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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF TICAGRELOR

PATEL JK*, THAKOR J, PATEL D, PATEL VK, PARIKH S AND PATEL R

Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur, Gandhinagar-382610

***Corresponding Author: Ms. Jaini K. Patel: E Mail: pateljainipharma22@gmail.com**

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ABSTRACT

The aim of present investigation was formulation and development of Ticagrelor Sustained Release Matrix Tablets. Study started from the preformulation study of the drug. Drug having good solubility in both dissolution mediums. The flow of API is low so directly compressible excipient used for tablet preparation. While studying IR spectrum, we can conclude that there is no interaction between drug and other excipients. Initially feasibility trials were taken using HPMC K4M and K100M. Tablets were found acceptable in physical parameters evaluation. During drug release evaluation amount of HPMC K4M increases the drug release for long period of time. In contrast less amount of HPMC K100M helps in drug release. So role of polymer concentration is very important in this formulation. Based on that F3 batch found satisfactory and considering for further factorial screening. 3^2 factorial design applied by taking HPMC K4M and PVP K-30 as independent factors. Factorial batch T1-T9 prepared by using direct compression method. Physical and chemical evaluation was done for all batches. PVP K-30 and HPMC K4M significantly impact on Drug release and hence the model found significant. Finally the optimized batch P12 taken based on Contour plot and evaluation done. Batch T12 load for stability for 1 month and found stable. Hence the batch T12 was optimized batch.

Keywords: Ticagrelor, Matrix Tablets, Sustained Release

INTRODUCTION

The controlled drug delivery system is that which delivers the drug at a specific rate locally or systemically for a specified period of time with minimum fluctuation in plasma

drug concentration, reduced toxicity and maximum efficiency. The oral controlled release formulations have been developed for those therapeutic agents that are easily absorbed from the G.I.T, having a shorter half-life, eliminated quickly from the blood circulation, narrow absorption window as these will release the drug slowly into the G.I.T. There are several terms used interchangeably viz. controlled release, programmed release, sustained release, prolonged release, timed release, extended release etc. **[1]**.

Sustained release dosage form is defined as well characterized and reproducible dosage form, which is designed to control drug release profile at a specified rate to achieve desired drug concentration either in blood plasma or at target site. This system will provide actual therapeutic control that would be temporal (time related), spatial (site related) or both. There are several advantages of sustained release drug delivery system such as reduced see-saw fluctuations, total amount of dose decreases, improved patient compliance and increased safety of drugs. The performance of a drug presented as a sustained release system which depends upon its release from the formulation and movement within the body during its passage to the site of action **[2, 3] (Figure 1)**.

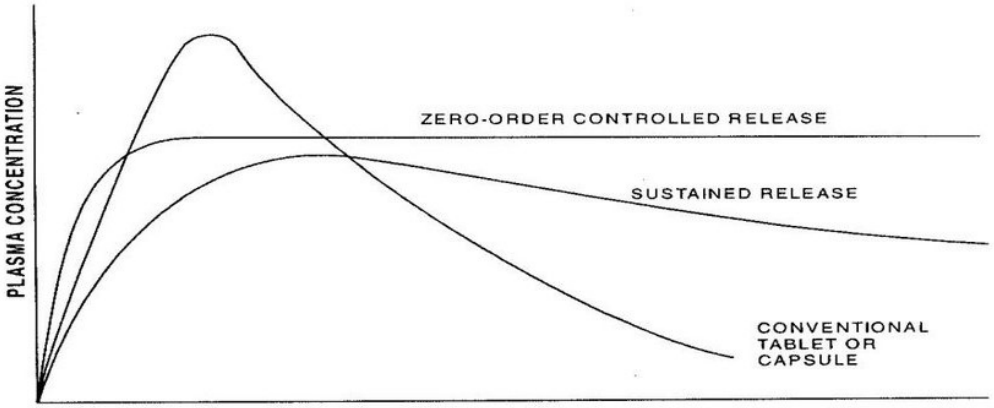

Figure 1: Plasma drug concentration vs. time profile

Ticagrelor is an ADP derivative developed for its P2Y12 receptor antagonism. It is a white crystalline powder. The chemical name of Ticagrelor is (1S,2S,3R,5S)-3-(7-{[(1R,2S)-2-(3,4-difluorophenyl) cyclopropyl] amino}-5-(propylsulfanyl)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol.

The molecular weight of the Ticagrelor is 522.568 g/mol **(Figure 2)**.

