AAPS PharmSciTech, Vol. 12, No. 1, March 2011 (© 2011)
DOI: 10.1208/s12249-011-9589-y

Research Article

Introduction of a Theoretical Splashing Degree to Assess the Performance of Low-Viscosity Oils in Filling of Capsules

Andreas Niederquell[1] and Martin Kuentz[1,2]

Received 10 November 2010; accepted 19 January 2011; published online 1 February 2011

Abstract. These days an alternative to soft capsules is liquid-filled hard capsules. Their filling technology was investigated earlier with highly viscous formulations, while hardly any academic research focused on low-viscosity systems. Accordingly, this work addressed the filling of such oils that are splashing during the dosing process. It was aimed to first study capsule filling, using middle-chain triglycerides as reference oil, in order to then evaluate the concept of a new theoretical splashing degree for different oils. A laboratory-scale filling machine was used that included capsule sealing. Thus, the liquid encapsulation by microspray technology was employed to seal the dosage form. As a result of the study with reference oil, the filling volume and the temperature were found to be significant for the rate of leaking capsules. The filling volume was also important for weight variability of the capsules. However, most critical for this variability was the diameter of the filling nozzle. We proposed a power law for the coefficient of weight variability as a function of the nozzle diameter and the obtained exponent agreed with the proposed theory. Subsequently, a comparison of different oils revealed that the relative splashing degree shared a correlation with the coefficient of the capsule weight variability (Pearson product moment correlation of r=0.990). The novel theoretical concept was therefore found to be predictive for weight variability of the filled capsules. Finally, guidance was provided for the process development of liquid-filled capsules using low-viscosity oils.

KEY WORDS: dosing; hard capsules; liquid-filling; low-viscosity oils; quality by design.

INTRODUCTION

Lipid-based drug delivery is a key formulation option for dealing with biopharmaceutically challenging drugs (1–3). However, the enhancement of oral bioavailability is not the only rationale for this formulation principle. Depending on the given drug, there are also other reasons why to develop such lipid-based systems. It is, for example, a good formulation principle for low-dose/high-potency drugs because a good content uniformity is reached, while the liquid-processing is further beneficial for the safety of technicians (4). Moreover, some drugs with a critical chemical stability or with extensive hygroscopicity can profit from the embodiment in lipid formulations.

Once the decision has been made to formulate such a lipid-based system, several technical options exist to obtain a final dosage form. These pharmaceutical technologies have recently been reviewed by Jannin *et al.* (5). Herein, the most widespread dosage form is still the soft capsule; however, the liquid-filled hard capsule has become a vital alternative. The technology has greatly evolved since the early days of filling hard capsules (6). For example, the sealing of two-piece capsules can either be done by band-sealing or using the more recent technique of liquid encapsulation by microspray (LEMS; 7,8). The latter method sprays a sealing liquid onto the join between the capsule halves and subsequently, capillary forces draw the liquid up between the cap and body. Such moisturization lowers the melting point of gelatin so that gentle heat of about 40°C leads to a melting of the polymeric material resulting in tight capsule sealing (9).

Apart from the sealing technology, it was especially the availability of laboratory-scale equipment that made the liquid-capsule filling attractive for early development. Thus, formulators can early initiate stability programs with only limited material. Even clinical supplies can be produced in-house so that outsourcing of this activity to a contract researcher is no longer mandatory.

The technical filling of two-piece capsules is these days a straightforward process so that a very low rate of capsule failures is easily obtained. However, the formulation has an impact on the performance of the filling step and some systems can be technically challenging. One example is the case of highly viscous fill masses. Depending on the viscoelastic properties, it has often been observed that the formulation was not breaking clean from the dosing nozzle so that a high variability of the fill weight resulted. Hawley, *et al.* and Shah *et al.* evaluated thermo-softening formulations for liquid-filled capsules, whereas Walters *et al.* studied silicon dioxide gels in oils (9–11). Later, the rheological behavior of

[1] Institute of Pharma Technology, University of Applied Sciences Northwestern Switzerland, Gründenstr. 40, CH-4132, Muttenz, Switzerland.
[2] To whom correspondence should be addressed. (e-mail: martin.kuentz@fhnw.ch)

particulate polymer dispersions was investigated with respect to a liquid-filling of capsules (12,13).

While most research was carried out with such highly viscous formulations, the low-viscosity systems were barely explored in scientific publications. This is in contrast to the importance of such formulations for liquid filling of capsules. A low viscosity is for example often encountered with drug delivery systems and it is a typical attribute of oils that are encapsulated as food supplements.

Industrial scientists often tried to avoid a technical issue by adhering to the proposal that the viscosity should not be lower than 0.1 Pas (14). However, the simple avoidance of a low viscosity is not always possible or meaningful. Formulation scientists should not be limited in their choice of oils. Moreover, the option of adding a viscosity enhancer is likely to affect the drug-release kinetics (15). Accordingly, there is the need to fill capsules at a low viscosity and this emphasizes the importance of gaining a better understanding of the involved technical issues.

