REPORT

NAPROXEN RELEASE FROM SUSTAINED RELEASE MATRIX SYSTEM AND EFFECT OF CELLULOSE DERIVATIVES

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ABSTRACT

The present study was conducted to investigate the low viscosity grades of hydroxypropylmethyl cellulose (HPMC) and ethyl cellulose (EC) in sustaining the release of water insoluble drug, naproxen from the matrix tablets. Both HPMC and EC were incorporated in the matrix system separately or in combinations by wet granulation technique. In vitro dissolution studies indicated that EC significantly reduced the rate of drug release compared to HPMC in 12 hour testing time. But, no significant difference was observed in the release profiles of matrix tablets made by higher percentages of EC. The tablets prepared with various combinations of HPMC and EC also failed to produce produce the desired release profiles. However, comparatively linear and desirable sustained release was obtained from EC-based matrix tablets prepared by slightly modifying the granulation method. Moreover, two different compression forces used in tableting had no remarkable effect on the release profile of naproxen.

Keywords: Naproxen, sustained release, hydrophilic matrix, lipidic matrix.

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INTRODUCTION

A controlled release dosage form may be formulated to provide drug for an immediate release as well as gradual and continuous release of remaining doses for an extended period of time (Bogner, 1997; Madan, 1985). One of the most important commonly used method for controlling drug release is to form a matrix system with hydrophilic or hydrophobic polymers. Hydrophilic polymers are widely used in oral sustained release matrix system (Lee and Robinson, 2000). These formulations are relatively flexible, well designed and gives reproducible release profiles. Among the various swellable hydrophilic polymers used to prolong the drug release, hydroxypropylmethyl cellulose (HPMC) has been widely used due to its rapid hydration (Huang *et al*., 2003), good compression and gelling characteristics along with its ease of use (Grassi *et al*., 2004; Gustafsson *et al*., 1999), availability and very low toxicity (Ebube and Jones, 2004; Fu *et al*., 2004). A hydrated viscous layer or gel layer is usually formed at the tablet periphery, which controls the drug release from the hydrophilic matrix tablets (Khanvilar *et al*., 2002; Kavanagh and Corrigan, 2004; Katzhendler *et al*., 2000). Similarly, hydrophobic polymers also provide several advantages ranging from good stability at varying pH values and moisture levels to well establish safe applications. Ethyl cellulose (EC) is a common example that has been extensively used in a number of dosage forms as a coating material for tablets and granules (Pearnchob *et al*., 2003; Biju *et al*., 2004), a tablet binder in preparing microcapsules (Sajeev *et al*., 2004) and also as film and matrix forming material for sustained release dosage forms (Iqbal *et al*., 2002; Pruthvipathy *et al*., 1995). There are few reported studies of sustained release wet-granulated matrix tablets that employ EC as rate controlling polymer. Commercial product of controlled release naproxen sodium is available but naproxen has been used rarely in controlled release dosage form. Naproxen is practically insoluble at low pH but freely soluble at high pH. It has been proved to be effective in rheumatoid arthritis, osteoarthritis, juvenile arthritis, and acute gout without any serious cardiovascular or respiratory side effects (Todd and Clissold, 1990). In the present study, low viscosity grades of HPMC, EC and their combinations were used separately to develop sustained release matrix system for naproxen by wet granulation. In addition, it was desired to study the effect of polymer concentration and the effect of compression force on the dissolution of naproxen from EC-based formulations.

MATERIALS AND METHODS

Materials

Naproxen (Shazoo laboratories, Lahore, Pakistan), hydroxypropylmethyl cellulose 300cps and ethyl cellulose 45cps (Highnoon laboratories, Lahore, Pakistan), lactose (BDH, Poole, UK), magnesium stearate (Fluka, Buchs, Switzerland), potassium dihydrogen phosphate (E-merk, Darmstadt, Germany) and disodium hydrogen phosphate (Sigma Aldrich, St. Louis, Mo, USA) were used as received.

Matrix tablets

For preparing hydrophilic and hydrophobic matrix tablets, naproxen (33.33% w/w), and various concentrations of HPMC/EC along with lactose (table 1) were first sieved and blended in a Kenwood mixer (Kenwood, Geesthacht, Germany) for 5 minute. The powder blend was granulated with small amount of alcohol (25ml/100g) and the wet mass was sieved through mesh No. 6 and dried at 60°C for 1 hour in an oven (Memmert, Schwabach, Germany). The dried granules were passed through sieve No.10 and the fractions of the granules retained on the sieve were discarded. Finally, magnesium stearate in 1.67% w/w was mixed for lubrication of granules which were then compressed with single punch tablet 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 200mg naproxen.