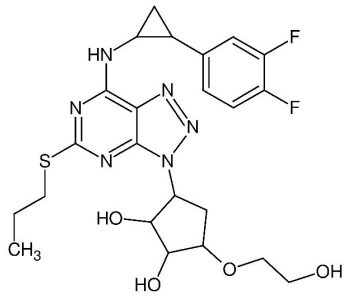

Figure 2: Sturcture of Ticagrelor

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers. CYP3A4 is the major enzyme responsible for ticagrelor metabolism. It is indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12ADP-receptor to prevent signal transduction and platelet activation **[4, 5]**.

MATERIALS AND METHODS [6, 7]

Table 1: List of materials

Sr. No.	Material	Function	Sources of Material
1.	Ticagrelor	API	Torrent Research Centre, Ahmedabad
2.	PVP K30	Binder	ACS Chemicals, Ahmedabad.
3.	HPMC K4M HPMC K100M HPMC K15M	Polymer	ACS Chemicals, Ahmedabad.
4.	Lactose	Diluent	ACS Chemicals, Ahmedabad.
5.	Talc	Glidant	ACS Chemicals, Ahmedabad.
6.	Magnesium Stearate	Lubricant	ACS Chemicals, Ahmedabad.

Preformulation Study

Organoleptic Characteristics:

Check the description by visual observation of the API powder and record the observation.

Flow Properties:

Bulk density and tapped density

Weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V0) was measured. After that by tapping 100 times manually, the volume was checked and calculated from below equation.

Bulk density = W/ V0 Tapped density = W/ VF

Compressibility Index (CI) / Carr's index

Compressibility index (CI) / Carr's index was calculated by using the following formula.

% Carr's index = (T.D. - B.D. /T.D.) × 100

Table 2: Relation between Carr's Index and Flow Property

(Carr's %)	Flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
>40	Very very poor

Hausner's ratio

Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

Hausner's ratio = (Tapped density / Bulk Density)

Angle of repose

Angle of repose of powder was determined by the funnel method. Accurately weight powder was taken in the funnel. Height of the funnel was attuned in such a way the angle of the funnel just touched the apex of the powder. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Table 3: Relation between Angle of Repose (θ) and flow properties

Angle of Repose (Θ)	Flow Properties
<25	Excellent Good Passable Very poor
25-30	
30-40	
>40	

Drug Identification and Drug-Excipients interaction study by FTIR [8]

FTIR studies were carried out to determine the compatibility of excipients with the drug. Pure drug sample and physical mixture of excipients with drug compared by FTIR and check the compatibility.

Determination of λmax and Development of Calibration Curve of Ticagrelor [9]

Standard stock solution of Ticagrelor (100 µg/ml) was prepared by dissolving 10 mg of Ticagrelor in 100 ml using 0.1 N HCl to get a concentration of 100 µg/ml. The prepared solution is sonicated for 10 minutes and filtered through the Whatman No. 41 filter paper. Appropriate volumes of this solution were further diluted to obtain final concentrations in the range of 1 to 10 µg/ml.

The spectrum of this solution was recorded from 200 nm to 400 nm using Shimadzu UV-VIS Spectrophotometer. Same process repeated for 6.8 phosphate buffer.

Dose Calculation

Optimum release profile for twice daily Sustained Release formulation was calculated by the below equation using available pharmacokinetic data.

$$Dt = Dose\ (1+ 0.693 \times t / t\ ½)$$
$$= 60\ (1+0.693\ (12/7))$$
$$= 131.28\ mg \sim 131.3\ mg$$

of Ticagrelor

Where,

Dt = total dose of drug,

Dose = dose of the immediate release part, (60 mg)

t = time during which the sustained release is desired (12 h)

t ½ = half -life of the drug (7 h).

Method of Preparation [10]

