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IN-VITRO DUAL RELEASE ANGIOTENSIN II RECEPTOR BLOCKER (LOSARTAN POTASSIUM) AND FORMULATION BY QbD APPROCH

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ABSTRACT

Multi-particulate drug delivery systems are utmost accepted and widely used dosage form as they offer so many benefits over unit dosage form like improved bio-availability because of increased surface area, reduced inter-subject variation and reduced chances of dose dumping. Pelletization is one of the most promising techniques for the multi-particulate drug delivery system. The purpose of this study to apply the QbD approach to optimize the formulation of a dual release pellets containing Losartan potassium prepared by extrusion and spheronization. A 3^2 full factorial design is the simple experimental design with two variables studied at three levels. In the present study, the type of polymers used HPMC (X1) and percent polymer replaced with MCC (X2) to achieve Sustained release of Losartan potassium taken as independent formulations variables. The Critical quality attributes (CQA) to be applied for formulation development is the response factors, such as the dissolution profiles at 2nd hr and 8th hr to be taken as dependent response variables. The optimized formulation to be characterized by comparison with the various physical properties and in-vitro pharmacokinetic parameters.

KEYWORDS: Dual Release Pellets, Sustained release, Immediate release, Losartan potassium.

INTRODUCTION

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00 mm. Pellets as suitable systems for extended-release formulations with respect to their spherical/ hemispherical shape, low surface area-volume ratios that provides ease of coating and reduction in the dosage regimen. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously. The pelletized

products can improve the safety and efficacy of the active agent. These are formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system. Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets.

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure typically does not cause symptoms. Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure atrial fibrillation, disease, vision, chronic kidney disease, and dementia. Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively. For most adults, normal blood pressure at rest is within the range of 100–130 millimeters mercury (mmHg) systolic and 60– 80 (mmHg) diastolic. For most adults, high blood pressure is present if the resting blood pressure is persistently at or above 130/80 or 140/90 (mmHg). Different numbers apply to children. Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office- based blood pressure measurement. It is divided into two types: Primary hypertension (Essential hypertension), Secondary hypertension (non-essential hypertension) The purpose of this study to apply the QbD approach to optimize the formulation of a dual release pellets containing Losartan potassium prepared by extrusion and spheronization. A 3^2 full factorial design is the simple experimental design with two variables studied at three levels. In the present study, the type of polymers used HPMC (X1) and percent polymer replaced with MCC (X2) to achieve Sustained release of Losartan potassium taken as independent formulations variables. The Critical quality attributes (CQA) to be applied for formulation development is the response factors, such as the dissolution profiles at 2nd hour and 8th hour to be taken as dependent response variables. The optimized formulation to be characterized by comparison with the various physical properties and in-vitro pharmacokinetic parameters.

MATERIALS AND METHODS

Losartan potassium (Losacar) from Zydus Cadila, Hydroxy Propyl Methyl Cellulose (HPMC K100M) obtained from Aualon, Gujarat. Sodium starch glycolate purchased from Parry's Chennai, Microcrystalline cellulose (W) from Chemspure, Chennai, and Ethyl cellulose Nanhang Indl.co, China.

Preparation of pellets by extrusion and spheronization:

Formulation of Losartan potassium immediate release pellets.

Formulation of pellets containing Losartan Potassium were prepared by extrusion and spheronization method. The components of the formulations were shown in Table 05. The solid powders of Losartan Potassium, MCC, and other ingredients were accurately weighed and mixed by hand in a polyethylene bag for 10 min to obtain a homogeneous physical mixture and add magnesium stearate, and mixed thoroughly. The powder mixture was mixed with water and isopropyl alcohol in the ratio of 1:1 as a binder for 20 minutes to achieve a consistency of a damp mass. The wet mass was then passed through a single screw extruder with a 1.0mm screen at 150 rpm. The extrudates were processed in a spheronizer fitted with a cross-hatched plate rotated at 300rpm for about 5 min. The obtained pellets were dried at 40oC for 12 h.

