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DESIGN, PREPARATION, EVALUATION, COMPATIBILITY AND *IN-VITRO* STUDIES OF NAPROXEN AND ESOMEPRAZOLE MULTILAYER TABLETS: LAYER BY LAYER TABLET TECHNOLOGY

Irin Dewan*, Sadiya Afrose Jahan, Mahjabeen Gazi, Joydeb Nath, Md. Asaduzzaman, Maksud Al- Hasan

Department of Pharmacy, University of Asia Pacific, Dhanmondi, Dhaka-1209, Bangladesh.

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***Correspondence for Author**
Irin Dewan
Department of Pharmacy, University of Asia Pacific, Dhanmondi, Dhaka-1209, Bangladesh.

ABSTRACT

The rationale of the present study was to design and prepare a combination product of naproxen and esomeprazole tablet by layer by layer tableting method. In this method shellac, cellulose acetate phthalate, methacrylic acid (copolymers), polyvinyl acetate phthalate and hypromellose phthalate were used as an enteric coating agent, to provide delayed action of naproxen, and esomeprazole was combined as an immediate release part which was added as a drug layer around the enteric coated naproxen core through a coating suspension. The granules and finished tablet were evaluated for their flow properties, diameters, thickness, hardness, friability and disintegration time. The selected core tablet was then sub coated with five different sub coating materials (E1-E5) in different concentrations (8%, 10% and 12%). Finally the product was completed with a finishing touch of coating layer with a coloring agent and polishing powder to provide a protection of esomeprazole layer and to improve the asthetic value of the product. The tablets were analyzed at several stages during development. FTIR studies revealed that there was no interaction between the drug and excipients used in the study. Core and enteric coating the delayed release profile was checked using USP II type dissolution apparatus in different media. The release mechanisms of naproxen enteric coated tablets were explored and explained with Zero order, first order, Higuchi, Korsmeyer and Hixon Crowell equations. The *in–vitro* release data were fitted with several mathematical models and mean dissolution time along with fractional dissolution time values (T25%, T50% and T80%) were calculated. The

final results indicate a complete combination of naproxen and esomeprazole and with good analytical results.

KEYWORDS: Layer by layer technology, Naproxen, Esomeprazole.

INTRODUCTION

In modern years, a rising attention has been developed in designing drug delivery systems that contain an immediate release (IR) component to controlled release (CR) dosages. The addition of an IR component allows one to design delivery systems having optimal pharmacokinetic profiles and enables the combination of different drugs thereby improving patient compliance.[1] Layered tablets are able to provide abundant advantages like to get immediate-release as well as controlled-release in single dosage form, to avoid incompatibility between two or more active pharmaceutical ingredient, cost reduction and stability enhancement. Multi-layer tablet dosage forms were designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredient(s) (API), to separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer, to modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release, to administer fixed dose combinations of different APIs, prolong the drug product life cycle, make novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery. The newest challenge has been seeking a balance with greatest benefit and least harm, often requiring a patient-individualized approach for these therapies.[2]

NSAID's are commonly used for the treatment of pain and inflammation in chronic conditions, such as rheumatoid arthritis and osteoarthritis. However these agents are associated with peptic ulcer disease and its complications. The pathogenesis of NSAID related ulcers is complex and multifactorial, involving primarily systemic effects. Therefore co therapy with agents that prevent and/or heal NSAID related mucosal damage (eg. proton pump inhibitors) is recommended. However co therapy for the prevention of NSAID related adverse effects are under prescribed and patients do not adhere to such treatment over time. Again combination product resulted in a statistically significant reduction in the incidence of gastric ulcers compared with esomeprazole alone.[3]

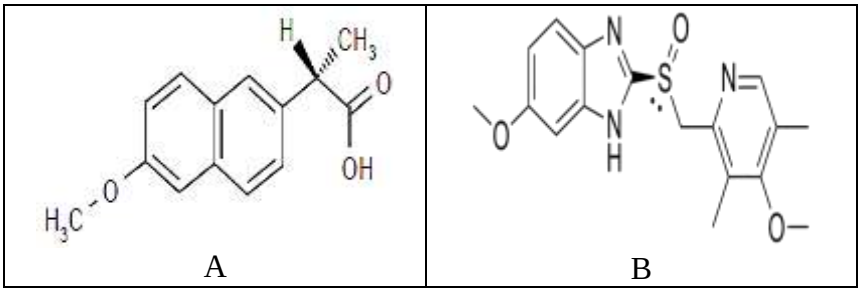

Figure 1 Chemical structure of A) Naproxen and B) Esomeprazole

Naproxen is a NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell, thus reducing gastric acidity. The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C. An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The enteric coated polymers remain unionize at low pH, and therefore remain insoluble. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers. Since enteric-coated tablets do not dissolve in the stomach, they are useful for the drugs which are not stable in gastric juice (i.e., at low pH) or are irritating to the gastric mucosa. By-passing the stomach and release of acid-labile drugs in the intestine will enhance the drug absorption significantly.[4]

So an oral single tablet fixed dose combination of the NSAID naproxen and proton pump inhibitor esomeprazole should be developed to provide pain relief and reduce the risk of gastric ulcer. The present invention comprises a multilayer sequential delivery tablet formulation combining an immediate release esomeprazole magnesium layer and a delayed release (DR) naproxen core. As a result, esomeprazole is deployed prior to the dissolution of the NSAID. The DR layer prevents naproxen release at pH levels below 5.5, providing protection against possible local gastric toxicity of naproxen.[5]

The major concern in enteric coating formulations is a risk of premature drug release through the enteric coating film in acid media. This problem could be solved by an application of a sub coating layer where the coating substrates are subject to coating with a small amount of a

soluble material prior to enteric coating. This thin film layer impedes water penetration through the cores and thus prevents the premature drug release. The sub coating layer reduces surface roughness of the coating substrate and improves adhesion of the enteric film on the substrate surface. This generates a robust film formation where a lower amount of enteric coating polymer may be required for enteric protection.[6]

The prime objectives of this study were: (i) to explain the release mechanisms from core and coated tablets; (ii) to design new multi- layer tablets based on this polymer to achieve different drug release; and (iii) to study process and formulation parameters affecting drug release. Naproxen and Esomeprazole were preferred as model drugs. The fixed dose combination of naproxen and esomeprazole (naproxen/esomeprazole) combines the efficiency of naproxen as an NSAID, with a lower incidence of NSAID-associated ulcers and better tolerated in the upper digestive tract, due to its association to esomeprazole, a PPI.[7] Its efficacy in osteoarthritis is equivalent to COX-2 and has proven to maintain its profile of GI and CV safety, even in the long term.[8]

