Thermal Treating of Acrylic Matrices as a Tool for Controlling Drug Release

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The purpose of the present study was to investigate the effect of thermal-treating on the release of ibuprofen from the granules prepared using aqueous dispersions of Eudragit. To accomplish this goal, different formulations were prepared using wet granulation method containing two different types of Eudragit aqueous dispersions, RS30D, RL30D and Avicel as filler. Tablets were prepared using direct compression method. The prepared tablets were thermally treated at 50 and 70 °C for 24 h. The drug release from tablets was assessed before and after thermal-treating. The results of release study showed that, thermally-treating the tablets at the temperatures higher than glass transition temperature (Tg) of the polymer can decrease the drug release from matrices. For mechanistic evaluation of the effect of thermal-treating, powder X-ray diffraction (XPD), scanning electron microscopy (SEM), differential scanning calorimeter (DSC), Fourier transform infrared (FT-IR) and helium pycnometer have been employed. The SEM graphs showed that the tablets have smoother surface with less porosity after thermal-treating. FT-IR spectra showed no change in the spectrum of thermally-treated tablet compared to control. In DSC graphs, no crystalline change was seen in the heat-treated samples of ibuprofen tablets, but decreased and widened peak size were related to the probable formation of solid solution of ibuprofen in Eudragit matrix. The results of helium pycnometer showed a significant decrease in the total porosity of some heat-treated samples. This study revealed the importance of thermal treating on the drug release from sustained release tablets containing Eudragit polymer.

Key words thermal-treating; ibuprofen; sustained release; Eudragit; dissolution; glass transition temperature

Thermal treatment of polymers refers to a process by which a polymer is heated to a certain temperature, for a specified time period.[1)] Annealing of amorphous polymers usually requires the heating of the polymer to temperature above the glass transition temperature (Tg), where the polymer orientation is the most rapid. After annealing at these high temperatures, the polymer sample is cooled gradually to avoid introduction of unwanted stresses or defects.[2)] This type of treatment often influences the mechanical properties of polymers and is associated with the time-dependent nature of the glass transition.[3)] In general, annealing increases the density within the polymer and decreases the rate of creep or stress relaxation at temperatures below the Tg.[4—6)] These changes tend to improve the dimensional stability of the polymer, as well as remove any residual stresses, strains, or defects that may have occurred during processing. Annealing generally produces polymers which display higher moduli and tend to be more brittle than unannealed polymers.[2,3)]

In reference to the annealing processes just described, the thermal treatment of polymeric pharmaceutical dosage forms has been studied in only a few cases.[7—9)] Omelczuk and McGinity studied the effect of thermal treatment on the physical-mechanical and dissolution properties of tablets containing polylactic acid (PLA).[7)] They showed that thermally treating the tablets to temperatures above the Tg of the PLA significantly retarded the drug release compared to tablets which were not thermally treated. However, thermal treatment had no significant effect on the molecular weight and the glass transition temperature of PLA alone and in combination with other components of the tablet formulation.

Polymethacrylates are widely used in pharmaceutical delivery systems for sustained drug delivery,[10)] hot melt extrusion,[11,12)] microencapsulation,[13)] nanoparticle,[14,15)] antiretroviral drug delivery,[15,16)] floating microspheres,[17)] colon delivery[18,19)] and transdermal drug delivery.[20)]

In our previous studies we showed the effect of thermal treating on the release of indomethacin[8)] and diclofenac sodium[9)] from acrylic matrix tablets and mechanistically studied the effect of heat-treating on physicochemical structure of tablet.[21)] These studies were performed on directly compressed tablets of indomethacin and diclofenac sodium which were prepared using Eudragit RS and RL powders. The purpose of this study was to investigate the effects of heat treating on drug release and characteristics of tablets prepared from granules which made using aqueous dispersions of Eudragit RL and RS. Also we wanted to study the effect of a non-traditional plasticizer, ibuprofen, on heat treating phenomenon.

Ibuprofen is a non-steroidal anti-inflammatory drug with a biological half-life of 2 h. It has low melting point (78—80 °C) which can make eutectic mixtures with several materials. There are many reports on the properties of ibuprofen and its conventional dosage forms.[22)] Also several studies are done on the controlled release products of this drug.[23—26)] Additionally it has been reported that ibuprofen can be used as a meltable binder of itself during the granulation.[27)] The previous studies showed the plasticization effect of ibuprofen on hot melt extrudates containing Eudragit RS polymer. However, no study has been performed on the plasticizing ability of ibuprofen on the granules and its effect on the ther-

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mal-treating process.

