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Research paper

FORMULATION DEVELOPMENT AND EVALUATION OF DELAYED RELEASE TABLET OF PROTON PUMP INHIBITOR

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These include physical and chemical stability, ability to be economically mass produced in a manner that assures the proper amount of drug in each and every dosage unit and in each batch produced and as far as possible patient acceptability. The set of batches from A-9 to A-12 were compressed with light grade of magnesium oxide in place of heavy magnesium oxide. It was assumed that due to fluffy nature (table 5.3) of light grade, it can effectively coat drug particles. Thus, to improve stability of core tablet, light magnesium oxide was decided to use. Seal coat was applied to prevent direct contact between acid labile core and enteric polymers. Crotts et al34. used concept of seal coat to stabilize the formulation and also to control the release rate. Oshlock et al37. used EC for intermediate "barrier" coating. In all cases, drug release in first 10 minutes was 0%, which is not acceptable. When f2 value was calculated for all the lots of batch A-10-III, f2 value was found below 50% and hence formulation is not considered as therapeutic equivalent with the innovator sample. It was concluded from the results that higher the concentration of hydrophobic polymer, drug release rate decreases. Present work is an attempt to formulate and evaluate rabeprazole into a delayed release tablet formulation, followed by enteric coating of the same.

Keywords: NSAIDs, GERD/PUD, GI market, PPI.

INTRODUCTION

The most important role of a drug delivery system is to get the drug ‘‘delivered’’ to the site of action in sufficient amount and the appropriate rate; however it must also meet a number of other essential criteria. A generic drug is identical or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counter parts, they are typically sold at substantial discounts from the branded price. Generic drugs can be legally produced for drugs.[1] Gastro resistant tablet also known as enteric coated table, actually enteric coating is aimed towards resisting the drug from coming in contact with the hostile acidic environment of the stomach. So it can correctly be called as gastro-resistant tablet also.[2] Some drugs are irritating to gastric mucosa when directly exposed to gastric mucosa. (eg. Aspirin, NH_4Cl). Finally the pylorus is the curved base of the stomach. Gastric contents are expelled into the proximal duodenum via the pyloric sphincter.[3] The secretory activities of the parietal cells can keep the stomach contents at a pH of 1.5–2.0. This highly acidic environment does not by itself digest chyme, If there is not enough acid, this valve does not open and the stomach contents are churned up into the esophagus. However, there is still enough acidity to irritate the esophagus. Gastric H2 receptor blockers (such as ranitidine, famotidine and cimetidine) can reduce gastric secretion of acid.[4] These drugs are technically antihistamines.

They relieve complaints in about 50% of all GERD patients. HPMCP may be plasticized with diethyl phthalate, acetylated monoglyceride or triacetin. Mechanically it is a more flexible polymer and on a weight basis will not require as much plasticizer as CAP or CAT.[5]

MATERIAL AND METHODS

Formulation of Gastro resistant tablet 20 mg of rabeprazole, with improved micromeritic properties of granules so that tablet granule blends can be fed into high speed tableting machines, without hampering the physical parameters, causing any tablet defects or compromising required specifications resulting in improved productivity and bioavailability of the drugs. To prevent degradation in acidic stomach environments, formulations are available as enteric coated tablets so that absorption begins only after the granules leaves the stomach.[6] pantoprazole (PROTONIX), omeprazole (PRILOSEC), Chloroform (Kay Cee Chemicals, Delhi), Methanol & ethanol (Chaudhary chemicals UP), Ether (Vats International, Delhi),, Glycerin (Chandra chemicals Delhi),Acetone (Trivalent Chemical, Vapi), Sodium Chloride(Vats International, Delhi), Nitric acid (Sigma chemical company, St. Louis Mo, USA), Isopropyl alcohol(Changshu yangyuan chemical, china), Benzene (Motion Aerosols, Delhi), sodium hydroxide(Vats International, Delhi), were provided by Rajasthan college Pharmacy, Udaipur. Spectral Analysis (IR, NMR & Mass) was done at NIPER Mohali.

EVALUATION TESTS

Weight variation

To maintain the coating uniformity, uniformity in weight of core tablet is necessary. The test was performed during and after compression process. Samples of 10 tablets were taken and weighed at fixed time intervals throughout the compression process. The USP weight variation test was carried out after the completion of the compression process, by weighing 20 tablets individually, comparing the individual weight with the average weight of tablets.[7]

The tablets meet the USP test if not more than 2 tablets were outside the percentage specification limit and if no tablet differs by more than 2 times the percentage limit.

Table 1:Weight variation Tolerance for Uncoated Tablets

Sr.No	Average Weight of Tablets (mg)	Maximum Percentage Difference Allowed
01	130 or less	10%
02	130-324	7.5%
03	More than 32	5%

Physical parameters of uncoated tablet

Thickness

Thickness is an important parameter which is required to maintain in fixed range. Vernier callipar was used for calculation of thickness and diameter of the tablets. For this test sample of 10 tablets were taken. The test was carried out during and after the compression process.[8]

Hardness

Hardness of tablets are maintained in optimal range

as too hard tablet takes more time to disintegrate while too less hardness may cause tablet to chip and crack. Hardness and thickness are having inverse relation. The hardness of 10 tablets was determined with a digital tablet hardness tester. The hardness was checked during tablet compression.

Friability[65]

The percentage friability of the uncoated tablet formulations was determined with Roche Friabilator. Tablets were weighed such that the weight of the tablets was not less than 6.5 gm. The tablets were carefully dedusted prior to testing. Accurately weighed the tablet sample and placed the tablets in the friabilator, which was then operated for 100 revolutions with a speed of 25 rpm. The tablets were then dusted and reweighed. When the weight loss is greater than the targeted value, the test was repeated twice and the mean of the three tests were determined. A maximum weight loss from the three samples of not more than 1.0 % was considered acceptable for most products. When capping was observed on friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss seen.[9]

$$\text{Friability (\%)} = \frac{\text{Initial Wt. – Final Wt.}}{\text{Initial Wt.}} \text{ X 100}$$

Disintegration time[66]

Disintegration test was performed on uncoated tablets during compression process as well as during coating process. Samples of uncoated tablets from batch A-1 to A-12 were subjected to disintegration test. The disintegration media was distilled water at a temperature of 37°C. The disintegration time of each tablet unit was checked separately by visual inspection.

Analytical process

Analysis was carried out using HPLC. Sample to be analyzed was injected into the HPLC, the chromatograms were recorded and the responses were measured for the principal peak area.

