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Research paper

Thermal treating as a tool to produce plastic pellets based on Eudragit RS PO and RL PO aimed for tableting

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Abstract

A 3^2 full-factorial design was used for preparation of pellets using extrusion–spheronization technique. Independent variables were %ibuprofen (40, 60, 80) and %Eudragit RS PO/RL PO (0, 50, 100). In all formulations 3% w/w PVP K30 and 10% Avicel PH101 were also used. The pellets were cured in oven at 60 °C for 24 h. The evaluated responses were crushing strength or yield point, elastic modulus and mean dissolution time (MDT) of pellets. The cured pellets were also compressed at 15 kN compaction force and then observed under scanning electron microscope.

It was shown that the cured pellets containing 40% or 60% drug exhibited a plastic deformation without any fracture under mechanical tests. The curing process resulted in significant decrease in the elastic modulus of the pellets. The SEM of the compressed pellets were also confirmed the plastic behavior of these pellets. The transition of pellet behavior from brittle to plastic upon curing was due to shift of Eudragit structure from glassy to rubbery state which was supported by DSC studies. However pellets with 80% drug showed brittle properties even after curing due to presence of less amount of Eudragit in their structure. Increasing the ratio of Eudragit RS in the pellets decreased the yield point and elastic modulus of cured pellets containing 40% or 60% drug, indicating more plastic behavior of these pellets. This was attributed to lower Tg of Eudragit RS than Eudragit RL.

The curing process also retarded drug release from pellets and increased MDT. Increasing the ratio of Eudragit RS in the pellets increased MDT in cured pellets containing 40% or 60% drug but had no effect in pellets with 80% drug.

Overall the results of this study revealed that thermal treating is a proper tool to produce plastic ibuprofen pellets based on Eudragit RS PO and Eudragit RL PO.

Keywords: Pellet; Extrusion–spheronization; Ibuprofen; Eudragit RS PO; Eudragit RL PO; Curing; Mechanical properties

1. Introduction

In our previous work we studied the application of Eudragit RS PO and RL PO in production of ibuprofen pellets using extrusion–spheronization technique and characterized the physicomechanical and release behavior of these pellets [1]. It was shown that both Eudragit RS PO and RL PO could be successfully applied in production of spherical pellets with good mechanical strength but brittle behavior and drug release was not considerably retarded. However in the case of need for Eudragit retard coating to slow down drug release, these pellets could be beneficial due to resemblance of core identity to coat identity and therefore one of the main sources for developing stresses in the film coating during storage which is difference between thermal expansion of core and coat will be reduced. Furthermore compaction of coated multiparticulates into tablets is becoming more popular. Pellets

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intended to be coated and compressed into tablets have to be strong, not brittle and have a low elastic resilience; they should deform under applied load without fracture. Schwartz and co-workers [2] stated that the pellet core should exhibit some degree of plasticity so that it can accommodate a possible change in shape when the coated pellets are subjected to tableting. Attempts in tableting of sustained release pellets have focused on preparation of hard pellets with plastic coat which were resistant to compression forces and tableting has been accomplished using high percentage of cushioning excipients [3–5]. This limits the amount of pellet that can be compressed as tablets and results in large size tablets.

Some studies have shown that curing could substantially affect the polymer structure and therefore alter the release and mechanical properties of matrix system. Curing process usually requires heating of polymers to temperatures above the glass transition temperature (Tg) [6]. It has been shown that curing of polyglycolic acid tablets [7] and polylactic acid microcapsules [8,9] caused changes of their polymer phase structure and release properties. Billa et al. [10] also reported that curing of diclofenac sodium granules containing Eudragit could increase the tensile strength of the tablets. However there is no report on the effect of curing on the mechanical properties and release behavior of Eudragit based matrix pellets prepared by extrusion and spheronization technology.

In the present study the physicomechanical and release properties of thermal treated (cured) pellets containing various percentages of ibuprofen, Eudragit RS PO and RL PO were studied and compared with those of uncured pellets in an attempt to identify those pellets able to withstand the compression process. This was necessary in order to minimize or prevent damage to the integrity of both pellet core and coat as a consequence of compression into tablets.

2. Materials and methods

2.1. Materials

Ibuprofen and microcrystalline cellulose (Avicel® PH101) were provided by Darupakhsh (Tehran, Iran), Eudragit® RS PO and Eudragit® RL PO were gifts from Rohm Pharma GmbH (Darmstadt, Germany), polyvinylpyrrolidone (PVP K30) was supplied by Fluka (Switzerland). All the materials were used as received.

