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Original Article

Effect of Polymer Concentration on the Release of Naproxen from Enteric Coated Sustained Release Tablets

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Abstract: Five different formulations of naproxen sodium core tablets were prepared using different amounts of Methocel K15M CR by direct compression method. From a particular formulation, 50 % of tablets were kept uncoated and enteric coating was applied to the remaining 50 % using cellulose acetate phthalate (6 % w/w). Dissolution, swelling and erosion tests of uncoated tablets were conducted 8 hours in phosphate buffer (pH 7.4). For enteric coated tablets, dissolution test was performed for first 2 hours in acidic medium (pH 1.2) then 8 hours in phosphate buffer (pH 7.4). Enteric coating was able to prevent the disintegration of the matrix tablets and dissolution of naproxen in the acidic medium. In the buffer medium, irrespective of the presence or absence of enteric coating, higher percentage of Methocel K15 MCR increased swelling of the tablets in first few hours which was followed by erosion of the tablet matrix. Dissolution studies revealed that high percentage of Methocel K15M CR retarded the release of naproxen for a longer period of time. Taking the swelling and erosion pattern and dissolution data together we concluded that with the increase of hydrophilic polymer content, the release mechanism of naproxen shifted towards swelling and erosion dependent processes.

Keywords: Methocel K15M CR; Enteric coating; Naproxen sodium; Swelling; Release mechanism

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1. Introduction

Conventional immediate release oral formulations offer faster and clinically effective therapy for many drugs. But by the same token, they have some limitations that include high dosing frequency and fluctuations of drug plasma concentrations [1]. For all drugs, to get an optimum therapeutic response without any toxic effect, it is important to maintain the plasma levels within the therapeutic window with minimal variations. Sustained release formulations help to overcome the drawbacks of conventional immediate release dosage forms. Especially for the oral

administration of many drugs, sustained-release matrix tablets have become dosage form of choice because they give more consistent plasma concentrations and reduce the frequency of dosing [2]. Hydroxypropyl methylcellulose (HPMC) is a hydrophilic semi-synthetic ether-based polymer which has been widely used in the sustained or controlled release formulations to control the release rate by forming a matrix system. It works well in the direct compression process because of its good compressibility [3].

Enteric coating prevents the disintegration and dissolution of solid oral dosage forms in the stomach and thus helps to bypass the stomach. For this reason, the enteric coating has become increasingly popular for drugs which cause gastric irritation and drugs which are degraded by the acidic environment of the stomach. Enteric coating polymers work by forming a layer which is stable at the acidic environment of the stomach but breaks down rapidly at relatively alkaline pH of the small intestine [4].

Naproxen, a propionic acid derivative, a non-steroidal anti-inflammatory drug, is readily absorbed in the gastrointestinal tract and has a bioavailability of 95 %. Naproxen can be administered either in acid form or in sodium salt form; both produce the same effects but differ in the rate and extent of absorption due to different solubility [5]. Though the drug is highly effective against diseases like rheumatoid arthritis osteoarthritis, ankylosing spondylitis, etc., it may cause an ulcer, kidney failure, and elevate bleeding after surgery [6]. Naproxen is a poorly water-soluble drug with high permeability and hence considered as a class II drug according to the Biopharmaceutics classification system [7]. Nevertheless, many pharmaceutical manufacturers are now formulating the drug in sustained release matrix tablets for prolonged relief of pain. On the other hand, it is a reversible inhibitor of cyclooxygenases and thus inhibits the biosynthesis of prostaglandins which play important role in the protection of gastric mucosa from the acidic condition [8]. Like other inhibitors of cyclooxygenases, naproxen is conventionally formulated in enteric coated dosage form [9]. By taking the necessity of prolonged drug release and its adverse effect on gastric mucosa in consideration, we hypothesized that preparing enteric coated sustained release matrix tablet of naproxen would be a safe and effective therapeutic strategy.

The main objective of this study was to compare sustained-release uncoated and enteric coated tablets of naproxen sodium. For doing this, sustained-release core tablets of naproxen sodium were prepared using different amounts of Methocel K15M CR. Then enteric coating was applied on half of the tablets of each formulation using cellulose acetate phthalate (CAP). Finally, physicochemical parameters, swelling, erosion, release rate, extent, and mechanisms were investigated in the aim of making comments about the impact of the varying amount of Methocel

K15M CR on swelling, erosion and drug release in the presence and in the absence of the enteric coating.

2. Materials and Methods

2.1 Materials

Naproxen Sodium, Methocel K15M CR and cellulose acetate phthalate (CAP) were generous gifts of IBN Sina Pharmaceuticals, Bangladesh. Ludipress was collected from BASF, Bangladesh. Aerosil and magnesium stearate were purchased from Merck, Germany. All other reagents and chemicals used in this experiment were analytical grade.

2.2 Micromeritic properties of the powder blend

2.2.1 Carr's index and Hausner ratio

Carr's index is the measurement of the powder consolidation tendency. It helps to measure the inter-particulate interactions among the powder particles. It was calculated by the following equation.

