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Formulation and Characterization of Time Release Press Coated Tablet of Rabeprazole Sodium for Treatment of Peptic Ulcer

Shivanee Yadav[1]*, Mr. Harikrishna Yadav[2], Dr. Nidhi Tyagi[3], Dr. Prashant Kumar Katiyar[4]

[1]*Research Scholar, Kanpur Institute of Technology and Pharmacy, Kanpur, UP
[2]Assistant Professor, Kanpur Institute of Technology and Pharmacy, Kanpur, UP
[3]Professor, Kanpur Institute of Technology and Pharmacy, Kanpur, UP
[4]Professor & Director, Kanpur Institute of Technology and Pharmacy, Kanpur, UP

Corresponding author: Shivanee Yadav[1*]
Research Scholar, Kanpur Institute of Technology and Pharmacy, Kanpur, UP

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ABSTRACT:

The present work was designed to develop pulsatile drug delivery system of Rabeprazole sodium. The Rabeprazole sodium degraded in acidic media of stomach and hence, reduced bioavailability. So, the core tablet containing drug and other excipients were press coated and enteric coated to protect and delay the drug release before the time as per the need of Chronomodulateddrugdeliverysystem.Presscoatingwasperformedwithdifferentgradesof HPMC and EC and ratios. The press coated tablets were optimized by the drug release study and finally 7:1 ratio of EC and HPMC K-4M was selected as optimized ratio. This press coated tablet was further enteric coated with Cellulose acetate phthalate (CAP) using PEG- 400 as plasticizer and acetone as solvent. The weight gain of enteric coating was optimized based on integrity of coating in acidic solution for about 2 hours. The 10 % weight gain was finally selected.Theoptimized formulation F21 showed drugreleasefrom 270 minutes,with rupturetime120minutes,hardness5.23±0.25kg/cm^{2}andaveragediameterof10.2±0.10mm. It revealed 95.4% drug release in about 7 hours. The optimized formulation was passed in weight variation as per Indian Pharmacopoeia.

Keywords: Rabeprazole sodium, formulation, press coated tablet,drug release, characterization.

1. INTRODUCTION

Itisused toprotect hygroscopic,light-sensitive, oxygenlabile oracid-labile drugs. Thesearerelatively simpleand cheap. Thesecaninvolvedirectcompressionofboththecoreandthecoat. Materials such as hydrophobic, hydrophilic can be used in press-coated pulsatile drug delivery system [1][2]. Itinvolvescompressionwhichiseasyonlaboratoryscale. Theseformulationsreleasedrugafter"lag-time". These formulations can be used to separate incompatible drugs from each other or to achieve sustained release [3][4].

Rabeprazole sodium is a substituted benzimidazole. Benzimidazoles are anti-ulcerouscompounds knownfordecreasinggastricacidsecretion.Thesecompounds,also known as Proton Pump Inhibitors (PPI) are commonly indicated for the treatment of Gastric ulcer, Peptic ulcer, Duodenal Ulcers, Erosive or Ulcerative GERD (Gastro Esophageal reflux Disease), Symptomatic GERD, PathologicalHypersecretory conditions (Zollinger - Ellison). Rabeprazole sodium is very soluble in water and in alkaline media. The stability of Rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions [5][6]. The degradation is catalyzed by acidic reacting compounds and PPIs are usually stabilized in mixtures with alkaline reacting compounds. Therefore, exposure of Rabeprazole sodium to the acidic content of the stomach would lead tosignificant degradation of the drug and hence, reduced bioavailability [6]. Delayed releasedosage form is best formulations which are used for drugs that are destroyed in the gastric fluids, or cause gastric irritation, or are absorbed preferentially in the intestine [7]. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer. The current research was based on the formulation and characterization of time release press coated tablet of Rabeprazole sodium for treatment of peptic ulcer [8][9]."

2. MATERIALS AND METHODS

Chemicals requirements

Table 1. Chemicals requirements

Materials used	Manufactured by
Rabeprazolesodium	Sheronpharmaceutical,dehradun
Lactose	Sd-finechem.Limited,Mumbai
Magnesium stearate	TitanbiotechLimited
Talc	LobaChemiePvt.Ltd. Mumbai
Microcrystallinecellulose(ph101)	Sd-finechem.Limited,Mumbai
PEG400	Sd-finechem.Limited,Mumbai
Croscarmelosesodium	LobaChemiePvt.Ltd. Mumbai
Ethyl cellulose	LobaChemiePvt.Ltd. Mumbai
Celluloseacetatephthalate	E-Merck
Starchpaste	E-Merck
HydroxyPropylMethylCellulose	Yarrowchem..products,Mumbai
Ethanol	RankamlaboratoryPvt.Ltd.
Methanol	RankamlaboratoryPvt.Ltd

Acetone	RankamlaboratoryPvt.Ltd
Sodium hydroxide	Labchemindustries. Mumbai
Potassiumdi hydrogen phosphate	Sd-finechem.Limited,Mumbai
Distilled water	Milliporewater purifier
Hydrochloric acid	E-Merck
Isopropyl alcohol	Labchemindustries. Mumbai

PREFORMULATIONSTUDIES [10][11]

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included important physico-chemical properties of drug and its solubility, stability and drug excipients compatibility study.

DeterminationofMeltingPoint

Melting point of rabeprazole sodium was determined by capillary method. Fine powder of rabeprazole sodium was filled in glass capillary tube (previously sealed at one end). The capillarytubewastiedtothermometerandthethermometerwasplacedin theThaistubeand this tube was placed on fire. The powder at what temperature it melted was noticed.

SolubilityStudies

The solubility of Rabeprazole sodium was determined in distilled water, acetone, methanol, ethanol, chloroform and ethyl acetate and different buffer, viz 0.1NHCl, pH 6.8 and pH 7.2 phosphate buffers.

PreparationofStandardCurveofRabeprazoleSodium

In different solvent like Distilled Water, Phosphate Buffer pH 6.8 And 0.1 N HCl standard curve was prepared. 100 mg of rabeprazole sodium was weighed accurately and dissolved in solvent. The volume of solution was made up to 100 ml. The solution was marked as stock solution-I, the 10ml of stock one was taken and volume of solution was made up to 100ml (stock-II).

1) From stock-II, dilution having concentration 1µg/ml, 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, 14µg/ml, 16µg/ml, 18µg/ml and 20µg/ml were prepared.
2) Above prepared solution were observed in double beam UV- Spectrophotometer (Shimadzu, Model No.1700) to measure the absorbance, in increasing order of concentration.

SELECTION OF PREPARATION TECHNIQUE OF RABEPRAZOLE SODIUM CORE TABLETS

1. Directcompression method
2. Wetgranulation Method:

Selected method WetGranulation

Drug along with other excipients, such as, diluents, binding agent and a part of disintegrating agent are moistened with a sufficient quantity of granulating agent in order to make acoherent mass. The coherent mass is then passed through sieve. If the maas sticks to the wire of the sieve it indicates over moistening. The wet granules are spread in trays and dried at 60˚c in a hot air oven. The dried granules are passed through again sieve to collect the granules of uniform size. The lubricating agents are mixed to these granules. And tablet compressed with cadmach (16 stations).

TableNo. 2. FormulationsofCoreTabletsof RabeprazoleSodium

Ingredient	**Formulationcode**			
	F1	**F2**	**F3**	**F4**
Rabeprazolesodium	**20**	**20**	**20**	**20**
MicrocrystallinecellulosepH101	**75**	**70**	**65**	**55**

Starchpaste(5%)	**q.s**	**q.s**	**q.s**	**q.s**
Lactose	**-**	**-**	**-**	**15**
Crosscarmellosesodium	**-**	**5**	**10**	**5**
Talc	**3.5**	**3.5**	**3.5**	**3.5**
Magnesium stearate	**1.5**	**1.5**	**1.5**	**1.5**
Total(mg)	**100**	**100**	**100**	**100**

SELECTIONOFPOLYMER/EXCIPIENTS

Polymers were selected on the basis of their solubility, release retention ability. Selected polymers are as follows:

TableNo. 3. Selectionof Polymer

S. No.	**Polymers**
1	MicrocrystallinecellulosepH101
2	Crosscarmellosesodium
3	Ethyl cellulose
4	HPMCK4M
5	CAP
6	PEG400

PRESS COATED TABLETS

Compression-coating presents an attractive alternative to spray-coating techniques for high molecular weight polymers. Thick coatings can be applied rapidly and it is a solvent-free coating process Compression-coating has been used in the pharmaceutical field for different purposes:

(1) Toprotecthygroscopic, light-sensitive,oxygen-labile oracid-labile drugs;
(2) To modify a drug release pattern (delayed, pulsatile and programmable release of different drugs in one tablet
(3) Various materials have been investigated as compression coatings to obtain time-controlled release: HPMC, hydroxypropyl cellulose, polyethylene oxidemicronized ethyl cellulose, Eudragit® RS, behenic acid.

Bimodal drug release usually obtained with multilayered matrix tablets can also be obtained with compression-coated tablets. Time-controlled or pulsatile drug delivery systems are often based on rupturable or erodible coatings/matrices.

A time-controlled delivery system named Chronotopic® system is based on a drug-containing core, spray-coated with the water-soluble polymer hydroxypropyl methylcellulose (HPMC).Uponcontact with gastrointestinal fluids, thecoating underwent swelling and drugs were released after erosion of the gel layer.

