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FORMULATION, DEVELOPMENT AND *IN-VITRO* EVALUATION OF RABEPRAZOLE SODIUM DELAYED RELEASE ENTERIC COATED TABLETS

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ABSTRACT

Rabeprazole sodium is a proton pump inhibitor used to treat peptic ulcer, duodenal ulcer, gastro oesophageal reflux disease by inhibiting the enzyme H^+ /K^+ATPase, the acidic pump. It is also used to treat Zollinger-Ellison syndrome, erosive esophagitis.This study is aimed to develop pharmaceutically equivalent and stable enteric-coated tablets of Rabeprazole sodium which protects it from acidic environment of the stomach. Six Formulations of Rabeprazole core tablets were developed using mannitol as diluents, crospovidone and polyplasdone-XL as super disintegrants, sodium carbonate anhydrous as stabilizer, magnesium stearate and talc as lubricant and glidant in different proportions, and the prepared core tablets were coated with enteric coating using hypromellose phthalate 55, myvacet, pigment blend yellow, ethanol and purified water. Compatibility studies were performed for drug, physical mixture tablet which shows no interaction. From the dissolution the formulation F6 shows highest percentage of drug release.

KEYWORDS: Rabeprazole sodium, crospovidonepolyplasdone-XL, direct compression and enteric coated tablets.

INTRODUCTION[1,2]

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Drug release only occurs some time after the administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy

of the drug, to improve the therapeutic outcome of the drug treatment and/or to increase patient compliance and convenience of administration. Modified Release dosage form may be classified as 1. Extended Release includes Sustained Release and Controlled Release 2. Delayed Release as given in fig.1.

Extended Release oral drug delivery systemallows the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release can be achieved using sustained or controlled-release dosage forms.

The term Sustained Release is constantly used to describe a pharmaceutical dosage form formulated to retard the release of the therapeutic agent such that its appearance in the systemic circulation is delayed and prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed, on the duration of its therapeutic effect is sustained.

Controlled Release Dosage form is generally accomplished by attempting to obtain "zero-order" release from the dosage form which independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained Release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug in a slow first order fashion (i.e., concentration dependent).

A Delayed Release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Delayed Release oral dosage forms can control where the drug is released, e.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms). Delayed Release systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. they do not release the drug immediately after ingestion, for example enteric-coated tablets, pulsatile-release capsules. Delayed Release dosage forms are designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to desired rate of drug release to target tissue over a specified period of time. The primary aim of using delayed release products is to protect the drug from gastric fluids, to reduce gastric distress caused by drugs particularly irritating to the stomach or to

facilitate gastrointestinal transit for drugs that are better absorbed from intestine. Delayed Release products are typically enteric-coated or targeted to the colon.

The oral route of drug delivery is typically considered the preferred and most patient-convenience means of drug administration. The release of drug from an oral dosage form may be intentionally delayed until it reaches the intestine.

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micromeritic or macromeritic properties of materials during manufacture and/or for providing a desired drug delivery system. The most commonly used pharmaceutical delayed release solid oral dosage forms today include tablets, capsules, granules and pellets.

T_{max}IR is the time for maximum plasma concentration of the drug released from an immediate-release dosage form and T_{max}DR is the time for maximum plasma concentration of the drug released from a delayed-release dosage form as given in fig 2.

Significance of Delayed Release Systems

The design of such system involves release of drugs only at a specific site in the gastrointestinal tract. The drugs contained in such a system are those that are.

- Destroyed in the stomach or by intestinal enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site
- Meant to exert local effect at a specific gastrointestinal site

In these cases drug release should be delayed until the dosage form has reached the small intestine. Often polymers are used to achieve this aim. The dosage form (for example, a tablet or the granules before tableting) can be coated with a suitable polymer. The polymer dissolves as a function of pH, so when the dosage forms travel from the low-pH environment of the stomach to the higher-pH environment of the small intestine, the polymer coat dissolves and the drug can be released. Once this occurs, the release is again immediate and the resulting plasma concentration versus time curve is similar to the one for immediate release dosage forms.

