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RESEARCH PAPER

Diclofenac Release from Eudragit-Containing Matrices and Effects of Thermal Treatment

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ABSTRACT

Ethyl acrylate–methyl methacrylate copolymer (Eudragit NE40D) was evaluated as matrix material for preparing controlled-release tablets of diclofenac sodium. Drug release could be modified in a predictable manner by varying the Eudragit NE40D content, but was pH dependent, being markedly reduced at lower pH. This could be attributed to the low solubility of the drug at these pH values. Thermal treatment of the tablets at 60°C was also found to affect the rate of drug release, which was found to decrease with an increase in the treatment duration, but could be stabilized after 96 hr of treatment. This was also associated with a corresponding increase in the tablet tensile strength. However, treatment of the granules for 5 hr prior to compaction into tablets could shorten the stabilizing time of the drug release to 48 hr and that of the tensile strength to 24 hr. The effect of thermal treatment may be ascribed to better coalescence of the Eudragit particles to form a fine network, resulting in matrix of higher tortuosity and lower porosity.

INTRODUCTION

Embedding a drug within an insoluble matrix provides a convenient means of controlling the drug release. In such a system, drug release is preceded by penetration of the dissolution medium into the porous matrix to dissolve the drug, followed by diffusion/leaching of the dissolved molecules out of the matrix. Solid drug on the matrix surface will be dissolved and released first. Upon exhaustion of the surface drug, the depletion zone will then increase progressively as the solid drug front recedes into the matrix.

The theoretical analysis of drug release from such solid matrices has been discussed by Higuchi (1). Both the porosity and tortuosity factor of the matrix are important factors that influence the rate of penetration of

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the dissolution media as well as the rate of drug release, and can be governed by the type of matrix materials used.

Various types of polymers, such as waxes (2), methyl acrylate–methyl methacrylate copolymer (3), and poly (DL-lactic acid) (4), have been used as the matrix materials for preparing controlled release dosage forms. Thermal treatment or heating the polymeric matrices above the glass transition temperature could significantly alter the physical–mechanical properties and the drug release, but only few polymer containing pharmaceutical dosage forms have been studied with regard to the effects of thermal treatment (4).

In the present study, ethyl acrylate–methyl methacrylate copolymer, available as an aqueous dispersion (Eudragit NE40D), was evaluated as the matrix material for preparing controlled-release tablets of diclofenac sodium. The influence of thermal treatment on the mechanical strength as well as the drug release of the tablets was also investigated.

MATERIALS

Microcrystalline cellulose was purchased from Wei Ming Pharmaceutical Manufacturing, South Korea. Both diclofenac sodium and magnesium stearate were purchased from Nutech Drugs, India. Eudragit NE40D was obtained from Rohm Pharma GmbH, Darmstadt, Federal Republic of Germany. All of these materials were used as received.

METHODS

Preparation of Tablets

A series of tablet formulations containing a constant amount of diclofenac sodium were prepared by varying the composition of Eudragit NE40D and microcrystalline cellulose (MCC) as shown below:

Diclofenac sodium	Eudragit NE40D	MCC
4	2.5	3.5
4	2.0	4.0
4	1.5	4.5
4	1.2	4.8
4	0.0	6.0

Eudragit NE40D was available as a 40% aqueous dispersion and the proportion indicated in the formulae refers to the solid content. Diclofenac sodium was first mixed with Eudragit NE40D in a Kenwood planetary mixer and blended for 5 min; MCC was then added and mixing continued for another 10 min. The wet powder mixture was then granulated by using a mortar and pestle, sieved using a 1.40-mm mesh, and the granules obtained dried in an oven (Memmert, Germany) at 60°C for 1 hr. After the granules were dried, they were again sieved using a 1.00-mm mesh before tabletting. Tablets of approximately 250 mg weight each were prepared from these granules after addition of 1% magnesium stearate, using a Rotary tabletting machine (Chung Yung Industrial, Taiwan) equipped with 8 mm diameter flat-faced punches. The tabletting equipment was adjusted to produce a consistent tablet weight and compaction force for all the different types of tablets. The drug release profiles of the tablets produced were then evaluated in vitro using a dissolution test apparatus.

Thermal Treatment

The preparation which comprised diclofenac sodium, Eudragit NE40D, and MCC in a proportion of 4:2:4 was selected for studying the effects of thermal treatment on the drug release. The drug and excipients were mixed as described previously, and the wet powder mixture sieved using a 1.40-mm mesh. The wet granules were then subdivided into six portions and each portion dried at 60°C in an oven for different durations, namely, 1, 2, 3, 4, 5, and 12 hr, respectively. After the granules were dried, they were again sieved using a 1.00-mm mesh, followed by compaction into tablets of 250 mg weight using the same tabletting equipment settings used previously.

