Model Dependent and Independent Approaches to Compare *In vitro* Release Profiles from Ethylcellulose and Eudragit L100 Based Matrix Tablets

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ABSTRACT: The main objective of the present study was to compare the release profiles of ethylcellulose and eudragit L100 based matrix tablets of naproxen. Dissolution studies were carried out by using United States Pharmacopoeia-XXIII type-II dissolution apparatus. The granules were evaluated for angle of repose, bulk density, compressibility index, total porosity and drug content. The tablets were subjected to thickness, diameter, hardness, drug content, disintegration test, friability and *in vitro* release studies. The release rate was quantitatively determined by a HPLC method. Matrix tablets based on 20% and 25% ethylcellulose and 25% eudragit L100 showed sustained release up to 8 hours. The release patterns were evaluated using model-dependent approaches (zero order, first order, Higuchi's, Korsmeyer's and Weibull's model) and model-independent approach (ANOVA and the similarity factor, f_2). Most of the release patterns were fitted to Korsmeyer's model with n values between 0.663 to 0.816, indicating the release mechanisms were governed by both diffusion and erosion. From the Weibull equation, the shape parameter was found to be sigmoid or S-shaped. Among the formulations, ECF-2 and EFU-6 were most similar to ECF-3 according to f_2 value. The MDT values were found to be increased with the increased concentration of polymers. Ethylcellulose found to be most rate retarding than eudragit L100.

Key words: Naproxen, ethylcellulose, eudragit L100, dissolution, dissolution profile comparison.

INTRODUCTION

Naproxen is a naphthylpropionic acid derivative. It is the only NSAID presently marketed as a single enantiomer and it is a nonselective COX inhibitor. Naproxen is effective for the usual rheumatologic indications.[1] Naproxen has been proved to be effective in both experimental and clinical pain like rheumatoid arthritis, osteoarthritis, juvenile arthritis and acute gout without any serious cardiovascular or respiratory side effects.[2,3] The drug is lipid soluble, practically insoluble at low pH and freely soluble at high pH. One of the most important commonly used methods for controlling drug release is to form a matrix system with the help of hydrophilic, inert and hydrophobic polymers.[4]

Ethylcellulose (EC) is a non-toxic, stable, compressible, inert, hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms. This polymer is often used as a rate-controlling membrane to modulate the drug release from dosage forms with organic or aqueous coating techniques but few references have focused on the use of EC as directly compressible excipient.[5]

Eudragits (EUD) are polymethacrylates. Eudragit L100-55 is an alternative to Eudragit L 30D-55,

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which is used as an enteric coating film former for solid dosage forms. Eudragit L100 is commonly available as redispersible polymers. The coating is resistance to gastric juice but readily dissolves at pH sbove 5.5. Eudragit L100 is soluble at pH> 6. Polymethacrylates are used as binders in both aqueous and organic wet granulation processes. Larger quantities (5-20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10-50%.[5]

Here approaches were used to compare the release kinetics of naproxen classified as: model independent approaches and model dependent approaches. Model independent approaches can be further differentiated as ANOVA based procedures, ratio test procedures or pair wise procedures. A third category of model independent methods examined is denoted pair wise procedures, which include the difference factor (f_1), the similarity factor (f_2) and two indices of Rescigno. Model-dependent approaches included zero order, first order, Hixson-Crowell, Higuchi, Weibull, Gompertz and logistic models.[6] The purpose of the present study is to compare the release profile of ethylcellulose (EC) and eudragit L100 (EUD) based matrix tablets by model-dependent and model-independent methods and to explain the possible release mechanism of Naproxen from the matrix tablets prepared by wet granulation method.

MATERIALS AND METHODS

Materials. Naproxen was a gift sample of Eskayef Bangladesh Ltd. Other materials used throughout the experiment were EC (Cornileus Pharmaceuticals Pvt. Limited, India), EUD (Colorcon Limited, India), povidon K-30 (BASF, U.S.A), IPA (Sasol, Germany), ortho-phosphoric acid 85% (Sigma-Aldrich, Switzerland). The reagents tribasic sodium phosphate, methanol (HPLC grade), methanol and hydrochloric acid (37%) were from Merck, Germany. A binary HPLC machine (Waters, Ireland), ultrapure water system (Sartorius, Germany), vaccum pump (Alltech, Germany), filter tips-0.22µm (Sartorius, Germany), dissolution tester (Pharmatest, Germany), tray dryer (Drug machineries, India), electronic balance (Denver Instrument M-310, Switzerland), pH meter (Lida, China) and a single punch tablet machine (Drug machineries, India) were used as the main instruments.

