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ORIGINAL ARTICLE

Preparation and in vitro evaluation of gliclazide sustained-release matrix pellets: formulation and storage stability

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Abstract

Objective: Gliclazide-loaded matrix pellets consisting of ethylcellulose, microcrystalline cellulose (MCC), and sodium carboxymethyl starch were prepared by extrusion-spheronization. *Method*: To control the initial fast release of the matrix pellets, three coating methods were used: hot-melt coating, polymer aqueous dispersion film coating, and MCC powder coating. An orthogonal experiment ($L_9(3)^4$) was applied to optimize the key process variables of MCC-powder coating. The in vitro dissolution profiles of the coating pellets were compared with the commercial tablets Diamicron® by the similarity factor (f_2). The storage stability was measured to choose the best coating method. *Result*: Initial fast release was overcome by using the three coating methods. Rotation speed of friction plate and time of coating (addition of binder/coating agents) were both found to have the more important influence to drug release. The f_2 values between the three coated pellets and the commercial product were all greater than 50. The results of storage-stability tests suggest that the pellets prepared by MCC-powder-coating method are stable for at least 6 months under stress conditions (40°C/75%RH), whereas the others failed. *Conclusion*: The MCC-powder-coating method offered the advantage of a one-step procedure compared with film coating and hot-melt coating.

Key words: *Gliclazide; matrix pellets; MCC-powder coating; storage ability; initial burst release*

Introduction

Gliclazide (Gz) is an oral hypoglycemic agent, belonging to the second generation of sulfonylureas, and is widely used in the treatment of non-insulin-dependent diabetes mellitus. The glucose-lowering effects are secondary to both enhanced insulin secretion and a decrease in insulin resistance. The former is because of closure of a K^+ adenosine triphosphate channel in the beta cells. Gz also has beneficial effects on platelet behavior and function, in addition to improving free radical status. These effects should be beneficial for the prevention of diabetic microangiopathy[1].

In contrast to tablets, pellets provide the advantages of multiple-unit dosage forms such as increased dosing flexible[2].The sustained-release matrix pellets of Gz were prepared for the advantages of the reduction in inter-subject variability of absorption and the incidence of adverse side effects compared with Diamicron® sustained-release tablets[3]. Usually, two techniques are used to prepare a controlled-release dosage form: coating and matrix systems. In the coating system, drug-loaded pellets are surrounded by a membrane that controls the release of drug. However, the procedure is a complex process, which is both time-consuming and expensive. By contrast, the preparation of using a matrix system is much simpler[4]. The matrix system involves the homogeneous dispersion of drug particles in either a hydrophobic or a hydrophilic polymer matrix and, therefore, the physicochemical nature of the matrix material controls the release rate of the drug and determines its release mechanism[5]. Hydrophobic and hydrophilic matrices are two types of matrix systems widely used to achieve sustained release[6]. However, the initial fast release frequently occurred in the development of sustained-release pellets because of their large surface,

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especially for matrix pellets. As a result, coating process is necessary in many cases. (1) Aqueous dispersion film coating: there are several advantages in using aqueous polymer dispersions instead of organic polymer solutions for film coating, such as the avoidance of environmental toxicity and the reduction of processing time. Surelease® (ethylcellolulose, EC) and Eudragit® have been used as sustained coating materials widely in pharmaceutical industry. But the high cost and time-consuming process restrict its development. It is difficult to ensure complete film formation even after curing and there is a risk of further coalescence of polymer particles during storage, which alter the structure of film and significantly decrease the release rate[7]. (2) Hot-melt coating, which is an attractive method developed in recent year. As a solvent-free method, the process can be closely controlled; moreover, it can offer taste masking and sustained-release characteristics[8]. Overall, the mentioned methods above were complicated, time-consuming, and too expensive. Therefore, it is necessary to develop a new coating method with a more simple procedure to control the drug release.

In this study, a novel microcrystalline cellulose (MCC)-powder-coating method was first adopted to sustain the drug release for the advantages of simplicity, convenience, and low cost. Pellets were manufactured by a one-step procedure, extrusion-spheronization, during which MCC was layered onto drug-loaded cores by direct pelletization in rotary processor with wetting agent. The pellets prepared with MCC-coating method exhibit well drug release profiles, and still remain stable under stress condition. Therefore, the MCC-powder-coating method can be regarded favorably by the pharmaceutical industry.

The major objectives of this study were (1) to prepare Gz-loaded matrix pellets; (2) to reduce the initial fast release of matrix pellets, for which hot-melt coating, aqueous dispersion film coating, and MCC-powder coating were applied respectively; and (3) to evaluate storage stability of sustained-release pellets under stress conditions (40°C/75%RH).