% of drug release was calculated using following formula[10]

Drug release % w/w = $\frac{Au}{As} \times \frac{W}{100} \times \frac{2}{50} \times \frac{1000}{20} \times \frac{P}{100} \times 100$

Assay

Assay was carried out for uncoated tablet, coated tablet and samples withdrawn from stability studies. Five intact tablets of the test substance being examined were transferred (equivalent to 100 mg) into a 100 ml volumetric flask. 60 ml diluents was added and sonicated. It was dissolved and diluted to volume with diluents and mixed. Solution was filtered through 0.45 µm nylon filter. 5 ml of this filtrate was diluted with 20 ml diluents.[11]

Content of drug in % were calculated using following formula

Drug release % w/w = $\frac{Au}{As} \times \frac{\text{W1}}{200} \times \frac{2}{50} \times \frac{100}{\text{W2}} \times \frac{20}{5} \times \frac{\text{Avg. wt}}{\text{L. C}} \times \text{P}$

Relative substance

Sample preparation was same as described in assay procedure. 10 µl of each blank preparation, system suitability solution and sample preparation were injected. Chromatogram was allowed to run

for 45 minutes and the chromatogram was recorded. Any peak due to blank preparation was not considered and calculated the percentage of purity, any individual unknown impurity, known impurity and total impurities by normalization method.

Calculation

% any individual unknown impurity = 5 area by normalization

% known impurity = % area by normalization X correction factor

% total impurities = % of sum of known impurities + % of sum of all unknown impurities

STABILITY STUDIES[67]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

Stability studies were performed on innovator samples and final development batches (A10-II–S3-E4, A11-S3-E4, A12-S-E). Stability studies were carried out as per ICH guidelines Q1A (R2). Approximately 30 tablets were packed in HDPE container with cotton and activated silica and kept in stability chamber.

Stability studies were carried out under long term condition (25°C ± 2°C/60% RH ± 5% RH) for 12 months and accelerated condition (40°C ± 2°C/ 75% RH ± 5% RH) for 6 months.

Stability protocols were prepared for all those batches charged for stability. Protocol contained storage condition, batch no. and date of manufacture, date of stability charging, sampling duration and evaluation tests to be carried out.

General tests to be carried out were physical appearance of tablet, film deformities if any, hardness, relative substances and assay. All test results were compared to the results of innovator sample. One month stability results of the optimized batches are shown in results and discussion section.

RESULTS

PRFORMULATION STUDIES-

Characterization of API-Drug Rabeprazole was found off white to light yellow powder, amorphous powder which was as per specification.

Identification of pure drug The IR spectrum of pure drug was found to be similar to the standard spectrum of Rabeprazole. The spectrum of Rabeprazole shows the following functional groups at their frequencies.

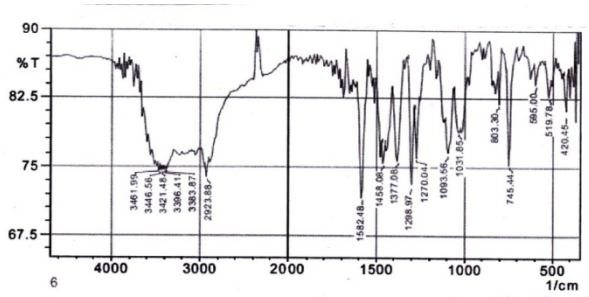

Fig.1: IR Spectra of Rabeprazole

Solubility Studies

Solubility tests of drug Rabeprazole was performed at different pH i.e.1.2, 6.8 and 8. Results are tabulated in table 5.1. It was concluded from the results that Rabeprazole was slightly soluble at

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acidic pH and solubility increased with increase in pH. Rabeprazole was found freely soluble in water and soluble in methanol and ethanol. Drug was analyzed for compliance with COA. Table 4.3 shows all analytical parameters are within specifications.

Table 2: Solubility results

Sr. No	Buffer pH	Solubility practically (gm/ml)	Solubility specification (gm/ml)
01	1.2	5.7	Slightly soluble
02	6.8	53.1	Sparingly soluble
02	8.0	86.8	Very soluble

Standard calibration curve of Rabeprazole

Method used to estimate Rabeprazole

The drug rabeprazole was dissolved in distilled water to get 10 µg/ml solution. Further diluted with the same and scanned for maximum absorbance (λmax) in a UV-VIS Spectrophotometer, (double beam) Shimadzu, Japan between a U.V range from 200 to 400 nm against distilled water as blank.

Calibration curve of Rabeprazole

Stock solution of Rabeprazole was prepared by dissolving 100 mg of accurately weighed amount of Rabeprazole in 10 ml of distilled water and then the volume was adjusted to 100 ml with the same solution.

Procedure

The above stock solution of drug was subsequently diluted with distilled water to get 2ug, 4ug, 6ug, 8ug, 10ug, 12ug, 14ug, 16ug, 18ug, and 20ug of drug per ml. Then the absorbance of these dilute solutions was measured at a l max of 284 nm by using double beam U.V. spectrophotometer against a blank of distilled water. Average of triplicate readings was taken and tabulated. The analytical method so developed was validated for precision, accuracy and linearity.

Table 3: Standard calibration curve for Rabeprazole

Sr.no	Concentration	Absorbance
1	0	0
2	2	0.085
3	4	0.17
4	6	0.259
5	8	0.342
6	10	0.428
7	12	0.519
8	14	0.596
9	16	0.689
10	18	0.768
11	20	0.872

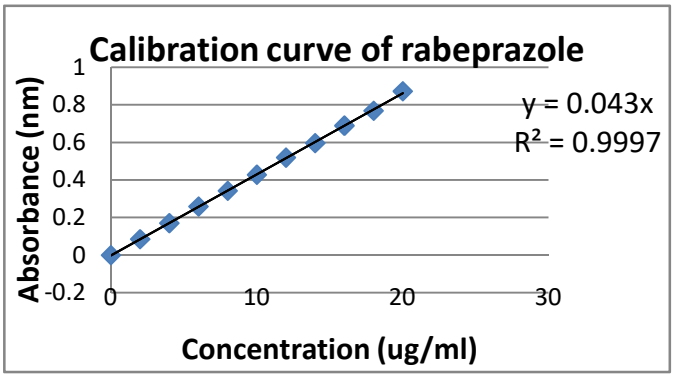

Fig. 1: Standard calibration curve of Rabeprazole

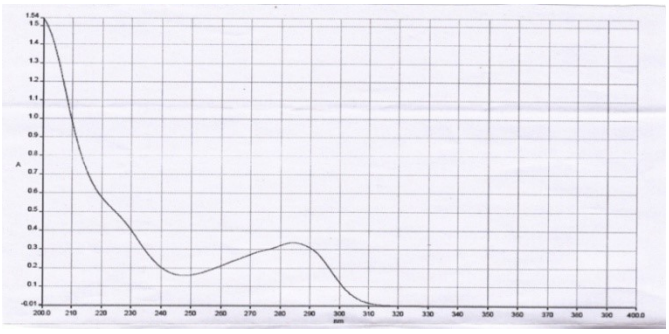

Fig. 2:U.V Spectra of Rabeprazole in Distilled Water (λ_{max} - 284nm)