Quantitative analysis through HPLC. A Waters HPLC system was used in quantification of naproxen in tablets, which consisting two Waters-1525 pumps. The drug analysis data were acquired and processed using Breeze (Version 3.30, Waters, Ireland) software running under Windows XP on a Pentium PC. Ultraviolet detection was achieved with a Dual λ absorbance detector (Waters-2487). Here, 0.1M ortho-phosphoric acid (pH = 3.03) and methanol in 35:65 ratio was used as mobile phase. Flow rate was 1 ml/minute, injection volume was 20 µl and λ_{max} of UV detection was 240 nm. Temperature was kept ambient and the sensitivity of the machine was 0.0005. Retention time of naproxen was found to be at 12.492 minutes (Figure 1).

Preparation of tablets by wet granulation method. According to the formulation given in table-1, naproxen, polymer and starch 1500 were blended carefully in a mortar with the help of a pestle. In a beaker binder solution was prepared by dissolving povidone K-30 in ethanol. Now, the previously blended powder mix was added gradually in the binder solution with continuously stirring until wet mass was formed. The wet mass was sieved through a sieve of 1 mm mesh size, the granules were collected and weighed in an electronic balance (sensitivity 0.001) and dried in a tray drier at 45^{o}C for 45 minutes. After proper drying the granules were again weighed and again sieved through a sieve of 125 nm mesh size. Then, it was blended with magnesium stearate and taken in a single punch machine equipped with 10 mm diameter die and punch. Finally the tablets were prepared using hand pressure (Table 1). The ethylcellulose based tablets were coded as ECF-1 to ECF-3 and eudragit L100 based tablets were coded as EUD-4 to EUD-6.

Evaluation of granules

Carr's Index and Hausner Ratio. Both poured density (PD) and tapped density (TD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a Pharmatest Densitometer (Germany) with 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. A useful empirical guide is given by Carr's Compressibility Index (equation 1). Tapped and poured densities of the powder mix of all formulations (without adding glident) were measured. A similar index (equation 2) has been defined by Hausner (1967).[7]

CI (%) = (TD-PD) X 100 / TD ..... (1)

Hausner Ratio = TD/PD ..... (2)

Where, TD = Tapped Density, PD = Poured Density, CI = Carr's Index.

Table 1. Formulation of ethylcellulose and eudragit L100 based naproxen matrix tablets

Ingredients (mg/tablet)	Formulation codes					
	ECF-1	ECF-2	ECF-3	EUF-4	EUF-5	EUF-6
Naproxen	365	365	365	365	365	365
Ethylcellulose	75	100	125	-	-	-
Eudragit L100	-	-	-	75	100	125
Povidon K-30	25	20	5	25	20	5
Starch 1500	33	13	3	33	13	3
Magnesium Stearate	2	2	2	2	2	2
% Polymer	15	20	25	15	20	25
Total tablet weight	500	500	500	500	500	500

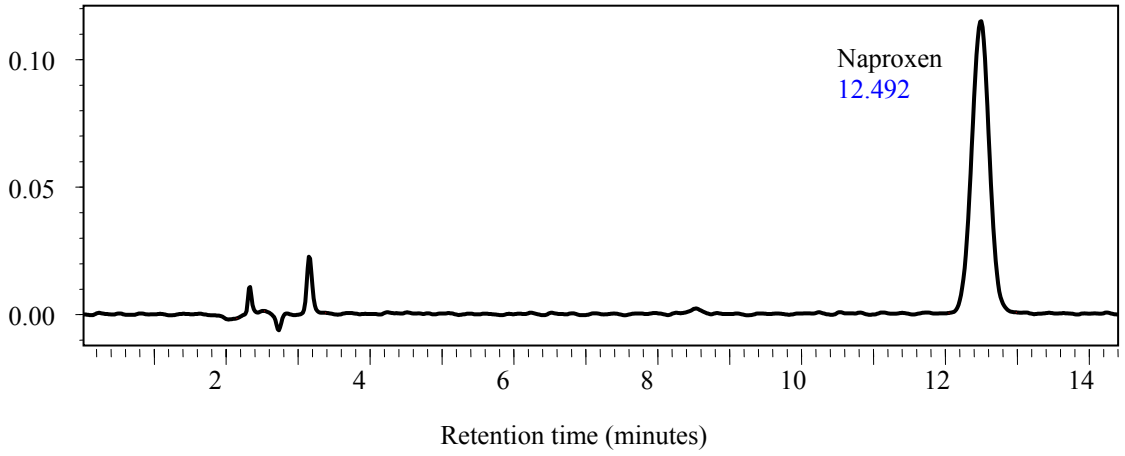

Figure 1. Chromatogram of naproxen at 240 nm using Water's binary HPLC machine.

