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ORIGINAL ARTICLE

Hot tabletting of slow-release tramadol hydrochloride microcapsules with cores obtained via compaction

Wiesław Sawicki[1], Jarosław Mazgalski[1,2] and Ilona Jakubowska[1]

[1]*Department of Pharmaceutical Technology, Medical University of Gdańsk, Gdańsk, Poland and* [2]*Preformulation Department, Pharmaceutical Works Polpharma SA, Starogard Gdański, Poland*

Abstract

Background: Coating, as a processing technique, applied to active pharmaceutical ingredient (API) crystals or particles (carriers) with an appropriate polymer allows to obtain a modified-release pharmaceutical dosage form. Such carriers can be the basic ingredient of a multi-unit dosage form. Additionally, coated API crystals (microcapsules) can provide an alternative to spherical granulate (pellets) as the main and most commonly used component of multi-unit dosage forms. Coating individual API crystals is a complicated process because of the crystals having insufficient size (below 100 μm), irregular shape, low mechanical durability and the fact that API crystals dissolve upon contact with the coating mixture, and other factors. *Method:* Compaction process was used to eliminate these inconveniences allowing us to obtain tramadol hydrochloride (TH) microcapsule cores in the size range of 212–500 μm. The coating of the cores was successfully conducted using a fluidized-bed coating technique with four different polymers that allowed us to attain slow release of TH. Then, the microcapsules were subjected to a hot tabletting process conducted by applying a low compression force of about 1 kN at 56°C. Semi-liquid granules containing melted PEG 3000 combined with TH microcapsules were compressed. A tablet matrix of good physical parameters was created when its temperature decreased to room temperature. In the proposed hot tabletting method, PEG 3000 included in the granulate provided the tableted microcapsules sufficient protection against rupture. *Results*: The compaction process allowed us to eliminate unwanted physical API properties, which could otherwise have an adverse effect on the fluidized-bed coating process. The microcapsule cores after compaction and coating using a fluidized-bed coating technique showed a TH-release profile similar to that of the compressed microcapsules after applying hot tabletting process. *Conclusions:* Multi-unit dosage forms can be obtained in a relatively simple way by combining three processes: (i) obtaining TH microcapsule cores by compaction, (ii) coating, and (iii) hot tabletting.

Key words: *Compaction; film coating; hot tabletting; slow-release microcapsules*

Introduction

Fluidized-bed coating has been often suggested as a suitable method for the microencapsulation of various substances[1,2].

A general aim of the research has been to establish a methodology for a certain active pharmaceutical ingredient (API) to be encapsulated successfully. In that context, the characteristics of the final product have been more important than the precise description of the technological aspects of the procedure itself. In this investigation three processes, coating, compaction, and hot tabletting, were briefly described with a focus mainly on critical aspects.

Microencapsulation of drugs is carried out for a variety of reasons such as taste/odor masking, stabilization of core content, but mainly for sustained-release purposes after oral administration[3]. Sustained-release dosage forms can be produced using an API in the form of crystals or granules. After coating with an appropriate polymer, the crystals or granules may be used as the basic ingredient of a multi-unit dosage form. Such dosage forms are more advantageous with respect to pharmacokinetics and safety of

Address for correspondence: Prof. Wiesław Sawicki, Department of Pharmaceutical Technology, Medical University of Gdańsk, Gdańsk, Poland. E-mail: wsawicki@amg.gda.pl

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use when compared to single-unit (monolith) dosage forms[4]. Additionally, coated crystals or granules (microcapsules) containing API as the main ingredient of multi-unit dosage forms offer an alternative to pellets.

Drug crystals are rarely coated directly because their small and irregular shape makes coating impossible by pan technique and very difficult by fluid bed coating[5].

Fluid bed coating, bottom-spray using Wurster (Glatt, Binzen, Germany), DiscJet™ (Oystar Huttlin, Schopfheim, Germany), and FlexStream™ (GEA Pharma Systems, Bubendorf, Switzerland), or top-spray technique applied to small particles (individual API crystals) can be a complicated process because the API crystals may be too small in size (below 100 μm), have inappropriate shape, insufficient mechanical durability, or they may dissolve upon contact with the coating suspension.

The model substance tramadol hydrochloride (TH) crystals, average size 100 μm, exist as fragile agglomerates that break easily during the coating process and are characterized by high solubility on contact with both water-based and organic coating suspensions. Microcapsule cores easily dissolve on contact with the atomized suspension droplets and the API penetrates (diffuses) into the film coating. This can introduce changes in the mechanical durability of the coating and its diffusion properties.

Additionally, mechanical durability of the TH agglomerates must be taken into account. If the friability is too high, larger particles break down into fines. The broken-off fragments adhere to large TH particles, which can have an adverse effect on the fluidized-bed coating process because the size of small fragments of API crystals is insufficient for the droplets of the coating suspension to cover them. Also, the ratio of the size of the coated cores to the size of the droplets of the coating suspension does not allow adequate coating. The size of the aerosol droplets must be sufficiently small to create a tight, adhesive, and smooth coating surface upon contact with the surface of API crystals[5,6].

To eliminate unwanted properties of the substance that appear during fluid bed coating process, roller compaction was used.

