International Journal for Pharmaceutical Research Scholars (IJPRS)

V-7, I-3, 2018 ISSN: 2277 - 7873

RESEARCH ARTICLE

Development and Characterization of Compression-Coated Tablet of Telmisartan Applying QbD Principles

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Manuscript No: IJPRS/V7/I3/00055, Received On: 28/07/2018, Accepted On: 06/08/2018

ABSTRACT

The objective of this study is to develop and evaluate compression coated drug delivery system, which involve rupturable coat around a rapidly disintegrated core tablet prepared by direct compression. Core tablet is containing an immediate dose of Telmisartan and mucoadhesive pellets for sustained release (SR) of Telmisartan. Sustained release pellets were prepared by extrusion-spheronization using quality by design (QbD) principle. Risk assessment was performed using fishbone diagram and failure mode and effect analysis (FMEA). A Plackett-Burman design (PBD) was used to screen seven potential high risk variables obtained from risk assessments study. Based on PBD out of seven potential high risk variables only two had significant effects on the quality of the pellets. This allowed to use 3^2 full factorial design for elucidation the relationship between the variable and critical quality attributes (CQAs). Optimized formulation of sustained release pellets was evaluated for different evaluation parameters. Core tablets and compression-coated tablets were subjected to various pre-compression and post-compression tests. Prepared compression-coated tablets were evaluated for lag time and *in-vitro* dissolution. DSC and FT-IR studies confirmed the compatibility between drug and excipients. Optimized formulation of SR pellets shows the satisfactory result. The core tablet shows the satisfactory disintegration time. Final batch of compression-coated tablet offered an immediate release (IR) of Telmisartan after predetermined lag time i.e., 4.5h, followed SR from mucoadhesive pellets. It can be concluded that bedtime dosing of chronomodulated compression coated tablets may offer a promising for controlling early morning surge in hypertension disease.

KEYWORDS

Telmisartan, Chronotherapy, Pellets, Quality by Design, Compression-Coating

INTRODUCTION

Human body shows 24 h variation in blood pressure (BP). BP is mainly increased in the early morning hours, declines form mid afternoon and is minimum at midnight[1].

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Telmisartan is a potent, long-lasting, non-peptide angiotensin II receptor (type AT1) antagonist used in the management of hypertension. It is well absorbed after oral administration. Peak plasma concentration is reached in 0.5 to 1 h after conventional drug dosage form administration[2-3]. Hence, the rationale of chronotherapy for hypertension is to deliver the drug in higher concentrations during the early morning post-awakening period. Thus, nighttime hypertensive medication is more specific for the early

 http://dx.doi.org/10.31638/IJPRS.V7.I3.00055

morning surge of BP in addition to 24 h BP control would be useful for the prevention of cardiovascular events in hypertensive patients[4].

Quality target product profile (QTPP) is a vital element of QbD approach which forms base for systematic product development. QbD is concerned with the product quality through linking the critical material attributes (CMAs) and critical process parameters (CPPs) into the critical quality attributes (CQAs) of drug product. Firstly, the potential risk variables are determined by risk assessment in the initial design during product development. Then, to improve process knowledge, multivariate experiments are carried out using design of experiments (DoE)[5]. DoE, as an important tool for QbD, can determine the relationship between CMAs, CPPs and CQAs of a process[6]. PBD is used for screening, which can screen the main variables among numerous inputs variables[5]. 3^2 full factorial design were usually used for optimization.

Pellets, as a drug delivery system, show remarkable advantages such as homogenous distribution in gastrointestinal tract thus maximizing drug absorption, reducing irritation of the gastrointestinal tract, lowered risk of side effects, less friable dosage form and easy coating. Extrusion-spheronization as pelletization technique is the most commonly and effectively used methods. There are many factors that impacts the extrusion-spheronization process, such as type of polymer, concentration of polymer, type of binder, type of spheronizer aid and concentration, kneading time, extruder speed, spheronizer speed, spheronizer time, drying technique, drying time[6].

The compression-coated approach offers several benefits, including that it is simple, versatile, has a solvent-free coating, and economical at the production scale compared to other pharmaceutical platform technologies which have been reported for such chronomodulated drug delivery[7].

In this work, we attempted to formulate chronomodulated compression-coated tablets of Telmisartan for administration at bedtime with a 4.5 - 5 h lag time for modulation of rapid release of Telmisartan during morning hours followed by sustained release up to 24 h. Compression-coated tablets dosage forms comprising of two components, (I) an inner core tablet which contain Telmisartan (for IR) and mucoadhesive pellets of Telmisartan (for SR) And (II) an outer coat layer is containing hydrophilic polymer.

MATERIALS AND METHODS

MATERIALS

Telmisartan was obtained as a gift sample from Zydus Cadila Healthcare Ltd, India. Microcrystalline cellulose (Avicel PH101; Signet Chemical Corporation, India). Eudragit RLPO, Eudragit RSPO, Hydroxy propyl methylcellulose (HPMCK100M), Polyox 303 WSR were received from Colorcon Asia Pvt. Ltd, Goa, India. All the chemicals used for analytical development were HPLC Grade.

METHODS

Preformulation Studies[7-10]

Micromeritics Properties

The angle of repose of Telmisartan and formulation mixture was determined by the fixed funnel method. The bulk density (BD) and tapped densities (TD) were determined by using standard density apparatus. The Carr's index (%) and the Hausner's ratio were calculated.

Drug-Excipients Compatibility Studies

Infrared Spectroscopy

The FTIR spectra of pure drug sample and excipients were acquired using the potassium bromide pellets technique on a Shimadzu Fourier transform-infrared spectrophotometer (Shimadzu, Kyoto, Japan) in the wavelength region of 4000 cm^{-1}- 400 cm^{-1}. The procedure consisted of dispersing a sample in potassium bromide, and compressing the sample into disc by applying a pressure of 5 tons for 5 min in a hydraulic press.

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Differential Scanning Calorimetry

The DSC analysis was carried out to investigate thermodynamic compatibility between pure drug and physical mixture of excipients selected for preparation based on their melting temperature and glass transition temperature. The drug-polymer physical mixture was prepared by simple mixing with the help of mortar and pestle. Approximately 3-5 mg of each sample was transferred in aluminium pan heated at a rate of 10^0C.min^{-1} up to 400^0C under nitrogen environment at a flow rate of 20 ml.min^{-1}. The thermograms were obtained using DSC-60 calorimeter (Shimadzu, Japan).

Preparation of Telmisartan Sustained Release Mucoadhesive Pellets[5-6]

Telmisartan sustained release mucoadhesive pellets were prepared by extrusion-spheronization method. Telmisartan (20%) was mixed with microcrystalline cellulose (Avicel PH 101, 43 %), polyvinylpyrrolidone (2.5%), Eudragit RLPO:RSPO (22.5%), HPMC K100M (10%) and PEG 400 (2%) using 60-mesh sieve. IPA:Water mixture was added slowly and the mixing was continued to get a wet mass of suitable consistency. The wet mass passed throgh a specially fabricated extruder with 2 mm die length and 1 mm diameter of the screened die. The collected extrudate product was then immediately transferred and rotated in a fabricated spheronizer. The obtained pellet were collected and dried at 40^0 C for 12 h in hot air oven.

