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Research paper

Preparation of delayed-release multiparticulate formulations of diclofenac sodium and evaluation of their dissolution characteristics using biorelevant dissolution methods

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ABSTRACT

Diclofenac sodium was used as a model drug for preparation of delayed-release (DR) multiparticulates, which were further processed into solid oral dosage forms such as capsules and tablets. Multiple unit pellets systems (MUPS) were prepared from different types of starter pellets (inert cores) including microcrystalline cellulose pellets, sugar spheres, isomalt pellets and novel calcium phosphate-based pellets. The study results showed that the material of the inert cores affected both mechanical properties of the drug-loaded pellets and the dissolution characteristic of the model drug. Biorelevant dissolution method carried out with the help of a pHysio-grad device allowed thorough examination of the developed formulations in the environment mimicking pH conditions along gastrointestinal tract. This method revealed significant differences between the formulations and their sensitivity to variable hydrodynamic conditions.

1. Introduction

Multiparticulate drug delivery systems (MDDS) are novel pharmaceutical dosage forms, which have been gaining increasing popularity in recent years when compared to single unit dosage forms. These multiple unit dosage forms (MUDF) are made of numerous independent subunits (microparticles), where each of them is an autonomous reservoir of a drug and releases the drug in a desirable way, independently of the other subunits. Multiparticulates are especially suitable for preparation of modified-release solid oral dosage forms (delayed- or sustained-release), which offer such benefits as less variable gastrointestinal transit or reduced risk of dose dumping. At the present time, the most commonly used multiparticulates are coated pellets which are formulated into oral dosage forms either by filling them into hard gelatin capsules or compacting into tablets (Multiple Unit Pellet System, MUPS) [1–4].

One of the well-established ways of preparation of multiparticulates is drug layering of spherical starter pellets (also called inert cores or beads) followed by coating these drug-loaded pellets with a thin polymer-based film. Drug layering of inert cores offers relatively easier technology compared to extrusion and spheronisation process. Moreover, it enables the production of multiparticulates with a very uniform particle size distribution as well as advantageous surface morphology [5,6]. There is a wide range of various types of neutral starter pellets commercially available on pharmaceutical market offering different characteristics [7,8]. Sugar spheres (nonpareils), which were introduced on the market and applied for the production of multiparticulates as first, are still the most popular. Sugar spheres are made of sucrose (usually up to 92%) and corn starch [9]. They are soluble in aqueous media and hygroscopic, which is often a challenge during coating [10]. Absorbed water can be problematic and impact stability of moisture sensitive drugs [8]. That is why alternative products have been introduced to the market and interest in their use is constantly growing. The most commonly employed substitutes are cellulose pellets consisting of 100% microcrystalline cellulose (MCC). They are insoluble in water and are characterized by high sphericity as well as good mechanical strength. Due to these properties, the drug layering can be carried out faster and with reduced formation of undesirable agglomerates, which shortens the coating time and reduces cost of production. However,

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problems such as the absorption of certain drugs on the surface of cellulose fibers or swelling in contact with water, which can affect dissolution pattern have been reported [11–13]. Another solution available on the market are starter pellets consisted of polyalcohols such as isomalt, mannitol, xylitol. Similarly to sugar spheres, they are hygroscopic and soluble in aqueous media, however, they are promoted due to their low glycemic index and lack of cariogenic effect [5,14]. Within this group, isomalt pellets offer especially interesting functionality of creating internal osmotic pressure, which modulates dissolution pattern of some drugs [15]. Recently, a new type of water-insoluble pellets based on anhydrous dibasic calcium phosphate (DCPA) has been introduced to the market. These pellets consist of 80% w/w of DCPA and 20% w/w of MCC. Due to their elevated density of above 1000 g/l, very low water content of less than 1%, and reduced hygroscopicity, they represent an attractive alternative to the other commercial products offered so far. A detailed comparison of various functional properties of calcium phosphate-based pellets with other commercially available inert cores can be found elsewhere [16].

Inert cores are made of excipients commonly used in the pharmaceutical industry, which are neutral and should not exhibit any pharmacological activity nor interact with the drug substance in a way, which may adversely affect its stability and/or effectiveness. Nevertheless, characteristics of starter pellets may have a significant impact on the course of the production process as well as can influence the rate of drug dissolution not less than the properties of coating polymer. Thus, the drug release pattern can be determined by the thickness of the coating and its permeability, but also by the geometry of the pellets, surface morphology or the osmotic pressure originating from the pellets cores [5,8,15,17–20].

As has been already mentioned, drug-loaded pellets can be filled into hard gelatin capsule shells or compressed into tablets. Especially, the latter technology of tabletting of microparticulates is very interesting and allows combining the advantages of both tablets and pellets-filled capsules in one dosage unit [21–23]. In this case, the properties of pellet cores together with the coating polymer will determine the durability of the drug-loaded pellets and protect them from damages during tabletting. It has been frequently reported that the size of pellets is a very important factor to be considered during compaction. Normally, small pellets are employed in preparation of tablets as they are less affected by the compression process. This is mainly due to the higher mechanical strength of smaller beads relative to their size as well as reduced contact force on each individual pellet resulting in significantly reduced degree of transformation [24,25].

In this work the suitability of different types of starter pellets in the development of delayed-release multiparticulate formulations containing diclofenac sodium as a model drug was evaluated. Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) having both analgesic and antipyretic activities. The drug is commonly used in the treatment of rheumatic disorders. Diclofenac sodium is available in a number of preparations of 25 mg, 50 mg or 75 mg strength [26–28]. The drug is a weak acid of BCS Class II and shows pH-dependent solubility in physiological pH range which increases with the increase of pH value [29,30]. Diclofenac sodium is often formulated as enteric-coated preparation to avoid direct contact of the drug with the mucosa resulting in local gastrointestinal toxicity. For this purpose pH-sensitive enteric polymers are commonly used. These polymers should limit the release of the drug in acidic conditions of stomach and allow rapid dissolution of the drug in duodenum and distal parts of the gastrointestinal tract (GIT) [31].