2.2. Methods

2.2.1. Experimental design

A 3^2 full factorial design was used as the experimental design for preparation of pellets. The studied independent variables and their levels were X_1: %ibuprofen (40, 60, 80) and X_2: %Eudragit RS/RL (0, 50, 100). The chosen dependent variables or responses were mean dissolution time (MDT), crushing strength (CS) and/or yield point (YP) and elastic modulus (EM) of pellets.

2.2.2. Preparation of pellets

The solid components of each formulation (Table 1) were mixed together using a kitchen mixer for 10 min. 3% PVP and 10% Avicel were used as binder and pelletization aid, respectively, in all formulations. Adequate amount of water was slowly added to the dry blend to make a wet mass with a suitable consistency. The wet mass was passed through a screw extruder (Khazar, Iran) with a 1 mm screen at 120 rpm. The extrudates were processed in a spheronizer (Khazar, Iran) fitted with a cross-hatched plate rotated at 1000 rpm for 2 min. The obtained pellets were dried at 40 °C (which is well below the Tg of Eudragit polymers) for 10 h in a conventional hot air oven. The pellets were sieved using nest of standard sieves (1180, 1000, 850 and 710 μm) shaken for 10 min on a sieve shaker (Retsch–Germany) and the pellets in the range of 850–1180 μm were collected. In this study these pellets are referred to as ''uncured pellets''.

2.2.3. Curing of pellets

The pellets were spread on a tray and placed in the oven pre-equilibrated to 60 °C for 24 h and then were allowed to cool at the ambient temperature for at least overnight or longer. Then they were kept in tightly closed containers. In this study these pellets are referred to as ''cured pellets''.

2.2.4. Mechanical tests

The crushing strength (the load needed to break the pellets) or yield point (the load needed to begin plastic deformation) of 15 pellets in the size range of 0.85–1.00 mm was determined using Material Testing Machine (Hounsfield, England). As mechanical strength of pellets is proportional to their size, for a better comparison between different formulations and in order to minimize the size dependent variations a narrower size range of pellets (0.85–1.00 mm) were fractioned. The speed of the upper mobile platen fitted with a 1 kN load cell was set at 1 mm/min. Elastic modulus and force–displacement graphs were obtained by a computer system attached to the apparatus (QMAT, Hounsfield, England).

2.2.5. Dissolution studies

The dissolution tests were carried out on accurately weighed samples ($n = 6$) containing 300 mg of ibuprofen in automated dissolution testing equipment (Pharma test, Germany) using USP apparatus I, at 100 rpm, in medium of phosphate buffer solution of pH 7.2, at 37 °C. The samples were taken from the vessels by a peristaltic pump (Alitea, Sweden), and assayed at 265 nm by a multi-cell transport spectrophotometer (Shimadzu, Japan). Ibuprofen has two distinct absorbance peaks in the UV range; a high peak at 221 nm and the shorter one at 265 nm. As dilution of samples during automated dissolution test was impossible, the shorter peak at 265 nm was chosen for determination of ibuprofen based on Costa et al. [11].

Model independent approach was used to compare the dissolution data. For this purpose mean dissolution time

Table 1
Composition of formulations and results of dissolution tests (MDT) and mechanical tests (crushing strength or yield point and elastic modulus) of uncured and cured pellets