$CI\ (\%) = (V_0-V_f)/V_0 \times 100$

Where, CI = Carr's index, V_0 = Untapped volume, V_f = Tapped volume

Hausner ratio has a close relation with Carr's index and it was calculated by the following equation [10].

$\text{Hausner ratio} = V_0/V_f$

In this equation, V_0 = Volume before tapping, V_f = Volume after tapping

2.2.2 Angle of repose

In this experiment angle of repose of the powdered materials was determined by funnel method. The powder was taken in a funnel and was permitted to flow via the funnel on a paper freely. The funnel height was adjusted in a way so that the funnel tip touched the apex of the powder mass. The diameter of the powder cone and the height of the powder cone from the surface were measured and the angle of repose was calculated by the following equation [11].

$\text{Angle of repose, } \theta = \tan^{-1}(h/r)$

Here, h = Height of the powder cone; r = Radius of the powder cone

2.3 Study of drug excipient compatibility by Fourier Transmitted Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC)

The infrared spectra of naproxen sodium, Methocel K15M CR, and physical mixture of the formulation (F-5) were recorded in the wavelength region of 2000 to 600 cm^{-1} using FTIR spectrometer (IR Affinity-1, Shimadzu, Japan). Samples IR spectra were acquired by potassium bromide (KBr) disk method [12]. DSC was performed for naproxen sodium, Methocel K15M CR and the optimized formulation (F-5) using Differential Scanning Calorimeter (DSC 60, Shimadzu, Japan). The measuring temperature was between 30°C to 400°C with a heating rate of 10°C/min [13].

2.4 Preparation of matrix tablets

All the tablets were prepared by using 500 mg naproxen for each tablet by direct compression method. This dose was determined by considering the recommended dosing regimen, which is generally 500 mg 2 to 3 times per day with a total daily highest dose of 1500 mg [14]. Formulations were prepared by different amount of polymer but keeping the amount of all other ingredients constant. In brief, naproxen sodium, Methocel K15M CR powder and other excipients except Mg-stearate was sieved through 60 mesh size and mixed thoroughly. Then Mg-stearate was added to the mixture to increase lubrication and was compressed to prepare the uncoated tablets of 600, 620, 640, 660, and 680 mg weight by a 3 stationed tablet compression machine using 13 mm die according to the compositions mentioned in **Table 1**.

Table 1: *Formula of naproxen sodium uncoated matrix tablets containing varying amounts of Methocel K15M CR and other excipients.*

Formulation code	Naproxen Sodium (mg	Methocel K15M CR (mg)	Ludipress (mg)	Aerosil (mg)	Mg-stearate (mg)	Total (mg)
F-1	500	40	50	5	5	600
F-2	500	60	50	5	5	620
F-3	500	80	50	5	5	640
F-4	500	100	50	5	5	660
F-5	500	120	50	5	5	680

F-6 was prepared by enteric coating of F-1 and F-7 was prepared by enteric coating of F-2 and so on.

2.5 Preparation of enteric coated tablets

The enteric coating was prepared in solution method using cellulose acetate phthalate (6 % w/w) as enteric coating polymer, PEG (1.5 % w/w) as plasticizer and acetone (60 % w/w) as a solvent. After adjustment of rest of the volume by diethyl phthalate, the mixture was constantly stirred by a mechanical stirrer (1000 rpm) for 1 hour and the solution was finally filtered through muslin cloth according to the previously described method [15]. Coating of tablets was done by using a perforated pan coating apparatus by maintaining the weight gain percentage within a specified range. Half of the tablets from each formulation were used for preparing the enteric coated tablets; for example, F-6 was prepared by enteric coating of F-1 and F-7 was prepared by enteric coating of F-2 and so on.

2.6 Physical properties of the uncoated and coated tablet

2.6.1 Weight variation and weight gain

Twenty uncoated tablets from each formulation were weighed individually using an electronic balance (Electronic Balance, Adam, UK). Average weight, the standard deviation of the weight of each tablet was calculated according to a previously described method [16]. On the other hand, percent weight gain due to enteric was calculated for enteric coated tablets according to the following equation [17]:

$$\% \text{ Weight gain} = (Wta - Wtb)/ Wtb \times 100$$

Here, Wta is the weight of tablet after coating and Wtb is the weight before coating.

2.6.2. Tablet hardness, thickness, and diameter

In the present study, tablet hardness was determined by using a dial type hardness tester and was measured in kg/cm^2. Tablet thickness and diameter were measured by using digital Vernier calipers. The tablets were positioned between the arms of the calipers to measure the thickness and diameter according to the procedure followed by Ahmed and co-workers [18].

2.6.3 Tablet friability

Friability test was done to confirm the physical strength of the tablet. For this, ten tablets from each formula both uncoated and enteric coated were weighed before putting them into the rotating disk of a tablet friability tester (Veego Friability tester, Model: VFT-2D). Then the disk was allowed to rotate at a speed of 25 rpm for four minutes, in order to complete 100 revolutions. After that, the tablets were taken out

of the drum and weight loss percentage was calculated by the following equation [19, 20].

