Department of Pharmaceutical Technology, Medical University of Gdansk, Poland

Influence of the components of Kollicoat SR film on mechanical properties of floating pellets from the point of view of tableting

R. Łunio, W. Sawicki

Received April 4, 2008, accepted April 24, 2008

Dr. hab. Wiesław Sawicki, Department of Pharmaceutical Technology, Medical University of Gdansk, Hallera 107, 80-416 Gdansk, Poland
wsawicki@amg.gda.pl

Pharmazie 63: 731–735 (2008) *doi: 10.1691/ph.2008.8096*

The influence of pellet core ingredients on pellet behaviour, e.g. during compression, is well known. In this study the influence of components of a Kollicoat SR polymer film on mechanical properties was investigated. The aim of this study was to evaluate the influence of polymer film components on the mechanical properties of the pellet as a whole, from the point of view of tableting. Tablets should disintegrate into undeformed pellets floating in this environment for 5–6 h, releasing the model drug – verapamil hydrochloride – if possible in a controlled way. The usefulness of texture analysis and work of compression measurement was also evaluated. Kollicoat SR in the form of a 30D aqueous dispersion was chosen as the main component of the polymer film. Polyvinyl pyrrolidone K-30 as a pore former, and propylene glycol, triethyl citrate and dibutyl sebacate plasticisers were selected as typical additives. The influence of different thickness of polymer film on behaviour during stress was also evaluated. After coating the cores with a 20 μm Kollicoat SR dispersion film, an increase in mechanical strength, in comparison to the pellet core, was observed (2.74 to 3.34 mJ). Addition of porophor increased the work of compression by 50% to 5.1 mJ. The investigation of the influence of plasticiser on film properties proved that the kind of plasticiser used in the polymer film had no effect on the mechanical properties of the film or pellets. Only in the case of the film with triethyl citrate was no distinct of the pellet core found. Pellets coated both with films with triethyl citrate and with dibutyl sebacate, in contrast to pellets with a film coating with propylene glycol, showed a significant decrease of the dissolution rate of verapamil hydrochloride (20, 10 and 40% at 6 hours, respectively). It is possible to compress pellets with a 50 μm polymer film without affecting the dissolution rate, as was confirmed during release studies. When using Kollicoat SR the most appropriate plasticizer seems to be triethyl citrate, and in this case a change of behavior during compression analysis by texture analyzer was observed. But so relationship was found between the type of plasticizer and the work needed to obtain a given deformation.

1. Introduction

In pharmaceutical technology there is an ever increasing desire to improve and optimize the function, quality and safety in use of pharmaceutical tablets. One idea is to develop multi-unit dosage forms, e.g. coated pellets compacted to a tablet form (Bodmeier 1997).

Usually pellets are filled into hard gelatin capsules. There are many advantages of a tablet dosage form. For the patients the method of dosing is easier because it is possible to divide the tablet in any way, and there is also less risk of adherence to oesophagus during swallowing. In addition there are lower production cost, higher production rate, and less sensitivity to tampering. The compressibility of the pellets also ensures there is a lower risk of the process technology of the drug form being copied by a competing producer (Abraham et al. 2004).

Tableting pellets is more complicated than compression of powders. Pellets coated with polymer film are independent containers releasing the active substance in a controlled way. The dominant mechanisms of compression of pellets to tablet form are deformation and densification. Data on compression of pellets indicate that pellets are compressed by deformation and the incidence of pellet fragmentation is low or non-existant (Santos et al. 2005).

There are a few important factors in pellet tableting. In many studies the authors evaluate the influence of the pellet core ingredients on the behaviour of the pellets during compression (Nicklasson et al. 1999; Tunón et al. 2003; Santos et al. 2004). The most common substance, forming the main part of the core (apart from the active substance) is microscrystalline cellulose (MCC). Pellets with MCC generally show a limited amount of fragmentation during

tableting while the main compression mechanisms are deformation and densification.
The mechanical properties of the pellet depend on the properties of the core and the polymer film, which is an important part of the coated pellet. The polymer film will also have an influence on the behaviour of the coated pellets during compression.
The aim of this study was to evaluate the influence of polymer film components on the mechanical properties pellet of the as a whole, from the point of view of tableting. Tablets should disintegrate into undeformed pellets floating in this environment for 5–6 h, releasing the model drug – verapamil hydrochloride (VH), as far as possible in a controlled way. The usefulness of texture analysis and work of compression measurement was also evaluated.

