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RESEARCH PAPER

Controlled-Release Naproxen Using Micronized Ethyl Cellulose by Wet-Granulation and Solid-Dispersion Method

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ABSTRACT

This study has been undertaken to develop a controlled-release tablet dosage form of naproxen using ethocel (ethyl cellulose) as the rate-controlling polymer. The formulations were made by employing the conventional wet-granulation method and the solid-dispersion method. Tablets made by both methods were compared for their controlled-release dissolution profiles. Both methods were useful in developing the controlled-release formulations of naproxen with desirable properties. However, the amount of polymer required to make a formulation with the desired release profile was 33% less via solid dispersion than via wet granulation. A cumulative 88% of naproxen was released from the solid-dispersion formulation, compared with 84% from the wet-granulation formulation.

INTRODUCTION

An ideal drug-delivery system should be able to deliver an adequate amount of drug, preferably for an extended period of time, for its optimum therapeutic activity. Most drugs are inherently not long-lasting in the body, and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problems, controlled-release and sustained-

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release delivery systems are receiving considerable attention from pharmaceutical industries worldwide. Controlled-release drug-delivery systems not only prolong the duration of action, but also result in predictable and reproducible drug-release kinetics (1).

A controlled-release product may be formulated to contain an immediately-available dose to provide immediate action. This is followed by a more gradual and continuous release of subsequent doses to maintain the plasma concentration of the drug over an extended period of time. One obvious advantage of controlled-release dosage forms is enhanced patient compliance (2–4).

Delivery systems employing polymeric matrices are simpler and easier to fabricate. Such systems normally control the rate of release via a diffusion mechanism. Delivery systems based on the principle of solid dispersion are multi-component mixtures of one or more active ingredients in an inert carrier or matrix in solid state. These are prepared either by dissolving the ingredients in a solvent followed by drying, or by melting the active and inert ingredients together followed by solidification, or a combination of the two methods. In solid dispersion, the dissolution of active ingredient is affected by the presence of other components. Therefore, the carrier selection ultimately influences the dissolution characteristics of the dispersed drug (5).

Ethocel (ethyl cellulose) is a hydrophobic polymer and is used extensively as a coating material, as a tablet binder in the preparation of microcapsules and microspheres, and in the preparation of matrix-type controlled-release tablets. It is also used in solid dispersion-type formulations of water-soluble drugs, or sparingly water-soluble drugs. There are only a few reported studies of controlled-release solid-dispersion or matrix-type wet-granulated tablets that employ ethocel as rate-controlling polymer. Controlled-release dosage forms of naproxene sodium are commercially available. However, naproxen has not been tested in controlled-release dosage forms. It is insoluble in water but soluble at alkaline pH.

The objective of the present study is to develop a controlled-release formulation of naproxen with a release profile greater than 12 hr in selected in vitro fluids. More specifically, it was also desired to study (i) the effect of polymer concentration and (ii) the effect of different manufacturing processes (solid dispersion and wet granulation) on the dissolution of naproxen from ethocel-based controlled-release formulations.

MATERIALS

Naproxen was obtained from Wyeth Ayerst Research, Pearl River, NY; Ethocel 10FP® (Ethyl Cellulose NF) was obtained from Dow Chemical Company, MI; lactose monohydrate was obtained from EM Industries, NY; magnesium stearate was obtained from Sigma Chemical Company, MO.

METHODS

Preparation of Tablets by Wet Granulation

Table 1 shows six tablet formulations prepared by wet granulation. The amount of ethocel in these formulations varies from 6% to 28%. The amount of drug was kept constant at 80 mg/tablet, or 16%. The final tablet weight was adjusted to 500 mg by adding lactose as filler.

Naproxen, ethocel, and lactose were first passed through a No. 20 sieve and then blended in a turbula mixer for 2 min. The powder blend was transferred into a wedgewood mortar and ethyl alcohol was added with constant grinding and mixing. The wet mass was then passed through a No. 8 sieve and the resulting granulation dried for 2 hr in an oven at 40°C. The dried granulation was passed through a No. 12 sieve, magnesium stearate was added and mixed for 2 min. The final powder blend was then compressed into tablets using a Carver single-punch machine employing 7/16″ SC tooling at 1400 psi pressure. The compression force was kept constant for all formulations, to eliminate its effect on dissolution.

