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PELLETIZATION OF NEEDLE-SHAPED PHENYLBUTAZONE CRYSTALS

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Abstract

The flowability of needle- or plate-shaped crystals is very poor and the direct compression of these crystals is difficult. Commercial phenylbutazone consists of needle crystals and it has three polymorphs.

The aim of this work was to investigate the solid-state thermal stability of phenylbutazone at condition of the pelletization process (40°C; 60 min). The other aim was the preparation of phenylbutazone pellets with centrifugal granulator.

Based non the flowability and the other parameters of, the pellets, they are suitable for capsule filling or tabletting. The centrifugal granulation and the conditions were favourable for the preparation of pellets from phenylbutazone in the form of needle crystals.

Keywords: centrifugal granulator, DSC, pelletization, phenylbutazone

Introduction

The flowability and deformability of materials are very important in tablet making. The flowability of needle- or plate-shaped crystals is very poor and the direct compression of these crystals is difficult.

Commercial phenylbutazone consists of needle crystals. Phenylbutazone is a non-steroidal anti-inflammatory analgetic drug, which inhibits prostaglandin synthesis in vitro and in vivo. It is completely absorbed after oral or rectal administration, and peak plasma levels are reached after 2 h [1, 2]. In spite of the many registered non-steroid antiinflammatory drugs phenylbutazone tablet is used for this therapy. [USP, Ph. Eur.].

Matsuda *et al.* [3, 4] have extensively investigated the solid-state stability of polymorphic drugs such as phenylbutazone. Matsunaga *et al.* [5] found that phenyl-

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butazone has three polymorphs, whereas Ibrahim *et al.* [6] reported the presence of four forms, with different solubilities (Table 1).

Müller [7] showed that forms I and II are pseudopolymorphs resulting from solvation, and assigned modification III as α and IV as δ. It was concluded by Matsuda *et al.* [3, 4] that δ is the stable form.

Miseta *et al.* [8] reported on the preparation of phenylbutazone tablets by direct compression, but for such crystals it is better to make tablets by wet granulation.

The possibility for wet granulation are the kneading process [9] or the fluidization process [10–13].

Table 1 Modifications of phenylbutazone

Form	Melting point/°C	Solubility/mg mL^{-1}
IV (δ) (anhydrous)	105	2.130
III (α) (anhydrous)	93	2.336
II (cyclohexane)	90	2.799
I (isobutanol)	80	2.887

Another possibility is pelletization. This is an agglomeration process that converts fine particles of drugs and excipients into small, free-flowing, spherical units with a compact texture [14]. Pelletization may be necessary to improve the compressibility of materials that are not directly processible into tablets. Pellets, however, can also be filled into capsules [15–17]. The mass uniformity of capsule filling is morphology- and particle size-dependent. The shape of pellets can improve the flowability and filling.

There are several possibilities for pelletization. One is the use of a centrifugal granulator, which is an open device. The powder mixture is fed onto a disk rotating at high speed in a barrel. The granulating fluid is constantly sprayed onto the disk, whereby a pelletizing powder can also be applied. With the temperature chosen correctly, the procedure can be continuous. Three forces act in the centrifugal granulator: centrifugal force, fluidization force and gravitation force. The centrifugal force has an important role in the formation of a spherical pellet shape [14] and its application may therefore be especially favourable in the case of needle-shaped crystals such as those of phenylbutazone.

Experimental

Materials

Core materials: Phenylbutazone (USP XXII, Ph. Eur. 2nd)
Mannitol (Ph. Eur. 3rd)
Microfine cellulose (Vitacel A 300®, J. Rettenmaier & Söhne GmbH, Germany)

Build-up powder:	Corn starch (Ph. Eur. 3rd)
	Sucrose (Ph.Hg.VII)
	Colloidal silica, hydrous (Ph. Eur. 3rd)
Granulating solution:	Polyvinyl-pyrrolidone (Kollidon 30®, BASF Aktiensges. Germany)
	Colloidal silica, hydrous (Ph. Eur. 3rd)
	Corn starch (Ph. Eur. 3rd)
	Distilled water (Ph.Hg.VII)

Methods

Morphological study

A Hitachi S2400 (Hitachi Scientific Instruments Ltd., Tokyo, Japan) scanning electron microscope (SEM) was utilized. A polaron sputter coating apparatus (Polaron Equipment Ltd., Greenhill, UK) was applied to induce electric conductivity on the surface of the samples. The air pressure was 1.3–13 mPa.

Homogenization

Powder mixing was performed with a Turbula mixer (Willy A. Bachofen Maschinenfabrik, Basel, Switzerland) (50 rpm for 10 min).