Establishment of Quality Target Product Profile[11]

Various elements of QTPP for development of Telmisartan mucoadhesive pellets have been summarized in Table 1. QTPP helps to determine critical quality attributes, which are prerequisites for establishment of risk assessment and failure modes.

Table: 1 QTPP for Compression-Coated Tablet of Telmisartan

QTPP element	Target	Justification
Dosage form	Compression-coated tablet	Tablet—commonly accepted unit solid oral dosage form; Compression coating - to achieve immediate drug release after desired lag time followed by sustained release; solvent-less and continuous processing, favorable in terms of formulation stability and productivity.
Route of administration	Oral	Dosage form designed to administer orally, most acceptable route of administration
Dosage strength	60 mg	It is the unit dose of Telmisartan which needs to be incorporated for once a daily administration
Quality drug product attributes	Drug release: 20-25 % immediate drug release after 4-6 h lag time followed by sustained release up to 18 h	Administration of the formulation before going to bed will restrict the drug release for 4–6 h followed by burst release to have peak effect explicitly in the early morning hours.

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Initial Risk Assessments Studies[5-6, 11]

Ishikawa fishbone diagram was constructed to identify initial list of potential high risk variables that affect the quality of the product. (Figure 1). Based on previous knowledge and initial experimental data, failure mode and effect analysis (FMEA) method were further applied in the risk analysis of the parameter of the pellets. To determine the priority of all the variables, a risk score matrix based on the total risk priority number (RPN) was used. Table 2 enlists the details of material attributes (MAs) and process parameters (PPs) employed during FMEA and their calculated RPN scores. In this study, the RPN threshold was set as 25. The variables associated with a RPN score above 25 were subjected to factor screening studies employing PBD.

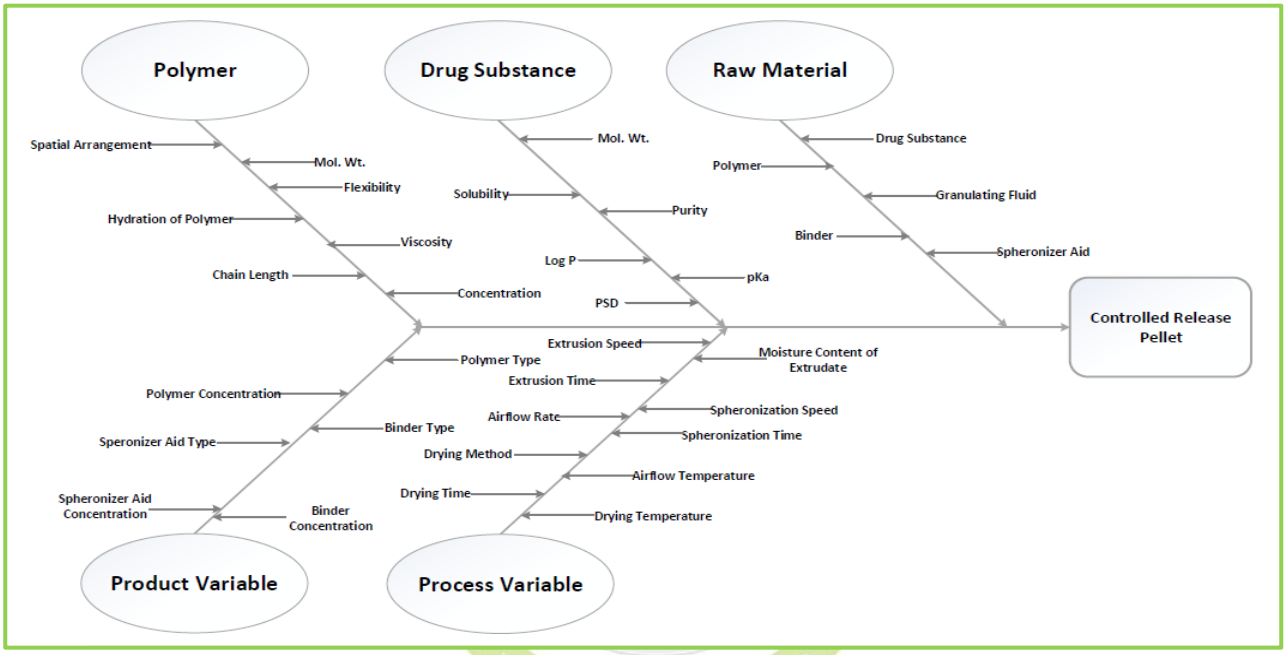

Figure: 1 Ishikawa Fish-Bone Diagram for Formulation and Process Variable of Mucoadhesive Pellets

Table: 2 Summary of FMEA Analysis Illustrating RPN Scores for Various Formulation VariablesAffecting the CQAs

Sr. No.	Failure modes	Severity (s)	Occurrence (O)	Detection (D)	RPN (S O D)
1	Eudragit Concentration (RLPO:RSPO) (1.5:1)	4	3	4	48
2	MCC Conc.	4	3	3	36
3	HPMC Conc.	3	4	4	48
4	Kneading Time	5	3	4	60
5	Extrusion Speed	2	3	2	12
6	Extrusion Time	2	3	2	12
7	Spheronization Speed	3	3	3	27
8	Spheronization Time	3	3	3	27
9	Drying Time	3	3	3	18

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Plackett-Burman Screening Design[5-6]

PBD was employing using the Minitab 17® Software (M/s Minitab Inc., Philadelphia, PA), to screen significant variables influencing selected CQAs. The parameters low (-1) and high (+1) level selection was based on preliminary screening and literature. The purpose of PBD was to evaluate the effects of the processing variables and identify the key one, influencing the % Yield, % Entrapment Efficiency, Q2h, Q8h, Q16h (Dependent variables). The Kneading Time (min), Spheronization speed, Spheronization time (min), MCC concentration (%), HPMC concentration (%), Eudragit RLPO:RSPO concentration (%), Amount of External Phase (ml), Stirring Speed (rpm), Stirring Time (h), Temperature (^{0}C) were selected as independent variables (Table 3). The Pareto charts were constructed to identify the influence of each factor on responses. High-risk variables were identified and further used for 3^2 full factorial experimental design.

3^2 Full Factorial Experimental Design

Systematic optimization of Mucoadhesive pellets was accomplished employing 3^2 Full Factorial Design i.e. two factor three level by determining the main and quadratic effects of variables on the selected responses. Table 4 illustrates the design layout as per 3^2 Full Factorial Design containing a total of 9 different formulations prepared employing Concentration of Eudragit (RLPO:RSPO) (X_1), and Kneading Time (X_2) as independent fators at three different levels, i.e. low (-1), intermediate (0) and high (+1) levels whereas the response (Y_1= %Yield, Y_2= %Entrapment Efficiency, Y_3= Q2h, Y_4=Q8h, Y_5=Q16h) were selected as dependent variables.

Preparation of Core Tablet

Core tablet containing 20 mg Telmisartan were prepared by direct compression. Accurately weighed amount of Telmisartan (20 mg), lactose (24 mg) as diluent, cross carmellose sodium (15 mg) as a fast disintegrant, PEG 8000 (5 mg) as cushioning agent, magnesium stearate (2 mg) and talc (1 mg) and 40 mg Telmisartan equivalent weight of pellets were mixed thoroughly in double cone blender for 10 minutes. The resultant powder blend was compressed into core tablets using rotary tablet machine (Karnavati Engineering, Ahmedabad, India) equipped with 6 mm round, flat, and plain punches. The force of compression was adjusted so that hardness of all the prepared core tablets ranged from 2-3 kg/cm^2.