In the roller compaction process primary powder particles are aggregated under high pressure. Handling of the powders is improved because of a larger particle size and a better flowability and the dust problem is thus minimized. Compaction of TH agglomerates composed of 100 μm particles produced a granulate containing particles in the size range of 212–500 μm. The granulate was subject to fluid bed coating process with one of the four coating systems: ethylocellulose (EC) aqueous dispersion—Aquacoat® ECD, organic solution of EC, aqueous dispersion of Eudragit® RS/Eudragit® RL mixture, and organic solution of Eudragit® RS/Eudragit® RL mixture. The granulate fraction used for coating, when compared to the original TH sample, had smaller surface area (Figure 2A) and higher mechanical durability (Figure 2B).

Microcapsules were obtained by means of coating compacted TH microcapsule cores. In the fluid bed coating process different polymers in the form of aqueous dispersions and organic solutions were used and compared. The tablets were produced by means of hot tabletting TH microcapsules. The compression force in the hot tabletting—as opposed to traditional tabletting process— is very low and the mechanisms responsible for forming tablet matrix such as fracture of particles, bond formation, and consolidation followed by elastic recovery during the decompression process are not present[7].

During hot tabletting process under low compression force the tablet matrix is formed as a result of the tablet ingredients being bound by a melted excipient present in a tablet composition. Above-mentioned aspects of the process, especially the low compression force, create new possibilities of tabletting pressure-sensitive materials, for example, modified- and slow-release pellets and enzymes[8,9].

The aim of this work was to develop a method of producing tablets composed of TH microcapsules of slow release. The target API-release rate assumed at the start of the research was equivalent to both the nontableted and the tableted microcapsules as well as commercially available Tramal Retard 100 mg tablets.

Materials and methods

Materials

TH (Polpharma, Starogard Gdański, Poland), microcrystalline cellulose, Avicel® PH101 (FMC, Brussels, Belgium), polyethyleneglycol 3000, PEG 3000 (Merck Schunchardt OHG, Hohenbrunn, Germany), ethylcellulose (Aquacoat® ECD, FMC BioPolymer, Philadelphia, PA, USA), triethyl citrate (Lancaster, Morecambe, UK), croscarmellose sodium (Vivasol®, JRS Pharma, Rosenberg, Germany), ethylcellulose N 100 (Aqualon, Dusseldorf, Germany), Eudragit® RS 30D (Evonik Röhm GmbH, Darmstadt, Germany), Eudragit® RL 30D (Evonik Röhm GmbH), Eudragit® RS 12,5 (Evonik Röhm GmbH), Eudragit® RL 12,5 (Evonik Röhm GmbH), magnesium stearate (Greatvista Chemicals, Zhejiang, China), talc (Luzenac, Milan, Italy), TH reference tablets (Tramal Retard 100 mg, batch no. 29L01; Grunenthal GmbH, Aachen, Germany). All the solvents were of analytic grade, unless specified.

Preparation of tramadol hydrochloride microcapsule cores

TH microcapsule cores were prepared by roller compaction of pure API. Roller compaction (using the GMP Alexanderwerk WP 150) was achieved under these conditions: roll speed 2.4 rpm, preselected roll gap size 1.5 mm, compaction pressure 8 and 16 kN/cm, roll type: grooved, rotor fine granulator speed 150 rpm, and mesh-size of sieve 1.4 mm.

Coating of the microcapsule cores

Microcapsule cores (600 g) were coated in a fluidized-bed coater using the Wurster bottom spray (Glatt GPCG3, Binzen, Germany) with aqueous dispersion of EC—Aquacoat® ECD, ethanol solution of EC (EC/EtOH), aqueous dispersion of Eudragit® RS/Eudragit® RL, and organic (acetone/isopropanol) solution of Eudragit® RS/Eudragit® RL. The quantitative composition of the mixtures and the parameters of the process are illustrated in Tables 1 and 2.

The film coating was sprayed onto drug-loaded pellets to achieve drug release over a period of 8 hours.

Microcapsule cores and their properties

Size distribution of the microcapsule cores was evaluated by sieve analysis. Analysis was performed on 100 g of material sieved on a sieve-shaker (Retsch, Haan, Germany) for 10 minutes at an amplitude of 1.5 mm. The sieves used were 212, 350, 425, 600, 850, 1000, and 1180 μm. The percentage of microcapsule cores remaining on each sieve was calculated.

Table 1. Coating composition and process parameters for ethylcellulose.

	Coating composition and coating parameters	
	Ethylcellulose water dispersion	Ethylcellulose ethanol solution
Aquacoat® ECD (g)	850	—
Ethylcellulose N100 (g)	—	200
Water (g)	210	—
Ethanol 96° (g)	—	3600
Triethyl citrate (g)	42	10
Inlet temperature (°C)	55	55
Outlet temperature (°C)	42	40
Bed temperature (°C)	38	34
Fluidizing air flow (m^3/h)	140	140
Coating rate (g/min)	4–7	5–10
Atomizing air pressure (bar)	1.5	2
Tray drying (°C/h)	60/24	60/2

Table 2. Coating composition and process parameters for Eudragit® RS/RL.

