Design and Formulation optimization by Using Design of Experiment of Trilayered Sustained Release Tablets containing an Antihypertensive Drug

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ABSTRACT

The purpose of this effort is to design, produce, and test extended-release trilayer matrix tablets that contain Ramipril for the purpose of administering the medicine over a longer period of time. Direct compression method with Response surface technique for polymers that included HPMC K4M, HPMC K15M, and xanthan gum (low, intermediate, and high concentrations) were used to construct a total of twelve different formulations (RTF1–RTF12) for the active layer (middle layer) by utilising Design of experiment software. These formulations were named RTF1–RTF12. One formulation was selected on the basis of its physicochemical qualities and drug release, and it was further made into prolonged release trilayered matrix tablets by altering amounts of polymers using the direct compression method. These tablets were then put through an evaluation. Characterization of the best possible optimised formulation was performed for the FTIR studies. RTF8 was selected as the best

formulation out of a total of 12 active layer formulations due to its maximal drug release of 99.35%. It was further developed into extended release trilayered matrix tablets (ARTF8-HRTF8) by altering the amounts of polymers used. The range of the swelling index for all batches (ARTF8- HRTF8) was 92 to 96%. Likewise, the range of the drug content was 78.66 to 99.11%, and the range of the drug released in 24 hours stably over an extended period was 86.76 to 99.35%, with GRTF8 exhibiting the greatest values for all of these parameters. When compared to the marketed product, which followed first order and exhibited an R2 value of 0.960, the results on the release order kinetics indicate that the zero-order release with the highest (R2) value for GRTF8 is superior. In addition, the formulation (GRTF8) demonstrated the best fit to the Korsmeyer-Peppas plots, with a value of 0.95, indicating that non-Fickian (anomalous) transport associated with erosion occurred. The results of the FT-IR analysis confirm that the medicine and the excipients are compatible with one another. GRTF8 was determined to be stable under accelerated settings for a period of three months.

Keywords: Extended release, Hypertension, Ramipril, Response surface method, Trilayer matrix tablets.

Introduction

Oral drug delivery has been recognized for many years as the most popular route of administration among all the routes that have been investigated for the purpose of systemic drug delivery using a variety of pharmaceutical products that come in a variety of dose forms. This is because oral drug delivery can be accomplished through ingesting the drug. The efficacy of medications, as well as their pharmacological effects and any potential adverse effects, have been the focus of research and development efforts that led to the creation and study of controlled-release pharmaceutical systems.[1] The vast majority of oral controlled release dose forms are classified as either matrix, reservoir, or multi-layer delivery systems. A multi-layer system typically consists of a hydrophilic matrix core that contains the active ingredient and one or two polymeric coatings that are either impermeable or semi-permeable and are put on one or both faces of the core during the tableting process. These coatings make up the barrier layer.

The barrier layers slow down the rate at which the active solute interacts with the dissolution medium. They do this by reducing the amount of surface area that is available for solute release while simultaneously restricting the rate at which solvent is able to penetrate. In the apparatus, the coat layers have a temporary protective effect on the protected core by preventing water from penetrating it.[2] In the succeeding process of dissolution, following this phase, the inflated barriers begin to disintegrate, and the surface area that is gradually accessible for drug release gradually rises. In this way, the drop in delivery rate that occurs as a result of an increase in the length of the diffusion channel is counterbalanced by an increase in the area that is simultaneously available for the release of the medication.

For the purpose of this study, the hypertension medication ramipril, which can be taken by mouth, was selected as the drug of choice. It is an excellent treatment for hypertension, which is why it is utilised. The recommended oral dose range is 0.5 to 3 grammes per day, to be taken in equal parts. The typical dosage for tablets is three times a day, as directed by the manufacturer. As the dose of ramipril is 10 mg (marketed immediate release formulations of ramipril are available in of (10, 20, and 25 mg). It has been determined that it can be used in the production of a dosage form with prolonged release. A biological half-life of ramipril of three hours has been determined. Because of this, it must be dosed three times every day. Because of this, ramipril is an excellent candidate for the development of a dosage form with extended release.[3]

Material and Methods

Wockhardt Pharmaceuticals in Aurangabad was where the purchase of ramipril was made. Hydroxypropyl methylcellulose HPMC K4M and HPMC K15M, xanthan gum, and lactose monohydrate are the ingredients in this formulation. At SD fine chemical in Mumbai, we were able to acquire magnesium stearate, polyethylene oxide N750, carbopol 934 P, Eudragit RSPO, and talc. Each and every one of the reagents that were utilised was of an analytical grade.

Formulation methods for preparation of Ramipril HCl Trilayered Matrix Tablets

The direct compression method was utilised in the manufacture of ramipril tablets using a trilayered matrix. The first thing that needed to be done in order to create the formulation was to create the middle active layer in a way that would allow for at least 90% of the drug to be released over the course of 12 hours. It's possible that this layer's release profile won't be of the constant rate type, but if it is, the profile should ideally be of the constantly declining rate type.