Preparation of Compression-Coated Tablet[11-12]

Polyox WSR-303 and lactose (2:1 mixture) were sifted through sieve no 120, and homogeneously mixed using a mortar pestle to obtain uniform powder blend and lubricated with magnesium stearate (6 mg) and talc (2 mg). Half of the total weight powder (300 mg) was weighed and transferred into a 9 mm die cavity. Next, the core tablet was centrally placed on powder bed. The remaining half of the powder blend was added into the die and compressed using rotary tablet machine. The force of compression was adjusted so that hardness of all the prepared tablets ranged from 5-6 kg/cm^2.

Characterization of Mucoadhesive Pellets[6,13-17]

% Yield and % Drug Entrapment Efficiency

Pellets (25 mg) were dissolved in 25 mL methanol and the resulting solution was filtered by whatman filter paper. The filtrate was diluted and analyzed by UV-Visible Spectrophotometer (UV-1800, Shmadzu, Japan) at 296 nm.

Yield (%) = Weight of pellets/Total expected weight of drug and polymer *100

Entrapment efficiency (%) = Actual loading/Theoretical Loading *100

Micromeritics Studies of Pellets

Micromeritic studies of pellets were performed as described earlier in preformulation study.

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Table: 3 Variables and Level in the Plackett-Burman Design

Independent Variables	**Levels**	
	Low Level (-1)	**High Level (+1)**
X_1: Kneading Time (min)	5	15
X_2: Spheronization Speed	Low	High
X_3: Spheronization Time (min)	10	20
X_4: MCC Concentration (%)	30	50
X_5: HPMC Concentration (%)	10	20
X_6: Eudragit Concentration (RLPO :RSPO) (%)	10	30
Dependent Variables Y_3: Q2h, Y_4: Q8h, Y_5: Q16h		

Table: 4 3^2 Full Factorial Experimental Design for Mucoadhesive Pellets

Batch code	**Coded values**	
	X_1	**X_2**
F1	-1	-1
F2	0	-1
F3	1	-1
F4	-1	0
F5	0	0
F6	1	0
F7	-1	1
F8	0	1
F9	1	1

Independent Variables	**Level**		
	Low (-1)	**Medium (0)**	**High (1)**
Concentration of Eudragit (RLPO:RSPO) (X_1)	20 %	25 %	30 %
Kneading Time (X_2) (min)	5 min	10 min	15 min
Dependent Variables Y_1: % Yield, Y_2: % Entrapment Efficiency, Y_3: Q2h, Y_4: Q8h, Y_5: Q16h			

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Aspect Ratio

At least 50 pellets from each batch were randomly selected for measurement of aspect ratio. The maximum and minimum diameters of the pellets were measured using digital micrometer (Mitutoyo Digimatic micrometer, Japan). Aspect ratio decreases with higher sphericity.

Aspects ratio = d_{max}/d_{min}

Friability

Two gram accurately weighed pellets were taken and placed in Roche Friabilator. The test apparatus was rotated at 25 rpm for 4 minutes. After friability testing, the pellets were sieved through sieve no. 40 to remove fines generated.

% F =[{(Initial Weight of pellets- Weight of Pellets after Friability)/ Initital Weight]* 100

***In-vitro* Dissolution Study**

In-vitro dissolution of pellets was carried out in pH 6.8 phosphate buffer using a USP Dissolution Apparatus I (Electrolab, India). The dissolution bath was maintained at $37^0 \pm 0.5^0$C at 50 rotations per minute (RPM) for 18 h. The 5 ml samples were withdrawn at suitable intervals and replaced with fresh medium. The aliquots were suitably diluted and analyzed by UV-Visible spectrophotometer at 296 nm.

Release Kinetic Study

Data obtained from *in-vitro* release study of optimized batch were fitted to various kinetics equations (zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Weibull models) to find out the mechanism of drug release from pellets Appropriate drug release kinetic model was selected based on least Fisher's ratio (F) and maximum R^2.

***In-vitro* wash-off test**[14]

The *in vitro* mucoadhesion study of pellets was assessed using Falling liquid film technique. A strip of Albino rat intestinal mucosa was mounted on a glass slide and 50 mg of accurately weighed pellets were sprinkled on the intestinal mucosa. This glass slide was incubated for 15 min in a desiccator at 80% relative humidity to allow the polymer to interact with the membrane and finally placed on the stand at an angle of 45°. Phosphate buffered of pH 6.8 previously warmed to 37±0.5° was allowed to flow over the pellets and membrane at the rate of 1 ml/min for 16 h with the help of a peristaltic pump. At the end of this process, the detached particles were collected and weighed.

% Mucoadhesion=[(weight of sample-weight of detached particles)/weight of sample]×100

Scanning Electron Microscopy

Scanning electron microscopy (SEM) was used for determining the surface morphology of optimized batch (JEOL JSM-5610V, JEOL, Tokyo, Japan). The pellets were fixed in slabs and coated with gold/ palladium using a sputter coater.

Characterization of Core and Compression-Coated Tablet of Telmisartan[6, 8, 18]

Physicochemical Characterization

The thickness, diameter, and hardness of the tablets (n = 6) were determined using a Vernier Calipers and the Monsanto hardness tester, respectively. The friability (%) of the tablets was determined using a Roche Friabilator and uniformity of tablet weight (n = 20) was evaluated as per pharmacopoeial guidelines using analytical balance (Sartorius, CP-224s, Germany). The disintegration time of the core tablets was determined using a disintegration test apparatus (Electrolab, India). The Telmisartan content of the tablets was assayed in triplicate by UV-Visible spectrophotometer.

***In-vitro* Dissolution Method**

The *in-vitro* dissolution study of compression-coated tablet was carried out using USP Type II dissolution apparatus. The study was carried out in 900 ml of phosphate buffer (pH 6.8). The dissolution medium was maintained at 37±0.5 °C. The paddle was rotated at 50 rpm. At different time intervals, 5 ml of sample was withdrawn and analyzed by UV–Visible spectrophotometer at 296 nm. At each time of withdrawal, 5 ml of fresh corresponding

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medium was replaced into the dissolution vessel. The lag time (after which tablet ruptured) was noted.

Stability Study

The optimized batch of compression-coated tablets was charged for the accelerated stabilities studies as per ICH guidelines (40 ± 2^0 C and 75 ± 5 % RH) for a period of 3 months in stability chambers (Model- TH 90 S, Thermolab, India). They were placed in amber glass bottles. The samples were taken out at 30, 60 and 90 days and evaluated for the various physicochemical parameters.