	Coating composition and coating parameters	
	Eudragit® RS/RL water dispersion	Eudragit® RS/RL organic dispersion
Eudragit® RS 30D (g)	900	—
Eudragit® RL 30D (g)	100	—
Eudragit® RS 12,5 (g)	—	2000
Eudragit® RL 12,5 (g)	—	200
Talk (g)	90	—
Magnesium stearate (g)	—	82
Water (g)	1000	—
Triethyl citrate (g)	60	14
Inlet temperature (°C)	40	40
Outlet temperature (°C)	27–32	26
Bed temperature (°C)	25–28	25
Fluidizing air flow (m^3/h)	170	140
Coating rate (g/min)	3–6	3–8
Atomizing air pressure (bar)	2	1.5
Tray drying (°C/h)	40/24	40/2

The friability was determined by placing 20 g of microcapsule cores in the size range of 212–500 μm in a friabilator (Erweka, Frankfurt am Main, Germany) rotating at 25 rpm for 10 minutes. Then, the remaining material was sieved through a 212 μm screen installed on a sieve shaker for 2 minutes at an amplitude of 1.5 mm. The material remaining on the screen was weighed and the friability percentage was calculated.

Breaking force [N] needed to break a TH microcapsule core was measured using a texture analyzer (TA XT Plus, Stable Micro System, Godalming, UK). The measurements were performed 24 times.

The ratio between the compression force (N) and the distance (mm) for the microcapsules coated with ethylcellulose organic solution and ethylcellulose water dispersion was measured. The measurements were performed 24 times. Then Texture Exponent 32 computer program was used to calculate the area under the curve as the work of 25% compression (mJ).

Granule porosity was measured by a combination of tapped density and true density of the granule using a gas pycnometer (AccuPyc 1340, Micromeritics, Norcross, GA, USA) with helium as the test gas.

The film-coating thicknesses of microcapsules that had been cut in half were measured under a microscope (Eclipse E200, Nikon,Tokyo, Japan) coupled with a digital camera (Altra 20, Soft Imaging System GmbH, Munster, Germany).

Hot tableted tramadol hydrochloride microcapsules

Tablet formulation was composed of a mixture of TH microcapsules (fraction 350–600 μm) as follows: 50%

microcapsules, 23% PEG 3000, 23% PH 101 microcrystalline cellulose, 3.5% croscarmellose sodium, and 0.5% magnesium stearate. PEG 3000 and PH 101 microcrystalline cellulose were granulated in a high-shear mixer (Glatt VG5, Dresden, Germany) using water as a binder (30/100 g of powder). The granulate was separately dried in a forced air-drying oven (Venticell BMT, Brno, Czech Republic) at 45°C for 12 hours. The dried granulate was then passed through a sieve with a mesh size of 1.0 mm. The coated TH microcapsules were combined with the dried PEG/MCC granulation, croscarmellose sodium as disintegrant, and magnesium stearate (to prevent the mixture from sticking to the punches during the hot tabletting process). The final mixture was blended for 5 minutes (Figure 1).

A ratio of 50% microcapsules and 50% granulate ensured that the tablet formulation had adequate flow, which could otherwise be adversely affected by tackiness of the heated tablet formulation.

The resulting tablet formulations were spread evenly on a paper tray and heated in a forced air-drying oven to a temperature not exceeding 56°C. A tablet press granulate feeder was heated in another forced air-drying oven. The feeder was then immediately mounted onto a rotary tablet press (Korsch XL 100, Berlin, Germany) filled with the heated tablet formulation. Tabletting process took 3 minutes and within this time the temperature was kept constant by heated granulate feeder at 56°C. The formulations were compressed into tablets with the use of the hot tabletting process in the same conditions. The tabletting parameters were as follows: spherical punches of 10.0 mm in diameter, curve radius 9 mm, main compression forces 1 and 10 kN, precompression forces 0.1 and 1 kN.

Physicochemical properties of tablets obtained by hot tabletting

Tests for disintegration, friability, and hardness of tablets obtained by hot tabletting were performed according to USP 31, which specifies requirements for compressed tablets.

Spectrophotometric assay for TH in tablets was determined using tablet powder (20 units) exactly equivalent to 100 mg of tablets. The TH concentration was read from the appropriate calibration graph.

In vitro release studies

Dissolution test was performed in 1000 mL of water at 37°C (±0.5°C). An automated Hansson Research Sr8+ paddle apparatus dissolution tester (Hansson Research, Chatsworth, CA, USA) with an online UV/Vis spectrophotometer (Agilent 8453, Wilmington, DE, USA) was used. At different time intervals (1, 2, 3, 4, 5, 6, 7, and 8 hours) the concentration of TH in the samples was analyzed spectrophotometrically at 272 nm. The dissolution results were calculated with reference to 100 mg of TH standard. All dissolution profiles are the mean of six dissolution tests performed under sink conditions.

Similarity of dissolution profile of the tablets was compared using a model-independent method by linear regression at specified time points and calculating an f_2 similarity factor. An f_2 value between 50 and 100 suggests that two dissolution profiles are similar (The European Agency for the Evaluation of Medicinal Products CPMP/EWP/QWP/1401/98, 2001).

Structure characteristics of microcapsules and tablets

The structure and appearance of the microcapsules and tablets were investigated using images obtained by scanning electron microscopy (SEM, Zeiss SUPRA 35VP, Carl Zeiss, Oberkochen, Germany) with extra high tension (EHT) voltage power of 1 kV.

