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RESEARCH ARTICLE

Preparing of pellets by extrusion/spheronization using different types of equipment and process conditions

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Abstract

Introduction: The focus of this work was to produce matrix pellets made by extrusion/spheronization using two types of equipment. The aim was to accomplish the laboratory-scale I process that has been already optimized and accepted with another type of equipment (laboratory-scale II).

Methods: A matrix pellet formulation consisting of MCC, Eudragit NE 30D and diclofenac sodium was used in the two types of equipment. Physico-chemical parameters and the dissolution profiles of the pellets in phosphate buffer pH 6.8 were compared.

Results: Pellets from both processes were similar in shape and tensile strength. They differed in particle size and dissolution profile. This may be contributed to different spheronization conditions.

Keywords

Aspect ratio, dissolution, extrusion/spheronization, pellets, tensile strength

History

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Introduction

Different types of extruders and spheronizers are available for the production of pellets. Extruders not only differ in terms of size but also in terms of the extrusion principle. A small-scale single screw extruder[1] should be compared with a larger flat die press[2]. Both are laboratory scale, but the single screw extruder has a lower throughput compared with the flat die press. Two spheronizers of different diameter are used for spheronization. The composition of the pellets is kept constant. The transferability of the formulation from one type of equipment to another type should be investigated.

To date, microcrystalline cellulose (MCC) remains the most frequently used excipient for the production of pellets by wet extrusion and spheronization. The manufactured pellets are particularly characterized by a narrow particle size distribution, a high sphericity, and suitable mechanical properties. However, with regard to low soluble drugs, MCC-based pellets show a tendency to have a prolonged drug release profile because of a lack of disintegration[3–5].

EUDRAGIT® NE 30D is the aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate that is highly suitable for sustained-release film coatings[6] and for sustained release granules[7,8]. The polymer is insoluble in water, has a low permeability and pH independent swelling property and it is highly flexible[9]. While MCC has hydrophilic characteristics, Eudragit NE is lipophilic.

Our aim was to compare different methods to produce matrix pellet composed of MCC and Eudragit NE 30D and to investigate the properties shape, particle size, mechanical properties and dissolution of the two types of pellets.

Methods

In the composition of pellets micronized diclofenac sodium (Teva Pharmaceutical Works PLC, Debrecen, Hungary) was used as an API, microcrystalline cellulose (Avicel PH 112, FMC Corp., Philadelphia, PA) and Eudragit® NE 30D (Evonik GmbH, Essen, Germany) as binder and matrix-forming agents and purified water was used as granulation liquid. According to pre-experiments it was established that the dissolution of API from MCC-based pellets without Eudragit NE 30D was too rapid.

In the Laboratory scale I (LI) the solid components of the powder mixtures (Table 1) were homogenized with Turbula mixer (W.A. Bachofen, Basel, Switzerland) at 50 rpm for 10 min.

Eudragit® NE 30D and purified water (62 g) were added to the mixture in a high shear granulator (ProCepT 4M8 granulator, ProCepTnv, Zelzate, Belgium) with the feed rate of 9 ml/min. Process parameters were the following: speed of impeller: 1500 rpm, speed of chopper: 2000 rpm. The wet mass obtained was extruded by a mini screw extruder (Caleva Ltd., Sturminster Newton, Dorset, UK) equipped with an axial screen with dies 1 mm in diameter and 4 mm in length, operating at 70 rpm. The jacked barrel of the extruder was cooled by water at $25 \pm 2\,^{\circ}C$. Each extrudate was collected in a container before it was spheronized. About 40 g of extrudate was spheronized at a time, on a spheronizer 12 cm in diameter (Model-120, G.B. Caleva Ltd., Sturminster Newton, Dorset, UK) fitted with a cross-hatch grooved plate, for 20 min at 1000 rpm. The pellets were dried at $40 \pm 2\,^{\circ}C$ for 24 h.

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In the Laboratory scale II (LII) the batch size was higher, so the quantity of purified water was adapted to reach a suitable wet mass. The ratio of powder and fluid was almost the same (1.015:1.065). The compositions can be seen in Table 1.

The weighed powders were transferred into a laboratory-scale blender (LM40, Bohle, Ennigerloh, Germany) and blended for 30 min at 35 rpm. The dry powders were then wetted first with Eudragit® NE 30D dispersion and after that with purified water using a high shear mixer (Mini-MGT, Bayer, Leverkusen, Germany) at 400 rpm and a peristaltic pump (Minipuls3, Gilson Inc., Middleton, WI) at 9 ml/min. The wetted mass was supplied to a flat die press 14-175 (Amandus Kahl, Reinbek, Germany) at a feeding screw rate of 180 rpm and extruded at a roller speed of 30 rpm through a flat screen with dies of 1 mm diameter. The distance between the screen and knife was adjusted to 3 mm.

Collected extrudate batches of approximately 300 g were transferred into a spheronizer (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) fitted with a cross-hatched rotor plate of 300 mm diameter and were spheronized for 8 min at a spheronization speed of 1000 rpm and a temperature of 25 °C. The resulting pellets were then transferred to a fluid bed drier (GPCG 1.1, Glatt, Dresden, Germany) and dried for 20 min at 60 °C with an air volume of 130 m^3/h.

The particle size and the shape of the pellets were studied by using a stereomicroscope (Zeiss Stemi 2000-C, Carl Zeiss GmbH, Vienna, Austria). A Quantimet 500 (Q500MC) image processing and analysis system (Leica Cambridge Ltd., Cambridge, UK) was used. The aspect ratio was utilized for the evaluation of the shape of the particles. 500 pellets of each sample were checked.

