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Formulation and Evaluation of Sustained Release Matrix Tablets of Tricagrelor

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ABSTRACT: The aim of present investigations was formulation and development of Ticagrelor sustained Release matrix tablets study started from the preformulation study of the drug. The drug have a good solubility in both discussions mediums. The flow of the API is low so it is directly compressible excipients used for tablet preparations. While studying IR spectrum, we can conclude that there is no direction between drug and other excipients. Tablets were found acceptable in physical parameters evolution. Initially feasibility trials were taken using HPMC K4M and K100M.The invention provides a ticagrelor sustained-release tablet system and a preparation method of the ticagrelor sustained-release tablet system. The preparation method comprises the following steps of: firstly uniformly mixing 10-60% of ticagrelor, 5-60% of a filler and 5-60% of high molecular polymer in percentage by weight, adding a granulating solution to granulate; fully drying the obtained granules at a temperature of 50-60 DEG C, uniformly mixing the sieved granules with 0.25-10% of a lubricant and/or 0-10% of a flow aid, carrying out tabletting to obtain the ticagrelor matrix type sustained-release tablets, wherein the granulating solution is preferably water, an alcohol-water solution or absolute ethyl alcohol; the granule size of the ticagrelor is below 100 micrometers; and the content of the ticagrelor is 50-300mg in the preparation process. The ticagrelor matrix type sustained-release tablet system provided by the invention has the advantages that a patient can take the ticagrelor once a day to ensure that the drug dependence of the patient can be improved and the risk of myocardial infarction or apoplexy caused by acute thrombosis due to a dose of the ticagrelor missing of the patient is reduced.

Keywords- Bioavailability, matrix, sustained release, histology, rabeprazole

I. INTRODUCTION

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.

Sustained release drug delivery system:

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal tract. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion. Plasma drug concentration-profiles for conventional tabletor capsule formulation, a sustained release formulation, and a zero order sustained release formulation.

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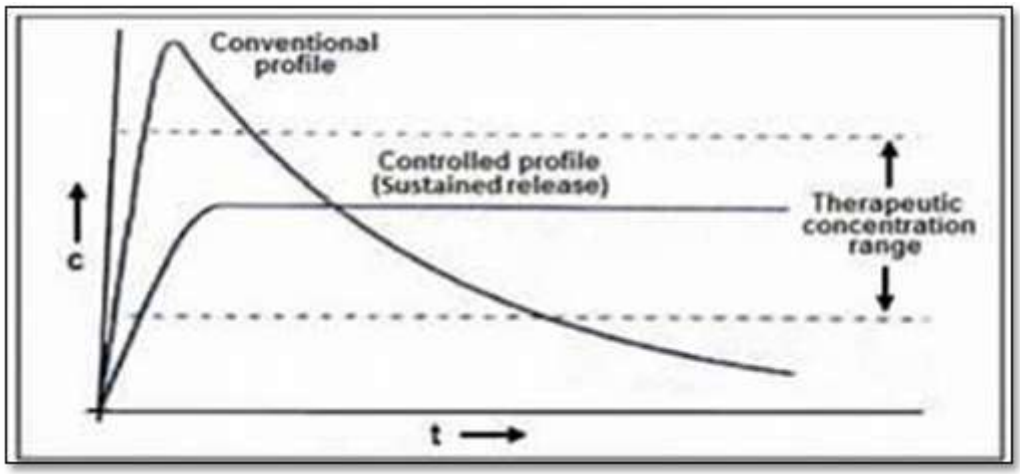

Fig1:Plasma Concentration-profiles Vs Time(sustained release formulation and zero order formulation)

Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval.

➢ **Advantages Of Sustain Release Dosage Forms:**

- Reduction in frequency of in takes.
- Reduce side effects.
- Uniform release of drug overtime.
- Better patient compliance.

➢ **Disadvantages Of Sustained Release Drug Delivery**

- Increased cost.
- Toxicity due to dose dumping.
- Unpredic table and often poor in vitro-in vivo correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Increased potential for first-pass clearance.

