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Research Article

Preparation and Evaluation of Extended Release Trilayered Matrix Tablets of Ramipril Using Design of Experiment

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ABSTRACT

The current work is aimed to design, prepare, and evaluate the trilayer matrix tablets incorporated with ramipril for extended drug release. Twenty-seven formulations (RF1-RF27) for active layer (middle layer) were prepared by direct compression method using 3^3 Response surface method of polymers of different HPMC K4M, HPMC K15M and xanthan gum (low, middle, and high concentrations) by using Design of experiment software. Based on physico-chemical properties and drug release one formulation was chosen and formulated into extended release trilayered matrix tablets were by varying proportions of polymers by direct compression method and they were evaluated. The best optimized formulation was characterized for FTIR studies. Out of 27 active layer formulations, RF23 was chosen as best based with maximum drug release of 98.11% and was formulated into extended release trilayered matrix tablets (ARF23-HRF23) by varying proportions of polymers. The range of swelling index for all batches (ARF23-HRF23) was 82.34 to 97.46%, similarly the range of drug content was 95.49 to 99.11% and drug released in 24 hours sustainably over an extended period was 84.98 to 98.26% with all highest values exhibited by GRF23. The release order kinetics data indicate the zero-order release with highest (R^2) = 0.983 for GRF23 better when compared to marketed product which followed first order showed R^2 value 0.962. Further the formulation (GRF23) showed best fit to Korsmeyer-Peppas plots i.e., 0.957 indicating non Fickian (anomalous) transport coupled diffusion and erosion. The FT-IR data assure the compatibility of drug and excipients. GRF23 was found to be stable for 180 days at accelerated conditions.

Introduction

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. Controlled release pharmaceutical systems have been developed and studied to improve the performance of drugs and to increase their pharmacological effect and reduce any side effects. Most oral controlled release dosage forms fall in the category of matrix, reservoir, or multi-layer systems. A multi-layer system consists, usually, of a hydrophilic matrix core containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (barrier-layer) applied on one or both faces of the core during tableting.[1]

The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate. In the device, the coat layers prevent the water penetration through the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erode and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase in diffusion path length is counter balanced by the simultaneous increase of the area available for drug release.[2]

The drug chosen for the present investigation was ramipril, orally active antihypertensive agent. It is effectively used in the treatment of hypertension. Its daily oral dose is 0.5 to 3 g/day in divided doses. Recommended dosage

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of conventional tablets is three times a day. As the dose of ramipril is 10 mg (marketed immediate release formulations of ramipril are available in of (10, 20, and 25 mg). It is found to be suitable for development of a sustained release dosage form. Ramipril has a biological half-life of 3 hours. Hence, it requires three-times a day dosing.[3] Therefore, ramipril is suitable candidate for development of an extended-release dosage form.

Material and Methods

Ramipril was purchased from Hetero drugs Ltd, Hyderabad. hydroxypropyl methylcellulose (HPMC) K4M, HPMC K 15M, xanthan gum, di-calcium phosphate. Magnesium stearate, Polyox WSR N 750, carbopol 934 P, ethyl cellulose and talc were purchased from Gattefosse, Mumbai. All the reagents used were of analytical grade.

Formulation of Trilayered Matrix Tablets of Ramipril HCl

The trilayered matrix tablets of ramipril 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 for 12 hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (upper & lower layers) to continue the drug release for 24 hours.[4] Formulations were designed using 3^3 Response surface methods (3 variables and 3 levels of polymers) by using Design of experiment software.

Design of Experiments (DOE)

Preparation of Middle Active Layer of Ramipril Tri-layered Tablets

Twenty-seven formulations (RF1-RF27) 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 K4M, HPMC K15M, xanthan Gum (Table 1).[5]

Response Surface Methodology

Study type: Response surface
Design type: Central composite
Design mode: Quadratic (Fig. 1)

Preparation of Upper and Lower Layers of Ramipril 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 carbopol 934P. The procedure adopted to make the compacts was via direct compressions. For the first procedure the carnauba wax, carbopol 934P and the filler was mixed in mortar and lubricated with magnesium stearate. Formulation of upper and lower layers was depicted in Table 3.[6]

Formulation of Extended Release Trilayered Tablets of Ramipril

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 die cavity; (9 mm, round) was adjusted equivalent to the weight of trilayered matrix tablets (400 mg). Then the pre weighed amount of powder equivalent to bottom layer (100 mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted and the granules equivalent to 100 mg of the drug was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with 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 them friability, hardness, drug content and drug release characteristics with a suitable number of tablets for each test (Tables 1 and 3).[7]

