Effects on the Quality of Granules Obtained in Conventionally Designed Fluid-bed Equipment Compared to Granules Obtained in a Washing In Place / Cleaning In Place Designed Unit

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Summary

Due to increasing demands for an automated cleanability of processing equipment, equipment manufacturers have improved their product design for an optimum performance of the Cleaning In Place (CIP) process with respect to GMP standards. In this context it is important to assess if and eventually how these design improvements do effect the properties of granules manufactured in this fluid-bed system. Besides other design variations especially the bottom plate and the product retention filters are considered as critical magnitudes of influence in a fluid-bed process. The conventional product retaining filter system used for this study consist of a seamed polyester fabric with a mesh size of approximately 20 μm. During a process this type of cloth filter is cleaned by means of pneumatic shaking cylinders which generate a periodically up and down movement of the bag type filter unit for a specified time. The product recovery filters developed for a WIP/CIP process are cylindrical filter cartridges consisting of stainless steel material with a mesh size of 10 μm in this study. Instead of the up an down movement the novel cartridges are periodically purged with bursts of compressed air at a pressure of 6 bar.

The study compares standard granule material obtained in a fluid-bed top spray granulator which was modified for a better cleanability during a WIP/CIP process with granules obtained in a conventionally designed unit. The granulations are carried out under equal process conditions with the same formulation. The goal of this study is to detect eventual differences between the granule properties. For the comparison of the quality of the granule properties the bulk and tapped density, loss on drying, angle of repose, particle size distribution and the uniformity of drug content were measured. Scanning Electron Micrographs were prepared to visualize possible morphological differences. Within this study it can be concluded that a top-spray granulation process optimized in a conventionally designed unit can be transferred to a WIP/CIP designed fluid-bed granulator without changing process variables. The investigated design improvements do not affect the granule quality.

Zusammenfassung

Vergleichende Untersuchung zur Granulatqualität nach einem Sprühgranulationsprozeß in einer konventionellen Wirbelschichtanlage und einer neuartigen Washing-In-Place-Cleaning-In-Place-Anlage

Aufgrund der hohen Anforderungen, die an automatische Reinigungsprozesse von Prozeßausrüstung gestellt werden, haben Anbieter von Wirbelschichtanlagen das Anlagendesign hinsichtlich eines Cleaning In Place (CIP)-Prozesses, der GMP-

Key words

- CIP (Cleaning In Place)
- Fluid-bed granulator, equipment design
- Granulation, granule quality, influence of processing equipment
- WIP (Washing In Place)

Standards entspricht, verbessert. Von besonderem Interesse ist hierbei, ob und inwieweit sich Veränderungen der Anlage auf die Granulatqualität auswirken. Neben anderen Designoptimierungen gelten als kritische Einflußgrößen in diesem Zusammenhang insbesondere das Design der Produktrückhaltefilter und des Anströmbodens. Die untersuchten konventionellen Produktrückhaltefilter sind aus Polyesterfasern mit einer Maschenweite von ca. 20 µm. Diese Art von Textilfilter werden zum Zweck der Abreinigung durch pneumatische Hubzylinder periodisch auf und ab bewegt. Die für den WIP/CIP-Prozeß entwickelten und in dieser Studie verwendeten Produktrückhaltefilter hingegen kommen in Form von runden Filterpatronen zum Einsatz,

deren Filterfläche aus einem Edelstahlsiebgeflecht mit einer definierten Maschenweite besteht. In dieser Studie wurden Filterpatronen mit einer Maschenweite von 10 µm eingesetzt. Im Gegensatz zu den Rüttelbewegungen werden diese Filterpatronen durch Druckluftimpulse mit 6 bar periodisch ausgeblasen.

In der vorliegenden Studie werden unter vergleichbaren Prozeßbedingungen formulierungsgleiche Standardgranulate zum einen auf einer WIP/CIP-designoptimierten Wirbelschichtanlage und zum anderen auf einer Wirbelschichtanlage konventioneller Bauart im Top-Spray-Verfahren hergestellt und verglichen. Hierbei soll die Fragestellung beantwortet werden, inwieweit die beiden Granulatqualitäten voneinander abweichen. Zur

vergleichenden Charakterisierung wurden verschiedene Kenngrößen wie Schütt- und Stampfdichten, Restfeuchten, Böschungswinkel, Korngrößenverteilung und die Einheitlichkeit des Wirkstoffgehalts einander gegenübergestellt. Rasterelektronenmikroskopische Aufnahmen der Partikel ermöglichen zudem eine morphologische Beurteilung der Granulatkörner.