PROCEDURE FOR PREPARATION OF PRESS COATING OF THE CORE TABLETS

The core tablets were press coated with mixed blend/granules of different polymers i.e. ethyl cellulose and HPMC K 4M, in different ratios. The barrier layer material was weighed and transferred in to a 10 mm punch die then the core tablet was placed manually at the centre,the remaining material of the barrier layer was added into the die and compressed at the cadmach (16 stations) punching machine.

TableNo.4. Composition ForPressCoating

S.no.	Ingredients	F5	F6	F7	F8	F9	F10	F11
1	HPMCK4M	200 mg	-	50 mg	100 mg	150mg	-	-
2	HPMCK15	-	-	-	-	-	50mg	200 mg
3	HPMCK100	-	-	-	-	-	-	-
4	Ethyl Cellulose	-	200 mg	150 mg	100 mg	50 mg	150mg	-
5	Magnesium Stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2mg	2mg

S.no	Ingredients	F12	F13	F14	F15	F16	F17	F18
1	HPMCK4M	-	-	-	-	-	25mg	175mg
2	HPMCK15	150mg	100mg	-	-	-		
3	HPMCK100	-	-	150mg	50mg	200mg	-	
4	Ethyl Cellulose	50mg	100mg	50mg	150mg	-	175mg	25mg
5	Magnesium Stearate	2mg	2mg	2mg	2 mg	2 mg	2mg	2mg

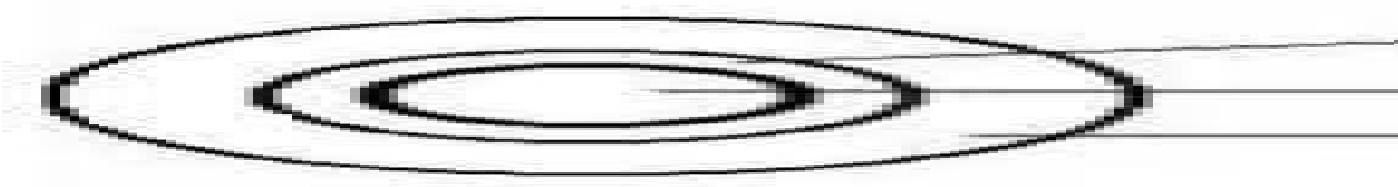


Fig. 1.(ETP)

ENTERICCOATING

An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word "enteric" indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. The entericcoated polymers remain unionise at low pH, and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionization, and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers.

Entericcoating is meant

- Topreventorreducethesideeffect (gastricdistressornausea) ofthedrugbyprotecting the gastric mucosa from some drugs (e.g. sodium salicylate).
- Todeliversomedrugs intendedforlocal actioninthe intestine.
- Toprovide adelayed-releasecomponentforrepeat-action tablets.
- Forthedeliveryofdrugsthatareoptimallyabsorbedinthesmallintestinetotheir primary absorption site in their most concentrated form
- For the protection of active pharmaceutical ingredients, from the acidic environment of the stomach (e.g. enzymes and certain antibiotics).
- Forminimizingfirst passmetabolismof drugs.

The enteric coating dissolves only at alkaline pH, thus preventing drug degradation in acidic environment of the stomach. The therapeutic concentration of a drug in blood can be maintained for a prolonged period of time by administering it in the form of a sustained release dosage form. This may minimize fluctuations of drug level in blood, prolong therapeutic drug level in blood, improve drug efficacy. Amongst sustained release formulations; sustained release tablet dosage forms have become extremely popular in modern therapeutics. Drugs with short half-lives are ideal candidates for sustained drug delivery.

The choice of the polymer and the thickness of the coated layer are critical to control the pH solubility profile of the enteric coated dosage form. The most common drugs which cause stomach ulcers like aspirin, diclofenac and naproxen are frequently available with enteric coatings. Omeprazole, which is a drug which stops the stomach from producing acid, is itself broken down in acid and therefore the drug generally has an enteric coating around it eitheras a granule in the capsules or as a granule in the dispersible form. Sulfasalazine is usedeither for the treatment of Crohn's disease which is inflammation of the intestines or for the treatment of arthritis. When used for Crohn's disease where it is needed in the intestines to work, it is given with an enteric coating whereas for arthritis it is very often given without an enteric coating so that it can be absorbed more quickly.

Delayed release dosage form is best formulations which are used for drugs that are destroyed in gastric fluids or cause gastric irritation, or areabsorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer & enteric coating layer.

IdealPropertiesofEntericCoating Material

- Resistancetogastric fluids
- Susceptible/permeabletointestinal fluid
- Compatibilitywithmostcoatingsolutioncomponentsandthedrug substrate
- Formationofcontinuousfilm
- Nontoxic,cheap and ease ofapplication
- Abilitytobereadily printed.

PolymersUsedForEntericCoating

Enteric polymers are becoming very popular due to their property of intact in the stomach,but will dissolve and release of the contents once it reaches the small intestine, their prime intension is to delay the release of drugs, which are inactivated by the stomach contents or may cause bleeding or nausea by the irritation of gastric mucosa. It is highly acid labile and presents many formulation challenges and to protect it from acidic environment of the stomach.Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers.

TableNo. 5.ListofEntericCoatedPolymersAndTheirDissolution pH

Polymers	Dissolution P^H
Shellac(estersofaleurticacid)	7.0
Celluloseacetatephthalate(CAP)	6.2
Poly(methacrylicacid-co-methyl methacrylate)	5.5-7.0
Celluloseacetatetrimellitate(CAT)	5.0
Poly(vinylacetatephthalate) (PVAP)	5.0
ydroxypropylmethylcellulosephthalate (HPMCP)	4.5-5.5

COATINGOFPRESSCOATEDTABLET

(A) Compression Coating

(B) Dip Coating

(A) CompressionCoating

It's a novel approach to producing coating layer over the core tablet for this accurate quantity of pH depended polymer was taken. Half quantity of weighed polymer was placed in the die cavity. Than the core tablet was placed. Over this remaining half part of coating polymer was poured. Than at optimum speed the tablet was compressed.

(B) Dip Coating

Prepared core tablet was coated by using dip coating technique. In this method selected polymerswasdissolveinorganicsolventlikemethanol,ethanol,acetone,ataconcentration of 10% w/v. Core tabletswerecoated usingcoating pan . Coating procedure repeated until10% over all weight gain was observed.

F17 wasselectedforthepreparationofacidresistantcoatinglayer.Itwasselectedonthebasis of their dissolution profile. The polymers which have less or no solubility in 0.1 N HCl were selected for enteric coating. The technique used for acid resistant coating is dip coating.

CAP(DipCoating).

- 3%w/vsolutionofCAPusingAcetoneassolventandPEG400(1.25%W/V)asa plasticizer.
- Tablet were dipped into coating solution and dried with the help of inlet air (temperature45-50˚c).Thecoatingprocesswasrepeatedtilldesiredlevelofcoating was achieved.

EVALUATIONOF POWDER BLEND

PowderblendwasevaluatedforAngleofrepose,Bulkdensityandtappeddensity, Compressibility Index, Hausner's ratio as described below [12][13][14]15][16].

MicromeriticProperties

AngleofRepose

Angleofreposeis used to determinetheflowproperties ofpowders,powderorgranules.The angle of repose of API powder was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder heap and height of heap was measured and angle of repose was calculated using the following equation.

$\tan\theta = h/r$

Where,h=heightof theheap, r= radiusoftheheap.

TableNo. 6. Angleof Repose

Sr. No.	Angleof repose(θ)	Typeof flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Verypoor

BulkDensity

Bulkdensityofthecoatedpowderwasdeterminedbypouringpowderintoagraduated cylinder via a large funnel and measuring the volume and weight.

Bulkdensity= weightofgranules/bulk volumeof granules

TappedDensity

Tapped density was determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which was operated for a fixed number of taps untilthepowderbedvolumehasreachedaminimumvolume.Usingtheweightofthedrugin the cylinder and this minimum volume, the taped density may be computed.

Tappeddensity=weightofgranules/tappedvolumeofgranules

Carr'sIndex

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

Carr'sIndex(%)=[(TD-BD) x100]/TD

Where,TD=Tapped density,BD=Bulk density

Hausner'sRatio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hausner's ratio. It is calculated by the following equation.

H =TD/BD

WhereTD=Tapped density,BD =Bulk density

EVALUATIONOFCOREAND PRESSCOATED TABLET PROPERTIES

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

Weight Variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets

individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentagelimitsandnotabletdiffers bymorethan2times the percentagelimit.USPofficial limits of percentage deviation of tablet are presented in the Table -10 Table 10: Weight variation limits

TableNo. 7. Weight variation

S.No	Avgwtoftablet (mg)	Max%differenceallowed
1	130 orless	10
2	130-324	7.5
3	324<	5

Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checkedbyusingMonsantohardnesstester.Thehardnesswasmeasuredintermsofkg/cm^2.

3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability

Friability generally refers to loss in weight oftablets in the containers due to removal offines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\%\text{Friability} = \frac{\text{Initialweightoftablet-finalweight oftablet}}{\text{Initialweightoftablet}} \times 100$$

Tablet Thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

Content Uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 500 mg was weighed accurately and dissolved in 100ml of phosphate buffer of pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whattman's filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 282.5nm. The concentration of the drug was computed from the standard curve of the NA in phosphate buffer of pH 6.8.

