IJPSR (2022), Volume 13, Issue 2 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 April 2021; received in revised form, 11 June 2021; accepted, 12 June 2021; published 01 February 2022

FORMULATION AND EVALUATION OF QUINAPRIL EXTENDED-RELEASE TRILAYERED MATRIX TABLETS BY DESIGN OF EXPERIMENT

K. Ashwin * and T. Rama Mohan Reddy

Department of Pharmacy, Mewar University, Chittorgarh - 312901, Rajasthan, India.

Keywords:

Quinapril, Hypertension, HPMC, Gellan gum, Release order kinetics

Correspondence to Author:
K. Ashwin

Research Scholar,
Department of Pharmacy, Mewar University, Chittorgarh - 312901, Rajasthan, India.

E-mail: dbpathi71@gmail.com

ABSTRACT: Objective: The present research was focused on designing, formulate and evaluate the trilayer matrix tablets incorporated with quinapril for extending drug release. **Methods:** Quinapril trilayer matrix tablets were formulated using response surface methodology wherein initially 27 formulations (QF1-QF27) were designed for active layer from which one best formulation was chosen based on drug content, swelling index, and in-vitro release studies. The chosen formulation was formulated into extended-release trilayed matrix tablet by varying proportions of polymers by direct compression technique and was evaluated for various physicochemical parameters, drug release and the drug release data were fitted into the various kinetic model to know the mechanism of drug release. The best-optimized formulation was further characterized by FTIR and stability studies. **Results:** 27 active layer formulations were evaluated for various physicochemical properties and drug release, out of which the highest drug release was exhibited by QF16 (98.85%). Thus, QF16 was used for formulation into trilayer matrix tablets (AQF16-HQF16). All the formulations were evaluated for drug content, swelling index, and percentage drug release in which EQF16 was found to exhibit the highest values with 98.42% swelling index, 99.56 % drug content, and 99.72 % drug release in 24h. The drug release data was fitted into kinetic models, which showed zero-order release kinetics for all quinapril trilayer formulations and the first order for a marketed product. The optimized formulation EQF 16 was further characterized by FTIR studies and found to exhibit no interaction with excipients, and no significant changes were observed in drug content, swelling index, and drug release after loading under accelerated stability conditions. Hence quinapril was successfully formulated into trilayer matrix tablet and found to be stable.

INTRODUCTION: The solid dosage forms of drugs administrated orally are considered an effective method of medication with the highest patient compliance. Numerous methods were adopted to modulate the drug dissolution rate from the specific drug delivery system.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(2).828-40

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(2).828-40

Most of the orally administrated dosage forms exist as polymer matrix, reservoir, or multi-layer systems. The multi-layer matrix systems are emerging as potential designs for sustained oral drug delivery.

These systems comprise of hydrophilic core embedding the drug molecules sandwiched between semi-permeable polymeric layers (barrier-layer). These layers retard the interaction between solute and dissolution medium by minimizing the availability of the surface for the release of solute and simultaneously checking solvent penetration

rate. Subsequently, the inflamed barriers erode, leading to an increase in the surface area accessible for drug release, thus simultaneously balancing the diffusion path length and area of drug release [1].

Hypertension has been identified by the world health organization (WHO) as one of the most significant risk factors for morbidity and mortality worldwide. It is responsible for the deaths of approximately nine million people annually. In the UK, the National Institute for Health and Care Excellence (NICE) defines high blood pressure (BP), also known as hypertension, as a clinic blood pressure of 140/90 mmHg or higher confirmed by a subsequent ambulatory blood pressure monitoring daytime average (or home blood pressure monitoring average) of 135/85 mmHg or higher [2].

Quinapril is an angiotensin-converting enzyme inhibitor (ACE inhibitor) indicated for the treatment of high blood pressure (hypertension) and as adjunctive therapy in the management of heart failure. Quinapril HCl has a short half-life of 2 hour. The objective of the present research work of trilayered matrix tablet containing quinapril as a drug candidate would remain for a prolonged period of time, thereby maximizing the drug release within the stipulated time [3].

MATERIALS: Quinapril was purchased from Hetero drugs Ltd, Hyderabad. HPMC K15M, HPMC K 100M, sodium carboxymethylcellulose, PVP K30. Magnesium stearate. Polyox WSR N 303, gellan gum, ethylcellulose, and talc were purchased from Gattefosse, Mumbai. All the reagents used were of analytical grade

Formulation of Trilayered Matrix Tablets of Quinapril HCl: The trilayered matrix tablets of Quinapril were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90% drug release during 12 hours. The release profile of this layer might not be of constant rate type but would preferably be of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) so as to continue the drug release for 24 h. [4]

Preparation of Middle Active Layer of Quinapril Trilayered Tablets: Twenty-seven formulations (QF1-QF27) for active layer were prepared by direct compression method using 3^3 Response surface methods (3 variables and 3 levels of polymers) by using design of experiment software with polymers like HPMC K100M, HPMC K15M, Sodium Carboxy Methyl Cellulose. All the formulations were varied in the concentration of polymers; magnesium stearate constituted in all the formulations. These materials were screened through #60 and mixed together in motor by using a pestle. Final mixtures were compressed by using 10 mm diameter flat punches on a sixteen-station rotary tablet press. The prepared tablets were subjected to dissolution studies.

Twenty-seven formulations (QF1-QF27) for active layer (Middle layer) were prepared by direct compression method using 3^3 Response surface method where 3^3 indicates 3 variables and 3 levels of polymers of different HPMC K100M, HPMC K15M, Sodium Carboxy Methyl Cellulose (low, middle and high concentrations) by using design of experiment software [5] **Fig. 1, Table 1**.

Response Surface Methodology (RSM):

Study type: Response surface

Design Type: central composite

Design Mode: quadratic

Preparation of Upper and Lower Layers of Quinapril Trilayered Tablets: The barrier layers were formulated employing hydrophobic swellable polymer carnauba wax the swelling erosion modeling fillers, which include water-soluble DCP, EC, and gellan gum. The procedure adopted to make the compacts was via direct compressions. For the first procedure, the carnauba wax, gellan gum, and the filler were mixed in a mortar and lubricated with magnesium stearate [6]. The formulation of upper and lower layers was depicted in **Table 2**.

Formulation of Extended-Release Try Layered Tablets of Quinapril: The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortar and pestle for about 20 minutes. Initially, the volume of the die cavity; (10 mm, round) was adjusted equivalence to the weight of trilayered matrix

tablets (300 mg). Then the pre-weighed amount of powder equivalent to the bottom layer (100 mg) was taken and placed in the die cavity, and slightly compressed for uniform spreading. The upper punch was lifted up and the granules equivalent to 100 mg of the drug were placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with a pre-weighed (100 mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain tri-layered tablets. Tri-layered matrix tablets of each composition were compressed and tested for their friability, Hardness, drug content and drug release characteristics with a suitable number of tablets for each test [7].

