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Research Article

Evaluation of Drug Release From Coated Pellets Based on Isomalt, Sugar, and Microcrystalline Cellulose Inert Cores

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Abstract. The objective of the present study was to investigate the effect of the pellet core materials isomalt, sugar, and microcrystalline cellulose on the *in vitro* drug release kinetics of coated sustained-release pellets as well as to evaluate the influence of different ratios of polymethacrylate copolymers exhibiting different permeability characteristics on the drug release rate. For characterization of the drug release process of pellets, the effect of osmolality was studied using glucose as an osmotically active agent in the dissolution medium. The pellet cores were layered with diclofenac sodium as model drug and coated with different ratios of Eudragit® RS30D and Eudragit® RL30D (ERS and ERL; 0:1 and 0.5:0.5 and 1:0 ratio) in a fluid bed apparatus. Physical characteristics such as mechanical strength, shape, and size proved that the inert cores were adequate for further processing. The *in vitro* dissolution tests were performed using a USP Apparatus I (basket method). The results demonstrated that, besides the ratio of the coating polymers (ERS/ERL), the release mechanism was also influenced by the type of starter core used. Sugar- and isomalt-type pellet cores demonstrated similar drug release profiles.

KEY WORDS: diclofenac sodium dissolution; inert pellet core; isomalt; microcrystalline cellulose; sugar.

INTRODUCTION

Multiparticulate drug delivery systems where pellets are used have come to the center of research attention during the past decades. Their numerous technological, physiological, and therapeutical advantages over single-unit dosage forms make them very useful both in drug carrier design and drug development (1–3). Consequently, several materials have been investigated to develop and produce inert cores as starting excipients for pharmaceutical pellet manufacturing with various particle sizes. These include inert cores based on saccharose and microcrystalline cellulose (MCC). Sugar spheres have been used as inert cores for a long time and are monographed in the major pharmacopeias [Eur. Ph., USP, JP] (4). MCC, the gold standard for extrusion–spheronization, is widely used, but possesses various disadvantages, such as drug adsorption to the surface of its fibers, its chemical incompatibility with a number of drugs, and its lack of disintegration when used in matrix pellets (5–8). Isomalt, a polyol produced from sucrose, is a novel potential carrier core exhibiting multiple health benefits as having low glycemic and low insulinemic responses, and thus is suitable for diabetics (9). Another advantage of this polyol is that it does not contain a carbonyl group (Maillard reaction is impossible); hence, it is chemically more stable than related saccharides (10). Using the inert carriers, a wide range of active ingredients can be layered on their surface, which may be followed by a second coating process applying a release-modifying polymer to ensure controlled release (11–13).

The drug release from such layered and coated pellets is usually governed by various mechanisms, such as diffusion, osmosis, or polymer erosion, and is influenced by several factors, such as the characteristics of the coats (polymer types, coating level), the coating process conditions, and one of the most important being the properties of the core (13). A number of the latter properties are already well described in the literature and the influence of size distribution, surface area, shape, surface roughness, density, and friability on the drug release and on the uniform coating thickness of the pellets has been shown to be very important factors (14,15). Besides the physical description of the pellets, characterization of the quality and quantity of the drug–excipient system forming the pellets is also of utmost importance. This was underlined by a study published by Ozturk *et al.* who pointed out that the mechanism of drug release from active pharmaceutical ingredient (API)-layered inert sugar cores coated with ethyl cellulose is mostly influenced by the combined osmotic pressure of the drug and the material of the core (16). Schultz and Kleinebudde investigated cellulose acetate-coated matrix pellets which were prepared with or without osmotic active ingredients. The drug release from these two types of pellets was very different (17). Sousa *et al.* reported that the solubility of both drug and filler influenced the drug release profile of matrix-structured pellets (18).

Alongside the properties of the core, the osmotic pressure in the gastrointestinal tract also plays a major role

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in the drug release profile of such pellets. The osmolality of the gastrointestinal tract varies between 100 and 400 mOsm/kg (19). Muschert *et al.* investigated different pellets containing various drugs under physiological (0.28–0.62 osmol/kg) conditions and concluded that the variation in the drug release rates from ethyl cellulose-coated pellets were only minor, irrespective of the type of the drug and pellet starter core (20,21).

Recently, isomalt became important in pharmaceutical development used as tablet or granule excipient. The objective of this study was to investigate the application possibility of isomalt as a starter pellet and to compare the most important characteristics of this core to the commonly used sugar and MCC-based inert spheres.

Furthermore, it was our purpose to investigate the difference of drug release rate from pellets coated with different ratios of polymethacrylate copolymers exhibiting different permeability characteristics.

An additional objective was to investigate and compare the effect of the three cores on the *in vitro* drug release of a poorly water-soluble drug when they were coated with a permeable membrane. For a better understanding of the drug release of the mentioned dosage form, we aimed to simulate the effect of the osmolality in the gastrointestinal tract using glucose as an osmotically active agent.

MATERIALS AND METHODS

Materials

Diclofenac sodium (Sigma-Aldrich Chemie GmbH, Germany) was used as model drug. Isomalt described in pharmacopeias [Eur. Ph., USP] is a pharmaceutically acceptable excipient, which was supplied by the manufacturer (BENEO-Palatinit GmbH, Germany) in the form of starter pellets (galenIQ™ 980) in the size range of 700–1,000 μm. Sugar spheres (850–1,000 μm; pharm-a-spheres®, H.G.Werner GmbH, Germany) and MCC spheres (710–1,000 μm; Ethispheres® 850, NPPharm Ltd., France) were chosen as inert cores for comparison with isomalt spheres. The sugar spheres used were of pharmacopeial grade and as such contain little amount of starch. The other two pellet cores do not contain any additive material.