After then, this layer would be placed in between two barrier layers—the upper and lower layers—so that the medication release would be maintained for a full day. By utilising Design of experiment software in conjunction with Response surface methods (consisting of three variables and three levels of polymers), formulations were developed. [4]

Design of Experiments (DOE)

Formulation of Middle Active Layer of Ramipril Tri-layered Tablets

In total, twenty-seven different formulations (RTF1–RTF12) for the active layer were created with the use of the direct compression method, Response surface methods (consisting of three variables and three layers of polymers), Design of experiment software, and polymers such as HPMC K4M, HPMC K15M, and xanthan Gum (all of which are represented in table 1).[5]

Table 1: Best twelve Formulation trials of extended release trilayered matrix tablets of Ramipril

Formulation Code	RTF_1	RTF_2	RTF_3	RTF_4	RTF_5	RTF_6	RTF_7	RTF_8	RTF_9	RTF_{10}	RTF_{11}	RTF_{12}
Ramipril	20	20	20	20	20	20	20	**20**	20	20	20	20
HPMC K4M	38	38	36	38	36	38	38	**40**	36	38	36	40
HPMC K15M	54	52	54	54	54	52	54	**52**	54	54	54	56
Xanthan Gum	62	62	60	62	62	62	60	**64**	62	62	64	62
PVP K-30	10	10	10	10	10	10	10	**10**	10	10	10	10
Lactose Monohydrate	61	63	65	61	63	63	63	**61**	63	61	61	57
Mg Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	**2.5**	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	**2.5**	2.5	2.5	2.5	2.5
Total	250	250	250	250	250	250	250	**250**	250	250	250	250

Formulation of Upper and Lower Layers of Ramipril Trilayered Tablets

Carnauba wax, which is hydrophobic and swellable, was used in the formulation of the barrier layers. The swelling erosion modelling fillers, which comprise water-soluble lactose monohydrate, Eudragit RSPO, and carbopol 934P, were also used into the formulation. Direct

compressions were chosen as the method to follow for the production of the compacts.[6] In the initial step of the process, a mortar was used to combine carnauba wax, carbopol 934P, and the filler while magnesium stearate was used to lubricate the process. Table 2 shows the formulation of both the top and bottom layers of the product.

Formulation design of Extended Release Trilayered Tablets of Ramipril

A mortar and pestle were used for approximately twenty minutes to completely combine the powder combinations that were necessary for the active and barrier layers. The powder was accurately weighed before being mixed. At first, the capacity of the die cavity, which was round and 10 millimetres in diameter, was modified to be identical to the weight of the trilayered matrix tablets, which was 500 milligrammes. After that, the quantity of powder that had been previously weighed and determined to be equivalent to the bottom layer (100 mg) was taken, placed in the die cavity, and then slightly compressed for uniform spreading. After lifting the upper punch, the granules representing 20 mg of the medicine were deposited over the previous layer in the die cavity, where they were then subjected to a second round of gentle compression. In order to obtain tri-layered tablets, the remaining space in the die cavity was filled with a quantity of powder equivalent to the top layer that had been pre-weighed at 100 mg. This mixture was then squeezed using the full force of the compression on a rotary tablet press. Compressed tri-layered matrix tablets of each composition were subjected to evaluations of their friability, hardness, drug content, and drug release properties, with an adequate quantity of tablets being used for each evaluation.[7]

Table 2: Composition various excipients used of Ramipril trilayered matrix tablet

Ingredients	$ARTF_8$	$BRTF_8$	$CRTF_8$	$DRTF_8$	$ERTF_8$	$FRTF_8$	$GRTF_8$	$HRTF_8$
Middle active layer (RTF8) (250 mg)								
Ramipril	20	20	20	20	20	20	20	20
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 K-30	10	10	10	10	10	10	10	10
Lactose Monohydrate	61	61	61	61	61	61	61	61

Mg Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Upper and lower layer (150 mg)								
Polyethylene oxide N750	10	15	20	25	30	35	40	45
Carbopol 934P	40	40	30	30	25	20	15	10
Eudragit RSPO	20	15	20	15	15	15	15	15
Lactose Monohydrate	76	76	76	76	76	76	76	76
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2

Evaluation Tests

Evaluation Tests of Pre-compression parameters

Following the processes that were alluded to, measurements were taken to determine the angle of repose (θ), bulk density, tapped density, carr's index, and Hausner's ratio. For the purpose of determining the flow qualities of dry powder mixes, all of these factors are determined. [8]

Evaluation Tests Post-compression parameters

In accordance with the process that was referred to, post-compression parameters that include variations in weight, thicknesses, and hardness as well as friability were examined. [9, 10]

Study of Drug Content (%)

A sample size of twenty pills was chosen at random, and their average weight was determined. A glass mortar was used to grind the tablets into a powder. A quantity of powder equal to 20 mg was weighed and then dispersed into 100 ml of phosphate buffer with a pH of 6.8 before being filtered and having its drug content measured spectrophotometrically using an ultraviolet spectrophotometer measuring at 222 nm. [11]

