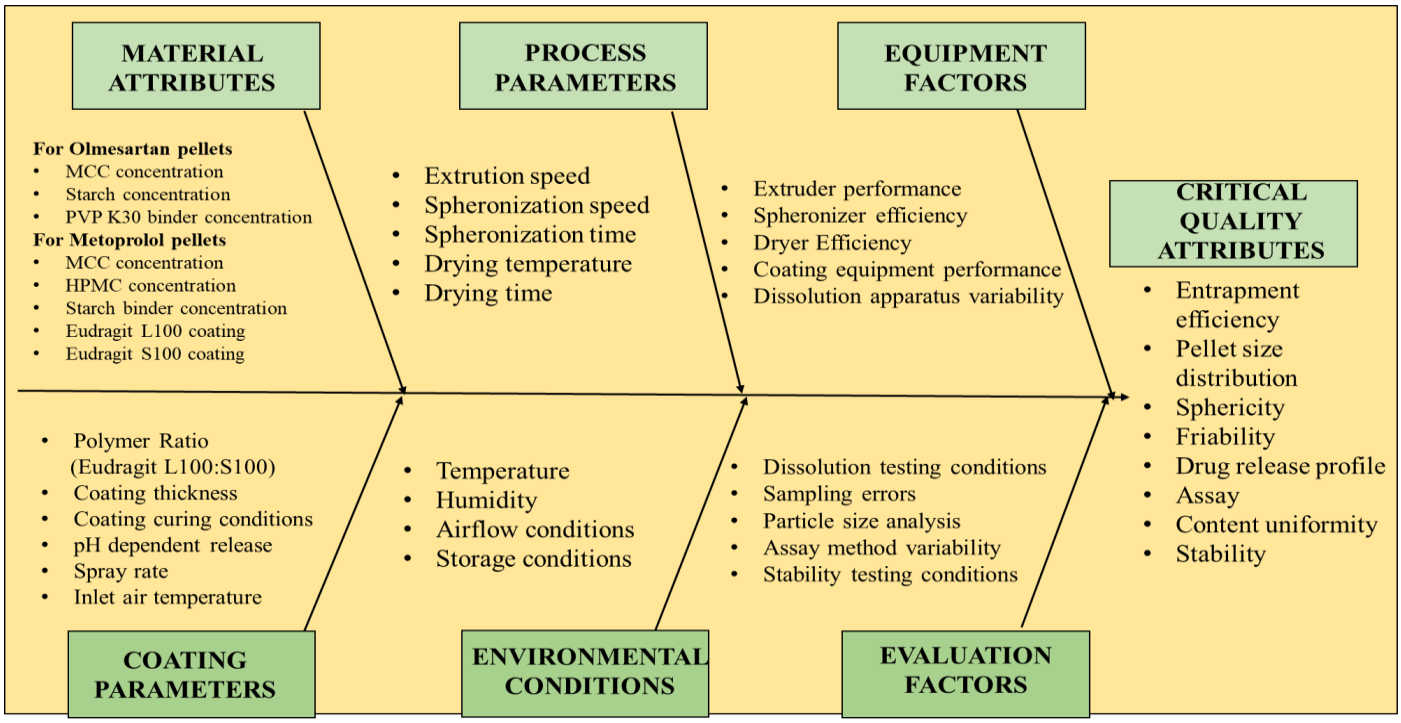
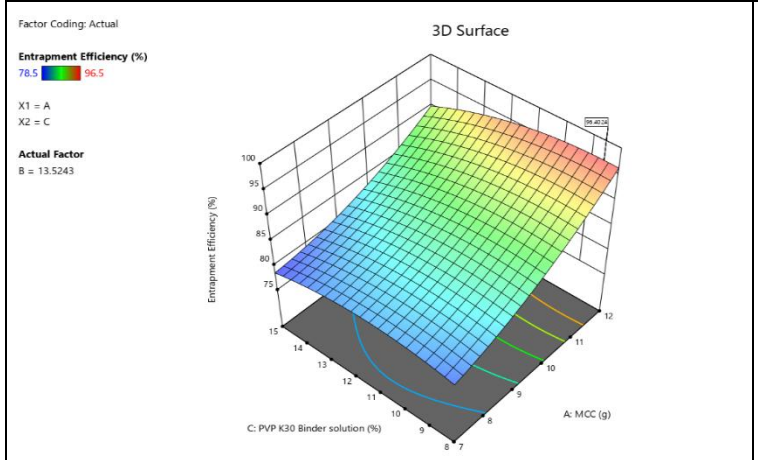
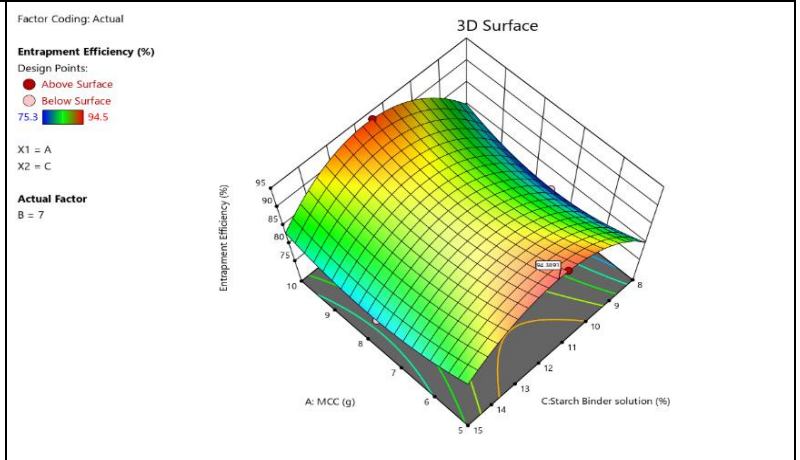