Rupturetest

The lag time of pulsatile release tablets is defined as the time when the outer CAP coating starts to rupture. It was determined visually by using the USP XXIV paddle dissolution apparatus (900 ml of 0.1 N HCl, 37.0F0.5 jC, 100 rpm, n = 3). In addition, the rupture behavior of pulsatile release tablets was photographed by a digital camera.

Disintegrationtime

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in electro lab USP disintegration test apparatus. It consists of 6 glass tubes which

are3 inches long, open at the top, and held against a10 mesh screen, at the bottom end ofthe basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing pH 6.8 Buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

In-vitroDissolution methods

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus().InordertosimulatethepHchangesalongwiththegastrointestinaltract(GIT) ,dissolution media with 0.1 N HCl and phosphate buffer(pH 6.8) were sequentially used.When performing the experiment ,0.1N HCl medium was used for 2 hrs (since the average gastric emptying time is 2 hrs).Then removedand fresh phosphate buffer(pH6.8) was added for subsequent hrs. 900 ml of the dissolution medium was used at each time and stirred at 100 rpm at 37 ± 0.5 ˚C.5 ml of dissolution media was withdraw at predetermindtime interval and fresh dissolution media was replaced. The withdraw samples were analyzed at 285.5 nm using a uv spectrophotometer.

3. RESULTSANDDISCUSSION

PreformulationStudies

MeltingPointDetermination

TableNo. 8. MeltingPoint Determination

Trial.No	Meltingpoint (^{0}C)	Average(Mean±S.D)n=3
1	139	139±0.577
2	140	
3	139	

Discussion:-Themeltingpointofdrugwasfoundtobe139±0.557˚C(n=3)whichiswithin limits of 138-141˚C.

SolubilityStudies

TableNo. 9.SolubilityStudies

Solvent	Solubility
Water	Freelysoluble
Chloroform	Soluble
Methanol	Soluble
Ethyl acetate	Soluble
Ether	Insoluble
n-hexane	Insoluble
0.1NHCL	Soluble
pH6.8phosphate buffer	Soluble
pH7.2phosphate buffer	Soluble

Discussion:- Solubility analysis of was performed in various organic solvents and distilled water .The drug was found to be freely soluble in water, soluble in chloroform, methanol, ethyl acetate, 0.1NHCl, phosphate buffer pH 6.8, phosphate buffer pH7.2, and insoluble in ether and n-hexane.

FTIR Spectroscopy

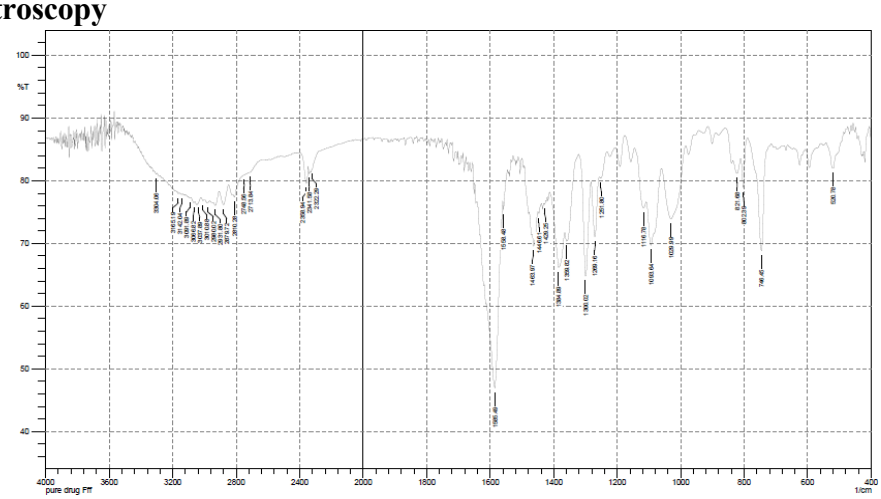


Fig. 2. IRSpectraofRabeprazoleSodium

TableNo. 10. MajorObservedPeaksForRabeprazoleSodium

S.NO	Peaks	FuntionalGroups
1	15.85	-C=C-Stretchingofanaromatic ring
2	1429.25	C=Nstr(inring)
3	1384.89	C-H-def(gem dimethyl)
4	1300-1359.82	C-Ostr
5	3010.88	-CHstrofanaromaticring
6	2960-2850	-CH3(C-Hstr)
7	1463.97	-CH3(C-Hdef)
8	1446.61	C-H-definCH3
9	2322.29	-C=N (Nitrite)
10	111.678	C-OstrinC-O-Cgroup
11	802.39	C-Sstr
12	746.45	C-Hdefoutofplane

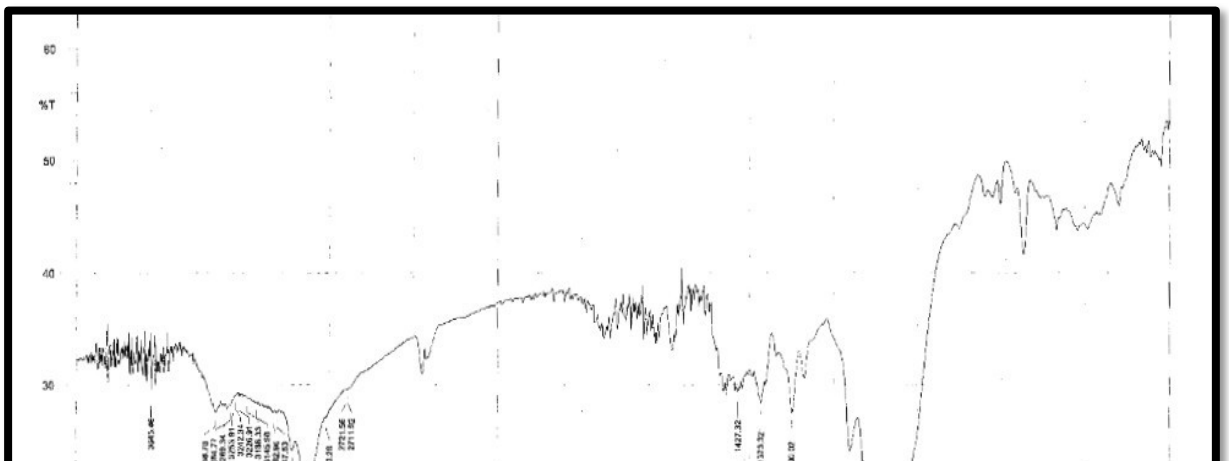
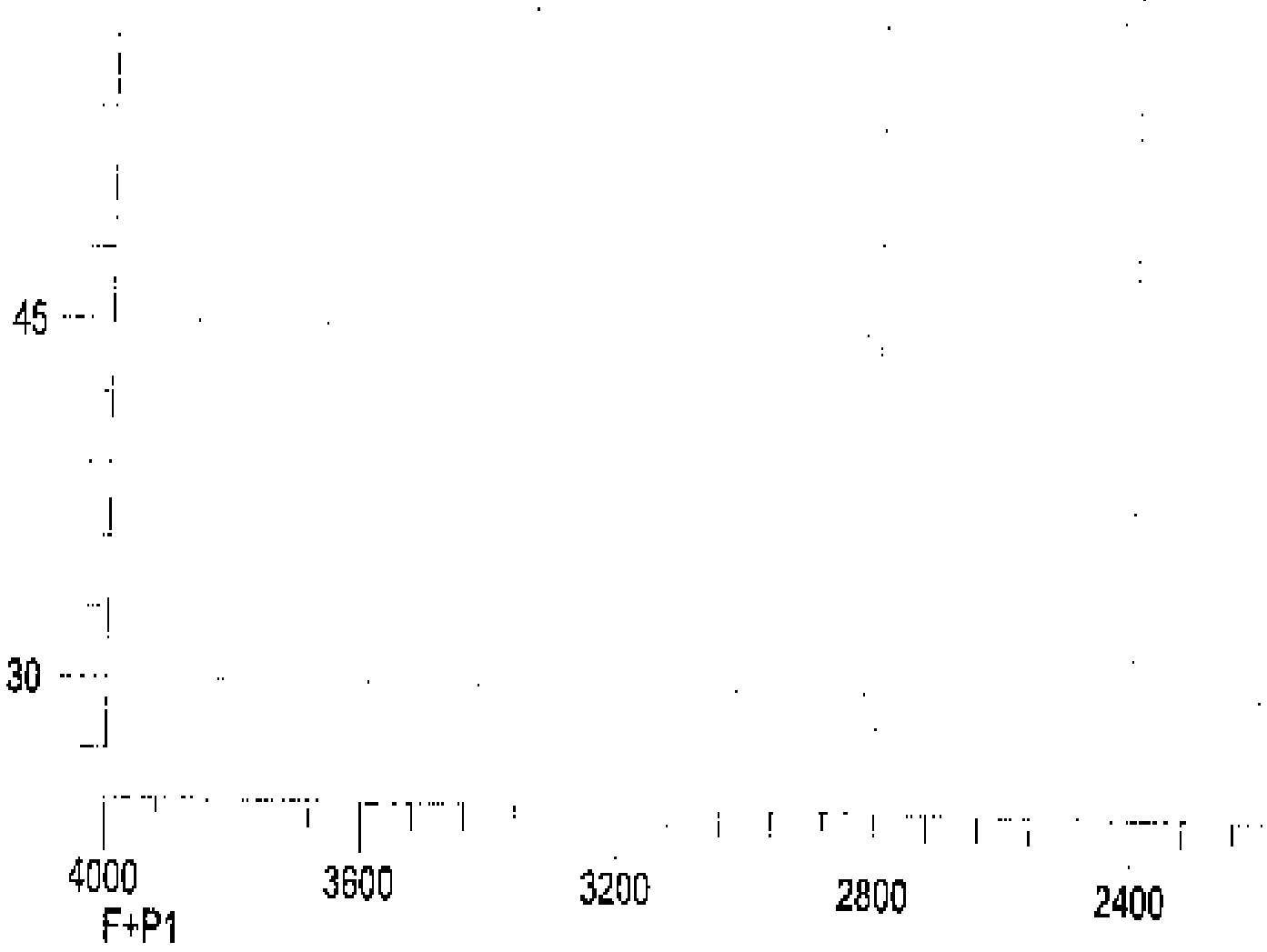