Materials and methods

Materials

Gz was purchased from Xiandai Hasen (Shanghai, China). Methacrylic acid copolymers (Eudragit® NE 30 D, Eudragit® L 30 D-55) were supplied by Römh GmbH Chemische Fabrik (Darmstadt, Germany). EC (EC-7cps) and Compritol 888 ATO were donated by Coloron (Shanghai, China). Talc was obtained from Yulin Talc Factory (Guangxi, China). MCC (Avicel PH101), sodium carboxymethyl starch (CMS-Na), and hydroxy-propyl methyl cellulose (HPMC-E5) were provided by Huzhou Zhanwang Pharmaceutical Co., Ltd. (Huzhou, China). Other excipients were of standard pharmaceutical grade.

Methods

Preparation of matrix pellets

Drug-loaded pellets of different formulations are listed in Table 1. Gz and excipents were mixed and passed through a 100-mesh screen three times. The required amount of water was slowly added to the dry mixer to produce a wet mass with a suitable consistency. The wet mass passed through a screw extruder (Wenzhou Pharmaceutical Equipment Factory, Wenzhou City, China) with a 1-mm screen on a laboratory scale (500 g) at 60 rpm. Then the extrudates processed in a spheronizator (Wenzhou Pharmaceutical Equipment Factory) fitted with a cross-hatched plate rotated at 200 rpm for 2 minutes to cut the material into smaller cylinders and further processed at a speed of 500 rpm for 10 minutes.The obtained pellets were dried at 40°C for 12 hours in a conventional hot air oven. The dried pellets were then screened and the 20–24 mesh (830–700 μm) fraction was collected for further study.

Hot-melt coating

The matrix pellets were coated with molten Compritol 888 ATO in a coating pan (B-300 Coating Pan, BaoJi JianHua Co., Ltd., Baoji, China) with a 20% weight gain. The coating conditions were batch size = 500 g, rotation speed = 30 rpm; the pellets were heated by hot air to 70°C then Compritol 888 ATO was added to the rolling pan. After coating, 2% (w/w) talc was added to prevent clumping and, finally, the pellets were cooled to room temperature.

Film coating

The matrix pellets were coated by a blend of Eudragit® NE 30 D and Eudragit® L 30 D-55 in a ratio of 5:1 (15%, w/v solid content) in a fluidized bed coater (Model: FD-MP-01, Powrex Corporation, Itami, Japan) to obtain a 5% weight gain. The coating aqueous dispersion kept agitating during the coating process.

The coating conditions were batch size = 500 g, inlet temperature = 25°C, product temperature = 25°C, air flow = 60 m^3/h, nozzle diameter = 1.2 mm, spray

Table 1. Composition of the different formulations.

Formulation	Gliclazide (%)	EC-7cps (%)	CMS-Na (%)	MCC (%)
F1	18	10	—	72
F2	18	10	2	70
F3	18	20	2	60

pressure = 1.2 MPa, spray rate = 3.5 g/min; and 0.1% talc was admixed into the pellets after coating. The coated pellets were then cured in an oven at 40°C for 24 hours.

MCC powder coating

As described in section 'Preparation of matrix pellets' after the extrudates being cut into smaller cylinders in the spheronizator for 2 minutes with the roating speed of 500 rpm, the cylinders turned into spheres. Then dropping wetting agent (2% HPMC-E5) until the surface of pellets was wetted. Subsequently, MCC was transferred slowly into the center of the spheronizator. MCC dispersed quickly by centrifugal force, and the surface of matrix pellets are covered with compact MCC powder; therefore, the pellets did not adhere with each other. The feeding rate of the coating powder onto the pellets cores was dependent on the capacity of the coating powder to adhere, which decreased with increasing coating levels; the wetting agent was dropped after the surface of cores turned dry. The binders and MCC were added alternately and the amount of binders was 10% (v/w) of MCC; MCC was controlled by the weight gain of the pellets, that is, 20% (w/w) of pellets. On a laboratory scale, this quantity of MCC can be added within 10 minutes at a constant rate. After all the MCC had been added, the spheronizator continued to rotate at a speed of 500 rpm for 5 minutes. The obtained pellets were dried at 40°C for 12 hours in a conventional hot air oven. The dried pellets were screened and the 20–24 mesh (830–700 μm) fractions were collected for further study.

