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FORMULATION AND EVALUATION OF DELAYED RELEASE TABLETS OF RABEPRAZOLE SODIUM

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ABSTRACT

The main aim of the work is to develop a stable, pharmaceutical equivalent and robust, delayed release tablets of Rabeprazole sodium. This is a proton pump inhibitor which is used in the treatment of Gastric and duodenal ulcer.To achieve this goal, various prototype trials were taken and evaluated with respect to the various quality parameters such as bulk density, sieve analysis, drug uniformity, and dissolution.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.Rabeprazole sodium Delayed release tablets (20mg) were developed by changes of Starch, PVP, CCS and Mannitol SD 200 of all the trials.From the dissolution the formulation F1 shows highest percentage of drug release. The F1 was found to respectively formulation compared to innovator product. Hence these two products were considered similar and comparable.The tablets were prepared by direct compression method. F1 was found to be best formulation compared to other formulations and that profile matching the innovator product.Further optimized formulation was coated with varying the compositions of seal coating and enteric coating.

Key Words: *Delayed release tablets, Enteric Coating, Polyvinyl Pyrrolidine (PVP), Sodium Starch Glycolate (SSG), Cross Carmellose Sodium (CCS), Mannitol, Dissolution Studies.*

INTRODUCTION

Drug delivery has metamorphosed from the concept of pill to molecular medicine in past 100 years. Better apeciation and integration of pharmacokinetics and pharmacodynamic principles in design of drug delivery system has been developed a lead to improve therapeutic efficacy. Drug research has evolved and matured through several phases beginning from pill to pharmaceutical dosage form.The most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally oral dosage forms refer to tablets, capsules, and liquid preparations taken orally, swallowed and transiting the gastrointestinal tract (GIT) for post buccal absorption. Oral route of drug administration has wide acceptance and of the drugs administered orally in solid dosage forms represents the preferred class of products .The reasons are as follows ; Tablets and Capsules represents unit dosage form in which one usual dose of drug has been accurately placed.

1. Tablet coating:

Coating may be defined as: "Tablets covered with one or more layers of mixtures of various substances such as natural or synthetic resin, gums, inactive or insoluble fillers, sugars, plasticizers, polyhydric alcohols, waxes, authorize coloring matters and sometimesflavouring agents".

2. Objectives of coating to the tablets:

1. To mask the taste, odour, or color of the drug.
2. To provide physical and chemical protection for the drug.
3. To control the release of the drug from the tablet.
4. To protect the drug from gastric environment of the stomach with an acid-resistant enteric coating.
5. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
6. To improve the pharmaceutical elegance by use of special colors and contrasting printing.
7. To reduce influence of moisture
8. To improve product identity.

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MATERIALS AND METHODS

1. Materials used:

Table No. 1: Materials used for Tablet Formulation

Sr. No.	Name	Category
1	Rabeprazole sodium	API
2	Alkalizing agent (A)	Stabilizing agent
3	Water insoluble compound(B)	Super disintegrant
4	Water soluble compound(C)	Binder
5	Mannitol SD-200	Diluent
6	Ethyl cellulose 7 cps	Coating agent
7	Crosspovidone –CLM	Disintegrant
8	Sodium stearylfumarate	Lubricant
9	**Coating Ingredients:** HPMCP-55, Pigment yellow, Myvacet.	Coating material (Film – coated)
10	Ethanol	Solvent
11	Distilled water	Solvent

2. Methods used:

2.1.Following are the steps involved in preparation of tablet formulation:

A) Preparation of tablet:

1. Shifting of active material, polymer and excipients from sieve no-30.
2. Shift twice to get a uniform mixing.
3. Dry mixing of step1 ingredient in a blender for 30 mins.
4. Lubrication - shifting of lubricants and blending with the above blend for 5-mins.
5. Compression of lubricated blend.
6. Coating of compressed tablet.

B) Film-coating:

1. Preparation of ethyl cellulose 7cps and crospovidone in the ratio (50:50) and ethyl cellulose and klucel –LF in the ratio

(20:80) with the help of magnetic stirrer in the ethanol and water solution.
2. The solution of ethanol: water is (80:20).
3. The strength of the seal coating solution is (10%W/W).

C) Enteric coating:

1. Ethanol and water is made in the ratio (80:20).
2. To the above solution HPMCP-55 is added and with the help of magnetic stirrer the Solution is mixed thoroughly.
3. To the above solution Myvacet (plasticizer) and pigment blend is added and Stirredwell.
4. The enteric coating solution strength was made 10% w/w.

