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In vitro drug release mechanism from lipid nanocapsules (LNC)

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ABSTRACT

Lipid nanocapsules are recently developed lipid nanocarriers for delivery of lipophilic drugs. Due to their small size and biocompatible nature, lipid nanocapsules (LNC) may be promising carriers for drug delivery with different routes of administration. The aim of this work was to study the effect of formulation variables on the in vitro drug release from LNC. Ibuprofen as a model drug was entrapped in the oily core while Cremophor A25 and Cremophor A6 were used as hydrophilic surfactants in different ratios ranging from 1:1 to 1:0. All the prepared LNC were of comparable particle sizes around 50 nm. Varying Cremophor compositions as well as the presence of lecithin, cetyl or stearyl alcohol had no significant effect on the in vitro drug release profiles. However, drug release rates increased significantly with increasing the temperature from 4 to 50 °C, i.e. the flux increased from 1.5 to 7 μg/(cm^2 min). This was explained by the increased ibuprofen–lipid interactions at reduced temperature where the increased viscosity of the lipid significantly slows down the drug diffusion to the external aqueous phase. In summary, the physicochemical properties of the drug as well as the oil phase have a high impact on the drug release rate while the surfactant type, composition or density exerted only a minor effect.

1. Introduction

Nanoparticles and nanoemulsions are attracting attention as they can provide improved therapeutic regimes for existing drug molecules. They have been investigated for diverse applications, among these mainly the improvement of the bioavailability of drugs (Zara et al., 1999; Chen et al., 2001; Peltier et al., 2006) and drug targeting (Lamprecht et al., 2002; Lu et al., 2008).

For lipophilic drugs, different lipid nanocarriers are known, which entrap the drug molecules in their lipid cores. Examples for such lipid nanocarriers are solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and lipid nanocapsules (LNC). SLN consist of a solid lipid core which is often stabilized by an external monolayer of steric or charged surfactant (Husseini and Pitt, 2008). SLN, however, suffer from several drawbacks such as limited drug loading, risk of gelation and leakage of the drug during storage caused by lipid polymorphism (Joshi and Patravale, 2008). NLC represent a new generation of lipid nanoparticles that were developed to overcome the limitations of the SLN. NLC are composed of a mixture of solid lipids with liquid lipids (oils) leading to an overall melting point depression but with keeping the solid state at body temperature (Müller et al., 2002). LNC, finally, are drug carriers in the nanometer range and are prepared by phase inversion of an emulsion (Heurtault et al., 2002). These nanocapsules are composed of a medium chain triglyceride core surrounded by a capsule shell made from hydrophilic and lipophilic surfactants. Due to their very small size in the range of 25–100 nm and their capacity to encapsulate lipophilic and hydrophilic drugs, LNC can be an excellent alternative to liposomes, emulsions, or microemulsions for pharmaceutical applications (Lamprecht et al., 2004; Anton et al., 2009).

Although several studies were conducted to optimize the formulation of LNC by investigating the effect of nature and ratio of the various components on the formulation results, the exact knowledge especially on the in vitro drug release is still lacking; only a very few incomplete studies on the in vitro drug release from LNC can be found. Lipid nanoparticles are mostly used for drug targeting purposes which makes some processes such as premature drug release or extremely retarded release lead to system failure. Since previous studies suggest LNC to exhibit a capsule structure, the drug release profile might be highly sensitive to changes in the physicochemical properties of the capsule and its shell, which is presumably a "molecular monolayer". Thus, a proper understanding of the release mechanism and of the influence of the surfactant monolayer barrier composition as well as the core material and drug properties in the drug release pattern is essential.

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The aim of this work was to elucidate the roles of the different formulation components in the mechanism of drug release. Different experiments were carried out for that purpose such as testing in vitro drug release kinetics, differential scanning calorimetry, measuring core oil viscosity as well as drug solubility and partitioning properties. Ibuprofen was taken as a model drug due to its physicochemical properties.

2. Materials and methods

2.1. Materials

Ibuprofen, Cremophor A25 and Cremophor A6 were kind samples from BASF (Ludwigshafen, Germany). Miglyol® 812 (medium chain triglyceride; MCT) was from Fagron GmbH (Barsbüttel, Germany). Soybean lecithin was purchased from Caelo, Germany. Lipoid® S75-3 (soybean lecithin) was a kind gift from Lipoid GmbH (Ludwigshafen, Germany). Cetyl and stearyl alcohols were from Sigma (Steinheim, Germany). Spectra/Por® dialysis membrane, molecular weight cut-off 12,000–14,000 Da was purchased from Spectrum Laboratories Inc., Rancho Dominguez, Canada. All other chemicals were of analytical grade or equivalent purity.

