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Research paper

Design and study of ibuprofen disintegrating sustained-release tablets comprising coated pellets

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Abstract

One challenge in tableting of sustained-release multiparticulates is maintaining the desired drug release after compaction. The aim of this study was to design sustained-release ibuprofen tablets which upon oral ingestion rapidly disintegrate into sustained-release pellets in which the integrity of the pellet core and/or coat is preserved.

First free films composed of Eudragit RS 30D and RL 30D in 4:1 ratio and containing different levels of triethyl citrate (TEC) were prepared and tested to optimize the plasticizer level. Cured Eudragit based pellets with 60% ibuprofen loading which in our previous study showed proper mechanical properties for compression were coated with Eudragit RS 30D/RL 30D (4:1) containing 20% triethyl citrate at different coating levels. The mechanical properties of the coated pellets were tested. Polymer coated pellets were compacted into tablets either alone or with a blend of excipients comprising Avicel, PEG 4000, cross-linked PVP. A 3^2 full factorial design was used to optimize the filler blend composition. Effects of pellet to filler ratio, compression force and granulation of filler on tablet characteristics were investigated.

Results of mechanical test showed that the coating of cured pellets had no significant effect on yield point and elastic modulus of the pellets. In the case of 5% coating level sustained release of ibuprofen over a period of 24 h was achieved. The results obtained from tableting procedure showed that by selecting suitable filler blend (60% Avicel, 10% cross-linked PVP and 30% PEG 4000), compression force, and granulation of filler it was possible to prepare sustained-release tablets containing high ratio of coated pellets (even 80%) with desirable strength, disintegration time, and drug release rate. It was observed that compression force, pellet to filler ratio, composition of filler blend and granulation of fillers had no effect on drug release rate from compacted pellets but had significant influence on tablet strength, friability, and disintegration time. SEM graphs and in vitro release profiles for compacted pellets showed no apparent damage to the coated pellets as a result of the compaction process.

Keywords: Ibuprofen; Eudragit; Pellet; Multiparticulate tablet; Sustained release

1. Introduction

Recently, there has been an increasing interest in the development of multiparticulate dosage form in the shape of tablets rather than hard gelatin capsules. The aim of most studies on the compaction of pellets is to convert multiple-unit dosage form into a single unit dosage form which is able to disintegrate into the primary individual multiparticles [1]. Administration of pellets as a tablet which disintegrates into their subunits upon ingestion combines the advantages of oral multiple-unit dosage forms (e.g. free dispersion in GI-tract to avoid local irritation and dose dumping, and provide uniform absorption and improve bioavailability) with those of tablets.

In our attempts for production of sustained-release Eudragit RS/RL based ibuprofen pellets as a tablet it was shown that the curing process had a significant

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retarding effect on drug release rate from these pellets, but due to presence of high drug loading in these pellets and consequently low polymer content, the polymer matrix could not have a desirable sustaining effect on drug release rate [2] and further coating is required to achieve sustained-release formulation. However alteration of mechanical properties of cured pellets from brittle to plastic makes them a suitable substrate for preparation of multiple-unit tablets either in the form of un-coated or coated pellets, as it can prevent cracking of pellets and/or their coating under the compression force and therefore prevent major changes in the release properties after compression.

It has been shown that the films prepared from acrylic polymers are more flexible and therefore more suitable for the compaction of coated pellets compared to ethylcellulose films [3]. It has been also reported that an aqueous dispersion of Eudragit polymers is more suitable than their solvent-based coatings for pellets which are intended to be compacted [1]. Eudragit RS 30D and RL 30D are widely used as coating materials to sustain drug release. The diffusion rate of dissolved drug molecules through membrane of Eudragit RS 30D is lower than Eudragit RL 30D. The mixed films prepared from two acrylic polymer latexes show intermediate permeability [4].

The aim of this study was to develop a coating formulation for cured Eudragit based ibuprofen pellets to achieve sustained release of drug over 24 h and to compress these pellets as a tablet. The tablets should disintegrate rapidly into their comprising pellets upon contact with dissolution medium. The influences of inclusion of filler, type of filler, compression force and pellet to filler ratio on the properties of compacts were also investigated.

2. Materials and methods

2.1. Materials

Ibuprofen and microcrystalline cellulose (Avicel® PH101) were provided by Darupakhsh (Tehran, Iran), Eudragit RL PO, Eudragit RS PO, Eudragit RL 30D and Eudragit RS 30D were gifts from Rohm Pharma GmbH (Darmstadt, Germany), polyvinylpyrrolidone (PVP K30) and cross-linked povidone (PVP XL) were supplied by Fluka (Switzerland), polyethylene glycol (PEG 4000), magnesium stearate, talc and triethyl citrate were obtained from Merck (Germany).

2.2. Methods

2.2.1. Preparation of cured pellets

Cured pellets containing 60% ibuprofen, 27% Eudragit RS/RL (1:1), 10% Avicel and 3% PVP K30 were prepared based on the procedure described by Abbaspour et al. [2]. Briefly, the components were mixed and kneaded to make a wet mass with suitable consistency. The wet mass was then extruded through a 1 mm screen at 120 rpm and spheronized at 1000 rpm for 2 min. The obtained pellets were dried at 40 °C for 10 h; those pellets in the range of 850–1180 μm were cured at 60 °C for 24 h and then were allowed to cool at the ambient temperature for at least overnight. Then they were kept in tightly closed containers until use.

2.2.2. Coating procedure

2.2.2.1. Preparation of free films. This part of study was performed in order to optimize the percent of plasticizer in coating formulation. It has been shown that Eudragit RS 30D is less permeable than Eudragit RL 30D and they can be mixed in any proportion to achieve intermediate permeability [4]. The 4:1 ratio of Eudragit RS 30D and Eudragit RL 30D was used for film preparation based on some preliminary studies performed in our laboratory. Free films composed of Eudragit RS 30D and Eudragit RL 30D in 4:1 ratio and different percents of TEC (10%, 20%, 30% w/w based on dry polymer) as plasticizer were prepared. The dispersions were diluted with distilled water to achieve 10% (w/v) dry polymer content. The plasticizer was added to dispersions by stirring 5 h prior to film preparation. Samples equal to 30 mL of resulted dispersions were poured into leveled flat-faced Teflon plates (casting area = 10 × 10 cm). The plates were placed in an oven at 40 °C for 48 h and then were transferred to a desiccator with 100% relative humidity (RH) resulted by water at room temperature for 10 h, to make the films flexible enough to be removed intact from the plate [5]. The softened films were then cut carefully with a sharp scalpel into several strips of 10 mm width and at least 50 mm length and then peeled off from the plate. Free films were stored in a desiccator with 50% RH resulted from a saturated solution of magnesium nitrate hexahydrate at room temperature until mechanical tests were performed [5].

2.2.2.2. Mechanical tests of free films. The thickness of the film strips was measured at five different points using a micrometer (Mitutoyo, Japan) and the mean thickness was calculated. Specimens with an average thickness of 250–300 μm were selected. Films with air bubble, nicks or tears and having mean thickness variations of greater than 5% were excluded from analysis.

Each specimen was placed between two grips of a Material Testing Machine (Hounsfield, England) fitted with a 1 kN load cell. The initial distance between two grips (initial length of the film specimens) was 30 mm and the speed of grip separation was set at 10 mm/min. The extension – force graphs, stress at break (the tensile stress at which the specimen ruptures), and % elongation (or % strain at break) were obtained with a computer system attached to the apparatus (QMAT, Hounsfield, England). The experiment was repeated 5 times for each formulation and the mean value was reported.