Evaluation Tests

Pre-compression Evaluation Tests

Angle of repose (θ), bulk density, tapped density and Hausner's ratio were evaluated as per the referred procedures.[8,9]

Post compression Evaluation Tests

Weight variations, thicknesses, hardness, and friability were evaluated as per the referred procedure.[10]

Drug Content (%)

Twenty tablets were randomly selected, and 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 222 nm.[11]

In-vitro Swelling Studies[12]

The degree of swelling of polymer is a key 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 hours at regular intervals of time (1, 2, 4,8,10 and 12 hours), the tablet was taken carefully by using filter paper and the swelling index was calculated.

In-vitro Drug Dissolution Study

In-vitro drug dissolution studies were carried out for both core middle layer (RF1-RF27) and prepared trilayer tablet formulations was carried out using USP Dissolution Apparatus Type II (Paddle) (Electrolab EDT-08Lx) at speed 100 rpm 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

Table 1: Formulation trials of extended release trilayered matrix tablets of ramipril

F. No	*Ramipril*	*HPMC K4M*	*HPMC K15M*	*XG*	*PVP K-30*	*DCP*	*Mg Stearate*	*Total*
RF1	10	36	52	60	8	30	4	200
RF2	10	40	54	62	8	22	4	200
RF3	10	36	56	60	8	26	4	200
RF4	10	40	56	60	8	22	4	200
RF5	10	36	52	64	8	26	4	200
RF6	10	38	52	64	8	24	4	200
RF7	10	36	56	64	8	22	4	200
RF8	10	40	56	64	8	18	4	200
RF9	10	36	54	62	8	26	4	200
RF10	10	40	54	62	8	22	4	200
RF11	10	38	56	62	8	24	4	200
RF12	10	38	52	60	8	28	4	200
RF13	10	38	54	60	8	26	4	200
RF14	10	38	54	64	8	22	4	200
RF15	10	40	54	64	8	20	4	200
RF16	10	38	54	62	8	26	4	200
RF17	10	38	52	62	8	26	4	200
RF18	10	36	54	60	8	28	4	200
RF19	10	38	54	62	8	24	4	200
RF20	10	36	54	62	8	26	4	200
RF21	10	38	52	62	8	26	4	200
RF22	10	38	54	60	8	26	4	200
RF23	10	40	52	64	8	22	4	200
RF24	10	36	54	62	8	26	4	200
RF25	10	38	54	62	8	24	4	200
RF26	10	36	54	64	8	24	4	200
RF27	10	40	56	62	8	20	4	200

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 222 nm.[13]

Drug Release Kinetics

Different mathematical models are applied for describing the kinetics of the drug-release process from matrix tablets and it was calculated using Microsoft® Office Excel. The kinetics of ramipril release from formulations was determined by finding the best fit of the dissolution data (drug-released fraction vs. time) to distinct models: zero-order, first-order and Higuchi.[14,15]

Characterization of Trilayer Matrix Tablets

Drug-excipient Compatibility Study by FTIR

An FTIR-8400S Spectrophotometer (Shimadzu, Japan) equipped with attenuated total reflectance (ATR)

