Acta Poloniae Pharmaceutica – Drug Research, Vol. 68 No. 5 pp. 725–733, 2011 ISSN 0001-6837
Polish Pharmaceutical Society

ANALYSIS OF WET GRANULATION PROCESS WITH PLACKETT-BURMAN DESIGN – CASE STUDY

KRZYSZTOF WOYNA-ORLEWICZ and RENATA JACHOWICZ*

Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University, Faculty of Pharmacy, 9 Medyczna St., 30-688 Kraków, Poland

Abstract: According to Process Analytical Technology perspective, drug product quality should be ensured by manufacturing process design. Initial step of the process analysis is investigation of critical process parameters (CPPs). It is generally accepted to type the CPPs based on project team knowledge and experience [5]. This paper describes the use of Design of Experiments tool for selection of the CPPs. Seven factors of wet granulation process were investigated for criticality. Low and high levels of each factor represented maximal and minimal settings of wide operational ranges. Granulates were produced in line with Plackett-Burman experimental matrix, blended with extra-granular excipients and compressed into tablets. Semi-products and final products were tested. Out of specification result of any critical quality attribute was treated as critical failure. The high-shear granulation factors, i.e. quantity of binding solution, rotational speed of impeller and wet massing time were considered of critical importance. Operational ranges of the parameters were optimized. The process performance was confirmed in qualification trials.

Keywords: criticality assessment, high-shear granulation, tablet manufacturing, Plackett-Burman, PAT, Quality by Design

Number of factors that impact drug product quality have driven worldwide regulatory authorities to modernize good manufacturing practices (GMP). The motto of XXI century GMP is "quality cannot be tested into products; it should be built-in or should be by design"(1).

Quality can be built-in the drug product by comprehensive understanding of many aspects related to its destination and manufacturing. The FDA's idea of Process Analytical Technology (PAT) treat the understanding as a cornerstone for innovativeness and risk-based regulatory approach (2).

The understanding is gained during drug product development stage. Extensive knowledge of active pharmaceutical ingredient (API) should be gathered with special interest in its chemical, physical and biopharmaceutical properties. Drug product Critical Quality Attributes (CQA) should be listed out and quantitatively described by target values and acceptance criteria. Excipients and packaging systems should be carefully selected taking into consideration drug product destination, patients compliance, API stability and pharmacokinetics as well as manufacturing process suitability.

The manufacturing process is well understood when target product profile is defined, product composition and production route are established, critical process parameters (CPP) are selected, control methods developed, proven acceptable ranges (PARs) and design space are established (3).

Level of the process understanding seems to be in an inverse relationship with risk of producing poor quality products. Therefore, scientific understanding of processes would substantially facilitate implementation of changes.

Among many development strategies, statistical Design of Experiments (DoE) is considered as the most beneficial tool for the scientific knowledge acquisition, since it is relevant for multi-factorial relationships investigation (2). Generally, for test of k factors each at 2 levels, the factorial design requires 2^k runs of experimentation. As the number of factors or levels increases, the number of runs increases rapidly: 4 factors at two levels need to be tested within 16 runs but 6 factors at two levels require 64 runs (4).

Since technological processes have many input and output variables, i.e., operational parameters

* Corresponding author: e-mail: mfjachow@cyf-kr.edu.pl

(speed, time, etc.) and possible product outcomes (dissolution, friability, etc.) it looks impossible to test all of them in a structured and organized manner, e.g., by application of DoE method. Therefore, it is accepted to use prior knowledge to establish the most important parameters, the so-called CPPs (3, 5). The CPPs are parameters whose variability in limited range impact drug CQA and hence should be monitored or controlled to ensure that the process produces the desired quality (6). Considering drug products as complex multifactorial systems, process parameters could influence quality attributes in a unique manner, hard to be estimated based on prior knowledge and single experiments (2). Therefore, to minimize risk of inadequate selection of the CPPs, it is proposed to use Plackett-Burman experimental design to screen out number of parameters in line with DoE principia. The design attributed to Plackett and Burman is a two level fractional factorial design. It enables to study $k = N\text{-}1$ variables in N runs, when N is a multiple of 4. In this way 7 factors can be tested within 8 runs, so number of trials may be reduced down to absolute minimum. The plan is dedicated for screening out numerous factors in order to chose the ones that mostly impact the process outcomes (4).

