European Journal of Pharmaceutical Sciences 99 (2017) 279–284

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

The influence of cetomacrogol ointment processing on structure: A definitive screening design

A.J.P. van Heugten [a,b,*], C.L. Braal [a,b], M. Versluijs-Helder [c], H. Vromans [a,b,d]

[a] Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, 3584 CG Utrecht, The Netherlands
[b] Research and Development Department, Tiofarma B.V., Hermanus Boerhaavestraat 1, 3261 ME, Oud-Beijerland, The Netherlands
[c] Department of Inorganic Chemistry and Catalysis, Debye Institute for Nanomaterials Science, Utrecht University, 3584 CG Utrecht, The Netherlands
[d] Department of Clinical Pharmacy, Division of Laboratory Medicine & Pharmacy, University Medical Centre Utrecht, P/O Box 85500, 3508 GA Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 3 November 2016
Received in revised form 20 December 2016
Accepted 28 December 2016
Available online 29 December 2016

Keywords:
Quality by design (QbD)
Ointment
Design of experiments (DoE)
Definitive screening design (DSD)
Rheology
Critical process parameters (CPPs)

ABSTRACT

Batch-to-batch variability is a challenge for the industrial scale production of ointments. Therefore the current investigation focussed on identifying and understanding critical process parameters (CPPs) for cetomacrogol ointment. This was evaluated using a definitive screening design (DSD) approach in which fourteen batches were produced under predefined and controlled conditions using the following variables: addition of SiO_2 nanoparticles, mixing speed, cooling rate, heating temperature, container filling temperature and isothermal mixing at the filling temperature.

Ointment structure was evaluated using a number of rheological parameters. One of these parameters, yield stress was found to be strongly influenced by filling temperature and mixing speed ($p = 0.0065$ and $p = 0.0013$ respectively). Both significantly affect ointment structure and they also have a significant interaction ($p < 0.05$). Understanding the ointment production process can help in defining a processing window to produce ointment of constant quality.

1. Introduction

Ointments are widely used in the therapy of various skin diseases. When ointments are produced on an industrial scale, inexplicable batch-to-batch variation in ointment structure may occur (Chang et al., 2013a). An example of a product that is prone to such batch-to-batch variation is the water free cetomacrogol ointment. Examples of reported complaints concerning cetomacrogol ointment involve the presence of agglomerates and the occurrence of a highly viscous product that cannot be easily removed from a tube or container (Scientific Institute for Dutch Pharmacists, 2013). The variation between batches remains high due to a lack of understanding and control of parameters in the production process. This leads to rejection of batches and decreases the productivity of pharmaceutical companies.

Until now, relatively few articles have described the influence of formulation and process parameters on ointment structure (Chang et al., 2013b; Lashmar et al., 1993; Xu et al., 2015). Furthermore, they report conflicting results. For ophthalmic ointments, formulation and process factors were studied for product quality and *in vitro* performance. Processing was found to have a minor impact on the particular ophthalmic ointment structure (Xu et al., 2015). On the other hand, a study on creams concluded that processing may impact product structure substantially (Lashmar et al., 1993).

This highlights the importance of a systematic study on the influence of the manufacturing process on consistency and physical stability of topical products (Chang et al., 2013a).

Structural properties of ointment-like products are generally characterized using rheological tests. These tests provide information that can be linked to results of sensory test panels and are therefore able to describe sensory properties well (Gilbert et al., 2013; Ozkan et al., 2012). In order to conduct a systematic study on the influence of formulation and processing variables on ointment structure a Quality by Design (QbD) approach seems preferable. QbD is a systematic tool to study the influence of formulation and process variables. The influence of process variables on product quality can be identified using a design of experiments (DoE) approach. With a screening design such as a fractional factorial design, the criticality of process variables can be estimated by determining the critical process parameters (CPPs) (Chang et al., 2013b).

These screening designs are available in many different varieties. Classical designs generally study variables at two levels and as such

* Corresponding author at: Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, 3584 CG Utrecht, The Netherlands.
E-mail address: tvheugten@tiofarma.nl (A.J.P. van Heugten).

http://dx.doi.org/10.1016/j.ejps.2016.12.029

can say nothing about whether a nonlinear relationship between the two tested levels exists. This has led to the recent development of a new type of screening design has been developed that seems more powerful. In this definitive screening design (DSD) variables are studied at three levels rather than two levels, and it is possible to examine possible interactions between variables (Jones and Nachtsheim, 2011).

In short, given the current lack of ointment process understanding, the aim of this study is to identify critical process parameters and their influence on ointment critical quality attributes. This will be done by using a definitive screening design approach.

