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RESEARCH PAPER

Lipid Based Formulations in Hard Gelatin and HPMC Capsules: a Physical Compatibility Study

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ABSTRACT

Purpose To investigate the compatibility between hard gelatin and HPMC capsules with a range of different isotropic lipid based formulations containing multiple excipients.

Methods The miscibility was investigated for 350 systems applying five different oils (Labrafac ™ lipophile WL1349, Maisine® CC, Captex 300 EP/NF, olive oil, and Capmul MCM EP/NF), five different surfactans (Labrasol ® ALF, Labrafil M 2125 CS, Kolliphor ® ELP, Kolliphor ® HS 15, Tween 80) and three different cosolvents (propylene glycol, polyethylene glycol 400, and Transcutol ® HP). For the isotropic systems capsule compatibility was investigated in both gelatin and HPMC capsules at 25°C at 40% and 60% relative humidity by examining physical damages to the capsules and weight changes after storage.

Results The miscibility of lipid based vehicles was best when the formulation contained monoglycerides and surfactants with a hydrophilic–lipophilic balance value <12. Gelatin capsules in general resulted in a better compatibility when compared to HPMC capsules for the evaluated formulations. Addition of water to the formulation improved the capsule compatibility for both capsule types. The expected capsule mass change could partly be predicted in binary systems using the provided data of the single excipients weighted for its formulation proportion.

Conclusions The capsule compatibility was driven by the components incorporated into the formulations, where more was compatible with gelatin than HPMC capsules. Prediction of the mass change from individual excipient contributions can provide a good first estimate if a vehicle is compatible with a capsule, however, this needs to be proved experimentally.

KEY WORDS capsule compatibility · hard gelatin capsules · HPMC capsules · lipid based formulation · lipid excipients · liquid filled capsule · SNEDDS · soft gel capsules

INTRODUCTION

Oral drug administration is often chosen as the favourable administration route as it offers unique advantages in terms of patient convenience and higher adherence, the possibility to self-administration, and lower production costs. For oral delivery, drug compounds with a poor aqueous solubility are a main concern for the pharmaceutical industry as these compounds present several challenges related to the formulation design. The poor solubility may constitute a limitation in the amount of compound that can be dissolved and hence made available for absorption after oral administration. To address this issue various formulation techniques have been developed to improve the bioavailability of these drugs, where in particular lipid based formulations have been demonstrated to be a very effective approach for some of the hardest to formulate compounds (1).

Lipid-based formulations constitute a broad range of formulation systems as also defined in Poutons lipid formulation classification system (2), where the selection of the exact formulation is driven by a number of parameters (3). Some of the formulations are liquid at ambient temperature whereas others are waxes, also termed semisolid, which become a

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liquid at slightly elevated temperatures. The critical formulation parameters are to firstly identify lipid excipients that are miscible, i.e. the ability of the combined excipients to form one phase, secondly a formulation that can solubilize the desired amount of active pharmaceutical ingredient wherein it is also stable, and not least ensure the needed biopharmaceutical behavior of the compound. Soft gelatin capsules were used to encapsulate the lipid based formulation, often also termed liquids and semi-solid. Up until year 2000, liquid and semi-solid formulations were almost exclusively filled into soft gelatin capsules whereas hard gelatin capsules were used for the encapsulation of powders (4, 5). A liquid formulation encapsulated within a hard gelatin capsule was already approved by FDA in 1941, however, only as of year 2000 several liquid filled hard gelatin capsules have entered the market (5). While soft-shell capsules can accommodate a higher fill volume and a wider range of excipients, hard gelatin capsules allow for higher filling temperature (as high as 70°C), in general less moisture migration from the capsule into the formulation and do not require the addition of plasticizers to the shell (6–9). Some plasticizers have been associated with higher oxygen permeability and a higher drug migration into the shell (6), both phenomena that may affect the formulations overall stability and performance. In addition, from an early drug product development perspective, hard gelatin capsules provide an advantage during early screening with very low amounts of API.

Major considerations of liquid/semisolid filled capsules are related to the compatibility between the formulation and the capsule shell (3, 7, 10–12). The choice of capsule type will depend upon a number of parameters, where the composition and physical characteristics of the formulation as well as the fill temperature needed is of importance. Where the formulation of the soft-gel capsules can be modified to the formulation vehicle, the hard gelatin capsules are locked in the composition. Hence the compatibility will be a critical parameter to define, if filling into a hard gelatin capsule is possible. Gelatin has historically been used as the capsule material; however, it has the major drawback of being susceptible to crosslinking reactions in the presence of aldehydes or high humidity (13), though this phenomenon has been shown to have no influence on the *in vivo* release and performance, hence it seems to be an issue isolated to the *in vitro* methodology (13, 14). Further, water is the sole plasticizer in hard gelatin capsules that optimally should be kept between 13 and 15% (*w*/w) for the capsules not to be become brittle (below 10% (w/w)) or sticky (above 18% (w/w)), respectively (15, 16). This makes hard gelatin capsules sensitive to low humidity or hygroscopic filling materials (17). As an alternative, hard capsules with hydroxypropyl methylcellulose (HPMC) have been developed. HPMC capsules have a lower water content (4–6% (*w*/w)) in comparison with the gelatin capsules and therefore also a lower possibility for water or hydrophilic excipient exchange with the capsule fill (18), which have been confirmed in a few studies (19, 20). Thus HPMC capsules are an interesting encapsulation option for lipid based formulations.

Lipophilic vehicles such as medium and long-chain free fatty acids and their esters (mono, di and tri-) are known to be compatible with hard gelatin and HMPC capsules (4, 7, 19). Polyethylene glycol (PEG) with a molecular weight of more than 4000 is known to be compatible with hard gelatin capsules, whereas lower molecular weights will make the gelatin capsules brittle due to the excipients hydrophobicity. In the case of HPMC, it has only been demonstrated that PEG 400 is not compatible with the capsules. A number of single excipients, including surfactants, have been reported compatible with both hard capsule types (6, 19), but in general very few studies have evaluated a range of different excipients and excipient mixtures in a head to head fashion for the two capsule types. The purpose of the present investigation was, therefore, to define miscible formulations and subsequently to assess the compatibility between hard gelatin and HPMC capsules with a wide range of different formulation types containing multiple excipients to obtain a better insight into when to select one capsule shell over the other.

MATERIALS AND METHODS

Materials

Polyethylene glycol 400 (PEG400) was obtained from Clariant, Germany**.** Propylene glycol was obtained from Caldic Belgium N.V**.** Transcutol® HP (Transcutol HP), Labrafac™ lipophile WL1349 (Labrafac lipophile), Maisine® CC (Maisine), Labrasol® ALF (Labrasol ALF), Labrafil® M 2125 CS (Labrafil 2125) were a gift from Gattefosse, France. Captex 300 EP/NF (Captex 300) and Capmul MCM EP/NF (Capmul MCM) were obtained from Abitec corporation, USA. Kolliphor® ELP (Kolliphor ELP) and Kolliphor® HS 15 (Kolliphor HS 15) were purchased from BASF, Germany. Tween 80 was obtained from Croda, USA. Olive oil was obtained from Henry Lamotte oils GmbH, Germany**.** Grey colored size 00 hard gelatin capsules and white-colored size 00 HPMC capsules were obtained from Capsugel, France. The used water was produced in-house using a Milli-Q water system. A presentation of the excipients investigated are summarized in Table I**.**

Miscibility Test

Two miscibility tests were performed in this study. The first test investigated the miscibility of the different excipients from Table I, i.e. oils, surfactants, and cosolvents, at different ratios, (Table II). In total 350 mixtures using five oils, five surfactants and three cosolvents were investigated. Since an isotropic

Table I Excipients Used in the Capsule Compatibility Test and Respective Information: Class, Chemical Composition, Trade Name, HLB, and Physical State at RT

Code	Trade name	Chemical composition	Abbreviation used	HLB	Physical state at ambient temperature
Oil (O1)	Labrafac™ lipophile WL1349	Medium chain triglyceridesCaprylic and capric acids	Labrafac lipophile	1 (21)	Liquid
Oil (O2)	Maisine® CC	Long Chain mixture of mono-, di- and triglycerides	Maisine	1 (22)	Liquid
Oil (O3)	Captex® 300 EP/NF	Medium-Chain TriglyceridesGlyceryl Tricaprylate	Captex 300	1*	Liquid
Oil (O4)	Olive oil	Long-chain triglyceride	na	1*	Liquid
Oil (O5)	Capmul® MCM EP/NF	Medium chain Caprylic/capric mono- & diglycerides Glyceryl caprylate/caprate	Capmul MCM	1*	Liquid
Surfactant (S1)	Labrasol® ALF	Caprylocaproyl Polyoxyl-8 glycerides(PEG 8, caprylic and capric acids)	Labrasol ALF	12 (23)	Liquid
Surfactant (S2)	Labrafil® M 2125 CS	Linoleoyl Polyoxyl-6 glycerides	Labrafil 2125	9 (24)	Liquid
Surfactant (S3)	Kolliphor® ELP	Polyoxyl-35-castor oil	Kolliphor ELP	12–14 (25)	Semisolid melts at 30 °C
Surfactant (S4)	Kolliphor® HS 15	Polyoxyl 15 Hydroxystearate	Kolliphor HS 15	15 (25)	Semisolid melts at 30 °C
Surfactant (S5)	Tween® 80	Polyoxyethylene (20) sorbitan monooleatepolysorbate 80	Tween 80	15 (26)	Liquid
Cosolvent (CS1)	Propylene glycol	propane-1,2-diol (2 hydroxyl groups)	Na	NA	Liquid
Cosolvent (CS2)	PEG400	low molecular weight polyethylene glycol	Na	NA	Liquid
Cosolvent (CS3)	Transcutol® HP	Diethylene glycol monoethyl ether	Transcutol HP	NA	Liquid