From a practical experience, it is known that oils at a low viscosity can splash during capsule filling. This mechanism is negatively affecting the weight variations as well as the sealing quality. Unfortunately, the physical description of the splashing event is complex. An interaction takes place between the dosing liquid and, first, the surface of the capsule and, later, the liquid surface of the formulation. The physics of how a droplet collides with a solid or liquid surface is a field of current research (16–19).

However, from a practical viewpoint of capsule filling, it is sufficient to have a parameter that describes the risk of splashing during the process. Such anticipation of splashing would provide guidance to optimize the formulation as well as to improve the process with respect to the filling precision.

Accordingly, the present study was aimed at introducing a new concept. A theoretical splashing degree was proposed for oils. The capsule dosing performance was first studied using middle-chain triglycerides as reference oil. Subsequently, different oils were to be filled into capsules and the results were to be interpreted considering the novel splashing degree. It was further intended to clarify a potential dripping from the dosing nozzle with respect to the accuracy of filling.

MATERIALS AND METHODS

Materials

The middle-chain triglyceride oil Miglyol® 812, peanut oil, linseed oil, peppermint oil as well as the lemon oil were obtained from the vendor Hänseler AG (Herisau, Switzerland). Capryol® 90 (propylene glycol monocaprylate) and Transcutol® HP (purified diethylene glycol monoethyl ether) were kindly supplied by Gattefossé (Lucerne, Switzerland). Ethanol (absolute) was purchased from J. T. Baker (Deventer, Netherlands). All excipients were used as supplied without any further purification. Finally, the used hard gelatin capsules were Licaps® of size 1 (Capsugel, Bornem, Belgium).

Physical Characterization of the Oils

All measurements of the physical characterization were conducted at 25°C in triplicate. The mean values were given together with their standard deviations for the different oils. Density was determined based on the oscillating body method. For this purpose, a density meter DA-100 M from Mettler-Toledo GmbH (Greifensee, Switzerland) was employed.

Dynamic surface tension was measured using the bubble pressure method. The differential pressure was measured along a capillary, while air bubbles were introduced into the sample. Depending on the measured pressure difference and taking the capillary diameter into account, the instrument determined a dynamic surface tension. This value was dependent on the bubble frequency and therefore on the age of the generated surface. We selected a comparatively long surface lifetime of 2,500 ms to obtain a good reproducibility of the data. A SITA DynoTester tensiometer ("SITA Messtechnik" GmbH, Dresden, Germany) was employed for this surface tensiometry.

Finally, the viscosity was determined using capillary viscosimetry. An Ubbelohde viscosimeter of type II was used for the experimental measurements. This glass instrument had a capillary with a suspending ball level and was supplied by SI Analytics GmbH (Mainz, Germany).

Capsule Filling Using the Licaps/LEMS Technology

A laboratory-scale capsule filling and sealing equipment of the type CFS1200™ (Capsugel, Colmar, France) was employed. Licaps™ (Capsugel, Colmar, France) of size 1 were filled in defined percentages of a 100% nominal fill volume of 0.5 ml. A reference value was also given with respect to the speed of the machine. Thus, a 100% speed was corresponding to about 1,200 capsules per hour and different speeds were selected in percentages of this reference value. Moreover, we used different temperatures from 25 to 45°C to heat the fill mass in the tank. Finally, various dosing nozzles were used with a diameter of 0.8–1.2 mm for the conduct of the statistical design (Table I) and later the range was extended up to 3.0 mm for the additional experiments.

During the manufacturing, the capsules were always maintained in a vertical position throughout the filling and sealing process. The latter sealing step employed a clamp system so that capsules were in contact from two opposing sides. A sealing solution (20 μL), consisting of ethanol/water (1:1, *w*/*w*), was sprayed through clamp holes. Capillary forces delivered the liquid between the two pieces of the gelatin capsule to enable a fusion of the material and excess fluid was removed by vacuum. Subsequently, the automated process blew heated air of 45°C across the capsule to complete the fusion and hence the sealing step.

To manufacture the individual batches, the targeted filling volumes were adjusted in runs of 20 capsules. The main batch was then manufactured with a rejection of the first 15 capsules. Finally, 60 capsules were randomly selected from each manufacturing batch (n=300) to check the mean coefficient of weight variability (CV).

The fraction of leaking capsules was obtained by visually inspecting 250 capsules from each batch. Prior to this assessment, the capsules were equilibrated for 12 h in a vacuum drying cabinet KVTS11 (Salvis AG, Switzerland) at constant pressure (150 mbar).

