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Ethyl Cellulose-Based Solid Matrix System for Sustaining Release of Naproxen

Muhammad Khan Sarfraz, Nisar-ur-Rehman,
Saeed Ahmed, Mohammad Ashraf and Sabeeh Mohsin
Department of Pharmacy, Islamia University Bahawalpur, Pakistan

Abstract: The present study was conducted to develop sustained release matrix tablets of naproxen with the help of a hydrophobic polymer, Ethyl Cellulose (EC). Matrix tablets were prepared by incorporating various proportions of EC in the matrix system using wet granulation technique. The rate of drug release from the matrix tablets was found to be very slow and could not produce the desired release profiles in 12 h testing time. However, the tablets prepared by slightly modifying the wet granulation method exhibited comparatively linear and desirable release rate. No significant difference in the release profiles of naproxen matrix tablets was observed at different stirring speeds and storage conditions.

Key words: Naproxen, sustained release, hydrophobic matrix

INTRODUCTION

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 (Uziel *et al*., 2000; Hashkes *et al*., 2003). 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. Ethyl Cellulose (EC) is hydrophobic polymer and is essentially tasteless, odorless, colorless and physiologically inert. It has been extensively used as a pharmaceutical vehicle, tablet binder in preparing microcapsules (Sajeev *et al*., 2002) coating material for tablets/granules (Pearnchob and Bodmeier, 2003; Sadeghi *et al*., 2003; Dashevsky *et al*., 2004) and matrix forming material for sustained release dosage forms (Zabed *et al*., 2002; Pruthvipathy *et al*., 1995). There are few reported studies of matrix tablets prepared by wet granulation for controlling the drug release. In the present study EC in various proportions was used to develop a sustained release matrix system for naproxen. In addition the release data of the optimum formulation was fitted in release kinetic models.

MATERIALS AND METHODS

Materials: Naproxen (Shazoo Labatories, Lahore, Pakistan), ethyl cellulose 45cps (Highnoon Labatories, Lahore, Pakistan), Lactose (BDH, Poole, England), Magnesium stearate (Fluka, Buchs, Switzerland), Potassium dihydrogen phosphate (Merck, Darmstadt, Germany) and Disodium hydrogen phosphate (Sigma Aldrich, St. Louis, Mo, USA) were used as received.

Matrix tablets: For preparing hydrophobic matrix tablet, naproxen (33.33%) and various percentages of EC and lactose as mentioned in Table 1 were first sieved and blended in a Kenwood mixer (Kenwood, Geesthacht, Germany) for 5 min. The powder blend was first granulated with small amount of alcohol (25 mL/100 g) and wet mass was sieved through mesh No. 6 and dried at 60°C for 1 h in an oven (Memmert, Schwabach, Germany). The dried granules were passed through sieve No.10 and the fractions of granules retained on the sieve were discarded. Magnesium stearate in 1.67% w/w was used for lubrication of various granules, which were compressed separately by single punch machine (Emmy, Lahore, Pakistan) using 12 mm punches and dies at fixed compression force of 1500 lb. The weight of tablet was adjusted to 600 mg containing 200 mg naproxen.

Test matrix tablets: Test matrix tablet was prepared using formulation I (Table 1) by slightly modifying the wet granulation method as described earlier. The granules were processed with 16.7% w/w of naproxen instead of 33.33% w/w, 5% EC and 60% lactose. The remaining amount of drug (16.63% w/w) was then dry mixed with the granules. Magnesium stearate (1.67% w/w) was then thoroughly mixed with the granules that were tabletted at a fixed (1500 lb) compression force.

Corresponding Author: Dr. Nisar-ur-Rahman, Department of Pharmacy, Islamia University Bahawalpur-63100, Pakistan
Tel: 92-0621-9255243 Fax: 92-0621-9250232

Table 1: Formulations of naproxen matrix tablets (values in percentage)

	Formulations			
Ingredients	F I	FII	FIII	FIV
Ethyl cellulose	5.00	10.00	15.00	20.00
Lactose	60.00	55.00	50.00	45.00
Naproxen	33.33	33.33	33.33	33.33
Magnesium stearate	1.67	1.67	1.67	1.67

Weight variation, hardness and friability of tablets: In order to determine the uniformity of tablet weight, twenty tablets of each formulation were randomly selected and weighed using class A weight balance (Precisa, Dietikon, Swizerland) and their percentage variation was determined. Hardness of tablets was determined using automatic hardness tester (Curio, Lahore, Pakistan). Twenty tablets of each formulation were used and the average hardness value was calculated. The tablets of each formulation were also subjected to friability testing employing friabilator (Emmy, Pakistan). Ten tablets were placed in the tumbling chamber and rotated precisely for 4 min at a speed of 25 rpm. The weight of ten tablets prior to their placement in the chamber and at the end of the test was recorded. The percentage weight loss was then calculated. Triplicate measurements were conducted for each formulation.