MATERIALS AND METHODS

Materials

Naproxen and Esomeprazole as an donation sample from Popular Pharmaceutical limited, Bangladesh, Hypromellose Phthalate (Colorcon Asia Pvt. Limited, India), Polyvinylacetate Phthalate (Colorcon Asia Pvt. Limited, India), Shellac (Evonik, Germany), Cellulose Acetate Phthalate (Colorcon Asia Pte. Limited, India), Hydroxypropyl Cellulose (Colorcon Asia Pte. Limited, India), Ethyl Cellulose (Colorcon Asia Pvt. Limited, India), Carnauba Wax (Saurav Chemical Com. India), D & C Yellow No. 10 (Colorcon Asia Pvt. Limited, India), Magnesium Oxide (Shijiazhuang Taiwnglida Import & Export Co. Ltd.Chaina), Opadry White OY-C-7000 A (Colorcon Asia Pvt. Limited, India), Acryl-EZE White (Colorcon Asia Pvt. Limited, India), Acryl-EZE White (Colorcon Asia Pvt. Limited, India), Croscarmellose Sodium (Colorcon Asia Pvt. Limited, India), Sodium Starch Glycolate (Yung Zip Chemical Co. Ltd. Taiwan), Microcrystalline Cellulose (PH 102) (Weiring Pharma Mfg. Co.Ltd. Taiwan), Magnesium stearate (Merck, Germany), Maize starch (Merck, Germany), Povidone (Kollidon 30) (BASF South Asia Pvt. Ltd. Singapore), Anhydrous Lactose (DVM Fonterra Excipients GMBH and Co. Ltd. Germany) etc.

Apparatus

SS vessel (Ruian Kaixinlong Pharmaceutical Machinery Tech Co.China), Blender (Ruian Kaixinlong Pharmaceutical Machinery Tech Co. China), Fluid Bed Dryer (Ruian Kaixinlong Pharmaceutical Machinery Tech Co.China), mesh# 24,30,40; punch, Clit Tablet compression machine(Shanghai Develop Machinery Co., Limited, China), Film and Sugar Coating Machine (Nanjing Hanyoo Machinery Co., Ltd. China),), USP Type II Dissolution Apparatus (Erweka, Germany) and UV Visible Spectrophotometer (Shimadzu, Japan).

METHODS

Preparation of Naproxen Core tablets

For the preparation of Naproxen core tablets, five cost effective formulations had selected shown in table 1. At first povidone (Kollidone 30) solution (1:7 ratio) in water was prepared by mixing with a stirrer into a SS vessel. Then accurate quantities of Naproxen, diluents and disintegrants were weighed. The raw materials were sifted through mesh # 30 and mixed thoroughly for 10 minutes. Then binder solution was added into the above blend and mixed for 3-4 minutes to prepare wet mass. Then extra water was added to effect good granulation and mix for extra 1-2 minutes. The wet mass was dried in a Fluid Bed Dryer (FBD) for about 15 to 20 minutes to obtain LOD 2.5% to 3.5%. The granules are then crushed with mesh#24 and collected separately. Then magnesium stearate was weighed and sieved through mesh # 40 and added to the granules and mixed for 5 minutes. In this procedure granules were prepared and then pre compression parameters were checked. Then tablets were compressed using 12 mm round shaped punch with both side plain surfaces with ten stations Clit tablet compression machine (shown in figure 2 and 3). After compression of granules the tablets were checked for post compression parameters. Depending on the Pre compression and Post Compression results one formulation would be selected for the next step.

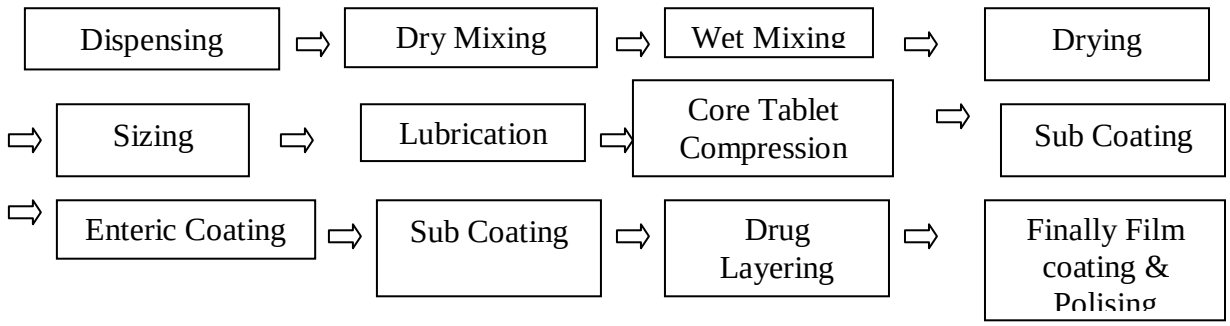

Figure 2 Flow diagram of Naproxen and Esomeprazole layer by layer tablet

A. Drying Granules in FBD

B. Granules of naproxen tablet

C. Compression of naproxen tablet

D. Naproxen core tablet

E. Sub Coating of Naproxen tablet

F. Sub coated Naproxen tablet

G. Enteric coated Naproxen Tablet

H. Sub coated over Enteric Coated Naproxen Tablet

I. Drug Layered with Esomeprazole of Naproxen Tablet

J. After film coating and polishing of Naproxen + Esomeprazole layer by layer tablet

Figure 3 Pictorial presentations of steps of manufacturing of Naproxen and Esomeprazole layer by layer tablet

Table 1 Formulation of Naproxen 500 mg Core Tablet

Material Name	Quantity (mg /tablet)				
	F1	F2	F3	F4	F5
Naproxen	500.00	500.00	500.00	500.00	500.00
Povidone (Kollidon 30)	21.00	10.00	15.00	15.00	12.50
Microcrystalline Cellulose (PH 101)	-	-	-	20.00	20.00
Anhydrous Lactose	-	-	15.00	-	-
Maize starch	-	20.00	-	-	10.00
Sodium Starch Glycolate (Type A)	-	15.00	-	10.00	-
Croscarmellose Sodium	21.00	-	15.00	-	-
Magnesium Stearate	8.00	5.00	8.00	5.00	7.50
Total Quantity	550.00	550.00	550.00	550.00	550.00

Preparation of Sub-coating Suspension of Naproxen Core Tablet

Sub coating was done with five formulations (S1 to S5) with methanol-methylene chloride solvent system at 20% solid dispersion in NR Film and Sugar Coating Machine shown in table 2.