Im Rahmen dieser Studie konnte gezeigt werden, daß ein Granulationsprozeß, der auf einer konventionellen Wirbelschichtanlage optimiert wurde, ohne Änderungen der Prozeßvariablen auf eine WIP/CIP-optimierte Wirbelschichtanlage übertragbar ist. Die erhaltenen Granulatqualitäten sind vergleichbar.

1. Introduction

Fluid-bed granulation plays an important role in the treatment of fine powders for the preparation of solid dosage forms. To deal with GMP requirements concerning the cleaning process of such equipment, new concepts have been established to minimize operator and environment exposure to the active ingredients. Nowadays, manual cleaning of the equipment is still the method used for standard applications. To facilitate the manual cleaning step a Washing In Place (WIP) unit could be installed in a conventionally designed fluid-bed system. If a fully automated cleaning process without any further manual cleaning steps is required a full Cleaning In Place (CIP) concept is advisable. This CIP concept has to consider the equipment design, the respective drug, the manufacturing process and the cleaning procedures. The technical installation can only be designed for the best possible cleaning (i.e. WIP), but the actual degree of cleaning achievable must always be determined in each individual case, e.g. reaching an acceptance criteria of a cleaning validation taking into account the cleaning variables like temperature, time, pH etc. To allow a fully automated cleaning process in the GMP sense of CIP, the fluid-bed equipment has to be completely redesigned [5]. Equipment as such therefore can always only be considered to be WIP able. Whether, based on this WIP system which describes the technical execution of a processing unit, a CIP process meeting the acceptance criteria is achievable, can only be determined on a case by case basis. From this point of view, equipment as such can't be considered "CIP". In comparison to the manual cleaning procedure, the CIP process requires no additional manual cleaning step [3].

If newly designed WIP/CIP fluid-bed equipment is to replace conventional equipment, pharmaceutical companies are required to assess whether the new design has any influence on the quality of the granule. Due to the fact that pharmaceutical production must take place under qualified conditions, each deviation with possible effects on the process has to be carefully assessed. This is the background for this study.

Hence, a spray granulation process was performed using a conventional fluid-bed unit as well as a WIP/ CIP fluid-bed equipment. The main technical modifications which could have an influence on the quality of the product are the bottom screen and the product-retaining filters in the filter chamber. The concept of a conventional bottom screen was improved by a newly designed bottom plate consisting of a wedge wire screen. The typical standard bag type filters which are available in a variety of different mesh sizes and materials were replaced with stainless steel filter cartridges [5]. Depending on the process demands, the mesh size of the stainless steel cartridges can be 2, 5 or 10 µm or larger.

During the process, the filters as well as the bottom plate have intense contact with the granule. This might generate friction which may influence the particle size distribution. The bottom screen and the product-retaining filters offer resistance to the process air which generates a fluidized-bed process. Changes in the geometry of these parts may also affect the quality of the granules. The powder load on the surface of the product-retaining filters has to be reintroduced to the fluidized bed frequently. In case of the conventional cloth filter, a frequent shaking prevents powder build-up on the filter's surface. The stainless steel filter cartridges of the WIP/CIP unit are cleaned by bursts of compressed air which allow the fine powder to fall back in the fluidized bed. It is therefore important to know if the type of filtration process has any influence on product quality.

2. Materials and methods

A standard granulation process with Acetaminophene USP [6] as the active ingredient was carried out using both fluid-bed equipment in a top-spray configuration [10]. Both systems are capable of granulating a batch load of approximately 20 kg depending on the bulk density and are equipped with the usual type of binary spray nozzle. The process parameters were determined during the first granulation and the process was repeated twice for the evaluation of the reproducibility of the granule properties.