Rabeprazolesodium[2,3,4]

Rabeprazole sodium is a proton pump inhibitor used to treat peptic ulcer, duodenal ulcer, gastro oesophageal reflux disease by inhibiting the enzyme H^+ /K^+ATPase, the acidic pump. It is also used to treat Zollinger-Ellison syndrome, erosive esophagitis.The Physico-Chemical Properties of Rabeprazole sodiumwere given in table.1 and Pharmacokinetics and Pharmacodynamics were given in table.2.the structure of Rabeprazole sodium was given in fig 3.

MATERIALS

Rabeprazole sodium, Mannitol, L Hydroxy propyl cellulose, Sodium Carbonate Anhydrous Crospovidone, Polyplasdone-xl, Talc, HPMCP 55, Myvacet, Pigment blend Yellow, Magnesium stearate, Ethanol,Purified water were of analytical grade and obtained from Hetero Labs.

METHODS

Preparation method

Direct compression method[1,5,6,7]**:** The enteric coated tablets were prepared by direct compression method. The weighed quantity of Rabeprazole sodium, mannitol, Sodium Carbonate Anhydrousand Hydroxy propyl cellulosewere sieved through30 # size. The above shifted materials were lubricated with crospovidone, talc and Magnesium stearatefor 5min octagonal blender. These blended materials were further subjected to compression. Thedifferent formulas were given in Table 3.

Organoleptic evaluation: These are preliminary characteristics of any substance which is useful in identification of specific material. The physical properties of API were given in table 4.

Calibration curve of Rabeprazole sodium

From the standard stock solution (1000 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made up to 10 ml with 6.8ph phosphate buffer so as to get concentration of 2, 4, 6, 8, 10 and 12 µg/ml. the absorbance of the solution were measured at 282 nm. The absorbance values for different known concentrations were given in table 5. A calibration graph was plotted as shown in fig 4.

Evaluation methods

Pre-compression studies[1,8,9,10]

Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

Db = M/ Vb

Where,

M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density (Dt)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference betweensuccessive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

Dt = M / Vt

Where,

M is the mass of powder

Vt is the tapped volume of the powder.

Angle of Repose (Ɵ)

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane. The flow Properties and Corresponding Angles of Repose were given in table 6.

tan(Ɵ) = h / ri.eƟ = tan-1 (h / r)

Where,

Ɵ is the angle of repose.

h is the height in cm, r is the radius in cm.

Carr's index (or) % compressibilit

It indicates powder flow properties. It is expressed in percentage and is give by,

I=Dt - Db / Dt×100

Where,

Dt is the tapped density of the powder

Db is the bulk density of the powder.

Hausnerratio: It is an indirect index of ease of powder flow. It is calculated by the following formula. The relation of flow property with HR & CI was given in table 7.

Hausner ratio=Dt /Dv

Where,

Dt is the tapped density,

Db is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post-compression Studies[11,12,13,14]

1. Weight variation test

Individual weights of 20 tablets were taken and the average weight was calculated by using the following formula. Weight variation specification as per IP/BP and USP are given in following table.The weight variation specification as per IP/BP and USP was given in table 8.

$$\textbf{Weight variation} = \frac{\text{(Weight of tablet-Average weight)}}{\text{Average weight of tablets}} \times 100$$

2. Hardness

Hardness of the tablets was observed by the use of hardness tester. Desired hardness was 6-8Kg/ in^2.

3. Thickness

Thickness of the tablets was calculated by the use of vernier calipers. Desired thickness was 2-3mm.

4. Friability

Friability of the tablets was calculated by the use of friabilator. Friability should be less than 1.

5. Disintegration time

Disintegration time of the tablet was observed with the help of disintegration test apparatus.

Dissolution study

Acidic Stage

Medium	: 0.1N HCl
Type of apparatus	: USP - II (paddle type)
RPM	: 100
Volume	: 900ml
Temperature	: 37ºC± 0.5
Time	: 2hrs

Buffer Stage

Medium	: pH 8.0 Tris buffer
Type of apparatus	: USP - II (paddle type)
RPM	: 100
Volume	: 1000ml
Temperature	: 37ºC± 0.5
Time	: 45 minutes

Drug excipient Compatibility studies

The objective of drug/excipient compatibility considerations and practical studies is to delineate, as quick as possible, real and possible interactions between potential formulation excipients and the active pharmaceutical excipient. Homogeneous mixtures of drug and excipients were prepared and filled in glass vials and self-seal LDPE (Low density Poly Ethylene) bags. The glass vials were maintained at 60□ 2^0 C for 2 weeks. Those packed LDPE bags were maintained at 40□2^0 C/75□ 5% RH for 1 month. Controlled conditions (2-8^0 C) maintained for comparison purpose. The results of Drug exicipients Compatibility study are given in table no 9.