Formulation of Losartan potassium sustained release pellets using different ratios of selected polymers

The required quantity of MCC as spheronization enhancer, HPMC and EC as polymeric material and losartan were weighed. To this mixture, sufficient quantity of isopropyl alcohol as granulating agent was added to get a wet mass. The solid blend was passed through the extruder to form the extrudates. The formed extrudates were introduced into the spheronizer to get spherical pellets by varying different spheronization speed. Preparation of Losartan potassium pellets using different concentrations of HPMC and EC by extrusion spheronization technique.

Table 1: Formulation of IR pellets.

S.no	Ingredients (mg)	Formulation
1	Losartan Potassium	25
2	Sodium starch Glycolate	16.5
3	Poly vinyl pyrrolidone	4.5
4	Microcrystalline cellulose	24
5	IPA and Distilled Water	1:1
*	**Total**	**70**

Table 2: Formulation of SR pellets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
DRUG	50	50	50	50	50	50	50	50	50
MCC	13.3	14.15	15	13.3	14.5	15	13.3	14.15	15
EC	7.5	6.5	5.5	6.5	5	5	5	5	5
PVP	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
HPMC	5	5	5	6.5	6.5	6.5	8	8	8
TOTAL	80	80	80	80	80	80	80	80	80

OPTIMIZATION

Design of Experiment (DOE)

Experimental design is a systematic and scientific approach to study the relationship and interaction between independent and dependent variables. A 2-factor, 3-level full factorial design (3^2) was employed for optimizing sustained release Losartan Potassium pellets using DESIGN EXPERT® (version 13) software available from Stat-Ease Inc., Minneapolis, MN. The concentration of MCC (A) and HPMC (B) were optimized by using Design of Experiment (DoE) at three different levels: low (-1), medium (0) and high (+1). Amount of drug release at 2nd hour, and amount of drug release at 8th hour, were selected as response variables. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the formulation responses; Equation.

$$Y=b_0+b_1A+ b_2A+ b_3A+ b_4A^2+b_5B^2$$

Where, Y is the response, b_0 is the arithmetic mean response of the 9 runs. The responses in the above equation Y are the quantitative effect of formulation components or independent variables A and B; b_0 is the arithmetic mean response; b_1, b_2, b_3, b_4 and b_5 are the estimated coefficient for the factors A and B.

Table 3: Full Factorial design layout.

S.NO	FORMULATIONS	FACTORS	
		A	B
1	F1	-	-
2	F2	0	-
3	F3	+	-
4	F4	-	0
5	F5	0	0
6	F6	+	0
7	F7	-	+
8	F8	0	+
9	F9	+	+

Evaluation of losartan potassium pellets

Micromeritic Properties

Angle of Repose, Bulk density, tapped density, Carr's Index, Hausner's ratio evaluated for the granules according to the standard method.

In vitro dissolution study

Dissolution testing of formulations F1-F4 was performed using USP XXVIII type I. The test Was performed using 500 ml solution of pH 6.8 phosphate buffer maintained at temperature 37 ± 0.5°C stirred at a speed of 50 rpm (United State Pharmacopoeia, 2005). A sample of 5 ml was taken out at an interval of 5 ml samples were withdrawn at 5,10,15,20,30,40,60 min for 1 hour to estimate the immediate release of losartan potassium pellets and at 1, 2, 4, 6, 8, 10 hours for estimating sustained release of losartan potassium pellets immediately replaced with 5 ml fresh pH 6.8 phosphate buffer solution to maintain sink conditions in the dissolution jar. The drug content was analyzed at 216 nm using a UV spectrophotometer.

Drug release kinetics

The release of drug from the tablet can be characterized using various kinetics like Zero order equation, Higuchi kinetics, Korsemeyer-peppas equation.

Optimization:

Optimization was carried out using **Design Expert version 13.**

Formulation of Losartan Potassium capsule dosage form:

The optimized formulation prepared as capsule dosage form by semi-automatic capsule filling machine. The empty hard gelatin capsule (size 2) obtained as gift sample. 70mg of formulated immediate release pellets and 80mg of optimized sustained release pellets were weighed and filled in the capsule which contain 25mg of Losartan potassium in IR and 50mg of Losartan potassium in SR. After capsulation, it will be analyzed as per IP including content uniformity, weight variation, etc.