Experimental

Ibuprofen was supplied by Chasun Chemicals, Japan. Microcrystalline cellulose (Avicel PH 101) was purchased from Merck, Germany. All meth-/acrylate copolymers (Eudragit RL 30D, RS 30D) were gifts from Röhm, Germany.

Preparation of Heat-Treating Tablets Granules were prepared using wet granulation method. The composition of each formulation has been showed in Table 1. Avicel and ibuprofen were first mixed and then aqueous dispersions of Eudragit added, the prepared wet mass was forced through 12 mesh size sieve and tray dried. The dried mass was then sieved using 16 mesh sieve and kept in tightly closed container for further studies. The prepared granules were directly compressed using a hydraulic press (Riken, Japan) equipped with 10 mm diameter flat faced punch and die set, under the pressure of 70 kg/cm^2 to have 100 mg ibuprofen in each tablet. For heat-treating, the prepared tablets were kept in an oven (Memmert, Germany) at 50 and 70 °C for 24 h.

Drug Release Studies For the evaluation of drug release, USP dissolution testing apparatus II (Erweka, DT6, Germany) was used. The dissolution medium (1000 ml), phosphate buffer solution pH 7.4, was maintained at 37±0.5 °C and stirred at 50 rpm. After inserting the tablets, 3 ml samples were withdrawn at predetermined time points and replaced with fresh dissolution medium. Sample concentration was determined by UV spectrophotometer (Shimadzu 160, Shimadzu Co., Kyoto, Japan) at 222 nm. Dissolution tests were performed in triplicate and the mean of three observations was reported.

Measurement of Drug Content For the measurement of drug content, each tablet was crushed and dissolved under constant stirring for 24 h in 1000 ml of dissolution medium, phosphate buffer solution pH 7.4. The drug concentration was measured using UV spectrophotometer as described before. The measurement was performed on tablets before and after heat treating at 50 °C and 70 °C. The test was performed on 6 tablets from each group and the results were analyzed using ANOVA test.

Scanning Electron Microscopy (SEM) Tablets were mounted on special aluminum pans, sputter-coated with a thin layer of gold palladium alloy. The micrographs from the surface of tablets before and after heat-treating were taken using a scanning electron microscope (Leo 440i, Leo Electron Microscopy Ltd., Cambridge, U.K.).

Differential Scanning Calorimeter (DSC) The thermal properties of tablets before and after heat-treating were determined by differential scanning calorimeter (DSC 60, Shimadzu, Japan). Samples were accurately weighed into aluminum pans that were then sealed. Each sample was analyzed at a heating rate of 10 °C/min, over a temperature range of 20 to 250 °C. The glass transition of Eudragit samples were determined as the midpoint of the transition using Shimadzu TA 60 version 1.51 software.

Powder X-Ray Diffraction (XRD) Powder X-ray diffractometer (Model D500, Siemens, Germany) was used to characterize the crystalline properties of the tablets before and after heat-treating. The samples were exposed to Cu$K\alpha$ radiation under 35 kV and 20 mA over the 2θ range from 2 to 60 degrees.

Fourier Transform-Infrared (FT-IR) Fourier transform-infrared spectra were obtained on a Bomem FT-IR system (Bomem 2000, Bomem, Quebec, Canada) using KBr disc method. Samples were mixed with KBr powder and compressed to 10 mm discs by hydraulic press at pressure of 10 tons for 30 s. For aqueous dispersions of Eudragit samples, 200 μl of sample was added on KBr disc and the spectra were obtained. The scanning range was 450—4000 cm^{-1} and the resolution was 2 cm^{-1}.

Porosity Analysis of Tablets The porosity of tablets before and after heat-treating was calculated using true volume and bulk volume values of the tablets. The true volume of the tablets was analyzed using helium pycnometer (Ultra pycnometer 1000, Quantachrome Instruments, U.S.A.). Bulk volume of the tablet was calculated by measuring diameter and thickness of the tablet using a digital micrometer (Mitutoyo, Japan). The total porosity of the tablet was obtained using Eq. 1:

$$\varepsilon_{\text{total}} = 1 - \frac{V_p}{V_b} \quad (1)$$

Where V_p and V_b are true volume and bulk volume of the tablets, respectively.