2. Investigations, results and discussion

VH has a low bioavailability after oral administration of conventional or modified release tablets (Busse et al. 2001; Vogelpoel et al. 2004). VH has more than six times better solubility in 0.1 HCl solution than in pH 6.8 buffer solution (Vogelpoel et al. 2004). Improved bioavailability can be obtained with a multiunit floating dosage form – e.g. tablets with floating pellets (Sawicki 2002).
It is most important in preparing tablets with pellets to avoid core or film damage during compression. The mechanical strength of the pellet depends on the consistency of the pellet core or the properties of the polymer film. Kollicoat SR 30D (polyvinylacetate dispersion (27%) stabilized with Povidone (25%) and sodium laureth phosphate) was selected for coating.
Work of compression over a distance 50% of the diameter (WC_{50}) of the pellet cores was low and amounted to 2.74 mJ. There are two maximum points on the graph illustrating the relationship between force and distance. The lower maximum point shows the force needed to break the core. In the case of the pellet core this force was 4.5 N (Fig. 1).
After coating the cores with a 20 μm Kollicoat SR dispersion A^1 film, an increase of mechanical strength was observed. The WC_{50} of pellets coated with film A^1 amounted to 3.34 mJ and the force needed to break the coated core was 5.7 N (Fig. 1). The results were compared using a one-way Anova test. Statistical analysis proved that the results obtained are statistically significantly different ($p = 0.009$). Ane increase of thickness of the Kollicoat SR film caused a significant decrease of the release rate of VH (Fig. 2).

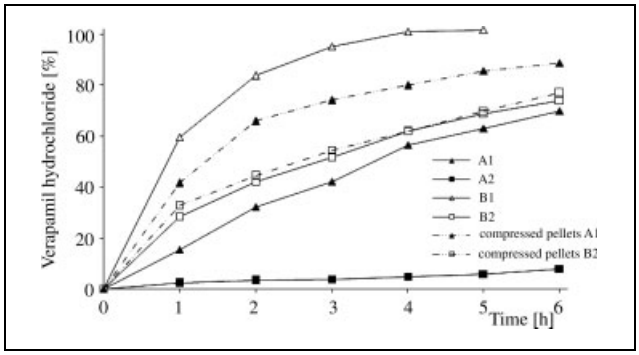

Fig. 2: *In vitro* verapamil hydrochloride release from pellets with film thickness A^1, B^1 – 20 μm, A^2, B^2 – 50 μm and pellets after tableting

To obtain a suitable release profile, the addition of a hydrophilic substance, which increases the diffusivity of the film, was necessary. PVP K-30 was chosen as a pore former. The influence of the presence of the pore former in the film on the mechanical proprieties of the pellets was investigated. It was found, that the addition of porophor PVP K-30 pore former increased the WC_{50} value. The WC_{50} of pellets coated with 20 μm film B^1 was 5.1 mJ. An increase of the force needed to break the pellet core was also observed, amounting to 9.5 N. Using PVP K-30 as a pore former improved the mechanical properties of the polymer film and increased the release rate of the active substance (Fig. 2). Obtaining an appropriate release profile was possible with a Kollicoat SR film of thickness 50 μm and 20% of pore former. Increasing film thickness to 50 μm (B^2) and 70 μm (B^3) did not cause a statistically significant change of WC_{50} value or the force needed to break the pellet core ($p = 0.16$). Results were compared with the one-way Anova test.
The plasticiser should have influence the mechanical properties of the polymer film and pellets. In the next part of the investigation, the effect of plasticiser on film properties was examined. The influence of PPG in formulation B^3, TEC in formulation C and DBS in formulation D was compared. The WC_{50} of pellets coated with film B^3 was 4.97 mJ (SD 0.5), C 5.27 mJ (SD 0.6) and D 5.56 mJ (SD 0.5), respectively (Fig. 3).
All results were compared with the one-way Anova test; there were no statistically significant differences. The investigation of the influence of plasticiser on film proper-