Test run	Ibuprofen (%)	Eudragit ratio %RL:%RS	PVP (%)	Avicel (%)	MDT (min)		Crushing strength (N)		Yield point (N)[a]	Elastic modulus (MPa)	
					Uncured[b]	Cured	Uncured[b]	Cured	Cured	Uncured[b]	Cured
1	40	47:0	3	10	45.40 ± 3.13	121.57 ± 0.27	5.55 ± 0.27	–	4.39 ± 0.19	123.72 ± 6.42	70.84 ± 5.85
2	40	23.5:23.5	3	10	53.73 ± 1.47	140.93 ± 4.97	5.16 ± 0.16	–	4.70 ± 0.16	117.53 ± 7.05	63.65 ± 4.84
3	40	0:47	3	10	43.42 ± 0.52	153.84 ± 2.72	4.09 ± 0.15	–	3.72 ± 0.15	133.44 ± 6.27	45.55 ± 5.23
4	60	27:0	3	10	41.09 ± 1.74	87.17 ± 3.22	3.10 ± 0.13	–	5.07 ± 0.16	87.20 ± 7.17	76.95 ± 6.26
5	60	13.5:13.5	3	10	33.83 ± 3.43	93.72 ± 1.91	3.12 ± 0.15	–	4.55 ± 0.15	86.77 ± 6.11	62.62 ± 6.41
6	60	0:27	3	10	34.86 ± 1.77	101.91 ± 3.18	2.00 ± 0.13	–	2.47 ± 0.12	71.56 ± 5.05	60.11 ± 5.05
7	80	7:0	3	10	63.94 ± 4.05	66.82 ± 4.63	2.30 ± 0.13	2.03 ± 0.09	–	80.12 ± 4.65	76.84 ± 6.29
8	80	3.5:3.5	3	10	63.71 ± 2.82	66.03 ± 3.28	2.08 ± 0.12	2.23 ± 0.10	–	65.02 ± 4.78	62.28 ± 6.17
9	80	0:7	3	10	40.54 ± 2.80	61.61 ± 3.47	2.09 ± 0.10	2.09 ± 0.10	–	84.68 ± 6.36	69.06 ± 6.25

[a] Yield points were not shown for uncured pellets due to their brittle behavior.
[b] Data for uncured pellets were taken from Ref. [1].

(MDT) was calculated for each formulation by the following equation [11]:

$$\mathrm{MDT} = \sum t_i^- \cdot \Delta M_i / \sum \Delta M_i \quad (1)$$

$$t_i = (t_i + t_{i+1})/2 \quad (2)$$

$$\Delta M_i = (M_{i+1} - M_i) \quad (3)$$

where t_i^- is the midpoint of the time period during which the fraction ΔM_i of the drug has been released from the dosage form. A high MDT value for a drug delivery system means that it has a slow in vitro drug release.

2.2.6. Statistical analysis of data

The effects of independent variables on each experimental response Y were modeled using a second order polynomial equation:

$$Y = C + b_1X_1 + b_2X_2 + b_3X_1^2 + b_4X_2^2 + b_5X_1X_2. \quad (4)$$

The models were simplified with a backward, stepwise linear regression technique. Only significant term ($p < 0.05$) was chosen for final model. The modeling was performed using SPSS (version 10.0) and related surface plots obtained by Statgraphics (version 5.1 plus).

2.2.7. Compression and deaggregation of lubricated pellets

The uncured or cured pellets were mixed with 0.5% w/w magnesium stearate as lubricant for 100 min in a tumbling mixer. This procedure was used to reduce bonding between the pellets in tablets to facilitate easy mechanical deaggregation [12]. Lubricated pellets (500 mg) was compacted in a single punch tableting machine (Korsch, Germany) equipped with a strain-gauge (ParsPaygeer, Iran) and flat-faced punches with a diameter of 1 cm at maximum compression force of 15 kN. The tablets made from cured pellets were then gently deaggregated into their comprising pellets by shaking them manually in a petri dish.

2.2.8. Scanning electron microscopy (SEM)

The surfaces of either cured and uncured pellets or their corresponding tablets were morphologically characterized using SEM. The samples were mounted on Al stub, sputter-coated with a thin layer of Pt using sputter coater (Polaron, England) under Argon atmosphere, and then examined using SEM (LEO1450VP, England).

2.2.9. Differential scanning calorimetery (DSC)

DSC analysis was performed on Eudragit RS PO or RL PO, ibuprofen and their physical mixtures before and after curing at 60 °C for 24 h using a differential scanning calorimeter (Mettler Toledo DSC 822e, Switzerland) and STARe software version 7.01 (Mettler Toledo, Switzerland). The instrument was calibrated with an indium standard. Samples (7–10 mg) were weighed and sealed into aluminum pans. The samples were cooled to 0 °C by an intra cooler (EK45-MT, Switzerland) and DSC runs were conducted over a temperature range of 0–100 °C at a rate

of 5 °C/min. All tests were run under a nitrogen atmosphere.