Tablets produced from granules thermally treated for 1, 2, 3, 4, 5, and 12 hr were further subdivided into four portions. The first portion was kept at ambient room temperature (20–24°C), while the other three were heated in an oven (Memmert, Germany) at 60°C but for different durations, namely, 24, 48, and 96 hr, respectively. The in vitro dissolution profiles of all the different thermally treated tablets were then evaluated using a dissolution test apparatus.

The hardness of the tablets before and after the various levels of thermal treatment was also determined using the tablet hardness tester (Erweka, Germany) and the tensile strength was then calculated using the relationship, $T = 2P/HD\pi$ (5) where T is tensile strength (N/m^2), H is the thickness of the tablet (mm), D is the diameter of the tablet (mm), and P is the applied force (N). For this purpose, larger tablets with diameter of 10 mm were prepared from granules dried at 60°C for 1, 5, and 12 hr. Twelve measurements were performed for

each type of thermally treated tablets and the results obtained analyzed using an analysis of variance (ANOVA) procedure appropriate for a completely randomized two factorial study design (6).

In Vitro Drug Dissolution Studies

Drug release from the various types of tablets was determined using the paddle method of the USP 23 dissolution test apparatus (Sotax, model AT7 CH 4008, Switzerland). The test was conducted in 900 ml of dissolution medium maintained at 37.0 ± 0.5°C at a paddle rotation speed of 100 rpm. Samples of 5 ml volume each were collected at predetermined time intervals using an automated fraction collector (model C613, Sotax) equipped with a piston pump (model CY7-50, Sotax) over 12-hr period. The drug concentrations of the samples were analyzed by UV spectroscopy (Hitachi UV/VIS Spectrophotometer, Japan) at 277 nm after appropriate dilution. One tablet was used in each vessel and each test was run in sets of six. The mean percentage of drug release was then calculated.

Throughout the studies, the dissolution medium employed was distilled water. In order to determine the influence of pH on the rate of drug release, different dissolution media, namely, 0.1M HCL, phosphate buffer BP of pH 4 and 7 were used. The batch of tablets containing diclofenac sodium, Eudragit NE40D, and MCC in a proportion of 4:1.6:4.5 was selected for these studies. In addition, the effect of agitation rate on the rate of drug release was also evaluated on this batch of tablets. The different agitation rates employed were 50, 75, 100, and 150 rpm, respectively.

RESULTS AND DISCUSSION

The drug release profiles of tablets containing different proportions of Eudragit NE40D and MCC are shown in Fig. 1. For tablets containing MCC as the sole matrix-forming material, drug release was rapid, being complete within 30 min. Thus, MCC alone was not sufficient to retard the drug release, consistent with the findings of Peh and Yuen (7) and O'Connor and Schwartz (8). However, sustained drug release could be achieved by incorporating Eudragit NE40D. Increasing the Eudragit NE40D content led to a corresponding decrease in the rate of drug release. At concentrations of 20% and above, the drug release could be adequately sustained up to 12 hr.

For tablets containing less than 20% of Eudragit NE40D, the profiles show an inflection followed by a

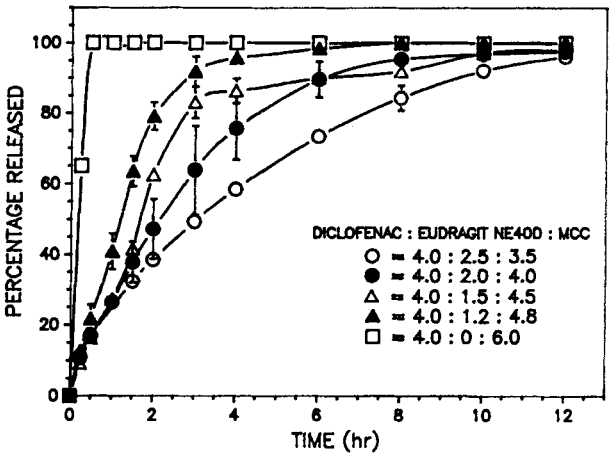

Figure 1. Diclofenac sodium release of tablets containing various proportions of Eudragit NE40D and microcrystalline cellulose (MCC). Mean ± SD, $N = 6$.

rapid drug release which could be ascribed to fragmentation of the tablets. The drug release was not sufficiently sustained and was virtually complete at 4–6 hr.

