IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN: 2278-3008, p-ISSN:2319-7676. Volume 9, Issue 5 Ver. I (Sep -Oct. 2014), PP 14-20
www.iosrjournals.org

Formulation Development and Evaluation of Enteric Coated Tablets of Rabeprazole Sodium

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Abstract: *Rabeprazole sodium is highly acid-labile and presents many formulation challenges and to protect it from acidic environment of the stomach an enteric coated tablet formulation is tried in the present study. This study is aimed to develop pharmaceutically equivalent and stable enteric-coated tablets of Rabeprazole sodium comparable to innovator product. Different Formulations of Rabeprazole core tablets were developed using mannitol as diluent and croscarmellose as super disintegrant in different proportions. Further optimized formulation was coated with varying the compositions of sub coating and enteric coating using opadry white and enteric yellow. 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. The kinetics of drug release for F6 & Innovator followed first order and 'n' value (0.5>n<1) shows that the mechanism may be erosion control rate release. The f1 and f2 were found to be 3.03 and 72.01 respectively for formulation F6 and innovator product. Hence these two products were considered similar and comparable. In the accelerated stability testing carried out at 40°c and 75% RH for three months, no significant change in the physical properties, drug content, and dissolution rate of formulation F6 was observed. From this it can be concluded that formulation F6 developed is found to be an efficient delayed release formulations of Rabeprazole comparable to the innovator product. Thus the study fulfilled the objective of developing efficient Rabeprazole delayed release tablets.*

Keywords: *Rabeprazole sodium, Enteric coated tablets, Dissolution rate.*

I. Introduction

Tablets may be defined as a solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. Some drugs resist compression in to dense particles, owing to their amorphous nature or flocculent, low-density character. Drugs with poor wetting, slow dissolution properties, intermediate to large dosage, optimum absorption high in the Gastro intestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet. Bitter tasting drugs with an objectionable odor, or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression. Enteric coatings are those, which remain intact in the stomach, but will dissolve and release 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 nausea or bleeding by irritation of gastric mucosa. Cracking of the film either during application or on storage will result in a loss of enteric properties. Therefore, consideration must be given to the mechanical properties of the applied film. Cracking problems can be effectively overcome by plasticization. Plasticizer can also be used to reduce the permeability of the polymer films to water vapor. The choice of suitable plasticizer is restricted as to non-water soluble materials because these are likely to be most effective. Rabeprazole sodium is highly acid-labile and presents many formulation challenges and to protect it from acidic environment of the stomach an enteric coated tablet formulation was carried out in the present study.

II. Materials

Rabeprazole sodium (Madras Pharma india), Mannitol (Roquette, France), Low substituted Hydroxy propyl cellulose (L-HPC, Shinetu Chemicals, Japan), Ethyl cellulose (Colorcon Asiapvtltd.,India). All other reagents were of analytical grade.

III. Methods:

Preformulation studies:

Calibration curve: Calibration curve was performed with 0.1N HCl and Phosphate buffer pH6.8. The results shows good Corelation coefficient with both the solvents. The results were shown in Fig 1.

Drug– excipient compatibility studies:

The compatibility studies were performed with excipients which may come in contact with the drug. The compatibility of drug with the physical mixture containing Drug, polymer and tablet were evaluated by FT-IR. The IR shows that all peaks are present in the drug are present in the physical mixture and tablet. The spectra was shown in Fig (2-5).

Determinationof bulkdensity and tapped density
Bulkdensity is the ratio of the weight of a powder to the volume it occupies. Itis expressed as gm/ml.

Angle of Repose[2]:
Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\text{Tan}\emptyset = h/r$$

Where, h =Height of pile; r =radius of the base of pile; Ø = angle of repose.

Compressibility Index

Compressibility is in directly related to the relative flowrate, cohesiveness and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density measurements[3].

Hausner ratio:

Hausner ratio is a number that is correlated to the flow ability of a powder or granular material[4]. It is calculated by the formula

$$H = \frac{\rho_T}{\rho_B}$$

Where, ρ_B- freely settled bulk density of the powder

ρ_T is the tapped bulk density of the powder.

Formulation of Tablets

Tablets were prepared by direct compression technique by mixing the drug with different concentrations of super disintegrants and other excipients (Table 1). Blended and compressed. Further Sub coating and Enteric coating was performed.

IV. Evaluation Of Developed Tablets

Thickness
Dimensions of the tablets was measured by usingthe calibrated Vernier calipers**.**
Ten tablets were selected randomly from a batch average thickness was calculated. The readings are shown in the table 3.