*No informations provided by suppliers, i.e. HLB given based upon classical understanding of HLB

Table II Percentage Ratios of All the Oils, Surfactants, and Cosolvents Used to Prepare the Formulations for the Miscibility Test

System	Oil (%w/w)	Surfactant (%w/w)	Cosolvent (%w/w)
1	40	60	0
2	40	50	10
3	40	40	20
4	60	40	0
5	60	30	10
6	60	20	20

mixture was targeted, the miscibility evaluation ensured that all components of the mixture to be filled in the capsules were in one phase. Binary (oil and surfactant) or ternary (oil, surfactant, and cosolvent) mixtures were prepared by mixing the different components in different ratios with a final mixture weight of 10 g. Semi-solid excipients were melted at 30°C before mixing with other excipients. The excipients were weighed in a 10 mL clear glass vial in the desired ratio followed by mixing the components using a magnetic rod at 500 rpm for 1 h at ambient temperature. Subsequently, the vials were placed against a black background and were visually inspected for isotropicity. Concepts that showed one phase solution were considered miscible (isotropic), concepts that were cloudy, turbid or had clear phase separation of the mixture were considered as immiscible (non-isotropic). Only isotropic mixtures were further investigated in capsule compatibility experiments, see section below**.**

For the isotropic concepts that failed in the capsule compatibility study, an additional miscibility test was conducted. Kuentz and Röthlisberger (27) argued that there exists a balanced amount of water, which when added to a lipid based formulation, prevent hygroscopic excipients from dehydrating the hard gelatin capsule shell thereby minimising the change in the capsules mechanical properties during storage (27). Thus, a second miscibility test was performed to determine the maximum amount of water that could be incorporated in the formulations that resulted in capsule incompatibility while maintaining an isotropic mixture. For the concepts that were not compatible with capsules in the first capsule compatibility test, water was added to 10 g of the formulations with increments of 1% (*w*/w) and stirred at 500 rpm for 1 h. Post 1 h, the mixtures were visually inspected for isotropicity as described above. If found isotropic, an additional 1% (w/w) water was added and the experiment continued until the mixture turned non-isotropic or the water addition reached 10% (w/w) of 10 g, whichever was earlier.

Capsule Compatibility

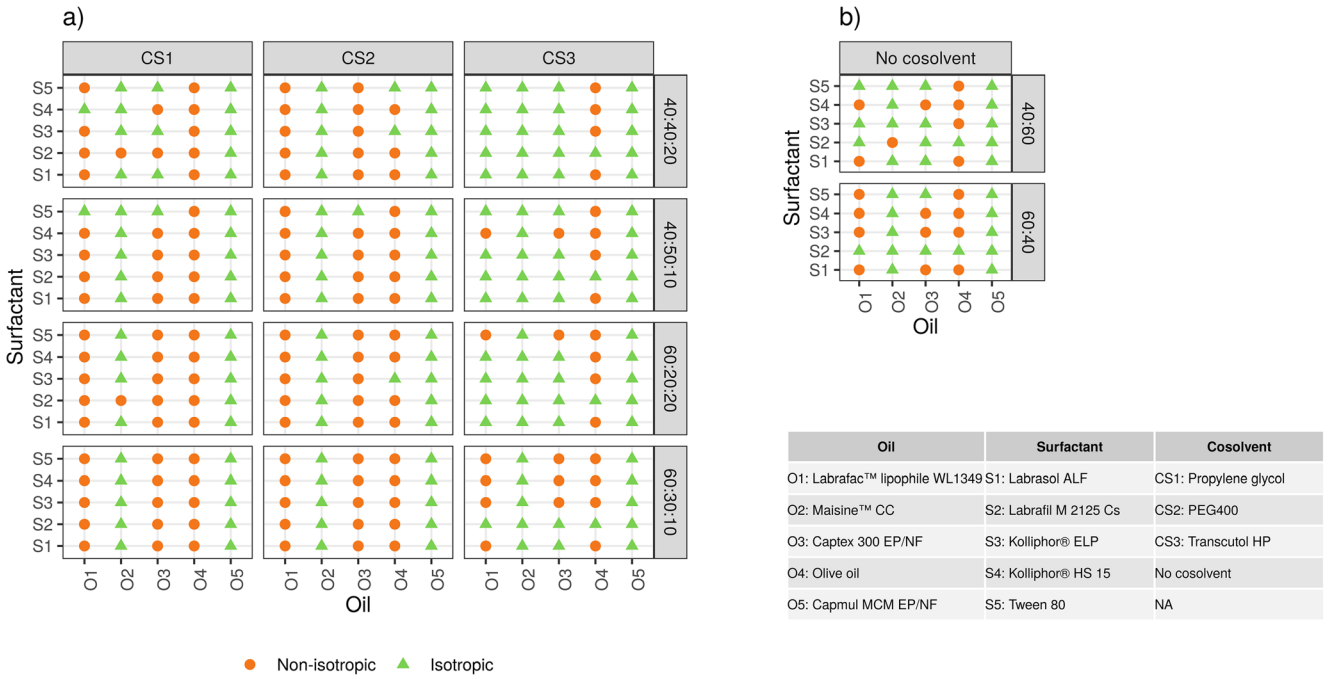
As for miscibility test, capsule compatibility was performed in two stages. In the first stage, the isotropic concepts from the first miscibility test were tested for compatibility either in hard gelatin or HPMC based capsule shells. In the second compatibility study, the isotropic concepts that were not compatible with the capsules were tested with the highest amount of water that could be added while maintaining the isotropicity (up to max 10% (*w*/w)), for compatibility either in hard gelatin or HPMC based capsule shells. The method used to determine the compatibility was as described by Cadé and Madit (28). The isotropic mixtures were prepared as described previously**.** The isotropic mixtures from either of the two miscibility tests were filled (0.5 mL) in a size 00 coni-snap capsule shell made of either hard gelatin or HPMC. The cap and body of the capsule was closed and capsules were placed standing in a holder placed in climate chambers maintained at 25°C/40 %RH as well as 25°C/60 %RH for a period of 4 weeks under open dish condition (Fig. S1**)**. The average weight of capsules ($n = 10$ for either shell type) was noted at time point 0 and after 2 and 4 weeks of storage at both condition. The average (n = 10) weight gain or weight loss was recorded as the difference between the start weight and the weight after 2 and 4 weeks, respectively. Apart from the weight gain or weight loss, the capsules (both shell type and both conditions) were also tested visually for any capsule defect at the 4 week period. The mixtures that showed a weight gain or weight loss within the 2% (*w*/w) window and that did not show any capsule defects at the end of the 4 week period were considered to be compatible (28). The compatibility of the individual oils and surfactants at 100% (*w*/w) concentration was also investigated in a similar manner. Individual cosolvents were not tested due to their well-documented incompatibility with capsules at concentrations more than 20% (w/w) (28).

RESULTS AND DISCUSSIONS

Miscibility Test

Miscibility of lipid based formulation vehicles containing oils (Labrafac lipophile, Maisine, Captex 300, olive oil, and Capmul MCM), surfactants (Labrasol ALF, Labrafil 2125, Kolliphor ELP, Kolliphor HS 15, and Tween80) and in the case of tertiary mixtures cosolvents (propylene glycol, PEG400, and Transcutol HP) at six different ratios was evaluated. The formulation excipients were melted and mixed in the respective ratios and evaluated visually for isotropicity. The results are shown in Fig. 1, and in Tables III, IV, V.

