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COMMUNICATION

Formulation Development of Oral Controlled-Release Pellets of Diclofenac Sodium

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ABSTRACT

In this study, various formulations of controlled-release pellets of diclofenac sodium were prepared. Selected polymeric film coatings were applied to the drug-loaded nonpareils and their effects on the in vitro drug release from the multiple-unit dosage form were examined. It was found that a combination of ethylcellulose, myvacet 9-40, and talc produced a stable film coating and controlled drug release was achieved. Dissolution data demonstrated that this formulation produced predictable and reproducible drug data release characteristics.

INTRODUCTION

Diclofenac sodium or sodium *2*-(2,6-dichloroanilino)- phenylacetate is a nonsteroid drug (1). Its anti-inflammatory, analgesic, and antipyretic actions are rated the same as indomethacin (2). Because of its high level of effectiveness, diclofenac sodium has been used clinically in the form of tablets and suppositories (1–3).

Oral tablets of diclofenac sodium are absorbed into blood within 30 min after administration and reach the maximum blood concentration at about 2 hr. However, its biological half-life is only 1.3 hr (2,4). As a result of the quick absorption and short half-life of the commercially available diclofenac sodium tablets, tablets must be administered orally three times a day. In addition, it has been reported that oral administration of diclofenac sodium often induces various side effects such as gastroenteritis (2). Therefore, a long-acting formulation that can sustain the action of diclofenac sodium in blood over an extended period of time would be very beneficial.

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The choice of an appropriate formulation for a selected drug may play a significant role in successful drug therapy. Although several different types of oral controlled-release tablets have been designed to release drug at various rates, all controlled-release products are designed so that the systemic rate of drug absorption is limited by the rate of drug release from the delivery system (5).

It has been asserted that products based on a multiunit system comprising many small pellets offer some advantages over single-unit preparations such as a matrix tablet. The gastric emptying of a multiunit dosage form occurs gradually, in a more consistent manner with small individual variations (6). Individual pellets also have the potential to distribute widely over a large area in the stomach and small intestine, thus yielding a more predictable drug release profile by reducing local differences in the gastrointestinal environment (7,8). Local effects of an irritant drug could similarly be reduced (9). Moreover, since each dose consists of many subunits, there is better statistical assurance of drug release (10) and the risk of dose dumping is equally subdivided (11).

Coating of drug pellets with a nonsolute barrier membrane offers a reliable method of regulating the drug's release (12). The coating can be varied in nature and thickness to give the desired release profile. In this regard, spherical pellets, which have low surface area-to-volume ratio, possess the ideal shape for application of the coating. Drug release from the coated pellets occurs via diffusion of dissolved molecules through the continuous phase and plasticizer channels of the barrier membrane (13), and aqueous-filled pores created by dissolution of soluble components incorporated into the coating (14).

The purposes of this study were to (i) develop a multiparticulate extended-release dosage form of diclofenac sodium, and (ii) to evaluate its sustained-release characteristics by in vitro dissolution. All coating procedures were performed in a rotor-process granulator and pellets were coated with an aqueous ethylcellulose-based coating mixture to control release of the drug.

EXPERIMENTAL

Materials

The following materials were used: diclofenac sodium (Chan-Fong Chem., Taiwan, lot 90302); ethylcellulose 100 cps (DOW Chem., USA, lot MM911001-2); nonpareil (Werner, West Germany, lot 08300); myvacet 9-40 (Chan-Chi, Taiwan, lot 12542); propylene glycol (DOW, USA, lot 44910). All other chemicals and solvents were reagent grade and used as received. Voltaren® 100 (Ciba-Geigy, USA, lot 073600) is a commercially available preparation containing 100 mg diclofenac sodium embedded in a controlled-release hydrophilic matrix. The release pattern of this preparation was used as reference.

