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Preparation and characterization of ibuprofen pellets based on Eudragit RS PO and RL PO or their combination

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Abstract

The aim of this study was to assess the application of Eudragit RL PO and RS PO and their combination for production of ibuprofen pellets by extrusion–spheronization. The pellets were prepared based on full factorial design. Independent variables were % ibuprofen (40, 60, 80), the ratio of Eudragit RS to Eudragit RL (1:0, 1:1, 0:1) and % PVP (1, 3, 5). The evaluated responses were mean dissolution time (MDT), crushing strength and elastic modulus of pellets. Surface characteristics, sphericity and aspect ratio of pellets were also evaluated. Linear regression and response surface modeling was used for analyzing results. It was shown that the amount of water required to prepare a proper wet mass was affected by composition of formulations. The required amount of water decreased with increasing drug load and percent of PVP. It was also shown that formulations containing Eudragit RL need more water. Increasing percent of PVP slightly decreased MDT and elastic modulus but had negligible effect on crushing strength. Increasing the percent of ibuprofen up to 60% decreased MDT but beyond that increased MDT. Increasing the percent of ibuprofen also decreased elastic modulus of pellets. Eudragit RL PO compare with Eudragit RS PO resulted in pellets with high crushing strength; however, Eudragit type did not have a significant effect on elastic modulus.

Keywords: Pellets; Extrusion–spheronization; Ibuprofen; Eudragit RS PO; Eudragit RL PO

1. Introduction

Multiple-unit dosage forms have several advantages compared with single-unit dosage forms including more stable plasma profiles and little risk of local side effects (Sandberg et al., 1988). Among the various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages. Extrusion–spheronization is one of the most popular methods of producing spherical pellets (Vervaet et al., 1995). A growing interest has been made in the development of matrix pellets formulations using some release retarding materials such as chitosan (Goskonda and Upadrashta, 1993), cellulose derivatives (O'Connor and Schwartz, 1985; Kojima and Nakagami, 2002) or waxes (Zhou et al.,

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1996; Vergote et al., 2001) to obtain a sustained release effect. There are a few reports on the production of matrix pellets by extrusion–spheronization based on pH-dependent acrylic polymers such as Eudragit S (Krogars et al., 2000) or Eudragit L100 55 and S100 (Mehta et al., 2001). pH-independent acrylic polymers such as Eudragit RL30D and RS30D have been used in preparation of granules by spraying or fluidized bed method (Tsai et al., 1998; Radtke et al., 2002). However, there is no report on production of pellets by extrusion–spheronization using this kind of acrylic polymers.

In the present work, the application of Eudragit RS PO, Eudragit RL PO or their 1:1 combination was studied for production of pellets. The effect on pellet characteristics of three formulation parameters namely drug loading, binder concentration and Eudragits ratio were evaluated.

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 3^3 full factorial design was used for the preparation of pellets. The independent variables studied (X_1, X_2 and X_3) and their levels are shown in Table 1. The chosen dependent variables or responses (Y_1, Y_2 and Y_3) were mean dissolution time (MDT), crushing strength (CS) and elastic modulus (EM) of pellets, respectively.

Table 1
Independent variables: factors and levels for full factorial design

Factors	Levels		
	−1	0	1
X_1: amount of ibuprofen (%)	40	60	80
X_2: polymer ratio (RS/RL)	0/1	1/1	1/0
X_3: amount of PVP (%)	1	3	5

2.2.2. Preparation of pellets

The solid components of each formulation (50 g) (Table 2) were mixed together using a kitchen mixer for 10 min. 10% Avicel was used as a pelletization aid in all formulations. The required amount of water (Table 2) 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 for 10 h in a conventional hot air oven.

2.2.3. Sieve analysis and yield of pellets

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). The pellets retained on each sieve were weighed and the obtained data was used to construct a frequency distribution. The size range of 850–1180 μm was considered appropriate and the weight of pellets in this range was reported as yield of pellets.

