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DP/BIH/96/027/0730D0/11-56

BOSNIA AND HERZEGOVINA

Technical report: Findings and recommendations*

Prepared for the Government of Bosnia and Herzegovina
by the United Nations Industrial Development Organization

Based on the work of Ms. S. Kocova
UNIDO consultant

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Industrial Sectors and Environment Division

United Nations Industrial Development Organization
Vienna

* This document has not been edited.

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INTRODUCTION

As continuation of the project for Bosnalijek Pharmaceutical and Chemical Industry Ltd. (Bosnalijek) and upon recommendation of Bosnalijek management a follow-up mission was organised to supervise training of a fellowship-recipient from Bosnalijek to conduct first principle trials for a product chosen by Bosnalijek management with the aim to:

A. Allow the trainee to learn the principles of fluid-bed granulation process which will replace the conventional granulation method in the new solid dosage forms department (UNIDO project).

B. Evaluate the suitability of the fluid-bed granulation process for large scale production of the selected product.

C. Set up the processing factors affecting granule formation and define the optimal processing parameters for preparation of granulations (and subsequently tablets) of specified characteristics.

D. Determine the formulation factors, i.e. change in the formulation parameters in order to adapt the conventional granulation method previously used for the product to fluid-bed granulator.

E. Prepare documentation protocol which will represent a basis for scale-up activities and towards implementation of the fluid-bed granulation process for large scale production in Bosnalijek.

F. Recommend guidelines for follow-up activities with regards to implementation of fluid-bed granulation technique in the new solid dosage form department at Bosnalijek.

Background

During the previous mission which took place in April/May 1997 in Sarajevo with the aim to assess the conditions in Bosnalijek, it was realised that there is need for training in the technology of fluid-

bed granulation. The technology, which will be used in the new solid dosage forms department (UNIDO project), is uncertain because of lack of experience with fluid-bed granulators. It was therefore recommended that in order to implement the fluid-bed granulation method to large-scale production in compliance with CGMP consultancy is provided for research and development activities prior to scale-up and validation of the manufacturing process (Draft report, DP/BIH/96/027/11-56, May 1997).

Upon discussion with Bosnalijek management a programme was set up for a fellowship-recipient, Ms. A. Kurtovic, head of solid dosage forms department, to carry out first principle trials for a priority product of Bosnalijek under supervision of UNIDO consultant. The facilities (not available at Bosnalijek) were provided by the Pharmaceutical Institute of the University of Basle, Switzerland, where a laboratory fluid-bed granulator, Type Strea-1 of capacity 0.2-2 l was rendered available for the study for the period, August 11 to 23 , 1997.

The outline of the programme of activity and description of the trials as well as the results of the test are described in full in the section entitled *Activities* and in the attached Annex 3.

SUMMARY

The fluid-bed granulation involves three major phases: premixing of the powder components, granulating with a suitable binder solution and drying to a suitable moisture content. All these operations are performed in a single piece of equipment, the fluid-bed granulator (FBG). Total processing hours in the fluid-bed process are considerably shorter in comparison to the conventional granulation method. Typically a two-fold decrease in total processing hours per kg batch results from incorporating a FBG in the manufacture of a solid dosage form. Other advantages of the fluid-bed technique are:

- there is better homogenization of the product due to the continuous fluidisation of the powder bed;

- the granules obtained by the fluid-bed technique are of lower density, are more spherical and have narrower size distribution;

- in comparison to the wet granulation method the product has superior flow properties which contribute to better tablettability on high-speed compression machines.

Because the mechanisms of granule formation and the effect of the process variables on the properties of the granules differ considerably between the two processes, unique problems are encountered during development and scale-up stages when a conventional granulation procedure is adapted to a FBG.

Although most products are suitable for fluid-bed granulation and have the potential to be manufactured in a FBG, a carefully planned feasibility study and an extensive process review followed by scale-up procedures are required in order to successfully convert the existing manufacturing method to a fluid-bed granulation process.