Orthogonal arrays

An $L_9(3)^4$ orthogonal array was used to investigate the key process variables of MCC-powder coating. Table 2 shows that the optimization experiment was carried out with three factors and three levels, namely, rotation speed of friction plate (400, 500, 600 rpm), time of rotation (3, 5, 7 minutes), and time of coating (addition of binder/coating agents) (5, 10, and 15 minutes). The range of each factor level was based on the results of preliminary trials. The percentages of the drug release of commercial product at 2, 4, and 12 hours were used as desirable drug release: 20%, 40%, and 90%. Q_2, Q_4, and Q_{12} were the cumulated release of experimental design preparations, K represented comprehensive score. K was smaller: the experimental preparation was more similar with commercial product ($K = |20 - Q_2| + |40 - Q_4| + |90 - Q_{12}|$). The key process variables could be obtained through the extreme difference analysis. Orthogonality Experiment Assistant software II (V3.1, Sharetop Software Studio, Beijing, China) was used for the evaluation of the statistical experimental design.

Table 2. Factors and levels for orthogonal test.

	Level[a]		
Variable	1	2	3
A, rotation speed of friction plate (rpm)	400	500	600
B, time of rotation (minutes)	3	5	7
C, time of coating (addition of binder/coating agents)(minutes)	5	10	15

[a]Level 4: unassigned.

Drug release test

To examine the effects of the investigated factors on drug release of the matrix pellets and coated pellets, respectively, drug release studies were carried out in a paddle apparatus (USP 29) using 900 mL phosphate buffer (pH 7.4), at 100 rpm, 37°C, $n = 6$. Samples were withdrawn at predetermined time points at 0.5, 1, 2, 4, 8, 10, and 12 hours and measured using UV-spectrophotometry ($\lambda = 226$ nm).

Higuchi[9] and Korsmeyer–Peppas[10] models were used for the analysis of the drug release mechanism of matrix pellets and coated pellets. The release of drugs from the matrix pellets can be analyzed by release kinetics theory as follows:

$$\text{Higuchi model}: \quad Q = K_1 t^{\frac{1}{2}} \tag{1}$$

where Q is the percentage of drug release at time t and K_1 is the Higuchi release rate constant that reflects the shape and the internal structure of the matrix as well as the drug concentration and solubility.

$$\text{Korsmeyer}-\text{Peppas model}: \quad Q = K_2 t^n \tag{2}$$

where K_2 is a constant incorporating the structural and geometric characteristics of the matrix pellets and n is the release exponent indicating the drug release mechanism. This model is generally used to analyze the drug release when the mechanism is not known or when more than one type of release process is involved.

To compare the differences in dissolution profiles between the commercial product and the experimental formulations, the similarity factor f_2[11] is defined by Equation (3):

$$f_2 = 501g\left\{\left[1+\frac{1}{n}\sum_{n=0}^{t} W_t\,(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \tag{3}$$

where n is the number of dissolution sample times and R_t and T_t are the individual percentages dissolved at each time point, t, for the reference and test dissolution profiles, respectively.

Storage stability

Aqueous dispersion film-coating pellets, hot-melt-coating pellets, and MCC-powder-coating pellets were stored in aluminum foil packing, and a constant temperature and a humidity test box was used in the drug stability experiment (LRH-150-Y, Guangdong, China) under stress conditions: 40°C/75%RH. The drug release was measured after 1, 2, 3, and 6 months of storage.

Scanning electron microscopy

The internal structures of the pellets prepared by the three methods were analyzed using scanning electron microscopy (SEM) (Model SHIMADZA SSX-550, Japan; HITACHI TM-100, Tokyo, Japan). Samples were mounted on double-side tape on aluminum stubs and sputter-coated with gold/palladium, and micrographs were taken at an appropriate magnification.

Results and discussion

Influence of matrix

Nowadays, MCC has been widely used as a filler for the extrusion/spheronization process and high MCC-based pellets tend to have a prolonged drug release profile for low solubility drugs[12]. However, it has obvious disadvantages, such as lacking of swelling ability and limited capability for controlling drug release. So, pellets were produced mixing with expansion and hydrophobic polymers, such as CMS-Na and EC, as a substitute or to reduce the use of MCC.

Table 1 shows the three formulations using a mixture of EC and MCC as the base matrix. It can be seen from Figure 1 that F3 was the most suitable formulation. The release of drug was found to be incomplete when only EC and MCC were used, but addition of 2% CMS-Na increased the release up to 95% at 12 hours. The release profiles of F2 and F3 showed that there was a slower release at 1 hour with 20%EC compared with 10%EC, and after 1 hour the difference of drug release was minimal. F3 was selected for the further studies.

