Verapamil hydrochloride (VH) is a calcium channel antagonist. It is used in the treatment of hypertension and angina pectoris. In medical practice it is mostly used in a conventional tablet form in a minimal dose of 40 mg and a maximal dose of 180 mg and in slow release form in doses of 120 and 240 mg, respectively. Only 10–20% out of the 90% of the dose absorbed from the digestive tract penetrates to the circulatory system in an unchanged form (1). This is due to a marked first pass effect, mostly in the liver. Improvement of bioavailability was obtained by the use of multiple-unit dosage forms e.g., pellets. The aim of this study was to compare the utility of the MCC and PC in the floating pellet cores comprising verapamil hydrochloride (VH) manufactured by extrusion and spheronization and influence on their physical properties like swelling, compressibility and VH release. It was found by scanning electron microscopy (SEM) investigation that porosity of surface of the pellets’ cores increased with an increase of PC amount in composition. Differential scanning calorimetry (DSC) analysis indicated the lack of physico-chemical interaction between PC and MCC either with VH or with any excipients in the pellet core. Formulation having the highest PC participation were characterized by the highest friability and compressibility and addition of MCC corresponded with a decrease of friability and compressibility. The results on pellets friability were not reflected by the results on the hardness test. It means that the PC contents growth contributes to the hardness growth. The swelling forces of physical mixture of powders containing PC and MCC was different and increased with increasing amount of PC in pellet’s core. Pellets’ cores were coated with Eudragit® NE dispersion. It was found that VH release rate from coated pellets with higher amount of PC was considerably slower in comparison to the pellets containing highest MCC participation.

**Keywords:** verapamil hydrochloride, floating pellets, microcrystalline cellulose, powdered cellulose, swelling, porosity.

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A gelatin capsule filled with target slow release floating pellets containing 40 mg VH in the stomach ensures obtaining better bioavailability parameters of that drug compared to conventional tablets (3). It was assumed that pellets should reside in the stomach, float for several hours and gradually release the VH in a controlled way.

The idea of floating pellets was realized taking advantage of a change in physical properties of the drug after its passing to the acidic environment of hydrochloric acid in vitro or to the acidic stomach environment in vivo. Thus, sodium hydrocarbonate was added as a component of the pellets core. This substance after reacting with hydrochloric acid creates carbon dioxide. Resulting bubbles adsorb on the surface of the spherical core of the pellets and cause their floating in the fluid in vitro or in vivo (4). The pellets are enclosed in hard gelatin capsules. Compression of pellets into tablets is a modern technological process (5). However, it is much more ideal than enclosing them in a hard gelatine capsule. A larger drug dose can be comprised just in the tablet. The method of dosing is also easier because

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**Abstract:** Microcrystalline cellulose (MCC) and powdered cellulose (PC) are commonly used excipients for solid dosage forms e.g., pellets. The aim of this study was to compare the utility of the MCC and PC in the floating pellet cores comprising verapamil hydrochloride (VH) manufactured by extrusion and spheronization and influence on their physical properties like swelling, compressibility and VH release. It was found by scanning electron microscopy (SEM) investigation that porosity of surface of the pellets’ cores increased with an increase of PC amount in composition. Differential scanning calorimetry (DSC) analysis indicated the lack of physico-chemical interaction between PC and MCC either with VH or with any excipients in the pellet core. Formulation having the highest PC participation were characterized by the highest friability and compressibility and addition of MCC corresponded with a decrease of friability and compressibility. The results on pellets friability were not reflected by the results on the hardness test. It means that the PC contents growth contributes to the hardness growth. The swelling forces of physical mixture of powders containing PC and MCC was different and increased with increasing amount of PC in pellet’s core. Pellets’ cores were coated with Eudragit® NE dispersion. It was found that VH release rate from coated pellets with higher amount of PC was considerably slower in comparison to the pellets containing highest MCC participation.

**Keywords:** verapamil hydrochloride, floating pellets, microcrystalline cellulose, powdered cellulose, swelling, porosity.

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of the possibility of dividing the tablet in required way. The method of preparation is simpler, cheaper, more efficient, and it does not require complex control of the process of capsules’ filling with pellets. Also ensures lower risk of copying the technology process of the drug form by competing producers.

In the process of pellet compressibility permanent deformation of cores and film is expected not to follow. As a result, a considerably faster VH release comparing to pellets in a hard gelatin capsule may be obtained.

It is more difficult to compress pellets having floating properties because tablets in the stomach must undergo fast disintegration into undeformed pellets, which should then emerge from the water and release VH in a controlled way.