Angle of Repose: Angle of repose of the powder mix of all formulations (without adding glident) was determined according to the fixed funnel and freestanding cone method. A glass funnel (75 mm) was secured with its tip at a given height (H) above a graph paper placed on a horizontal surface. Powder (2.5 g) was poured through the funnel until the apex of conical pile touched the tip of the funnel and then the angle of repose (θ) was calculated using the following formula (equation 3),

Tan θ =H/R..... (3)

Where R is the radius of conical pile,[8] which was measured by taking the radius of the circle (conical pile) produced by the powder mix on the graph paper.

Total Porosity: Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V)[9] :

$$\textbf{Porosity (\%)} = (V_{bulk} - V)/V_{bulk} \times 100 \ldots (4)$$

Moisture content: Weight of the prepared granules before drying and after drying were measured using an electronic balance and the moisture content (%) was determined by calculating the difference of the weights of the granules and dividing the value by the weight of the granules before drying. The percentage of this value was calculated.

Evaluation of Tablets.

Hardness and tensile strength: Five tablets of each of the formulations were taken and hardness was measured by Hardness tester (Veego, India). The average value was calculated and the testing unit was kg. Measurement of tensile strength was conducted in the axial and radial directions with the intact matrix discs according to Fell and Newton (equation 6 and 7):

$$T_{axial} = 4F/(\pi \times D^2) \ldots\ldots\ldots\ldots\ldots\ldots (6)$$

$$T_{radial} = 2F/(\pi \times D \times H) \ldots\ldots\ldots\ldots\ldots (7)$$

Where F, D and H are the crushing force (kg/mm^2), diameter (mm) and thickness (mm) of the naproxen matrix tablets respectively.

Thickness Measurement: Six tablets of each of the formulations were taken and thickness was measured by Vernier Caliper (E-Base Measuring Tools co., Taiwan). The values were reported in millimeter (mm).

Diameter Measurement: Six tablets of each of the formulations were taken and diameter was measured by Vernier Caliper. The values were reported in millimeter (mm).

Friability Test: Ten tablets of each of the formulations were weighed out and taken into the rotating disk of a Friability tester (Pharmatest, Germany). It was allowed to rotate at 25 rpm for 4 minutes. At the end of the rotation, tablets were collected, dedusted and reweighed. The friability was calculated as the percent of weight loss.

Disintegration Time: Six tablets of each formulation were taken to measure their disintegration time. One tablet of each formulation was introduced into each tube of Tablet Disintegration test Apparatus (Pharmatest, Germany). The assembly was suspended in a beaker containing phosphate buffer of pH 7.4 and observed continuously during operation. The tablets were observed for signs of cracks or disintegration. The disintegration time (minute) taken to disintegrate each tablet was recorded. The tablets passed the test till all the tablets were disintegrated.

Drug content assay: Five tablets of each formulation were weighed, then placed in a mortar and powdered with a pestle. Now, an amount equivalent to 25 mg of naproxen was dissolved with l00 ml pH 7.4 phosphate buffer and it was shaken for 15 minutes to dissolve the drugs completely. The solution was filtered through Whatmaan filter paper (0.45 μm), properly diluted with the buffer solution and the content of naproxen was determined by HPLC method.

In vitro release studies: The release rate of naproxen from the matrix tablets was determined by using US Pharmacopoeia dissolution apparatus 2 (perfect sink conditions). The dissolution test was performed using 750 ml 0.1N HCl solution at 37 ± 0.5°C using 50 rpm for first 2 hours. After 2 hrs, the acid stage was changed into buffer stage followed by addition of 180 ml 0.3 M trisodium phosphate and 50 ml of distilled water into 750 ml of 0.1N HCl to raise the pH up to 7.4. Now the release rate of naproxen in buffer was measured for next 8 hrs, withdrawing 10 ml of sample at 2 hour intervals and replacing with 10 ml of the fresh medium to maintain the volume constant. The samples were filtered through a

Whatmaan filter paper (0.45 μm) and diluted to a suitable concentration with required media.