2. Materials and Methods

2.1. Materials

All materials complied with the quality requirements of the European Pharmacopoeia (Ph. Eur. 2016). White petrolatum Snowwhite N® (Sonneborn International, Amsterdam, The Netherlands), cetomacro golwax Galenol® 1618 AE (Sasol GmbH, Brunsbüttel, Germany), isopropylmyristate Kollicream® IPM (BASF Personal Care and Nutrition GmbH, Düsseldorf, Germany), paraffin 110–230 mPa·s (Gustav Heess GmbH, Stuttgart, Germany) and SiO_2 particles Aerosil® 200 vv Pharma (Evonik, Paris, France).

2.2. Batch Production

The batches (0.5 kg) were produced under controlled conditions in a 4M8-Trix homogenizer (ProCePt, Belgium). Cooling rate was defined in the range from 45 °C to filling temperature. In this range the solidification of the ointment occurs. A cooling rate of 0.15 °C/min was achieved by cooling down the mass without water. Cooling rates of 0.575 and 1.00 °C/min were achieved by cooling the wall of the vessel with water (low *versus* high flow). After production samples were stored for two weeks at room temperature. After this initial period of storage, samples were analysed. Prior to analysis, the samples were preconditioned for at least 1 h in a peltier-cooled incubator (Memmert IPP30) at 20 °C. Production and analysis of the sequence was randomized.

2.3. Rheological Characterization

The stress-controlled rheometer (TA Instruments Discovery HR-2, Etten-Leur, The Netherlands) used was equipped with a step-peltier stage (20 °C) and a 40 mm sandblasted parallel plate (TA-instruments Cone plate geometry 40 mm, Etten-Leur, The Netherlands). After approximately 5 g of ointment sample was placed on the peltier plate, the upper plate was slowly lowered to the preset trimming gap of 1050 μm. After trimming excessive ointment the geometry gap was set at 1000 μm. Before analysis, samples were equilibrated for 5 min at 20 °C. All rheological studies were performed in triplicate and results were expressed as mean ± relative standard deviation (RSD %). To characterize the rheological characteristics, the following procedures were performed in sequence on each sample:

- Oscillatory stress sweep: a logarithmic stress sweep at a frequency of 1 Hz was conducted within the range of 10 to 2000 Pa. The point of intersection with the G′ and G″ was defined as yield stress.
- Flow ramp: a linear flow ramp from 0.1 to final 200 s^{-1} was measured for 120 s. Outcomes zero shear viscosity and viscosity were determined using this measurement.
- Axial compressibility: 5 g ointment was compressed to a distance of 1000 μm (distance upper and lower plate), gap speed 10.0 μm·s^{-1} and angular velocity 0.0 rad·s^{-1}. The total axial force was measured at 1000 μm.
- Axial tension: after reaching 1000 μm, the direction of the upper plate was moved in the opposite direction, gap speed 10.0 μm·s^{-1}.

2.4. Critical Quality Attributes (CQAs)

The following critical quality attributes (CQAs) were studied: yield stress, RSD in yield stress, linear viscoelastic region (LVR)-height, viscosity, zero shear viscosity, axial compression and axial tension. Yield stress and LVR-height are measures for ointment spreadability. Zero shear viscosity, axial compression and axial tension are parameters to evaluate ointment structure in its container. Zero shear viscosity is the viscosity of the ointment when no shear is applied. Axial compression is the amount of force that is needed to compress a certain volume of ointment and axial tension is a measure for the stickiness of ointment to the geometry.

2.5. X-Ray Diffractometry

Room temperature XRD measurements were carried out on a Bruker-AXS D8 Advance powder X-ray diffractometer, in Bragg-Brentano mode, equipped with automatic divergence slit and a PSD Våntec-1 detector. The radiation used was Cobalt $K\alpha_{1,2}$, $\lambda = 1.79026$ Å, operated at 30 kV. Crystallite size was calculated using the Scherrer equation (Eq. 1) by using a K-value of 0.89 and calculating the β value by measuring half the maximum intensity of the crystalline peak and substracting the instrumental line broadening. Crystallinity was determined using the ratio between background and peak area, calculated with the XRD analysis program DiffracEVA (Bruker, The Netherlands).

$$\tau = \frac{K\lambda}{\beta \cos\theta} \quad (1)$$

2.6. Design of Experiments

Each batch consisted of: white petrolatum (38.25%), paraffin 110–230 mPa·s (21.25%), cetomacrogolwax (25.5%) and isopropylmyristate (15%). A DoE with 14 runs (Table 1), made of a mixture design with 5 continuous variables at 3 levels combined with 1 discrete factor at 2 levels, was used during this study. Six parameters were varied: maximum product temperature: ProdT (60.0–80.0 °C), SiO_2 particles: SilP (0.0–0.10%), mixing rate: MixR (10–100 rpm), cooling rate: CoolR (0.15–1.0 °C·min^{-1}), exit temperature: ExitT (30.0–37.0 °C) and 10 min mixing in the last step before filling: MixF (Yes/No) (Table 1). The resulting products were analysed for a number of CQAs; these are

Table 1
Detailed experimental conditions for the DoE. ProdT = Product temperature, MixS = Mixing speed, CoolR = Cooling rate, ExitT = Exit temperature and MixF = 10 min isothermal mixing before filling.