2.2.2.3. Coating of the pellets. Ten percent (w/v) of coating formulation containing Eudragit RS 30D and Eudragit RL 30D in 4:1 ratio was prepared. Triethyl citrate was added

to the dispersion as plasticizer (20% w/w related to dry polymer) and the formulation was stirred for 5 h prior to coating. Talc (2% w/v) was also added as an antiadherent. The coating was performed using a fluidized bed coater (Wurster insert, Werner Glatt, Germany) fitted with a Wurster column and a 1 mm nozzle. The inlet air temperature was set at 40 °C and the outlet temperature was in the range of 25–35 °C. The atomizing pressure was 2.0 bar and the spray rate was 10 g/min. The pellets were spray coated until a weight gain of 5%, 10% and 15% w/w. Coating dispersion was stirred during coating process. After coating, the pellets were spread out on trays in an oven for 24 h at 40 °C to ensure the completion of curing. The resulted coated pellets were kept in tightly close containers until use.

2.2.3. Mechanical testing of coated pellets

The yield point (the load needed to begin plastic deformation) and elastic modulus of 15 coated pellets were determined using a Material Testing Machine (Hounsfield, England). The speed of the upper mobile platen fitted with a 1 kN load cell was set at 1 mm/min. Yield point and elastic modulus were obtained by a computer system attached to the apparatus (QMAT, Hounsfield, England).

2.2.4. Preparation of filler blends

In order to select the best blend of fillers for compaction a 3^2 full factorial design was used as the experimental design for preparation of different blends of fillers. The independent variables studied (X_1 and X_2) and their levels are shown in Table 1. The chosen dependent variables or responses were tablet hardness and disintegration time.

2.2.5. Granulation of fillers

Ten grams of Avicel or PVP XL was wetted with addition of 15 or 40 mL ethanol 70%, respectively. The resulted wet mass was then passed through a 1 mm sieve manually and then dried in an oven for 8 h at 40 °C. The dried granules were sieved and the size fraction of 850–1000 μm was used in tableting process. Granules of PEG 4000 were obtained by milling of its flakes with a mortar and pestle and separating the size fraction of 850–1000 μm.

2.2.6. Tableting procedure

2.2.6.1. Selection of best filler blends for compaction. Tablets containing 60% pellet and 40% filler blend in form of powder (Table 2) were prepared using maximum compression force of 5 kN. A constant compression speed was used to make all tablets. Coated pellets and filler blends as a powder were weighed separately and mixed with a laboratory size tumbling mixer for 10 min at 90 rpm. Magnesium stearate (0.25%) (as lubricant) was added to the mixture and mixed for additional 5 min. The resulted mixture was then manually filled into the die and compressed using flat-faced punches with a diameter of 1 cm. The prepared tablets were stored in tightly closed containers at room temperature for at least 48 h before being subjected to any characterization.

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

Factors	Levels		
	−1	0	1
X_1: amount of Avicel (%)	20	50	80
X_2: ratio of PVP XL/PEG	0/1	1/1	1/0

Table 2
Composition of different filler formulation

Test run	Avicel (%)	PVP XL (%)	PEG (%)
1	20	0	80
2	20	40	40
3	20	80	0
4	50	0	50
5	50	25	25
6	50	50	0
7	80	0	20
8	80	10	10
9	80	20	0

2.2.6.2. Preparation of tablets under different compaction forces. Coated ibuprofen pellets and filler blends were compacted in a single punch tableting machine (Korsch, Germany) equipped with a strain-gauge (ParsPaygeer, Iran) at maximum compression forces of 5, 10, and 15 kN. The tableting machine was equipped with flat-faced punches with a diameter of 1 cm. Tablets weighing 500 mg were prepared by direct compression of either pellets or mixture of pellets and fillers.

2.2.6.3. Preparation of tablets containing different percent of pellets. Tablets containing 60%, 80%, and 100% pellet and filler blend (in the form of powder or granules) were prepared with maximum compression force of 5, 10, and 15 kN. For the tablets containing 100% pellet, lubricated pellets were unable to make a tablet and the pellets did not make coherent mass upon ejection from die therefore tablets containing 100% pellet were prepared without any lubrication.

2.2.7. Evaluation of tablets

2.2.7.1. Dissolution testing. The dissolution tests were carried out on pellets or tablets containing 300 mg of ibuprofen ($n = 6$) 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. [6].

The mean dissolution time (MDT) was calculated for each formulation by following equation [6]:

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

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

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

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.

2.2.7.2. Disintegration testing. The disintegration time was tested on 6 tablets according to the British Pharmacopoeia using a disintegration apparatus (Erweka ZT3, Germany) with discs. Thousand milliliters distilled water was used as disintegration medium and the temperature was set at 37 °C. The time taken until no material from any of the tablets was left on the mesh was recorded.

The European Pharmacopoeia requires that rapid release tablets disintegrate in maximum 15 min (i.e. 900 s). This rule can also be applied to tablets consisting of pellets for multiple-dose prolonged release formulations [7,8]. Disintegration time measurements, as such, are indicative of whether, and when, the tablet formulations start to act as true multiple-dose preparations [7].

2.2.7.3. Hardness testing. Tablet hardness was determined from the force required to fracture tablets by diametrical compression using a tablet hardness Tester (Erweka TBH200, Germany). Mean hardness of 5 tablets from each formulation was reported as tablet hardness.

2.2.7.4. Friability testing. Five tablets were weighed on an analytical balance and run in a Roche friabilator (Erweka TA3R, Germany) for 5 min at 25 rpm. The tablets were then dusted and reweighed. The friability was subsequently calculated as percentage of weight lost. A limiting value of 1% for friability tests of tablets has been suggested by the European Pharmacopoeia.

2.2.7.5. Scanning electron microscopy (SEM). The morphology of the surface of compressed pellets, tablets and cross-section of tablets was 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).

3. Results and discussion

3.1. Effect of film coating on pellet characteristics

An ideal film coat, with respect to retaining its physical continuity, should be hard and tough without being brittle [9]. A hard and tough film must have a high tensile stress and a large extension before breaking.

Fig. 1 shows the mechanical properties of free films, obtained from tensile tests. The desired situation is to optimize the plasticizer level in order to reduce the brittle character of the polymer without adding excess plasticizer which would cause adhesion of the coated pellets during curing and storage. It is evident from Fig. 1 that addition of TEC as a plasticizer (from 10% to 30%) increased elongation of films and lowered their stress at break significantly ($p < 0.001$). As the optimum free film must have the maximum stress at break and elongation, the free films containing 10% TEC (which have the lowest elongation) and those containing 30% TEC (which have the lowest stress at break) were not suitable. Free films containing 30% TEC were also sticky and caused adhesion problems. It was also claimed that the elongation of the coating at break should be at least 75% to avoid coating rupture during compaction [4]. According to these results 20% TEC in free film formulations was considered as optimum plasticizer concentration, and therefore coating formulation with 20% TEC was used in coating process.

Visual inspection and SEM photographs of coated pellets showed that a complete, uniform and integrated coating was achieved even with 5% coating level (Fig. 2).