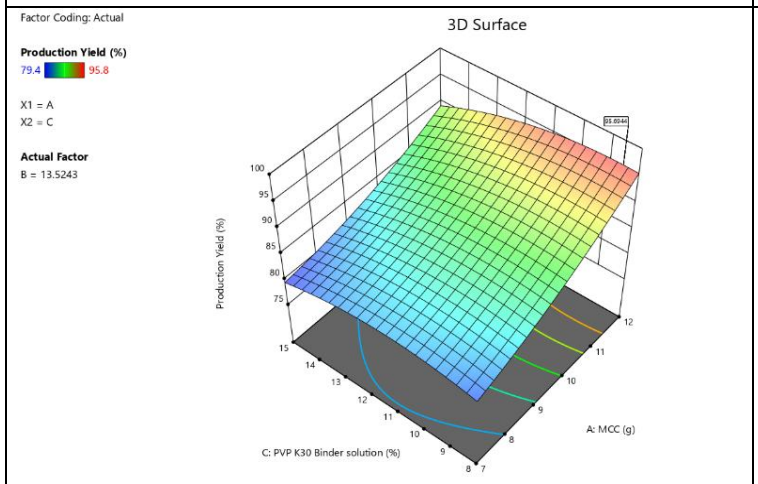
Fig 2: Fishbone diagram for CQAs of dual-release pellets



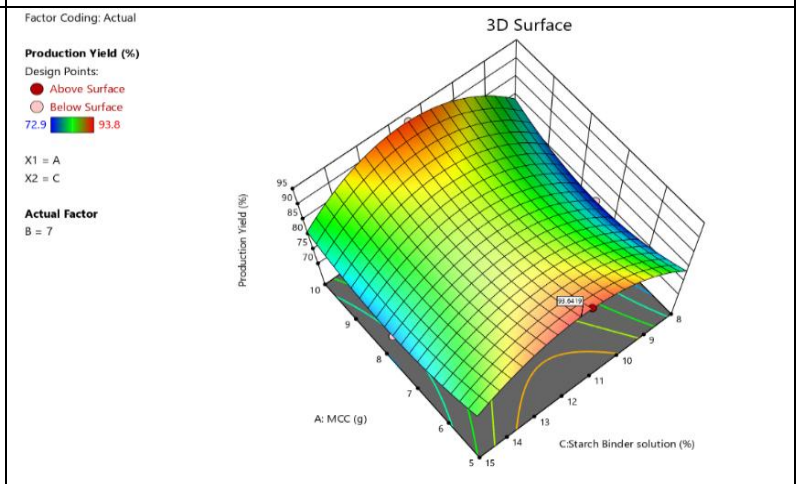
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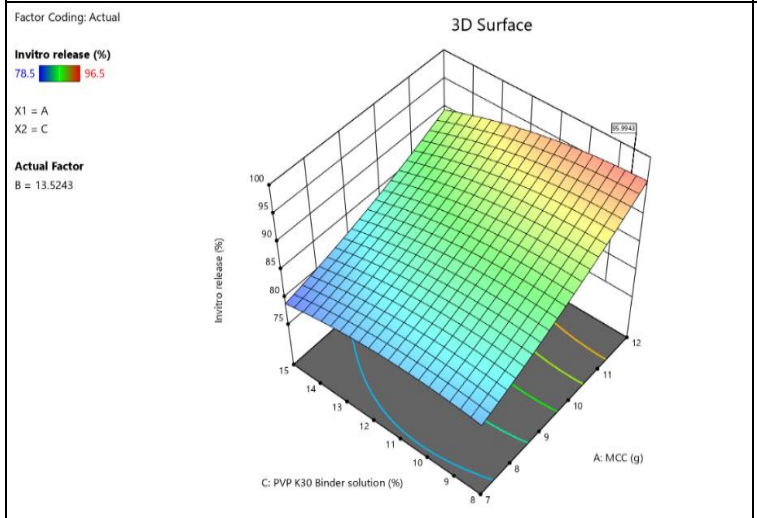
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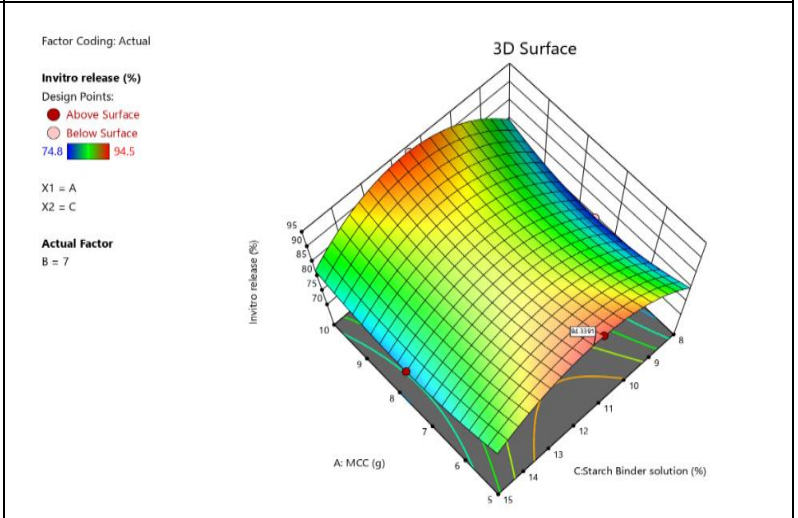
3.c)



3.d)



3.e)



3.f)

Fig.3 : 3.a) 3D surface plot for entrapment efficiency of olmesartan pellets and Fig.3b) 3D surface plot for entrapment efficiency of metoprolol pellets. Fig.3c) 3D surface plot for production yield of olmesartan pellets and Fig.3 d)3D surface plot for production yield of metoprolol pellets. Fig.3 e) 3D surface plot for in vitro drug release of olmesartan pellets and Fig.3 f) 3D surface plot for in vitro drug release of metoprolol pellets.

