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Studies of the production and testing of fluidized-bedrotor granules with modified release

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Dedicated to Prof. Dr. B. C. Lippold, Düsseldorf, on the occasion of his 60th birthday

The influence of product parameters on drug release of granules was evaluated using a rotary fluidized-bed equipment. When croscarmellose sodium was employed as a disintegrant, faster release resulted. An increase of release could also achieved by incorporation of lactose instead of microcrystalline cellulose. The incorporation of croscarmellose sodium and lactose showed the fastest release. The coating of the granules using a commercially available ethyl-cellulose pseudo-latex coating system (Aquacoat®) led to a decrease of drug release depending on the thickness of the coated layer. A second coating of the granules with a theophylline containing layer showed the effect of a fast released initial dose.

1. Introduction

Fluidized-bed granulation of pharmaceuticals was first described by Wurster in 1959 [1]. Now fluidized-bed systems are widely used in pharmaceutical industry for the production of granules, for drying processes and for film coating.

Comparison of the fluidized-bed technique with conventional processes has been discussed by Story and Thiel [2]. The ability of the fluid-bed equipment to approach isothermal conditions quickly is the outstanding advantage of this method over other methods [3]. The greatest merit of the method is that it allows to meet the requirements of GMP very well, since mixing, wetting, coating and drying are combined in a single process [4].

An important development in fluidized-bed processing equipment was the tangential spray or centrifugal granulator, commonly referred as the rotor granulator. The basics of the rotary granulator design were originally reported by Bauer [5]. This technique was conceived to combine high shear granulation speed and energy with fluid-bed drying efficiency for producing granules with higher density than typically possible in conventional fluid-bed granulators [6]. During spraying of the binder solution, the flow is tangentional and co-current, leading to a more homogeneous material distribution and allowing a wide range in working capacity.

Aulton et al. [7] have classified the possible variables during fluidized-bed process into three groups: 1. apparatus parameters, 2. process parameters and 3. product parameters. These three parameters and their influence on product properties are widely described in the literature but there are only a few reports about the applications of the rotary fluidized-bed equipment.

For example, Turkoglu et al. [8] evaluated the rotary fluidized-bed equipment as a mixer, granulator and dryer and determined the mixing and granulating efficiency. Turkoglu et al. [9] studied the rotary fludized-bed aqueous coating process and used this coated pellets for in vivo experiments with beagle dogs [10]. Jaeger et al. [11] studied the effect of different molecular weights of polyvinylpyrrolidone blends in the rotary fluidized-bed granulator. Veccio et al. [12] evaluated the influence of different amounts of spheronization enhancer and of different fillers on both processing and physical properties.

The objective of this study was to modify the drug release of fluidized-bed rotor granules by varying the product parameters.

Theophylline was chosen as a model drug at 10% levels.

2. Investigations, results and discussion

2.1. Increase of drug release

Croscarmellose sodium as a disintegrant was incorporated in the basic formula with 0.25, 0.5, 1.0, 2.0 and 4.0%. Fig. 1 illustrates the dissolution profiles.

There is no significant difference between the basic formulation and the formulations with 0.25, 0.5 and 1.0% of disintegrant. 100% of theophylline release was achieved after around 4 h. The double amount of disintegrant could

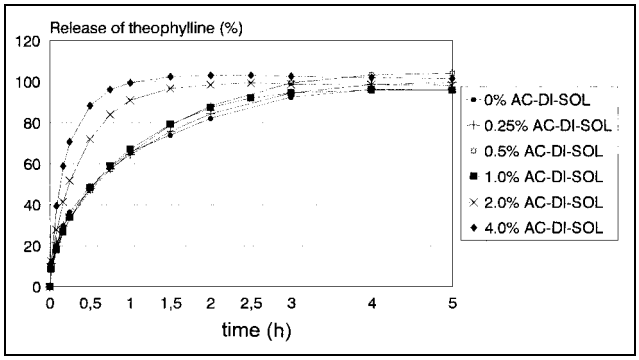

Fig. 1: Effect of disintegrant content on release from theophylline granules

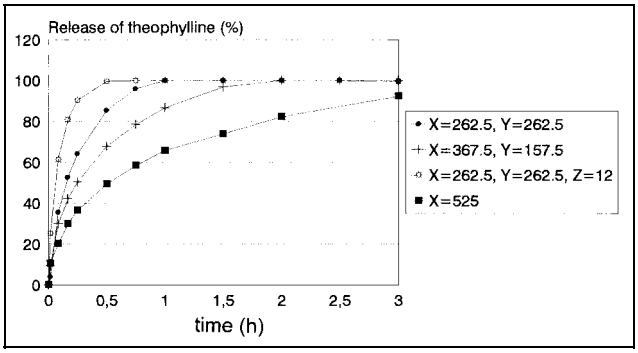

Fig. 2: Effect of lactose and disintegrant on release from theophylline granules (theophylline 60 g, PVP 15 g, Emcocel 50M Xg, lactose Yg, Ac-Di-Sol Zg)