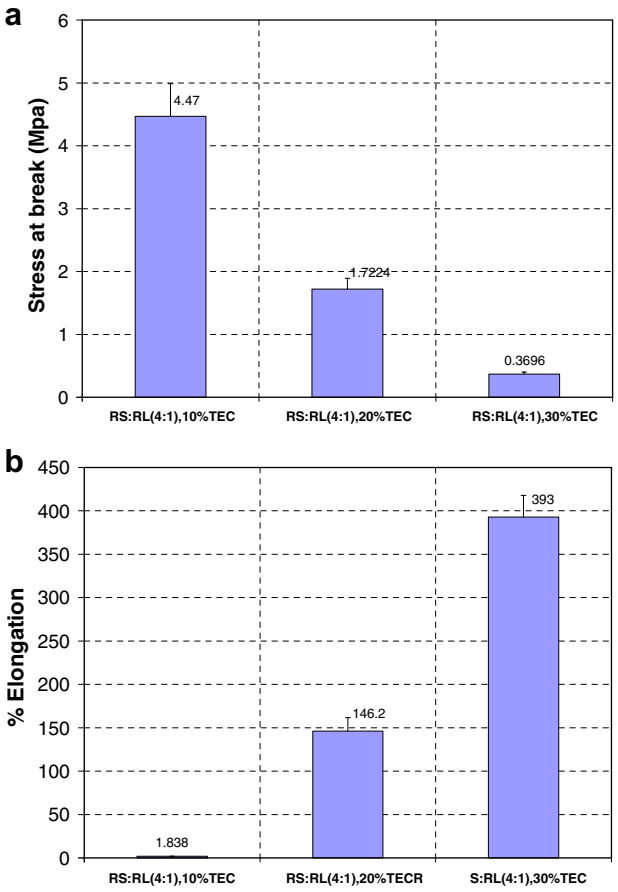

Fig. 1. The effect of different levels of TEC on (a) stress at break and (b) % elongation of Eudragit RS/RL films.

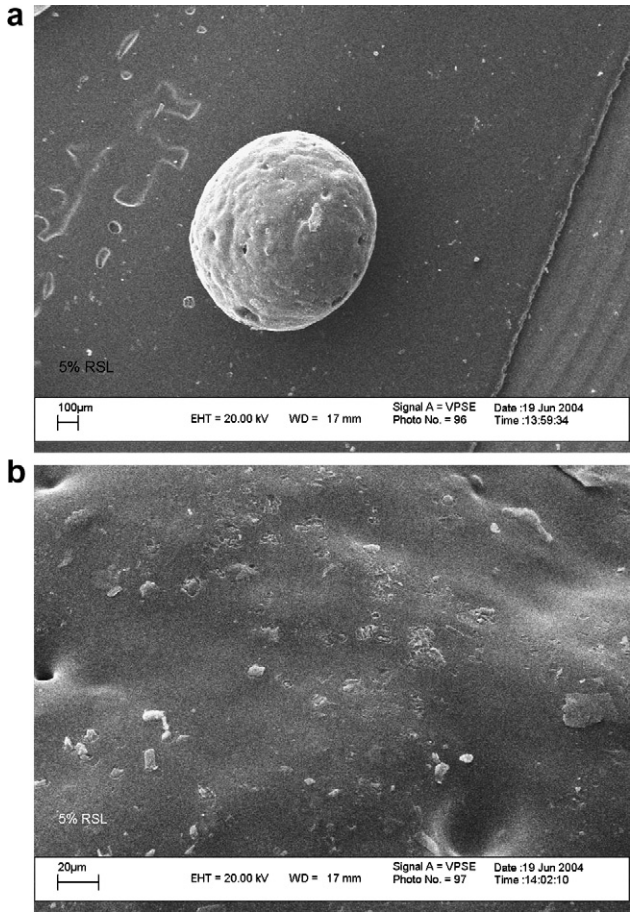

Fig. 2. Scanning electron micrographs of surface of the pellets coated with 5% coating level: (a) 40×, (b) 400×.

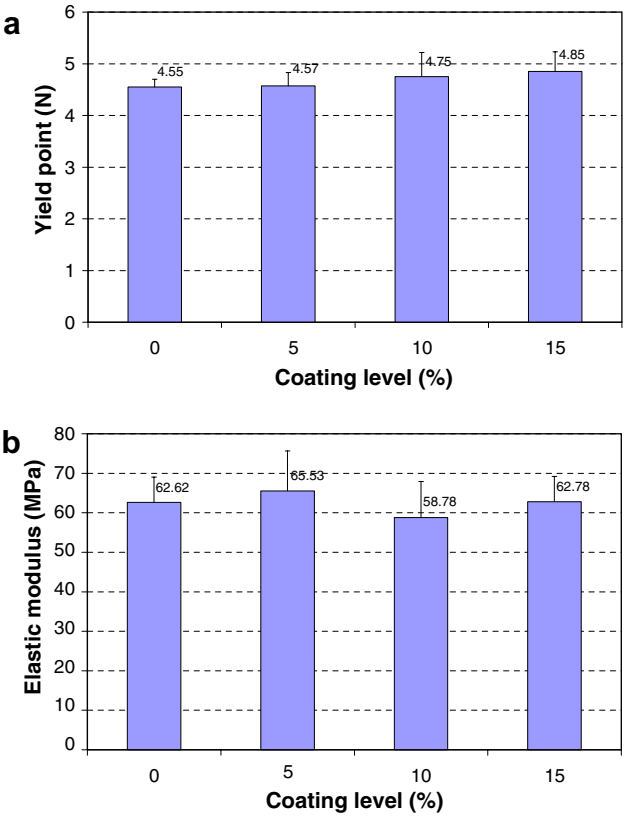

Fig. 3. The effect of different coating levels on (a) yield point and (b) on elastic modulus of coated pellets.

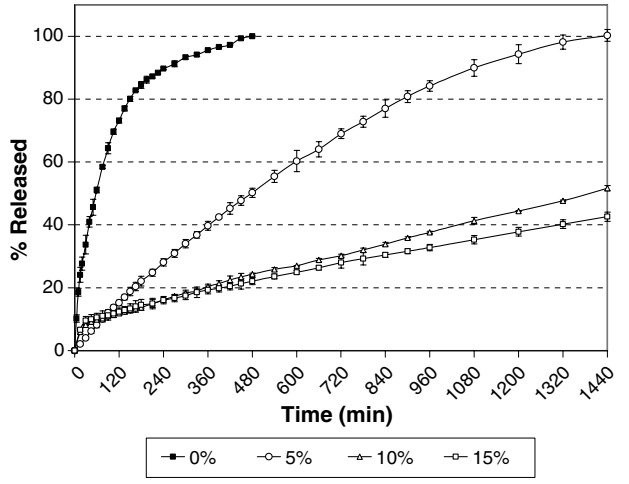

Fig. 4. Dissolution profiles of un-coated pellets and pellets coated with different coating levels.

Results for mechanical test of coated pellets (Fig. 3) show that the coating of cured pellets with 5%, 10%, and 15% coating levels had no significant effect on yield point and elastic modulus of the pellets ($p > 0.05$). Previously Bashaiwoldu et al. [10] demonstrated that the film coating affected the mechanical properties of the pellets differently depending on the properties of the core pellets. The effects of the coating material on the mechanical properties of the rigid pellets were significant, while there was no significant effect on mechanical properties of soft pellets. The plastic nature of core pellets in our study [2] and resemblance of core and coat substances may be the reason for negligible effect of coating on the mechanical properties of pellets.