Fig.3.IRSpectraofRabeprazoleSodium+Avicel+CMS+HPMC+EC


45
30
4000
F+P1
3600
3200
2800
2400

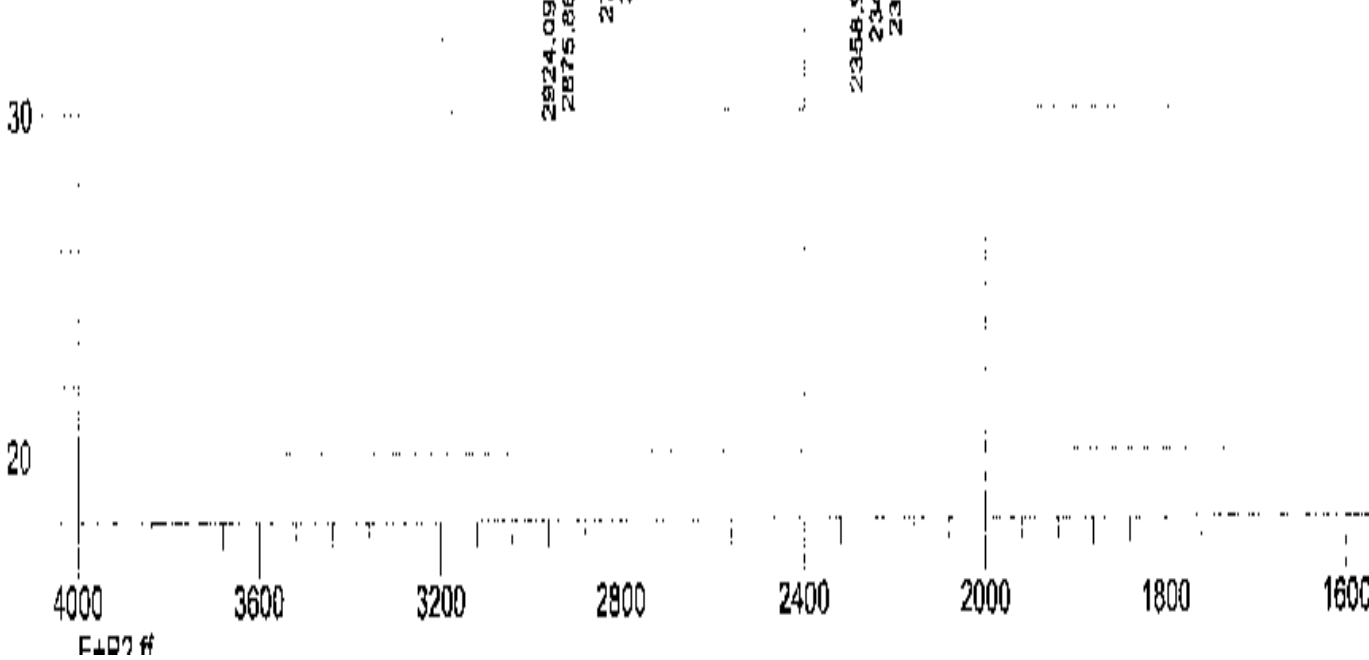

30
20
4000
3600
3200
2800
2400
2000
1800
1600

Fig.6. IRSpectra ofRabeprazoleSodium+HPMC

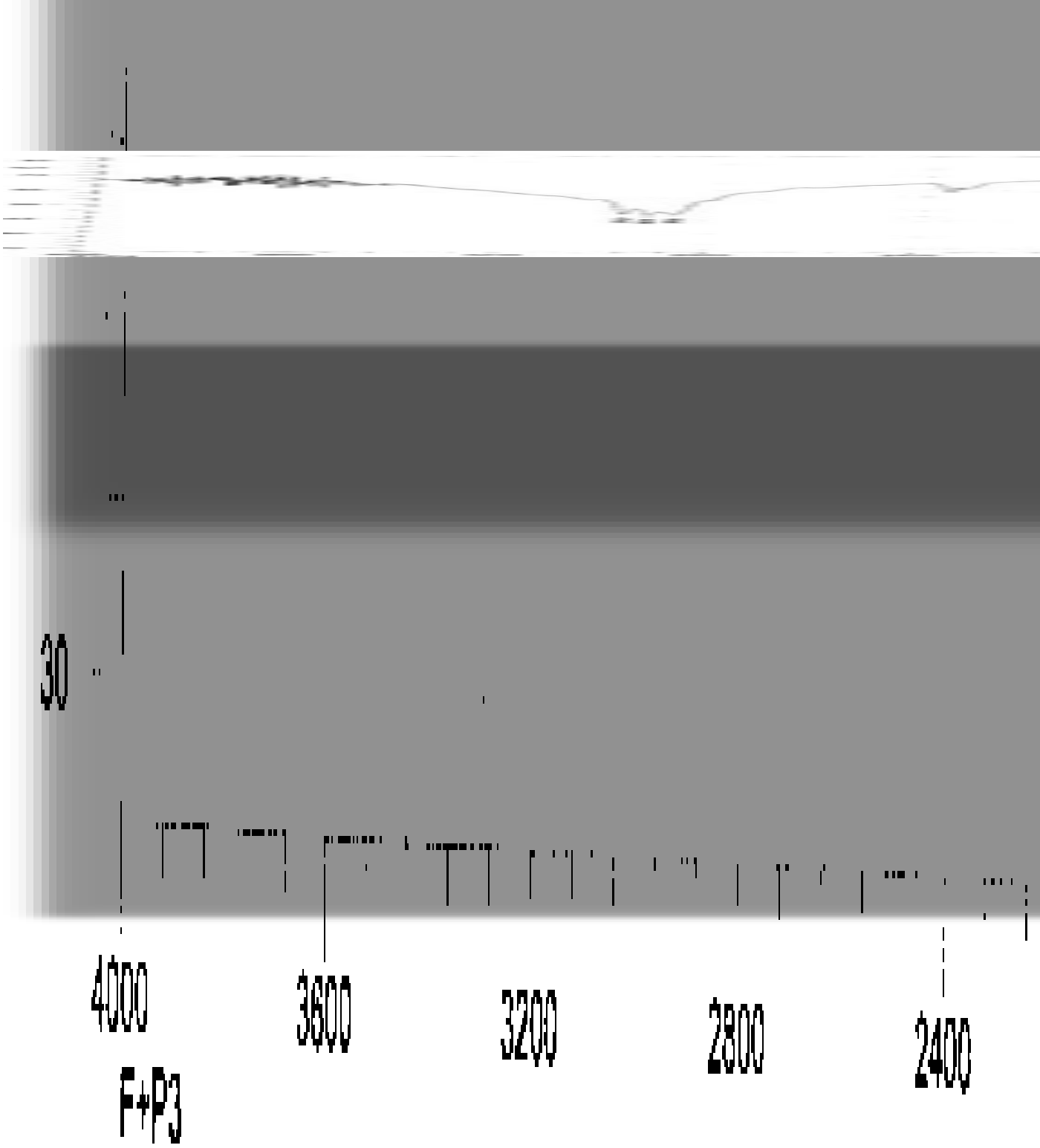
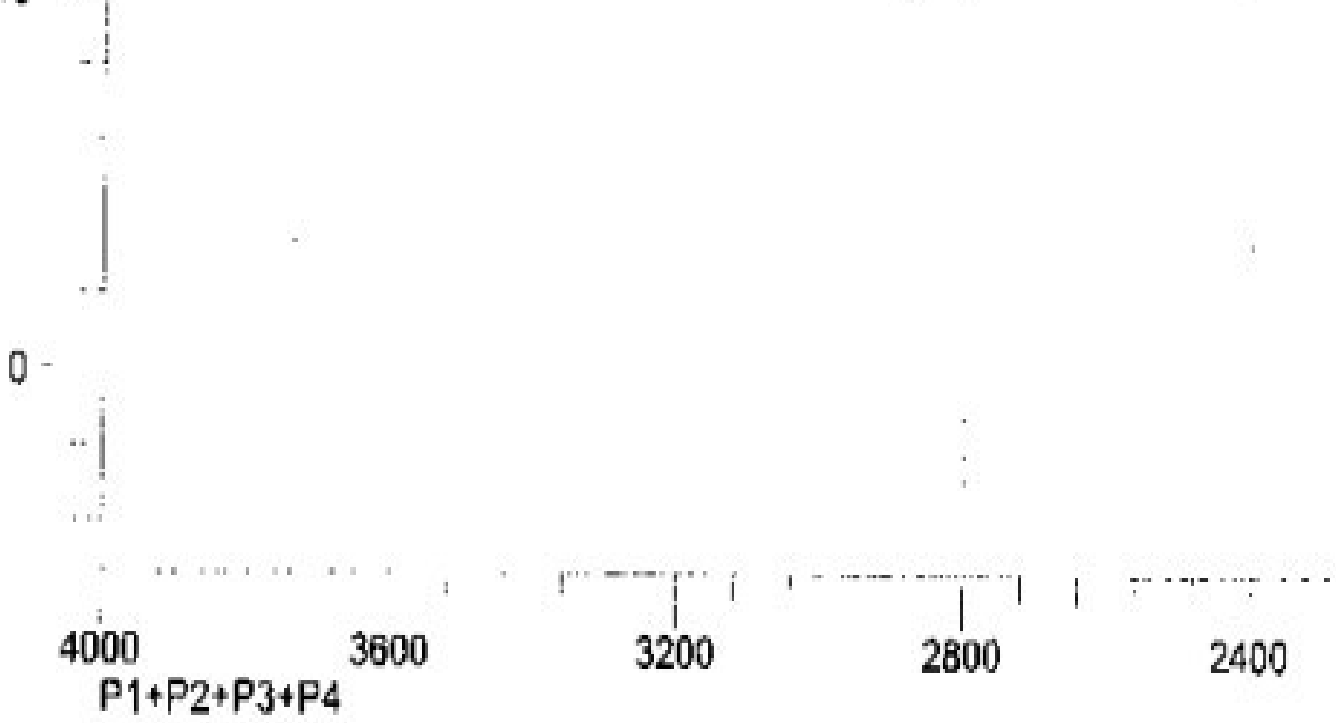