The aim of this paper was to study the utility of the microcrystalline cellulose (MCC) and powdered cellulose (PC) in the VH pellet cores and influence on their physical properties like swelling, compressibility and VH release rate. That research should be helpful in designating a proper kind of cellulose for pellet contents, which are going to be compressed.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride (Recordati, Milano, Italy), sodium hydrocarbonate (Merck, Darmstadt, Germany), microcrystalline cellulose (Avicel PH 101°, mean particle size 50 µm, FMC, Brussels, Belgium), (Avicel PH 102°, mean particle size 100 µm, FMC, Brussels, Belgium), powdered cellulose (Arbocel P 290°, mean particle size 70 µm, IRS, Rosenberg, Germany), lactose (Ubichem, Eastleigh, United Kingdom), Povidone K-30 (BASF, Ludwigshafen, Germany), Eudragit NE 40D (Röhm Pharma, Darmstadt, Germany), Macrogol 6000 S (Fluka Chemie, Buchs, Switzerland), gelatin (Loba Feinchemie AG, Fischamend, Austria), talc (Ph. Eur.).

Preparation of floating pellets cores

Pellets were prepared by means of extrusion and spheronization. The contents of particular core formulations is presented in Table 1. Powder mixtures were moistened with portions of 5% Povidone K-30 solution.

The obtained moist mass was inserted into the extruder chamber in portions of approximately 80 g. Caleva Extruder 25 was used (Caleva, Dorset, UK). The process was carried out using a sieve division with opening diameter of 1.2 mm at extruder head rate of 40 rpm.

Spheronization process was performed in Caleva Model 120 apparatus (Caleva, Dorset, UK). Spheronizer shield rotation speed was measured by means of tachometer Caleva (1200-1300 rpm). Spheronization time of a 20 g portion of granule was 4 min. Wet cores were dried in a drying cabinet with circulating hot air at 40°C for 12 h and then separated into fractions of 0.8-1.0, 1.0-1.25 and 1.25-1.6 mm by means of a sieve set. Pellets of 1.0-1.25 mm comprised the largest fraction (about 80%) under the given conditions of spheronization.

Thermal analysis

Differential Scanning Calorimetry (DSC) thermograms were performed using DSC model 822 equipped with STAR® software (Mettler Toledo, Boston, USA). 3-mg samples were heated under an air atmosphere at a heating rate of 10°C/min up to the final temperature of 300°C.

Morphology

The morphology of the pellets were 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.

Table 1. Composition [%] of pellets’ cores with verapamil hydrochloride.

<table>
<thead>
<tr>
<th>Substance</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil hydrochloride</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Avicel PH 101</td>
<td>45.2</td>
<td>33.5</td>
<td>22.2</td>
<td>10.9</td>
</tr>
<tr>
<td>Arbocel P 190</td>
<td>–</td>
<td>11.2</td>
<td>22.2</td>
<td>32.8</td>
</tr>
<tr>
<td>Sodium hydrocarbonate</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>12.3</td>
<td>12.3</td>
<td>12.3</td>
<td>12.3</td>
</tr>
</tbody>
</table>
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Physical properties of 1.0-1.25 mm pellets cores

Bulk density. Bulk density \( [g/m] \) was determined by means of an electromagnetic voltmeter. Cores were poured into a 25 mL capacity metal cylinder at a constant rate. The container was weighted after removing the excess of cores. The activity was conducted in triplicate.

Disintegration time. 1 g pellets cores were placed in three 100 mL conical flasks containing 50 mL of 0.1 mol/L hydrochloric acid (37 ± 2°C). The flasks were rotated every 30 s. The experiment was continued until total disintegration of the granulated mass. The total disintegration time was determined at the moment when there were no particles bigger then 0.5 mm. Sieve Retch (Retsch, Hann, Germany) 0.5 mm mesh diameter was used.

Hardness. Cores hardness was measured by means of an automatic hardness tester type TBH 20 (Erweka, Hensenstamm, Germany). 50 pellets cores (1.0-1.25 mm diameter) were placed in the apparatus in turn and the force needed to crush them was registered.

Cores friability. Cores friability was assayed with the Erweka TAB apparatus (Heusenstamm, Germany). 20 g of vacuum-cleaned pellets cores and 60 g of 3.3 mm i.d. steel globules were placed in the apparatus drum. The globules were applied in order to increase the friability force. The rate was 25 drum rpm. After 20 min the cores were taken out, vacuum-cleaned by means of the 0.63 mm mesh diameter sieve and weighed again in order to indicate the mass loss.