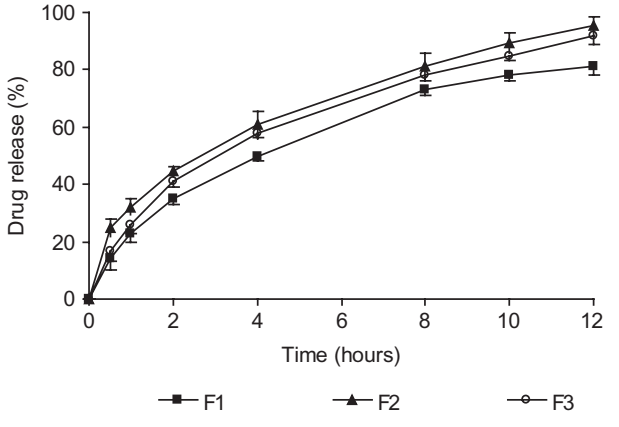

Figure 1. Dissolution profiles of gliclazide from matrix pellets according to experimental matrix design (see Table 1).

According to the dissolution criteria of Diamicron® sustained-release tablets, the percentage of drug release at 2, 4, and 12 hours was restricted to 17–31, 35–55, and more than 85%, respectively. Desired dissolution profiles meeting with sustained-release requirements were not achieved, and there was an initial fast release even for pellets with a loading of 20% EC (Figure 1). There were several reasons for this initial fast release: (1) the larger surface areas of the pellets result in faster dissolution rates, (2) the drug on the surface of the pellets is comparatively free to the matrix and, thus, dissolution is rapid[13], (3) in the early phase of dissolution process, the diffusion pathways are short, resulting in steep concentration of gradients that become the driving forces for diffusion and, thus, high drug release rates are obtained initially[5], and (4) the gel layer of the pellets needs a certain time to become effective for controlling the drug release[14]. So, coating methods were adopted to solve the initial fast release problem and the similarity factor was used to validate the coating results compared with the dissolution profile of Diamicron®.

Influence of the MCC-powder coating

As a new coating technique, there were no references provided for the MCC-powder coating. MCC was chosen as coating material, because it was thermostable and suitable to the coating process. As can be seen from Figure 2, the release of drug was decreased with increasing of the coating level. For the big surface of pellets, just a thin layer covered the pellets with 5% coating level. The thin layer could not prevent the penetration of dissolution media and the diffusion of drug on the edge of pellet. The drug release met the requirement when the coating level was up to 20%. The thick layer would prevent the penetration of dissolution media for a while and the drug on the edge would need some time to diffuse, so the initial fast release was solved at 20% coating level. According to the *R*-values (shown in Table 3), the order of the influence of MCC-powder coating to the drug release was as follows: $A > C > B$. Rotation speed of friction plate and time of coating (addition of binder/coating agents) were both found to have the more important influence on drug release. No. 4 ($A_2B_1C_2$) was most close to the commercial product in Table 3. To increase the spherical degree, $A_2B_2C_2$ was chosen because factor *B* had little influence on drug release.

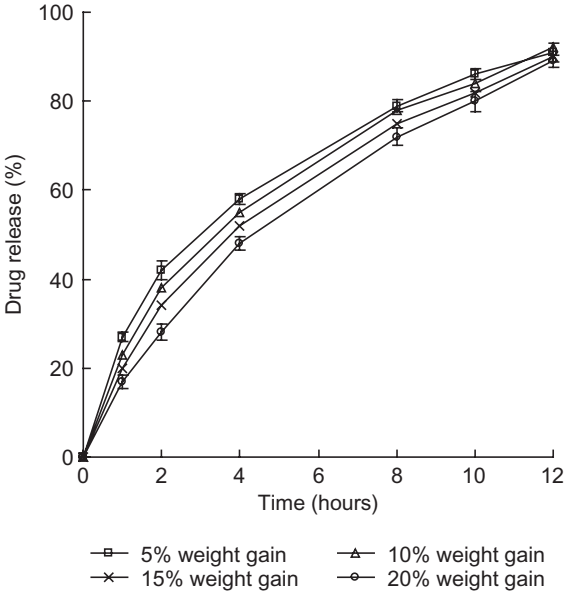

Figure 2. The influence of different coating level of MCC-powder-coating pellets on the dissolution profiles.

Table 3. Analysis of $L_9(3)^4$ test results.

No.	*A*, rotation speed of friction plate (rpm)	*B*, time of rotation (minutes)	*C*, time of coating (addition of binder/ coating agents)	*K*
1	1 (400)	1 (3)	1 (5)	39
2	1 (400)	2 (5)	2 (10)	32
3	1 (400)	3 (7)	3 (15)	23
4	2 (500)	1 (3)	2 (10)	9
5	2 (500)	2 (5)	3 (15)	12
6	2 (500)	3 (7)	1 (5)	26
7	3 (600)	1 (3)	3 (15)	14
8	3 (600)	2 (5)	1 (5)	28
9	3 (600)	3 (7)	2 (10)	24
*T*1	31.333	20.667	31.000	
*T*2	15.667	24.000	21.667	
*T*3	22.000	24.333	16.333	
R	15.666	3.666	14.667	

T, average deviation of error; *R*, the result of extreme analysis.