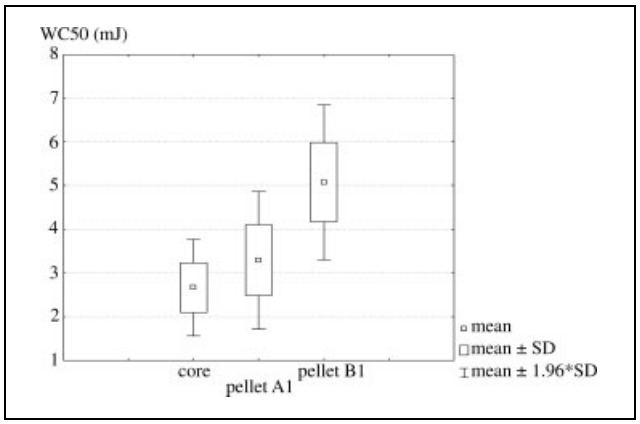

Fig. 1: Work of compression 50% (WC_{50}) [mJ] of pellet core and pellets A^1 and B^1 with 20 μm film

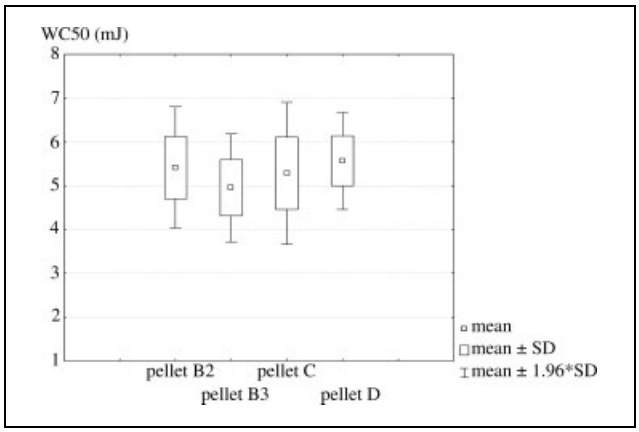

Fig. 3: Work of compression 50% (WC_{50}) [mJ] of pellet core and pellets coated with B^2 – 50 μm, B^3, C and D – 70 μm

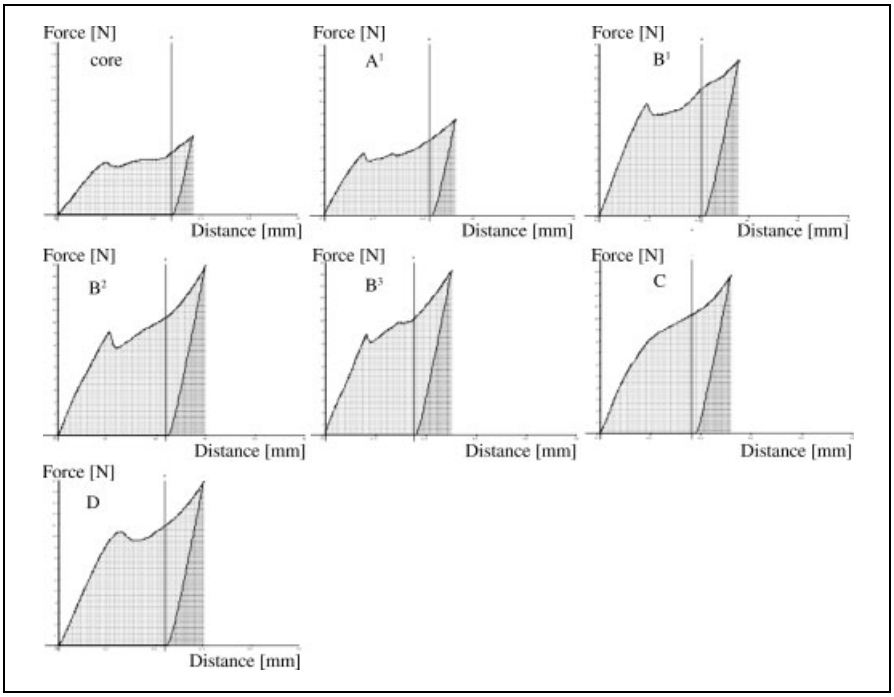

Fig. 4:
Examples of texture analysis, relationships between applied crushing force [N] and distance [mm] for pellet core and pellets coated with films A^1, B^1, B^2, B^3, C and D (area under curve – work of compression 50% [mJ])