The following report illustrates the development activities which were required in order to convert a formula based on diclofenac sodium from the originally used wet granulation method to a fluid-bed granulator.

First principle trials for the development of diclofenac tablet were conducted in a laboratory scale FBG as part of a training seminar for a trainee from Bosnalijek.

The principles of the fluid-bed process and the operation of the apparatus were introduced as described in part A of *Training Activities* .

The product and its potential to be granulated in the fluid-bed granulator are described in section B of the training.

A number of process variables which have an effect on the properties of the granules were investigated and are described in detail under section C of the training.

The formulation factors and the need for change in the formula in order to successfully convert the product from wet granulation to a granulation in the fluid-bed were also investigated as described in section D of the training activities.

The effects of all the variables investigated on the physical properties of diclofenac-containing fluid-bed granulations were characterized and are documented in Table 3.1 and 3.2 of *Annex 3*.

The results of the first principle studies and the information gathered during the development stage (laboratory phase) can be used as a basis for scale-up activities (pilot plant and production scale-up phase) which can begin only after a number of identified process variables have been tested.

The documentation of the data obtained during the development phase is essential in order to determine which parameters of the process can be used as possible tools to ensure quality control of the product in compliance with CGMP. The documentation protocol may be helpful in solving technical questions that might arise in later phases of production and in validation of the process if the process is implemented.

For the initial development trials a table-top FBG, e.g. an Aeromatic, Type Stea-1 is recommended as most suitable size. Provided that it is procured with the options for fluid-bed drying and for coating, it can also be used in first principle trials when adapting the fluid-bed method for drying of granules prepared in the high speed mixer and for coating of products.

However, although laboratory scale granulation is essential for the first principle trials, it is recommended that proper feasibility studies for scale-up should be conducted with at least 15 kg batch.

Recommendations for equipment and batch size were made as follows:

- for the development phase, e.g. a laboratory fluid-bed apparatus (Aeromatic, Type Strea-1) and
- for the scale-up activities, e.g. a minimum batch size of ~ 15 kg.

Essential (minimum) equipment and apparatus as well as methods for testing of physical properties of the granules were also recommended as indicated in Annex 2.

Adequate literature on the relevant subjects to assist in development and scale-up activities involving other products at Bosnalijek is listed in Annex 4.

RECOMMENDATIONS

The recommendation listed below were made bearing in mind the future tasks by the R&D, Production and QC/QA departments at Bosnalijek with regards the activities to convert all old products from conventional granulation to fluid-bed granulation process or to develop new products for granulating and/or drying using the fluid-bed technique.
These tasks should have the aim to:

1. Limit the fluid-bed granulation process to granulation with water. This is necessary because of : a) environmental considerations, b) reduced safety risks and c) avoiding spray-drying which happens when organic solutions are employed.

2. Select the product - candidates by conducting preformulation studies on the starting material especially the active ingredient. This is necessary in order to determine whether the product under development is suitable or not for manufacture by the fluid-bed technique and whether (in the latter case) enhancement of the properties of the drug will be economically justified. For example: for a readily soluble drug the granule formation in fluid-bed is easier than for a drug with poor water solubility and wettability. This implies that if aqueous process is to be used, more extensive development is needed in the latter case in order to adapt the fluid-bed granulation technique (binder-type, addition of suitable tenside etc.). Water insoluble drugs on the other hand represent a real challenge and decision-making based on cost effectiveness.

3. Since granulation in fluid bed is very much affected by the physical properties of the starting materials these must be held within the specified range to avoid revalidation activities. The effect of particle size distribution of the active ingredient is illustrated in Table 3.2 which compares data obtained with two grades of diclofenac sodium.

4. Development studies in the form of first principle trials are necessary to characterize each product. Sufficiently robust formulations (e.g. the diclofenac formula studied during the training activities) can be manufactured in the fluid-bed granulator once the parameters and the scaling-up factors have been determined. Other products may be difficult to convert to fluid-bed system. In such cases the fluid-bed granulator can serve as a fluid-bed drier and the granulation process can be conducted in the high speed mixer. Fluid-bed drying too requires

first principle trials and scale-up activities as the fluid-bed granulation process. (Consideration must also be given to the capacities of both equipment which should be compatible with one another.)