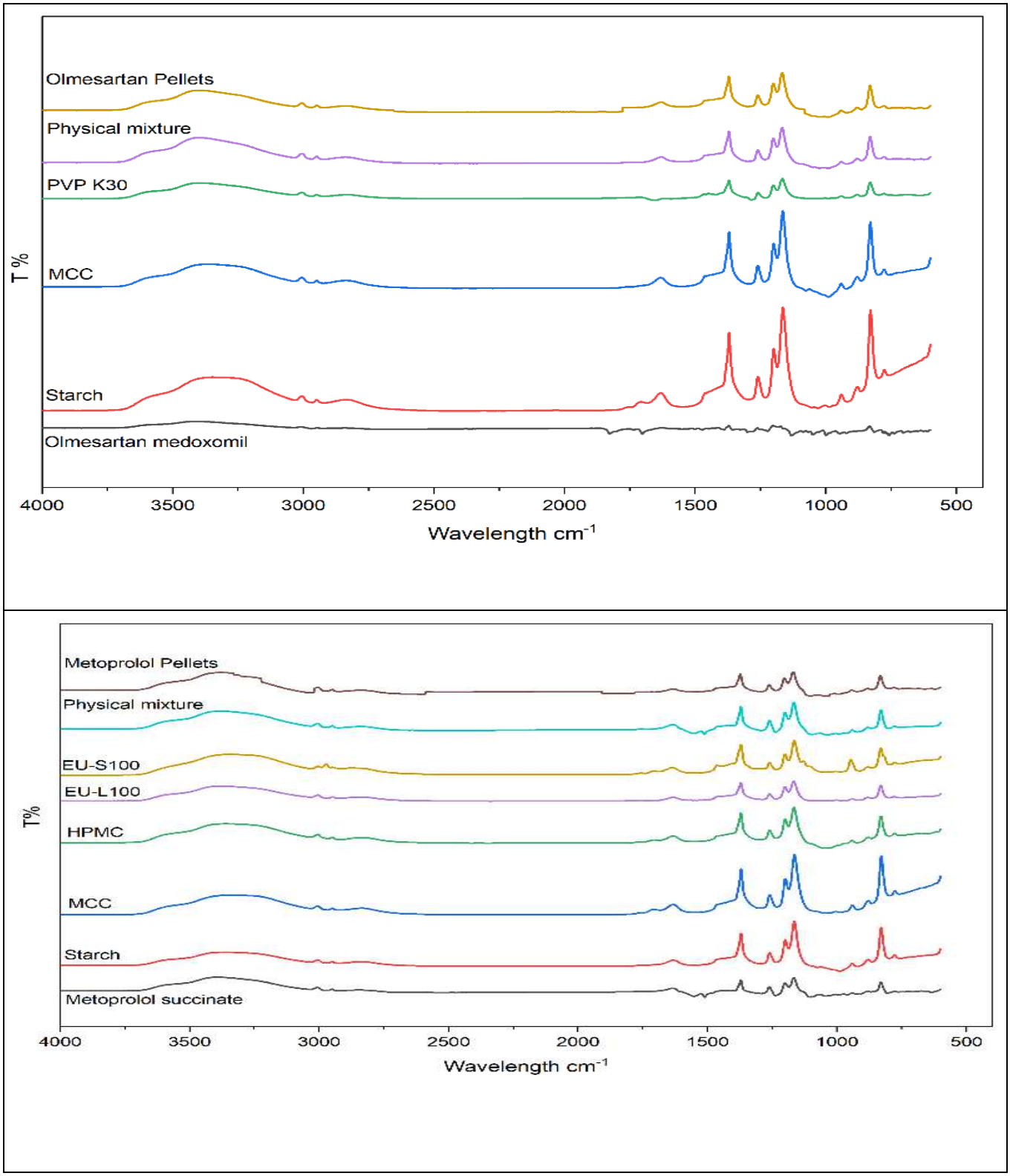
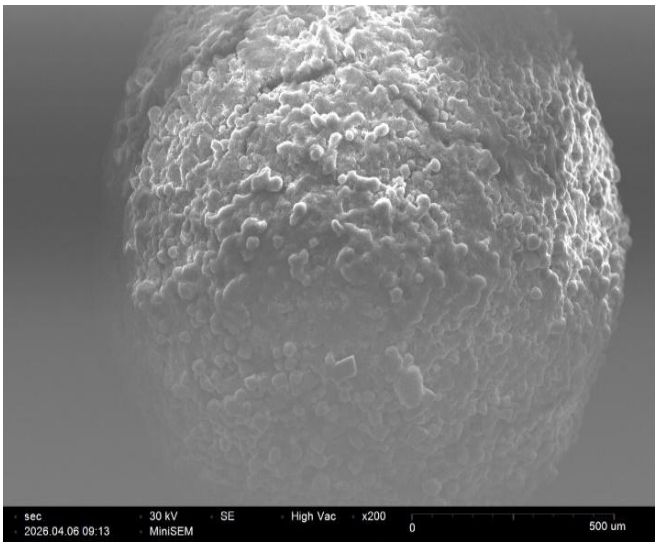
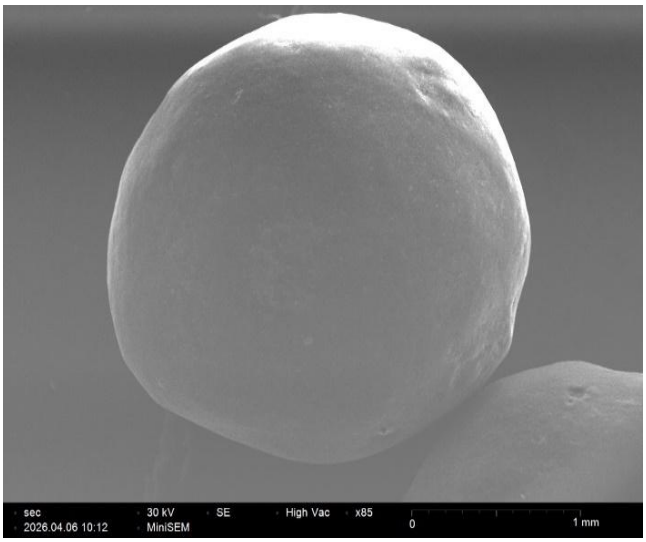


Fig 4: FTIR spectra of drug, excipients, physical mixtures, and optimized pellet of Olmesartan and Metoprolol formulations.