Water uptake determination

The Enslin number (g mL^{-1}) was determined with the use of a glass sieve and a pipette with 0.01 mL accuracy.

Flow properties

The flow time, the angle of repose and the mass by volume were tested with a powder testing apparatus (PTG-1) (Pharma Test GmbH, Hainburg, Germany).

DSC study

A DSC 821^e (Mettler–Toledo GmbH, Switzerland) apparatus was applied to check the features of the material on exposure to heat.

8.6 mg phenylbutazone was measured into the aluminium pan. The measurement involved an isothermal segment (25°C, 3 min) and a dynamic segment (25–120°C, 5°C min^{-1}).

Pelletization

A Freund centrifugal granulator (Freund CF-360, Japan) was applied.

Parameters:	rotor speed:	200 rpm
	granulating fluid feed rate:	20 rpm (=20 mL min^{-1})
	atomizing pressure:	4 atm
	inlet temperature:	40°C

flow rate of slit air:	120 L min^{-1}
flow rate of spray air:	15 L min^{-1}
build-up powder feed rate:	20 rpm (uncontinuously)

Breaking (deformation) process

The modified breaking hardness tester (Chinoin Chemical and Pharmaceutical Works Ltd., Budapest, Hungary) used is suitable for the recording of breaking (deformation) curves.

Dissolution

The dissolution of phenylbutazone was studied with the rotating basket method.

Apparatus:	Pharma Test PTW II, equipped with a rotary basket (Pharma Test Apparatebau GmbH, Hainburg, Germany)
Dissolution medium:	900 mL artificial intestinal juice (pH=7.5±0.1)
Temperature:	37±0.5°C
Rotation speed:	50 rpm
Sampling time:	5, 10, 20, 30, 60 min
Number of samples:	6
Measurement:	at 264 nm with an UV spectrophotometer (Spectromom 195D, MOM Bp. Hungary)

Results and discussion

Phenylbutazone consists of needle-shaped crystals (Fig. 1) which form a heterodisperse system without any flow time. (The measurement of flow time was impossible.)

Fig. 1 Phenylbutazone crystals (SEM)

The thermoanalytical characterization revealed that the crystals were crystals of the stable modification (IV). The DSC curve (Fig. 2) exhibits an endothermic peak at about 105°C, which is the melting peak of modification IV.

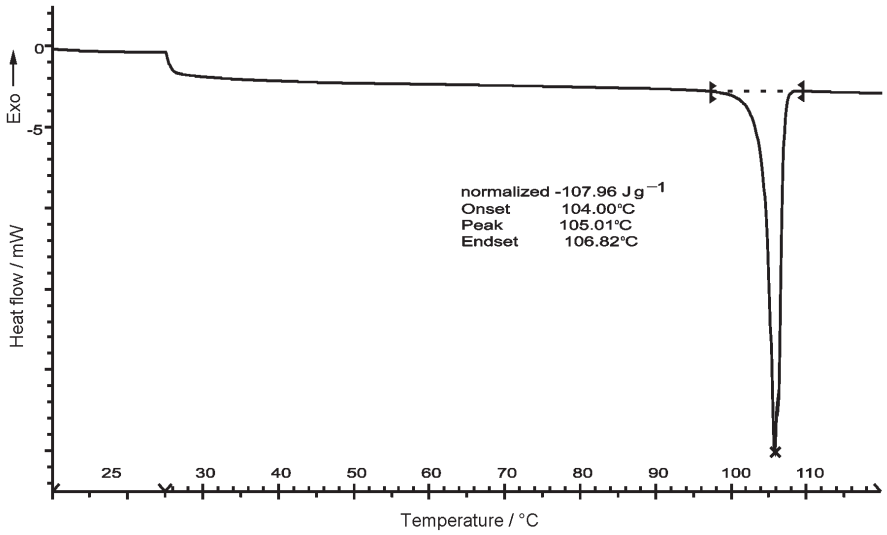

Fig. 2 DSC curve of phenylbutazone crystals

Table 2 Composition of pellets

	Components	Pellet 1/g	Pellet 2/g	Pellet 3/g
In core	Phenylbutazone	200.00	300.00	200.00
	Mannit	300.00	250.00	300.00
	Vitacel A300	500.00	450.00	500.00
	Colloidal silica hydrous	–	–	10.00
In gran. fluid.	Kollidon 30	50.53	76.73	51.15
	Sucrose	404.26	613.81	409.21
	Corn starch	128.84	195.81	130.43
	Colloidal silica hydrous	10.11	15.35	10.23
In build-up powder	Corn starch	135.18	125.82	141.90
	Sucrose	135.18	125.82	141.90
	Colloidal silica hydrous	15.43	14.36	16.20
Sum of dry materials		1879.54	2267.54	1911.02

Granulating fluidum:		Build-up powder:	
Kollidon 30	100 g	Corn starch	236.5 g
Sucrose	800 g	Sucrose, milled	236.5 g
Corn starch	255 g	Colloidal silica hydrous	27.0 g
Colloidal silica hydrous	20 g		
Distilled water	780 g		

In consequence of the unfavourable habit and the very poor flow properties, it was necessary to perform wet granulation before tabletting. The compositions are displayed in Table 2.

