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Formulation and Evaluation of Naproxen and Esomeprazole Film Coated Delayed Release Tablets

Parsi Swetha[1*], Dr. M. Sunitha Reddy[2]

[1]Department of Pharmaceutics, CPS, UCEST, JNTUH, HYD
[2]Department of Pharmaceutics, UCPSC, Sultanpur, JNTUH, HYD
Mail Id: parsiswetha1099@gmail.com

ABSTRACT

The present study was an attempt to formulate and evaluate enteric coated tablets for esomeprazole and naproxen. FTIR studies revealed that there was no interaction between the drug and excipients used in the study. Different core tablets were prepared and formulation (F-8) was selected for further enteric coating, based on the disintegration time. Enteric coating was carried out using different polymers. In the present study, Naproxen (500mg) is prepared in combination with Esomeprazole, a proton pump inhibitor as a multi-layer coated tablet. Results from disintegration time and dissolution rate studies indicate that all the esomeprazole enteric tablets prepared possess good integrity, desirable for enteric coated tablets. The *in-vitro* drug release studies were conducted for Naproxen core tablets, Naproxen enteric coated tablets and multi-layered tablets in 0.1N HCl and 6.8 pH phosphate buffer. The analytical results obtained at several stages of preparation of the product were found to be satisfactory. The release mechanisms of naproxen enteric coated tablets were explored and explained with Zero order, first order, and Higuchi, Korsmeyer and Hixon Crowell equations. The in–vitro release data were fitted with several mathematical models. Stability studies indicate that the prepared formulations were stable for a period of three months.

Keywords: Esomeprazole, Naproxen, FTIR studies, Polymers, direct compression technique, In-vitro drug release studies

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. Pharmaceutical products designed for oral delivery are mostly the immediate-release type. Because of their clinical advantages over immediate-release pharmaceutical products containing the same drugs, delayed release pharmaceutical products have gradually gained medical acceptance and popularity since their introduction into the market place[1] Delayed release drug delivery systems (DRDDS) indicates that the drug is not released immediately but is being released at a later time. Therefore, the formulation is designed in order to increase the stability of the drug and optimizing the therapeutic effect of a drug by controlling its release in the body in the lower part of the gastrointestinal tract i.e. releasing drug into the colon.[2,3] Esomeprazole is a proton pump inhibitor which reduces acid secretion through inhibition of the H+ / K+ ATP ase in gastric parietal cells. By inhibiting the functioning of this transporter, the drug prevents formation of gastric acid. Naproxen is an NSAID of the propionic acid class, works by reversibly inhibiting both the COX-1 and COX-2 enzymes as a non-selective coxib. But it poses an intermediate risk of stomach ulcers. To reduce stomach ulceration risk, it is often combined with a proton-pump inhibitor to reduce stomach acid production during long-term treatment for those with pre-existing stomach ulcers or for those having history of developing stomach ulcers while on NSAIDs. Naproxen used in the treatment of Rheumatoid arthritis, Osteoarthritis, Ankylosing spondylitis, Tendinitis, Bursitis, Acute gout. [4,5] Therefore the primary objectives of the study were to develop a suitable dosage form for two active ingredients, NSAID (in the enteric coated layer) and esomeprazole and to overcome the under prescribed combination of these two drugs.[6] In this study, the combination product of Naproxen and esomeprazole is prepared by using multi-layer tablet coating technology. Naproxen core tablet is prepared by compression and then enteric coated. Upon this enteric coated tablet, Esomeprazole drug layer is applied. The number of ingredients were tried to reduce as much as possible which would make it a cost-effective formulation.

MATERIALS

Naproxen, Esomeprazole was obtained from Hetero labs, HYD. Croscarmellose, Povidone, Eudragit L100-55 were procured from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Fourier Transform Infrared Spectroscopy: FTIR spectra of Esomeprazole and Naproxen was obtained using Shimadz FTIR spectrophotometer using diffuse reflectance technique (KBr disc technique) as a part of qualitative analysis by comparing it with the spectra of Esomeprazole IP standard. Samples of powder was previously ground and mixed with KBr, an infrared transparent matrix. The weighed amount of the drug (3 mg) was mixed with 100 mg of Potassium bromide (dried at 40°-50°C), which was then compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The scans were obtained in the mid-infrared regions of the spectrum form 4000 cm-1 – 400 cm-1 at resolution of 1 cm-1.[7]