Hydroxypropyl methylcellulose (HPMC; Pharmacoat 606, Shin-Etsu Chemical Ltd., Japan) was used as binder for the drug-layering process. Polymethacrylate copolymers (Eudragit® RL30D and Eudragit® RS30D, Degussa, Germany)—ERL and ERS—were used as film-forming polymers. Triethyl citrate (TEC; Fluka Chemie AG, Switzerland) served as plasticizer and micronized talc (Sigma-Aldrich Chemie GmbH, Germany) was used as an antiadhesion agent. Glucose anhydrate (MOLAR, Hungary) served as an osmotically active ingredient.

Manufacture of Drug-Layered and Coated Pellets

Drug Layering

Diclofenac sodium (5.0% *w*/*w*) was dissolved in HPMC (Pharmacoat 606; 2.0% *w*/*w*) solution and the solution was layered on the different inert cores in a bottom spray configured fluidized bed apparatus (Aeromatic Strea I., Aeromatic-Fielder AG, Switzerland); 5.0% *w*/*w* drug concentration was achieved. During the layering process, the dispersion was stirred and tempered (about 55–60 C) continuously to keep the diclofenac sodium in solution. The process parameters are given in Table I.

Coating of Drug-Layered Pellets

The drug-layered sugar, isomalt, and MCC cores were coated with different ratios of ERS and ERL (0:1 and 0.5:0.5 and 1:0 ratio) using the equipment described above. The mixing of the coating polymers results in a coat exhibiting permeability properties which fall between the permeability of ERL and ERS where the level of permeability is dependent on the ratio of the applied polymers (22,23). TEC (20% *w*/*w* on dry polymer) and micronized talc (75% *w*/*w* on dry polymer) were added to the coating composition. The concentration of the polymers was 10% *w*/*w* in the coating suspension. The dispersions were gently stirred continuously during the coating processes to prevent sedimentation of the talc. The coating level was 0.65 mg polymer/cm^2 of applied drug-layered pellets. The process parameters are shown in Table I. The coated beads were stored in tightly closed containers.

Characterization Methods

Physical Properties of Pellets

Shape and Size of the Pellets. Two hundred pellets were randomly chosen from each batch to be analyzed. The pellets were placed on the nonshiny black surface of the microscope (black–white contrast plate) serving as the background. The pellets were illuminated from the top using a cold white coherent fiber optic light (230 V, 185 W, 50/60 Hz, diameter of bundle 5.4 mm) of halogen light source (Intralux 5000-1 type, Volpi, Switzerland). One pixel corresponds to 3.048 μm. Maximum of 10–15 pellets could be photographed at a time. Therefore, 15–20 photos were taken of each batch, and the images produced were digitized and analyzed using the computer program Image Pro Plus 4.5 (Media Cynerbetics, USA). For each pellet, 52 shape parameters were determined. In this study, the pellet size and shape were characterized by roundness, aspect ratio (AR), and Feret diameter.

Roundness (C) was calculated using the following formula (24):

$$C = \frac{p^2}{4 \times \pi \times A} \quad (1)$$

where p is the perimeter and A is the area of the pellet (25).

Table I. Layering and Coating Conditions

Condition	Drug layering	Coating
Batch size (g)	450	150
Spray nozzle diameter (mm)	0.8	0.8
Inlet air temperature (°C)	60	45
Outlet air temperature (°C)	51–53	37–40
Atomizing air pressure (bar)	0.8	0.8
Fluid air flow rate (m^3/h)	80–100	80–100
Spray rate (g/min)	2–5	3
Drying temperature (°C)	60	45
Drying time (min)	10	10

Table II. Physical Characteristics of Inert Core (Mean ± SD)

Core type	Tensile strength (N/mm^2)	True density (g/cm^3)	Feret$_{max}$ (mm)	Shape parameters	
				AR	Roundness
Sugar	4.5±1.0	1.55±0.03	1.02±0.06	1.094±0.046	1.005±0.006
Isomalt	6.7±1.7	1.53±0.05	0.90±0.05	1.129±0.056	1.019±0.010
MCC	18.5±7.5[a]	1.38±0.04	0.93±0.09	1.097±0.065	1.013±0.019

[a] Deforming pellets

AR is the ratio of the maximum Feret diameter to the minimum Feret diameter, which is perpendicular to the maximum Feret diameter.

In both cases, the value for an ideal sphere is 1. The more the value differs from 1, the more the object differs from a perfect round particle. The values presented for each type of pellet are the average and standard deviation (SD) calculated from the measurement of 200 individual pellets.

Tensile Strength of the Pellets. Twenty pellets of each batch were measured with a texture analyzer (TA-HD*i*®plus Texture Analyser, Stable Micro System Ltd., UK) operating with a 5-kg load cell. Single pellets were placed onto a flat steel plate. A cylindric punch of 5 mm diameter was moved from the top with a speed of 0.1 mm/s towards the pellet. The crushing load (F) and the diameter (d) of each individual pellet were recorded during the test. The surface tensile strength was calculated using Eq. 2 (26):

$$\sigma_f(s) = \frac{1.6 \times F}{\pi \times d^2}. \quad (2)$$

The average of 20 values was reported as the tensile strength for each batch.

True Density

True density measurements of pellets were performed using a helium pycnometer (Ultrapycnometer 1000, Quantachrome, Germany). Sample preparation consisted of storing the beads at 60 C for 20 h. The pycnometer tested each pellet 15 times and the results were presented as the mean values of the measurements. The sample pellets were examined in triplicate.