The peak area of naproxen was measured at 240 nm by using a HPLC machine (Waters, USA). By finding out the area produced by naproxen, percentage of drug release was calculated using an equation obtained from the standard curve.

Release kinetics: The suitability of several equations that are reported in the literature to identify the mechanisms for the release of naproxen was tested with respect to the release data. The data were evaluated according to the following equations:

Zero-order model: [10]

$$M_t = M_0 + K_0 t \quad \text{..... (7)}$$

Higuchi model: [11,12]

$$M_t = M_0 + K_H t^{0.5} \quad \text{..... (8)}$$

Korsmeyer-Peppas model: [13,14]

$$M_t = M_0 + K\, t^n \quad \text{..... (9)}$$

Where M_t is the amount of drug dissolved in time t, M_0 is the initial amount of drug, K_0 is the zero-order release constant, K_H is the Higuchi rate constant, K is a release constant, and n is the release exponent that characterizes the mechanism of drug release.

First order model:[15]

$$\text{LogC} = \text{LogCo} - kt/2.303 \quad \text{..... (10)}$$

Where, C = cumulative percent of drug release at time t, Co = the initial concentration of drug at t = 0 and k = first order rate constant.

Table 2. Release mechanism with variation of n* values[16]

n value	Mechanism	dM_t/d_t dependence
n<0.5	Quasi-Fickian diffusion	$T^{0.5}$
0.5	Fickian diffusion	$T^{0.5}$
0.5<n<1.0	Anomolous (non-Fickian) diffusion	t^{n-1}
1	non-Fickian case II	Zero order
n>1.0	non-Fickian super case II	t^{n-1}

To characterize the drug release rates in different experimental conditions, mean dissolution time (MDT) was calculated from dissolution according to Mockel and Lippold[17] using the following equation:

$$MDT = n \text{ X } (K^{-1/n})/ (n+1) \quad \text{..... (11)}$$

Where n is the release exponent and K is the kinetic constant calculated from Equation 9.

Weibull equation:[18]

$$F = F^{\alpha} [1\text{-e-}(t\text{-}t_0/t_d)^{\beta}] \quad \text{.....(12)}$$

Where, F = Fraction of the dose dissolved at time 't', F^{α} = amount dissolved at infinite time, t = time, t_0 = the lag time for dissolution after disintegration, t_d = mean dissolution time, β = shape factor (Weibull slope) and $\alpha = (t_d)^{\beta}$ = time scale of the process.

The similarity factor was used to compare the difference of dissolution profiles of the test matrix tablets is given below:

$$f_2 = 50\log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad \text{... (13)}$$

where R_t and T_t are the percentage of drug dissolved at each time point for the test and reference products, respectively and n is the number of dissolution samples taken.[19]

RESULTS AND DISCUSSION

The granules of different formulations were evaluated for angle of repose, PD, TD, Carr's index, Hausner ratio, total porosity and moisture content (Table 3). The results of angle of repose and Carr's index (%) ranged from 27.47 to 30.11 and 18.79 to 21.47 respectively. Hausner ratio was from 1.20 to 1.27. The results of PD and TD ranged from 0.061 to 0.062 and 0.074 to 0.079 respectively. The results of % porosity of granules ranged from 27.33 to 31.63 and percent moisture content ranged from 2.10 to 2.30.

The average diameter and thickness of the tablets ranged from 9.95 to 9.98 mm and 1.940 to 2.095 mm respectively. The average % deviation of 6 tablets of each formula was less than ± 0.30. The average hardness, axial tensile strength and radial tensile strength were from 9.220 to 9.540 kg, 0.119 to 0.122

kg/mm^2 and 0.282 to 0.314 kg/mm^2 respectively. The average % friability and average disintegration time were from 0.14 to 0.22 and 12.20 to 12.80 minutes respectively. Drug content of the six formulations ranged from 98.23 to 100.10 % with standard deviation among five tablets was 0.56% (Table 3).