Need for additional patient education and counselling. Characteristics of drugs unsuitable for oral sustained release forms:

- Not effectively absorbed in the lower in testinee. g.riboflavin, ferroussalts.
- Absorbed and excreted rapidly; short biologic half-lives (< 1hr) e.g. penicillin G, furosemide.
- Long biologic half-lives (>12hr.) e.g.diazepam, phenytoin
- Large doses required (>1g)e.g. Sulphonamides.
- Cumulative action and undesirable side effects; drugs with low the rapeutic indices e.g. phenobarbital, dig toxin.
- Precise dosage titrated to individualis requirede.g. anticoagulants, cardiac glycosides.
- No clear advantage for sustained release for mulation e.g. Griseofulvin.

A) Diffusion and Dissolution Controlled System.

In a bio erodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack.

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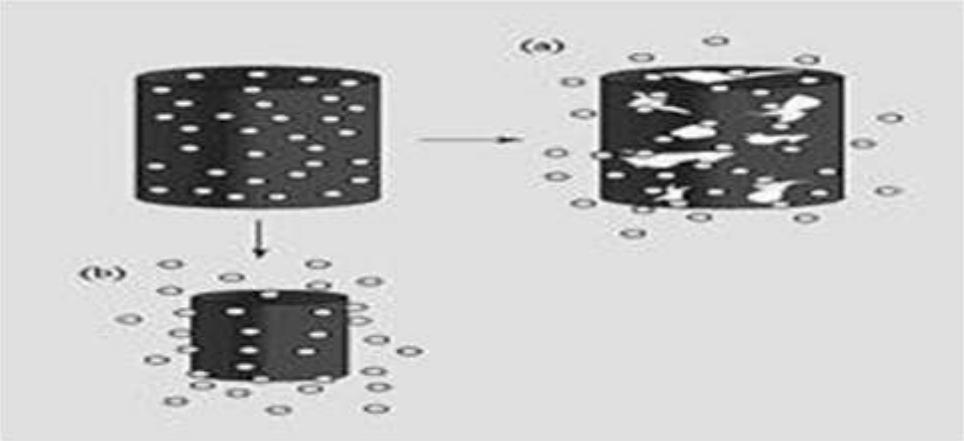

Fig2: Drug delivery from(a) bulk-eroding and(b) surface-eroding Bio erodible systems

The classification of the matrix-based systems is based on the following criteria.

- Matrix structure
- Release kinetics
- Controlled release properties (diffusion, erosion and swelling).
- Chemical nature and the properties of the applied release retardant(s).

Based on the chemical nature of the release retardant(s), the matrix systems are classified as given in Table 1.

Type of the Matrix System	**Mechanism**
Hydrophilic	• Unlimited swelling delivery by diffusion • Limited swelling controlled delivery • e.g.: Hydroxypropyl methyl cellulose
Inert	• Inert in nature • Controlled delivery by diffusion • e.g.:Ethyl cellulose
Lipidic	• Delivery by diffusion & erosion • e.g.: Carnaubawax
Biodegradable	• Nonlipidic nature • Controlled delivery by surface erosion
Resin Matrices	• Drug release from drug-resin complex • e.g.: Ionex change resins

Advantages Of Matrix Tablet

- Easy to manufacture
- Versatile, effective and low-cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain the rapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improvement the bioavailability of some drugs.

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- Improvement of the ability to provide special effects.
- Ex: Morning relief of arthritis through bed time dosing.

Derivation of the mathematical model to describe this system involves the following assumptions:

1) A pseudo-steady state is maintained during drug release.
2) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
3) The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation:
$dM/dh = C0.dh - Cs/2$ (i)

Where,
dM= Change in the amount of drug released per unit area.

dh=Change in the thickness of the zone of matrix that has been depleted of drug. C0 = Total amount of drug in a unit volume of matrix.