Scanning Electron Microscopy study (SEM):

The external and surface morphology of Losartan potassium pellets was analyzed by Scanning Electron Microscopy (SEM). The pellets are fixed on supports with carbon-glue, and coated with gold- palladium under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Samples were then observed with a FEI, Quanta 200 scanning electron microscope (FEI, Quanta 200 SEM, USA) at 20 kV. The results were shown in the **Fig.8**

RESULT AND DISCUSSION

Pre-formulation study

Drug –excipient compatibility (FT-IR) study of tri-layer formulations

The FT-IR analysis of the drug and polymer gave thermal profile characteristic of the substances are shown in **Fig 1,2**: Principal peaks of tri-layer formulation containing drug and polymer are intact in the formulations.

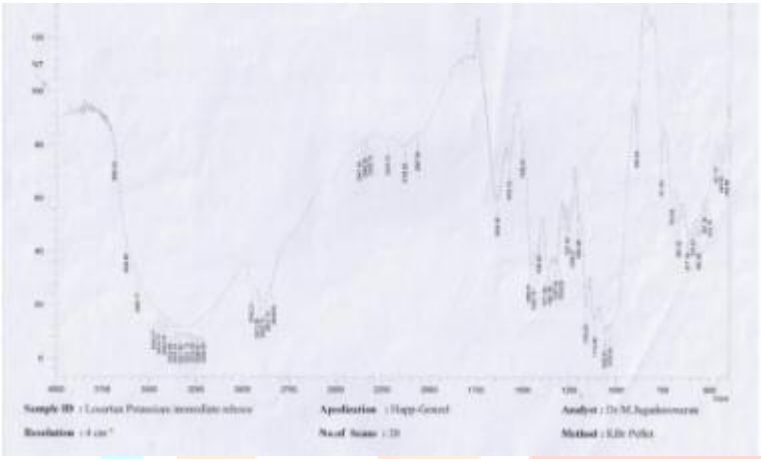

Fig 1: FT-IR Spectrum of Losartan Potassium with MCC.

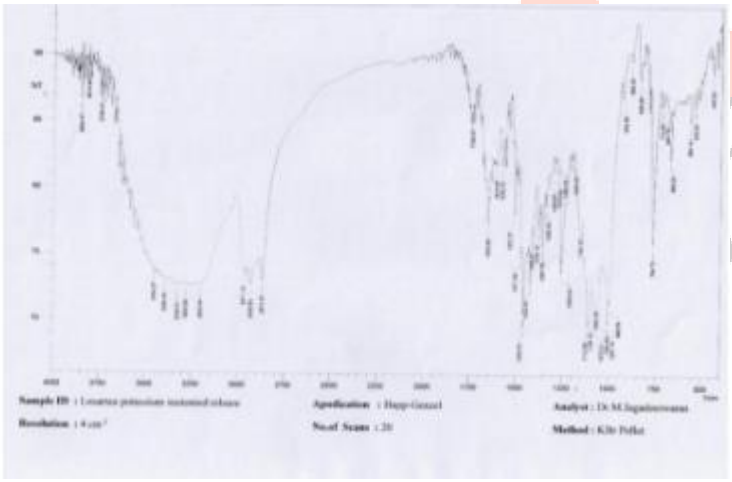

Fig 2: FT-IR Spectrum of Losartan Potassium with HPMC and Ethyl Cellulose.

The characteristic absorption of the Losartan potassium SR was the band at 1502 cm-1, and 1538 cm-1, which is assigned to the stretching vibration of aliphatic and aromatic C-H of Losartan potassium and 1723 cm-1 assigned to stretching vibration of C=C. Another band at 2898 cm-1 is due to C=N symmetric vibration. The characteristic absorption of the Losartan potassium IR was the band at 3264.55 cm-1, which is assigned to the stretching vibration of O-H group of Losartan. Another band at 1032 cm-1 is due to N-H stretching vibration. As the identical peaks were observed in all the cases, hence it was confirmed that no interaction exists between drugs and excipients.