2.2. Preparation of lipid nanocapsules

The preparation of lipid nanocapsules was based on solvent free phase inversion method that allows the preparation of very small nanocapsules by thermal manipulation of oil/water system (Heurtault et al., 2003; Lamprecht et al., 2004). Briefly, an ibuprofen amount equivalent to 2% (w/w) was dissolved in the internal oily triglyceride phase MCT (18%, w/w) prior to all preparation steps by magnetic stirring for 5 min. The oil phase was then mixed with Cremophor A25 either alone or with Cremophor A6 (the concentration of the total Cremophor mixture was always kept at 20%). Distilled water (final concentration w/w: 60%), sodium chloride (100 mg), and soybean lecithin (100 mg) were also added to give a total weight of 5 gm. The mixture was heated under magnetic stirring up to 85 °C (until a distinct drop of conductivity occurs) to ensure that the phase inversion temperature was passed and a w/o emulsion was formed. Then the emulsion was cooled to 55 °C. During the cooling, another complete phase inversion to an o/w emulsion occurs. This cycle was repeated twice before adding 5 ml of distilled water at 4 °C. The LNC suspension was then stirred for 10 min before further analysis.

To study the effect of the lipophilic co-surfactant on the capsule membrane properties and on the in vitro drug release, soybean lecithin was omitted or replaced by cetyl alcohol, stearyl alcohol, and Lipoid®, respectively.

2.3. Measurement of particle size of lipid nanocapsules

The LNC were analysed for their particle size and size distribution in terms of the average volume diameters and polydispersity index by photon correlation spectroscopy using a particle size analyser (Brookhoven Instruments Corporation, New York, USA) at a fixed angle of 90° at 25 °C. The nanocapsules suspension was diluted with distilled water before analysis and samples were analysed in triplicate.

2.4. Determination of in vitro drug release kinetics

The study was carried out using a modified USP dissolution apparatus II as described elsewhere (Abdel-Mottaleb et al., 2009). After fixation to the apparatus, the tubes were immersed in the dissolution vessel which contained100 ml of the release medium (Sorenson phosphate buffer pH 7.4). The glass baskets were rotated at 25 rpm and aliquots each of 3 ml were withdrawn from the release medium at predetermined time points. The samples were assayed spectrophotometrically for ibuprofen content at λ_{max} = 264 nm using online UV spectrophotometer and the concentration of the drug was determined from a previously constructed calibration curve.

The effect of temperature on the in vitro drug release was analysed by performing the dissolution tests at 4, 25, 37, and 50 °C. To detect potential differences in release rates, the data for the different formulations at different temperatures were analysed using f2 test (FDA, 1995; Moore and Flanner, 1996).

2.5. Differential scanning calorimetry (DSC)

DSC was studied using PerkinElmer Pyris 1 differential scanning calorimeter. Each sample of 5 mg was hermetically sealed into aluminium pans and heated at a rate of 10 °C/min from 0 to 150 °C and cooled again to 0 °C at the same rate. A second heating cycle was run from 0 to 150 °C to simulate the preparation procedure of the LNC. All measurements were scanned against an empty aluminium pan.

2.6. Measurement of MCT viscosity at different temperatures

The rheological properties of MCT samples were determined using rotational rheometer of concentric cylinder structure, Haake RheoStress1. Measurements were made at 4, 25, 37 and 50 °C to investigate the effect of temperature on the oil viscosity and at shear rates ranging from 0.1 to 300 s^{-1} with 10 s between each two successive speeds and then in a descending order. The type of flow was determined from the dynamic viscosity (η).

2.7. Determination of ibuprofen solubility and partition coefficient

To find out the effect of temperature on the solubility of ibuprofen in MCT and phosphate buffer pH 7.4 and 4.5 which may help to understand the different release rates at different temperatures, the solubility of ibuprofen was measured at 50, 37, 25 and 4 °C. An excess amount of ibuprofen was added to the oil or the buffer and mixed by magnetic stirring for 72 h at the four different previously mentioned temperatures. The concentration of ibuprofen was determined directly or after dilution in ethanol by UV spectrophotometry at λ_{max} = 264 nm. All experiments were carried out in triplicates.