3. Results and discussion

Table 1 shows the results of mechanical tests (crushing strength or yield point and elastic modulus) and dissolution tests (MDT) for cured and uncured pellets (the data for uncured pellets were taken from Abbaspour et al. [1]. In the present study curing process was carried out at 60 °C for 24 h. This temperature is above the Tg of Eudragit RS and RL to facilitate the coalescence of polymer particles and well below the melting point of ibuprofen to avoid drug instability and polymorphism. The most appropriate temperature for curing of Eudragit RL and RS based matrix tablets has also been reported to be 60 °C by Azarmi et al. [13]. The least release rate for drugs was achieved after 24 h curing at 60 °C for Eudragit RL and RS based matrix tablets [13] and 4 h curing at 80 °C for ethylcellulose pellets [14] indicating maximum coalescence of polymer and curing over these periods had no further retarding effect. In our preliminary studies it was also observed that there was no further change in drug release rate from pellets upon curing over 8 h in 60 °C. The difference between duration of complete curing for matrix tablets as reported by Azarmi et al. [13] and pellets (in this study) could be due to smaller size of pellets compared with tablets which facilitate heat transfer through smaller matrices. Nevertheless in this study the pellets were kept at 60 °C for 24 h to ensure the maximum coalescence of polymer particles.

Table 2 shows the results of regression of responses (EM and MDT) against X_1 and X_2. The obtained model's elastic modulus (EM) and MDT for cured pellets are given below:

$$\mathrm{EM} = 73.641 - 0.440X_2 + 0.005X_1X_2 \quad R^2 = 0.832 \qquad (5)$$

$$\mathrm{MDT} = 237.922 - 3.640X_1 + 0.702X_2 + 0.01883X_1^2 - 0.00937X_1X_2 \quad R^2 = 0.991. \qquad (6)$$

Because the cured pellets behaved differently under the mechanical tests i.e. those containing 40% or 60% polymer did not break, it was not possible to define a model for crushing strength of these pellets. Fig. 1a and b are examples of force–displacement graphs obtained by Material testing machine for pellets with brittle and plastic behavior, respectively.

Eqs. (5) and (6) represent the quantitative effect of the formulation variables on the responses. The values of the coefficients X_1, X_2 relate to the effects of these variables on the corresponding responses. Coefficients with more than one-factor term represent the interaction terms and coefficients with higher order terms indicate the quadratic (non-linear) nature of the relationship. A positive sign indicates a synergistic effect while a negative sign represents an antagonistic effect. The resulted surface plots of Eqs. (5) and (6) are demonstrated in Figs. 5 and 8, respectively.

As it was reported in our previous work, all uncured pellets showed brittle behavior under the mechanical tests and were found to break into fragments [1]. Table 1 indicates that cured pellets containing 80% drug also showed brittle behavior similar to uncured pellets. In fact the crushing strength and elastic modulus of pellets containing 80% ibuprofen did not show significant changes after curing compared to uncured pellets. This was due to the presence of less amount of polymer in the structure of these pellets. However the cured pellets containing 40–60% ibuprofen underwent a plastic deformation without any fracture. The obtained yield points have been presented in Table 1.

The uncured pellets containing 40% and 60% ibuprofen exhibited an elastic modulus between 71 and 133 MPa [1], while after curing the elastic modulus decreased to 45–76 MPa. This indicates reduced rigidity and high tendency to plastic deformation for these pellets. To further confirm the change in compression behavior of the pellets under

Table 2
Results of the multiple linear regression analysis (based on $Y = C + b_1X_1 + b_2X_2 + b_3X_1^2 + b_4X_2^2 + b_5X_1X_2$), with backward elimination method for MDT and EM

Dependent variable (response)	Predictors (factors)	Regression coefficients	Sig.[a]	R^2
EM		73.641 [C]	0.000	
	X_2	−0.440	0.000	
	X_1X_2	0.005	0.000	0.832
MDT		237.922 [C]	0.000	
	X_1	−3.64	0.000	
	X_2	0.702	0.000	
	X_1^2	0.019	0.000	
	X_1X_2	−0.009	0.000	0.991

[a] Level of significance $p < 0.05$.