A total of 350 concepts were evaluated of which 192 (54.9%) concepts were isotropic, i.e. clear, transparent and one phase. Of the 192 visually isotropic concepts, 31 were



Oil	Surfactant	Cosolvent
O1: Labrafac™ lipophile WL1349	S1: Labrasol ALF	CS1: Propylene glycol
O2: Maisine™ CC	S2: Labrafil M 2125 Cs	CS2: PEG400
O3: Captex 300 EP/NF	S3: Kolliphor® ELP	CS3: Transcutol HP
O4: Olive oil	S4: Kolliphor® HS 15	No cosolvent
O5: Capmul MCM EP/NF	S5: Tween 80	NA

Fig. 1 Miscibility of lipid excipients. Each point represents an isotropic (▲, green) or non-isotropic (●, red) lipid based vehicle. (**a**) ternary formulation vehicles, (**b**) binary formulation vehicles.

binary mixtures of oils and surfactants and 161 tertiary mixtures included a cosolvent. In approximately half of the tested formulation vehicles, the evaluated excipients were not miscible, also demonstrating the value of generating pseudo-phase diagrams when engaging into lipid based formulations to define the relevant ranges of the different components.

In the case of oils, all evaluated lipid vehicles containing Capmul MCM led to a visually isotropic mixture. Vehicles containing Maisine resulted in isotropic mixtures in 96% of the cases investigated. The lowest amount of isotropic mixtures was observed with the long chain triglyceride olive oil, with 13% of isotropic vehicles. In addition, Captex 300 and Labrafac lipophile also resulted in a relatively low amount of isotropic vehicles of 37% and 29%, respectively. This indicated that monoglycerides were in general better miscible with other lipid excipients than triglycerides, resulting in an increased amount of isotropic lipid vehicles. Furthermore, the results showed that a lower lipid load in the formulation, i.e. 40%, resulted in a better miscibility and an increased amount of isotropic vehicles was obtained when compared to a lipid load of 60%. In addition, binary mixtures appeared to result in a higher amount of isotropic formulations when compared to tertiary mixtures.

All surfactants resulted in isotropic formulation vehicles when mixed with both monoglycerides (Maisine and Capmul MCM). In the case of binary surfactant-triglyceride mixtures, Labrafil M2125 resulted in the most isotropic vehicles, especially in an oil:surfactant ratio of 60:40 (*w*/w). Overall, Labrafil 2125 resulted in the highest amount of isotropic vehicles of 61% and in combination with Transcutol HP all vehicles were isotropic regardless of the oil component. In the case of semi-solid Kolliphor ELP and Kolliphor HS 15, a temperature dependent miscibility was observed. While at elevated temperatures (>30°C), a visually isotropic mixture

Table III Number and Percent of Isotropic Lipid Vehicles as a Function of the Investigated Oil

Mixture (oil: surfactant: cosolvent)	Labrafac lipophile	Maisine	Captex 300	Olive oil	Capmul MCM	Total
40:40:20	6/15 (40%)	14/15 (93%)	8/15 (53%)	3/15 (20%)	15/15 (100%)	46/75 (61.4%)
40:50:10	5/15 (33%)	15/15 (100%)	6/15 (40%)	1/15 (7%)	15/15 (100%)	42/75 (56%)
40:60	3/5 (60%)	4/5 (80%)	4/5 (80%)	1/5 (20%)	5/5 (100%)	17/25 (68%)
60:20:20	4/15 (27%)	14/15 (93%)	4/15 (27%)	2/15 (13%)	15/15 (100%)	39/75 (52%)
60:30:10	1/15 (7%)	15/15 (100%)	2/15 (13%)	1/15 (7%)	15/15 (100%)	34/75 (45.4%)
60:40	1/5 (20%)	5/5 (100%)	2/5 (40%)	1/5 (20%)	5/5 (100%)	14/25 (56%)
Total	20/70 (29%)	67/70 (96%)	26/70 (37%)	9/70 (13%)	70/70 (100%)	

Table IV Number and Percent of Isotropic Lipid Vehicles as a Function of Surfactants

Mixture (oil: surfactant: cosolvent)	Labrasol ALF	Labrafil 2125	Kolliphor ELP	Kolliphor HS 15	Tween 80	Total
40:40:20	9/15 (60%)	8/15 (53%)	10/15 (67%)	9/15 (60%)	10/15 (67%)	46/75 (61.4%)
40:50:10	8/15 (53%)	9/15 (60%)	8/15 (53%)	6/15 (40%)	11/15 (73%)	42/75 (56%)
40:60	3/5 (60%)	4/5 (80%)	4/5 (80%)	2/5 (40%)	4/5 (80%)	17/25 (68%)
60:20:20	8/15 (53%)	8/15 (53%)	9/15 (60%)	8/15 (53%)	6/15 (40%)	39/75 (52%)
60:30:10	7/15 (47%)	9/15 (60%)	6/15 (40%)	6/15 (40%)	6/15 (40%)	34/75 (45.4%)
60:40	2/5 (40%)	5/5 (100%)	2/5 (40%)	2/5 (40%)	3/5 (60%)	14/25 (56%)
Total	37/70 (53%)	43/70 (61%)	39/70 (56%)	33/70 (47%)	40/70 (57%)	

was formed, a decrease in temperature to 25°C resulted in a cloudy formulation. Overall, Kolliphor ELP and Kolliphor HS 15 resulted in the formation of isotropic formulations in 56% and 47% of the evaluated cases, respectively. In the case of Labrasol ALF and Tween 80, approximately half of the formulation vehicles were visually isotropic. While it appeared that a higher surfactant concentration (60% (*w*/w)) was needed for Labrasol ALF, Kolliphor ELP, and Tween 80 to produce isotropic formulations, the factor had less influence for Labrafil 2125 and Kolliphor HS 15. This indicated that a higher amount of surfactants may in part contribute to the isotropicity of a formulation, however, the type of surfactant and the type of oil were clearly important components for the development of an isotropic lipid based formulation.

In the case of cosolvents, a better miscibility with monoglycerides (Maisine and Capmul MCM) was observed when compared to triglycerides (Labrafac lipophile, Captex 300, and olive oil). However, Transcutol HP containing vehicles also resulted in isotropic mixtures with triglycerides and thereby showed the overall highest percentage of visually isotropic concepts among the investigated cosolvents (73%). Transcutol HP showed exceptional miscibility with olive oil in combination with Labrafil 2125, since all evaluated vehicles containing these three excipients resulted in visually clear mixtures irrespective of concentration. Unlike Transcutol HP, both propylene glycol and PEG400 containing vehicles resulted only in 44% of the investigated cases with an isotropic mixture. Vehicles containing olive oil and propylene glycol were all non-isotropic. In fact, compared to the cosolvent free binary systems, the addition of propylene glycol and PEG400 in general led to a reduction in the number of isotropic mixtures regardless of the amount of added cosolvent, i.e. 10% (*w*/w) or 20% (w/w). With respect to cosolvent concentration, it was observed that a higher cosolvent concentration (20% (w/w)) resulted in a higher number of isotropic formulations, when compared to a lower cosolvent concentration (10% (w/w)). In summary, from a miscibility perspective the addition of cosolvents was not advantageous in all cases and highly dependent upon the type and amount of cosolvent.

Evaluation of Compatibility: Capsule Appearance

Excipient compatibility with hard gelatin and HPMC capsule shells was assessed for miscible vehicles (see Fig. 1**)** after 4 weeks of open dish storage at 25°C/40% RH and 25°C/60% RH. The formulation mixture was considered incompatible in case of observed capsule damage or a weight change of the filled capsules outside ±2% (*w*/w). Capsule damages comprised leakages, softening or deformation. Examples of capsule damages are depicted in the supporting information (Fig. S2). Capsule damages were observed for 31 binary (oil/surfactant) and 161 tertiary (oil/surfactant/cosolvent) isotropic mixtures. An overview of all evaluated formulations is illustrated as an alluvial plot in Fig. 2 and Fig. S3-S7. A summary of the observed capsule damage for oils, surfactants, and cosolvents is provided in

Table V Number and Percent of Isotropic Lipid Vehicles as a Function of Cosolvent

Mixture (oil: surfactant: cosolvent)	Propylene glycol	PEG400	Transcutol HP	No cosolvent	Total
40:40:20	13/25 (52%)	12/25 (48%)	21/25 (84%)	NA	46/75 (61.4%)
40:50:10	12/25 (48%)	11/25 (44%)	19/25 (76%)	NA	42/75 (56%)
40:60	NA	NA	NA	17/25 (68%)	17/25 (68%)
60:20:20	9/25 (36%)	11/25 (44%)	19/25 (76%)	NA	39/75 (52%)
60:30:10	10/25 (40%)	10/25 (40%)	14/25 (56%)	NA	34/75 (45.4%)
60:40	NA	NA	NA	14/25 (56%)	14/25 (56%)
Total	44/100 (44%)	44/100 (44%)	73/100 (73%)	31/50 (62%)	