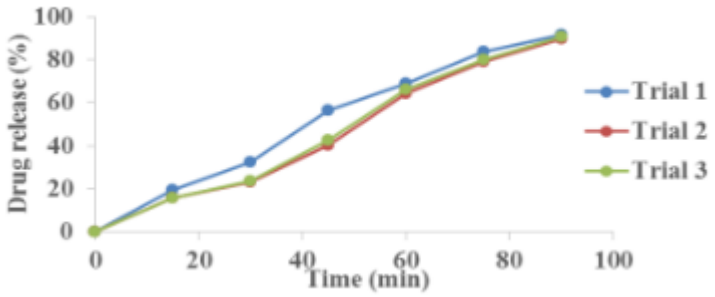

Fig 3: In Vitro drug release profile of Losartan potassium pellets (IR).

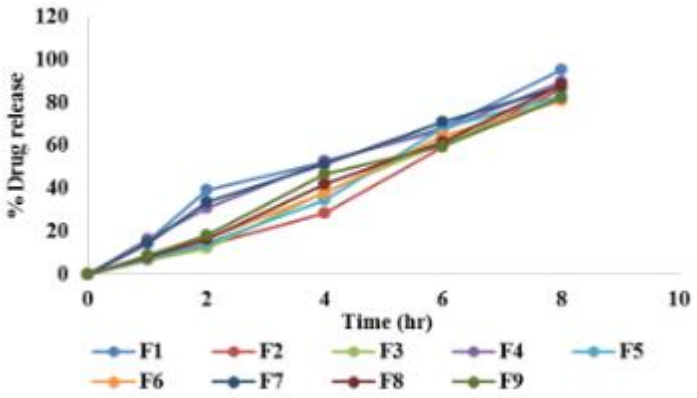

Fig 4: Comparative In-vitro Drug release profile of SR Losartan potassium pellets.

Dissolution study of Losartan potassium

The Losartan potassium of IR which contains MCC as a polymer batch was studied for one batch and 3 trials were carried out. The release at 90 mins was found to be 91.56%. This Losartan capsule consisted of equal quantity of three variables. hydrophilic and hydrophobic Polymer containing pellets (EC: HPMC) in SR. During dissolution, the dissolution medium penetrated into the pellets, leading to the hydrophilic polymer hydration and swelling. A gel layer was formed around the pellet surface, and the drug began to release; the thickness of the gel layer increased while the drug was released continuously from the erosion gel or diffused through the diffusion channels; and as the study time went on, after 6 hour the losartan pellets with EC continues to infiltrate in to dissolution medium until the drug released completely. Moreover, increasing quantity of EC did not result in retardation of drug release especially after 6 hour of drug release. Therefore, either rupture or fissure formation of membrane or formation of pore lead to complete drug release, which is 25% to 30% of Losartan potassium after 6 to 7 hours of dissolution.

Table 1: Response surface values of Dissolution at 8 hrs.

SOURCE	SUM OF SQUARES	DF	MEAN SQUARE	F-VALUE	P-VALUE	
MODEL	**123.40**	**1**	**123.40**	**17.87**	**0.0039**	**SIGNIFICANT**
A-mcc	**123.40**	**1**	**123.40**	**17.87**	**0.0039**	**-**
RESIDUAL	**48.33**	**7**	**6.90**	**-**	**-**	**-**
COR TOTAL	**171.73**	**8**	**-**	**-**	**-**	**-**