Table 2: Formulation of Sub Coating Suspension of Naproxen 500 mg tablet

Material Name	Quantity (mg /Tablet)				
	S1	S2	S3	S4	S5
Ethyl Cellulose	3.5	-	-	-	-
HPMC 15 CPS	-	3.5	-	-	-
Opadry OY-C-7000A	-	-	3.5	-	-
Hydroxypropyl Cellulose	-	-	-	3.5	-
HPMC 15 CPS+ HPMC 5 CPS (1:1)	-	-	-	-	3.5

Enteric Coating of Naproxen Sub Coated Tablet

Enteric coating was applied over Sub Coated Naproxen tablets (S3 formulation has followed specification) with five different enteric coating materials at three different concentrations with aqueous solvent system at 20% solid dispersion. Total 15 trials had done with 15 enteric coating formulations shown in table 3.

Table 3 Formulation of Enteric Coating Suspension

Initial Formulation code	Material Name	Polymer Concentration And Formulation Code		
		8%	10%	12%
E1	Aquateric (Cellulose Acetate Phthalate) FMC	E1i	E1j	E1k
E2	EmCoat 120 N (Shellac) Emerson	E2i	E2j	E2k
E3	Acryl EZE White (Methacrylic Acid Co Polymer) Colorcon	E3i	E3j	E3k
E4	Sureteric (Polyvinylacetate Phthalate) Colorcon	E4i	E4j	E4k
E5	HP-55 (Hypromellose Phthalate) Seppic	E5i	E5j	E5k

Sub Coating over Enteric Coated Naproxen Tablet

Before starting of drug layering, half portion of enteric coated tablets were sub coated with the same formulation that was previously selected as sub-coating formulation shown in table 4. So drug layering was done over two types of tablets, i) Enteric coated tablets and ii) Sub coated (over enteric coated) tablets.

Table 4: Formulation of Sub coating over Enteric Coating

Material Name	Quantity (mg /tablet)
Opadry OY-C-7000A	19.25
Methanol	58.326
Dichloromethane	116.65

Drug Layering Through Coating Suspension

Tablets of selected formulations were coated with Esomeprazole containing coating suspension. Total six trials were performed with formulations D1 to D6 shown in table 5.

Table 5 Formulations of Drug Layering Coating suspension containing Esomeprazole magnesium

Material Name	Quantity (mg /tablet)					
	D1 pH 6-8	D2 pH 8-10	D3 pH 6-8	D4 pH 8-10	D5 pH 6-8	D6 pH 8-10
Esomeprazole Magnesium Trihydrate*	26.76	26.76	26.76	26.76	26.76	26.76
Opadry OY-C-7000A	26.76	26.76	26.76	26.76	26.76	26.76
Magnesium Oxide (Heavy)	6.00	10.00	-	-	-	-
Calcium Carbonate	-	-	10.00	15.00	-	-
Calcium Hydroxide	-	-	-	-	4.00	8.00
Isopropyl Alcohol	423.30	423.30	423.30	423.30	423.30	423.30
Purified Water	105.80	105.80	105.80	105.80	105.80	105.80

22.30 mg Esomeprazole Magnesium Trihydrate is equivalent to 20 mg Esomeprazole *20 % overage given to compensate process loss

Finally preparation of Film Coating and Polishing Suspension

To improve the esthetic value of the final product and to prevent degradation of Esomeprazole coating layer in contact with environmental moisture the final tablets were film coated (with a coloring agent) and polished with 0.002% Carnauba Wax shown in table 6.

Table 6: Formulation of Final Film Coating Suspension

Sl. No.	Material Name	Qty. (mg /tablet)
1	Opadry OY-C-7000A	19.25
2	Methanol	58.326
3	Dichloromethane	116.65
4	D & C Yellow No. 10	0.0057

Evaluation Parameters of Pre-compression Stage (granules)

Bulk Density and Tapped density: Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index (Carr's Index): The compressibility index of the granules was determined by Carr's compressibility index. Carr's index (%) = [TBD-LBD] /TBD X 100
Hausner Ratio: A similar index has been defined by Hausner (1967).

Angle of repose (θ): The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. Tan θ = h/r, where h and r are the height and radius of the powder cone.

Evaluation Parameters of Post compression stage (tablets)
Averag Weight Variation: For weight variation test, twenty tablets were selected at random and weighed individually. The individual weights were compared with average weight for determination of weight variation.

Thickness: The thickness of the tablets in mm was measured using Digital Vernier calipers.

Diameter: The diameter of the tablets in mm was measured using vernier caliper.

Hardness: The tablets to be tested are held between a fixed and a moving jaw of hardness test apparatus (Schleuniger pharmatron) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet breaks and the force required to break the tablet was noted.

Friability: Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed.[9] The percentage friability was determined using the formula,

$$\text{Percentage friability} = \text{Initial weight - Final weight/Initial weight} \times 100$$

Disintegration Time
This test is provided to determine whether tablets disintegrate within the prescribed time when placed in a liquid medium under the experimental conditions presented below. Operate the apparatus using water as the immersion fluid unless another liquid is specified and maintain its temperature at 35-39 °C. At the end of the specified time, lift the basket from the fluid and observe the dosage units: all of the dosage units have disintegrated completely.

***In-Vitro* Drug Release Studies**

Dissolution of Naproxen Core Tablet

Preparation of Buffer for dissolution medium

Phosphate buffer of pH 7.4 was prepared by dissolving 2.62 gm of sodium dihydrogen orthophosphate monohydrate and 11.5 g of anhydrous disodium hydrogen orthophosphate in sufficient water to produce 1000 ml and adjusted the pH to 7.4 by dilute phosphoric acid.

Preparation of 0.1 M hydrochloric acid for dissolution medium

To prepare 0.1 M hydrochloric acid, 8.5 ml concentrated hydrochloric acid (37%) was added in 1000 ml water.