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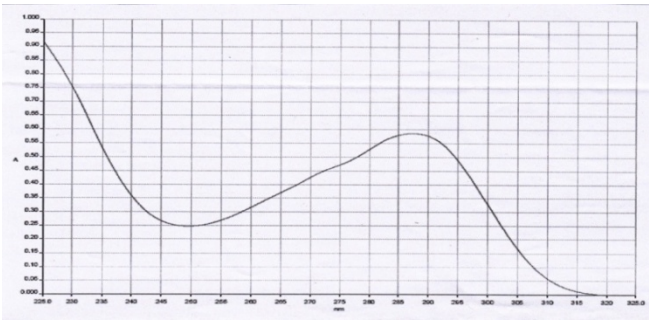

Fig. 3: U.V Spectra of Rabeprazole in HPLC Water (λ_{max} - 287nm)

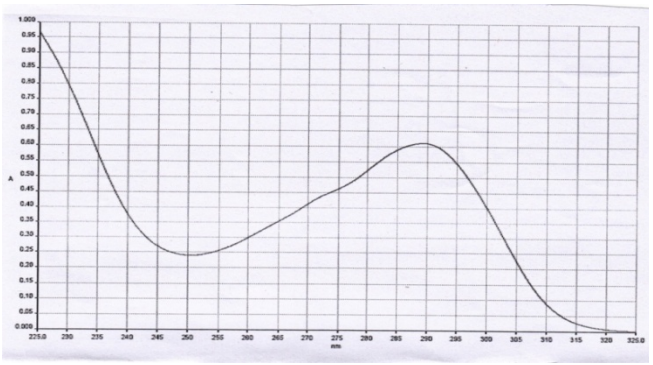

Fig. 4: U.V Spectra of Rabeprazole in Water (pH-8.0)(λ_{max} - 289nm

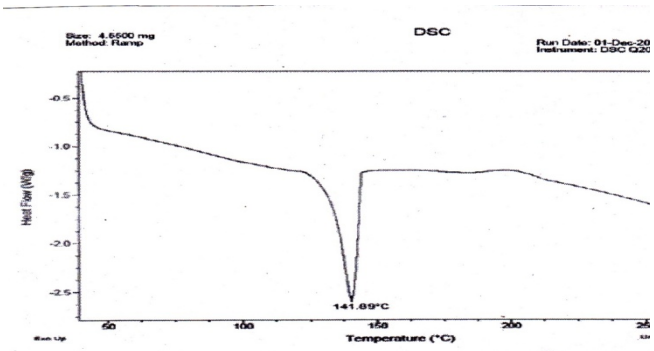

Fig. 5: DSC of pure drug Rabeprazole

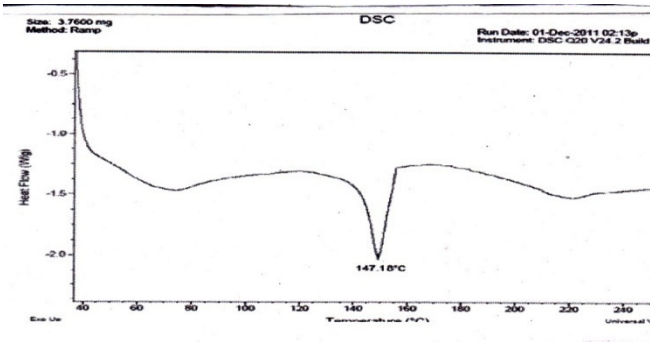

Fig. 6:- DSC of Formulation with HPMC

Micromeritic Studies

Micromeritic Studies- Active pharmaceutical ingredient

Table 4: Micromeritic results of API

Parameters	Drug
Bulk density (gm/ml)	0.69
Tapped density (gm/ml)	0.79
Carr's index (%)	12.66
Hausner's ratio	1.14
Angle of repose (α)	43.60

Loss on drying

Table 5: Loss on drying results drug andexcipients

Sr. no	Ingredients	Loss on drying (%w/w) At 105°C
1	Rabeprazole	3.51%*
2	Mannitol 25	0.2%
3	Heavy magnesium oxide	1.78 %
4	Light Magnesium Oxide	1.69 %
5	Hydroxypropyl cellulose	4.51 %
6	L -HPC	6.36 %
7	Talc	3.8 %
8	Magnesium Stearate	3.56 %
9	Ethyl cellulose	1.36 %
10	Hydroxypropyl methyl cellulose	4.29 %
11	Hydroxypropyl methyl cellulose Phthalate	4.07 %

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Micromeritic Studies- Excipients

Table 6: Micromeritic results of excipients

Parameters	Mannitol 25	Heavy MgO	Light MgO	HPC	L-HPC	Talc	Mg stearate
Bulk density (gm/ml)	0.40	0.67	0.40	0.52	0.83	0.25	0.22
Tapped density (gm/ml)	0.76	0.84	0.47	0.67	0.90	0.42	0.38
Carr's index (%)	47.39	20.2	14.9	23.23	7.78	40.41	42.1
Hausner's ratio	1.9	1.25	1.17	1.28	1.08	1.68	1.73
Angle of repose (α)	51.34	52.22	No flow	39.80	43.60	53.13	49.63

Table 7: Excipient compatibility results

Sr.no	Blend	Ratio	Storage condition	Time period	Description
01	Drug	1		Initial	White to off-white powder
			40°C/75%RH	4W	Slightly yellow
			60°C± 2°C	4W	Black melt
02	Drug + Mannitol	1:1		Initial	White to off-white powder
			40°C/75%RH	4W	Slightly yellow
			60°C± 2°C	4W	Slightly yellow
03	Drug+ Light MgO	1:1		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	Black dots with white to off white powder
04	Drug+ Light MgO	1:1.5		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change
05	Drug +light MgO	1:2		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change
06	Drug+ HPC	1:1		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change
07	Drug +L-HPC	1:1		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change
08	Drug + Mg. stearate	1:0.5		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change
09	Drug +Talc	1:0.5		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change
10	Drug + EC	1:0.5		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change

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11	Drug+ HPMC	1:0.5		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change
12	Drug +IPA	1:0.5		Initia	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	No change
13	Drug + (HPMC-P)	1.1		Initial	White to off-white powder
			40°C/75%RH	4W	Brownish black
			60°C± 2°C	4W	Black melt
14	Drug +Water	1:0.5		Initial	White to off-white powder
			40°C/75%RH	4W	No change
			60°C± 2°C	4W	Slightly brown

Formulation Deveopment
Core Optimization Trials
Formulation Batch A-1: Tablets compressed by direct compression method
Table 8a Micromeritics Batch A1

Parameters	Batch A1
Bulk density (gm/ml)	0.50
Tapped density (gm/cc)	0.71
Carr's index (%)	29.57 %
Angle of repose	No flow
Partilce size distribution	% remained
#20	0.0
#40	3.06
#60	8.23
#80	30.78
Below #80	57.93