RESULTS AND DISCUSSION

Preformulation Study

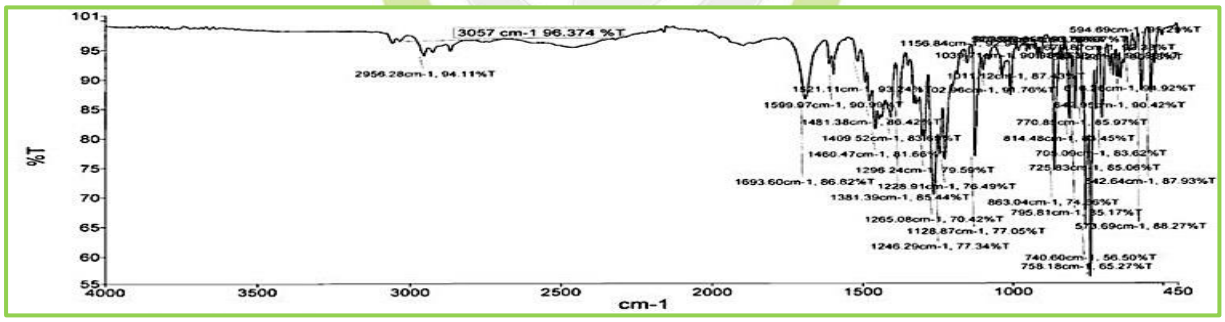
Micromeritic Properties

For direct compression of materials, it is required to possess good flow and compacting properties. The drug Telmisartan exhibited angle of repose of 36±0.22° indicating poor flow property. The Carr's index (16.49±1.09%) and Hausner's ratio (1.19±0.013) values were also high. The prepared formulation mixtures showed good flow properties as indicated by low values of angle of repose, Carr's index and Hausner's ratio.

Drug-Excipients Compatibility Studies

Drug–excipient compatibility studies were carried out by FT-IR spectroscopy and DSC. The FT-IR spectra of pure Telmisartan and its physical mixture with other excipients (Figure. 2) are showed characteristic peak at 740 and 757 cm^{-1} (ring vibration due to 1,2- distributed benzene), 1266 cm^{-1} (-CH_3 Bending), 1448 cm^{-1} (-CH_2), 1455 and 1381 cm^{-1} (-CH_3 bending vibration), 1460 cm^{-1} (C-H bend), 1599 cm^{-1} (C-C aromatic band and stretching), 1693 cm^{-1} (C=O stretching vibrations), 2965 cm^{-1} (-CH_3 Stretching), and 3057 cm^{-1} (Aromatic ring). Since these peaks were found to be unchanged in drug and excipients mixture, Telmisartan is physically compatible with excipients used.

(A)



(B)

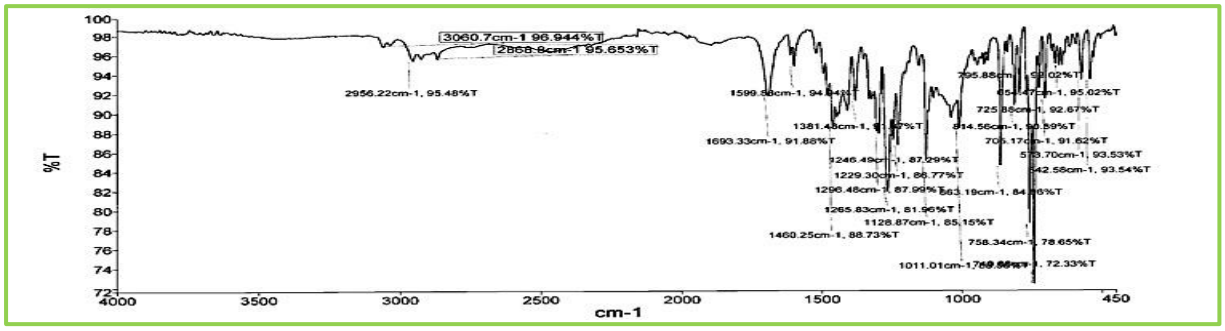


Figure: 2 FT-IR spectra of (A) Telmisartan Drug and (B) Physical Mixture of Telmisartan Drug with Excipients of Pellets

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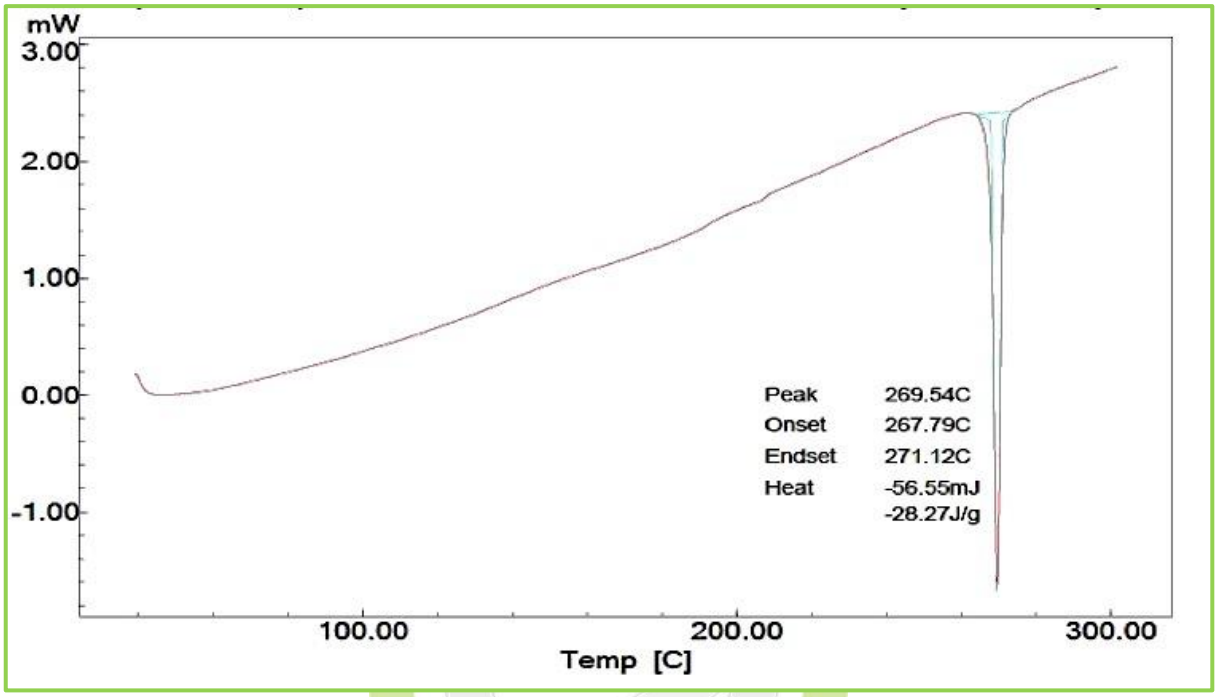
The thermal curve of Telmisartan showed melting endothermic peak at 269.54 °C (Figure. 3). There was no considerable change in the endotherm peak (261.07 °C) of Telmisartan when mixed with excipients.