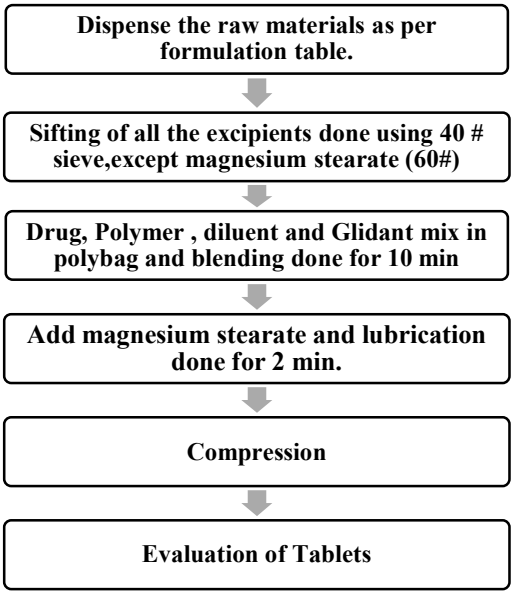

Figure 3: Method of Preparation

Formulation of Ticagrelor Trial Batches

Table 4: Formulation of Ticagrelor F1-F7

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Ticagrelor (1:1)	262.6	262.6	262.6	262.6	262.6	262.6	262.6
Microcrystalline Cellulose (Avicel)	97.4	87.4	77.4	97.4	87.4	77.4	77.4
Lactose (DCL 11)	90	90	90	90	90	90	90
PVPK 30	10	10	10	10	10	10	10
HPMC K4M	30	40	50	-	-	-	25
HPMC K100M	-	-	-	30	40	50	25
Colloidal silicon dioxide	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Magnesium Stearate	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Total	500.0	500.0	500.0	500.0	500.0	500.0	500.0

Based on feasibility trial results, F3 batch which contains 50.0 mg of HPMC K4M gives satisfactory drug release up to 12 hours. Hence F3 batch composition selected for factorial design. Design and formulation of factorial batches are given below **(Table 4, 5)**.

Table 5: Formulation of Ticagrelor factorial batches

Ingredients (mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9
Ticagrelor	262.6								
HPMC K4M	45	45	45	50	50	50	55	55	55
PVPK 30	5	7.5	10	5	7.5	10	5	7.5	10
Microcrystalline Cellulose (Avicel)	87.4	84.9	82.4	82.4	79.9	77.4	77.4	74.9	72.4
Lactose (DCL 11)	90	90	90	90	90	90	90	90	90
Colloidal silicon dioxide	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Magnesium Stearate	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Total	500	500	500	500	500	500	500	500	500

Evaluation of Sustained Release Matrix tablets of Ticagrelor [11, 12]

Weight variation

The weight variation test was conducted by weighing 20 randomly selected tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The specification of weight variation is 10%.

Thickness

The thickness was measured by using digital vernier caliper.

Hardness

The hardness of the tablets was determined by diametric compression using a Hardness testing apparatus. A tablet hardness of about 4-5 kg is considered adequate for mechanical stability. Determinations were made in triplicate.

Friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_0) de dusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

% Friability = $(W_0 - W/ W_0) \times 100$

Drug Content

Tablets were individually finely ground in a mortar. Accurately weighed quantity of the powder tablet equivalent to 131.3 mg of the drug was transferred to 100 ml volumetric flask dissolve in 100 ml 0.1 N HCl Aliquots were filtered and assayed spectrophotometrically (by UV) at 255 nm for drug content.

In-vitro dissolution study

In vitro release studies were carried out for all the formulations as per USP-II tablet

dissolution tester employing rotating paddle at 50 rpm using 900 ml 0.1 N HCl of pH 1.2 for first two hour and phosphate buffer of pH 6.8 for 10 hours as dissolution medium. 5ml aliquot samples were collected at 1 hour interval up to 4 hours and at 2 hours interval up to 12 hours. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 um membrane filter. Absorbance of these solutions was measured at 255 nm using a UV/V is double beam spectrophotometer.

Drug Release Kinetics

The release kinetics will be fitted to different mathematical models like Zero order, First order, Higuchi's and Peppas plot to understand the drug release kinetic of tablets.

Accelerated stability study: Ticagrelor sustained release tablets will be kept for one month and the stability of the tablets will be monitored up to 1 month at accelerated stability conditions (40 ºC temperature and 75 $\pm$ 5% RH). Samples will be removed and characterized by appearance and in-vitro drug release study

RESULTS & DISCUSSION

Preformulation Study Results

From the Results of Preformulation studies of the API, It was concluded that Ticagrelor has poor flow property and compressibility property. So, to improve the flow and compressibility property, it was beneficial to use the directly compressible grade components in the formulation of tablet **(Table 6)**.

Drug Excipient Compatibility Study by FTIR

From the FTIR Study, it was concluded that there was no significant Drug- Excipient interaction was observed. So we can conclude that drug and other excipients are compatible which each other **(Table 7, Figure 4, 5)**.

Calibration curve of Ticagrelor

The calibration curve of Ticagrelor was found to over a concentration range 1-10 µg/ml. (R^2=0.9998) the data for calibration curve is given below in **Table 8**, **Figure 6, 7**.