The rate of drug dissolution was noted to be markedly affected by pH. Only the drug release profiles under pH 7 and distilled water are shown (Fig. 2), since release of diclofenac under pH 1 and 4 was not detectable. This observation could be ascribed to diclofenac sodium being poorly soluble at low pH values. On the other hand, the drug release profiles under different agitation rate were almost superimposable, being independent of agitation rate as depicted in Fig. 3. This indicates that the drug release which proceeded via a

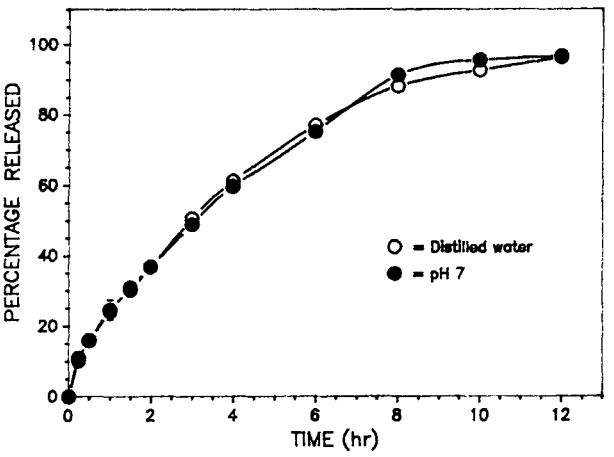

Figure 2. Diclofenac sodium release under pH 7 and distilled water.

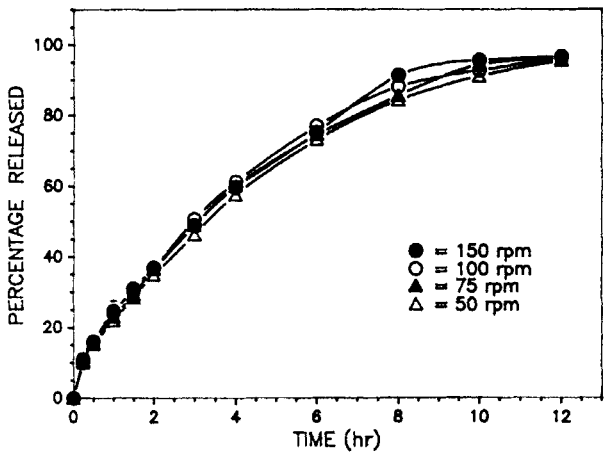

Figure 3. Diclofenac sodium release under different agitation rates.

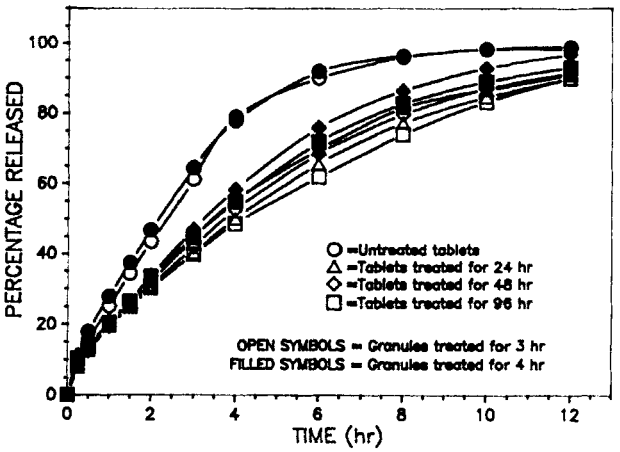

Figure 5. Diclofenac sodium release of thermally treated and untreated tablets compressed from granules treated for 3 and 4 hr.

diffusion process is internalized within the nonsoluble tablet matrix and is not limited by the drug diffusion from the tablet surface (9).

Thermal treatment of the tablets, however, was found to cause a decrease in the rate of drug release, and the effect was influenced by pretreatment of the granules used to prepare the tablets. Figures 4 and 5 show that when the tablets were prepared from granules treated for 4 hr or less, the decrease in the rate of drug release was more pronounced with longer treatment time of the tablets. In comparison, when the tablets were prepared from granules treated for 5 hr or more, the decrease in the rate of drug release could be stabilized after 24 hr of treatment as shown in Fig. 6. There was no further decrease in the rate of drug release when the tablets were treated for 48 and 96 hr.