Hardness
Ten tablets were selected randomly from a batch and hardness of the tablet was determined by using Monsanto hardness tester. The mean value and standard deviation for each batch was calculated.

DisintegrationTime[7]

The disintegration time was determined by using USP tablet disintegration apparatus Disintegration of tablet was observed first in 0.1N HCl at 37 ± 2^0C for 2 hour and replace with Phosphate buffer pH6.8 and observe it for 1 hr. The time taken for all the tablets to disintegrate was noted. The readings were shown in table 3.

Assay[8,9]

Drug content was determined by HPLC. Phosphate buffer pH 6.8: Acetonitrile was used as mobile phase in the ratio of 530:470 in an Lichrosorb RP-18, 250*4.0 mm, 5µ column maintanind at a temperature of 30º C and the flow rate is 1.0 mml /min. The injection volume is 10 µl.

***In vitro* drug release studies**

In vitro studies were carried out using a USP type II dissolution apparatus. The tablet was placed in 900ml of 0.1N HCl at paddle speed of 100 rpm maintained at 37°C ± 0.5°C for 2 hrs. 10 ml of Sample was taken and analyzed using UV spectrophotometer at 263 nm. Then the dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and tested for drug release for 1 hr at same temperature and same rotation speed. 10 ml of the samples were taken out at 10, 20, 30, 45, 60 minutes and the same volume of medium was replaced. Sample was analyzed using UV spectrophotometer at 281nm. The results are shown in table 6, 7 and fig 13.

Kinetics release

Kinetic release studies were performed for best formulation and innovator to find out the order of release and mechanism of release. The readings were shown in table8.

Similarity Factor and Dissimilarity Factor Calculation[10,11]:

The similarity factor (f2) was defined by CDER, FDA, and EMEA as the logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles. Dissimilarity or difference factor (f1) describes the relative error between two dissolution profiles. There are several methods for dissolution profile comparison. Similarity factor is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f1 &f2

$$f1=\{ [\Sigma_{t=1}^{n} R_t - T_t \Sigma] / [\Sigma_{t=1}^{n} R_t]\} . 100$$

$$f2=50. \text{Log}\{1 +(1/n)\Sigma_{t=1}^{n}(R_t-T_t)^2]^{-0.5}.100$$

Where 'R_t'"T_t' are the cumulative percentage dissolved at each of the selected time point of the reference & test product respectively.

Accelerated Stability Studies

Rabeprazole sodium tablets 20mg were evaluated for accelerated stability studies at 40^0C /75%RH condition[12] carried out for a period of 3months

V. Discussion

Seven formulations of Rabeprazole were developed by preparing core tablets using Carscarmellose as super disintegrant. Once the core tablet was optimized Further the formulations was enteric coated with varying compositions of Drug CoatL100. The compatability studies were studied by FT-IR (Fig 2-5). Pure drug shows peaks at 3436.4 cm^{-1}(Ar-H), 2810cm^{-1} (Ali-H), 1584 cm^{-1} (aromatiC=C), 1300 cm^{-1} (C-N), 1092 cm^{-1} (C-O arylalkylether), 1009cm^{-1} (S-Osulphoxide), 745 (Ar-H bending), same peaks were shown in the physical mixture i.e drug with polymers and tablets. This showsn there is no interaction between drug and polymers. In the preformulation studies the micromeritic flow properties of the API along with excipients were assessed (table 2). The results indicate good free flow of blend and further the blend was compressed into tablets.

In the formulation F1,F2 (Table 1) by using the Croscarmellose concentration at high concentration(4%) and (2%) shows initial burst effect in which is of only 2 mins and drug release was 99% and 93% at the end of 5 mins and 10 mins (Table 6). Since there was initial burst effect at high concentration of Croscarmellulose, the concentration was reduced to 1% in F3 Formulation (Table 1) which fulfills all the specifications of the core tablet as that of innovator. Further The core tablets formulated without superdisintegrant in F4 formulation failed to fulfillthe core specifications. Hence the F3 formulation is considered as best formulation and further coating step was processed.

For F5, F6, F7 formulations sub coating and enteric coating was done with varying concentration of 5%, 6.5% and 7.5% of solid dispersion until the weight build upto 10%, 15%, 20% (Table 1). The F5 formulation fulfilled the core specifications but due to insufficient coating, this formulation failed in the acid resistant stage. So, increased the coating concentration.