Evaluation of Ticagrelor factorial batches T1 – T9

Based on trial batches results, 3^2 factorial design is applied to optimize the polymer and binder concentration. Formulation T1-T9 prepared by taking HPMC K4 M and PVP K-30 as independent factors. The results of factorial batches are given in below **Table 9**.

The results were showed in above tables and the inference for the same also listed in

table. Most of the batches have a good to passable flow in nature. Additionally the flow of all batches blend was enough for compression operation. By changing the dry binder and polymer concentration, no major difference observed in bulk density and tapped density parameters.

After completion of Pre compression parameters evaluation, batches T1-T9 compressed as per required weigh and post compression parameters were evaluated for all batches. During compression no any critical observation listed with respect to flow property. The results of post compression parameters were recorded in below **Table 10**.

Based on **Table 10** of post compression parameters, it seems that the weight variation in all batches found well within acceptable limit. The weight variation is within 2% range which was more stringent than the acceptable range. Further the thickness found within range as per desired parameters. Hardness was good enough to give a proper mechanical strength to tablets and hence the friability was observed below 1 %.

Drug release study of factorial batches T1-T9

Drug release study shows the impact of HPMC K4M in formulation. Higher the amount of HPMC retards the drug release and vice versa. It also seems that the amount of PVP K-30 which was used as dry binder also impact on drug release. The actual impacts of both factors analyzed by using factorial design regression study. From the results of drug release study, T7 batch which contains 45 mg HPMC K4M and 10 mg PVP K-30 shows good drug release up to 12 hours which also match the profile with theoretical drug release profile **(Table 11, Figure 8)**.

Drug release kinetic study

To establish the order and mechanism of drug release, dissolution data of the optimized batch (T7) were fitted to different kinetic models, namely, Zero order model, first order model, Hixon crowell, Higuchi model and Korsmeyer peppas model. The model for best fit was predicted from the value of R^2. For an ideal fit, value of R^2 was 1. Hence, the model which gives the R^2 value nearest to 1 describes the order of drug release. The results were shown in below **Table 12**.

From the results of data fitting to various models, it was found that the optimized batch T7 showed zero order drug release.

Validation of Design:

A checkpoint batch was designed accordance to the desirability function, as shown in below table. To assess the validity of prediction, a checkpoint batch T10 and T11 was prepared and evaluated under the same conditions as outlined for the other batches. The response data was compared with that of required data **(Table 13)**.

Optimized batch:

Based on Factorial Design data, final optimized batch selected from the Contour plot to achieve desired drug release. Complete analysis of this batch done and recorded below **(Table 14, Figure 9)**.

Stability Study

Stability study on optimized batch T12 carried out and the results were recorded in below table. Formulation found stable and no any critical observation seen during stability. The results were given in below **Table 15**.

Table 6: Characterization of Ticagrelor

Drug	Angle of Repose (^{0})	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Carr's Index (%)	Hausner's Ratio
Ticagrelor	27.34	0.375	0.516	27.32	1.376