Evaluation of *In vitro* Swelling Studies

The extent to which the polymer swells is one of the most important factors that determines adhesion. In order to carry out the research, a tablet was measured in terms of its weight and then put into a petri dish that held 5 millilitres of phosphate buffer with a pH of 6.8. After a period of 12 hours, the tablet was removed from the dish for various points of time (1, 2, 4, 8, and 10 hours), then the index of swelling was determined. [12]

Evaluation of *In vitro* Drug Dissolution Study

In vitro drug dissolution studies were conducted for both the core middle layer (RTF1- RTF12) and the prepared trilayer tablet formulations. These studies were conducted using a USP Dissolution Apparatus Type II (Paddle) (Electrolab EDT-08Lx) at a speed of 100 rpm with 900 mL of phosphate buffer (pH 6.8) as the dissolution medium while maintaining the temperature at 37 0.5°C. At various time intervals, aliquots of 5 millilitres of the dissolving medium were removed, filtered, and then replaced with fresh 5 millilitres of the dissolution medium. UV spectrophotometer (Shimadzu UV 1800) readings taken at 222 nm were used to determine the amount of medication that was emitted. [13, 14]

Evaluation of Drug Release Kinetics

When attempting to describe the kinetics that govern the drug-release process in matrix tablets, a variety of mathematical models are utilised, and the results were derived utilising Microsoft Office Excel. The kinetics of Ramipril release from formulations were analysed by selecting the models that provided the best match with the dissolution data (drug-released fraction vs. time). The models that were considered were Higuchi, zero-order, and first-order models. [15]

Characterization of Trilayer Matrix Tablets

Drug-excipient Compatibility Study by FTIR Analysis

To obtain the infrared spectra of the medicine in the isotropic mixtures of excipients, an FTIR-8400S Spectrophotometer (Shimadzu, Japan) equipped with an attenuated total reflectance (ATR) accessory was employed. The technique of diffuse reflectance spectroscopy (DRS)-FTIR with a KBr disc was utilised in order to perform analyses on both the pure drug, which was identified as ramipril, and on physical mixes of the drug with the excipients. Before any spectra were taken, every sample was dried in a vacuum to remove any impact that could have been caused by moisture that had been left behind. For each spectra, eight scans were taken with a resolution of four cm-1 throughout a frequency range of four hundred to four thousand cm^{-1}.

Stability Studies of optimised formulation

Testing for stability was carried out in a stability chamber from Thermo Lab in Mumbai for three months at a temperature of 40°C ± 2°C and a relative humidity of 75% ± 5%. In accordance with the recommendations provided by the ICH, samples were taken at regular intervals of 0, 30, 60, and 90 days during the testing period. A number of different in vitro criteria, such as drug content, in vitro drug release studies, and swelling index, were examined.

Results and Discussion

Percentage Drug Content and Swelling Index

The percentage of medication contained in every ramipril core layer varied from 78.66 ± 1.27 to 99.39 ± 1.45%, while the swelling index ranged from 92 ± 1.32 to 98 ± 1.89%, with the highest value being recorded for RTF8 (the results are provided in table 3).

Table 3: Results showing Drug content and Swelling index of Ramipril middle active layer

Formulation Code	*Drug content (%)*	*Swelling index (%)*
RTF$_1$	96.45 ± 1.05	93 ± 1.32
RTF$_2$	90.36 ± 1.21	94 ± 1.40
RTF$_3$	79.28 ± 1.32	96 ± 1.50
RTF$_4$	78.66 ± 1.27	93 ± 1.37
RTF$_5$	96.51 ± 1.38	95 ± 1.45
RTF$_6$	96.37 ± 1.36	93 ± 1.36
RTF$_7$	95.48 ± 1.62	94 ± 1.53
RTF$_8$	99.39 ± 1.45	98 ± 1.89
RTF$_9$	97.29 ± 1.26	92 ± 1.32
RTF$_{10}$	95.32 ± 1.15	96 ± 1.41
RTF$_{11}$	94.45 ± 1.30	96 ± 1.38
RTF$_{12}$	94.38 ± 1.42	95 ± 1.64

Values are expressed in mean ± SD (n=3)

In vitro Drug Dissolution Studies of Core Middle Layer

The matrix tablets of Ramipril were prepared without the upper and lower layers (RTF_1-RTF_{12}). All the formulation trials were subjected to *in vitro* dissolution studies to determine their release profiles and is represented in Figures. All formulations showed complete drug release in 12 hours. Out of all 12 formulations RTF_8 was chosen as best optimized as it showed highest drug release of 99.15 ± 1.32% and was chosen to form the active layer of the trilayer matrix tablets which were formulated later.