Storage Conditions

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time till it covers the proposed shelf life.

RESULTS AND DISCUSSION

Pre-compression studies: The pre-compression studies were performed for all the formulations. The results of F2, F3& F6 were found to be fair and the results for F1, F4 & F6 were found to be passable as given in table 10.

Post-compression Studies

Physical Evaluation of Core tablet: All the physical evaluation tests of core tablet was performed for all the formulations and results are found to be satisfactory. The results were given in table 10.

Physical Evaluation After Enteric Coating: All the physical evaluation tests of coated tablet was performed for all the formulations and results are found to be satisfactory. The results were given in table 11.

Ivitro drug release profile

Acidic stage: No release of drug was seen.

Buffer stage: The dissolution test was performed for all the formulations and results are found to be with in the limit i.e not less than 75% release in 30min and a comparative graph of all formulations was plotted against Time versus Percent drug release in Fig5.

Table 1: Physico-Chemical Properties of Rabeprazole sodium.

Description	white to slightly yellowish-white solid
Chemical name	2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]- methyl] sulfinyl]-1H–benzimidazole sodium salt.
Molecular formula	$C_{18}H_{20}N_3NaO_3S$
Molecular weight	381.43
Solubility	very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane.
Functional category	In the treatment of peptic ulcer mainly for gastro-esophageal reflux diseases.
Pharmacopoeial status	USP
Storage conditions	Store in air tight containers, Protect from light, at a temperature between 2^0C and 8^oC

Table 2: Pharmacokinetics and Pharmacodynamics of Rabeprazole sodium

Parameters	Data
T_{max}	2 to 5 hours
AUC	0.8 µg-h/ml
Bioavailability	52% - 58%
C_{max}	0.41 µg/ml
Biological half life	1 to 2 hours.
Site and Mechanism of absorption	Oral absorption is~50%but as the gastric pH raises a higher fraction (upto ¾) may be absorbed
Serum protein binding	Highly serum protein bound (96.3%)
Route of metabolism	Rapidly metabolized in liver
Metabolites	Two metabolites have been identified in plasma. Thioether and sulfone derivatives. These metabolites have very little or no antisecretory activity.
Activity of metabolites	Have very little or no antisecretory activity
Route of excretion	Urinary excretion is a primary route of excretion of rabeprazole metabolites (90%)
Route of administration	Oral
Indications	Gastric ulcers, Duodenal ulcers, Gastro-esophageal reflux disease, Zollinger-Ellison syndrome,infection caused by H. pylori
Adverse effects	Headache, pain, pharyngitis, flatulence, infection, constipation.

Table 3: Composition of Rabeprazole Enteric Coated Tablets.

S. No.	Ingredients	mg/tab					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
1.	Rabeprazole sodium	20	20	20	20	20	20
2.	Mannitol	73..5	59	44.5	71	56.5	49.5
3.	Sodium Carbonate Anhydrous	6	8	10	6	8	10
4.	Crospovidone	30	40	50	-	-	25
5.	Polyplasdone-xl	-	-	-	40	50	25
6.	L Hydroxy propyl cellulose	-	2.50	5.00	2.50	5.00	-
7.	Talc	0.5	0.5	0.5	0.5	0.5	0.5
8.	Magnesium stearate	5.00	5.00	5.00	5.00	5.00	5.00
Enteric coating stage							
9.	HPMCP 55	17	17	17	17	17	17
10.	Myvacet	1.72	1.72	1.72	1.72	1.72	1.72
11.	Pigment blend Yellow	2.28	2.28	2.28	2.28	2.28	2.28
12.	Ethanol	q.s	q.s	q.s	q.s	q.s	q.s
13.	Purified water	q.s	q.s	q.s	q.s	q.s	q.s

Table 4: Organoleptic evaluation of Rabeprazole sodium.