5.a)



5.b)

Fig.5: 5.a) Uncoated Pellets. 5.b)Coated Pellets

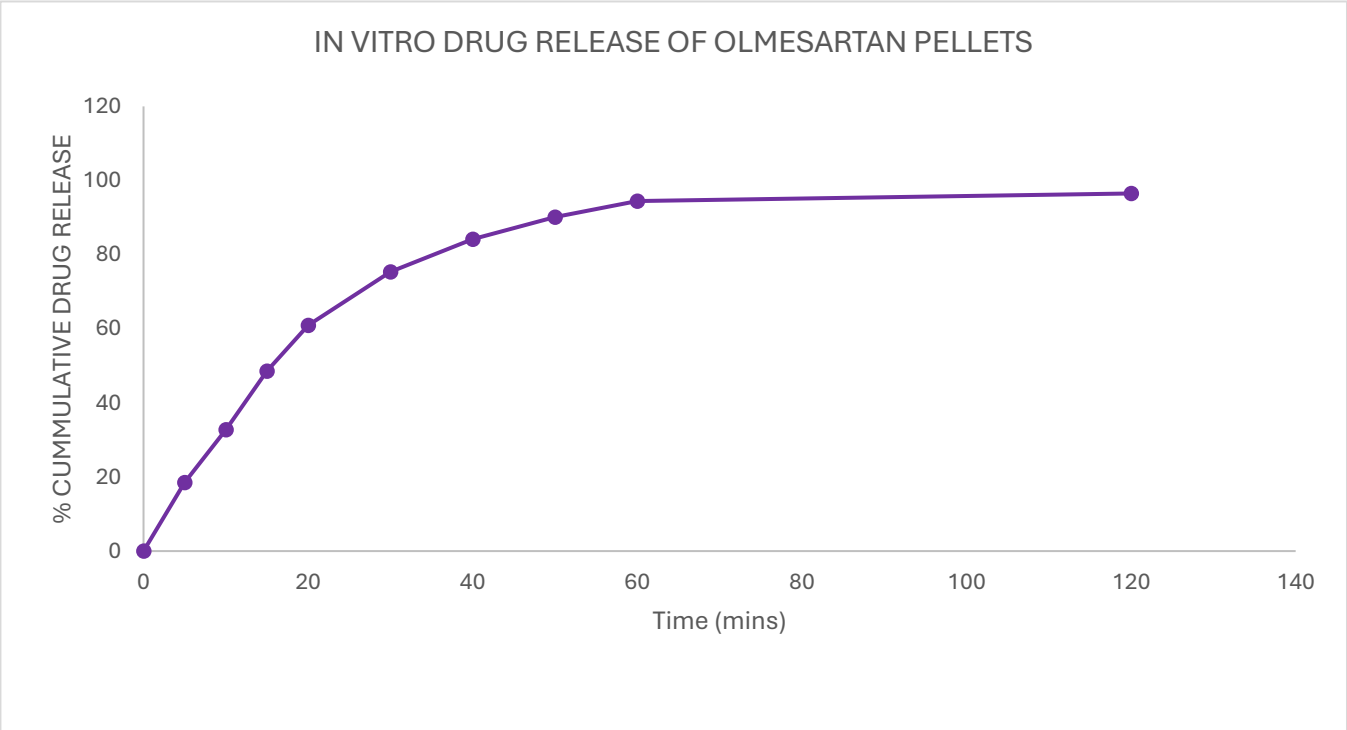


Fig 6: In vitro drug release profile of optimized olmesartan pellets.

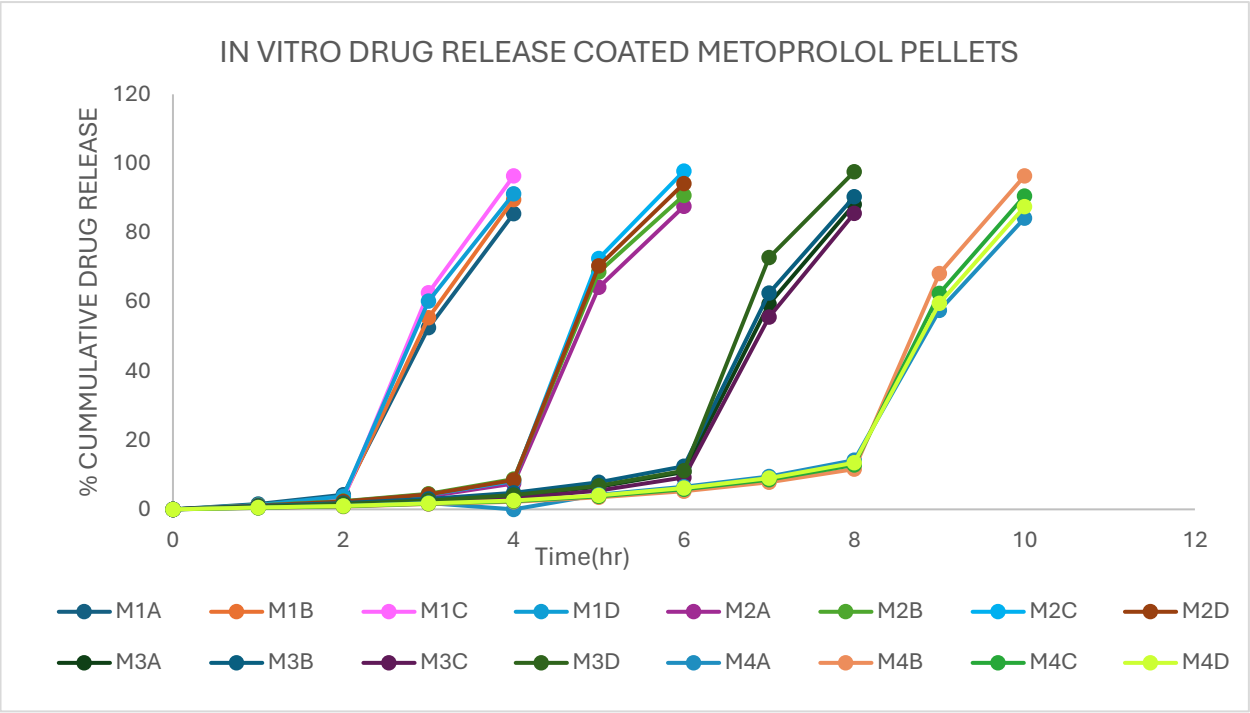


Fig 7: In vitro drug release profile of coated metoprolol pellets.