Friability= $(W_0 - W)/W_0 \times 100$

Here, W_0 = initial weight; W = final weight

2.7 In vitro dissolution studies

Dissolution studies of the formulated tablets were performed by using USP type II apparatus (Logan Instruments, USA) with 900 ml medium at 37±0.5°C and in 100 rpm [18]. For uncoated tablets, the total duration of the dissolution was 8 hours and phosphate buffer at pH 7.4 was used as a dissolution medium. 5 ml of samples were withdrawn, from each dissolution vessel, at the interval of 1, 2, 3, 4, 5, 6, 7 and 8 h. After every withdrawal, 5 ml of fresh buffer solution was added to each vessel to readjust the volume of the medium. After filtration and dilution absorbance values were measured at 249 nm for naproxen sodium by using a UV visible spectrophotometer (UV-1800, Shimadzu Corp). On the other hand, dissolution study of enteric coated tablets was performed in same test conditions except for the fact that first two hours dissolution was done using 900 ml 0.1 N HCl solution as medium followed by 8 hours in phosphate buffer (pH 7.4).

2.8 Release kinetics studies

Release kinetics study was done by data obtained from the *in vitro* drug release and plotting it in various release kinetic models like zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas [21, 22].

Zero-order equation: $Q_t = Q_0 + K_0t$

Where, Q_t = dissolved drug amount at time t, Q_0 = initial drug amount, K_0 = release constant of zero order expressed in units of concentration/time.

First-order equation: $\log C = \log C_0 - Kt/2.303$

In the above equation, the initial concentration of the drug is C_0, first-order rate constant is K and time is t.

Higuchi equation: $Q = KHt^{1/2}$

Where, Q = drug release amount at time t; KH= Higuchi diffusion rate constant.

Korsmeyer–Peppas equation: $Q = M_t / M_\infty = Kt^n$

Where Q is the amount of drug release, Mt is the amount of drug release at time t and M∞ is the drug release amount at an infinite time, K is the constant of release rate and n is the exponent of release. In order to characterize the release of cylindrically shaped matrices, n is used.

Hixson-Crowell equation:

The cube root equation of Hixson and Crowell is a frequently used model for explaining the effect of change in diameter and surface area of tablets or particles due to swelling and erosion [23]. In the present study, the release data were fitted with Hixson-Crowell equation in the aim of investigating the impact of tablet matrix swelling and erosion upon the release of naproxen.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t$$

Where Q0 is the initial amount of drug, Qt is the remaining amount of drug at time t, and KHC is the Hixson-Crowell constant.

2.9 Determination of mean dissolution time (MDT)

Mean dissolution time (MDT) was calculated with the help of dissolution data. It helps in the drug release rate characterization from the dosage form polymer retarding efficiency [24].

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

Where, n = release exponent and K = release rate constant obtained from Korsmeyer–Peppas equation.

2.10 Swelling index studies

Swelling index of the uncoated matrix tablets from each formula was evaluated by using phosphate buffer at pH 7.4. Initial weights (w_1) of the tablets were taken and then tablets were immersed in a Petri dish containing phosphate buffer at 370C temperature. For enteric coated tablets, this was done in two phases: first two hours in acid medium (pH 1.2) and then 8 hours in buffer medium (pH 7.4). The tablets were taken out of the buffer 1, 2, 3, 4, 5, 6, 7, and 8 hours and then final weight (w_2) was taken using the balance. In case of enteric coated matrix tablets first two hours swelling was evaluated by using 0.1 N HCl solution and then for 8 hours in phosphate buffer and final weights were calculated in each hour as was done in case of uncoated tablets. The swelling index was calculated using the following formula [25].

Swelling index = 100 $(w_2-w_1)/w_1$

Where, w_1 = initial weight, w_2 = final weight

2.11 Erosion studies

Erosion study of the core and coated tablets was carried out according to the method of Ravi et al. [26]. Briefly, the uncoated tablets (F-1 to F-5) were immersed in the buffer medium (pH 7.4) which was maintained under the same conditions as specified in the dissolution study. For the enteric coated tablets, it was performed in a combination of two phases as it was done in case of swelling study. After each hour matrix tablet was taken away from the dissolution vessel using a small basket and was dried at a temperature of 45°C until a constant weight was obtained. Erosion of the formulated matrix tablets after each hour was calculated by using a previously reported equation of Sriamornsak and co-workers [27]:

Erosion = 100 $(W_0-W_2)/W_0$

Where, W_0 = initial weight, W_2 = final weight after drying

2.12 Statistical evaluation

All the experiments related to average percent release with time, mean dissolution time (MDT) percent erosion and swelling index were done in triplicate. Statistical significance was calculated by the student's t-test, and the difference was considered as significant when the value of p was less than 0.05.

