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International Journal of Pharmaceutics 246 (2002) 171–177

international journal of pharmaceutics

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Thermal treating as a tool for sustained release of indomethacin from Eudragit RS and RL matrices

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Received 23 April 2002; received in revised form 26 June 2002; accepted 9 July 2002

Abstract

Eudragit RS and RL are biocompatible non-swelling polymers that widely used in the preparation of sustained release drug delivery systems. In this study, the effect of thermal treating on the tensile strength of tablets and release of indomethacin from Eudragit RS and RL matrices were investigated. The results showed that thermal treating at 40 °C has no effect on the release of the drug, whereas heat-treating at temperatures higher than 50 or 60 °C decreases the release rate of indomethacin from Eudragit RS or RL, respectively. It was shown that the duration of the heat treatment was also an important factor in controlling the release rate of indomethacin from Eudragit matrices. The results showed that an increase in the duration of the heat treatment from 2 to 24 h resulted in a reduction in the release rate of the drug. The heating of the matrices over 24 h had no significant effect on the release rate of indomethacin. It was shown that heat treatment of the matrices over the glass transition temperature of the polymer can prolong the drug release but had no significant effect on the tensile strength of tablets. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Eudragit RS; Eudragit RL; Sustained release; Heat-treating; Thermal treating; Dissolution efficiency

1. Introduction

Eudragit RS and RL are biocompatible copolymers synthesized from acrylic and methacrylic acid esters. The structures of Eudragit RS and RL differ only in the extent of the quaternary ammonium substitutions, with Eudragit RS containing much less such substitution than Eudragit RL. Their permeability to water is unaffected by pH, but water can permeate more freely into Eudragit RL than it can into Eudragit RS, due to the relative hydrophilicity of the RL polymer (McGinnity, 1989). The acrylate–methacrylate polymers have been used in the preparation of matrix tablets for oral sustained release, in tablet coating and in the microencapsulation of drugs (Boza et al., 1999; Mitrevej et al., 1998; Ammar and Khalil, 1997; Kristmundsdottir et al., 1996).

Embedding a drug within an insoluble matrix is a convenient way of controlling the drug release. In such a system, drug release is preceded by the

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PII: S0378-5173(02)00378-2

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 the drug release from such matrices has been discussed by Higuchi (1963). Both the porosity and tortuosity of the matrix are important factors that influence the rate of the penetration of the dissolution media as well as the rate of the drug release, and can be governed by the type of the matrix materials.

Thermal treatment or heating the polymeric matrices above the glass transition temperature could significantly alter the physical–mechanical properties and the drug release. However, the effects of thermal treating have only been studied for a few such matrices (Omelczuk and McGinnity, 1993; Billa et al., 1998). Billa et al. investigated the effect of thermal treatment on the release rate of sodium diclofenac from Eudragit NE40D matrices at a constant temperature of 60 °C. They found that the release rate of the drug decreased with an increase in the treatment duration, but could be stabilized after 96 h of treatment. This was also associated with a corresponding increase in the tablet tensile strength (Billa et al., 1998).

Therefore, the purpose of this study was to investigate the effect of heat-treating on the release of indomethacin from Eudragit RS and RL matrices. Indomethacin is a non-steroidal anti-inflammatory agent, which is widely used in the treatment of rheumatic disorders.

2. Materials and methods

Indomethacin was provided by Zahravi (Tabriz, Iran), Eudragit RS PO and RL PO were gifts from Rohm Pharma GmbH (Darmstadt, Germany), anhydrous lactose and potassium dihydrogen phosphate were supplied by Merck (Darmstadt, Germany). Distilled water was freshly prepared in the laboratory. All the materials were used as-received.

2.1. Preparation of tablets

Two formulations containing indomethacin, Eudragit RS PO or RL PO and lactose with ratios of 3:3:4, respectively, were prepared. The components of each formulation (drug and excipients) were mixed together using the tumbling method (Erweka, Type UG, Germany) for a period of 10 min. The tablets of 250 mg weight were prepared from these mixtures using IR press (Riken, Japan) equipped with 10 mm diameter flat faced punches. The tableting equipment was adjusted to produce tablets with a consistent weight using a constant compaction force of 60 kg/cm^2.