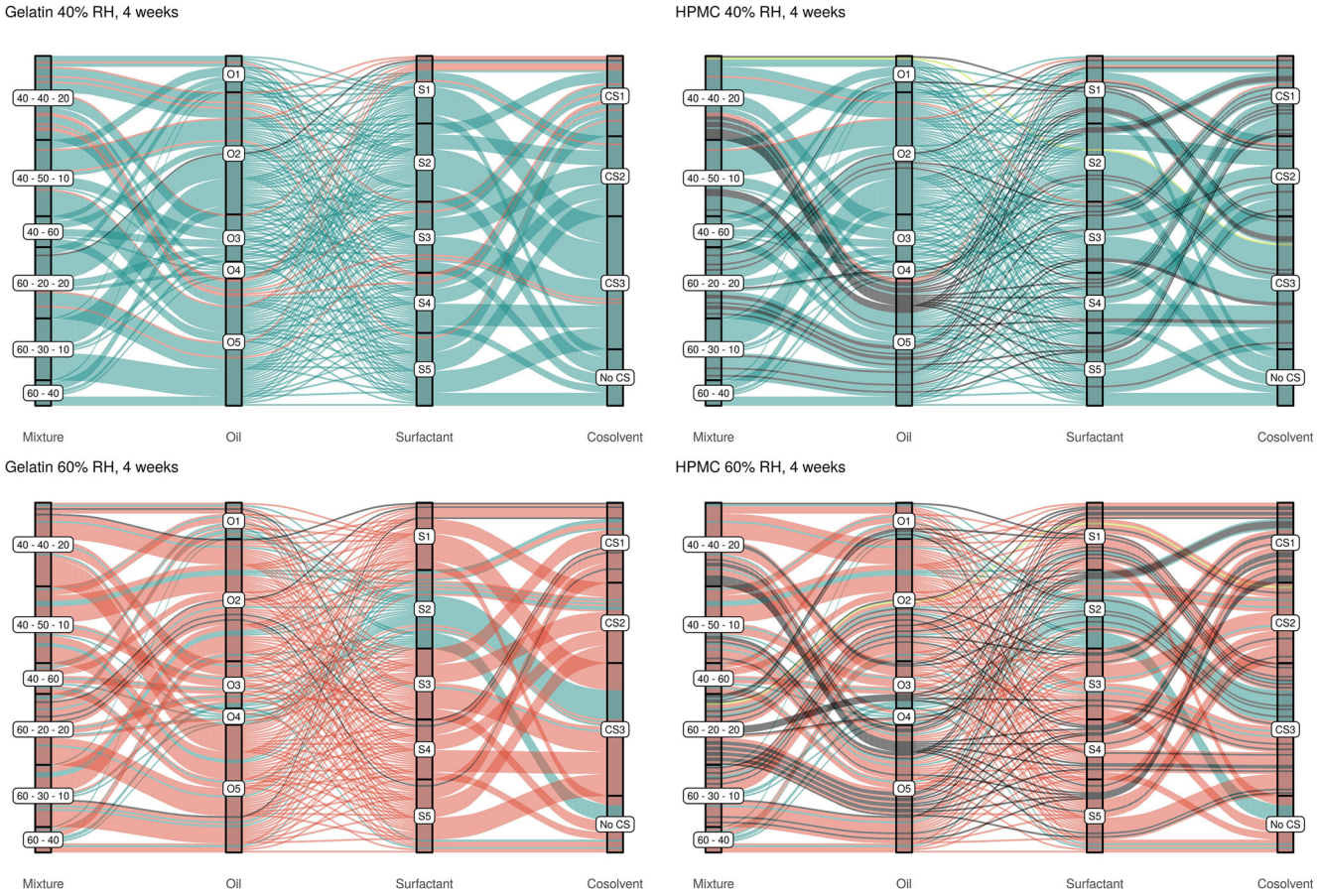


Fig. 2 Capsule compatibility for all evaluated concepts in both gelatin (left) and HPMC (right) capsules, respectively, after 4 weeks of storage at 25°C/40% RH (upper pane) and 25°C/60% RH (lower pane), respectively. Each colored line connecting specific mixture, oil, surfactant and cosolvent represents a specific formulation of the specified mixture ratio. Depicted are compatible formulations with a weight change between −2% and 2% (w/w) (green); incompatible formulations with a weight change < −2% or > 2% (w/w) (red); and formulations resulting in capsule damages (black). O1: Labrafac lipophile; O2: Maisine; O3: Captex 300; O4: olive oil; O5: Capmul MCM; S1: Labrasol ALF; S2: Labrafil 2125; S3: Kolliphor ELP; S4: Kolliphor HS 15; S5: Tween 80; CS1: propylene glycol; CS2: PEG400; CS3: Transcutol HS.

Table VI, VII and VIII, respectively and the entire data set can be found in the supporting information (Table SI). The alluvial plot should be read like a flow diagram from left to right, exact formulations that were compatible cannot be identified, but the plot can provide a quick visual oversight, e.g. that the combination of S2 (Labrafil 2125) and CS3 (Transcutol HS) is critical for compatibility with gelatin at 60 %RH.

In general, a higher number of capsule damages was observed in HPMC based capsules when compared to a gelatin based capsule shell, as illustrated in Fig. 2 by the black curves. For both gelatin and HPMC capsules the amount of damaged capsules increased when increasing the relative humidity during storage from 40% to 60%. While the individual oils and surfactants did not cause damages to gelatin capsules after 4 weeks at 25°C/40% RH and 60% RH, damages in the case of Capmul MCM (25°C/40% RH), Labrafac lipophile (25°C/60% RH) and Labrasol ALF (25°C/60% RH) were observed after 4 weeks storage in HPMC capsules.

Table VI Observed Capsule Damage as a Function of Oil Type After 4 weeks of Open Dish Storage at 25 °C/40% RH and 25°C/60% RH

Capsule material	Storage condition	Labrafac lipophile	Maisine	Captex 300	Olive oil	Capmul MCM	Total
Gelatin	25 °C/40% RH	2/20 (10%)	3/67 (4%)	0/26 (0%)	1/9 (11%)	25/70 (36%)	31/192 (16%)
	25°C/60% RH	0/20 (0%)	1/67 (1%)	0/26 (0%)	0/9 (0%)	0/70 (0%)	1/192 (1%)
HPMC	25 °C/40% RH	4/20 (20%)	8/67 (12%)	6/26 (23%)	1/9 (11%)	25/70 (36%)	44/192 (23%)
	25 °C/60% RH	1/20 (5%)	4/67 (6%)	0/26 (0%)	0/9 (0%)	1/70 (1%)	6/192 (3%)

Table VII Observed Capsule Damage as a Function of Surfactant Type After 4 weeks of Open Dish Storage at 25 °C/40% RH and 25°C/60% RH

Capsule material	Storage condition	Labrasol ALF	Labrafil 2125	Kolliphor ELP	Kolliphor HS 15	Tween 80	Total
Gelatin	25 °C/40% RH	9/37 (24%)	5/43 (12%)	6/39 (15%)	6/33 (18%)	5/40 (12%)	31/192 (16%)
	25 °C/60% RH	1/37 (3%)	0/43 (0%)	0/39 (0%)	0/33 (0%)	0/40 (0%)	1/192 (1%)
HPMC	25 °C/40% RH	12/37 (32%)	9/43 (21%)	5/39 (13%)	10/33 (30%)	8/40 (20%)	44/192 (23%)
	25 °C/60% RH	3/37 (8%)	0/43 (0%)	0/39 (0%)	2/33 (6%)	1/40 (3%)	6/192 (3%)

Among the oils in the evaluated mixtures an increased amount of capsule damages was observed in HPMC capsules when compared to gelatin capsules and during storage at higher relative humidities. Especially, formulations containing Capmul MCM damaged the HPMC capsule shell in 36% of the cases at both evaluated storage conditions. This was in agreement with the observed incompatibility of Capmul MCM alone in HPMC capsules. The ranking of capsule damages from low to high after 4 weeks of storage at 25°C/60% RH was Captex 300 EP/NF = olive oil < Capmul MCM < Labrafac lipophile < Maisine in gelatin capsules and olive oil < Maisine < Labrafac lipophile < Captex 300 < Capmul MCM in HPMC capsules.

In the case of surfactants, an increased relative humidity led to a slight increase in the fraction of gelatine capsules damaged when using Labrasol ALF, Kolliphor HS15, and Tween 80. No capsule damages were observed for Labrafil M2125 CS and Kolliphor ELP in gelatin capsules at 40%RH. Formulation mixtures stored in HPMC capsules resulted in an increased amount of capsule damages with increasing relative humidity for all surfactants except for Kolliphor ELP. The ranking of capsule damages from low to high after 4 weeks of storage at 25°C/60% RH was Labrafil M2125 CS = Kolliphor ELP < Tween 80 < Kollipjhor HS15 < Labrasol ALF in gelatin capsules and Kolliphor ELP < Tween 80 < Labrafil M2125 CS < Kolliphor HS15 < Labrasol ALF in HPMC capsules, indicating that Labrasol ALF carries the highest risk followed by Kolliphor HS15 for capsule damages in both gelatin and HPMC based capsule shells for the investigated systems.