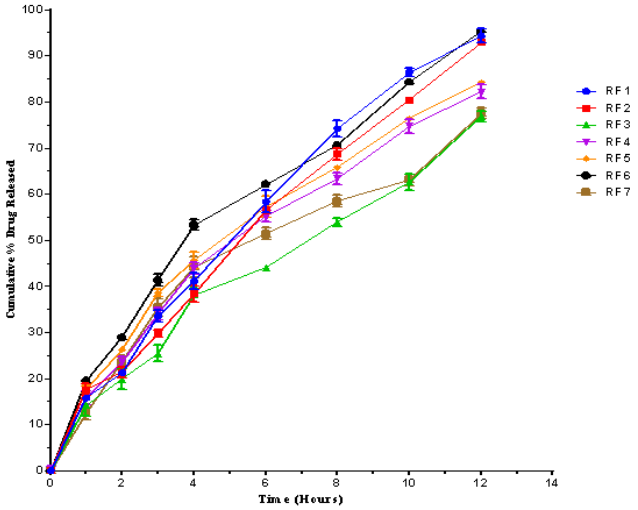

Fig. 1: List of dependent and independent variables in RSM

Table 2: Composition of ramipril trilayered matrix tablet

Ingredients	*ARF23*	*BRF23*	*CRF23*	*DRF23*	*ERF23*	*FRF23*	*GRF23*	*HRF23*
Middile active layer (RF23) (200 mg)								
Ramipril	10	10	10	10	10	10	10	10
HPMC K4M	40	40	40	40	40	40	40	40
HPMC K15M	52	52	52	52	52	52	52	52
Xanthan Gum	64	64	64	64	64	64	64	64
PVP K30	8	8	8	8	8	8	8	8
DiCalcium Phosphate	22	22	22	22	22	22	22	22
Magnesium stearate	4	4	4	4	4	4	4	4
Upper and lower layer (100 mg)								
Polyox WSR 750	10				30	35	40	45
Carbopol 934P	45				25	20	15	10
Ethyl cellulose	15				15	15	15	15
Di Calcium phosphate	26				26	26	26	26
Magnesium stearate	2				2	2	2	2
Talc	2				2	2	2	2

accessory was used to obtain the infrared spectra of drug in the isotropic mixtures of excipients. Analysis of pure drug i.e., Clopidogrel and physical mixtures of the drug with the excipients were carried out using diffuse reflectance spectroscopy (DRS)-FTIR with KBr disc. All the samples were dried under vacuum prior to obtaining any spectra to remove the influence of residual moisture. For each the spectrum, 8 scans were obtained at a resolution of 4 cm^{-1} from a frequency range of 400 to 4000 cm^{-1}.

Stability Studies

Stability testing was conducted at 40°C ± 2°C /75% RH ± 5% RH for 3 months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0-, 30-, 60-, and 90-days period according to ICH guidelines. Various in vitro parameters like drug content, in vitro drug release studies and swelling index were evaluated.

Results and Discussion

Percentage Drug Content and Swelling Index

The %drug content of all ramipril core layer ranged from 74.78 ± 1.29 to 99.42 ± 1.55% and the swelling index varied between 90.05 ± 1.37 to 99.26 ± 1.62% with maximum value recorded for RF23 (Table 3).

In-vitro Drug Dissolution Studies of Core Middle Layer

The matrix tablets of ramipril were prepared without the upper and lower layers (RF1-RF27). All the formulation trials were subjected to *in-vitro* dissolution studies to determine their release profiles and is represented in Figs 2–5. All formulations showed complete drug release in 12 hours. Out of all 27 formulations RF23 was chosen as best optimized as it showed highest drug release of 98.26 ± 1.47 and was chosen to form the active layer of the trilayer matrix tablets which were formulated later.

The physical evaluation of prepared powder blends of ramipril tablet (ARF23-HRF23) was found to be satisfactory (Table 4).

The bulk densities of all the formulations ARF23 to HRF23 were measured and they are ranged from 0.51g/cc to 0.59 g/cc.

The tapped density of all the formulations ARF23 to HRF23 was measured and they are ranged from 0.54g/cc to 0.69 g/cc.

Angle of repose of all the formulations was found satisfactory result. The formulation GRF23 was found to be 20.16 having good flow property.

The compressibility index values were found to be in the range of 8 to 12%. These findings indicated that the all the batches of formulations exhibited good flow properties.

The Hausner' s ratio values were found to be in the range of 1.05 to 1.12%. These findings indicated that the all the batches of formulations exhibited good flow properties.

The results of the physical tests of the prepared blends were within the limits (Table 5).

The weight variation of all the formulations within the 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., ARF23 to HRF23 were ranged between 5.0 to 6.2 Kg/cm^2 and the results are shown in Table 6.

The thickness of the tablets was found to be almost uniform in all formulations ARF23 to HRF23. The friability of all prepared formulation between 0.52 to 0.63. The friability properties limits are in between 0 to 1%.