2.2. Thermal treatment

To study the effect of the duration of heat-treating, the tablets were thermally treated at 50 °C for 2, 3, 5, 24, 48 and 72 h in an oven (Memmert, Germany). To investigate the effect of temperature, tablets were stored at different temperatures of 40, 50, 60 and 70 °C for a period of 5 h. The tablets were then kept in tightly closed containers.

2.3. Tensile strength

The hardness of the tablets was determined before and after the various levels of thermal treatment using the tablet hardness tester (Erweka, Germany). The tensile strengths were then calculated using the relationship, $T = 2P/HD\pi$ (Fell and Newton, 1971), where T is the tensile strength (N/m^2), H the thickness of the tablet (mm), D the diameter of the tablet (mm), and P the applied force to fracture the tablet (N). Six measurements were performed for each type of the thermally treated tablet and the results were statistically analyzed using analysis of variance (ANOVA) procedure appropriate for a completely randomized two factorial study design.

2.4. In vitro drug dissolution study

The drug release from the different formulations before and after thermal treatment was run using the No. 1 USP 24 dissolution test apparatus

(Erweka, Germany). The test was conducted in 900 ml phosphate buffer pH 7.2 USP medium maintained at 37.0±0.5 °C at a basket rotation speed of 100 rpm. Samples of 5 ml volume each were collected over 8 h period and replaced by 5 ml of the phosphate buffer pH 7.2. One tablet was used in each vessel and each test was run in triplicate. The drug concentration of the samples was analyzed by UV spectrophotometer (Shimadzu, Japan), at 266.2 nm after appropriate dilution. The mean of at least three determinations was used to calculate the drug release from each of the formulations.

2.5. Scanning electron microscopy

Morphology of the surface of tablets was characterized by scanning electron microscopy (SEM). The tablets were mounted on aluminum stubs, sputter-coated with a thin layer of Au/Pd and examined using an SEM (Jeol, Japan).

3. Results and discussion

The drug release profiles of indomethacin from Eudragit matrices are shown in Figs. 1–5. As shown in these figures, sustained drug release could be achieved by incorporating Eudragit polymers. Fig. 1 shows that increasing the heat-treating time decreases the drug release rate from Eudragit RS matrices. However, the release profiles of the drug from the matrices that were treated for 48 or 72 h are superimposable to that of 24 h. In other words, increasing the time of heat-treating of matrices to more than 24 h does

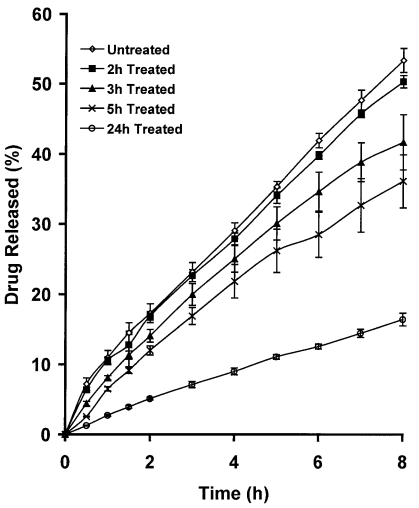


Fig. 1. The effect of the duration of heat-treating at 50 °C on the release of indomethacin form Eudragit RS matrices.

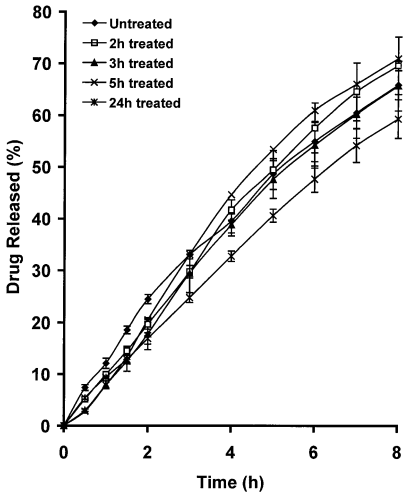


Fig. 2. The effect of the duration of heat-treating at 50 °C on the release of indomethacin form Eudragit RL matrices.