Due to PAT guides, manufacturing process should be well understood in order to minimize risk of poor quality product delivery to the public (1, 2). Influence of operational parameters on drug characteristics should be investigated. Critical parameters should be established and further optimized. Therefore, the aim of the study was to analyze the impact of wet granulation process parameters on the drug product quality attributes. The following steps were performed:

– CQAs of the product were characterized,

– process parameters (factors) of potentially critical impact on the CQAs were typed,

– high and low levels were assigned to each factor,

– experimental matrix was designed,

– the experimentation was realized in line with the matrix,

– process outcomes were noticed,

– effects of the factors influence on the CQAs were estimated,

– the CPPs were typed.

The CPPs were further optimized in order to produce quality drug product in repeatable manner. The newly established operational ranges of critical factors were verified.

Table 1. Critical parameters investigation of granulate containing A06 substance manufacturing: Plackett-Burman Design (n = 8, k = 7) supplemented by three additional runs with central levels of tested factors (C1, C2, C3). The main effects of the processes are presented.

Run [n]	Factors [k] screened for criticality							Main effects		
	Wetting	Massing			Drying		Sizing			
	Water amount* [g]	Impeller speed [rpm]	Chopper speed [rpm]	Massing time [min]	Drying temp. [°C]	Granulate LOD [%]	Screen size [mm]	Tablet weight range [mg]	Friability [%]	Dissolution [%]
	1	2	3	4	5	6	7	NMT 35 mg	NMT 1 %	NLT 80%
1	200	150	500	5	60.0	2.0	1.00	9.1	0.1	96.0
2	350	150	500	1	35.0	2.0	2.50	9.7	0.2	100.3
3	200	450	500	1	60.0	1.0	2.50	13.3	0.2	111.9
4	350	450	500	5	35.0	1.0	1.00	6.5	0.1	42.5
5	200	150	3000	5	35.0	1.0	2.50	11.9	0.1	95.4
6	350	150	3000	1	60.0	1.0	1.00	5.7	0.0	101.4
7	200	450	3000	1	35.0	2.0	1.00	6.2	0.0	98.4
8	350	450	3000	5	60.0	2.0	2.50	15.6	0.3	27.5
C1	275	300	1750	3	47.5	1.5	1.75	4.4	0.1	101.0
C2	275	300	1750	3	47.5	1.5	1.75	7.2	0.1	98.3
C3	275	300	1750	3	47.5	1.5	1.75	6.4	0.1	101.1

* binding solution containing 46 g of povidone and 200 g of water was used for wetting of powders as a standard; 150 g of additional water was poured into the high shear granulator in runs 2, 4, 6, 8 and 75 g of water was poured in runs C1–C3.