5. Scaling up: Parameters which need scaling-up activities include inlet air temperature during the granulating stage, binder spraying rate, the ΔT value (or the difference between the product temperature at the endpoint and at the equilibrium) and the total process time. In general the scaling-up activities will involve feasibility trials with 10-15 kg, since the parameters determined with smaller product size can not be used directly for larger scale production. In the absence of equipment for such trials a contracting manufacturer or the equipment supplier's facilities can be used.

6. Validation : For the first-time-use equipment it is recommended to choose a *prospective product validation* (solid dosage formulation) and *process validation* (fluid-bed granulation or fluid-bed drying).

   a. Equipment : On the basis of the preliminary experiments carried out during the training seminar and in order to fully utilize the Aeromatic fluid-bed granulator (UNIDO project), first principle trails during development stage need to be conducted for both old and new products. Old products, i.e. those based on conventional granulation method, may have to be reformulated: change in formulation may involve binder concentration and amount of water needed for granulation. The experimental data shown in Table 3.2 (Annex 3) indicate that fluid-bed granulation required higher binder concentration and larger amounts of liquid for granulation of diclofenac than the wet granulation method. New products can be developed directly for fluid-bed granulation or fluid-bed drying The need for a laboratory fluid-bed apparatus must therefore be given a high priority. For first principle trials a Strea-1 laboratory apparatus is recommended equipped with options for fluid-bed drying and fluid-bed coating. Furthermore, equipment for physical testing of granules is also needed for the evaluation of the physical properties of the granules. Basic equipment for testing along the lines described in the present training activities is listed in Annex 2.

ACTIVITIES

Outline of working programme for the implementation of the fluid-bed granulation process for manufacture of solid dosage forms as part of UNIDO project for Bosnalijek

Trainee:	UNIDO fellowship recipient as part of humanitarian aid for Bosnalijek, Sarajevo, Bosnia and Herzegovina
Time duration:	11 - 23 August 1997.
Place of training:	University of Basle, Basle-Switzerland (courtesy of Pharmaceutical Department of University of Basle).
Equipment:	Laboratory fluid-bed granulator, Strea-1, capacity 1 - 1.5 *l*.
Product:	Diclofenac Sodium tablet.
Supervisor:	UNIDO consultant, project number DP/BIH/96/027/11-56.

This working programme was prepared with the objectives as outlined in the section *Introduction.*

A. Training of the fellowship-recipient in the operation of the fluid-bed granulator and in the principles of the fluid-bed granulation process.

B. Evaluation of the suitability of the fluid bed granulation process for a large scale production of the product.

C. Setting up of processing factors affecting granule formation and selection of the optimal processing parameters for preparation of tablets of specified characteristics.

D. Determination of the formulation factors, i.e. change in formulation parameters in order to adapt the conventional granulation method previously used for this product to fluid bed granulator.

E. Preparation of documentation protocol which will represent the basis for scale-up activities towards implementation of the fluid-bed granulation process for large scale production in Bosnalijek.

F. Recommendations and guidelines for prospective validation of the product/process development on the example of the selected product.

Training Activities

A. Training of the fellowship-recipient in the operation of the fluid-bed granulator and in the principles of the fluid-bed granulation process

1. Background

Because the technique is new to Bosnalijek, experience in the principles of operation and in the technicality of the apparatus is lacking. Experiments were therefore carried out to familiarize the trainee with the technique. This involved a series of experiments to be run with a placebo formulation of the product.