Table 1

Formulation(s) of Tablets Prepared by Wet Granulation

	Amount (mg/tablet)					
Ingredients	1	2	3	4	5	6
Naproxen	80	80	80	80	80	80
Ethocel	140	100	80	60	40	30
Lactose	270	310	330	350	370	380
Magnesium stearate	10	10	10	10	10	10
Total	500	500	500	500	500	500

Table 2

Formulation(s) of Tablets Prepared by Solid Dispersion

	Amount (mg/tablet)					
Ingredients	1	2	3	4	5	6
Naproxen	80	80	80	80	80	80
Ethocel	240	160	80	60	40	20
Lactose	170	250	330	350	370	390
Magnesium stearate	10	10	10	10	10	10
Total	500	500	500	500	500	500

Table 3

Formulation(s) of Naproxen Tablets of Higher Strength

	Amount (mg/tablet)			
	Wet Granulation		Solid Dispersion	
Ingredients	1	2	1	2
Naproxen	160	240	160	240
Ethocel	60	90	40	60
Lactose	270	160	290	190
Magnesium stearate	10	10	10	10
Total	500	500	500	500

Preparation of Tablets by Solid Dispersion

Table 2 shows six tablet formulations prepared by solid dispersion. The amount of ethocel in these formulations varies from 4% to 48%. The amount of drug was kept constant at 80 mg/tablet, or 16%. The final tablet weight was adjusted to 500 mg by adding lactose as filler.

Naproxen and ethocel were transferred to a 100-mL beaker containing a magnetic stirrer. A 50-mL portion of a mixture of ethyl ether/methanol (50/50) was added to the beaker and stirred for 15 min until dissolved. Lactose was then added and mixed for 10 min. The beaker containing the dispersion was then incubated at 40°C and stirred constantly until complete evaporation of the solvent. This was done under a gentle stream of nitrogen gas. After evaporation of the solvent, the mass was passed through a No. 8 sieve. The resulting granules were then dried further in an oven at 40°C for 2 hr. The dried granules were passed through a No. 12 sieve. Magnesium stearate was added and blended for 2 min. The final powder blend was then compressed into tablets using a Carver single-punch machine employing 7/16″ SC tooling at 1400 psi pressure.

Naproxen Tablets of Higher Strength

Once the formulations displaying the desired release profiles from both wet-granulation and solid-dispersion techniques were established, tablets were prepared with two- and threefold increases in naproxen content (Table 3). In these formulations the ratio of drug to polymer was kept constant, whereas lactose was used to adjust the tablet weight to 500 mg. These tablets were used to evaluate the suitability of the formulation and the manufacturing process to prepare tablets of higher strength.

In Vitro Dissolution Studies

The dissolution studies were performed using USP method 1 (6). Simulated intestinal fluid (SIF) or simulated gastric fluid (SGF) was used as dissolution medium (900 mL). The temperature of the medium was maintained at 37 ± 0.5°C. The agitation rate was 100 rpm. Six tablets were used in each test. The dissolution assembly was calibrated as per USP. A 3.0-mL sample was removed at 1, 2, 4, 6, 8, and 12-hr intervals for measuring drug release. An equal volume of fresh dissolution medium was used to maintain a constant volume. The aliquot samples were filtered and the drug concentration was determined by ultraviolet (UV) method at 271 nm.

A directly-compressed tablet formulation of naproxen without ethocel was used as a reference in dissolution studies. The dissolution data of these tablets (Fig. 1) were compared with formulations prepared by wet granulation and solid dispersion having the desired release profile.

Investigation of Drug-Release Kinetics

Drug-release kinetics were investigated by fitting the dissolution data to a zero-order, first-order, and square-root-of-time equation to find the equation that fits best.

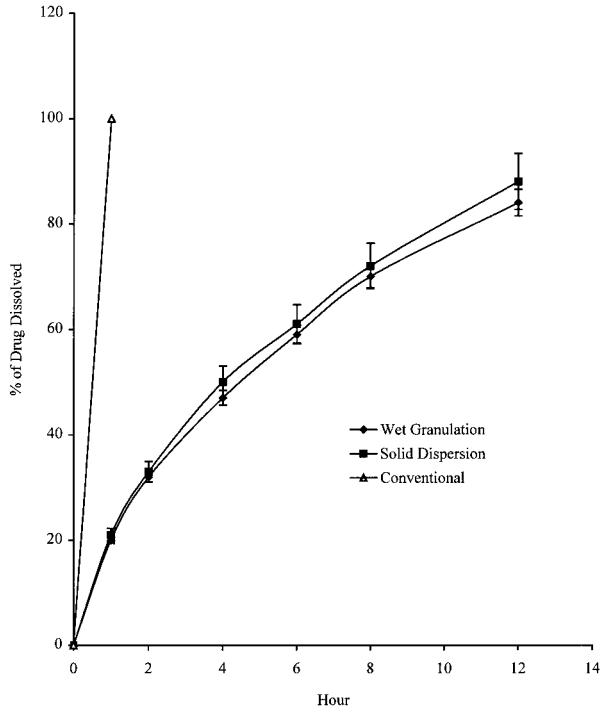

Figure 1. Comparison between directly-compressed tablets without ethocel and controlled-release tablets made by wet granulation and solid dispersion.