To determine the ibuprofen MCT/buffer partition coefficients at pH 7.4 and 4.5 at different temperatures, 20 mg of ibuprofen were dissolved in 5 ml oil and mixed with 5 ml phosphate buffer in a thermostatically controlled shaking water bath at 4, 25, 37, and 50 °C for 24 h. The aqueous phase was then separated and analyzed for ibuprofen content by UV spectrophotometry at λ_{max} = 264 nm and partition coefficient was then calculated.

2.8. Interfacial tension measurement

Interfacial tension measurements were carried out using a drop tensiometer (EasyDrop Standard, KRÜSS GmbH, Hamburg, Germany). To investigate the changes occurring on LNC surfaces during drug release, ibuprofen was dissolved in MCT to give the same concentration used in the LNC formulations. A drop of drug oily solution was formed in phosphate buffer pH 7.4 representing the aqueous release medium. The surfactants Cremophor A25 and Cremophor A6 were dissolved in the buffer and the oil, respectively, employing the same ratios used previously in preparing the different ibuprofen loaded LNC. The changes in the interfacial tension occurring due to

the adsorption of surfactant molecules on drop surface during drug release were monitored until a constant value was obtained.

3. Results

During the preparation of LNC, the proportions of both surfactants used were determined according to preliminary trials which showed that Cremophor A6 alone, unlike Cremophor A25, could never be used for LNC preparation. Still large particles were obtained when only small amounts of Cremophor A25 were incorporated in the capsule shell (data not shown). LNC could be prepared successfully starting from a 1:1 mixture of both the surfactants and preparation remained convenient by increasing the Cremophor A25 percentage gradually up to 100%.

Data on particle size and size distribution of LNC containing ibuprofen are shown in Table 1. All LNC prepared with the different Cremophor A25/A6 ratios had a mean particle size in the range from 44 to 47.5 nm with the only exception being the LNC prepared with Cremophor A25 alone. These LNC had a mean diameter of 54 nm, which was slightly larger than that of the other formulations. All batches of LNC had a polydispersity index ranging from 0.151 to 0.265. Also when changing the lipophilic co-surfactant in the formulation of the LNC replacing lecithin with cetyl and stearyl alcohols, a mean size remained in the range of 40–50 nm (Table 2).

Results of the interfacial tension measurements showed a very high value of 64 mN/m in case of MCT-buffer interface without adding surfactants. For the measurements made using Cremophor A25 only, the initial value of 11.3 mN/m decreased gradually, until reaching a stable value of 7.58 mN/m after 20 min (Table 1). For the other A25:A6 mixtures, lower initial values were obtained and the final stable values were reached faster.

In the drug release experiments, all formulations exhibited zero order like release kinetics at all temperatures. The temperature was found to be a dominating parameter while surprisingly varying the formulations had little effect: Neither using different Cremophor compositions (Fig. 1) nor exchanging the lipophilic co-surfactants (Fig. 2) had a high influence of the release profile or release rate. To compare the formulations, the fluxes were calculated and were found to increase from 1.5 to 7.0 μg/(cm^2 min) with increasing the temperature from 4 to 50 °C.

The differential scanning calorimetry of the three individual surfactants Cremophor A25, Cremophor A6, and lecithin revealed that the melting points of them (49, 36 and 44, and 46 °C for Cremophor A25, Cremophor A6, and lecithin, respectively) did not change with temperature cycling (Fig. 3). Similarly, DSC of ternary mixture of surfactants showed the same melting points in the first heating cycle. After the second heating cycle, however, the different peaks of the three surfactants disappeared and were replaced by a single peak at 37 °C. This indicates that the three components interacted after their heating and yielded one homogenous mixture that forms the capsule shell.