The results of dissolution tests (Fig. 4) show that increase in coating level from 5% to 10% significantly decreased drug release rate, however further increase in coating level from 10% to 15% only had a little retarding effect on drug release. This can be explained by the term critical coating level; below which core coverage by the polymer is incomplete and drug release is diffusion controlled through pores, and above that sufficient polymer is applied to cover the cores so drug release appears to be membrane controlled [9]. In the case of 5% coating level sustained release of ibuprofen over a period of 24 h was achieved so that the MDT for pellets before coating and after 5% coating was 93.72 ± 1.91 min and 534.277 ± 12.84 min, respectively. However 10% and 15% coating levels gave a very slow drug release about 50% and 40% after 24 h, respectively, which was not acceptable. Therefore pellets with 5% coating level were considered for further studies on tableting.

3.2. Selection of best filler blend for tableting

Maintaining the modified drug release after compaction of barrier-coated sustained-release pellets is a major

challenge in the production of tablets from these pellets. The application of compaction pressure can lead to structural changes in the film coating and, consequently results in alteration in drug release. The compression-induced changes in the structure of the film coating can depend on formulation factors, such as the type and amount of coating, the properties and structure of the pellet core and the incorporation of excipients with protective properties [1]. The protective effect of excipients depends on material properties such as compression characteristics and particle size [1]. The ideal filler materials used for the tableting of pellets should prevent the direct contact of the pellets (e.g. polymer coatings) and act as cushioning agent during compression. The excipients should also result in hard and rapidly disintegrating tablets at low compression forces and should not affect the drug release [1].

Torrado and Augsburger [11] studied the possible protective effect of different excipients on the tableting of theophylline granules coated with Eudragit RS and reported that the order of least damage to the coating was PEG 3350 < Avicel PH 101 < PVP XL < lactose < dicalcium phosphate. The order of least damage to enteric-coated bisacodyl pellets during compression has also been reported to be as cellactose < PEG 6000 < Avicel PH 200 < dicalcium phosphate [12].

Avicel is mostly used excipient for direct compression of tablets and also acts as a disintegrant [13]. PVP XL is an excipient used in tablet formulation to achieve fast disintegration [13] and PEG has been used as a cushioning agent in tableting of coated particles [11].

In order to investigate the effect of these mostly used excipients (Avicel, PEG, and PVP XL) and effect of their interaction and also to select an optimum composition as filler for tableting of coated pellets, a full factorial design with 9 test run was carried out. The primary experiments showed that the use of different filler blends had no significant effect on drug release rate or MDT of compacted pellets, thus the disintegration time and the hardness of tablets (which are most important parameters influenced by the filler type and ratio) were selected as dependent parameters or responses.

All tablets contained 60% coated pellets and compressed at 5 kN force. Theoretically, 29% of excipient is needed to fill the void space between densely packed pellets in tablet formulation. This can be explained by percolation theory [14]. Although several researchers have used different percents of pellets (ranging from 10% to 90%) in preparation of tablets, the percents of pellets below 60% showed acceptable results [7,14–22]. Therefore in this study 60% pellet in tablet formulations was chosen to ensure maximum pellet protection by excipients. Table 3 shows the resulted responses for different composition of filler blends.

The models obtained for hardness ($Y1$) and disintegration time ($Y2$) by regression analysis are given below:

Table 3
Experimental responses for different formulations

Test run	$Y1$: hardness (kg)	$Y2$: disintegration time (min)
1	4.3 ± 1.2	70
2	4.5 ± 0.4	0.5
3	5.6 ± 0.9	0.25
4	5.0 ± 0.7	45
5	5.4 ± 0.9	1
6	7.1 ± 0.6	0.05
7	6.3 ± 0.2	1.5
8	6.5 ± 0.9	0.25
9	8.8 ± 0.3	0.05

$$Y1 = 3.982 + 0.000382X_1^2 + 0.000194X_2^2 \quad (R^2 = 0.755) \tag{4}$$

$$Y2 = 86.444 - 0.952X_1 - 1.712X_2 + 0.00757X_2^2 + 0.01138X_1X_2 \quad (R^2 = 0.917) \tag{5}$$

The regression analysis and ANOVA for these models are shown in Tables 4 and 5, respectively. Related surface and contour plots of the responses (Figs. 5 and 6) show the influence of % Avicel and ratio of PVP XL/PEG in filler blends on mechanical strength and disintegration times of tablets, respectively. It is evident from these plots that increase in percent of Avicel leads to harder tablets which disintegrate very fast. Avicel powder is known to be very compressible and forms hard tablets at low compression forces [1]. The plots also indicate that by increasing ratio

Table 4
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 $Y1$ (hardness) and $Y2$ (disintegration time)

Dependent variable (response)	Predictors (factors)	Regression coefficients	Sig.[a]	R^2
$Y1$ (hardness)		3.982 [C]	0.000	
	x_1^2	3.820E−04	0.000	
	x_2^2	1.941E−04	0.000	0.755
$Y2$ (disintegration time)		86.444 [C]	0.003	
	x_1	−0.952	0.014	
	x_2	−1.712	0.009	
	x_2^2	7.557E−03	0.044	
	x_1x_2	1.138E−02	0.032	0.917

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

Table 5
ANOVA of models $Y1$ and $Y2$

Model	Sum of squares	df	Mean square	F	Sig.
$Y1$					
Regression	56.951	2	28.476	50.846	0.000
Residual	18.481	33	0.560		
Total	75.432	35			
$Y2$					
Regression	4920.833	4	1230.208	11.660	0.019
Residual	444.912	4	111.228		
Total	5365.746	8			

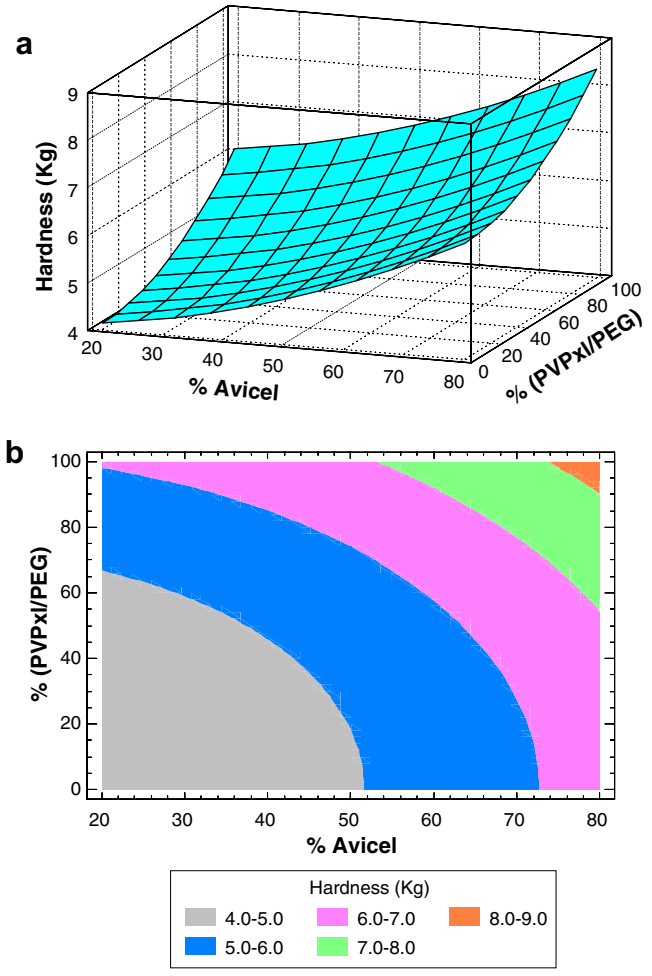

Fig. 5. Influence of % Avicel and % (PVP XL/PEG) on hardness of tablets containing 60% coated pellets: (a) surface plot, (b) contour plot.