#	ProdT (°C)	Addition SiO_2 (%)	MixS (rpm)	CoolR (°C/min)	ExitT (°C)	MixF
1	70	0.05	55	0.575	33.5	Yes
2	80	0.10	100	0.15	33.5	No
3	80	0.05	10	1.0	37	No
4	60	0.10	55	1,0	30	No
5	70	0.05	55	0.575	33.5	No
6	60	0.05	100	0.15	30	Yes
7	80	0.10	10	0.575	30	Yes
8	80	0.00	55	0.15	37	Yes
9	60	0.00	10	1.0	33.5	Yes
10	70	0.00	10	0.15	30	No
11	60	0.10	10	0.15	37	No
12	80	0.00	100	1.0	30	Yes
13	60	0.00	100	0.575	37	No
14	70	0.10	100	1.0	37	Yes

specified in the paragraph critical quality attributes. After model analysis optimal formulation and process variables were identified; this model was subsequently validated in triplicate by producing at optimal settings and measuring the CQAs.

2.7. CQA Target Windows

Critical quality attributes were established beforehand based on rheological properties commonly described in literature and on results of sensory testing by an internal test panel (N = 10). In the latter case, panel members were asked to evaluate different batches of cetomacrogol ointment and determine what they felt appropriate for patient use. Based on the results the following targets were set: yield stress (500–800 Pa), RSD yield stress, expressed as Ln RSD (minimization), LVR height (400.000–600.000 Pa), zero shear viscosity (500–750 Pa·s), viscosity 20 °C (6.0–9.0 Pa·s), axial compressibility (10–25 N) and axial tension (10–30 N).

2.8. Statistical Analysis

Analysis was conducted according to the methodology for definitive screening designs (Jones and Nachtsheim, 2011) by an independent statistical expert (Stanwick, Merelbeke, Belgium). Software from SAS, JMP-12 was used. For every CQA, a statistical analysis was conducted and finalised by analysing the residuals plot for potential outliers and for confounding using the VIF function (VIF < 5). The analysis results in a model function by which values for CQAs can be predicted based on input variable settings.

For every single CQA the analysis was stored and subsequently all CQAs were analysed together in order to optimize all input variables for all CQAs. This optimization produced desirability graphs that showed whether chosen settings for a variable could produce ointment on target, a value of 1.0 means completely on target and 0.0 completely off target.

The outcomes of the statistical analysis for single CQAs or for all CQAs are referred to as "model".

3. Results and Discussion

The following outputs were evaluated in the current study namely yield stress, homogeneity (in %RSD), LVR-height, viscosity, zero shear viscosity, axial compression and axial tension.

On all outcomes, stepwise regression analysis was conducted to design a model that estimates the influence of formulation and process variables on CQAs. The model for yield stress is described below as an example. Subsequently all CQAs were analysed together to design a final model for the optimization of cetomacrogol ointment production process.

3.1. Model for Yield Stress

In the current study, yield stress (at 20 °C) of the products was found to lie between 272 and 1309 Pa. (Fig. 1) As can be seen, only 5 of the 14 produced batches are within the specification for yield stress. Yield stress was shown to be an important parameter for pharmaceutical and cosmetic materials when considering storage stability and sensory features such as spreadability (Park and Song, 2010). Based on sensory testing by an internal test panel (N = 10), yield stress values may be roughly categorized as follows: yield stresses <400 Pa are more cream-like and ointments with yield stress >800 Pa are too thick to be removed from a tube. Therefore the observed differences in yield stresses for the different tested products (272–1309 Pa) will have a substantial impact. To assess the impact of formulation and process variables on ointment yield stress, a non-linear statistical model was created; a summary is shown in Fig. 2.