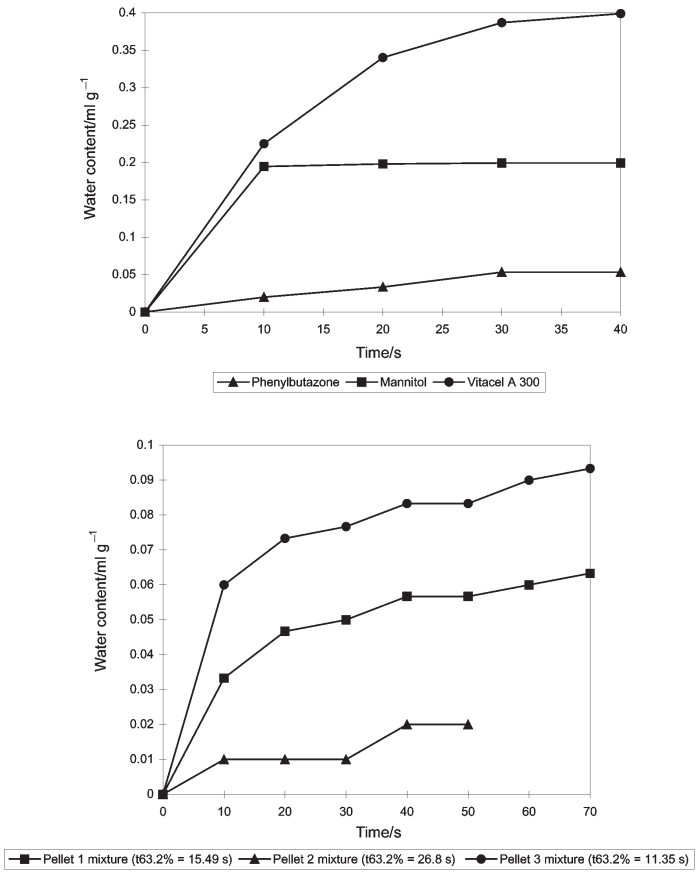

Fig. 3 Water uptake of the materials

Before wet granulation, it is important to know the extents of water uptake of the components. Comparison of the water-uptake curves of the materials (Fig. 3A) demonstrated that mannitol and Vitacel A 300 are more hydrophilic than phenylbutazone. The amount of the drug in the core-powder mixture of Pellet 1 is smaller than in the core of Pellet 2, and the water-uptake of the powder mixture of Pellet 1 is better (Fig. 3B). This is well shown by the characteristic water-uptake time ($t_{63.2\%}$), calculated via the modified Weibull equation (RRSBW equation) [18]. It can be observed that the presence of colloidal hydrous silica (Pellet 3) promoted the water uptake of the powder mixture ($t_{63.2\%}$=11.35 s).

During the pelletization process, the inlet temperature was 40°C. There was no peak in the DSC curve at this temperature (Fig. 2).

