PŮVODNÍ PRÁCE

Evaluation of pellet friability

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SUMMARY

Evaluation of pellet friability
Pellet friability and hardness are important particle characteristics as they predict pellet behavior during technological processes such as film coating, filling into hard gelatin capsules or compressing into tablets. At present no methods for testing of these pellet properties are present in pharmacopoeias and various methods adapted from tablet evaluation are used. A number of methods and different equipment are used to determine pellet friability. These methods in addition differ also in the testing conditions. Therefore pellets of different hardness and composition were chosen on purpose for this experiment to show the influence of method variables on the friability of brittle and hard pellets prepared by different techniques. Pellet friability was tested in the same equipment under different conditions, but always with the equal amount of sample and equal total number of revolutions. All the samples exhibited also similar residue moisture content. As different friability values were obtained for the same sample under different testing conditions it is necessary to pay attention to the method used and its parameters. This experiment indicates that pellet friability is influenced not only by pellet composition but also by the technique of their manufacture.
Key words: pellets – hardness – friability – methods of evaluation – testing conditions

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SOUHRN

Hodnocení oděru pelet
Pevnost a oděr jsou důležitými vlastnostmi pelet, protože umožňují předpovídat jejich chování v průběhu technologických procesů, např. při filmovém obalování, plnění do tvrdých želatinových tobolek nebo při lisování do tablet. V současné době lékopisy neuvádějí žádné metody k testování uvedených vlastností u pelet a v praxi se používají metody odvozené z metod doporučených pro hodnocení tablet. Ke stanovení oděru pelet slouží různé přístroje a aplikuje se řada metod, které se navíc liší i podmínkami testů. Pro vyhodnocení vlivu rozdílných podmínek metody na hodnoty oděru pelet se pro tento experiment vybraly pelety různé pevnosti a složení, připravené několika technologiemi. Oděr pelet se testoval vždy ve stejném zařízení za odlišných podmínek, zkoušené množství vzorků a celkový počet otáček však zůstávaly konstantní. Všechny vzorky měly také podobný obsah vlhkosti. Vzhledem k tomu, že se hodnoty oděru u téhož vzorku často významně lišily, je bezpodmínečně důležité u zvolené metody dodržovat vždy stejné podmínky k dosažení reprodukovatelných a srovnatelných výsledků. Experiment naznačil, že oděr pelet je ovlivněn nejen jejich složením ale také způsobem výroby.
Klíčová slova: pelety – pevnost – oděr – metody hodnocení – podmínky testování

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Introduction

Pellets are small spherical particles used for oral application; their diameter for pharmaceutical purposes lies usually in the range of 0.5–2.0 mm. As multiparticulates, i.e. higher number of particulate drug units in one dose, they exhibit several advantages comparing to single unit dosage forms such as tablets. In pharmacotherapy, they offer the drug delivery independent on the stomach emptying, a reduction of gastrointestinal tract irritation and minimizing of side effects. Flexibility in dosage form design, possible combination of several drugs in one dose, improved stability and easy coating due to pellet spherical shape belong among their advantages in technology. Therefore pellets are very often used for controlled drug release preparations, i.e. they undergo subsequent processes such as coating, filling into hard gelatin capsules or compressing into tablets. Thus their mechanical properties especially pellet hardness and friability are very important parameters. In fluid bed film coating the friability of pellet cores can significantly influence the coating quality. A high amount of attrition of the core material during the coating procedure could modify drug release behavior due to the incorporation of small particles into the film coating [1]. For this and above mentioned reasons mechanical pellet properties should be evaluated using appropriate well defined methods.

Pellet hardness is usually measured using tablet strength testers equipped with a cell for pellet evaluation. However it is significantly dependent on pellet diameter, composition and manufacturing process [2]. Hardness is characterized as a resistance against the crushing under defined conditions. It is measured in a tester consisting of two clips the sample is inserted in. The clips are moving against each other and the force when the sample breaks is registered [3]. Hardness is determined either in Newtons or kilograms: 1N = 9.81 kg.