The development of drug products is a time-consuming process and involves high costs. Thorough examination of drug formulations with the help of reliable in vitro biorelevant techniques facilitates screening of the candidates and makes this process more efficient. Biorelevant dissolution methodologies allowing an adequate prediction of the in vivo performance of drugs come here with help [32,33]. In the present work a novel device, pHysio-grad, which enables biorelevant simulation of the intestinal pH was employed [34]. The pHysio-grad can precisely monitor and adjust the pH value of hydrogen carbonate buffer, which is considered to be one of the most biorelevant medium for simulation of intestinal conditions [35,36]. The carbonate buffer is a complex system and its pH is an effect of dynamic interplay between all its constituents. The thermodynamic instability leads to spontaneous increase of pH due to the loss of carbon dioxide (CO_2). This effect might be minimized by either preventing CO_2 evaporation (by using appropriate sealing or covering a dissolution medium with an organic layer) or by compensating the loss of CO_2 with the help of an automated system. Moreover, carbonate buffers give the opportunity for simulation of dynamic intraluminal pH changes, however, continuous and dynamic adjustment of pH value must be provided in order to use them in routine dissolution testing.

The main objective of this work was to investigate the suitability of different types of starter pellets in the development of delayed-release multiparticulate formulations containing diclofenac sodium as a model drug. The planned scope of research included the use of commercial inert cores made of microcrystalline cellulose, sugar, isomalt as well as novel calcium phosphate-based pellets in preparation of both hard gelatin capsules and compressed tablets. The additional objective was to examine and compare the effect of the core material on the in vitro drug release of the model drug using compendial as well as biorelevant dissolution methods.

2. Materials and methods

Diclofenac sodium (Amoli Organics, Mumbai, India). Film coating systems: Vivacoat® FM-1M 000 (JRS Pharma, Rosenberg, Germany) and Aquarius® Control ENA (Ashland, Covington, KY, USA). Inert cores: calcium phosphate-based (DCPA) pellets - PharSQ® Spheres CM M (Chemische Fabric Budenheim, Budenheim, Germany), microcrystalline cellulose pellets - VIVAPUR® MCC Spheres 500 (JRS Pharma, Rosenberg, Germany), sugar spheres - pharm-a-spheres™ MESH 35-25 (Hanns G. Werner GmbH, Tornesch, Germany), isomalt starter pellets - galenIQ™ 960 (BENEO-Palatinit GmbH, Mannheim, Germany). Microcrystalline cellulose VIVAPUR® 200 (JRS Pharma, Rosenberg, Germany). Low-substituted hydroxypropyl cellulose (L-HPC) LH-11 (ShinEtsu, Wiesbaden, Germany). Magnesium stearate (Peter Greven Fett-Chemi, Venlo, The Netherlands). Transparent hard gelatin capsule shells, size "0" (Kapselwelt, Hude, Germany).

2.1. Preparation of drug-loaded DR pellets

The starter pellets used in this study were initially calibrated between two sieves, 500 μm and 710 μm, in order to obtain grains of similar dimensions and to avoid the effect of different particle sizes on the coating process as well as on analyses results. Sieved pellets were drug-layered with diclofenac sodium in a ProCepT 4M8-Trix Fluid-bed system (FBS) equipped with a Wurster column (ProCepT nv, Zelzate, Belgium). Around 100 g of starter pellets were first coated with a aqueous suspension containing 5% w/w of the drug substance and 5% w/w of Vivacoat® system up to about 20% of weight gain. Subsequently, without breaking the process, the pellets were sprayed with purified water (intermediate coating) and finally coated with 20% w/w aqueous suspension of Aquarius® Control ENA (enteric-coating) until around 10% of weight gain was reached. The use of an intermediate coating step allowed maintaining the continuity of the entire process and adjusting the process parameters before the following coating phase. Moreover, it reduced interactions between the two layers and the accumulation of static charges. During all phases the machine settings were maintained at the following values: air speed of around 0.21 m^3/min, inlet air temperature of around 63 °C, product temperature of around 40 °C, nozzle pressure of 1 bar.

2.2. Preparation of multiparticulate dosage forms

Enteric-coated pellets containing the model drug were used to formulate two types of solid oral dosage form - hard gelatin capsules and compressed tablets. Developed MUPS formulations consisted of around: 50.0% w/w of the diclofenac sodium pellets (equivalent to 25 mg of diclofenac sodium), 44.5% w/w of MCC type 200, 5.0% w/w of L-HPC and 0.5% w/w of magnesium stearate. Hard gelatin capsules were prepared by manual filling of the diclofenac sodium pellets into capsule shells of "0" size. Tablets were compressed on a Korsch EK0 eccentric tablet press (Korsch, Berlin, Germany) using concave punches (R 25 mm) of 12 mm diameter under a compaction forces of 18–20 kN.

2.3. Scanning electron microscopy

To visualize surface properties of the drug-loaded DR pellets alone, as well as compressed into tablets, a scanning electron microscope Phenom Pro (Phenom World Thermo Fisher, Eindhoven, Netherlands) was employed. Standard sample holder and a carbon tape were used to fix a sample and acceleration voltage of 5–10 kV was applied to record images at a magnification of 300x.

2.4. Mechanical strength

The mechanical strength of starter pellets as well as drug-loaded DR pellets was assessed with a texture analyzer equipped with a 6 mm diameter cylindrical stainless steel probe in compression mode (TA.XT Plus, Godalming, Surrey, England). The probe was moved vertically downwards at a speed of 2.0 mm/s until the triggering force of 0.1 N was detected and further with a speed of 0.05 mm/s until a pellet was crushed. The maximum force at the point of fracture and the distance to break were recorded. All measurements (for each type of sphere $n = 12$) were performed at room temperature.