FORMULATION OF NAPROXEN CORE TABLET[8,9,10]

Table1-: Formulation of naproxen core tablet

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Naproxen	500	500	500	500	500	500	500	500	500	500
Povidone	10	20	10		-	10	-	-	-	10
MCC		-		10	20	10	10	-	-	-
Lactose	10	-	10	10	-	-	10	20	10	-
Mannitol	-	-	-	-	-	-	-	-	10	10
Croscarmellose	20	20	20	20	20	20	20	20	20	20
Magnesium stearate	10	10	10	10	10	10	10	10	10	10
Total wt	500	550	500	500	500	500	500	500	500	500

Sub Coating material

Table-2: Sub coating material

Ingredients	**Quantity of material**
Eudragit L100-55	5
Methanol	0.1 ml
Methylene chloride	0.1ml

Formulation of enteric coating suspension

Table-3: Formulation of enteric coating suspension

Ingredients	**Quantity of tablet (mg)**
Eudragit L100-55	15
PEG	0.2
Iso propyl alcohol	0.1ml
Water	0.2

Formulation of drug layering coating suspension containing Esomeprazole

Table-4: Formulation of drug layering coating suspension containing Esomeprazole

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Esomeprazole	20	20	20	20	20	20	20	20	20	20
HPMC E15 LV	10	20	30	40	50	-	-	-	-	-
Eudragit L100-55	-	-	-	-	-	10	20	30	40	50

Magnesium oxide	5	10	15	20	25	-	-	-	-	-
Calcium carbonate	-	-	-	-	-	5	10	15	20	25
MCC	63.5	48.5	33.5	9.5	3.5	63.5	48.5	33.5	18.5	3.5
Isopropyl alcohol	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
PEG	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Yellow iron oxide	1	1	1	1	1	1	1	1	1	1

Core tablet

1. Naproxen and Croscarmellose sodium were sifted through #20 mesh and transferred into FBP bowl (Top spray granulation).
2. Povidone K90 was taken and dissolved in purified water and kept under stirring until clear binder solution is obtained.
3. The binder solution was sprayed onto the above step 1 material to get the desired granules. The obtained granules were dried for about 5-10 minutes to get the desired LOD with NMT 2.0 %.
4. The above obtained granules were sifted through #40 mesh.
5. To the sifted material required quantity of Croscarmellose sodium was added by sifting through #40 mesh ASTM. The sifted material was prelubricated for about 10 minutes in blender.
6. To the prelubricated blend required qty of magnesium stearate sifted through #60mesh was added and lubrication was done for 5 minutes.
7. The above lubricated blend was compressed into tablets.

II) Enteric coating

1. Talc and sodium hydroxide were homogenized using a suitable homogenizer for about 10 minutes.
2. Required qty of polymer was taken in a beaker and kept under stirring. To the polymers dispersion above step 1 dispersion was added and continued the stirring up to few minutes until uniform dispersion appears.
3. The core tablets were loaded into coating pan.
4. The tablets were prewarmed for few minutes and continued the coating with selected process parameters until target weight build up 11% w/w is achieved.
5. After achieving target weight build up the tablets were cured for about 120 minutes at 40°C.

III) Sub coating

1. To the above enteric coated tablets Sub coating is done as per the below mentioned procedure. Few steps for the preparation of Sub coating dispersion.
2. Opadry clear is added purified water which is sunder mechanical stirring and the stirring ids continued until uniform dispersion appears.
3. The enteric coated tablets were loaded into Auto coater and prewarmed the tablets for few minutes.
4. To the prewarmed tablets Opadry clear dispersion was coated until the target weight build up 6% w/w is achieved.

IV) Esomeprazole Drug layering

1. Esomeprazole drug layering is done by using Methanol and water mixture of solvent.
2. Initially Methanol and water was taken in 80:20 ratio for 8% w/w solids and to that Magnesium oxide light was added slowly under Homogenizer
3. Esomeprazole Magnesium Trihydrate added to the mixture under Homogenizer until clear solution is obtained.
4. To the clear solution required qty of polymers, PEG are added and Homogenization continued for 30minutes for uniform distribution of contents.
5. Dispersion was coated onto the Sub coated tablets by using Auto coater.

V) Protective agents coating

1. polymer, binders, Iron oxide yellow were added to purified water Under mechanical stirring and the stirring continued for 30minutes Drug layered tablets were coated with film coating dispersion.