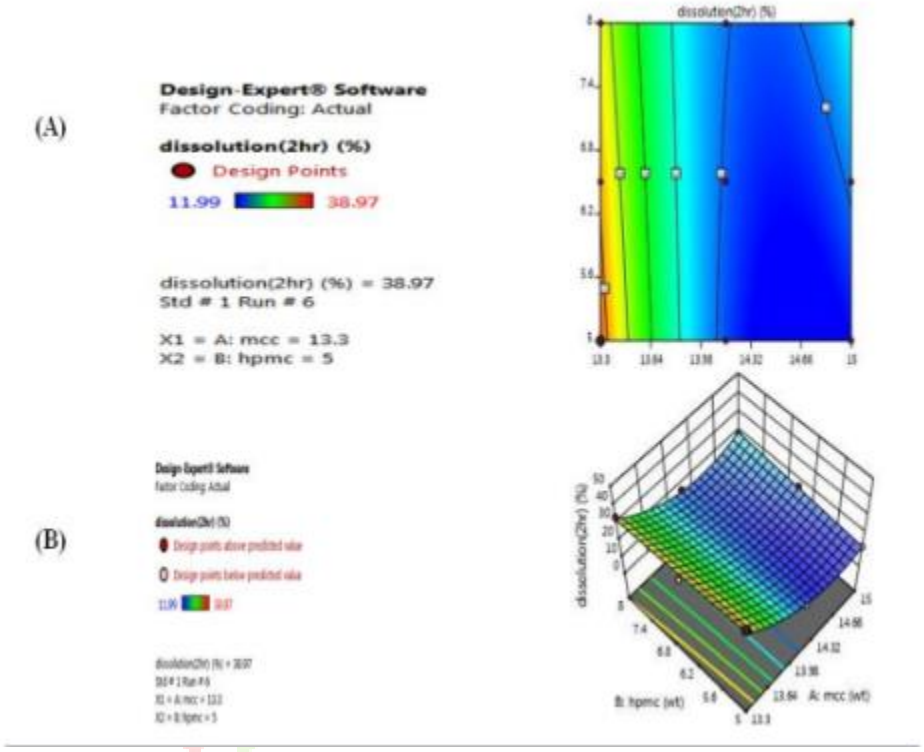

Fig 5: Effect of EC and HPMC on 2 (hour) presented by response surface plot (a), and contour plot (b).

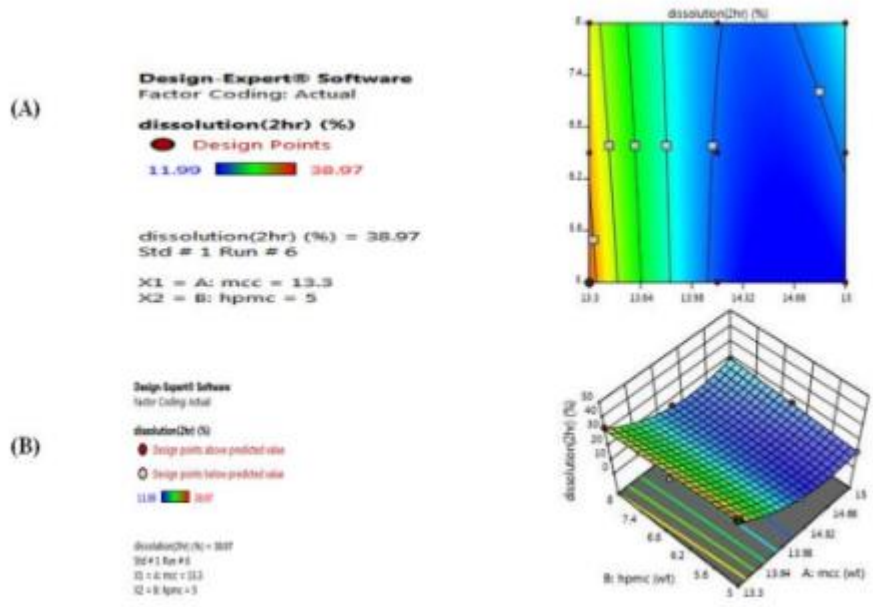

Fig 6: Effect of EC and HPMC on 8(hour) presented by response surface plot (a), and contour plot (b).

Effect of MCC and HPMC on drug release at 2nd hour and 8th hour:

When the polymer concentration decreased with increased the concentration of drug release. As increase concentration of polymer, the drug release was decreased at end of 2 hours were found to be f2 (13.21%) & amp; f3 (11.99%) respectively. Release rate determined from mg/hour or %/HR as per zero order release kinetics for all formulation to find out the effect of polymers interaction. More than 9% of drug release from all formulation but F2 and F3 gave lesser average RR (13.21%, 11.99%) due to high level of polymer (12%) at 2nd hr. The release rate of F6 and F9 shows lesser release rate due to high concentration of HPMC and low concentration of MCC.