(A)



(B)

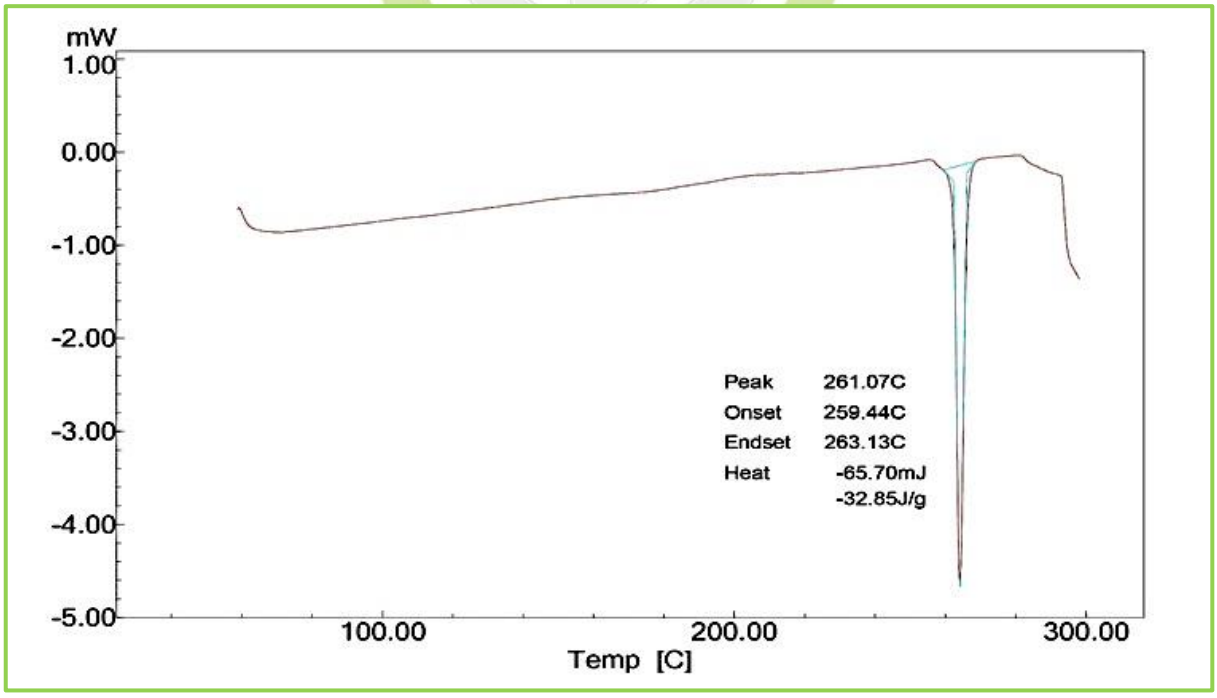


Figure: 3 DSC Thermogram of (A) Telmisartan drug and (B) Physical Mixture of Telmisartan Drug with Excipients

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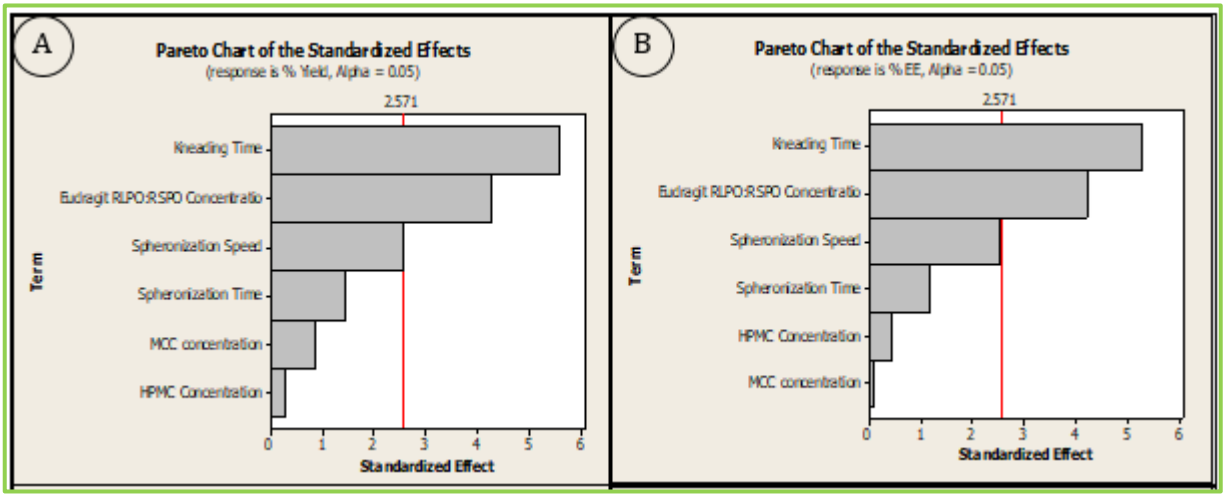
Plackett-Burman Screening Design

The goal of this study was to identify the most significant variables affecting the CQAs using PBD. The experimental run with variables and corresponding responses are presented in Table 5.

Table: 5 PBD for Screening of Processing and Formulation Parameters

Runs	X_1	X_2	X_3	X_4	X_5	X_6	Y_1	Y_2	Y_3	Y_4	Y_5
1	-1	1	1	-1	1	-1	40.23	42.34	30.07	65.09	100.34
2	1	1	1	-1	1	1	87.23	88.23	14.89	44.56	95.43
3	-1	1	1	1	-1	1	58.32	60.3	25.87	47.9	98.32
4	1	1	-1	1	1	-1	67.23	64.54	28.88	60.43	99.98
5	-1	-1	-1	1	1	1	54.23	49.54	23.25	59.65	97.32
6	1	1	-1	1	-1	-1	80.32	79.45	28.67	60.12	99.45
7	1	-1	1	1	-1	1	75.43	77.31	17.82	46.65	96.32
8	-1	-1	1	1	1	-1	41.09	38.9	31.07	66.43	100.45
9	-1	-1	-1	-1	-1	-1	38.33	41.9	28.05	59.32	98.32
10	1	-1	1	-1	-1	-1	45.89	48.54	26.78	52.34	97.33
11	-1	1	-1	-1	-1	1	64.32	68.9	23.83	50.32	98.43
12	1	-1	-1	-1	1	1	79.23	81.54	16.12	48.23	96.09

Pareto charts are shown in Figure 4 indicates that among all of the variables, concentration of Eudragit RLPO:RSPO and kneading time strikingly influenced dependent variables.