Test matrix tablets

Test matrix tablets were prepared with EC (F5, table 1) by slightly modifying the standard wet granulation method as described above. The granules were processed with 16.7% w/w naproxen, 5% EC and 60% lactose. The remaining amount of drug (16.63% w/w) was mixed for 10 minutes with the dried granules. Magnesium stearate (1.67% w/w) was then thoroughly mixed with the granules that were compressed at a fixed (1500 lb) and higher compression force (3000 lb).

Weight variation and hardness test

In order to determine the uniformity of tablet weight, twenty tablets of each formulation were taken and weighed using

Table 1: Formulations of Naproxen matrix tablets. Each formulation contains naproxen 33.33% and magnesium stearate 1.67%

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
HPMC	20	35	50	65	0	0	0	0	1	1.5	2	3
EC	0	0	0	0	5	10	15	20	5	5	5	5
Lactose	45	30	15	0	60	55	50	45	59	58.5	58	57

HPMC, hydroxypropylmethyl cellulose and EC, ethyl cellulose.

class A weight balance (Precisa, Dietikon, Swizerland) and their percentage variation were determined. The weight variations of all the compressed tablets were well within the acceptable limits of BP, which confirmed that the filling of the granules in the die of compression machine is uniform. Hardness of twenty tablets of all the formulations was recorded using automatic hardness tester (Curio, Lahore, Pakistan) and averaged.

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° and stirred at 50 rpm. Samples (5ml) were withdrawn at predetermined time intervals (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10,12) hours with automatic sampling unit (Watson Marlo, Stockholm, Sweden). Samples were filtered through 10µm Sinter filter (Pharma Test, Hainburg, Germany) to remove suspended and insoluble tablet components and analyzed by UV spectrophotometer (Shimadzu, Kyoto, Japan) at 332nm. A directly compressed naproxen tablet was used as reference in determining the percentage dissolution. In the data analysis of each formulation, cumulative percentage of drug release was calculated using mean of six samples readings.

RESULTS AND DISCUSSION

The objectives of sustained release delivery systems is to provide desirable *in vitro* release profiles so that predictable plasma drug levels can be achieved. Formulation factors and the manufacturing difficulties are important considerations when designing a new formulation. Some aspects of a new sustained release matrix tablets for insoluble drug, naproxen are presented. All dissolution studies were performed in phosphate buffer solutions (pH 7.4) due to greater solubility of naproxen in this medium.

Influence of low viscosity grade of HPMC on drug release

Usually, high viscosity grades of HPMC forms a strong viscous gel when comes in contact with aqueous media, and very useful in drug delivery of highly water-soluble drugs. During dissolution study, such HPMC-based matrix tablets does not disintegrate and remains intact in the media. In the present study, low viscosity HPMC-based tablets were prepared to sustain the release of naproxen. Figure 1 shows the dissolution profiles of naproxen from hydrophilic matrix tablets containing 20-65% HPMC (F1-4). The release rate of naproxen is appreciably influenced by increasing amounts of HPMC in the matrix tablets. As evident in fig. 1, increasing the contents of HPMC decreased naproxen release. All the four formulations released almost 100% of the drug in about 4 hours and the rate of drug release could not be sustained for more than 4 hours even by incorporating 65% of HPMC in the formulation. This was due to similar swelling and disintegration characteristics of the matrix tablets. Tablets were disintegrated just after one sampling intervals during dissolution as no gel layer was formed around the tablets. The drug release process therefore, seemed to be mainly erosion controlled from the matrix tablets. Hence, low viscosity grades of HPMC are inappropriate for sustaining the release profiles of naproxen.