The release rate of naproxen in first two hours in acid media was so negligible (less than 4%), that's why the result was not shown in the release curve (Figure 2). At this pH (1.2) naproxen (pKa = 4.2) exists in its acidic form, which is well known to be practically in soluble in the stomach. When the dissolution media was changed to pH 7.4 Phosphate buffer media, the drug release rate was slightly increased; this is possibly because the naproxen was partially converted to naproxen salt, which is soluble form.

Table 3. Properties of granules (values are expressed as mean)

Formulation	Angle of repose(θ)	Tapped density (g/ml)	Poured density (g/ml)	Carr's Index (%)	Hausner ratio	Total Porosity (%)	Moisture content (%)
ECF-1	29.680	0.077	0.061	19.820	1.250	28.050	2.100
ECF-2	29.250	0.074	0.062	16.560	1.200	31.630	2.200
ECF-3	27.470	0.075	0.061	18.790	1.230	27.330	2.100
EUF-4	27.920	0.077	0.061	20.120	1.250	29.410	2.100
EUF-5	28.800	0.079	0.062	21.470	1.270	30.020	2.300
EUF-6	30.110	0.078	0.061	21.340	1.270	29.540	2.200

Table 4. Properties of Tablets (values are expressed as mean)*

Formulation	DIA (n=6) (mm)	THK (n=6) (mm)	HAD (n=6) (kg)	Ta (kg/mm^2)	Tr (kg/mm^2)	FRA (n=10)	DT (min)	DC (%)
ECF-1	9.980	1.940	9.540	0.122	0.314	0.140	12.700	98.230
ECF-2	9.950	2.060	9.260	0.119	0.288	0.140	12.500	99.050
ECF-3	9.950	1.960	9.450	0.122	0.309	0.170	12.600	100.100
EUF-4	9.980	2.095	9.550	0.122	0.291	0.220	12.800	99.540
EUF-5	9.950	2.095	9.230	0.119	0.282	0.210	12.200	98.980
EUF-6	9.950	2.065	9.220	0.119	0.286	0.210	12.300	99.640

*DIA = Diameter, THK = Thickness, HAD = Hardness, Ta = Axial tensile strength, Tr = Radial tensile strength, FRA = % Friability, DT = Disintegration time and DC = Drug content.

The results of dissolution studies of formulations ECF-1 to ECF-3 composed of EC at 15, 20 and 25% concentrations respectively are shown in Figure 2. Tablets ECF-1 to ECF-3 release about 25.52, 20.54 and 15.56% respectively at the end of 1 hour in pH 7.4 phosphate buffer media. ECF-1 released 89.86% at 6 hours, ECF-2 and ECF-3 released 94.63% and 85.84% naproxen respectively at the end of 8 hours. The results of dissolution studies of formulations EUF-1 to EUF-3 composed of EUD at 15, 20 and 25% concentrations respectively are shown in figure-2. EUF-1 to EUF-3 release about 28.52, 23.59 and 21.23% respectively at the end of 1 hour in pH 7.4 phosphate buffer media. EUF-1 and EUF-2 released 95.45 and 91.98 %at 6 hours, EUF-3 released 86.12% naproxen respectively at the end of 8 hours. Considering ECF-3 as the reference release pattern, the release pattern of ECF-2 and EUF-6 showed the least deviation from the theoretical release pattern (Table 5 and Figure 2).

The granules for tablet preparation were prepared according to the formula given in Table 1. Granulation is the key process in the production of many dosage forms involving the controlled release of a drug from coated or matrix-type particles. A granule is an aggregation of component particles that is held together by the presence of bonds of finite

strength. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation. The granules of different formulations were evaluated for angle of repose, PD, TD, Carr's index, total porosity and moisture content (Table 3). The results of angle of repose (<30) indicate good flow properties of the granules.[8] This was further supported by good to passable (the flow can be improved by using glident) index values (Table 3). Generally, compressibility index values up to 15% result in good to excellent flow properties and 18 to 21 result in fair to passable flow properties.[7] Hausner ratio <1.25 indicates good flow properties.[7] Here except EUF-5 and EUF-6, all formulations showed good flow properties. So, in general magnesium stearate was used to compensate the poor flow problem. In addition, granule density may influence compressibility, tablet porosity, dissolution, and other properties. The porosity values of the granules ranged from 27.33 to 31.63%, indicates that the packing of the granules may range from close to loose packing and also further confirming that the particles are not of greatly different sizes. Generally, a percentage porosity value below 26 shows that the particles in the powders are of greatly different sizes and a value greater than 48% shows that particles in the powder are in the form of aggregates or flocculates.[9] The moisture content found to be satisfactory from pharmaceutical point of view.