Cosolvents are generally freely soluble with water and hence could theoretically constitute an important factor for capsule incompatibilities since cosolvents could interact more easily with the capsule shell. This study, however, revealed that the type of cosolvent and capsule shell were pivotal for the observed damages. In gelatin capsules only propylene glycol resulted in capsule damages at the tested concentrations, which increased from 2% to 14% with increasing relative humidity. For HPMC capsules, it was observed that all mixtures without a cosolvent were compatible with no observed damages, whereas significant amount of incompatibilities was observed when a cosolvent was added. This clearly indicated that formulations with a cosolvent, which may be added to a formulation e.g. to increase the compound solubility in the vehicle, carry a higher risk of incompatibility with HPMC capsules. These data therefore suggest that in cases where a cosolvent is needed, a gelatin capsule may have a higher level of success. The ranking of capsule damages from low to high after 4 weeks of storage at 25°C/60% RH was PEG400 = Transcutol HP < propylene glycol in gelatin capsules and PEG400 < Transcutol HS < propylene glycol in HPMC capsules, i.e. in particular propylene glycol may be a challenge to include into a formulation.

Evaluation of Compatibility: Weight Change of Capsules

In addition to the capsule appearance evaluation, excipient compatibility with gelatin and HPMC based capsule shells was also assessed by means of capsule weight changes. The average weight of 10 capsules was measured after capsule filling as well as after 2 and 4 weeks of open dish storage at 25°C/40% RH and 25°C/60% RH. While in the case of a mass change of up to ±2% (*w*/w) compatibility with the capsule shell was assumed, in the case of a mass change > ± 2% (w/w) the excipient mixture was considered non-compatible with the tested capsule shells (28). The capsule weight change was evaluated for the same 192 isotropic mixtures that were previously used for appearance assessment. The observed weight changes for the single excipients (oils and surfactants) and for all formulation mixtures is illustrated in Figs 3 and 4,

Table VIII Observed Capsule Damage as a Function of Cosolvent Type After 4 weeks of Open Dish Storage at 25 °C/40% RH and 25°C/60% RH

Capsule material	Storage condition	Propylene glycol	PEG400	Transcutol HP	No cosolvent	Total
Gelatin	25 °C/40% RH	14/44 (32%)	5/44 (11%)	12/73 (16%)	0/31 (0%)	31/192 (16%)
	25 °C/60% RH	1/44 (2%)	0/44 (0%)	0/73 (0%)	0/31 (0%)	1/192 (1%)
HPMC	25 °C/40% RH	22/44 (50%)	3/44 (7%)	19/73 (26%)	0/31 (0%)	44/192 (23%)
	25 °C/60% RH	6/44 (14%)	0/44 (0%)	0/73 (0%)	0/31 (0%)	6/192 (3%)

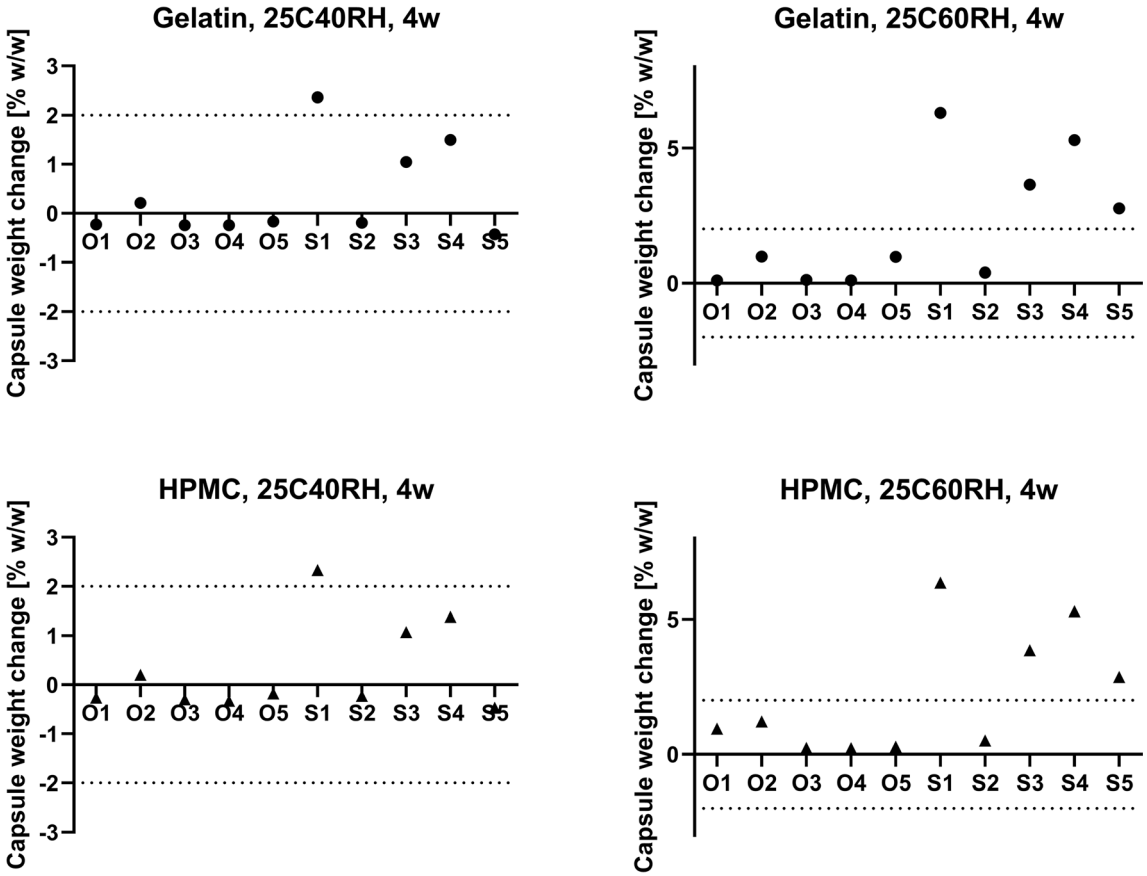


Fig. 3 Weight change (% *w/w*) of single excipients (oils and surfactnats) in gelatin and HPMC capsules after storage at 25°C/40% RH and 25°C/60% RH, respectively after 4 weeks of storage. The maximum accepted weight change of ± 2% (w/w) is illustrated as dotted lines. O1: Labrafac lipophile; O2: Maisine; O3: Captex 300; O4: olive oil; O5: Capmul MCM; S1: Labrasol ALF; S2: Labrafil 2125; S3: Kolliphor ELP; S4: Kolliphor HS 15; S5: Tween 80.

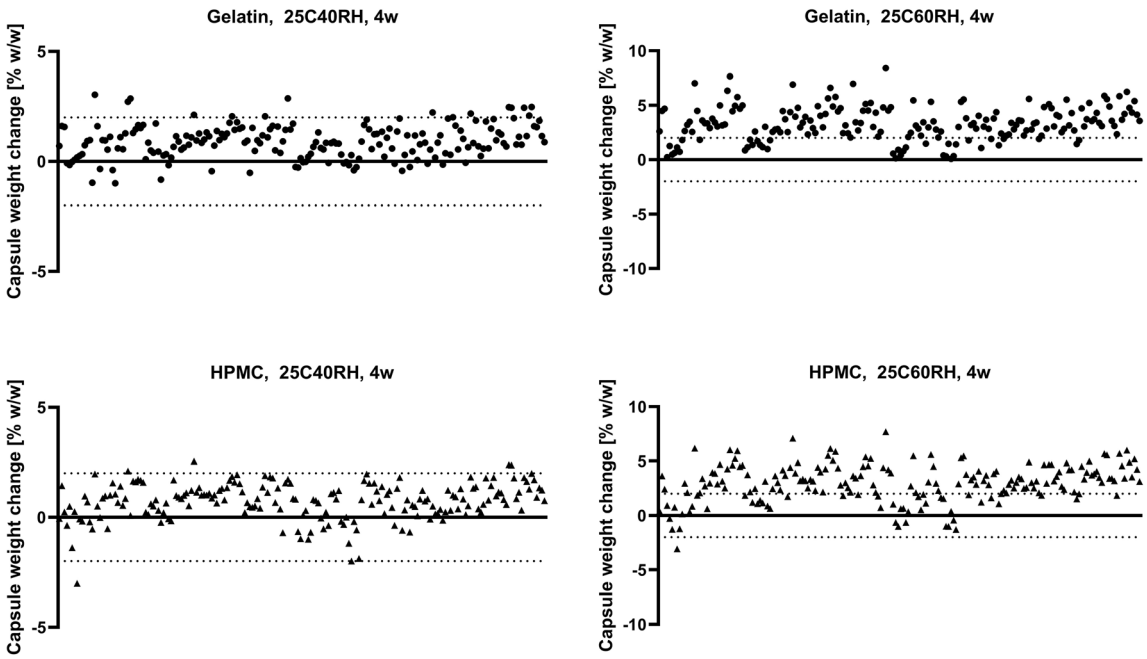


Fig. 4 Weight change of the evaluated formulation vehicles in gelatin and HPMC capsules after 4 weeks of storage at 25°C/40% RH and 25°C/60% RH, respectively. The maximum accepted weight change of ±2% (w/w) is illustrated as dotted lines.

respectively. A summary for all formulation mixtures is provides in Tables IX, X, and XI for oils, surfactants, and cosolvents, respectively. Alluvial plots for the compatibility study can be found in the supporting information (Fig. S3 to S7) as well as weight change as a function of time (Fig. S8 to S10).