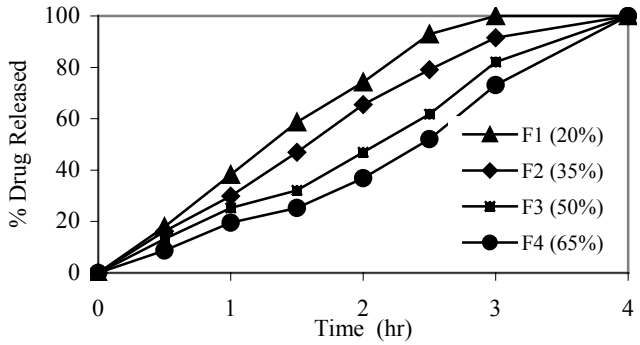

Fig. 1: Effect of various percentages of HPMC on *in vitro* release from naproxen tablets.

Influence of ethyl cellulose on drug release

A hydrophobic polymer ethyl cellulose (EC) having viscosity 45 cp was used to formulate the matrix system in this part of study. Fig. 2 shows the release of naproxen from hydrophobic matrix tablet containing 5-20% EC (F5-8). Incorporating EC in the matrix tablets considerably decreased the drug release profiles. The slow drug release rate from such tablets was due to formation of EC coating around the individual drug particles. However, increasing the percentage of EC had no significant effect on the release rates. This was due to the fact that during granulation the amount of ethanol used for higher percentages of EC was insufficient to wet the drug particles and in turn provided less uniform coating. About 50% of the drug was released in 12 hours from EC-based matrix tablets while almost 100% dug was released from HPMC-based matrix tablets in 4 hours. This clearly indicates that EC had pronounced effect in decreasing the drug release rate from hydrophobic matrix tablets compared to HPMC. The dissolution data of HPMC-based formulations (F1-4) and EC-based formulations (F5-8) was statistically analyzed using student t-test and significant difference was found in their release rates ($p < 0.05$). However, the results of the present study were not in good agreement with the reported study (Iqbal *et al*., 2002) in which increasing percentages of micronized EC produced slower drug release rates. As in the reported study, micronized form of EC was used which could be more easily wetted by the granulating liquid and provided more uniform coating compared to the granular form of EC used in this study.

Influence of HPMC-EC mixtures on drug release

Mixed matrix formulations containing both HPMC and EC were also investigated due to undesirable release profiles obtained from HPMC and EC-based matrix tablets. To produce the mixed granules, increasing amounts of HPMC

(1%, 1.5%, 2%, 3%) were mixed separately into the fixed amount of EC (5%). Fig. 3 shows the release of naproxen from the mixed matrix tablets. The release rate of naproxen in eight hour was 38%, 86%, 98%, 100% from the formulations containing 1%, 1.5%, 2%, 3% HPMC respectively as compared to 29% drug release from 5% EC alone (fig. 2). By comparing figures 2 and 3, it is apparent that HPMC in the mixed matrix tablets had increased the drug release rate while EC acted as release retardant. A close examination of Fig. 3 indicated that incorporation of 1% HPMC in the mixed matrix had little effect on the release rate whereas slightly higher percentages of HPMC had remarkable effect on the drug release rate due to formation of channels which facilitated the entry of dissolution medium at faster rate.

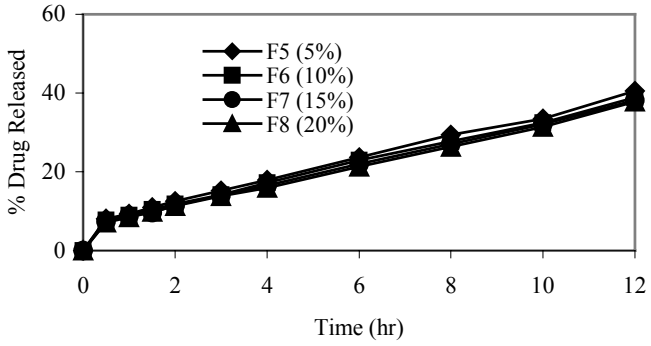

Fig. 2: Effect of various percentages of ethyl cellulose on *in vitro* drug release from naproxen tablets.