Table 8b: *In-process* tests during compression of Batch A1

Test	Batch A1
Average weight (mg)	180.0
Hardness (N)	60-80
Thickness (mm)	3.9-3.92
Diameter (mm)	7.5-7.52
Friability	
After 100 RPM (%w/w)	0.04 %
After 500 RPM (%w/w)	0.2 %
Disintegration Time (minutes)	8-9

Formulation Batch A-2 to A-8: using heavy magnesium oxide and wet granulation method
Table 9a: Micromeritics Batch A-2 to A-8

Parameters	Batch A-2	Batch A-3	Batch A-4	Batch A-5	Batch A-6	Batch A-8
Bulk density (gm/ml)	0.5	0.53	0.65	0.62	0.55	0.60
Tapped density (gm/cc)	0.6	0.60	0.83	0.81	0.71	0.76
Carr's index (%)	16.67	11.67	21.68	22.83	28.16	21.1
Angle of repose	37.27	37.02	47.23	45.75	45	44.29
Partilce size distribution	% remained	% remained	% remained	% remained	% remained	% remained
#20	0.4	0.58	0.0	0.0	1.0	0.0
#40	30.2	37.2	34.8	29.68	26.8	36.67
#60	18.2	13.6	16.8	19.36	16.5	14.5
#80	8.4	7.76	21.6	20.08	22.08	6.46
Below #80	40.2	40.16	25.2	28.8	32.4	40.3

Table 9b: *In-process* tests during compression of Batch A-2 to A-5

	Batch A2			Batch A3	Batch A4			Batch A5		
	X	Y	Z		X	Y	Z	X	Y	Z
Average weight (mg)	180.0	180.0	180.0	180.0	180.0	180.0	180.0	180.0	180.0	180.0
Hardness(N)	50-60	80-100	120-140	85-100	50-60	70-85	125-130	45-55	75-85	125-135
Thickness (mm)	4.2-4.3	3.9-4.0	3.7-3.8	4.0	4.1-4.15	3.8-3.95	3.7-3.8	4.1-4.15	3.8-3.9	3.7-3.75
Diameter (mm)	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52
Friability (%w/w)										
After 100 RPM	0.7%	0.09%	0.1%	0.5%	0.07%	0.41%	0.14%	0.07%	0.41%	0.16%
After 500 RPM	0.91%	0.16%	0.78%	0.12%	0.10%	0.55%	0.2%	0.10%	0.55%	0.22%
Disintegration Time (min)	7-8	9-10	12-13	7-9	7-8	10-11	12-13	5-6	6-7	7-8

Table 9c: *In-process* tests during compression of Batch A-6 to A-8

	Batch A6			Batch A8		
	X	Y	Z	X	Y	Z
Average weight (mg)	180.0	180.0	180.0	180.0	180.0	180.0
Hardness (N)	140-150	95-115	70-80	100-120	80-100	60-80
Thickness (mm)	3.75-3.79	3.8-3.84	4.01-4.06	4-4.05	4.05-4.1	4.11-4.17
Diameter (mm)	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52
Friability(%w/w)						
After 100 RPM	0.15	0.07	0.11	0.11	0.17	0.16
After 500 RPM	0.22	0.16	0.21	0.13	0.2	0.22
Disintegration Time (min)	12-13	11-12	9-10	11-12	9-10	8-9

Table 9d: Analytical results of batch A-2 to Batch A-8

	Innovator	Batch A-2	Batch A-3	Batch A4-Y*	Batch A5-Y*	Batch A-6	Batch A8-Y*
Acid stage	0.35	ND	ND	NA	NA	ND	-
Buffer Stage				% release	% release		% release
10 minutes	13			63	55		60
20 minutes	69	ND	ND	98	93	ND	100
30 minutes	97			100	102		100
45 minutes	93			96	98		95
f1 %	-	-	-	-	-	-	-
f2 %	-	-	-	-	-	-	-
Assay	99.9%	ND	ND	101.2%	103.0%	ND	106.6%
Relative substance	Known1:0.39 % Known2: 0.26 % Known 3: 0.08%	ND	ND	Known1: 0.13 % Known2:	Known1: 0.13 % Known2:	ND	Known1: 0.14 % Known2:

	Known 4: 0.5% Known 5: 0.45% TI:1.68%			0.12 % TI 0.25%	0.13 % TI:0.26%		0.11 % TI :0.25%
Water content	1.07 %W/W	-	-	2.45 %W/W	2.21 %W/W	-	1.56 %W/W
pH	10.9	-	-	10.12	9.9	-	10.62

Note: ND= not done, NA= not applicable, TI= Total Impurities

• Uncoated tablets were selected for dissolution and dissolution was carried out directly in pH 8 Tris-HCl buffer dissolution media.

Table 10b: *In-process* tests during compression of Batch A-9 to A-12

Parameters	Batch A-9	Batch A-10	Batch A-11	Batch A-12
Average weight (mg)	180.0	180.0	180.0	180.0
Hardness (N)	80-100	85-110	85-95	80-100
Thickness (mm)	4.0-4.06	3.8-4.0	3.95-4.0	3.90-3.95
Diameter (mm)	7.5-7.52	7.5-7.52	7.5-7.52	7.5-7.52
Friability After 100 RPM (%w/w) After 500 RPM (%w/w)	 0.31 0.46	 0.27 0.53	 0.29 0.36	 0.05 0.16
Disintegration Time (minutes)	9-10	10-11	10-11	10-11

Table 10c: Analytical results of batch A-9 to Batch A-12

	Innovator	Batch A-9*	Batch A-10-I*	Batch A-11*	Batch A-12*
Acid stage	0.35	-	-	ND	ND
Buffer Stage 10 minutes 20 minutes 30 minutes 45 minutes	 13 69 97 93	 48 84 98 95	 47 86 97 93	 71 99 97 93	 52 95 97 94
f1 %	-	-	-	-	-
f2 %	-	-	-	-	-
Assay	99.9%	105 %	101.6%	105.0%	102.2%
Relative substance	Known1:0.39 % Known2: 0.26 % Known 3: 0.08% Known 4: 0.5% Known 5: 0.45% TI:1.68%	Known1: 0.14 % Known2: 0.09 % TI:0.23%	Known1: 0.11 % Known2: 0.10 % TI:0.21%	BDL	BDL
Water content	1.07	1.3	1.3	1.76	1.86
pH	10.9	10.48	10.65	10.58	10.75

Note: ND= not detected, NA= not applicable, TI= Total Impurities, BDL- below detectable limits

*: Uncoated tablets were selected for dissolution and dissolution was carried out directly in pH 8 Tris-HCl buffer dissolution media.