Dissolution Studies

The dissolution test for each batch of coated pellets was carried out in 900 ml pH 6.8 (phosphate buffer) solution using the USP basket method (1) with 100 rpm at 37±0.5 C (Hanson SR8-Plus™ Dissolution Test Station, Hanson Research, USA); 500 mg pellets (equivalent to 25 mg drug) were exposed to the media. At predetermined time points, 5 ml samples were withdrawn. The medium was kept at a constant volume by refilling it with fresh buffer solution. The concentration of released diclofenac sodium was measured spectrophotometrically ($\lambda_{diclofenac}$=276 nm; UNICAM UV/VIS Spectrometer UV2, UNICAM Ltd., UK). All results were the mean of six parallels and SD was <5%.

In order to study the influence of osmolality on the release kinetics, pH 6.8 phosphate buffer solutions containing different amounts of glucose anhydrate (0.25 or 0.50 mol/L) were prepared and additional experiments were run under the same conditions. Since the film-forming polymer was cationic, glucose was used as osmotic agent instead of a salt (27).

The osmolality of the media was determined by an osmometer (Knauer-OSMO, model 2320, Germany), applying the freezing point depression method. The osmolality of the three dissolution media were: 0.106±0.004 osmol/kg (without glucose), 0.483±0.007 osmol/kg, and 0.706±0.002 osmol/kg, respectively, with the addition of glucose anhydrate.

Swelling Properties of Coated Pellet

Image analysis was used to determine the swelling properties of coated pellets. Single pellets (n=3) were placed

Table III. Physical Characteristics of Layered, Coated Pellets (Mean ± SD)

Core type	Coating system		Tensile strength (N/mm^2)	True density (g/cm^3)	Feret$_{max}$ (mm)	Shape parameters	
	ERL (%)	ERS (%)				AR	Roundness
Sugar	100	0	7.6±1.1	1.47±0.04	1.08±0.06	1.082±0.042	1.045±0.049
	50	50	7.1±1.0	1.48±0.05	1.08±0.05	1.083±0.039	1.009±0.012
	0	100	7.6±1.3	1.46±0.05	1.08±0.06	1.089±0.052	1.009±0.009
Isomalt	100	0	12.3±2.5	1.44±0.03	0.99±0.06	1.131±0.061	1.020±0.013
	50	50	10.9±1.7	1.42±0.06	0.98±0.06	1.121±0.059	1.019±0.010
	0	100	10.3±2.0	1.43±0.04	0.99±0.06	1.128±0.059	1.017±0.011
MCC	100	0	18.7±2.5[a]	1.29±0.05	1.03±0.07	1.090±0.055	1.020±0.022
	50	50	18.7±2.8[a]	1.30±0.06	1.01±0.08	1.090±0.059	1.017±0.022
	0	100	20.2±4.4[a]	1.29±0.04	1.02±0.07	1.090±0.048	1.011±0.011

[a] Deforming pellets

in aqueous media of different osmolality (5 ml), which was then shaken horizontally (Vibrotherm LE-204/2, Germany, rpm=50) at 37 C. At predetermined time intervals, the pellets were withdrawn and their shape parameters were measured using image analysis as described above. The increase of pellet diameter was calculated using the following equation:

$$\text{Change in pellet diameter } (\%) = \frac{d_t}{d_{t_0}} \times 100 \qquad (3)$$

