AAPS PharmSciTech, Vol. 19, No. 5, July 2018 (© 2018)
DOI: 10.1208/s12249-018-1063-7

Research Article

Scale up of Semisolid Dosage Forms Manufacturing Based on Process Understanding: from Lab to Industrial Scale

Anton J. P. van Heugten[1,2,4] and Herman Vromans[1,2,3]

Received 21 February 2018; accepted 3 May 2018; published online 29 May 2018

Abstract. The scale up of production processes is a major challenge in pharmaceutical industry. Using a quality by design approach, upscaling can be based on the design space, which can be assessed on a small scale. In a previous study, the critical process parameters were identified by a definitive screening design on cetomacrogol ointment. In the current study, this lab scale (0.5 kg) study was scaled up to industrial scale (2000 kg, filling 100g tubes at 75 tubes/min). A similar trend for the influence of filling temperature on ointment yield stress was found for lab and industrial scale production. Furthermore, a process window for ointment filling viscosities was established. It was shown that between 26 and 170 Pa.s ointment could be filled into tubes with a low weight variation (< 0.5% RSD) resulting in a product with a yield stress that meets the pre-set criteria. This approach was subsequently verified using several creams and ointments and showed general applicability.

KEY WORDS: quality by design (QbD); design space; scale up; ointment; design of experiments (DoE).

INTRODUCTION

Upscaling is a major challenge in pharmaceutical industry. In order to successfully scale up a process, the similarity principle can be adopted**.** This principle assumes that across all equipment and process scales equal ratios between for example dimensions, forces, and temperature gradients are achieved (1). Here, often dimensionless numbers are used as an expression of these ratios. In practice, it is impossible to fully meet the requirement of similarity**.** Therefore, scale up is a serious point of attention in drug development (2). The upscaling of a process can be performed on the basis of process understanding, by using a quality by design (QbD) approach (3). Through such an approach, the criticality of the process parameters is determined. The knowledge of the critical parameters that really contribute to the final product specifications (critical quality attributes (CQAs)) enables the selection of the appropriate settings at larger scale. Normally**,** the initial assessment of critical process parameters is conducted on lab scale level since experiments at industrial scale batches are associated with high costs (2).

In ointment production, several process parameters may influence the CQAs. A major product property is the spreadability onto the skin. This can be characterized by measuring the yield stress. Yield stress was shown to be an important parameter when considering product spreadability (4,5). In a lab scale (0.5 kg) study, it was shown that the yield stress of cetomacrogol ointment was significantly influenced by mixing speed and filling temperature (5).

The effect of mixing and filling temperature on ointment yield stress was studied using a definitive screening design (DSD). This DSD is a statistical method to study the influence of different variables on predefined CQAs. The DSD distinguishes itself from more conventional two-level factorial designs since it allows the study of interactions between variables and detection of curvature in the influence of variables (6). Curvature can only be studied when variables are studied on more than two levels since only then non-linearity in the influence of a variable can be detected. This would also be possible with more conventional designs but using a DSD, this can be achieved highly efficient**ly** using only $2n + 1$ experimental runs. This results in fewer experiments compared to conventional two-level (2^n) or three-level (3^n) designs.

The aim of this study was to translate the outcomes of the lab scale design to industrial scale and to establish a process window for an industrial scale filling process.

MATERIAL AND METHODS

Materials

The following products were studied: cetomacrogol ointment, cetomacrogol cream, and lanette cream II. The composition of these products is shown in Table I. The