Methods

Coating of Diclofenac Sodium Pellets

All batches of pellets were prepared by coating a layer of diclofenac sodium onto nonpareils and then coating a polymer membrane around the diclofenac sodium-loaded pellets. This method is convenient, simple, and suitable for preparation of potent drugs.

The formulation for the drug-coated pellets consisted of 100 mg of diclofenac sodium (per capsule) coated onto nonpareils with the aid of ethylcellulose as binder and ethyl alcohol as the coating solvent. The nonpareils were charged into the prewarmed chamber of the rotor-process granulator (Glatt D-7852 Binzen), dried, and then fluidized at 50°C for 30 min (spray rate: 10.0 ml/min).

The diclofenac sodium-loaded pellets were coated by ethylcellulose solution in ethyl alcohol with a plasticizer (myvacet 9-40) in a rotor-process granulator. The pellets were then dried at 50°C for a further 60 min in the roto-process granulator. The prepared pellets were cured overnight at 25°C (room temperautre) before dissolution studies. Six samples were tested for each batch.

Further batches of pellets were coated with known concentrations of ethylcellulose using myvacet 9-40 as plasticizer and talc as lubricant.

In Vitro Disolution Studies

Dissolution studies were performed using the paddle method (USP 22, apparatus 2) at 50 rpm in a six-station dissolution apparatus (Hanson Research Northridge, USA). The dissolution medium was 900 ml of pH 6.8 0.2 M KH_2PO_4–NaOH buffer and maintained at 37 ± 0.5°C (15).

Aliquots (2 ml) were removed at 1, 2, 3, 4, 6, 8, 10, and 12 hr and were filtered through 0.45 μm filters before they were analyzed by a high-performance liquid chromatographic (HPLC) method (16).

RESULTS AND DISCUSSION

Fig. 1 shows the difference in dissolution rates between two pellets of the same formulation (Tables 1 and 2) and coating conditions (Tables 3 and 4), but with different particle sizes. These results indicate that the diclofenac sodium release rate of the coated pellets is significantly ($p < 0.05$) higher in small-size pellets (30–35 mesh) than in large-size pellets (25–30 mesh). This may be due to the higher diclofenac sodium loading capacity in the small-size pellets. This would result in an increased ratio of diclofenac sodium to polymer.

Fig. 2 describes the difference in dissolution rates between the pellets coated with different concentrations of ethylcellulose. The release rate decreased as the film thickness increased, suggesting that the diclofenac sodium has to diffuse through a thicker membrane before dissolution into the surrounding medium. Donbrow and Samuelov (17) have also shown that drug release through ethylcellulose film is a function of membrane thickness and composition. During the coating of the batches, it became evident that the high concentration of the ethylcellulose solution caused the agglomeration of pellets in the rotor-process granulator. In order to prevent the agglomeration, more-dilute solutions were used.

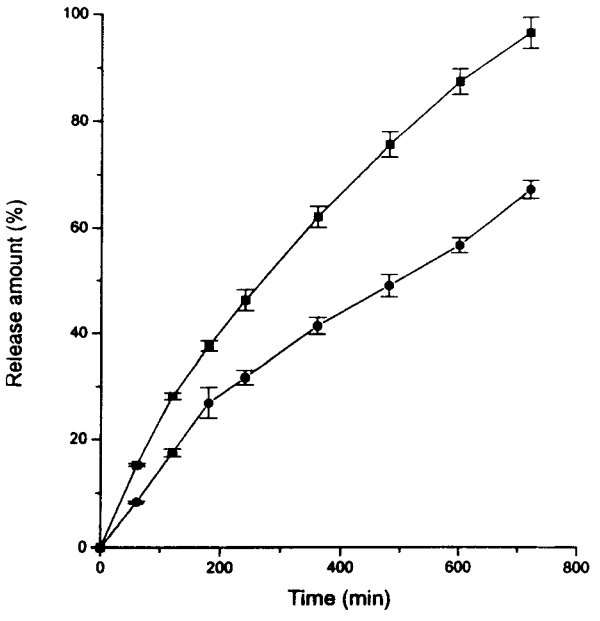

Figure 1. Drug dissolution of different particle size nonpareils coated with ethylcellulose as a function of time. ■ 30–35 mesh, ● 25–30 mesh.