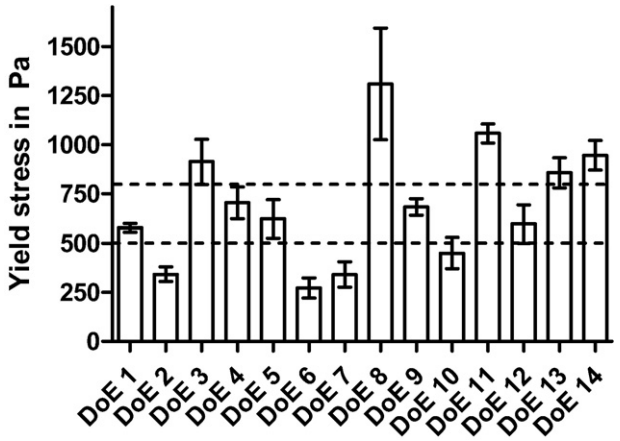

Fig. 1. Yield stress results for DoE ointment batches measured at 20 °C, CQA window is defined in the range of 500–800 Pa (shown in dashed lines). Yield stress is expressed as mean ± SD.

Exit temperature, mixing rate and addition of SiO_2 particles all showed a significant effect. (p-values: 0.0065, 0.0013 and 0.0073 respectively). Furthermore, mixing rate and exit temperature showed a statistically significant interaction (p-value 0.0116).

The statistical function for this model given by Eq. 2 can be used to estimate the yield stress with a certainty shown in the ANOVA of F = 50.2336 and a probability of p = 0.0009. This means that statistical significant differences have been found in the analysed data. Furthermore the model is able to explain 97.2% of variation in the yield with a R^2adjusted = 0.97198 and no lack of fit p > 0.05. Therefore this model can be considered as a reliable way to describe cetomacrogol ointment yield stress.

$$\begin{aligned}\text{Yield stress (Pa)} = {} & -1909,074 - 1155,90 * SiO_2 \\ & + (SiO_2 * SiO_2 * 75815,70) - 0,96 * \text{MixR} \\ & + (\text{MixR} * \text{MixR} * -0,13) + 91,78 * \text{CoolR} \\ & + 77,06 * \text{ExitT} + (\text{ExitT} * \text{ExitT} * 14,74) \\ & + (\text{MixR} * \text{CoolR} * 1,86) \\ & + (\text{MixR} * \text{ExitT} * -0,57) \end{aligned} \quad (2)$$

For all six other CQAs (overview shown in Fig. 2) similar statistical functions were calculated using the same approach and subsequently analysed together to design a model for all CQAs.

3.2. Optimizing Formulation and Process Variables for all CQAs

The overview of the effects of the five process variables is shown in Fig. 3; all significant effects are marked with an asterisk (*) and acceptable ranges for the CQAs are shown in grey bars.

In Fig. 3, it can be seen that mainly mixing rate and exit temperature had an important and statistical significant effect on several of the CQAs, namely yield stress, LVR-height, zero shear viscosity, axial compression and axial tension. The addition of SiO_2 particles (within the tested range of 0.0%–0.1%) also has statistical significant effects, however this effect does not influence any CQA enough for it to be out of specification. Therefore addition of SiO_2 particles to the formulation is not considered critical. Interestingly, research from the Dutch pharmaceutical association (FNA) has shown that the addition of 0.1% of SiO_2 particles is critical for large scale production (Scientific Institute for Dutch Pharmacists, 2013). As shown in this study, apparently this is not the case for at least small scale production.

The desirability graphs for all CQAs in the bottom of Fig. 3 show the optimal settings for the process variables. From these graphs it can be concluded that mixing rate is critical and that the optimal rate lies in the middle; 60 rpm. Furthermore, exit temperature, which is the temperature at which containers are filled, has a significant influence and