Table 1. Composition of Each Formulation for Preparing Ibuprofen Granule

Code	Ibuprofen (g)	Eudragit RS 30D (ml)	Eudragit RL 30D (ml)	Avicel (g)
RS	2.5	10	—	7.5
RL	2.5	—	10	7.5

Results and Discussion

In this research ibuprofen was selected as model drug with low melting point (79 °C). The granules were prepared by wet granulation method and tablets were prepared by direct compression of granules. The prepared tablets were treated at 50 and 70 °C and drug release studies were carried out using tablets before and after heat-treating.

Release from Heat-Treating Tablets The results of drug release studies were shown in Fig 1. It can be seen that heat-treating at these temperatures decreased drug release from the tablets. Heat-treating of Eudragit RL tablets at 70 °C had more pronounced effect compared to heat-treating at 50 °C. In Eudragit RS containing tablets no significant difference was seen between drug release profile from tablets treated at 50 and 70 °C. This effect can be explained by considering the glass transition temperature (Tg) of Eudragit RS polymer. Tg value for Eudragit RS is equal to 50 °C, therefore heat-treating at 50 °C can lead to rearrangement of polymer network through the matrix of tablet and forming a matrix with less porosity which can make a barrier against drug release out of the tablet.[21] Heat-treating of Eudragit RL tablets at both temperatures showed decreased drug release. 70 °C is well above the Tg of Eudragit RL (55 °C), therefore it was expected to have decreased drug release after heat-treating at 70 °C. But in our previous works[8,9] which we used indomethacin and sodium diclofenac as model drugs, heat-

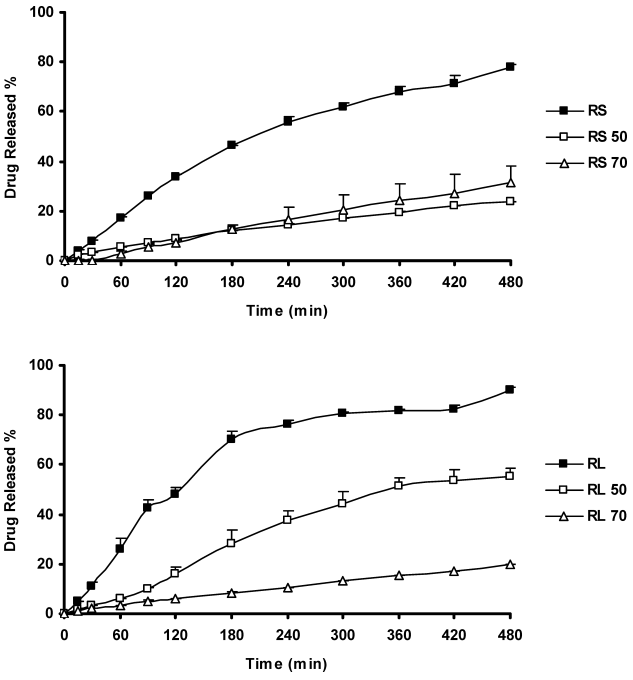

Fig. 1. Profile of Ibuprofen Release from Eudragit RS and RL Containing Tablets before and after Heat-Treating at 50 (RS 50 and RL 50) and 70 °C (RS 70 and RL 70) for 24 h

treating of Eudragit RL containing tablets at 50 °C, did not change the drug release compared to non-treated tablets. It has been shown that ibuprofen can have plasticizing effect on Eudragit polymers.[2,3] Wu and McGinity showed that by increasing the concentration of ibuprofen in Eudragit films, the glass transition temperature decreases.[3,20] They showed that "the addition if ibuprofen enhances the plasticization of the Eudragit RS 30 D polymer and results in a highly amorphous polymer structure due to the disordered placement of the polymer chains in the polymeric matrix." They related the plasticization effect of ibuprofen to the disrupted interactions between the chains of Eudragit RS through hydrogen-bond formation between the carboxylic acid group of ibuprofen and ammonium and ester groups of Eudragit RS.

Also Kidokoro *et al.* showed that the Tg for Eudragit RS in the absence of ibuprofen is approximately 55 °C which this amount decreases by increasing levels of ibuprofen in Eudragit granules.[2] They reported that the minimum film formation temperature (MFT) of Eudragit RS containing 30% ibuprofen was 40—50 °C.