Table 1

Formulation of the Diclofenac Sodium-Coated Nonpareils

Ingredients	Amount
Nonpareil	2000 g
Diclofenac sodium	200 g
Ethylcellulose	10 g
Talc	2 g
95% Ethyl alcohol	1500 ml
Deionized water	100 ml

Table 2

Formulation of Coated Diclofenac Sodium Pellets

Ingredients	Amount
Diclofenac sodium pellets	500 g
Ethylcellulose	30 g
Myvacet 9-40	10 g
Talc	30 g
95% Ethyl alcohol	1000 ml
Deionized water	100 ml

Table 3

Operating Conditions for Diclofenac Sodium-Coated Nonpareils

Operating Conditions	Setting
Inlet temperature	65°C
Outlet temperature	55°C
Solution temperature	60°C
Flow rate of coating solution	10 ml/min
Atomizing air pressure	2 bars
Rotor speed	90 rpm
Drying time	60 min

Table 4

Operating Conditions for Diclofenac Sodium-Coated Pellets

Operating Conditions	Setting
Inlet temperature	65°C
Outlet temperature	55°C
Solution temperature	60°C
Flow rate of coating solution	10 ml/min
Atomizing air pressure	2 bars
Rotor speed	180 rpm
Drying time	60 min

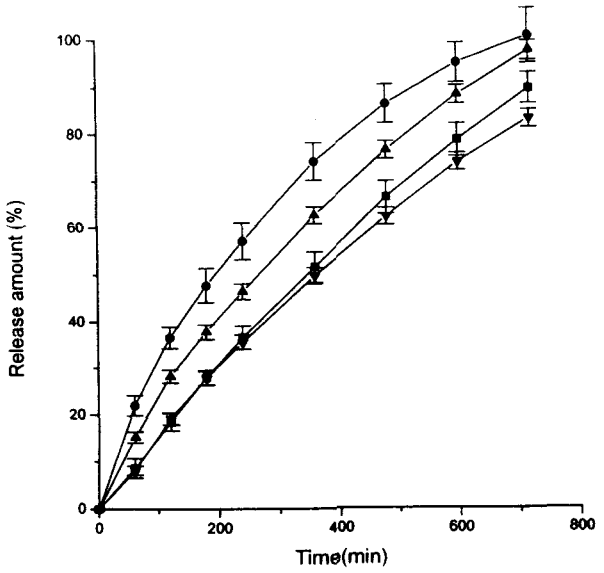

Figure 2. Drug dissolution of pellets coated with different concentrations of ethylcellulose (EC) as a function of time. ● 4% EC, ■ 8% EC, ▲ 6% EC, ▼ 10% EC.

A plasticizer was included in the coating formulation in order to improve the stability of the film by increasing the flexibility of the membrane. The inclusion of suitable plasticizer in polymeric films has been studied (18–20). By lowering the glass transition temperature of the polymer (21), the plasticizer serves to alter physical properties such as flexibility, hardness, tensile strength, and elasticity. Polymer–plasticizer systems differ widely and compatibility is often specific. In this study, the influence of plasticizer was investigated by formulating pellets with 2% myvacet 9-40 (acetylated monoglyceride) or 2% propylene glycol. Fig. 3 shows that the rate of diclofenac sodium released from the coated pellet containing 2% myvacet 9-40 as plasticizer was similar to the Voltaren reference standard but slower than the pellet with 2% propylene glycol. Myvacet 9-40 was therefore chosen as the plasticizier for the preparation of subsequent batches of ethylcellulose-coated pellets.