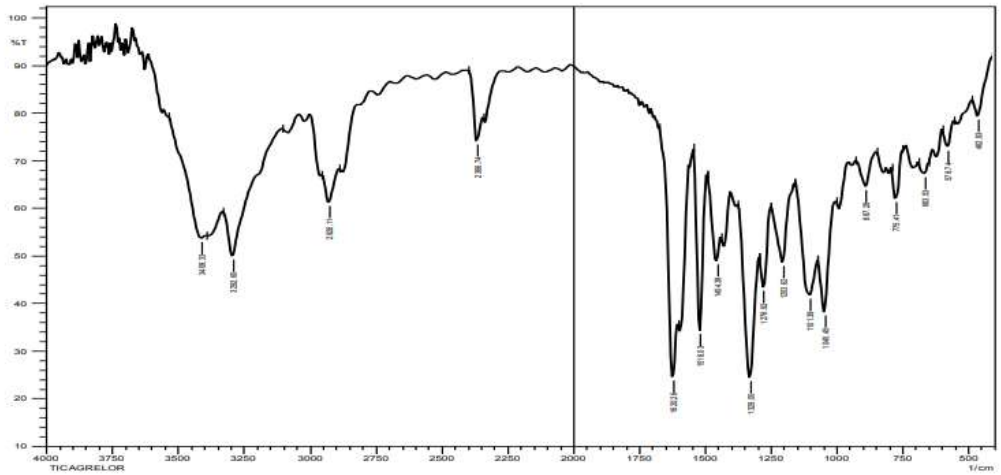

Figure 4: FTIR Spectra of Pure Drug Ticagrelor

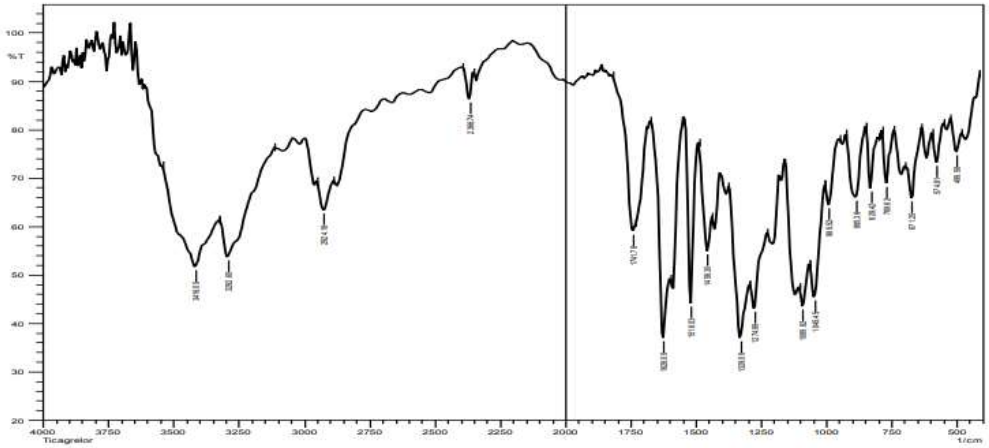

Figure 5: FTIR Spectra of Physical Mixture

Table 7: FTIR Data of Drug and Formulation

Stretching	Pure Drug Peak (cm^{-1})	Formulation Peak (cm^{-1})
C=O	1737	1735
N-H	1629.88	1632.44
C-N	1290.37	1290.12

Table 8: Calibration curve of Ticagrelor

Sr. No	Concentration (µg/ml)	0.1 N HCl	6.8 Phosphate Buffer
		Absorbance ± SD (n=3)	Absorbance ± SD (n=3)
1	0	0	0
2	1	0.073 ± 0.005	0.086 ± 0.001
3	2	0.142 ± 0.004	0.156 ± 0.002
4	3	0.219 ± 0.003	0.243 ± 0.001
5	4	0.290 ± 0.006	0.319 ± 0.002
6	5	0.360 ± 0.004	0.402 ± 0.001
7	6	0.425 ± 0.003	0.478 ± 0.001
8	7	0.499 ± 0.005	0.558 ± 0.002
9	8	0.562 ± 0.001	0.641 ± 0.002
10	9	0.640 ± 0.006	0.725 ± 0.002
11	10	0.723 ± 0.002	0.810 ± 0.001