Generally, to achieve a good miscibility between two components, the solubility parameters should be equal or have difference not more than ± 6.3 $(J/cm^3)^{1/2}$.[29] The solubility parameters for ibuprofen and Eudragit RS polymer are 19.0 and 19.2 $(J/cm^3)^{1/2}$, respectively.[20,30] The plasticization of Eudragit by ibuprofen is related to their miscibility at 50 °C.[2] Therefore, heat-treating of Eudragit RL containing tablets at 50 °C showed decreased drug release, which can be related to the plasticizing effect of ibuprofen on Eudragit polymer.

Drug content study before and after heat treating at 50 °C and 70 °C showed no significant change in drug content after heat-treating in different temperatures ($p>0.05$). This fact demonstrates the stability of ibuprofen during the thermal treatment as it has been shown in hot melt extrudes of ibuprofen and Eudragit polymers.

Release Mechanism Following Heat-Treatment For comparing the drug release profiles DE_8 values were used. Dissolution efficiency (DE) is calculated according to Eq. 2:

$$DE_t = \frac{\int_0^1 f \cdot dt}{f_{100}t} \tag{2}$$

Where f is percent drug released at time t (8 h).

The results of DE_8 values have been shown in Table 2. It can be seen from this table that DE_8 values for RS tablets have been decreased after heat-treating at both temperatures. The decrease in DE_8 values for Eudragit RL tablets thermally treated at 70 °C is more pronounced compared to tablets treated at 50 °C.

To elucidate the mechanism of drug release from tablets before and after heat-treating, drug release data were fit to the following mathematical models:

1. Zero Order Kinetics:

$$Q_t = Q_0 + K_0 t \tag{3}$$

Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0=0$) and K_0 is the zero order release constant.

2. First Order Kinetics:

$$Q_t = Q_0 e^{-k_1 t} \tag{4}$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant.

3. Higuchi Model:

$$f_t = Q = \sqrt{D(2C - C_s)C_s t} \tag{5}$$

Where Q is the amount of drug released in time t per unit area, C is the drug initial concentration, C_s is the drug solubility in the matrix media and D is the diffusivity of the drug molecules (diffusion constant) in the matrix substance. Higuchi equation can be simplified as follows:

$$f_t = K_H t^{1/2} \tag{6}$$

Where K_H is the Higuchi dissolution constant

4. Korsmeyer–Peppas Model:

$$f_t = at^n \tag{7}$$

where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and the function of t is M_t/M_∞ (fractional release of drug).

The results have been showed in Table 2. It can be seen that, in most cases RSQ (square of the Pearson product moment correlation) values are higher for Peppas model. Therefore it can be concluded that diffusion controlled release is prominent mechanism of release either in heat-treated and control tablets, in other words heat-treating did not change the mechanism of drug release from tablets.

Table 2. The Results of Fitting Drug Release Data before (RS and RL) and after Heat-Treating at 50 °C (RS 50 and RL 50) and 70 °C (RS 70 and RL 70) for 24 h to Different Kinetic Models and DE_8 Values

		RS	RS 50	RS 70	RL	RL 50	RL 70
Zero order	K_0	0.0016	0.0005	0.0007	0.0017	0.0013	0.0004
	RSQ	0.9438	0.9893	0.9960	0.8365	0.9632	0.9975
First order	K_1	−0.0031	−0.0005	−0.0008	−0.0046	−0.0019	−0.0004
	RSQ	0.9952	0.9947	0.9987	0.9531	0.9808	0.9987
Peppas	n	0.9636	0.6824	1.6866	1.1523	1.0664	0.7915
	a	0.0030	0.0035	0.0000	0.0022	0.0009	0.0014
	RSQ	0.9879	0.9952	0.9400	0.9925	0.9853	0.9960
Higuchi	K_H	0.0428	0.0122	0.0180	0.0485	0.0342	0.0102
	RSQ	0.9939	0.9910	0.9774	0.9418	0.9725	0.9780
DE_8 values		49.10	13.96	15.80	63.98	33.01	10.55

Morphological Properties of Tablets To study the effect of heat-treating on the morphological properties of tablets, the tablet surfaces were evaluated before and after heat-treating. The pictures were shown in Figs. 2 and 3. It can be seen from these pictures that the tablets show smoother surfaces with less fractures on surface after heat-treating. These findings are consistent with the findings of other researchers.[1—3,7] It seems that during heat-treating at temperatures higher than the Tg of the incorporated polymer,