2.2.4. Image analysis

The shape and the area of pellets were investigated by optical microscopic image analysis. Fifty pellets from each batch were placed on black backgrounds and a top cold light source was used to reduce the influence of shadow on the image processing. The image analyzer consisted of a computer system linked to a color video camera (Sony, Japan) and a stereomicroscope (magnification 8.5×) (Kyowa, Japan). The digitized images were analyzed by Scion image analyzing software (Scion Image for Windows, Release Beta 4.0.2). The area (A), perimeter (P_m) and Feret diameters of pellets were measured and two shape factors were calculated as follow:

$$\text{Aspect ratio} = \frac{d_{max}}{d_{min}} \quad (1)$$

$$\text{Sphericity} = \frac{4\pi A}{P_m^2} \quad (2)$$

Table 2
Composition of different formulation and the pellet yields in the range of 850–1180 μm

Test run	Ibuprofen (%)	Eudragit ratio %RL:%RS	PVP (%)	Avicel (%)	Water (%)	850–1180 μm pellet yield (%)
1	40	49:0	1	10	68	71
2	40	47:0	3	10	64	75
3	40	45:0	5	10	60	72
4	40	24.5:24.5	1	10	64	73
5	40	23.5:23.5	3	10	60	70
6	40	22.5:22.5	5	10	56	74
7	40	0:49	1	10	48	73
8	40	0:47	3	10	44	72
9	40	0:45	5	10	40	76
10	60	29:0	1	10	60	73
11	60	27:0	3	10	56	75
12	60	25:0	5	10	52	71
13	60	14.5:14.5	1	10	56	74
14	60	13.5:13.5	3	10	52	78
15	60	12.5:12.5	5	10	48	71
16	60	0:29	1	10	52	75
17	60	0:27	3	10	48	75
18	60	0:25	5	10	44	74
19	80	9:0	1	10	48	74
20	80	7:0	3	10	44	76
21	80	5:0	5	10	40	75
22	80	4.5:4.5	1	10	44	72
23	80	3.5:3.5	3	10	40	75
24	80	2.5:2.5	5	10	36	75
25	80	0:9	1	10	40	70
26	80	0:7	3	10	36	75
27	80	0:5	5	10	32	73

where d_{max} and d_{min} were the longest and shortest Feret diameters measured, respectively.

2.2.5. Scanning electron microscopy (SEM)

The morphology of the surface of pellets was characterized using SEM. The pellets were mounted on aluminum stub, sputter-coated with a thin layer of Platinum using sputter coater (Polaron, UK) under Argon atmosphere, and then examined using SEM (LEO1450VP, UK).

2.2.6. Mechanical tests

The crushing strength (the load needed to break the pellets) and elastic modulus of 15 pellets (850–1000 μm size fraction) were determined using a Material Testing Machine (Hounsfield, UK). 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, UK).

2.2.7. 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).

Model independent approach was used to compare the dissolution data. For this purpose mean dissolution time was calculated for each formulation using following equation (Costa et al., 2003):

$$\mathrm{MDT} = \frac{\sum t_i^- \times \Delta M_i}{\sum \Delta M_i} \quad (3)$$

$$t_i^- = \frac{t_i + t_{i+1}}{2} \quad (4)$$

$$\Delta M_i = M_{i+1} - M_i \quad (5)$$

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.

2.2.8. Statistical analysis of data

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

$$Y = C + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1^2 + b_5X_2^2 + b_6X_3^2 + b_7X_1X_2 + b_8X_1X_3 + b_9X_2X_3 \quad (6)$$

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

3. Results and discussion

It has been shown that the amount of water required for preparation of a suitable wet mass depends on the amount and properties of formulation components including drug and excipients (Lustig et al., 1999). It has also been reported that the amount of water added in the granulation step affects the pellet size and shape (Wan et al., 1993). The compositions of different formulations prepared are shown in Table 2. It is evident that the amount of water used in the massing stage was different. The results showed that all formulation produced acceptable yield at desired range, i.e. more than 70% of the pellets were in the size range of 850–1180 μm (Table 2).

Water has two major roles in the granulation and spheronization process. It is required to bind the powder mix during granulation and its plasticizing and lubricating properties also aid the extrusion process (O'Connor and Schwartz, 1989). As shown in Table 2, by increasing percent of PVP and also percent of ibuprofen, the amount of water needed for granulation decreased. These can be attributed to the plastic nature of both PVP (Buhler, 1998) and ibuprofen (Nokhodchi et al., 1995), which can enhance deformation and promote plasticity of the wet mass and decreases the need for excess water. It has been reported that the hydrophilic polymers, which have the least adhesive strength, such as HPC and PVP have a remarkable effect on production of highly spherical pellets (Funk et al., 1991; Law and Deasy, 1998). A comparison between the formulations containing Eudragit RL PO and Eudragit RS PO showed that less water was required for the formulation containing Eudragit RS PO. Eudragit RL contains much more quaternary ammonium substitutions; these substitutions make Eudragit RL more hydrophilic than Eudragit RS (McGinity, 1989), thus more water is required to achieve a suitable consistency with formulations containing Eudargit RL.