Parameter	RABEPRAZOLE SODIUM
Organoleptic Evaluation	White to slightly yellowish-white solid
Solubility Analysis	Very soluble in water and methanol, Freely soluble in ethanol, chloroform, and ethylacetate, insoluble in ether and n-hexane.

Table 5: Calibration curve values of Rabiprazole sodium.

s.no	Concentration	Absorbance
1	0	0
2	2	0.061
3	4	0.119
4	6	0.180
5	8	0.241
6	10	0.310

Table 6: Flow Properties and Corresponding Angles of Repose.

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair - aid not needed	36–40
Passable - may hang up	41–45
Poor - must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Table 7: Relation of flow property with HR & CI.

Compressibility Index (%)(CI)	Flow Character	Hauser's Ratio(HR)
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Table 8: Weight variation specification as per IP/BP and USP.

Monograph	Average weight	Deviation (%)
IP/BP	<80 mg	10
	Between 80 and 250 mg	7.5
	>250 mg	5
USP	<130 mg	10
	Between 130 and 325 mg	7.5
	>325 mg	5

Table 9: Drug/ exicipients Compatibility study.

S. No	Composition Details	D:E ratio	Observation at various storage conditions and durations					
			Initial	40/75% RH		60□ 2^0 C		2-8^0 C	
				2W	4W	1W	2W	2W	3W
1	Rabeprazole Sodium (D)		Off White	NC	NC	NC	NC	NC	NC
2	D + Mannitol	1:10	Off White	NC	NC	NC	NC	NC	NC
3	D + Polyplasdone-XL	1:3	Off White	NC	NC	NC	NC	NC	NC
4	D + Crosspovidone	1:3	Off White	NC	NC	NC	NC	NC	NC
5	D + L-hydroxypropyl cellulose	1:10	Off White	NC	NC	NC	NC	NC	NC
6	D + Talc	1:0.5	Off White	NC	NC	NC	NC	NC	NC
7	D + Mg.Stearate	1:5	Off White	NC	NC	NC	NC	NC	NC
8	D + Sodium carbonate Anhydrous	1:10	Off White	NC	NC	NC	NC	NC	NC

NC: No change

Table 10: Flow properties of different formulations.

Formulation	Blend Property					
	B.D (gm/ml)	T.D (gm/ml)	C.I (%)	H.R	Angle of repose	Property
F1	0.480	0.679	22.22	1.275	42	Passable
F2	0.712	0.869	17.17	1.192	37	Fair
F3	0.458	0.715	17.23	1.201	36	Fair
F4	0.503	0.601	23.31	1.264	41	Passable
F5	0.540	0.686	23.26	1.272	43	Passable
F6	0.500	0.600	17.11	1.191	35	Fair

Table 11: Physical Evaluation of Core tablet:

S. No	Physical parameter	F1	F2	F3	F4	F5	F6
1	**Weight variation**	1.41	1.65	1.35	1.23	1.54	1.38
2	**Hardness (kP)**	7	7.2	7.1	7.3	7.4	7.5
	Thickness (mm)	3.97	3.96	3.96	3.95	3.97	3.95
4	**Friability %**	0.18	0.45	0.57	0.48	0.49	0.48
5	**Disintegra-tion time**	1min 44sec	2min 44sec	3min 18sec	2min 44sec	2min 22sec	2min 10sec

Table 12: Physical Evaluation After Enteric Coating.

		F1	F2	F3	F4	F5	F6
Enteric coated Tablet	Hardness (kP)	9.1	9.2	9.3	9.3	9.3	9.2
	Thickness (mm)	4.01	4.01	4.08	4.01	4.08	4.05

Table 13: Ivitro drug release profile of prepared Rabeprazole 20mg DR tablets F1 to F6.