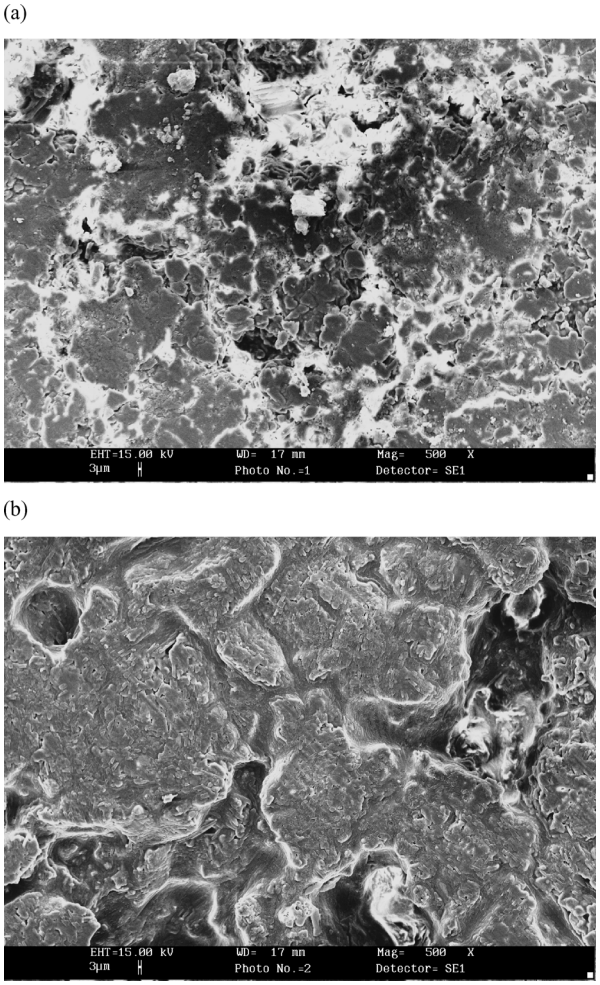

Fig. 2. Surface of Eudragit RS Tablets (a) before Heat-Treating and (b) after Heat-Treating at 70 °C for 24 h (Magnification 500)

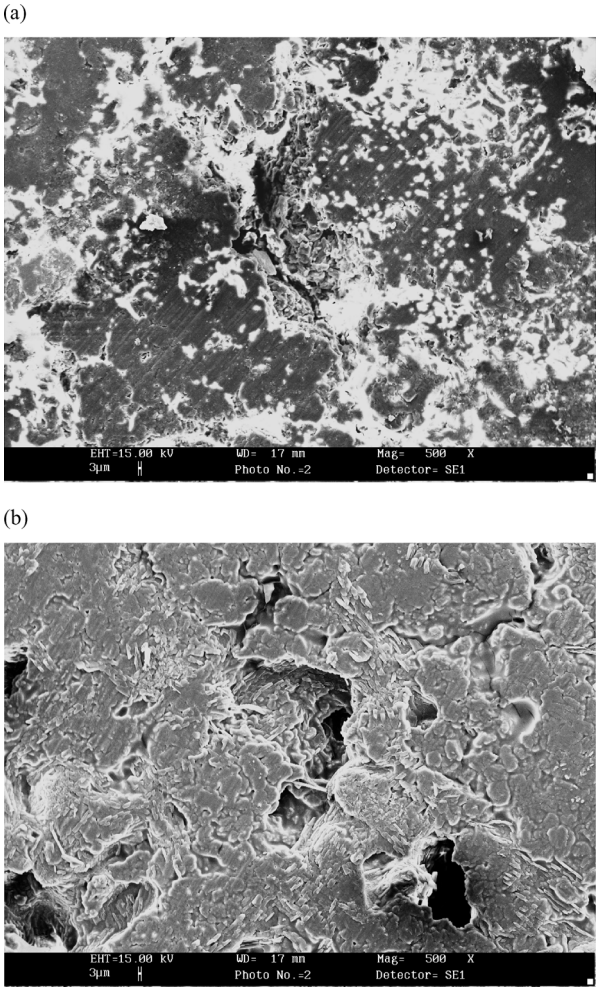

Fig. 3. Surface of Eudragit RL Tablets (a) before Heat-Treating and (b) after Heat-Treating at 70 °C for 24 h (Magnification 500)