2.1. Fluid-bed equipment

The GPCG 15 (Glatt, Binzen, Germany) is a conventionally designed fluid-bed unit. The multi-layered bottom screen con-
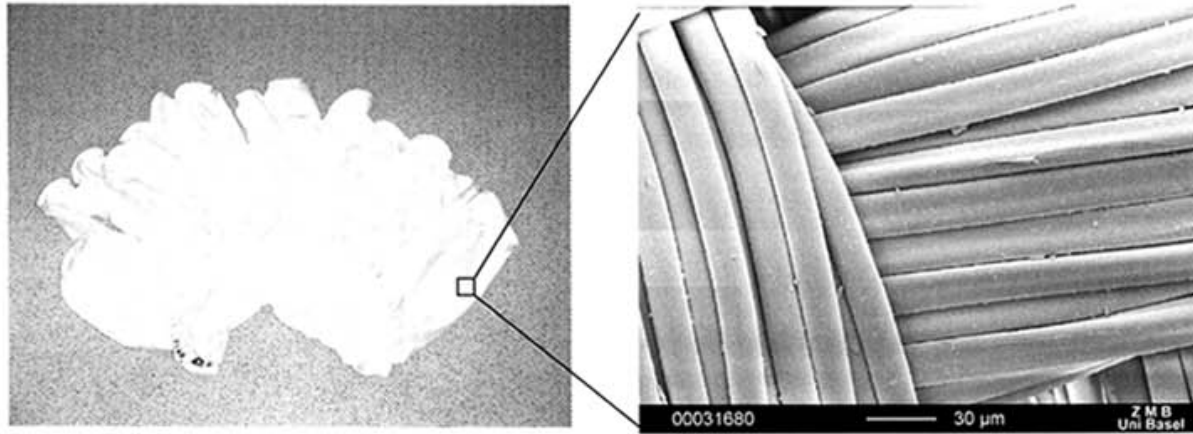
Fig. 1: Conventional bag type filter and the textile filaments (scanning electron micrograph).

sists of a perforated stainless steel plate, a fine mesh ("PZ fabric"; 100 μm mesh size) and stainless steel rods on the top of the fine sieve mesh. Due to the fact that the mesh is only fixed at the circumference, above a certain circular area of the mesh this stabilization construction is necessary to ease the strain of the fine sieve [5]. As the product-retaining filter conventional textile bag type filter (T165P, approximately 20 μm mesh) are used. The filter cleaning procedure during the process is based on a vertical movement of stroke cylinders. Two exhaust air filter chambers allow continuous spraying even if one chamber is being shaken for cleaning which reduces the filtration surface in the process area down to 50 %. During shaking the outlet air flap of the concerning chamber is closed and no process air may pass through, therefore particles can effectively be removed from the filter. The machine is charged with the powder mixture (Table 1) by means of a manual filling of the product bowl. The GPCG 15 has to be opened for both the charging and discharging. After a campaign is carried out, the whole machine is dismantled and manually cleaned.

The GPCG 15 Super Clean (Glatt, Binzen, Germany) is a specially designed fluid-bed unit which allows automated CIP processes. Many details like gaskets, windows, flanges, sensors, filters, bottom screen etc. are different to the GPCG 15 in order to meet the demands of an automated cleaning process [5]. The bottom screen for example is a so-called wedge wire sieve (wedge distance 100 μm). It does without the multi-layered construction and minimizes product residues after WIP/CIP cleaning [5]. The product-retaining filters are cylindrical stainless steel cartridge filters with a mesh size of 10 μm as the outer surface fixed to a support mesh construction. The fine filtration mesh (10 μm) is therefore not covered by an additional outer coarser supporting membrane (for stabilization purposes) as is usually seen with WIP/CIP-compatible pleated stainless steel filter cartridges [5]. Periodic bursts of compressed air having a pressure of up to 7 bars provide the cleaning process during the granulation and the WIP/CIP process. Due to the fact that only one cartridge is in the purge sequence the reduction of the filtration surface is less than 50 %, regarding the GPCG 15 SC 16.6 %. The discharge of the product is carried out by means of a turning bottom plate and a vacuum product transfer without opening the equipment (total containment philosophy) [5].

2.1.1. Product-retaining filters

One important point of the study was to assess the influence of two different filtration concepts on the quality of the granule material.

Conventional textile filters are unsuitable for use in WIP/CIP processes: The filters sewn together and product can become irreversibly embedded in the fabric. The fact that the filaments are loosely interwoven means that the mesh size is alterable, thus allowing particles to migrate through the structure.

On the other hand, the patented WIP/CIP stainless steel cartridges are manufactured out of stainless steel filaments fixed to an inner reinforcement mesh. This construction guarantees a defined mesh size. The filter cartridge's round shape is completely welded for both avoiding process air and compressed air during the purge sequence bypassing the filter mesh and cleaning requirements. In comparison to the conventional bag type filter concept, the cartridge concept enables WIP processes, eventually leading to CIP in the sense of GMP [5]. Fig. 1 illustrates the fine structure of the textile bag type filter used for these trials. The fabric is loosely interwoven so that the matrix is in continuous movement especially during the filter shaking sequence while fine powder particles are returned to the process.