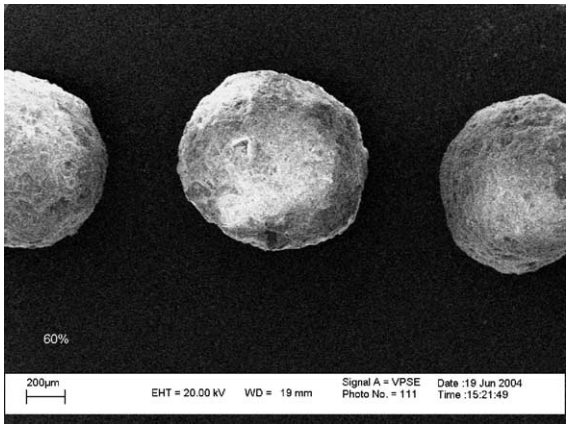

Fig. 1. Scanning electron micrograph of pellets containing 60% ibuprofen (formulation 14) (magnification 40×).

The pellets obtained from all formulations were spherical and uniform in shape. Fig. 1 shows the scanning electron micrograph of pellets containing 60% ibuprofen (formulation 14) as an example.

As shown in Table 3, both sphericity and aspect ratio have little variation from 1, indicating that near spherical pellets were obtained by these formulations. The results of Table 3 also indicate that there is no significant relation between the sphericity of pellets and drug load, binder concentration and also the type of Eudragit used. Overall the results showed that the drug loading, binder concentration and type of Eudragit did not affect the shape and sphericity of pellets.

Table 4 shows the results of dissolution (MDT) and mechanical tests (crushing strength and elastic modulus) as experimental responses (Y_1, Y_2 and Y_3).

Table 3
Results of image analysis

Run	Aspect ratio	Sphericity
1	1.17 ± 0.10	0.85 ± 0.03
2	1.13 ± 0.07	0.85 ± 0.02
3	1.17 ± 0.09	0.86 ± 0.02
4	1.15 ± 0.10	0.87 ± 0.03
5	1.12 ± 0.05	0.87 ± 0.02
6	1.10 ± 0.06	0.87 ± 0.02
7	1.18 ± 0.09	0.86 ± 0.01
8	1.19 ± 0.12	0.86 ± 0.02
9	1.15 ± 0.08	0.87 ± 0.02
10	1.14 ± 0.08	0.86 ± 0.03
11	1.12 ± 0.08	0.86 ± 0.03
12	1.14 ± 0.09	0.86 ± 0.02
13	1.13 ± 0.08	0.84 ± 0.03
14	1.16 ± 0.09	0.84 ± 0.02
15	1.14 ± 0.08	0.87 ± 0.02
16	1.14 ± 0.08	0.87 ± 0.02
17	1.17 ± 0.10	0.86 ± 0.02
18	1.21 ± 0.10	0.86 ± 0.02
19	1.12 ± 0.07	0.87 ± 0.02
20	1.15 ± 0.08	0.87 ± 0.06
21	1.15 ± 0.09	0.88 ± 0.02
22	1.14 ± 0.10	0.87 ± 0.02
23	1.14 ± 0.06	0.88 ± 0.02
24	1.13 ± 0.06	0.88 ± 0.01
25	1.12 ± 0.07	0.88 ± 0.02
26	1.15 ± 0.08	0.88 ± 0.02
27	1.13 ± 0.07	0.88 ± 0.01