Influence of the three coating methods

Table 4 showed the release kinetic data for the Higuchi and Korsmeyer–Peppas models and Figure 3 showed the dissolution profiles of Gz from the commercial product and experimental formulations. The drug release data for the film-coated pellets fitted the Higuchi equation well, whereas the hot-melt-coated pellets and the MCC-powder-coated pellets fitted the Korsmeyer–Peppas equation well. A good fitness to the Higuchi equation indicated that the release of drug from

Table 4. The similarity factor f_2 and the release kinetics of the commercial product and experimental formulations.

	Higuchi model		Korsmeyer–Peppas model			
Formulation	r^2	k_1	r^2	$K_2\times10^3$	n	f_2
Commercial product	0.9907	0.0373	0.9998	2.108	0.9518	—
Film-coated pellets	0.9998	0.0421	0.9952	2.88	0.9267	66.69
Hot-melt-coated pellets	0.9982	0.034	0.9992	5.78	0.7784	60.54
MCC-coated pellets	0.9955	0.0403	0.9995	7.87	0.7487	61.10

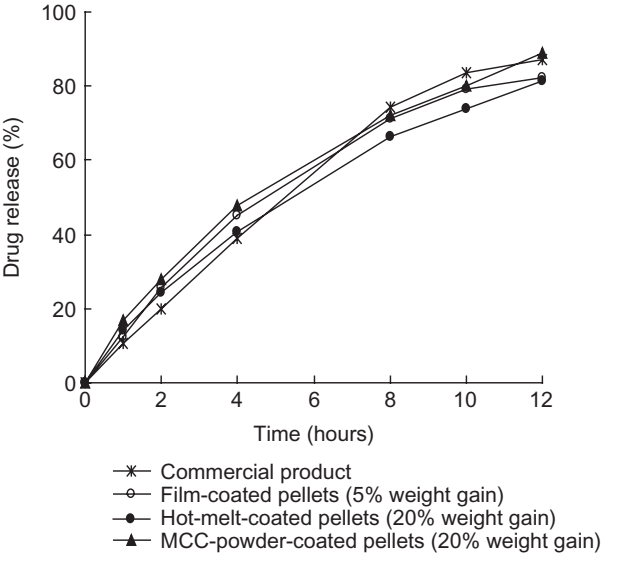

Figure 3. Dissolution profiles of gliclazide from the commercial product and experimental formulations.

the film-coated pellets can be attributed to diffusion. Eudragit® L 30 D-55 was used as a pore-foaming agent. However, the use of Eudragit® L 30 D-55, which is an enteric dissolution polymer, is insoluble in acid and soluble at pH values above 5.5, resulting in a coating layer that acts as a porous sustained-release membrane in pH 7.4 phosphate buffer[15]. The formed pores induce drug diffusion. Drug release from the hot-melt-coated pellets and MCC-powder-coated pellets was both controlled by the combined effect of diffusion and erosion mechanisms for a value of n between 0.43 and 0.89[16]. Coating at 70°C, which is close to the melting point of Compritol 888 ATO (67–70°C), ensured that the Compritol melted and the particles coalesced. This resulted in the matrix pellet being encapsulated by a denser structure (as shown in the SEM photograph, Figure 4) that was less permeable for the dissolution medium. The diffusion pathlength was increased before the hot-melt coating was removed by the medium, and the diffusion of the surface drug from the matrix pellets was