In F6 formulation with the solid dispersion of 6.5% w/w, coating as done until the weight build upto15%. The F6 formulation fulfills all the specifications of core tablet, passes the acid resistant stage and also shows a good invitro release profile when compared to the innovator (I) (table 7).

Further F7 formulation was prepared with amount of coating material at concentration of 7.5% and weight build upto 20% passes the acid resistant stage, but there was a lack of drug release in the buffer stage which was only 85% when compare to that of F6 formulation. Hence formulation F6 is considered as effective formulation.

The release kinetics of Rabeprazole was developed and the data was given in (Table 8) indicates that F6 followed first order kinetics. When mechanism of release was analyzed by Peppas equation the'n' value was found to be 0.5839-0.5939 indicatingthat non-fickian (Anomalous) diffusion as the release mechanism may be erosion control rate release.

The dissolution profiles of formulation F6 and innovator product were compared by calculating differential factor (f1) and similarityfactor (f2).The results of f1and f2 (Table 9) were found to be 3.03 and 72.01 respectively for the comparison of dissolution profiles of formulation F6 and innovator product.Hence these two products were considered similar and comparable.

Stability studies conducted on Rabeprazole sodium enteric coated tablets storing in high density polyethylene container at 40^0C / 75 % RH for 3 months. No significant change was observed with hardness, dissolution and assay. The drug release was 95.8% at the end of 60 mins. The drug content was19.95 mg.

VI. Conclusion

Rabeprazole sodium is highly acid-labile and presents many formulation challenges and to protect it from acidic environment of the stomach an enteric coated tablet formulation is tried in the present study. The F6 formulation is quite stable with regard to drug content, physical properties and dissolution rate in the accelerated stability testing and the data is comparable with innovator product. Hence pharmaceutically equivalent and stable enteric-coated tablets of Rabeprazole sodium were prepared which are comparable to innovator product.

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Table 1: Formulation Of Rabeprazole Enteric Coated Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7
Rabeprazole Sodium	21.5	21.5	21.5	21.5	21.5	21.5	21.5
Croscarmellose	5	3	1.5	-	1.5	1.5	1.5
Hydroxy Propyl Cellulose LH-11	7	5	5	8	5	5	5
Hydroxy Propyl Cellulose LH F	3	2.5	2.5	4	2.5	2.5	2.5
Mannitol	81.25	86.5	87.75	84.75	87.5	87.5	87.5
Light Magnesium Oxide	6.75	6	6.75	6.75	6.75	6.75	6.75
Purified Talc	3	2.5	3	3	3	3	3
Magnesium Sterate	7.5	8	7	7	7.5	7.5	7.5

Coating Parameters

Seal Coating	F1	F2	F3	F4	F5	F6	F7
Instacoat IC-S-010	-	-	-	-	4.05(6%)	4.05(6%)	4.05(6%)
Isopropyl Alcohol	-	-	-	-	27	27	27
Methylene Chloride	-	-	-	-	40.05	40.05	40.05
Enteric coating							
Drug CoatL100	-	-	-	-	16(5%)	16(6.5%)	16(7%)
P. Talc	-	-	-	-	3.2	3.2	3.2
Titanium Dioxide	-	-	-	-	1.6	1.6	1.6
Triethyl Citrate	-	-	-	-	0.6	0.6	0.6
Iron oxide Red(Lake)	-	-	-	-	0.84	0.84	0.84
Isopropyl alcohol	-	-	-	-	177	132	132
Methylene Chloride	-	-	-	-	266	199	199
%Weight Gain					10%	15%	20%

Figure 1 : Calibration curve of Rabeprazole sodium in pH 6.8 Phosphate buffer and 0.1N HCL

