Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 37–43
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

A technical feasibility study of surfactant-free drug suspensions using octenyl succinate-modified starches

Martin Kuentz *, Peter Egloff, Dieter Röthlisberger

F. Hoffmann-La Roche Ltd, Pharmaceutical & Analytical R&D, Basel, Switzerland

Received 1 July 2005; accepted in revised form 10 October 2005
Available online 13 December 2005

Abstract

Many new drugs exhibit poor wetting behaviour and low aqueous solubility. This is particularly an issue for preclinical studies like toxicological trials, in which considerably higher doses and volumes are being administered compared to clinical studies. Preclinical vehicles typically contain high levels of surfactants that can exert biological effects. However, the biological inertness of vehicles is pivotal for the application in preclinical studies stressing the need in finding new excipients to solve formulation problems of today's drug discovery. The present study investigated the technical feasibility of surfactant-free suspensions using a new poorly soluble drug as model. It was shown that octenyl succinate-modified starches adequately wetted the drug and homogenous tasteless suspensions were obtained. The polymer xanthan gum was identified as macroscopically compatible gelling agent. Concentration effects of xanthan, drug and different modified starches were studied in a *D*-optimal design with respect to rheological properties. The suspensions were also tested in an analytical centrifuge using NIR transmission profiles to obtain a measure of sedimentation stability under accelerated conditions. The modified starches exhibited only little influence on the viscosity as well as on the yield point in contrast to the rheological effects of xanthan gum. This gelling agent was the main stabilising excipient as the modified starches hindered to a lesser extent sedimentation. The most stable suspensions displayed convenient flow properties. The viscosity at 100 s^{-1} and 25 °C was in technically acceptable range of 120–140 mPa s in view of a application via gavage or a syringe in animal studies.

The results demonstrated that surfactant-free drug suspensions with excellent technical performance can be obtained using octenyl succinate-modified starches. The vehicles were tasteless and based on the experience of modified starches in the food industry, the vehicles should exhibit good tolerability. The future use of such surfactant-free drug suspensions in toxicological, pharmacokinetic and pharmacodynamic studies will have to determine their advantage in terms of biological inertness.

Keywords: Octenyl succinate; Modified starch; Surfactant-free; Suspension stability; *D*-optimal design

1. Introduction

Surfactants are widely used in pharmaceutical preparations [1,2], even though surface active ingredients are able to disrupt normal membrane structure [3] and may thus lead to cytotoxicity [4]. Accordingly, it is not surprising that only few surfactants are acceptable for the oral route of administration [5,6]. These currently used ingredients, however, do not solve all the formulation problems that arise from modern drug discovery. A considerable number of new chemical entities show very poor wetting behaviour and lack of aqueous solubility. High amounts of wetting agents are needed to suspend such drugs and, if a micellar solution can be obtained, considerable levels of surfactants are required. The tolerability of such drug vehicles is particularly an issue for pre-clinical studies, in which formulations with much higher concentrations and volumes are administered compared to clinical formulations. Vehicles are generally tested in a control group to verify their tolerability, but sometimes a vehicle interacts with the drug, e.g. the toxic effects of a drug can depend on the vehicle used. Such confounded effects may also be a problem for studies of metabolism, pharmacodynamics or pharmacokinetics. An example for the latter case is reported on the influence of the surfactant Solutol on the pharmacokinetic parameters of colchicin [7] and midazolam [8] following intravenous administration of the drugs. A recent article [9] reviews general pharmacological effects of formulation vehicles.

* Corresponding author. F. Hoffmann-La Roche Ltd, Pharmaceutical & Analytical R&D, Building 072/338, CH-4070 Basel, Switzerland. Tel.: +41 61 688 3870; fax: +41 61 688 8689.
E-mail address: martin.kuentz@roche.com (M. Kuentz).

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2005.10.004

The formulators increasingly realize that surfactants fulfil not only their technical function in drug formulations, but also bear the potential to interact with biological processes. A recent study reported for example effects on P-glycoprotein inhibition, as well as on lipoprotein processing by Cremophor EL and Pluronics [10]. Another example is Cremophor RH40 that is known to affect P-glycoprotein and CYP3A in vitro [11].

Accordingly, such excipients must be regarded as bioactive substances. Effects can also have clinical relevance. The influence of Cremophor RH40 on P-glycoprotein drug efflux was, for example, shown to be relevant for digoxin [12].