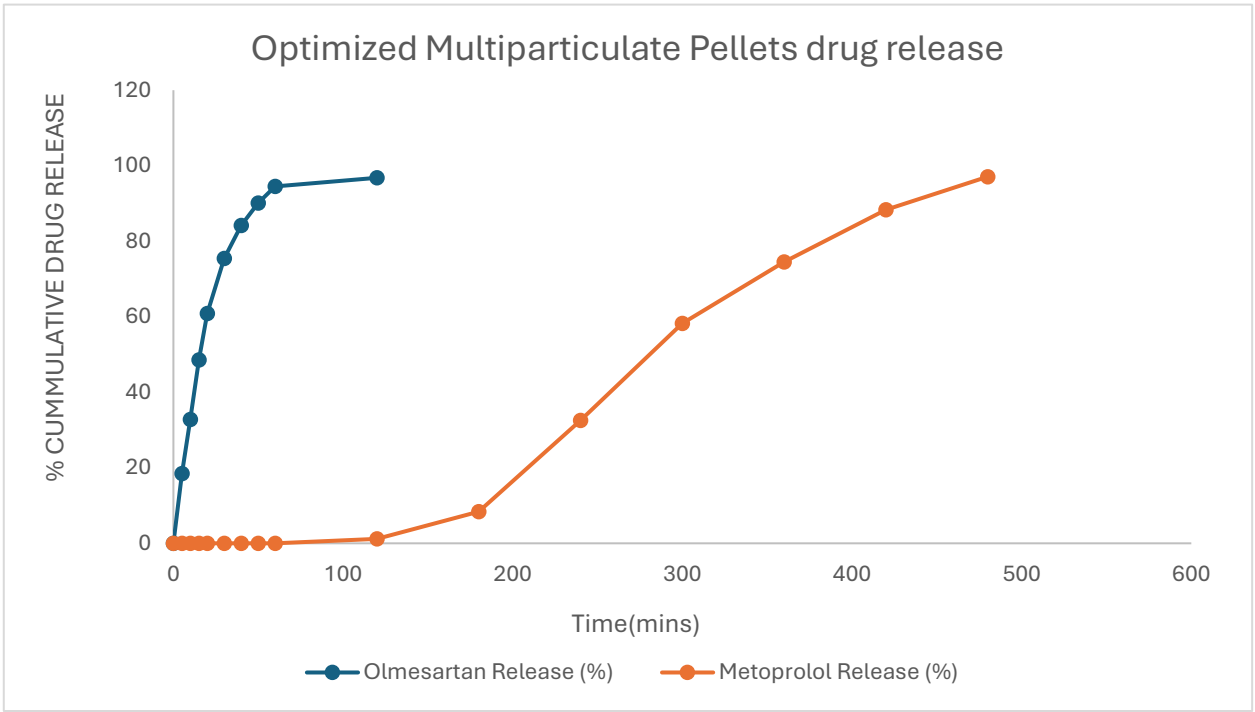


Fig.8: In vitro drug release profile of optimized dual-release multiparticulate pellets.

Tables

Table 1: QTPP of dual-release capsule formulation

QTPP Element	Target	Rationale
Dosage form	Dual-release multiparticulate capsule containing immediate-release olmesartan medoxomil pellets and delayed-release metoprolol succinate pellets	Designed to achieve sequential drug delivery, providing rapid RAAS inhibition followed by delayed β1-adrenergic blockade to effectively control the early morning blood pressure surge.
Route of administration	Oral	Oral administration is convenient, non-invasive, and promotes better patient adherence for long-term antihypertensive treatment.
Dosage strength	Olmesartan medoxomil 20 mg + Metoprolol succinate 50 mg	Selected to deliver the recommended therapeutic doses for combination therapy in the management of hypertension.
Drug release design	Immediate release of olmesartan with pH-dependent delayed release of metoprolol	Provides rapid onset of antihypertensive action while delaying metoprolol release to coincide with the circadian increase in cardiovascular risk during the early morning hours.
Pellet size	Uniform spherical pellets (710–1000 μm)	Uniform pellet size promotes consistent coating thickness, predictable drug release, and uniform dose distribution within capsules.
Drug release profile	Immediate release of olmesartan within approximately 2 h followed by delayed release of metoprolol after the desired lag time	Mimics the circadian rhythm of hypertension by synchronizing drug release with disease progression.
Entrapment efficiency	>90%	High entrapment efficiency ensures effective drug incorporation while minimizing drug loss during pellet manufacturing.
Production yield	>90%	A high production yield reflects an efficient, reproducible, and scalable extrusion–spheronization process.
Friability	<1%	Low friability preserves pellet integrity during coating, filling, packaging, transportation, and storage.
Content uniformity	95–105%	Ensures accurate dosing and uniform distribution of both drugs among individual capsules.

Stability	Physically and chemically stable throughout the intended shelf life	Maintains product quality, drug potency, and release performance during storage.
Container–closure system	Hard gelatin capsule packed in aluminium–PVDC blister	Provides effective protection against moisture, oxygen, and environmental conditions, thereby enhancing formulation stability.