Table 5. f_2 and MDT values of ECF-1 to ECF-2 and EUF-4 to EUF-6 (considering ECF-3 as reference)

Formulation	f_2	MDT
ECF-1	41.167	2.865
ECF-2	54.223	3.448
ECF-3	-	4.179
EUF-4	33.509	2.45
EUF-5	35.173	2.62
EUF-6	62.656	3.747

The tablets of different formulations were subjected to various evaluation tests, such as diameter, thickness, uniformity of weight, drug content, hardness, axial and radial tensile strength, friability, disintegration time and *in vitro* dissolution. All the formulations showed uniform thickness. Good uniformity in drug content was found among all different batches of tablets and the percent of drug content was more than 98%. All of the formulations showed high hardness value. In case of EUF-1 to ECF-3, this may due to the presence of more EC, which is generally responsible for more hardness of tablets.[3] Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. The disintegration time was also found to be acceptable (Table 4).

The *in vitro* drug release characteristics were studied in simulated gastric and intestinal fluids for a period of 10 hrs using USP XXIII dissolution apparatus 2. Among the six formulations, release rate was increased with the increasing concentrations of EC and EUD. At higher concentration (20 and 25%) of EC, there was no significant difference in the release rates of the drug. This was due to the fact that the amount of ethanol used during granulation of various formulations was insufficient to wet all the particles of EC, which were in granular form and could not provide a uniform coating around the drug particles.[3] The results found in this study, increase of higher concentration of EC (not increase of lower concentration of EC), were not in good agreement with the reported study[20] in which increasing percentage of micronized EC produced slower drug release rate. As in the reported study,[20] micronized EC was used which could be more easily wetted by the granulating liquid and provide more uniform coating around the drug particles. EUD found to be less retarding polymer than EC as at only EUF-6 (containing 25% EUD) showed sustained drug release up to 8 hours. Eudragit L100 contains a carboxyl group in their structure, whereas eudragit RS and RL contains a quarternery ammonium group,

that's why when the pH started to rise above 6, the carboxylate group started to form salt and became soluble. For this reason, EUD was not able to sustain to release naproxen as long as EC. However, processing factors including wetting on granulation, particle size and hardness also affect the release of drug from tablets (Figure 2).

To know the mechanism of drug release from these formulations, the data were treated according to model-dependent methods, that is, zero order, first order, Higuchi's model, Weibull's equation and Korsmeyer's model (Table 6). According to table 6, ECF-2 having a high regression coefficient (0.974) towards Higuchi's model, indicating Fickian diffusion through a porous matrix. Diffusion is related to transport of drug from the dosage matrix. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi's kinetics.

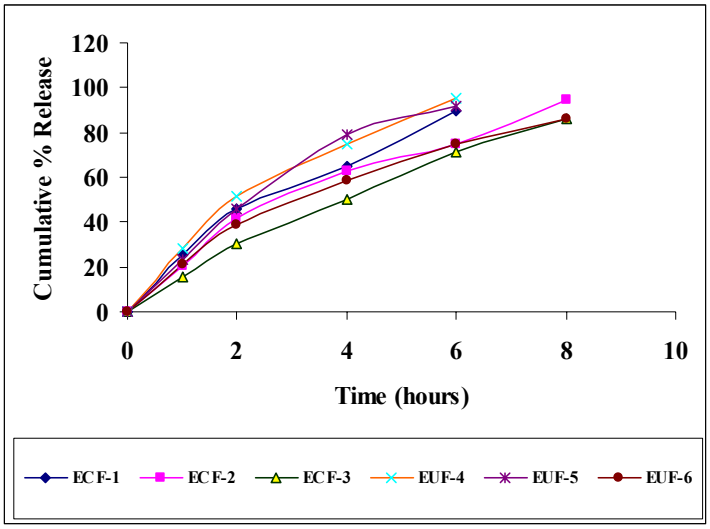

Figure 2. Zero order release profiles of ethylcellulose and eudragit L100 based naproxen matrix tablets.