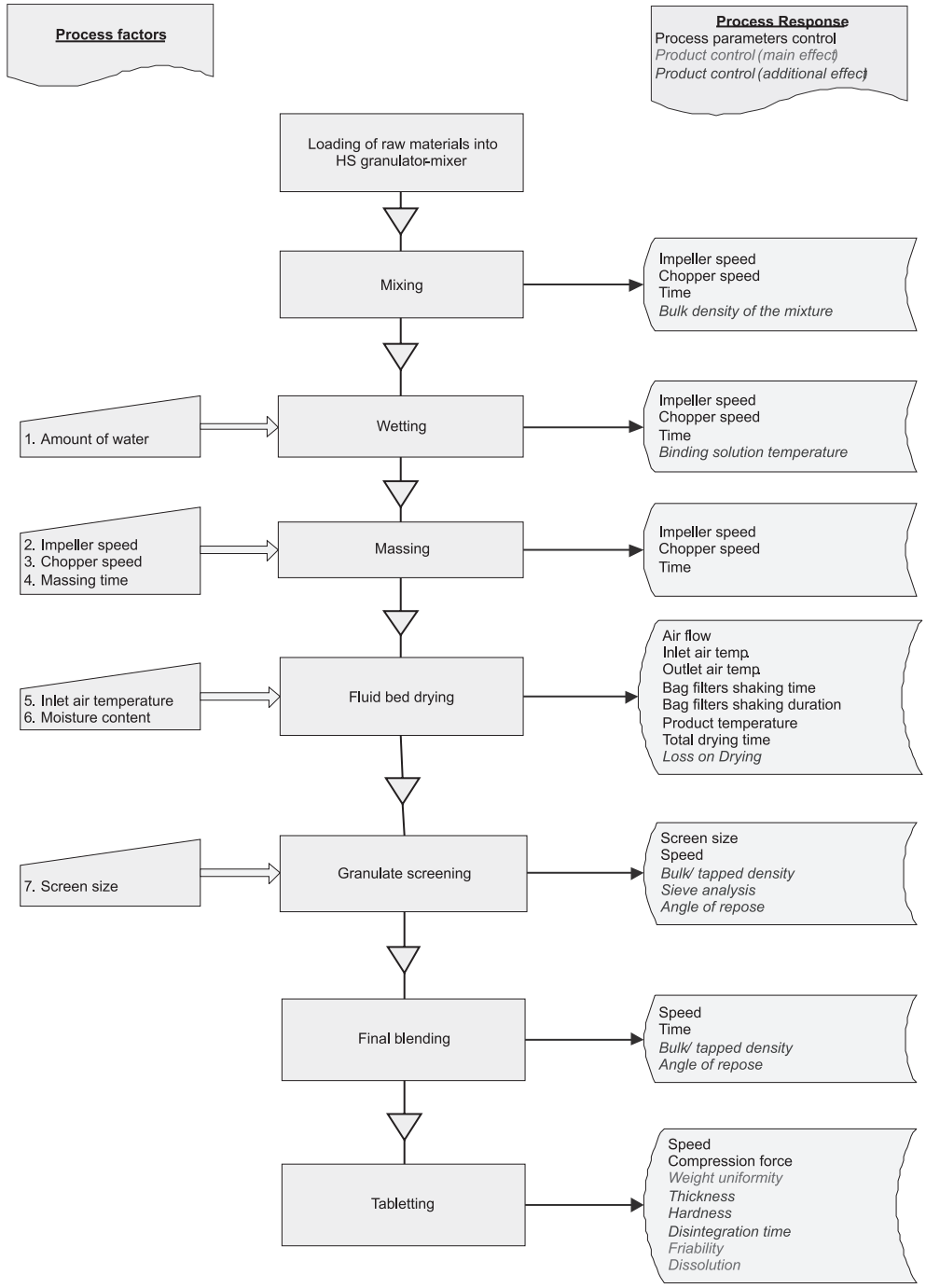

Figure 1. Process flow chart

EXPERIMENTAL

Materials

Active substance coded A06 (API), lactose monohydrate (Pharmatose Milled 200 M, DMV International), microcrystalline cellulose (Vivapur types 101 and 102, JRS), povidone (Plasdone K29/32, ISP), pregelatinized starch (Starch 1500, Colorcon), sodium starch glycolate (type A, Vivastar, JRS), colloidal silica (Aerosil 200, Evonik), magnesium stearate (Ligamed MF-2-V, Peter Greven). Pharm. Eur. water purified was used as a granulating fluid.

Tablets preparation

Active substance was mixed-up with microcrystalline cellulose type 101, lactose monohydrate, pregelatinized starch, sodium starch glycolate in the high-shear mixer (Diosna P10). The mixture was wetted with povidone solution. In some runs additional water was poured in accordance to experimental matrix (Tab. 1). The wet mixture was massed to form granulate. The granulate was transferred to fluid-bed processor (Glatt GPCG3.1) and dried with air of controlled temperature until the predefined loss on drying was confirmed. Dry granulate was screened (Erweka oscillating granulator) using sieves of apertures given in Table 2. Afterwards, the granulate was mixed with microcrystalline cellulose type 102, lactose monohydrate, pregelatinized starch, povidone, colloidal silicon dioxide, magnesium stearate (L.B. Bohle LM10/20). The final blend was compressed into tablets (Korsch PH 106) at three compression forces: 5 kN, 10 kN and 15 kN at constant tabletting speed of 39 rpm.

Product control

The process control scheme is presented in Figure 1.