A model-independent approach like the similarity (f2) and dissimilarity (f1) factor were used to compare the dissolution profiles of the uncoated and coated formulation. In this instance equation proposed by Moore and Flanner was used which are given below [28].

$$\mathbf{f_1 = \{[\sum_{t=1}^{n}(R_t - T_t)]/\ \sum_{t=1}^{n} R_t]\} * 100}$$

$$\mathbf{f_2 = 50\ log\ \{[1+ (1/n) \sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} * 100}$$

Where f_1= dissimilarity factor

f_2 = similarity factor

n = number of observations

R_t = % drug dissolved from reference formulation

T_t = % drug dissolved from test formulation

3. Results and Discussion

3.1 Physical properties of powder blends

For proper tableting, measurement of powder flow is a key requirement as it is directly related to tablet weight, integrity and content uniformity [11]. For the evaluation of flow-ability and compressibility, Carr's index (CI) and Hausner ratio (HR) of different powder blends were investigated. Carr's index (CI) and Hausner ratio (HR) of all formulations were found to be within passable range (CI, 21-25 and HR, 1.26-1.34) according to the specification of United States Pharmacopoeia. Additionally, the measured angle of repose of F-1, F-2, F-3 was within passable range (41◦-45◦), F-4 and F-5 were found within fair range (36◦-40◦) [18] **(Table-2).**

Table 2: *Pre-compression physical properties of powder blends of different formulations.*

Formulation code	Carr's index (%)	Hausner ratio	Angle of repose (θ^0)
F-1	22.0 ± 0.352	1.30 ± 0.03	43.0 ± 1.22
F-2	21.6 ± 0.241	1.27 ± 0.04	44.2 ± 1.15
F-3	21.8 ± 0.326	1.28 ± 0.05	43.0 ± 1.31
F-4	22.3 ± 0.561	1.31 ± 0.02	38.7 ± 0.84
F-5	23.2 ± 0.785	1.33 ± 0.03	38.2 ± 0.91

3.2 Drug-excipient compatibility studies

Formulation-5 (F-5) which contained the highest amount of K15M CR and found to control the release for the longest period of time with minimum fluctuation was selected for compatibility study by Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Pure naproxen sodium, Methocel K15M CR, and the physical mixture of F-5 were characterized by FTIR **(Figure 1A).** Naproxen sodium gives several strong and weak absorption bands in between 1450 and 1600 cm^{-1} due to C-C stretching vibration modes of the aromatic rings [29]; visible strong peaks at 1363 and 1388 cm^{-1} resemble -CH3 bending vibration group [30]; it shows a weak absorption band due to C=O stretching at 1558 cm^{-1} [31] **(Figure 1A).** Methocel K15M CR shows weak intensity peak at 1732 cm^{-1} that confirms C=O stretching vibration [32]; weak absorption peak at 1633 cm^{-1} because of the presence CO six-member cyclic rings [33]; weak absorption bands at 570 and 507 cm^{-1} are due to C-C stretching [31] **(Figure 1B).** Formulation F-5 gives a weak peak at 1631 cm^{-1} due to C=C stretching vibration; strong to medium intensity peaks at 856 and 688 cm^{-1} are observed due to the presence of =C-H bending vibration group [32]; medium to weak intensity peaks at 688 and 522 cm^{-1} are because of C-C stretching [31] **(Figure 1C).**

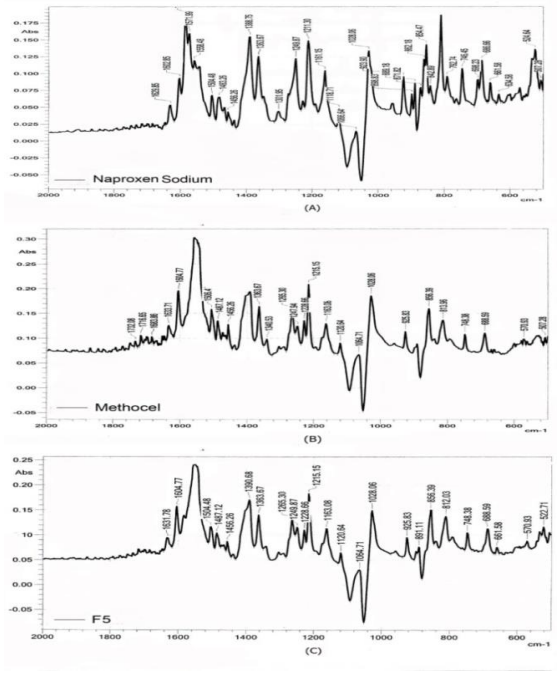

Figure 1: FTIR spectrum of (A) Naproxen Sodium (B) Methocel K15M CR and (C) Formulation F-5

Study shows that all characteristic peaks of pure naproxen and Methocel K15M CR were easily detectable before mixing and there was no sharp change in the absorption peaks in the physical mixture of our selected formulation (F-5) indicating that there was no major incompatibility between the drug and the excipients.