Table 1 shows the mean tensile strength values (N = 12) of the tablets before and after various levels of thermal treatment. Both treatment of the granules and treatment of the tablets were found to significantly increase ($p < 0.05$) the tensile strength. In addition, a significant interaction was also observed between the two treatment effects, indicating that pretreatment of the granules could influence the treatment effects of the

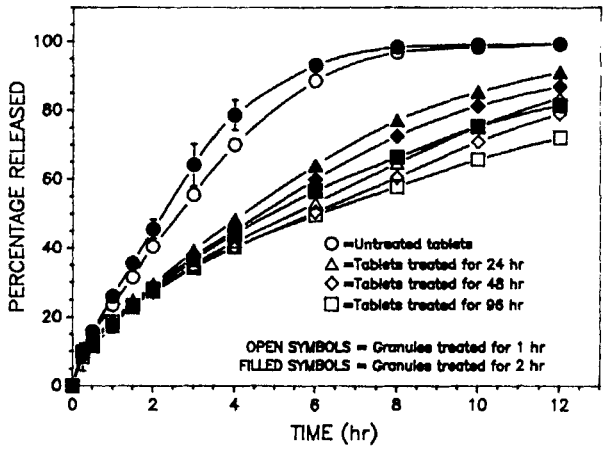

Figure 4. Diclofenac sodium release of thermally treated and untreated tablets compressed from granules treated for 1 and 2 hr.

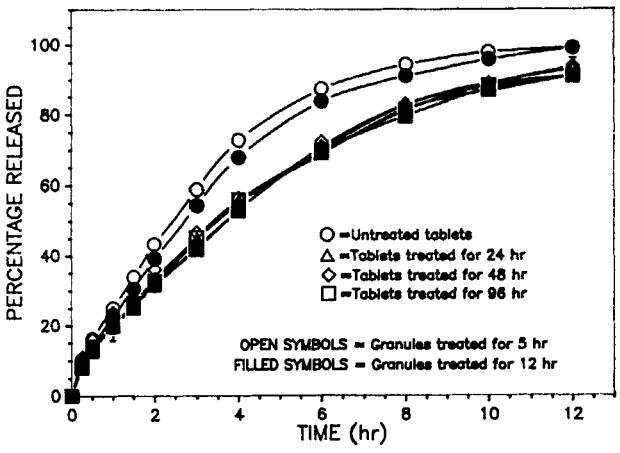

Figure 6. Diclofenac sodium release of thermally treated and untreated tablets compressed from granules treated for 5 and 12 hr.

Table 1

Mean Tensile Strength ($\times 10^5$ N/m^2) of Tablets Treated at Various Durations Compressed from Granules Thermally Treated for 1, 5, and 12 hr

Treatment Duration of Granules (hr)	Treatment Duration of Tablets (hr)			
	0	24	48	96
1	13.8	16.5	17.7	18.3
5	14.0	18.1	18.2	18.3
12	14.2	18.1	17.8	18.2

tablets. For example, when the tablets were prepared from granules treated for 1 hr only, the tensile strength was significantly increased ($p < 0.05$) with an increase in the treatment duration up to 48 hr. On the other hand, for tablets prepared from granules treated for 5 hr or 12 hr, the tensile strength was stabilized after 24 hr of treatment, indicating that 5 hr treatment of the granules was sufficient to reduce the treatment time of the tablets to 24 hr.

The effect of thermal treatment on the tablets is essentially similar to that on film formation during coating of dosage forms using aqueous polymer dispersion. Thermal treatment or curing of the dosage forms after the coating process will accelerate the rate of coalescence of the polymer particles to achieve complete film formation, thus avoiding physical changes of the coat and consequently the drug release properties during storage (10–12). In the present study, thermal treatment of the granules/tablets could have resulted in polymer chain movement and hence inter-diffusion of Eudragit polymer chains in the tablet matrix. There was thus better coalescence of the polymer particles to form a fine network, resulting in a matrix of better mechanical strength, as well as higher tortuosity and lower porosity. Similar effects of thermal treatment have also been observed by Omelczuk and McGinity (4) with tablets containing poly(DL-lactic acid). These workers also attributed the changes in the mechanical strength and drug release of the tablets to polymer chain movement and redistribution of the poly(DL-lactic acid) in the tablet matrix during thermal treatment.

Coalescence of the Eudragit particles is influenced by the softness of the polymer, which in turn is influenced by the minimum film forming temperature (MFT). Above this temperature, coalescence will take place, but may take several hours or even days to complete (4). However, it can be hastened by increasing the temperature. For Eudragit NE40D, the MFT is around 5°C, thus treating the tablets at 60°C could hasten the coalescence after their processing at a room temperature of approximately 24°C, yielding tablets of better mechanical strength and retardant effects. Based on the above findings, it is thus important that matrices containing Eudragit NE40D be sufficiently thermal treated so that changes in mechanical strength and drug release will not occur during their storage.

CONCLUSION

In summary, the release of diclofenac sodium could be adequately sustained using Eudragit NE40D. However, the drug dissolution was found to be affected by pH, but was essentially independent of agitation rate. In addition, thermal treatment could affect the mechanical strength as well as the rate of drug release of the tablets, but could be stabilized with sufficient duration of treatment. Thermally treating the granules prior to their compaction into tablets could shorten the treatment time.

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