Bulk and tapped density

The bulk and tapped density were measured in accordance with Ph. Eur 2.9.15 Apparent volume method by using Erweka SVM22 apparatus.

Loss on drying

Loss on drying was analyzed in Mettler Toledo LJ16 apparatus. Granulate in quantity of ca. 5 g was dried at 105^{o}C to constant mass. The loss of mass was presented as percent m/m.

Particle size distribution (PSD)

The PSD of granulate was measured by sieve analysis performed in Fritsch Analysette Pulverisette 03.502 set. Test sample of 50 g was treated for 10 min under vibrations of 1.5 cm amplitude. Mass of granulate retained at each sieve was determined and presented as m/m percent.

Angle of repose

The flow properties of granules were measured by using apparatus made by ZMR s.c. The method relies on the USP <1174> angle of repose testing principle. The granulate was poured out of the funnel down to the round base of fixed radius (r). High (h) of the powder cone-like pile was measured. The result was converted to angle of repose according to the following equation:

$$\text{Angle of repose } (\text{tg}\,\alpha) = h / r$$

Mass uniformity, hardness, thickness

Tablets were tested for mass uniformity and hardness according to Ph. Eur. methods 2.9.5.and 2.9.8, respectively. Thickness of the tablets was also measured. All the parameters were tested using Erweka Multicheck apparatus.

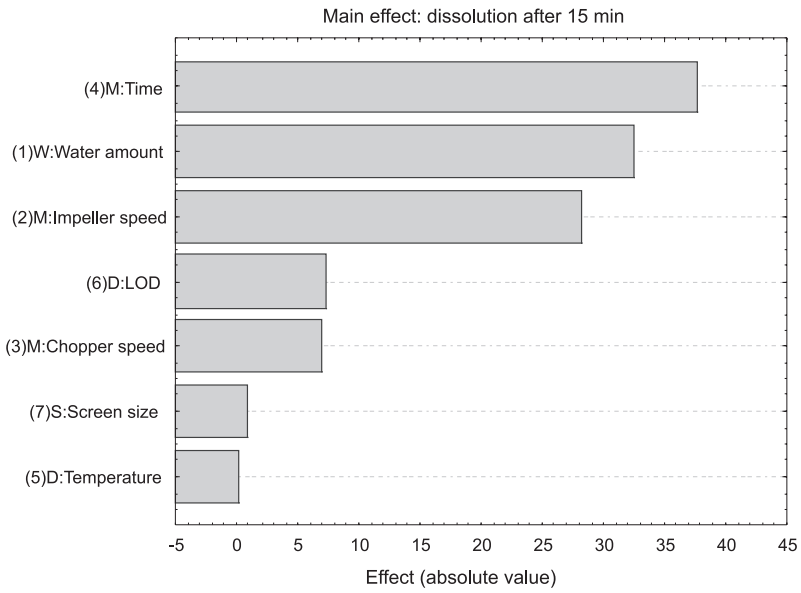

Figure 2. Pareto diagram showing effects of individual factors on the A06 substance dissolution. The unit operations of granulation process are marked with symbols: W – wetting, M – massing, D – drying, S – screening