Preparation of Standard Curve of Naproxen

Naproxen Working Standard 28 mg was accurately weighed and taken into a 50 ml volumetric flask. Then about 30 ml of phosphate buffer pH 7.4 was added and sonicated for 10 minutes and diluted to volume with the same. After that 5 ml of this solution was diluted to 25 ml with phosphate buffer pH 7.4. From the standard solution, Naproxen solution of concentration 0.02 mg/ml, 0.04 mg/ml, 0.06 mg/ml, 0.08 mg/ml, 0.10 mg/ml, 0.12 mg/ml, 0.14 mg/ml were prepared by appropriate dilution and absorbance was taken by UV – Spectrophotometer at 332 nm to prepare a standard curve of Naproxen shown in figure 4a.

Preparation of Standard Curve of Esomeprazole

Esomeprazole magnesium trihydrate working standard (22.3 mg) was accurately weighed into a 100 ml volumetric flask. Methanol (5 ml) was added and dissolves by hand shaking; then diluted to volume with diluting solution and sonicated for 10 minutes. Then 5 ml of this solution is dilute to 100 ml with diluting solution. From the standard solution Esomeprazole, solutions of concentration 0.02 mg/ml, 0.04 mg/ml, 0.06 mg/ml, 0.08 mg/ml, 0.10 mg/ml, 0.12 mg/ml was prepared by appropriate dilution and absorbance was taken by UV Spectrophotometer at 302 nm and standard curve of Esomeprazole was preparedshown in figure 4b.

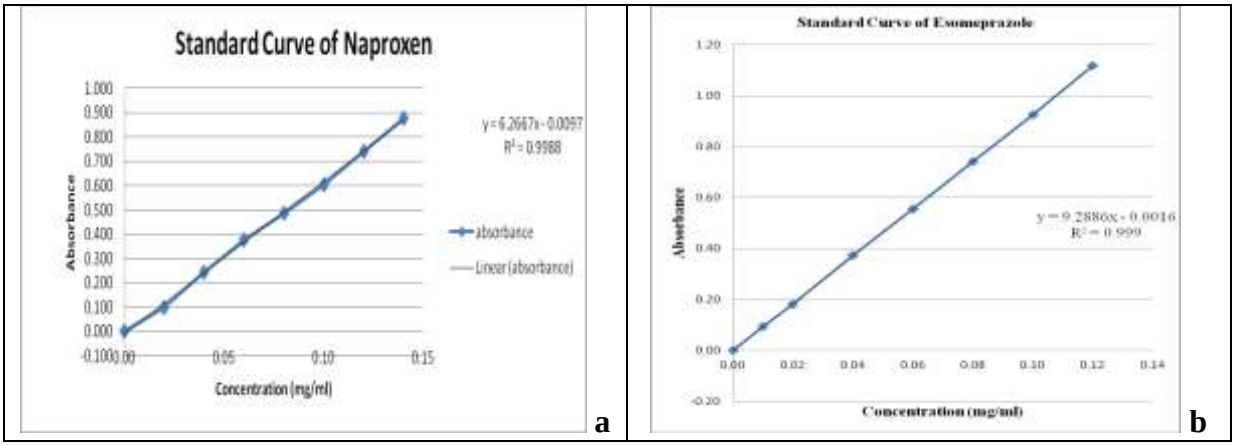

Figure 4 : Standard curve of a) Naproxen and b) Esomeprazole Magnesium Trihydrate

Analysis of Dissolution Profile

Absorbance values obtained from the dissolution studies were converted into percent release of drug from the formulations of enteric coated tablets. This is done by comparing the absorbance values with the standard curve.

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero order,[10] first order, Higuchi[11] and Korsmeyer[12] equations to ascertain the kinetic modeling of drug release.

Curve Fitting Analysis

To analysis the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as.

1) Cumulative percentage drug released vs time (*In-Vitro* drug release plots)
2) Cumulative percentage drug released vs Square root of time (Higuchi's Plots)
3) Log cumulative percentage drug remaining vs time (First order plots)
4) Log percentage drug released vs log time (Peppas plots)
5) Cube root percent remaining vs time (Hixon – Crowell)

Successive Fractional Dissolution Time (MDT)

To characterize the drug release rate in different experimental conditions, $T_{25\%}$, $T_{50\%}$ (mean dissolution time) and $T_{80\%}$ were calculated from dissolution data according to the following equations.

$$T_{25\%} = (0.25/k)^{1/n}$$

$$T_{50\%} = (0.5/K)^{1/n}$$

$T_{80\%} = (0.8/k)^{1/n}$

Mean dissolution time can also be calculated by the following equation

$MDT = (n/n+1).k^{-1/n}$

Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice –versa. The MDT value was also found to be a function of polymer loading, polymer nature and physic-chemical properties of the drug molecule.[9]

Drug–Excipient Compatibility studies by Fourier transform infrared (FTIR) spectroscopy.

Appropriate quantity of KBr and sample (in the ration 100: 0.1) were mixed by grinding in an agate mortar. Pellets were made with about 100 mg mixture. FTIR spectra were recorded with FT-IR 8400S Shimadzu spectrophotometer in the range 4000 – 400 cm^{-1}.

RESULTS AND DISCUSSIONS

Pre and post compression Parameters of Naproxen Core Tablets (F1 to F5)

Naproxen core tablets are prepared by wet granulation method. Prior to compression granules were evaluated for their characteristic parameters. Angle of repose was measured by Fixed Funnel method. Bulk density and Tapped density was measured by Cylinder method and Carr's index (CI) and Hausner ratio were calculated. In figure 5, it has shown Physical parameters of pre and post compression of naproxen core tablets from F1 to F5 respectively.