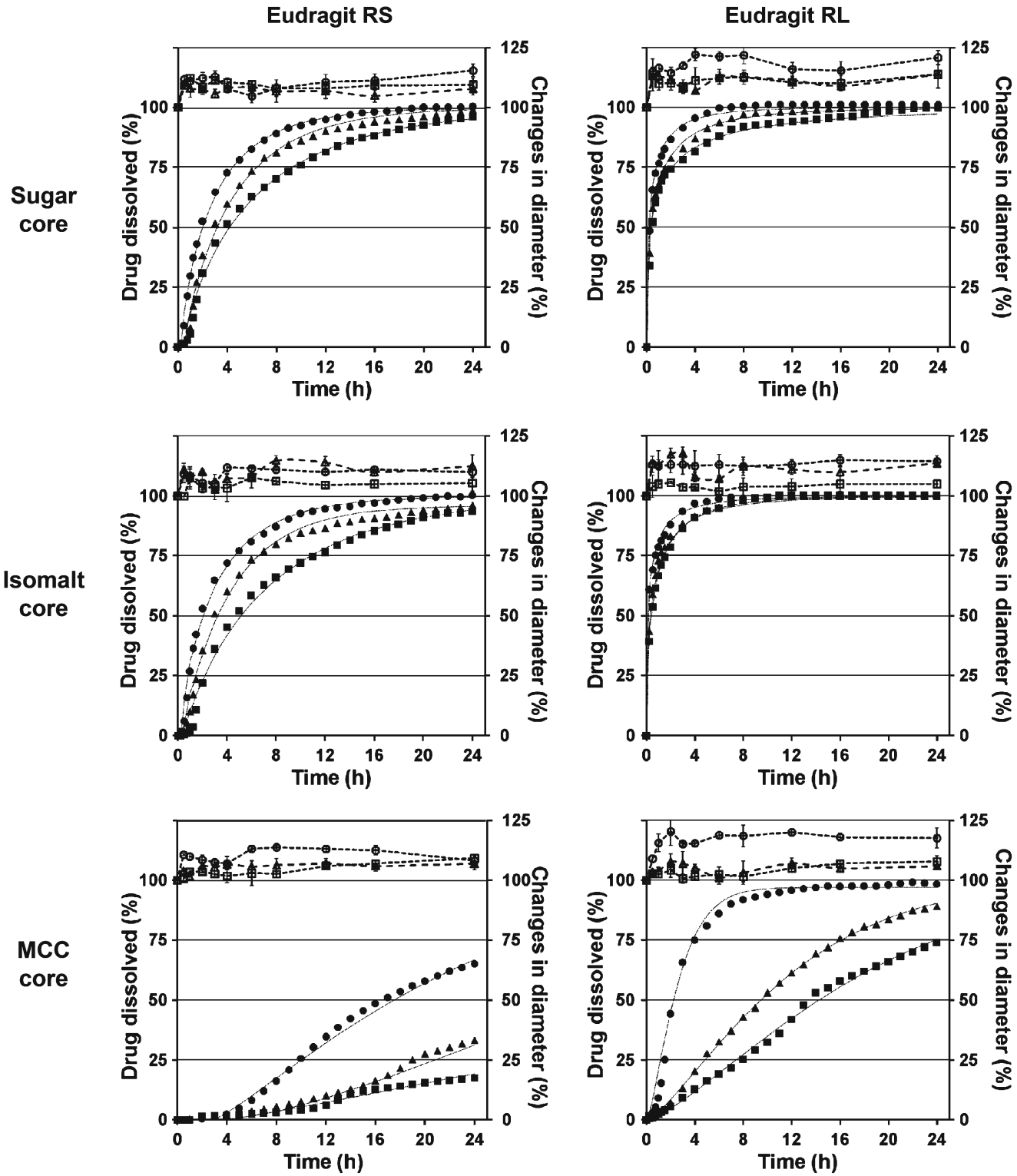

Fig. 1. Drug release profile (*filled circles*, *filled triangles*, *filled squares*) with fitted Weibull model and swelling behavior (*open circles*, *open triangles*, *open squares*) in dissolution media exhibiting different osmolality: 0.106 osmol/kg (*filled circles*/*open circles*), 0.483 osmol/kg (*filled triangles*/*open triangles*), and 0.706 osmol/kg (*filled squares*/*open squares*).The types of polymers are shown at the *top*, the type of cores is indicated on the *left*

where d_t is the maximum Feret diameter at time t and d_{t_0} is the maximum Feret diameter of the investigated pellets before the trial.

Drug Release Kinetic Study

Several theories or kinetic models describe drug release from multiparticulates (28). Although Weibull distribution provides no information about the possible mechanism of dissolution control, in cases where dissolution profiles exhibit differently shaped curves, Weibull distribution serves as a suitable mathematical model to compare the estimated kinetic parameters of the curves (29,30). Since the shape of the dissolution curves of present study was different, the Weibull distribution function was used for the characterization of the dissolution profile of the pellets:

$$M_t = M_\infty \left[1 - \exp - \left(\frac{t - t_0}{\tau_d}\right)^\beta\right] \quad (4)$$

where M_t is the percentage of the dissolved drug at time t, M_∞ is the drug infinite concentration (in percent), t_0 is the lag time of the dissolution, β is the shape parameter of the curve, and τ_d represents the time (in hours) when 63.2% of drug has been dissolved.

The statistical analysis of the data was performed using the TableCurve®3D v4.0 (Systat Software Inc., London, UK). The effect of the independent variables on response y was modeled by the following polynomial equation:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2 \quad (5)$$

where x are the factors (x_1, coating system ratio of the film-forming polymers; x_2, osmolality of the medium) and b parameters mark the coefficients characterizing the main (b_1, b_2), the quadratic (b_{11}, b_{22}), and the interaction effects (b_{12}). These equations were used in a two-factorial, three-level study to determine the τ_d in various media and pellets exhibiting different permeability characteristics.

RESULTS

Physical Properties of Pellets

Image Analysis, Tensile Strength

The roundness and AR as informative shape parameters are shown in Tables II and III.

As seen from the tables, the average value of roundness (for all investigated pellets) varies between 1.005 and 1.045. Assessing the Feret_{max} values in Table III, it can also been seen that the particle sizes increase during the drug-layering and film-coating processes as could be expected.

The tensile strength of starter sugar and isomalt cores is lower, and the true density of these cores are higher than inert MCC pellets (Table II). After the layering and coating processes, the true density of all nine pellet formulations is decreased. Pellets containing sugar or isomalt as a neutral core had a little higher values of true density than the pellets containing MCC (Table III).