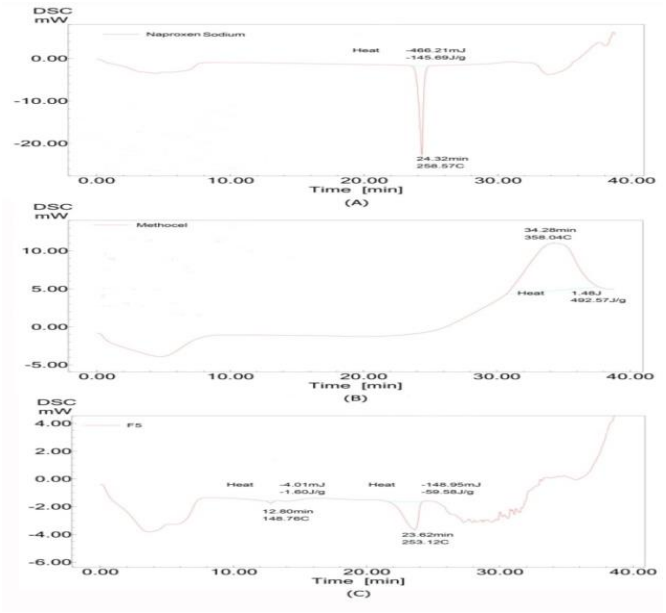

Figure 2: DSC thermogram of (A) Naproxen Sodium (B) Methocel K15M CR and (C) Formulation F-5

This finding was further confirmed by DSC analysis **(Figure 2).** The DSC thermogram of pure naproxen sodium showed a sharp melting endotherm at 2580C with normalized energy of -145.69 J/g **(Figure 2A),** which is consistent to its actual melting point [30]. The thermograms of solid admixtures of naproxen with various excipients showed a similar peak at 2530C with same normalized energy, indicating that naproxen is unaffected in the presence of various excipients used in the preparation of sustained release matrix tablet. Methocel K15M CR showed a sharp exothermic peak at 358°C (492.57 J/g) followed by a broad endothermic peak which might be due to the re-crystallization of the polymer [34] **(Figure 2B).** However, minor changes of peaks observed in formulation F-5 are due to the mixture of the drug and the excipients which don't indicate the incompatibility of the drug with excipients **(Figure 2C).**

3.3 Physical characteristics of the uncoated and enteric coated tablets

Naproxen sodium sustained release uncoated and enteric coated tablets were prepared by using different amounts of Methocel K15M CR and fixed the amount of ludipress, aerosol, and magnesium stearate as mentioned in the previous section (Table-1). Results of the hardness, thickness, diameter, weight variations, and friability for uncoated tablets are presented in **Table-3** and enteric coated tablets in **Table-4**.

Table 3: *Physical properties of core tablets of different formulations.*

Formulation code	Average hardness (kg/cm^2)	Average Friability (%)	Average thickness (mm)	Average diameter (mm)	Average Weight (mg)
F-1	6.7 ± 0.11	0.61 ± 0.00(	7.30 ± 0.08	11.51 ± 0.1(	601 ± 4.3(
F-2	6.4 ± 0.20	0.27 ± 0.00	7.34 ± 0.11	11.52 ± 0.12	619 ± 3.75
F-3	6.5 ± 0.12	0.31 ± 0.00	7.40 ± 0.10	11.50 ± 0.11	642 ± 3.74
F-4	6.6 ± 0.20	0.47 ± 0.00	7.44 ± 0.09	11.50 ± 0.0	661 ± 4.2(
F-5	6.3 ± 0.12	0.45 ± 0.00	7.50 ± 0.08	11.52 ± 0.0	682 ± 4.5

Physical evaluation of the tablets revealed that the tablets average thickness, diameter, weight of core tablets and weight gain due to enteric coating was uniform. Friability values of the tablets were less than 1 % and the hardness of the tablets was between 6.3 to 6.7 kg/cm^2 indicating that the results were within specification [18] and tablet surfaces were strong enough to withstand the mechanical shock or attrition during storage and transportation.

Table 4: *Physical properties of naproxen sodium tablets after enteric coating.*

Formulation code	Average thickness (mm	Average diameter (mm)	Weight gain due to coatin (%)	Average Weight (mg)
F-6	7.55 ± 0.071	12.48 ± 0.107	6.67 ± 0.119	640 ± 4.31
F-7	7.62 ± 0.121	12.51 ± 0.112	6.13 ± 0.213	658 ± 3.60
F-8	7.70 ± 0.122	12.50 ± 0.102	6.09 ± 0.109	679 ± 5.10
F-9	7.82 ± 0.092	12.52 ± 0.092	6.21 ± 0.182	701 ± 4.22
F-10	7.85 ± 0.088	12.53 ± 0.101	6.03 ± 0.154	721 ± 4.40

3.4 Dissolution study of uncoated and coated tablets

The dissolution test of uncoated tablets was performed in the buffer medium (pH 7.4). On the other hand, the dissolution test of enteric coated tablets was conducted in two phases: 2 hours in acid medium, followed by 8 hours in a buffer medium. It was observed from the release profile that the variation in the amount of the polymer Methocel K15M CR had a variable effect on the release rate and extent of the drug. In case of uncoated tablets, the initial drug release was rapid and inconsistent for the formulations having lower amount (F-1, F-2, and F-3) of polymer; as the amount (F-4 and F-5) of the polymer was increased the release patterns became slower and steady **(Figure 3A).**

On the other hand, the enteric coating effectively prevented the release of naproxen from the matrix tablets in acid medium. But, in the buffer medium, the enteric coating dissolved immediately and matrix tablets released the drug almost in the same pattern as it did in case uncoated tablet **(Figure 3B).**