ties proved that the type of plasticiser used in the polymer film had no effect on the mechanical properties of the film or the pellets as a whole. Only in the case of film formulation C was there no distinct maximum point in the graph of the relationship between force and distance, indicating a break of the pellet core (Fig. 4).

SEM examination confirmed the differences observed during texture analysis. Pellets were compressed by 10% of their diameter. Pellets with formulation B^3 were coated with the most brittle film. There were many cracks with sharp edges, what confirming a brittle failure mechanism during compression (Fig. 5a, e). A purely plastic, ductile mechanism of compression was visible in the case of pellets C. During compression by 10% of diameter there were no cracks. The surface of the pellet was smooth, with a visible site of compression impact (Fig. 5b, e). The brittle mechanism but with some plastic, ductile phenomena was observed with formulation D. The edges visible on the SEM photo were not so sharp as in the case of film B^3, and the number of cracks was also smaller (Fig. 5c, f).

There were significant differences in release rate between pellets coated with films B^3, C and D of thickness 70 μm (Fig. 6).

Both pellets coated with film C with TEC and with film D with DBS showed a significant decrease of dissolution rate of VH. By 6 h of release test pellets with film B^3 had released about 40%, C 20% and D only 10% (Fig. 4). The decrease in release rare can be explained by the lipophilic properties and low solubility in water of both TEC and DBS in comparison with PPG (Lippold and Monells Pagés 2001).

The behaviour of pellets during the tableting process was investigated. Pellets releasing VH for 6 h with films A and B^2 were chosen for tableting. Avicel PH 102 (13.5%), mannitol (37.8%), Kollidon Cl (9.5%) and magnesium stearate (1%) were selected as components of the tablet mass. Kollidon Cl was added as a disintegrating agent, to ensure disintegration of the tablet to pellets. Tableting was carried out using a laboratory Korsch tableting machine, equipped with a compressive force measuring device. Tab-

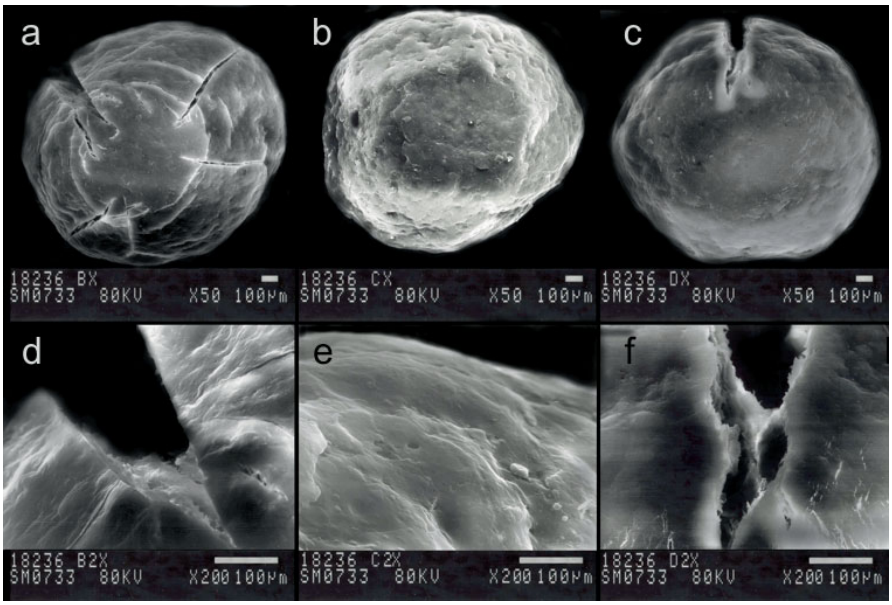

Fig. 5:
Scanning electron micrographs of pellets after compression 10% of for diameter (formulation B^3 – a, d; formulation C – b, e; formulation D – c, f)