Table 3: Physico-chemical parameters of ramipril middle active layer

F. No	*Drug content (%)*	*Swelling index (%)*
RF1	96.57 ± 1.38	93.43 ± 1.63
RF2	98.42 ± 1.66	90.29 ± 1.12
RF3	78.59 ± 1.34	96.51 ± 1.78
RF4	94.37 ± 1.25	93.21 ± 1.45
RF5	91.18 ± 1.73	98.36 ± 1.52
RF6	83.69 ± 1.48	96.23 ± 1.69
RF7	92.75 ± 1.42	94.77 ± 1.97
RF8	95.21 ± 1.51	96.23 ± 1.64
RF9	92.95 ± 1.60	95.49 ± 1.72
RF10	83.69 ± 1.36	93.15 ± 1.54
RF11	74.78 ± 1.29	90.05 ± 1.37
RF12	92.75 ± 1.68	95.89 ± 1.42
RF13	96.11 ± 1.38	90.35 ± 1.66
RF14	98.26 ± 1.16	93.32 ± 1.25
RF15	91.89 ± 1.78	96.44 ± 1.63
RF16	97.44 ± 1.81	92.51 ± 1.45
RF17	89.25 ± 1.32	92.67 ± 1.67
RF18	77.68 ± 1.48	97.76 ± 1.37
RF19	76.28 ± 1.34	92.95 ± 1.68
RF20	95.61 ± 1.85	94.27 ± 1.94
RF21	95.21 ± 1.56	94.22 ± 1.62
RF22	94.28 ± 1.87	93.42 ± 1.26
RF23	99.42 ± 1.55	99.26 ± 1.62
RF24	96.44 ± 1.38	91.38 ± 1.18
RF25	94.45 ± 0.37	97.25 ± 1.26
RF26	93.22 ± 1.74	97.33 ± 1.49
RF27	93.23 ± 1.26	94.59 ± 1.78

The drug content of all formulation is in between 95.49–99.11%, 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 ramipril 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 Ramipril Trilayered Matrix Tablets (ARF23-HRF23)

In-vitro dissolution of ramipril trilayered matrix tablets (ARF23-HRF23) was conducted and found that all formulation exhibited extended drug release up to 24 hours, and out of all GRF23 was found to show highest drug release of 98.26 ± 1.15% and is best optimized formula based on its physical properties as well as release profile (Fig 6).

The release order kinetics data with highest regression coefficient value closer to unity (R^2) = 0.983 for GRF23 indicate the zero-order release. GRF23 which showed best fit for Korsmeyer-Peppa's model indicating diffusion and non-Fickian diffusion process of drug release.

Design of Experiment

About 27 experiments performed according to experimental runs generated by 3^3 Response surface method. Stat-Ease Design Expert® software V8.0 was utilized for analyzing data, to get regression equation, regression coefficient and analysis of variance (ANOVA).

Percentage Swelling Index

A larger swelling index may permit a faster release rate. The swelling index of the tablets was found to be in the range of 82.34 to 97.46%. The quadratic model generated

Table 4: Physical evaluation of prepared powder blends of ramipril tablet (ARF23-HRF23)

Formulation	*Bulk density (g/cc)*	*Tapped density (g/cc)*	*Angle of repose(Θ)*	*Carr' s index (%)*	*Hausner ratio*
ARF23	0.54 ± 0.11	0.55 ± 0.36	24.29 ± 0.4	12.45 ± 0.8	1.11 ± 0.02
BRF23	0.51 ± 0.26	0.54 ± 0.12	24.88 ± 0.3	10.39 ± 1.0	1.08 ± 0.07
CRF23	0.52 ± 0.51	0.55 ± 0.02	25.19 ± 0.1	09.61 ± 0.8	1.12 ± 0.05
DRF23	0.55 ± 0.16	0.58 ± 0.08	24.58 ± 0.3	11.78 ± 0.8	1.09 ± 0.03
ERF23	0.57 ± 0.38	0.66 ± 0.05	22.47 ± 0.8	10.75 ± 0.45	1.06 ± 0.05
FRF23	0.53 ± 0.13	0.59 ± 0.12	23.63 ± 0.1	09.36 ± 0.59	1.07 ± 0.06
GRF23	0.59 ± 0.44	0.69 ± 0.29	20.16 ± 0.5	08.21 ± 0.89	1.05 ± 0.12
HRF23	0.54 ± 0.78	0.60 ± 0.07	25.21 ± 0.1	10.75 ± 0.7	1.10 ± 0.09

Table 5: Physico-chemical evaluation properties of ramipril trilayered tablets (ARF23-HRF23)