For the analysis of the relationship between the coefficient of weight variability and the inner nozzle diameter, all

Table I. Design Plan for the Study of the Reference Oil Middle-Chain Triglycerides

Run	A: temperature (°C)	B: nozzle diameter (mm)	C: filling volume (%)	D: filling speed (%)
1	25	1	95	90
2	35	1	87.5	90
3	35	0.8	80	90
4	35	1	87.5	90
5	35	1.2	95	90
6	45	1.2	87.5	90
7	35	1	95	80
8	25	1.2	87.5	90
9	25	1	80	90
10	45	1	80	90
11	45	0.8	87.5	90
12	35	1.2	87.5	100
13	25	1	87.5	80
14	35	1	80	100
15	25	0.8	87.5	90
16	35	1	80	80
17	45	1	87.5	100
18	35	1.2	87.5	80
19	45	1	87.5	80
20	35	1.2	80	90
21	45	1	95	90
22	35	1	87.5	90
23	25	1	87.5	100
24	35	1	95	100
25	35	0.8	87.5	100
26	35	0.8	87.5	80
27	35	0.8	95	90

batches (n=150) were manufactured in triplicate with the same parameter settings as selected for the center point of the statistical design (Table I).

Statistical Analysis and Design of Experiment

The program STATGRAPHICS® Centurion XV ed. Professional from Statpoint Technologies Inc. (Warrenton, USA) was used for the statistical data treatment including the planning and evaluation of the statistical design. A response surface design was selected to investigate the process parameters of the reference oil medium-chain triglycerides and Table I shows the corresponding factor settings.

Part of the design evaluation was an analysis of the variance and a presentation of the factors as a Pareto chart. This data evaluation was based on a characteristic data transformation. Each effect was converted to a t statistic dividing it with its standard error. The standardized effects were then plotted in decreasing order for absolute magnitude.

Following this statistical study plan, the influence of the nozzle diameter on the weight variability of the capsules was investigated in more detail. Thus, data were analyzed here by a non-linear regression that employed the Marquardt algorithm to minimize the residual sum of squares until a convergence was obtained. The quality of the model fit was then assessed with respect to the R^2 value and the residuals were inspected to see potential trends. The absence of such trends underlined the suitability of the chosen mathematical equation.

RESULTS AND DISCUSSION

Theoretical Development

The filling of low-viscosity oils is often accompanied by a splashing around the dosing nozzle. It is mainly the portion of oil that is spilling out of the capsule, which is critical here. This splashed oil decreases the filling adequacy and oil contamination of the capsule rim further leads to issues of the sealing process. It would be beneficial to anticipate such a splashing of liquids and therefore the work of Rodrigues and Mesler (20) is of interest. The authors delineated the process of coalescence and splashing of droplets impacting upon a liquid pool. Different regimes of the Froude and Reynolds number were proposed that indicate whether or not a drop impact results in a splash.

The current article follows a different approach and introduces a single non-dimensionless parameter for a liquid's potential for splashing. We call this parameter the splashing degree and it is defined in the following way.

Given that a small mass Δm is passing through the filling nozzle, it will impact with velocity v on a surface. The impact can result either in a splash or not. A splash would in any case lead to generation of a new surface. The maximal new surface in the splashing event minus the surface before the impact of Δm is named a "splashing surface" ΔS. Subsequently, a "splashing degree" δ_s can be defined by normalizing ΔS by the mass fraction Δm:

$$\delta_s \equiv \frac{\Delta S}{\Delta m} \tag{1}$$

The impact of Δm comes with a kinetic energy and it is assumed that a fraction f of this energy is transferred to generation of ΔS. Taking the surface tension γ_s into account and by neglecting the potential energy of Δm we find:

$$f\frac{1}{2}\Delta m v^2 = \gamma_s \Delta S \tag{2}$$

$$\delta_s = \frac{f v^2}{2\gamma_s} \tag{3}$$

The Hagen-Poisseuille law defines a volume flow per time, Q along a tube or nozzle length L_n with radius R_n, given a pressure difference ΔP along the dosing nozzle and the dynamic viscosity η:

$$Q = v\pi {R_n}^2 = \frac{\pi {R_n}^4 |\Delta P|}{8\eta L_n} \tag{4}$$

Accordingly, we find for the splashing degree:

$$\delta_s = \frac{f Q^2}{2\pi^2 {R_n}^4 \gamma_s} \tag{5}$$

and

$$\delta_s = \frac{f {R_n}^4 \Delta P^2}{128\eta^2 {L_n}^2 \gamma_s} \tag{6}$$

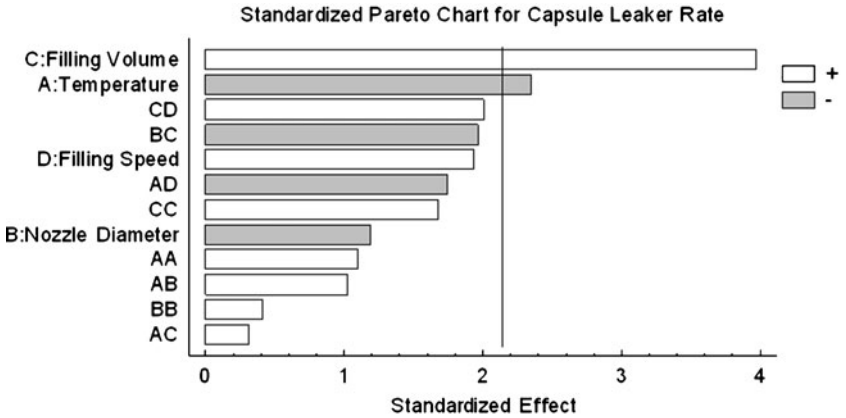

Fig. 1. Standardized effects for the leaker rate of the capsules using middle-chain triglycerides