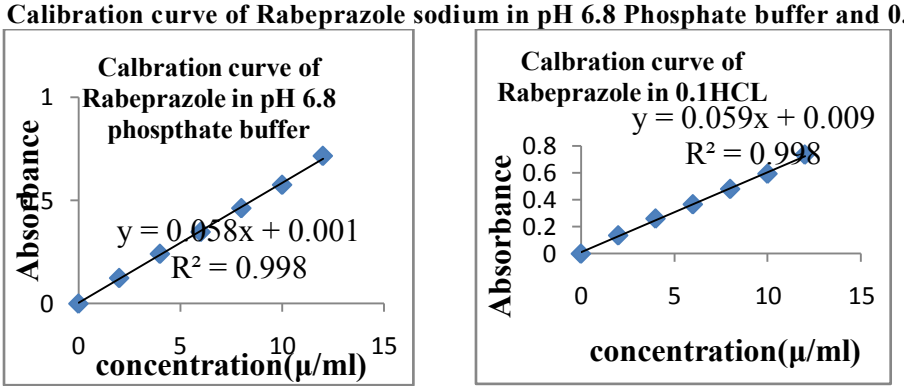


Figure 2 : FTIR Of Drug

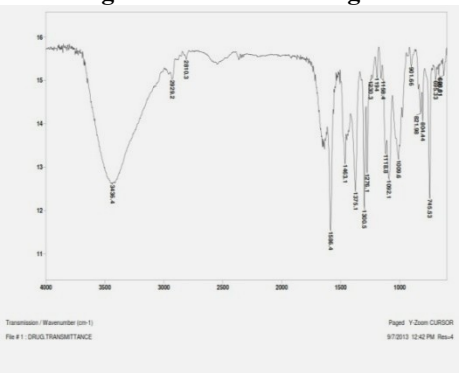


Figure 3 : FTIR Of Drug +CCS Mixture

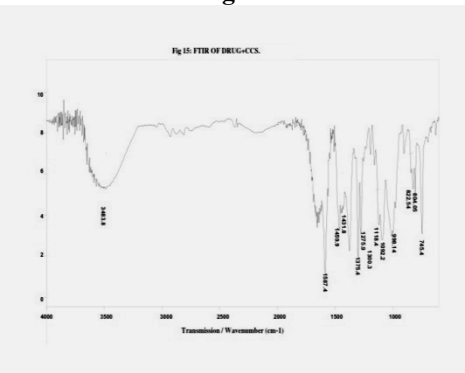


Figure 4 : FTIR Of Drug + HPC Mixture

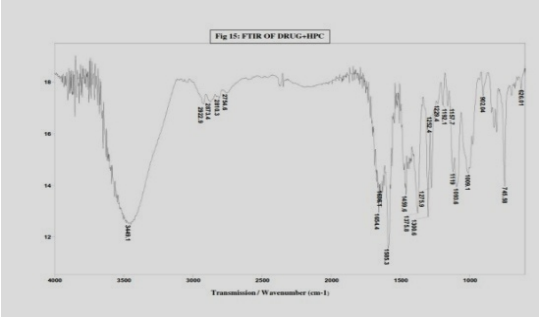


Figure 5 : FTIR Of Tablet

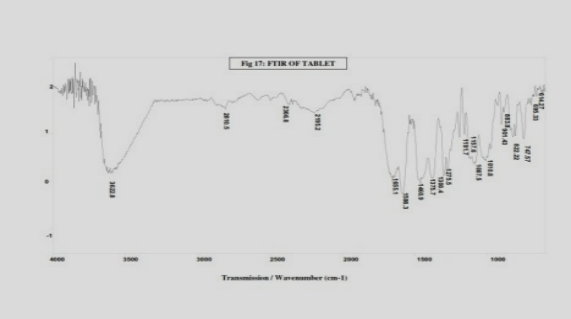


Table 2: Precompression Specifications

Parameters	F1	F2	F3	F4	F5	F6	F7
Bulk density(g/ml)	0.31±0.1	0.31±0.3	0.31±0.1	0.31±0.2	0.32±0.1	0.31±0.2	0.306±0.4
Tapped density(g/ml)	0.37±0.3	0.37±0.1	0.37±0.4	0.36±0.1	0.37±0.2	0.37±0.4	0.36±0.2
Compressib-ilityindex(%)	16.0±0.1	15.8±0.3	15.1±0.1	16.5±0.2	15.5±0.2	15.3±0.2	15.85±0.3
Hausners ratio(%)	1.2±0.2	1.2±0.1	1.17±0.2	1.1±0.4	1.18±0.1	1.18±0.3	1.18±0.1
Angle of Repose	27.9^0± 0.3	29.9^0± 0.3	24.0^0± 0.2	29.5^0± 0.1	27.6^0± 0.4	26.1^0± 0.3	25.5^0 ±0.2

Table 3 : Core Tablets Specifications

Parameters	F1	F2	F3	F4	F5	F6	F7
Average weight (mg)	135±3.5	134.5±4.5	135.1±4	135.7±3.5	134.3±5	134.2±6	135.9±4
Thickness (mm)	2.9±0.02	2.8±0.1	2.9±0.2	2.9±0.2	2.7±0.3	2.9±0.2	2.8±0.1
Friabiity (%)	0.23±0.09	0.19±0.09	0.17±0.01	0.41±0.1	0.27±0.02	0.19±0.01	0.28±0.08
Hardness (Kg/cm^2)	4.5±0.5	5.10±.5	4.90±0.5	5.50±0.5	5.20±0.5	5±0.5	4.8±0.5
Disintegra-tion (min)In buffer solution*	2±1	3±1	9±2	17±2	8±2	7.5±1	9±2