F.NO	**Weight variation (mg)*	*#Thickness (mm)*	*#Hardness (Kg/Cm^2)*	*#Friability (%)*	*Drug content (%)*	*Swelling index (%)*
ARF23	301 ± 1.5	4.5 ± 0.12	5.8 ± 0.12	0.58 ± 0.01	96.29 ± 0.63	89.21 ± 0.26
BRF23	300 ± 1.2	4.1 ± 0.06	5.4 ± 0.81	0.55 ± 0.02	98.17 ± 0.06	86.79 ± 0.47
CRF23	298 ± 1.9	4.6 ± 0.00	5.5 ± 0.38	0.63 ± 0.02	95.49 ± 0.8	82.34 ± 1.32
DRF23	300 ± 0.8	4.5 ± 0.12	5.4 ± 0.89	0.58 ± 0.01	98.65 ± 1.01	95.67 ± 0.92
ERF23	300 ± 1.4	4.0 ± 0.06	6.2 ± 0.15	0.56 ± 0.03	96.41 ± 0.14	96.32 ± 0.45
FRF23	302 ± 0.6	4.3 ± 0.10	5.8 ± 0.63	0.63 ± 0.01	98.22 ± 0.31	88.04 ± 0.31
GRF23	300 ± 1.5	4.2 ± 0.13	5.4 ± 0.15	0.52 ± 0.08	99.11 ± 0.56	97.46 ± 0.57
HRF23	301 ± 1.8	4.4 ± 0.25	6.0 ± 0.78	0.57 ± 0.01	96.34 ± 0.51	89.27 ± 0.62

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

Table 6: Regression equations of the fitted models

Response	*Equation*
Swelling Index (Y1)	$78.19 +12.42 X1 - 11.65 X2 - 3.15 X3 -1.23X^2_1 + 1.49X_1X_3 +09.34 X^2_2 -1.19 X_2X_3 +2.65 X^2_3$
Drug Content (Y2)	$83.24 + 11.63X1 + 7.25 X2 +2.75 X3 +0.13X^2_1 - 1.19X_1X_3 -10.83 X^2_2 -3.56 X_2X_3 -2.35 X^2_3$
% Cumulative drug released (Y3)	$71.66 -4.52 X1 + 18.74 X2 -15.40 X3 +1.82X^2_1 -14.89X_1X_3 +4.14 X^2_2 -26.51 X_2X_3 +3.77 X^2_3$

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.

revealed that the amount of HPMC K4M, amount of HPMC K15M and amount of sodium CMC have a considerable influence on the swelling index. The theoretical (predicted) values and the observed values were in good agreement. The mathematical model generated for %swelling index (Y1) was found to be significant with F-value of 0.0367 implies the model is significant. The interaction between B and C on swelling index at a fixed level of A is shown in Fig. 7A. The respective contour plots are as shown in Fig 7B. The increase in the swelling index with concomitant increase in the amount of HPMC K4M (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 amounts of polymers.

Drug Content

The drug content of the trilayer tablets was found to be in the range of 95.49 to 99.11%. The quadratic model generated revealed that the amount of HPMC K15M and amount of xanthan gum have a considerable influence on the drug content. The theoretical (predicted) values and the observed values were in good agreement as seen. The mathematical model generated for drug content (Y2) was found to be significant with F-value of 0.0219 implies the model is significant. The interaction between A and B on drug content at a fixed level of C is shown in Fig. 8A. The respective contour plots are as shown in Fig. 8B.

Cumulative Percent Drug Released

The cumulative percent drug release in 24 hours from the tablets was found to be in the range of 84.98–98.26%.

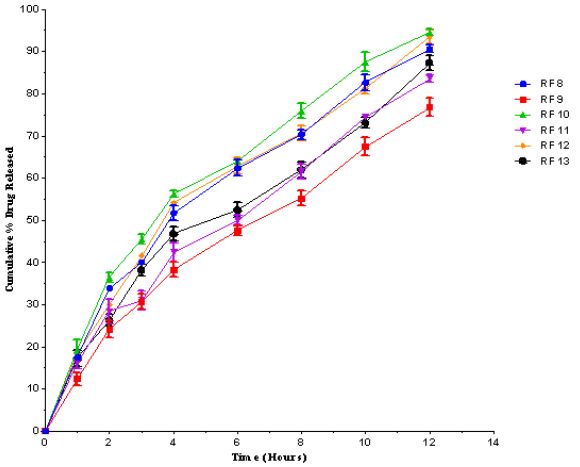

Fig. 2: *In vitro* drug release profile for prepared middle active layer of ramipril tablets RF1-RF7

The quadratic model generated revealed that the amount of HPMC K4M, amount of HPMC K15M and amount of sodium CMC have a considerable influence on the %CDR. The theoretical (predicted) values and the observed values were in good agreement as seen. The mathematical model generated for percent drug release in 24 hours (Y3) was found to be significant with F-value of 0.0347 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. 9A. The respective contour plots are as shown in Fig. 9B. The amount of surfactant was responsible for the increase in cumulative percentage of drug released from the formulation. The increase in cumulative drug release was attributed to rapid self-

emulsification of the formulations due to instantaneous dispersion in the medium after dissolution of the capsule shell. It was also seen that the cumulative percentage of drug released was further improved by adding 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 hours (Y3) were transformed into the desirability scale, respectively. Among them, Y1 and Y2 had to be minimized, while Y3 had to be maximized. For 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 X1:40, X2:52 and X3:64. 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 7. The model was proven to be validated since a fine agreement existed between the predicted and observed results. The experimental values were in very close agreement with the predicted values, indicating the success of the CCD combined with a desirability function for the evaluation and optimization of Tablets formulations.