Cs=Saturated concentration of the drug within the matrix. Additionally, according to diffusion theory:
$dM = (Dm.Cs/h)\,dt$. (ii)

Where,
Dm = Diffusion coefficient in the matrix. h=Thickness of the drug-depleted matrix.
dt = Change in time.
By combining equation(i) and equation(ii) and integrating:
$M = [Cs.Dm(2C0 - Cs)t]1/2$ (iii)

When the amount of drug is in excess of the saturation concentration then: $M = [2Cs.Dm.C0.t]\ 1/2$ (iv)

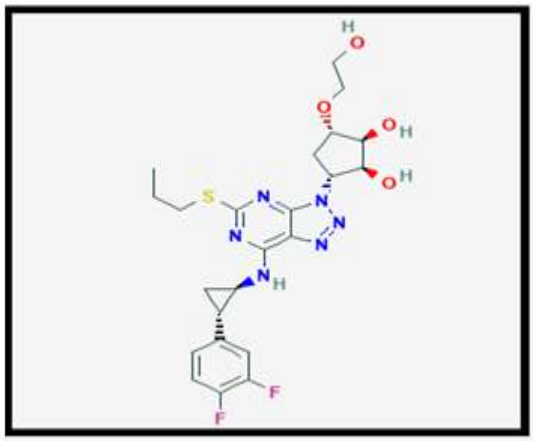
Equation (iii) and eq. (iv) relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from aporous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:
$M = [Ds.Ca.p/T.(2Co - p.Ca)t]1/2$ (v)
Where,
p =Porosity of the matrix
t = Tortuosity
Ca = solubility of the drug in the release medium
Ds=Diffusion coefficient in the release medium. T = Diffusional path length

For pseudo steady state, the equation can be written as:
$M = [2D.Ca.C0(p/T)t]1/2$ (vi)
The total porosity of the matrix can be calculated with the following equation: $p = pa + Ca/\rho + Cex/\rho ex$ (vii)

Where,
p =Porosity
ρ=Drug density
pa = Porosity due to air pockets in the matrix ρex = Density of the water soluble excipients
Cex=Concentration of water soluble excipients
For the purpose of data treatment, equation (vii)can be reduced to:
$M = k.t1/2$ (vii)
Where,
k =constant.
So the amount of drug released versus the square root of time will be line ar, if the release of drug from matrix is diffusion controlled

Drug profile:
TICAGRELOR:

➢ **Structural formula:**



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➢ **Brand name:**
Brilianta

➢ **Drug class:**
P2Y12 plate let in hibitor

➢ **CAS Number:**
274693-27-5

➢ **IUPAC Name:**
(1S,2S,3R,5S)-3-[7-[[(1R,2S)-2-(3,4-difluorophenyl) cyclopropyl] amino]- 5-propylsulfanyltriazolo [4, 5-d] pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1, 2-diol

➢ **Molecular formula :**
C23H28F2N6O4S

➢ **Appearance:**
White to off-white crystalline powder

➢ **Solubility:**
Solubility in water: approximately 10ug/Ml

➢ **Melting point:**
140-142°C

➢ **Pharmacokinetic profile:**

- Absorption: The mean absolute bioavailability of ticagrelor is about 36%, (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor Cmax, but resulted in a 21% increase in AUC. Absorption of ticagrelor occurs with a median Tmax of 1.5 h (range 1.0-4.0) Ticagrelor can be taken with or without food.

- Distribution: The steady state volume of distribution of ticagreloris 88
  L. Extensively bound to human plasma proteins (>99%).

- Metabolism: CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors.
- Elimination: The primary route of ticagrelor elimination is hepatic metabolism. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean t1/2 is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

POLYMER PROFILE:

i. Hypromellose:

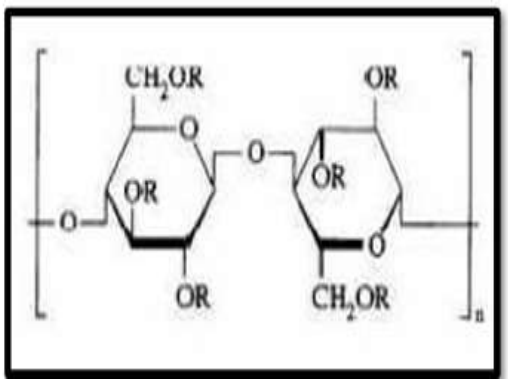
➢ **Nonproprietary Names:**
BP: Hypromellose
JP: Hydroxypropylmethyl cellulose Ph Eur: Hypromellosum
USP: Hypromellose

➢ **Synonyms:**
Benecel MHPC; E464; hydroxypropylmethyl cellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

➢ **Chemical Name and CAS Registry Number:**
Cellulose hydroxypropylmethyl ether

➢ **Empirical Formula and Molecular Weight:**
The PhEur 2005 describes hypromellose as a partly Omethylated and O-(2- hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 208C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group(OCH3).These condtwodig its refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH (OH) CH3), calculated on a dried basis. Molecular weight is approximately 10 000–1 500 000.