From a practical viewpoint, it is meaningful to compare an oil of unknown filling performance with well-characterized reference oil. Thus, a sample with the viscosity η_x and surface tension γ_{sx} can be linked to a reference material of viscosity η_{ref} and surface tension γ_{sref} under the following simplifying assumptions. The factor f for both materials shall be of the same order of magnitude and also the filling pressure difference should be in the same range. Using the same nozzle diameter and length, we can define a relative splashing degree δ_{srel} as follows:

$$\delta_{\text{srel}} \equiv \frac{\delta_{\text{sx}}}{\delta_{\text{sref}}} \cong \left(\frac{\eta_{\text{ref}}}{\eta_x}\right)^2 \frac{\gamma_{\text{sref}}}{\gamma_{\text{sx}}} \tag{7}$$

Apart from droplet splashing, there is another potential mechanism of fill weight inadequacy. Thus, a formulation can be dripping from the nozzle, which increases the variability of the dosing weight. However, some capsule machines apply a backpressure at the end of the filling cycle so that a hanging drop would be retracted into the nozzle. Without such a negative pressure, it is simple to calculate the force equilibrium of a hanging drop at the dosing nozzle. Accordingly, a hanging drop of volume V_d and density ρ has a force equilibrium at a defined nozzle radius R_{ne}:

$$2\pi R_{\text{ne}}\gamma_s = V_d\rho g \tag{8}$$

where g is the acceleration of gravity. Based on Eq. 8 an equilibrium nozzle radius or the corresponding equivalent nozzle diameter D_{ne} can be defined:

$$D_{\text{ne}} \equiv \sqrt{\frac{6\gamma_s}{\rho g}} \tag{9}$$

For nozzle diameters larger than D_{ne}, a hanging drop would theoretically fall down.

Study of Capsule-Filling Parameters Using Middle-Chain Triglycerides as Reference Oil

Before we started comparing different oils, it was important to study varying process parameters using a reference oil. We selected middle-chain triglycerides for this purpose, since the viscosity at 25°C was clearly below 100 mPas. This excipient was deemed a good candidate for low-viscosity oil in capsule filling.

Table I shows the different experimental parameters. Thus, temperature of the filling process was factor A, whereas different filling nozzle diameters provided a second parameter B. We evaluated filling volumes, as factor C, from 80% to 95% of the available nominal capsule volume. The capsules were in this range still adequately filled, which was of industrial relevance. We further considered the industrial relevance with respect to factor D. This factor of filling speed was only studied in a comparatively narrow range, which avoided a low machine speed that is unrealistic for manufacturing.

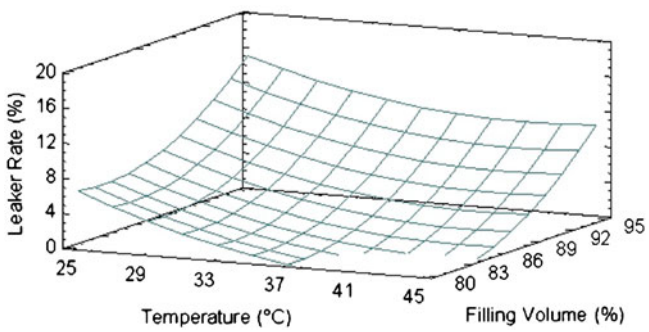

Fig. 2. Surface plot—influence of temperature and filling volume on the leaker rate using middle-chain triglycerides

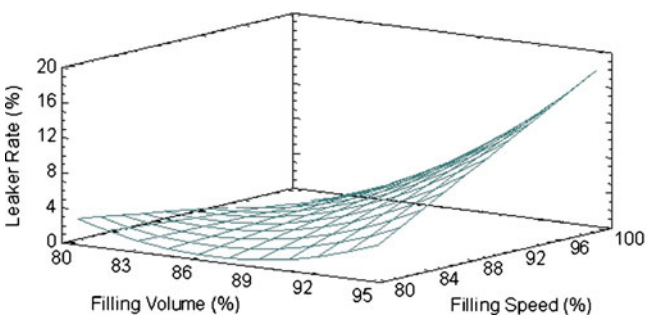

Fig. 3. Surface plot—influence of filling volume and filling speed on the leaker rate using middle-chain triglycerides