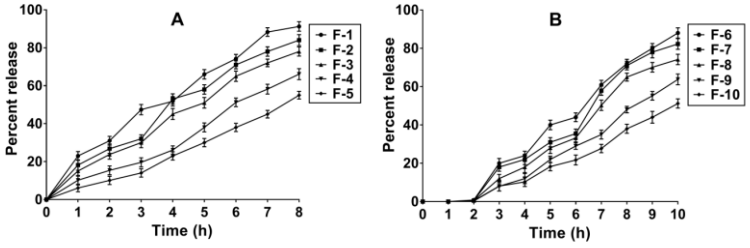

Figure 3: Average percent release of naproxen sodium calculated from dissolution data for different formulations of uncoated (A) and enteric coated (B) matrix tablets. The dissolution test of uncoated tablet was conducted in buffer medium (pH 7.4) for 8 hours. On the other hand, dissolution study of enteric coated tablets was performed in 0.1 N HCl solution for first 2 hours which was followed by 8 hours in phosphate buffer (pH 7.4).

It is clear from the data that there was no initial burst release of naproxen in the buffer medium, which is also consistent with the previous finding, where Manjula and co-workers demonstrated that initial rapid release from hydrophilic matrix is associated with highly soluble drugs [35]. Both in case of uncoated and enteric coated tablets after 8 hours of dissolution test in the buffer medium (pH 7.4) the total percent release was approximately 90 % for the matrix tablets which were prepared by using lowest amount (40 mg) of Methocel K15M CR. Conversely, for the tablets prepared by the highest amount of polymer (120) the average percent release at the end of 8 hours dissolution in the buffer medium was close to 55 %. In the present study, the amount of polymer in each formulation has been increased from the previous one by 20 mg (Table-1). Comparison between F-1 and F-2 revealed that due to this 20 mg change of polymer content, the average percent release at the end of 8 hours was not changed significantly. But the comparison between F-1 and F-3 revealed that 40 mg increase was able to change the percent release significantly (p<0.05) both in case of coated and uncoated tablets.

Drug release mechanism from the matrix to the dissolution medium involves the participation of different physical and/or chemical phenomena making it difficult to get a perfect mathematical model for describing it [36]. The most frequently used mathematical models for the last few years, in general, are the zero-order model, Higuchi model, first-order model, Korsmeyer-Peppas model and Hixson-Crowell model [37]. From the Korsmeyer and Peppas equation, the values of release exponent (n) were calculated which are 0.831, 0.823, 0.859, 0.911, and 0.942 for F-1 to F-5 for uncoated matrix tablets of naproxen sodium in that order **(Table-5)**. According to the Korsmeyer-Peppas model F-1, F-2, and F-3 followed non-Fickian diffusion and formula F-4 and F-5 followed super case II transport mechanism [38].

Table 5: Release rate constants and R^2 values of different release kinetics and mechanism of naproxen sodium release from uncoated matrix tablets.

Formulation	Zero Order		First Order		Higuchi		Hixson-Crowe		Korsmeyer	
code	K_0	R^2	K_1	R^2	K_h	R^2	K_{hc}	R^2	n	R^2
F-1	12.77	0.981	-0.23	0.805	37.94	0.931	0.744	0.696	0.831	0.961
F-2	12.34	0.979	-0.17	0.907	36.80	0.937	0.728	0.719	0.823	0.972
F-3	11.62	0.976	-0.12	0.942	34.45	0.923	0.718	0.741	0.859	0.955
F-4	6.77	0.983	-0.04	0.964	19.64	0.903	0.695	0.812	0.911	0.977
F-5	6.13	0.964	-0.03	0.944	17.09	0.866	0.669	0.849	0.942	0.975

The values of release exponent were also calculated for enteric coated tablets by using 8 hour's release data in the buffer phase. The values of release exponent (n) obtained for the enteric coated tablets are 0.847, 0.872, 0.892, 0.915 and 0.987 for F-6 to F10 respectively **(Table-6).**

Table 6: Release rate constants and R^2 values of different release kinetics and mechanism of naproxen sodium release from enteric coated matrix tablets.

Formulation	Zero Order		First Order		Higuchi		Hixson-Crowe		Korsmeyer	
code	K_0	R^2	K_1	R^2	K_h	R^2	K_{hc}	R^2	n	R^2
F-6	13.74	0.958	-0.17	0.795	38.85	0.982	0.691	0.723	0.847	0.979
F-7	12.76	0.959	-0.16	0.948	12.76	0.959	0.670	0.771	0.872	0.964
F-8	10.50	0.953	-0.08	0.987	10.50	0.953	0.686	0.833	0.892	0.970
F-9	6.87	0.941	-0.03	0.946	6.87	0.941	0.658	0.853	0.915	0.873
F-10	4.85	0.936	-0.02	0.908	4.85	0.916	0.635	0.884	0.987	0.976