To compare the hardness of tablets differing in shape there exist formulas describing their diameter and thickness [4]. Similar formula can be used also for pellets:

$$\delta_{f(s)} = \frac{0.4 \times F}{\pi \times r^2}$$

$\delta_{f(s)}$ is the tensile strength, F is the crushing force, r is the pellet diameter. The unit of $\delta_{f(s)}$ is Pascal[5, 6].

Pellet friability can be determined by a number of different methods using various equipments. Widely used are rotating drums like friability testing apparatus for tablets, e.g. Erweka [7, 8] or Roche [9–12] Friabilator. Due to the electrostatic charge and low weight of pellets providing insufficient mechanical stress during these tests, their stainless steel variation and the addition of glass or steel balls are used. However the friability conditions among these methods differ significantly, for instance the number of balls from 10 [11] to 200 [7, 12], their material, i.e. glass [7, 9–12] or steel [8], the amount of pellets 5 g [9, 11] or 10 g [7, 8, 10, 12], testing time from 3 [8] to 10 [7, 10, 12] minutes, and rotating speed of 10 [8], 25 [12] or 36 [9] rpm. Another group of tests is based on the use of a Turbula blender [13, 14] or horizontal shakers [15, 16]. All these described methods work in closed systems. Thus the attrition remains in the apparatus and can get into a contact with the surface of pellets.

As friability testing apparatus should simulate the conditions the product will be exposed to in the production process later on, e.g. during coating or drying processes in fluid bed devices an open system would be more appropriate as the attrition is removed immediately from the tested system [17, 18].

Friability is characterized as the weight loss of a sample (%) [17], the mean pellet diameter reduction (%) [19, 20] or the difference in areas under the curve of pellet size distribution before and after the friability testing [21].

Limit value of pellet friability should correspond to their intended use [21], for instance for pellets proposed for subsequent coating value lower than 1.7% is recommended [22].

In this experimental study pellet hardness and friability were tested, and the influence of pellet composition, preparation process and variables of friability test on pellet mechanical properties was observed.

EXPERIMENTAL

Materials

In this experiment, pellets of different composition prepared using various pelletization techniques were chosen (Table 1). Freely soluble diltiazem hydrochloride (DHCl, kindly donated by Zentiva, Czech Republic) or sparingly soluble diclofenac sodium (DNa, Amoli Organics, Mumbai, India) were used as model drugs. Microcrystalline cellulose (MCC, Avicel® PH 101, Mingtai Chemical Co., Ltd., Taiwan), lactose monohydrate (Cerapharm, Vienna, Austria) and povidone (PVP, Kollidon® 25, BASF, Germany) were excipients, and Celphere® (Asahi Kasei Kogyo, Japan) were used as inactive cores. All substances were of pharmaceutical grade (Ph.Bs. 2005; Ph. Eur. IV); other materials used for pellet evaluation were of analytical purity.

Pellet preparation

Pellets were prepared either by a layering technique or by an agglomeration in a Rotoprocessor (Multiprocessor MP 1, Aeromatic Fielder, Switzerland). For layering, MCC inactive cores Celphere® (CP 305) or lactose/MCC cores prepared in our laboratory were used as starters. Lactose/MCC cores were prepared as follows: 350 g of MCC and 650 g of lactose were mixed for 5 min in a Stephan mixer (UMC 5, Germany). One kilogram of powder blend was loaded into the inner bowl of the Rotoprocessor and water was sprayed into the container at the optimal, experimentally determined rate [23]. Once all the water was sprayed, spheronization was performed

Table 1. Composition of the samples, pellet preparation and size

Sample	Composition (%)					Technology used for preparation	Pellet size(mm)
	DHCl[a)]	DNa[b)]	MCC[c)]	LM[d)]	PVP[e)]		
1	48.5	–	48.5	–	3.0	layering of DHCl on MCC cores	0.5–0.8
2	55.0	–	35.0	10.0	–	rotoagglomeration	0.8–1.0
3	48.5	–	17.0	31.6	2.9	layering of DHCl on LM/ MCC cores	0.8–1.0
4	–	–	100.0	–	–	Celphere®	0.5–0.71
5	–	10.0	35.0	55.0	–	rotoagglomeration	0.8–1.0
6	–	–	35.0	65.0	–	rotoagglomeration	0.8–1.0