S.NO	Time(min)	F1	F2	F3	F4	F5	F6
1	**0**	0	0	0	0	0	0
2	**10**	0	11	16	9	18	24
3	**20**	58	66	68	61	78	81
4	**30**	78	84	88	83	88	91
5	**45**	85	90	94	90	92	97

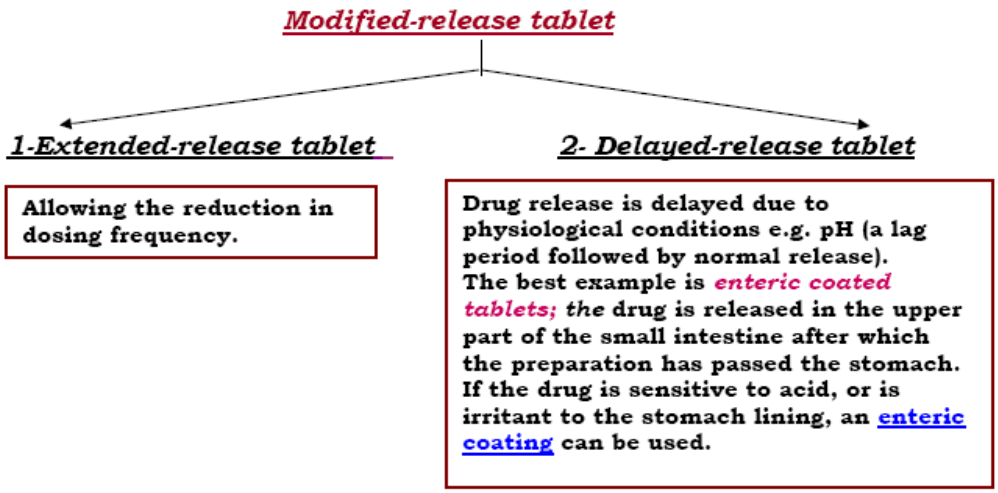

Fig 1: Types of Modified Release Tablet.

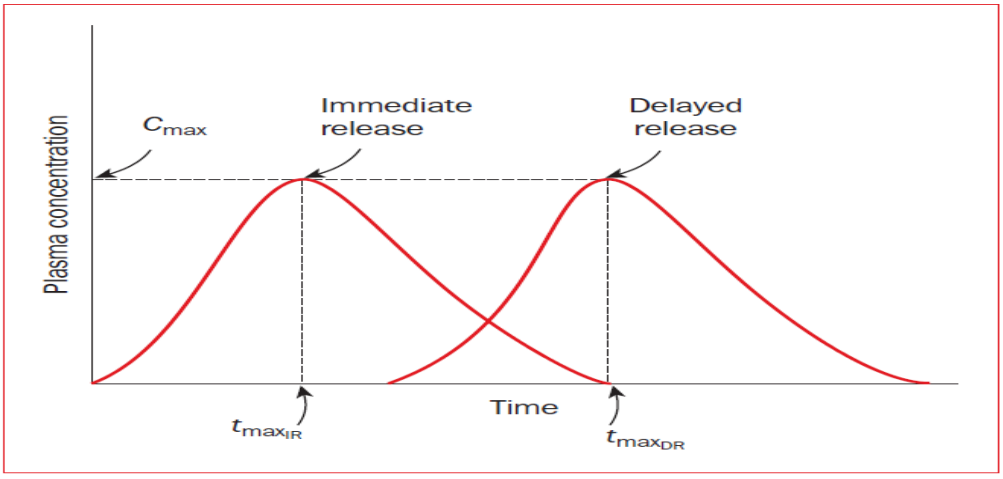

Fig 2: Oral Dosage Form Compared to an Immediate-Release Dosage Form.

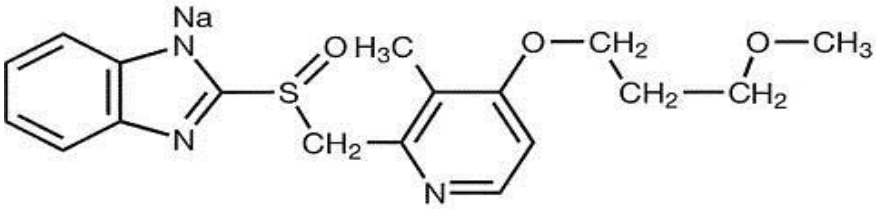

Fig 3: Chemical structure of Rabeprazole sodium ($C_{18}H_{20}N_3NaO_3S$).