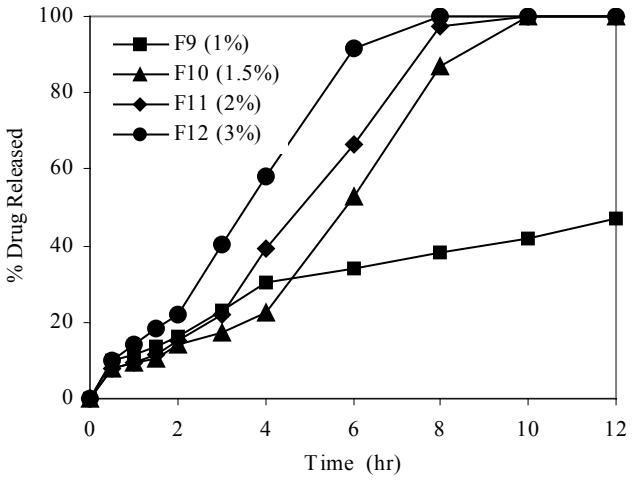

Fig. 3: Effect of HPMC (1-3%) on *in vitro* release from naproxen tablets containing 5% ethyl cellulose.

Drug release from the test matrix tablet

From the above results, hydrophilic, hydrophobic and mixed matrix formulations failed to show the linear and sustainable drug release profile during 12 hours. Finally, EC-based matrix tablets were prepared by modifying the granulation method using formulation F5 and the drug release profile obtained from this test matrix tablet is shown in fig. 4. The drug release pattern from the test matrix tablet appeared to be linear and the extent of drug release was also improved in comparison to standard granulation method used in various formulations. About 65% of drug was released in 8 hours from the test matrix tablets compared to only 29% of drug release from the same formulation. Moreover, about 22% of drug was released as burst release from the test matrix tablet and was probably attributed to the dissolution of drug from the surface of tablet. Further penetration of the dissolution medium was hindered due to hydrophobic nature of EC around drug particles leading to slow drug release for longer period of time. Fig. 5 shows the naproxen release profile of test matrix tablets, which were compressed, at a fixed compression force (1500 lb) and at higher compression force (3000 lb). The release rate of test matrix tablets was almost super-imposable (f_2 =97.79) indicating that the drug release is not dependent on the compression force applied to the granules. Although at higher compression force, an average hardness of the tablets was almost doubled than the hardness of tablets using fixed compression force but the rate of flux of dissolution media through the inner core seemed to be similar. Moreover these findings were comparable with the reported study (Ebube and Jones, 2004).

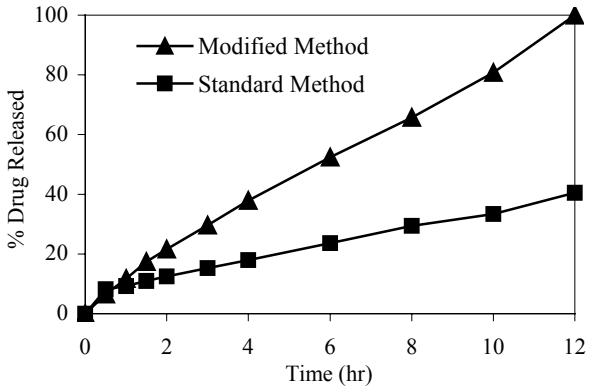

Fig. 4: Effect of granulation process on in vitro release from naproxen tablet containing 5% ethyl cellulose.

CONCLUSION

In hydrophilic matrix, increasing the amount of HPMC resulted in decreasing the release rate of drug while increasing the amount of EC in hydrophobic matrix did not affect the rate of drug release. Although the drug release rate in hydrophobic matrix tablet was significantly reduced in comparison to hydrophilic matrix tablet. A mixed matrix system containing both HPMC and EC showed that major part of the drug was released during 8 hours compared to hydrophilic matrix in which almost 100% drug was released within 4 hours. Therefore, in the mixed matrix system the rate of drug release could be manipulated by varying HPMC

contents in the fixed amount of EC. However, the test matrix tablets prepared by modifying the wet granulation method were found to produce desirable release rate.

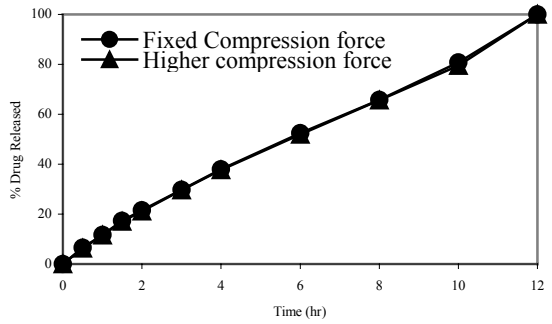

Fig. 5: Effect of compression force on in vitro naproxen release from test matrix tablets.

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