These examples highlight the need to better characterize known oral excipients, e.g. surfactants, in view of their potential interference with pre-clinical studies. Also the need for new excipients is emphasized. New additives must be found that are technically useful and bear the potential to be less bioactive than commonly used surfactants.

The scope of the present study was to technically evaluate modified starches of the type octenyl succinate (OSA) to overcome the hurdle of poor drug wettability. The OSA starches are approved food additives in the US and are being considered safe for oral consumption as regulated under 21 CRF 172.892 (revised April 2, 2001). In Europe OSA starches are classified as E1450 and therefore permitted food additives. Based on knowledge in the food industry, the OSA starches demonstrated both good tolerability and surface-active properties. Another great advantage of OSA starches is the absence of taste, since most oral surfactants are bitter. Such bitter additives can lead at high concentrations to problems like vomiting even by administration via gavage.

The present study aimed to test OSA-modified starches in combination with a new poorly wettable CNS drug without further aid of a surfactant. Accordingly, the technical performance of such surfactant-free suspensions was to be evaluated.

2. Materials and methods

2.1. Materials

The drug R1500 was synthesized by the chemical development department of F. Hoffmann-La Roche Ltd in Basel. The excipients Hi-Cap® 100 (OSA H) and Capsul® HS (OSA C) were obtained from National Starch (US). The schematic structure of these octenyl succinate-modified starches is given by Fig. 1. The xanthan gum Rhodigel® 80 was used from Rhodia (France). The Simethicone Emulsion USP as well as the parabens was purchased from Fluka (Switzerland). All excipients were used as received.

2.2. Manufacture of the dispersions

The different suspensions had constant levels of 0.18% methyl paraben, 0.02% propyl paraben, and 0.2% Simethicone Emulsion USP. The latter additive was needed for small-scale manufacture, as no vacuum was applied during the dispersion step. The other ingredients varied according to the statistical design (Table 1).

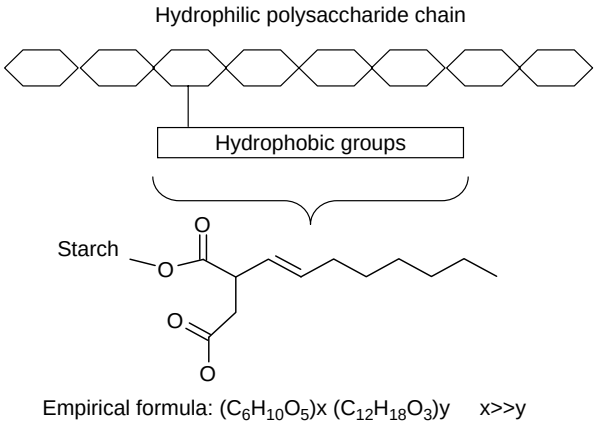

Fig. 1. Schematic structure of octenyl succinate-modified starches.

Manufacturing of the suspensions started with dissolving the preservatives in water followed by addition of the Simethicone Emulsion. The OSA starches, drug substance, and xanthan gum were weighed, blended and added to the preserved water, while continuous stirring. An Ultra-Turax T25 was then used for homogenization at 24,000 rpm during 5 min. The dispersions were kept under vacuum over night to remove residual foam.

Table 1
Experimental design

Exp. no.	Run order	Xanthan gum (%)	OSA H (%)	OSA C (%)	API (%)
1	2	0.2	10	5	1
2	14	0.2	10	10	1
3	1	0.2	5	6.6667	1
4	19	0.2	5	8.3333	1
5	25	0.2	8.3333	10	1
6	27	0.4	5	10	1
7	12	0.4	10	8.3333	1
8	10	0.4	6.6667	5	1
9	9	0.6	5	5	1
10	17	0.6	10	5	1
11	29	0.6	5	10	1
12	22	0.6	8.3333	10	1
13	7	0.2	6.6667	5	4
14	20	0.4	8.3333	10	4
15	24	0.6	10	6.6667	4
16	23	0.6	5	5	4
17	18	0.2	5	5	7
18	26	0.2	10	10	7
19	21	0.2	5	10	7
20	3	0.2	10	6.6667	7
21	11	0.4	10	5	7
22	5	0.6	5	5	7
23	16	0.6	10	10	7
24	6	0.6	5	10	7
25	15	0.6	10	7.5	7
26	8	0.6	7.5	7.5	7
27	13	0.6	7.5	7.5	7
28	4	0.6	7.5	7.5	7
29	28	0.6	7.5	7.5	7

2.3. Sedimentation analysis using NIR transmission profiles during centrifugation

An accelerated physical stability test was performed, using a recently introduced separation analyser LUMiFuge® 114 (LUM Ltd, Berlin, Germany) [13–15]. This analytical centrifuge monitors phase separations with an optic-electronic sensor system that measures NIR transmission profiles along horizontally inserted sample tubes at ambient temperature.