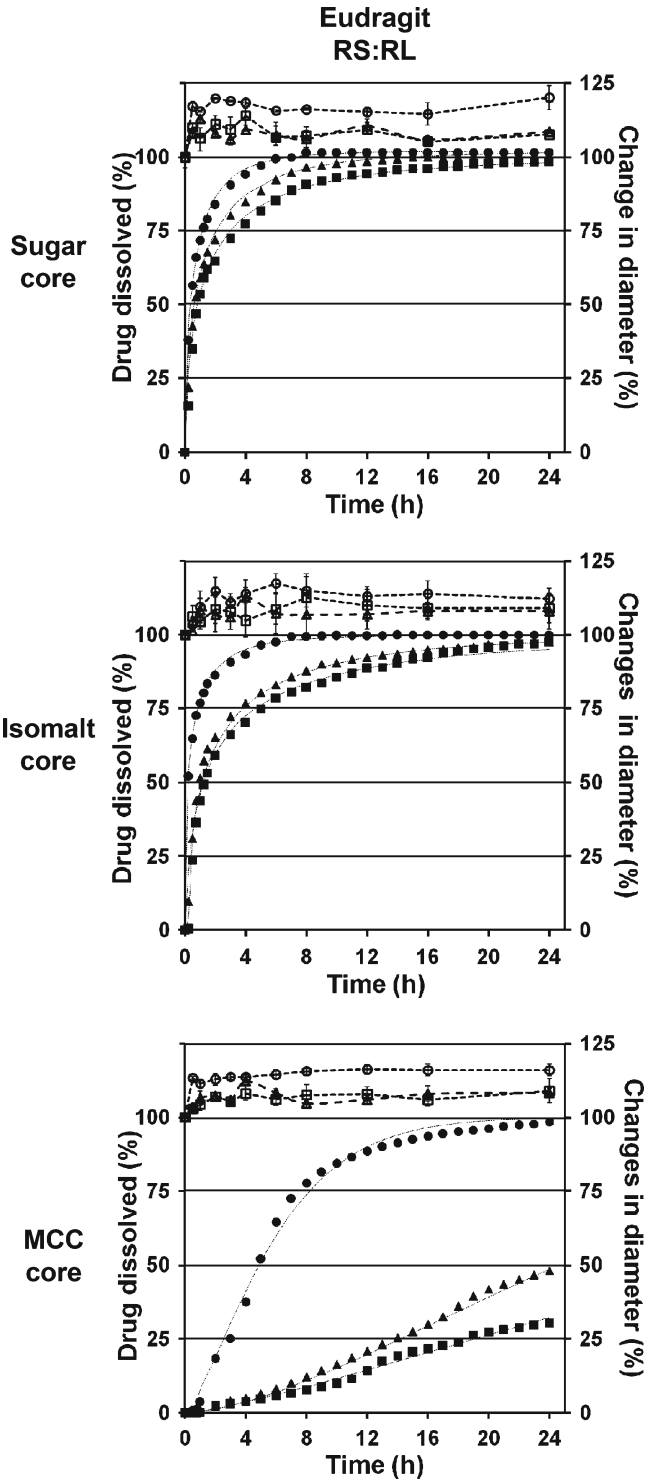

Fig. 2. Drug release profile (*filled circles*, *filled triangles*, *filled squares*) with fitted Weibull model and swelling behavior (*open circles*, *open triangles*, *open squares*) in dissolution media exhibiting different osmolality: 0.106 osmol/kg (*filled circles*/*open circles*), 0.483 osmol/kg (*filled triangles*/*open triangles*), and 0.706 osmol/kg (*filled squares*/*open squares*).The type of polymer is shown at the *top*, the type of cores is indicated on the *left*

Table IV. Independent Variables and Their Variation Interval: Factors and Their Coded Levels

	Actual values	
Coded value	x_1, coating system amount of film-forming polymer (%)	x_2, osmolality of medium (osmol/kg)
−1	ERS/ERL (100:0)	0.106
0	ERS/ERL (50:50)	0.483
1	ERS/ERL (0:100)	0.706

Dissolution Studies of Coated Pellets

Influence of Starter Core on the Dissolution of the Pellets

Figures 1 and 2 show the diclofenac sodium release profile of the nine different formulations. In general, not taking into consideration the effect of the osmolality of the dissolution media, it can be seen that the dissolution rates for the soluble sucrose- and isomalt-based pellets were similar and were significantly higher compared to those of the MCC-based pellets.

Taking into consideration the different polymer coatings, it can be seen that their effect is in correlation with their permeability. As seen in the figures, the more permeable coat (ERL) results in a fast drug release profile, while the less permeable (ERS) polymer exhibits slower drug release profiles. The dissolution of diclofenac sodium from the coat comprising 1:1 ratio of ERL and ERS falls between the dissolution curves of 100% ERL and 100% ERS, but is closer to the curve of the more permeable coat. This correlates well with data previously published (22).

The Influence of Release Medium Osmolality on the Dissolution of the Pellets

Figures 1 and 2 show that, in the case of each pellet, the osmolality of the dissolution media greatly influences the diclofenac sodium release profile. Generally, as the osmolality of the medium is increased, the dissolution of the drug is decreased. The magnitude of decrease in dissolution rate for MCC with the shift from low to medium osmolality is substantially higher, as observed with the shift from medium to high osmolality.

Swelling Properties of Coated Pellet

In Figs. 1 and 2, the swelling properties of the pellets is demonstrated as a second axis in the dissolution media exhibiting different osmolality. An increase in osmolality results in a slight decrease in the change of diameter.

Table V. Matrix of the Two-Factor, Three-Level Face-Centered Factorial Design and Kinetic Parameters of Dissolution Estimated According to Weibull Distribution Function (Mean ± SD, n=6)

		Experimental matrix					
Core type	Trial number	x_1	x_2	τ_d (h)	β	t_0 (h)	r
Sugar	1	−1	−1	2.80±0.111	0.80±0.037	0.23±0.01	0.999
	2	0	−1	0.70±0.025	0.60±0.023	0.00±0.00	0.999
	3	1	−1	0.40±0.019	0.48±0.014	0.00±0.00	0.997
	4	−1	0	4.10±0.173	0.88±0.035	0.46±0.03	0.998
	5	0	0	1.23±0.042	0.56±0.019	0.00±0.00	0.997
	6	1	0	0.75±0.028	0.48±0.022	0.00±0.00	0.998
	7	−1	1	5.90±0.195	0.81±0.035	0.43±0.02	0.998
	8	0	1	1.50±0.065	0.50±0.018	0.10±0.01	0.997
	9	1	1	0.90±0.028	0.39±0.017	0.00±0.00	0.995
Isomalt	1	−1	−1	2.90±0.115	0.80±0.028	0.23±0.02	0.998
	2	0	−1	0.44±0.012	0.50±0.021	0.00±0.00	0.999
	3	1	−1	0.30±0.011	0.43±0.014	0.00±0.00	0.998
	4	−1	0	4.05±0.183	0.96±0.031	0.30±0.01	0.998
	5	0	0	1.99±0.088	0.53±0.018	0.14±0.01	0.995
	6	1	0	0.70±0.027	0.49±0.019	0.00±0.00	0.999
	7	−1	1	7.10±0.188	0.87±0.035	0.49±0.07	0.997
	8	0	1	2.15±0.082	0.46±0.013	0.25±0.02	0.998
	9	1	1	0.80±0.033	0.54±0.025	0.00±0.00	0.999
MCC	1	−1	−1	21.00±1.010	1.22±0.037	2.80±0.07	0.998
	2	0	−1	6.36±0.218	1.33±0.046	0.00±0.00	0.996
	3	1	−1	2.80±0.117	1.30±0.033	0.00±0.00	0.996
	4	−1	0	38.80±1.540	1.60±0.055	3.00±0.12	0.996
	5	0	0	30.98±1.149	1.59±0.061	0.00±0.00	0.999
	6	1	0	12.46±0.423	1.30±0.048	0.00±0.00	1.000
	7	−1	1	77.00±2.850	1.15±0.038	3.80±0.18	0.987
	8	0	1	49.27±1.864	1.31±0.049	0.00±0.00	0.995
	9	1	1	18.69±0.657	1.35±0.037	0.00±0.00	0.998