Design Summary

Study Type	Response Surface	**Runs**	27
Initial Design	Central Composite	**Blocks**	No Blocks
Design Model	Quadratic		

Factor	Name	Units	Type	Low Actual	High Actual	Low Coded	High Coded	Mean	Std. Dev.
A	HPMC K100M	%	Numeric	13.00	15.00	-1.000	1.000	14.000	0.711
B	HPMC K15M	%	Numeric	18.00	20.00	-1.000	1.000	19.000	0.711
C	Na CMC	%	Numeric	21.00	23.00	-1.000	1.000	22.000	0.711

Response	Name	Units	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio	Trans	Model
Y1	SI	%	27	Polynomial	80.150	98.420	94.296	3.461	1.228	None	2FI
Y2	DRUG CONTENT	%	27	Polynomial	88.360	99.130	94.412	2.734	1.122	None	Linear
Y3	%CDR	%	27	Polynomial	78.340	98.850	88.144	4.886	1.262	None	Quadratic

FIG. 1: LIST OF DEPENDENT AND INDEPENDENT VARIABLES IN RSM

TABLE 1: FORMULATION TRIALS OF EXTENDED-RELEASE TRILAYERED MATRIX TABLETS OF QUINAPRIL

F. no.	Quinapril	HPMC K100M	HPMC K15M	Na. CMC	PVP K-30	DCP	Mg Stearate	TOTAL
QF1	40	39	54	63	12	86	6	300
QF2	40	45	57	66	12	74	6	300
QF3	40	39	60	63	12	80	6	300
QF4	40	45	60	63	12	74	6	300
QF5	40	39	54	69	12	80	6	300
QF6	40	45	54	69	12	74	6	300
QF7	40	39	60	69	12	74	6	300
QF8	40	45	60	69	12	68	6	300
QF9	40	39	57	66	12	80	6	300
QF10	40	45	57	66	12	74	6	300
QF11	40	42	53	66	12	81	6	300
QF12	40	42	54	63	12	83	6	300
QF13	40	42	57	63	12	80	6	300
QF14	40	42	57	69	12	74	6	300
QF15	40	45	57	69	12	71	6	300
QF16	40	42	57	66	12	77	6	300
QF17	40	42	54	66	12	80	6	300
QF18	40	39	57	63	12	83	6	300
QF19	40	42	57	67	12	76	6	300
QF20	40	39	57	66	12	80	6	300
QF21	40	42	54	66	12	80	6	300
QF22	40	42	57	63	12	80	6	300
QF23	40	42	57	68	12	75	6	300
QF24	40	39	57	66	12	80	6	300
QF25	40	45	54	69	12	74	6	300
QF26	40	39	57	69	12	77	6	300
QF27	40	45	60	66	12	71	6	300

TABLE 2: COMPOSITION OF QUINAPRIL TRILAYERED MATRIX TABLET

Ingredients	AQF16	BQF16	CQF16	DQF16	EQF16	FQF16	GQF16	HQF16
Middile active layaer (QF16) (300 mg)								
Quinapril	40	40	40	40	40	40	40	40
HPMC K100M	42	42	42	42	42	42	42	42
HPMC K15M	57	57	57	57	57	57	57	57
Sodium CMC	66	66	66	66	66	66	66	66
PVP K30	12	12	12	12	12	12	12	12
Di Calcium Phosphate	77	77	77	77	77	77	77	77
Magnesium stearate	06	06	06	06	06	06	06	06
Upper and Lower Layer (100 mg)								
Carnauba wax	10	15	20	25	30	35	40	45
Gellean Gum	45	40	35	30	25	20	15	10
Ethyl cellulose	15	15	15	15	15	15	15	15
Di Calcium Phosphate	26	26	26	26	26	26	26	26
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2

Evaluation Tests:

Pre-Compression Parameters:

Micromeritic Properties: The lubricated blend was evaluated for angle of repose, bulk density, tapped density, Carr's index and hausner's ratio [8].

Angle of Repose (θ) Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using following formula [9, 10]. Angle of repose is calculated by the following formula.

$$\Theta = \text{Tan}^{-1} (h / r)$$

Where Θ = angle of repose, r = radius of pile, h= height of the pile

Bulk Density and Tapped Density: Bulk density is defined as a mass of a powder divided by the bulk volume. Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined.

The bulk volume was calculated using the formula

$$b = M / V^*$$

The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula [11].

$$^*t = M / V_t$$

Carr's Compressibility Index (Carr's Consolidation Index): The compressibility index of the powder blend was determined from bulk density and tapped density. It was calculated by the formula given as below [12]

C.I (%) = Tapped density – Bulk density × 100 / Tapped density

Hausner's Ratio: Hausner's ratio is an index of ease of powder flow. It is calculated by using the formula

Hausner's ratio = *dt/*db

Where *dt = tapped density, *db = bulk density

Post Compression Evaluation Tests:

Weight Variations: Twenty tablets were randomly selected and the average weight was determined. Then individual tablets were weighed, and percent deviation from the average was calculated [13].

Thicknesses: Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, the thickness must be controlled to facilitate packing. The thickness in millimeters was measured individually for 10 pre-weighed tablets by using a screw gauge. The average thickness and standard deviation were reported.

Hardness: The strength of the tablet is expected as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester. Three tablets from each formulation batch were tested randomly, and the average reading was noted.

Friability: Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes, dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

$$F\ \% = (1\text{-}W_0/W) \times 100$$

Where, $W_{0\ is}$ weight of the tablets before the test and W is the weight of the tablets after the test.

Content Uniformity: 20 tablets were randomly selected, and the average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 10 mg was weighed and dissolved in 100 ml of Phosphate buffer pH 6.8 filtered and drug content analyzed spectrophotometrically in UV spectrophotometer at 224 nm.

***In-vitro* Swelling Studies:** [14] The degree of swelling of polymer is an important factor affecting adhesion. For conducting the study, a tablet was weighed and placed in a petri dish containing 5 ml of phosphate buffer pH 6.8 in 12 h at regular intervals of time (1, 2, 4,8,10, and 12 h), the tablet was taken carefully by using a filter paper. The swelling index was calculated using the following formula

$$\text{Swelling Index (S.I)} = (Wt\text{-}Wo) / Wo \times 100$$

Where S.I = swelling index, Wt = weight of tablet after swollen at time t Wo= weight of the initial tablet.

***In-vitro* Drug Dissolution Study:** [15] *In-vitro* drug dissolution studies were carried out for both core middle layer (QF1-QF27), and prepared trilayer tablet formulations was carried out using USP Dissolution Apparatus Type II (Paddle) at speed 100rpm with 900 ml of phosphate buffer (pH 6.8) as dissolution medium by maintaining at 37 ± 0.5°C. Aliquots of 5 ml of dissolution medium were withdrawn at different time intervals, filtered, and replaced with fresh 5 ml of dissolution medium. The amount of drug released was determined by UV spectrophotometer (Shimadzu UV 1800) at 224 nm.