30
4000
3600
3200
2800
2400
F+P3

Fig.8.IRSpectraofRabeprazoleSodium+Avicel+ CMS

F+P1+P2



TableNo.11.StandardCurveofRabeprazole SodiumInDistilled Water

S. no	Concentration(µg/ml)	Absorbance (Mean±S.D)
1	1	0.034±0.135
2	2	0.80±0.0156
3	4	0.160±0.300
4	6	0.250±0.0423
5	8	0.311±0.0508
6	10	0.392±0.1075
7	12	0.492±0.1040
8	14	0.540±0.1305
9	16	0.609±0.1421
10	18	0.688±0.1511
11	20	0.766±0.1621

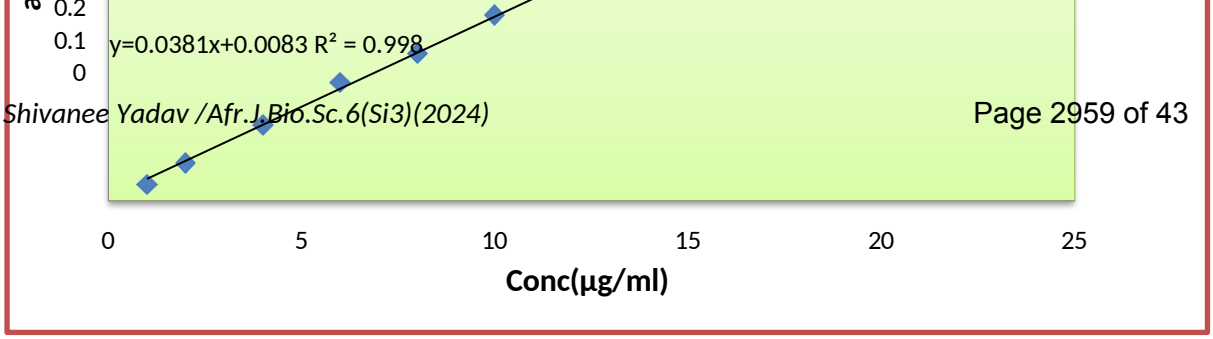


Fig. 10.Standardcurveofrabeprazolesodium indistilledwater

Standard Curveof RabeprazoleSodium In0.1N HCl

Table.No. 12.StandardCurveof Rabeprazole SodiumIn0.1N HCl

S. no	Concentration(µg/ml)	Absorbance(Mean±S.D)
1	1	0.036±0.115
2	2	0.057±0.0156
3	4	0.106±0.210
4	6	0.163±0.0513
5	8	0.227±0.0483
6	10	0.274±0.0579
7	12	0.329±0.0799
8	14	0.389±0.0749
9	16	0.450±0.0892
10	18	0.504±0.1213
11	20	0.571±0.1532

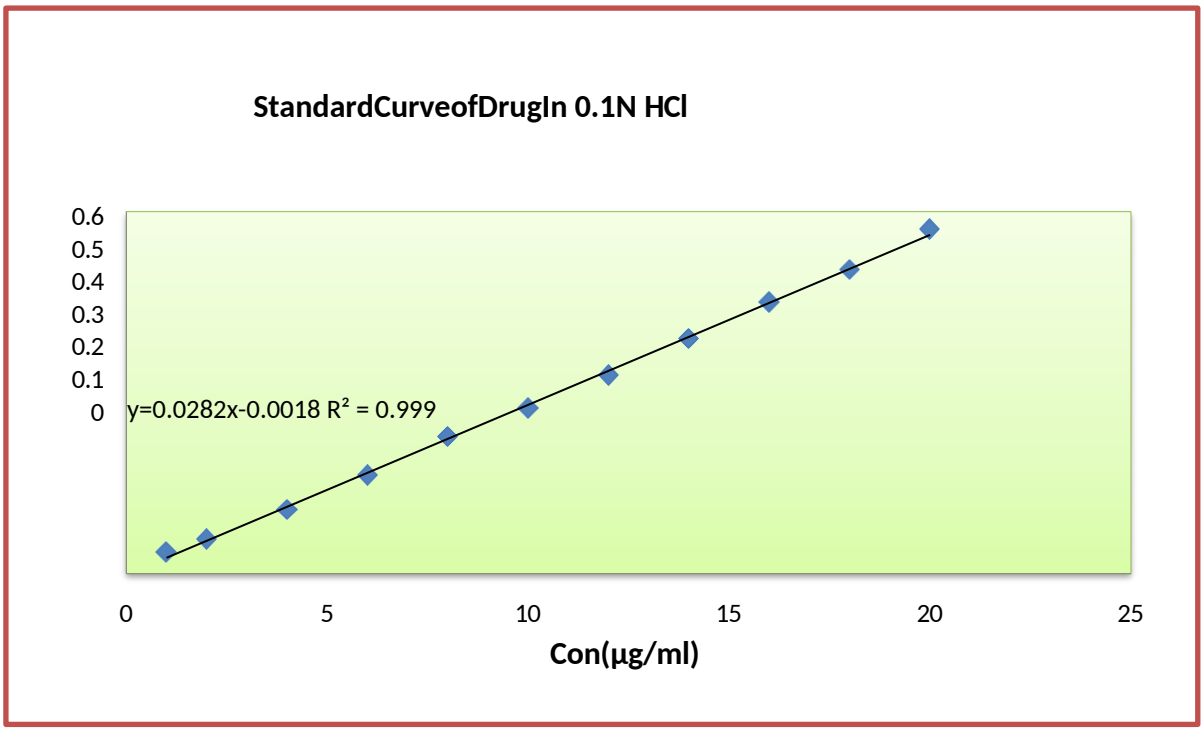


Fig. 11.Standardcurveofrabeprazolesodium in 0.1NHCl

StandardCurveofRabeprazoleSodium InPhosphateBufferpH 6.8

TableNo.13.StandardCurveof RabeprazoleSodium InPhosphateBufferpH 6.8

S. no	Concentration(µg/ml)	Absorbance (Mean±S.D)
1	1	0.072±0.024
2	2	0.118±0.212
3	4	0.253±0.311
4	6	0.29±0.417
5	8	0.34±0.612
6	10	0.401±0.887
7	12	0.446±0.871
8	14	0.55±0.912
9	16	0.6±0.992
10	18	0.635±0.129
11	20	0.705±0.872