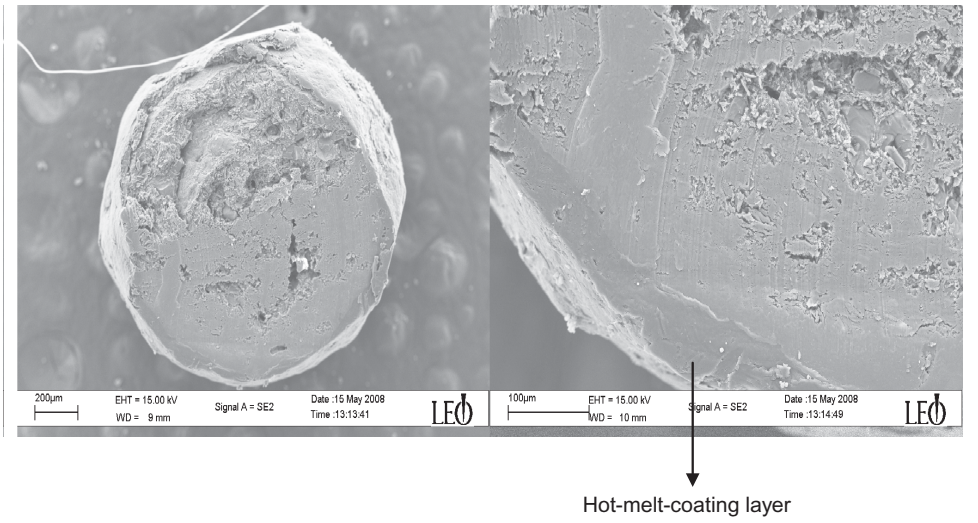

Figure 4. SEM photographs of hot-melt-coating pellet.

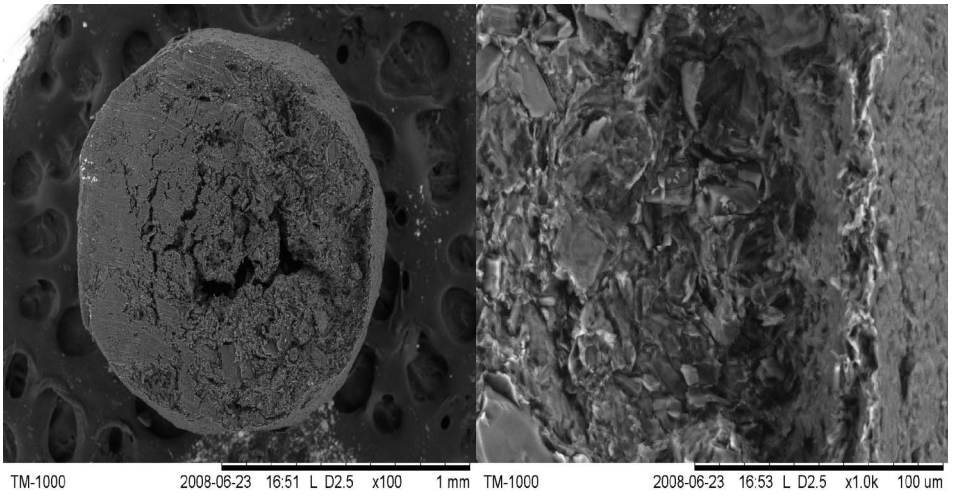

Figure 5. SEM photographs of MCC-powder-coating pellet.

delayed and so the problem of initial drug release was solved. Coating pellets with powder MCC could also control the initial drug release, although no visible coating layer was formed (as shown in the SEM photograph, Figure 5). After the matrix pellets were wetted, MCC-powder adhesion to the wetting surface of matrix pellets by liquid capillary force and the powder layer was formed. MCC added during the process of spheronization allowed combination with the matrix pellets to form an integral, with MCC covering the surface of the pellets. After the solvent evaporation, the liquid-bridge was replaced by solid-bridge, the bonding force between particles was enhanced strongly. Because of the formation of the MCC hydrophilic expansion layer, the dissolution medium needs time to penetrate the MCC layer and then the layer takes up water, swells slightly, and erodes. Accordingly, the diffusion path length is also increased and thus the initial drug release is closely controlled. When the MCC layer is exhausted, the release of drug is similar to that with matrix pellets, so the MCC-powder-coating method does not influence the later release of drug and this is suitable for some water-insoluble drugs. It can be seen from Table 3 that the f_2 values of film-coated pellets, hot-melt-coated pellets, and MCC-powder-coated pellets compared with the commercial product were all greater than 50, which shows the equivalence of the two curves (as shown in Table 4). The dissolution storage stability of three coating methods was studied to select the best coating method.

Influence of storage stability

Although the film-coating technique can control the release of drug with only a 5% weight gain, resulting in a coating film that is very thin (as shown in the SEM