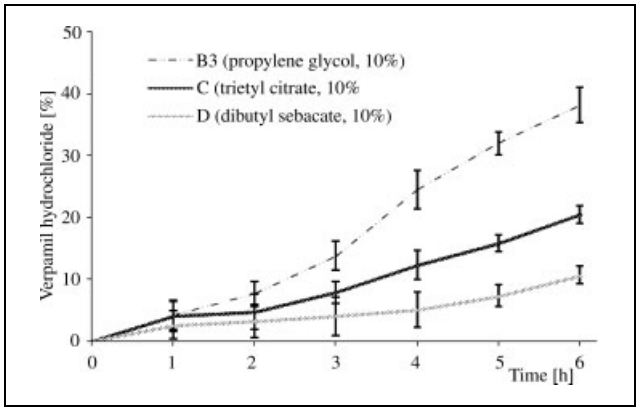

Fig. 6: *In vitro* verapamil hydrochloride release from floating pellets with films B[3], C and D (70 μm) with different plasticizers

leting of both formulations proceeded without problems, no segregation being observed. All tablets fulfilled the quality requirements of Ph. Eur.

It was found that 20 μm of film A was too thin, and fractured during the tableting process, which was apparent as an increase in the dissolution rate of VH (Fig. 2).

However, film B[2] appeared most appropriate. The release profile from tableted pellets was similar to that of the pellets before tableting (in hard gelatine capsules) when the compression force was 8 kN. A slight decrease of release rate was found with compression at 12 and 18 kN. Release test results were compared with one-way ANOVA and no significant differences were observed ($p = 3 \cdot 10^{-5}$). Increasing the compression force from 8 to 12 and 18 kN caused a significant increase of hardness and decrease of friability of the tablets, as expected (Fig. 7).

3. Experimental

3.1. Materials

Dibutyl sebacate (DBS) (Flukachemie, Steinheim, Germany), Kollidon® Cl (BASF, Ludwigshafen, Germany), Kollicoat® SR 30 D (BASF, Ludwigshafen, Germany), lactose (Ubichem, Eastleight, UK), microcrystalline cellulose (MCC) (Avicel® PH 101, mean particle size 50 μm and Avicel® PH 102, mean particle size 100 μm, FMC, Brussels, Belgium), mannitol (POCh, Gliwice, Poland), magnesium stearate (Riedel-de Hean, Seelze, Germany), povidone K-30 (PVP K-30) (Kollidon K-30 BASF, Ludwigshafen, Germany), propylene glycol (PPG) (Merck, Darmstadt, Germany), triethyl citrate (TEC) (Lancaster, Morecambe, UK), sodium bicarbonate (Merck, Darmstadt, Germany), talc (Ph. Eur.), verapamil hydrochloride (VH) (Recordati, Milano, Italy).

Statistical analysis of the results was performed with Microsoft Excel (Microsoft, Washington, USA) and Statistica v 7.1 (Stat Soft. Inc., Tulsa, USA).

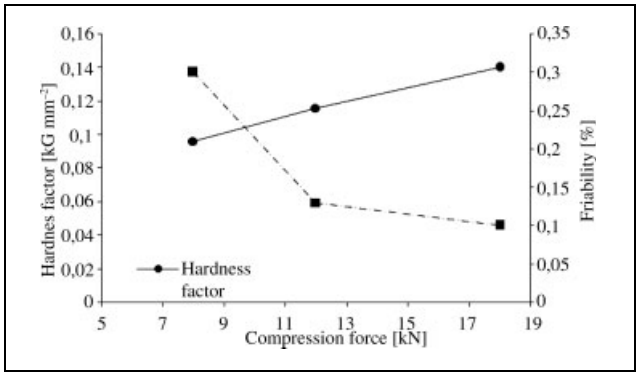

Fig. 7: Hardness factor and friability of tablets with pellets as a function of compression force