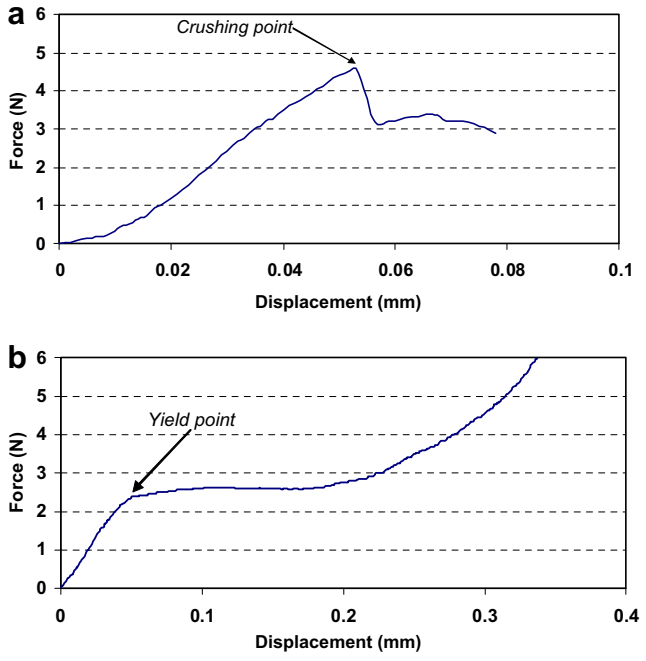

Fig. 1. Typical force–displacement diagram for a pellet with; (a) brittle nature, (b) plastic behavior.

load the pellets were mixed with magnesium stearate and compressed using tableting machine. SEM photographs of surface of the tablets prepared from uncured and cured pellets are shown in Fig. 2a and b, respectively. SEM of tablets prepared from cured pellets revealed that pellets remained as coherent individual units in tablet even after compression and the boundaries between individual pellets were readily observable. These tablets were deaggregated into their comprising pellets easily by shaking manually due to their plastic nature and presence of magnesium stearate. However the surface of tablets made from uncured pellets showed a uniform structure and no distinct boundary was observed between individual pellets indicating the breaking and subsequent fusion of broken pellets into each other. Therefore, these tablets could not be deaggregated.

Fig. 3a and b show the SEM of cured individual pellets before and after compression. The SEM of the deaggregated compressed pellets also confirmed the plastic deformation of these pellets induced by compression. As it was mentioned the plastic behavior of the cores could be beneficial when tableting of coated cores is intended.

The transition of pellet behavior (for those containing 40% or 60% drug) from brittle to plastic upon curing was due to the softening of the polymer and shift of polymer structure from a glassy to a rubbery state. These findings were supported by DSC analysis of either polymer or their physical mixtures with drug before and after curing. The thermograms for Eudragit RL and its physical mixture with ibuprofen before and after curing are depicted in Fig. 4. The onset of the peak for glass transition temperature of uncured Eudragit RL appeared at about 55 °C. This peak is also clearly visible in physical mixture of drug and polymer before curing. However no peak for this transition could be detected in thermograms of polymer or its physical mixture with drug after curing. The corresponding Eudragit RS mixtures showed a very similar behavior (data are not shown). The plasticizing effect of ibuprofen on polymer structure may also improve the plasticity of pellets after curing. It has been shown that the ibuprofen could plasticize the Eudragit RS 30D film [15]. Kidokoro et al. [16] also demonstrated that ibuprofen was an effective plasticizer for Eudragit RS PO in the thermal processes and lowered the glass transition temperature of Eudragit RS PO in matrix tablets. However the plasticizing effect of ibuprofen on Eudragit polymer could not be detected by DSC analysis performed in this study (Fig. 4).