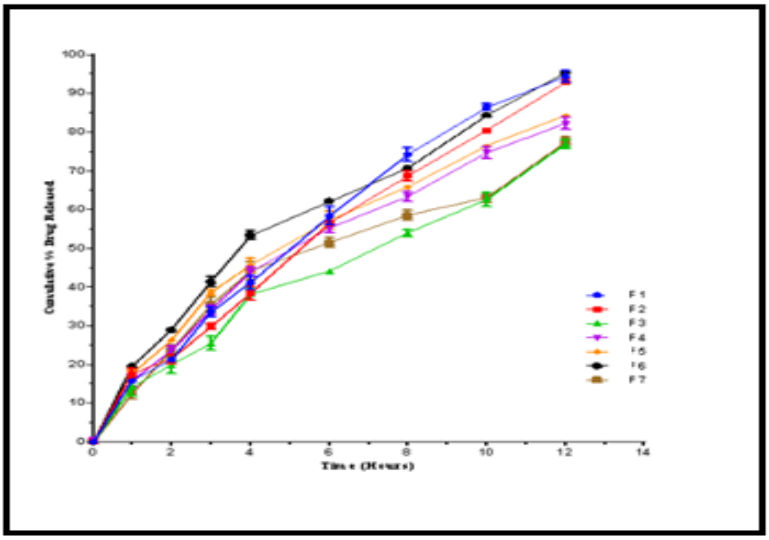

Figure 1: *In vitro* drug release profile for prepared middle active layer of Ramipril tablets RTF_1- RTF_7

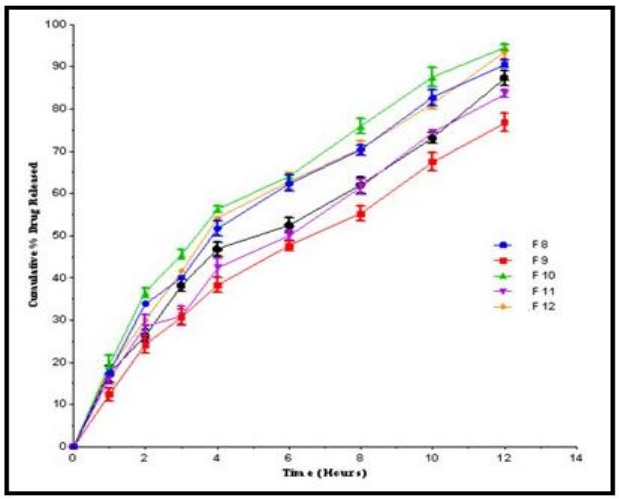

Figure 2: *In vitro* drug release profile for prepared middle active layer of Ramipril tablets RTF_8- RTF_{12}

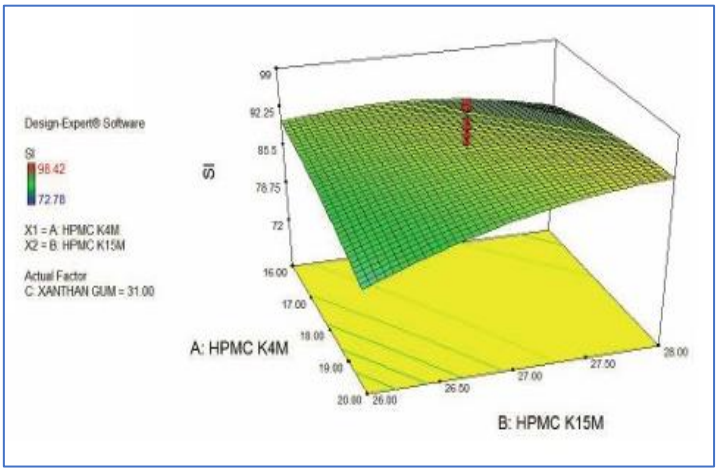

Figure 3: Response 3D surface plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on swelling index fixed

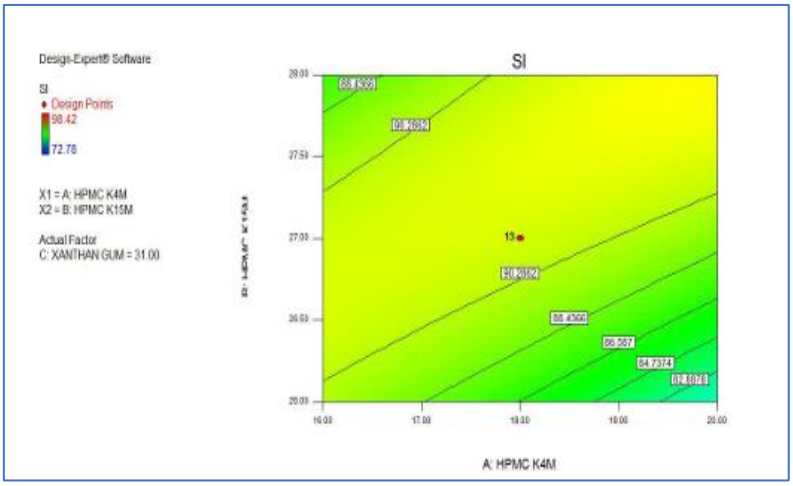

Figure 4: Contour plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on swelling index fixed level of C