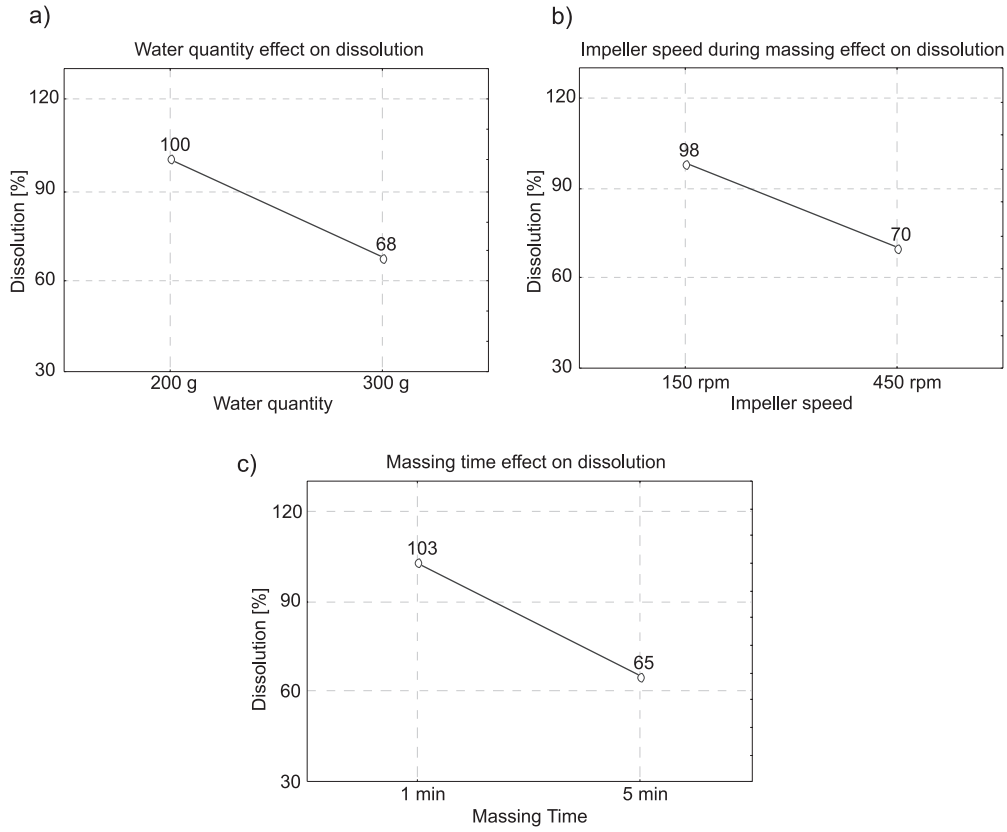

Figure 3. Impact of granulation parameters on A06 substance dissolution

Friability

The friability of tablets was checked using Erweka TA40 tester. The analysis was done in accordance with Ph. Eur. 2.9.7 method.

Disintegration time

Disintegration of tablets was measured by using Erweka ZT72 tester in line with Ph. Eur. 2.9.1. method.

Dissolution

Tablets were tested for dissolution in Ph. Eur. paddle apparatus (Hanson Research SR8Plus) operated at 50 rpm. Nine hundred mL of 0.01 M HCl was used as dissolution medium. Samples were withdrawn from the media after 15 min and were analyzed in Agilent 1100 HPLC apparatus using Eclipse XDB-Phenyl column 3,5 µm (4.6 mm × 150 mm) with guard column 5 µm (4.6 mm × 12.5 mm). The mobile phase consisted of phosphate buffer/methanol (60/40). The compound was detected by UV at 270 nm.

Criticality assessment

Qualitative and quantitative composition of tablets has been defined. Each tablet contained 80 mg of A06 substance and the total tablet mass was 350 mg. Process flowchart is shown in Figure 1.

The following factors were examined: amount of binding water, impeller speed, chopper speed, massing time, drying temperature, granulate loss on drying, mesh of screen used for dry granulate sizing. The drug product CQAs were typed: dissolution, mass uniformity and friability. Acceptance criteria were established for each the CQA, as follows:

– not less than 80% of API dissolved from tablets,

– tablet weight range not more than target 350 mg ± 5 %,

– friability not more than 1 %, none tablet capped.

Since tablets were made under wide range of compression forces, the main outcomes at the worst case scenario conditions were studied, i.e., dissolution at high compression (15 kN), friability at low