Lubricants or antiadherents are solid inclusions that decrease the tackiness of coating solutions. Lubricants also have an inhibitory effect on the rate of drug release due to their hydrophobic nature (20). Subsequent batches were coated with known concentrations of

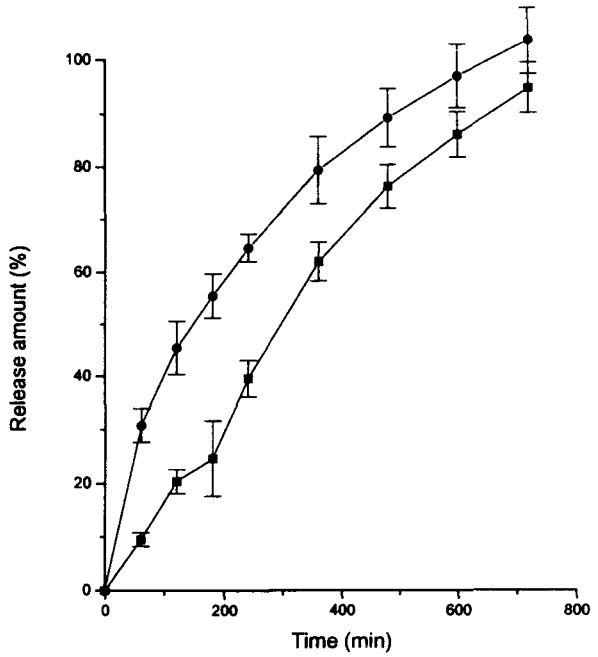

Figure 3. Drug dissolution of pellets coated with ethylcellulose and plasticizers as a function of time. ■ 2% myvacet 9-40, ● 2% propylene glycol.

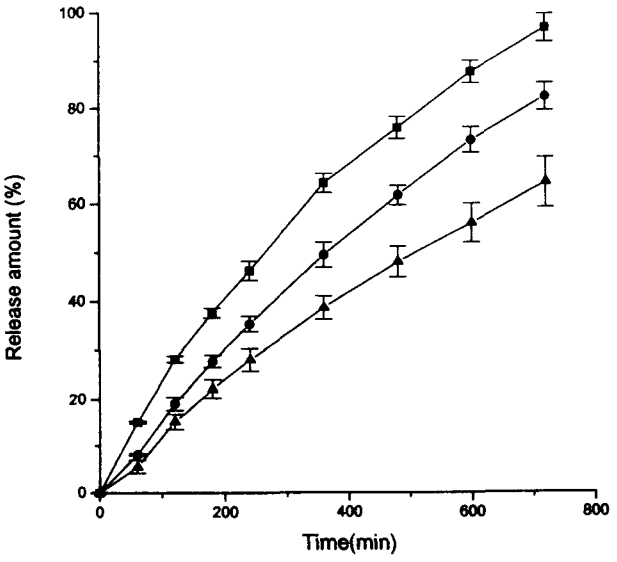

Figure 4. Drug dissolution of pellets coated with ethylcelluose, plasticizer, and lubricant as a function of time. ■ 6% EC, ● 8% EC, ▲ 10% EC.

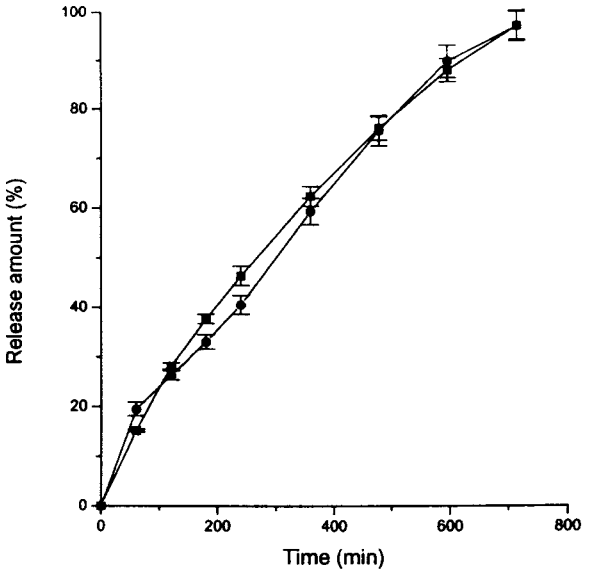

Figure 5. Drug dissolution of the prepared pellets and Voltaren as a function of time. ■ sample, ● Voltaren 100.