2.5. Dissolution test (modified compendial method)

According to The United States Pharmacopeia monograph for diclofenac sodium delayed-release tablets, dissolution test is carried out in two steps, between which test samples must be transferred from the one medium to the other. In the case of enteric-coated tablets a paddle apparatus is applicable because the transfer of such tablets is not a major problem. However, in the case of microparticulates the use of a basket apparatus is more convenient. In this study both hard gelatin capsules and tablets containing enteric-coated diclofenac sodium pellets were placed in a basket apparatus (USP apparatus 1) PTWS 820D (PharmaTest AG, Hainburg, Germany) and the dissolution test was carried out according to the monograph for Diclofenac Sodium Delayed-Release Tablets given in USP42/NF37 using a rotational speed of 100 rpm. During the first phase the capsules were incubated in 0.1 M hydrochloric acid for 2 h. In acidic stage, according to both USP/NF and Ph.Eur. gastro-resistant pellets should not release more than 10% of labeled content of a drug. In the subsequent buffer stage, release of the drug should be rapid and reach minimum 80% of the labeled amount of diclofenac sodium within 45 min. The amount of the dissolved drug was determined using a T70 UV/VIS Split-Beam Spectrophotometer (PharmaTest AG, Hainburg, Germany) at the detection wavelength of 276 nm using flow-through quartz cuvettes with 1 cm path length.

2.6. Biorelevant dissolution in hydrogen carbonate buffer using a pHysio-grad device

The pHysio-grad device used in this study was composed of a microcomputer, which controlled independently each measurement channel and a valve island. pH probes assured constant pH measurement in each vessel and triggered adjustment of pH when necessary. The adjustment of pH values was obtained by addition of a titrant, which was CO_2 and compressed air in this case (Fig. 1).

Dissolution was carried out in a paddle apparatus (USP apparatus 2) at a 50 rpm paddle rotational speed. Dissolution test was composed of two stages. In the first stage tablets or pellets (taken out from capsule shells) were placed in a vessel filled with 250 mL of 0.01 M HCl for 30 min. After this time 750 mL of Hank's buffer concentrate was added and the test continued for 60 min. After addition of buffer, the pH of hydrogen carbonate medium was controlled by pHysio-grad device and set at 6.8. The amount of the dissolved drug was determined using an Agilent 8453 UV/VIS Spectrophotometer (Agilent Inc. Santa Clara, CA, USA) at the detection wavelength of 276 nm using quartz cuvettes with 1 cm path length.

3. Results

3.1. Mechanical strength

Mechanical strength of starter pellets and drug-loaded DR pellets was assessed with a texture analyzer. The maximum force at the point of fracture (hardness) and the distance to break vs. pellets breaking strength [N] are shown in Figs. 2 and 3. The highest value of hardness was recorded for MCC spheres, and the lowest for sugar-based inert cores. Generally, it was observed that for all types of starter pellets the coating process significantly improved the mechanical strength of the particles. The increase in robustness was the most pronounced in case of water-insoluble pellets (MCC and DCPA). It can be noted that for isomalt-, sugar- and MCC-based pellets values of the standard deviation are relatively high which could result from their not quite spherical shape. Drug-loaded enteric-coated pellets based on isomalt and sugar exhibited very similar response to the compression. They deformed relatively fast when exposed to external force until reaching the point of fracture as shown in Fig. 3. Deformation of DCPA-based pellets was significantly slower. It can be noted that the maximum force at the breaking point is at similar level as for isomalt pellets, but the distance to reach fracture point was significantly extended. This can be the effect of the specific composition of DCPA-based inert cores, which combine the features of brittle calcium hydrogen phosphate and a ductile material (microcrystalline cellulose).

3.2. Scanning electron microscopy

Surface structure and cross-sections of the drug-loaded DR pellets before and after compression into tablets were studied with a scanning electron microscope. Fig. 4 shows SEM micrographs of drug-loaded diclofenac sodium pellets before compression (left column), compressed pellets inside tablets (middle column) and pellets extracted from the surface of tablets (right column). SEM images of cross-sections show

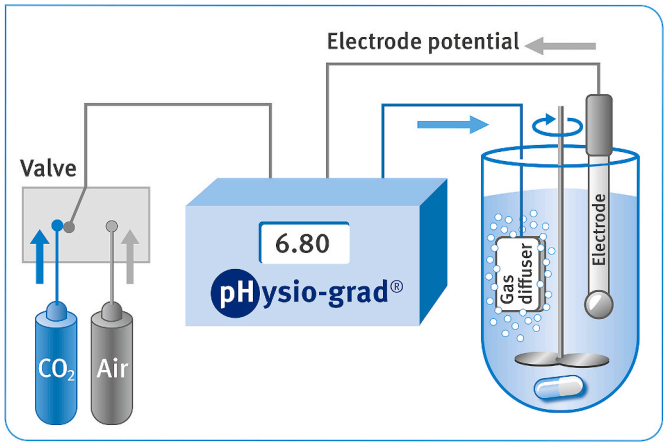

Fig. 1. Schematic diagram of the pHysio-grad device.

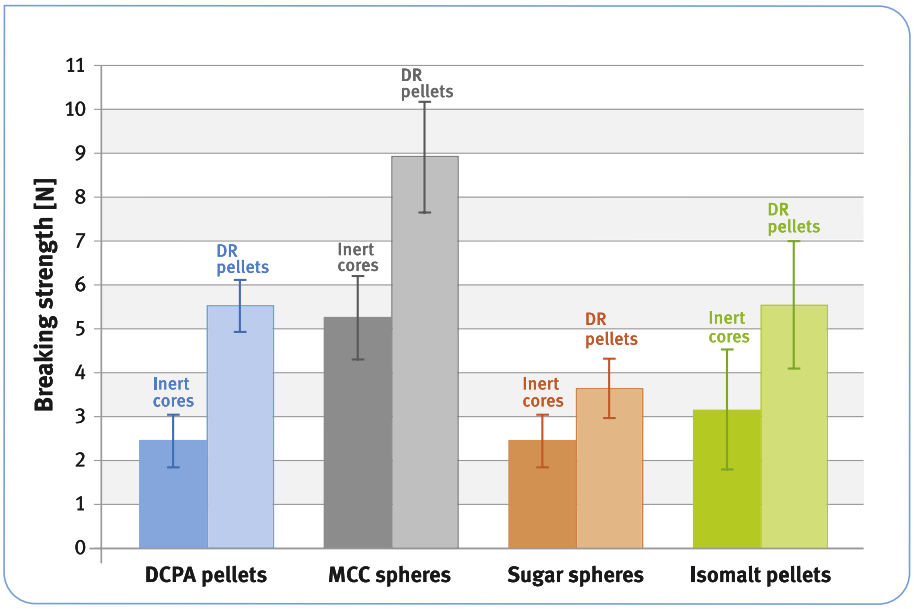

Fig. 2. Comparison of breaking strength (hardness) of inert cores made of DCPA, MCC, sugar and isomalt with corresponding drug-loaded DR pellets (given are means of min. 10 repetitions, SD is indicated by the error bars).