Kinetic Model Fitting: To elucidate the mode and mechanism of drug release, the data from the invitro release study were fitted into various kinetic models such as zero-order, first-order, Higuchi's, and Korsmeyer-Peppas model [16].

RESULTS AND DISCUSSION:

Percentage Drug Content and Swelling Index: The % drug content of all quinapril core layer ranged from 92.12±0.78 to 99.13±0.98%, and the swelling index varied between 90.87±0.10 to 98.42±0.069% with the maximum value recorded for QF16 **Table 3**.

TABLE 3: PHYSICO-CHEMICAL PARAMETERS OF QUINAPRIL

F. no	#Content uniformity (%)	% Swelling Index
QF1	96.19±0.21	95.29±0.043
QF2	98.23±0.19	96.35±0.051
QF3	96.89±0.65	90.87±0.10
QF4	97.67±1.59	94.12±0.043
QF5	96.73±0.19	95.61±0.022
QF6	94.27±0.49	93.18±0.067
QF7	92.12±0.78	94.28±0.053
QF8	96.42±0.15	98.26±0.079
QF9	93.32±0.66	97.68±0.073
QF10	95.38±0.45	95.53±0.035
QF11	98.76±0.13	97.44±0.039
QF12	97.51±0.62	96.57±0.095
QF13	95.59±0.89	97.67±0.084
QF14	98.51±0.39	94.59±0.070
QF15	97.36±0.78	96.88±0.067
QF16	99.13±0.98	98.42±0.069
QF17	96.29±0.79	94.45±0.018
QF18	94.15±0.62	95.21±0.095
QF19	95.29±0.62	94.37±0.018
QF20	93.21±0.39	92.75±0.059
QF21	95.89±0.27	94.45±0.070
QF22	96.36±0.26	91.18±0.085
QF23	93.28±0.48	93.11±0.062
QF24	94.35±0.48	92.75±0.035
QF25	92.85±0.37	91.89±0.037
QF26	94.39±0.41	92.95±0.010
QF27	93.23±0.48	93.41±0.066

***In-vitro* Drug Dissolution Studies of Core Middle Layer:** *In-vitro* dissolution studies conducted for the core middle layer tablets of quinapril (RF1-RF27) is represented in figures. All 27 formulations exhibited complete drug release up to 12 h. Out of all QF16 showed the highest drug release of 98.85± 1.52. Based on drug content, swelling index, and drug release QF16 was chosen as the best active layer formulation for further studies **Fig. 2-5**.