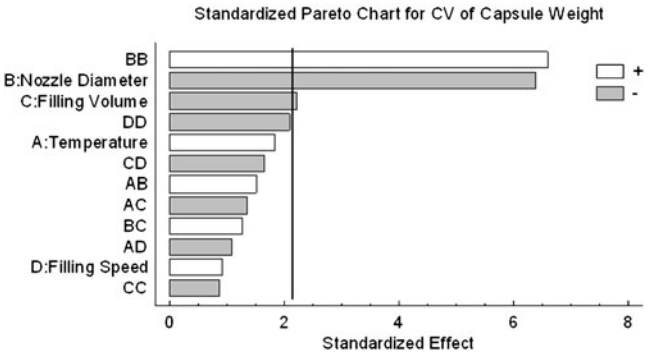

Fig. 4. Standardized effects for CV of the capsule weight in case of middle-chain triglycerides

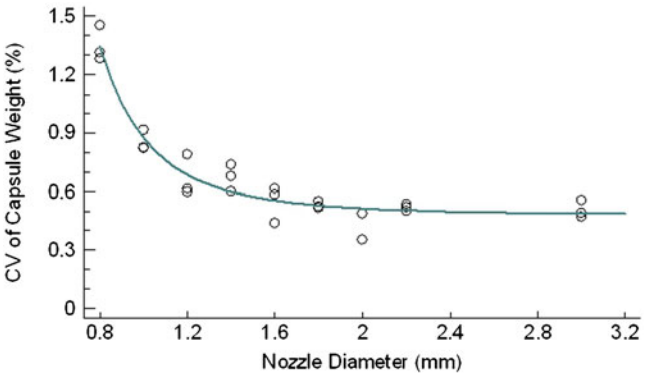

Fig. 6. Non-linear fit according Eq. 10 describing the influence of the nozzle diameter on the CV of the capsule weight using the reference oil

As a first response variable, we studied the fraction of leaking capsules. This percentage was determined following an equilibration of the capsules under vacuum by visual inspection. Under normal industrial conditions, these leaking capsules would be removed from the production batch. However, in view of the quality by design concept, it is favorable to minimize the number of defective capsules right in the production step, before any testing is conducted. An understanding of the influential parameters and their optimization is therefore crucial.

Figure 1 shows the results for the portion of leaking capsules (leaker rate) as a Pareto chart. The standardized effects were ordered according to their magnitude and the solid line separates the significant factors (on the 95% confidence level) from the others. An R^2 of 0.749 was obtained for the model that neglected the two least significant interactions. Most important was apparently the filling volume ($p=0.001$). Certainly, it is known among scientists that capsules should have a lower filling volume than their nominal volume, but no quantitative values have yet been reported for low-viscosity oils. Thus, a selection of an optimal fill volume is expected to be dependent on the type of material that is being processed. For middle-chain triglycerides, it was obviously important to select a comparatively low filling volume. Such low-filling volume is already theoretically advantageous for low-viscosity oils because there is less liquid expected to splash out of the capsule. Such splashing can contaminate the capsule rim and this was most likely leading to the high leaker rate that was observed with the 95% filling volume.

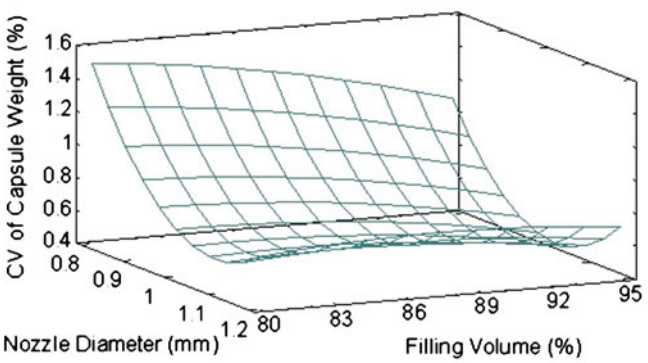

Fig. 5. Surface plot—influence of nozzle diameter and filling volume on CV of the capsule weight using the reference oil

Figure 2 shows the response plot of the leaker rate as a function of the temperature ($p=0.034$) and the aforementioned filling volume. The latter influence of the filling volume was highly non-linear. Once the filling volume approached 95% of the nominal volume, the leaker rate greatly increased. On the other hand, a lower fill volume of 80% significantly reduced this portion of leaking capsules. The combined setting with a filling temperature of 45°C was even leading to the absence of any capsule leaking. This effect of the temperature was remarkable as it was difficult to explain thinking of splashing only.

It is possible that some oil splashing still occurred during the dosing, but it was here of lower importance for the subsequent sealing step. Eventually, the filling at 45°C was beneficial for sealing, since the LEMS technology involves a subsequent warming sequence to this temperature for adequate fusion of the capsule pieces. Slightly elevated filling temperatures seemed to increase the robustness of the sealing step if low-viscosity oils are filled into capsules.