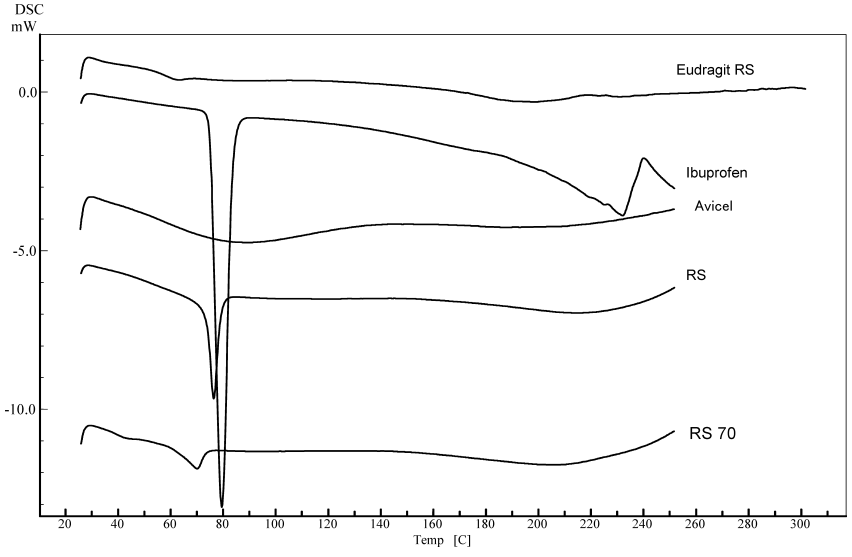

Fig. 4. DSC Spectra of Eudragit RS, Ibuprofen, Avicel and Eudragit RS Tablets before (RS) and after Heat-Treating at 70 °C for 24 h (RS 70)

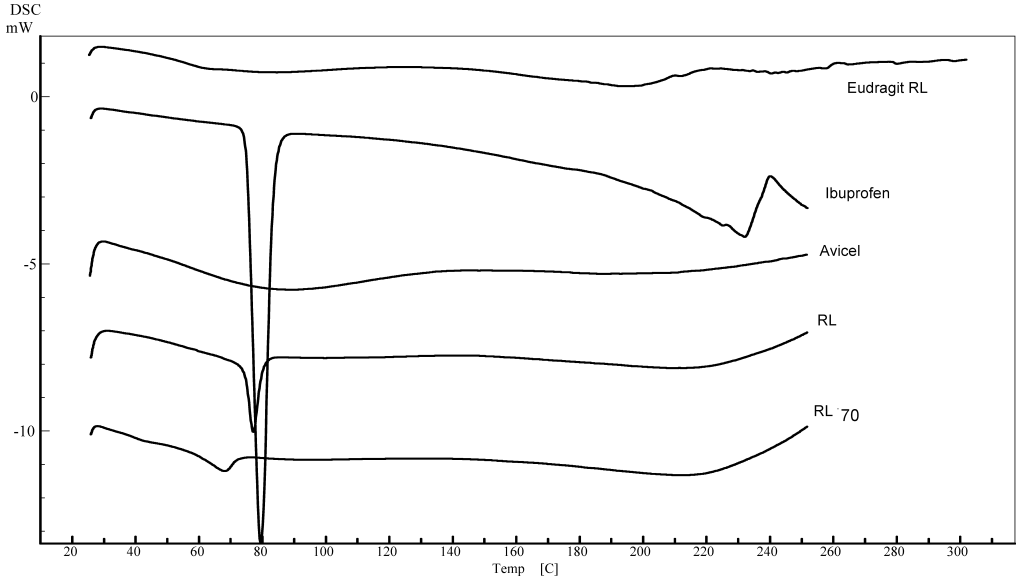

Fig. 5. DSC Spectra of Eudragit RL, Ibuprofen, Avicel and Eudragit RL Tablets before (RL) and after Heat-Treating at 70 °C for 24 h (RL 70)

the polymer softens and moves through the interstitial spaces inside the tablet to fill these spaces and render a tablet with less porosity and smoother surfaces.

To demonstrate the occurrence of such phenomenon the total porosity of the tablets before and after heat-treating was analyzed. The results were shown in Table 3. It can be seen that after heat-treating the total porosity in tablets has been decreased. The decrease in porosity after heat-treating was statistically significant (p values, 0.001 and 0.002 for RS and RL tablets, respectively). Therefore the findings of SEM were consistent with the total porosity analysis of the tablets.