DISCUSSION

Physical Properties of Pellets

The morphological characteristics of pellets are critical for the final quality of the dosage form because their physicochemical features depend on the size, shape, and surface geometry of the particles. Another important property of inert cores is a high mechanical stability, which is important for further processing such as layering, coating, and compression into tablets.

The maximum acceptable AR value is 1.200 as was previously proposed (5,7). For that reason, the results of shape parameters—*C* (varies between 1.005 and 1.019) and AR (varies between 1.094 and 1.129)—of inert cores indicate spherical geometry.

The tensile strength of sugar and isomalt cores is lower than that of MCC pellets, but there was no attrition observed during fluid bed layering. Therefore, the values prove that the inert cores are adequate for further processing.

Results of the layered, coated pellets show that the shape parameters (AR, *C*) did not change during the process, but the pellets are larger and mechanical strength is somewhat higher compared to the starter cores.

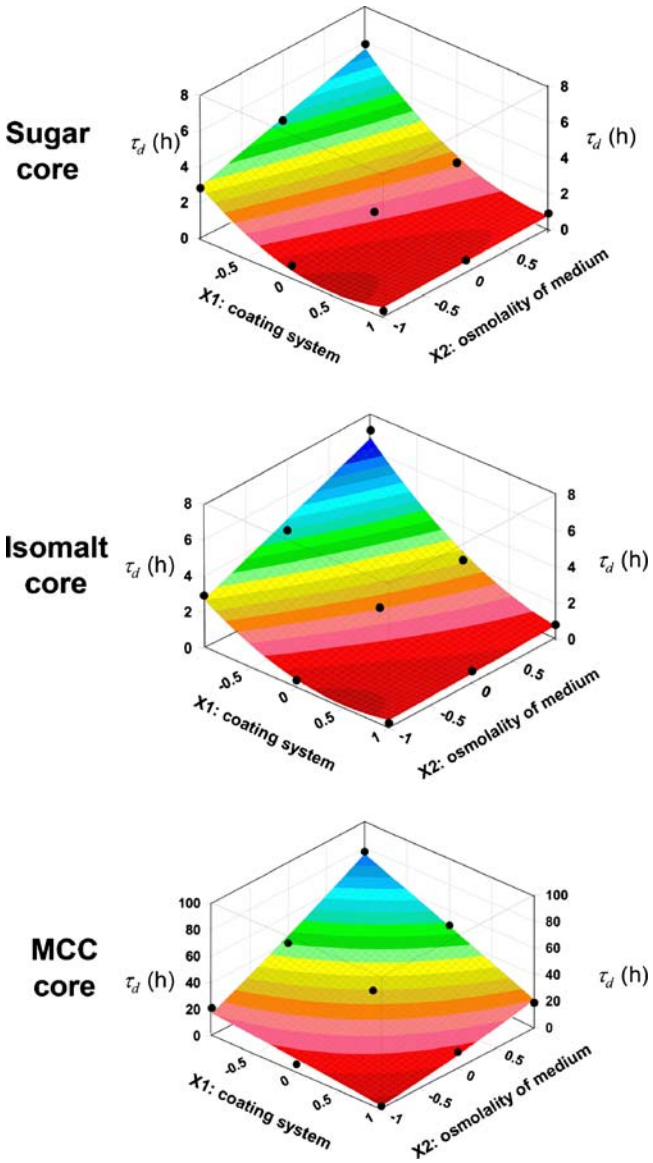

Fig. 3. Surface plot of the effects of polymer type and osmolality on the dissolution (τ_d demonstrates time value when 63.2% of drug is dissolved)

Dissolution Studies of Coated Pellets

Influence of Starter Core on the Dissolution of the Pellets

MCC is not soluble, but swells in water, and it is assumed that van der Waals interactions are the main interparticle bonding mechanism (31). On the other hand, a dissolution study using sugar spheres, built up mainly of sucrose, proved that the sugar-based pellets possess good water solubility properties (32). Isomalt is also water-soluble, showing 25 g/100 ml solubility at 20 C (10). These properties of the pellets also play an important role in the dissolution of the drugs from the different cores.

