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Development of a quasi-continuous production line for granules - a concept to avoid scale-up problems

1. Introduction

A new plant for quasi-continuous wet granulation and multiple-chambered fluid-bed drying has been developed by Glatt AG CH-Pratteln, F. Hoffmann-La Roche Ltd. Basel and the Basel School of Pharmacy.
The system gives a new possibility for industrial manufacturing and galenical development of pharmaceutical solids specialities and has following purposes:
Automatized unattended production, withdrawing from scale-up experiments and thus a shorter development time for new specialities, with the aim of a shorter time to market. Manufacturing procedures can be simplified, validated faster, and the quality of granules, tablets and kernels compared to common production is equal until better.
Different solids specialities have been tested and validated.

2. Aims of quasicontinuous wet granulation in comparison to traditional aqueous granulation

2.1. Unattended production

One of the general aims of quasi-continuous granulation and fluid-bed drying is unattended production. The production of small subunits of 4-9 kg instead of a whole batch allows an automatized, iterative granulation and drying procedure. The division of the process into different compartments (mixing, sieving and drying compartments) guarantees the reproducibility of the galenical properties of each subunit.

2.2. Withdrawing from scale-up experiments

The granulation and drying of subunits of 4-9 kg instead of a whole batch gives the possibility to use the plant for laboratory and production scale, because the batch size is no more characterized by the machine size but by the number of produced subunits. Using the same plant in galenical research, development and production may shorten the time to market for new solids specialities.

2.3. Simplification of manufacturing procedures

Existing manufacturing procedures can be taken over from common equipment without changing components. In certain cases it's possible to simplify the procedures. The small mixer size and the geometry of the mixing elements allow to add the binders into the premixture and just to granulate with water.

2.4. Equal until better quality of granules and tablets

The quality of the produced granules and tablets is equal until better and fulfills the product specifications.

3. Results

Constant values and reproducibility of the process are important facts of quasi-continuous granulation. The tests could also show equal until better quality of granules and tablets compared to common granulation equipment (Diosna® P-600 high speed granulator)

3.1. Constant values and reproducibility

3.1.1. Yield

[Fig. 1, 2]

Fig. 1 - Yield (Formulation 1)

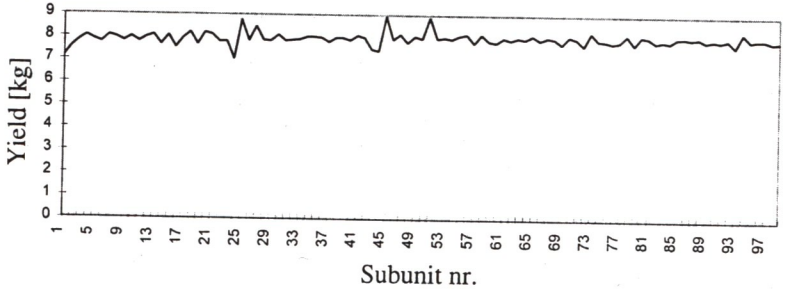
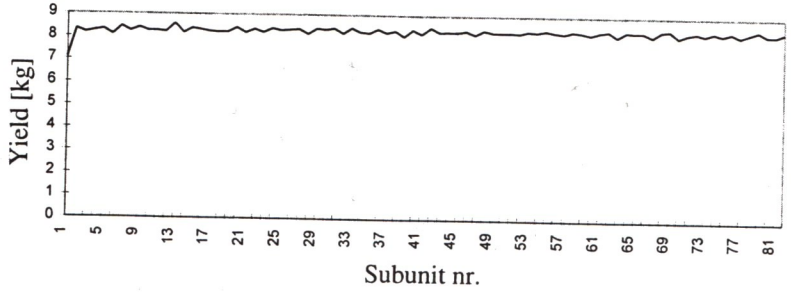


Fig. 2 - Yield (Formulation 2)



3.1.2. Sieve analysis

[Fig. 3, 4]

Fig. 3 - Sieve analysis (Formulation 1)