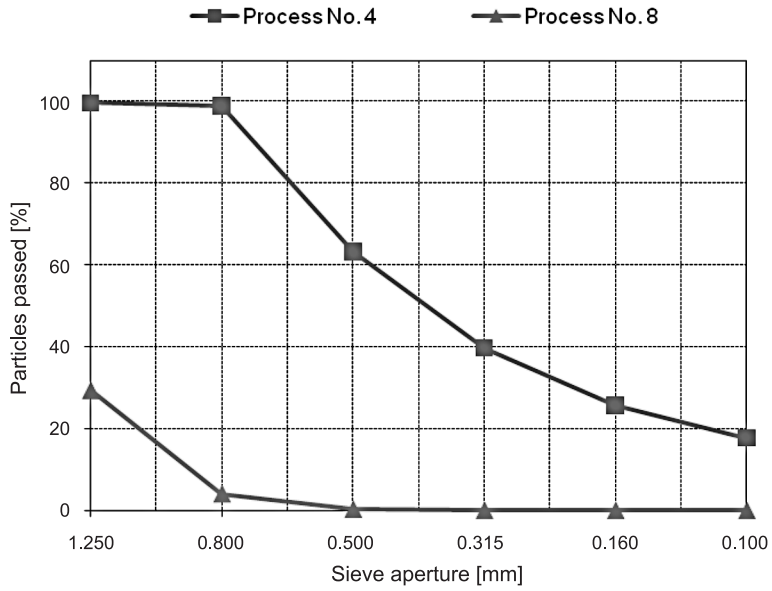

Figure 4. Particle size distributions of granulates that provided tablets of poor A06 substance dissolution

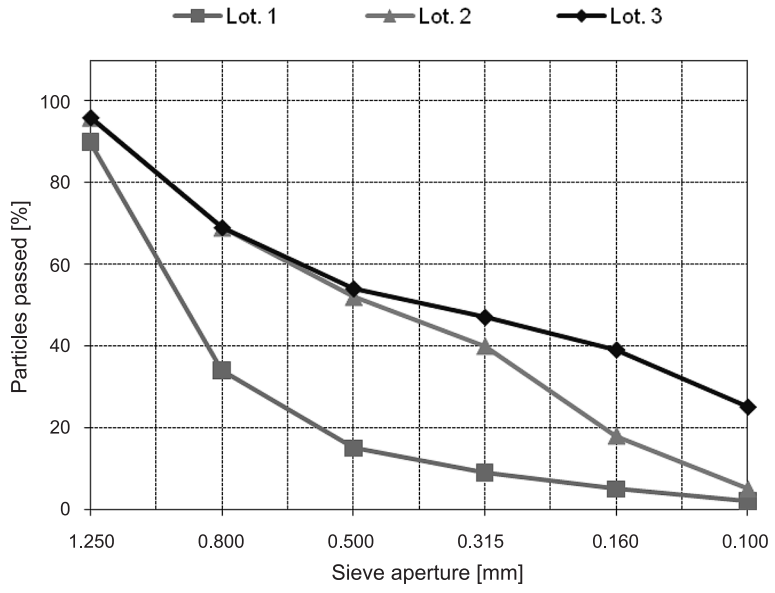

Figure 5. Particle size distributions of granulates made under narrowed operational ranges

compression (5 kN) and the widest observed ranges of tablet weight.

The process parameters (factors) were screened out for criticality using randomized two-level fractional factorial design of resolution III attributed to Plackett and Burman. The upper and lower levels of each process parameter represented minimum and maximum settings of wide operational ranges. Three runs at the central level of each factor were added to the design. The experimental

design and the process response analysis were performed using StatSoft Statistica 6 software. The levels of factors, composition of the experimental matrix and the processes (runs) outcomes are presented in Table 1.

RESULTS AND DISCUSSION

The processes were run in accordance with experimental matrix (Tab. 1). Runs 1–8 were conducted under various levels of factors. During runs, C1–C3 factors were set at intermediate, so called central levels. Tablets made in each run were tested for main and additional outcomes.

Critical drug product failures were noticed: runs No. 4 and 8 produced tablets of unacceptable dissolution. Effects of each factor influence on drug dissolution are presented at Pareto diagram (Fig. 2). It is demonstrated that active substance dissolution depends mainly on three factors, i.e., amount of binding water, impeller speed and massing time The absolute effect values indicate magnitude of each factor impact on active substance dissolution. The following values were noticed: amound of binding water (effect –32; $p < 0.01$), impeller speed (effect –28; $p < 0.01$) and massing time (effect –38; $p < 0.01$). Considering the minus sign of the values it is supposed to observe an increase in dissolution rate of ca. 30% to 40% after change of considered factor from up to low level (Fig. 3). Although the low dissolution was determined when high levels of the three factors contributed together, i.e., granulates were made using large quantity of water, at high impeller speed and after long massing, the Plackett-Burman design due to its messy alias structure does not allow to estimate interactions among screened parameters (4). Therefore, it was decided to assess criticality of each of the parameters.