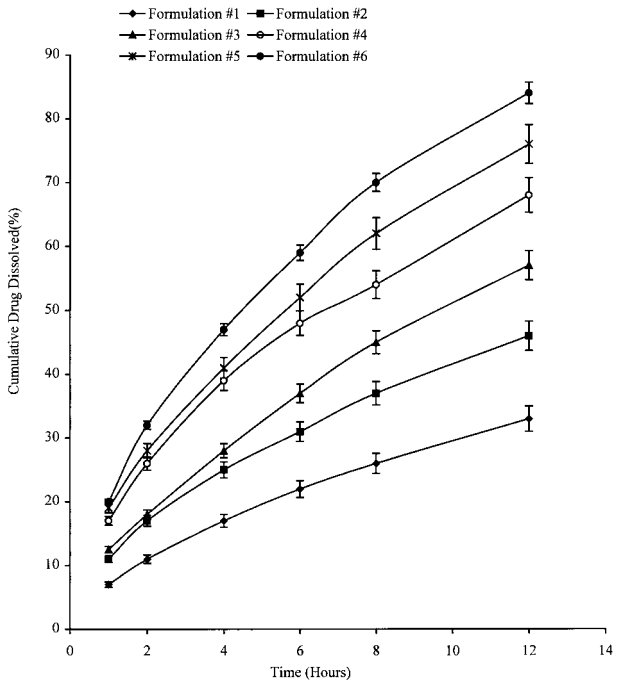

Figure 2. Dissolution profiles of tablets prepared by wet granulation.

RESULTS AND DISCUSSION

Dissolution of Tablets Prepared by Wet Granulation

Figure 2 shows the dissolution results for tablets prepared by wet granulation. It shows that increasing the contents of ethocel decreases naproxen release. The formulation containing 6% ethocel released 84% of the drug in 12 hr, while the formulation containing 28% ethocel released 30% of the drug in 12 hr. None of the formulations released 100% of the drug.

Dissolution of Tablets Prepared by Solid Dispersion

Figure 3 shows the dissolution results for tablets prepared by solid dispersion. It shows that increasing the contents of ethocel decreases naproxen release. The formulation containing 4% (20 mg) ethocel released 88% of the drug in 12 hr, while the formulation containing 48% (240 mg) ethocel released 30% of the drug in 12 hr. None of the for-

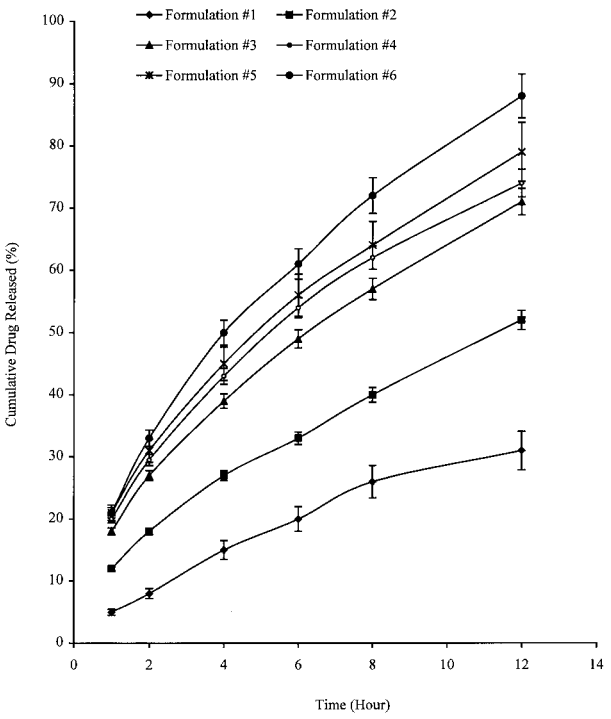

Figure 3. Dissolution profiles of tablets prepared by solid disperson.

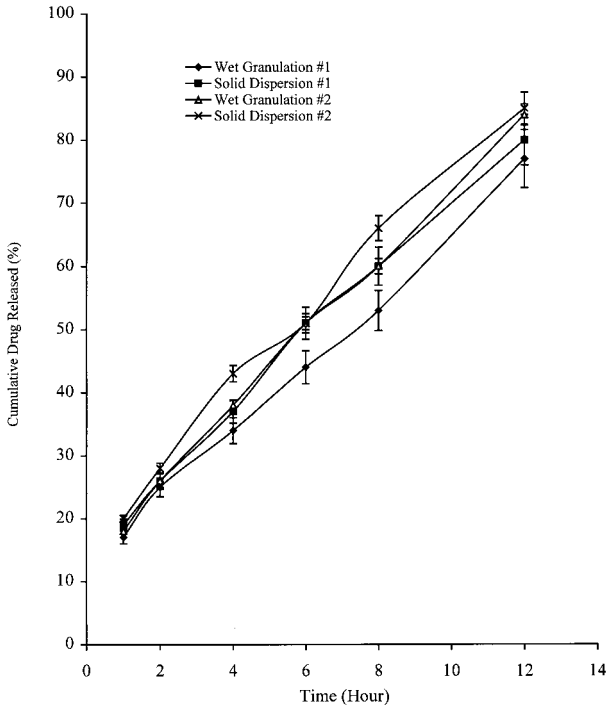

Figure 4. Dissolution profiles of tablets of higher strength.