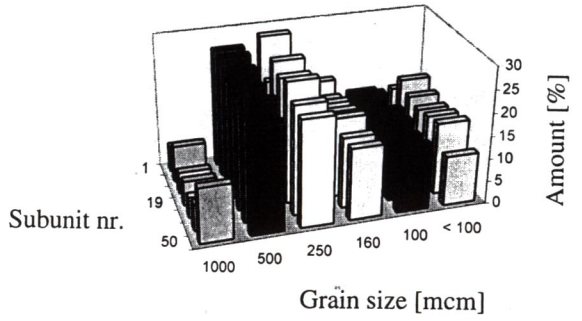
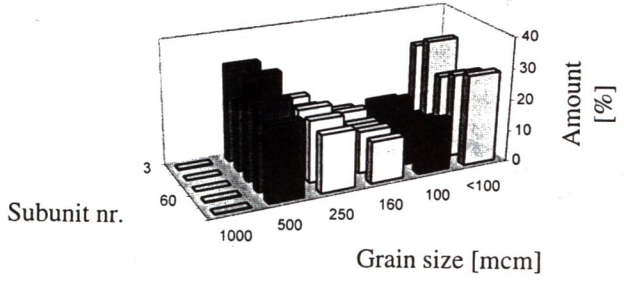


Fig. 4 - Sieve analysis (Formulation 2)



3.1.3. Bulk volume/tapped volume

[Fig. 5, 6]

Fig. 5 - Bulk volume/tapped volume (Formulation 1)

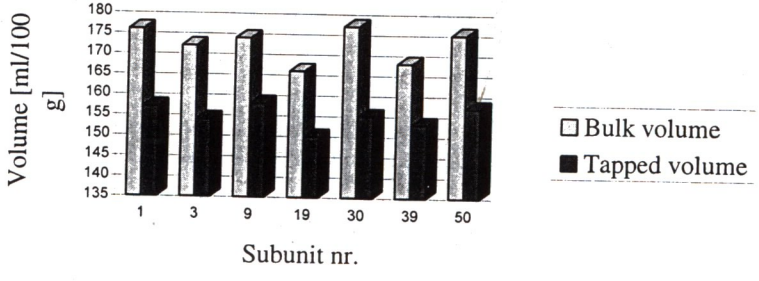
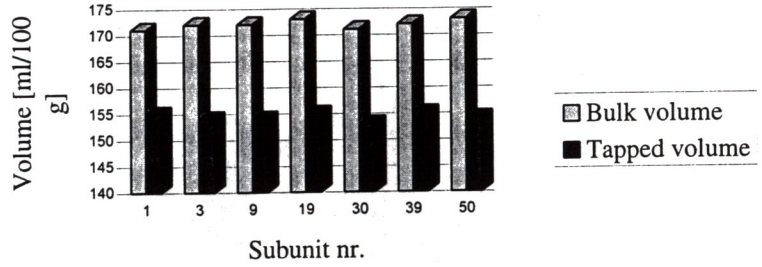


Fig. 6 - Bulk volume/tapped volume (Formulation 2)



3.1.4. Compression force/hardness profile

[Fig. 7, 8]

Fig. 7 - Compression force/hardness profile (Formulation 1)

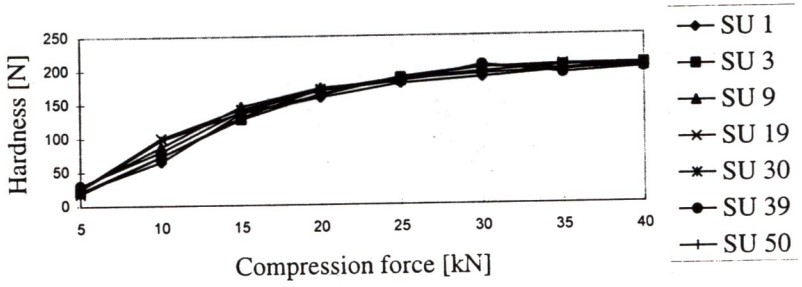
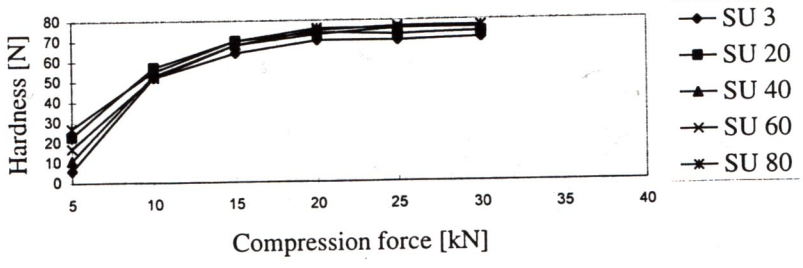