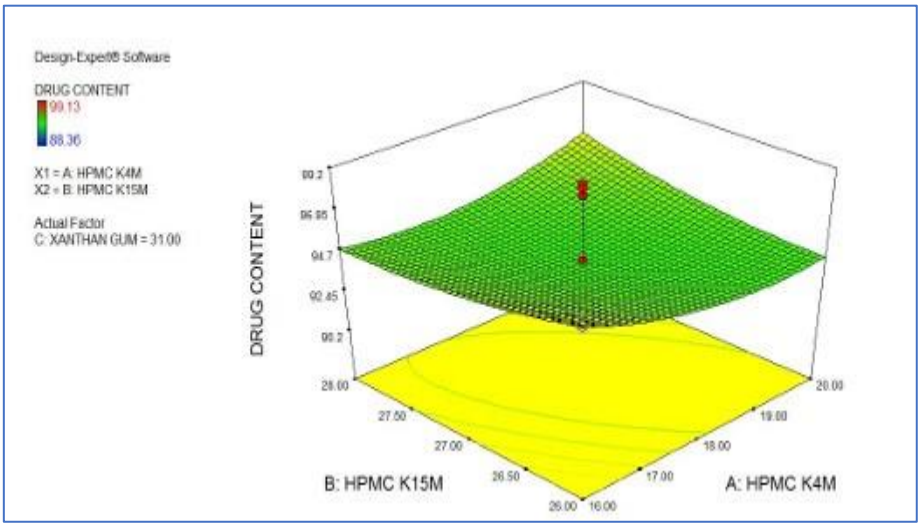

Figure 5: Response 3D surface plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on drug content fixed level of C

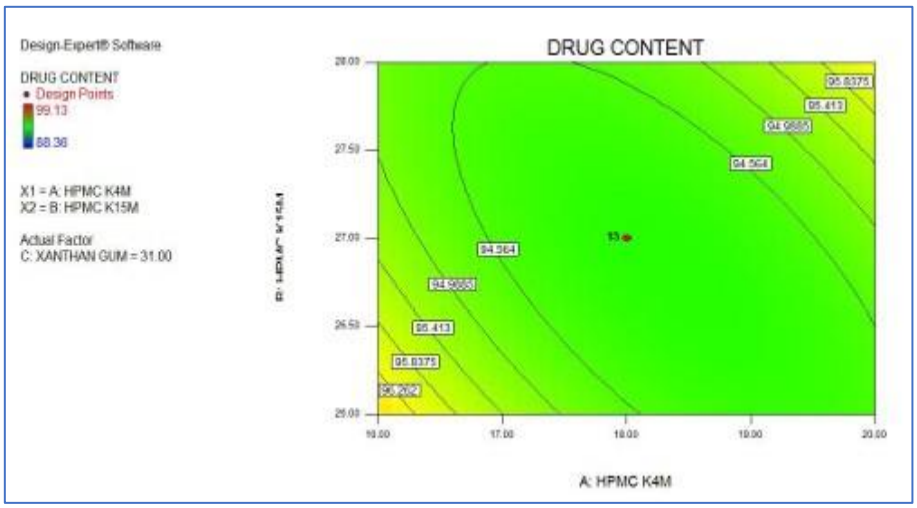

Figure 6: Contour plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on drug content fixed level of C

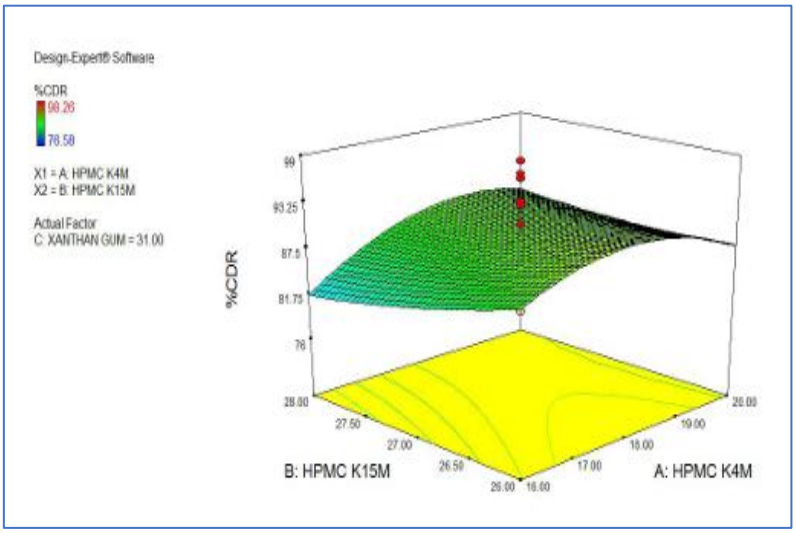

Figure 7: Response 3D surface plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on cumulative % drug released level of C