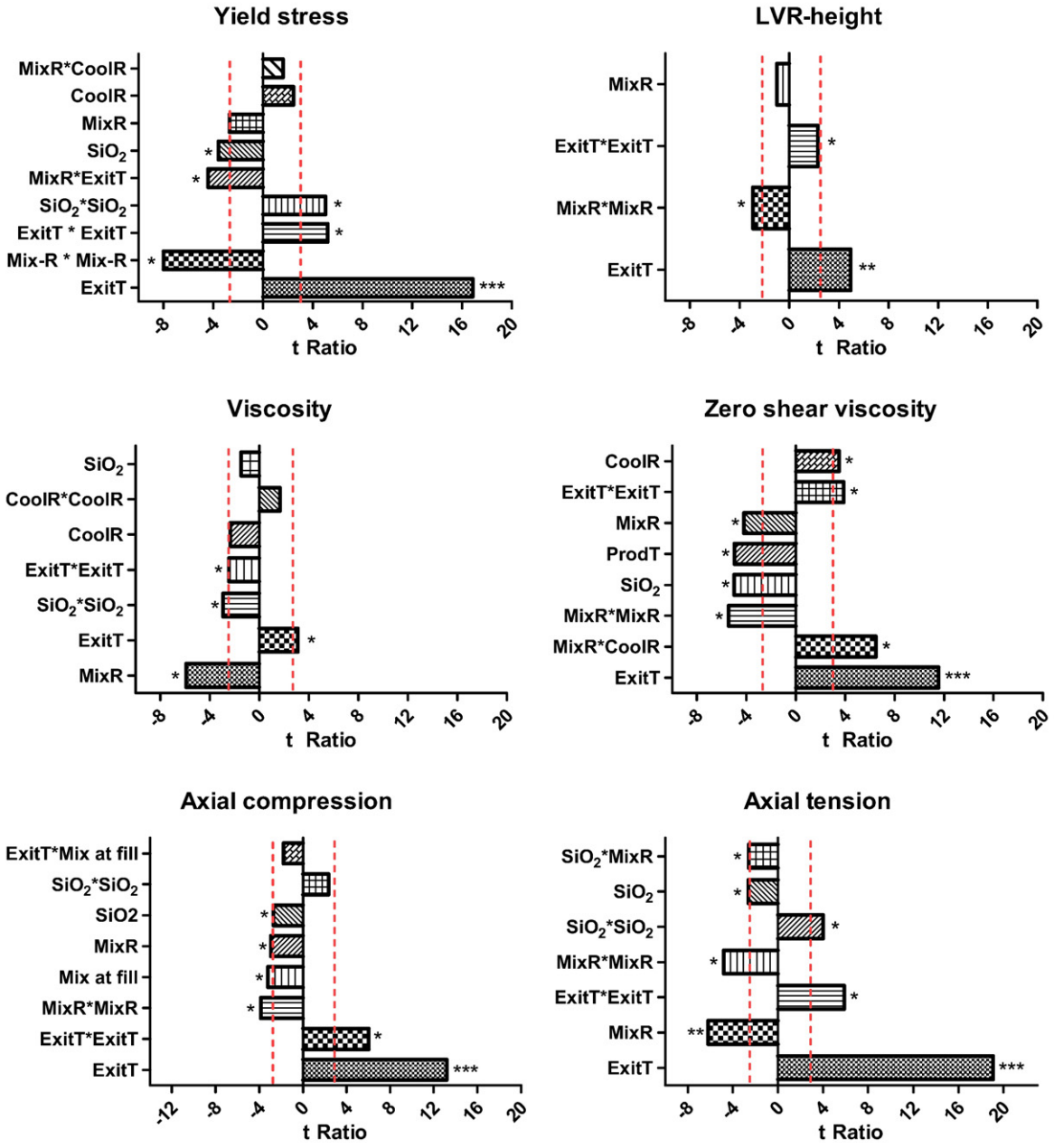

Fig. 2. Sorted parameter estimates based on t-ratio for various formulation and process parameters. *p-value < 0,05, **p-value < 0,001, ***p-value < 0,0001.

should therefore be precisely controlled. Preferably, temperature for filling cetomacrogol ointment containers should be 31.9 °C. Furthermore, it can be concluded that for any tested cooling rates between 0.15 and 1.0 °C/min, all CQAs are within specification. Heating temperature (ProdT) has no significant impact on any of the CQAs, nor did mixing at filling temperature for 10 min.

To estimate whether this model is able to predict the influence of all studied parameters on cetomacrogol ointment structure, verification was conducted in triplicate. For this verification, ointment was produced at the optimal settings (shown at the bottom of Fig. 3) and all in the DoE studied CQAs were analysed. Results (see Table 2) show that the RSD between the three batches was between 1.0 and 11.6%. The deviation of the average outcome from the target value is relatively high for LVR-height and axial tension (8.6% and 15.3% respectively). However, deviations in rheological analyses are prone to be high: from 10 to 20% depending on the used equipment and methods. Therefore, this variation between measurements can be considered to be normal; and additionally, important parameters such as yield stress show values close to the target setting (−2.8%).

Thus, all three individual batches were within specification and based on these results, the model can be considered valid.

3.3. Understanding Mechanisms Behind Significant Parameters

In order to understand why mixing rate and exit temperature have a significant impact on ointment structure, further experiments were conducted.

To study the effect of mixing rate in more detail, fresh ointment batches were produced, similar to the DoE batches, with mixing rate as the only variable. Batches used in the DoE were not used, since in this design no batches were produced with only this process variable. Data are shown in Fig. 4. It can be seen that the pattern is similar to the pattern found in the model. Since it is known that crystallinity