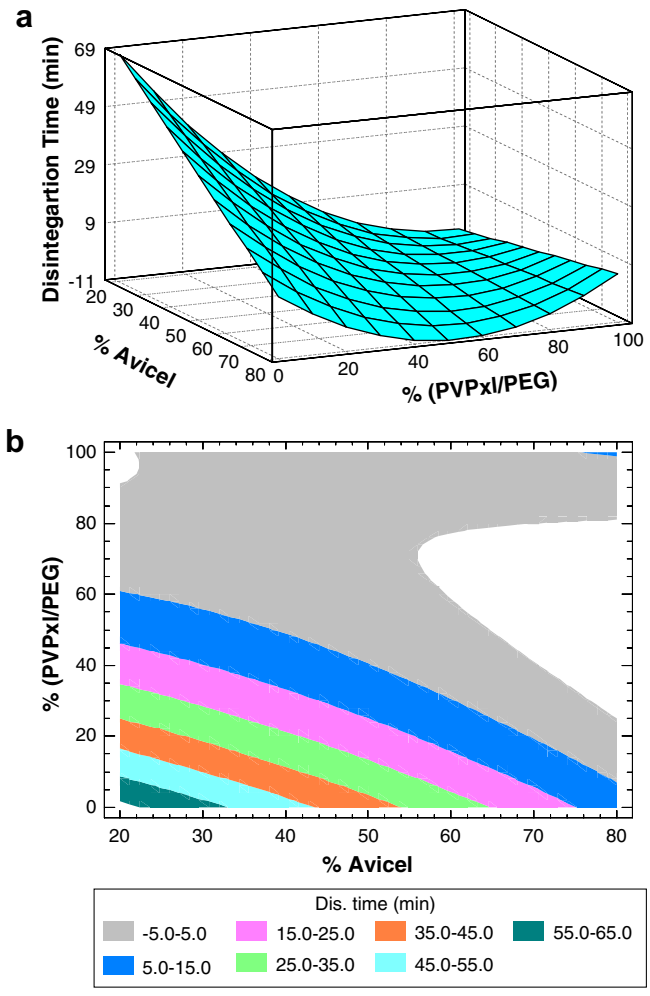

Fig. 6. Influence of % Avicel and % (PVP XL/PEG) on disintegration time of tablets containing 60% coated pellets: (a) surface plot, (b) contour plot.

of PVP XL or decreasing ratio of PEG, the tablet hardness increased. At lower ratios of PVP XL/PEG the disintegrating effect of Avicel was predominant while at higher ratios of PVP XL/PEG the amount of Avicel had no significant effect on disintegration time and PVP XL had the major role in reduction of disintegration time.

It can also be concluded from Figs. 5 and 6 that presence of PEG led to production of weaker tablets which disintegrated more slowly. It was shown that PEG had excellent cushioning effect in tableting of coated pellets due to its high plastic deformation but increased disintegration time of tablets through particle bonding [11].

In order to select the optimized filler blend for production of tablets with proper hardness and disintegration time the graphical approach was used. In this approach the optimization is performed by superimposing the contour plots of different response variables and locating the area of interest (optimal surface) considering a desirable criterion.

Fig. 7 shows the contour plots of tablet hardness and disintegration time superimposed on each other. According to European Pharmacopoeia to have a fast disintegrating tablet the disintegration time of the tablets should be less than 15 min. On the other hand it seems that tablets with range

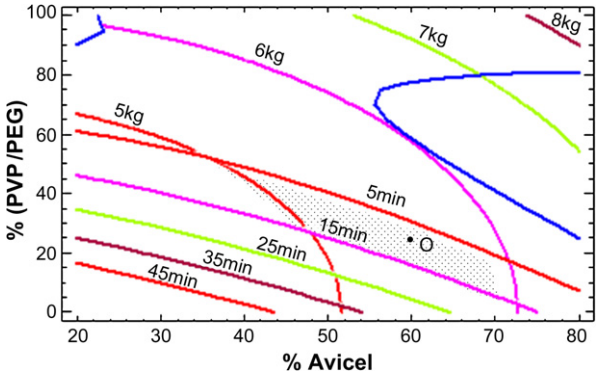

Fig. 7. Superimposed contour diagrams of tablet hardness and disintegration time; O is selected as an optimum point.

of disintegration times lower than 5 min disintegrate too fast to be swallowed by patient. Therefore disintegration time between 5 and 15 min and proper mechanical strength or hardness between 5 and 6 kg were considered as responses.

It can be seen in Fig. 7 that any point between lines representative of 5 and 15 min disintegration time and also

between 5 and 6 kg tablet hardness fulfills the above mentioned criteria. In our study we have selected the point O as an optimum point which is related to 60% Avicel and PVP XL/PEG in 25/75 ratio.

In Table 6 the comparison between the observed and predicted values of the responses for the selected point (point O) is presented. At this point there was a reasonable agreement between the predicted and the experimental values and therefore Eqs. (1) and (2) describe adequately the influence of the selected independent variables on the studied responses.

3.3. Effect of compression force and percent of pellets on tablet properties

To study the effect of percent of pellets and compression force on tablet properties, tablets containing 60%, 80%, and 100% (lubricated and un-lubricated) pellets were prepared under the compression forces of 5, 10, and 15 kN. The filler blend composition was constant for all tablets and consisted of 60% Avicel and 40% PVP XL/PEG 4000 (in 25/75 ratio). The resulted tablets were assessed by dissolution tests, hardness testing, and disintegration testing. The results are shown in Table 7. In the case of tablets containing 100% pellet it was impossible to make a tablet with lubricated pellets and pellets were disaggregated after ejection from die. Thus no data were shown for tablet hardness, disintegration time and friability. In order to study the effect of compression force on drug release from these pellets, the compressed pellets were collected and analyzed by dissolution test. Tablets with 100% pellet content were also prepared using un-lubricated pellets and evaluated for their hardness, friability and dissolution. The results are presented in Table 7. Due to slow and incomplete drug release from these compacts it was impossible to calculate MDT values for them.

The dissolution profiles of un-coated pellets, un-compressed coated pellets and tablets with different percent of pellets prepared under different compression forces are shown in Fig. 8. It is evident from Fig. 8 that drug release rate from different tablet formulations is similar. The comparison of MDT for different tablet formulations by ANOVA and Tukey–Kramer multiple comparison test confirmed no significant differences between MDT of tablets containing 60% and 80% pellets and also compressed lubricated pellets ($p > 0.05$). It means that the pellet/filler ratio and compression forces did not influence the drug release rate.

There are several reports on the effect of compression force on drug release rate from compacted reservoir pellets such as enteric-coated bisacodyl pellets [12] and coated diltiazem pellets [18]. However Young et al. [23] reported that increasing compression force had no significant effect on drug release rate from matrix pellets prepared by hot–melt extrusion method. They reported that hot–melt extruded materials produced dense extrudates during thermal extrusion and tableting process did not influence the effective porosity or surface area of pellets. It seems that curing process in our work had similar effect on the structure of pellets.

Table 6
Comparison between predicted and observed values for the test responses at point O

Response	Predicted value	Observed value	Expected range	% Bias[a]
Tablet hardness (kg)	5.4	5.1	5–6	6.7
Disintegration time (min)	8.3	7.0	5–15	15.8

[a] Bias was calculated using the equation: [(predicted value − observed value)/predicted value] × 100.