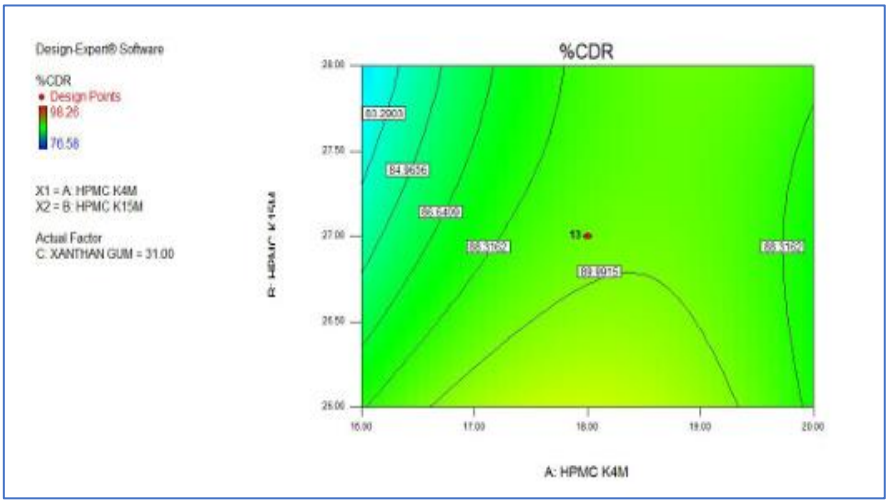

Figure 8: Contour plot showing the influence of amount of HPMC K4M and amount of HPMC K15M on Cumulative % drug released level of C

According to Table 4, the results of the physical evaluation of the manufactured powder blends of the Ramipril tablet (ARTF8- HRTF8) were considered to be satisfactory. After taking readings, it was determined that the bulk densities for each of the formulations, from ARTF8 to HRTF8, varied from 0.52 g/cc to 0.56 g/cc. After taking readings, it was determined that the average density of all of the formulations, from ARTF8 to HRTF8, varied between 0.50g/cc to 0.65 g/cc. The angle of repose for each of the several formulations yielded a result that was deemed satisfactory. It was determined that the formulation GRTF8 had a flow property of

21.29 and was satisfactory. The values of the compressibility index were discovered to fall somewhere in the region of 8 to 12%. According to these observations, each batch of formulations displayed good flow qualities. This was true for all of the formulations. The values of the Hausner's ratio were discovered to be in a range that went from 1.05 to 1.12%. According to these observations, each batch of formulations displayed good flow qualities. This was true for all of the formulations. The outcomes resulting from the physical tests conducted on the created mixtures showed that they fell within the acceptable ranges. The acceptable level of tablet hardness is an essential need for customer acceptance and handling, as is the amount of weight variation of all formulations that falls within the limit. The determined hardness of the tablets for every batch of all formulations, from ARTF8 to HRTF8, ranged between 5.0 and 6.2 Kg/cm2, and the results are presented in Table 5 below.

It was revealed that the tablet thickness was essentially the same throughout all of the formulations, ranging from ARTF8 to HRTF8, and this was found to be the case. The level of friability of every formulation that was made fell somewhere in the range of 0.61 and 0.64, giving the range the value of 0.61 to 0.64. The limits of the friability qualities are specified anywhere between 0% and 1% of the total weight. The distribution of the medicine is dependent on the angle of repose because if the angle of repose was good, then the distribution of the drug would likewise be uniform. This is due to the fact that if the flow quality was satisfactory, then the medicine was dispersed evenly across the entirety of the formulation. The amount of active ingredient included in each formulation varies anywhere from 96.25% to 99.45%. The angle of repose affects the amount of drug present. The findings of the research conducted on the swelling of a trilayered matrix tablet containing ramipril can be found shown in Table 5. These findings demonstrate that the swelling index of the tablet increases with an increase in the amount of time up to a period of 24 hours. There is a possibility that this occurrence is connected to the fact that the biodegradable polymer xanthum gum is deteriorating with time. This indicates that the medication will remain in the intestinal region until it is completely released from the delivery system, and once it is released, it will stimulate the normal process of elimination that occurs within the body.

Table 4: Physical evaluation of prepared dry powder blends of Ramipril tablet ($ARTF_8$- $HRTF_8$)

Formulation Code	*Angle of repose (θ)*	*Carr's index (%)*	*Hausner ratio*

***RTF*$_1$**	22.40 ± 0.4	11.25 ± 0.5	1.20 ± 0.01
***RTF*$_2$**	21.36 ± 0.3	10.37 ± 0.3	1.34 ± 0.02
***RTF*$_3$**	23.28 ± 0.1	11.52 ± 0.4	1.26 ± 0.04
***RTF*$_4$**	22.36 ± 0.1	12.63 ± 0.2	1.12 ± 0.02
***RTF*$_5$**	20.27 ± 0.1	13.38 ± 0.5	1.13 ± 0.01
***RTF*$_6$**	22.45 ± 0.1	11.48 ± 0.4	1.10 ± 0.02
***RTF*$_7$**	21.38 ± 0.1	10.66 ± 0.3	1.13 ± 0.04
***RTF*$_8$**	21.29 ± 0.1	14.74 ± 0.5	1.11 ± 0.03
***RTF*$_9$**	20.65 ± 0.1	13.48 ± 0.6	1.12 ± 0.01
***RTF*$_{10}$**	24.75 ± 0.1	14.27 ± 0.4	1.13 ± 0.03
***RTF*$_{11}$**	22.36 ± 0.1	12.81 ± 0.5	1.20 ± 0.03
***RTF*$_{12}$**	23.25 ± 0.1	15.80 ± 0.6	1.18 ± 0.02