The 2 ml sample volume (in a 1.15 cm diameter tube) forms a rather shallow suspension sample compared to the distance from the axis of rotation to the base of the tube (11.5 cm). This minimizes the lateral particle movement that could invalidate the analogy with gravitational settling [16]. The 3000 rpm rotor speed is equivalent to 1200 *g* acceleration with reference to the base of the tube. NIR transmission profiles were recorded continuously during the 4 h separation process.

The LUMiFuge® software—SEPView V.3.2. (LUM Ltd)—calculates the integral of every transmission curve over the chosen sample radius. Integral transmission increases linearly as a function of time in the initial sedimentation phase. This linear range provides a slope of integral transmission, or so-called *clarification* (%/1000 s), calculated by the software under control of the correlation coefficients. This clarification is a measure of sedimentation instability and was recently used in an accelerated stability study of pharmaceutical bentonite dispersions [17].

2.4. Rheology

A rotational/oscillatory viscometer (CSL 500, Carri-Med/TA Instruments, New Castle, DE, USA) was used. All measurements were performed with a stainless steel cone-plate sensor (6 cm diameter and 2°) at 25 ± 0.1 °C. Viscosity, η, was obtained from the down-curve of rotational measurements at a shear rate of 100 s^{-1}; the yield point, σ_Y, was calculated from the up-curve using Casson extrapolation [18].

2.5. Dynamic surface tension measurement

The surface tension was measured using a PocketDyne® (Krüss Ltd, Germany). In this type of dynamic surface tensiometry, air passes through an orifice and into water, forming a succession of bubbles. During inflation of a bubble, its pressure increases from the hydrostatic value, p_0 to a maximal bubble pressure, p_{max}. At this maximal pressure the bubble radius equals to that of the capillary, r. The dynamic surface tension, σ_d was calculated using the following equation:

$$\sigma_d = \frac{(p_{max} - p_0)r}{2}$$

The measurement was performed at three arbitrarily set bubble frequencies. Since the lifespan of a bubble is less of interest than the true age of the surface, the latter parameter was determined. This surface age was obtained from the time point of bubble initiation to that when maximal inflation pressure was recorded.

2.6. Statistical design and evaluation of data

Statgraphics® Plus software (version 5.0, Quality and Design Edition, Manugistics, USA) was used for data evaluation and graphical presentation of the dynamic surface tension results. The software MODDE® V.6.0 (Umetrics, Sweden) was used for all other statistical calculations. The concentration of the OSA C, OSA H, xanthan gum and drug were chosen as factors in a *D*-optimal design according to Table 1. A general introduction to these response surface designs is given by Lewis et al. (1999) [19].

3. Results and discussion

The model drug R1500 displayed poor wetting behaviour. Different drug amounts were added to water and floated entirely. Vigorous stirring energy forced the drug in dispersion, but the particles floated within hours again. In another initial test, OSA H was added together with the drug to water and macroscopically homogenous drug dispersions were obtained that did not exhibit drug floating following two days under vacuum. It was probably due to the amphiphilic nature of the modified starch (Fig. 1) that considerably improved drug wetting was observed.

To further characterise the general surface activity of octenyl succinate-modified starches, dynamic surface tension measurements were conducted. Aqueous solutions of 5 and 15% (w/w) OSA type C and type H were measured in triplicate for three different surface ages: 50, 200 and 1000 ms. Consequently, an analysis of the variance was performed for the individual excipients with the factors OSA starch concentration and surface age. Both factors as well as the interaction were found highly significant for both modified starches. Fig. 2 shows the interaction of the surface tension at 5 and 15% OSA C with the different surface ages. All measured values showed reduced surface tension compared to the known reference of water. The effect of the concentration depended on the surface age and was most pronounced at 1000 ms, as here the polymer was given the longest time to diffuse to the surface. This interaction was also seen with OSA H (Fig. 3), where the