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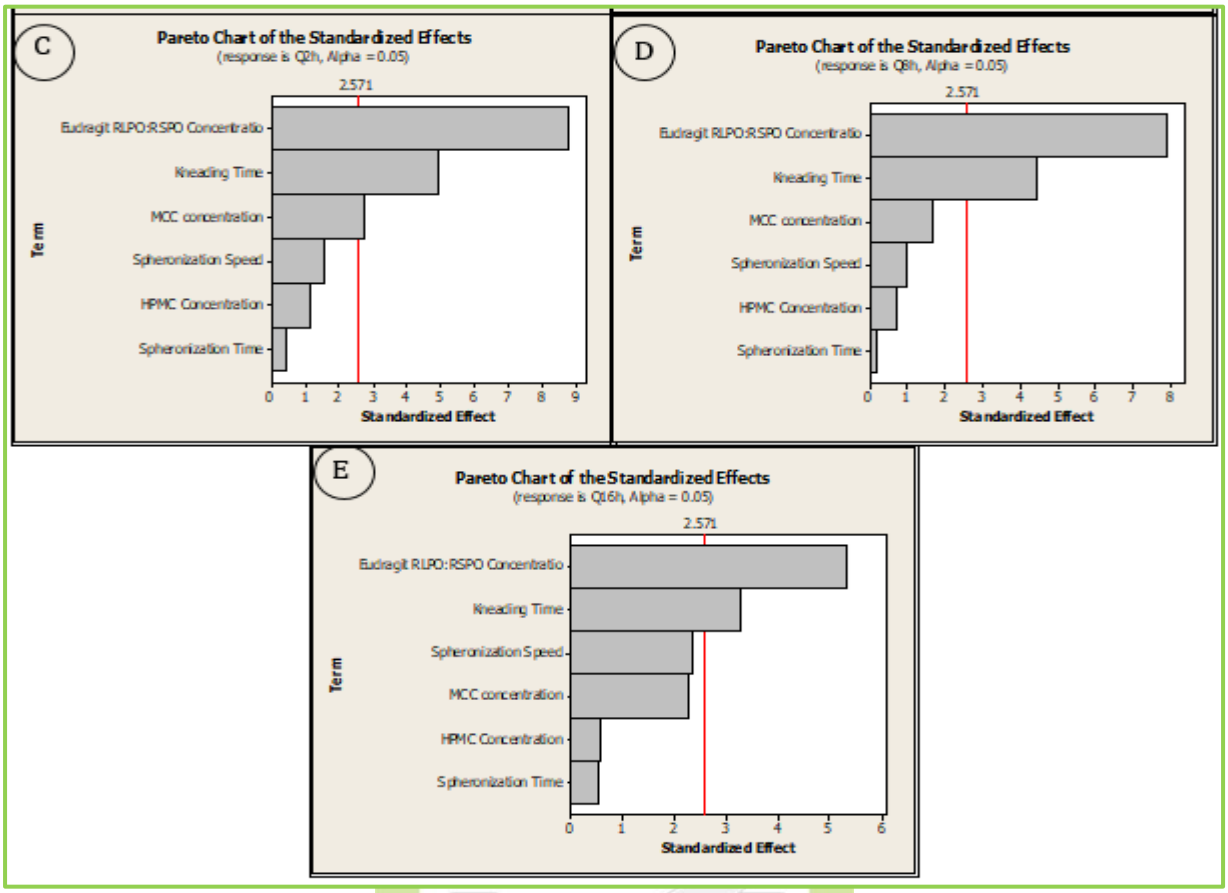

Figure: 4 Pareto Chart for Screening of Influencing Variables as per PBD

Table: 6 Responses for Factorial Batches of Mucoadhesive Pellets

Batch No.	Responses				
	Y_1	Y_2	Y_3	Y_4	Y_5
F1	57.54 ± 0.12	52.36 ± 0.25	28.9 ± 0.34	70.03 ± 0.10	100.32 ± 0.27
F2	54.32 ± 0.31	50.76 ± 0.17	26.87 ± 0.29	66.43 ± 0.65	99.45 ± 0.53
F3	58.08 ± 0.22	60.49 ± 0.33	23.63 ± 0.23	65.43 ± 0.22	98.76 ± 0.33
F4	70.32 ± 0.18	72.56 ± 0.15	25.86 ± 0.19	68.43 ± 0.28	98.45 ± 0.27
F5	74.32 ± 0.15	71.56 ± 0.27	22.56 ± 0.22	65.43 ± 0.15	97.65 ± 0.39
F6	71.66 ± 0.22	68.32 ± 0.19	20.65 ± 0.43	63.43 ± 0.25	96.78 ± 0.25
F7	84.34 ± 0.34	87.45 ± 0.27	19.45 ± 0.37	58.54 ± 0.32	98.57 ± 0.21
F8	85.42 ± 0.25	89.43 ± 0.23	17.65 ± 0.28	56.78 ± 0.27	96.34 ± 0.14
F9	87.78 ± 0.17	90.45 ± 0.41	14.89 ± 0.11	52.34 ± 0.41	94.56 ± 0.22

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3^2 Full Factorial Experimental Design

% Yield, % Entrapment Efficiency, In-vitro dissolution parameters, are presented in Table 6 as response of factorial batches for optimization of mucoadhesive pellets. All the tests were performed in triplicates (n=3).

The model explaining the effect of various variables on each dependent response are as follows:

$Y_1 = 71.53 + 0.89X_1 + 14.60X_2$

$Y_2 = 71.48 + 1.15X_1 + 17.29X_2$

$Y_3 = 23.02 – 2.51X_1 - 4.57X_2 – 1.12X_2^2$

$Y_4 = 65.76 - 2.63\ X_1 – 5.71X_2 - 4.17X2^2$

$Y_5 = 97.63 – 0.84\ X_1 – 1.51X_2 – 0.61X_1X_2 + 0.3X_2^2 - 0.56X_1X_2^2$

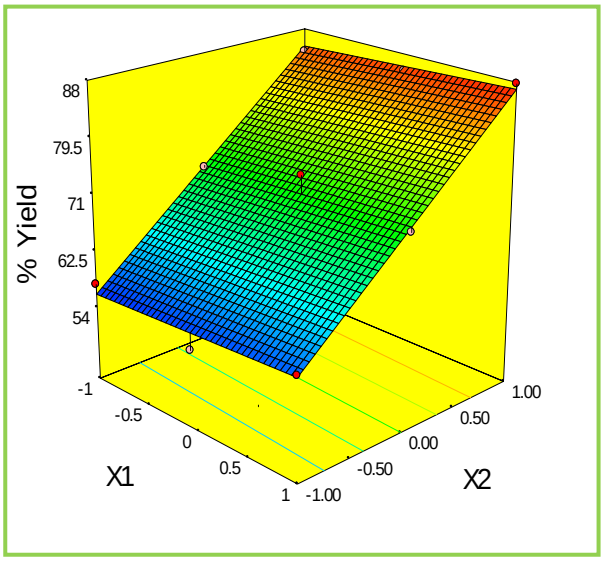
Co-efficient of X_1 (concentration of Eudragit RLPO:RSPO) and X_2 (Kneading time) show positive effect on Y_1 and Y_2.

In contrast, both X_1 and X_2 exhibits negative effect on Y_3, Y_4 & Y_5 responses. The effect of variables on responses is shown in Figure 5**.** The 3D response surface plot depicts in Figure 5 A and B reveal that kneading time is linearly increasing influence on % Yield and % Entrapment Efficiency. The 3D-response surface plot depicts in Figure 5 C revels that the concentration of Eudragit RLPO:RSPO has linearly descending influence on Q2h. The 3D-response surface plot depicts in Figure 5 D & E revel that the concentration of Eudragit RLPO:RSPO has linearly descending influence on Q8h and Q16h. The yellow region in the Figure 5 F represents as an overlay plot shows the optimized parameters suggested by the Design-Expert 7® (Stat-Ease Inc., Minneapolis, MN) software to get the CQA in the required range. By applying desirability function, optimized batch for mucoadhesion pellets was derived.

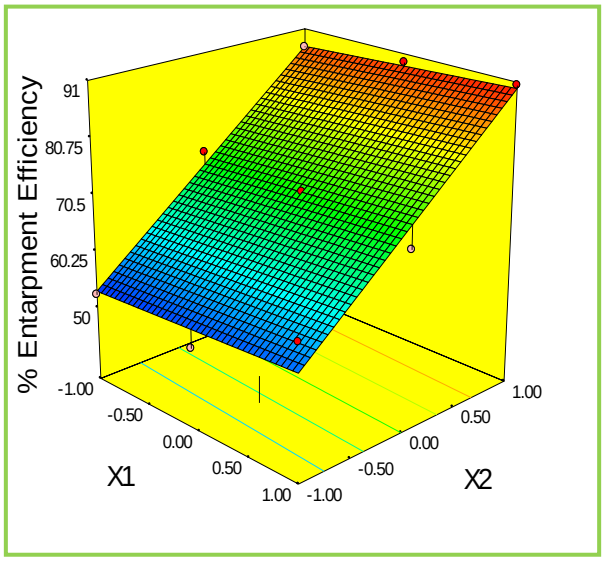
Evaluation of Optimized Batch

The prepared optimized batch of mucoadhesive pellets exhibited 82.87 % yield and 85.76%, good entrapment indicating superior drug loading. 84.12 % mucoadhesion revels that pellet formulation remained under mucoadhesive for at least 18h. Evaluation of the micromeritics properties revealing favorable flow characteristics of the prepared pellets. The drug release profile of the formulation showed sustained release profile of drug upto 18h. The comparative *in-vitro* dissolution profiles of optimized batch with desired release profile and market product (Telmiride®) are shown in Figure 6.