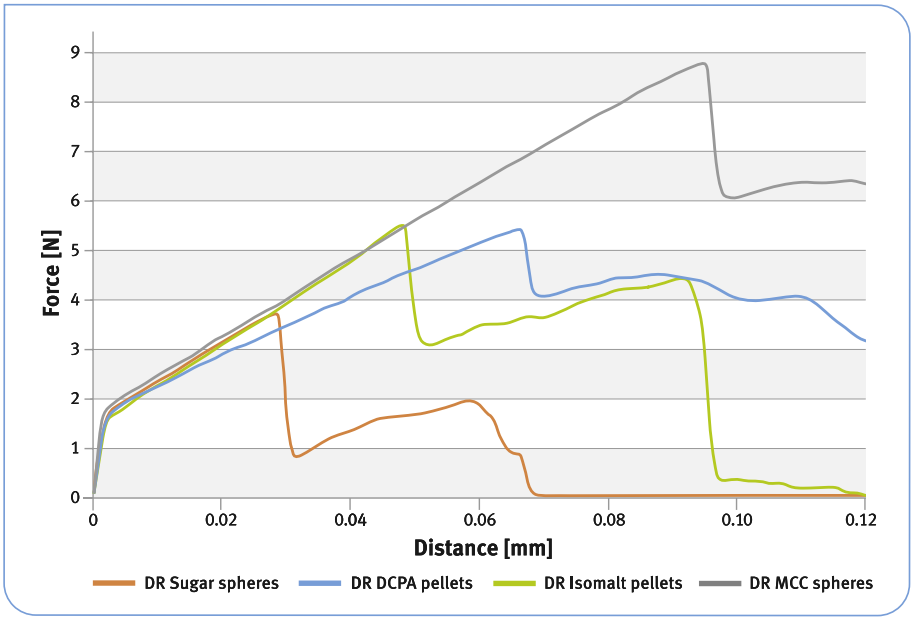

Fig. 3. The distance to break and the maximum force at the point of fracture of drug-loaded enteric-coated pellets based on DCPA, MCC, sugar and isomalt (given are examples of single deformation profiles).

that the shape of sugar- and DCPA-based drug-loaded pellets is spherical, whilst isomalt and MCC show more ellipse-like character. In all cases a clear distinction between a core and a coating layer can be spotted with no visible deformation of the coating layer. The coating layer is uniform through the whole cross-sections with layer thickness of approximately 30 μm. Although the irregular shape of the some types of examined inert cores could have caused a variation in the coating thickness, no such observations were made. It can be seen that even after compression the original shape of the pellets located inside the tablets generally remained unchanged, without visible deformations or damages of the coating layer. However, it should be noted here that many pellets positioned on the very surface of the tablets, which were in direct contact with the punches during compaction, displayed cracks in the polymer layer and partial shape deformation. The most pronounced cracks are visible for pellets made of sugar, isomalt and MCC. Especially sugar-based pellets were heavily deformed, which led to partial exposure of their cores.

3.3. Dissolution test (modified compendial method)

Four types of commercially available inert cores (DCPA pellets, MCC spheres, sugar spheres and isomalt pellets) were used to prepare delayed-release multiparticulate formulations (hard gelatin capsules and tablets) of diclofenac sodium at a dose of 25 mg. All of them were analyzed using modified compendial methods for diclofenac sodium delayed-release tablets (USP42/NF37). Comparison of the amount of the drug released in the acidic medium is given in Fig. 5. During this phase both hard gelatin capsules and tablets disintegrated completely and