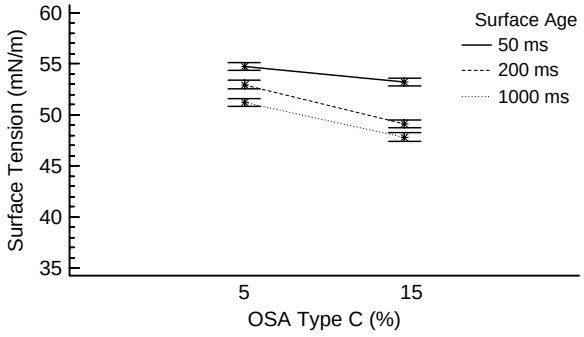

Fig. 2. Dynamic surface tension of aqueous solutions of 5 and 15% (w/w) OSA type C as a function of surface age (95% confidence intervals shown).

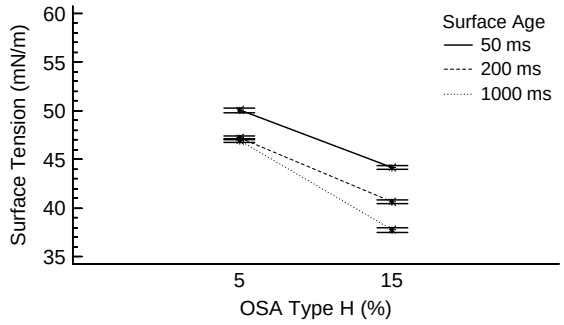

Fig. 3. Dynamic surface tension of aqueous solutions of 5 and 15% (w/w) OSA type H as a function of surface age (95% confidence intervals shown).

concentration effect was again most evident for the longest surface age. Interestingly, the measured surface tension of the solutions was generally lower with OSA type H in comparison with that of type C.

Further pre-tests identified xanthan gum as visually compatible polymer with the OSA starches. The concentration limits of the pre-tests were in line with the main experimental design according to Table 1. Along with the two types of OSA starches, the concentration of the drug and the amount of the thickening agent xanthan gum were considered as factors.

The different suspension formulations were easily manufactured from a technical point of view and resulted all in homogenous drug dispersions. No visual physical incompatibilities were observed with regards to the vehicles of the different compositions from Nos 1 to 29.

The suspensions exhibited different flow properties and the viscosity under shear (100 s^{-1}) was used as a first response of the *D*-optimal design. Since the self-interaction term of the OSA H starch (OSAH*OSAH) was not found to be significant for all tested responses, this coefficient was subsequently neglected in the models. The adj. R^2 value for the model of the viscosity was 0.996. This regression was found to be significant and no lack of fit was detected. A value of $P = 0.218$ indicated the validity of the chosen model. Fig. 4 displays the coefficients of the model of viscosity with 95% confidence intervals. The magnitude of the coefficients is of main interest, being considered as effects that are by definition a factor 2 greater than their corresponding coefficient in factorial designs.

Xanthan gum had a predominant effect on viscosity within the examined concentration limits of 0.2–0.6% (w/w).The polymers OSA H and OSA C affected the viscosity of the suspensions much less, considering also their concentration range of up to 10% (w/w). Accordingly, the modified starches were not viewed as thickening agent and co-addition of a polymer like xanthan gum was required to improve the physical stability of the dispersions.

The drug concentration between 1 and 7% (w/w) also affected the viscosity (Fig. 4). From theory is known that the particle volume fraction impacts on the viscosity and non-linear effects occur at higher volume fractions of the dispersed phase [20]. Such non-linearity was also in the present case observed, which is indicated by the existence of the quadratic term 'API*API' (Fig. 4). The coefficient had similarly small extent like the term 'Xan*API'. The latter interaction must be understood as a dependence of the xanthan effect on the drug concentration. Such dependence could be due to polymer adsorption on drug particle surfaces. However, the contribution of this interaction to overall flow behaviour is rather small in comparison to the interaction of xanthan.

The model of the yield point also provided a high adj. R^2 value of 0.998 and no significant model error was observed. Again the effect of xanthan gum dominated (Fig. 5). It was in a range of several Pa and could prevent particle settling of a micronized drug suspension [21]. The quadratic term of xanthan, 'Xan*Xan' was of clearly lesser importance, as was also the effect of the drug concentration 'API'. The modified starches hardly influenced the yield point of the suspensions.