Both for uncoated and coated tablets, the value of release exponent (n) obtained from Korsmeyer's equation, indicates that formulations containing a lower amount of polymer followed anomalous transport mechanisms; whereas formulations having a relatively higher amount of polymer followed case II and super case II transport mechanisms. This suggests that irrespective of the presence of enteric coating the drug release mechanism shifted towards the same direction in the buffer medium. Moreover, the gradual increase of the values of release exponent with an increase of polymer content in the tablet indicated that polymer chain relaxation and consequent swelling and erosion of the tablet matrix play key roles in controlling the release of sparingly water-soluble drug from the hydrophilic matrix [39]. These findings are also reinforced by the poor fitting with the Higuchi model as indicated by the R^2 values **(Table 4 and 5).** Generally, water-soluble drugs are released in diffusion-controlled mechanisms shows better fitting with the Higuchi model [40]. On the other hand, the release mechanism of the poorly soluble drug, like naproxen, from hydrophilic matrix tablet is relatively complex because it is mainly dependent on the erosion of tablet matrix and relaxation of the hydrated polymer chains [41]. Our observations are also in agreement with the findings of several other researchers who have already reported that soluble component of the dosage form is released by Fickian diffusion and the insoluble portion of the dosage form is released due to the erosion of the solid matrix [1, 42, 43].

The dissolution data were also used to make a comparison between uncoated and coated tablet; for example, F-1 was compared with F-6 and F-2 with F-7 and so on for evaluating the similarity and dissimilarity. According to Center for Drug Evaluation and Research (CDER) of the US Food and Drug Administration (FDA), a value of f2 from 50 to 100 indicates that the dissolution profiles of the formulations are similar [28]. Based on that standard it can be considered that F-1 and F-6 are pharmaceutically equivalent; similarly, any formulation from the uncoated group and its corresponding formulation from the coated group are also found to be pharmaceutically equivalent **(Table-7).**

Table 7: Similarity and dissimilarity between uncoated and enteric coated tablets based on dissolution data.

Reference Formulation (R_t)	Test Formulation (T_t)	Similarity Factor (f_2)	Dissimilarity Factor (f_1)
F-1	F-6	70.07 ± 2.39	6.35 ± 0.45
F-2	F-7	67.77 ± 2.54	5.42 ± 1.33
F-3	F-8	60.20 ± 3.09	8.89 ± 0.79
F-4	F-9	78.30 ± 2.14	6.39 ± 1.39
F-5	F-10	82.65 ± 3.31	5.47 ± 0.84

The main benefit of using f1 and f2 is that it is an easy way to compare the dissolution data as well as their equivalence. However, this method lacks the effectiveness of using variability and correlation of the data [44]. For this reason, different model dependent approaches, as mentioned above, were also used in this study to understand the drug release mechanism more comprehensively.

3.5 Polymer content altered the mean dissolution time (MDT)

Sustained release matrix tablets should be able to retard the drug release rate which is necessary for the consistent and prolonged drug delivery for the maintenance of plasma drug concentration in the therapeutic window with minimum fluctuation. This release controlling ability is achieved generally through the judicious use of an optimum amount of polymer with appropriate viscosity grade [45]. Therefore, to evaluate the impact of the different amount of Methocel K15M CR on release, we also calculated mean dissolution time (MDT), by using the value of release exponent (n), according to Mockel-Lippold equation [46]. In case of uncoated core tablets formula F-1, which contained the lowest amount (40 mg) of polymer, has the lowest MDT (3.51 hours) and formula F-5, which contained the highest amount (120 mg) of polymer, has the highest MDT (7.5 hours). Same was the pattern in case of enteric coated tablets (7.62 hours) which were not significantly different from the corresponding formulation of the uncoated tablet. Similar to the percent release in this case 20 mg change of polymer was not able to change the MDT significantly but 40 mg change of polymer content was able to change the MDT value significantly ($p<0.05$) **(Figure 4).** Moreover, these findings were in agreement with the observation of Reza and co-workers, where they demonstrated that release retarding ability of matrix tablets increased due to the increase of HPMC content in diltiazem and theophylline-based matrix tablets [47].

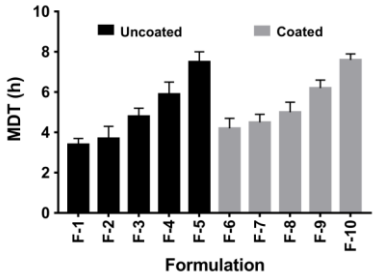

Figure 4: Mean dissolution time (MDT) of naproxen sodium from different formulations of uncoated (F-1 to F-5) and enteric coated (F-6 to F-10) tablets based on the release of drug in buffer medium (pH 7.4) for 8 hours.

3.6 Impact of swelling and erosion on drug release from matrix tablets

This part of our present study was aimed to investigate how the swelling and erosion pattern of hydrophilic matrix tablets influences the release of naproxen. When drug loaded HPMC type hydrophilic matrices are exposed to dissolution fluid, water molecules are absorbed into the polymeric matrix due to the water concentration gradient between the dissolution fluid and the outermost surface of the matrix tablet. Thus, the dissolution medium exerts a plasticizer effect which causes the dramatic lowering of glass transition temperature (Tg) of the polymer [39]. As the Tg approaches the temperature of the system (37°C), the polymer chains continue to relax and eventually disentangle which increases the molecular surface area [48]. The continuous infiltration of water breaks the existing intermolecular hydrogen bonds which were formed during tablet compression and leads to the development of new hydrogen bonds for accommodating incoming water molecules. Therefore, the reduction of Tg, dissociation of old hydrogen bonds between the polymer and other ingredients of tablet and formation of new hydrogen bonds between polymer and water results in the increase of the volume of the tablet matrix [49]. This phenomenon of polymer chain relaxation due to the absorption of solvent and resultant conversion of the polymer from an amorphous glassy state to gel-like rubbery state is termed as ‘swelling’.