Characterization of Optimized Formulation of Ramipril Trilayered Tablet

FTIR Studies

The FTIR spectra of pure ramipril and optimized formulation (GRF23) are shown Fig. 10A and 10B respectively. The chemical interaction between the drug and excipients often leads to identifiable changes in the infrared profile of dispersion. Drug spectrum shows prominent peaks at IR spectra of ramipril showing the peaks at 3342.75 cm^{-1} for –NH and -OH, 2928.04 cm^{-1} for –CH aromatic streaching,1720.56 cm^{-1} for -C=O, 1319.05 cm^{-1} for–CH aliphatic bending. The same characteristic peak its slight variations were also noticed in the spectra of optimized formulation.

Stability Study

There were no physical changes in appearance and flexibility. After subjecting the optimized formulation

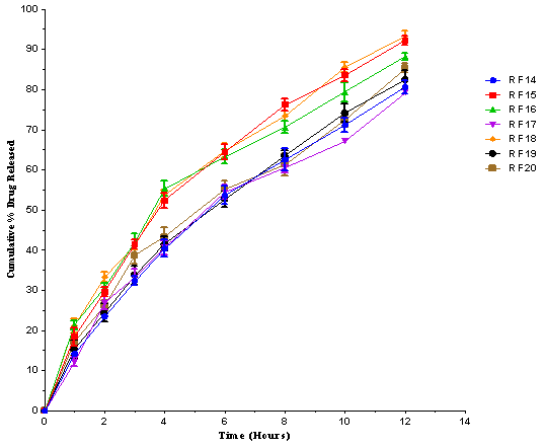

Fig. 3: *In vitro* drug release profile for prepared middle active layer of ramipril tablets RF8-RF13

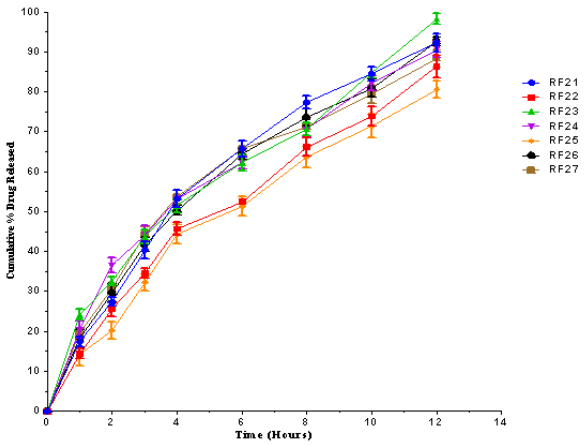

Fig. 4: *In vitro* drug release profile for prepared middle active layer of ramipril tablets RF14-RF20

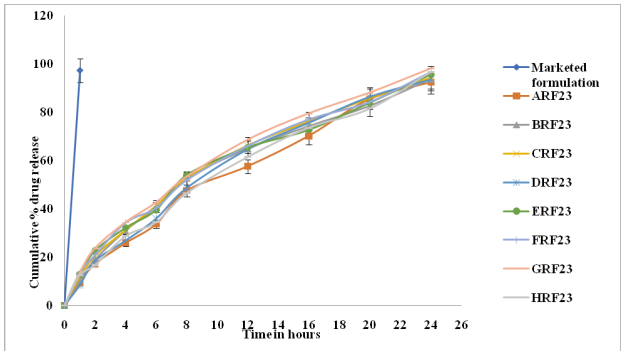

Fig. 5 : *In-vitro* drug release profile for prepared middle active layer of ramipril tablets RF21-RF27

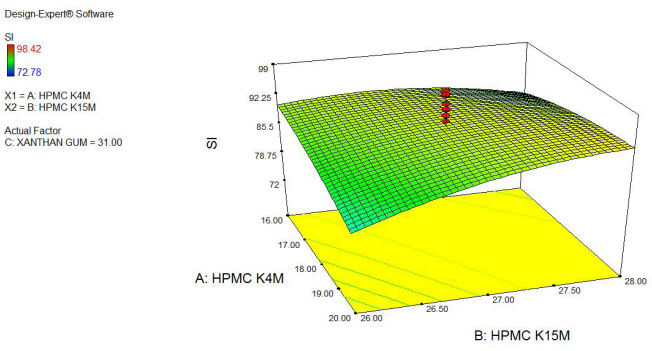

Fig. 6: *In-vitro* dissolution of ramipril trilayered matrix tablets (ARF23-HRF23) and marketed product