2. Apparatus

The apparatus used in the study was an AEROMATIC table-top laboratory fluid-bed granulator, Type Strea-1, Aeromatic-Fielder AG, Bubendorf, Switzerland, with two-fluid nozzle system and a peristaltic pump for the delivery of the binder solution. The apparatus is suitable primarily for the first principle trials. The apparatus is equipped with an exhaust ventilator and air heating aggregate which draw and pre-heat the environmental air in the powder container through a distributor and a double sieve (300 μm). The air escapes through the exhaust air filter consisting of four filter bags, which are cleaned in a consecutive order every 15 sec. by compressed air. A two-fluid nozzle for spraying of granulating solutions can be placed in three different position determining the distance from the powder bed.

3. Method

For this activity three experiments were conducted based on the following placebo formula using aqueous binder solution:

Lactose	86% w/w	for 500 g :	430 g
Maize starch	10% w/w		50 g
PVP K30	4% w/w		20 g

N.B. : For all experiments, it was important to introduce the amount of water equivalent to ~30% w/w calculated on the total load.

Placebo experiment 1:

Total load = 500 g

Binder solution = 10% w/w ; 200 ml (containing the total of 20 g PVP + 160 ml water = 32%)

Nozzle position : middle

Spraying rate: beginning ~ 6 g/min. then increase to 9 g/min.

Inlet air temperature: during granulation: R.T.; during drying: 40 ∘C.

Result: fine granules with narrow range of particle sizes.

Placebo experiment 2:

As in exp. 1 except:

Total load = 400 g

nozzle position : low

Result : not much bigger granules

Placebo experiment 3:

As in exp. 2 except:

Binder solution : 20% w/w (contains 16 g PVP in 80 g solution i.e. 64 g water; since 30% of 400 g =120 g the rest 120-64=56g is added after introducing the 80 g of the binder solution).

Result : larger granules obtained.

4. Conclusions

As a result of these activities the trainee was aquaint with the operation of the apparatus and was able to select and vary the parameters which will affect the end product. This was an appropriate preparation for conducting the activities described under the following headings (B - D).

B. Evaluation of the suitability of the fluid bed granulation process for a large scale production of the product

1. Introduction

To evaluate the suitability of the method for the selected product it is important to determine the ability of the components (active ingredient and excipients) to form granules in the fluid-

bed granulator. Since the later is determined by the solubility of the active ingredient it is important to determine whether water or organic solvent will be used in the process.

In view of environmental concerns and safety risks involved with organic solvents, water granulation was the method used. With water soluble drugs this is easily accomplished. If the substance exhibits poor wettability but it is readily soluble in water, the method can be applied upon rendering the substance more easily wettable, e.g. by introducing in the formula a surface active agent which can reduce the angle of contact of the drug. The problem arises when the drug is insoluble and has poor wettability in which case organic solvent can be avoided only by selecting a soluble form of the drug or solubilization of the drug prior to granulation. Cost effectiveness of the procedure will play important role in the final decision regarding the suitability of the fluid-bed method for the particular product.

The physical properties of the starting materials are other important factor to be considered and it is recommended that preformulation studies are made to determine the range of variation in these properties which will maintain the process suitable for the product.

2. Product

The product selected for the training course was suggested by the management of Bosnalijek. It reflects high priority for the new unit for solid dosage forms. The product was originally developed for the conventional wet granulation method. Thus the implementation of fluid bed granulation if evaluated as a suitable technique represents change in manufacturing process and involves process validation activities during development and scale-up to ensure that the product manufactured at the production site meets specific quality for GMP compliance.

The product formula for granulations for the un-coated tablet included: Diclofenac Sodium as the active ingredient and Lactose 200 mesh, Maize Starch, Microcrystalline Cellulose (Avicel PH 102) as excipients, and Polyvinylpyrrolidone, PVP K30 as binder. All the materials except for the active ingredient were obtained from the Pharmaceutical Institute in Basle.

The active ingredient used for the experimental work was shipped from Bosnalijek. This was necessary because Bosnalijek uses two sources for Diclofenac which had different appearance. In order to specify the active ingredient sieve analysis was performed using a laboratory Air

jet sieve 200 (Alpine AG, Germany). The two types of Diclofenac Sodium differed significantly in their particle size and distribution.