Coming to the results of the analytical centrifugation, the clarification, being indicative for phase separation, was analysed as response. The model showed a goodness of fit with adj. R^2 of 0.80, the lack of fit not being significant at 95%

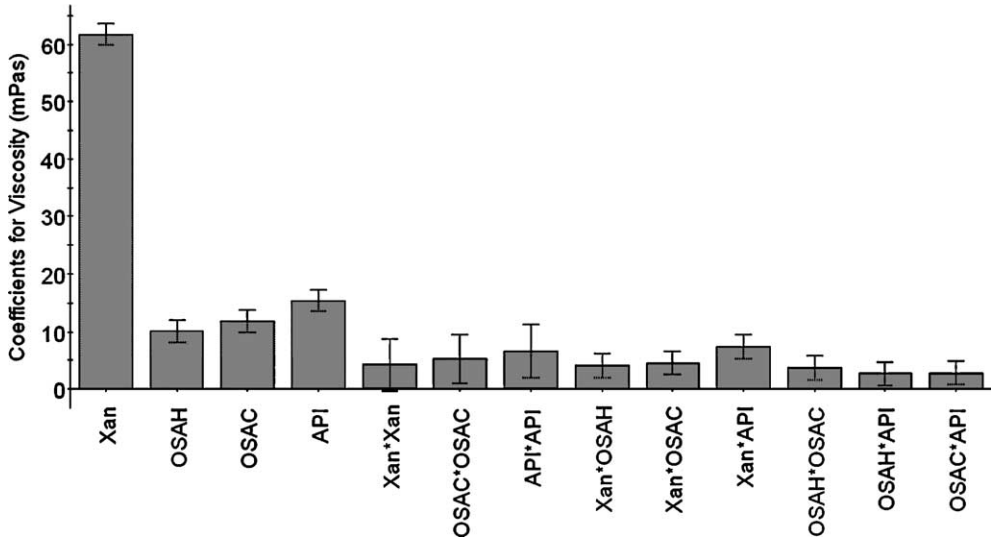

Fig. 4. Coefficient plot (centered and scaled data) for the viscosity at 100 s^{-1} and 25 °C (mPa s) with 95% confidence intervals.

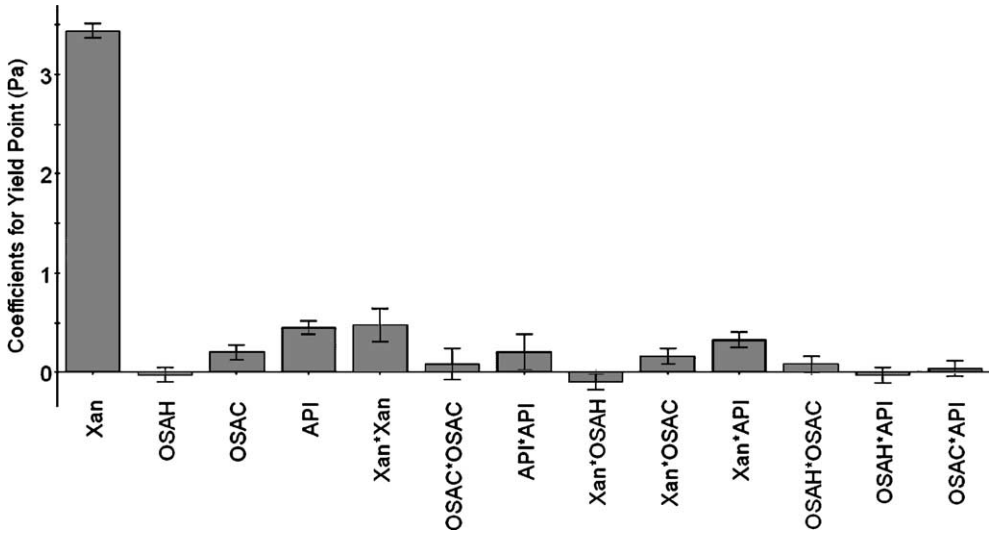

Fig. 5. Coefficient plot (centered and scaled data) for the yield point (Pa) with 95% confidence intervals.

confidence level. The most negative influence on clarification was observed for xanthan gum (Fig. 6). This confirms the rheological view that xanthan gum generates structure thus exerting a negative effect on clarification leading to stabilisation against particle settling. The positive sign of the quadratic term 'Xan*Xan' indicates the existence of a minimum in the response surface whereas confidence intervals of this coefficient indicate the uncertainty of its broadness. Accordingly, there must be an optimal stabilising concentration of xanthan in terms of particle settling. Such an optimum is known for other particle dispersions stabilised with a polymer [22,23] and is also reported for xanthan gum with bentonite [17]. In these examples a coherent network of polymer with particles is formed that entraps all liquid and minimises particle settling. An excess concentration of xanthan will not further stabilise the dispersion, but only leads to unwanted increase in viscosity.