Fig. 8 - Compression force/hardness profile (Formulation 2)



3.1.5. Disintegration time in water 20°C

[Fig. 9, 10]

Fig. 9 - Disintegration in water 20°C (Formulation 1)

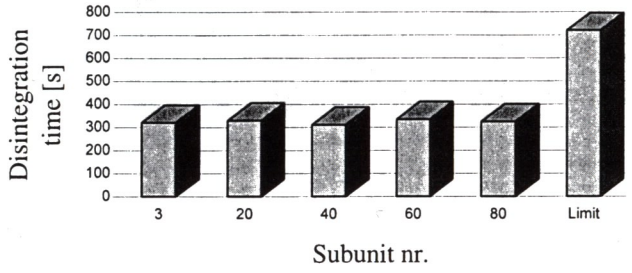
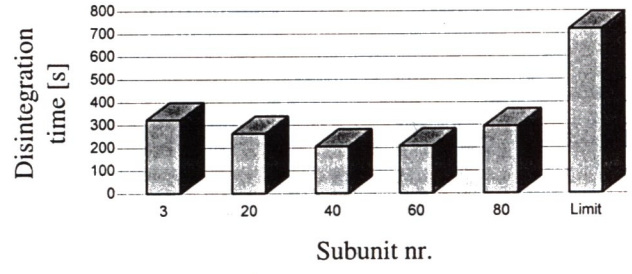


Fig. 10 - Disintegration in water 20°C (Formulation 2)



3.1.6. Friability/abrasion

[Fig. 11, 12]

Fig. 11 - Friability/Abrasion (Formulation 1)

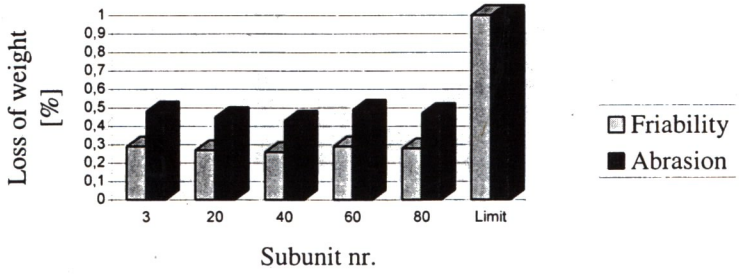
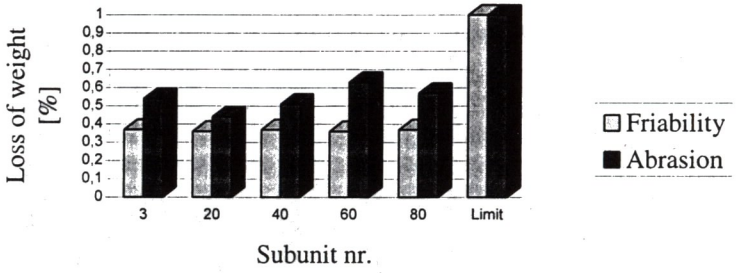


Fig. 12 - Friability/Abrasion (Formulation 2)



3.2. Comparison Glatt® Multicell - Diosna® P-600

3.2.1. Sieve analysis

[Fig. 13, 14]

Fig. 13 - Sieve analysis (Formulation 1)

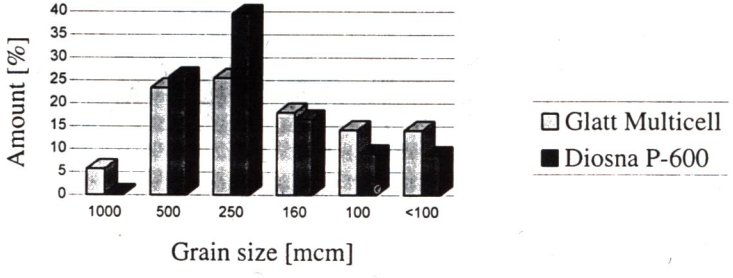
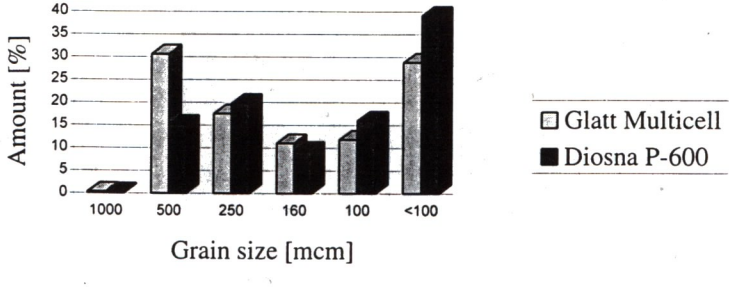