A



B



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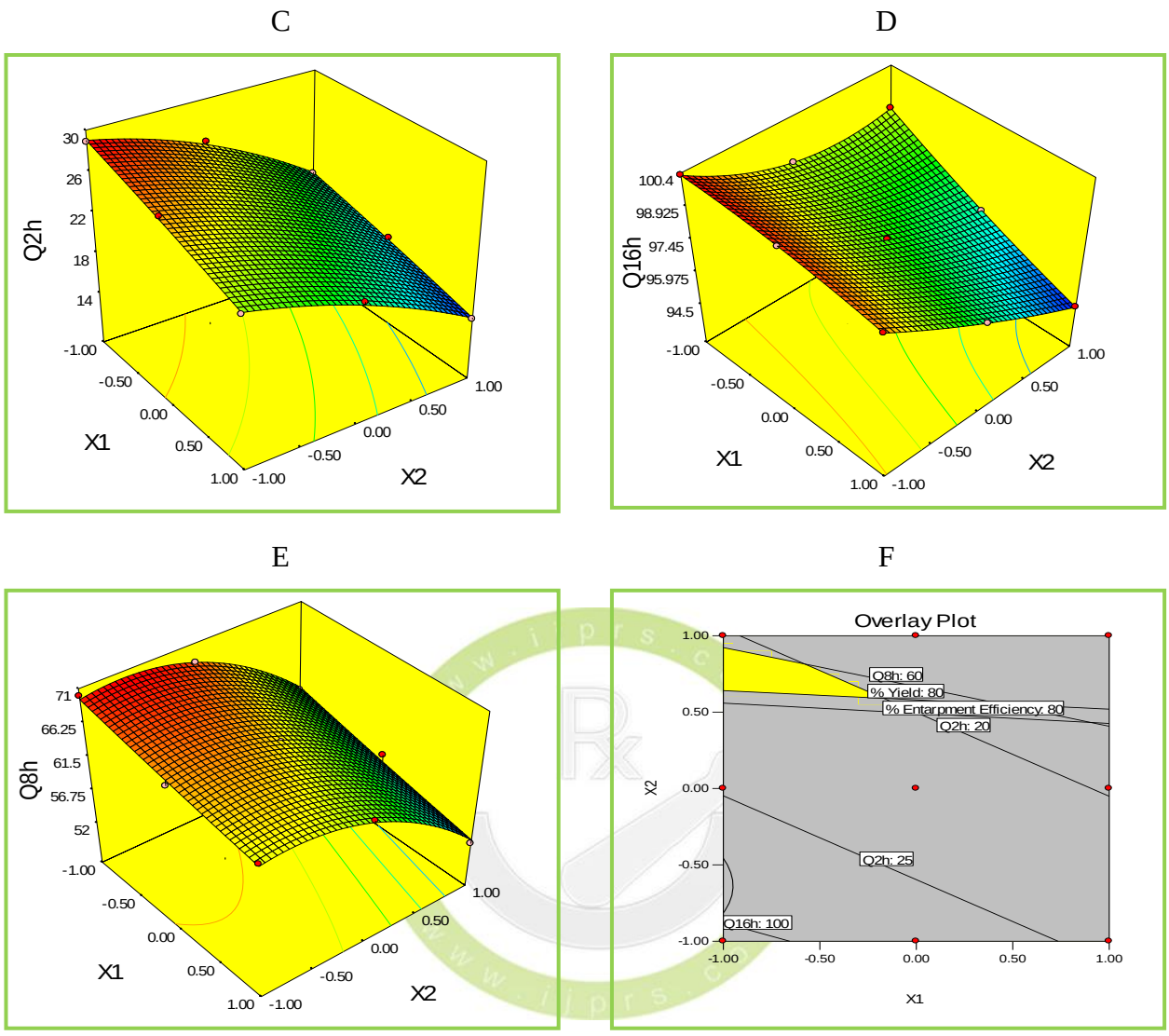

Figure: 5 Response Surface Plots and Overlay Plot of Mucoadhesive Pellets

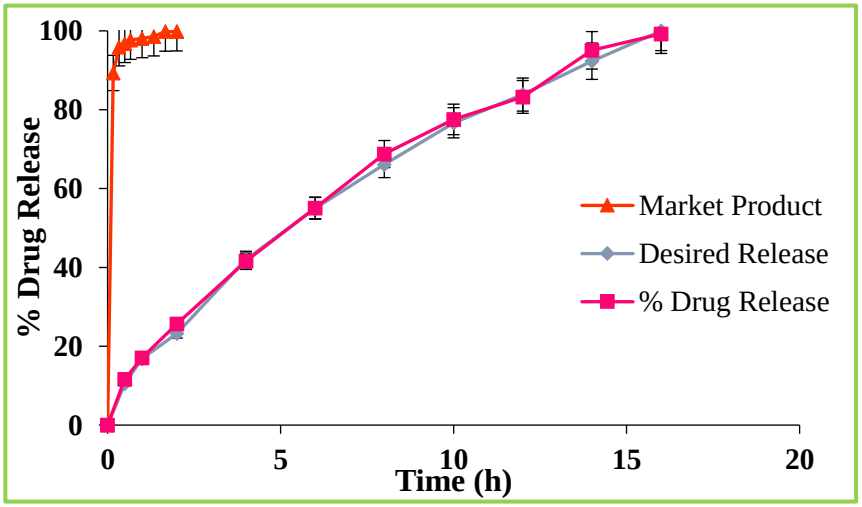

Figure: 6 Comparative *In-Vitro* Drug Release Profile of Optimized Batch of Mucoadhesive Pellets, Desired Release and Market Product

 http://dx.doi.org/10.31638/IJPRS.V7.I3.00055

The marketed tablet showed almost complete drug release in less than 2 h owing to its immediate release nature, while the pellets showed complete release upto 18 h. There was good similarity between the obtained drug release profile and desired release profile (evidenced by similarity factor f_2 = 87.41).

Release Kinetic Study

It was observed that the drug release followed Korsmeyer-Peppas model (Table 7). The value of diffusional release exponent (n) of 0.629 for optimized pellets formulation indicated non-fickian, i.e. anomalous behavior.

Tablet: 7 Release Kinetic Study of Optimized Formula of Mucoadhesive Pellets

Parameters	Kinetic Model					
	Zero order	**First order**	**Higuchi**	**Korsmeyer-Peppas**	**Hixon**	**Weibull**
F	104.0496	18.2909	24.1141	**3.1614**	10.9640	18.8186
R^2	0.9827	0.9931	0.9953	**0.9989**	0.9968	0.9938

Scanning Electron Microscopy

Figure 7 shows the SEM images of optimized pellets, which are found spherical in shape with smooth surface. Approximate particle size of pellets was found 1.1-1.5 mm.