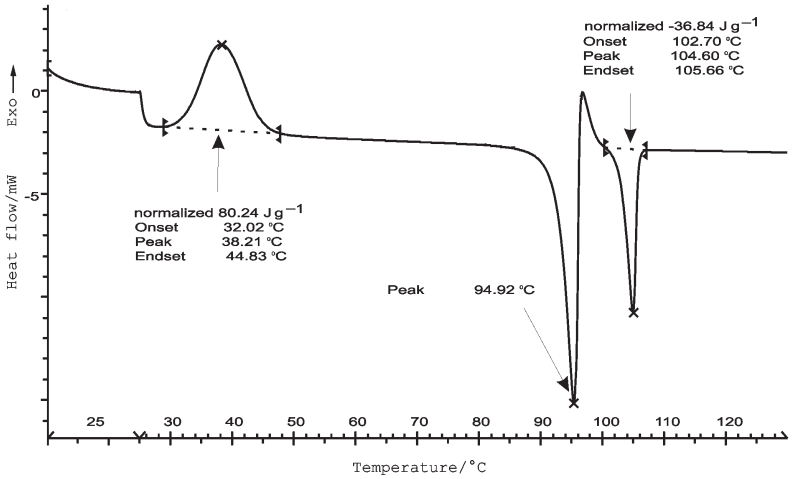

Fig. 4 DSC curve of the melted phenylbutazone crystals

After cooling, the melted sample was again heated (Fig. 4). An exothermic peak was then observed at about 35°C (onset: 32.02°C, end: 44.83°C), and also two endothermic peaks. The first was at 94.92°C (onset: 92.29°C, end: 96.24°C), which is the melting peak of modification III. The second endothermic peak was at 104.98°C, which is characteristic of the original crystals (modification IV). This curve clearly demonstrates that some change occurred during cooling, involving the formation of modification III. On the base of enthalpy values, it can be stated that the sample is solidified as an amorph form upon cooling during the second heating, the exothermic peak showed the recrystallization of amorph phase to modification III.

Since an exothermic peak appeared at 40°C and the pelletization process took longer at this temperature, repetition of the thermoanalytical test under isothermal circumstances at this temperature was justified. In the repeated measurement, the sample was held for 60 min at 40°C. No change was seen in the DSC curve relative to that in Fig. 2. This result proved that the pelletization process causes no change in the

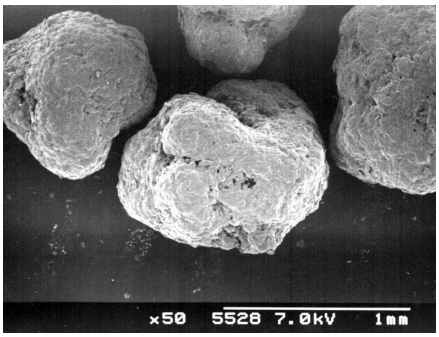

Fig. 5 Phenylbutazone pellets (SEM)

phenylbutazone crystals, and the process with the conditions applied is suitable for pellet preparation.

After the preparation pellets were also tested. The shape was investigated by means of a SEM. Figure 5 depicts a spherical pellet. The flowability data on the pellets are presented in Table 3. It can be seen that the flow properties of Pellet 1 and 2 were good and practically the same. Furthermore, the presence of colloidal hydrous silica in the composition decreased the flow time and the angle of repose (Pellet 3).

Table 3 Flow properties of pellets

Preparations	Mass by volume/ g(100 mL)$^{-1}$	Flow time/ s	Angle of repose/ degree
Pellet 1	60.73	15	35.25
	(SD=0.05)	(SD=0)	(SD=0.31)
Pellet 2	58.64	15.06	35.82
	(SD=0.08)	(SD=0.06)	(SD=0.62)
Pellet 3	58.91	9	34.14
	(SD=0.1)	(SD=0)	(SD=0.11)

Angle of repose (degrees)	Type of flow
<25	excellent
25–30	good
30–40	passable
>40	very poor

Angle of repose as an indication of powder flow properties [19]

The mechanical properties of pellets were also studied. For mechanical hardness testing of pellets and granules the friability test is described in the Pharmacopoeas. This result gives the abrasive resistance of a heap of pellets and it can not reflect the

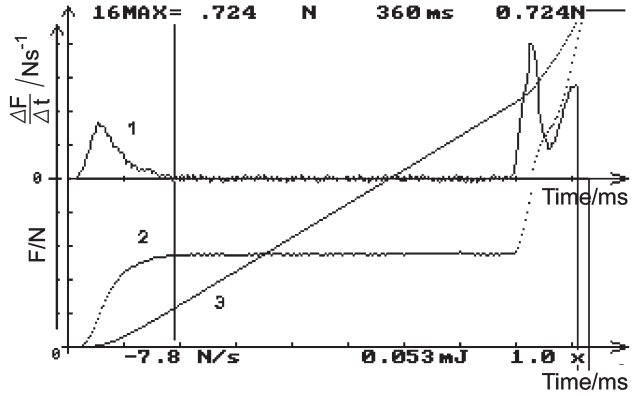

Fig. 6 Breaking process of Pellet 1. 1 – differential curve, 2 – breaking curve, 3 – integral curve. Breaking force 0.724 N, breaking time: 360 ms, breaking work: 0.053 mJ

resistance of an individual pellet. Some papers are to be found in the literature regarding this matter [19–21].

Figure 6 demonstrates the breaking (deformation) process of one pellet, while Table 4 reports breaking data.