Interestingly, the filling volume and filling speed shared an interaction that had a borderline p value of 0.064. This interaction was further observed in the corresponding response surface plot (Fig. 3). Accordingly, the parameter of the filling volume depended on how fast the machine was operating. A fast-filling speed was leading to an inacceptable high leaker rate, if the capsules were filled close to their maximal filling volume. On the other hand, the influence of filling speed was barely observed for a comparatively low filling volume. This result again underlined the importance of a low filling volume for avoiding capsule leakers with the given reference oil. Optimal process conditions were shown to substantially reduce this rate of leakers with medium-chain triglycerides, which was a remarkable finding. It was, however, still an open question, whether the identified critical factors were equally important for other quality attributes like the weight variations of capsules.

The CV was analyzed for the capsule weight and Fig. 4 shows the Pareto chart with a model of $R^2=0.897$ (by omitting the least important interactions AA, BD). Most critical was the nozzle diameter that had a significant linear effect ($p<0.0001$) as well as a quadratic contribution ($p<0.0001$). A significant effect was again obtained with the filling volume of the capsules ($p=0.044$). However, this factor was expected to have a complex influence on the weight variations. On the one hand, the filling volume defined the average weight of the capsules. Selection of a higher filling volume was therefore

Table II. Physical Characteristics of Selected Oils Used in the Statistical Evaluation

Oil[a]	ρ (g/cm^3)	γ (mN/m)	η (mPas)	δ_{srel}	D_{ne} (mm)
Miglyol 812	0.937±0.00	28.6±0.0	23.54±0.04	1.00	3.77
Peanut oil	0.909±0.00	32.3±0.0	59.20±0.01	0.14	3.87
Linseed oil	0.919±0.00	32.4±0.0	38.98±0.03	0.32	3.86
Transutol HP	0.982±0.00	30.5±0.2	3.90±0.01	34.17	3.78
Capryol 90	0.935±0.00	28.1±0.1	11.58±0.01	4.20	3.76
Peppermint oil	0.893±0.00	27.8±0.0	4.63±0.00	26.60	3.78
Lemon oil	0.843±0.00	26.7±0.0	1.14±0.00	453.34	3.79

[a] Experimental values were determined at 25°C

expected to primarily reduce capsule weight variation relative to its mean. On the other hand, a higher filling volume was likely to promote oil splashing out of the capsules. This combined mechanism was the reason why the net effect of filling volume was different for the weight CV as opposed to the corresponding influence on the leaker rate.

Figure 5 displays the impact of the inner nozzle diameter on the weight variability of the capsules. This factor was highly influential at a comparatively low nozzle diameter, leading to significant variability of the filling weight. However, for diameters wider than about 1 mm, there was barely any effect observed so that a near constant weight variability was attained. The nozzle diameter obviously made a difference between a rather accurate filling and a comparatively variable filling process if, for example, a nozzle of 0.8 or 0.9 mm was selected. Interestingly, these filling trials using the thin nozzle exhibited marked oil splashing. Considerable amounts of oil were found close to the filling nozzle outside of the capsule. Unfortunately, it was not possible to reproducibly quantify this amount of splashed oil. An attempt was therefore made to correlate the relative splashing degree with the capsule weight CV.

Role of the Theoretical Splashing Degree and Equilibrium Diameter for the Capsule-Filling Variability

Equation 5 tells that for a given material with constant product flow Q, the splashing degree would be proportional to R_n^{-4} or proportional to the corresponding diameter D_n^{-4}. Unfortunately, it was not possible to determine an experimental splashing degree and to correlate it with the nozzle opening. We further did not know about the correlation of the splashing degree and the CV of the capsule weight. It was accordingly of interest to study the latter capsule attribute as a function of the nozzle diameter.

A series of dosing experiments was conducted keeping Q constant by adjusting a dosing knob in preliminary runs. The machine speed was set to 90% and all experiments were conducted at 25°C. In line with the previous experimental design, a strong non-linear function of capsules weight CV and nozzle diameter was recorded (Fig. 6). For nozzle diameters of about 1.6–3.2 mm, the variability leveled off to a minimal value. This minimal variability was less than about half of the CV that was observed using the 0.8 mm nozzle.

We fitted the following heuristic Eq. 10 to the data, where CV_0 is a minimal limiting coefficient of variability, D_n is the dosing nozzle diameter and k is a constant:

$$CV = CV_0 + kD_n^{-q} \quad (10)$$

The non-linear regression produced a high R^2 of 0.938 and the model described the data excellently (Fig. 6). The value CV_0 was 0.482% with an asymptotic standard error of ±0.028%. This value CV_0 was of practical interest as it indicated, which dosing precision could be attained by selecting the optimal nozzle for the given oil. Remarkable was the finding of the exponent q with 3.56±0.479. This exponent in Eq. 10 was reasonably close to how the splashing degree was depending on D_n^{-4} under constant Q (Eq. 5).