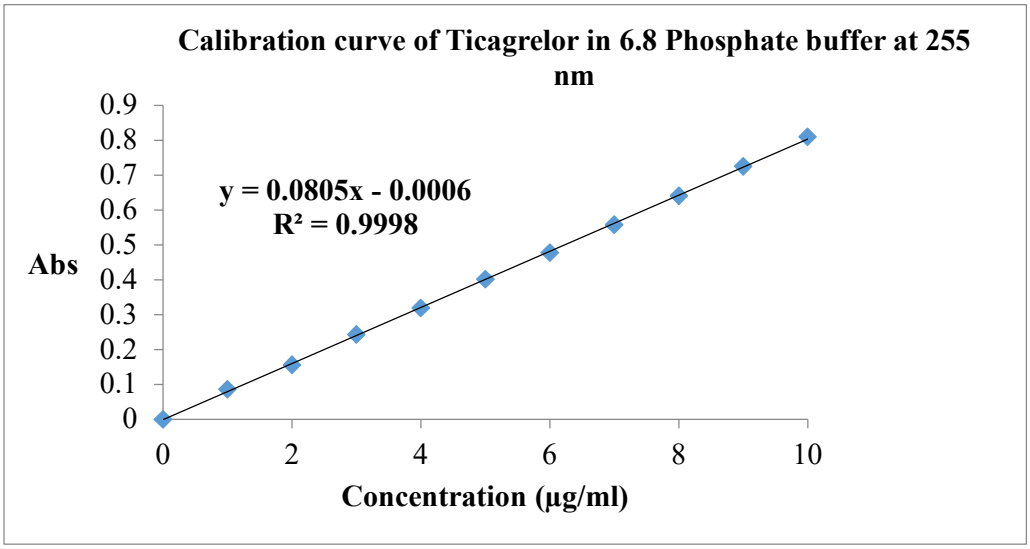

Figure 6: Calibration curve of Ticagrelor in 6.8 Phosphate buffer at 255 nm

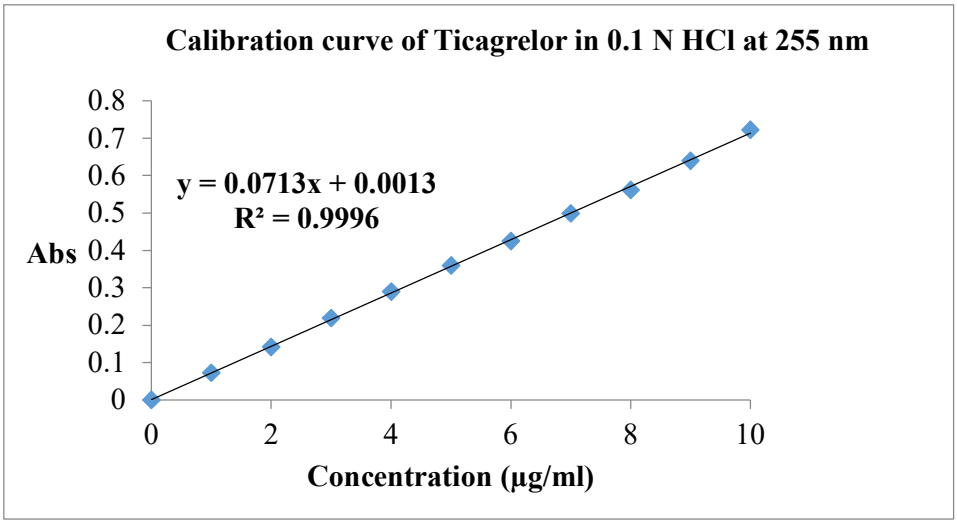

Figure 7: Calibration curve of Ticagrelor in 0.1 N HCl at 255 nm

Table 9: Pre compression parameters of batches T1 to T9

Batch	Bulk density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner Ratio	Angle of Repose (ϕ)	Inference
T1	0.43±0.01	0.49±0.02	12.24±0.05	1.14±0.05	33.50±0.07	Good
T2	0.42±0.02	0.47±0.03	10.64±0.06	1.11±0.04	34.12±0.03	Good
T3	0.40±0.01	0.51±0.04	21.57±0.04	1.28±0.07	42.33±0.05	Passable
T4	0.41±0.03	0.50±0.02	18.00±0.09	1.22±0.03	39.41±0.04	Fair
T5	0.43±0.01	0.49±0.01	12.24±0.03	1.14±0.05	33.92±0.05	Good
T6	0.42±0.02	0.49±0.03	14.29±0.02	1.17±0.03	38.63±0.03	Fair
T7	0.40±0.01	0.53±0.01	24.53±0.07	1.33±0.07	41.52±0.07	Passable
T8	0.41±0.03	0.48±0.03	14.58±0.05	1.17±0.02	37.61±0.06	Fair
T9	0.43±0.02	0.50±0.01	14.00±0.03	1.16±0.02	38.43±0.09	Fair

Table 10: Post compression parameters of batches T1 to T9

Batch code	Weight Variation (mg) (n=10)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	% Friability	% Drug Content (n=10)
T1	499 ± 0.58	3.50 ± 0.16	6.5 ± 1.20	0.55	99.5 ± 0.65
T2	500 ± 0.68	3.45 ± 0.34	7.0 ± 0.89	0.60	98.3 ± 0.60
T3	498 ± 0.98	3.49 ± 0.47	6.8 ± 0.55	0.62	99.4 ± 0.87
T4	497 ± 0.47	3.53 ± 0.31	7.2 ± 0.89	0.40	97.9 ± 0.36
T5	500 ± 0.23	3.64 ± 0.18	6.9 ± 1.20	0.45	98.6 ± 0.47
T6	497 ± 0.34	3.35 ± 0.37	6.4 ± 0.98	0.49	99.2 ± 0.35
T7	500 ± 0.65	3.86 ± 0.34	7.1 ± 1.20	0.52	98.7 ± 0.79
T8	501 ± 0.78	3.36 ± 0.15	6.4 ± 0.98	0.35	97.3 ± 0.15
T9	502 ± 0.85	3.45 ± 0.25	6.9 ± 0.98	0.47	98.1 ± 0.50