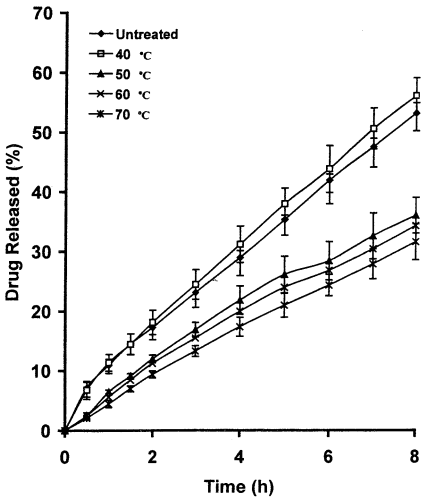


Fig. 3. The effect of the temperature of heat-treating on the release of indomethacin form Eudragit RS matrices.

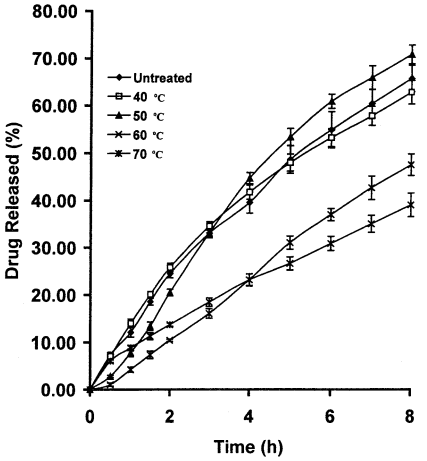


Fig. 4. The effect of the temperature of heat-treating on the release of indomethacin form Eudragit RL matrices.

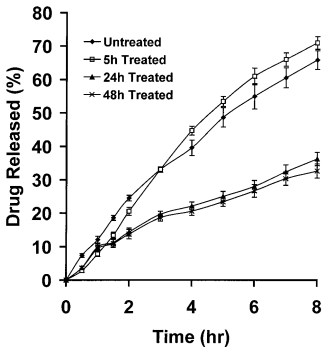


Fig. 5. The effect of the duration of heat-treating at 70 °C on the release of indomethacin form Eudragit RL matrices.

not retard the drug release rate further. As shown in Fig. 2, thermal treatment of matrices containing Eudragit RL PO at 50 °C did not show a pronounced effect on the drug release rate. Dissolution efficiency (DE_8) was used as the criterion for comparing the effect of thermal treatment on the release rate (Khan, 1975). The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. The DE value can be calculated by the following equation:

$$DE = \frac{\int_0^t y\,dt}{y_{100}t} \times 100\%,$$

where y is the drug percent dissolved at time t.

Figs. 3 and 4 show the release profiles of the drug from the Eudragit RS and RL matrices, respectively, thermally treated at 40, 50, 60 and 70 °C for 5 h. In Fig. 3, it can be seen that thermal treating at 40 °C has no effect on the release of the drug, whereas heat-treating at temperatures higher than 50 °C decreases the release rate. Furthermore, there is no significant difference ($P > 0.05$) between the release profiles of the matrices treated in 50, 60 and 70 °C. This can also be concluded from DE_8 values of the matrices in Tables 1 and 2. Fig. 4 shows that heat-treating of indomethacin matrices containing Eudragit RL for 5 h at 40 and 50 °C has no obvious effect on the release profiles, while heat-treating at 60 and 70 °C cause a decrease in drug release.

Eudragit RL matrices were also treated thermally at 70 °C for periods of 5, 24 and 48 h. Fig. 5 shows the effect of this on the release of the drug from the matrices. As shown in this figure, heat-treating for a period of 5 h slightly decreases the drug release rate during the first 2 h. Increasing the duration of heating from 5 to 24 h or 48 h has considerable effect on prolongation of the drug release ($P < 0.05$). However, increasing the duration of heating from 24 to 48 h has no further effect on the prolongation of the drug release ($P > 0.05$).

Although Billa et al. (1998) reported that heat-treating of diclofenac sodium granules containing Eudragit NE40D is able to increase the tensile strength of the tablets, in the present study, the tensile strength of the indomethacin matrices was not significantly affected by the heat treatment at 50 and 70 °C for Eudragit RS and RL, respectively ($P > 0.05$).