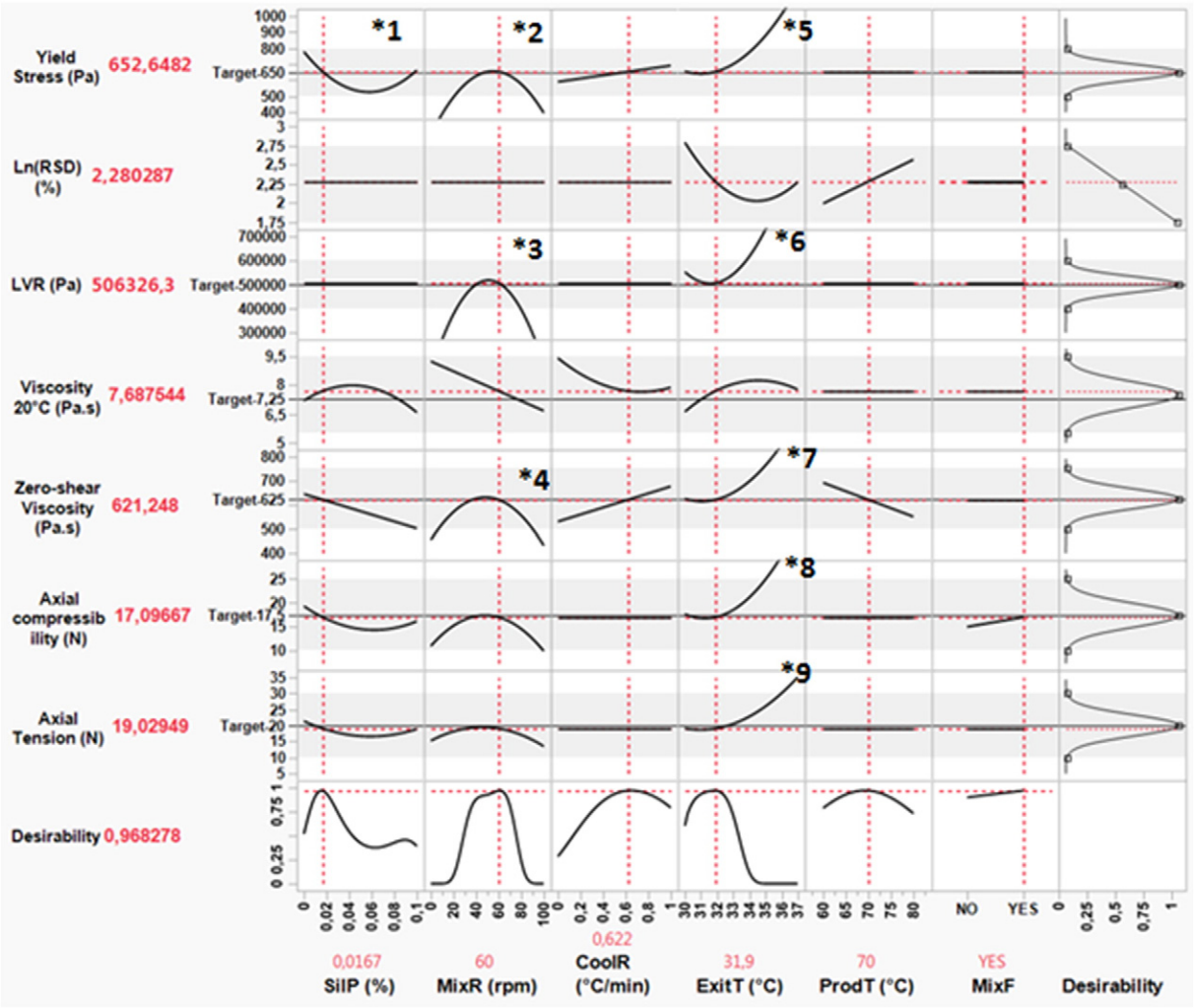

Fig. 3. Summary of all outcomes from DoE study, significant results*. Acceptable target range shown in grey. 1) p = 0.02307 2) p = 0.0013 3) p = 0.01757 4) p = 0.00292 5) p = 0.0065 6) p = 0.04679 7) p = 0.01159 8) p = 0.00180 9) p = 0.00109. SilP = silica nano particles; MixR = Mixing rate; CoolR = Cooling rate; ExitT = Exit temperature; ProdT = Product temperature; MixF = 10 min isothermal mixing.

may influence structure, X-ray analysis was conducted on these samples (Larrañaga et al., 2014).