[a)] diltiazem hydrochloride, [b)] diclofenac sodium, [c)] microcrystalline cellulose, [d)] lactose monohydrate, [e)] povidone

Table 2. Variables in friability measurements

Number of glass balls	Rotation time (min)	Rotation speed (rpm)	Total number of rotations	Definition of friability (mm)
200	10	20		
100	10	20		
10	10	20	200	< 0.25
100	5.5	36		
10	5.5	36		

for 2 min. After completion of the pellet formation, the pellets were dried at 50 °C by lifting the inner wall of Rotoprocessor. Required pellet size fractions, i.e. 0.5–0.8 mm and 0.8–1.0 mm, were separated on sieves of appropriate apertures. To prepare the active pellets of samples 1 and 3, concentrated solution (i.e. 50% w/w) of DHCl in purified water with PVP was sprayed onto the smaller starters surface in a fluid bed unit equipped with a Wurster column (Multiprocessor MP 1, Aeromatic Fielder, Switzerland) until the theoretical drug amount reached 50% of the pellet weight. Pellets were dried in the same equipment and stored in plastic bags at room temperature for further evaluation. The other pellet samples, i.e. samples 2 and 5 were prepared in a Rotoprocessor by wetting and spheronizing the homogenized powder mixture (Table 1) as described above. Purified water was used as the wetting agent. Celphere® (CP 507) produced commercially were used as sample 4 for mechanical pellet properties comparison.

Pellet properties evaluation

Particle size and size distribution of both, starters and prepared pellets, were determined by a sieve analysis for each sample. The set of stainless steel sieves with apertures in the range of 0.5–1.0 mm and a sieve shaker (type AS 200, Retsch, Germany) were used. Particles smaller than 0.5 mm were considered as a dust and particles bigger than 1.0 mm (for sample 1 bigger than 0.8 mm) as agglomerates and were excluded from the total yield. Selected pellet fractions were used for further evaluation.

The particle shape and internal structure were examined using a JEOL JSM-6700F scanning electron microscope (JEOL Ltd., Japan). Samples were mounted on a cylindrical stub using a double-sided sticky tape. The samples were coated with an approx. 70 nm thick gold layer in a SCD 030 sputter coater (Balzers Union Ltd., Balzers, Liechtenstein) and observed under the microscope operating at 5.0 kV.

The hardness of used starters and prepared pellets was tested on the C 50 Tablet Hardness Tester (Engineering Systems, England) equipped with a C5 cell for pellet evaluation. The hardness of ten randomly selected particles of each sample was evaluated.

For friability testing, 10 g of dust free particles (pellets or starters) were precisely weighed, put into the friabilator Roche (type TAR 10, Erweka, Germany) with stainless steel drum along with 200, 100 or 10 pieces of 4 mm glass beads, respectively, and rotated for 10 or 5.5 minutes at 20 or 36 rpm. The experimental conditions are described in Table 2. Particles smaller than 0.25 mm were regarded as the attrition. The friability was expressed as a percentage of the weight loss after agitation. The measurement was repeated three times.

RESULTS AND DISCUSSION

Pellets of different composition, size and hardness (Table 1) were chosen on purpose for this experiment to show the influence of method variables on the friability of brittle and hard pellets prepared by different techniques. Pellet friability was tested in the same equipment (Roche Friabilator) under different conditions (Table 2), but always with the equal amount of sample (10 g) and equal total number of revolutions (200). All the samples exhibited similar residue moisture content (1.41–2.59%). Table 3 indicates hardness and friability of pellet samples.

It is obvious that with increasing pellet hardness friability values of samples decrease despite of the friability test conditions (Table 3). When tensile strengths of samples are compared the lowest values, i.e. 0.26 MPa