Table 4
Experimental responses for different formulations

Test run	Y_1: MDT (min)	Y_2: CS (N)	Y_3: EM (MPa)
1	62.71 ± 0.63	5.07 ± 0.24	133.86 ± 9.30
2	45.40 ± 3.13	5.55 ± 0.27	123.72 ± 6.42
3	49.43 ± 4.00	5.67 ± 0.31	113.43 ± 6.41
4	49.75 ± 3.93	4.77 ± 0.20	119.80 ± 5.92
5	53.73 ± 1.47	5.16 ± 0.16	117.53 ± 7.05
6	48.03 ± 1.93	5.49 ± 0.19	107.67 ± 6.32
7	51.99 ± 3.46	3.83 ± 0.15	138.64 ± 6.11
8	43.42 ± 0.52	4.09 ± 0.15	133.44 ± 6.27
9	55.70 ± 5.69	4.51 ± 0.16	128.46 ± 6.61
10	40.58 ± 1.03	3.01 ± 0.09	114.38 ± 6.78
11	41.09 ± 1.74	3.10 ± 0.13	87.20 ± 7.17
12	38.76 ± 2.59	3.45 ± 0.15	75.72 ± 6.32
13	33.30 ± 3.42	2.48 ± 0.15	61.96 ± 6.17
14	33.83 ± 3.43	3.12 ± 0.15	86.77 ± 6.11
15	34.39 ± 3.98	3.19 ± 0.19	95.55 ± 4.37
16	43.91 ± 1.36	2.74 ± 0.12	94.68 ± 6.28
17	34.86 ± 1.77	2.00 ± 0.13	71.56 ± 5.05
18	30.46 ± 2.29	2.19 ± 0.15	82.28 ± 5.05
19	63.94 ± 4.05	2.30 ± 0.13	80.12 ± 4.65
20	60.24 ± 4.27	2.18 ± 0.09	72.08 ± 6.11
21	63.71 ± 2.82	2.08 ± 0.12	65.02 ± 4.78
22	59.37 ± 5.80	1.94 ± 0.12	69.52 ± 5.08
23	53.14 ± 4.47	1.98 ± 0.14	61.39 ± 5.05
24	50.93 ± 4.25	1.98 ± 0.08	58.19 ± 3.76
25	44.79 ± 0.71	1.67 ± 0.09	62.95 ± 6.41
26	40.54 ± 2.80	2.09 ± 0.10	84.68 ± 6.36
27	50.53 ± 4.15	2.26 ± 0.14	73.83 ± 6.56

By regression of these results against X_1, X_2 and X_3 we can obtain following models for MDT (Y_1), crushing strength (Y_2) and elastic modulus (Y_3):

$$Y_1 = 178.96 - 4.557X_1 - 5.677X_3 + 0.0398X_1^2 + 0.001X_2^2 + 0.808X_3^2 - 0.003X_1X_2, \quad R^2 = 0.776 \tag{7}$$

$$Y_2 = 13.441 - 0.276X_1 - 0.19X_2 + 0.285X_3 + 0.00167X_1^2 - 0.00005\,X_2^2 + 0.00027X_1X_3 - 0.00334X_1X_3, \qquad R^2 = 0.960 \tag{8}$$

$$Y_3 = 290.118 - 4.824X_1 - 0.423X_2 - 8.107X_3 + 0.02835X_1^2 + 0.00398X_2^2 - 0.00211X_1X_2 + 0.05665X_1X_3 + 0.05209X_2X_3, \quad R^2 = 0.839 \tag{9}$$

Eqs. (7)–(9) represents the quantitative effect of the formulation variables on the three responses. The values of the coefficients X_1, X_2 and X_3 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 resultant surface plots of Eqs. (7)–(9) are shown in Figs. 2, 4 and 5, respectively.

As seen in Eq. (7), Eudragit type has no significant effect on MDT of pellets. Fig. 2 demonstrates the effect of amount of drug and PVP on MDT, it is obvious from the plot that overall mean dissolution times calculated for pellets with 60% drug loading were shorter than for other pellets. Higher amounts of Eudragit present in pellets with 40% drug load was a possible explanation for higher MDT of these pellets compared with pellets containing 60% drug. In pellets with high drug loads

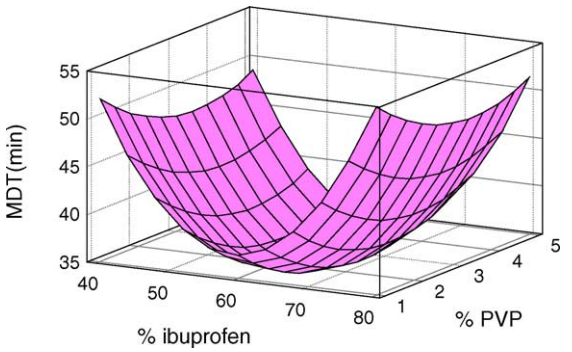

Fig. 2. Influence of % ibuprofen and % PVP on MDT of pellets.