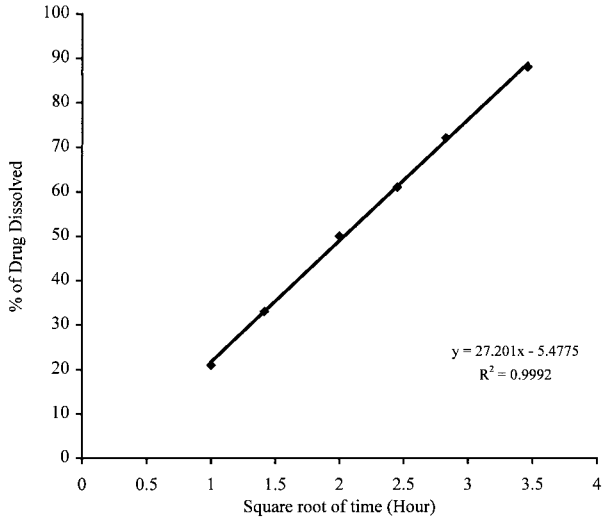

Figure 5. Diffusion-controlled release in tablets prepared by solid dispersion.

mulations released 100% of the drug. The results also show that solid dispersion requires lower amounts of polymer (4%) than wet granulation (6%) to produce a similar release profile.

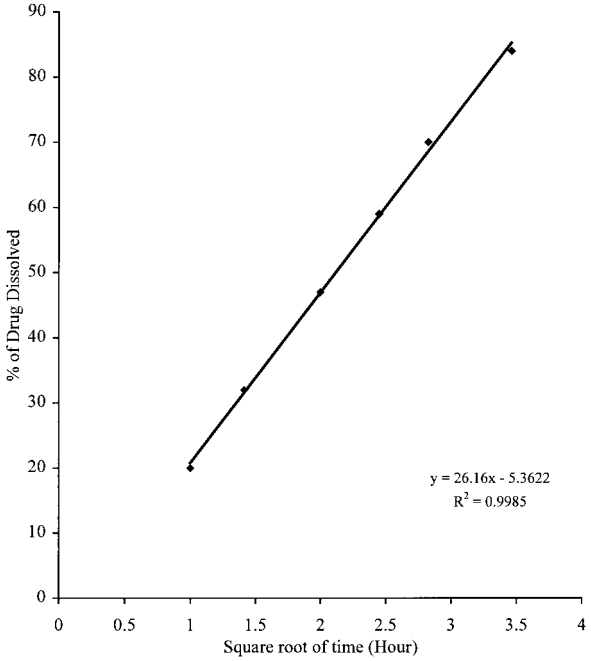

Figure 6. Diffusion-controlled release in tablets prepared by wet granulation.

Dissolution of Tablets of Higher Strength

Figure 4 shows the dissolution profiles of naproxen tablets of higher strength. It shows that different strengths of controlled-release tablets of naproxen have similar release characteristics, as long as the drug-to-polymer ratio is constant. Changes in lactose content have no effect on the naproxen dissolution.

Drug-Release Kinetics

The plot of percent drug remaining in the matrix, or log of percent remaining in the matrix, against time was found to be nonlinear, indicating lack of zero-order or first-order kinetics. When the percent drug dissolved was plotted against the square root of time, a linear curve with positive slope was obtained (Figs. 5 and 6). No positive deviations were observed over a period of 12 hr. Therefore, the geometry of tablets did not change during the course of dissolution for either formulation. The slopes of these plots for the two formulations are approximately the same. These results suggest a diffusive mechanism for obtaining naproxen from the

ethocel tablet matrix. However, this needs further verification.

CONCLUSIONS

Ethocel can be used successfully to formulate controlled-release naproxen tablets. Both methods of manufacturing ethocel-based controlled-release tablets, i.e., wet granulation and solid dispersion, were found useful in preparing these tablets. Solid dispersion was found relatively more efficient in preparing controlled-release tablets using ethocel as rate-controlling polymer. This may be due to more efficient drug trapping in the tablet matrix. Solvents were employed to prepare ethocel-based formulations. This may be useful in formulating moisture-sensitive drugs.

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