None of the investigated process factors has critical impact on tablet mass uniformity and friability (Tab. 1).

Based on the trial results, it is concluded that critical parameters of the granulation process are: the amount of binding solution, impeller speed during massing and massing time. High levels of the factors operational settings could lead to manufacture of tablets of unacceptable dissolution. High-shear wet granulation is still not fully explained, since it is a complex and highly dynamic process (7). Impeller and chopper blades operated at high speed cause high-energy collisions between particles. Wet particles bind together and create agglomerates of limited surface area and porosity. The subsequential phases of granulation are particles nucleation, consolidation, granules attriction and breakage. The granule growth is attributed to the maximum pore liquid saturation and the amount of granule deformation during impact. Increasing quantity of binding solution contributes to maximum pore liquid saturation. Free liquid available at the surface of particles after saturation of their pores promotes nucleation and coalescence phenomena resulting in enlargement of agglomerates. Speed of impeller blade affects collisions between granules. Fast agitation of wet mass increases both energy and frequency of particles collisions. High impeller speed additionally increases temperature of agitated mass which may impact viscosity of binder solution and plasticity of particles. Duration of wet massing process magnify influence on granule growth that amount of binding solution and impeller speed have. The three factors seemed to interact. It was found that size of granules used for tabletting is not correlated with retardation of active substance dissolution. Tablets of unacceptable dissolution were made with granulates prepared under impact of high levels of the critical factors, i.e., big quantity of binding solution, high impeller speed and long massing. The conditions created large, regular and strong agglomerates. The initially big granules were screened using both – fine (run 4) and coarse (run 8) sieves, which provided extreme differences in particle size distribution (Fig. 4). In consequence, inadequate amount of dissolved drug was observed during testing of tablets containing coarse and fine granules. The fact could be explained by assumption that strong bindings were created between particles of powder during granulation runs 4 and 8. Wetting of powder with binding solution lead to decrease of distance between individual particles and to increase of interparticle contact area. Bindings are created among them. Various mechanisms of the bonding creation can be considered, e.g., diffusion of molecules from one particle to another, chemical reaction, van der Waals forces, hydrogen bonds, hardening of binder. High levels of critical factors during agglomeration runs 4 and 8 resulted in strong bindings creation between agglomerated particles. In consequence, densification of materials, reduction of their surface area and porosity occurred. The phenomena have direct impact on active substance dissolution rate. The solid-liquid contact area was limited, water penetration into agglomerate was inhibited and solids dissolution prolonged. The other process runs were performed in milder conditions than created in runs 4 and 8. The three factors of the most significant influence on drug dissolution were not set simultaneously at high level anymore. As a

result, the structure of agglomerates was not so dense and tablets were of adequate dissolution. Knowing the CPPs, it was of primary importance to set their operational ranges at levels that provide quality product within robust manufacturing process. The ranges tested so far were too wide which caused poor drug dissolution. The CPPs operational ranges were narrowed in the following way. During the trials, 874.6 g of dry mixture was wetted with binding solution containing 200 g, 275 g and 350 g of water. The dry mass/water quotient was 4.4, 3.2 and 2.5, respectively. For purpose of further testing, the range of water quantity was narrowed in order to keep the dry mixture/water quotient at the levels of 2.9–3.5. Low impeller speed was not recommended due to potential risk of not sufficient agglomeration and, in consequence, punches sticking. Therefore, it was decided to keep it in range of 350–450 rpm. The massing time was shorten and set in the range of 1.5–3.5 min. In order to check out the mentioned above assumptions, three consecutive lots of the drug product were made. The three critical process parameters were set in order to represent the worst case scenarios, i.e., intense and mild agglomeration (lots 1 and 3, respectively) as well as agglomeration under moderate conditions (lot 2), i.e.,:

1) lot 1 (high levels of CPPs)
   - high quantity of binding water (dry mixture/ water quotient is 2.9),
   - impeller speed during massing at 450 rpm,
   - massing time of 3.5 min
2) lot 2 (intermediate levels of CPPs)
   - water for wetting at the intermediate level (dry mixture/ water quotient is 3.2),
   - impeller speed during massing at 400 rpm,
   - massing time of 2.5 min
3) lot 3 (low levels of CPPs)
   - low quantity of water (dry mixture/ water quotient is 3.5),
   - impeller speed during massing at 350 rpm,
   - massing time of 1.5 min