Assay:

Table 4 : Standard Profile

Title	R.T	Area	Theoretical plate	Tailing factor	Area%
Check standard Inj.1	8.71	9704707	4463	1.06	100
Check standard Inj.2	8.72	9588778	4507	1.05	100
Avg	8.71	9646743	4485	1.06	100
%RSD	0.108	0.85	0.686	0.0872	0

Fig 6 :Chromatogram Of Standard 1

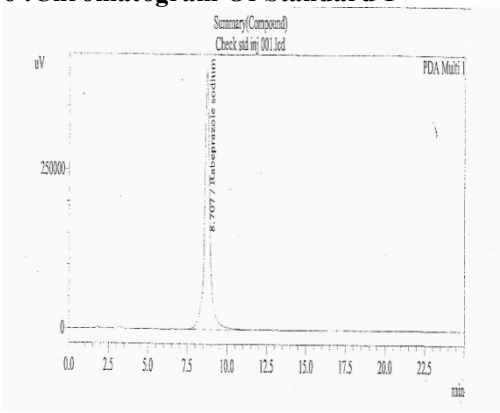


Fig 7 : Standard 2

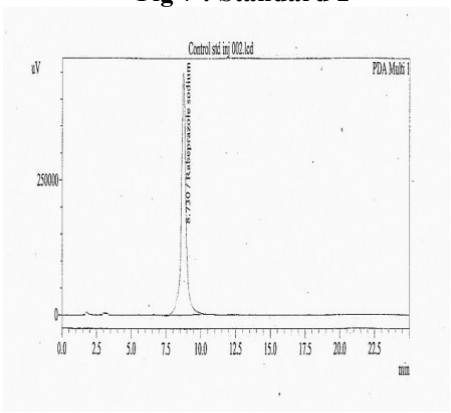


Table 5: Assay Profiles

Title	F3	F5	F6	F7
R.T	8.7	8.73	8.72	8.7
Area	1090188	1093162	10569508	10699508
Theretocal plate	4319	4507	4507	4485
Tailing factor	1.05	1.06	1.06	1.06
Area%	100	100	99.99	100
Assay(mg/tab)	19.078473	18.7385	20.49836	20.278378
Assay%	95.4	93.7	102.5	101.5