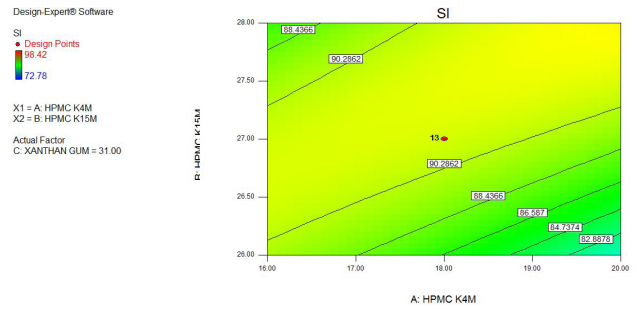

Fig. 7A: Response 3D surface plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on swelling index fixed

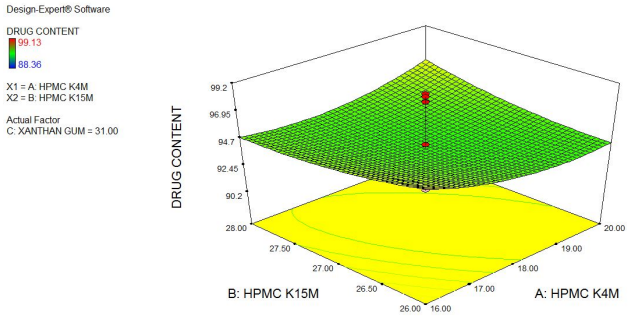

Fig. 7B: Contour plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on swelling index fixed level of C

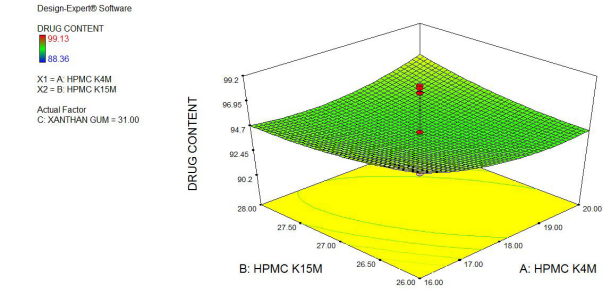

Fig. 8A: Response 3D surface plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on drug content fixed level of C

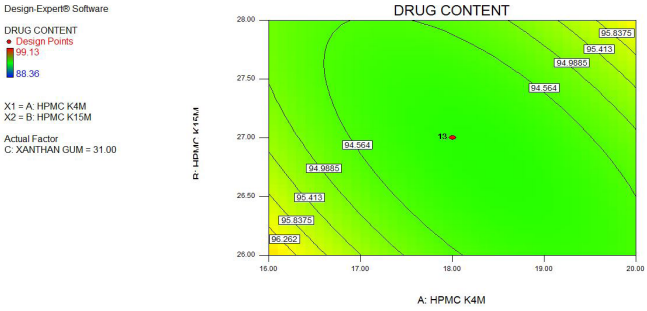

Fig. 8B: Contour plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on drug content fixed level of C

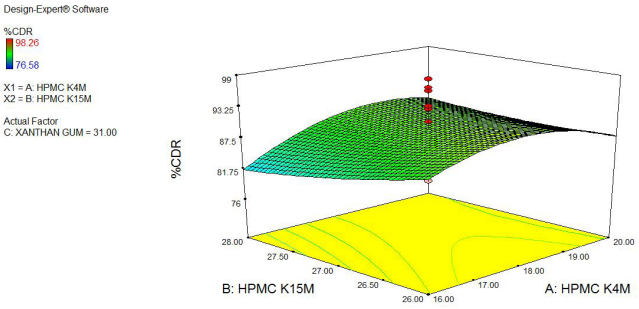

Fig. 9A: Response 3D surface plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on cumulative % drug released level of C