Results and discussion

TH microcapsule cores were obtained by means of roller compaction process. TH was compacted without the excipients, because it already had sufficient compression properties and was able to form sufficiently mechanically durable microcapsule cores (Figure 2B). Microcapsule cores were coated with EC and Eudragit® RS/RL polymer system. This work compares the compacted TH microcapsule cores coated with the polymer-based coating suspensions (aqueous dispersions and organic solutions). The coating systems allowed us to obtain slow release of TH from the resulting microcapsules.

In the compaction process two different pressure values were used (8 and 16 kN/cm). Under both pressure forces the TH powder behaved similarly, creating ribbons of identical length and tightness and generating similar amounts of dust. Roller compaction process parameters apart from the pressure were identical. That no variables had to be altered was because the granulate had appropriate bulk density, particle size, and TH powder flow properties, which guaranteed that the work of the compactor would be correct.

The results from force analysis, hardness tests, friability, and porosity of the compacted TH cores for both pressure values did not show significant differences. Application of 8 kN/cm pressure yielded 36.8% of compacted TH microcapsule cores in the size range of 212–500 μm, whereas 16 kN pressure yielded 45.4% of compacted TH microcapsule cores that were then subject

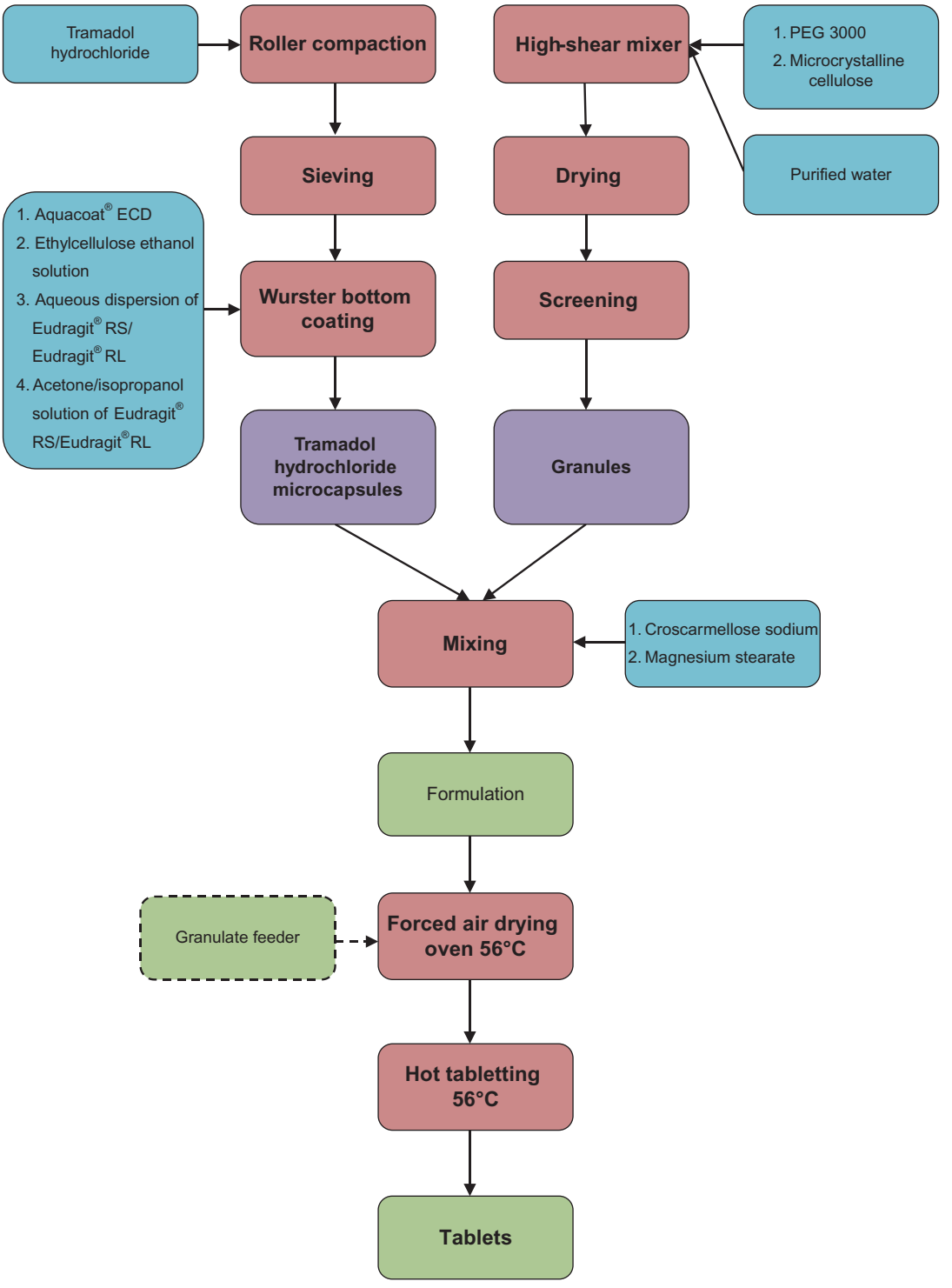

Figure 1. Flowchart of obtaining tablets with microcapsules by hot tabletting process.

to fluid bed-coating process. The friability of the microcapsule cores fraction was 0.95% and 0.70% for 8 and 16 kN/cm pressures, respectively. Microcapsule core hardness, which is a factor directly connected with friability, was 2.8 and 3.2 N, whereas the porosity was 45% and 42% for 8 and 16 kN/cm pressures, respectively.