Accordingly, the CV of capsule weight variability minus its limiting value CV_0 must have been proportional to the theoretical splashing degree δ_s. Such a correlation between the splashing degree and the weight variability of capsules had a practical aspect. It was of interest to know if the theoretical splashing degree could help in anticipating issues regarding capsule dosing with a given oil.

A series of pharmaceutical oils was selected and physically characterized. Table II shows the values of measured density, surface tension, as well as obtained viscosity. The differences among the oils were already revealed by their density values. Middle-chain triglycerides had a slightly higher density than the two long-chain triglycerides, i.e., peanut and linseed oil. On the other hand, the lemon and peppermint oil exhibited a clearly lower density. The different types of oils were also differentiated with respect to the measured surface tension and viscosity. Accordingly, the reference oil Miglyol 812 had both, a lower surface tension and viscosity as opposed to the values of the long-chain triglycerides. The lowest values in surface tension and

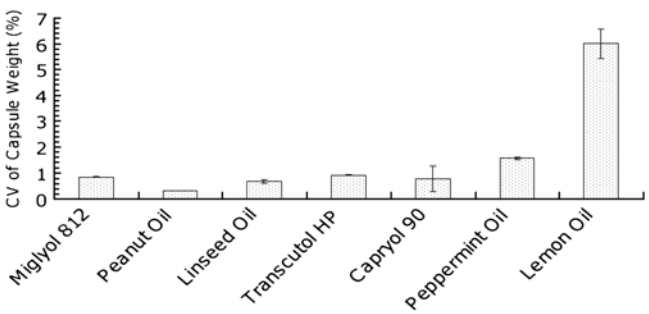

Fig. 7. Comparison of the capsule weight variability as obtained from liquid-filling of different oils at constant filling parameters (according to the center of the statistical design in Table I)

viscosity were, however, observed with peppermint and lemon oil. Especially the latter oil showed a particularly low viscosity that was even close to the value of water.

Despite their differences in physical characteristics, the different oils provided calculated equilibrium nozzle diameters that were all in close range (Table II). This calculated equilibrium value included the ratio of surface tension to density according to Eq. 9. This ratio was apparently less variable among the oils than absolute values of the surface tension or density. Oils with comparatively large or small values in both parameters resulted therefore in similar estimates of the equivalent nozzle diameter. This proximity of these estimates was one remarkable aspect and the other was that all values were comparably high, i.e., all values were close to 4 mm. Smaller openings of the dosing nozzle were therefore deemed uncritical with respect to a dripping of formulation. Most dosing nozzles have a smaller opening than D_{ne} so that an extensive dripping is not expected using common pharmaceutical oils. Even though excessive dripping seems unlikely to occur, a retracting pressure at the end of dosing can still be meaningful. This mechanism can retract a hanging drop and thereby avoiding the contamination of a following capsule in the filling cycle.

Unlike the equivalent nozzle diameter D_{ne}, the relative splashing degree δ_{srel} (Table II according to Eq. 7) displayed great differences among the oils. The unity value was defined for middle-chain triglyceride that was selected as reference oil. Values smaller than unity were observed with long-chain triglycerides oils. In contrast, the peppermint and especially the lemon oil produced substantially higher values.

A next step was to compare the dosing performance of the different oils on the capsules filling machine. Figure 7 demonstrates the obtained CV values for the capsule-filling trials. In line with the predicted splashing degree, it was the peppermint and lemon oil that produced the highest weight variability. These oils also exhibited the most pronounced oil splashing that was visually observed during filling. On the other hand, the experiments with long-chain oils did not reveal any oil splashing to the naked eye. This observation was in line with the yield of low CV values. The value close to 0.3% CV demonstrated how accurate a filling can be in case of an oil that is not splashing.

Correlation of the relative splashing degree and the mean CV of capsule weight provided a Pearson product moment correlation of $r=0.990$ with $p<0.0001$. This result supported our view of an existing strong relationship between the variables. It therefore seems possible to anticipate the dosing performance of an oil if the relative splashing degree is known. A relative splashing degree of greater than unity is considered as a risk for the dosing adequacy of liquid-filling of capsules. This information can guide the formulation scientist in developing an adequate system for liquid-filled capsules.