➢ **Structural Formula:**



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➢ **Functional Category:**

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

II. MATERIALS AND METHODS

LISTOF MATERIALS:

SR.NO.	MATERIALS
1	Ticagrelor
2	HPMCK100 M
3	Xanthangum
4	Microcrystalline cellulose
5	Magnesium tea rate
6	Talc

1.1 LIST OF EQUIPMENT/ INSTRUMENTS:

SR.NO.	INSTRUMENTS
1	Electronic analytical balance
2	Sieve no 40
3	Tablet compression machine
4	Tablet hardness tester
5	Friability test apparatus
6	Tablet dissolution tester
7	FTIR spectrophotometer
8	UV-Visible spectrophotometer
9	Digital Ph meter
10	Sonicator
11	Hotair oven
12	Water distillation unit
13	Stability chamber

III. RESULT AND DISCUSSION:

1.1 Determination of λ max of Ticagrelor:

The λ max of the ticagrelor was found to be254 n min methanol and acetonitrile.

1.2 Calibration curve of ticagrelor:

The absorbance of ticagrelor was measured in a UV spectrophotometer at 254 nm against methanol and acetonitrile as blank. The absorbance obtained was tabulated (table no.) and graph was obtained by plotting absorbance Vs concentration(figure no.).

Table no.7 calibration curve

Sr.no	Concentration(µg/ml)	Absorbance at 254 nm
1	**2**	**0.0738**
2	**4**	**0.1548**
3	**6**	**0.2359**
4	**8**	**0.3345**
5	**10**	**0.4301**

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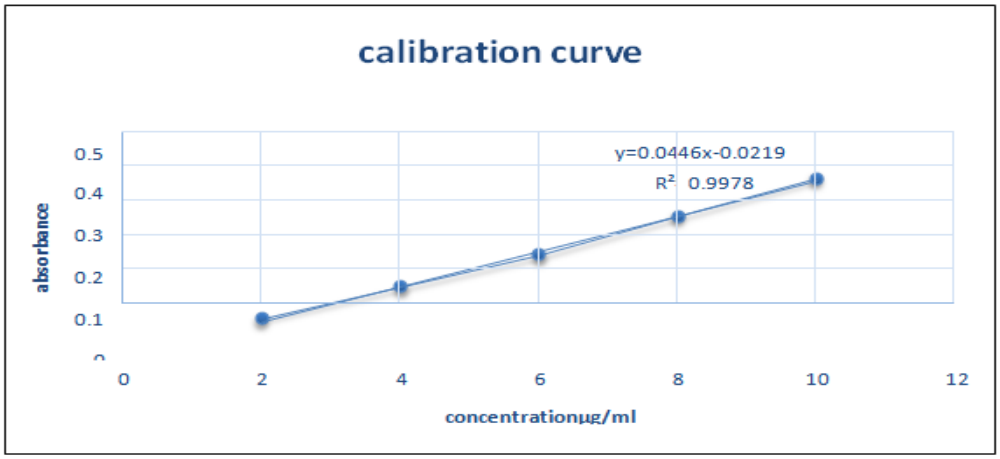

1.3 Compatibility studies using FT-IR:

All the characteristic peaks of ticagrelor were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. From the results, it was concluded that there was no interference of the functional group as the principle peaks of the ticagrelor were found to be unaltered in the drug- polymer physical mixtures, indicating that they were compatible chemically. The spectrum confirmed that there is no significant change in the chemical integrity of the drug. agents are most commonly prescribed: acetylsalicylic acid (aspirin), P2Y12 receptor

Compatibility study

ingredient	(O-H) s	(N-H)s	(C=C)s	(C=N)s	(N=N)s	(C-F)s
Drug	3435.86	3280	1620	1585	1519	1270
Drug+HPMC						
mixture						