Diclofenac C (coarse): 48% < 125 μm; 28% < 90μm; 20% < 63 μm; 10% < 45 μm.
Diclofenac F (fine): 82% < 125 μm; 72% < 90 μm; 54% < 63 μm 22% < 45 μm.

3. Conclusions

Preliminary experiments using both types of diclofenac showed that the fluid-bed granulation method is suitable for manufacturing granulations based on the formula used in the conventional granulation method. The granules obtained in the fluid-bed system however differ from those from the conventional method and in order to vary their particle size within the existing formula a series of activities described bellow were planned whereby the process parameters affecting granule size were varied.

C. Setting up of processing factors affecting granule formation and selection of the optimal processing parameters for preparation of granules (and subsequently tablets) of specified characteristics

1. Processing factors affecting granule formation

This involved setting up of the major processing parameters since they influence the physical properties of the granulations and thus the performance of the tablets prepared from these granulations. Processing factors studied included:

- height of the spraying nozzle over the fluidized solids
- temperature of the fluidizing air during the granulating phase
- temperature of the fluidizing air during the drying phase
- rate of binder addition
- time for pre-mixing in the fluidized state
- time for drying to reach equilibrium moisture content of the product

Summary of the process parameters investigated is given in Table 3.1 in Annex 3. The physical properties of the granules obtained from optimization of the process parameters are summarized in Table 3.2 in Annex 3.

2. Conclusions

On the basis of the data obtained during this activity it can be concluded that the process parameters can influence the properties of the granules within a limit of particle size and size distribution. The product in all the cases was however finer than the expected and in order to increase its size it is necessary to change the original formulation in order to accommodate for higher amount of binder per batch size. This was studied in the series of experiments described below.

D. Determination of the formulation factors, i.e. change in formulation parameters in order to adapt the conventional granulation method previously used for this product to fluid bed granulator

1. Selection of the optimal formulation parameters for preparation of fluid-bed granulations based on diclofenac.

The critical formulation factor affecting granule formation is the concentration of the binder. Since generally the fluid-bed method requires higher binder concentration than the conventional method, the amount of binder (PVP) may have to be adjusted to obtain satisfactory granule formation. This will involve modification of the amounts of the other excipients (e.g. lactose or maize starch).

Other important factor is the amount of liquid (water) needed for building the granules. Due to the different mechanisms involved in the two processes, higher amount of liquid is required in fluid-bed method compared to the conventional wet granulation.

A series of experiments was therefore conducted in order to study the following formulation parameters:

- binder concentration (% of total mass)
- strength of spraying solution
- amount of water added as spraying solution and as pure water
- type of diclofenac (coarse or fine)
- addition of avicel to the granulating mass

In order to evaluate the effect of the above parameters the following physical properties of the granules obtained were tested (see Annex 2):

- particle size expressed as mean and median size;
- size distribution expressed as % of fraction < 90 μm;
- powder flow properties expressed as the time needed for a known amount of powder to flow through an opening of a given size;
- density / porosity expressed as bulk, tap density and the Hausner Factor;
- wear resistance / friability expressed as the amount of fines obtained during a defined number of rotations in Roche friabilator or a suitable mixer.

A detailed summary of the formulation parameters and the physical properties of the resulting granules is given in Table 3.2 in Annex 3.

2. Conclusions

Based upon the granules properties the following conclusions can be drawn about the optimal formulation parameters for the product under study.

In order to obtain granules with properties comparable to those obtained from the conventional granulating method the amount of binder and the quantity of spraying liquid will have to be increased when converting to fluid-bed granulator.