The coefficients in Fig. 4 for the OSA starches H and C displayed overlapping confidence intervals, but there seems to be the tendency that OSA H better stabilised the drug suspensions. Such a tendency would also correspond to the observation that OSA type H exhibited greater surface tension decrease in aqueous solutions than that observed with OSA type C.

The response surface of the clarification (%/1000 s) as a function of the xanthan and OSA type H concentration (w/w) is depicted by Fig. 7. The influence of xanthan is dominating and a minimal concentration of about 0.5% (w/w) seems to be needed to minimise sedimentation. The influence of the OSA H was less pronounced and a broad minimum of clarification was observed between 7 and 10% (w/w). This optimal region was further investigated using a contour plot in terms of the viscosity (Fig. 8). The viscosities were all below 200 mPa s, which is in general acceptable for drug suspensions that are administered via gavage or syringe. The viscosity was in the range of 120–140 mPa s at 0.5% (w/w) xanthan and 5–10% (w/w) OSA H. This is reasonably low in view of drug

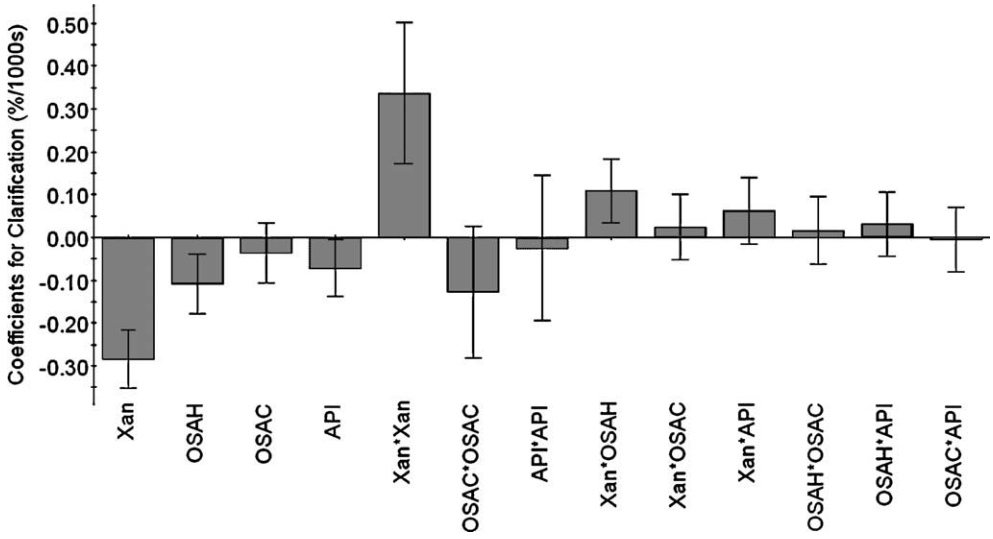

Fig. 6. Coefficient plot (centered and scaled data) for the clarification (%/1000 s) with 95% confidence intervals.

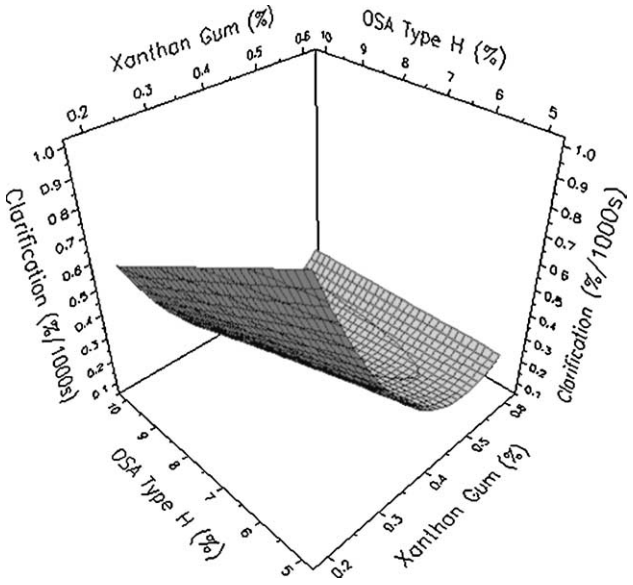

Fig. 7. Response surface plot in terms of clarification (%/1000 s) as a function of the OSA H and xanthan gum concentration (%).