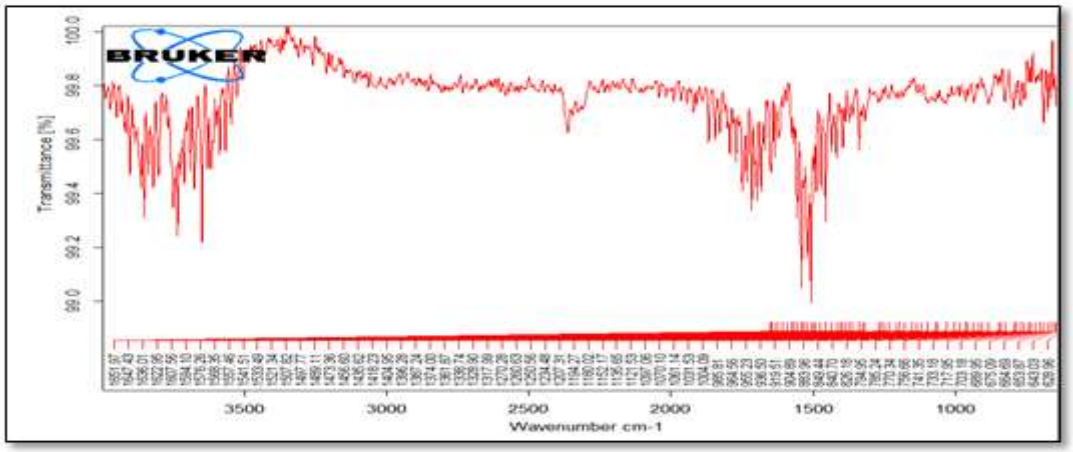

Figure: IR Spectrum of ticagrelor

FORMULATION DESIGN:

The main aim of present study was to formulate sustain release matrix tablets of ticagrelorusingHPMCK-100 Minor der to improve it's the rapeutic efficacy and decrease the adverse effects by minimizing the dosing frequency.

Evaluation Parameters:

Evaluation of powder blended characteristics of matrix tablet formulation of ticagrelor For each type of formulation, blends of ticagrelor and other excipients were prepared and evaluated for various parameters such as bulk

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density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose. Bulk density was found in the range of 0.3420 to 0.3844 g/cm3 and the tapped density between 0.3881to 0.4221 g/cm3 indicating both parameters were found to be within the limits. Using the above two density data, Carr's compressibility index were calculated. The compressibility index and Hausner's ratio was found in the range of 9 to 24 % and 1.1 to 1.3 respectively indicating that all powder blends showed excellent to acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found in the range 27.02to 32.36 the results of angle of repose showed all powder blends exhibited well to acceptable flow property. The results of pre-compression parameters are shown in table no. 9

Table no.9 pre-compression parameter

Formulations Number	Bulk Den sity (gm/cc)	Tapped De nsity (gm/cc)	Carr' sIndex (%)	HausnrRatio	Angleof Repose (θ)
F1	0.3420	0.45	24	1.33	27.02
F2	0.3425	0.3881	11.85	1.134	29.55
F3	0.3844	0.4220	19.36	1.097	31.19
F4	0.3649	0.4020	9	1.100	28.63
F5	0.3550	0.4660	23.20	1.31	32.36
F6	0.3720	0.4120	21.60	1.10	27.58

Physical evaluation of tablets:

After compression various quality control tests were carried out, which demonstrated following organoleptic properties viz. color, odor and shape. All formulations (F1 to F6) were found to be white in color, odorless and concave round flat with break-line on one side.