The parabolic relationship for yield stress dependency on mixing rate can possibly be a consequence of a higher percentage of crystalline material in the 55 rpm sample compared to the 10 and 100 rpm samples (5.6% compared to 4.7% and 4.3%). These small differences in crystallinity may contribute to a significant difference in yield stress, because the crystallites are very small (approximately 20–50 nm). Crystallite size was determined using X-ray diffractometry, a convenient method for determining the mean size of nanosized crystallites and sample preparation that is less destructive (Monshi, 2012). As was shown in (van Heugten et al., 2016) particles of nanosize have a major effect on ointment yield stress. Since SiO_2 particles of approximately 15 nm were used in the current study it was expected that these would also have a major effect on ointment yield stress. However as Fig. 5 shows, an apparent threshold for the ability of SiO_2 to increase the yield stress in cetomacrogol ointment lies above the concentrations used in the DoE. Therefore it can be understood why SiO_2 did not have a significant impact on the consistency of cetomacrogol ointment. Similar phenomena have been described for other materials such as polymer composites, polyhydroxyalkanoates and inulin. (Larrañaga et al., 2014; Mermet-Guyennet et al., 2015; Ronkart et al., 2010)

Table 2
Summary of verification batches produced at optimal settings: ProdT 70 °C, ExitT 31.5 °C, MixS 50 rpm, SiO_2 0.0167%, CoolR 0.6 °C/min.

Output parameter	Target	RSD between validation batches (%)	Deviation of average from target (%)
Average yield stress (Pa)	653	3.6	−2.8
Ln (RSD)	2.28	11.6	2.3
Average LVR height (Pa)	506,326	8.1	8.6
Average viscosity 20 °C (Pa·s)	7.7	4.2	−2.0
Average zero shear viscosity (Pa·s)	621	1.0	3.1
Average axial compressibility (N)	17.1	8.9	7.8
Average axial tension (N)	19.0	6.1	15.3

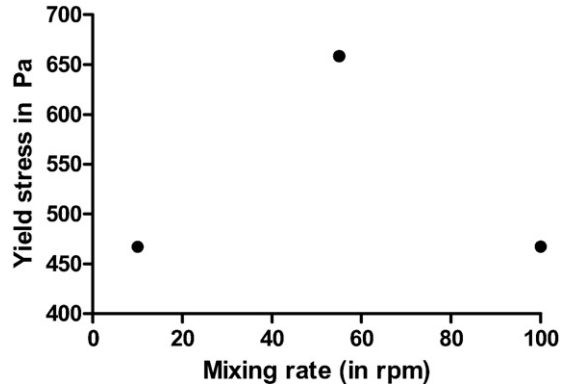

Fig. 4. Influence of mixing rate on yield stress. Processing conditions: ProdT 70 °C, ExitT 31.5 °C, MixS 50 rpm, SiO_2 0.014%, CoolR 0.6 °C/min.

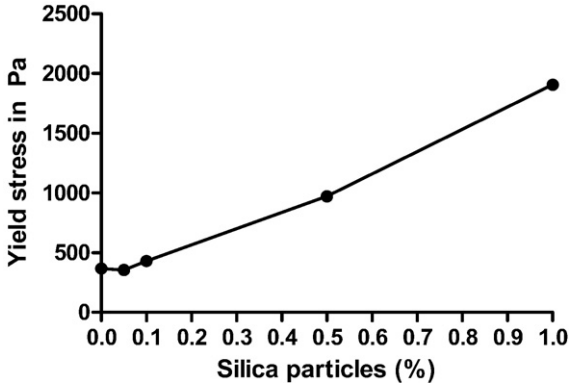

Fig. 5. Effect of SiO_2 particles on yield stress of cetomacrogol ointment. Processing conditions: ProdT 70 °C, MixS 55 rpm, CoolR 0.5 °C/min , ExitT 30 °C.

A possible explanation for the parabolic relationship between yield stress and mixing rate may also be found in the crystallinity. It can be argued that nuclei growth during cooling is dependent upon the agitation of the mass. When mixing is optimal nucleus growth exhibits a similar rate compared to the transport of molecules to and from the nuclei. At lower rate, the supply of molecules that fit in the crystal structure is sub-optimal, while at higher rate the shear leads to abrasive effects. Consequently, an optimum may be observed at 55 rpm. A similar phenomenon has been described for the influence of mixing rate on emulsion polymerization in a batch reactor (Fathi Roudsari et al., 2015).

When the approach of using a definitive screening design (DSD) is compared to the traditionally used fractional factorial designs, remarkable differences can be observed. For example, in traditional fractional factorial designs, variables are usually studied on two levels while in a DSD variables are studied on three levels. Studying variables on only two levels allows no estimation to be made of curvature, meaning nonlinear patterns of variables. When our results are reflected it can be seen that in this study, every single variable showed nonlinear or curvature effects (Fig. 3). These patterns would not have been observed in standard two-level screening designs. Thus, a DSD can be viewed as a highly efficient screening design with significant advantages over the more traditionally used fractional factorial designs. Statistical analysis however should be conducted according to the methodology for DSDs. (Dougherty, 2013; Jones and Nachtsheim, 2011).

4. Conclusion

This study shows that a definitive screening design is a helpful tool to gain insight into a production process such as the production of cetomacrogol ointment. For this ointment it has been shown that processing had a substantial influence on important rheological parameters such as yield stress. Of all testes process variables, filling temperature and mixing speed are critical. These two variables also have a significant interaction. With these findings a process window was established within which cetomacrogol ointment of constant quality can be produced.