The viscosity measurements performed at different shear rates showed that MCT has an ideal Newtonian flow behaviour. As

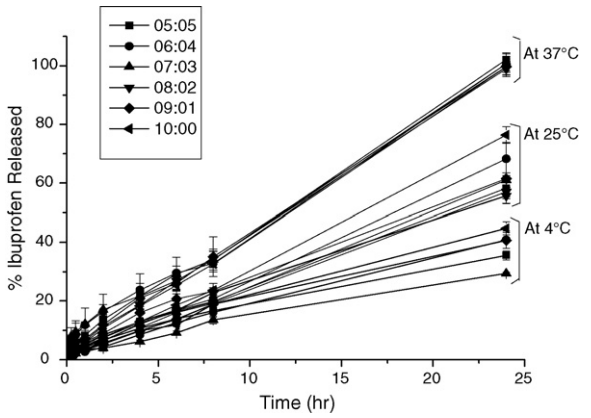

Fig. 1. In vitro release of Ibuprofen from different LNC at 37 °C, 25 °C and 4 °C.

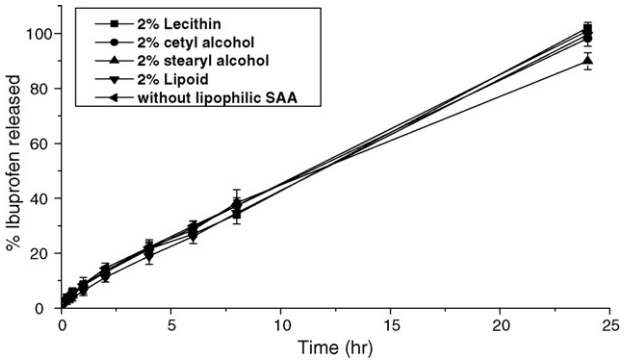

Fig. 2. Effect of lipophilic surfactant type on the in vitro release of ibuprofen from different LNC at 37 °C.

Table 1
Particle size and the interfacial tension analysis for different ibuprofen LNC.

Ratio of Cremophor A25:A6	PD (nm)	PI	Initial IFT (mN/m)	Stabilized IFT (mN/m)
0.5:0.5	47.5 ± 1.2	0.247 ± 0.008	7.82 ± 2.34	4.11 ± 1.22
0.6:0.4	46.2 ± 0.6	0.242 ± 0.004	6.06 ± 0.48	3.13 ± 1.01
0.7:0.3	44.0 ± 0.5	0.265 ± 0.006	8.48 ± 2.51	4.65 ± 2.45
0.8:0.2	46.7 ± 0.5	0.253 ± 0.006	9.69 ± 3.04	3.82 ± 0.62
0.9:0.1	45.4 ± 0.3	0.201 ± 0.005	10.11 ± 2.62	4.19 ± 2.37
1.0:0.0	54.0 ± 0.8	0.151 ± 0.012	11.3 ± 1.38	7.58 ± 1.85

Interfacial tension between Miglyol and buffer without adding any surfactants was 64 mN/m. PD: average particle diameter in nm. PI: polydispersity index.

Table 2
Effect of lipophilic surfactant type on the particle size of different LNC.

Type of the lipophilic surfactant	PD (nm)	PI	Initial IFT (mN/m)	Stabilized IFT (mN/m)
Lecithin	47.5 ± 1.2	0.247 ± 0.008	7.82 ± 2.34	4.11 ± 1.22
Cetyl alcohol	45.0 ± 0.4	0.087 ± 0.005	5.82 ± 0.18	4.91 ± 0.35
Stearyl alcohol	50.3 ± 0.6	0.153 ± 0.004	8.36 ± 1.26	6.01 ± 0.95
Lipoid	46.8 ± 0.6	0.207 ± 0.013	9.36 ± 2.18	6.06 ± 0.53
No surfactant	40.9 ± 0.4	0.070 ± 0.010	5.87 ± 1.85	5.42 ± 1.91

PD: average particle diameter in nm. PI: polydispersity index.

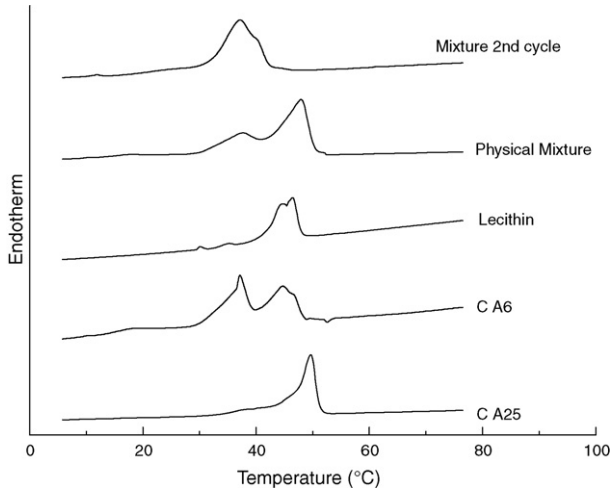

Fig. 3. DSC of Cremophor A25, Cremophor A6, soybean Lecithin and a ternary mixture of them.

expected, increasing the temperature from 4 to 25 to 37 to 50 °C led to a decrease in the viscosity (Fig. 4).