These findings can be well described by considering the glass transition temperature (T_g) values of the polymers. The T_g-values for Eudragit RS and RL are 50 and 55 °C, respectively (Petereit et al., 1994). 40 °C is lower than the T_g of the polymers and cannot affect the glassy state.

Table 1
DE_8 values for matrices that thermally treated at various levels

	Duration of heat-treating (h)						
	0	2	3	5	24	48	72
RS[a]	29.14	27.86	23.99	20.27	8.78	8.72	8.56
RL[a]	38.40	38.44	36.05	40.15	32.04	33.15	31.87
RL[b]	38.40	–	–	40.15	21.07	19.79	–

[a] Matrices thermally treated at 50 °C.
[b] Matrices thermally treated at 70 °C.

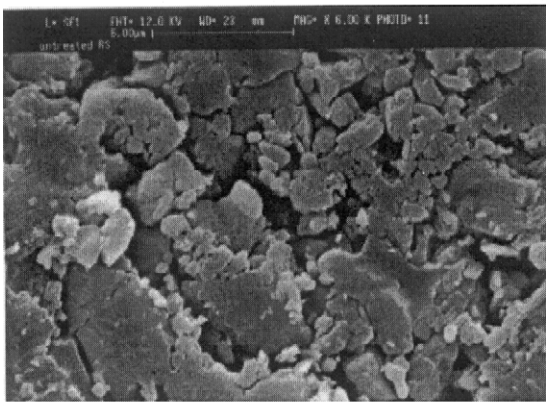
Table 2
DE_8 values for matrices that thermally treated at various levels

	Heat treated for 5 h			
	40 °C	50 °C	60 °C	70 °C
RS	30.79	20.27	18.85	16.72
RL	38.38	40.15	23.15	22.15

On the other hand, 50 °C is equal to the T_g of Eudragit RS and can change the glassy state of the polymer to the rubbery state. Increasing the treating temperature over 50 °C has no further effect on the glassy state of the Eudragit RS. Likewise heat-treating of Eudragit RL matrices up to 50 °C could not change the glassy state of the polymer, while heat-treating over the T_g, i.e. 60 and 70 °C, changes the glassy state of the polymer. The duration of the heat treatment is also an important factor. As shown in Figs. 1 and 2, increasing the duration of the heat treatment from 2 to 24 h reduces the release rate of the drug, with further heating showing no significant release prolongation effect. This could be due to a specific time required for the penetration of heat into the core of the matrices. The effect of thermal treatment of the tablets is similar to that of film formation during coating of dosage forms using aqueous polymer dispersions (Cole et al., 1995). To achieve the complete and smooth film formation in film coating process, inlet air temperature must be little above the glass transition temperature of the applied polymer. In this study, the effects of thermal treatment of the tablets on the release rate of the drug were attributed to the polymer chain movement and inter-diffusion of the Eudragit polymer chains in the tablet matrix, which causes a better coalescence of the polymer particles to form a fine network and a matrix with lower porosity and higher tortuosity. In this way, the drug is surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug. In this study, the SEM micrographs of the surface of the tablets (Fig. 6) were studied in order to find evidences. As shown in Fig. 6, the surface of the tablet is smoother and the porosity is decreased after heat-treating. Similar effects of thermal treatment have also been observed by Omelczuk and McGininty (1993) with poly (DL-lactic acid) and Billa et al. (1998) with Eudragit NE40D containing granules. Billa et al. (1998) studied the thermal treatment technique at a constant temperature of 60 °C, which was above the glass transition temperature of the polymer they used. However, they did not investigate the effect of temperature, nor they discussed the importance of the T_g on the release rate of the drug. They also attributed the change in the mechanical strength and drug release of the tablets to the polymer chain movement and redistribution of the polymer in the tablet matrix structure 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 need several hours or even days to complete.