The different pressures had a small impact on friability test results. A higher degree of TH compression and consolidation was achieved by applying a higher

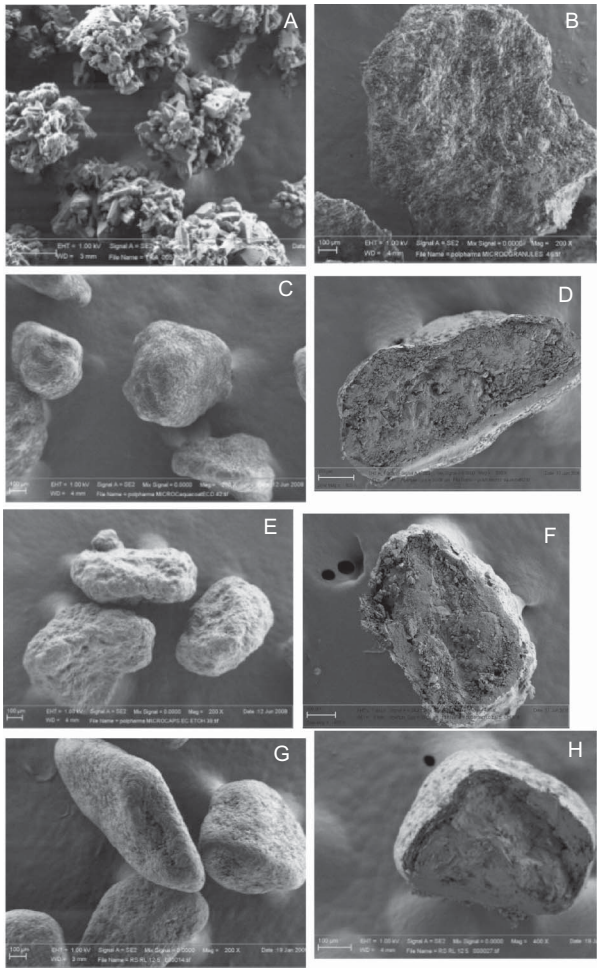

Figure 2. SEM images of tramadol hydrochloride (A) and compacted tramadol hydrochloride (microcapsules cores) (B). EC/EtOH microcapsule surface (C) and cross-section (D). Aquacoat® ECD microcapsule (E) and cross section (F). Eudragit® RS/RL organic solutions 12,5 microcapsule surface (G) and cross section (H).

pressure, which—because of a very small particle size and good compressibility of the particles—created bigger agglomerates (granules) (Figure 2A).

The EC/EtOH coating mixture was chosen because of the lowest toxicity of the solvent's vapors, the economic-environmental aspect (cheaper than solvents such as acetone/isopropanol), and in order to test the possibility of coating with the EC/EtOH system, of a much higher viscosity, when compared to EC used as an acetone/isopropanol mixture[10].

The TH core 212–500 μm fraction was coated with EC/EtOH, aqueous dispersion of EC—Aquacoat® ECD, and an organic solution of Eudragit® RS/RL. Coating the TH cores with aqueous dispersion of Eudragit® RS/RL was not successful, because of the clogging of the spraying nozzle with talc. All the other coating types resulted in a slow-release profile of TH from the microcapsules.

The SEM images of the surfaces of the microcapsules and their cross sections show a regular and tight structure of the coating (Figure 2C–H). The studies on all three types of the coating suspensions showed that high level of coating suspension (10–20%)[2] was required to obtain a slow-release profile. As a result the rough, uneven surface of the microcapsules cores was completely covered with a thick and tight film coating, which created smooth and even surface of the microcapsules.

The microcapsules coated with Aquacoat® ECD exhibited the thickest film coating, which was 59.9 ± 6.4 μm SD. The organic coating suspensions were less thick with 45.5 ± 4.4 μm SD for Eudragit® RS/RL and 32.3 ± 3.0 μm SD for EC/EtOH. It can be rather surprising that, despite high viscosity of the EC/EtOH coating system, tight film coating was obtained and the minute roughnesses in the surface of the microcapsules cores were filled.

The reason why the coating layer of Aquacoat® ECD applied to microcapsules was the thickest can be explained by the fact that more polymer was necessary to achieve the required release profile. Organic coating suspensions produced a less thick coating layer still ensuring the adequate release profile. When using aqueous dispersion more polymer is required because of a different film-forming mechanism, which can have a direct effect on the coating structure and the final thickness[11].

It should be kept in mind that the coating structure and the rate of drug release from microcapsules can vary as they may get affected by the process parameters (even though the ingredients, the amounts, and the order of addition remain the same), such as stirring rates, coating suspension temperature, amount and temperature of fluidizing air, and cooling rates. These parameters suggest that the rate of the microcapsules film formation is an important formulation factor and could have impact on film formation changes and topography[3,12].

Additionally, the surface of those microcapsules was marked with characteristic dried-up droplets of the coating suspension, which did not fully coalesce on the surfaces of the microcapsules.