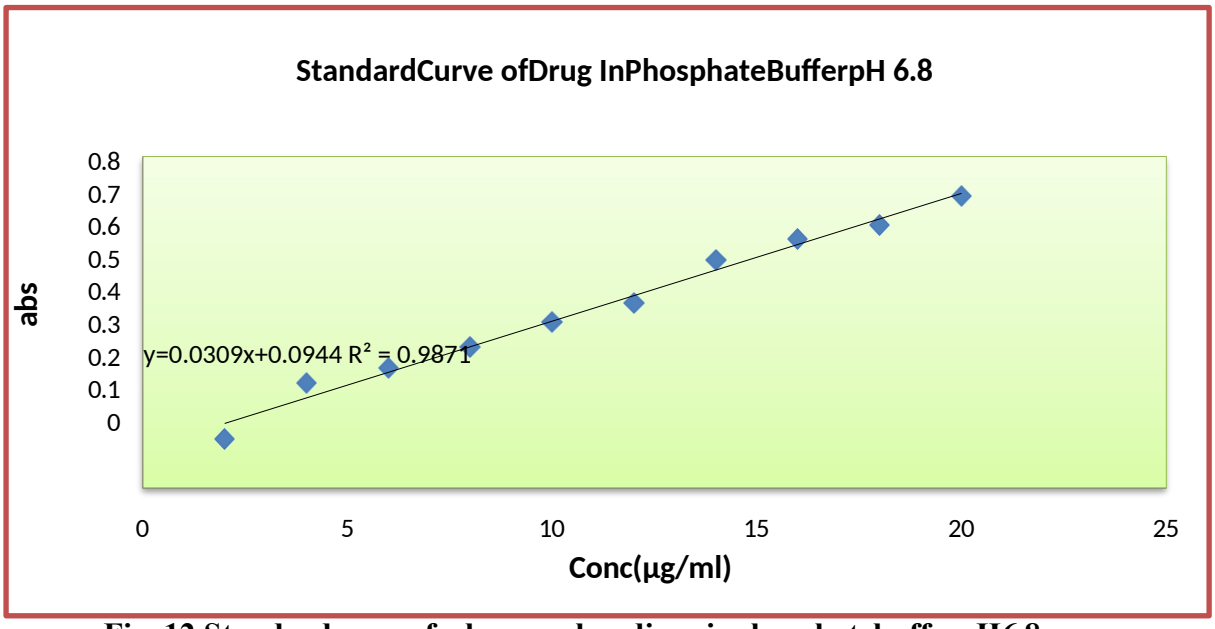


Fig. 12.Standardcurveofrabeprazolesodium inphosphatebufferpH6.8

Discussion: - The standard curves were prepared for rabeprazole sodium in different P^H buffersolutionsanddistilledwaterbydoublebeamUVspectrophotometer.Itwasobserved thatrabeprazolesodiumfollowstheBeerLambert'slawandcorrelationcoefficientswere found to be near to one for all the media used.

FORMULATIONSOFCORETABLETSOFRABEPRAZOLESODIUM

TableNo. 14. FormulationsofCoreTabletsof RabeprazoleSodium

Ingredient	Formulationcode			
	F1	F2	F3	F4
Rabeprazolesodium	20	20	20	20
MicrocrystallinecellulosepH101	75	70	65	55
Starchpaste(5%)	q.s	q.s	q.s	q.s
Lactose	-	-	-	15
Crosscarmellosesodium	-	5	10	5
Talc	3.5	3.5	3.5	3.5
Magnesium stearate	1.5	1.5	1.5	1.5
Total(mg)	100	100	100	100

SELECTIONOFPOLYMER/EXCIPIENTS

Polymerswereselectedonthebasisoftheirsolubility,releaseretentionability.Selected polymers are as follows

TableNo. 15. Selectionof Polymer

S. No.	Polymers
1	MicrocrystallinecellulosepH101
2	Crosscarmellosesodium
3	Ethylcellulose
4	HPMCK4M
5	CAP
6	PEG400

EVALUATIONOFPOWDER BLEND

TableNo.16.PrecompressionParametersofPreparedGranules

Formulation code	Bulkdensity (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index(%)	Hausner'sratio (%)	Angle of repose
F1	0.55±0.015	0.62±0.0152	11.2±0.152	1.12±0.012	23.79±0.67
F2	0.66±0.1	0.76±0.0057	12.4±0.36	1.14±0.021	20±0.28
F3	0.55±0.015	0.66±0.0152	16.7±0.21	1.2±0.022	18.2±0.255
F4	0.57±0.0152	0.66±.0152	14.3±0.24	1.16±0.017	24.7±0.69

Dicussion :- Precompression parameters of prepared granules with respect to bulk density wasfoundtobeintherangeof0.55to0.66gm/cm^3,tappeddensitywasfoundtobe0.62to 0.76 gm/cm^3 , angle of repose was found to be 18.2 to 24.7 , carr's index values were foundto be in the range 11.2 to 16.7 and Hausner's ratio was found to be in the range of 1.1 to 1.2. All

these pre-compression parameters values were within the pharmacopoeial limit.

IN-VITRORELEASEPROFILEOFPREPAREDCORETABLET

TableNo. 17.In-VitroReleaseProfileofPreparedCoreTablet

Time(min)	%Drugrelease			
	F1	F2	F3	F4
0	0	0	0	0
5	14.6	30.5	46.68	16.45
10	19.5	31.92	48.79	22.78
15	29.10	44.57	55.12	27.70
20	39	52.31	62.85	37.54
25	41	60.75	73.40	44.57
30	52.45	69.89	80.43	52.31
35	55.3	75.5	90.28	60.75
40	58.21	83.95	93.09	72.00
45	60	88.17	96.60	74.81
50	66.4	91.68	98.01	83.95

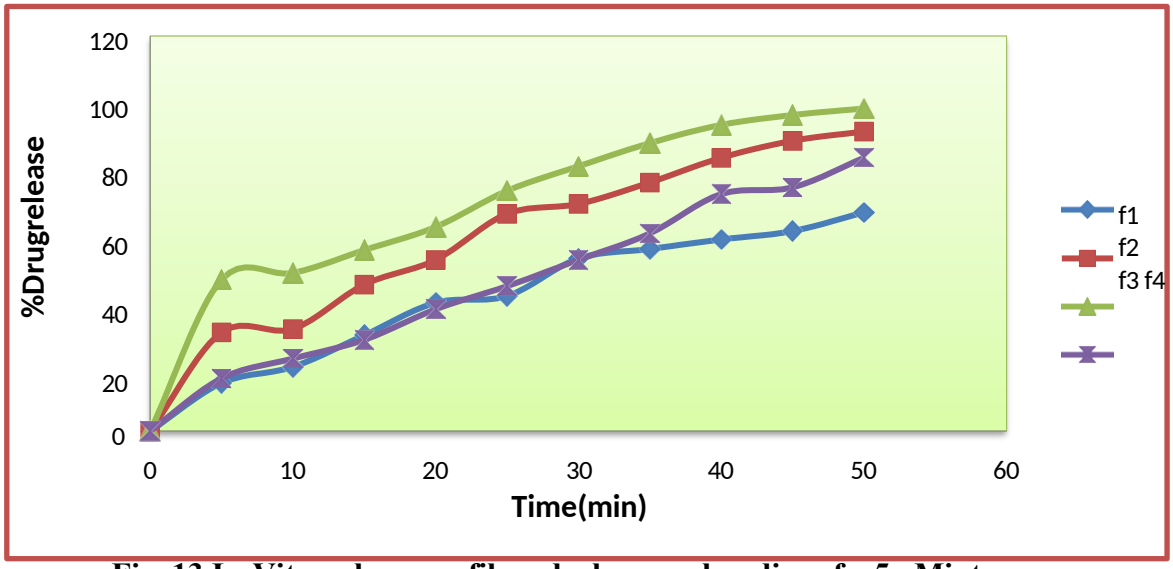


Fig. 13.In-Vitroreleaseprofileandrabeprazolesodium for5o Mintus

Discussion: - In vitro release of rabeprazole sodium from core tablet. From formulation F1, F2,F3,and F4(coretablet),F3 showedfasterdrug releasefromotherformulation.Fasterdrug releasecanbecorrelatedwiththehighdisintegrationandfriabilityobservedinthisstudy .Based on the above characters formulation. F3was selected as best formulation and press coated.

POSTCOMPRESSIONPARAMETEROFRABEPRAZOLESODIUMCORE TABLET

TableNo. 18. PostCompressionParameterofRabeprazoleSodiumCore Tablet

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time(sec)	Weight variation(%)
F1	1.5±0.70	0.124±0.0035	0.38±0.010	4.8±0.76	101.5±2.06
F2	1.5±0.70	0.126±0.0034	0.79±0.025	3.83±0.86	100.2±3.5
F3	2.25±0.35	0.123±0.0032	0.19±0.012	2.23±0.28	101.8±2.77
F4	1.5±0.70	0.118±0.009	0.49±0.02	3.20±0.44	101.42±2.98

Dicussion :-Post compression parameter of rabeprazole sodium of core tablet was studied. Hardness of core tablet were found to be 1.5 to 2.2 kg/cm^2, thickness of core tablet were found to be 0.118 to 0.126 mm, friability of core tablet were found to be 0.19 to 0.79 %, disintegrationtimeofcoretabletwerefoundtobe2.2to4.8sec,weightvariationofcore tablet were found to be 100 to 101. All these pre-compression parameters values were within the acceptable limit.