CONCLUSION

The newly introduced splashing degree provided a valuable concept for capsule filling of low-viscosity oils. Results of the reference oil middle-chain triglycerides revealed the optimal process conditions to obtain a low rate of leaking capsules as well as to minimize the weight variability. This reference oil was further employed to form a relative splashing degree. A correlation of this parameter with the variability of filling weight was demonstrated for several low-viscosity oils. This result was highly interesting from a practical viewpoint because it is possible to anticipate the technical dosing precision of an oil before it is filled into capsules. Oils could be classified according to the relative splashing degree. Some oils have a clearly lower relative splashing degree than unity. For such oils issues of splashing are not expected during a capsule filling. On the other hand, oils with clearly higher splashing degree than unity are likely to produce high capsule weight variability due to extensive splashing. These oils should ideally be modified to increase viscosity or surface tension by for example adding another excipient. Finally, a third case is given with oils having a relative splashing degree being close to unity. Based on the results of the middle-chain triglycerides, it does not seem mandatory to change the oil properties. It is, however, critical to choose a sufficiently large nozzle diameter and to optimize the filling volume with respect to leakers and weight variability of the capsules. A further minimization of the leaker rate is obtained by slightly increasing the filling temperature to 40–45°C. Such optimization of the filling parameters was in our study sufficient for the middle-chain triglycerides to exhibit adequate process performance and capsule quality.

The presented concept was aiming at designing quality into liquid-filled capsules. Thus, an early anticipation and understanding of technical filling issues helps the scientist to finally obtain a robust capsule-filling process. It is important to transfer the research results to a manufacturing environment; a first step is to keep the capsules in an upright position throughout the entire filling and sealing cycle, which is the case with the used CFS1200, but it is not a standard in current manufacturing. Apart from such transfer work, there is also more research needed. The present study was focusing on oils with Newtonian flow behavior so a next step is to study complex mixtures to explore the filling performance of low-viscosity formulations.

ACKNOWLEDGMENTS

The authors wish to thank the University of Applied Sciences, Northwestern Switzerland for funding the research project. The authors would also like to thank Capsugel for providing the CFS1200™.

REFERENCES

1. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov. 2007;6:231–48.
2. O'Driscoll CM. Biopharmaceutical challenges associated with drugs with low aqueous solubility—the impact of lipid-based formulations. Adv Drug Deliv Rev. 2008;60:617–24.
3. Kuentz M. Oral self-emulsifying drug delivery systems: from biopharmaceutical to technical formulation aspects. J Drug Deliv Sci Technol. 2011 (in press).
4. Cole ET, Cade D, Benameur H. Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. Adv Drug Del Rev. 2008;60 (6):747–56.

5. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. Adv Drug Del Rev. 2008;60:734–46.
6. Lahr W. Liquid filled hard gelatine capsules. Pharm Ztg. 1986;131 (15):871–4.
7. Bowtle WJ. Materials, process, and manufacturing considerations for lipid-based hard-capsule formats. In: Hauss, editor. Oral Lipid-Based Formulations, 2007. pp. 79–106.
8. Cole ET. Liquid-filled and sealed hard gelatin capsule technologies. In: Rathbone MJ, Hadgraft J, Roberts MS, editors. Modified-release drug delivery technology. New York: Marcel Dekker; 2003. p. 177–88.
9. Hawley AR, Rowley G, Lough WJ, Chatham S. Physical and chemical characterization of thermosoftened bases for molten filled hard gelatin capsule formulations. Drug Dev Ind Pharm. 1992;18(16):1719–39.
10. Shah N, Phuapradit W, Ahmed H. Liquid/semi-solid filling in hard gelatin capsules: formulation and processing considerations. Bull Tech Gattefossé. 1996;89:27–37.
11. Walters PA, Rowley G, Pearson JT, Taylor CJ. Formulation and physical properties of thixotropic gels for hard gelatin capsules. Drug Dev Ind Pharm. 1992;18(15):1613–31.
12. Rowley G, Hawley AR, Dobson CL, Chatham S. Rheology and filling characteristics of particulate dispersions in polymer melt formulations for liquid fill hard gelatin capsules. Drug Dev Ind Pharm. 1998;24(7):605–11.
13. Kattige A, Rowley G. Influence of rheological behaviour of particulate/polymer dispersions on liquid-filling characteristics for hard gelatin capsules. Int J Pharm. 2006;316:74–85.
14. Cole ET. Liquid filled and sealed hard gelatin capsules. Bull Tech Gattefossé. 1999;92:67–76.
15. Patil P, Joshi P, Paradkar A. Effect of Formulation Variables on Preparation and Evaluation of Gelled Self-emulsifying Drug Delivery Systems (SEDDS) of Ketoprofen. AAPS Pharm Sci Tech. 2004;5(3):1–8.
16. Rein M. Phenomena of liquid drop impact on solid and liquid surfaces. Fluid Dyn Res. 1993;12(2):61–93.
17. Mundo CHR, Sommerfeld M, Tropea C. Droplet–wall collisions: experimental studies of the deformation and breakup process. Int J Multiph Flow. 1995;21(2):151–73.
18. Manzello SL, Yang JC. An experimental study of a water droplet imprinting on a liquid surface. Exp Fluids. 2002;32:580–9.
19. Yarin AL. Droplet impact dynamics: splashing, spreading, receeding, bouncing. Annu Rev Fluid Mech. 2006;38:159–92.
20. Rodrigues F, Mesler RJ. Some drops don't splash. J Colloid Interface Sci. 1985;106:347–52.