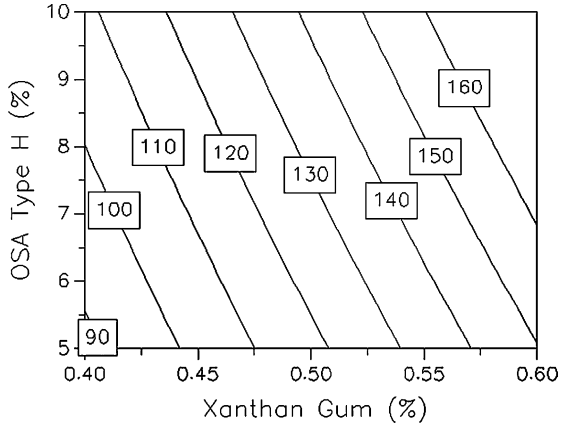

Fig. 8. Contour plot in terms of the viscosity at 100 s^{-1} and 25 °C (mPa s) as a function of the OSA H and xanthan gum concentration (%).

administration. Another advantage of this flow behaviour is the reduced foam stabilization. The manufacture on a small-scale without vacuum often leads to entrapped air that can be removed unless the viscosity is too high.

It should be noticed that the discussed polymer effects in Figs. 7 and 8 hold for the average levels of the other factors, i.e. 4% drug substance and 7.5% OSA C. Since OSA C and H showed no relevant interaction in terms of the tested parameters, no technical advantage was seen with regard to combination of the modified starches. For future studiers it seems reasonable to use only one of the two polymers, preferably OSA type H.

The next step towards the development of drug dispersion using R1500 would be to initiate long-term stability tests. A starting point for a 4% drug dispersion would be to add about 0.5% xanthan gum and for example about 10–15% OSA H. The higher concentration level is outside the examined design space, but is meaningful to compensate for the abandoned OSA C.

4. Conclusions

The study demonstrated that surfactant-free suspensions of a poorly wettable drug were technically feasible using OSA modified starches.

Xanthan gum was found to be a compatible gelling agent for these drug suspensions and prevented particle settling in the analytical centrifuge. The dispersions with best stability did also show convenient flow behaviour in view of a drug administration via gavage or syringe.

Further long-term stability tests are certainly needed for a full technical assessment; however, this would be part of a drug suspension development, which was beyond the scope of the present feasibility tests. It also remains to be proven that octenyl succinate-modified starches interfere less with biological processes than commonly used oral surfactants. The octenyl succinate-modified starches are known from the food industry to be well tolerable and to have no inconvenient taste. Future toxicological, pharmacokinetic and pharmacodynamic

studies are needed to test the inertness of the presented vehicles, being of pivotal importance for preclinical studies in drug development.

Acknowledgements

The authors wish to thank Jean-Michel Clavey for his technical support.