It was found that different CPP levels provide granulates of diversified particle sizes (Fig. 5). The lot 1 granulate was composed of coarse particles, the lot 3 granulate contained significant fraction of fines and the lot 2 granulate was of medium size. All the granulates produced tablets that dissolved ca. 100% API after 15 min of testing. The other drug product parameters like tablet mass uniformity, friability, hardness, disintegration, complied with European Pharmacopoeia requirements. It was proved that quality tablets can be produced by narrowing the CPPs operational ranges . With respect to the Quality by Design (QbD) perspective, the process optimization should be performed by applying statistical response surface methodology, e.g., a central composite design. The experiment should allow to define combination of parameter ranges that deliver tablets of required dissolution in repeatable manner (3), i.e., to determine a design space. In-process control (IPC) methods should be developed in order to monitor key high-shear granulation phenomena. Changes of agglomerated mass could be controlled by power consumption or torque fluctuations monitoring (8, 9). The other methods that can be considered are control of motor slip (9) or conductivity of damp mass (10), probe vibration analysis (11), positron emission particle tracking (12), acoustic emission detection (13), NIR moisture analysis (14), focus beam reflectance measurement (15) or application of rapid image processing system 16).

CONCLUSION

Understanding of manufacturing process is of key importance to successful implementation of QbD approach. The understanding requires the CPPs to be adequately typed. In order to select the CPPs, it is suggested that processing factors are set at high and low levels, i.e., max and min settings of their operational ranges. Plackett-Burman design can be used for screening-out numerous factors and finding out the CPPs. Out of specification (OOS) results of CQAs indicate critical influence of factors. Process parameter that impacts the OOS outcome significantly is the CPP. Process outcomes within the spec limits indicate a lack of CPPs. Operational ranges of critical parameters should be optimized in order to produce quality product in a repeatable manner.

Acknowledgment

The authors wish to acknowledge the technical support received from Pliva Kraków, Pharmaceutical Comp., where the experimental part was performed.

REFERENCES

1. FDA, Guidance for industry: Pharmaceutical CGMPs For the 21st Century – A Risk-Based Approach, Final Report. 2004.
2. FDA, Guidance for industry: PAT — A framework for innovative pharmaceutical development, manufacturing and quality assurance. 2004.

3. ICH: Q8 Pharmaceutical development. 2008.
4. Montgomery D.C.: Design and Analysis of Experiments, 6th edn., J. Wiley & Sons, Inc., Hoboken NJ 2005.
5. Yu L.X.: Pharm. Res. 25, 781 (2008).
6. PQRI: Process robustness – a PQRI white paper, Pharm. Eng. 26, 1 (2006).
7. Iveson S.M. Litster J.D., Hapgood, K., Ennis B.J.: Powder Technol. 117, 3 (2001).
8. Terashita K., Watano S., Miyanami K.: Chem. Pharm. Bull. 38, 3120 (1990).
9. Parikh D.M.: Handbook of pharmaceutical granulation technology, Marcel Dekker, New York 1997.
10. Spring M.S.: Drug Dev. Ind. Pharm. 9, 1507 (1983).
11. Staniforth J.N., Quincey S.M.: Int. J. Pharm. 32, 177 (1986).
12. Hassanpour A., Kwan C.C., Ng B.H., Rahmanian N., Ding Y.L., Antony S.J., Jia X.D., Ghadiri M.: Powder Technol. 189, 304 (2009).
13. Gamble J.F., Dennis A.B., Tobyn M.: Pharm. Dev. Technol. 14, 299 (2009).
14. Rantanen J. Räsänen E., Tenhunen J., Känsäkoski M., Mannermaa J.-P., Yliruusi J.: Eur. J. Pharm. Biopharm. 50, 271 (2000).
15. Ganguly S., Gao J.Z.: Application of focused beam reflectance measurement technology in high-shear wet granulation, AAPS 2005 General Meeting, Nashville TN; AAPS J. 7(S2), Abstract No. T3216 (2005).
16. Watano S.: Powder Technol. 117, 163, (2001).

Received: 7. 07. 2010