Table 2: Critical quality attributes (CQAs) of dual-release pellet formulation

Critical Quality Attribute (CQA)	**Justification**
Pellet size distribution	A narrow pellet size distribution is essential for achieving uniform coating, reproducible dissolution behaviour, and accurate dose delivery.
Sphericity	Highly spherical pellets exhibit improved flow properties, uniform coating deposition, and consistent drug release characteristics.
Friability	Low friability minimizes pellet damage during manufacturing, coating, capsule filling, packaging, and handling.
Entrapment efficiency	High drug entrapment is necessary to achieve the intended dose while reducing material loss during formulation.
Production yield	High production yield reflects process robustness, manufacturing efficiency, and batch-to-batch reproducibility.
Drug release (Olmesartan)	Rapid drug release is required to produce an immediate antihypertensive effect through early inhibition of the renin–angiotensin–aldosterone system (RAAS).
Drug release (Metoprolol)	Controlled, pH-dependent delayed release is necessary to synchronize β1-blockade with the early morning surge in blood pressure, supporting chronotherapeutic treatment.
Assay	Drug content should comply with pharmacopeial specifications to ensure potency, quality, and therapeutic effectiveness.
Content uniformity	Uniform drug distribution among pellets and capsules is essential for dose accuracy and consistent clinical performance.
Stability	Adequate physical and chemical stability is required to preserve pellet integrity, drug potency, and the intended release profile throughout the product shelf life.

Table 3:Risk estimation matrix for material attributes and process parameters

OLMESARTAN						
Drug Product CQAs	**MCC**	**Starch**	**PVP 30 Binder Solution**	**Extrusion Speed**	**Spheronization Speed**	**Drying Temp**
Entrapment Efficiency	High	High	High	Medium	Medium	Low
Production Yield	High	Medium	High	High	High	Medium
Pellet Size Distribution	High	Medium	High	High	High	Medium
Sphericity	High	Medium	High	Medium	High	Medium
Friability	High	Medium	High	Medium	High	Medium
Drug Release	High	High	High	Medium	Medium	Medium
Assay	Low	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low	Low
METOPROLOL						
	MCC	HPMC	Starch Binder Solution	Extrution Speed	Spheronization speed	Drying Temp
Entrapment Efficiency	High	High	High	Medium	Medium	Low
Production Yield	High	Medium	High	High	High	Medium
Pellet Size Distribution	High	Medium	High	High	High	Medium
Sphericity	High	Medium	High	Medium	High	Medium
Friability	High	Medium	High	Medium	High	Medium
Drug Release	Medium	High	Medium	Low	Medium	Medium
Assay	Low	Low	Low	Low	Low	Low

Content Uniformity	Low	Low	Low	Low	Low	Low

LOW	**A broad acceptable risk. Further investigation is not required.**
MEDIUM	**An acceptable risk. Further investigation might be required for the reduction of risk**
HIGH	**Unacceptable risk. Further investigation will be required for the reduction of risk**

Table 4: FMEA-Based Risk Assessment and RPN Scoring

OLMESARTAN PELLETS				
Factor	**S**	**O**	**D**	**RPN**
MCC	4	4	4	64
PVP 30 Binder Solution	4	4	4	64
Starch	4	4	3	48
Extrusion Speed	4	3	3	36
Spheronization Speed	4	3	3	36
Drying Temperature	3	3	2	18
METOPROLOL PELLETS				
MCC	4	4	3	48
HPMC	4	4	3	48
Starch Binder Solution	4	4	3	48
Extrusion Speed	3	3	3	27
Spheronization Speed	4	3	3	36
Drying Temperature	3	3	2	18

Table 5:The experiment trials were performed via a Box-Behnken design.

	Independent Variables	**Response Values**

RUN	MCC(g)	Starch(g)	PVPK30 Binder Solution(%)	Entrapment Efficiency (%)	Production Yield (%)	In-vitro Release (%)
Olmesartan Pellets						
1	9.5	14	11.5	86.4	87.2	87.2
2	9.5	17	15	80.2	81.1	81.8
3	9.5	14	11.5	85.6	86.4	86.4
4	9.5	11	8	83.5	84.6	85.9
5	9.5	14	11.5	86	86.8	87
6	9.5	17	8	84.1	83.8	85.5
7	9.5	11	15	79.8	80.5	82.2
8	7	14	8	79.2	80.1	80.8
9	7	14	15	78.5	79.4	78.5
10	9.5	14	11.5	86.2	87	87.2
11	12	17	11.5	92.1	91.4	91.2
12	12	14	15	90.5	89.8	89.8
13	7	17	11.5	78.8	79.9	80.1
14	12	11	11.5	93.4	92.6	93.5
15	12	14	8	96.5	95.8	96.5
16	9.5	14	11.5	85.8	86.6	86.6
17	7	11	11.5	79.5	80.3	80.4
Metoprolol pellets						
RUN	**MCC(g)**	**HPMC(g)**	**Starch Binder Solution(%)**	**Entrapment Efficiency (%)**	**Production Yield (%)**	**In-vitro Release (%)**
1	7.5	9.5	11.5	86.8	83.6	86.2
2	7.5	7	8	75.3	72.9	74.8
3	7.5	9.5	11.5	85.6	82.4	85.9
4	7.5	12	15	78.2	75.1	77.1
5	5	7	11.5	94.5	93.8	94.5
6	7.5	12	8	77.8	74.5	76.5
7	7.5	9.5	11.5	86	84	86.4

8	7.5	7	15	79.5	76.2	78.3
9	7.5	9.5	11.5	86.4	83.2	86.1
10	10	9.5	8	79.1	76.5	78.9
11	10	9.5	15	80.2	77.4	79.5
12	7.5	9.5	11.5	88.6	82.8	86.7
13	10	12	11.5	93.8	92.9	93.8
14	10	7	11.5	93.2	92.5	93.2
15	5	9.5	15	81.5	78.8	80.4
16	5	9.5	8	78.4	75.2	77.9
17	5	12	11.5	94.1	93.1	94.1