The swelling study of uncoated tablets (F-1 to F-5) was performed for 8 hours in a buffer medium and of enteric coated tablets (F-6 to F-10) this was done in two phases: first 2 hours in acidic medium and then 8 hours in buffer medium (pH 7.4). At the end of the first two hours immersion in acidic medium, the enteric coated tablet dimensions remained unchanged with very insignificant swelling (data not shown). As the enteric coated tablets were immersed in the buffer medium (pH 7.4) the enteric coating started to dissolve and tablets started to swell. In both cases, it was observed that formulations containing a lower amount of Methocel K15M CR continued to swell up to the first two hours and then started to lose weight due to the erosion of the matrix. On the other hand, formulations containing a higher amount of

Methocel K15M CR continued to swell up to first 3 hours and then started to lose weight **(Figure 5A and Figure 5B).** Both in case of core and coated tablets release of naproxen sodium from tablet matrix and erosion of the tablet matrix, in the buffer medium, followed the similar trends **(Figure 6A and Figure 6B).** To make the understanding even more quantitative in the pattern, the release data was analysed with Hixson-Crowell's cube root model which is being used to describe the release mechanism by considering the gradual erosion of the surface of the matrix tablets or tablet particles during the dissolution [50]. This erosion dominated release observed in formulations containing the highest amount of polymer (F-5 and F-10) was highly supported by higher correlation co-efficient values of Hixson-Crowell model **(Table 4 and 5).**

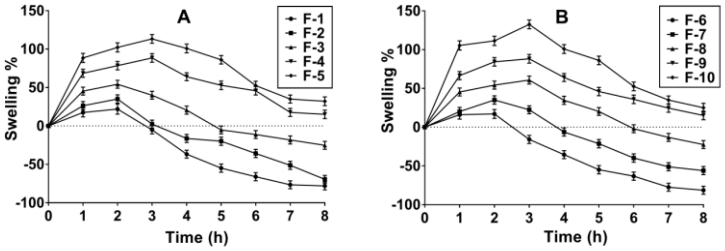

Figure 5: Swelling index for different formulations of naproxen sodium uncoated (A) and enteric coated (B) matrix tablets for 8 hours in buffer (pH 7.4) medium.

The thickness and rheological properties of the gel layer is crucial in describing the release mechanisms of swellable and erodible matrices [27]. When the outer layer becomes completely hydrated, the relaxation of polymer chains reaches to the maximum level and hence can no longer maintain the integrity of the gel layer which results in the erosion of the tablet matrix. Dissolution medium continues to infiltrate towards the center of the matrix until the tablet is completely disintegrated [39]. Hence initial swelling and subsequent erosion can be attributed to control the drug release mechanism from the formulations evaluated in the present study.

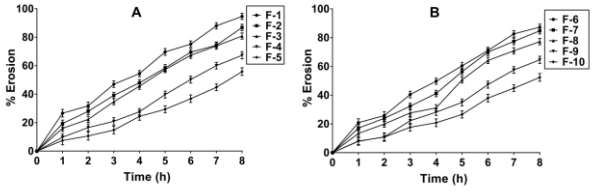

Figure 6: Percent erosion of different formulations of naproxen sodium uncoated (A) and enteric coated (B) matrix tablets for 8 hours in buffer (pH 7.4) medium.

4. Conclusions

Hydroxypropyl methylcellulose containing solid dosage forms are considered as swelling controlled systems in which drug release is mainly affected by the penetration of dissolution medium in the tablet matrix and subsequent relaxation of the polymer chain which culminates in swelling and erosion of the tablet matrix. In the present investigation, tablets prepared by using a higher amount of Methocel K15M CR exhibited higher swelling index at the first few hours which was followed by mechanical erosion of the tablet. Higher MDT values of formulations made from higher amounts of Methocel K15M CR indicates that it has high release retarding efficiency which was also consistently represented in the lower value of average percent release at the end of 8 hours dissolution test. The release of naproxen from all of the 5 uncoated formulations and corresponding 5 enteric-coated formulations were controlled primarily by non-Fickian processes which are dominated by relaxation of the polymer chain followed by swelling and erosion of the matrix tablet. There was no initial burst release of naproxen from the matrix which is generally the pattern of highly soluble drugs and is the characteristic of Higuchi release mechanism. By analyzing all these results, it can be concluded that development of enteric coated sustained release matrix tablets of naproxen sodium using Methocel K15 MCR, or similar grade as a release-controlling polymer, could be a new approach for sustained pain relief with reduced harmful effects on the gastric mucosa.

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