Evaluation of core tablets

Weight variation test: Ten tablets were selected randomly from each batch were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.[11]

Friability Test: Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. It is usually measured by the use of the Roche Friabilator. Ten tablets are weighed (W1) and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed (W2) and the weight is compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up.[12] normally, when capping occurs, friability values are not calculated. The percent friability was determined using the following formula.

Friability=w1-w2/w1*100

Where,

W1 = weight of ten tablets before test

W2 = weight of ten tablets after test

Hardness test: Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The force is measured in kilograms. The hardness was tested using Monsanto Tester. The tablets were placed horizontally in contact with the lower plunger of the Monsanto Hardness Tester and zero reading was adjusted. The tablet was then compressed by forcing the upper plunger until the tablets breaks. This force was noted. [13]

Thickness, width and length: Control of physical dimension of the tablets such as thickness, width and length is essential for consumer acceptance and to maintain tablet to tablet uniformly. The dimensional specifications were measured using digital micrometre callipers. The thickness of the tablet is mostly related to the tablet hardness which can be used as initial control parameter. [14]

Drug content uniformity: From each batch of the formulation, 10 tablets were collected randomly and powered using a mortar and pestle. A quantity of the powder equivalent to the weight of one tablet (300mg drug) was transferred to a 100ml volumetric flask. To this, about 50ml of distilled water was added and subjected to sonication for 15 minutes. The volume was then made up to 100ml with the same solution. This solution was suitably diluted using distilled water to get a concentration between 5µg/ml to 25µg/ml. These solutions are then analyzed by UV spectrometer as per the calibration graph method by recording the absorbance at 289 nm.[15]

In vitro Drug release studies: In vitro drug release of the samples was carried out using USP– type II dissolution apparatus (paddle type). The dissolution medium, 900 ml 0.1N HCl solution, after 6.8 phosphate buffer was placed into the dissolution flask maintaining the temperature of 37 + 0.5oC and rpm of 50. One film coated tablet was placed in each paddle of dissolution apparatus. The apparatus was allowed to run for 12hours. Samples measuring 1 ml were withdrawn at regular intervals up to 12 hours using 1 ml syringe. The fresh dissolution medium (37oC) was replaced every time with the same quantity (1ml) of dissolution medium. Collected samples were suitably diluted with 0.1N HCl and 6.8 phosphate buffer and analysed at 283nm and 289 nm using 0.1N HCl and 6.8 phosphate buffer as blank. The cumulative percentage drug release was calculated.[16]

Disintegration time: The disintegration time of the coated tablets was determined using the The USP model disintegration apparatus (EI). Six tablets were placed in the basket rack assembly, and was run for 2 hours in 0.1 N HCl media with the discs. The tablets were removed from the solution, gently dried by bloating. The test was then continued by placing the tablets in phosphate buffer pH 6.8, for 1 h, maintaining the temperature at 37±2 ºC[17]

Dissolution of Esomeprazole from coated tablets

The in vitro drug dissolution studies was conducted in an eight stage dissolution apparatus (TDT-08L, Electro lab) using an rotating paddle, at 50 rpm, in 900 ml of simulated gastric fluid, maintained at 37± 0.5 ºC. Samples were withdrawn of the gastric media at 2 h and then, the vessel was drained off the acid and was replaced with 900 ml of phosphate buffer pH 6.8.The samples were withdrawn at regular intervals, filtered and suitably diluted. The concentration in acid media and phosphate buffer was measured with a spectrophotometer (Lambda 25, Perkin Elmer) at 283 and 289 nm, respectively, by comparison to a calibration curve1[18]

Drug release kinetics[19]

The results of in vitro release data obtained for all formulations were fitted in four popular models of data treatments as follows:

1. Zero-order kinetic model (cumulative percentage drug release versus time),

2. First-order kinetic model (log cumulative percentage drug remaining versus time),

3. Higuchi's equation (cumulative percentage drug release versus square root time).

4. Korsmeyer-Peppa's equation (log cumulative percentage drug release versus log time

Stability Testing: To evaluate the stability of enteric coated tablets of esomeprazole and naproxen, the optimized formulations were packed in polyethylene bottles. Accelerated stability studies were conducted by reserving the tablets at room temperature 40± 2 oC and 75± 5 % RH, in a humidity chamber. The samples were withdrawn at the intervals of 0, 1, 2 and 3 months from the date of packing. The physical appearance, assay and the percentage drug release were evaluated to assess the constancy of the tablets.[20]