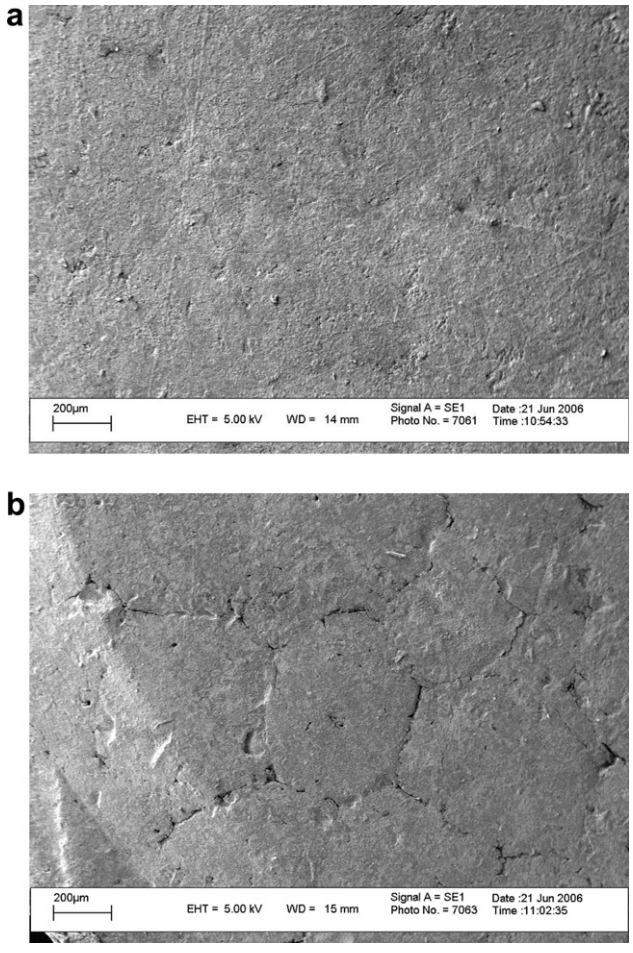

Fig. 2. Scanning electron micrograph of surface of tablet prepared from; (a) uncured pellets, (b) cured pellets.

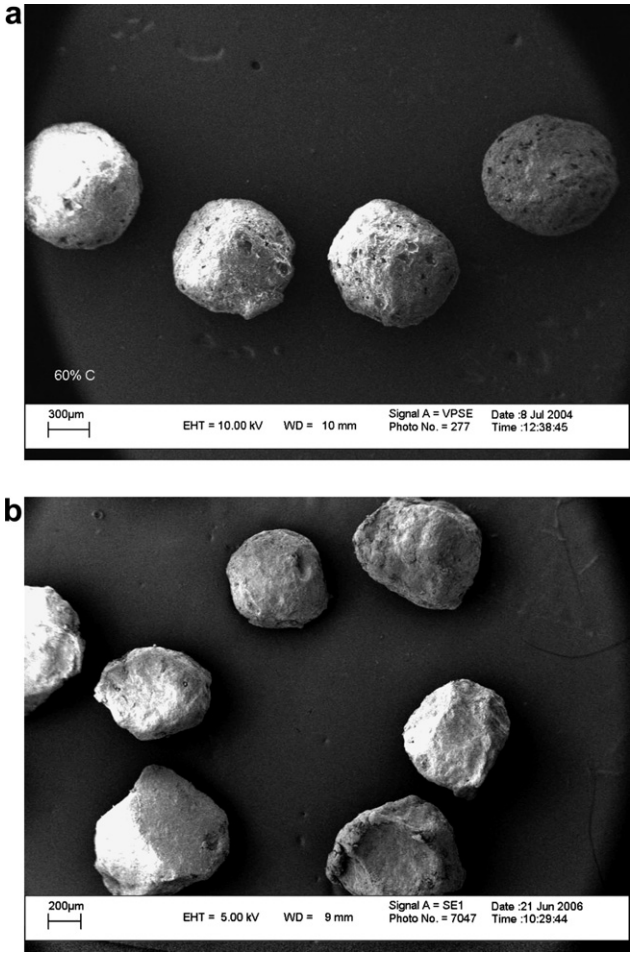

Fig. 3. Scanning electron micrograph of cured pellets; (a) before compression, (b) after compression.

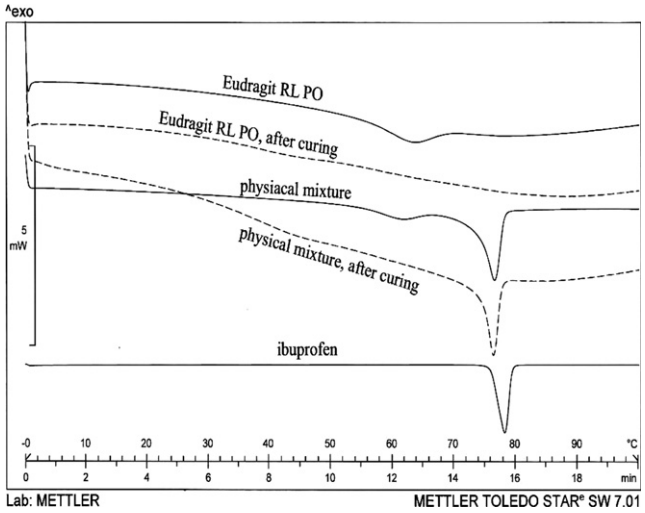

Fig. 4. DSC graphs of Eudragit RL PO and ibuprofen and their physical mixture, before and after curing.