ethylcellulose using 2% myvacet 9-40 as plasticizer and 6% talc as lubricant. Batches containing 4%, 6%, 8%, and 10% ethylcellulose were prepared. The results of dissolution studies on these batches are presented graphically. It was observed that batches coated with 6%, 8%, and 10% of polymer released diclofenac sodium at a constant rate (zero-order) over a 12-hr period (Fig. 4). The batch coated with 6% ethylcellulose displayed release characteristics comparable to the reference standard, Voltaren 100 (Fig. 5).

CONCLUSION

In the present study, drug release characteristics of newly formulated controlled-release pellets of diclofenac sodium were evaluated by means of in vitro dissolution tests. The design of this product involved the logical development of a formulation by optimizing processing variables until a desirable product was achieved. Further studies, including in vivo bioavailability tests, need to be conducted in order to correlate the in vitro/in vivo relationship of the prepared dosage forms.

REFERENCES

1. P. A. Todda and E. M. Sorkin, Drugs, 35, 244 (1988).
2. United States Patent, patent numer 4,948,581.
3. Y. Hirotani, Y. Arakawa, Y. Maeda, A. Yamaji, A. Kamad, and T. Nishiha, Ta. Chem. Pharm. Bull., 3049–3053 (1987).
4. P. D. Fowler, Voltarol: diclofenac sodium, Clin. Rheum. Dis., 5, 427–464 (1979).
5. Ganderton, Manuf. Chem., 56, 3, 27–31 (1985).
6. H. Bechgard, Acta Pharm. Tech., 28(2), 149–157 (1982).
7. K. S. Murthy, R. V. Nesbitt Jr., and H. R. Harris, Pharm. Eng., 3, 19–21 (1983).
8. A. H. Beckett, Pharm. J., 233, 509–510 (1984).
9. J. S. Rowe, Pharm. J., 231, 538 (1983).
10. *The Theory and Practicle of Industrial Pharmacy*, 1986, p. 430.
11. H. Bechgard and G. H. Nielson, Drug Dev. Ind. Pharm., 4, 53–67 (1978).
12. R. F. Shangraw, Drug Dev. Ind. Pharm., 14, 319 (1988).
13. A. G. Ozturk, S. S. Ozturk, B. O. Palsson, T. Wheatley, and J. B. Dressman, in "Proceedings of 9th Pharmaceutical Technology Conference", Veldhoven, Holland, 1990, vol. 1, p. 253.
14. B. C. Lippold and H. Forster, Acta Pharm. Tech., 27, 169 (1981).
15. D. P. Wang, M. C. Yan, C. Y. Wong, and M. K. Yeh, J. of Hosp. Pharm., 10 (3,4), 191–194 (1993).
16. D. P. Wang, M. K. Yeh, C. Y. Wong, and D. K. T. Lee, Chin. Pharm. J., 42(6), 484–491 (1990).
17. M. Donbrow and Y. Samuelov, J. Pharm. Pharmacol., 32, 463–470 (1980).
18. M. E. Aulton, Int. J. Pharm. Prod. Mfr., 3, 9–16 (1982).
19. R. C. Rowe, A. D. Kotaras, and F. T. White, Int. J. Pharm., 22, 57–62 (1982).
20. O. E. Ononokpono and M. S. Spring, J. Pharm. Pharmacol., 40, 313–319 (1988).
21. C. Eskison, Manuf. Chem., 56, 33–39 (1985).