In Fig. 2 a magnification of the WIP/CIP stainless steel cartridge filter mesh can be seen. To return the fine particles back to the product container during the process, bursts of compressed air are used. Therefore, it is necessary that a mesh array can withstand an air pressure of up to 7 bar. To get comparable results, a filter mesh size of 10 μm is used which is similar to the mesh size of the bag type filters.

2.2. Formulation

For reasons of universality the study is carried out using a standard granulation formulation. Acetaminophene (USP Quality, Mallinckrod, St. Louis, MO, USA) a well known antipyretic drug was used as the active ingredient. Corn starch (Meritena 100, Tate & Lyle/Amylum Group, Aalst, Belgium), Lactose (Granulac 200, Meggle, Wasserburg, Germany) and Polyvinylpyrrolidon (Kollidon 25 and 90 F, BASF, Ludwigshafen, Germany) are also widely used as excipients in the pharmaceutical technology. To obtain better physical stability of the granule, a mixture of Kollidon 25 and Kollidon 90 dissolved in water is used as 7.5 % binder solution to be sprayed.

Table 1 shows the amount of active and excipient used for the granulation process. The blending of the powder is carried out by fluidizing the mixture a few minutes in the fluid-bed granulator.

2.3. Charging / discharging process

The two fluid-bed units are loaded with product in different ways:

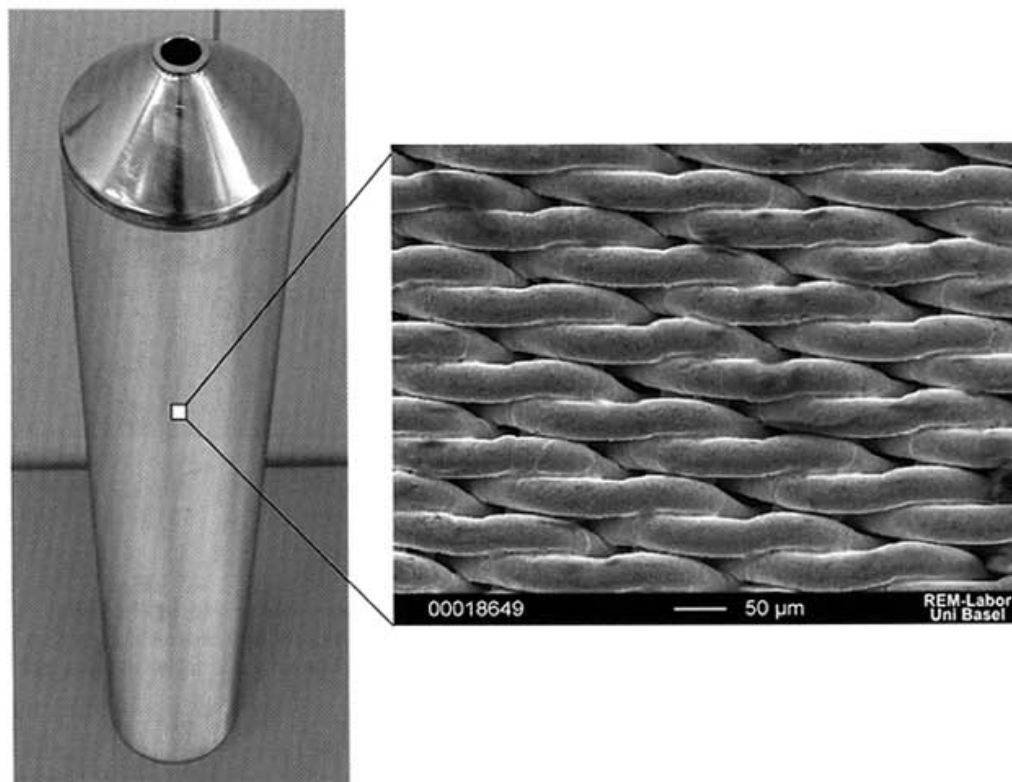The GPCG 15 is opened and the powder is manually filled into the product bowl. The WIP/CIP equipment, on the other

Fig. 2: WIP / CIP stainless steel filter cartridge. The scanning electron micrograph demonstrates the uniformity of the top filtration mesh.

hand, allows a completely closed filling process (Total Containment Philosophy) [5]. Charging is performed by gravity using a charge port and a hopper. The discharging of the granule is done using a vacuum transfer line and a pneumatic conveying system. Both systems were cleaned between the batches using a standard cleaning procedure.