COMPOSITIONFORPRESS COATING

TableNo. 19. CompositionForPressCoating

S.no	Ingredients	F5	F6	F7	F8	F9	F10	F11
1	**HPMC K4M**	200 mg	-	50 mg	100 mg	150mg	-	-
2	**HPMC K15**	-	-	-	-	-	50mg	200mg
3	**HPMC K100**	-	-	-	-	-	-	-
4	**Ethyl Cellulose**	-	200 mg	150 mg	100 mg	50 mg	150mg	-
5	**Magnesium Stearate**	2 mg	2 mg	2 mg	2 mg	2 mg	2mg	2mg

S.no	Ingredients	F12	F13	F14	F15	F16	F17	F18
1	**HPMC K4M**	-	-	-	-	-	25mg	175mg
2	**HPMC K15**	150mg	100mg	-	-	-		
3	**HPMC K100**	-	-	150mg	50mg	200mg	-	
4	**Ethyl Cellulose**	50mg	100mg	50mg	150mg	-	175mg	25 mg

5	**Magnesium Stearate**	2mg	2mg	2mg	2 mg	2 mg	2mg	2mg

***IN-VITRO*RELEASEPROFILEOFPRESSCOATEDTABLET**

TableNo. 20. In-VitroReleaseProfileofPressCoatedTablet

Time(min)	**%Drugrelease**					
	F5	**F7**	**F8**	**F9**	**F17**	**F18**
15	0	0	0	0	0	0
30	0	0	0	0	0	0
45	0	0	10.5	0	0	0
60	0	0	12.1	0	0	0
75	0	6.1	15.9	7.05	0	0
90	0	21.0	23.0	12.15	0	0
105	0	63.4	30.0	17.4	0	0
120	0	73.0	33.9	25.6	0	0
135	0	75.3	42.0	30	0	0
150	0	76.2	73.8	36.30	7.6	0
165	0	78.0	75.9	82.0	45.6	0
180	0	78.6	80.7	82.5	80.7	0
195	0	78.6	81.9	83.1	82.8	13.5
210	0	79.9	84.1	84.3	83.1	37.6
225	7.5	81.9	84.4	85.6	86.1	58.0
240	69.00	81.9	84.6	87.6	86.2	71.2
255	84.75	84.1	84.4	89.1	87.9	76.3
270	87.9	85.2	87.1	93.4	92.4	83.4
285	90.9	86.7	87.5	95.4	92.5	91.6
300	96.15	87.1	87.9	97.5	92.9	99.15

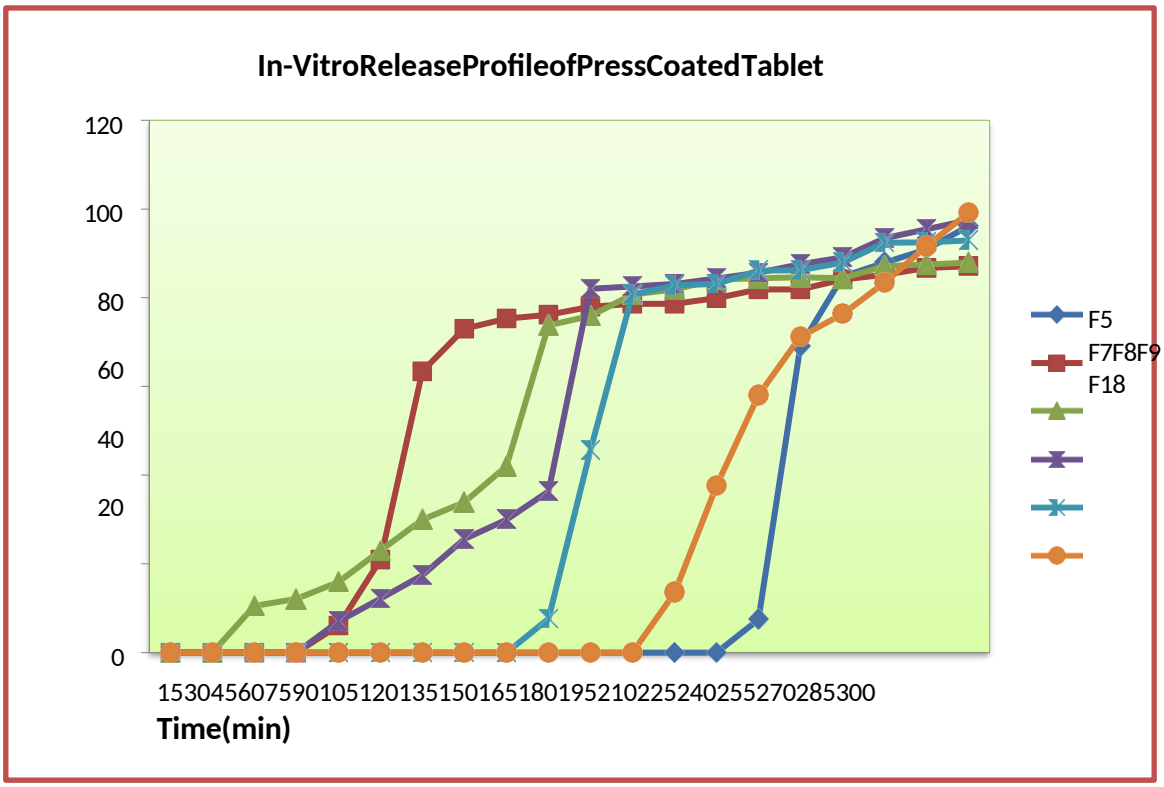


Fig. 14.In -Vitroreleaseprofileofvariouspresscoated tablet

Discussion: - F3was selected as best formulation and press coated and enteric coated to find out the changes in the release rate of the rabeprazole sodium from enteric coated tablet. F6, F10, F11, F12, F13, F14, F15and F16 showed the extensively less drug release due to increased concentrationofwaterinsoluble ethylcelluloseandhighviscositygradepolymersi.e. HPMC K15 and HPMC K100 as compared to HPMC K4. But F5,F7,F8,F9,F17and F18showed the maximum drug release after 3 hrs 45 minute, 1hrs, 30 minute, 1hrs, 2 hrs30 minute and 3hrs respectively but F17and F18showed the better result as compared to others. Therapeutic level and time dependent pulsatile drug delievery system has been achieved from the tablet of formulation F17 with 92.9 % drug release which meet demand of chronotherapeutic drug delievery.

EVALUATION OF PHYSICAL PARAMETER OF COMPRESSED TABLET OF RABEPRAZOLE SODIUM

TableNo.21. PhysicalParameterofCompressedTabletofRabeprazoleSodium

Formulation code	Hardness (kg/cm^2)	Friability (%)	Diameter (mm)	%Drugcontent
F5	4.3±0.27	0.52±0.14	10.01±0.005	98.7±1.7
F6	4.8±0.20	0.21±0.21	10.02±0.006	97.9±2.4

F7	4.2±0.37	0.40±0.03	10.01±0.005	97.5±3.1
F8	4.1±0.56	0.39±0.19	10.01±0.005	96.5±3.5
F9	5.0±0.42	0.68±0.03	10.01±0.005	97.4±2.4
F10	4.9±0.19	0.40±0.13	10.02±0.006	98.1±3.4
F11	4.3±0.42	0.37±0.26	10.03±0.006	99.1±1.1
F12	4.5±0.38	0.33±0.16	10.04±0.007	96.4±3.5
F13	4.3±0.45	0.43±0.24	10.02±0.006	97.6±3.5
F14	4.6±0.46	0.15±0.03	10.03±0.006	97.9±2.5
F15	4.8±0.38	0.38±0.22	10.01±0.005	99.4±1.4
F16	5.1±0.16	0.32±0.13	10.01±0.005	95.6±3.1
F17	4.5±0.27	0.68±0.17	10.02±0.006	99.6±1.1
F18	4.2±0.33	0.35±0.01	10.01±0.005	98.4±2.5

WEIGHT VARIATIONTEST

TableNo. 22. WeightvariationTestofCompressedTabletofRabeprazoleSodium

Formulation code	**Observed weightvariation**	**Weight variation limit**	**Inferences**
F5	(-)0.06 to(+) 0.43	5%	Acceptable
F6	(-)0.33 to(+) 0.66	5%	Acceptable
F7	(-)1.97 to(+) 1.64	5%	Acceptable
F8	(-)0.66 to(+) 0.99	5%	Acceptable
F9	(-)2.64 to(+) 0.33	5%	Acceptable
F10	(-)0.33 to(+) 1.00	5%	Acceptable
F11	(-)0.33 to(+) 0.66	5%	Acceptable
F12	(-)0.33 to(+) 0.66	5%	Acceptable
F13	(-)0.33 to(+) 0.53	5%	Acceptable
F14	(-)2.65 to(+) 0.31	5%	Acceptable
F15	(-)0.66 to(+) 0.66	5%	Acceptable
F16	(-)0.86 to(+) 0.33	5%	Acceptable
F17	(-)2.3 to(+) 0.33	5%	Acceptable
F18	(-)1.6 to(+) 0.33	5%	Acceptable

Discussion:-

Weightvariationtest

Weightvariationfor allthebatcheswerefoundtobewithinacceptablelimit(lessthan5%).

Hardnesstest

The measured hardness of tablet of all the formulations ranged between 4.1±0.56 to 5.1±0.16 kg/cm^2. This ensures good handling characteristics of all batches.

Friabilitytest

The values of friability test were tabulated in above table. The % friability was less 0.7 % in all the formulations ensuring that the tablets were mechanically stable

Diametertest

Diameter of the coated formulations was measured with digital verniercalliper. Themeasured diameter of coated tablets of each formulations ranged between 10.04±0.007 mmto 10.01±0.005 mm. This ensures uniform coating to all batches.