The oils and surfactants evaluated in the formulation mixtures were assessed as a single component for their weight change upon storage at 25°C/40% RH and 25°C/60% RH (Fig. 3). The tested oils resulted in a minor weight change in gelatin and HPMC based capsules at both evaluated storage conditions. Thus, all oils were considered compatible with the tested capsule shells. With respect to the evaluated surfactants, it was observed that at lower relative humidity only Labrasol ALF resulted in a significant weight change of >2% (*w*/w), whereas at higher relative humidity of 60% all surfactants resulted in a significant mass increase except Labrafil 2125 (Fig. 3). Labrafil 2125 exhibited only a minor weight change and was hence considered compatible with both capsule types. This was in agreement with the observations of capsule damages where formulation vehicles with Labrafil 2125 resulted in one of the lowest number of capsule damages when compared to the other surfactants. In general, it appears that oils were not the root cause for capsule incompatibility with respect to weight change upon storage, but rather the surfactants and cosolvents.

Overall, it was observed that at 25°C/40% RH weight changes were low and 92% of tested concepts in gelatin capsules and 81% of tested formulation vehicles in HPMC capsules resulted in a weight change of < ± 2% (w/w). Thus, the majority of tested formulation vehicles was considered compatible with the capsule shells. However, at elevated relative humidity of 60%, a significant increase in capsule mass was observed for both capsule types, as illustrated in Figs. 2 and 4 (and Fig. S3), indicating that a careful evaluation of formulation concept compatibility with the capsule shell during drug product development is crucial for the development success.

As shown above in Fig. 3**,** the single oils were compatible with both capsule shell materials, which was also reflected in the results of the formulation mixtures (see Table IX). For gelatin at 25°C/40% RH, 92% of the formulations were compatible with the capsule shell, for HPMC at the same conditions this was 81%, which for both capsule types dropped to approximately 20% at 25°C/60% RH. In particular, the inclusion of one of the two glyceride mixtures in the formulation, i.e. Maisine and Capmul MCM stood a bit out for both shell types at both storage conditions, however, no firm conclusions on to lipid chain length or type could be drawn.

While the oils did not appear to be the root cause of increasing weight change, it was evident that the surfactants contributed considerably to the observed mass increase at elevated relative humidity of 60%. Especially Labrasol ALF and Kolliphor HS 15 resulted in a significant mass increase with no concept being within the −2% (*w*/w) to 2% (w/w) limits at 25°C/60% RH in gelatin capsules. Kolliphor ELP and Tween 80 also resulted in a significant reduction in compatible formulations when stored at 25°C/60% RH over 4 weeks in gelatin capsules. Only Labrafil 2125 showed a high degree of compatibility with gelatin capsules with 100% and 79% of tested vehicles being compatible at 25°C/40% RH and 25°C/60% RH, respectively. This is especially visible in Fig. 2, where the area of Labrafil 2125 is highlighted in green, i.e. compatible formulation vehicles. In the case of HPMC capsule compatibility, a similar trend of incompatibility of Labrasol ALF, Kolliphor ELP, Kolliphor H S15, and Tween 80 was observed. In HPMC capsules, Labrafil 2125 resulted in a superior capsule compatibility (see Fig. 2 and Table X), albeit the amount of compatible concept was lower with 86% and 60% of compatible formulation mixtures at 25°C/40% RH and 25°C/60% RH, respectively when compared to gelatin capsule compatibility.

Cosolvents impacted the capsule compatibility of the tested formulation vehicles significantly. While the absence of cosolvents resulted in 100% compatibility in both gelatin and HPMC capsules at the low relative humidity condition, the addition of especially propylene glycol and PEG400 resulted in an increase of incompatibility at higher relative humidity of 60% (see Table XI). While Transcutol HP also showed an increased incompatibility with increasing relative humidity during storage, this was evident to a lesser extent. Especially the combination of Labrafil 2125 and Transcutol HP resulted in capsule shell compatible formulations as illustrated in Fig. 2 by the green lines from Labrafil 2125 to Transcutol HP for both gelatin and HPMC capsules at 25°C/60% RH.

Balanced Amount of Water

A significant weight change of the capsule was influenced by the storage conditions as well as by the formulation mixture.

Table IX Number and Percent of Capsules with a Weight Change < ± 2% as a Function of Oil

Capsule material	Storage condition	Labrafac lipophile	Maisine	Captex 300	Olive oil	Capmul MCM	Total
Gelatin	25 °C/40% RH	19/20 (95%)	61/67 (91%)	25/26 (96%)	9/9 (100%)	62/70 (89%)	176/192 (92%)
	25 °C/60% RH	8/20 (40%)	9/67 (13%)	7/26 (27%)	6/9 (67%)	7/70 (10%)	37/192 (19%)
HPMC	25 °C/40% RH	17/20 (85%)	62/67 (93%)	26/26 (100%)	8/9 (89%)	43/70 (61%)	156/192 (81%)
	25 °C/60% RH	8/20 (40%)	10/67 (15%)	9/26 (35%)	5/9 (56%)	6/70 (9%)	38/192 (20%)

Table X Number and Percent of Capsules with a Weight Change < ± 2% as a Function of Surfactant

Capsule material	Storage condition	Labrasol ALF	Labrafil 2125	Kolliphor ELP	Kolliphor HS 15	Tween 80	Total
Gelatin	25 °C/40% RH	29/37 (78%)	43/43 (100%)	35/39 (90%)	30/33 (91%)	39/40 (98%)	176/192 (92%)
	25 °C/60% RH	0/37 (0%)	34/43 (79%)	1/39 (3%)	0/33 (0%)	2/40 (5%)	37/192 (19%)
HPMC	25 °C/40% RH	25/37 (68%)	37/43 (86%)	32/39 (82%)	27/33 (82%)	35/40 (88%)	156/192 (81%)
	25 °C/60% RH	1/37 (3%)	26/43(60%)	4/39 (10%)	2/33 (6%)	5/40 (12%)	38/192 (20%)

Depending on the residual water content in the formulation vehicle, water may migrate from the capsule shell to the formulation, or vice versa resulting in capsule damage and capsule weight change. Thus, the addition of water to the formulation vehicle was investigated to mitigate the observed capsule damages and weight changes as incompatibility. A total water amount of 1–5% (*w*/w) was added to the formulation vehicles that were incompatible with the tested hard gelatin or HPMC capsules at 25°C/60% RH. The amount of added water was determined by the miscibility of the formulation vehicle with water. The maximum amount of water resulting in an isotropic mixture was used for the stability assessment. Capsules were stored open dish at 25°C/40% RH and 25°C/60% RH for 4 weeks and appearance and weight changes were assessed. The mass change of the capsules as a function of water addition is illustrated in Fig. 5 and in the supporting information (Fig. S11 and S12).

The water addition was limited to 1% (w/w) to most of the formulations due to the occurrence of a two phase/micellar system upon mixing. While the addition of 1% (w/w) water to the lipid mixtures resulted in increased and decreased weight change after 4 weeks of storage at the tested conditions, the addition of 2% - 5% (w/w) of water resulted in a clear decrease of weight change when compared to the same formulation mixtures without additional water. In fact, for several concepts the weight change could be reduced to stay within the acceptable limits of ±2% (w/w) by adding water to the formulation before the encapsulation. While the general trend towards a decrease in weight change was observed, it was not correlated to a specific oil, surfactant or cosolvent (see supporting information Fig. S11 and S12). This indicated that the addition of a certain amount of water may improve the formulation with respect to capsule compatibility. Nevertheless, the addition of water to the formulation vehicle requires balancing the drug's solubility as well as the capsule compatibility, hence a balance ensuring both parameters may need to be considered in concrete cases.

Prediction of Capsule Compatibility

During formulation development, the compatibility of the desired vehicle with the capsule shell is crucial for the formulation selection. Thus, a predictive model based on the observed mass change of the tested individual excipients was assessed for the binary systems. The predictions were calculated using the mass change of the individual excipients in hard gelatin or HPMC capsules after storage at 25°C/40%RH for 4 weeks weighted for the proportion in the formulation mixture. The calculations were only conducted for binary mixtures. The fit between the predicted change in mass and the measurements in this study is illustrated in Fig. 6.

The developed predictive model was based on pure additive effects of the single excipients and was able to predict capsule compatibility for the tested formulation excipients. The correlation between the measured and predicted mass change exhibited an R^2-value of 0.91. Since the effect of the single oils on the mass change was rather low, the model was especially influenced by the observed mass change of the surfactant. Synergistic effect of oils and surfactants were hence not included in the prediction, which in part may explain the underprediction of some of the concepts. Nevertheless, the predicted mass change correlated well with the measured mass change in that no observed incompatible formulation vehicle was predicted to be compatible and vice versa.