2.4. Process parameters

The parameters for the granulation process are shown in Table 2. The values are equal for both types of fluid-bed equipment to guarantee the equal process conditions during the trials. The granulation trials are carried out on the same day to avoid deviations in the granulating and drying performance due to different environmental conditions, e.g. air humidity.

2.5. Analytical procedures

2.5.1. Bulk / tapped density

The bulk / tapped density of the granules are determined according to USP 25 [6] using a Erweka SVM-20 system (Erweka, Heusenstamm, Germany)

2.5.2. Hausner factor

The Hausner factor (HF) is calculated as the ratio of the tapped (d_t) and bulk density (d_b) as shown in equation 1.

$$HF = \frac{d_t \left(\frac{g}{cm^3}\right)}{d_b \left(\frac{g}{cm^3}\right)} \qquad Eq. 1$$

2.5.3. Yield

The yield (y) is calculated as the ratio of the weight of the manufactured granule (m_g) and the weight of the introduced solids (m_i).

Table 1: Formulation.

	Weight (g)	% (m/m)
Basic material		
Acetaminophene	4290	35.7
Corn starch	1800	15
Lactose	5460	45.5
Binder[a]		
Kollidon 90 F	200	1.7
Kollidon 25	250	2.1
Total	12000	100

[a] Used as 7.5 % solution in water.

$$Y(\%) = \frac{m_g \ (kg)}{m_i \ (kg)} \times 100 \ \% \qquad Eq. 2$$

2.5.4. Angle of repose

A modified test equipment based on Dr. Pfrengle, DIN 4324 was used. A funnel with an opening of 10 mm is fixed 7.5 cm above a circular plate with a radius r of 2.5 cm. A volume of 150 ml granule material is used for the determination of the angle of repose. The height of the granule on the plate is measured and the result is calculated as given in equation 3.

$$\tan \alpha = \frac{h \ (cm)}{r \ (cm)} \qquad Eq. 3$$

2.5.5. Flow properties

The flow rate is measured using the same experimental setup but with the difference that a balance is placed below the col-

Table 2: Process parameter.

Heating	*2 min*
Air volume	550 m³
Inlet air temperature	55 °C
Outlet air temperature	45 °C
Product temperature	37 °C
Spraying	*46 min*
Spray pressure	2 bar
Spray rate	120–140 g/min
Air volume	550–600 m³
Inlet air temperature	45 °C
Outlet air temperature	32–23 °C
Product temperature	30–24 °C
Drying	*10 min*
Air volume	500 m³
Inlet air temperature	55 °C
Product temperature	39 °C
Outlet air temperature	32 °C
Total process time	*58 min*

lecting pan. The flow rate (v_g) is calculated as the ratio of the mass of granule (m_g) and flow time (t_f) seen in equation 4.

$$V\left(\frac{g}{s}\right) = \frac{m_g\,(g)}{t_f\,(s)} \qquad \text{Eq. 4}$$

2.5.6. Loss on drying

For the determination of the loss on drying (LOD), the infrared dryer type PJ 300 MB (Mettler-Toledo, Giessen, Germany) is used. An amount of 1.5 g is weighed out into the sample plate and dried with an infrared lamp (temperature = 105 °C, time = 10 min). The results were taken directly from the balance.

2.5.7. Particle size distribution

The particle size distribution is assessed using an analytical sieve shaker AS200 digit (Retsch, Haan, Germany) and a laser diffraction system MasterSizer X (Malvern Instruments, Malvern, UK) [8].

In case of the sieve shaker, an amount of 100 g granule material is placed on the top of the mounted test sieves (DIN-ISO 3310/1). The shaking time is adjusted to 10 min. According to European Pharmacopoeia [7], test sieves with mesh sizes of 90, 125, 250, 355, 500, 710, 1000 and 1400 µm are used.

Using the Mastersizer an adequate amount of granule material is placed on the ultrasonic feeder system for measuring the particle size with the laser diffraction unit. A dispersion pressure of 1 bar was found to be an optimal value to prevent the granule cluster breaking. The feed rate is set to 5 to obtain optimal obscuration. The focus lens with 1000 mm is normally used for measuring particles with sizes between 1.8 and 2000 µm. The measuring time is fixed to 300 000 sweeps and the obscuration level is optimized to 10 %. The alignment and background correction is carried out for every trial. The raw data presentation is calculated with the Fraunhofer theory (Malvern Software Ver. 1.1a) [9]. Three samples of each granule batch are measured.