Acknowledgements

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

References

Chang, R.-K., Raw, A., Lionberger, R., Yu, L., 2013a. Generic development of topical dermatologic products: formulation development, process development, and testing of topical dermatologic products. AAPS J. 15:41–52. http://dx.doi.org/10.1208/s12248-012-9411-0.

Chang, R.-K., Raw, A., Lionberger, R., Yu, L., 2013b. Generic development of topical dermatologic products, Part II: quality by design for topical semisolid products. AAPS J. 15: 674–683. http://dx.doi.org/10.1208/s12248-013-9472-8.

Dougherty, S.A., 2013. A Comparison Study of Second-Order Screening Designs and Their Extension.

Fathi Roudsari, S., Dhib, R., Ein-Mozaffari, F., 2015. Mixing effect on emulsion polymerization in a batch reactor. Polym. Eng. Sci. 55:945–956. http://dx.doi.org/10.1002/pen.23963.

Gilbert, L., Savary, G., Grisel, M., Picard, C., 2013. Predicting sensory texture properties of cosmetic emulsions by physical measurements. Chemom. Intell. Lab. Syst. 124: 21–31. http://dx.doi.org/10.1016/j.chemolab.2013.03.002.

van Heugten, A.J.P., Versluijs-Helder, M., Vromans, H., 2016. Elucidation of the variability in consistency of Pharmacopoeia quality Petrolatum. Drug Dev. Ind. Pharm. http://dx.doi.org/10.1080/03639045.2016.1274902.

Jones, B., Nachtsheim, C.J., 2011. A class of three-level designs for definitive screening in the presence of second-order effects. J. Qual. Technol. 43:1–15. http://dx.doi.org/10.2514/6.2000-4890.

Larrañaga, A., Fernández, J., Vega, A., Etxeberria, A., Ronchel, C., Adrio, J.L., Sarasua, J.R., 2014. Crystallization and its effect on the mechanical properties of a medium chain length polyhydroxyalkanoate. J. Mech. Behav. Biomed. Mater. 39:87–94. http://dx.doi.org/10.1016/j.jmbbm.2014.07.020.

Lashmar, U.T., Richardson, J.P., Erbod, A., 1993. Correlation of rheological properties of an oil in water emulsion with manufacturing procedures and stability. Int. J. Pharm. 91: 59–67. http://dx.doi.org/10.1016/0378-5173(95)00149-D.

Mermet-Guyennet, M.R.B., Gianfelice De Castro, J., Varol, H.S., Habibi, M., Hosseinkhani, B., Martzel, N., Sprik, R., Denn, M.M., Zaccone, A., Parekh, S.H., Bonn, D., 2015. Size-dependent reinforcement of composite rubbers. Polymer 73:170–173 (United Kingdom). 10.1016/j.polymer.2015.07.041.

Monshi, A., 2012. Modified Scherrer equation to estimate more accurately nano-crystallite size using XRD. World J. Nano Sci. Eng. 2:154–160. http://dx.doi.org/10.4236/wjnse.2012.23020.

Ozkan, S., Gillece, T.W., Senak, L., Moore, D.J., 2012. Characterization of yield stress and slip behaviour of skin/hair care gels using steady flow and LAOS measurements and their correlation with sensorial attributes. Int. J. Cosmet. Sci. 34:193–201. http://dx.doi.org/10.1111/j.1468-2494.2012.00702.x.

Park, E.-K., Song, K.-W., 2010. Rheological evaluation of petroleum jelly as a base material in ointment and cream formulations: steady shear flow behavior. Arch. Pharm. Res. 33:141–150. http://dx.doi.org/10.1007/s12272-010-2236-4.

Ronkart, S.N., Paquot, M., Deroanne, C., Fougnies, C., Besbes, S., Blecker, C.S., 2010. Development of gelling properties of inulin by microfluidization. Food Hydrocoll. 24: 318–324. http://dx.doi.org/10.1016/j.foodhyd.2009.10.009.

Scientific Institute for Dutch Pharmacists, 2013. Cetomacrogolzalf. commentary. Formularium Der Nederlandse Apothekers (FNA), fifth ed., pp. 133–135.

Xu, X., Al-Ghabeish, M., Rahman, Z., Krishnaiah, Y.S.R., Yerlikaya, F., Yang, Y., Manda, P., Hunt, R.L., Khan, M.A., 2015. Formulation and process factors influencing product quality and in vitro performance of ophthalmic ointments. Int. J. Pharm. http://dx.doi.org/10.1016/j.ijpharm.2015.07.066.