Compressibility of pellet cores. 150 g of cores of each formulation were directly compressed using Korsch single stroke tablet press (Korsch EKO, Berlin, Germany) by means of 11.0 mm diameter flat punches. Next, the obtained tablets were weighed on the analytical balance and their theoretical capacity after compression was calculated according to the equation for cylinder capacity.

Pellets’ capacity before compression was measured according to p. Bulk density.

Compressibility of pellet cores was calculated according to the following equation:

\[
\text{Compressibility} \% = (1 - \frac{C_{AC}}{C_{BC}}) \times 100
\]

where: \( C_{AC} \) – capacity after compression; \( C_{BC} \) – capacity before compression.

Swelling. 100 g of a sample of physical mixtures of I-IV formulations powders were placed in a 100 mL glass cylinder put on a 0.01 g measuring accuracy electronic balance. A small metal piston (diameter of piston – 46.5 mm) was applied to the surface of powder mixtures. Then, 60 g of water were slowly poured into the beaker. By moistening the powder mixture the water caused swelling of the mixtures. The powder swelling force pressed the piston which was immobilized in the stand and at the same time pressed the scale. The obtained value of the pressure force \( [g] \) was calculated per force unit \([N]\) according to the equation:

\[
F = m \times g
\]

where: \( F \) – swelling force \([N]\), \( m \) – pressure exerted on the scale caused by a powder mixture swelling \([kg]\), \( g \) – acceleration of gravity \((9.81 \text{ m/s}^2)\).

Coating of the pellets cores. Formulations I and IV were designated for the coating process. The contents of the coating mixture was as follows (%): Eudragit NE 40 D 43.2, tcalc 6.9, Macrogol 6000S, 1.3, and distilled water 48.6.

Core coating (bath 200 g) was done in an Uni-Glatt apparatus (Glatt GmbH, Systemtechnik, Dresden, Germany) with the use of the following conditions: incoming air temperature of 45°C, outgoing air temperature of 30°C, incoming air pressure of 6 bar, air pressure in spray nozzle of 2 bar, peristaltic pump feeding rate of 5.2 mL/min. Pellets were dried in a drying cabinet with circulating hot air at 35°C for 30 h precisely.

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

In vitro drug release test. The measurement of release rate of VH from pellets was performed using the Ph. Eur. paddle apparatus Pharma Test Model FIGURE 1. Apparatus for the measurements of the swelling force.
PTWS–3 (Pharma Test, Hainburg, Germany). At the temperature of 37 ± 0.5°C vessels were filled with 750 mL of hydrochloric acid (0.1 mol/L). The concentration of VH in the samples was determined spectrophotometrically at 278 nm. Spectrophotometer JASCO V-530 (Jasco Corporation, Tokyo, Japan) was used for investigation. For a given pellet formulation, in vitro drug release test was repeated five times.

**RESULTS AND DISCUSSION**

Pellets cores with VH were obtained directly by means of extrusion and spheronization. Particular pellets cores formulations consisted of MCC (I) and 70 µm grain size PC in the following proportion 3:1 (II), 1:1 (III), and 1:3 (IV), respectively (Table 1). It was impossible to obtain pellets cores containing only PC as excipient substance. Such a granulated mass did not undergo spheronization to the spherical shape regardless of the amount of 5% Povidone K-30 solution added at the stage of powder moistening.

The amount of 5% Povidone K-30 was determined individually for I–IV pellets cores formulations. It increased together with PC increasing in the formulation contents and e.g., for core formulation II achieved 60 mL per 100 g of powders mixture and for formulation IV 80 mL per 100 g of powders mixture.

According to the literature (6), MCC constitutes the basic excipient making the possible preservation of pellets. This substance binds water in the intermolecular space easily, undergoes deformation soon and shows proper flexibility for granulated spherically drug forms (7). Therefore, it exceeds e.g., lactose, poly(ethylene glycol), crospovidone and calcium hydrophosphate in this respect. Also PC has similar properties to MCC (8).

Figure 3 presents the DSC thermograms of physical mixture of components of the pellet core.

The shape of curves reflects the composition of analyzed mixtures. The weak endothermic peak
relating to the presence of Povidone K-30 and Avicel PH 101 or Arbocel P 290 is observed at 110°C. There are two interfering endothermic peaks at about 150°C relating to the decarboxylation of NaHCO₃ into Na₂CO₃ and melting of VH and lactose. The wide peak at over 200°C is connected with the disintegration of lactose.

Comparing the surface, shape and temperature of the respective peaks on thermograms A and B revealed no differences. Therefore, the conclusion is that MCC (Avicel PH 101) in formulation I and PC (Arbocel P 290) in formulation IV do not interact physicochemically either with VH or any excipient in the pellet core.