Table 3. Hardness and friabilities of prepared pellets

Sample	Pellet hardness (N)	Calculated tensile strength (MPa)	Friability (%)				
			200/10/20*	100/10/20	10/10/20	100/5.5/36	10/5.5/36
1	0.87 ± 0.33	0.26	3.16 ± 0.30	1.56 ± 0.19	0.50 ± 0.15	1.85 ± 0.11	0.71 ± 0.15
2	1.67 ± 0.59	0.26	2.62 ± 0.04	1.49 ± 0.06	0.35 ± 0.02	1.64 ± 0.03	0.47 ± 0.02
3	2.84 ± 0.36	0.45	1.91 ± 0.08	0.82 ± 0.07	0.29 ± 0.01	1.04 ± 0.07	0.29 ± 0.02
4	3.41 ± 1.08	1.19	0.38 ± 0.07	0.24 ± 0.08	0.19 ± 0.07	0.26 ± 0.04	0.24 ± 0.07
5	3.61 ± 0.69	0.57	0.26 ± 0.06	0.22 ± 0.06	0.14 ± 0.04	0.24 ± 0.05	0.19 ± 0.03
6	4.89 ± 0.54	0.77	0.18 ± 0.01	0.09 ± 0.04	0.07 ± 0.03	0.17 ± 0.03	0.13 ± 0.05

* number of glass beads/rotation time (min)/rotation speed (rpm)

were noticed for pellet samples 1 and 2 with low hardness values. Equal tensile strength to break pellets is probably given by the predominant properties of DHCl either in pellets (sample 2: 55%) or in the active layer (sample 1 : 88%). The highest tensile strength (1.19 MPa) was calculated for MCC starters Celphere® that are generally considered as very hard. Other tensile strength values corresponded to the increasing pellet hardness and decreasing pellet friability. Pellets prepared using the drug layering technique generally showed higher sensitivity to friability conditions than pellets produced by a rotoagglomeration (samples 1 and 3, Table 3, Figure 1 and Figure 2). Furthermore when the inactive cores are compared, better mechanical properties were obtained for active pellets with LM/MCC cores than pellets started with only MCC cores (pellet hardness of 2.84 vs. 0.87 N, calculated tensile strength of 0.45 MPa vs. 0.26 MPa, and friabilities 0.29–1.91% vs. 0.50–3.16%). This can be explained by different cores solubility and wettability. While MCC cores are insoluble in water, which was used as wetting agent for the layering, LM/ MCC cores were partly soluble due to high lactose content (65%). For successful drug solution layering process it is necessary to wet properly the solid surface of the starter. Only under these conditions, droplets of the drug solution could spread all over the solid surface and create a continuous drug layer. As LM/ MCC cores are partly soluble in water, one might presume their surface is better wetted by the drug solution making the layering process more effective and the drug layer adhering more tightly to the core surface. The consequence indicates higher pellet hardness and lower pellet friability. This theory was supported by SEM images of layered pellets (Figure 3) and also photos of pellets after the friability test (Figure 2). The left part of Figure 3 (sample 1) shows clearly defined drug layer on MCC starter surface while on the right side of this picture (sample 3) drug layer and starter surface are not well distinguishable. On Figure 2a, the core surface without active layer is clearly visible (sample 1) indicating thus that drug layer is not binding tightly to the starter's core.

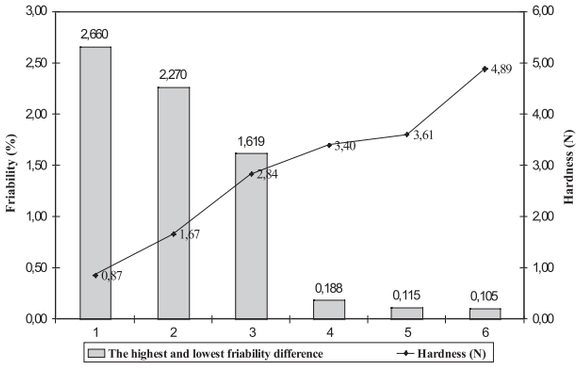


Fig. 1. Sensitivity of different pellet samples to variable conditions of friability tests