E. Preparation of documentation protocol which will represent the basis for scale-up activities towards implementation of the fluid-bed granulation process for large scale production in Bosnalijek

Useful information regarding the scaling-up factors in adapting a conventional granulating process to a fluid bed granulator can be obtained from the first laboratory trials of the product in development similar to those conducted during the training. Documentation protocol outlining the experience and the results of the trials can be used as a basis for scale up activities towards implementation of the fluid bed granulator for large scale production. For example the comprehensive list of the results of the trials tabulated as shown in Annex 3 represents basis for such documentation protocol. This is because during the early stages of

development it is possible to fix some process parameters necessary to achieve uniform spraying of the binder solution into the fluidized powder bed. These include: nozzle height (i.e. nozzle setting in Table 3.1), nozzle orifice size (i.e. 0.8 mm in Table 3.1) atomizing air pressure (i.e. 1 bar in Table 3.1), the rate of spraying of binder solution and the volume and the temperature of the fluidizing air (i.e. spray rate and inlet air temperature in Table 3.1). The values at which these parameters are fixed depend upon the height of powder bed and the viscosity of the binder solution. During the development stage it is also possible to fix some formulation parameters. These include the amount of binder needed for granule formation, normally between 3% and 5% w/w calculated on the total mass in the container (i.e. binder conc. in Table 3.2), and the strength of the binder solution used for spraying (i.e. spray solution in Table 3.2).

Scale-up activities can begin with ~ 15 kg batch size. The parameters obtained with this size can be scaled-up directly to a batch size of ~ 100 kg, although larger production (i.e. up to 600 kg) may require several levels in order to be scaled-up. Tables of scale-up factors which summarize the processing parameters in fluid-bed granulators at four levels of scale-up can be found in Reference 4.2.1 in Annex 4. Although they were developed for Glatt granulators, the relationships among the various processing parameters can be applied to the Aeromatic granulators of equivalent sizes (i.e. Glatt-500 corresponding to Aeromatic S-9, etc.).

Conclusions

Based on the findings during the present training activities, a feasibility and scale-up program is needed for each product in order to convert successfully from the conventional wet granulation method to a process based on fluid-bed granulation.

F. Recommendations and guidelines for prospective validation of the product/process development on the example of the selected product

Validation of a pharmaceutical product and/or process is required in order to 1- confirm to CGMP, 2- avoid the possibility of rejected or recalled batches, 3- ensure that the marketed product consistently meets the specified quality requirements. Although validation is usually associated with full-scale production, the documentation of the earlier development steps of the product and/or process is critical to the subsequent validation of scaled-up batches. The

activities pertaining to validation start during the development when pertinent data or information is collected and generated in order to determine which parameters of the process can be used as possible tools for monitoring of the product. It is therefore important to prepare a documentation of all the data collected during the first principle trials in order to use them as a basis in the further process and during full-scale manufacture. For example, the tabulation of data collected during the first principle trials for diclofenac tablet (see Tables 3.1 and 3.2) to support the validation of the fluid-bed granulation process can be an useful guide in the development of other products at Bosnalijek.

Prospective validation - Implementation of the fluid bed granulator (Aeromatic) for large-scale production in the solid dosage unit requires process validation for both the old products which will be switched from the conventional granulating process to fluid bed granulation/drying and for any new products to be manufactured in the fluid bed granulator. In both cases and especially in the case of a new product development a prospective validation is the more reasonable approach, since it makes validation an integral part of a planned product/process developmental programme.

A comprehensive guide to pharmaceutical process validation in compliance with CGMP can be found in Reference 4.3.1 in Annex 4.

ACKNOWLEDGMENTS

This training seminar was made possible by the Pharmaceutical Institute of the University of Basle who provided free facilities and materials for the experimental work. Special acknowledgments are due to Professor H. Leuenberger for valuable discussions related to fluid-bed granulation of pharmaceuticals and to his entire staff for their assistance and support.

ANNEXES

Annex 1

JOB DESCRIPTION*

Post title Quality Assurance Specialist

Duration 1 month

Date required beginning April 1997

Duty station Sarajevo, Bosnia and Herzegovina

Duties In co-operation with the Team Leader, the international consultants and the national consultant (National Project Director), the quality assurance specialist shall carry out the following duties:

1. Assess and review the conditions at Bosnalijek.
2. Assist in preparing the final list of QA/QC equipment to be procured.
3. Assist in installing, validating and running up of the facilities in compliance with current good manufacturing practices (CGMP).
4. Prepare a list of equipment to be procured specifically for quality assurance such as the office equipment.
5. Organize in plant training courses in quality assurance and CGMP at all levels. Assist in improving the quality assurance system in compliance with CGMP.
6. Prepare a detailed report on the above work.