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COATING OPTIMIZATION TRIALS
Coating optimization Batch A-10

Table 11: Analytical results of batch A-10-I, A-10-II

	Innovator	A10-I	A10-I S1	A10-II S1	A10-II S2	A10- II S3	A10-II S3-E1	A10-II S3-E2	A10-II S3-E3	A10-II S3-E4
Acid stage	0.35	-	-	-	-	-	7.4	5.5	2.1	0.5
Buffer Stage 10 min. 20 min. 30 min. 45 min.	13 69 97 93	48 84 98 95	0 0 12 54	29 90 101 97	54 92 98 93	47 92 100 94	36 74 97 93	24 64 93 98	25 66 96 96	12 61 95 98
f1 %	NA	-	-	-	-	-	10.29	9.19	6.9	6.0
f2 %	NA	-	-	-	-	-	46.39	48.03	49.48	65.0
Assay	99.9%	101.6 %	-	101.8	101.4	102.1	-	-	-	99.2
Relative substance	Known1:0.39% Known2:0.26% Known3:0.08% Known4: 0.5% Known5:0.45% TI:1.68%	Known1: 0.14 % Known2: 0.09 % TI:0.23%	-	Known1: 0.24 % Known2: 0.28 % TI:0.52%	Known1: 0.24 % Known2: 0.29 % TI:0.53%	Known1: 0.29 % Known2: 0.23 % TI:0.52%	Known1: 0.33 % Known2: 0.16 % TI:0.49%	Known1: 0.50 % Known2: 0.27 % TI:0.97%	Known1: 0.48 % Known2: 0.24 % TI:0.72%	Known1: 1.81 % Known2: 0.16 % TI:1.97%
Water content	1.07 %W/W	1.3 %W/W	-	-	-	-	1.44 %W/W	1.7 %W/W	1.56 %W/W	1.76 %W/W
pH	10.9	10.48	-	-	-	-	10.72	10.65	10.46	10.54

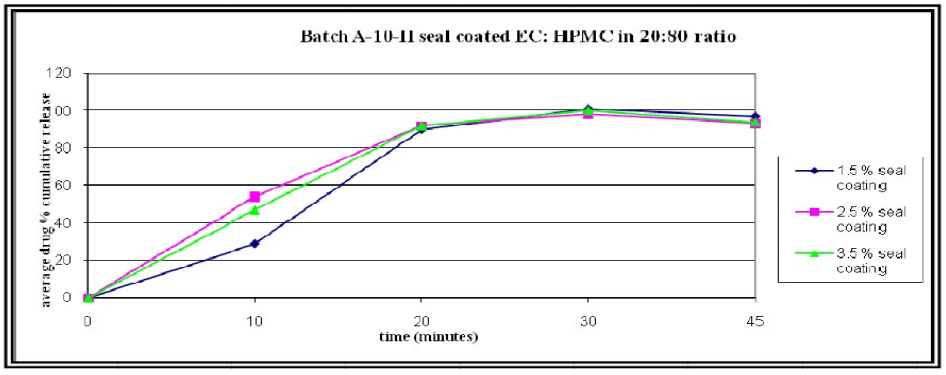

Fig.7: comparison of drug release profile between seal coated tablets with different percentage of EC: HPMC combined polymer coating of batch A-10-II-S1, batch A-10-II-S2 and batch A-10-II-S3

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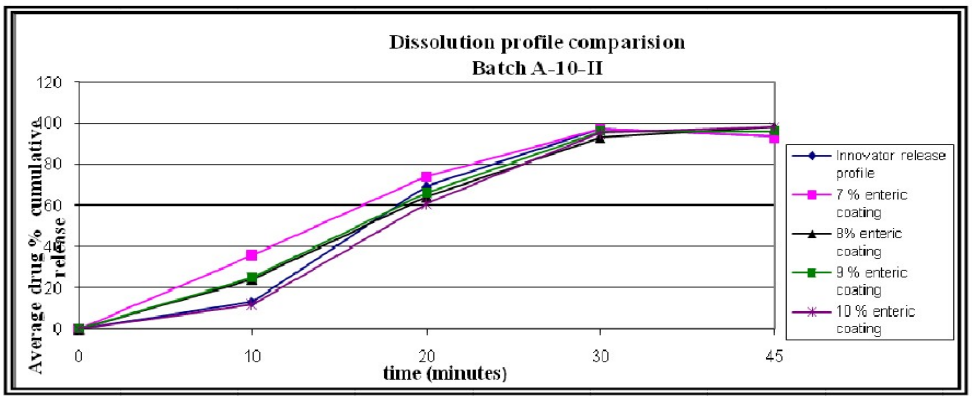

Fig.8: comparison of drug release profile between innovator tablets with different percentage of enteric polymer coating of batch A-10-II-S3-E1, batch A-10-II-S3E2, batch A-10-II- S3E3, and batch A-10-II-S3E4

Table 12a: One month stability results– physical parameters. Batch A10-II-S3-E4

Batch	Condition After 1M	Description	Hardness (N)	Coated tablet surface	Disintegration time in pH 8 (minutes)
Innovator Sample	Initial	Round shaped, Yellow colored, coated tablets	160-170	Yellow and Smooth	17- 19
	25°C/60%RH	No change	160-170	No change	17- 19
	40°C/75%RH	No change	170-180	No change	17- 19
A10-II S3-E4	Initial	Round shaped, Yellow colored, coated tablets plain on both side	170-190	Yellow and Smooth	19-20
	25°C/60%RH	No change	170-190	No change	18-20
	40°C/75%RH	No change	170-190	No change	18-20

Table 12b: One month stability data –analytical results. Batch A10-II-S3-E4

Batch No.: Innovator 20 mg DR tablet in HDPE bottles						
	Duration	Known Impurity 1%	Known Impurity 2%	All %	Total Imp. %	Assay %
Storage condition	Initial	0.39	0.26	0.06	1.68	99.9
25°C/60%RH	1M	0.44	ND	0.02	0.54	99.5
40°C/75%RH	1M	0.48	0.03	0.07	0.75	99.0
Batch No.: A10-II-S3-E4/Enteric coated 20 mg tablets in HDPE bottles						
	Duration	Known Impurity 1%	Known Impurity 2%	All %	Total Imp. %	Assay %
Storage condition	Initial	0.18	0.14	0.04	0.36	99.2
25°C/60%RH	1M	0.2	0.16	0.05	0.52	101.7
40°C/75%RH	1M	0.36	0.37	0.37	1.96	97.3

Coating optimization Batch A-10

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Table 13: Analytical results of batch A-10-III