2.5.8. Scanning electron micrographs (SEM)

Samples of the granules are investigated by means of a scanning electron microscope Philips XL 30 ESEM (Zentrum für Mikroskopie, Pharmazentrum University of Basel, Switzerland) with a size enlargement factor of 100 and 500.

2.5.9. Content uniformity

The method used is described in the USP 25, p. 17, Acetaminophene Capsules. An amount of approximately 30 mg granule material is weighed out and dissolved in methanol. The samples are introduced into a UV/VIS spectrometer Lambda 20 (Perkin Elmer, Fremont CA, USA) and the absorption is measured (wavelength 248 nm). The concentration of the samples are calculated with a generated calibration curve.

3. Results and discussion

The powder mixture is granulated on both systems three times, leading to a total number of 6 batches. The batch code of the Glatt Process Technology Center is used. The suffix "WIP/CIP" means the granules are produced on the WIP/CIP fluid-bed equipment and "conventional design" means the granules are produced on the conventionally designed unit".

3.1. Powder analytic

The different characteristics are shown in Table 3. The yield of the "WIP/CIP" granules were approximately 3 % lower in comparison with the "conventional design" granules. This can be explained by the discharging process: The WIP/CIP unit is discharged by means of a pneumatic conveying system, having a larger equipment surface which can be occupied with granule residue leading to higher product loss. On the other hand the conventional unit is discharged directly into a vessel manually. Between the batches the equipment was cleaned, thus the yield cannot increase and is more or less constant. In practice no cleaning would be performed after the first and also after the following batches. In such a case the surfaces are "powder saturated" and a "dynamic equilibrium" is achieved leading to higher yields.

The slightly higher bulk and tapped density of the "WIP/CIP" granule is possibly caused by the mechanical impacts during pneumatic conveying. The high speed of the granule particles during the "extraction by suction" could possibly destroy the granule cluster and also generate a certain amount of small particles which fill up the gaps between the larger granule particles. The Hausner ratio is known to be an index of flowability and shows no major deviations. The values of the angle of repose and the flow rate of all batches are comparable.

3.2. Grain size distribution

In Fig. 3 results of the granule size distribution of the laser diffraction measurement for both granule types are shown. The curve is averaged with 3 batches measured three times (n = 9). The maximum of both curves including the inflection points are on equal ordinate positions. The granule size distribution of the "WIP/CIP" granules has a small parallel shift to smaller sizes but broadness of the distribution is identical. Due to this parallel shift, the slight deviation can be considered as systematic. However there are no effects on the final product performance expected due to this minor shift.

In Table 4 the percentiles d_{10}, d_{50}, d_{90} of the particle size analysis of both granules including the mean value and the relative standard deviation of the laser diffraction and the sieve measurement are shown. In Fig. 4 the

Table 3: Powder analytics.

Equipment	Conventional design					WIP/CIP design				
Batch No.	406	407	408	MV	RSD (%)	409	410	411	MV	RSD (%)
Yield (%)	98.3	99.2	99	98.8 (n = 3)	0.4	96	96.2	96	96.1 (n = 3)	0.1
Loss on drying (%)	2.1	2.2	2.1	2.16 (n = 3)	2.2	2.2	2.1	2.1	2.13 (n = 3)	2.3
Bulk density (g/cm^3)	0.43	0.45	0.45	0.44 (n = 12)	2.1	0.47	0.46	0.48	0.47 (n = 12)	1.7
Tapped density (g/cm^3)	0.48	0.48	0.48	0.48 (n = 12)	1.25	0.52	0.51	0.52	0.516 (n = 12)	1.4
Hausner ratio	1.12	1.07	1.07	1.09 (n = 12)	2.2	1.11	1.11	1.08	1.1 (n = 12)	1.3
Angle of repose (°)	29.7	30.4	29.7	29.9 (n = 9)	1.1	29.7	29.3	29.3	29.4 (n = 9)	0.6
Flow ratio t(g/s)	4.63	4.6	4.6	4.61 (n = 9)	0.3	4.6	4.62	4.6	4.6 (n = 9)	0.2

MV = mean value; RSD = relative standard deviation.

granule size distribution of the laser diffraction measurement is represented as percentiles including minimal and maximal deviations for d_{10}, d_{50}, d_{90} of both granules. The granule sizes of the "WIP/CIP" granules are slightly smaller due to the mechanical forces during pneumatic discharging described in chapter "Powder analysis". Due to the fact that the d_{10}, d_{50} and d_{90} values of the "WIP/CIP" granules are inside the deviation of the "conventional design" granules, thus a possible influence during tabletting is not expected. Both analytical methods, the laser diffraction and the sieve shaker lead to the same conclusions.