Table 7
The results of dissolution test, hardness and disintegration time for tablets containing powder filler and various percent of pellets, prepared under different compression forces

Pellet content	Tablet property	Force (kN)		
		5	10	15
60%	MDT (min)	407.18 ± 31.22	401.34 ± 25.89	401.69 ± 38.21
	Hardness (kg)	5.1 ± 0.3	12.2 ± 1.4	19.3 ± 1.1
	Disintegration time (min)	7	15	60
	Friability (% weight loss)	2.6	0.4	0.05
80%	MDT (min)	371.88 ± 33.32	364.1 ± 25.38	367.99 ± 22.98
	Hardness (kg)	5.2 ± 0.7	14.8 ± 1.8	21.4 ± 1.9
	Disintegration time (min)	12	30	70
	Friability (% weight loss)	8.2	0.7	0.5
100% (lubricated)	MDT (min)	424.39 ± 38.38	418.55 ± 40.21	422.61 ± 32.45
	Hardness (kg)	–	–	–
	Disintegration time (min)	–	–	–
	Friability (% weight loss)	–	–	–
100% (un-lubricated)	MDT (min)	–	–	–
	Hardness (kg)	28.7 ± 1.8	30.5 ± 1.9	35.9 ± 1.6
	Disintegration time (min)	>120	>120	>120
	Friability (% weight loss)	0.05	0.02	0.01

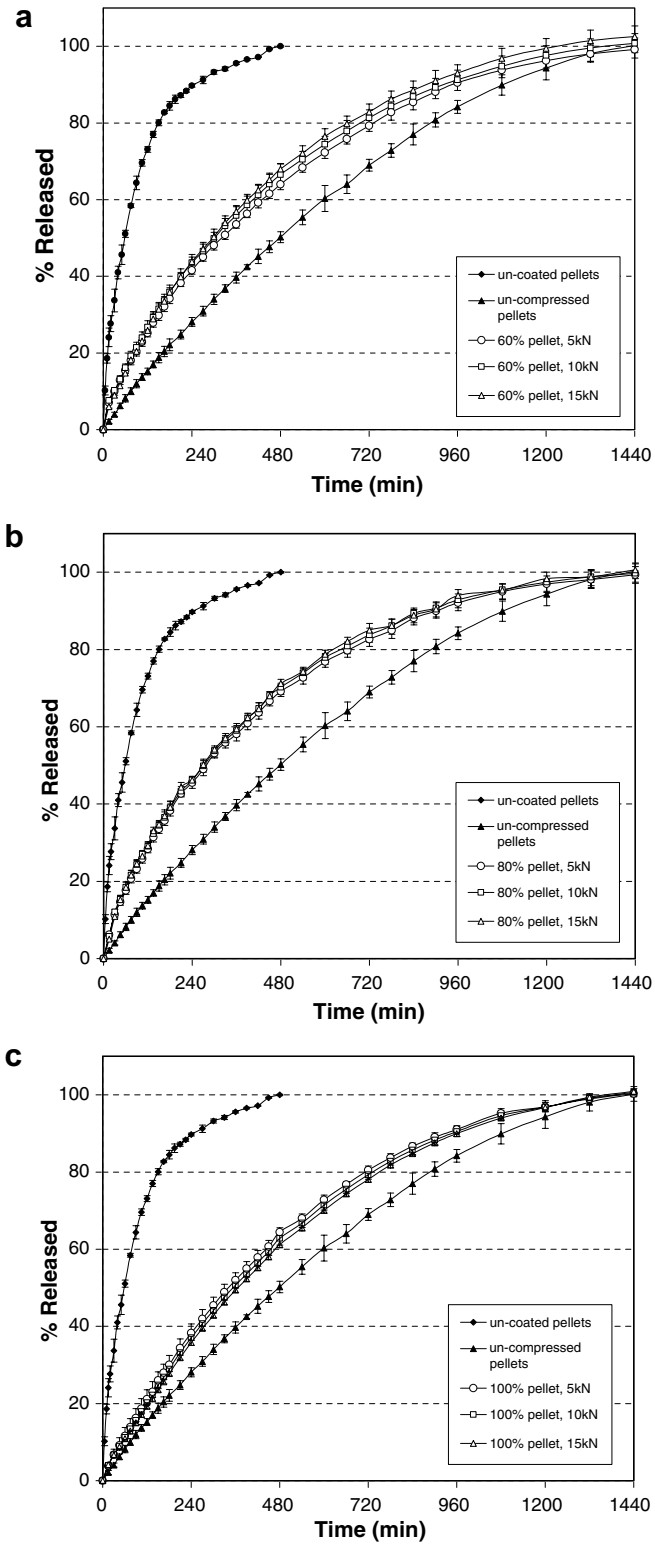

Fig. 8. Dissolution profiles for un-coated pellets, un-compressed coated pellets and tablets containing 60%, 80%, and 100% lubricated pellet prepared under compression forces of 5, 10, and 15 kN.

Release profiles obtained for compacts with 100% pellet contents and those with 60% and 80% pellet contents indicate that core pellets and their coating had enough mechanical strength and flexibility to withstand compression forces. However drug release rate from compressed pellets showed little deviation from non-compressed pellets. It was claimed that the elongation of the coating at break should be at least 75% to avoid coating rupture during compaction [4]. The SEM photographs of the surface of lubricated pellets after compression (without filler) are shown in Fig. 9. This figure indicates that the pellets underwent plastic deformation and compression-induced changes in shape however the integrity of their coating remained intact after compression. Inability of lubricated pellets to make a stable compact is another reason to prove that the plastic deformation of pellets is the major mechanism for tableting of these pellets.

As SEM photographs did not show major defects on pellet coating (Fig. 9) the changes in dissolution rate after compression could be due to intensive deformation of pellets which leads to stretching of polymer film and also film thinning during deformation of pellets especially at tablet surfaces where it is in direct contact with punches and die walls. It was shown that stretching of an intact polymer layer affects the permeability of the film [24]. Similar findings also have been reported by Vergote et al. [19]. Another reason could be the deformation of pellets under compression force which may cause a departure from spherical

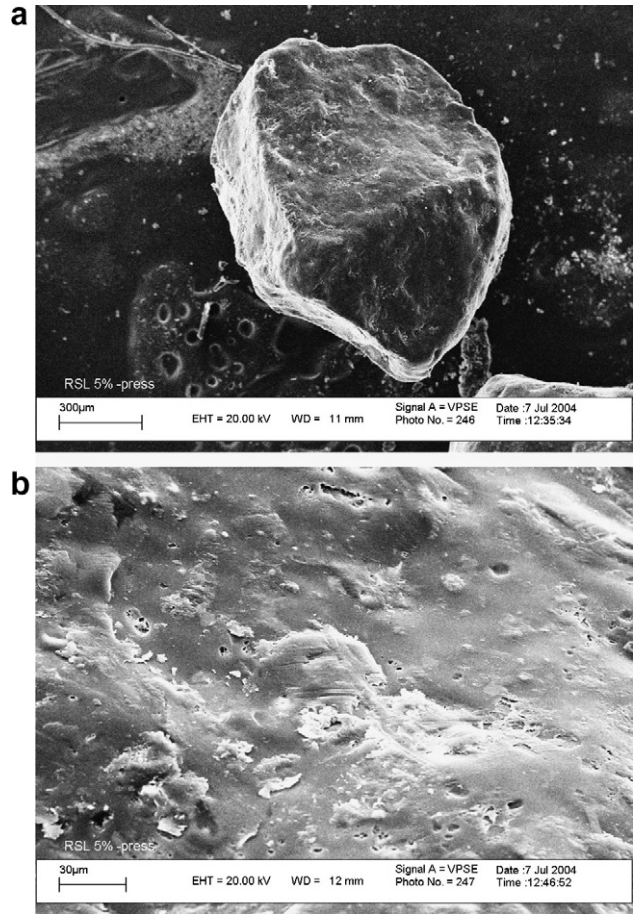

Fig. 9. Scanning electron micrographs of a lubricated pellet after compression without filler excipient under 15 kN force: (a) 40×, (b) 400×.

shape that in turn could increase the surface area of pellets and hence increase drug release rate.