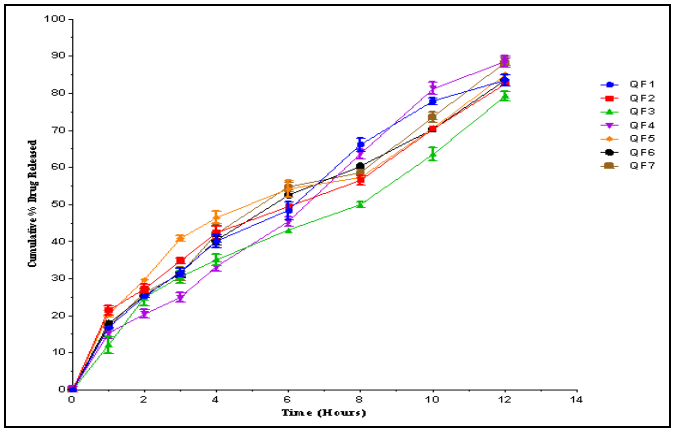

FIG. 2: *IN-VITRO* DRUG RELEASE PROFILE FOR PREPARED MIDDLE ACTIVE LAYER OF QUINAPRIL TABLETS QF1-QF7

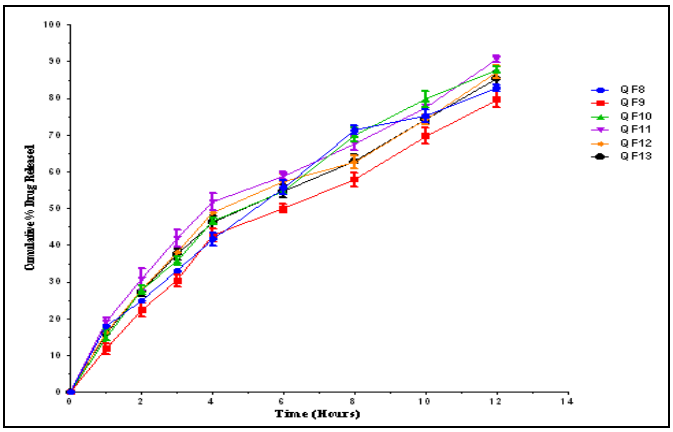

FIG. 3: *IN-VITRO* DRUG RELEASE PROFILE FOR PREPARED MIDDLE ACTIVE LAYER OF QUINAPRIL TABLETS QF8-QF13

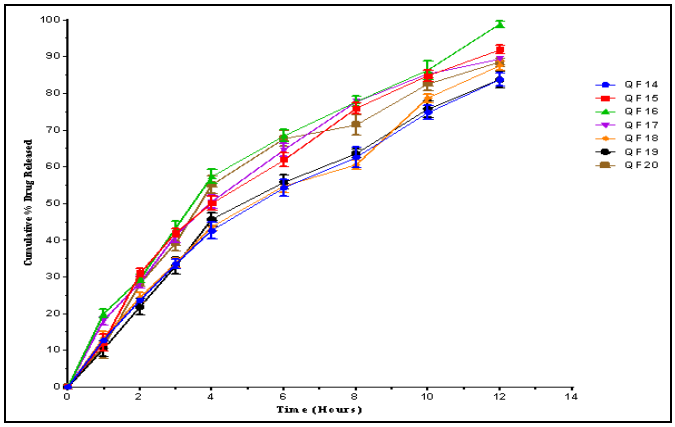

FIG. 4: *IN-VITRO* DRUG RELEASE PROFILE FOR PREPARED MIDDLE ACTIVE LAYER OF QUINAPRIL TABLETS QF14-QF20

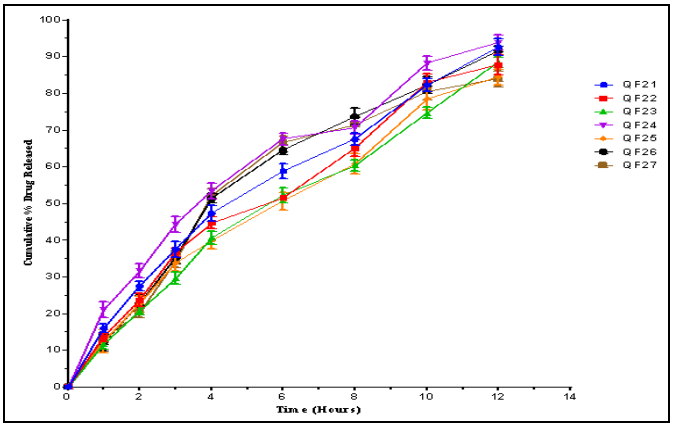

FIG. 5: *IN-VITRO* DRUG RELEASE PROFILE FOR PREPARED MIDDLE ACTIVE LAYER OF QUINAPRIL TABLETS QF21-QF27

TABLE 4: PHYSICAL EVALUATION OF PREPARED POWDER BLENDS OF QUINAPRIL TABLET

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (Θ)	Carr's index (%)	Hausner ratio
AQF16	0.53±0.02	0.57±0.01	23.34±0.4	10.11±0.8	1.10±0.02
BQF16	0.50±0.12	0.55±0.04	25.56±0.3	09.23±1.0	1.08±0.07
CQF16	0.51±0.02	0.54±0.02	24.56±0.1	10.23±0.8	1.11±0.05
DQF16	0.53±0.01	0.59±0.03	25.67±0.3	11.11±0.8	1.10±0.03
EQF16	0.58±0.06	0.67±0.08	20.22±0.8	08.75±0.4	1.06±0.05
FQF16	0.53±0.21	0.57±0.12	24.30±0.1	10.23±0.59	1.09±0.06
GQF16	0.530.06	0.56±0.03	25.56±0.2	10.34±1.0	1.10±0.06
HQF16	0.53±0.04	0.58±0.05	24.54±0.1	11.12±0.7	1.11±0.09

All the parameters were found to be within limits, as shown in **Table 4**.

The bulk densities of all the formulations AQF16 to HQF16 were measured, and they are ranged from 0.50g/cc to 0.58 g/cc. The tapped density of all the formulations AQF16 to HQF16 was measured, and they are ranged from 0.54g/cc to 0.67 g/cc.

The angle of repose of all the formulations was found satisfactory result. The formulation EQF16 was found to be 20.22, having good flow property.

The compressibility index values were found to be in the range of 8 to 11%.

These findings indicated that all the batches of formulations exhibited good flow properties.

The Hausner's ratio values were found to be in the range of 1.06 to 1.11%.

These findings indicated that all the batches of formulations exhibited good flow properties.

TABLE 5: PHYSICO-CHEMICAL EVALUATION PROPERTIES OF QUINAPRIL TRILAYERED TABLETS

F. no.	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	# Content uniformity (%)	Swelling index (%)
AQF16	302±1.2	4.5±0.12	5.7±0.12	0.57±0.01	97.23±0.63	88±0.76
BQF16	299±0.8	3.6±0.06	5.6±0.06	0.59±0.02	96.04±0.06	87±0.72
CQF16	300±0.4	4.5±0.00	5.8±0.00	0.61±0.02	96.23±0.8	80±1.03
DQF16	300±0.0	4.4±0.12	5.2±0.12	0.57±0.01	97.71±1.01	94±0.81
EQF16	300±0.2	4.0±0.06	6.0±0.06	0.54±0.03	99.56±0.14	97±0.64
FQF16	303±0.4	4.3±0.10	5.9±0.06	0.65±0.01	97.45±0.31	85±0.84
GQF16	301±0.3	3.7±0.10	5.1±0.10	0.60±0.02	96.11±0.49	87±0.72
HQF16	300±0.2	4.5±0.25	5.7±0.40	0.56±0.01	95.23±0.51	86±0.79

*values are expressed in mean± SD (n=20) #values are expressed in mean± SD (n=3)

The results of the physical tests of the prepared blends were within the limits as shown in **Table 5**. The weight variation of all the formulations with in limit, the adequate tablet hardness is necessary requisite for consumer acceptance and handling. The measured hardness of the tablets of each batch of all formulations *i.e.* AQF16 to HQF16 were ranged between 5.0 to 6.0 Kg/cm^2 and the results are shown in **Table 5**. The thickness of the tablets was found to be almost uniform in all formulations AQF16 to HQF16. The friability of all prepared formulation between 0.54-0.65. The friability properties limits are in between 0-1%. The drug content of all formulation is in between 95.23-99.56%; drug content depends on angle of repose because if the angle of repose was good then drug content is also uniform because if the flow property is good then the drug is evenly distributed in the formulation. The Swelling study of trilayered matrix tablet of Quinapril was given in **Table 6**, showed that the swelling index of the tablet increases with increase in time upto 24 hours, this may be attributed to the fact that the erosion of biodegradable polymer Guar Gum. This indicates that the drug will remain in intestinal region till drug is released completely from the delivery system and promotes evacuation after its release.

***In-vitro* Dissolution of Quinapril Trilayered Matrix Tablets (AQF16-HQF16):** The drug release from quinapril trilayered matrix tablets (AQF16-HQF16) was found to extend drug release sustainably up to 24 h, and out of all EQF16 was found to show highest drug release of 99.72±1.11 **Fig. 6**. The drug release was better when compared with the marketed product (98.16±1.23) and is as shown in **Fig. 7**. Based on other physicochemical properties and drug release EQF16 was chosen as best optimized formulation and is further characterized for FTIR and stability studies.

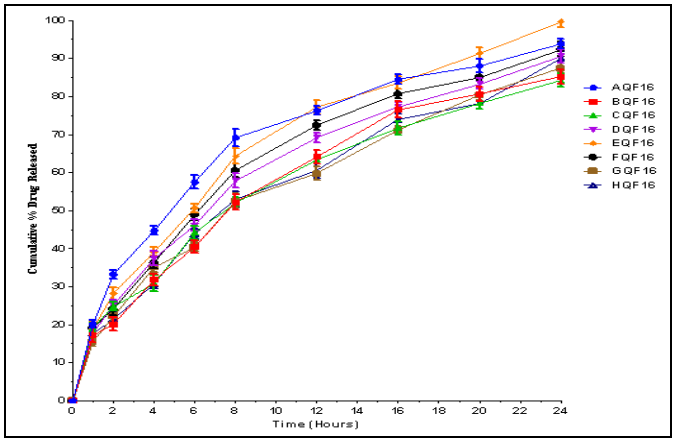

FIG. 6: *IN-VITRO* DISSOLUTION OF QUINAPRIL TRILAYERED MATRIX TABLETS (AQF16-HQF16)