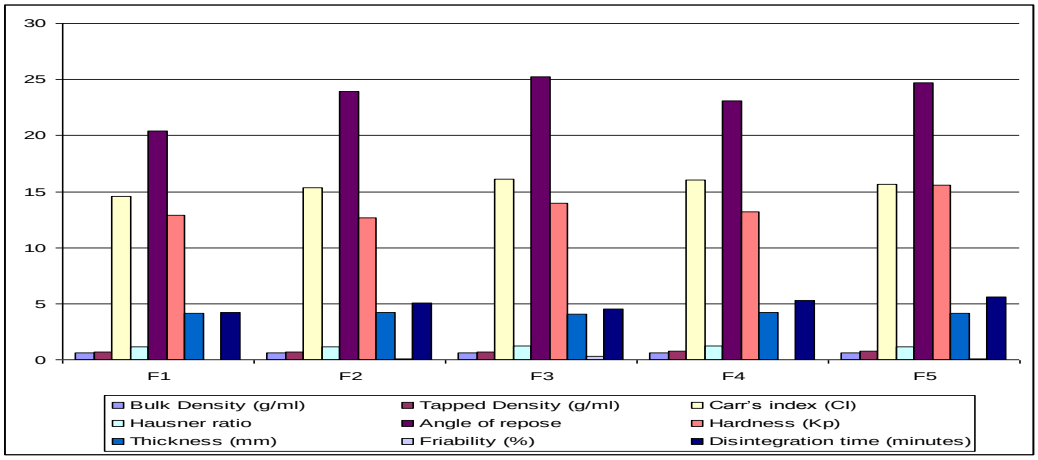

Figure 5 Physical parameters of pre and post compression of naproxen core tablets from F1 to F5 respectively

Studies of Dissolution Profile of Naproxen Core Tablet (F1 to F5)

The release profile of Naproxen core tablets was studied by UV spectrophotometer at 332 nm for 45 minutes. According to BP-2013 Naproxen immediate release tablet monograph dissolution specification is, not less than 85% of the labeled amount of Naproxen is released in 45 minutes. From the results obtained F1 to F5 shown in figure 6, one formulation F1 complies the specification. The release profile of F1 is better than the rest.

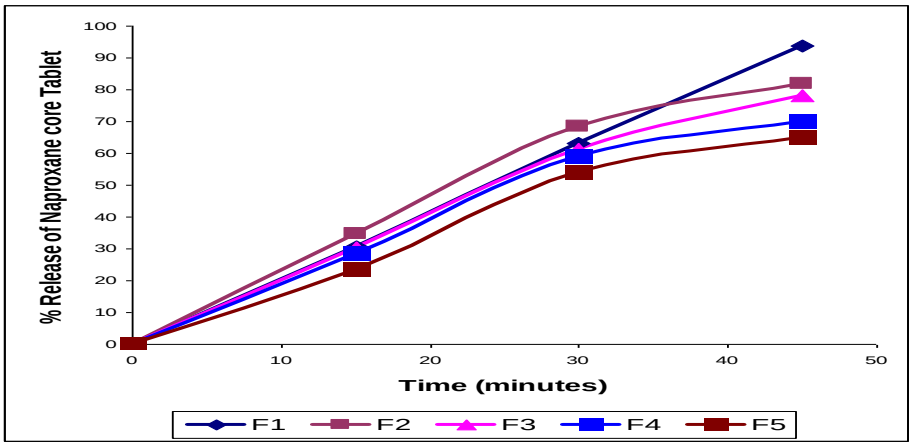

Figure 6 Release Profile of Naproxen Core Tablet From Formulations F1 to F5

Sub Coating of Naproxen Core Tablet

The tablets of formulation F1 were sub coated with the five formulations S1 to S5 in NR Film Coating Machine. The sub coated tablets were checked for weight gain percentage and DT in phosphate buffer (pH 7.4) shown in figure 7. Formulation **S3** was selected for sub coating of the core tablets as it provides tough and smooth film than other formulations and disintegration time is relatively less in phosphate buffer which can be taken as an indication of good drug release in alkaline media of intestine.

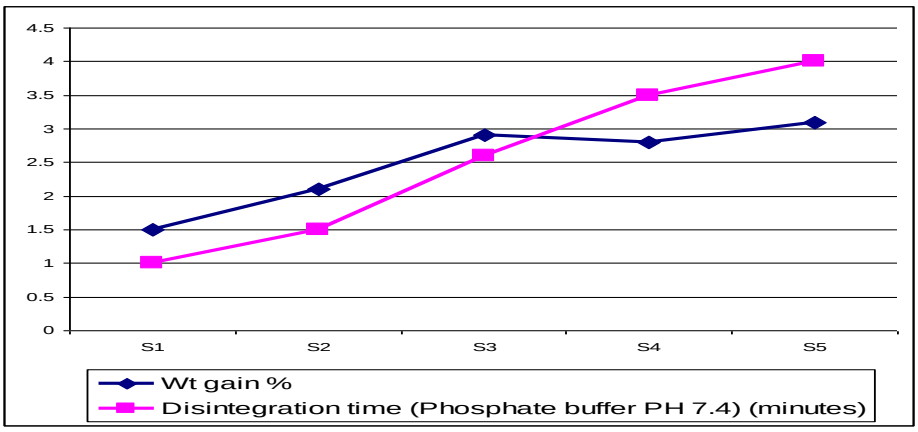

Figure 7 Physical properties of Sub coated tablets of Formulations S1 to S5

Enteric coating of Naproxen Sub Coated Tablet with Formulations E1 to E5

Sub coated tablets were subjected to enteric coating with five different coating materials with formulations E1-E5. Each formulation was prepared in three different concentrations (8%, 10% and 12%). Total 15 trials with 15 formulations (E1i, E1j, E1k, E2i, E2j, E2k, E3i, E3j, E3k, E4i, E4j, E4k, E5i, E5j, E5k) had done with the aqueous solvent system at 20% solid dispersion. All the 15 formulations were subjected to disintegration test in 0.1M Hydrochloric acid for two hours and then in phosphate buffer (pH 6.8) for 45 minutes shown in figure 8.