The breaking force was tested for pellets with diameters between 1000 and 1250 µm. The strength tester and the software were developed in our institute. The tester contains a special specimen holder and a stamp, and it is connected to a computer via an interface and the deformation/breaking force was measured. Twenty measurements per batch were performed. Tensile strength of pellets was also determined with the following equation[10]:

$$\sigma_s = \frac{0.4F}{\pi R^2} \quad (1)$$

where
σ_s = tensile strength
F = breaking force
R = radius of pellets

Pellets (160 mg) were placed into the basket of a dissolution tester (Erweka DT 700, Heusenstamm, Germany). The dissolution medium consisted of phosphate buffer (pH 6.8) for 4 hours kept at 37.0 ± 0.5 °C. The rotational speed of the baskets was set at 100 rpm. The dissolution system was combined with an automatic sampling station. Samples of 5 ml were withdrawn from the phosphate buffer medium at 10, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min. Absorbance was measured spectrophotometrically (Unicam Heλios Alpha, Spectronic Unicam, Cambridge, UK) at λ_{max} = 276 nm. Three parallel tests of dissolution were performed.

Results

The results are summarized in Table 2. The data show that aspect ratio is small indicating spherical pellets and similar for both processes. The size of the pellets is smaller in case of LII. Spheronization was performed for 20 min at a tip speed of 6.3 m/s

Table 1. Composition of powder mixture for LI and LII.

Components	Quantity for LI (g)	Quantity for LII (g)
1. Diclofenac sodium	50	120
2. Avicel PH 112	85	204
3. Eudragit® NE 30D	75	180
4. Purified Water	62	165

Table 2. Shape parameters (n = 500) and mechanical properties (n = 20) of pellets (mean ± SD).

	Length (mm)	Breadth (mm)	Aspect ratio	Breaking force (n)	Tensile strength (MPa)
LI	1.33 ± 0.11	1.23 ± 0.09	1.08 ± 0.04	38.2 ± 4.2	11.9
LII	1.15 ± 0.14	1.05 ± 0.12	1.10 ± 0.08	25.8 ± 3.2	10.9

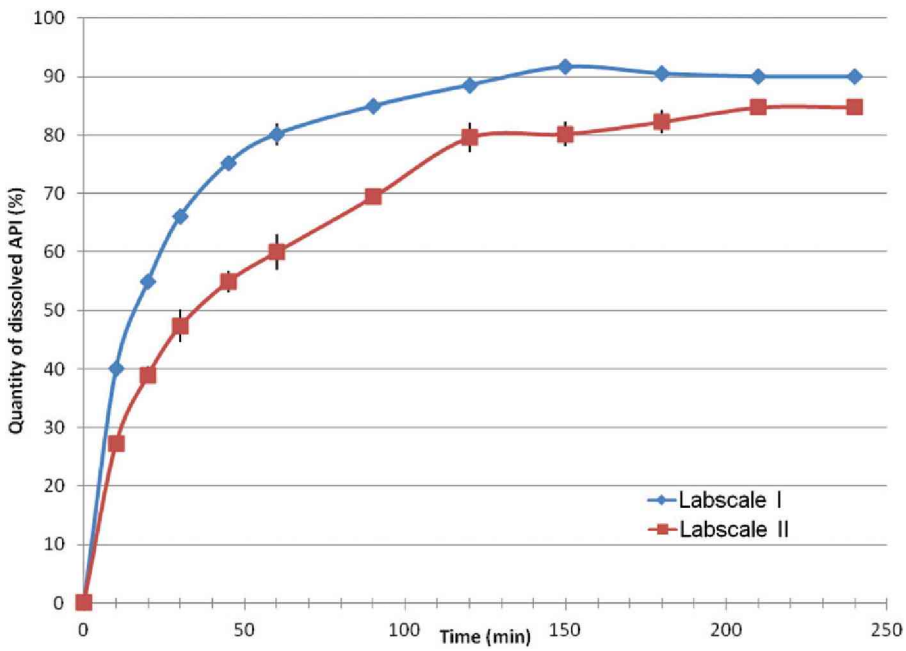

Figure 1. Dissolution from pellets of LI and LII in phosphate buffer pH = 6.8 (mean ± SD, n = 3).

in LI while 8 min at 15.7 m/s were applied for LII. The higher velocity of spheronization in LII might have caused a different breaking behavior of the extrudates resulting in smaller pellets.

According to previous results of our institute[1,11], breaking force of both batches was high enough for further processing, e.g. coating. The pellets were not deformed or abraded due to mechanical stress. In spite of the different pellet sizes and breaking forces the tensile strengths of the two pellets types is comparable.

The results of dissolution studies show, that the drug release from the different samples follows the same kinetic. Eudragit® NE 30D shows a pH independent swelling in aqueous media, which resulted in burst effect in the first stages of drug release. In all cases, the pellets show a matrix type of release because of the missing disintegration caused by the presence of MCC and Eudragit® NE (Figure 1). It can be seen that the quantity of dissolved API differs significantly. Surprisingly the smaller pellets of LII show the slower dissolution profile. A matrix dosage form of given composition and structure is expected to result in slower dissolution with increasing particle size. A reason for this behaviour is not obvious. Probably the porosity and/or the pore structure is different for the two pellet types. A higher densification of LII pellets might occur due to the spheronization conditions. However, such a change is not reflected in the tensile strength values of the pellets.

Discussion and conclusion

It can be concluded that the process could be accomplished by the use of different equipment. Pellets of suitable shape and mechanical properties were produced with both types of equipment. However, the size of the pellets and the dissolution profile of the pellets differed. Further work is required to produce pellets of equal properties by the two types of equipment.

Declaration of interest

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