The capability for shape-changing: compression of the microcapsules was checked by assessing the relationship between the distance (mm) and the force (N) needed to obtain 25% deformation of the microcapsules. The result of the deformation of microcapsules is represented by the area under the curve (mJ). The bigger the area under the curve (mJ), the higher the mechanical durability and the elasticity of the microcapsules. The proposed deformation was considered a realistic value achievable during the tabletting process. The force and the area under the curve for the microcapsules coated with EC/EtOH were 1.55 ± 2.7 N SD and 0.14 ± 2.2 mJ SD, Aquacoat® ECD—1.97 ± 4.4 N SD and 0.16 ± 4.0 mJ SD, and for Eudragit® RS/RL 12.5% organic solution—1.82 ± 3.1 N SD and 0.20 ± 3.1 mJ SD.

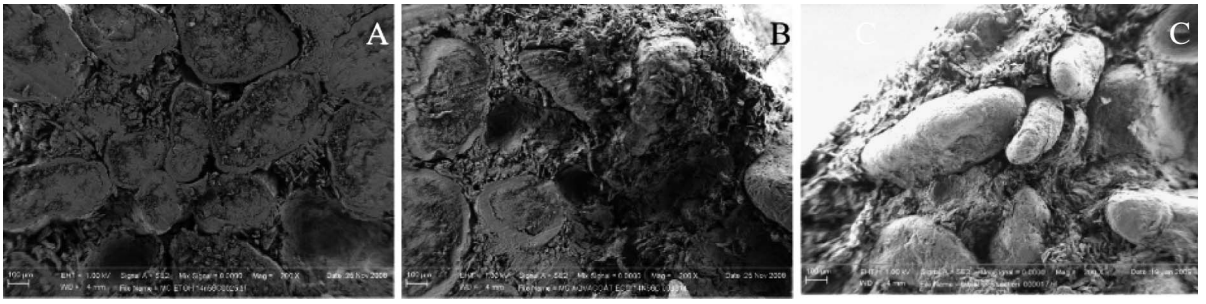

Figure 3. SEM images of compressed microcapsules. Tablet cross section with microcapsules-coated EC/EtOH (A), Aquacoat® ECD (B), and Eudragit® RS/RL 12,5 (C).

Taking into account only mechanical durability parameters indicates that Aquacoat® ECD produces the most durable microcapsules, whereas EC/EtOH-coated capsules are the least durable.

Based on the SEM results it has been observed that the structure of the tablets obtained by hot tabletting shows absence of the microcapsule deformation. The tablet matrix is slightly compact with visible empty spaces, which leads to the conclusion that there was no direct contact between the TH microcapsules and the granulate composed of PEG 3000 and microcrystalline cellulose (Figure 3A–C). The cross-section SEM image of the tablets confirms that the element, which undergoes deformation during the hot-tabletting process, is melted PEG 3000 as a part of the tablet formulation.

The compressibility of different excipients was assessed with respect to the cushioning properties during the hot tabletting process of pellets coated with aqueous dispersion of Aquacoat® ECD. The excipients were granulated with PEG 3000 in the ratio of 1:1. The resulting granulate was mixed with the pellets creating a tablet formulation, which was then tabletted. No effect on the release profile was observed. This is proof that the formation of the tablet matrix was not directly associated with the compaction properties of the excipients but with the cushioning properties of melted PEG 3000, which in combination with the excipients, created inter-granular bonds in the tablet formulation[13]. The bonds among the granules are formed because the melted PEG makes the granules more cohesive. As a result only a very low compression force is required to form tablet matrix and the mechanical deformation of granules does not occur. The bonds immediately solidified after tabletting creating a solid tablet matrix.

Unchanged shape and lack of deformation and fragmentation of the film coating of the TH microcapsules could be achieved by compressing the microcapsules via a hot tabletting method in which it was mainly the fillers and the binder (PEG 3000 in the form of granules) that were deformed and the TH microcapsules were kept intact. Semi-liquid granules accommodated their shape to the microcapsules without adverse impact on the coating and the cores of the microcapsules.

The physical properties of the tablets with hot tableted TH microcapsules and traditionally tableted TH microcapsules showed significant differences in the tablet thickness and the time of the tablet disintegration time. With hot tableted formulations the minimum compressing force is sufficient to bind the TH microcapsules with the PEG 3000 granulate and thus create a tablet matrix. Traditional tabletting requires a significantly higher compressing force, which results in producing tablets of visibly smaller thickness[6].

The longest disintegration time was observed for tablets with an Eudragit® RS/RL coating. This is a consequence of the coating substance properties, which exhibits a tendency toward mechanical consolidation and creating strong bonds between the coated microcapsules with the use of Eudragit® RS/RL. Strong bonds between the microcapsules, apart from a longer tablet disintegration time, had an impact on the tablet hardness, much higher than for tablets with EC/EtOH-coated and Aquacoat® ECD-coated microcapsules (Table 3).