***In vitro* release studies:** The dissolution studies were performed using USP apparatus type II (Pharma Test, Hainburg, Germany). The dissolution medium consisted of 900 mL of phosphate buffer solution pH (7.4) maintained at 37±0.5°C and stirred at 50 rpm. Samples (5 mL) were withdrawn at predetermined time intervals (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h) with automatic sampling unit (Watson Marlo, Stockholm, Sweden). Samples were filtered through Sinter filter 10 μm (Pharma Test, Hainburg, Germany) to remove suspended and insoluble tablet components and analyzed by UV spectrophotometer (Shimadzoo, Kyoto, Japan) at 332 nm. In addition to the release profile at pH 7.4, the test matrix tablets were also tested at two different pH values namely pH 1.0 (0.1 M HCl) and pH 4.0 (phosphate buffer). The effect of stirring speed on drug release rate was also evaluated on the test matrix tablets. The different stirring speeds used were 50, 100 and 150 rpm. Moreover, test matrix tablets were divided into two portions and packed in an airtight amber glass bottles and kept at 8 and 37°C. The samples of tablets were drawn after 3 months and 6 months and evaluated for stable *in vitro* release profile. In the data analysis of each formulation, cumulative percentage of drug release was calculated using mean of six samples readings.

***In vitro* drug release kinetics:** The dissolution data of matrix tablet formulations (Table 1) and the test matrix tablets were fitted to zero order, Higuchi and Peppas model for determining the release rates. Equations for (a) zero-order release (Xu and Sunada, 1995) and (b) Higuchi model (Higuchi, 1963) are given below.

$$Q = k_1 t \quad (a)$$

$$Q = k_2 (t)^{0.5} \quad (b)$$

Where Q is the percentage of drug released at time t. k_1 and k_2 are the release rate constants for zero-order and Higuchi models, respectively. Regression analysis was performed to obtain the release rate constant and the values of coefficient of determination (r) were also compared. Moreover, equation for drug release mechanism from the matrix system was also used as explained by Ritger and Peppa (1987).

$$M_t/M_\infty = k_3 t^n \quad (c)$$

Where Mt/M_∞ is the fraction of drug released at time t, k_3 is the kinetic constant and n is the so-called diffusion exponent, indicative of the mechanism of the drug release. The equation generally holds for M_t/M_∞>70% of drug release (n = 0.45 or 0.45<n<0.89 or n>0.89, indicates Fickian diffusion or anomalous transport or Case II transport kinetics, respectively). In addition, the similarity factor f_2 (Moore and Flanner, 1996) was used to compare the difference of dissolution profiles of the test matrix tablets prepared at different stirring speeds and is given below:

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

Where n is the number of dissolution samples taken, R_t and T_t are the individual percentages dissolved at each time point for the reference and test dissolution profiles, respectively and the f_2 value between 50 and 100 suggests that the data of two dissolution profiles are similar.

RESULTS AND DISCUSSION

The weight variation of all the compressed tablets was well within the acceptable limits of British pharmacopoeia indicating that the filling of the granules in the die of tablet machine was uniform. The hardness of each tablet formulation was above 5 kg and negligible weight loss (less than 0.8%) in the friability test was observed. Furthermore, the tablets exhibited good physical appearance with no defects such as capping,

Table 2: Percentage weight variations, hardness and weight loss in friability test of various formulations

Formulation	Weight variation (± %)	Hardness (kg)	Friability (± %)
F I	2.0	6.0	0.01
F II	1.3	6.0	0.01
F III	1.4	6.5	0.01
F IV	1.8	6.0	0.01
Test matrix	1.0	6.3	0.01

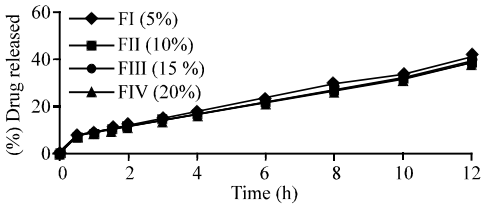

Fig. 1: Effect of various percentages of ethyl cellulose on *in vitro* drug release from naproxen tables

lamination, picking and sticking during compression. The results of weight variation, hardness and friability are presented in Table 2. Dissolution profiles of all the compressed tablets having standard deviation less than ±2 were determined and explained in the following sections.