	Innovator	A10-III-S1	A10-III-S2	A10-III-S3	A10-III S3-E1	A10-III S3-E2	A10-III S3-E3	A10-III S3-E4
Acid stage	0.35	ND	ND	ND	13.0	9.0	5.0	3.0
Buffer Stage								
10 min.	13	54	12	01	00	00	00	00
20 min.	69	89	63	16	00	25	05	09
30 min.	97	94	87	51	12	71	39	43
45 min.	93	88	87	90	56	94	84	93
f1 %	NA	-	-	-	75.0	30.88	52.94	46.69
f2 %	NA	-	-	-	11.77	28.93	17.87	19.42
Assay	99.9%	102.4	103.0	103.1	101.3	103.5	101.2	108.4
Relative substance	Known1:0.39% Known2:0.26% Known3:0.08% Known4: 0.5% Known5:0.45% TI:1.68%	ND	ND	ND	ND	ND	ND	Known1: 0.40 % Known2: 0.27 % TI:0.67%
Water content	1.07 %W/W	2.15 %W/W	2.30 %W/W	1.94 %W/W	1.06 %W/W	1.37 %W/W	1.22 %W/W	1.22 %W/W
pH	10.9	10.84	10.93	10.99	10.62	10.7	10.57	10.60

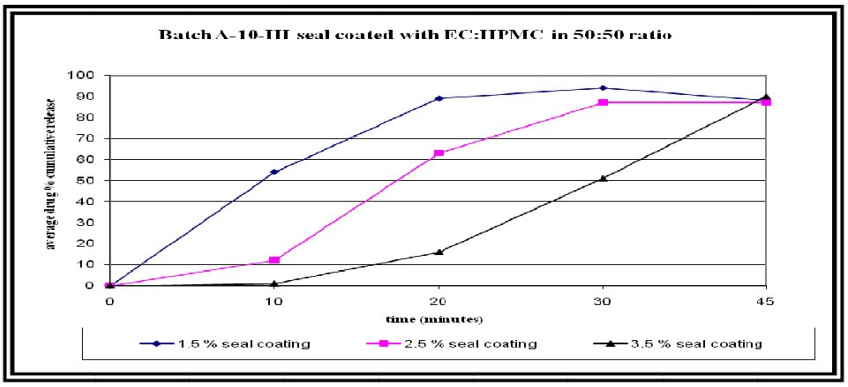

Fig. 9: comparison of drug release profile between seal coated tablets with different percentage of EC: HPMC combined polymer coating of batch A-10- III-S1, batch A-10- III-S2 and batch A-10- III-S3

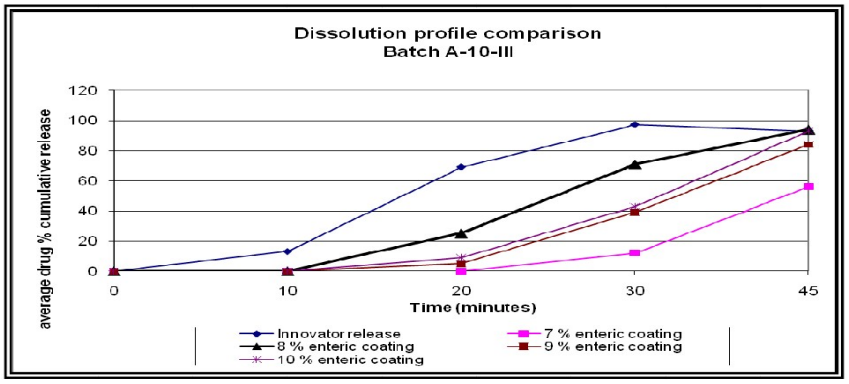

Fig. 10: comparison of drug release profile between innovator tablets with different percentage of enteric polymer coating of batch A-10-III-S3-E1, batch A-10-III-S3E2, batch A-10-III-S3E3, and batch A-10-III-S3E4

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Coating optimization Batch A-11, Batch A-12

Table 14: Analytical results of Batch A-11, Batch A-12

	Innovator	A11	A11-S1	A11-S2	A11-S3	A11-S3-E2	A11-S3-E3	A11-S3-E4	A12-S-E
Acid stage	0.5	ND	ND	ND	ND	0	0.3	1.9	1.2
Buffer Stage									
10 min.	13	71	64	58	56	26	42	10	09
20 min.	69	99	99	96	90	99	98	80	75
30 min.	97	97	92	90	85	104	108	104	104
45 min.	93	93	96	88	83	101	104	100	97
f1 %	-	-	-	-	-	21.32	29.41	12.29	7.72
f2 %	-	-	-	-	-	38.20	32.92	55.92	62.98
Assay	99.9%	105	107.3	106.5	107.3	106.6	104.2	99.2	99.8
Relative substance	Known1:0.39% Known2:0.26% Known3:0.08% Known4: 0.5% Known5:0.45% TI:1.68%	ND	Known1: 0.17 % Known2: 0.11 % TI:0.28%	Known1: 0.18 % Known2: 0.12 % TI:0.29%	Known1: 0.18 % Known2: 0.12 % TI:0.30%	Known1: 0.18 % Known2: 0.12 % TI: 0.38%	Known1: 0.18 % Known2: 0.12 % TI: 0.38%	Known1: 0.18 % Known2: 0.12 % TI: 0.38%	Known1: 0.17 % Known2: 0.13 % TI:0.35%
Water content	1.07 %W/W	1.76 %W/W	0.81 %W/W	0.90 %W/W	1.19 %W/W	0.95 %W/W	0.84 %W/W	1.15 %W/W	1.25 %W/W
pH	10.9	10.58	10.73	10.88	10.9	10.88	10.87	10.89	10.70

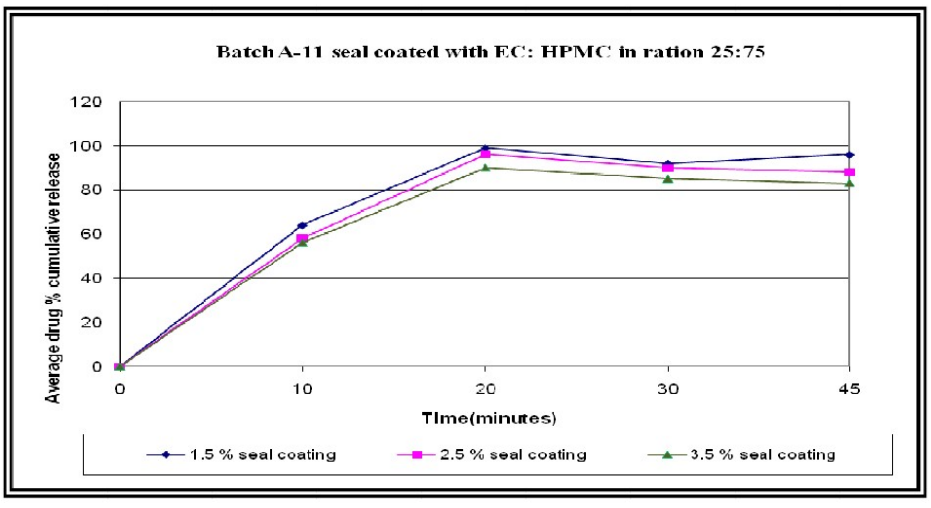

Fig. 6.5: comparison of drug release profile between seal coated tablets with different percentage of EC: HPMC combined polymer coating of batch A-11-S1, batch A-11 -S2 and batch A-11-S3