Evaluating the carried out studies on pellets cores physical properties (Table 2) it can be ascertained that their disintegration time meets the Ph. Eur. requirements for uncoated drug i.e., below 15 min.

The disintegration time got slightly longer together with the increasing of in the PC contents and amounted to 9.5 min for pellets IV cores. It was the effect of pellets agglomerates showing considerable viscosity.

Formulation IV cores having the greatest PC participation were characterized by the highest friability amounting to 0.76%. However, together with the PC contents drop in the cores composition, fri-
ability decreased to 0.3% for formulation I – inclusive on the basis of MCC.

The result of pellets friability is not reflected by the results of their hardness test. It means that the PC contents growth contributes to the hardness growth. Higher cores friability should be reflected by their lower mechanical durability. Higher value of the hardness tester reading may be explained by the fact that some pellets underwent crushing, not cracking. Such behavior of cores with MCC may prove their high flexibility and therefore hardness test was unable to measure pellets cores crack precisely.

However, cores friability increasing together with PC contents increasing is fully justified by their greater porosity. PC causes creating higher porosity.

Table 2. Physical parameters of pellets’ cores with verapamil hydrochloride.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Moisture content [%]</td>
<td>3.0</td>
</tr>
<tr>
<td>Bulk density [g/mL]</td>
<td>17.8</td>
</tr>
<tr>
<td>Disintegration time [min]</td>
<td>8.3</td>
</tr>
<tr>
<td>Friability [%]</td>
<td>0.30</td>
</tr>
<tr>
<td>Hardness [N]</td>
<td>15.3</td>
</tr>
<tr>
<td>Compressibility [%]</td>
<td>49.1</td>
</tr>
<tr>
<td>Swelling force [N]</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Figure 4. Scanning electron micrographs of the surface of pellet’s core formulation I (A) and IV (B).
Influence of the type of cellulose on properties of multi-unit cores. Porosity of the pellets’ cores corresponding to their compressibility. Pellets’ II cores of PC contents amounting to 11.2% had 48.1% compressibility and cores IV of PC contents amounting to 32.8% had 56% compressibility. Much greater surface porosity of pellets IV cores compared to II is depicted in Figure 4.

In this study we also suggested our own method for measurement of swelling force of pellets cores of physical powder mixtures used for the formulation of pellet cores. Powder, granulated mass and tablet swelling force is hard to measure as there are no standardized, routine methods of such analysis. The described concepts of measurement are based on home-made ideas and apparatuses (9,10).

All results were statistically compared with one way ANOVA test and there were statistically significant differences (df =29, p=4.13-10^{-25}). It was found that together with PC contents increasing in the composition of physical mixtures I – IV its swelling force rises (Figure 5). It was also found that PC itself swells twice stronger than MCC. For comparison, gelatin swelling force amounted to 5.5 N.

The evaluation of the influence of MCC and PC contents in the composition of pellets cores on VH release rate was performed for formulation I and IV cores. In order to do that they were coated fluidally with a 41.0 µm thick film of Eudragit NE.

In all formulation of pellets after 2-3 min carbon dioxide vesicles were getting outside, as a result of hydration and swelling of film. Carbon dioxide bubbles carrying pellets on the surface of the receptor solution – hydrochloric acid (0.1 mol/L). It was discovered that 15-20% of sodium hydrocarbonate concentration in core pellets ensured the most favorable constant floating effect (11).

It was found that VH release from pellets IV with higher amount of PC is considerably slower comparing to formulation I with MCC (Figure 6). That result merely justifies longer pellets IV disintegration time. However, differences in other properties of both kinds of cellulose do not favor such a release profile. PC porosity and swelling force are higher compared to those of MCC, which should increase VH release rate.
Such an effect was obtained by Alvarez et al. in experiments with furosemide (8).

Also, the experiment testing VH released solution viscosity in macroscopic pellets model conditions helped in explaining slower VH release from pellets IV. Designated kinematic viscosity of processed formulation IV powder mixture was above 1 and amounted to 1.2 and 1.0 mm² s⁻¹, respectively (Figure 7).

Hence, it may be concluded that in the case of pellets IV, considerable viscosity and outer core layers swelling were so strong that they caused restraint of outer layers moistening and because of that it slowed down VH release rate. VH release rate may be increased by introducing poly(ethylene glycol) or hydroxypropyl methyl cellulose to the pellets IV film composition in order to increase its permeability. However, undoubtedly, the advantage of PC presence in pellets is their greater porosity and compressibility. Such pellets with VH or placebo will be more susceptible to deformation, fill empty spaces and allow for obtaining tablets with VH release profile similar to pellets enclosed in a gelatin capsule.

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REFERENCES


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