Drug release from matrix tablets: Figure 1 shows the release of naproxen from hydrophobic matrix tablets containing various percentages of EC. The tablets containing 5, 10, 15 and 20% EC released about 41, 39, 38 and 37.8% in 12 h testing intervals as shown in Table 3, respectively. EC had pronounced effect in decreasing the drug release rate from hydrophobic matrix tablets. The slower drug release rate from such tablets was due to formation of uniform ethyl cellulose coating on the individual drug particles. However, increasing the percentage of EC had no significant difference in the release rates of 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. The results found in this study were not in good agreement with the reported study (Zabed *et al*., 2002) in which increasing percentages of micronized EC produced slower drug release rate. As in the reported study, micronized EC was used which could be more easily wetted by the granulating liquid and provide more uniform coating around the drug particles.

Moreover, the release profiles of tablet formulations were fitted to zero order, Higuchi and Peppas model. Regression analysis was performed to obtain co-efficient of determination (r) and was compared as shown in Table 4. The values of r obtained from zero order

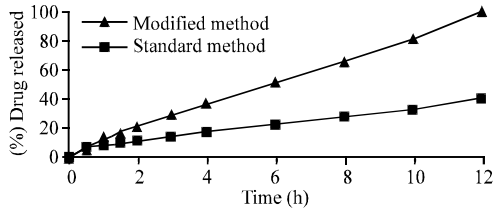

Fig. 2: Effect of granulation process on *in vitro* release from naproxen table containing 5% ethyl cellulose

models are almost greater than Higuchi model and therefore the drug release rate from these formulations followed the zero order kinetics. Drug release data was also fitted to Peppa's model, which showed slope values in the range of 0.737 to 0.740 indicating a Fickian diffusion release mechanism.

Influence of granulation process on drug release: Only about 40% of the drug was released in 12 h from all the hydrophobic matrix tablets containing various percentages of EC and failed to improve the extent of drug release. Therefore, the matrix tablets were also prepared by slightly modifying the granulation process. Drug release profile of the matrix tablets prepared with different granulation processes is shown in Fig. 2. Surprisingly, the drug release pattern of the matrix tablets prepared with modified method (test tablets) was linear and the extent of drug release was also improved in comparison to standard method used in tablet formulations (Fig. 1). About 65% of drug was released in 8 h from test matrix tablets compared to only 29% of drug released from the same formulation using standard granulation method (Table 3). Moreover, about 22% drug was released in 2 h as burst release from test matrix tablets and was probably attributed to the dissolution of drug from the surface of tablets. But, further penetration of the dissolution medium was hindered due to the hydrophobic nature of EC on the drug particles leading to slower drug release for prolong period of time. The r-values obtained from test matrix tablets using zero order and Higuchi models were 0.998 and 0.973, respectively and are shown in Table 4. This clearly indicates that test matrix tablets follow zero order release kinetic. Drug release data of test matrix tablet was also fitted to Peppas model, which showed the slope values of 1.074 indicating anomalous diffusion mechanism.

Influence of pH and stirring speed on drug release rate: Figure 3 shows the drug release profile from the test matrix tablets at pH 1, 4 and 7.4. At the lower pH (pH 1 and 4) the release profiles were essentially similar and negligible amount of drug was released during 12 h testing interval indicating the poor dissolution of naproxen at lower pH.

Table 3: Mean *in vitro* release of naproxen from hydrophobic matrix tablets containing various percentages of EC (n = 6)

	Percentage drug released			
Time (h)	F I (5%)	F II (10%)	F III (15%)	F IV (20%)
0.0	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
0.5	8.11 (0.9)	7.77 (0.9)	7.43 (0.5)	7.11 (0.3)
1.0	9.29 (0.7)	8.95 (0.5)	8.78 (0.7)	8.42 (0.4)
1.5	10.98 (0.7)	10.47 (0.7)	9.63 (0.4)	9.87 (0.9)
2.0	12.50 (0.6)	11.82 (0.6)	11.49 (0.7)	11.30 (0.3)
3.0	15.20 (1.2)	14.19 (1.2)	14.02 (0.6)	13.90 (0.6)
4.0	17.91 (0.5)	17.23 (1.1)	16.55 (0.9)	15.90 (0.7)
6.0	23.65 (0.7)	22.97 (1.2)	21.96 (1.1)	21.30 (1.1)
8.0	29.39 (0.6)	27.70 (0.9)	27.03 (0.8)	26.40 (1.5)
10.0	33.45 (1.1)	32.43 (0.5)	32.09 (1.1)	31.40 (0.8)
12.0	40.54 (1.5)	38.85 (0.7)	38.18 (1.1)	37.80 (1.2)