Table 6: ANOVA for response : Entrapment Efficiency, Production Yield, In-vitro drug release

Response	**Entrapment Efficiency**		**Production Yield**		**In-vitro drug release**	
Source	**F-value**	**P-value**	**F-value**	**P-value**	**F-value**	**P-value**
Olmesartan Pellets						
Model (Significant)	173.00	<0.0001	232.10	<0.0001	136.48	<0.0001
A – MCC	1282.76	<0.0001	1666.35	<0.0001	1027.21	<0.0001
B – Starch	0.40	0.5463	2.17	0.1844	4.53	0.0708
C – PVP K30 binder	82.17	<0.0001	121.96	<0.0001	105.39	<0.0001
AB	0.29	0.6073	0.86	0.3855	3.13	0.1199
AC	22.58	0.0021	37.60	0.0005	15.17	0.0059
BC	0.03	0.8628	2.62	0.1493	0.00	1.0000
A^2	60.40	<0.0001	51.57	0.0002	12.81	0.0090
B^2	63.30	<0.0001	115.39	<0.0001	32.33	0.0007
C^2	50.81	0.0002	93.58	<0.0001	28.33	0.0011
Metoprolol Pellets						
Model (Significant)	91.17	<0.0001	326.31	<0.0001	657.55	<0.0001
A – MCC	0.75	0.4164	1.14	0.3217	2.26	0.1761
B – HPMC	0.30	0.5997	0.02	0.8977	0.49	0.5052
C – Starch Binder	11.93	0.0106	31.34	0.0008	52.17	0.0002
AB	0.31	0.5961	1.07	0.3343	2.01	0.1989
AC	1.23	0.3035	6.48	0.0384	7.27	0.0308

BC	4.45	0.0728	6.48	0.0384	16.93	0.0045
A^2	112.72	<0.0001	554.43	<0.0001	871.33	<0.0001
B^2	34.02	0.0006	214.62	<0.0001	223.89	<0.0001
C^2	691.27	<0.0001	2268.09	<0.0001	5008.12	<0.0001

Table 7: Independent variable ranges and response goals for the Box–Behnken optimization of olmesartan medoxomil immediate-release pellets.

Name	**Goal**	**Lower Limit**	**Upper Limit**
A – MCC (g)	In range	7	12
B – Starch (g)	In range	11	17
C – PVP K30 Binder Solution (%)	In range	8	15
Entrapment Efficiency (%)	Maximize	78.5	96.5
Production Yield (%)	Maximize	79.4	95.8
In vitro Drug Release (%)	Maximize	78.5	96.5

Table 8:Multi-objective optimization constraints for delayed-release metoprolol succinate pellets using Box–Behnken Design.

Name	**Goal 1**	**Goal 2**	**Goal 3**	**Goal 4**
A – MCC	Minimize (5–8)	Maximize (8–10)	Maximize (8–10)	Minimize (5–8)
B –HPMC (g)	Minimize (7–9)	Minimize (7–9)	Maximize (9–12)	Maximize (9–12)

C – Starch Binder Solution (%)	In range (8–15)	In range (8–15)	In range (8–15)	In range (8–15)
Entrapment Efficiency (%)	Maximize (75.3–94.5)	Maximize (75.3–94.5)	Maximize (75.3–94.5)	Maximize (75.3–94.5)
Production Yield (%)	Maximize (72.9–93.8)	Maximize (72.9–93.8)	Maximize (72.9–93.8)	Maximize (72.9–93.8)
In vitro Drug Release (%)	Maximize (74.8–94.5)	Maximize (74.8–94.5)	Maximize (74.8–94.5)	Maximize (74.8–94.5)

Table 9:Predicted and observed responses of the optimized olmesartan and metoprolol succinate pellet formulations.

Code	**MCC (g)**	**Starch (g)**	**Binder Solution (%)**	**Entrapment Efficiency (%)**	**Observed (± SD)**	**Production Yield (%)**	**Observed (± SD)**	**In vitro Drug Release (%)**	**Observed (± SD)**
				Predicted		**Predicted**		**Predicted**	
O	12	13.53	8.50	96.402	96.18 ± 0.42	95.694	95.32 ± 0.51	95.995	95.61 ± 0.47
Code	**MCC (g)**	**HPMC (g)**	**Binder Solution (%)**	**Predicted**	**Observed (± SD)**	**Predicted**	**Observed (± SD)**	**Predicted**	**Observed (± SD)**

M1	5	7	11.84	94.389	94.10 ± 0.38	93.642	93.28± 0.44	94.333	94.02 ± 0.41
M2	10	7	11.68	93.249	92.98 ± 0.46	92.596	92.21 ± 0.52	93.402	93.05 ± 0.49
M3	10	12	11.45	94.053	93.76 ± 0.35	93.177	92.88 ± 0.40	94.052	93.71 ± 0.43
M4	5.	12	11.62	94.109	93.82 ± 0.39	93.046	92.70 ± 0.47	93.933	93.55 ± 0.45

Table 10: Composition of Eudragit coating dispersions for pH-dependent delayed-release metoprolol succinate pellets.