[1] Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, 3584 CG, Utrecht, The Netherlands.
[2] Research and Development Department, Tiofarma B.V, Hermanus Boerhaavestraat 1, 3261 ME, Oud-Beijerland, The Netherlands.
[3] Department of Clinical Pharmacy, Division of Laboratory Medicine & Pharmacy, University Medical Centre Utrecht, P/O Box 85500, 3508 GA, Utrecht, The Netherlands.
[4] To whom correspondence should be addressed. (e–mail: tvheugten@tiofarma.nl)

ingredients were as follows: white petrolatum (Snowwhite N®, Sonneborn international, Amsterdam, the Netherlands), cetomacrogol wax (Galenol® 1618 AE, Sasol GmbH, Brunsbüttel, Germany), isopropyl myristate (Kollicream(R) IPM, BASF Personal Care and Nutrition GmbH, Düsseldorf, Germany), paraffin oil (110–230 mPa.s, Gustav Heess GmbH, Stuttgart, Germany), colloidal silicon dioxide (Aerosil(r) 200 vv Pharma, Evonik, Paris, France), sorbic acid (Merck, Darmstadt, Germany), cetiol V (BASF Personal Care and Nutrition GmbH, Düsseldorf, Germany), sorbitol (Neosorb 70/70, Roquette, Vecquemont, France), and lanette wax SX (BASF Personal Care and Nutrition GmbH, Düsseldorf, Germany). Distilled water was prepared by a Elga Centra R 60/120 system (Woodridge, Illinois, USA).

Rheology

A stress-controlled rheometer (TA instruments HR-2, Etten-Leur, The Netherlands) equipped with a peltier plate and a 40-mm sandblasted parallel plate (TA instruments plate geometry 40 mm) was used. Approximately 5 g of ointment was placed on the peltier plate before slowly lowering the upper plate to the pre-set trimming gap of 1050 μm. After trimming excessive petrolatum, the geometry gap was set to 1000 μm.

The yield stress was determined using oscillatory stress sweep (OSS) experiments in a wide stress range (1–2000 Pa) at 20 °C. Yield stress was defined as the point where the storage and loss modulus lines cross. Data was analyzed using Trios v3.3.0.4055 software. Yield stress can be used as a measure for the spreadability of a product and can therefore be considered as a relevant product characteristic for patient use (4,5).

The viscosity was determined as a function of temperature using temperature ramps at a heating rate of 1.0 °C/min between 20 and 70 °C. Geometry velocity was set at 0.1 rad/s. Viscosity is a measure of a material's resistance to flow. This can therefore be considered as an important attribute for the processability of a product.

The internally trained test panel ($n = 10$) was first trained to evaluate a series of different dermatological products (*e.g.*, gel, cream, ointment, and paste). This panel mainly focussed on the spreadability of a product. Subsequently, panel members were asked to evaluate the spreadability of different batches of cetomacrogol ointment and determine what they felt appropriate for patient use. Based on these results, the specifications for product yield stress were set.

Ointment Filling

Industrial scale filling tests were conducted using a Comadis C1110 with a temperature controlled filling hopper. This is an automated filling machine for pharmaceutical products such as ointments. The filling hopper was filled with ointment (approximately 30 kg per experiment) and conditioned at the required temperature (the temperature required for the experiments) while stirring. Filling rate was set at 75 tubes/min; polyethylene tubes were filled with 100 g of ointment. For every experiment, 100 tubes were weighed using a checkweigher (OCS HC-A-2000-2, Kaiserslautern, Germany) for weight variation (%RSD).

RESULTS AND DISCUSSION

Upscaling Cetomacrogol Ointment Process

Lab scale production of cetomacrogol ointment was studied. The yield stress was used as a measure for the spreadability of the product. Batches of 0.5 kg were produced under controlled conditions. The following variables were studied: heating temperature, the addition of SiO_2 particles, mixing rate, cooling rate, filling temperature, and isothermal mixing before filling. Figure 1 shows the resulting yield stress for 14 differently produced cetomacrogol ointment batches.

The yield stress of the cetomacrogol ointment batches (at 20 °C) was found to lie between 272 and 1309 Pa (Fig. 1). To determine the impact of differences in yield stress, an internally trained test panel ($n = 10$) was consulted. The experimental yield stress values can be roughly categorized as follows: a yield stress < 500 Pa corresponds to a cream-like product, values > 800 Pa to products too thick to be removed from a tube. Dashed lines in Fig. 1 show that only 5 of the 14 lab scale batches are within these specifications. Clearly, the majority of the batches produced are not within the set requirements. From this, it can be concluded that processing has a significant influence on the products rheological properties. To assess which variable has a dominant impact on the yield stress, a non-linear statistical model was designed using software from SAS, JMP 12. This is described in more detail by van Heugten *et al.* (5). The impact of several variables on ointment yield stress is shown in Fig. 2.