3.3. Content uniformity

In Table 5 the percentage arithmetic mean of the content of acetaminophene in the certain batches is shown. The minimum and maximum deviation of the acetaminophene content in all batches is inside the pharmacopoeia acceptance criteria [7].

3.4. "Visual inspection" of the granule particles

In Fig. 5 the "conventional design" granule and in Fig. 6 the "WIP/CIP" granule particles are shown. The morphology of both granules does not show any visible difference.

4. Conclusion

The comparison of the granules manufactured on different fluid-bed units show that the differences in equipment design have no major influence on the qual-

ity of the granule material. All values are inside the acceptable limits for use in pharmaceutical production. It has been proven that both designs are completely interchangeable without affecting the granule quality. All analytical markers both physically and chemically show no major deviations. The slight shift to smaller "WIP/CIP" granule particles can be explained by the mechanical effect during discharging with the pneumatic conveying system, this should be investigated in further studies. The slightly smaller standard deviation of the WIP/CIP granules is perhaps caused by the differing methods of filter cleaning: In the case of the bag type filters the up and down movement peels the stacked powder/binder mixture away only by inflexion, so the size of the "clusters" has a wider particle size range. The periodic bursts of compressed air in the case of the

Table 4: Grain size distribution: percentiles.

Analytical equipment			Laser analysis		Sieve analysis	
Fluid bed unit (design)			Conventional	WIP/CIP	Conventional	WIP/CIP
d_{10} (n = 9)	MV	(µm)	118	112	140	118
	RSD	(%)	21.7	9.9	2.1	2.7
d_{50} (n = 9)	MV	(µm)	268	253	257	223
	RSD	(%)	12.9	7.3	2.6	2.3
d_{90} (n = 9)	MV	(µm)	529	500	460	439
	RSD	(%)	8.4	5.5	1.0	2.2

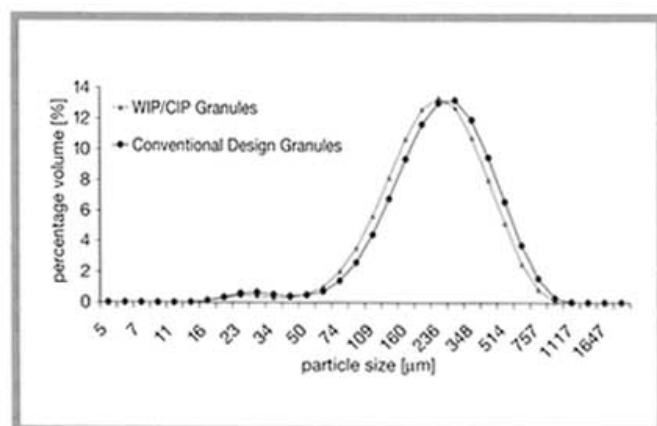MV = mean value; RSD = relative standard deviation.

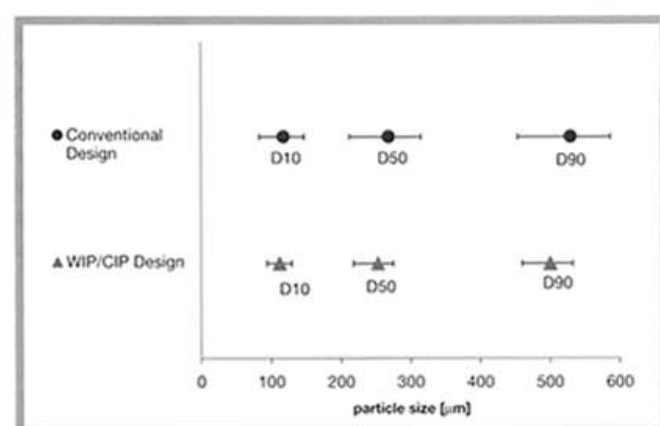**Fig. 3: Laser diffraction measurement (n = 9), granule size distribution.**