Qualifications: Quality assurance specialist/ industrial microbiologist/ industrial pharmacist/ chemical engineer/ chemical analyst with personal experience in developing countries and countries of transition economy.

Language: English

* See Amendment to special service agreement - Expert on mission

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Annex 2

LIST OF APPARATUS, EQUIPMENT AND TESTING INSTRUMENTS USED FOR PREPARATION AND CHARACTERIZATION OF FLUID BED GRANULATIONS

1. Fluid bed granulation: AEROMATIC table-top laboratory fluid-bed granulator, Type Strea-1, Aeromatic-Fielder AG, Bubendorf, Switzerland.
2. Moisture content measurement: 110 ∘C; 10 minutes; Mettler LP16 IR Dryer.
3. Sieve analysis: Particles > 70 µm; method DIN 53477 with sieves in geometrical order with factor √2 (at least 5 sieves): 1000, 750, 500, 355, 250, 180, 125, 90 µm; sample size = 100 ± 0.1 g ; time = 10 min. Apparatus: Shaker sieve, Type Vibro, Retsch GmbH, Haan, Germany. For determination of parameters of the particle size distribution: computer program using Excel 5.0 (courtesy of Pharmaceutical Institute, University of Basle). For particles < 70 µm; apparatus: Laboratory Air-jet Sieve® 200, Alpine AG, Augsburg, Germany.
4. Bulk density : Method DIN 53912 with 100 ± 0.1 g in 250 ml graduated cylinder.
5. Tapping density : Method DIN 53194 according to Engelsman using at least 1250 taps.

Annex 3

SUMMARY OF RESULTS OBTAINED DURING TRAINING COURSE ON FLUID-BED GRANULATION

1. Summary of process parameters investigated for converting conventional granulation of diclofenac tablet to fluid-bed granulator

Exp	Nozzle	Inlet Air[c] Temp		Binder	Process Time (min)			Endpoint data		
#[a]	Setting[b]	Granu-lating °C	Dry-ing °C	Spray Rate g/min	Mixing	Granu-lating	Drying	Inlet Air °C	Outlet Air °C	Moist. Cont. % w.b.
1	low	38	50	5 ; 11	3	12	30	60	29	5.7
2	low	50	60	na	2	11	14	70	32	4.3
3		pump	failed							
4	low	40	50	8 ; 10	2	15	20	na	na	6.6
5	low	30	60	6 ; 7	2	14	21	68	33	na
6	low	30	60	10	5	10	20	60	31	6.7
7	low	40	60	15	2	8	na	na	na	6.7
8		spoilt:	rate	too	high					
9	middle	40	60	7 ; 12	2	15	15	84	30	8
10	middle	40	60	8.6	3	15	20	80	32	na
11	middle	40	60	9	3	23	25	69	33	4.8
12	middle	60	65	8 ; 15	3	17	9	77	30	9
13	middle	40	70	12 ; 15	2	16	13	84	30	9.8
14	middle	50	70	12 ; 15	2	17	16	75	30	9
15	middle	50	70	12 ; 15	3	18	17	84	28	10
16	middle	50	70	13 ; 15	3	13	18	86	31	na
17	middle	50	80	13 ; 15	3	12	25	81	32	~8
18	middle	50	80	13 ; 15	3	14	20	90	31	na

a) all experiments were with 500 g powder
b) low = 24 cm, medium = 28 cm from bed support plate; nozzle orifice size: 0.8 mm; atomizing air pressure: 1 bar
c) the inlet air was adjusted so as to obtain complete fluidization; max = 130 m^3 /min.; av. air throughput for the experiments was ~ 50 m^3 /h

2. Formulation parameters and physical properties of granules investigated for converting conventional granulation of diclofenac tablet to fluid-bed granulator