Table: Composition [%] of coating mixtures with Kollicoat SR 30D

Substance	Coating mixtures			
	A*	B*	C	D
Kollicoat SR 30D	50.80	48.20	48.20	48.20
Propylene glycol	–	1.45	–	–
Triethyl citrate	–	–	1.45	–
Dibutyl sebecate	–	–	–	1.45
Polyvinyl pyrrolidone K-30	–	5.05	5.05	5.05
Talc	3.40	3.40	3.40	3.40
Water	45.20	41.90	41.90	41.90

* thickness of film
1 – 20 μm
2 – 50 μm
3 – 70 μm

3.2. Preparation of floating pellet cores with verapamil hydrochloride

Pellets were prepared by extrusion and spheronization. On the basis of initial experiments the composition of cores was selected as: VH 20.0%; sodium bicarbonate 20.0%, MCC (Avicel® PH 101) 43.4%, lactose 12.3%, PVP K-30 4.3%. The first four substances were mixed in a mixer and moistened with portions of 5% aqueous solution of PVP K-30 (up to 60 g per 100 g of the powder mixture). The wet mass was extruded in a Caleva Extruder 25 (Caleva, Dorset, UK). Then the extrudate obtained underwent a spheronization process.

The spheronization process was performed in a Caleva Model 120 apparatus (Caleva, Dorset, UK). The spheronizing disk rotation speed, measured by the Caleva tachometer, was 1500–1600 rpm, and the spheronization time of a 20 g portion of granulate was 4 min. Wet cores were dried in a blow-dryer at 40 °C for 12 h and then separated into fractions of 0.8–1.0, 1.0–1.25, 1.25–1.6 and 1.6–2.0 mm by means of a sieve set. Pellets of 1.0–1.25 mm diameter comprised the largest fraction (about 85%) in the given spheronization conditions.

3.3. Coating pellet cores

Films A–D, having different thicknesses and comprising different components, were prepared based on Kollicoat® SR 30 D. The composition of the coating mixtures is summarised in the Table. The process of preparing coating mixtures was as follows. The appropriate amount of Kollicoat® SR 30 D was introduced to a beaker with a magnetic stirrer. Next, portions of water were added during stirring. At the same time PVP K-30 was dissolved in the water. Then, the appropriate plasticizer, PPG, TEC or DBS, was added and the mixture stirred for 2 h. Core coating (200 g) was performed in a Uni-Glatt apparatus (Glatt, Systemtechnik, Dresden, Germany): incoming air temperature 40 °C, outgoing air temperature 30 °C; air pressure in spray nozzle 2 bar and peristaltic pump feeding rate 3 ml/min. Pellets were dried in a blow-dryer at 40 °C for 24 h precisely.

3.4. Measurement of film thickness

Coated pellet film thickness was measured after cross sectioning on 10 randomly selected pellets from each formulation. The hemispheres obtained were placed under a microscope (Motic, Wetzlar, Germany) connected with a digital camera (Panasonic, Osaka, Japan) and film thickness was measured. Average value was calculated on the basis of the results obtained.

3.5. Compressibility of floating pellets containing verapamil hydrochloride (VH)

Compression was carried out using a single stroke tablet press (Korsch EK0, Berlin, Germany). The device was equipped to permit measurement of the compression force. Tablets weighing 0.55 g were compressed by means of round punches ($\varnothing = 12.0$ mm, $R = 12$ mm) using a force of 6, 12 or 18 kN. It was assumed that the pellets in a single tablet contained 40 mg of VH.

3.6. In vitro drug release test

The determination of the release rate of VH from pellet and tablet formulations was performed using the Ph. Eur. paddle apparatus, Pharma Test Model PTWS–3 (Pharma Test, Hainburg, Germany). Six vessels were filled with 750 ml of hydrochloric acid (0.1 mol/l) at a temperature of 37 ± 0.5 °C. The concentration of VH in the samples was determined spectrophotometrically at 278 nm. A JASCO V-530 spectrophotometer (Jasco Corporation, Tokyo, Japan) was used for the investigation.