MCT/buffer partition coefficient for ibuprofen decreased slightly when increasing the temperature from 4 to 50 °C at pH 7.4 (Fig. 5a) while a more significant decrease was observed at pH 4.5 (Fig. 5b). On the other hand, the solubility in both MCT and aqueous buffers increased with increasing the temperature by exhibiting a comparable slope.

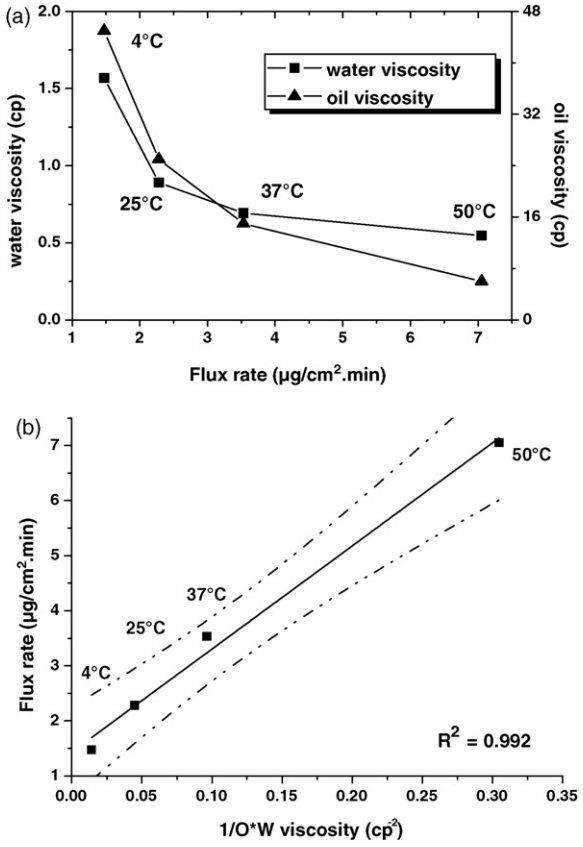

Fig. 4. (a) Relationship of viscosity of MCT and water with ibuprofen flux rates at different temperatures, (b) Inverse correlation of ibuprofen flux rates and the product of MCT and water viscosity.

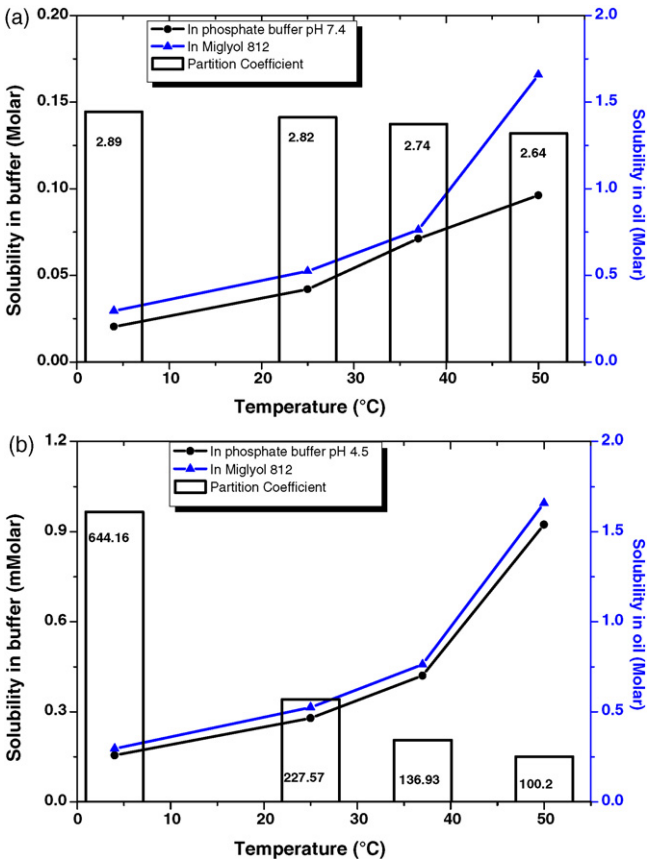

Fig. 5. Effect of temperature on the solubility of Ibuprofen in MCT and phosphate buffer and partitioning between them at (a) pH 7.4 and (b) pH 4.5.