Tableno.10 physical evaluation of tablet

Formulation code	Color	Odour	Shape
F1	White color	Odour less	Concave, round and flat with break-line on oneside
F2	White color	Odour less	Concave, round and flat with break-line on one side
F3	White color	Odour less	Concave, round and flat with break-line on one side
F4	White color	Odour less	Concave, round and flat with break-line on One side
F5	White color	Odour less	Concave, round and flat with break-line on one side
F6	White color	Odour less	Concave, round and flat with break-line on one side

Tableno.11Post-compression parameters results

Formulation	Thickness (mm)±SD	Weightvariation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug conte nt(%)
F1	4.2	350.12	6.2	0.521	101.2
F2	4.6	352.78	6.9	0.698	97.56
F3	5.2	348.16	6.8	0.832	99.54
F4	4.8	349.66	8.2	0.632	102.36
F5	5.3	346.79	7.8	0.885	98.63
F6	5.7	351.24	6.4	0.755	100.2

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Post compression parameter:

- Thickness of tablets
- Hardness
- Friability
- Weight Variation
- Drug content

- **Thickness of tablets:** All the formulations were evaluated for their thickness using "Vernier callipers" as per procedure in methodology and the results are shown in table no. The average thickness for all the formulations was found in the range of 4.2 to 5.4 mm which is within the allowed limit of deviation i.e. 5% of the standard value.
- **Hardness:** Tablet hardness is one of the critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before its administration. All the controlled release matrix tablet formulations of ticagrelor were evaluated for their hardness as per procedure in methodology and the results were dissipated in table no 11Hardness test was performed by "Monsan to hardness tester". All the formulations have an average hardness in between 6.2 to 8.4 kg/cm2. This ensures good handling characteristics of all formulation batches.
- **Friability:** Friability is determined to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. Friability of prepared tablets was determined by using "Roche friabilator". The entire controlled release matrix tablet formulations were evaluated for their percentage friability and the results are shown in table no.11 The average percentage friability for all the formulations was found in between 0.55 to 0.88% to ,which is found within the pharmacopoeia limit (i.e. lessthan1%).

Table In vitro drug release

Time (Hrs)	Percentage Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	19.50	18.12	21.10	14.92	21.79	12.86
2	30.03	27.05	33.23	24.08	33.23	21.79
4	41.47	38.72	41.24	32.77	41.93	26.82
6	53.37	49.71	51.77	44.90	54.52	38.95
8	64.81	57.72	66.19	57.95	65.27	49.25
10	70.08	67.10	74.66	63.44	76.94	57.03
12	76.94	72.14	87.24	72.08	87.47	64.09
14	87.70	79.23	95.48	85.63	96.86	70.99
16	95.25	84.50		90.45		78.55
18		90.45		96.86		87.47
20		96.86				92.28

Table: In-vitro drug release profile of ticagrelor sustain release matrix tablets

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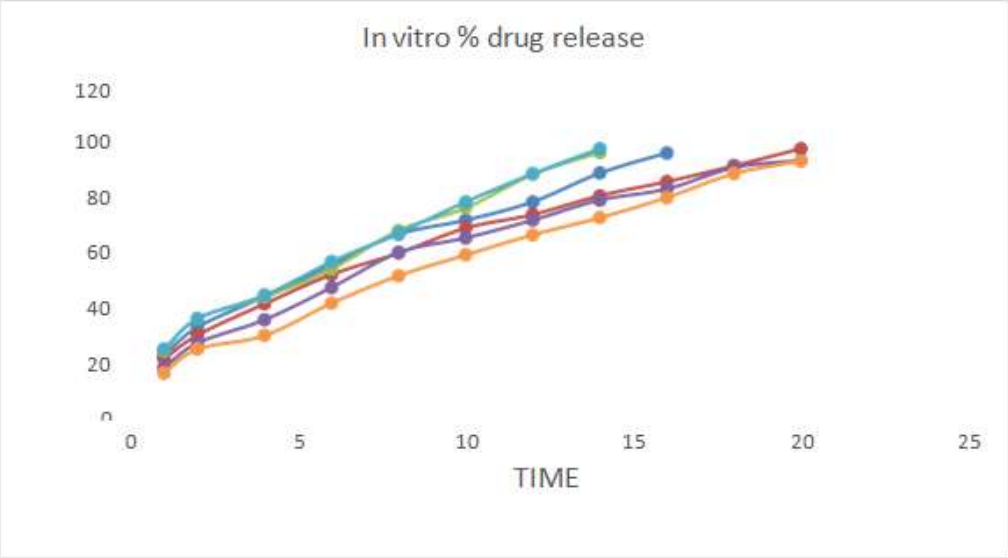

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