reduce the time for 100% release to the half. A formulation with 2% of croscarmellose sodium reduced the time of 100% release to 2 h and a formulation with 4% croscarmellose sodium reduced the time of 100% release of 1 h.
The incorporation of 4% croscarmellose sodium led to a clear prolongation of production time, around 45 min. To reach the same particle size, it was necessary to spray more water. That means also a prolongation of drying time.
This results show, that the increase of the amount of croscarmellose sodium over 2% is not an effective method to decrease the time until 100% release is achieved.
The dissolution profiles in Fig. 2 show the substitution of microcrystalline cellulose with lactose. The same results like incorporation of 2% croscarmellose sodium could achieved by substitution of one third microcristalline cellulose with lactose – 100% theophylline release after 2 h. The substitution of the half of microcristalline cellulose with lactose decreased the time until 100% release to 1 h. The combination of microcrystalline cellulose : lactose 1 : 1 plus 2% of croscarmelose sodium could finally decrease the time until 100% release to 30 min. By incorporation of lactose, the production time was also clearly decreased. Veccio et al. found, that a decrease of cellulose led to an increased stickiness of the material and produced irregular large granules. The cellulose acts by controlling the movement of the water through the wet powder mixture during the various stages of processing. When a part of the cellulose is substituted with a filler, the amount of the water required can vary depending on the physical properties of the specific employed material. The substitution of a part of cellulose with a corresponding amount of lactose led to pellets more irregular in shape, larger in size, with a wider size distribution [12].
In accordance to the results of Veccio et al., the spraying of 500 ml of binder solution caused irregular large granules. To reach the desired particle size, only 250 ml of binder solution was necessary. Thus, the drying time is also decreased.
This formulation appears as a suitable and effective method to increase the drug release of rotary fluidized-bed granules.

2.2. Decrease of drug release

An aqueous ethylcellulose dispersion +30% dibutyl sebacate was used as coating material to modify the drug release in the other direction. The following formula was used as the core material. Theophylline 60.0 g, Emcocel 50M 262.5 g, Lactose 262.5 g, PVP 15.0 g and Ac-Di-Sol 12.0 g. In Fig. 3 the dissolution profiles of coated granules with different thickness of the layer are shown.

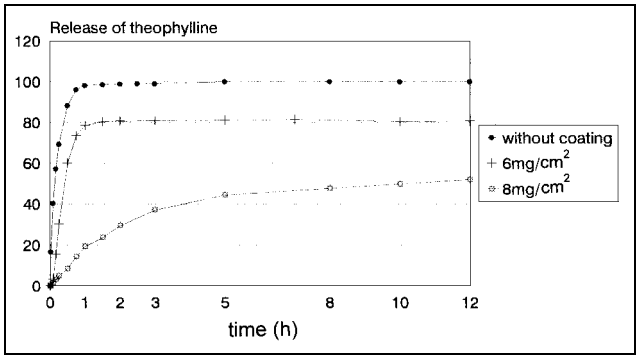

Fig. 3: Effect of coating on theophylline release in dependance on the thickness of the layer

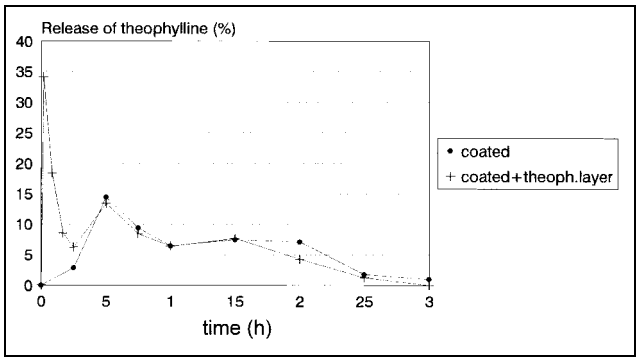

Fig. 4: Effect of a second theophylline layer on the initial drug release in comparison to the coated granules

By coating of 6 and 8 mg coating material/cm^2 significant difference in the release profiles is obvious. By coating of 6 mg/cm^2 the drug release was 80% after 12 h and by coating of 8 mg/cm^2 the drug release was only 52% after 12 h. It is clear to say, that the drug release is depending on the thickness of the coated layer.
The feasibility to produce granules with modified release by varying the product parameters using a rotary fluidized-bed equipment was confirmed. An increase of drug release could be achieved by incorporation of disintegrant or substitution of cellulose with filler. As a suitable method for decrease the drug release, the coating of the pellets with anqueous cellulose dispersion was shown.