4. Discussion

The preparation of LNC was not possible using Cremophor A6 as the sole surfactant. This may be explained by the higher hydrophobicity of the Cremophor A6 for which a HLB around 10 was reported whereas the HLB of Cremophor A25 is in the range of 15–17 according to the product sheet. This means that the polyoxyethylene head group was too short to undergo a successful phase inversion as it is not sensitive enough to the temperature. This confirms that although nonionic polyethoxylated surfactants can perform the emulsion inversion, the affinities of the surfactant for the aqueous and oily bulk phases have to be relatively balanced (Anton et al., 2007).

Results obtained from particle size measurements indicated that the variation of the Cremophor A25 fraction from 50 to 100% had a minor effect on the particle size. This finding was interesting for the aim of our study, since the barrier properties of the capsule shell could be varied by changing the surfactants proportions without affecting the oil/water interface areas. Thus, the effect of particle size on the in vitro drug release rates could be neglected. The results also indicate that the type of lipophilic co-surfactant or even its complete absence from the formulation has a minor effect on the LNC size and the size distribution. This is well in agreement with a previous study, where it was shown that increasing the concentration of Lipoid from 1 to 5% had no effect on the mean particle size of LNC (Heurtault et al., 2003).

At 37 °C, the different formulations showed similar in vitro release profiles for 24 h. To clarify the true reason for the non-significant difference between the different formulations, in vitro drug release studies were also carried out at room temperature (25 °C), which is supposed to be below the melting point of the shell components. The release profiles of the different formulations

were still following zero order kinetics, but the total amount of ibuprofen released after 24 h decreased significantly and was well below the 100% obtained at 37 °C. This observation could indicate that rigidity of LNC shell had increased upon decreasing the temperature to 25 °C. This interpretation is underpinned by the fact that the A25:A6 ratio had no effect on the in vitro drug release mechanism or on the release rate. Therefore, it could be concluded that the ratio of surfactants is not an important factor as long as the total emulsifier concentration is constant. This total emulsifier concentration determines the surfactant packing density at the oil–water interface leading to different barrier properties of the interface (Lamprecht et al., 2002).

Another in vitro release experiment was carried out at 4 °C to further investigate the effect of changing the temperature below 37 °C on drug release profiles. Again, no differences were detected between the different formulations at this temperature. The drug release rate was significantly lower than in the above two experiments at 25 and 37 °C. This finding indicated that – at least at such low temperatures – the temperature affects not only the rigidity of the capsule shell but exerts another influence on the drug release mechanism, too.

Regarding the effect of lipophilic surfactant on the in vitro drug release behaviour, the four different lipophilic surfactants used were reported in literature to have different melting points 45, 50, 58 and 81 °C for the lecithin, cetyl alcohol, stearyl alcohol and Lipoid, respectively (Smolkova et al., 1979; Kester and Fennema, 1989). These different melting points were expected to have an impact on the solid state properties of the LNC shell, which should be reflected by the in vitro ibuprofen release from the nanoparticles. Surprisingly, we did not observe any significant difference between the in vitro release profiles of the different LNC at 37 °C and were even similar to the release profile of the formulation without any lipophilic surfactant. This confirmed that the structure of the capsule shell is not the most decisive parameter in the in vitro drug release process.

Our observations led us to further investigate the viscosity of the lipophilic triglyceride core material (MCT) at different temperatures and also the solubility of ibuprofen in and its partitioning between the core material and external aqueous phase, the release medium.

The viscosity of oil is extremely sensitive to the operating temperature and falls rapidly with increasing temperature (Knezevic and Savic, 2006). It is negatively related to the release of active substances from formulations and their penetration of the diffusion barriers (Tsai et al., 1999; Welin-Berger et al., 2001). This decrease in drug release with decreasing temperature could be attributed to an increased microviscosity of the oil delaying the drug diffusion out of LNC core into the aqueous release medium. This effect of ambient temperature on viscosity, however, is not limited to the internal oily core material but applies also to the external aqueous phase. The inverse proportionality of drug flux rate and viscosity of oil and that of water at different temperatures is shown in Fig. 4. The product of both was calculated and its reciprocal was plotted against ibuprofen flux rate where a linear correlation with correlation coefficient R^2 value of 0.992 was obtained. This indicates that the drug release rate is highly dependent on the viscosities of both the donor and acceptor phases, which were changing significantly with temperature.