Our findings show that the cured pellets containing Eudragit RS have lower yield points compared to Eudragit RL (Table 1). Also Fig. 5 shows that increasing the ratio of Eudragit RS decreased elastic modulus of cured pellets. These findings could be attributed to the lower Tg of Eudragit RS than Eudragit RL [17].

Dissolution profiles of different cured formulations and their MDT values are shown in Fig. 6 and Table 1, respectively. Comparison of the results presented in Table 1 for uncured and cured pellets shows that significant decrease in drug release could be achieved after curing of pellets containing 40% and 60% drug. However due to presence of fewer polymers in pellets with 80% drug, release behavior remained unchanged after curing. As it can be seen in Table 1 the MDT of uncured pellets was in the range of 33.83–63.94 min but after curing it increased to a range of 61.61–153.84 min. A similar retarding effect upon curing was reported for release of indomethacin [13], diclofenac [10], and ibuprofen [16] from Eudragit based matrix tablets. These effects can be attributed to the softening of the polymer due to polymer chain movement and inter-diffu-

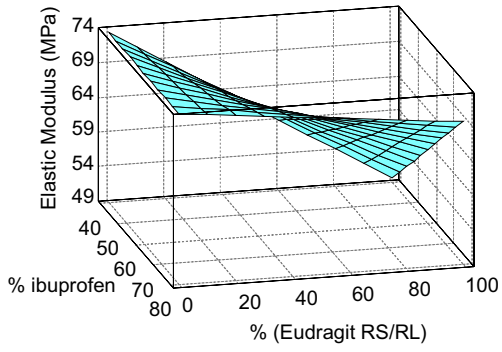

Fig. 5. Influence of % ibuprofen and % (Eudragit RS/RL) on elastic modulus of cured pellets.

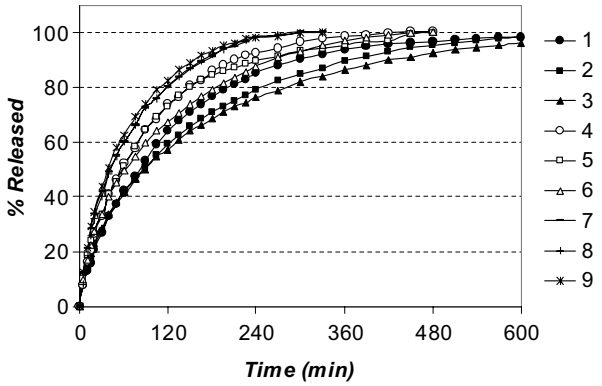

Fig. 6. Dissolution profiles of cured ibuprofen pellets (formulations 1–9).

sion of Eudragit chains in the pellet matrix following curing. This results in better coalescence of the polymer particles and formation of a fine polymer network amongst the other particles that surrounds and entangles the drug. These findings can be well described considering the glass transition temperature (Tg) values of polymers. The Tg-values for Eudragit RS and RL are 50 and 55 °C, respec-