Figure in brackets = Standard deviation

Table 4: Coefficient of determination r and diffusion exponent of various formulations using drug release kinetic models

Formulations	Zero order (r)	Higuchi model (r)	Peppas model (n)
F I	0.987	0.987	0.737
F II	0.988	0.986	0.734
F III	0.989	0.985	0.738
F IV	0.989	0.983	0.740
Test matrix-tablet	0.998	0.973	1.074

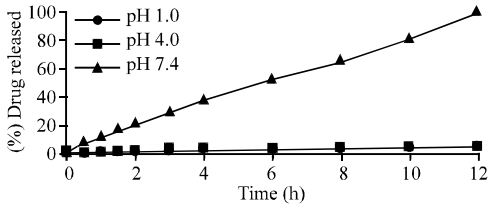

Fig. 3: Effect of pH on *in vitro* drug release from test matrix tables

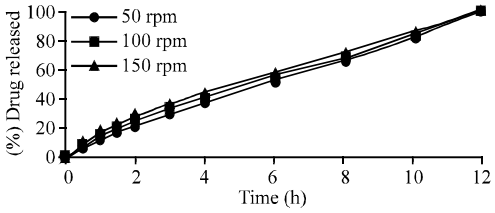

Fig. 4: Effect of stirring speed on *in vitro* drug release from test matrix tables

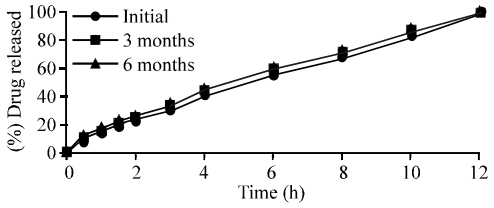

Fig. 5: Effect of storage at 8°C on *in vitro* drug release from test matrix tables

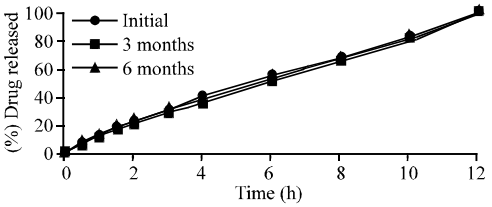

Fig. 6: Effect of storage at 37°C on *in vitro* drug release from test matrix tables

At pH 7.4 there was apparent difference in drug release profile and almost 100% of the drug was released during 12 h. From the results, it can be concluded that naproxen release from the test matrix tablets is pH dependent. The pH dependency is due to difference in the solubility of naproxen at various pH values. As the naproxen has maximum solubility at pH 7.4 in contrast to pH 1 and 4, therefore greater amount of drug was released from the test matrix tablets at higher pH.

Figure 4 shows the drug release profile from the test matrix tablets at different stirring speeds. The drug release was seemed to increase slightly as the stirring speed was increased. The data was statistically compared using f_2 equation and it was found that the dissolution data obtained at 50, 100 and 150 rpm were similar. The f_2 values obtained from dissolution data at 50 rpm vs 100 rpm and 50 rpm vs 150 rpm were 64.5 and 77.6, respectively suggesting that the rate of drug release is independent of stirring speed.

Influence of storage conditions on drug release rate of test matrix tablets: Figure 5 and 6 shows the drug release profile of test matrix tablets at 8 and 37°C after six months of storage, respectively. The release profiles were similar and comparable at both temperatures. It seemed that the drug and the polymer in the test matrix tablets are insensitive to moisture and temperature during storage. As no significant change in the release profiles of test

matrix tablets was observed at different temperatures, therefore no further change in the rate of drug release is expected for prolong storage.

CONCLUSIONS

The drug release rates from various hydrophobic matrix tablets were comparable and no significant change in the drug release profile was observed even by incorporation of increasing proportions of ethyl cellulose. However, the test matrix tablets prepared by modifying the wet granulation method were found to produce desirable release rate. The release of test matrix tablets was found to be pH dependent due to difference in the solubility of naproxen in various dissolution media. Moreover, the drug release profile of test matrix tablets was independent of stirring speed and stable upon storage at different temperatures.

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