Drug solubility in the aqueous release medium and the core oil as well as the partitioning between them are considered key factors in predicting the in vitro drug release behaviour. Inspection of the literature suggests that little attention has been given to defining or controlling temperature accurately during partition coefficient measurements (Songster, 1989). In our experiment, it was of interest to study the effect of temperature on the MCT/buffer 7.4 partitioning to further analyze the previous results from drug release experiments. MCT/buffer partition coefficient for ibuprofen decreased slightly from 2.89 to 2.64 upon heating from 4 to 50 °C (Fig. 5). Decreasing the buffer pH to 4.5 gave a more significant depression of the partition coefficient from 644.16 to 100.2 at 4 and 50 °C, respectively. This indicated that the partitioning of the drug from the oil core of LNC to the external release medium will increase upon increasing the temperature. This finding was previously reported by Bahadur et al. (1997) for some chlorobenzenes where enhanced partitioning to lipid phases was observed by lowering temperature. In our study, there was an enhanced interaction between ibuprofen and MCT with decreasing temperatures which delayed the drug release rate. It can be seen from the solubility studies that the ratio between ibuprofen solubility in the oil and buffer was nearly constant which means that the solubility increased with increasing temperatures in both oil and buffer with the same pattern. Increased lipid partitioning with lowering temperature can be explained by the increased drug lipid interaction upon cooling which enhance the drug entrapment into the oil droplets.

Zur Mühlen et al. (1998) had also shown that the interactions between drug and lipid molecules plays important role in controlling the drug release. These interactions could affect the viscosity of the solid lipid matrix leading to different release rates for different drugs although having similar lipophilic properties. They demonstrated that the development of sustained release SLN is possible by the proper choice of the drug and the lipid and their degree of interaction.

Investigation of the drug release from SLN also showed that burst release of drugs could be controlled via the solubility of the drug in the water phase during the production process. Increasing the production temperature and surfactant concentration leads to increased drug solubility in the water phase. Cooling the SLN suspension again will decrease the water solubility and the drug repartition to the lipid forming shell-enriched or core-enriched with the drug depending on the lipid recrystallization temperature (Müller et al., 2000). These two models lead to too fast and too slow drug release rate, respectively. Decreasing the water solubility of drugs by lowering production temperature and surfactant concentration used will avoid this repartitioning and forms homogenous solid solution of the drug (the drug is molecularly dispersed in the lipid matrix). In that last case, the drug release rate will be solely dependent on the extent of drug lipid interaction and the rate of drug partitioning to the aqueous release medium. For the LNC, the oily core is liquid and thus ensures a homogenous dispersion of the drug throughout the whole particle. Therefore, the rate of drug release will only be affected by the extent of drug oil interaction and sustained or fast drug release rates could be achieved by changing the oil used as a core material.

Investigation of drug release from different wax matrix pellets using theophylline as a lipophilic drug showed that as the hydrophobicity of the wax increases, the drug release rate decreases. The more hydrophilic is the wax, the more it is susceptible for hydration by the release medium and therefore the faster the drug release. The drug release pattern was also highly dependant on the drug aqueous solubility. The release process was mainly affected by the relative affinity of the drug to the wax and the aqueous release medium (Cheboyina and Wyandt, 2008).

It can be stated that however, minor temperature changes around 37 °C will not significantly influence the drug release from these LNC which excludes the option of a temperature-dependent release under in vivo conditions.

5. Conclusion

Ibuprofen loaded lipid nanocapsules were prepared successfully using mixtures of Cremophor A25 and Cremophor A6 as hydrophilic

surfactants with a small particle size ranging from 40 to 50 nm. The in vitro drug release from LNC followed the zero order kinetics. The release rate seemed to be mainly dependent on the drug lipid interactions and partitioning between the liquid oily core of the capsule and the external aqueous phase. Therefore, it may be concluded that the physicochemical properties of the oil core and the drug are of primary importance, while the surfactant type and packing density are not affecting the in vitro drug release from the LNC.

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