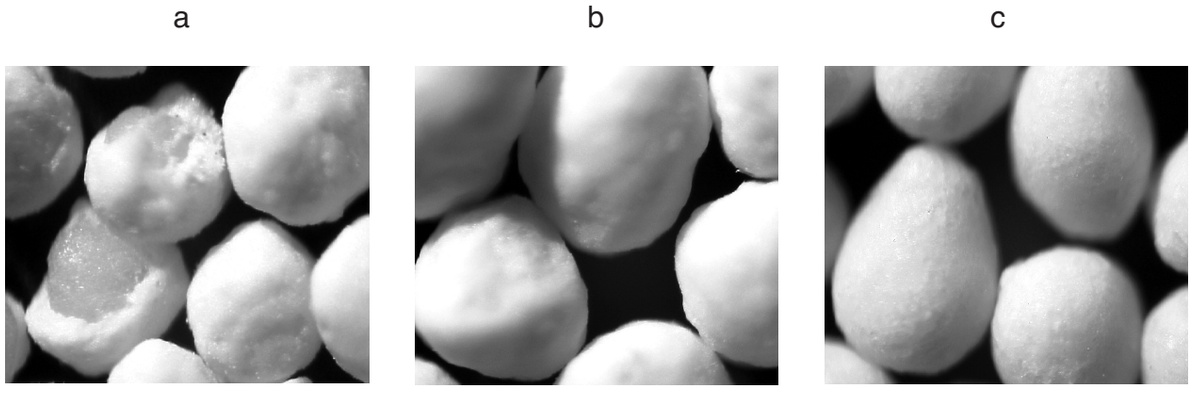
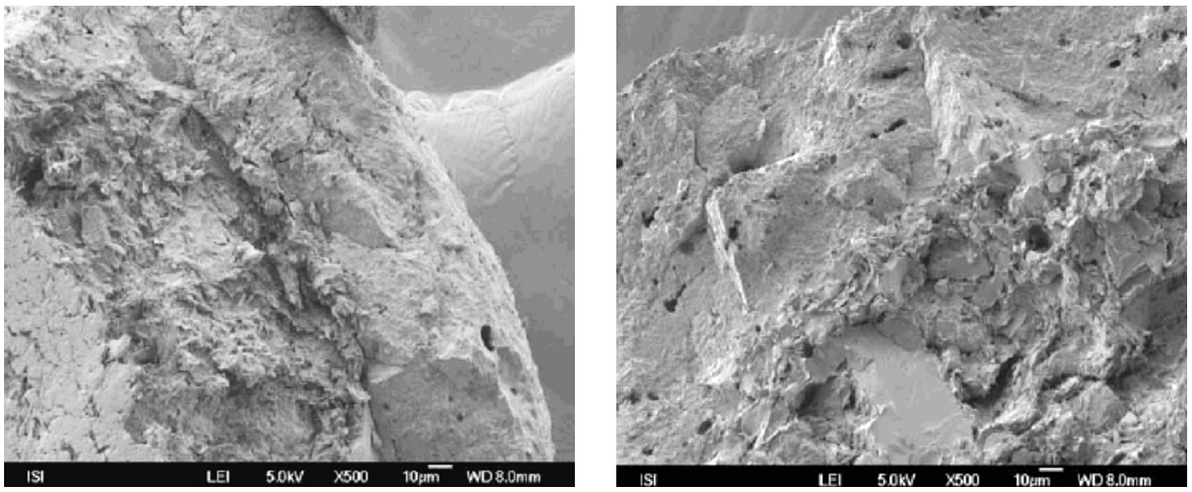


Fig. 2. Sample 1 (a), sample 3 (b) and sample 6 (c) after friability test under condition 200/10/20 (magnification 25×)



A B

Fig. 3. The cross-section of the layered pellet (left) containing the MCC and LM / MCC (right) as observed under the scanning electron microscope (magnification 500×)

This feature is less obvious on Figure 2b (sample 3) signalizing better active layer to core sticking. On the other hand the surface of a sample prepared by rotoagglomeration (Figure 2c) remains almost untouched after agitation under comparable conditions showing thus high resistence against a friction.

Pellets obtained by an agglomeration process in a Rotoprocessor containing lower drug amount (sample 5) or drug free pellets (sample 6) showed the highest hardness values (3.61 N and 4.89 N) and the lowest friability (0.14–0.26% and 0.07–0.18%, respectively). These values were comparable to those obtained for sample 4, i.e. commercially produced starters Celphere® considered as mechanically highly resistant.

Since limit values for pellet friability were published in the literature, i.e. less than 1.7% [22], it is necessary to pay attention to the method used and its parameters. As shown in our experiment, different friability values of one sample can be obtained indicating either satisfactory or unsatisfactory friability values. Especially brittle pellets are very sensitive to the variables of friability method used.

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