Table 11: Cumulative % drug release of factorial batches T1 to T9

Time (hrs)	T1	T2	T3	T4	T5	T6	T7	T8	T9
0	0	0	0	0	0	0	0	0	0
1	32.9±5.9	30.1±4.1	29.4±3.8	28.5±5.1	24.9±3.9	23.8±4.5	26.9±5.5	21.5±1.4	19.0±5.2
2	50.1±1.8	46.9±2.6	41.5±2.4	49.1±3.2	45.2±2.4	41.1±6.4	36.4±4.1	34.9±2.1	30.2±2.8
3	56.9±2.3	51.3±3.1	50.1±2.6	59.6±2.6	56.3±3.1	52.1±1.9	43.2±2.8	39.7±3.4	35.4±3.6
4	68.4±3.4	65.4±2.9	61.9±1.9	66.3±1.6	61.2±2.4	56.4±2.1	50.4±1.6	46.7±2.6	41.9±2.1
6	74.6±2.1	70.9±1.8	68.2±1.7	73.9±3.4	70.3±1.9	66.9±3.4	62.5±2.3	60.3±2.9	56.8±1.3
8	82.9±2.5	78.2±3.2	74.1±3.4	79.5±2.6	78.6±3.5	76.2±2.4	75.6±2.6	74.1±1.8	71.3±1.1
10	93.5±0.9	93.0±0.9	91.5±2.8	93.9±0.9	87.5±0.9	90.4±2.1	86.4±0.9	82.3±3.4	79.5±1.0
12	99.9±0.4	99.9±0.4	99.8±0.9	99.9±0.4	98.4±0.3	99.1±0.9	98.5±0.4	94.5±0.9	89.4±0.5

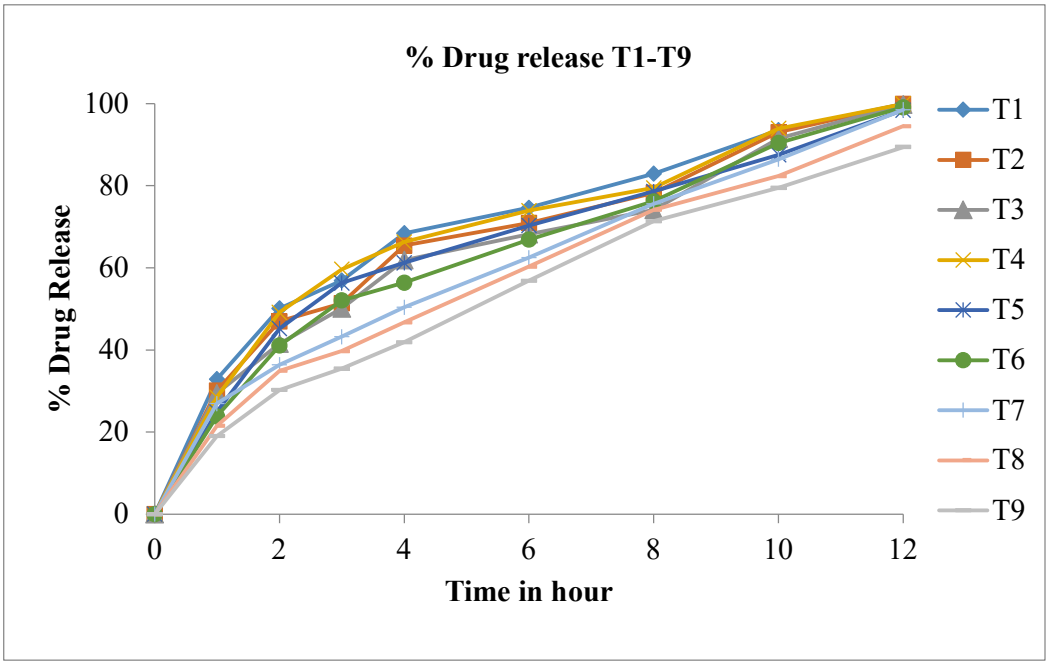

Figure 8: Drug release study of factorial batches T1 to T9

Table 12: Drug release kinetic study of T7 batch

Formulation Code	R^2				
	Zero Order	First Order	Higuchi model	Korsmeyer Peppas model	Hixon crowell
T7	0.998	0.975	0.994	0.997	0.925

Table 13: Check point batch

Batch	Amount of PVP K-30 (mg)	Amount of HPMC K4M (mg)	% Drug release in 2 hours			% Drug release in 8 hours		
			Predicted	Observed	% Bias	Predicted	Observed	% Bias
T10	7.40	50.61	41.55	42.30	1.02	76.28	75.30	1.01
T11	5.26	45.76	50.87	48.90	1.04	80.82	81.54	1.00