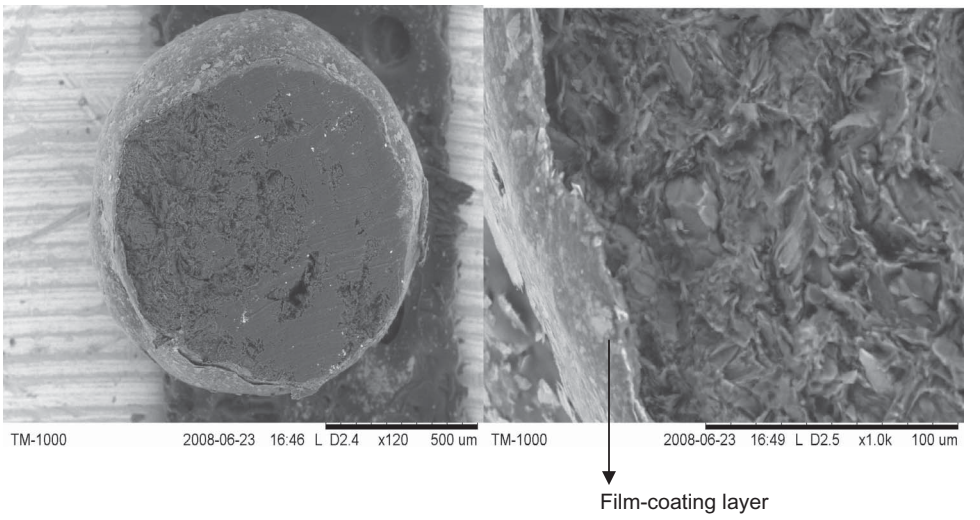

Figure 6. SEM photographs of film-coating pellet.

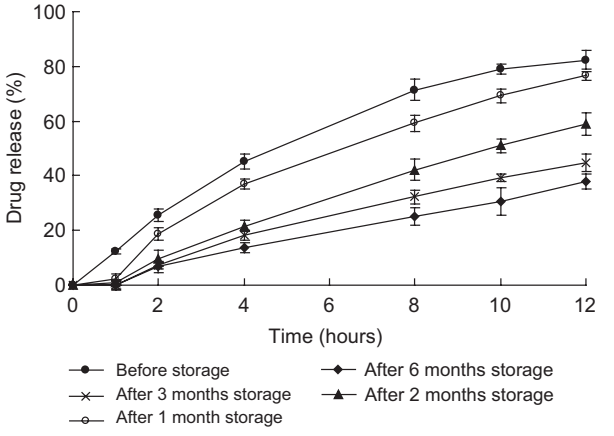

Figure 7. Storage stability of film-coated pellets: drug release in pH 7.4 phosphate buffer before and after 1, 2, 3, and 6 months of storage under stress conditions: 40°C/75%RH.

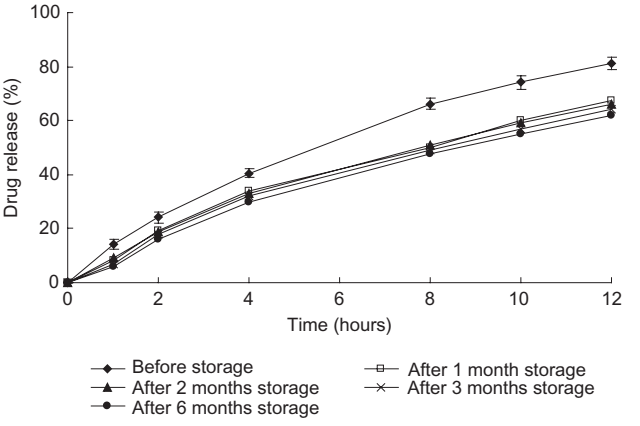

Figure 8. Storage stability of hot-melt-coated pellets: drug release in pH 7.4 phosphate buffer before and after 1, 2, 3, and 6 months of storage under stress conditions: 40°C/75%RH.

photograph, Figure 6), the MCC-powder coating and the hot-melt coating need 20%, and the MCC-powder-coating and hot-melt-coating systems are faster and cheaper compared with Eudragit®, which is expensive because it requires water evaporation and curing. Compared with the traditional liquid-coating technology, hot-melt-coating and MCC-powder-coating methods are very attractive because of the savings in energy, environmental friendliness, and consequent low operation costs.

The drug release profiles of the film-coated pellets showed a significant reduction between initial pellets and those stored for 6 months (Figure 7). The same phenomenon was observed in the hot-melt pellets (Figure 8). However, there was no significant difference of drug release from MCC-powder-coated pellets during 6 months storage (Figure 9). Therefore, a long shelf life was obtained using the MCC-powder-coating method. In contrast, drug release rates from film-coated pellets and hot-melt-coated pellets significantly slowed down during 6 months storage; thus, the film-coated pellets and hot-melt-coated pellets were unstable. There may be two reasons for film-coated pellets being unstable: (1) although the blend of Eudragit® NE 30 D and Eudragit® L 30 D-55 was completely miscible at a ratio of 4:1[17], different glass transition temperatures between Eudragit® NE 30 D and Eudragit® L 30 D-55 resulted in an incompatibility of the two polymers. Eudragit® NE 30 D exhibited a lower glass transition temperature (T_g = –8°C) than Eudragit® L 30 D-55, leading to different rates of coalescence that can lead to significant changes in the structure of the polymeric membranes under stress