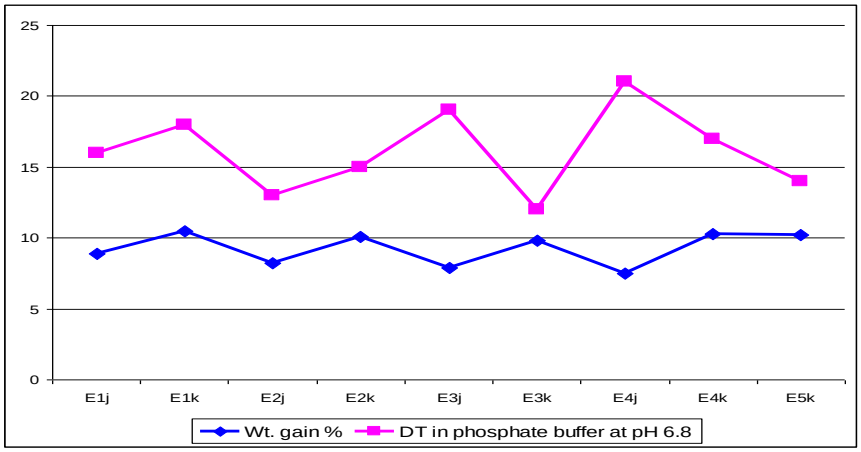

Figure 8 Disintegration Time of Enteric Coated Tablet (E1 to E5)

Dissolution Profile study of Enteric Coating of Naproxen Tablets of Formulations - E1j, E1k, E2j, E2k, E3j, E3k, E4j, E4k, E5j, E5k in Acid and Buffer Media:

Tablets of the ten formulations were analysed for drug release profile in acid and buffer media has shown in figure 9 and figure 10. Data obtained from dissolution profiles were plotted in different models.

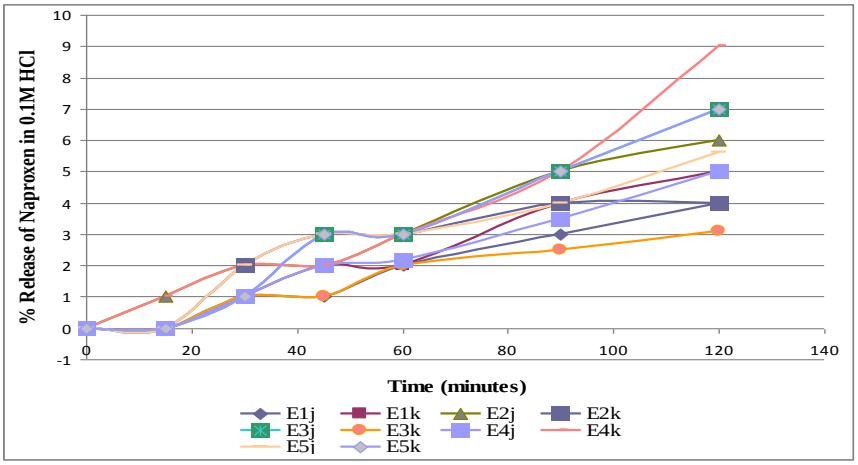

Figure 9 Percent Release of Naproxen in 0.1M HCl in 120 minutes from formulation E1j, E1k, E2j, E2k and E3j, E3k, E4j, E4k, E5j and E5k respectively

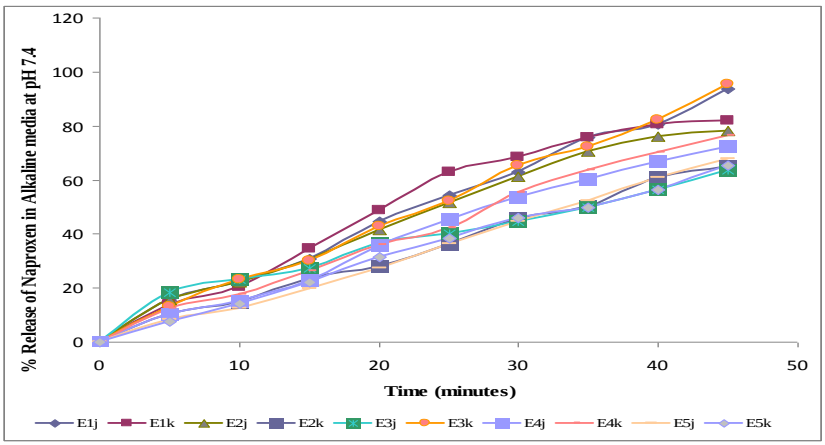

Figure 10: Percent release of Naproxen in alkaline media at pH 7.4 from formulations - E1j (Aquateric-10%), E1k (Aquateric-12%), E2j (EmCoat 120 N -10%), E2k (EmCoat 120 N-12%) and E3j (Acryl EZE-10%) respectively

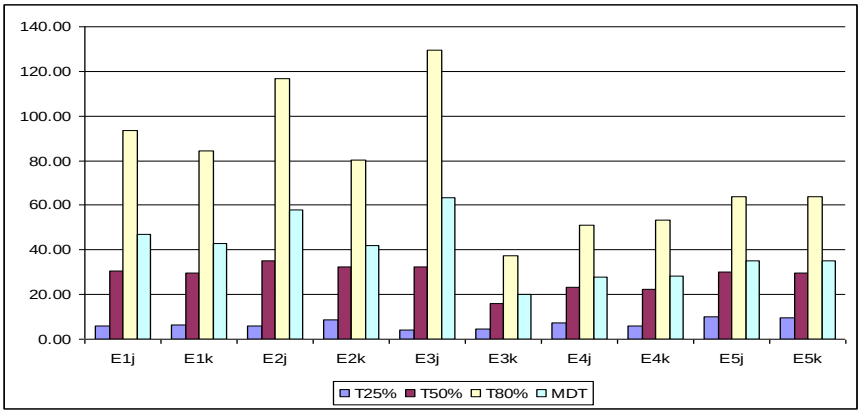

Figure 11: MDT values of formulation E1j, E1K, E2j, E2k, E3j, E3k, E4j, E4k, E5j and E5k respectively

Table 7: Interpretation of release rate constants and R^2 values for Different Release Kinetics

Formulation Code	Zero order		First order		Higuchi		Korsmeyer		Hixon Crowell	
	R^2	K_0	R^2	K^1	R^2	Kh	R^2	n	R^2	K_C
E1j	0.995	2.025	0.868	-0.024	0.928	14.280	0.928	0.502	0.946	0.056
E1k	0.988	1.936	0.978	-0.018	0.943	14.000	0.954	0.535	0.962	0.048
E2j	0.991	1.780	0.982	-0.016	0.947	12.760	0.935	0.472	0.984	0.042
E2k	0.995	1.440	0.972	-0.01	0.917	10.100	0.933	0.520	0.985	0.030
E3j	0.981	1.249	0.973	-0.008	0.973	9.154	0.904	0.340	0.967	0.026
E3k	0.997	2.066	0.827	-0.026	0.920	14.490	0.957	0.554	0.926	0.058
E4j	0.992	1.664	0.988	-0.013	0.920	11.710	0.944	0.581	0.991	0.036
E4k	0.995	1.718	0.971	-0.014	0.921	12.080	0.935	0.536	0.985	0.039
E5j	0.996	1.528	0.969	-0.011	0.892	10.570	0.934	0.621	0.979	0.032
E5k	0.995	1.438	0.984	-0.011	0.927	10.130	0.978	0.609	0.992	0.029

Drug Layering

Formulation E3k was selected for the drug layering step as it showed better physical and analytical performance than the rest of the formulations shown in table 8. Tablets of formulation E3k were drug layered with six formulations (D1to D6) containing three different alkaline stabilizers at two different pH values. The drug layering was done in two different ways. In the first way drug layer was given directly over the enteric coated Naproxen tablet. In the second way a sub coating layer was given over the enteric coated Naproxen tablet before drug layering. Then the tablets of formulations D1 to D6 were checked for physical appearance and only three formulations (D2, D4 and D6) were has followed the specification shown in figure 12.