DISCUSSION

The oral administration of liquid or semisolid filled capsules has been demonstrated to be a successful approach to increase

Table XI Number and Percent of Capsules with a Weight Change < ± 2% as a Function of Cosolvent

Capsule material	Storage condition	Propylene glycol	PEG400	Transcutol HP	No cosolvent	Total
Gelatin	25 °C/40% RH	31/44 (70%)	43/44 (98%)	71/73 (97%)	31/31 (100%)	176/192 (92%)
	25 °C/60% RH	3/44 (7%)	4/44 (9%)	19/73 (26%)	11/31 (35%)	37/192(19%)
HPMC	25 °C/40% RH	27/44 (61%)	38/44 (86%)	60/73 (82%)	31/31 (100%)	156/192 (81%)
	25 °C/60% RH	2/44(5%)	2/44 5%)	23/73 (32%)	11/31 (35%)	38/192 20%)

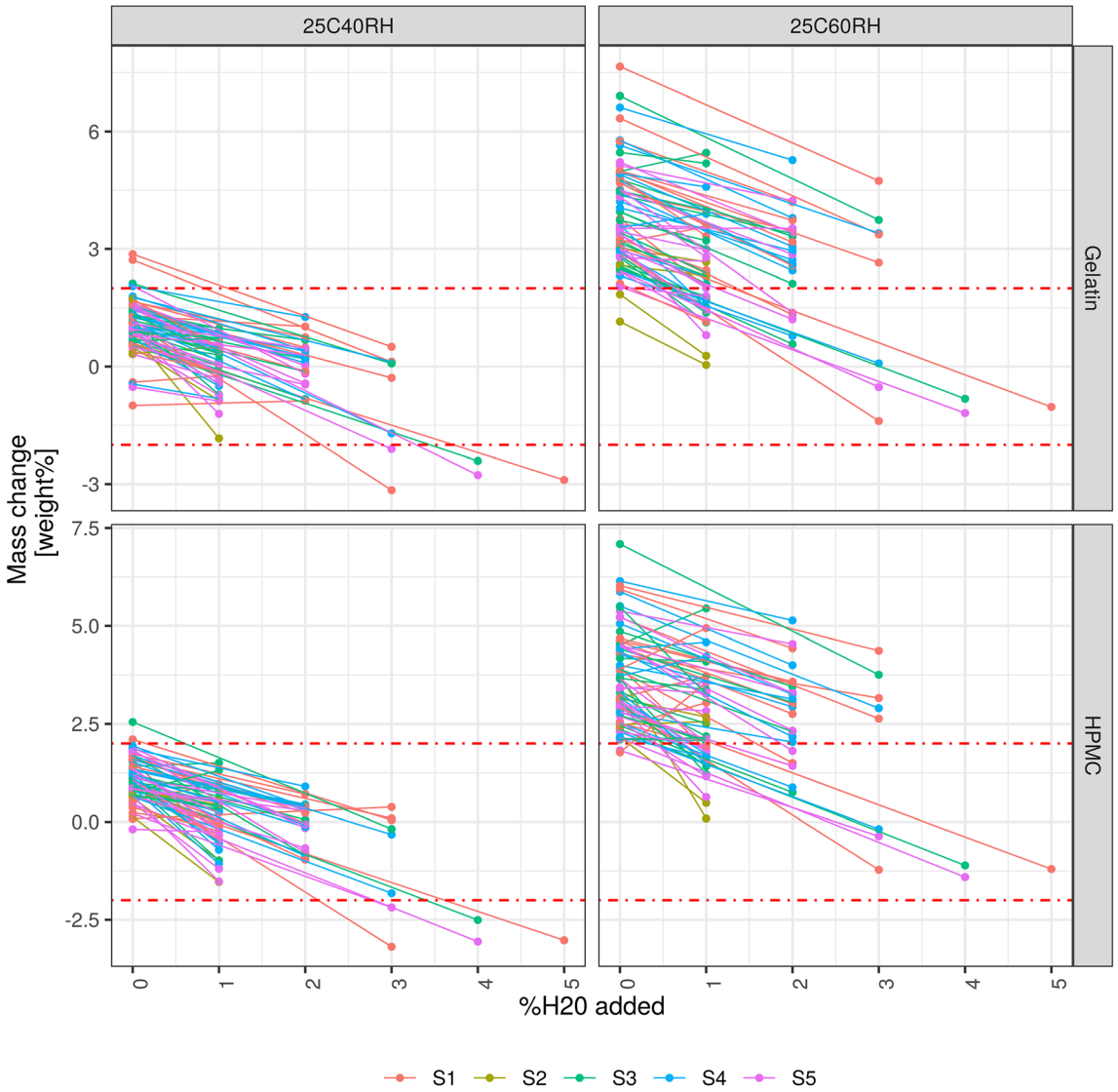


Fig. 5 Change of mass at a water addition to the formulation vehicles after 4 weeks of open dish storage at 25°C, 40%RH and 25°C, 60%RH in gelatin and HPMC capsules, respectively. Coloured according to the surfactant type: S1: Labrasol ALF (red); S2: Labrafil 2125 (army green); S3: Kolliphor ELP (green); S4: Kolliphor HS 15 (blue); S5: Tween 80 (purple).

oral bioavailability for poorly water soluble drugs. Such liquid or semisolid formulations mainly comprise of lipid-based formulations in soft gelatin capsules (5). However, the development of a soft gelatin capsule and formulation is lengthily and resource intensive, while the use of a hard gelatin or HPMC based capsule shell allows for a rather simple processing at higher product temperatures resulting in a quicker and more cost-effective development (18). In addition, hard gelatin or HPMC capsules result in a drug product with a lower moisture content in the formulation, which does not require the addition of plasticizers to the capsule shell (6–9). Independent of the capsule shell, the final formulation must be evaluated for capsule compatibility with the desired capsule shell. Visual damages and weight changes beyond ±2% (*w*/w) upon storage of the formulation in the capsules are deemed non-acceptable (28). Therefore, this study provides an improved insight into the compatibility between hard gelatin and HPMC capsules with a wide range of different formulation types containing multiple excipients providing guidance on the selection of capsule shell type. In addition, a predictive model allowing for an early screening of possible formulation candidates was developed and successfully applied.

The miscibility assessment of the formulation vehicles revealed that monoglycerides resulted in a superior number of isotropic vehicles when compared to triglycerides. In addition, the surfactant Labrafil 2125 resulted in a relatively high amount of isotropic mixtures, especially in combination with Transcutol HP. These results were expected based on the chemical nature of the evaluated excipients. Monoglycerides or mixed glycerides such as Maisine or Capmul MCM contain

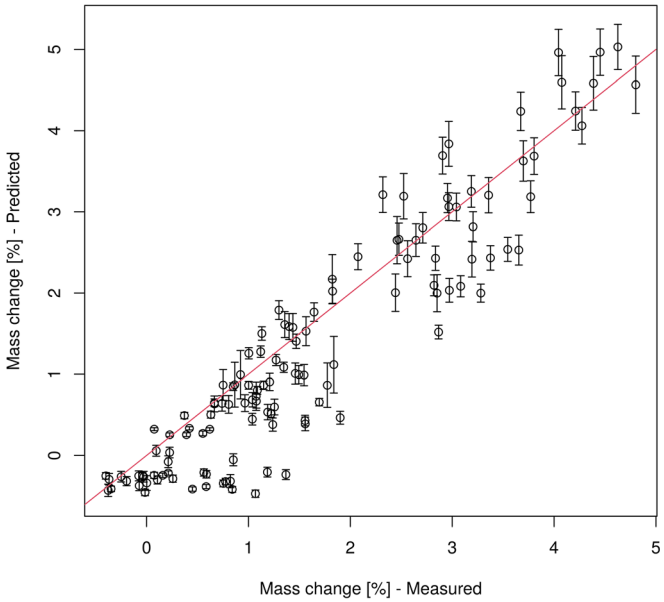


Fig. 6 Relationship between the measured and predicted mass change (weighted form single excipients in the binary mixture) at 25°C, 40%RH . Whiskers depict the 95% confidence interval of the predicted values.

both lipophilic and hydrophilic parts, allowing for hydrogen bonding and van-der-waal interactions with other formulation components. This distinct difference to the rather lipophilic triglycerides seems to enhance the miscibility of monoglycerides when compared to triglycerides, regardless of the other formulation components. The superior miscibility of Labrafil 2125 (HLB value: 9) observed in this study may relate to the co-existing fractions of mono-, di- and triglycerides as well as PEG-6 (MW 300) mono- and diesters of linoleic (C18:2) acid facilitating the interaction towards e.g. triglycerides such as olive oil and cosolvents such as Transcutol HP. While individual researchers may generate pseudo-phase diagrams to define the different ranges for mixtures of different excipients, there is to the best of our knowlegde no overview of lipid excipient miscibilities available in public domain that can support this observation. However, such a database could be very valuable for the formulation scientist working with lipid based formulations. In the present study the mixtures were allowed to stand for one hour before the miscibility was observed, which potentially could lead to false positives for mixtures with a high viscosity. However, since the two investigated semi-solid surfactants, Kolliphor ELP and Kolliphor HS 15, were mixed at elevated temperature, the viscosity of the obtained mixtures were significantly lower mitigating the aforementioned issue. Another point for these two specific surfactants was the observation that they had a temperature dependent miscibility in some cases. For some of the formulations an isotropic mixture was observed at >30°C, but as the temperature was lowed to below 25°C a cloudy formulation was obtained. These observations were in agreement with data presented by Reichert and co-workers (29), who in their study concluded that the thermal treatment of surfactants can have a major impact on their phase behavior through modified interactions between the surfactant and the system (29). While in the present study a temperature dependency was only observed for the two semi-solid surfactants, it cannot be excluded that a temperature dependency also exists for other excipients or mixtures. Therefore, when the isotropicity of formulations is evaluated it is important to consider the potential temperature impact that may occur during manufacturing and storage to ensure the quality of the end product.