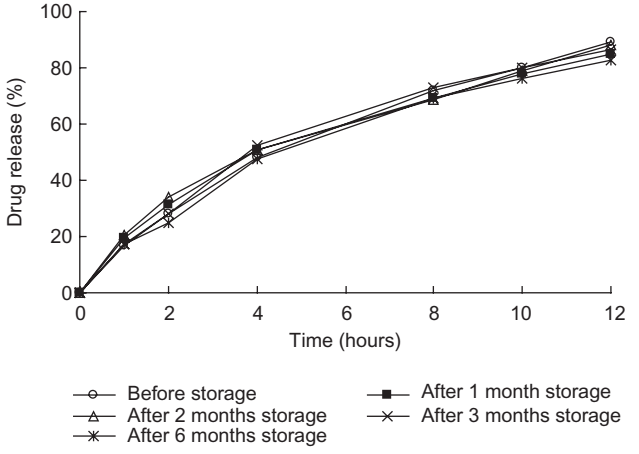

Figure 9. Storage stability of MCC-powder-coated pellets: drug release in pH 7.4 phosphate buffer before and after 1, 2, 3, and 6 months of storage under stress conditions: 40°C/75%RH.

conditions. Even a minor change in the polymeric membranes would influence the release of drug because Gz is water-insoluble; (2) it is difficult to ensure complete film formation during curing period, and under stress conditions, uncured polymer particles may continue to come into contact with each other and gradual coalescence would result in a significant reduction in the release rates[18]. As shown in Figure 7, the release of drug from hot-melt-coating pellets after 1-month storage changed markedly, especially the later drug release, and then it did not change over 2–6 months. This suggests that the stress conditions of 40°C/75%RH changed the structure of the hot-melt-coating layer that made the waxy molecules to coalesce. It is difficult for the dissolution medium to penetrate the hot-melt coating and so the drug release was slower than before. The diffusion pathlength for the drug in the pellet core was much longer when the coating layer was solidified under the stress conditions. Over 2–6 months, the release curve of the pellets was similar, which indicated that the structure of the coat was no longer changing and later the drug release decreased markedly between 4 and 12 hours compared with that of the MCC-powder-coated pellets. Because of the hydrophobic effect of Compritol 888 ATO, it took a longer time for the drug in the core of pellet to diffuse than in the case of the MCC-powder-coated pellet that was hydrophilic.

As can be seen from Figure 9, good storage stability was seen with MCC-powder-coating pellets, the drug release profiles had little change, there was no significant difference before and after 1, 2, 3, and 6 months of storage, indicating that there was no significant change in the structure of solid-bridge of the MCC-coating layer proving that the MCC-powder-coating technique confers long-term stability. The storage conditions did not influence the MCC-coating layer, which was stable to both heat and humidity. Comparing Figures 7 and 8 with Figure 9, the MCC-powder coating was stable for at least 6 months when stored under stress conditions: 40°C/75%RH. During 6-month storage, the drug release of film-coating pellets showed a significant reduction because of the unstable structure of the film coating. The release of drug from hot-melt-coating pellets altered markedly after 1-month storage, while it did not change over 2–6 months, which suggested that the structure of hot-melt coating was steady during that period. Drug release from MCC-powder coating was stable under the same storage condition for 6 months. Although the storage stability of film-coated pellets was obtained by adding PVA-PEG graft copolymer to Aquacoat ECD[19], it was time-consuming to blend the two substances and the curing conditions were severe, whereas, in contrast, the MCC-powder-coating method offered a one-step procedure that not only solved the storage stability problem but also saved time. MCC powder could be coated on pellets by one-step procedure to provide sustained drug release. Compared with film-coating and hot-melt-coating methods, MCC powder-coating method has many advantages, such as a shorter processing time, one-step procedure, and good storage stability.

Conclusion

In this study, Gz sustained-release matrix pellets were successfully prepared using a stable, simple, and economical MCC-powder coating. Initial fast release was existed even by a loading of 20% EC. Hot-melt-coating, aqueous dispersion film-coating, and MCC-powder-coating methods were investigated to solve this problem, and the release of drug was similar to the commercial product because the f_2 values were all greater than 50. The MCC-powder-coating method was chosen because of the storage stability under stress conditions (40°C/75%RH). Using this method, the problem of the initial fast release can be solved, and it has the advantage of one-step production procedure compared with film-coating and hot-melt-coating methods. Other water-insoluble drugs with the similar problem of initial fast release could adopt this method.

Declaration of interest

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

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