In Fig. 2, the influence of several variables on cetomacrogol ointment yield stress is shown. On the *y*-axis in some cases, "variable" * "variable" is shown. This, in the case of "variable A * variable B", indicates that two variables have a combined effect on ointment yield stress or in other words show an interaction. In the case of "Mix-R * Mix-R", this variable shows a non-linear effect, or curvature. This curvature can be observed in the parabolic pattern for the influence of mixing rate on yield stress (shown in (5)). A range of 10–100 rpm was studied and 55 rpm showed the highest yield stress. Clearly, the most significant variables are filling temperature, mixing rate and the addition of SiO_2 particles (p values 0.0065, 0.0013, and 0.0073 respectively). Furthermore, mixing rate and filling temperature showed a statistically significant interaction (p value 0.0116**).** A more elaborate discussion on the results is described in more detail by van Heugten *et al.* (5). For the scope of this study, knowing that the mixing rate and filling temperature obviously are the most critical process parameters in the production of cetomacrogol ointment is the most important outcome. This helps in focusing attention during scale up.

Interestingly, on industrial scale production, the influence of mixing rate was not found to affect product quality. Especially for a mixing process, the hydrodynamic similarity is important. In the current study, a scale up investigation was conducted from a lab scale 1.5 L mixer (ProCept 4M8-Trix) to an industrial scale 2400 L mixer-homogenizer with an additional top-down flow through the homogenizer and pipe (Dinex H2400). The lab scale mixer is a low shear mixer without a top-down flow; the industrial scale mixer is a low shear mixer with a top-down flow and homogenizer. Clearly, these represent two completely different mixing

Table I. Composition of Cetomacrogol Ointment, Cetomacrogol Cream, and Lanettecream II

Cetomacrogol ointment	Cetomacrogol cream	Lanettecream II
38.2% white petrolatum	15% cetomacrogol wax	24% lanette wax SX
25.5% cetomacrogol wax	0.2% sorbic acid	0.15% sorbic acid
15% isopropyl myristate	20% cetiol V	16% cetiol V
21.2% paraffin oil	4% sorbitol	4% sorbitol
0.1% SiO_2 particles	60.8% water	55.85% water

principles with different Reynolds numbers. This Reynolds number describes flow patterns and is dependent on the vessel diameter and material velocity (1). Most likely, the homogenizer and additional top-down flow on the industrial scale production will greatly influence material velocity. In addition, the homogenizer is likely to play a significant role in the formation of ointment structure on colloidal dimensions due to the high shear forces. Furthermore, the Froude number (Eq. 1) can be used to determine whether the ratio of inertial to gravitational forces is constant for both scales of manufacturing (7), in which n represents the agitator speed measured in revolutions per second, D_a the impeller diameter in meters and g the acceleration due to gravity (9.81 m/s^2).

$$Fr = \frac{n^2 * D_a}{g} \quad (1)$$

For the small scale vessel, the Froude number is 0.026 and for the large scale 0.020. These Froude numbers are slightly different which may be another reason why the effect of mixing rate is different on a small compared to a large scale.

Figure 3 confirms that the yield stress of the finished product is dependent on the filling temperature used in production. This phenomenon is independent of the manufacturing scale and/or specific equipment used. In Fig. 3, the data points for temperatures higher than 33 °C are lacking for the industrial process. Here, the ointment viscosity was found to be too low for operating the filling machine. Therefore, higher temperatures were not studied. Clearly, not only the critical influence of filling temperature on ointment yield stress is important when translating lab scale outcomes to industrial scale**.** In this case, also processability parameters such as the ointment viscosity were found to be important.