Table 8: Physical Parameters of formulation D1 to D6 after Drug Layering

Test Parameter	**Quantity (mg /tablet)**					
	D1 pH 6-8	**D2 pH 8-10**	**D3 pH 6-8**	**D4 pH 8-10**	**D5 pH 6-8**	**D6 pH 8-10**
Physical Appearance of Drug layered tablet **without sub coating** over enteric Layer(After 15 days)	Black colored	Black colored	Black colored	Black colored	Black colored	Black colored
Physical Appearance of Drug layered tablet **with sub coating** over enteric Layer (After 15 days)	light grey colored	Ok	Ash colored	Ok	Ash colored	Ok

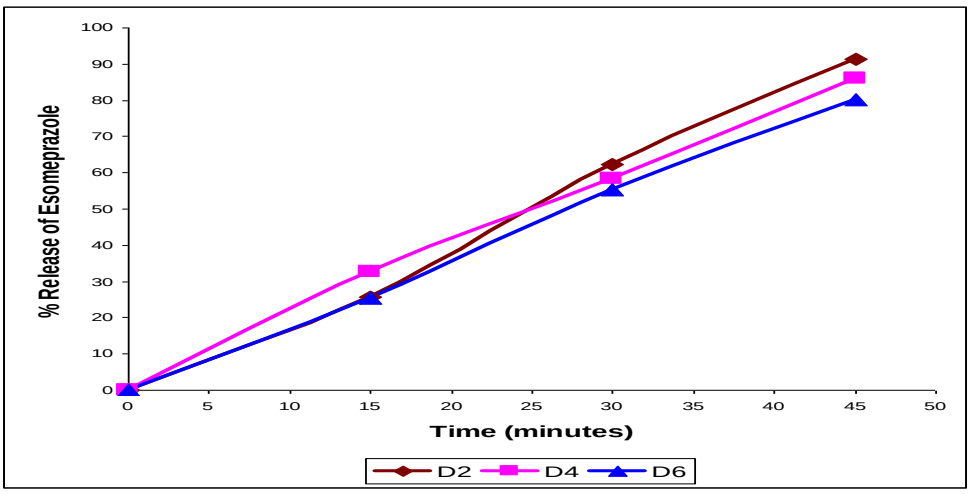

Figure 12 Percent release of Esomeprazole from formulations D2, D4 and D6 respectively

DISCUSSIONS

The release profile of Naproxen from formulation E1j-Aquateric (10%), E1k-Aquateric (12%), E2j-EmCoat 120 N (10%), E2k-EmCoat 120 N (12%) and E3j-Acryl EZE (10%), E4j-Sureteric (10%), E4k-Sureteric (12%), E5j-HP-55 (10%), E5k-HP-55 (12%) and E3k-Acryl EZE (12%) were plotted in Zero Order , 1st Order, Higuchi, Korsmeyer, and Hixon Crowell model and T25%, T50%,T80% and MDT values were calculated. It was apparent that all ten formulations (E1k, E1j E2j,E2k and E3j) were best fitted with Zero order model which reveals that the release mechanisms were independent of the concentration of the drug and drug was released through Non Fickian Diffusion and erosion.

Exception was seen in case of Sureteric (Polyvinylacetate Phthalate) formulations -E4j (10% Polymer) and E4k (12% Polymer). Increasing the polymer concentration increases the MDT value a very small. In formulation E5k and E5j with HP-55 (Hypromellose Phthalate) increase of 2% Polymer shows a very small decrease in MDT values. Among the ten Enteric coating formulations, E1j [Aquateric (Cellulose Acetate Phthalate)-10%] released 93.80% drug in alkaline media in 45 minutes and E3k [Acryl EZE White (Methacrylic Acid Co Polymer)-12%] released 95.45%. Between two formulation E3k has shown the highest dissolution in alkaline media shown in figure 11.

So, among the 10 formulations E3k (Acryl-EZE-12%) released the least amount of Drug in Acid media and highest amount of Drug in Alkaline media, which could be taken as an indication of best formulation. So Formulation-E3k was selected for the next step (Drug Layering) of the study.

Drug layering was done with six different formulations of three different alkalinizing agents at two different pH conditions. For this purpose the Opadry White OY-C-7000A is chosen as the carrier of drug solution as this material is used as sub coating agent previously and was proven compatible with Esomeprazole. As stability of Esomeprazole Magnesium was a function of pH; and it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. For this reason we had added the alkalinizing agent into the formulation to create an alkaline environment of the entire coating formulation, which prevent the degradation of the Esomeprazole Magnesium. At first we disperse the alkalinizing agent into IPA+ Water (1:1) solution at selected concentration to provide specific alkaline condition. Then added the Esomeprazole Magnesium into the solution and homogenize for 15-20 minutes for uniform dispersion. At the same time Opadry White OY-C-7000A was

reconstituted separately at 20% solid dispersion in the same ratio of IPA+ Water solution. The drug solution part was then added to Opadry OY-C-7000A part carefully to the region of vortex in a steady stream as quickly as possible but avoiding undue accumulation of foam in the liquid surface. Stirring was continued for 45 minutes. Finally the pH of the coating suspensions are found between 6.0 to 10.0 according to the formulations, which might be suitable for Esomeprazole Magnesium's stability. Esomeprazole Magnesiumis was given with 20% overage, to adjust the process loss during coating operation.