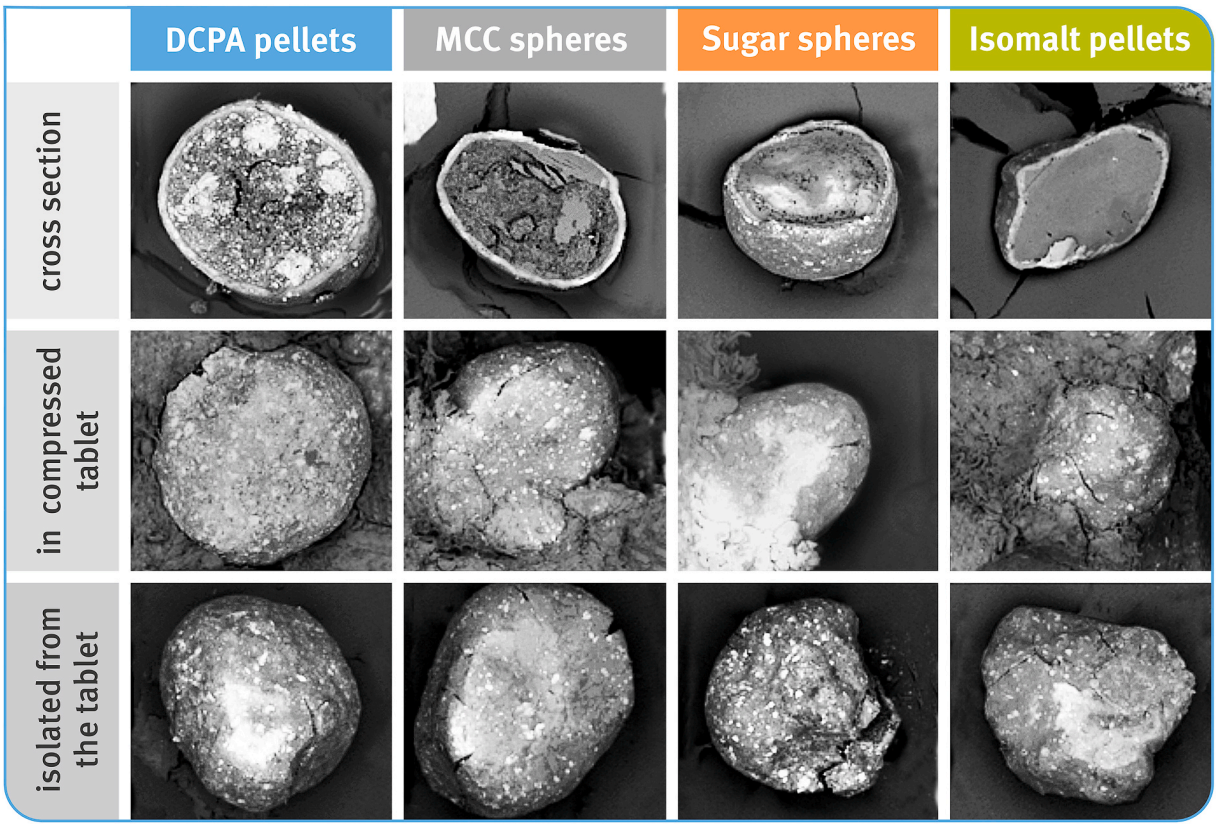

Fig. 4. SEM micrographs of drug-loaded diclofenac sodium DR pellets (magnification of 300x).

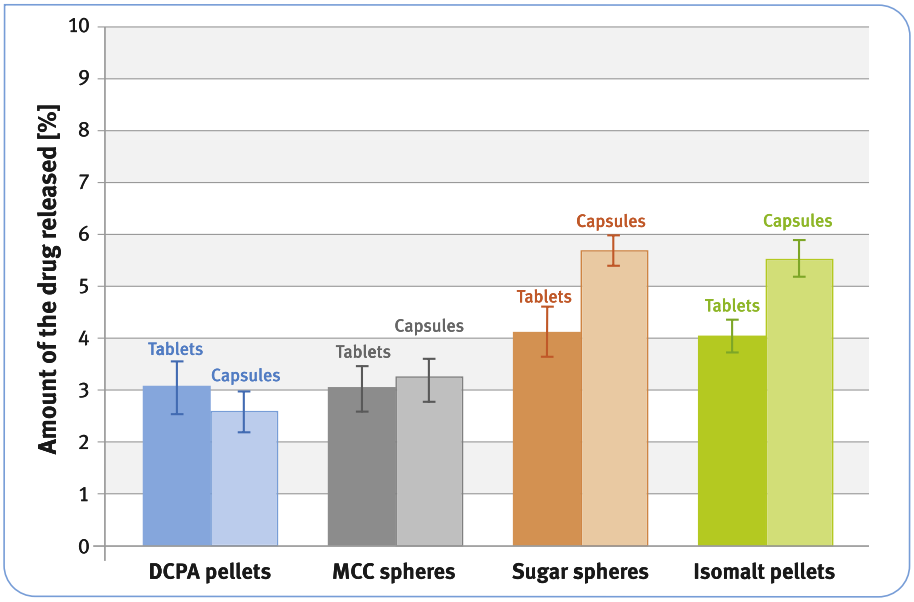

Fig. 5. The release of diclofenac sodium from gastro-resistant diclofenac sodium preparations in acid phase (after 2 h incubation in 0.1 M HCl) (given are mans of n = 6, SD is indicated by the error bars).

water-insoluble ingredients formed a cone at the bottom of dissolution vessels. In the baskets remained practically only pellets with very small residue of excipients. It was observed that the water-soluble inert cores (made of sugar and isomalt) tended to float in the upper part of baskets, whereas the insoluble ones (DCPA and MCC) remained mostly at the bottom of baskets. All examined formulations demonstrated their gastro-resistance and released much less than 10% of the labeled amount of diclofenac sodium within 2 h of the test. However, in case of preparations containing water-soluble starter pellets higher dissolution of the drug substance can be detected. It can also be noticed that tablets containing inert cores with MCC, sugar and isomalt released less amount of the drug than analogous capsules. The opposite situation occurred in case of phosphate pellets, where the release of diclofenac sodium from tablets is slightly higher than from capsules.

In the buffer stage all tested formulations demonstrated rapid dissolution and released the whole amount of the drug within required 45 min (Fig. 6). It can be noted that multiparticulates containing water-soluble substances showed identical, measurably faster dissolution rate in comparison to insoluble MCC and DCPA cores. In the case of phosphate pellets, the release of diclofenac sodium from tablets is slightly slower than from hard gelatin capsules, while in the other examined formulations these differences are not so visible. After completing this phase in the baskets containing DCPA and MCC microparticulates still the whole quite spherical cores could be observed while for water-soluble sugar and isomalt beads the baskets were practically empty. In the case of MCC spheres, a large amount of retained red dye (which is a component of the enteric-coating) can be seen. (Fig. 7).

3.4. Biorelevant dissolution in hydrogen carbonate buffer using a pHysiograd device

Biorelevant dissolution test has shown the high discriminatory power and revealed significant differences between the tested formulations in terms of the impact of the dosage form as well as the core material on the dissolution rate. Moreover, the use of a paddle apparatus enabled visual observation of the tested samples directly in dissolution vessels.

The results presented in Fig. 8 show that drug-loaded pellets containing sugar and isomalt, both alone (without capsule shells) and compressed into tablets, released diclofenac sodium faster than corresponding MCC and DPCA cores. In addition, the release of the model drug from these tablets and free pellets was virtually identical and the dosage form had no effect on its dissolution rate. These findings are in line with the results obtained in the dissolution test based on the compendial method (Fig. 6). A different situation can be observed in the case of pellets containing water-insoluble MCC and DCPA. Here, the differences between the two dosage forms are clearly visible. The dissolution rate from pellets is much slower than from corresponding tablets. This difference is noticeably larger in the case of DCPA cores.