2.3. Initial dose

Theophylline with 5% PVP and 20% propylene glycol in water was used for spraying a second layer on the coated theophylline granules. As shown in Fig. 4 (non-cumulative dissolution profile) this layer has no retardant effect on the

Table 1: Conditions of granulation, drying and coating

	Granulation	Drying	Coating
Inlet air temperature (°C)	25	50	40
Product bed temperature (°C)	14	20	18
Bottom plate: – typ	waffle plate	waffle plate	smooth plate
– rpm/min	720	720	280
Spray nozzle: – diameter (mm)	1.2		1.2
– air pressure (bar)	1.5		1.5
Batch size (g)	600	600	200
Binder spray rate (ml/min)	44		8.5
Filter shaking: – duration (s)	3	3	
– interval (s)	5	5	5
Pressure drop in product chamber (kPa)	1.5	1	1.5
Fluidization air flow rate (m/h)	65 (25%)	195 (70%)	65 (25%)

Table 2: Theophylline content

Sample	Granules (mg)	Released amount (mg)	Content* (%)	85–115.0%
1	26.9	2.635	9.797	+
2	25.8	2.481	9.618	+
3	27.6	2.751	9.968	+
4	26.3	2.468	9.386	+
5	25.7	2.463	9.582	+
6	26.7	2.525	9.456	+
7	25.4	2.583	10.171	+
8	27.0	2.634	9.757	+
9	25.7	2.391	9.305	+
10	27.4	2.621	9.566	+
Avg			9.661	
SD			0.267741	

* Label claim: 10%

drug release. 50% of theophylline from the outer layer are released within 1 min and 100% of theophylline from this layer within 10 min. Thus, this second layer can be applicated if there is a need for an initial dose.

3. Experimental

3.1. Formula and materials

The basic formula used for granulation was a powder mixture of 60 g theophylline anhydrous USP (China) and 525 g of microcrystalline cellulose (Emcocel 50 M, Mendell Co. Inc., Carmel, NY, USA). The binder solution consisted of 15 g polyvinyl-pyrrolidone (Plasdone K-29/32, ISP Technologies, Inc., Wayne, NY, USA) and around 500 ml of purified water. The film coating was an aqueous dispersion of ethylcellulose (Aquacoat, FMC Corp., Newark, DE, USA) with 30% of sebacid acid dibutyl ester (SIGMA Chemical Co., St. Louis, MO, USA) as the softening agent. Further, croscarmellose sodium (Ac-Di-Sol, FMC Corp., Newark, De, USA) was used as a disintegrant and lactose hydrous (Sheffield Products, Norwich, NY, USA) as a filler instead of microcrystalline cellulose. For the second coating propylene glycol (Fisher Chemical, Fair Lawn, NJ, USA) was used. Emcocel 50M, Plasdone K-29/32, Aquacoat and Ac-Di-Sol were used as received.

3.2. Granulation, drying and coating

A laboratory size fluidized-bed (Versa-Glatt, GPCG-1, Glatt Air Techniques, Inc., Ramsey, NJ, USA) with the rotary insert was used. The conditions of granulation were determined from Turkoglu et al. [9] upon preliminary experiments in order to achieve a fast and reproducible granulating process with spherical and dense particles. Table 1 summarizes the conditions of granulation, drying and coating.
After spraying of around 500 ml binder solution, samples were withdrawn from the bed every 10 s to monitor the granule growth. When granules reached 0.85–1.00 mm size, the inlet air temperature was set to 50 °C and the pressure drop in the chamber was reduced to 1.0 kPa by elevating the bottom plate and increasing the fluidization air flow from 25 to 70%. Hence, granule growth was inhibited.

3.3. Theophylline and moisture contents

The moisture content was determined using an automated gravimetric moisture content analyzer (Computrac, Max-50, Arizona Instruments, Tempe, AZ, USA). From each batch three samples, 7 g each, were tested at 105 °C after drying. The batches were dried to a content of 2–4% of water.

The theophylline content of each batch was determined by UV spectrophotometry (Beckmann DU-70 UV/VIS Spectrophotometer, Beckmann, Inc., Fullerton, CA, USA) at 271 nm. Samples of around 0.025 g granules were weighed accurately into 100 ml volumetric flasks. After appropriate dilutions with distilled water, the flasks were shaken for 20 min, then the contents were filtered. A blank was prepared under identical conditions without drug. A series of theophylline standards were run along with the samples.
The USP content uniformity was examined and the requirements were meet for all batches. A sample is shown in Table 2.

3.4. Sieve analysis

The granules were subjected to a sieve analysis using a number of U.S. standard sieves (1.70, 1.40, 1.18, 1.00, 0.85 mm opening sizes) to determine the mean statistical particle size (d 63.5%) and the idealized specific surface area (Asp) for each batch using a particle size distribution nomogram (Rosin, Rammler, Sperling and Bennet function, DIN 4190) in order to calculate the amount of coating material.
For coating and all examinations sieve fractions above 1.70 mm and below 0.85 mm were excluded, because the surface area calculation based on the range between 1.70 and 0.85 mm. So, before and after coating the surface areas could be compared within as well as among the batches.

3.5. Dissolution test

Granules of the sieve fractions between 1.40 and 1.18 mm were tested for *in vitro* theophylline release using the USP basket apparatus with 900 ml of distilled water as the dissolution medium at 37 °C and 50 rpm. Samples were withdrawn after 1, 5, 10, 15, 30, 45, 60, 90, 120 min, 3, 5, 8, 10, 12 h and assayed by UV spectroscopy at 271 nm.

Acknowledgements: The authors would like to thank the Mendell Co. Inc., the ISP Technologies and the FMC Corp. for their generous donation of chemicals.

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Received March 3, 1999
Acepted May 1, 1999

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