Values are expressed in mean ± SD (n=3)

Table 5: Post compression evaluation parameters of Ramipril trilayered tablets (ARTF8-HRTF8)

Formulation Code	*#Weight variation (%)*	*#Thickness (mm)*	*#Hardness (Kg/Cm^2)*	*#Friability (%)*	*#Swelling index (%)*
***ARTF*$_8$**	3.6± 0.42	4.2 ± 0.11	5.2 ± 0.12	0.62 ± 0.02	91 ± 1.31
***BRTF*$_8$**	3.2± 0.32	4.3 ± 0.13	5.3 ± 0.13	0.61 ± 0.03	94 ± 1.55
***CRTF*$_8$**	3.4± 0.43	4.4 ± 0.14	5.4 ± 0.12	0.63 ± 0.04	93 ± 1.42
***DRTF*$_8$**	3.1± 0.54	4.5 ± 0.11	5.6 ± 0.13	0.64 ± 0.02	95 ± 1.34
***ERTF*$_8$**	3.2± 0.42	4.2 ± 0.13	5.1 ± 0.12	0.62 ± 0.01	94 ± 1.40
***FRTF*$_8$**	3.3± 0.31	4.3 ± 0.14	5.4 ± 0.13	0.63 ± 0.03	92 ± 1.62
***GRTF*$_8$**	**3.1± 0.52**	**4.2 ± 0.11**	**5.5 ± 0.15**	**0.63 ± 0.02**	**97 ± 1.32**
***HRTF*$_8$**	3.0± 0.43	4.3 ± 0.13	5.6 ± 0.12	0.64 ± 0.03	96 ± 1.17

Values are expressed in mean ± SD (n=3)

In vitro Dissolution of Ramipril Trilayered Matrix Tablets (ARTF$_8$-HRTF$_8$)

The in vitro dissolution of ramipril trilayered matrix tablets (ARTF8-HRTF8) was carried out, and the results showed that all formulations exhibited extended drug release for up to 24 hours.

However, GRTF8 was discovered to show the highest drug release of 99.35 ± 1.48%, and it is the best optimised formula based on its physical properties as well as its release profile. The release order kinetics results for GRTF8 imply a zero-order release since they have a regression coefficient value that is closest to unity and has the largest absolute value. GRTF8, which demonstrated the best match for Korsmeyer-Peppa's model, demonstrating that the drug release process involves both diffusion and non-Fickian diffusion.

Design of Experiment

Approximately 12 different tests were carried out in accordance with the experimental runs that were generated using the Response surface method. We performed the analysis of the data using the Stat-Ease Design Expert® software version 8.0. This allowed us to obtain the regression equation as well as the regression coefficient and analysis of variance (ANOVA).

Percentage Swelling Index

A higher swelling index may make it possible to achieve a higher release rate. The tablets were discovered to have a swelling index that fell somewhere in the range of 91 ± 1.31 to 97 ± 1.32 % when measured. According to the findings of the quadratic model that was developed, the quantity of sodium CMC, the quantity of HPMC K4M, and the amount of HPMC K15M all have a significant impact on the rise in the index. Both the theoretical (predicted) readings and the observed values showed a high degree of congruence with one another. With an F-value of 0.0365, the mathematical model that was developed for the percentage swelling index (Y1) has been determined to be significant. This indicates that the model is significant. Figure illustrates the effect of the interaction between B and C on the swelling index when kept at a constant level of A, as well as the respective contour plots. In many of the articles that have been written about trilayer tablets, an increase in the swelling index has been observed to occur in conjunction with a simultaneous increase in the amount of HPMC K4M (X1) or a decrease in the amount of HPMC K15M (X2) and vice versa. This phenomenon can also occur in reverse. It's possible that this can also explain why there's such a significant relationship between the polymer quantities.

Drug Content

It was discovered that the drug concentration within the trilayer tablets ranged anywhere from 95.49 to 99.11% of their total weight. The quadratic model that was developed demonstrated that the quantity of HPMC K15M as well as the quantity of xanthan gum having a significant impact on the amount of medication that is present. As could be clearly seen, the assumed (predicted) values and the observed values were very closely aligned with one another. With an F-value of 0.0217, it was determined that the mathematical model that was developed considering drug content (Y2) was significant. This indicates that the model is significant. Figures show the interaction between A and B on drug content at a constant level of C, as well as the respective contour plots for the different levels of drug content.