3.7. Physical properties of tablets

Tablets crushing strength was tested using an automatic hardness tester type TBH 20 (Erweka, Heusenstamm, Germany). Crushing strength was determined for 10 randomly selected tablets. Hardness of the tablets was determined by calculating the hardness factor (T) according to the following equation:

$$T = \frac{P_{max}}{2rh}$$

where: P_{max} – force needed to crash a tablet [kG], r – tablet radius [mm], h – tablet thickness [mm].
Friability of uncoated tablets was determined according to Ph. Eur. 6.

3.8. Texture analysis; determination of work of compression 50% (WC_{50})

For this measurement a TA.XT.plus texture analyser (Stable Micro System, Surrey, UK) was used. The device was equipped with a 5000 g capacity load cell and a cylindrical aluminum probe. The probe was moved down at a the pre-test speed of 0.1 mm/s. After detecting the surface of pellet, the pellet was crushed at a test speed of 0.05 mm/s over a distance of 50% of its diameter. The relationship between force (N) and distance (mm) was obtained. Then the area under curve was calculated as the work of compression 50% (mJ).

3.9. Morphology

The morphology of the pellets was studied by scanning electron microscopy (SEM). The samples were sputter-coated with gold for SEM analysis. The pellet structure was examined in a JEOL JEM-1200 EX II electron microscope equipped with an EM-ASID 11 Scanning Image Observation Device using secondary electron imaging.
The observed pellets were compressed using texture analysis, over a distance of 10% of the diameter with parameters as in Section 3.

Acknowledgements: The authors gratefully acknowledge Prof. Jolanta Kubasik-Juraniec and Ph.D. Olga Walentynowicz from the Department of Electron Microscopy, Medical University of Gdansk for scanning electron microscopy analysis. This work was a part of project financially supported by the Ministry of Science and Higher Education (Grant no. N40500332/0125).

References

Abraham B, Bashaiwoldu F, Podczeck JM (2004) Newton application of dynamic mechanical analysis (DMA) to determine the mechanical properties of pellets. Int J Pharm 269: 329–342.

Bodmeier R (1997) Tableting of coated pellets. Eur J Pharm Sci 43: 1–8.

Busse D, Fromm MF, Mörike K, Drescher S, Kühlkamp V (2001) Disposition and pharmacologic effects of R/S-verapamil in patients with chronic atrial fibrillation: An investigation comparing single and multiple dosing. Clin Pharm Ther 69: 324–332.

Lippold BC, Monells Pagés R (2001) Film formation, reproducibility of production and curing with respect to release stability functional coatings from aqueous polymer dispersions. Pharmazie 56: 5–17.

Nicklasson F, Johansson B, Alderborn G (1999) Tabletting behaviour of pellets of a series of porosities – a comparison between pellets of two different compositions. Eur J Pharm Sci 8: 11–17.

Santos H, Veiga F, Pinia M[a]E, Sousa JJ (2004) Compaction, compression and drug release characteristics of xanthan gum pellets of different compositions. Eur J Pharm Sci 21: 271–281.

Santos H, Veiga F, Pinia M[a]E, Sousa JJ (2005) Compaction, compression and drug release properties of diclofenac sodium and ibuprofen pellets comprising xanthan gum as a sustained release agent. Int J Pharm 295: 15–27.

Sawicki W (2002) Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans. Eur J Pharm Biopharm 53: 29–35.

Tunón Å, Börjesson E, Frenning G, Alderborn G (2003) Drug release from reservoir pellets compacted with some excipients of different physical properties. Eur J Pharm Sci 20: 469–479.

Vogelpoel H, Welink J, Amidon GL, Junginger HE, Midha KK, Möller H, Olling M, Shah VP, Barends DM (2004) Biowaiver monographs for intermediate release solid oral dosage forms based on Biopharmaceutics Classification System (BCS) literature data: verapamil hydrochloride, propranolol hydrochloride, and atenolol. J Pharm Sci 93: 1945–1956.