References

[1] L. Prokai, V. Nguyen, B.R. Jasti, T.K. Gosh, Principles and applications of surface phenomena, in: T.K. Gosh, B.R. Jasti (Eds.), Theory and Practice of Contemporary Pharmaceutics, CRC Press, Boca Raton, 2005, pp. 172–196.
[2] M. Malmsten, Surfactants and Polymers in Drug Delivery, Marcel Dekker, New York, Basel, 2002. pp. 1–17.
[3] R.L. Oberle, T.J. Moore, D. Krummel, Evaluation of mucosal damage of surfactants in rat jejunum and colon, J. Pharmacol. Toxicol. Methods 33 (2) (1995) 75–81.
[4] R.L. Grant, Ch. Yao, D. Gabaldon, D. Acosta, Evaluation of surfactant cytotoxicity potential by primary cultures of ocular tissues: I. Characterization of rabbit corneal epithelial cells and initial injury and delayed toxicity studies, Toxicology 76 (1992) 153–176.
[5] R.G. Strickley, Solubilizing excipients in oral and injectable formulations, Pharm. Res. 21 (2) (2004) 201–230.
[6] M.J. Lawrence, G.D. Rees, Microemulsion-based media as novel drug delivery systems, Adv. Drug Deliv. Rev. 45 (2000) 89–121.
[7] B. Bittner, R.C.B. Gonzáles, I. Walter, M. Kapps, J. Huwyler, Impact of solutol HS15 on the pharmacokinetic behaviour of colchicine upon intravenous administration to male wistar rats, Biopharm. Drug Dispos. 24 (2003) 173–181.
[8] B. Bittner, R.C.B. Gonzáles, H. Isel, Ch. Flament, Impact of solutol HS 15 on the pharmacokinetic behaviour of midazolam upon intravenous administration to male wistar rats, Eur. J. Pharm. Biopharm. 56 (2003) 143–146.
[9] A.J. Tije, J. Verweij, W.J. Loos, A sparreboom, Pharmacological effects of formulation vehicles. Implications for cancer chemotherapy, Clin. Pharmacokinet. 42 (7) (2003) 665–685.
[10] F. Seeballuck, M.B. Ashford, C.M. O'Driscoll, The effect of pluronics block copolymer and cremophor EL on intestinal lipoprotein processing and the potential link with P-glycoprotein in caco-2 cells, Pharm. Res. 20 (7) (2003) 1085–1092.
[11] Ch. Wandel, R.B. Kim, C.M. Stein, 'Inactive' excipients such as cremophor can affect in vivo drug disposition, Clin. Pharmacol. Ther. 73 (5) (2003) 394–396.
[12] Y. Tayrouz, R. Ding, J. Burhenne, K.D. Riedel, J. Weiss, T. Hoppe-Tichy, W.E. Haefeli, G. Mikus, Pharmacokinetic and pharmaceutic interaction between digoxin and cremophor RH40, Clin. Pharmacol. Ther. 73 (5) (2003) 397–405.
[13] D. Lerche, Th. Pense, D. Frömer, St. Strowich, A new opto-electronic system to evaluate sedimentation and packing in a centrifugal field, in: Testing and Analysis for Industrial Competitiveness and Sustainable Development, Eurolab-D, NW-Verlag für neue Wissenschaft, Bremerhaven, 1996, pp. 624–635
[14] T. Sobisch, D. Lerche, Application of a new separation analyzer for the characterisation of dispersions stabilized with clay derivatives, Colloid Polym. Sci. 278 (2000) 369–374.
[15] D. Frömer, D. Lerche, An experimental approach to the study of the sedimentation of dispersed particles in a centrifugal field, Arch. Appl. Mech. 72 (2002) 85–95.
[16] M. Ungarish, On the separation of a suspension in a tube centrifuge, Int. J. Multiphase Flow 27 (2001) 1285–1291.
[17] M. Kuentz, D. Röthlisberger, Rapid assessment of sedimentation stability in dispersions using near infrared transmission measurements during centrifugation and oscillatory rheology, Eur. J. Pharm. Biopharm. 56 (2003) 355–361.
[18] L. Gehm, Rheologie. Praxisorientierte Grundlagen und Glossar, Vincentz, Hannover, 1998, p 78.
[19] G.A. Lewis, D. Mathieu, R. Phan-Tan-Luu, Pharmaceutical Experimental Design, Marcel Dekker, New York, 1999, pp. 265–270.
[20] J. Mewis, C. Macosk, Suspension rheology, in: C. Macosco (Ed.), Rheology Principles, Measurements and Applications, Wiley/VCH, New York, 1993, pp. 425–474.
[21] M. Kuentz, D. Röthlisberger, Sedimentation analysis of aqueous microsuspensions based on near infrared transmission measurements during centrifugation. Determination of a suitable amount of gelling agent to minimize settling in the gravitational field, STP Pharma Sci 12 (6) (2002) 391–396.
[22] D. Heath, Th.F. Tadros, Influence of pH, electrolyte, and poly(vinyl alcohol)addition on the rheological characteristics of aqueous dispersions of sodium montmorillonite, J. Colloid Sci. 93 (2) (1993) 307–319.
[23] S. Rossi, P.F. Luckham, Th.F. Tadros, Influence of non-ionic polymers on the rheological behaviour of Na+-montmorillonite clay suspensions—I nonylphenol-polypropylene oxide-polyethyleneoxide copolymers, Colloids Surf. 201 (2002) 85–100.