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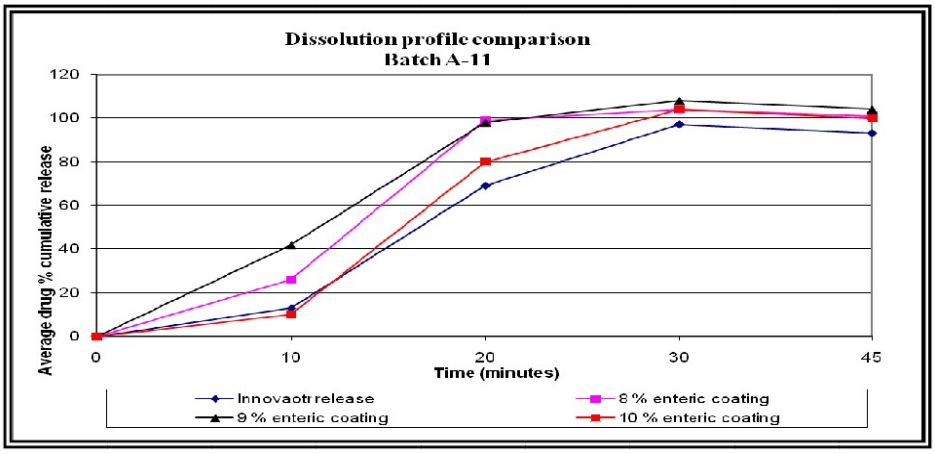

Fig. 11: comparison of drug release profile between innovator tablets with different percentage of enteric polymer coating of batch A-11-S3E2, batch A-11-S3E3, and batch A-11-S3E4

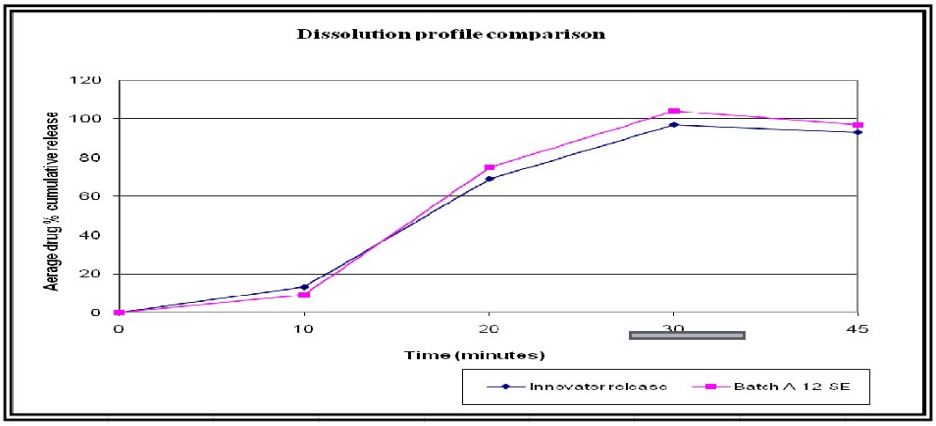

Fig. 12: comparison of drug release profile between innovator tablets with different percentage of enteric polymer coating of batch A-12-SE

Table 15a: One month stability results – physical parameters. Batch A11-S3-E4, A12-S-E

Batch	Condition After 1M	Description	Hardness (N)	Coated tablet surface	Disintegration time in pH 8 (minutes)
Innovator Sample	Initial	Round shaped, Yellow colored, coated tablets	160-170	Yellow and Smooth	17- 19
	25°C/60%RH	No change	160-170	No change	17- 19
	40°C/75%RH	No change	170-180	No change	17- 19
A10-II S3-E4	Initial	Round shaped, Yellow colored, coated tablets plain on both side	170-190	Yellow and Smooth	19-20
	25°C/60%RH	No change	170-190	No change	19-20
	40°C/75%RH	No change	170-190	No change	19-20
A12-S-E	Initial	Round shaped, Yellow colored, coated tablets plain on both side	180-190	Yellow and Smooth	19-20
	25°C/60%RH	No change	170-190	No change	19-20
	40°C/75%RH	No change	170-190	No change	19-20

Table 15b: One month stability data –analytical results. Batch A11-S3-E4, A12-S-E

Batch No.: Innovator 20 mg DR tablet in HDPE bottles						
	Duration	Known Impurity 1%	Known Impurity 2%	All %	Total Imp. %	Assay %
Storage condition	Initial	0.39	0.26	0.06	1.68	99.9
25°C/60%RH	1M	0.44	ND	0.02	0.54	99.5
40°C/75%RH	1M	0.48	0.03	0.07	0.75	99.0
Batch No.: A11-S3-E4/Enteric coated 20 mg tablets in HDPE bottles						
	Duration	Known Impurity 1%	Known Impurity 2%	All %	Total Imp. %	Assay %
Storage condition	Initial	0.17	0.13	0.05	0.30	99.8
25°C/60%RH	1M	0.21	0.16	0.26	0.63	104.6
40°C/75%RH	1M	0.26	0.06	0.41	0.73	100.2
Batch No.: A12-S-E/Enteric coated tablets 20mg in HDPE bottles						
	Duration	Known Impurity 1%	Known Impurity 2%	All %	Total Imp. %	Assay %
Storage condition	Initial	0.17	0.13	0.05	0.30	99.8
25°C/60%RH	1M	0.21	0.16	0.26	0.63	104.6
40°C/75%RH	1M	0.26	0.06	0.41	0.73	100.2

Compatibility studies

Compatibility studies were performed between drug and various excipients at 40^{0}C/75 RH and 60^{0}C for 4 weeks. Table 5.6 shows that drug: excipient compatibility results.

DISCUSSION

Carr's index and hausner's ratio were calculated on the basis of bulk density and tapped density. Carr's index and hausner's ratio were calculated as 12.66 and 1.14 respectively, showing good compressibility properties (Table 5.2).Flow properties were evaluated and compared with flow of scalability in USP/NF 31/26 (table 4.8, 4.9) more Batch A-1 was compressed by direct compression method. **Batch A-2** granulated using non aqueous solvent, showed fair compressibility and flow property (table 5.7a). Batch was compressed at different hardness but capping was observed while compressing tablets at 80-100 N. **Batch A-3** was compressed with increasing concentration of binder[69] and Micromeritics of lubricated granules and IPQC tests during compression were found acceptable. (Table 5.7a, 5.7b). **Batch A-4** was compressed with decreased concentration of disintegrant but disintegration time was increased to at required hardness. Dissolution profile (table 5.7d) was not good enough. **A-5** was compressed. **batch A-6.** Disintegration time was increased up to 9-10 minutes. **batch A-7** was processed with increasing concentration of alkalizer **Batch A-8** was processed to study the effect of granulating solvent on granulation process. **Batch A-9** was