2.2. Parameter for Evaluation of Designed Formulation:

2.2.1. Pre-compression parameters:

Bulk density:

Bulk density of Diclofenac potassium & Thiocolchicoside was determined by pouring gently 14.6 gm and 15.3 gm of sample (rabeprazole sodium) through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density = weight of sample in gram /volume occupied by the sample

Tapped density:

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylindermounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

Tapped density = Wt. of sample in gm / Tapped volume

Compressibility Index and Hausner ratio:

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics.

Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density of a powder.

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hauser's Ratio = Tapped Density / Bulk Density

Table No. 2: Relation of flow property with HR & CI

Compressibility Index (%)	Flow Character	Hauser's Ratio
≤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

Angle of Repose:

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\tan\theta = h / r$$
$$\theta = \tan^{-1} h / r$$

Where,θ = angle of repose, h = height, r = radius.

Table No. 3: Flow Properties and Corresponding Angle 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

2.2.2.Post compressional parameters:

Uniformity of weight:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation, if not more than two of the individual weights deviates from the average weight by more than the percentage shown in the Table and none should deviate by more than twice the percentage shown. The average weight and standard deviation of the tablets of each batch were given in the table.

Table No. 4: Weight Variation Specification

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

Thickness:

The control of physical dimension of the tablet such as thickness is essential for consumer acceptance and to maintain uniformity of tablet weight. Six tablets were randomly selected from each batch and their thickness was measured by using vernier callipers. The average thickness with standard deviation of the tablets from each batch were measured and tabulated.

Hardness:

The tablet crushing load is the force required to break a tablet by compression. Hardness was measured by using hardness tester (Dr.Schleniger hardness tester). For each batch, six tablets were selected randomly and evaluated.

Friability:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for this purpose. Pre weighed sample of twenty tablets were placed in the friabilator, which was then operated for 100 revolutions. After 100 revolutions the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

$$\text{Percentage Friability} = \frac{(\text{Initial Weight} - \text{Final Weight})}{\text{Final Weight}} \times 100$$

Disintegration Time:

Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in water (37 ± 0.5 °C) using United States Pharmacopeia (USP) disintegration apparatus.

Disintegration time (D.T.):

It is determined by using USP device which consist of 6 glass tubes that are 3 inches long, open at one end and held against 10 mesh screen at the bottom end of basket rack assembly.

To test for disintegration time, one tablet is placed in each tube and the basket arck is positioned in a1 liter beaker of water at 37^0C ± 2^0C.A standard motor driven device is used to move the basket assembly up and down.

In vitro Dissolution studies:

Table No. 5: Dissolution parameters

Dissolution medium	**0.1 N Hcl followed by PH- 8 buffers.**
Dissolution medium volume	**1000 ml**
Apparatus	**USPII, Paddle.**
Speed	**100 rpm**
Time	**180 min**
Sampling interval	**125,130,140,150,&180(min)**

RESULTS

Table No. 6: Formulation of the product F1-F4 (Tablet)

Sr. No.	Ingredients	Formulation Codes			
		F-1	F-2	F-3	F-4
Tablet:: quantity(mg/unit)					
1	Rabeprazole sodium	20.00	20.00	20.00	20.00
2	Alkalizing agent(A)	10.00	10.00	10.00	10.00
3	Water soluble compound(B)	50.00	50.00	40.00	40.00
4	Water insoluble compound(C)	------	------	2.50	2.50
5	Mannitol SD-200	52.30	52.30	59.80	59.80
6	Sodium stearyl fumarate	2.70	2.70	2.70	2.70
Weight / Tablet		135.00	135.00	135.00	135.00
Seal coating %weight build up		4%w/w	6%w/w	4%w/w	6%w/w
1	Ethyl cellulose 7cps	2.7	2.7	2.7	2.7
2	Crospovidone CLM	2.7	2.7	2.7	2.7
3	Hydroxypropyl cellulose(HPC)	-------	-------	-------	------
Seal coated tablet weight/tablet		140.50	143.20	140.50	143.20
Enteric coating %weight build up		15%w/w	15%w/w	15%w/w	15%w/w
1	HPMCP-55	16.30	16.30	16.30	16.30
2	Myvacet	1.60	1.60	1.60	1.60
3	Pigment blend	2.50	2.50	2.50	2.50

Table No. 7: Formulation of the product F5-F8 (Tablet)