Exp #	Binder Conc. (total) (%)	Spray Solut. (%)	Amount added as Solut. (g)	Water (%)	Type Dicl. C/F[a]	Avi-cel (%)	Physical Properties of Granules Mean / Median (µm)	<90 µm (%)	Bulk Dens. (g/ml)	Tap Dens. (g/ml)	HF[b]
1	2.25	7.5	150	27.8	C	0	196/187	12	0.41	0.48	1.16
2	2.25	7.5	100	18.5	C	0	na	na	na	na	na
3	2.25	20	exp. stopped; pump failure								
4	2.25	7.5	100	18.5	C	0	180/169	20	na	na	na
5	2.25	15	100	17.8	C	0	na				
6	2.25	15	100	17.8	C	0	237/210	21	na	na	na
7	3.7	15	125	21.3	C	0	258/224	30	0.41	0.48	1.17
8	spoilt										
9	3.7	10	120	21.7	C	0	167/158	23	0.41	0.48	1.17
10	3.7	10	160	28.8	F	0	267/217	17	0.40	0.48	1.17
11	3.7	10	188	33.8	F	0	145/135	28	na	na	na
12	2.9	10	188	33.8	F	23	177/161	19	0.21[c]	0.39	1.36
13	5	10	188	33.8	F	0	258/226	12.6	0.36	0.41	1.12
14	5	10	250	45	F	0	313/290	2..9	0.35	0.38	1.09
15	5	10	250	45	F	23	252/222	5.7	0.33[c]	0.37	1.13
16	5	15	167	28	F	0	220/198	11.9	0.33	0.39	1.17
17	5	15	167	28	F	0	289/267	6.7	0.34	0.39	1.14
18	5	15	167	28	C	23	251/232	8.5	0.33[c]	0.38	1.14

a) C/F ; C = coarse diclofenac sodium (28% < 90 µm)
F = fine diclofenac sodium (72% < 90 µm)
b) HF is the Hausner Factor: HF = Tap density/ Bulk density
c) measured with 50 g only of granules

Annex 4

RECOMMENDED READING

Fluid-bed granulation

1. Factors to consider in fluid-bed processing: D. M. Jones, Pharmaceutical Technology, April 1985, 50-62.
2. Fluidized bed granulation - factors influencing the quality of the product: M. E. Aulton and M. Banks, Int. J. Pharm. Tech. & Prod. Mfr., 2 (4), 1981, 24-29.
3. Batch production of pharmaceutical granulations in a fluidized bed I: effect of process variables on physical properties of final granulation: W. L. Davis and W. T. Gloor, J. Pharm. Sciences., 60 (12), 1971, 1869-1873.
4. Some factors influencing the properties of tablets made from fluid-bed granulations: S. K El-Arini and J. Polderman, Drugs made in Germany, 26, 1983, 205-211.
5. Evaluation of small scale fluidized bed granulation unit: M. C. R. Johnson, J. E. Rees and F. Sendall, J. Pharm. Pharmacol., 27, 1975, Suppl. 80P
6. Wirbelschichtgranulation - Verfahrensoptimierung mittels Factorial Design: S. K. El-Arini, Pharm. Ind. 43 (70, 1981, 674-679.

Scale - up

1. Fluid-bed granulation: factors affecting the process in laboratory development and production scale-up: A. Y. Gore, D. W. McFarland and N. H. Batuyios, Pharmaceutical Technology, September 1985, 114-122.
2. Scale-up factors in adapting a conventional granulating process to a fluid-bed granulator: F. A. Rowley, Pharmaceutical Technology, September 1987, 76-79.

Validation

1. Pharmaceutical process validation: I. R. Berry and R. A. Nash (eds), Marcel Dekker Inc., 1993, pp. 167-248.
2. Principles of qualification and validation in pharmaceutical manufacture: T. Berg, P. Humphreys and B. Scherz, Convention for the mutual recognition of inspections in respect of the manufacture of pharmaceutical products, Document PH 1796, January 1996.