Formulation	**Weight Gain (%)**	**Drug Loaded Pellets (g)**	**Eudragit L100:S100 (Ratio)**	**Acetone (mL)**	**Water (mL)**	**TEC (g)**	**Talc (g)**
M1A	20	15	80:20	70	10	0.45	0.30
M1B	20	15	60:40	70	10	0.45	0.30
M1C	20	15	20:80	70	10	0.45	0.30
M1D	20	15	40:60	70	10	0.45	0.30
M2A	12	20	30:70	70	10	0.36	0.24
M2B	12	20	70:30	70	10	0.36	0.24
M2C	12	20	40:60	70	10	0.36	0.24
M2D	12	20	60:40	70	10	0.36	0.24
M3A	16	25	70:30	70	10	0.60	0.40
M3B	16	25	80:20	70	10	0.60	0.40

M3C	16	25	20:80	70	10	0.60	0.40
M3D	16	25	30:70	70	10	0.60	0.40
M4A	24	20	90:10	70	10	0.72	0.48
M4B	24	20	10:90	70	10	0.72	0.48
M4C	24	20	40:60	70	10	0.72	0.48
M4D	24	20	60:40	70	10	0.72	0.48

Table 11: Pellet Size Distribution of Optimized Olmesartan (O) and Coated Metoprolol Formulations (M1C–M4C)

Sieve Size (µm)	**O (%)**	**M1C (%)**	**M2C (%)**	**M3D (%)**	**M4B (%)**
1700	0.30 ± 0.06	0.79 ± 0.10	0.40 ± 0.07	0.54 ± 0.08	1.18 ± 0.14
1180	1.30 ± 0.18	4.08 ± 0.26	2.30 ± 0.18	2.93 ± 0.21	5.25 ± 0.30
1000	96.23 ± 0.31	93.23 ± 0.34	95.43 ± 0.27	94.80 ± 0.29	91.53 ± 0.39
710	2.17 ± 0.16	2.39 ± 0.18	2.07 ± 0.16	1.99 ± 0.15	2.60 ± 0.20

Table 12: Comparison of Production Yield Before and After Coating of the Optimized Pellet Formulations

Formulation	**Observed Production Yield Before Coating (%)**	**Observed Production Yield After Coating (%)**
O	95.32 ± 0.51	97.48 ± 0.45
M1C	93.28 ± 0.44	95.62 ± 0.40
M2C	92.21 ± 0.52	94.86 ± 0.42
M3D	92.88 ± 0.40	95.34 ± 0.39
M4B	92.70 ± 0.47	96.12 ± 0.44

Table 13: Friability of the Optimized Pellet Formulations

Formulation	**Friability (%)**
Olmesartan (O)	0.40 ± 0.10

M1C	0.50 ± 0.10
M2C	0.40 ± 0.10
M3D	0.50 ± 0.10
M4B	0.60 ± 0.10

Table 14: Micromeritic Properties of the Optimized Pellet Formulations

Formulation	**Angle of Repose (°)**	**Bulk Density (g/cm³)**	**Tapped Density (g/cm³)**	**Carr's Index (%)**	**Hausner Ratio**
O	24.8 ± 0.7	0.47 ± 0.02	0.54 ± 0.02	12.96 ± 0.84	1.15 ± 0.02
M1C	25.6 ± 0.6	0.46 ± 0.02	0.53 ± 0.02	13.21 ± 0.91	1.15 ± 0.02
M2C	24.3 ± 0.5	0.48 ± 0.01	0.55 ± 0.02	12.73 ± 0.77	1.14 ± 0.01
M3D	26.2 ± 0.8	0.45 ± 0.02	0.52 ± 0.02	13.46 ± 0.95	1.16 ± 0.02
M4B	27.1 ± 0.9	0.44 ± 0.02	0.51 ± 0.02	13.72 ± 1.02	1.16 ± 0.02

Table 15: Weight Variation of the Capsule Formulation

Capsule	**Weight (mg)**
1	644.8
2	645.1
3	644.2
4	645.3
5	644.6
6	644.9
7	644.3
8	645.0
9	644.7

10	644.4
11	645.2
12	644.8
13	644.5
14	645.1
15	644.6
16	644.9
17	644.3
18	645.0
19	644.7
20	644.4

Table 16: Content Uniformity of the Capsule Formulation

Capsule	**Olmesartan (%)**	**Metoprolol (%)**
1	96.5	97.0
2	97.4	97.9
3	96.9	97.4
4	96.2	96.6
5	97.8	98.3
6	97.0	97.5
7	96.4	96.9
8	97.6	98.0
9	96.8	97.2
10	96.1	96.5
Mean ± SD	96.87 ± 0.55	97.33 ± 0.60
%RSD	0.57	0.62

Table 17: Drug Release Kinetics of the Optimized Olmesartan and Metoprolol Pellet Formulations

Olmesartan Pellets	**Zero-order**	**First-order**	**Higuchi**	**Korsmeyer-Peppas**
R^2 Value	0.9076	0.9972	0.8654	0.9090
Metoprolol Pellets	**Zero-order**	**First-order**	**Higuchi**	**Korsmeyer-Peppas**
R^2 Value	0.9076	0.8125	0.6698	0.9727

Table 18: Stability Study Results of the Optimized Dual-Release Multiparticulate Capsule Formulation

Storage Period	**Visual Appearance**	**Olmesartan Drug Content (%)**	**Metoprolol Drug Content (%)**
Initial	White colored pellets with no visible defects	96.8 ± 0.42	97.1 ± 0.38
1 Month	No visible change in appearance	96.5 ± 0.40	96.8 ± 0.36
2 Months	No noticeable change observed	96.2 ± 0.39	96.5 ± 0.35
3 Months	Formulation remained physically unchanged	95.9 ± 0.37	96.2 ± 0.34

Table 19: In Vitro Drug Release Profile of the Optimized Formulations During Stability Studies

Storage Period	**Olmesartan Drug Release at 120 min (%)**	**Metoprolol Drug Release at 480 min (%)**
Initial	96.8 ± 0.45	97.1 ± 0.40

1 Month	96.5 ± 0.43	96.8 ± 0.38
2 Months	96.2 ± 0.41	96.4 ± 0.36
3 Months	95.8 ± 0.39	96.0 ± 0.35

Table 20: Similarity Factor (f_2) and Difference Factor (f_1) Analysis of the Optimized Multiparticulate Formulations During Stability Studies

Storage Period	**Olmesartan f_1**	**Olmesartan f_2**	**Metoprolol f_1**	**Metoprolol f_2**
1 Month	0.55	98.74	0.67	99.37
2 Months	1.08	95.72	1.33	97.62
3 Months	1.66	91.70	2.03	95.19