The SEM photographs of tablets with 60% and 80% pellet contents after compression are shown in Fig. 10. This figure shows that pellets remained as coherent individual units after compression and therefore filler blends could successfully separate the pellets from each other and prevent pellet coating from fusion and formation of matrix system.

Fig. 11 shows the release profiles of tablets prepared from 100% un-lubricated pellets under the compression forces of 5, 10, and 15 kN. The retardation effect on drug release from these pellets compared to lubricated pellets (Fig. 8) can be attributed to the fusion of pellet coating during compression and formation of a stable matrix system especially in central parts of the compacts. Drug release rate decreased with increasing compaction force. This was attributed to the formation of highly compacted matrix especially in central parts of the tablets by increasing the compression force. SEM micrographs of surface and cross-section of tablets prepared from 100% un-lubricated pellets (Fig. 12) confirmed the above theory.

Visual inspection after dissolution tests of these tablets showed that the compacts remained intact in the dissolution baskets even after 24 h however the compacts were loosened due to swelling effect of pellets or their coating in dissolution media. The high mechanical strength of tablets containing 100% un-lubricated pellets and their high

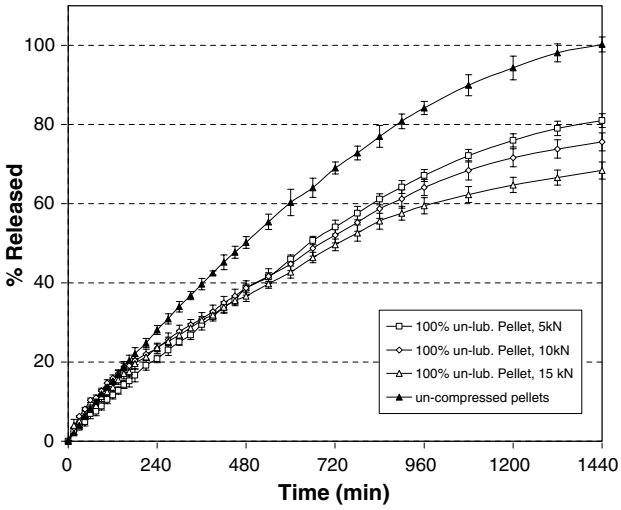

Fig. 11. Dissolution profiles of un-compressed pellets and tablets prepared from 100% un-lubricated pellets under compression forces of 5, 10, and 15 kN.

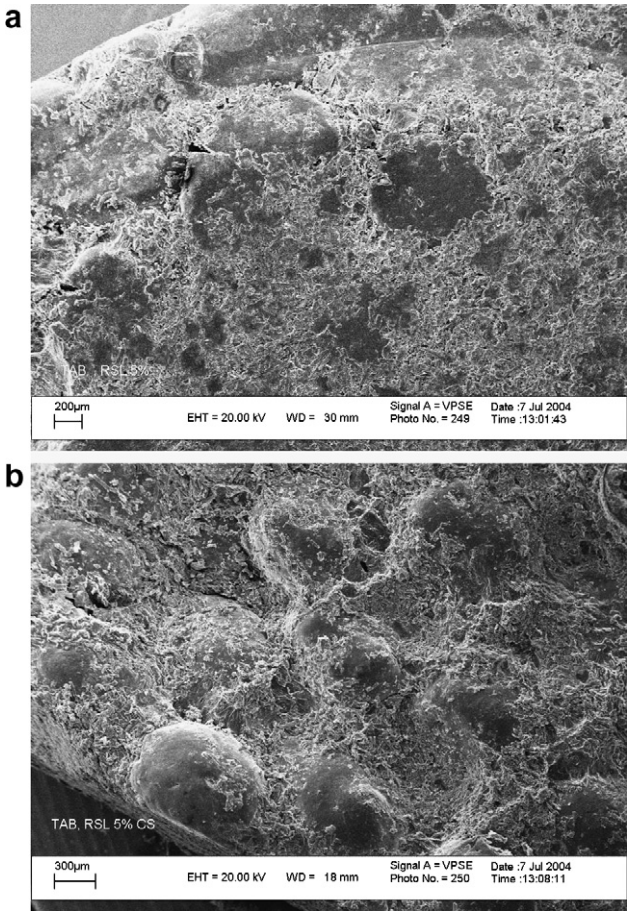

Fig. 10. Scanning electron micrographs of a tablet prepared from 60% pellet under 15 kN compression force: (a) surface, (b) cross-section (magnification 40×).

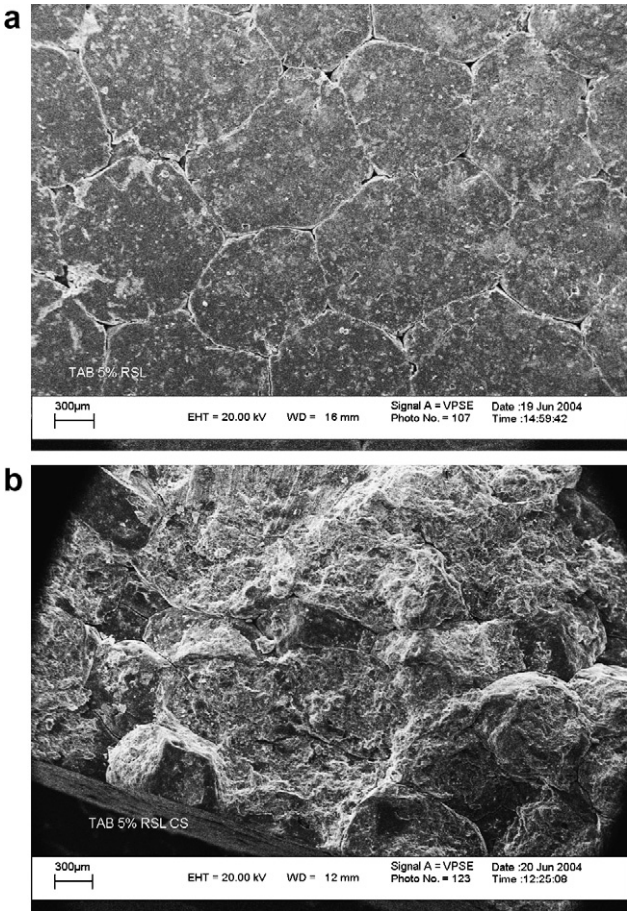

Fig. 12. Scanning electron micrographs of a tablet prepared from 100% un-lubricated pellet under 15 kN compression force: (a) surface, (b) cross-section.

disintegration time (above 120 min) and low friability (Table 7) are also in agreement with the dissolution results.