Fig. 14 - Sieve analysis (Formulation 2)



3.2.2. Compression force/hardness profile

[Fig. 15,16]

Fig. 15 - Compression force/hardness profile (Formulation 1)

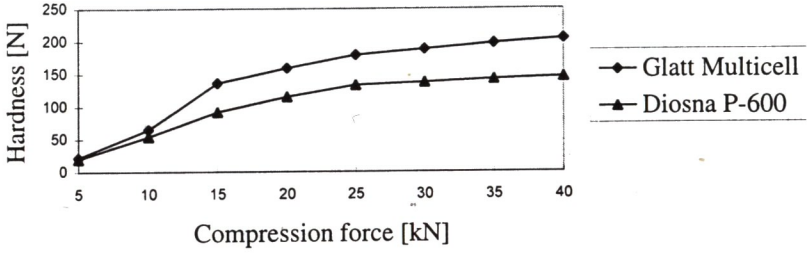
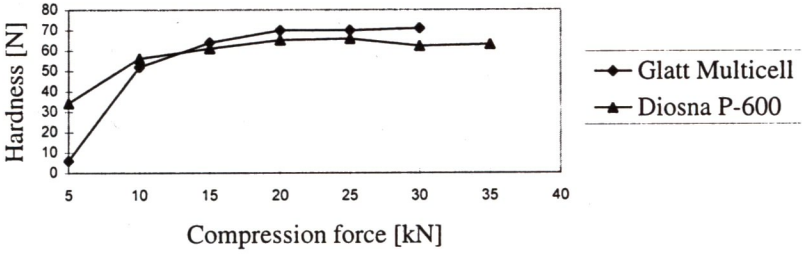


Fig. 16 - Compression force/hardness profile (Formulation 2)



4. Materials and methods

4.1. Materials

Formulation 1:	
Lactose 350 M	65,5 %
Maize starch	25,5 %
Povidone K-30	6,5 %
Primojel	2,5 %

Granulation liquid: Aqua purificata Ph. Eur. II

Formulation 2:

Lactose 350 M	68,7 %
Maize starch	27,0 %
HPMC 2910/3 cP	4,3 %

Granulation liquid: Aqua purificata Ph. Eur. II

4.2. Production parameters

Subunit size: 7,0 kg
Rotational speed of mixer: 206 rpm
Granulation liquid per subunit: 1,0 kg (Formulation 1)/1,3 kg (Formulation 2)
Spray rate: 800 g/min. (Formulation 1)/900 g/ min. (Formulation 2)
Mixing time: 85s (Formulation 1)/ 90 s (Formulation 2)
Sieve diameter: 5 mm wet sieving, 1,5/1,0 mm dry sieving
Drying temperature: 60 °C
Inlet air quantity: 600 m^3/h