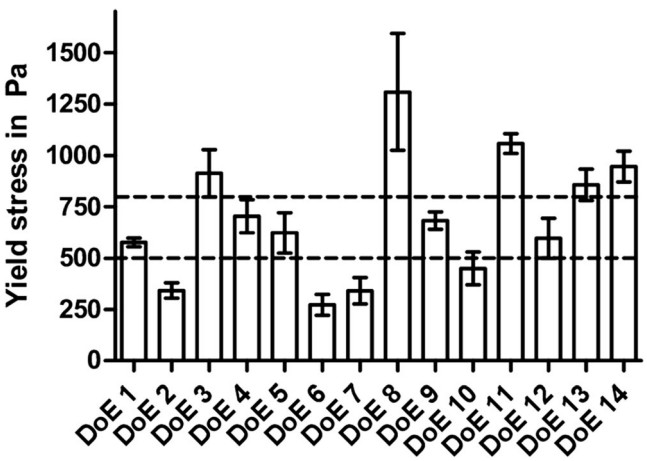

Fig. 1. Yield stress results for batches of cetomacrogol ointment measured at 20 °C. CQA window is defined in the range of 500–800 Pa (shown in dashed lines). Yield stress is expressed as mean ± SD. Figure is acquired under the creative commons attribution license (CC BY) from (5)

Process Window for Industrial Scale Ointment and Cream Filling

In order to establish a process window for the ointment filling temperature, additional experiments were conducted. For ointments and creams, it is known that their rheological behavior is complex and highly temperature dependent (8,9). The influence of the filling temperature on the weight variation in filled tubes was determined first (Fig. 4).

Figure 4 shows that the variation in tube weight (expressed as % RSD) is highly dependent on ointment temperature. At a temperature somewhere between 24 and 26.4 °C, a high increase in weight variation was found. Between 26.4 and 33 °C, the filling was accurate and reproducible, < 0.35% RSD. At 34 °C, however, it was found that ointment was too thin to be filled into tubes. In this

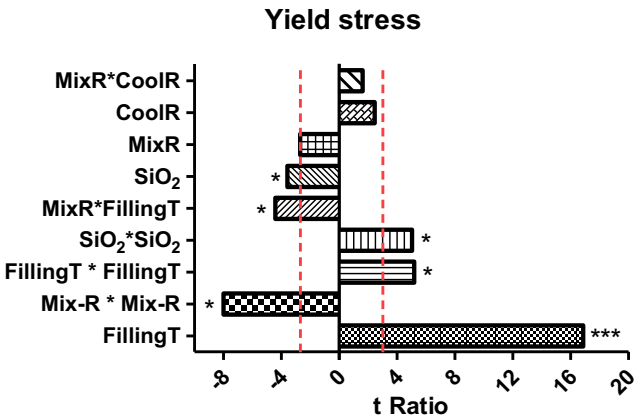

Fig. 2. Effect of the formulation and process variables on cetomacrogol ointment yield stress, the sorted parameter estimates. *p value < 0.05, **p value < 0.001, ***p value < 0.0001. Mix-R, mixing speed; CoolR, cooling rate; SiO_2, addition of Aerosil 200 *v/v*; FillingT, temperature at which containers were filled. The t ratio provides an indication for the significance of an effect. Figure is acquired under the creative commons attribution license (CC BY) from (5). The original "ExitT" was changed in this figure to "FillingT" the match the accompanying text