Examination of free pellets allowed observation of their different dissolution behavior which might be related to the core material. Sugar- and isomalt-based pellets were mobile and tended to float in the entire volume of dissolution medium. Dosing of a gaseous titrants in the second stage of the test additionally stimulated the movement of pellets in the vessel which could promote dissolution of diclofenac sodium. On the contrary, MCC- and DCPA-based pellets exhibited more stationary behavior. Especially pellets containing DCPA, due to their elevated density, were lying still at the bottom of the vessels even during addition of gaseous titrants. The limited movement resulted in much lower dissolution rate, particularly in comparison with sugar and isomalt cores. DCPA-based pellets did not release the whole of the labeled amount of diclofenac sodium within 60 min of the test. Additional intensive mixing was needed to release all the substance (results not included in the diagram).

Significant differences in dissolution pattern between tablets and free pellets could be observed, especially at the very beginning of the second stage of the dissolution test. First samples were withdrawn in 1 min after addition of Hank's buffer (Fig. 9). All tested tablets have released more than 20% of label amount of diclofenac sodium within this time, which could be caused by the presence of excipients that promoted movement of freed pellets and increased their exposure to the dissolution medium. For comparison, at the same time the free pellets released a much smaller amount of the drug substance (about 12–13% for sugar and isomalt pellets, 11% for MCC cores and only 4% for DCPA cores). In case of pellets based on water-insoluble material, contrary to tablet formulations, free pellets showed less tendency to move and were lying at the bottom of the dissolution vessels. It could be also observed that dosing of the gaseous titrant had a greater effect on movement of isomalt and sugar cores and facilitated their floating in the entire volume of the dissolution medium.

4. Discussion

The aim of this work was to compare the suitability of different types of starter pellets in the development of delayed-release multiparticulate formulations containing the model drug - diclofenac sodium. Four types of commercial inert cores of pharmaceutical grade were selected for the research. Two of them were soluble in aqueous media – sugar spheres and isomalt pellets. Other two, microcrystalline cellulose spheres and calcium phosphate-based pellets, were insoluble in water. Starter pellets available on the market differ significantly in size which can significantly impact properties of multiparticulate formulations including their dissolution characteristics [37–39]. In order to eliminate impact of particle diameters on results of analyses the cores used in this study were normalized and only the 500–710 μm fraction was utilized. A chemical nature of the core material determined not only the solubility but also

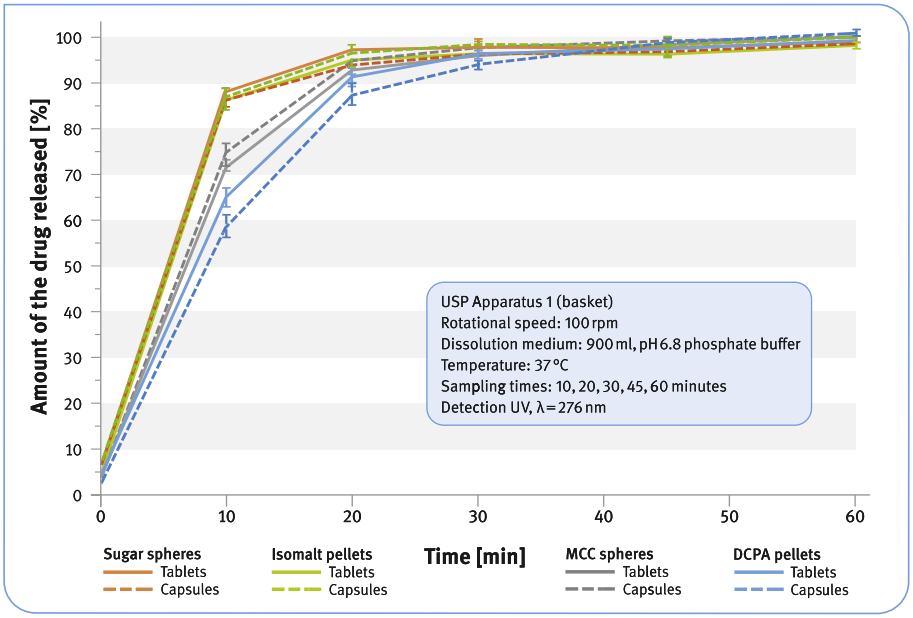

Fig. 6. Dissolution rate of diclofenac sodium from various multiparticulates in the buffer stage (given are mans of n = 6, SD is indicated by the error bars).

Fig. 7. Residues of diclofenac sodium DR pellets (DCPA, MCC, sugar, isomalt) at the bottom of basket after completing the buffer stage.

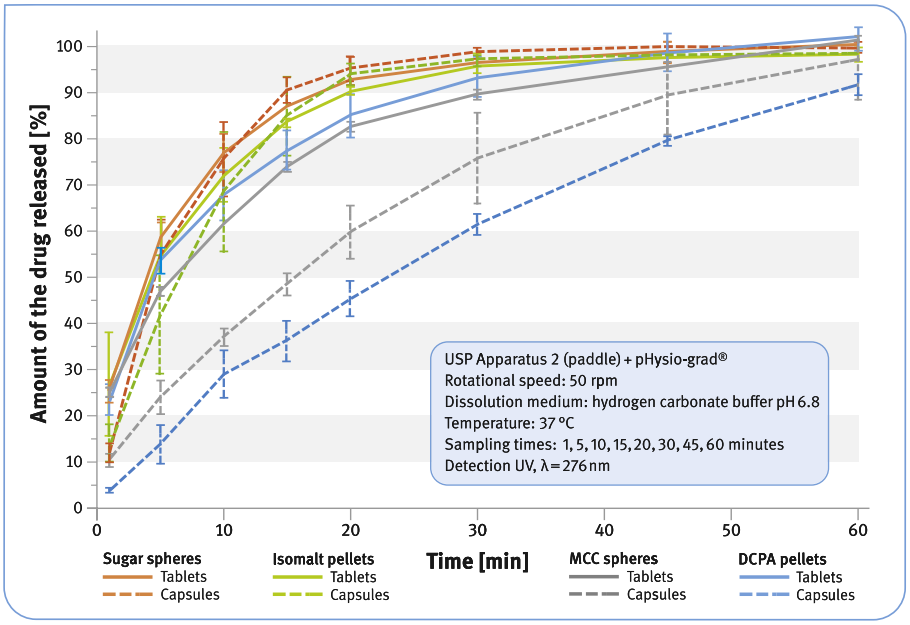

Fig. 8. Dissolution rate of diclofenac sodium from various multiparticulates in the hydrogen carbonate buffer pH 6.8 (biorelevant test condition) (given are mans of n = 3 SD is indicated by the error bars).