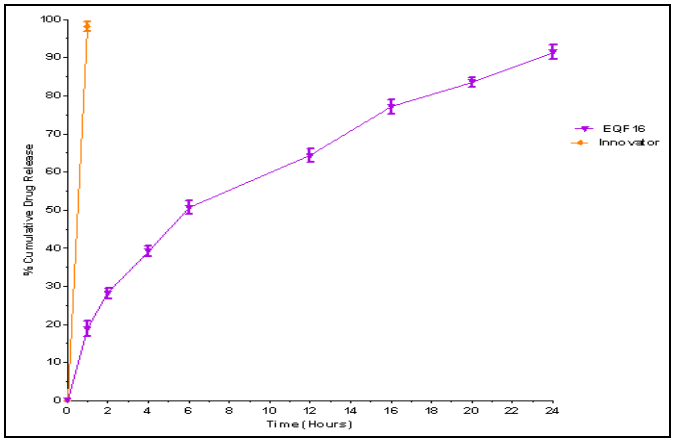

FIG. 7: COMPARATIVE *IN-VITRO* STUDY PLOT OF OPTIMIZED FORMULATION (EQF16) AND CONVENTIONAL MARKETED TABLET

From the results, it is apparent that the regression coefficient value (R^2) closer to unity in case of zero order plot for all the formulations (AQF16-HQF16) and out of all EQF16 with highest (R^2) *i.e.*,0.9853 indicates that the drug release follows a zero-order mechanism **Table 6**. This data indicates a lesser amount of linearity when plotted by the first order equation. Hence, it can be concluded that the major

mechanism of drug release follows zero order kinetics. Further the n value obtained from the Korsmeyer-Peppas plots *i.e.*, 0.959 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion For the marketed product the (R^2) closer to unity in case of first order plot *i.e.*, 0.982 hence it follows first order kinetics.

TABLE 6: RELEASE KINETICS OF QUINAPRIL TRILAYERED TABLETS (AQF16-HQF16) AND MARKETED FORMULATION

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppa's R^2	Korsmeyer-Peppa's n value
AQF16	0.9879	0.6744	0.8797	0.9191	0.7801
BQF16	0.9914	0.6885	0.8776	0.9202	0.7842
CQF16	0.9867	0.6953	0.8793	0.9212	0.7904
DQF16	0.9935	0.7123	0.8742	0.9222	0.7941
EQF16	0.9853	0.793	0.913	0.959	0.743
FQF16	0.9917	0.7019	0.8769	0.9215	0.7915
GQF16	0.9786	0.6657	0.8794	0.9183	0.7805
HQF16	0.9903	0.6877	0.8767	0.9201	0.7866
Marketed product	0.6985	0.982	0.9010	0.892	0.9028

Design of Experiment: About 27 experiments were performed according to experimental runs generated by 3^3 Box-Behnken design. All responses fitted into second-order quadratic equations and the competence of model validated by ANOVA tests provided by Design-Expert software **Table 7**.

Response Surface Analysis: Stat-Ease Design Expert ® software V8.0 was utilized for analyzing data, for getting regression equation, regression coefficient and analysis of variance (ANOVA).

TABLE 7: REGRESSION EQUATIONS OF THE FITTED MODELS

Response	Equation
Swelling Index (Y_1)	$85.42 + 09.67\ X_1 - 14.23\ X_2 - 2.60\ X_3 - 0.88X^2_1 + 0.21X_1X_3 + 12.54\ X^2_2 - 2.15\ X_2X_3 + 1.79\ X^2_3$
Drug Content (Y_2)	$79.54 + 08.13X_1 + 13.41\ X_2 + 3.74\ X_3 + 0.18X^2_1 - 0.45X_1X_3 - 13.59\ X^2_2 - 2.52\ X_2X_3 - 3.15\ X^2_3$
% Cumulative drug released (Y_3)	$68.13 - 2.84\ X_1 + 22.18\ X_2 - 19.63\ X_3 + 0.47X^2_1 - 12.33X_1X_3 + 06.75\ X^2_2 - 38.65\ X_2X_3 + 2.40\ X^2_3$

Where Y1, Y2 and Y3 are the predicted response and X1, X2 and X3 are the coded values of the test variables in respective concentrations.

% Swelling Index: % Swelling index is a critical value for assessing trilayer tablets. A larger swelling index provides a larger surface area for drug absorption.

In addition, a larger swelling index may permit a faster release rate. The swelling index of the tablets was found to be in the range of 80.15-98.42%.

The quadratic model generated revealed that the amount of HPMC K100M, amount of HPMC K15M and amount of sodium CMC have a significant influence on the swelling index.

The theoretical (predicted) values and the observed values were in reasonably good agreement.

The mathematical model generated for % swelling index (Y1) was found to be significant, with an F-value of 0.0128 implies the model is significant.

The interaction between B and C on the Swelling Index at a fixed level of A is shown in figure 8A. The respective contour plots are as shown in figure 8B. The increase in the Swelling Index with a concomitant increase in the amount of HPMC K100M (X1) or decrease in the amount of HPMC K15M (X2) and vice versa has been reported in many papers pertaining to trilayer tablets.

This may also explain the significant interaction between the number of polymers.

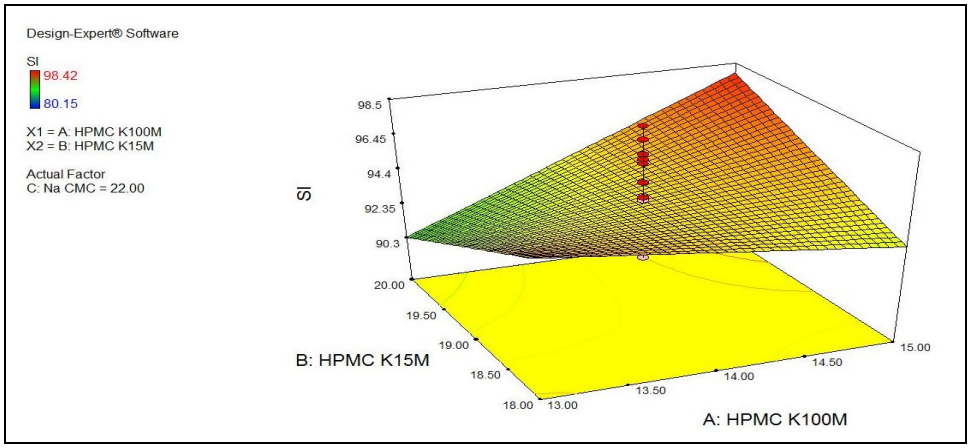

FIG. 8A: R**ESPONSE 3D SURFACE PLOT SHOWING THE INFLUENCE OF AMOUNT OF HPMC K100M AND AMOUNT OF HPMC K15M ON SWELLING INDEX FIXED LEVEL OF C**