Fig 8 : Chromatogram Of F3

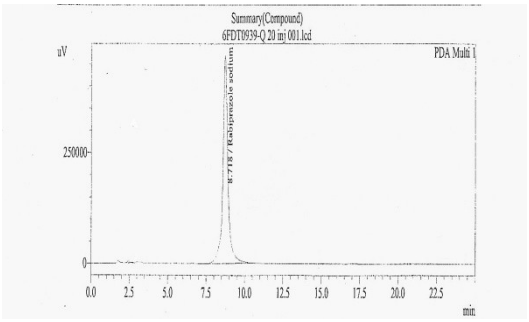


Fig 9 : Chromatogram Of F4

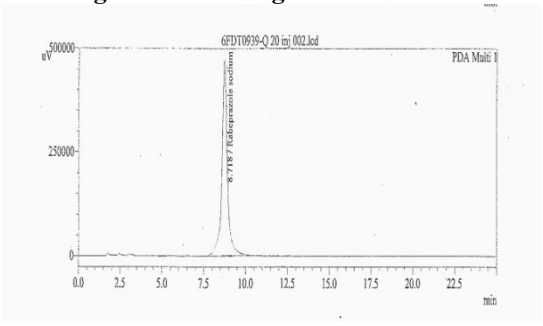


Fig 10 : Chromatogram Of F5

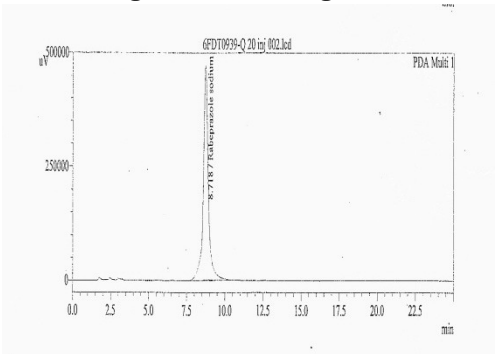


Fig 11 : Chromatogram Of F6

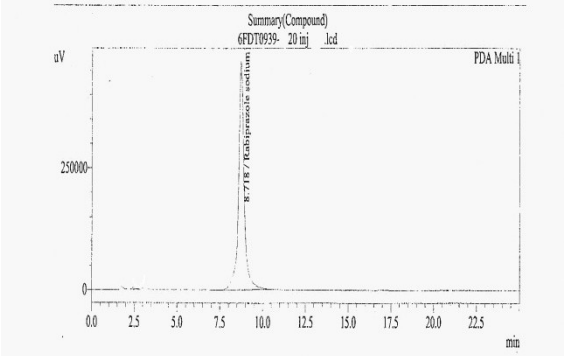
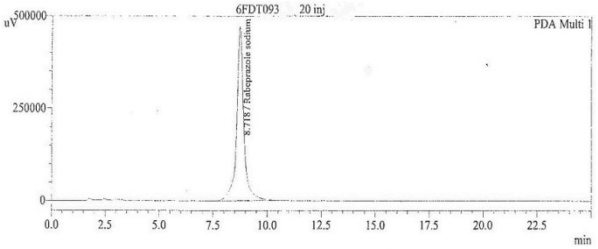


Fig 12 : Assay Chromatogram For F7



***In Vitro* Dissolution**

Table 6 : Cumulative % Drug Release For Core Tablets In pH 6.8 Buffer

Time	% of Drug release			
(mins)	F1	F2	F3	F4
0	0	0	0	0
5	99.1±0.1	79.6±0.9	23.3±0.6	12.3±0.5
10	-	93.3±1.2	32.1±0.9	18.3±0.5
15			65.3±1.2	29.8±0.9
30			81.4±0.1	42.6±0.5
45	-		89.9±0.6	51.9±0.5
60	-	-	96.2±0.4	55.4±0.6

Table 7 : Cumulative % Drug Release For Coated Atblet

	% of drug release			
Time (mins)	F5	F6	F7	I
0	0	0	0	0
30	9.6±1.2	1.5±0.3	1.2±0.2	1.9±0.6
60	12.8±1.4	2.1±0.4	2.1±0.7	3.1±0.2
90	19.9±1.6	4.9±0.2	3.5±0.6	4.2±0.1
120	34.5±0.9	16.7±0.5	15.4±0.9	15.3±0.3
150	-	78.2±0.5	52.4±1.3	82.4±0.2
180	-	95.8±0.9	82.5±0.7	97.2±0.5

Figure 13 :In Vitro Dissolution Data For Coated Tablets (F5-F7& Innovator)

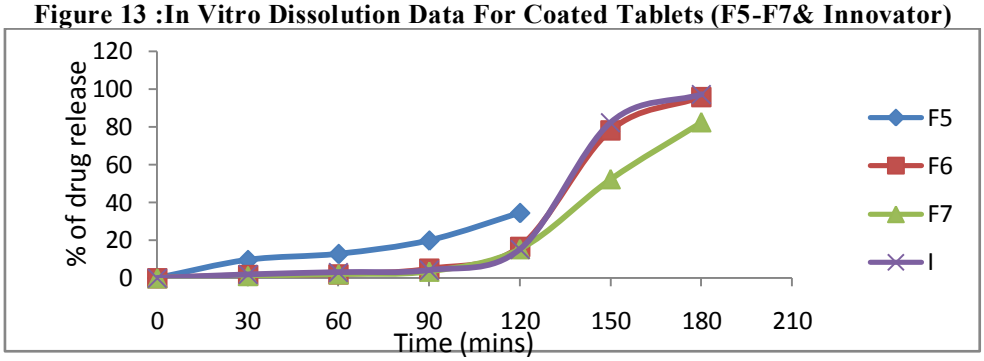


Table 8: Co-Relation Coefficient Values For F6 And I

	Release kinetic model				
Formulation	Zero order R^2	First order R^2	Higuchi model R^2	Peppes model R^2	n
F6	0.8122	0.9906	0.8785	0.8341	0.5839
I	0.8005	0.9899	0.8423	0.8443	0.5251

Similarity Factorand Dissimilarity Factor

Table 9: F1 And F2 Value Of The Rabeprazole Sodiumtablets

Time	Test Release profile	Reference Release profile
0	0	0
130min	29.4	34.1
135min	61.8	64.8
150min	78.2	82.4
165min	89.4	92.3
180min	95.8	97.2

f1=3.03 f2=72.01