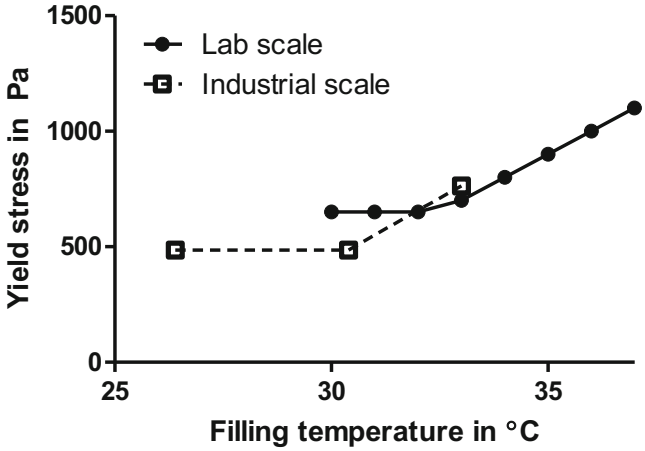

Fig. 3. Yield stress at 20 °C for cetomacrogol ointment after filling single tubes at different temperatures on lab scale (0.5 kg). On industrial scale, PE tubes of 100 g were filled at a rate of 75 tubes/min

situation, ointment splashed from the hopper onto the filling equipment, making it impossible to operate the filling machine. The limits for the filling of the cetomacrogol ointment studied here are therefore 26.4 to 33 °C.

In the aforementioned experiments, the yield stress was studied. This is an important parameter when considering end product characteristics such as spreadability. When focusing on the processability of a material, the viscosity should be studied. This viscosity provides insight into the flow properties of a material. Therefore, the relationship between viscosity and temperature for cetomacrogol ointment was studied (Fig. 5).

Figure 5 shows that with increasing temperature from approximately 35 °C a steep decrease in ointment viscosity can be observed. Temperature clearly has a significant impact on ointment viscosity. Dashed lines correspond to the limits for filling (see also Fig. 4). The process window was set from 26.4 to 33.0 °C; the corresponding viscosities are 107 and 26 Pas.

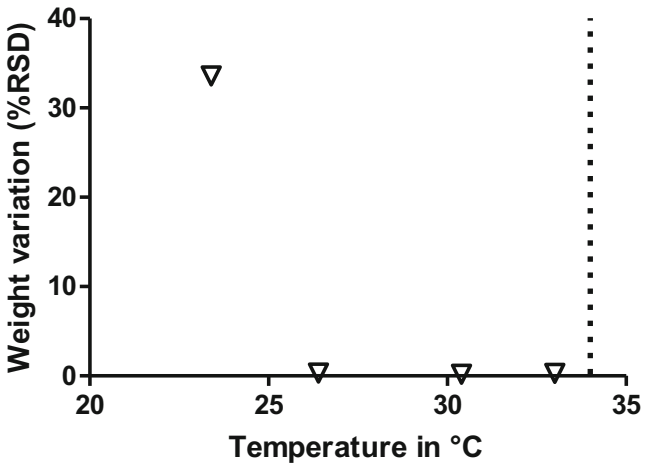

Fig. 4. Relationship between cetomacrogol ointment filling temperature and weight variation between filled tubes at industrial scale (expressed as % RSD). The temperature at which ointment was too thin to be filled is shown in a dashed line. All other filling parameters were kept constant during the experiments

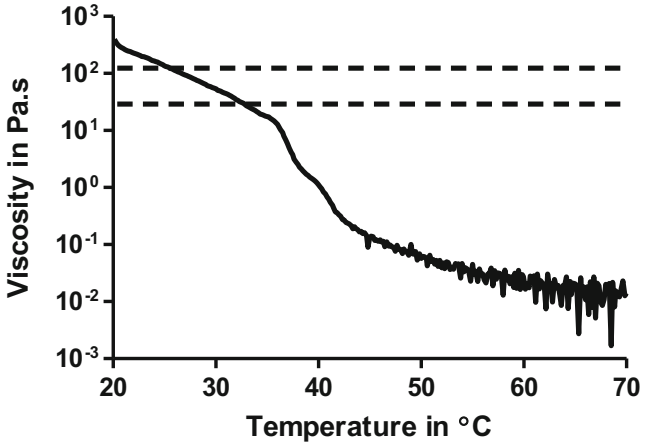

Fig. 5. Relationship between temperature and viscosity for cetomacrogol ointment. The process window for filling viscosity is shown in dashed lines

Verification of Process Window for Product Viscosity on Industrial Scale

This process window for product filling was subsequently verified using both creams and ointments, listed in Table II. The same rheometry experiments as shown in Fig. 5 were conducted and results are shown in Table II.