The initial linear section of the force-time curve reflects elastic deformation and then first plastic and later plastoelastic deformation. This demonstrates the breaking (=deformation) point, when the rate of force change (N s^{-1}) is zero or negative. The software presents the deformation work computed from the onset of loading to the completion of deformation. The relative standard deviation of the hardness was within a 5% range, whereas that of the deformation work and time was higher (Table 4). The reason for this lies in the unequal distribution of the binding bridges. The mean values were calculated from 20 measured values.

Table 4 Breaking parameters of pellets

Preparations	Breaking force/N	Breaking time/ms	Breaking work/mJ
Pellet 1	0.7255	324.8	0.0484
	(RSD=±1.3003%)	(RSD=±13.3%)	(RSD=±16.695%)
Pellet 2	0.705	338.6	0.0456
	(RSD=±3.6062%)	(RSD=±18.9%)	(RSD=±26.1188%)
Pellet 3	0.6863	336.9	0.049
	(RSD=±2.6952%)	(RSD=±12.7)	(RSD=±18.2825%)

The ratio of phenylbutazone to Kollidon was the same in every case (Pellet 1=1:0.25; Pellet 2 and Pellet 3=1:0.26) and the ratio of phenylbutazone to excipients was as follows: Pellet 1=1:8.41; Pellet 2=1:6.56; Pellet 3=1:8.56. It can be seen

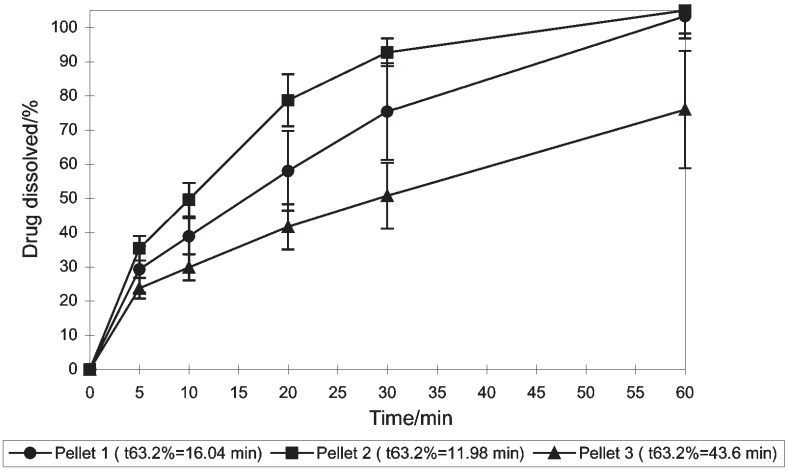

Fig. 7 Dissolution rate of phenylbutazone from pellets

from the data that there was only a small difference in hardness between Pellet 1 and Pellet 2 (Table 4). Furthermore, in spite of the same drug to excipients ratio, the hardness of Pellet 3 was smaller. This difference was significant ($p<0.05$), but the difference in the breaking time and work was not significant (Statgraphics, Copyright STSC, Inc. and Statistical graphics Co., USA, two-sample analysis). It is well known from the literature [22] that the particles of colloidal hydrous silica are located on the edges of the crystals, and the possibility of the formation of stronger bonding is therefore smaller. This is the reason for the smaller hardness of Pellet 3.

The composition also influenced the rate of drug dissolution. In Pellets 1 and 2, the drug to excipients ratios and the amounts of build-up powder were different. Pellet 2, with a smaller drug to excipients ratio, exhibited faster dissolution (Fig. 7). The excipients plays an important role in the dissolution. It is well known that particles of corn starch swell in an aqueous medium and that particles of colloidal hydrous silica form a gel in a fluid medium. In the case of Pellet 1, where the ratio was higher, the swelling and gel formation hindered the dissolution process to a higher degree, but the drug liberation was complete in 60 min. In the case of Pellet 3, where the ratio was the same as for Pellet 1, some colloidal hydrous silica was also situated in the pellet core, and the dissolution was the slowest: only about 75% of the drug dissolved in 1 h. The characteristic dissolution time ($t_{63.2\%}$) demonstrated the differences between the three preparations very well.

Conclusions

Finally, it can be stated that the flowability indicates that the phenylbutazone pellets obtained with a centrifugal granulator are suitable for capsule filling or tabletting. This method and the conditions were favourable for the preparation of pellets from phenylbutazone in the form of needle crystals. The temperature applied did not cause any change in the phenylbutazone modification, and the crystals were stable during the process. The components influenced the properties. In spite of the fact that the powder mixture of Pellet 3 displayed the best water uptake, and the flow time of this pellet was the shortest, the rate of dissolution of drug from this pellet was slower.

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