RESULTS AND DISCUSSION

FTIR Studies

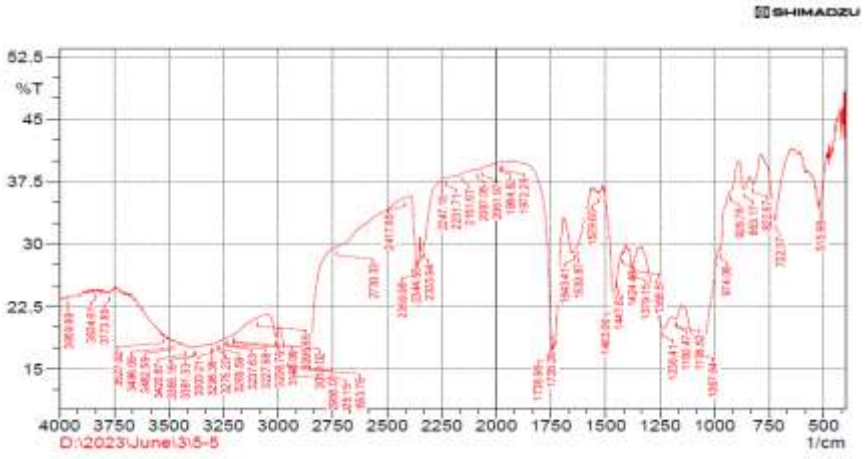

Fig-1: FTIR Studies of Naproxen

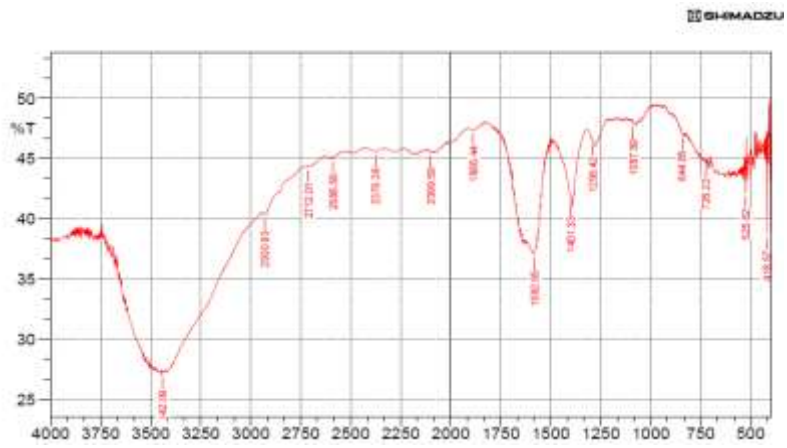

Fig-2: FTIR Studies of Esomeprazole

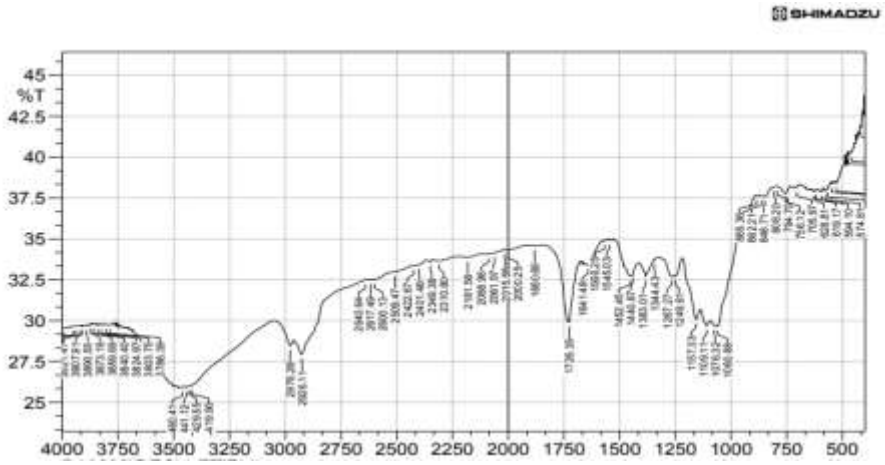

Fig-3: FTIR studies of Optimized formulation

EVALUATION STUDIES

Weight variation:

All the formulated (F1 to F10) tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F10 formulations and were found to be in the range of 3.0mm to 3.6 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 6.3 to 7 kg / cm^2. This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F10 was found to be between 75.38 % and 89.65 % of delayed film tablets it complies with official specifications.