Studies of crystallization of many materials from the amorphous state shown that significant crystallization rates most often occur above the

A. Untreated



B. Treated

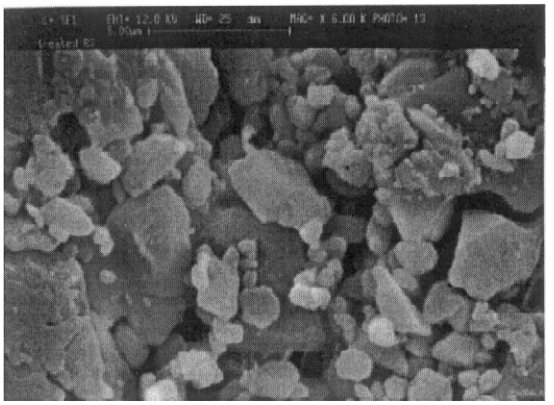


Fig. 6. SEM micrographs of the surface of the tablets (A) before heat-treating and (B) after heat-treating.

glass transition temperature (T_g), where sufficient molecular mobility exists to allow rapid nucleation and crystal growth. However, some studies also have shown that significant crystallization can occur at temperature well below T_g (Chryssikos et al., 1991; Grincourt et al., 1995). Using indomethacin as a model, Yoshioka et al. (1994) showed that dry amorphous material completely crystallized at 30 °C, well below its T_g, within a period of 3 weeks and that the rate was greatly increased at higher temperatures, presumably because of an increased molecular mobility. It was further shown that below T_g, only the most stable γ-crystal form of indomethacin appeared, whereas above T_g, both the more unstable α-crystal form and the γ-form appeared, with the α-form dominating as the temperature was raised above 60 °C. It is well established that water absorbed by amorphous solids lowers the T_g of the solid, acting as a plasticizer and increasing molecular mobility, and that the tendency of such absorbed water is to enhance the rate and extent of crystallization. The increased crystallinity may be responsible for declining indomethacin release upon exposure to high temperature. Imaizumi et al. (1983) reported that amorphous indomethacin held at 30 °C and exposed to high RHs, exhibited greatly enhanced crystallization. Interestingly, whereas exposure at 69 and 79% RH produced only γ-crystal forms, exposure to 89% RH produced a mixture of α- and γ-forms and 100% RH produced only the α-form.

In our study, the RH was kept constant (RH = 45%), and so according to the information mentioned above only γ-form of indomethacin will produce. As we have used elevated temperature above 30 °C, thus at higher temperature α-form was produced. SEM shows that the shape of the indomethacin crystals is altered when matrices are heated (Fig. 5) indicating recrystallization of indomethacin at high temperature.

Pharmaceutical literature on indomethacin has shown that crystallization temperature and humidity alter the physicochemical properties of indomethacin crystals such as crystallinity, dissolution, T_g, etc. (Androins et al., 1997; Androins and Zografi, 1998; Khan et al., 2000; Lovrecich et al., 1996). These alterations in properties of indomethacin in turn would cause changes in dissolution and release of the drug from matrices. It has been shown that crystallization from the amorphous state can occur in the temperature range 20–45 °C below the T_g of 50 °C (Imaizumi et al., 1980; Fukuoka et al., 1986; Otsuka and Kaneniwa, 1988). These studies have reported that indomethacin above 20 °C, i.e. at temperatures starting from 30 °C below its T_g exhibits sufficient molecular mobility to induce crystallization. The uptake of water decreases the T_g of amorphous solid by acting as a plasticizer (Androins and Zografi, 1998). Because of this plasticization, there was a significant increase in the free volume, which

in turn increases the molecular mobility of segments of molecules in the solid system. The enhanced mobility is manifested in enhanced degree of crystallinity and lower dissolution rate.

Yoshioka et al. (1994) reported that dry ground amorphous indomethacin was recrystallized below T_g on rather short time scales. Changes in molecular mobility are believed to be responsible in part for the alteration of dissolution rate of indomethacin.

4. Conclusion

Heat-treating can prolong the release rate of indomethacin from Eudragit RS and RL matrices, provided that the heat-treating is above the glass transition temperature of the polymers. The decreased porosity of the matrix may be responsible for this observation. The procedure can provide a cost-benefit method to achieve a sustained release of indomethacin from the Eudragit matrices.

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