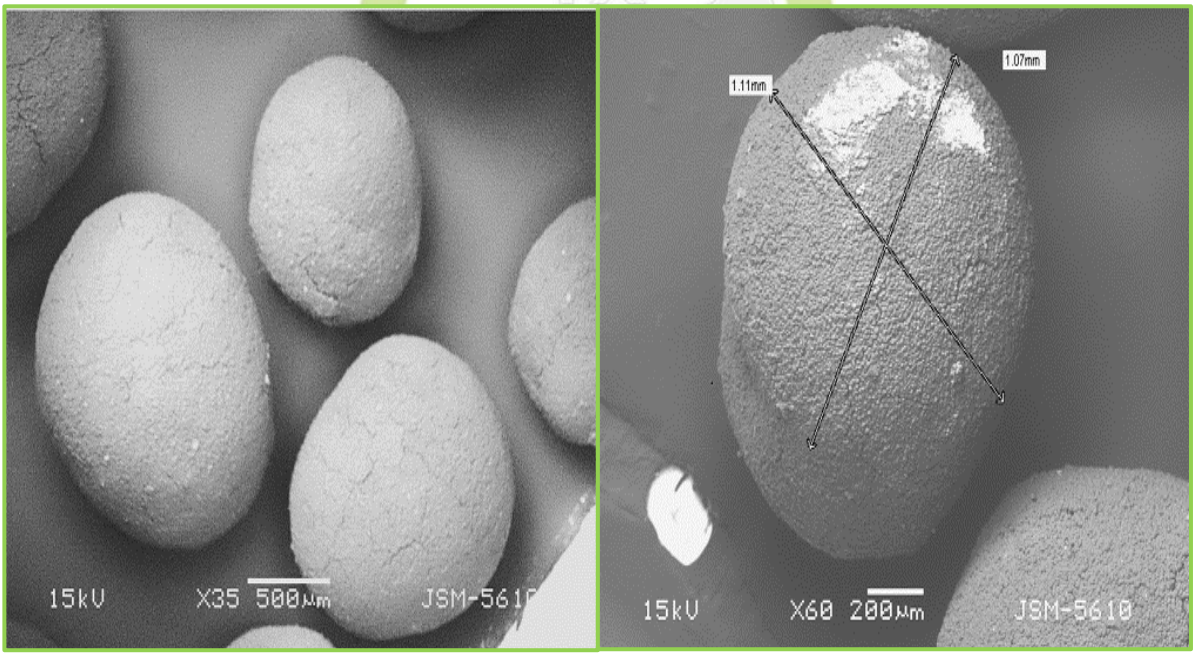

Figure: 7 Scanning Electron Microscopy Images of the Optimized Mucoadhesive Pellets

Evaluation of Telmisartan Compression-Coated Tablet

The appearance of Telmisartan compression-coated tablet was found to be satisfactory. Table 8 depicts the result of core and compression-coated tablet evaluation.

 http://dx.doi.org/10.31638/IJPRS.V7.I3.00055

In-vitro Study of Compression-Coated Tablet

Compression-coated tablet showed immediate release with distinct lag time of 4.5 h, during which the dissolution medium reaches the core after eroding or rupturing the outer layer followed by sustained release from pellets (Figure 8). A cumulative drug release profile produced by all the components of compression-coated tablet together was in accordance with the target release profile, evidenced by similarity factor f_2 value (87.82).

Stability Study

The optimized formulations subjected to short-term stability studies were evaluated for physical appearance, hardness, friability and *in-vitro* drug release and results of stability studies reveled stable characterization of formulation.

Table: 8 Physical Characterizations of Core & Compression-Coated Tablet

Sr. No.	Characterization parameter	Core Tablet	Compression-coated tablet
1	Weight of Tablet (mg)	301 ± 2.51	605 ± 3.12
2	Thickness (mm)	2.5 ± 0.42	4.5 ± 0.31
3	Hardness (kg/cm$^{2)}$	2.8 ± 0.33	5.2 ± 0.33
4	Friability	< 1 %	< 1 %
5	Disintegration Time (sec)	9 ± 2.23	-
6	Lag time (h)	-	4.5 ± 0.45 h

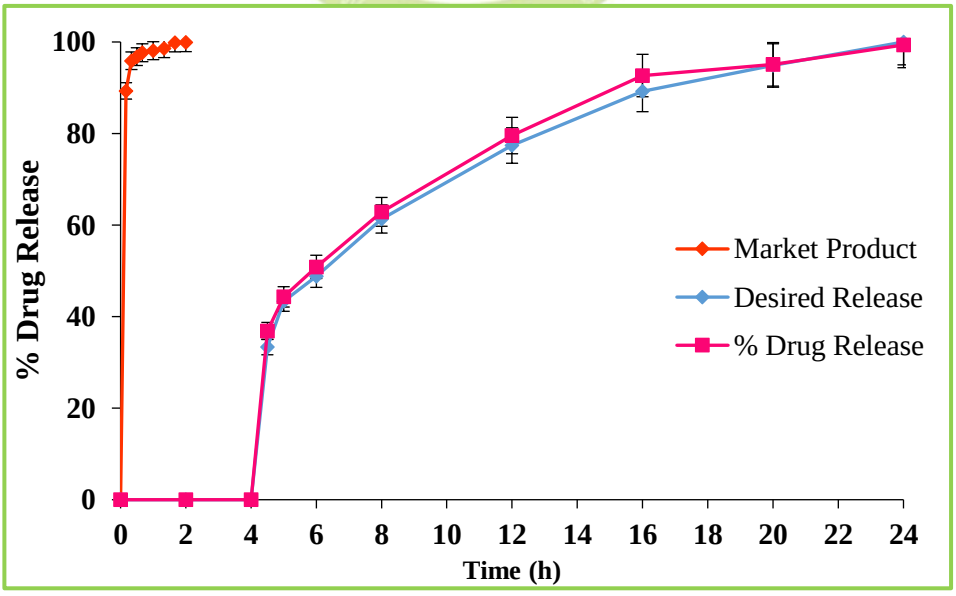

Figure: 8 Comparative Dissolution Profile of Compression-Coated Table, Desired Release Profile and Market Product

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CONCLUSION

The current study demonstrated the usefulness of the application of QbD principle to gain fundamental understanding of formulation and processing variables affecting the Telmisartan sustained release pellets. Compression-coated tablet for Telmisartan was prepared successfully for providing the desired drug release characterized by immediate release after 4.5 h lag time followed by sustained release for 18 h. We conclude that chronomodulated drug delivery using a compression-coated approach may be promising for controlling early-morning surge of hypertension when administered at bedtime to patients suffering from hypertension.

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HOW TO CITE THIS ARTICLE

Trivedi, P. J., Mehta, D. M., Suthar, D. D., Parejiya, P. B., & Shelat, P. K. (2018). Development and Characterization of Compression-Coated Tablet of Telmisartan Applying QbD Principles. *International Journal for Pharmaceutical Research Scholars(IJPRS), 7(3),* 58-76. http://dx.doi.org/10.31638/IJPRS.V7.I3.00055

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