Table-5: Evaluation parameters of delayed release tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)	Disintegration time(min)
F1	750±0.23	3.0±0.05	6.7±0.35	0.52±0.41	86.39±7.5	8.3±7.5
F2	750±0.28	3.2±0.12	6.3±0.37	0.45±0.43	88.15±7.5	7.8±7.5
F3	751±0.15	3.1±0.31	6.5±0.34	0.54±0.44	78.92±0.43	8.2±0.12
F4	750±0.24	3.4±0.62	6.9±0.43	0.51±0.47	82.63±35	6.6±0.18
F5	752±0.16	3.5±0.04	6.6±0.41	0.53±0.40	77.94±0.46	5.9±0.20
F6	749±0.14	3.6±0.08	6.4±0.44	0.54±0.43	75.38±72	6.3±0.14
F7	750±0.35	3.4±0.04	6.9±0.45	0.51±0.47	85.63±0.25	7.9±0.86
F8	750±0.16	3.2±0.05	7.0±0.46	0.53±0.42	89.65±0.85	7.5±0.82
F9	751±0.32	3.1±0.30	6.8±0.47	0.54±0.48	79.38±0.83	7.9±0.76
F10	753±0.29	3.0±0.25	6.4±0.43	0.55±0.43	80.25±0.85	8.1±0.72

In-vitro Dissolution Study

All the 10 formulation of prepared delayed release matrix tablets of naproxen and esomeprazole were subjected to in-vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

Table-6: Dissolution Profile of F1 to F10

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
0	0	0	0	0	0	0	0	0	0	0
1	19.24±7.08	18.31±8.54	17.27±8.36	20.14±15.02	21.37±13.87	19.16±13.49	20.18±12.30	24.12±11.65	18.25±13.81	19.35±7.70
2	22.45±10.09	25.30±9.67	23.11±10.06	31.45±13.06	30.29±11.05	28.79±11.72	27.59±11.71	31.18±11.65	30.32±12.41	24.57±14.54
3	32.80±12.81	35.32±12.07	33.76±9.17	49.90±7.64	48.58±8.45	45.81±8.30	44.21±10.02	46.89±11.81	45.81±11.64	34.52±16.52
4	42.63±10.78	44.65±12.04	43.23±11.06	56.70±7.77	50.18±10.23	51.28±12.33	50.19±12.33	53.95±12.30	54.87±10.41	53.21±9.96
5	58.21±10.41	59.28±10.43	52.11±11.56	65.16±8.59	63.96±5.65	62.12±10.42	63.78±11.08	69.95±9.30	68.93±7.83	67.48±6.47
6	63.35±14.00	68.55±11.81	65.22±14.19	72.22±11.11	70.18±10.44	75.89±7.67	74.81±9.24	78.15±9.85	75.21±10.14	72.39±11.29
7	78.26±38.94	80.10±40.21	75.16±38.06	82.26±39.14	75.25±37.47	82.56±38.75	85.95±37.95	88.52±43.51	84.50±41.15	80.32
8	91.35±40.30	92.17±41.66	93.22±39.33	94.42±39.85	90.27±38.57	91.20±39.04	93.17±37.99	97.85±42.89	95.48±42.52	94.67