In case of the MCC-based pellets, a sustained release is notable, which can be accounted for by the fact that MCC is insoluble in water. Compared to the sugar and isomalt cores, it does not dissolve in the water that penetrated into the pellet; therefore, a difference of osmotic pressure between the outer and inner part of the coat cannot be expected. This difference of pressure may be responsible for the release of the active ingredient. In case of the soluble cores, the pressure difference is achieved, thus the active ingredient is released from the pellets. The action of release is not fully understood, but results of swelling behavior detailed in Figs. 1 and 2 prove that the major role of cracking can be excluded. This is underlined by the change in pellet diameter and by the lack of change in roundness. The constant flow of water into the pellet would initially increase its size up to a limit when the crack appears (33). At this point, the inner liquid would flow out of the pellet and its diameter would decrease suddenly. This is not the case in the tested samples. The increase of diameter is similar for all three pellets and can be characterized by an initial, slow increase and an even slower swelling. In spite of this similar swelling behavior, the dissolution from water-soluble-based pellets is much faster and is more complete than from the pellets based on water-insoluble cores. Later, in the case of pellets based on water-soluble core functioning as an osmotically active agent, forces the active ingredient out of the pellet through the pores of the coat formed through the dissolution of pellets.

Based on the difference encountered in the dissolution of the pellets, it can be concluded that the diclofenac sodium release mechanism is mainly determined by the type of starter pellet.

The Influence of Release Medium Osmolality on the Dissolution of the Pellets

For all nine pellet formulations, it can be concluded that, as the osmolality of the dissolution medium is increased, the dissolution of the diclofenac sodium is decreased. The decreased release rate is substantial, even under physiological conditions that were investigated. Muschert *et al.* (20) also found a decrease in the diltiazem HCl release rate from ethyl

cellulose-coated beads, but their study proved this at higher osmolality of the dissolution media. The results found here can be explained by the fact that, as previously described, an internal osmotic pressure is formed in the pellets and that the rate of dissolution correlates with the osmotic pressure difference encountered between the inner and outer part of the pellet. Therefore, in the case where the osmolality of the medium is higher, the osmotic gradient is lower, which leads to a slower dissolution of the API. Examining the three dissolution curves (media with different osmotic pressures) of each batch one by one, it can also be stated that, for the water-soluble cores, the difference between the dissolution at various medium osmotic pressures is mainly dependent on the type of film-forming polymer coat. It can be concluded that the difference between the three dissolution curves is larger in the case of ERS than in the case of ERS/ERL, which is larger than ERL. Therefore, there is a correlation between the permeability of the coat and the difference of active ingredient dissolution (in different media with different osmotic pressure). In the case of the water-insoluble core (MCC), a similar tendency can be observed, with the exception that the difference between the three dissolution curves is much more dependent on the osmolality of the medium than in case of sugar and isomalt.

Drug Release Kinetic Study

The kinetic parameters (τ_d, β, t_0) that were calculated using the Weibull distribution function are shown in Tables IV and V. Coated pellets prepared by layering the drug onto sugar or isomalt cores demonstrated similar drug dissolution profiles. In case of pellets coated with ERS polymer, drug release started later ($t_0>0$) by increasing osmolality in the dissolution medium, especially for MCC pellet cores.

A surface plot was fitted onto τ_d parameters applying the polynomial Eq. 5 and it is shown in Fig. 3. The results show that the effect of the two factors (osmolality of medium and ratio of ERS/ERL) on τ_d is very similar for isomalt and sugar, but were different in case of MCC. It can be seen that, in the case of highly permeable coats, drug release rate is not as pronouncedly affected by the change in the osmolality of the medium as in the case of coats exhibiting lower permeability. The strength of this effect is not only determined by the permeability of the coat, it also varies with the type of starter core (water-soluble or water-insoluble):

$$\tau_{d,\text{sugar}} = 1.14 - 1.79x_1 + 0.73x_2 + 1.33x_1^2 - 0.65x_1x_2$$
$$(\text{with } r_{\text{sugar}} = 0.993, \text{standard error of fit} = 0.36),$$
$$\tau_{d,\text{isomalt}} = 1.50 - 2.04x_1 + 1.07x_2 + 1.12x_1^2 + 0.04x_2^2 - 0.925x_1x_2$$
$$(\text{with } r_{\text{isomalt}} = 0.986, \text{ standard error of fit} = 0.60),$$
$$\tau_{d,\text{MCC}} = 27.69 - 17.14x_1 + 19.13x_2 - 0.41x_1^2 + 1.77x_2^2 - 10.03x_1x_2$$
$$(\text{with } r_{\text{MCC}} = 0.990, \text{ standard error of fit} = 5.41).$$

The fitted polynomial equations demonstrate the similar behavior of sugar- and isomalt-based pellets. However, in the case of poorly water-soluble diclofenac sodium, the dissolution rate was more sensitive to the osmolality (x_2) for MCC pellets, which is demonstrated by the amplitude of the coefficients.

CONCLUSION

Pellets comprising water-soluble and water-insoluble inert cores were prepared. There was no substantial difference in the shape characteristics of different layered pellets; however, MCC-based pellets exhibited higher mechanical strength.

Dissolution studies with all pellets proved that, besides the ratio of the coating polymer (ERS/ERL), the release rate from such layered pellets was also influenced by the type of starter core. In general, it can be concluded that sugar- and isomalt-type pellet cores demonstrated a similar drug release rate as shown by almost identical drug release profiles. The dissolution of poorly water-soluble diclofenac sodium conducted in dissolution media exhibiting different osmolality demonstrated that pellets prepared with water-soluble sugar or isomalt cores are similarly less sensitive to the change in osmolality, compared to the MCC-based pellets.