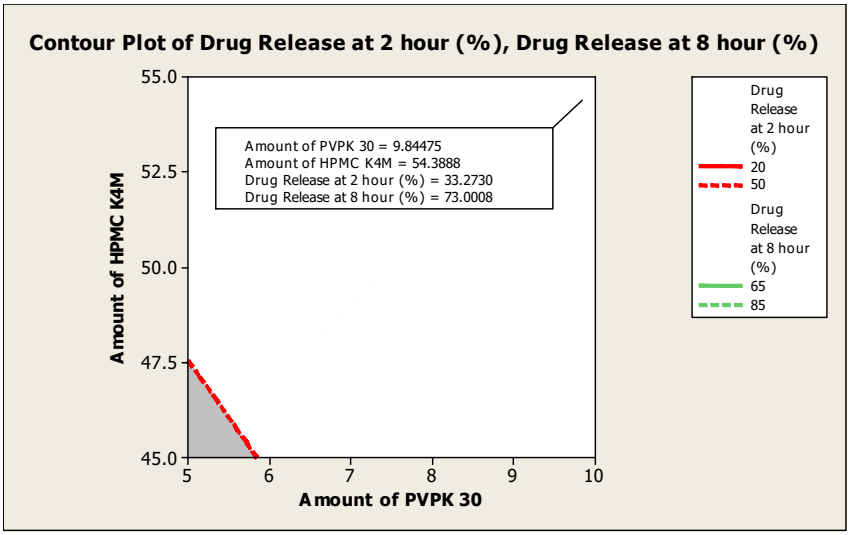

Figure 9: Overlay plot of optimized batch

Table 14: Composition of Optimized batch formulation (T1)

Ingredients (mg)	P12
Ticagrelor	262.6
Lactose (DCL 11)	90
Microcrystalline Cellulose (Avicel pH 102)	73.1
PVP K-30	9.8
HPMC K4M	54.4
Colloidal silicon dioxide	5.0
Magnesium Stearate	5.0
Total	500.0

Table 15: Optimized batch T12

Physical parameter	Initial	1 Month
Appearance	White coloured, round tablet	White coloured, round tablet
Average Weight (mg)	500 ± 2.8	500 ± 1.9
Thickness (mm)	3.75 ± 0.6	3.75 ± 0.9
Hardness (kg/cm^2)	6.9 ± 0.9	7.0 ± 0.6
Friability (%)	0.45	0.49
% Drug Content	99.3 ± 0.8	99.1 ± 0.5
% Drug release after 12 hours	99.5 ± 1.9	98.9 ± 2.6

Table 16: stability study

Parameter	Results	
Appearance	White coloured round shape tablet plain on both side	
Average weight (mg)	500 ± 2.8	
Thickness (mm)	3.75 ± 0.6	
Hardness (kg/cm^2)	6.9 ± 0.9	
Friability (%)	0.45	
Drug content (%)	99.3 ± 0.8	
% Drug Release	Time (hour)	%Drug Release
	0	0
	1	25.7 ± 0.4
	2	33.1 ± 1.7
	3	40.1 ± 1.1
	4	47.0 ± 2.1
	6	60.8 ± 0.4
	8	72.9 ± 0.9
	10	86.8 ± 1.2
	12	99.5 ± 1.9

CONCLUSION

The aim of present investigation was the formulation and development Ticagrelor Sustained Release Matrix tablets. Study started from the preformulation study of the drug. Drug having good solubility in both dissolution mediums. Also the flow of API is low so directly compressible excipient used for tablet preparation. While studying IR spectrum, we can conclude that there is no interaction between drug and other excipients. Initially feasibility trials were taken using HPMC K4M and K100M. Tablets were found acceptable in physical parameters evaluation. During drug release evaluation amount of HPMC K4M increases the drug release for long period of time. In contrast less amount of HPMC K100M

helps in drug release. So role of polymer concentration is very important in this formulation. Based on that F3 batch found satisfactory and considering for further factorial screening. 3^2 factorial design applied by taking HPMC K4M and PVP K-30 as independent factors. Drug release at 2 hours and 8 hours considered the dependent factors. Factorial batch T1-T9 prepared by using direct compression method. Physical and chemical evaluation was done for all batches. Drug release study for T1-T9 batch shows the significant impact of both factors. PVP K-30 and HPMC K4M significantly impact on Drug release and hence the model found significant. Finally the optimized batch T12 taken based on Contour plot and evaluation done. Batch T12 load for stability for 1 month and found stable. Hence the batch T12 was optimized batch.

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