Fig. 4: Laser diffraction measurement (n = 9), percentiles.
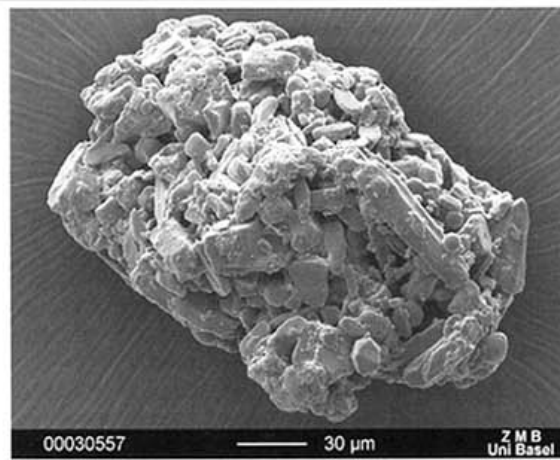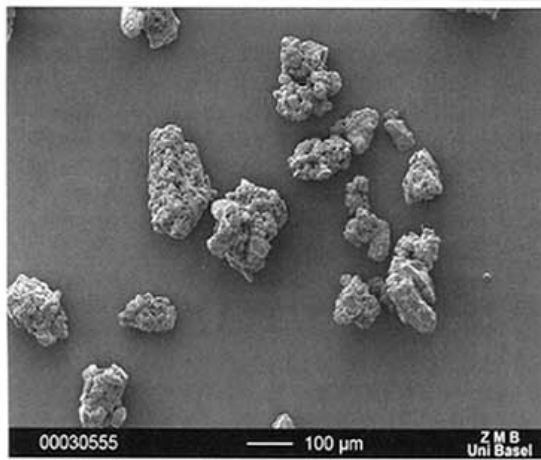
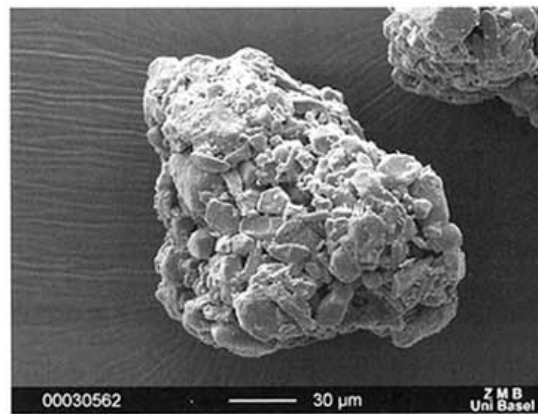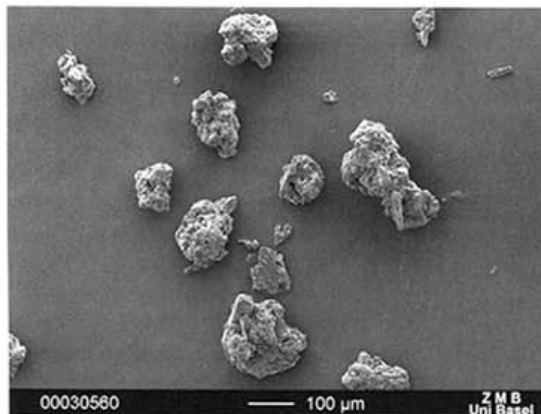**Fig. 5:** "Conventional design" granule particles (enlargement factor 100 and 500).

Fig. 6: "WIP / CIP" granule particles (enlargement factor 100 and 500).

Table 5: Content uniformity.

Equipment	Conventional design			WIP/CIP design		
Batch No.	406	407	408	409	410	411
MV (n = 10) (%)	98.3	98.6	98.2	99.2	98.9	99
Min. value (%)	96.9	96.9	95	98.6	98.1	98
Max. value (%)	99.7	102.5	100.3	99.7	100.8	101.1
RSD (%)	0.8	1.6	1.4	0.5	0.9	1

MV = mean value; SD = standard deviation; min. value = minimum value; max. value = maximum value; RSD = relative standard deviation.

stainless steel filters generate a high speed air stream which divides the powder/binder layer into many fine particles.

Under the experimental conditions the present study shows that the exchange of a conventional production unit to a novel WIP/CIP fluid-bed equipment can lead to equal granule quality. Therefore it is possible to transfer a granulating process validated on a conventionally designed equipment to a novel WIP/CIP fluid-bed unit without changing the formulation and process variables.

5. Literature

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