the functional properties of starter pellets that were influencing the process of drug layering of the cores. For instance, different tendencies to accumulate electrostatic charges have been observed. Fig. 10 shows pictures of FBS chamber taken about 5 min after the start of the process. In case of MCC, sugar and isomalt cores, high adherence of the particles to the glass walls of the granulator, caused by static electricity, is clearly visible. Fluidization of DCPA beads is smooth and undisturbed. Moreover, in the case of water-soluble inert cores, especially made of isomalt, initial extensive formation of dust has been noticed. This observation corresponds to the data published earlier and showing higher friability of these inert cores [16].

Starter pellets differed in terms of hardness expressed here as breaking strength (see Fig. 2) The most durable were MCC spheres, the lowest mechanical strength was observed for sugar- and DCPA-based inert cores. The coating of inert cores – in this case with a water suspension of hydroxypropyl methylcellulose (HPMC) mixed with the equal amount of diclofenac sodium – significantly improved mechanical strength of the pellets. The greatest improvement was observed for DCPA pellets for which hardness value increased by over 2.25 times. In the course of research, no clear relationship between pellets hardness and resistance to crush during tabletting could be observed. Considering that the coating thickness for all pellets was identical (around 30 μm), the differences in their robustness had to be due to the properties of the core material. Drug-loaded enteric-coated sugar spheres with the lowest value of breaking strength were affected the most during compression (see Fig. 4). Nevertheless, when comparing coated pellets of similar hardness, i.e. based on isomalt and DCPA, one can notice much less compression damages of these latter. This difference is probably due to

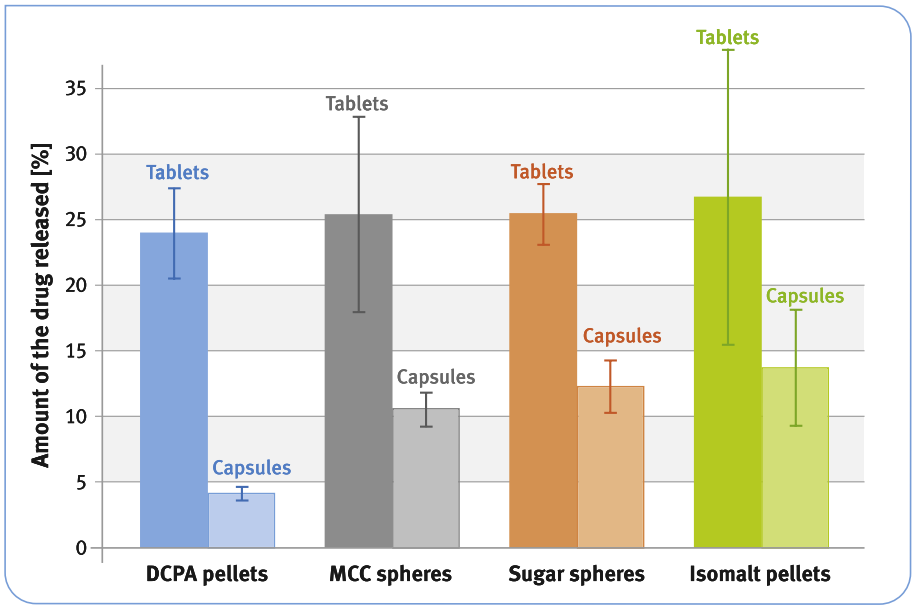

Fig. 9. The release of diclofenac sodium after 30 min incubation in 0.01 M HCl and 1 min after addition of hydrogen carbonate buffer (given are mans of n = 3 SD is indicated by the error bars).

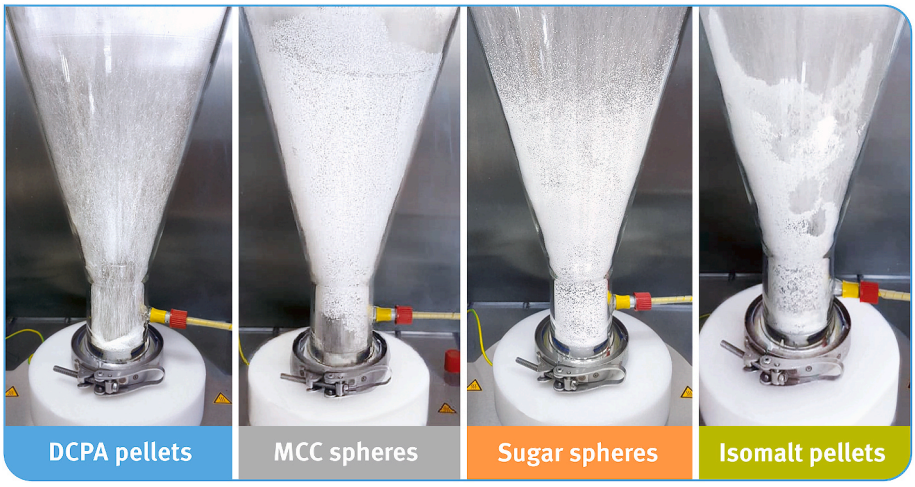

Fig. 10. Chamber of fluid bed system after around 5 min of the coating process containing 1) DCPA pellets, 2) MCC spheres, 3) sugar spheres, 4) isomalt pellet.

the longer time needed to reach the fracture point for the phosphate-based pellets, as shown in Fig. 3. Furthermore, the inert cores made of ductile MCC with the highest value of breaking strength were damaged even more than previous two types. It should be mentioned here that the pellets of the sizes used in this study (500–710 μm) are normally not employed for preparation of MUPS tablet. However, a similar approach has been successfully applied for research purposes and reported by Hiew et al. [40] In this case, however, such particle dimensions allowed precise observation of the coating layer and its deformation or damages arose during compression into tablets. It is also important that the damages were limited to the pellets located on the very surface of the tablets, which had direct contact with steel parts of tableting tooling. It can therefore be assumed that many of the observed cracks were caused mechanically and the use of larger amounts of cushioning excipients could significantly reduce the damages.