The capsule appearance assessment revealed that gelatin capsules were more compatible with the evaluated lipid excipients when compared to HPMC capsules at both evaluated storage conditions of 25°C/40% RH and 25°C/60% RH. Especially, the cosolvent containing formulations resulted in capsule damages and hence incompatibility. Besides increasing the drug solubility in a lipid based formulation, cosolvents such as propylene glycol and PEG400 also act as plasticizers, e.g. in soft gelatin capsules (30). In addition, both PEG400 and propylene glycol are well known hygroscopic excipients. Thus, the formulation vehicles containing these cosolvents may inherently possess a higher affinity for water adsorption leading to capsule shell defects due to an increased capsule shell brittleness (8). In addition, the migration of cosolvents into the capsule shell may lead to a capsule softening and hence the observed integrity issues, also leading to capsule shell incompatibility. These factors appear to be more pronounced in HPMC based capsule shells compared to gelatin capsules, which in part may be due to the lower water content (18). In addition, this study showed that oils and surfactants alone were compatible with the capsule shells in most of the cases, which is in agreement with other studies in the field of capsule shell compatibility (7).

From the weight change assessment, it appeared that incompatibility did not originate from the investigated oils, but rather from the surfactants and cosolvents. However, formulations containing Labrafil 2125 or a combination of Labrafil 2125 and Transcutol HP resulted in the most capsule shell compatible formulations in both HPMC and gelatin capsules. In fact, among the evaluated surfactants in this study, Labrafil 2125 was the only surfactant that did not show an increase in mass upon storage for 4 weeks at 25°C/40% RH and 25°C/60% RH. All evaluated surfactants in the present study with a HLB value >10 resulted in capsule incompatibility for both gelatin and HPMC based capsules upon storage due to an increase in mass > 2% (*w*/w). Labrafil 2125 has a HLB value of 9 and contains a relatively high fraction of mono-, di and triglycerides of linoleic acid (C18:2), thus the lipophilic characteristics of Labrafil 2125 may in part have improved the capsule compatibility of the formulation vehicles containing the excipient. In addition, in this and in previous studies it has been shown that lipophilic lipid excipients such as oils and

Labrafil 2125 did not show any incompatibilities with gelatin capsules (7). The excipients resulting in the lowest compatibility were Labrasol ALF and propylene glycol. Both resulted in a significant amount of incompatibilities with especially HPMC capsules already at 25°C/40% RH. This may be linked to the hygroscopicity of the excipients and the hydrophilicity of the excipients. Hence, the interaction between the excipients and the capsule shell or other mechanisms of actions, though the mechanism was not explored in the present work. In addition, a simple prediction model to evaluate the mass increase of the capsules based upon the mass increase from the individual excipient was applicable reflecting that the compatibility was driven by the balanced hygroscopicity of the formulation components. While the model was not 100% accurate, it should be seen as a quick and simple prediction that may guide during the initial concept screening, allowing to move faster forward with the most promising formulation vehicles, but not replace experimental conformation of the compatibility.

In the present study the compatibility between the vehicle and the capsules was investigated by physical changes to the capsule shell combined with weight changes at two different relative humidities. Work by Kuentz and Röthlisberger (27) on PEG filled capsules used a texture analyzer to detect capsule compatibility sooner. While the visual observation and weighing is a fast analysis, obtaining data earlier during formulation development could be of high value and hence could be considered in such situations.

Besides the capsule content, also the storage conditions impact the capsule integrity and stability. Since the acceptable moisture content of gelatin and HPMC capsules range from approximately 10% – 18% (*w*/w) (7) and 4% - 6% (w/w) (18), respectively, a too low relative humidity may result in brittle capsule shells, while a too high relative humidity may soften the capsule shell and make them sticky. In the case of gelatin capsules, the acceptable atmospheric relative humidity to obtain satisfactory capsule shell characteristics is between approximately 35% and 65% (31). In the present study, a clear effect of the relative humidity upon storage was observed. The amount of incompatible formulation vehicles increased significantly with increased relative humidity from 40% to 60% at constant temperature for both gelatin and HPMC capsules. Both mass as well as the amount of physical damaged capsules increased. Depending on the excipients in the liquid capsule fill, the formulation vehicle absorbs water from the capsule shell which in turn absorbs water from the atmosphere, resulting in a mass increase and a potentially capsule shell softening. This equilibrium may be shifted to either side by the atmospheric relative humidity and the hygroscopicity as well as moisture content of the lipid formulation vehicles. Kuentz and Röthlisberger (27) suggested to consider a balanced amount of water to the formulation to compensate for these equilibriums and thereby ensure a formulation, which was compatible with the encapsulation material. This approach was investigated for the incompatible formulations in the present study. The mass gain was in general lowered after addition of water to the formulation, in a way so most of the vehicle was compatible at 25°C/40%RH, to a lower extend at 25°C/60%RH, but still sufficient to suggest that the addition of water to the formulation may be considered as an option in case of a capsule incompatible formulation.

Hard gelatin or HPMC capsules can withstand a higher temperature during manufacturing than soft gelatin capsules, which enables the use of semi solid excipients as vitamine E-TPGS, Gelucire and higher molecular weight PEGs. In addition, the manufacturing process of soft gelatin capsules results initially in water diffusion in the formulation until dried, which may be a challenge for low water soluble compounds incorporated into the lipid based formulations. Besides, these pro/con considerations, feasibility with a formulation approach is often conducted internally in pharmaceutical companies as a part of the formulation strategy definition. It may be percieved faster to start with hard gelatine capsules before engaging with one of the specialised companies in the field of soft gelatin capsule development and manufacturing. The present study supports some of these internal formulation work and provides some guidance to how to consider the compatibility aspect, though a number of limitations are also present in this work, which need to be considered by the formulation scientist in a concrete situation. For instance, only placebo formulations were evaluated, however, an active compound solubilized in the lipid vehicle may change both the miscibility as well as the compatibility. Both these elements may be affected by the drug loading as well as the compound characteristics. In the present study, liquid formulations were filled into hard gelatin capsules, which were positioned up-right to avoid leakage of the vehicle. No influence of sealing, either by banding or use of the LIMS technology (7), on the capsule compatibility is expected, though not demonstrated in the present study. Lastly, vehicle fill volume was in this study 60%, however, this should be considered as an important parameter – the higher the vehicle to capsule ratio, the more sensitive the system would be with respect to compatibility as there would be relative more mass to absorb the water and hence lead to a potential capsule incompatibility.

CONCLUSION

The encapsulation of lipid based formulation appears to be well recognised in soft gelatin capsules, but less for hard gelatin and HPMC based capsules. Therefore, the current study

evaluated capsule shell compatibility with lipid based formulation vehicles to guide the formulation of such liquid and semisolid formulation towards the capsule shell selection. In the current study the miscibility of lipid based vehicles was especially promoted by monoglycerides and surfactants with a HLB value <12, i.e. Labrafil 2125. Overall, hard gelatin capsules resulted in a better compatibility for the evaluated formulation vehicles when compared to HPMC capsule shells. While capsule shell incompatibility originated in this study from both hydrophilic surfactants and cosolvents, a superior capsule compatibility was achieved with formulations containing the water insoluble surfactant Labrafil 2125 and/or the cosolvent Transcutol HP. In case of a suboptimal compatibility the addition of water to the formulation was able to improve capsule shell compatibility for both gelatine and HPMC capsules. This study also provided evidence that the expected capsule mass change can be predicted in binary systems using the provided data of the single excipients weighted for its proportion in the formulation. However, further studies with an increase amount of excipients are required to fully conclude whether such predictions hold true for a large variety and types of lipid formulations.

DECLARATIONS

Disclosures of Financial Interest The authors declare no financial interest

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