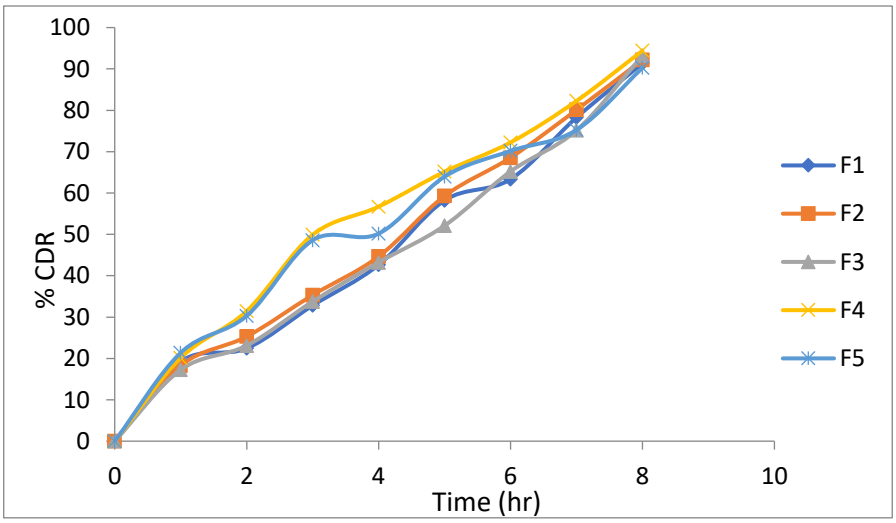

Fig-4: Dissolution profile of (F1-F5) Formulations

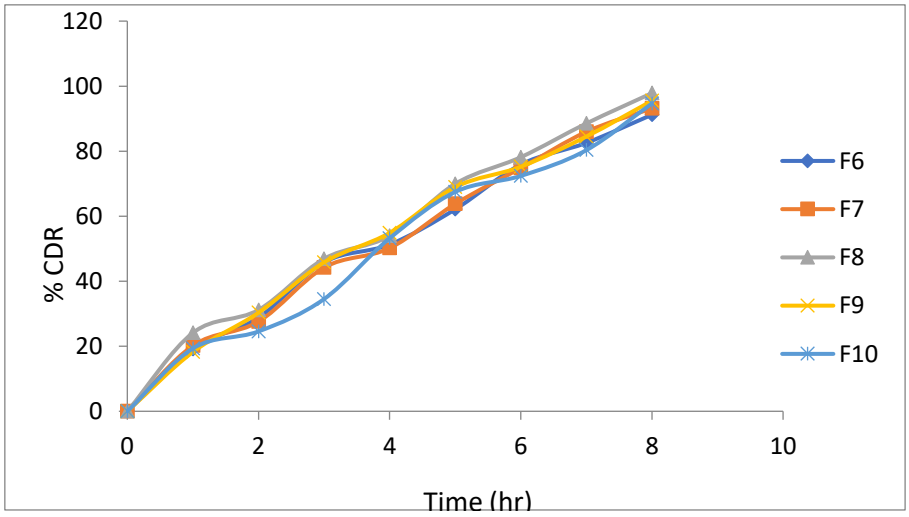

Fig-5: Dissolution profile of (F5-F8) Formulations

Release order kinetics:

Zero order kinetics:

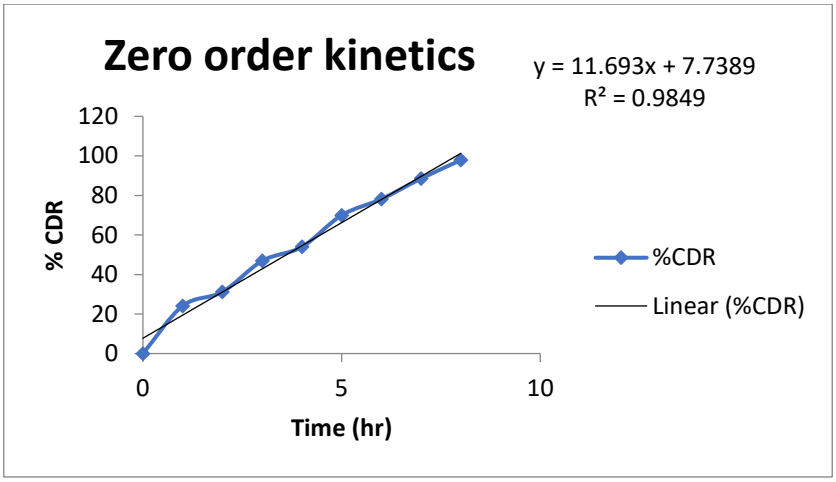

Fig-6: Zero order plot for optimized formula

First order kinetics

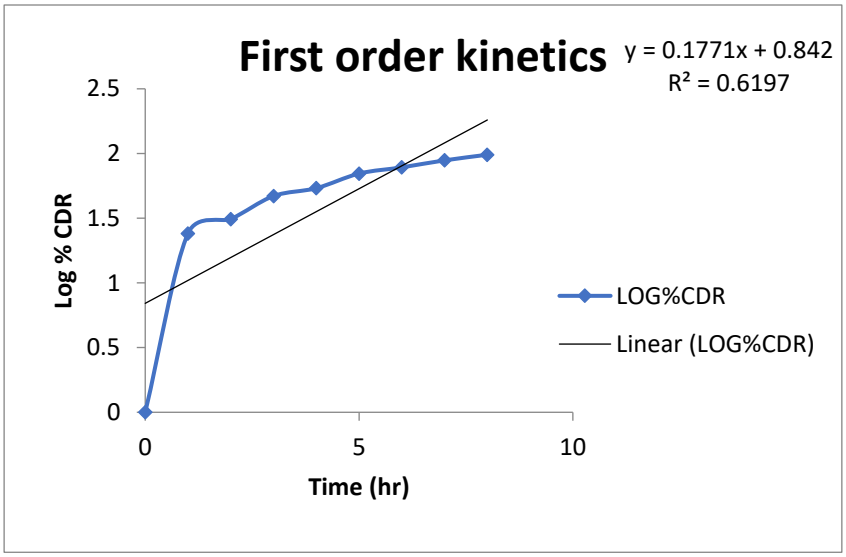

Fig-7: First order for the optimized formula

Higuchi plot

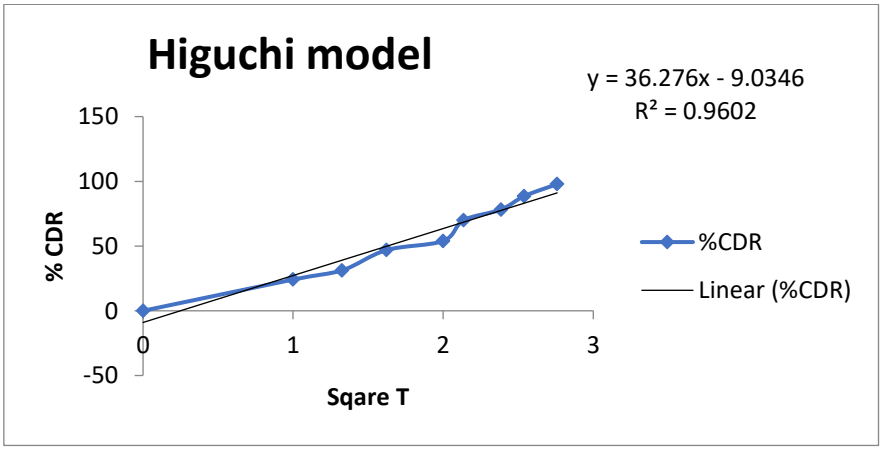

Fig-8: Higuchi plot for optimized formula

Korsmeyer peppas

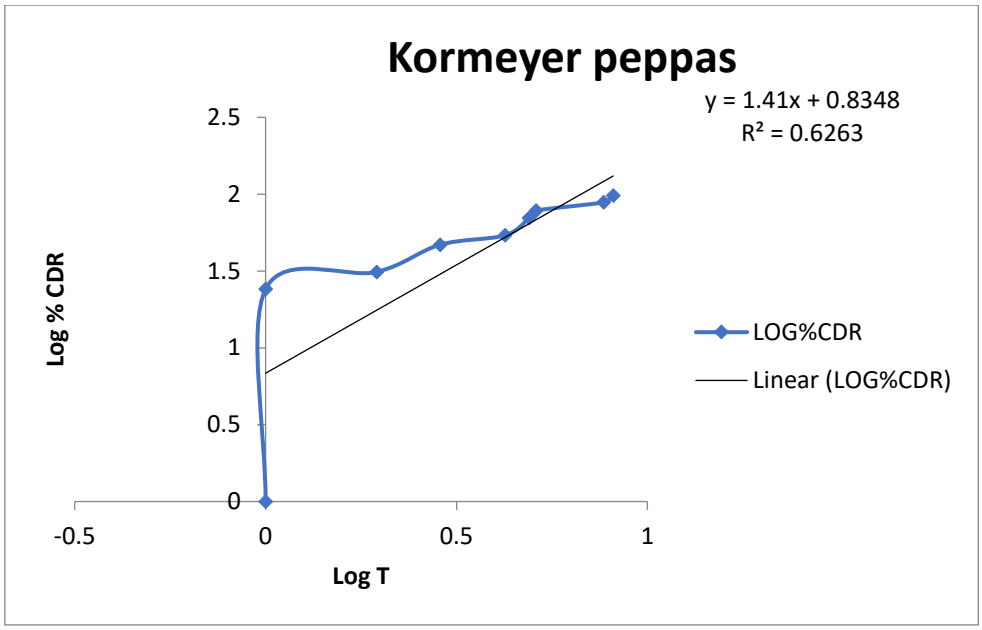

Fig-9: Korsmeyer peppas plot for optimized formula Hixson crowell

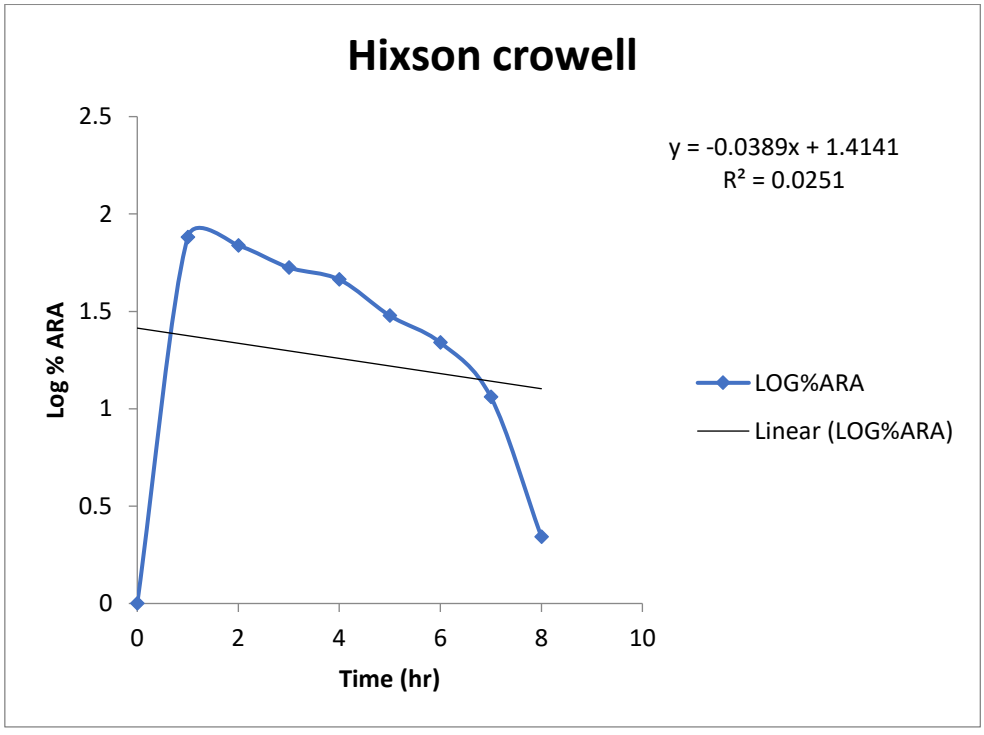

Fig-10: Hixson crowell plot for optimized formula

The drug release from the sustained release tablets was found to follow Zero order release based on the "r" value obtained for Zero order (0.984) and first order (0.627) for F8 formulation. Also, the drug release mechanism was found to be "Diffusion" based on the "r" value of 0.960 obtained for Higuchi's plot. Similarly, the drug release mechanism was found to be of Anomalous diffusion mechanism based on the "n" value of 0.626 obtained for Peppa's equation.

Stability studies

DR tablets formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 25, 30, 40^{o}c and 2-8^{o}c for a period up to 90 days.

Table-7: Results of stability studies of optimized formulation F-8

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-8	**25^{0}C/60%RH % Release**	97.85%	97.21%	96.95%	95.86%	**Not less than 85 %**
F-8	**30^{0}C/75% RH % Release**	97.85%	97.18%	96.27%	95.43%	**Not less than 85 %**
F-8	**40^{0}C/75% RH % Release**	97.85%	97.07%	96.12%	95.28%	**Not less than 85 %**

CONCLUSION

Optimization of the formulation and coating parameters, all the enteric polymers used in the study, could be successfully used to prepare the delayed release formulation of the naproxen and esomeprazole drugs. The performance of the polymers however, greatly depend upon the nature of the polymers, its solubility in a particular pH and the coating level and coating method used. Though requires a shorter processing time. The use of organic solvents in the coating of pharmaceutical dosage forms has become problematic due to regulatory requirements, flammability and limits on solvent residues in the coated product. As the studies substantiate the effectiveness of the aqueous coating systems in par with the organic coating polymers, it may well be suggested that a delayed release tablet formulation of proton pump inhibitors can be effectively formulated with aqueous based enteric polymers. The future of coating technology thus ensue aqueous coating process as customary rather than the indemnity.

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