Physical and Chemical Properties of Tables For evaluating the effects of heat-treating on the solid state of the drug in tablets, DSC and XRD methods were employed. Solid state properties of a drug such as polymorphism, pseudo-polymorphism and crystalline state, are determining properties in a formulation, therefore these properties have been studied after heat-treating. DSC and XRD spectra of different formulations have been shown in Figs. 4, 5 and 6, 7 respectively. DSC spectra of Eudragits show amorphous structure for these polymers. DSC spectrum for pure ibuprofen exhibited a single melting endothermic peak at 79 °C (enthalpy of melting 111.4 J g^{-1}). The thermal profile corresponding to the control tablet showed combined thermal characteristics. In the case of the heat-treated sample, melting peak of ibuprofen was observed too. As seen in Figs. 4 and 5, a shift of the endothermic peak from 79 to 75 °C was observed. In addition, a concomitant reduction in peak size and enthalpy per unit mass of ibuprofen was evident. These results could be attributed to the miscibility of ibuprofen in Eudragit and formation of solid solution. The observed peak in the heat treated samples can be related to the ibuprofen content of the granules which exceeded the drug solubility in polymer.[2)]

In XRD spectra of both heat-treated and control tablets, ibuprofen exists in its crystalline state. XRD spectrum for ibuprofen shows peaks at 5.9, 12.1, 13.9, 16.5, 17.5, 18.5, 18.9, 19.3, 20.1, 22.2, 22.8, 25.1, 27.2, 28.1, 28.6 and 29.8 2θ. These distinguished peaks can be seen in both control and heat-treated tablets containing different Eudragits; how-

Table 3. Total Porosity of Tablets before and after Heat-Treating at 70 °C for 24 h

Formulation	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Average
Before heat-treating					
RS	13.3677	14.4169	25.8570	22.5381	19.0449
RL	17.9495	19.6114	21.7537	19.9044	19.8047
After heat-treating					
RS	5.9196	8.7572	17.9473	14.6645	11.8222
RL	10.2862	8.7325	8.6680	8.3884	9.0188

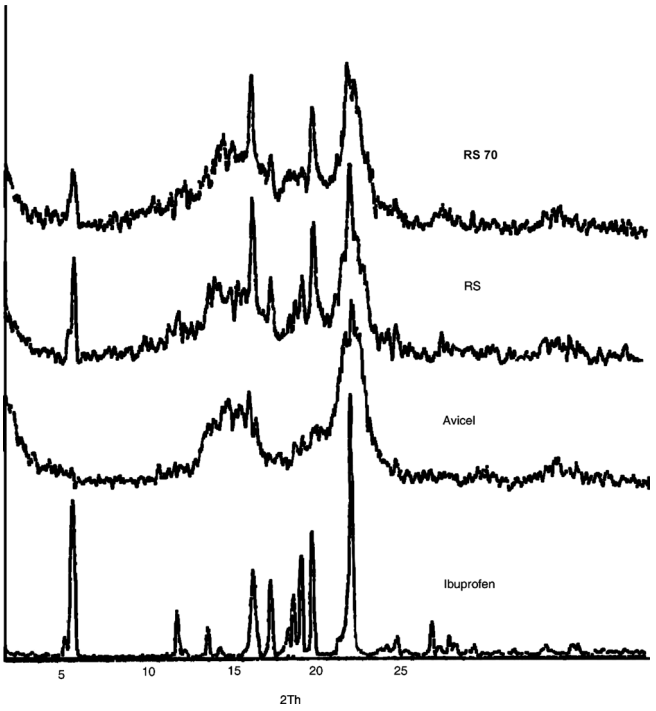

Fig. 6. XRD Spectra of Ibuprofen, Avicel and Eudragit RS Tablets before (RS) and after Heat-Treating at 70 °C for 24 h (RS 70)