The tests of TH release from the microcapsules coated with three types of polymers allowed us to obtain a prolonged 8-hour release profile in all but one case (aqueous dispersion of Eudragit® RS/RL). To show the similarities between the release profiles, f_2 similarity factor in comparison with the reference tablets (Tramal Retard 100 mg) was assessed. The most similar release profile was that exhibited by EC/EtOH-coated microcapsules where f_2 was 73 and for hot tableted microcapsules f_2 was 64, whereas for traditional tabletting f_2 was 56 (Figure 4). For Aquacoat® ECD-coated microcapsules f_2 was 65, for hot tableted microcapsules f_2 was 54, and for traditionally tableted ones f_2 was 45 (Figure 5).

The TH-release profile from the tableted microcapsules coated with EC/EtOH was closer to the release profile of untableted microcapsules when compared to Aquacoat® ECD-coated microcapsules. This was a consequence of the coating structure and mechanical durability, which in turn is a result of a difference in the

Table 3. Physical properties of tablets obtained by hot and traditional tabletting microcapsules.

	Compression force/tabletting temperature					
	1 kN/56°C			10 kN/20°C		
	Microcapsule coating polymer					
Parameter	EC/EtOH	Aquacoat® ECD	Eudragit® RS/RL	EC/EtOH	Aquacoat® ECD	Eudragit® RS/RL
Hardness (N)	64 ± 3.3	53 ± 2.7	72 ± 4.5	60 ± 4.2	48 ± 5.2	69 ± 3.5
Friability (%)	0.3	0.5	0.2	0.6	0.6	0.5
Thickness (mm)	6.20 ± 1.5	6.13 ± 1.7	6.21 ± 2.3	5.30 ± 0.8	5.51 ± 1.2	5.58 ± 1.1
Disintegration time (minutes)	10	8	14	7	4	20
Assay (%)	99.2	97.7	97.6	97.5	98.2	99.0
Mass of tablets (mg)	403.2 ± 4.8	396.7 ± 2.7	398.5 ± 3.9	399.2 ± 1.5	396.0 ± 2.1	397.4 ± 1.8

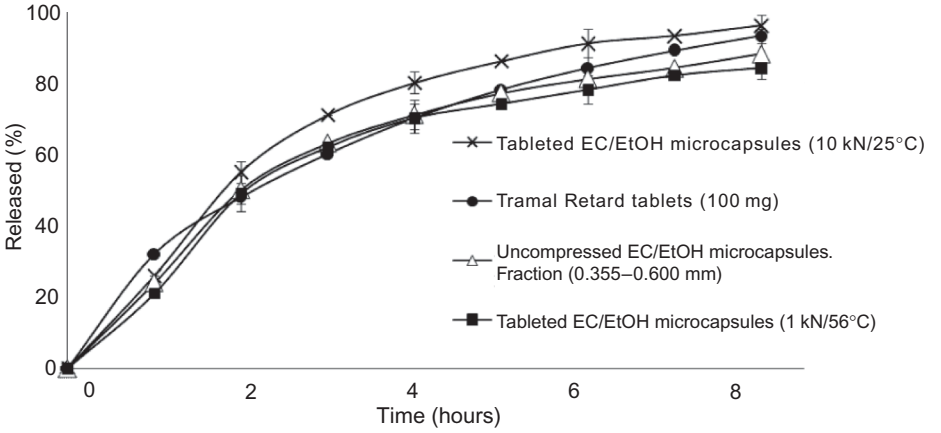

Figure 4. Effect of traditional and hot tableting on tramadol hydrochloride dissolution profile of coated EC/EtOH microcapsules as such.

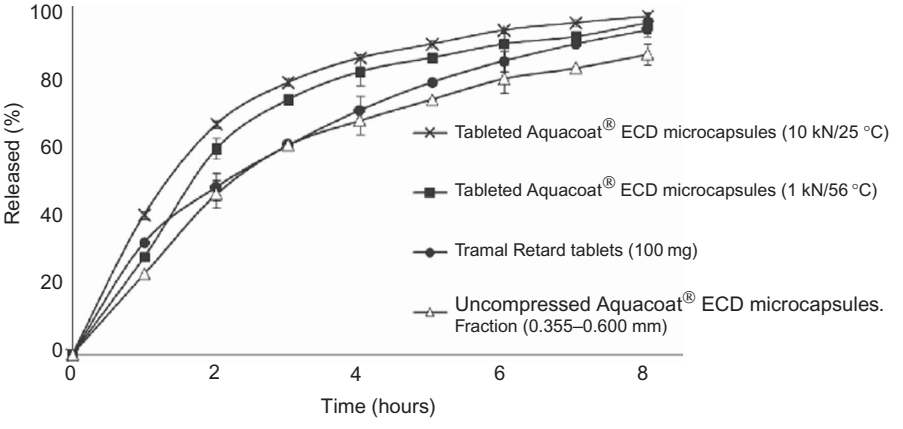

Figure 5. Effect of traditional and hot tabletting on tramadol hydrochloride dissolution profile of coated Aquacoat® ECD microcapsules as such.

coating forming mechanism when using organic coating suspensions[14].

The least similar release profiles in comparison with the reference product were noted for Eudragit® RS/RL-coated microcapsules: f_2 was 51 for uncompressed microcapsules, 59 for hot tableted capsules, and 43 for traditionally tableted ones (Figure 6). Additionally, tablets with Eudragit® RS/RL-coated TH microcapsules did not disintegrate during the release tests but behaved similarly to not swelling matrix tablets. Similarly to the long disintegration time, this is a result of the mechanical consolidation, creating strong bonds between the Eudragit® RS/RL-coated microcapsules with 10 kN compression force used. The above phenomenon results in an s-shaped release profile.