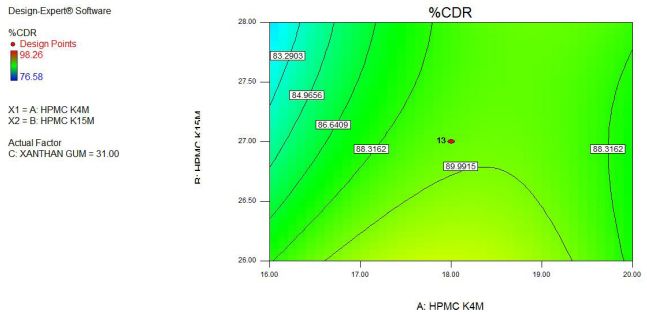

Fig.9B: Contour plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on Cumulative % drug released level of C

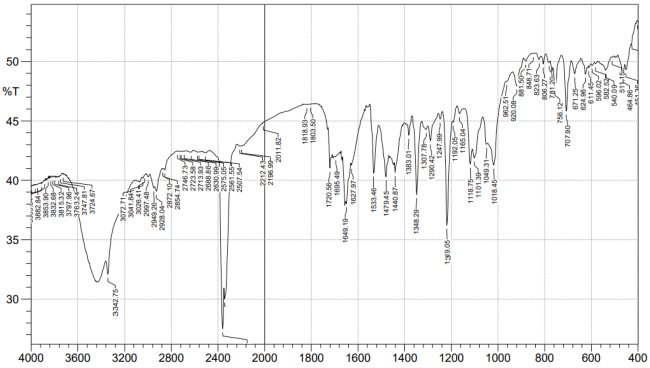

Fig. 10A: FTIR Spectrum of ramipril pure drug

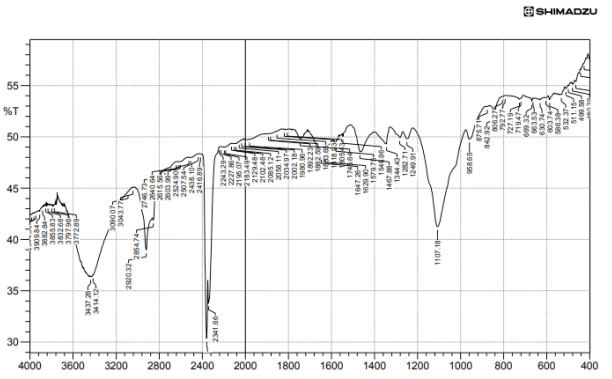

Fig. 10B: FTIR spectrum of ramipril optimized formulation (GRF23)

(GRF23) 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 8).

Table 7: Optimized values obtained by the constraints applies on Y1, Y2 and Y3

	Predicted values							
Independent variable	*Nominal values %*	*Swelling index (Y1) (%)*	*Drug content (%) (Y2)*	*%CDR (Y3)*	*Batch*	*Swelling index (Y1) (%)*	*Drug content (Y2)*	*Percent drug released (Y3)*
Amount of HPMC K4M	40	97.46	99.11	98.26	1	96.40	98.36	96.89
Amount of HPMC K15M (B)	52				2	97.21	98.54	97.13
Amount of Xanthan Gum (C)	64				3	96.37	97.16	97.49

Table 8: Parameters after accelerated stability study of formulation ERF16

	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 (%)	99.11 ± 0.56	99.09 ± 1.53	99.05 ± 1.42	99.02 ± 1.35
In Vitro drug release (%)	98.26 ± 1.15	99.56 ± 1.68	99.43 ± 1.37	99.361 ± 1.22
Swelling index	97.46 ± 0.57	98.33 ± 1.78	98.26 ± 1.55	98.18 ± 1.24

Conclusion

In present study was conducted to achieve extended drug release with controlled manner up to 24 hours from the trilayered matrix tablets of ramipril form. Twenty-seven formulations (RF1-RF27) 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 K4M, HPMC K15M and xanthan gum (low, middle and high concentrations) by using Design of experiment software. Out of all RF23 was chosen as best and extended release trilayered matrix tablets were formulated by varying proportions of polymers by direct compression method and they were evaluated. All the Physico-chemical properties of the formulations were within the limit. From *in-vitro* drug release studies maximum drug was released from the formulation GRF23 (98.26 ± 1.15%) within 24 hours and was concluded as the best formulation. No prominent changes in physico-chemical properties of formulation after its exposure to accelerated conditions of temperature (40 ± 2°C) and humidity conditions (75 ± 5%RH) were seen. Hence the developed formulation was found to be stable even after subjecting to accelerated stability conditions. It can be concluded that the extended release trilayered matrix tablets of ramipril formulations can be an innovative and promising approach for the delivery of ramipril for the treatment of hypertension.

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