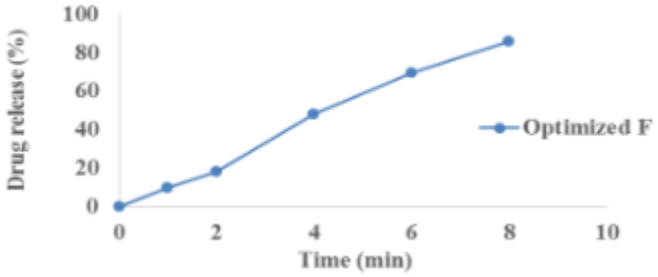

Fig 7: In Vitro drug release profile of optimized Losartan potassium pellets.

Dissolution data of the optimized formulation was fitted to various mathematical models (zero- order, first-order, Higuchi and korsemeyar-peppas) in order to describe the kinetics of drug release. Regression coefficient and slope (rate) were compared in all the formulations to study their effect on drug release. Further, optimized formulation fitted with selectively zero order and peppas model to calculate the value of sum of squared residuals (SSR) and Akaike information criterion (AIC), best goodness-of-fit test (R2). High value of Mean selection criterion (MSE) was taken as criteria for selecting the most appropriate model. Accordingly, optimized formulation fitted with all dissolution model and values found to be

followed zero-order and korsemeyer-peppas kinetics. The release exponent of peppas model (n=1) indicate case II transport drug release mechanism and rates as a function of time follows zero order release. Similarly adjusted R2, AIC, some of square residues (SSR) and mean selection criterion were satisfied with korsemeyer-peppasmodel.

Scanning Electron Microscopy:

The SEM studies were carried out on optimized batch at both lower (x270) and higher (x1000) magnifications. Views of SEM in **(Fig.8)** of F-He surface of the Formulation -10 was continuous but granular compared to smooth and homogenous confirmed the aforementioned release results and give evidence that the presence of ethyl cellulose in the core caused porous, non-intact film during coating. The surface of Formulation 10 was more compact, continuous and uniform. Therefore, the diffusion length for dissolution medium to enter the drug layer and dissolved drug to diffuse out would be increased levels that would result in slower release rate as in the case of optimized formulation.

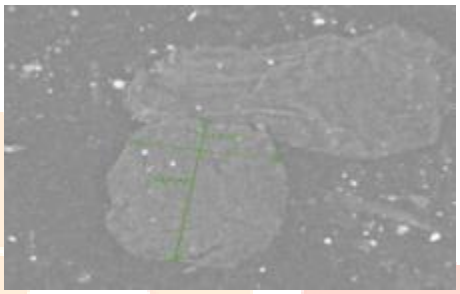

Figure 8: SEM of optimized batch

CONCLUSION

The present study demonstrated for the feasibility of developing an Immediate release Losartan potassium contains MCC as a polymer and sustained release contains HPMC and EC as a polymer in the different ratios of formulation from F1-F9 and the developed formulation was undergone in- vitro dissolution study and the optimized batch were prepared and evaluated. 70mg of IR Losartan potassium and the 80mg of optimized batch of sustained release Losartan potassium pellets were taken and filled in the capsule size no: 2 to develop the dual release formulation. The developed dual release system was able to deliver a first fraction of the dose in short time and deliver a second fraction at a sustained rate for a longer period of time to overcome significant variation in drug concentration in the plasma.

Losartan potassium capsule for dual release application were successfully developed by response surface methodology based on 32 full factorial design. The variable ratio of MCC:HPMC, in capsule on the release properties of Losartan sustained release capsule with RR 2nd hour, and 8th hour were analyzed and optimized. The three-dimensional response surface plots and corresponding contour plots relating R2h and hardness indicate the decreased values of 8th hour and increased values of RR with the increment of proportionate amount of MCC: HPMC. The optimized Losartan batch (F-10) showed RR 2nd hour of 18.3%, 8th hour of 86.01%. These developed optimized batch showed sustained release of Losartan over 12 hours, with release of almost 10 mg after 6th hour for planned delivery which might be beneficial over the conventional tablet to reduce the dosing frequency with improved patient compliance.

CONFLICT OF INTEREST:

None.

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