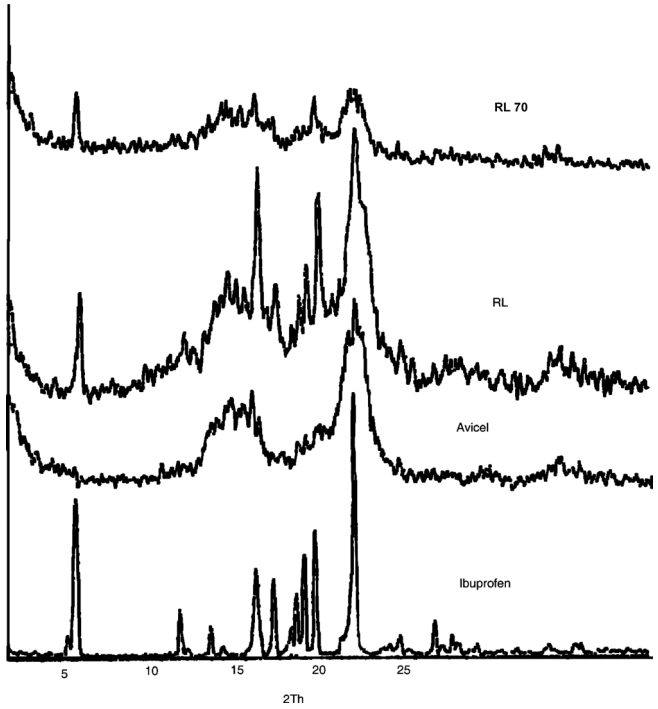

Fig. 7. XRD Spectra of Ibuprofen, Avicel and Eudragit RL Tablets before (RL) and after Heat-Treating at 70 °C for 24 h (RL 70)

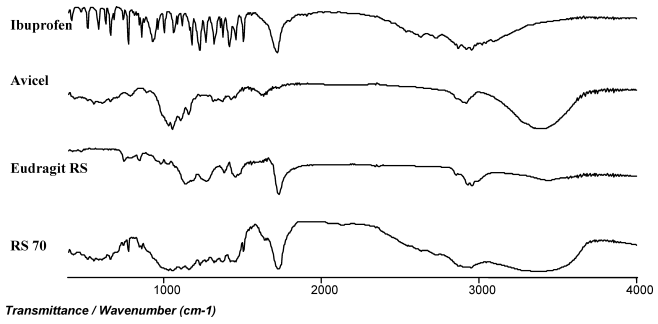

Fig. 8. FT-IR Spectra of Ibuprofen, Avicel and Eudragit RS Tablets before (RS) and after Heat-Treating at 70 °C for 24 h (RS 70)

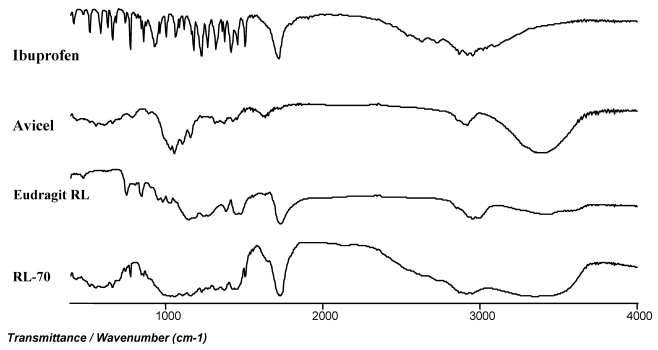

Fig. 9. FT-IR Spectra of Ibuprofen, Avicel and Eudragit RL Tablets before (RL) and after Heat-Treating at 70 °C for 24 h (RL 70).

ever, a reduction in the peak intensities was observed in XRD patterns of heat treated samples, indicating reduced crystallinity of the drug.

To rule out any chemical interaction during heat-treating and after that, FT-IR spectroscopy was employed. FT-IR spectra of different formulations have been shown in Figs. 8 and 9. Ibuprofen shows a stretching peak of its aromatic ring at 3050—3150 cm^{-1}, bending peak of aromatic ring at 360—900 cm^{-1} and a stretching peak of carbonyl group at 1721 cm^{-1}. At 1820 cm^{-1} (C–O stretching), 1465 cm^{-1} (–CH_2– bending), 1375 cm^{-1} (–CH_3– bending), 1720—1740 cm^{-1} (C=O aldehyde) and 1700—1725 cm^{-1} (carboxylic acid) important peaks of ibuprofen can be seen. These peaks can also be seen in spectra of control and heat-treated tablets of both Eudragit RS and RL. Therefore it can be concluded that no chemical interaction occurred during heat-treating, and decreased drug release after heat-treating cannot be attributed to possible drug–polymer interaction.

Conclusions

This study shows the application of thermal-treating in the sustaining of drug release from polymethacrylate matrices. Ibuprofen can play a significant role as non-traditional plasticizing agent in by decreasing the Tg of the incorporated polymer. The decrease in drug release can be related to the decrease in the porosity of the whole matrix by softening the polymer and re-arranging inside the matrix. In part the formation of solid solution and entrapment of drug molecules in the polymer chains making them non-accessible to dissolution medium can be responsible for decreased drug release. This process is a physical phenomenon and no chemical reaction or interaction happens during the thermal-treating process.

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