Sr. No	Ingredients	Formulation codes			
		F-5	F-6	F-7	F-8
Tablet:: quantity(mg/unit)					
1	Rabeprazole sodium	20.00	20.00	20.00	20.00
2	Alkalizing agent(A)	10.00	10.00	10.00	10.00
3	Water soluble compound(B)	50.00	50.00	40.00	40.00
4	Water insoluble compound(C)	5.00	5.00	5.00	5.00
5	Mannitol SD-200	47.30	47.30	59.80	59.80
6	Sodium stearyl fumarate	2.70	2.70	2.70	2.70
Weight / Tablet		135.00	135.00	135.00	135.00
Seal coating %weight build up		4%w/w	6%w/w	6%w/w	8%w/w
1	Ethyl cellulose 7cps	2.7	2.7	1.60	2.00
2	Crospovidone CLM	2.7	2.7	------	------
3	Hydroxypropyl cellulose(HPC)	------	------	6.40	8.00
Seal coated tablet weight/tablet		140.50	143.20	143.20	145.50
Enteric coating %weight build up		15%w/w	15%w/w	15%w/w	15%w/w
1	HPMCP-55	16.30	16.30	16.30	16.30
2	Myvacet	1.60	1.60	1.60	1.60
3	Pigment blend	2.50	2.50	2.50	2.50

Table No. 8: Pre Compression parameters of Tablets

Trial No.	Tablet blend				
	B.D (gm/ml)	T.D (gm/ml)	C.I (%)	H.R	Property
F2	0.672	0.829	18.98	1.234	Fair
F3	0.541	0.691	21.62	1.276	passable
F4	0.541	0.691	21.62	1.276	passable
F5	0.501	0.605	17.19	1.207	passable
F6	0.501	0.605	17.19	1.207	Fair
F7	0.501	0.605	17.19	1.207	Fair
F8	**0.501**	**0.605**	**17.19**	**1.207**	Fair

Table No. 9: Evaluation Parameters for Prepared formulations

Formulation	Avg. Weight (Mean± S.D) (n=20)	Thickness (mm) (n=10)	Hardness (Kp) (n=10)	Friability (%w/w) (n=10)	Disintegration time
F1	164±1.06	3.53±0.23	5.2±1.1	0.12	7Min 58sec
F2	163±1.13	3.51±0.11	5.3±0.92	0.11	8Min 30sec
F3	163±1.19	3.51±0.12	5.3±0.89	0.14	7Min 40sec
F4	164±1.69	3.50±0.30	5.4±0.81	0.13	7Min 50sec
F5	164±1.65	3.50±0.01	5.2±1.16	0.15	7Min 50sec
F6	164±1.82	3.50±0.10	5.1±1.4	0.08	8Min 25sec
F7	164±1.85	3.50±0.09	5.2±1.6	0.12	7Min 35sec
F8	164±1.25	3.50±0.28	5.2±1.5	0.13	7Min 50sec

Table No. 10: Results of Compatibility study

Sr. No	Name of the Excipient	Ratio API: Expt	Initial Observation	Final observation 40°C/75% RH		conclusion
				1 month	2 month	
1	API (rabeprazole sodium)	---	White to yellowish white	White to yellowish white	White to yellowish white	Compatible
2	API+ alkalizing agent (A)	1 :0.5	White fine powder	White fine powder	White fine powder	Compatible
3	API + WSC (B)	1 : 1	off-white	off-white	off-white	Compatible
4	API + WIC(C)	1 : 1	White	White	White	Compatible
5	API + Mannitol SD-200	1 : 1	Off white	Off white	Off white	Compatible
6	API + Sodium stearyl fumarate	1 : 0.05	White	White	White	Compatible
7	API 1 + Mg. Stearate	1 : 0.05	White	Colour change	Colour change	incompatible
8	API + ethyl cellulose 7cps	1 : 2	White	White	White	Compatible
9	API + Water insoluble compound (D)	1: 1	White	White	White	Compatible

Table No. 11: Standard data of Rabeprazole Sodium

S. No.	Concentration (µ/ml)	Absorbance
1	0	0
2	2	0.152
3	4	0.315
4	6	0.462
5	8	0.623
6	10	0.75

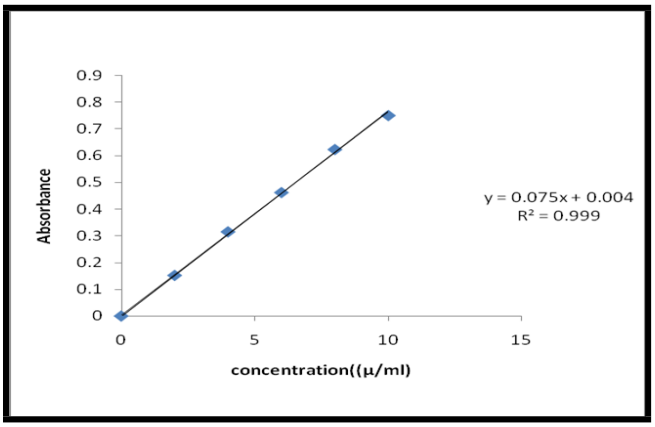

Fig. 1: Stanadard plot of Rabeprazole Sodium

Table No. 12: Dissolution profiles of Rabeprazole sodium (F1-F4)