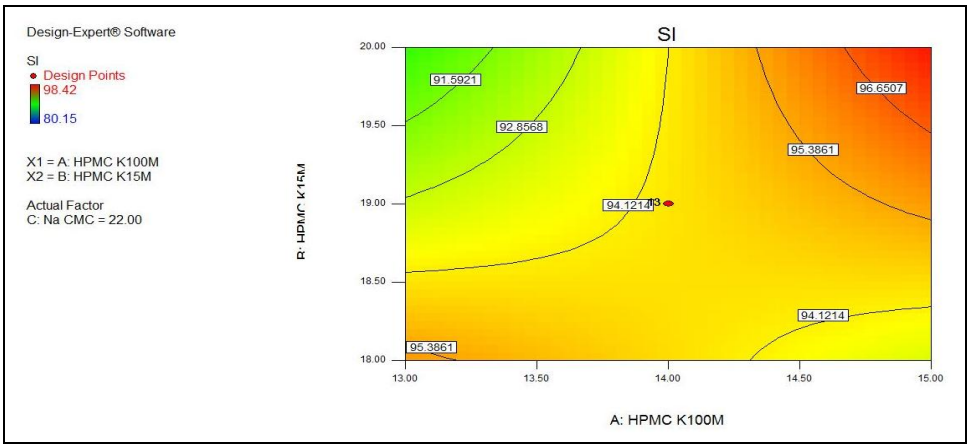

FIG. 8B: CONTOUR PLOT SHOWING THE INFLUENCE OF AMOUNT OF HPMC K100M AND AMOUNT OF HPMC K15M ON SWELLING INDEX FIXED LEVEL OF C

Drug content: The drug content of the trilayer tablets was found to be in the range of 95.23 to 99.56%. The quadratic model generated revealed that the amount of HPMC K15M and amount of Sodium CMC have a significant influence on the drug content. The theoretical (predicted) values and the observed values were in reasonably good agreement as seen. The mathematical model generated for drug content (Y2) was significant with an F-value of 0.0345 implies the model is significant. The interaction between A and B on drug content at a fixed level of C is shown in **Fig. 9A**. The respective contour plots are as shown in **Fig. 9B**.

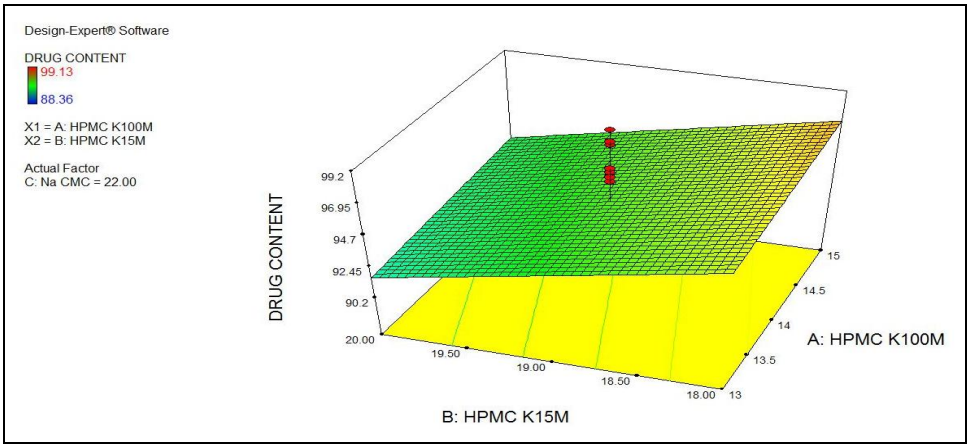

FIG. 9A: RESPONSE 3D SURFACE PLOT SHOWING THE INFLUENCE OF AMOUNT OF HPMC K100M AND AMOUNT OF HPMC K15M ON DRUG CONTENT FIXED LEVEL OF C

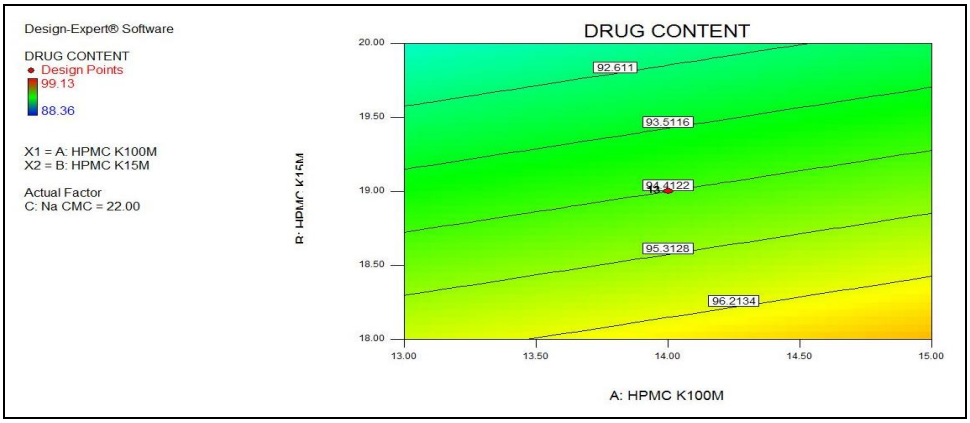

FIG. 9B: CONTOUR PLOT SHOWING THE INFLUENCE OF AMOUNT OF HPMC K100M AND AMOUNT OF HPMC K15M ON DRUG CONTENT FIXED LEVEL OF C

Cumulative Percent Drug Released: The cumulative percent drug release in 24 h from the Tablets was found to be in the range of 84.24-99.72%. The quadratic model generated revealed that the amount of HPMC K100M, amount of HPMC K15M and amount of Sodium CMC have a significant influence on the %CDR. The theoretical (predicted) values and the observed values were in reasonably good agreement as seen.

The mathematical model generated for percent drug release in 24 h (Y3) was found to be significant with an F-value of 0.0191 implies the model is significant.

The interaction between A and B on percent drug release at a fixed level of C is shown in **Fig. 10A**. The respective contour plots are as shown in **Fig. 10B**.