For all products listed in Table II, the proposed temperature ranges were tested on industrial scale. The verification of these ranges was conducted by testing the upper limit of the filling temperature. For the three products in Table II, the shown upper limit was indeed a correct temperature to accurately fill product. No additional data is shown here since verification runs were only conducted for the upper limits. Subsequently, the operation specifications were set 2 °C lower in order to establish a safe operating window. Similar process windows were established and verified for a number of other commercial products that cannot be disclosed due to confidentiality. The process window can thus be translated to different products such as other creams and ointments, assuming the same equipment constraints.

CONCLUSION

Our study shows that the scale up of a production process can be performed based on process knowledge. Thorough characterization of a lab scale process yields information about the criticality of process parameters. Especially these parameters should subsequently be evaluated on industrial scale. The mixing rate of the equipment

Table II. The Process Windows That Were Established Using Rheometry on Commercial Scale

Product name	Process window for filling (in °C)
Cetmacrogol ointment	26.4–33.0
Cetomacrogol cream	20.0–41.3
Lanettecream II	48.0–60.0

investigated in this study was critical on a lab scale, but not on an industrial scale. Filling temperature on the other hand was found to be critical on both scales of production. The influence of ointment viscosity at filling temperature was shown to be critical for processability on industrial scale with the equipment used in this study. A process window for product viscosity to successfully fill tubes on industrial scale was established for the equipment used in this study. This process window was shown to be applicable to a number of creams and ointments using the same equipment.

FUNDING INFORMATION

This work was supported by the R&D tax credit of the Ministry of Economic Affairs, The Netherlands (grant number S016053527).

REFERENCES

1. Levin M. Pharmaceutical process scale-up [Internet]. Marcel Dekker; 2002 [cited 2018 Jan 11]. 566 p. Available from: https://books.google.nl/books/about/Pharmaceutical_Process_Scale_Up.html?id=-HBRzGQRpHkC&redir_esc=y.
2. Pandey P, Badawy S. A quality by design approach to scale-up of high-shear wet granulation process. Drug Dev Ind Pharm [Internet]. 2016;42(2):363–9045. Available from: http://www.tandfonline.com/action/journalInformation?journalCode=iddi20%0Awww.tandfonline.com/iddi
3. Chang R-K, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products, part II: quality by design for topical semisolid products. AAPS J [Internet]. 2013 Jul [cited 2014 Aug 20];15(3):674–83. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3691439&tool=pmcentrez&rendertype=abstract.
4. Park EK, Song KW. Rheological evaluation of petroleum jelly as a base material in ointment and cream formulations: steady shear flow behavior. Arch Pharm Res. 2010;33(1):141–50.
5. van Heugten AJP, Braal CL, Versluijs-Helder M, Vromans H. The influence of cetomacrogol ointment processing on structure: a definitive screening design. Eur J Pharm Sci [Internet] 2017;99:279–284. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0928098716305693
6. Jones B, Nachtsheim CJ. A class of three-level designs for definitive screening in the presence of second-order effects. J Qual Technol. 2011;43(1):1–15.
7. Agrawal AM, Pandey P. Scale up of pan coating process using quality by design principles. J Pharm Sci [Internet]. Elsevier Masson SAS. 2015;104(11):3589–611. https://doi.org/10.1002/jps.24582.
8. van Heugten AJP, Versluijs-Helder M, Vromans H. Elucidation of the variability in consistency of pharmacopoeia quality petrolatum. Drug Dev Ind Pharm [Internet] 2017;43(4):595–599. https://doi.org/10.1080/03639045.2016.1274902
9. Pandey P, Ewing GD. Rheological characterization of petrolatum using a controlled stress rheometer. Drug Dev Ind Pharm [Internet]. 2008 Feb [cited 2014 Dec 8];34(2):157–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18302034