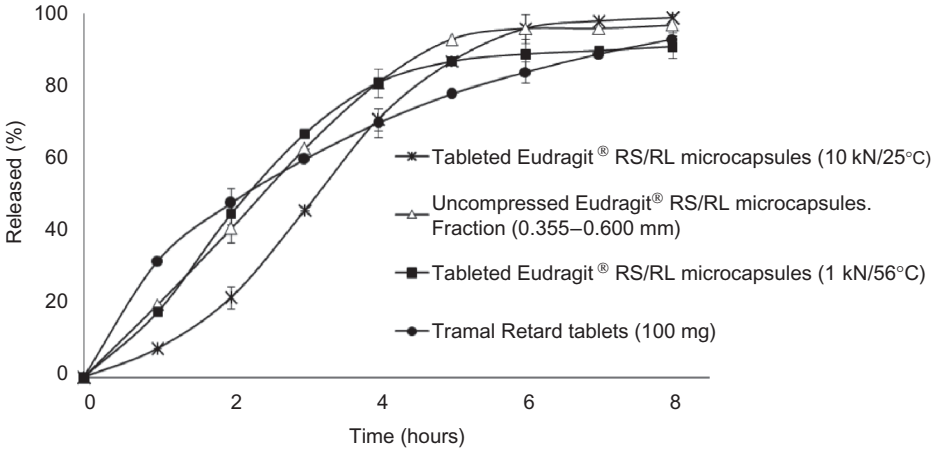

Figure 6. Effect of traditional and hot tabletting on tramadol hydrochloride dissolution profile of coated Eudragit® RS/RL 12,5 microcapsules as such.

Conclusion

TH is characterized by good compression properties, which in the roller compaction process allowed us to obtain microcapsule cores with very good mechanical parameters. After hot tabletting, the resultant tablets produced drug-release characteristics similar to the commercial brand.

The physical parameters for the tablets containing microcapsules were noticeably better than those for hot tableted slow-release TH pellets[10]. Low compression force applied during hot tabletting could create new possibilities of tabletting pressure-sensitive materials, for example, modified- and slow-release pellets, microcapsules, and enzymes.

The use of other excipients than microcrystalline cellulose is possible in hot tabletting because the formation of the tablet matrix cannot be directly attributed to the compaction properties of excipients, but to melted PEG 3000 in the tablet formulation. This can be advantageous in the production of multilayer tablets.

Hot tabletting process of creating the tablet matrix could allow us to incorporate a high percentage of API (whose compaction properties are not good) into tablet formulation. It could also allow us to embed disintegrating substances and, as a result, to obtain tablets with high porosity that is favorable during the production of orally dispersible tablets.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Lehmann K. (1992). Fluid-bed spray coating. In: Donbrow M ed. Microcapsules and nanoparticles in medicine and pharmacy. Boca Raton: CRC Press, 73–97.
2. Deasy PB. (1984). Microencapsulation and Related Drug Processes. Drug and Pharmaceutical Science Series. In: Deasy PB, ed. 20, Marcel Dekker Inc.
3. Deasy PB. (1994). Evaluation of drug-containing microcapsules. J Microencapsul, 11(5):487–505.
4. Antal I, Kallai N, Angyal N, Balogh E, Dredan J, Devay A, et al. (2007). Development of modified release multiple unit dosage forms. J Pharm Sci, 32S:S10.
5. Guignon B, Duquenoy A, Dumoulin ED. (2002). Fluid bed encapsulation of particles: Principles and practice. Dry Technol, 20(2):419–47.
6. Nienaltowska K, Depypere F, Dewettinck K, Van Der Meeren P, Ronsse F, Pieters JG. (2009). Water-soluble cellulose derivatives as coating agents in fluidized bed processing. Particulate Sci Technol, 27:389–403.
7. Jain S. (1999). Mechanical properties of powders for compaction and tabletting: An overview. Pharm Sci Technol Today, 2:20–31.
8. Picker KM. (2004). Soft tableting: A new concept to tablet pressure-sensitive materials. Pharm Dev Technol, 9:107–21.
9. Debunne A, Vervaet C, Mangelings D, Remon JP. (2004). Compaction of enteric-coated pellets: Influence of formulation and process parameters on tablet properties and in vivo evaluation. Eur J Pharm Sci, 22:305–14.
10. Dias VD, Ambudkar V, Fegely KA, Rajabi-Siahboomi AR. (2008). The influence of solvent type on extended release coating with ethylcellulose barrier membranes. Controlled Release Society Annual Meeting, New York.
11. Siepmann F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. (2008). Polymer blends for controlled release coatings. J Control Release, 125:1–15.
12. Moldenhauer MG, Nairn JG. (1991). The effect of rate of evaporation on the coat structure of ethylcellulose microcapsules. J Control Release, 17:49–60.
13. Sawicki W, Mazgalski J. (2009). Hot tabletting as a new method for obtaining tablets from slow release–coated pellets. Drug Dev Ind Pharm, 35:1–9.
14. Bodmeier R, Wesseling M. (1998). Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat®, or an organic ethylcellulose solution. Int J Pharm, 152:17–26.