Diclofenac sodium is known to cause adverse GI side effect after oral administration [29]. Thus its preparations are commonly enteric-coated in order to reduce gastric exposure. Enteric-coating should limit release of the active substance in the stomach as much as possible and then allow quick dissolution in the duodenum and distal GIT. In the present studies, the quality of the coating layer has been evaluated after prolonged storage under acidic conditions, reflecting those prevailing in the stomach, as it is recommended in Ph.Eur. (chapter 2.9.3.) or USP/NF (chapter 711). After 2 h of maceration in 0.1 M HCl, it was found that all tested microparticulates met the compendial requirements and did not release more than 10% of the labeled content of the active substance (see Fig. 5) proving their gastro-resistance. It can be noted, however, that the drug-loaded pellets based on water-insoluble cores released less diclofenac sodium than water-soluble ones. When comparing MUPS tablets and capsules, one can also observe slight differences in the amount of the drug substance dissolved. For tablets containing sugar, isomalt or MCC cores, the release of diclofenac sodium under acidic conditions was lower than from corresponding capsules. The smallest change was observed in the case of microparticulates based on MCC. This observation is unexpected as the analysis of SEM micrographs (see Fig. 4) revealed damages to the polymer layer of many pellets after compression. Probably during prolonged maceration in aqueous solution of hydrochloric acid, the polymer coating was hydrated and formed hydrogel

which sealed microparticulates interior. Interestingly, however, this phenomenon has a larger magnitude in the case of pellets compressed into tablets which might result from the very close contact of drug-loaded pellets surface with excipients caused by compaction forces. DCPA-based DR pellets behaved differently and after compression into tablets released more active substance. This could be explained by a less effective sealing of the enteric-coating during maceration. It should be noted that the difference between tablets and capsules formulation was not big and the amount of dissolved diclofenac sodium in this case was at the same level as for MCC cores and furthermore, much lower than for both sugar- and isomalt-based multiparticulates. The assumption about the sealing of the coating layer is to a certain degree justifiable, taking into account the results shown in Fig. 9 where four times shorter maceration in much smaller volume of diluted acid did not cause such sealing effect and allowed much higher release of active substance from tablets when compared to the corresponding free pellets (taken out from capsule shells). The highest difference was observed for DCPA-based microparticulates, nevertheless, it should be noted that the release of diclofenac sodium from the tablets containing calcium phosphate cores is lower that from other tested MUPS tablets. For formulation containing MCC- and isomalt-based DR pellets, big error values can be spotted. In the first case, this may be due to the plastic nature of the cores and their significant deformation during compression resulting in a different coating thickness. For isomalt-based drug-loaded pellets this phenomenon is related to the high solubility of the core material in water. From the very beginning of the dissolution test, both uncompressed and compressed multiparticulates were partly floating on the surface of the dissolution medium, where parts of the pellets were not immersed in the medium.

Comparing results of the dissolution carried out in buffers of neutral pH using modified compendial method in a basket apparatus (see Fig. 6) and the biorelevant method in a paddle apparatus (see Fig. 8), a very similar relationship between the drug release rate and the chemical nature of inert cores was found: dissolution rate from water-soluble sugar- and isomalt-based multiparticulates was much faster than from insoluble ones. Furthermore, in the case of drug-loaded pellets based on water-soluble inert cores the release of diclofenac sodium from both tablets and hard gelatin capsules was insensitive to differences in hydrodynamic conditions generated in a paddle or a basket apparatus, showing similarly fast dissolution rate, normally exceeding 85% of the amount of the drug substance within first 15 min of the test. The dissolution rate from tablets containing MCC- and DCPA-based multiparticulates was slightly slower and their release profiles had a similar shape. In the case of uncompressed DR pellets filled in capsules, a very high susceptibility of the drug release to the hydrodynamic conditions in an apparatus was found. Comparing the results obtained using the basket and paddle methods, one can observe much slower dissolution rate for the latter method. This is due to the fact that the water-insoluble pellets cores, especially DCPA-based ones, had a higher density and tended to lay on the bottom of dissolution vessel directly under the paddles, where mixing intensity is normally the lowest. Interestingly though, under these conditions the release profile observed for calcium phosphate pellets was very close to 0-order kinetics.

5. Conclusions

In the course of this study, delayed-release multiparticulate formulations of diclofenac sodium in the form of tablets and hard gelatin capsules were developed. As a basis for the preparation of the multiparticulates, the starter pellets containing sucrose, isomalt, microcrystalline cellulose and anhydrous dibasic calcium phosphate were used. It has been shown that the core material significantly influenced the coating process, the properties of drug-loaded pellets as well as their dissolution behavior. For diclofenac sodium, it seems more advantageous to use starter pellets based on water-insoluble substances such as MCC or DCPA, which showed the lowest degree of the drug release in the acid phase. This may result in lower concentration of diclofenac sodium in the gastric lumen and reduce stomach irritation.

The tableting of drug-loaded enteric-coated pellets revealed slightly different resistance to compression and susceptibility to mechanical damages of investigated inner cores. It can be assumed, the use of starter pellets of smaller size would result in obtaining more rugged multiparticulates, more suitable for formulation into tablets as reported elsewhere [37,39,41].

The dissolution rate of diclofenac sodium from developed formulations in neutral conditions mimicking these in the distal GIT was clearly related to the solubility of the core material in water – very rapid for soluble cores made of isomalt and sugar, slower for insoluble ones (MCC- and DCPA-based).

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