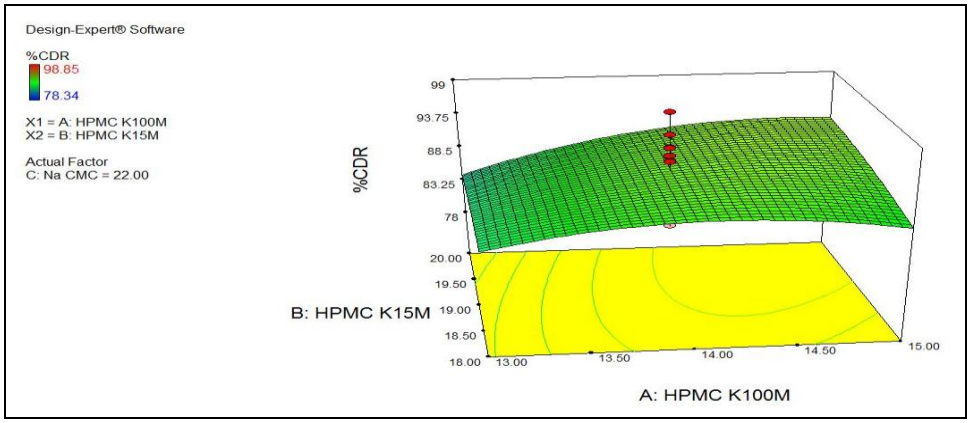

FIG. 10A: RESPONSE 3D SURFACE PLOT SHOWING THE INFLUENCE OF AMOUNT OF HPMC K100M AND AMOUNT OF HPMC K15M ON CUMULATIVE % DRUG RELEASED LEVEL OF C

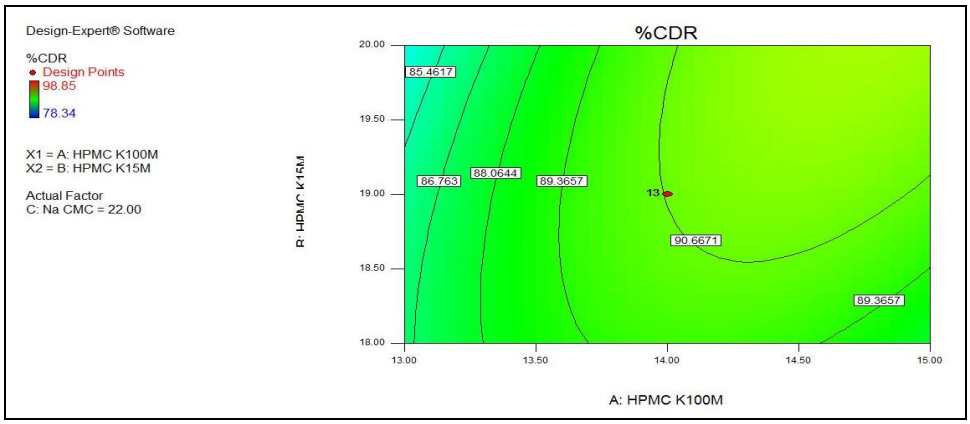

FIG. 10B: CONTOUR PLOT SHOWING THE INFLUENCE OF AMOUNT OF HPMC K100M AND AMOUNT OF HPMC K15M ON CUMULATIVE % DRUG RELEASED LEVEL OF C

The amount of surfactant was mainly responsible for the increase in the cumulative percentage of drugs released from the formulation. The increase in cumulative drug release was mainly attributed to rapid self-emulsification of the formulations due to instantaneous dispersion in the medium after the dissolution of the capsule shell. It was also seen that the cumulative percentage of drug released was further improved by the addition of suitable polymers.

Optimization by Desirability Function: An optimization process was undertaken with desirability function to optimize the three responses simultaneously. The responses: Swelling Index (Y1), Drug Content (Y2), and cumulative percentage of drug released in 24 h (Y3) were transformed into the desirability scale, respectively. Among them, Y1 and Y2 had to be minimized, while Y3 had to be maximized. For the individual desirability function, Y_{max} and Y_{min} were taken as the highest objective function (D) was calculated by Equation (3) for each response. Finally, the global desirability value was calculated by combining the individual desirability function as the geometric mean by an extensive grid search and feasibility search over the domain by the Design-Expert software. The maximum function value was obtained at X1:42, X2:57, and X3:66. To confirm the model adequacy for prediction, three batches of formulations under the optimum composition were prepared, and the three responses were evaluated for each formulation. The results are shown in **Table 8**. The model was proven to be validated since a fine agreement existed between the predicted and observed results. It can be seen that the experimental values were in very close agreement with the predicted values, indicating the success of the central composite design combined with a desirability function for the evaluation and optimization of tablet formulations.

TABLE 8: OPTIMIZED VALUES OBTAINED BY THE CONSTRAINTS APPLIES ON Y1, Y2 AND Y3

Independent variable	Nominal values %	Predicted values			Batch	Swelling Index (Y1) (%)	Drug Content (Y2)	Percent drug released (Y3)
		Swelling Index (Y1) (%)	Drug Content (%) (Y2)	%CDR (Y3)				
Amount of HPMC K100M	42	98.42	99.56	99.72	1	97.13	98.54	97.61
Amount of HPMC K15M (B)	57				2	96.85	98.61	96.32
Amount of Sodium CMC (C)	66				3	97.63	97.69	97.73

Characterization of Optimized Quinapril Trilayer Matrix Tablet Formulation:

FTIR Studies: Characteristics peaks of pure drug FTIR **Fig. 11A** were seen at 2856.67 cm^{-1} for N-H stretching and C=O stretching of acid at 1739.85 cm^{-1}. The other principal peaks are at 1535.39 cm^{-1} for C=C stretching, 2505.62 cm^{-1} for =C-H stretching, 3387.11cm^{-1} strong and broadband for O-H stretching, 1444.73 cm^{-1} and 1342.50 cm^{-1} for asymmetric and symmetric bending vibration of CH_3 group, respectively, 1294.28 cm^{-1} bending vibration for C-H, 1143.83 cm^{-1} for C-F stretching vibrations.

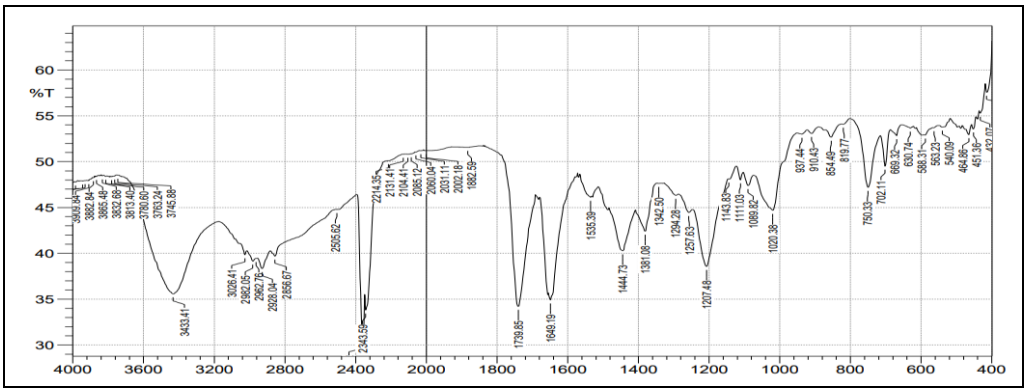

FIG. 11A: FTIR SPECTROSCOPY OF QUINAPRIL PURE DRUG

The same peaks were observed in optimized formulation **Fig. 11B** and concluded that there was no incompatibility between drug and polymers used in the formulation.