(80%), the total polymer content is relatively low, since the weight fraction of drug per unit weight of the drug-polymer mixture is high, particles of drug associate to form drug agglomerates (Nystrom and Westerberg, 1986) and this agglomeration tendency of the drug at high drug loads will reduce the number of pores in the matrix structure and the total pore surface area. In such a system, the hydrophilic pathways for entrance of water molecules into pellets will be reduced resulting in low contact surface area with the dissolution medium. This can explain the increasing MDT in 80% of drug loading. Increasing binder concentration (X_3) slightly decreased MDT. This could be due to increasing the wetability of ibuprofen in the presence of PVP as a hydrophilic excipient. Similarly Deasy and Law (1997) showed that the rate of drug release from indomethacin pellets (a poorly soluble drug) increased in the presence of PVP. However, it was shown that in the case of theophylline there was no significant difference between drug release from beads containing 2% PVP and the control beads with no PVP (Funk et al., 1991).

In our study, all the pellets show brittle behavior under the mechanical tests. Fig. 3 is an example of force–displacement graphs obtained by mechanical test on pellets.

As shown in Eq. (8), the amount of PVP has a positive effect on crushing strength of pellets (increasing hardness); however, as shown in Eq. (9), it has a negative effect on elastic modulus of pellets that can be explained by the cohesive and plastic characteristics of PVP, respectively.

Figs. 4 and 5 demonstrate the effect of amount of drug and type of Eudragit on crushing strength and elastic modulus of pellets, respectively. It can be seen that

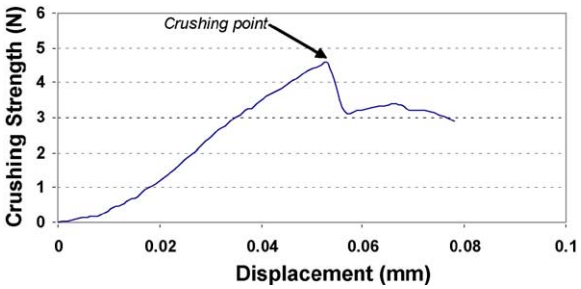

Fig. 3. Force–displacement diagram for a pellet (formulation 9).

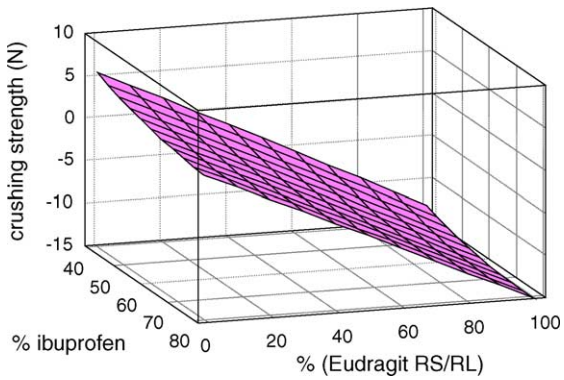

Fig. 4. Influence of % ibuprofen and % (Eudragit RS/RL) on crushing strength of pellets.

the amount of drug has negligible effect on crushing strength but decreases the elastic modulus significantly. This is probably due to the plastic nature of ibuprofen.

Also Eudragit type does not have a significant effect on elastic modulus, but has considerable effect on crushing strength of the pellets, i.e. increasing the ratio of Eudragit RL, increases the crushing strength of pel-

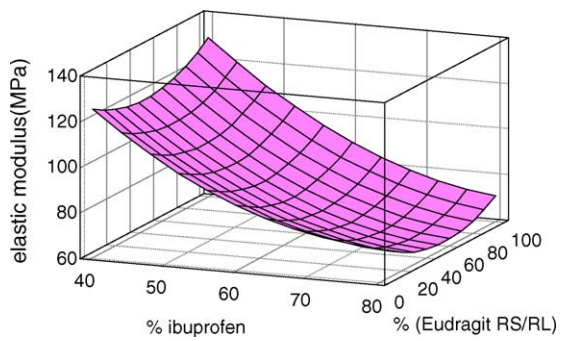

Fig. 5. Influence of % ibuprofen and % (Eudragit RS/RL) on elastic modulus of pellets.

lets. This can be explained by the hydrophilic characteristic of Eudragit RL compared with Eudragit RS. As mentioned before, formulations containing Eudragit RL required more water in the granulation step that can provide more plastic mass and promote densification of the pellets, thus harder pellets are produced after drying.

4. Conclusions

The ibuprofen pellets based on Eudragit RL PO or Eudragit RS PO and their combination were produced successfully using extrusion–spheronization technique. The pellets obtained exhibited adequate size, shape and hardness; however, the retarding effect of Eudragit RS PO and RL PO on drug release from pellets was not considerable. It was shown that the amount of water required to prepare a proper wet mass was affected by composition of formulations. Drug loading has a significant effect on drug release and mechanical properties of pellets. Eudragit type had also a significant effect on the crushing strength of pellets.

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