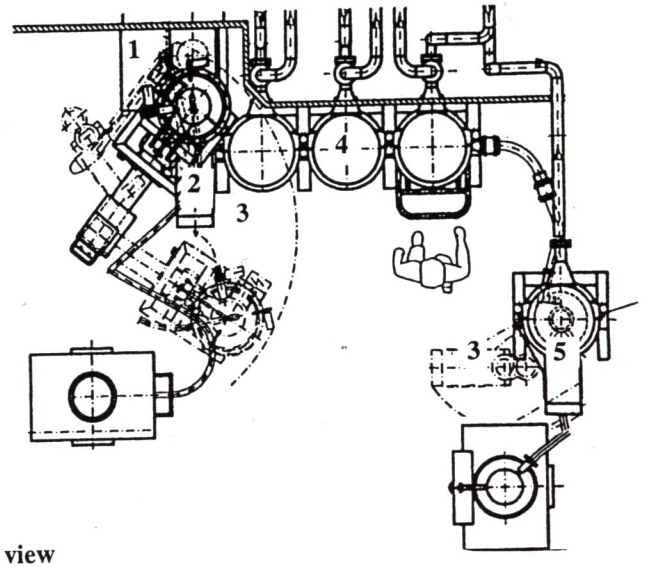
4.3. Test methods

Relative humidity (Rotronic® hygroscope)
Loss on drying (Mettler® LP 16/PM 480 Deltarange infrared balance)
Sieve analysis (Fritsch® Analysette laboratory sieving machine)
Bulk volume/tapped volume (Jel STAV® 2003 volumeter)
Compression force/hardness profile (Manesty® Deltapress tabletting machine with Tegimenta® Pharmatest PTB 301 hardness tester)
Hardness (Tegimenta® Pharmatest PTB 301 and Krämer® Computest hardness tester)
Disintegration time (Tegimenta ® Pharmatest PT 21 and Krämer® DES-2A disintegration tester)
Friability/abrasion (Roche® friabilator)

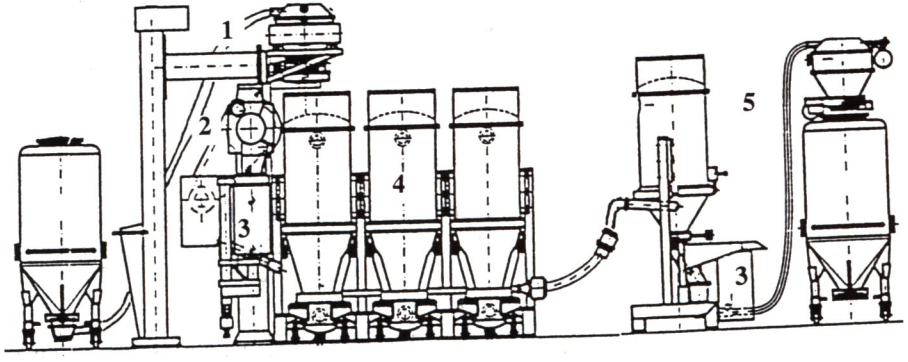
5. Description of the production plant

The Glatt® Multicell unit for quasi-continuous granulation and fluid-bed drying consists of the following elements: A transport and dosage system for mixer filling (1), a horizontal high-speed plough-share mixer (subunits of 4-9 kg of premixture can be granulated) with an airless spray pump for the granulation liquid (2), rotary sieving machines for wet and final sieving (3), a 3-chambered fluid bed dryer for predrying, final drying and cooling down to roomtemperature (4), a transport system to collect the granulated subunits in a container (5) and an integrated washing-in-place system.

5.1. Layout



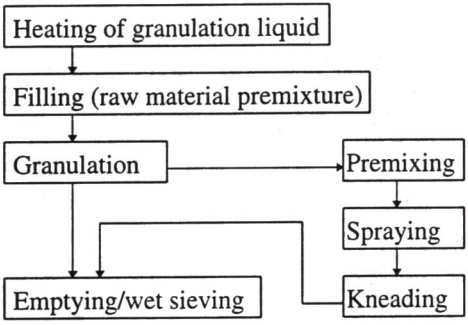
5.2. Front view



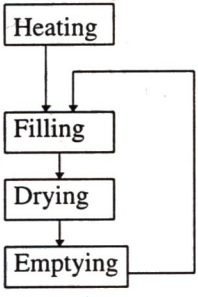
1: Transport and dosage system for mixer filling
2: Horizontal high-speed plough-share mixer
3: Rotary sieving machines for wet and final sieving
4: 3-chambered fuid-bed dryer
5: Transport system

5.3. Granulation and drying process

5.3.1. Mixer



5.3.2. Fluid-bed dryer



6. References

1) Schade A., Herstellung von pharmazeutischen Granulaten in einem kombinierten Feuchtgranulations- und Mehrkammer-Wirbelschichttrocknungsverfahren, Dissertation Universität Basel, 1992

2) Schade A., Leuenberger H., Herstellung pharmazeutischer Granulate in einem kombinierten Feuchtgranulations- und Mehrkammer-Wirbelschichttrockungsverfahren, Chem.- Ing.- Tech. 64 (1992) Nr. 11, 1016-1018

3) Dörr B., Entwicklung einer Anlage zur quasikontinuierlichen Feuchtgranulierung und Mehrkammer-Wirbelschichttrocknung von pharmazeutischen Granulaten, Dissertation Universität Basel, 1996