During the checking of Physical appearance of drug layered tablets, there were two types of observations in table 8. The tablets of Formulations D1, D3 and D5 develops a light grey or Ash color, might be due to some degradation of the drug layer. The pH of Formulations D1, D3 and D5 was between (6-8), which might not be sufficient for Esomeprazoles stability. On the other hand Formulations D2, D4 and D6 (pH 8-10) were completely good in appearance which was an indication of Esomeprazoles stability. So the formulations having pH 8-10, provided the most suitable alkaline environment for Esomeprazoles stability. Among the formulations D2, D4 and D6, Formulation D2 was considered best of all according to the results of dissolution profile study in figure 12. Though the results found within the range, but for the safety of the product and to improve the asthetic value we have given a final coating with the same coating material with a coloring agent followed by a polishing with Carnauba Wax. Thus some stable formulations of Naproxen and and Esomeprazole combination product is developed, which also shows good analytical results in every step.

FTIR Spectroscopy for Compatibility Study

FTIR had done to examine Drug –Excipient and Drug –Polymer interaction. IR spectra of pure drugs (Naproxen and esomeprazole) was carried out for qualitative compound identification. The compatibility study for drugs and various excipients were performed by FTIR spectrophotometric analysis. From the results of FTIR it was observed that the both drugs were compatible with the excipients used. The comparison of the spectrums reveals that there is no incompatibility exists between the excipients and polymers used in the drug shown in figure 13.

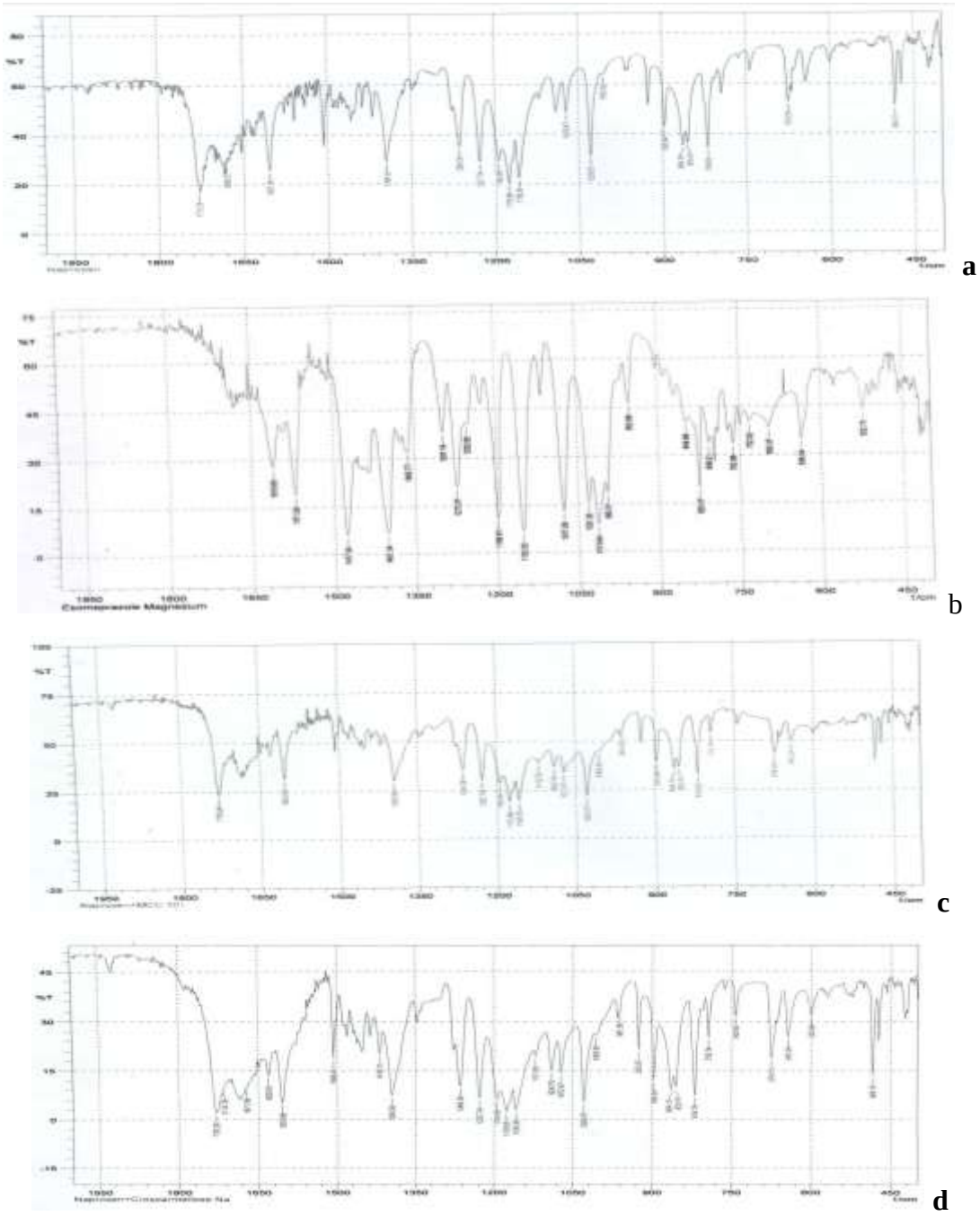

Figure 13: FTIR Spectrum of a) Pure Naproxen b) Esomeprazole c) Naproxen and Microcrystalline Cellulose PH 101d) Naproxen and Croscarmellose Sodium respectively

CONCLUSION

Nonsteroidal anti-inflammatory drugs (NSAIDs), naproxen, cause an increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at a greater risk for serious GI events. Concomittent use of proton pump inhibitors may not be feasible all times. So combination therapy of

naproxen and esomeprazole must provide better support. In the combined product of naproxen and esomeprazole, the layer of esomeprazole will release inside the stomach immediately after administration and as a proton pump inhibitor suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell and blocks the final step in acid production, thus reducing gastric acidity. Naproxen is a NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, related to prostaglandin synthetase inhibition. The enteric coating prevents naproxen release at pH levels below 5.5.

Layer by layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Layering tablet technology can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. This technology is suitable for sequential release of two drugs in combination and also for delayed release of tablet in which one layer is for immediate release as loading dose for specific purpose and second layer is maintenance dose for the same purpose or for another purpose.
The current invention offers an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products' efficacy, and protect against impersonator products. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity, and improved patient compliance and convenience.

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