Cumulative Percent Drug Released

The pills were discovered to have an aggregate percent drug release over 24 hours that ranged from 86.76 to 99.35% of its total potential. According to the findings of the quadratic model that was developed, the quantity of sodium CMC, the quantity of HPMC K4M, and the quantity of HPMC K15M all have a significant impact on the percentage of CDR. As could be clearly seen, the assumed (predicted) values and the observed values were very closely aligned with one another. With an F-value of 0.0346, the mathematical model that was developed for calculating the percentage of drug release in 24 hours (Y3) was found to be significant. This indicates that the model is significant. Figure illustrates the effect of the interaction between factors A and B on the percentage of drug release when C is held constant, as well as the respective contour plots. The increase in the cumulative percentage of medication that was released from the formulation was caused by an increase in the amount of surfactant that was used. The quick self-emulsification of the formulations was thought to be responsible for the increase in cumulative drug release. This was because of the instantaneous dispersion in the medium that occurred once the capsule shell was dissolved. It was also observed that the addition of suitable polymers led to a further improvement in the cumulative percentage of medication that was released.

Optimization by Desirability Function

In order to achieve the best results for all three responses at the same time, an optimisation procedure using a desirability function was carried out. The following responses were converted into the respective desirability scale: swelling index (Y1), drug content (Y2), and

cumulative percentage of drug discharged in 24 hours (Y3). Among these, Y1 and Y2 were to be reduced as much as possible, whereas Y3 had to be increased as much as possible. Ymax and Ymin were computed as the highest objective function (D) was obtained by equation (3) for each response. This was done so that the individual desirability function could be determined. In the end, the global desirability value was determined by merging the individual desirability functions in order to determine the geometric mean. This was done with the help of the Design-Expert programme, which conducted an exhaustive grid search and a feasibility search across the domain. At X1:40, X2:52, and X3:64, we were able to obtain the highest possible value for the function. In order to verify that the model is enough for prediction, three batches of formulations with the optimum composition were made, and the three responses were analysed for each formulation. This was done so that the model could be used to make accurate predictions. The validity of the model was demonstrated by the fact that the results that were predicted and those that were actually observed agreed quite closely. Indicating the efficacy of the CCD paired with a desirability function for the evaluation and optimisation of Tablets formulations, the experimental values were in extremely close agreement with the anticipated values.

Characterization of Optimized Formulation of Ramipril Trilayered Tablet

FTIR Studies

Figures illustrate the FTIR spectra of both pure ramipril and the optimised formulation (GRTF8). The chemical reaction that takes place between the active ingredient and the excipients almost always results in observable shifts in the infrared profile of the dispersion. IR spectra of ramipril exhibit strong peaks at 3342.72 cm^{-1} for –NH and -OH, 2928.02 cm^{-1} for CH aromatic streaching, 1720.53 cm^{-1} for -C=O, and 1319.05 cm^{-1} for–CH aliphatic bending. The peaks at 3342.75 cm^{-1} for –NH and -OH are seen in the drug spectrum. In the spectra of the formulation that was optimised, the same distinctive peak was observed, along with its modest modifications.

Stability Study

There was no discernible change in either the outward appearance or the degree of flexibility. When the optimised formulation (GRTF8) was put through accelerated stability tests, the results showed that there were no significant shifts in the amount of drug present, the amount

of drug that was released in vitro, or the swelling index. As a result, it was determined that the formulation could withstand repeated uses (the results are provided in table 6).

Table 6: Parameters after accelerated stability study of formulation GRTF8

Parameters	Initial	After 30 days	After 60 days	After 90 days
In Vitro drug release (%)	99.35 ± 1.48	98.43 ± 1.27	98.18 ± 1.23	97.05 ± 1.39
Swelling index	94 ± 1.32	92 ± 1.43	91 ± 1.32	90 ± 1.40
Drug content (%)	99.26 ± 0.45	98.42 ± 0.30	97.86 ± 0.52	97.05 ± 0.28

Values are expressed in mean ± SD (n=3)

Conclusion

In the current investigation, an effort was made to achieve extended drug release in a regulated manner for up to twenty-four hours using trilayered matrix tablets containing ramipril in pill form. Direct compression method using Response surface method where three variables and three levels of polymers of different HPMC K4M, HPMC K15M, and xanthan gum (low, middle, and high concentrations) were used to prepare twelve formulations (ARTF8-HRTF8) for the active layer (middle layer) by using Design of experiment software. These formulations were for the active layer (middle layer). After considering all of the options, RTF8 was selected as the top contender, and extended release trilayered matrix tablets were created by combining different quantities of polymers using the direct compression method. These tablets were then tested. Each and every one of the formulations' physicochemical parameters fell within the acceptable range. Based on the findings of in vitro drug release trials, the formulation GRTF8 was determined to be superior since it allowed for the largest amount of drug to be released within 24 hours (99.35%). After being subjected to accelerated conditions of temperature (40 °C) and humidity conditions (75%RH), the formulation did not show any significant changes in its physico-chemical properties. Therefore, after putting the newly produced formulation to accelerated stability conditions, it was discovered that the formulation was stable. It is possible to draw the conclusion that the extended release trilayered matrix tablets of ramipril formulations might be an original and potentially fruitful strategy to the administration of ramipril for the therapy of hypertension.

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