	Marketed prod.	% Drug release of the Trials			
Time(in min)	PARIET 20mg	T --- 1	T --- 2	T --- 3	T --- 4
125	0	0	0	0	0
130	2	0	0	0	0
135	21	46	1	37	1
140	87	93	71	89	84
150	95	94	92	97	97

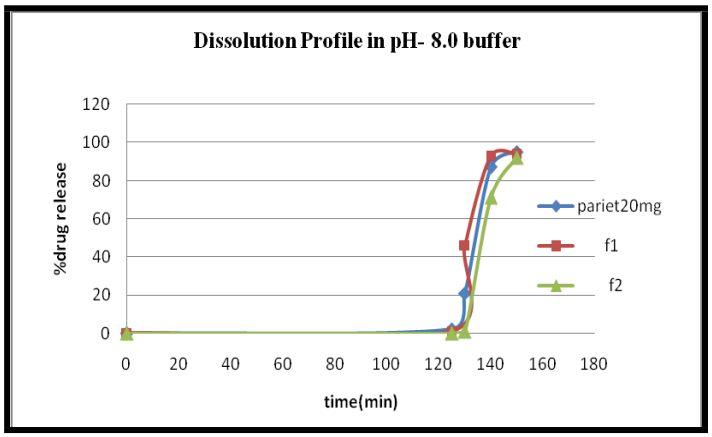

Fig. 2: Dissolution profile for F-1 and F-2 Formulation

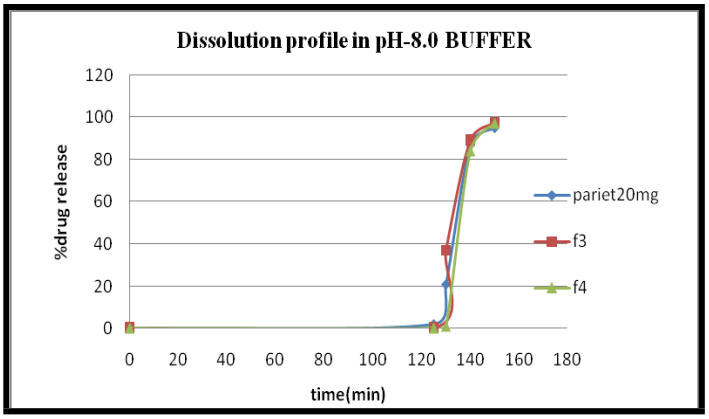

Fig. 3: Dissolution profile for F-3 and F-4 Formation

Table No. 13: Dissolution profiles of Rabeprazole sodium (F1-F4)

	Marketed prod.	% Drug release of the Trials			
Time(in min)	PARIET 20mg	T --- 5	T --- 6	T --- 7	T --- 8
125	0	0	0	0	**0**
130	2	0	0	0	**0**
135	21	1	0	11	**0**
140	87	64	55	93	**59**
150	**95**	**83**	**87**	**94**	**97**