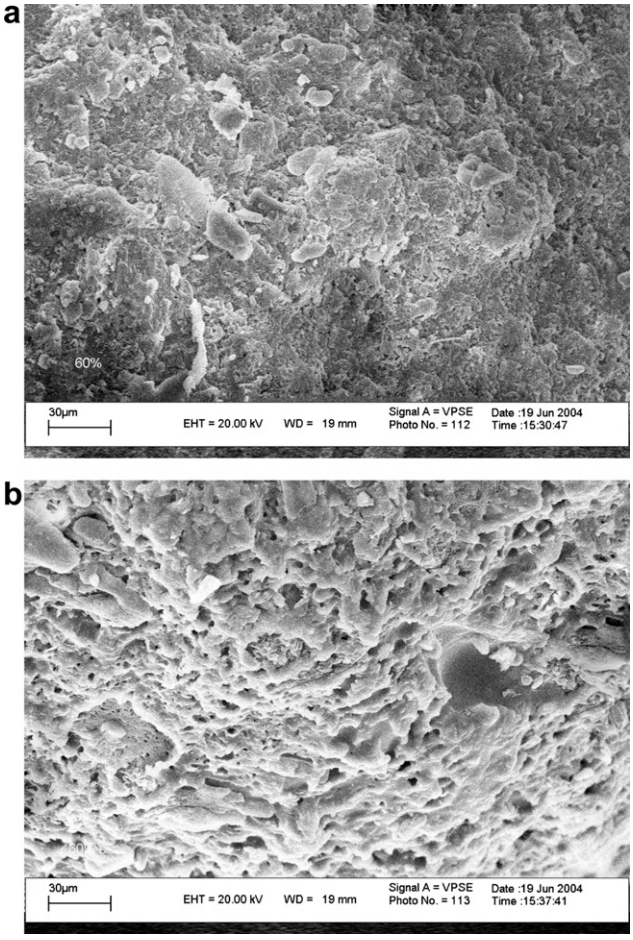

Fig. 7. Scanning electron micrograph of surface of pellet containing 60% ibuprofen (formulation 5); (a) before curing, (b) after curing.

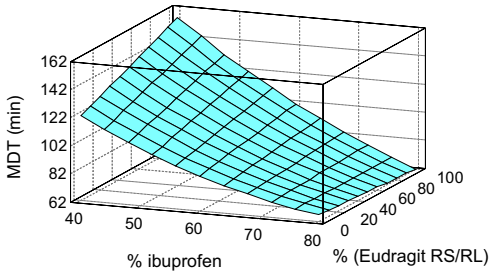

Fig. 8. Influence of % ibuprofen and % (Eudragit RS/RL) on MDT of cured pellets.

tively [17], and therefore, the coalescence of the Eudragit particles is promoted by the softness of the polymer at temperatures above the Tg of polymer. However the retardation effect observed in this study was not sufficient to provide sustained release of drug and therefore, coating layer is still necessary to slow down drug release rate.

The surface characteristics of the pellets were examined under the electron microscope. SEM of surfaces of pellets before and after curing (Fig. 7a and b) showed that curing has led to alterations in pellet structure. In uncured pellets, the individual polymer particles could be easily distinguished. However in cured pellets the matrix structure was formed of coalesced polymer particles. Sufficient curing probably softens the polymer causing it to fill in the interstices. The same findings were reported by Kojima and Nakagami [14] and Kidokoro et al. [16] in the case of ethyl cellulose pellets and Eudragit tablets, respectively. Marked reduction in porosity of Eudragit matrices upon curing was reported by Azarmi et al. [18] and accounted for considerable decrease in drug release rate. Although the retardation in drug release rate after curing was not sufficient to produce sustained release formulation this could minimize the level of coating required for controlling drug release.

Fig. 8 shows that as the percentage of ibuprofen increased in the cured pellets, the ibuprofen release rate also increased or MDT decreased. The negative sign of X_1 coefficient in Eq. 6 also demonstrates this linear antagonistic effect. It is speculated that the formation of continuous matrix structure was physically inhibited by the presence of the more ibuprofen particles. Fig. 8 shows that Eudragit type has significant effect on MDT of cured pellets containing 40–60% drug. Increasing ratio of Eudragit RS increased MDT; the positive sign of X_2 coefficient in Eq. (6) demonstrates this agonistic effect as well. This may be due to the less hydrophilic nature and water permeability of Eudragit RS compared to Eudragit RL, which can decrease the permeation of dissolution medium through the polymer matrix. Fig. 8 also shows that curing had no effect on the release properties of pellets containing 80% drug, which had lower amounts of polymer. It means that both uncured [1] and cured pellets containing 80% drug had almost the same MDT values, about 60 min (Table 1).

4. Conclusion

Curing process affected the mechanical and release properties of ibuprofen pellets based on Eudragit RS PO and RL PO. This effect was dependent on the percent of the polymer and the ratio of Eudragit RS to RL.

Overall the results of this study revealed that thermal treating is a proper tool to produce plastic ibuprofen pellets based on Eudragit RS PO and Eudragit RL PO. Compaction of lubricated uncured and cured pellets and subsequent examination of compacts confirmed the plastic behavior of Eudragit RS/RL based cured pellets.

Changes of mechanical and release properties of cores have advantages for those pellets which are intended to be coated in order to sustain the drug release and administered as a single unit dosage form because this plastic behavior can probably prevent damage to the cores or their coating under the compression. Further studies on tabletting of cured pellets using suitable fillers and pellet/filler ratio are in progress in order to obtain acceptable tablets in terms of drug release rate, disintegration time, hardness and friability.

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