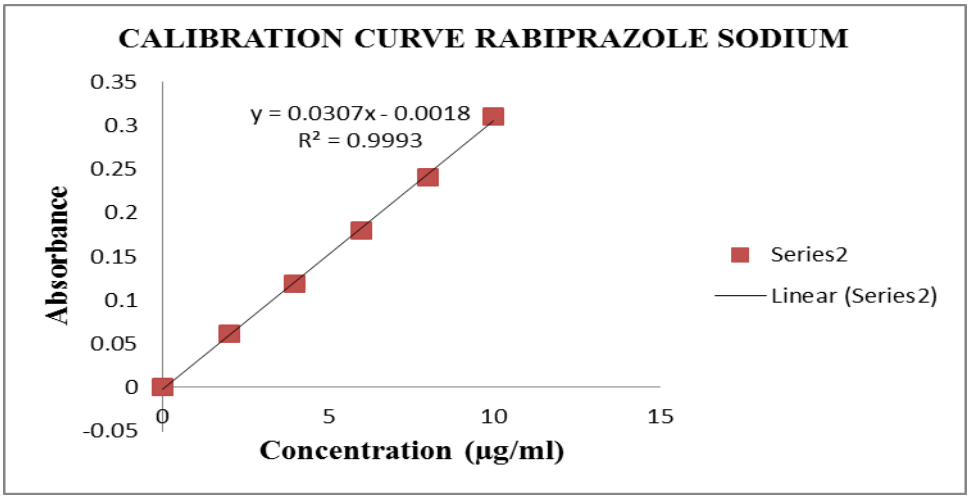

Fig 4: Caliberation curve of Rabeprazole sodium in water (make up with 6.8ph buffer).

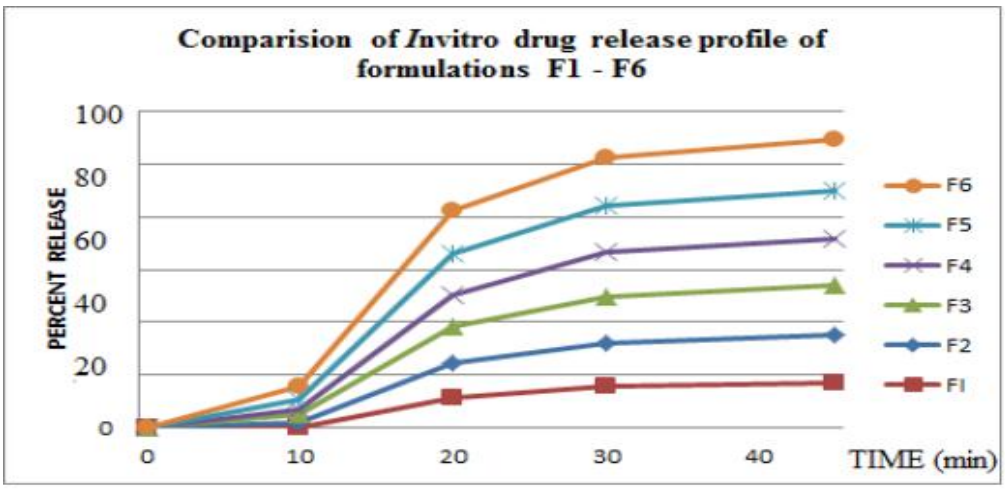

Fig 5: Comparision of *I*nvitro drug release profile of formulations F1 - F6.

CONCLUSION

Delayed release enteric coated tablets of Rabiprazole sodium were prepare and evaluated. Total six formulations of enteric coated tablets of Rabeprazole were developed by preparing core tablets using mannitol as diluents, croscpovidone and polyplasdone-XL as super disintegrants, sodium carbonate anhydroys as stabilizer, magnesium stearate and talc as lubricant and glidant in different proportions and and the prepared core tablets were coated

with enteric coating using hypromellose phthalate 55, myvacet, pigment blend yellow, ethanol and purified water. The core tablets were prepared by Direct compression method. F6 was found to be best of all the formulations showing high drug release than other formulation. Stability study is carried out for 3 months at 25°C; 60% RH: and 40°C; 75%RH, according to ICH guidelines. The identified formula shall be utilized for the formulation development and other studies for successful launching of the product.

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