The results in Table 7 show that by increasing compression force tablet hardness and disintegration times increased but friability decreased. The results can be explained by the formation of more condensed compact with increasing the compression force.

The results also showed that by increasing the pellet ratio from 60% to 80%, tablet hardness, disintegration times and % friability increased. Lundqvist et al. [15] and Debune et al. [22] reported that increase in pellet ratio up to 60% in tablet formulation increased tablet friability and decreased the hardness and disintegration time. The results obtained for friability can be explained by this fact that in tablets with 80% pellet content there might be some regions with lack of filler due to insufficient amount of filler to cover the pellets completely and/or segregation phenomena during tableting process. Therefore in these tablets there are some parts with high concentration of filler and some parts with localized pellet aggregates. These two regions do not show enough mechanical strength due to non-homogeneity especially at tablet edges. The higher values of tablet hardness and disintegration times compared to tablets with 60% pellet also can be explained by the formation of matrix system due to fusion of pellet coating in the regions with lack of filler and/or by decrease in proportion of disintegrants.

3.4. Effect of filler granulation

In order to avoid or reduce the probability of segregation phenomena and achieve uniformity within the mixture of pellets and excipients, it is preferred that the excipients have almost the same size as the pellets [15,25]. In order to find out weather the change in particle size of fillers could affect the tablet properties the fillers were either granulated or sieved to achieve the same size range as pellets. Avicel and PVP XL powders were successfully granulated with ethanol 70%. PEG 4000 was also milled and sieved to achieve the desired particle size. It has been shown that most fillers especially Avicel lose their unique properties after granulation with water. For example Avicel pellets or granules do not have the same swelling, compaction characteristics and disintegrating effects as Avicel powder [26,27]. In order to achieve granules or pellets of Avicel with high porosity and weak mechanical strength one approach was granulating the Avicel with ethanol/water mixture [28].

Our preliminary experiments showed that resulted Avicel and PVP XL granules easily fractured under the compression while PEG yielded very soft granules with clear plastic behavior.

Tablets containing 60% or 80% pellets and granulated fillers were prepared and evaluated for their hardness, disintegration time and dissolution profiles and the results are shown in Table 8.

It is evident from MDT values in Table 8 and also dissolution profiles of tablets prepared from granulated fillers (Fig. 13) that different compression forces and percent of pellets had no significant effect on drug release rate. Also there were no significant differences between MDT of tablets prepared with granulated fillers and those of powder fillers (Table 7) ($p > 0.05$).

Table 8 also shows that pellet hardness and disintegration time increased and % friability decreased by increasing the compression forces. Increasing pellet ratio from 60% to 80% also increased hardness, disintegration time, and % friability of tablets. In general these findings were similar to those tablets prepared from powder fillers.

Comparisons of results obtained from tablets prepared with granulated excipients with those of powder excipients show that granulation of fillers slightly increased tablet hardness. Increase in hardness of tablets with use of granulated filler could be explained by brittle effect of Avicel and PVP XL granules that fractured under the compression and made fresh bonding sites. Percent of friability of tablets prepared from granulated fillers is lower than those of powder fillers. These results are in agreement with tablet hardness results. The results also show that disintegration time of tablets prepared from granulated fillers is reduced. This can be attributed to the greater swelling volume of large PVP XL particles, which could give more rapid disintegration [29].

Table 8
The results of dissolution test, hardness and disintegration time for tablets containing granulated filler and various percent of pellets, prepared under different compression forces

Pellet content	Tablet property	Force (kN)		
		5	10	15
60%	MDT (min)	360.06 ± 41.32	340.58 ± 35.36	371.83 ± 25.43
	Hardness (kg)	8.8 ± 0.6	14.5± 2.0	22.6 ± 1.2
	Disintegration time (min)	1	3	15
	Friability (% weight loss)	2.3	0.05	0.02
80%	MDT (min)	365.11 ± 31.44	344.40 ± 38.39	368.43 ± 40.87
	Hardness (kg)	9.6 ± 0.6	17.6 ± 1.2	23.1 ± 1.41
	Disintegration time (min)	2	5	20
	Friability (% weight loss)	5.4	0.2	0.08

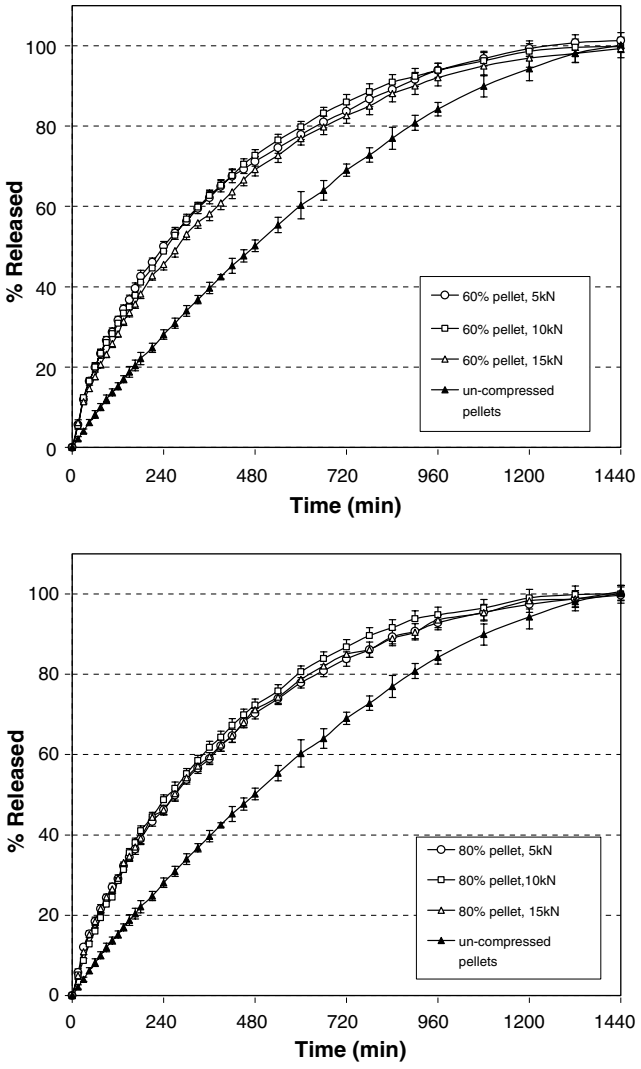

Fig. 13. Dissolution profiles of un-compressed pellets and tablets containing 60% and 80% pellet prepared with granulated filler under compression forces of 5, 10, and 15 kN.

4. Conclusions

Cured Eudragit based ibuprofen pellets coated with Eudragit polymers were found to be an ideal substrate for compression into tablets. These pellets could be successfully compressed as a tablet using proper filler blends and excipients. It was shown that compression force, pellet to filler ratio, and composition of filler blend did not influence the ibuprofen release rate from their disintegrating compacts. However tablet hardness, disintegration time, and % friability were markedly influenced by compression force and pellet ratio. Selected filler blend consists of 60% Avicel, 10% PVP XL and 30% PEG 4000 and provided desirable mechanical strength and disintegration time for resulted tablets. It was also found that granulation of fillers had no significant effect on drug release rate but had clear effects on tablet hardness, disintegration time, and friability.

In general the results showed that the studied coated pellets had proper mechanical behavior to withstand the compression force and retain the drug release rate of pellets after tableting process. It was also possible to prepare tablets containing high ratio of pellets (even 80%) with suitable strength and disintegration time by selecting optimum filler formulation, compression force and granulation of filler.

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