compressed by replacing heavy MgO with light MgO in formula. **Batch A-10** was repetition trial of batch A-9. Significant changes were not observed in compressibility, flow of lubricated granules and disintegration time. Dissolution profile was also found similar to that of batch A-9.**Batch A-11** was compressed with aqueous granulation. Table 5.8a shows good micromeritics, IPQC during compression. **Batch A-12** was repetition trial of Batch A-11. Table 5.8a, 5.8b and 5.8c show no major changes in micromeritics, flow properties of lubricated granules, **Batch A-10-I** was coated with EC only up to 2.5% weight gain. Dissolution profile for seal coated tablets shows 0% drug release till 20 minutes. Hence, seal coat approach using EC alone was discontinued., **Batch A-10-II** was coated with HPMC: EC combination in the ratio of 80:20 for different percentages of polymer coatings like 1.5%, 2.5% and 3.5%. Dissolution profile for seal coated tablets up to 3.5% weight gain was comparatively better and further taken for enteric coating.**Batch A-10-III** Seal coating was done by EC: HPMC in combination of 50:50 for 1.5%, 2.5% and 3.5 % polymer coating. Samples from all batches were analyzed for release pattern. 3.5% seal coated tablets were further enteric coated for 7%, 8%, 9% and 10% weight gain.**Batch A-11** was seal coated with EC: HPMC in ratio of **25:75** upto 1.5%, 2.5% and 3.5% polymer coating. Tablets with 3.5% seal coat were found suitable for further enteric coating. Enteric coating was done for 8%, 9% and 10% weight gain. **Batch 12** was taken for coating reproducibility. Dissolution when carried out, results show similarity factor value (f2) 62.98% for tablets having 3.5% seal coating and 10% enteric coating. **Batch A-11-S3-E4** and **Batch A-**. Batch A-12-SE can be considered one month stability results of Batch A-11-S3E4 and Batch A-12-SE are acceptable. Batch A-12-SE can be considered as therapeutically equivalent with the innovator product for one month.

CONCLUSION

Final formulation was enteric coated to prevent the release of proton pump inhibitor in the stomach. Following conclusions were drawn from the series of experimental studies.

Preformulation

• API was analyzed for its specification and it was complied with the COA supplied by API vendor.

• From compatibility studies, following conclusions were drawn

➢ Drug was compatible with almost all selected excipients except that excipient which was acidic in nature (HPMC-P).

➢ Drug was found to be stable under alkaline condition. To maintain the alkalinity of drug, drug initially mixed with magnesium oxide. Magnesium oxide forms hydrophobic coat over drug particles, so moisture effect can be minimized.

7.2 Formulation Development

- Light magnesium oxide provided better water proofing effect as compared to heavy magnesium oxide.
- Wet granulation method was best for manufacturing tablets when compared to direct compression.

- Core tablet compressed with formula of batch A-10, A-11 and A-12 produced good results. Seal coating with HPMC: EC in the ratio 75:25 upto 3.5% polymer coating gave controlled release profile. Enteric coating using HPMC-P upto 10% polymer coating, helped in getting gastric release less than 5%.
- Initial impurity profile as well one month stability impurity profile showed that aqueous granulation was better as compared to non-aqueous granulation. Even, economically aqueous granulation is better than non-aqueous granulation.
- Hydrophilic polymer HPMC can be act as pore former in hydrophobic film of EC.

Release of drug from the combination coating can be controlled by two ways.

1) Changing of hydrophobic polymer: hydrophilic polymer ratio

2) Release rate can be decreased by increasing polymer coating. Higher percentage of polymer coating, lesser drug release in prescribed time limit.

- 10 % enteric coating with HPMC-P showed very less amount of drug release in 0.1 N HCl for 2 hrs. Thus, drug can be prevented from degradation in acidic juices.
- Batches A-11, A-12 when stored at two different storage conditions (40 ± 2 °C/75 ± 5 % RH and 25 ± 2 °C/60 ± 5 % RH) for the period of 30 days, no significant changes were observed in any of the physicochemical parameters studied including related substances by HPLC method.
- **Batch A-12-SE** was considered therapeutically equivalent with innovator sample as batch shows f2 value is 62.98%. after one month stability at 40 ± 2 °C/75 ± 5 % RH and 25 ± 2 °C/60 ± 5 % RH, total impurities are less than 1% for Batch A-12-SE and hence batch is considered stable.

REFERENCE

1. Shargel L, Kanfer L. *Introduction to Generic Drug Product Development, Generic Drug Product Development-Solid Oral Dosage Forms,* Marcel Dekker, Inc., NY, 2005, 1-16,

2. Leopold C. *Coated dosage forms for colon-specific drug delivery,* Pharmaceutical Science & Technology Today. 1999, 2(5); 197-204,

3 Hoogerwerf HA, Pasricha PJ. *Pharmacotherapy of gastric acidity, peptic ulcers and gastroesophageal reflux disease; Goodman & Gilman's pharmacological basis of therapeutics Brunton LL, Lazo JS, Parker KL,* editors. 11th ed, USA: McGraw- Hill Companies, Inc.2006; p 967-81.

4 Yong CS, Jung JH, Rhee JD, Kim CK, Choi HG, *Physicochemical Characterization and Evaluation of Buccal Adhesive Tablets Containing Omeprazole,* Drug Development and Industrial Pharmacy, 2001, 27(5): 447 – 455.

5 Crotts G, Sheth A, Twist J, Ghebre-Sellassie I. *Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acid.* European Journal of Pharmaceutics and Biopharmaceutics, 2001, 51(1):71-76,

6. Miller RA, Vadas EB. *The physical stability of tablets coated using an aqueous dispersion of*

ethylcellulose, Drug Development and Industrial Pharmacy, 1984, 10(10):1565 – 85,

7. Rowe RC. The effect of the molecular weight of ethyl cellulose on the drug release properties of mixed films of ethyl cellulose and hydroxypropylmethylcellulose, International Journal of Pharmaceutics. 1986, 29(1):37-41,

8. Ramakrishna N, Mishra B, *Plasticizer Effect and Comparative Evaluation of Cellulose Acetate and Ethylcellulose-Hpmc Combination Coatings as Semipermeable Membranes for Oral Osmotic Pumps of Naproxen Sodium,* Drug Development and Industrial Pharmacy. 2002. 28(4);403 – 412.

9. Dabbagh MA, Pooladi F, *Sustained release formulation of Metoclopramide Hydrochloride, Daru,* Journal of Faculty of Pharmacy Tehran University of Medical Sciences. 20003, 4(8): 15-19.

10. Gowda DV, Darsha J, Shivakumar HG, Ravi SV, *Influence of a microporous membrane coating on theophylline drug delivery,* Asian Journal of Pharmaceutical Sciences, 2007, 2(2): 56-67.

11. Soyeux P, Delacourte A, Delie B, Lefevre P, *Boniface B. Influence and optimizations of operating parameters with a new binder in wet granulation. I: use in powder form.* Eur J Pharm Biopharm., 1998. 46(1):95-103.