DrugContent Uniformity

The percentage of drug content was found to be between 95.6± 3.1 and 99.6±1.1. It complies with official specifications and indicate the well entrapment efficiency of prepared formulation. The results were shown in above table.

RuptureTest

TableNo. 23. RuptureTest

Formulationcode	Timeinminute
F19	75
F20	105
F21	120

Fig. 15.Differentformulationofrupturetest

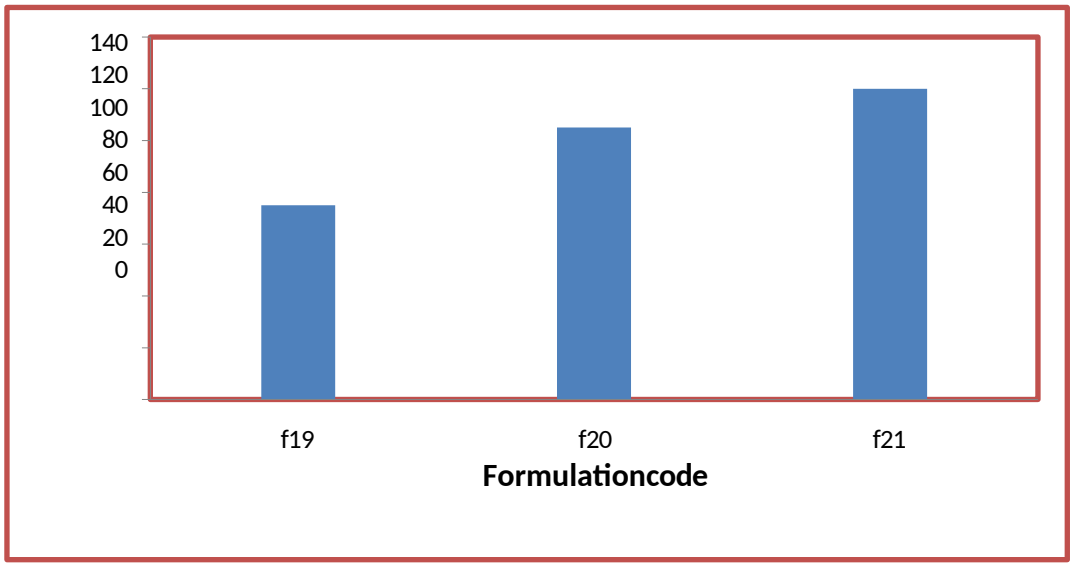


Fig. 16.Rupturetimeofdifferentformulations

Discussion: - The rupture test clearly revealed that F21 formulation should be selected as comparedto F20and F19asrupturetimeofentericcoatingis120,105 and75respectively. SotheF21formulationwith10%coating gainisoptimizedforentericcoating performance.

WEIGHTGAINFORACIDRESISTANTCOATINGLAYER

TableNo. 24.WeightGain ForAcid ResistantCoating Layer

Formulationcode	**%Weight gain of coating layer**
F19	**5**
F20	**7.5**
F21	**10**

S.NO	**% Weight Gain**	**COMMENTS**
1	5%	Notselected(Uniformcoatingwasnotachieved)
2	7.5%	Notselected(Uniformcoatingwasnotachieved))
3	10%	**Selected(Uniformcoatingwasachieved)**

5.1 IN-VITRORELEASEPROFILEOFENTERICCOATEDTABLETS

TableNo.25. In-VitroReleaseProfileof EntericCoated Tablets

Time(min)	**%Drugrelease**		
	F19	**F20**	**F21**
15	0	0	0
30	0	0	0
45	0	0	0
60	0	0	0
75	0	0	0
90	0	0	0
105	0	0	0
120	0	0	0
135	0	0	0
150	0	0	0
165	0	0	0
180	0	0	0
195	0	0	0
210	0	0	0

225	21.4	0	0
240	42.7	0	0
255	44.4	10.6	0
270	47.4	15.1	1.2
285	54.9	15.9	7.6
300	60.9	23.7	15.1
315	61.2	26.7	18.7
330	65.2	30.9	45.3
345	66.9	31.6	46.6
360	72.0	36.9	54.1
375	75.1	57.1	57.1
390	75.9	63.9	60.9
405	83.4	90.0	68.4
420	89.7	90.9	75.9
435	89.7	90.9	89.4
450	90.9	92.0	90.9
465	92.2	92.4	95.4

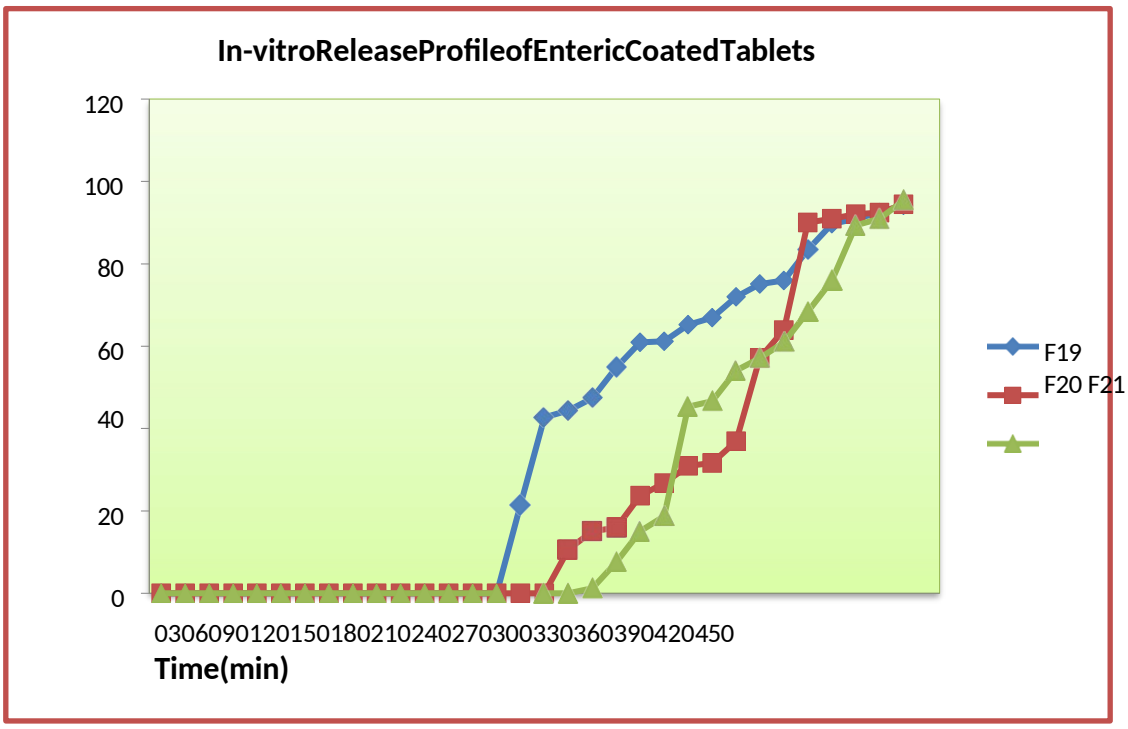


Fig. 17.In-Vitroreleaseprofileofenteric coated tablets

Discussion: - Formulation F17 was further coated with 3% w/v solution of CAP in Acetone

using 1.5 % w/v PEG-400 as plasticizer .The dip coating was performed with above solution to achieve weight gain of 5% , 7.5% and 10%. All three formulation were evaluated for drug releasefirstlyin0.1NHClfor2hrs,then0.1NHClwasreplacedwithphosphatebufferP^H 6.8.Thedrugreleaseprofileofthese3formulationsrevealednodrugreleaseinfirst2hrsin 0.1 N HCl instead of formulation f19,which indicate the integrity of coating membrane. The drug release was started after 210 minutes in formulation with 5% coating weight gain, whereas drug release was started after 255 minutes with 7.5% coating weight gain and 270 minuteswith10%coatingweightgain .Wherethedrugreleaseafter300 minutes(5hrs)was only 7.6 % and after 7 hrs the drug release was 75.4 %. The decrease drug release after 2 hrs may be due to press coating along with enteric coating with 10% weight gain.

EVALUATION PARAMETERS OF THE OPTIMIZED BATCH F21OF RABEPRAZOLE SODIUM

TableNo. 26.ParametersofTheOptimizedBatchF21ofRabeprazoleSodium

Formulation code	Hardness (kg/cm^2)	Diameter (mm)	% Drug content	Average mean± SD	%weight gainin entericcoating
F21	5.23 ±0.25	10.2 ±0.10	97.2 ±1.1	334.3 ±0.57	10%

Discussion: - The optimized formulation F21 showed 95.4% drug release after 7.75 hours and it successfully inhibit drug release in initial hours. The tablet had 5.23 ±0.25 kg/cm^2 hardness which is adequate for packaging with a diameter of 10.2 ±0.10 mm and 97.2 ±1.1 % drug content. The press coated tablet was enteric coated with 10 % of weight gain. It showed good inhibition of drug release in acidic media as compared to F19and F20as shown in figure 5.19.

4. CONCLUSSION

In this research work we formulated and characterize the pulsatile drug delivery of rabeprazole sodium and optimize different ratios of excipients and polymer using with the other processing parameters and characteristics of finish product. The optimized formulation successfully prevents the drug release as per need of therapy.

FUNDING
Nil.

CONFLICT OF INTEREST
None.

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