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REFERENCES

1. Digenis GA. The *in vivo* behavior of multiparticulate *versus* single unit dosage formulations. In: Ghebre-Sellassie I, editor. paticulate oral drug delivery. New York: Marcel Dekker; 1994. p. 333–55.
2. Nastruzzi C, Cortesi R, Esposito E, Genovesi A, Spadoni A, Vecchio C *et al*. Influence of formulation and process parameters on pellet production by powder layering technique. AAPS PharmSciTech. 2000;1(2):E9.
3. Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. J Control Release. 2009;134:74–80.
4. Werner D. Sugar spheres: a versatile excipient for oral pellet medications with modified release kinetics. Pharmaceut Tech Eur. 2006;18:35–41.
5. Dukić-Ott A, Thommes M, Remon JP, Kleinebudde P, Vervaet C. Production of pellets via extrusion–spheronisation without the incorporation of microcrystalline cellulose: a critical review. Eur J Pharm Biopharm. 2009;71:38–46.
6. Charoenthai N, Kleinebudde P, Puttipipatkhachorn S. Influence of chitosan type on the properties of extruded pellets with low amount of microcrystalline cellulose. AAPS PharmSciTech. 2007;8(3):E64. doi:10.1208/pt0803064.
7. Kranz H, Jürgens K, Pinier M, Siepmann J. Drug release from MCC- and carrageenan-based pellets: experiment and theory. Eur J Pharm Biopharm. 2009;73:302–9.
8. Thommes M, Kleinebudde P. Use of k-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. I. Influence of type and fraction of filler. Eur J Pharm Biopharm. 2006;63:59–67.
9. Liversey G. Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. Nutr Res. 2003;16:163–91.
10. Bolhuis GK, Engelhart JJP, Eissens AC. Compaction properties of isomalt. Eur J Pharm Biopharm. 2009;72:621–5.
11. Jones DM. Solution and suspension layering. In: Ghebre-Sellassie I, editor. Pharmaceutical pelletization technology. New York: Marcel Dekker; 1989. p. 145–64.
12. Goodhart FW, Jan S. Dry powder layering. In: Ghebre-Sellassie I, editor. Pharmaceutical pelletization technology. New York: Marcel Dekker; 1989. p. 165–86.

13. Tang ESK, Chan LW, Heng PWS. Coating of multiparticulates for sustained release. Am J Drug Deliv. 2005;3:17–28.
14. Mehta AM. Evaluation and characterization of pellets. In: Ghebre-Sellassie I, editor. Pharmaceutical pelletization technology. New York: Marcel Dekker; 1989. p. 241–65.
15. Felton LA. Characterization of coating systems. AAPS PharmSciTech. 2007;8(4):E112.
16. Ozturk AG, Ozturk SS, Palsson BO, Wheatley TA, Dressman JB. Mechanism of release from pellets coated with an ethylcellulose-based film. J Control Release. 1990;14:203–13.
17. Schultz P, Kleinebudde PA. New multiparticulate delayed release system. Part I: dissolution properties and release mechanism. J Control Release. 1997;47:181–9.
18. Sousa JJ, Sousa A, Moura MJ, Podczeck F, Newton JM. The influence of core materials and film coating on the drug release from coated pellets. Int J Pharm. 2002;233:111–22.
19. Beckwith MC, Feddema SS, Barton RG, Graves C. A guide to drug therapy in patients with enteral feeding tubes: dosage form selection and administration methods. Hosp Pharm. 2004; 39:225–37.
20. Muschert S, Siepmann F, Leclercq B, Carlin B, Siepmann J. Prediction of drug release from ethylcellulose coated pellets. J Control Release. 2009;135:71–9.
21. Muschert S, Siepmann F, Leclercq B, Carlin B, Siepmann J. Drug release mechanisms from ethylcellulose: PVA-PEG graft copolymer-coated pellets. Eur J Pharm Biopharm. 2009;72:130–7.
22. Amighi K, Moes AJ. Evaluation of thermal and film forming properties of acrylic aqueous polymer dispersion blends: application to the formulation of sustained-release film coated theophylline pellets. Drug Dev Ind Pharm. 1995;21:2355–69.
23. Siepmann F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. Polymer blends for controlled release coatings. J Control Release. 2008;125:1–15.
24. Cespi M, Bonacucina G, Misici-Falzi M, Golzi R, Boltri L, Palmieri FG. Stress relaxation test for the characterization of the viscoelasticity of pellets. Eur J Pharm Biopharm. 2007;67:476–84.
25. Kristensen J. Direct pelletization in a rotary processor controlled by torque measurements. III. Investigation of microcrystalline cellulose and lactose grade. AAPS PharmSciTech. 2005;6(3): E495–503.
26. Newton M, Petersson J, Podzcek F, Clarke A, Booth S. The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture. J Pharm Sci. 2001;90:987–95.
27. Wagner KG, McGinity JW. Influence of chloride ion exchange on the permeability and drug release of Eudragit RS 30 D films. J Control Release. 2002;82:385–97.
28. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Biopharm. 2001;13:123–33.
29. Langenbucher F. Linearization of dissolution rate curves by the Weibull distribution. J Pharm Pharmacol. 1972;24:979–81.
30. Dévay A, Mayer K, Pál SZ, Antal I. Investigation on drug dissolution and particle characteristics of pellets related to manufacturing process variables of high-shear granulation. J Biochem Biophys Methods. 2006;69:197–205.
31. Dreu R, Širca J, Pintye-Hódi K, Burjan T, Planinšek O, Srčič S. Physicochemical properties of granulating liquids and their influence on microcrystalline cellulose pellets obtained by extrusion–spheronisation technology. Int J Pharm. 2005;291:99–111.
32. Marabi A, Mayor G, Burbidge A, Wallach R, Saguy IS. Assessing dissolution kinetics of powders by a single particle approach. Chem Eng J. 2008;139:118–27.
33. Lecomte F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. pH-sensitive polymer blends used as coating materials to control drug release from spherical beads: elucidation of the underlying mass transport mechanisms. Pharm Res. 2005;22:1129–41. doi:10.1007/s11095-005-5421-2.