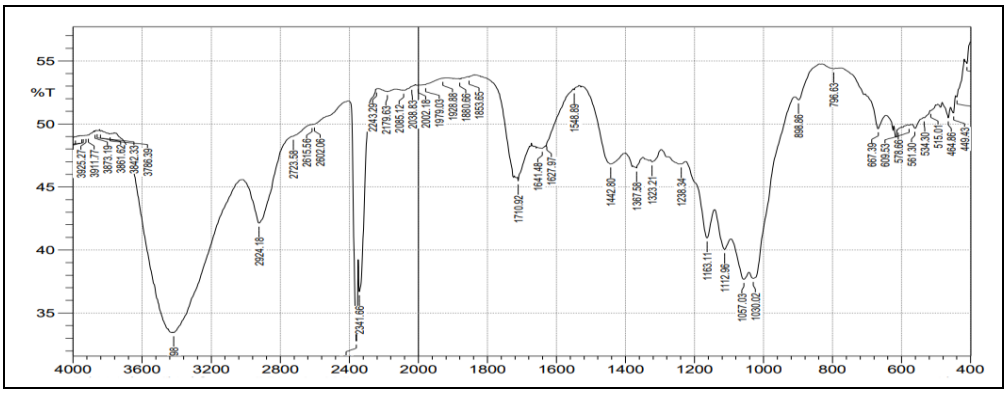

FIG. 11B: FTIR SPECTRUM OF QUINAPRIL OPTIMIZED FORMULATION EQF16

Stability Study: There were no physical changes in appearance and flexibility. After subjecting the optimized formulation (EQF16) to the accelerated stability studies, the results were shown that there were no major changes in drug content, *in-vitro* drug release, and swelling index. Hence the formulation was found to be stable **Table 9**.

TABLE 9: PARAMETERS AFTER ACCELERATED STABILITY STUDY OF FORMULATION EQF16

	Temperature Maintained at 40 ±2°C; Relative Humidity (RH) Maintained at 75%±5%RH			
Parameters	**Initial**	**After 1 month**	**After 2 months**	**After 3 months**
Drug Content (%)	99.56±0.14	99.09±1.53	99.05±1.42	99.02±1.35
In-vitro Drug Release (%)	99.72±1.11	99.56±1.68	99.43±1.37	99.361±1.22
Swelling Index	98.42±0.64	98.33±1.78	98.26±1.55	98.18±1.24

CONCLUSION: Trilayered matrix tablets of quinapril were successfully prepared by direct compression method using 3^3 Response surface method by using design of experiment software. Initially, active layer formulations (QF1-QF27) were prepared and the preformulation properties were carried out, and the values obtained were within the range. Out of 27 formulations, QF16 was found to exhibit good physicochemical properties and the highest drug release of 98.85% and was chosen for formulation into trilayer tablet. Thus, extended-release trilayered matrix Tablets were formulated by varying proportions of polymers by direct compression method, and they were evaluated (AQF16-HQF16). The physicochemical properties like swelling index, which ranged from 80.15-98.42%, and drug content of 95.23-99.56 % were within limits with the highest values exhibited by EQF16.

In vitro drug release studies were carried out to know the drug release with respective of the time. The maximum drug was released from the formulation EQF16 (99.72) within 24 h. Based on the physicochemical properties and *in-vitro* drug release, the formulation EQF16 was concluded as the best formulation. FTIR studies indicated no interaction of drug with excipients, and EQF16 was loaded for stability exhibited no significant changes in swelling index, drug content and drug release, hence found to be stable.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTERESTS: Nil

REFERENCES:

1. Ho-Wah H, Robinson J and Lee V: Design and fabrication of oral controlled release drug delivery systems. In: Controlled Drug Delivery. New York: Marcell Dekker Inc, 1987: 373.
2. Conte U and Maggi L: Multi-layer tablets as drug delivery devices. Pharm Techn 1998; 2: 18-25.
3. Kitt and Jamie: New Approaches in Hypertension Management: a Review of Current and Developing Technologies and Their Potential Impact on Hypertension Care. Current Hypertension Reports 2019; 21(6): 44.
4. Syed IA, Mangamoori LN and Rao YM: Formulation and characterization of matrix and triple-layer matrix tablets for controlled delivery of metoprolol tartrate. International J of Pharma Sci and Drug Research 2011; 3(1): 23-28.
5. Gohel MC and Bariya SH: Hypromellose and polyethylene oxide: comparative formulation design of triple-layer tablets. J Pharm Res 2010; 3: 2223-27.
6. Srinivas MP and Chaitanya N: Formulation and evaluation of sitagliptin phosphate and metformin hydrochloride trilayered tablets, Inter J of Drug Delivery 2017; 5: 15-27.

7. Efentakis M and Peponaki C: Formulation study and evaluation of matrix and three-layer tablet sustained drug delivery systems based on carbopols with isosorbite mononitrate. AAPS PharmSci Tech 2008; 9(3): 917-23.
8. Krishnaiah YSR, Karthikeyan RS, Bhaskar P and Satyanarayana V: Bioavailability studies on guar gum-based three-layer matrix tablets of trimetazidine dihydrochloride in human volunteer. J Control Release 2002; 83: 231-39.
9. Lordi NG: Sustained release dosage forms. The theory and practice of industrial pharmacy. Varghese Publishing house, Mumbai, Edition 3, 2008: 430-54.
10. Patil R, Vishal, P and Sonawane R: Nano and microparticulate chitosan based system for formulation of carvedilol rapid melt tablet. APB 2015; 5: 169-79.
11. Srinivas MP and Chaitanya N: Formulation and evaluation of sitagliptin phosphate and metformin hydrochloride trilayered tablets. Int J of Drug Deliv 2013; 5: 15-27.
12. Talukdar MM, Mooter VD, Augustijns P, Maga TT, Verbeke N and Kinget R: *In-vitro* evaluation of Guar gum as potential excipients for oral controlled release matrix tablet formulation. Int J Pharm 1998; 169: 10513.
13. Yang L and Fassihi R: Accessibility of solid core tablet for dissolution in a asymmetric triple-layer matrix system. J Pharm Pharmcol 2003; 55: 1331-33.
14. Karadag E: *In-vitro* swelling studies and preliminary biocompatibility evaluation of acrylamide-based hydrogels. Biomaterials 1996; 17(1): 67-7.
15. Bozal-Palabiyik B, Uslu B, Ozkan Y and Ozkan SA: In-Vitro Drug Dissolution Studies in Medicinal Compounds. Curr Med Chem 2018; 25(33): 4020-36.
16. Chidambaram N, Porter W, Flood K and Qiu Y: Formulation and characterization of new layered diffusion matrices for zero-order systained release. J Control Release 1998; 52: 149-58.

How to cite this article:
Ashwin K and Reddy TMM: Formulation and evaluation of quinapril extended release trilayered matrix tablets by design of experiment. Int J Pharm Sci & Res 2022; 13(2): 828-40. doi: 10.13040/IJPSR.0975-8232.13(2).828-40.