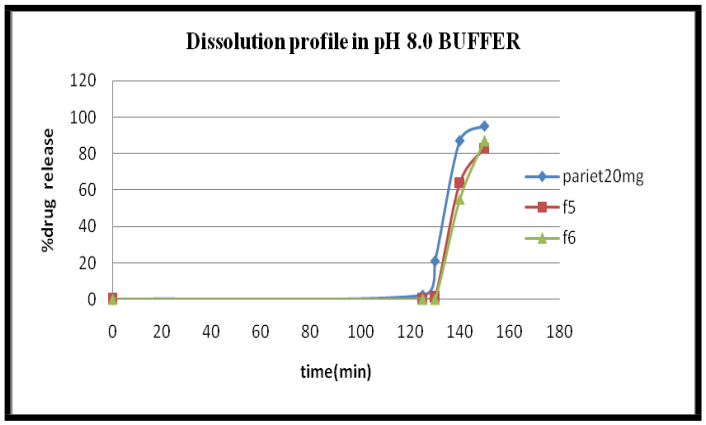

Fig. 4: Dissolution profile for F-5 and F-6 Formation

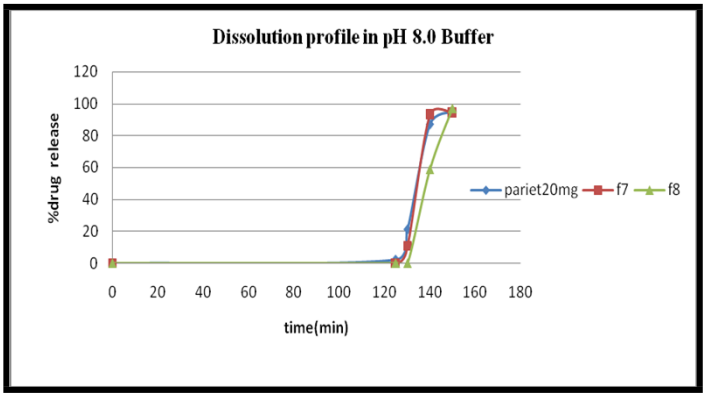

Fig. 5: Dissolution profile for F-7 and F-8 Formation

Table No. 14: Physical observations for core tablets of all the trials

Trial no.	Physical observations	
	After 1 month	After 2 months
F-1	No colour change and tablets appeared good.	No colour change and tablets appeared good.
F-2	No colour change and tablets appeared good.	No colour change and tablets appeared good.
F-3	Brown spots appeared on the tablet surface.	Tablets were broken.
F-4	Brown spots appeared on the tablet surface.	Tablets were broken.
F-5	No colour change and tablet appeared good	No colour change and tablet appeared good
F-6	No colour change and tablet appeared good	No colour change and tablet appeared good
F-7	Light brown spots appeared on the tablets.	Light brown spots appeared on the tablets and tablets are broken.
F-8	Light brown spots appeared on the tablets.	Light brown spots appeared on the tablets

Table No. 15: Results of stability studies of optimized formulation F-1.

Time points	F-1	40°C/ 75%RH	
	Initial	1 month	2 months
0	0	0	1
125	0	0	0
130	46	53	31
140	93	84	75
150	94	94	86

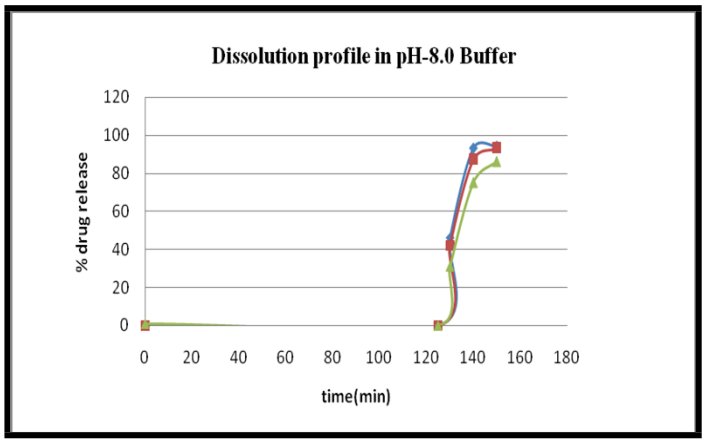

Fig. 6: Dissolution profile of Final trial (F-1)

SUMMARY

Suitable analytical method based on UV- Visible spectrophotometer was developed for Rabeprazole sodium wave length of 280 nm was identified in 0.1N Hcl buffer solution pH 8.

Different ratios of pvp, starch,cross carmellose sodium,mannitol SD-200 using in different formulations by direct compression method.

Direct compression Method was established to delayed release tablets of Rabeprazole sodium.

Delayed release tablets of Rabeprazole sodium were successfully prepared using cross carmellose sodium and mannitol SD-200.

In the present study,delayed release tablets were using single super disintegrate and two times coating in each formulation.

Evaluation of parameters like hardness,friability,weight variation,disintegration, thickness values were within permissible limit for all formulations.

In vitro drug release study was carried out and basedon the results F-1 was identified as the best formulation among all the other formulations and invitro release profile was 95%. Hence the formulation F-1 was optimized after 3 months of accelerated stability studies developed formulation was found to be stable for the tablets of formulation F1.

The delayed release tablets of Rabeprazole sodium in this investigation release .Thus we are able to achieve our objective, with using minimum excipients and simple method.

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.Rabeprazole sodium Delayed release tablets(20mg) were developed by changes of Starch, PVP, CCS and Mannitol SD 200 of all the trials.From the dissolution the formulation F1 shows highest percentage of drug release.The F1 was found to respectively formulation compared to innovator product. Hence these two products were considered similar and comparable.The tablets were prepared by direct compression method. **F1** was found to be best formulation compared to other formulations and that profile matching the innovator product.Further optimized formulation was coated with varying the compositions of seal coating and enteric coating.

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