Table 6. Kinetic values obtained from various plot of ethylcellulose and eudragit L100 based naproxen matrix tablets

Formulas	Zero order	Higuchi model	First order	Korsmeyer		Weibull		
	R^2	R^2	R^2	R^2	n	R^2	β	α
ECF-1	0.935	0.973	0.955	**0.988**	0.681	0.950	1.105	3.200
ECF-2	0.916	**0.974**	0.947	0.941	0.700	0.959	1.126	4.030
ECF-3	0.976	0.941	0.977	**0.996**	0.816	0.954	1.216	5.691
EUF-4	0.909	0.983	0.950	**0.987**	0.663	0.972	1.174	2.863
EUF-5	0.930	0.959	**0.991**	0.981	0.773	0.982	1.258	3.359
EUF-6	0.905	0.983	**0.995**	0.991	0.667	0.969	1.020	3.847

EUF-5 and EUF-6 fitted to First order model (R^2 were 0.991 and 0.995 respectively). EUD based matrix tablets release naproxen according to their salt formation in buffer media, that's why they showed drug concentration independent release mechanism from depot. ECF-1, ECF-3 and EUF-4 showed best fitting with Korsmeyer's model (R^2 values were 0.988, 0.996 and 0.987 respectively). Their n values were 0.681, 0.816 and 0.663 respectively. From their n values their release might be a coupling of diffusion and erosion mechanisms (so called anomalous diffusion). The relatively complexity of these formulations and their components may indicate that the drug release is controlled by more than one

process. Similar results were observed by Fassihi and Ritschel[20] with matrix tablets of theophylline containing EC; they considered the n value of about 0.70 to be indicative of an anomalous release mechanism. None of the drug release pattern fitted to zero order model. Formulations from EUF-4 to EUF-6 were more fitted to Weibull equation (R^2 ranged from 0.950 to 0.959) than ECF-1 to ECF-3 (R^2 ranged from 0.969 to 0.982). β values were greater than 1. β values of EUD-4 to EUD-6 were decreased where as α values were increased with the increased value of t_d. In Equation 12, α defines the time scale of the process, and β characterizes the shape of the curve as exponential (β = 1), sigmoid or S-shaped with upward curvature followed by a turning point (β > 1) or parabolic, with a higher initial slope and after that consistent with exponential (β < 1).[21] As dissolution was slowed across the formulations, Weibull t_d grew larger, which is in agreement with the interpretation that this parameter reflects the scale of time for the process (α). Weibull β, a shape factor, decreased across the formulations and indicates that the formulations possessed lesser sigmoid shape. The dissolution data (time versus percent release) were treated with one way repeated measures ANOVA (using SPSS software, version 16.0). From the output it can be stated that the within subject effect showed calculated F value $5.806X10^4$ for all methods p = 0.000. So, time is highly significant at any reasonable level of significance. Thus it can be concluded that the percent release on time differed significantly. The multiple comparisons (Bonferroni and Dunnett) were also carried out. Dunett t tests treat one group as a control and compare all other groups against it. The paired comparison of the six groups with the control group give p value = 0.000, indicating the significant difference among the release pattern of all groups ($p<0.05$). The f_2 values of only ECF-2 and EUF-6 lied between 50 to 100. The f_2 values of others were less than 50.[19] So, it can be stated that ECF-2 and EUF-6 were similar to ECF-3, where ECF-3 was considered as the reference as it showed close to zero order release pattern (Table 5).

MDT is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher MDT indicates a higher drug-retarding ability of the polymer and vice versa. The MDT value was found to be a function of polymer loading. Table 5 shows that the higher the polymer level, the higher the value of MDT. These findings were in accordance with those of Reza *et al.*[22] They investigated the effect of plastic, hydrophilic and hydrophobic types of polymers; their content level; and drugs of different aqueous solubility values on MDT. The studies showed that a direct relationship could be found with MDT value and polymer loading irrespective of drug and polymer type, and that this relationship was linear.

CONCLUSION

Observing the release kinetics of naproxen in EC and EUD based matrix tablets, none of the both polymers showed sustained action at their 15, 20 and 25% concentrations. EC showed sustained action till 8 hours at 20 and 25% concentrations and EUD at 25% concentration. EC gave more sustained action than EUD. While fitting the release kinetics in model-dependent approaches, most of the release patterns were fitted to Korsmeyer's model with diffusion-erosion coupled release mechanism. When the data were fitted to model-independent approach ECF-2 and EUF-6 were found to be more similar towards ECF-3. So, it might be stated that ECF-2, ECF-3 and EUF-6 were the most sustained formulations which were more similar among themselves.

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