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Do drug release studies from SEDDS make any sense?

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ABSTRACT

Self-emulsifying drug delivery systems (SEDDS) are considered as a potential platform for mucosal drug delivery. The in vitro–in vivo correlation, however, is in particular for this type of delivery systems considerably poor resulting quite often in a simple trial and error approach in order to optimize formulations. One reason for this situation is certainly the lack of appropriate methods to determine the drug release from SEDDS in vitro, as the process is particularly troublesome. For quantification of the drug in the release medium the oily droplets need to be separated. In most studies this is achieved by utilizing a separating membrane such as dialysis membranes or filters having a huge impact on the obtained release profile. Moreover, sink conditions are very often not provided. As drug release from SEDDS is based on a simple diffusion process from a lipophilic liquid phase into an aqueous liquid phase, a likely more meaningful way to characterize the release behaviour might be just the determination of the distribution coefficient (log $D_{SEDDS/RM}$) of the drug between the SEDDS pre-concentrate and the release medium (RM). As log D is simply the measure of the difference in solubility of a compound in two phases, it can be determined by measuring solubility of drug or drug complex in the SEDDS pre-concentrate and in the release medium in a separate manner. The impact of log $D_{SEDDS/RM}$ on the in vivo drug release behaviour is discussed including various case studies.

1. Introduction

Self-emulsifying drug delivery systems (SEDDS) are considered as a potential platform for mucosal drug delivery. They can be administered as a form of surfactant-oil mixture or water-in-oil (w/o) microemulsion and are expected to convert to oil-in-water (o/w) microemulsions on the target mucosa such as the intestinal, intraoral or ocular mucosa. Apart from the delivery of poorly water-soluble drugs, SEDDS have shown great potential for the delivery of therapeutic peptides [1]. Moreover, SEDDS are promising vehicles for the delivery of DNA- and RNA-based drugs [2]. Although SEDDS experience a renaissance likely because of these newer developments, the in vitro-in vivo correlation is in particular for this type of delivery systems considerably poor [3,4,5]. One reason for this situation is certainly the lack of appropriate methods to determine the drug release from SEDDS in vitro, as the process is particularly troublesome. In case of membrane diffusion methods sink conditions are mostly violated and drug release profiles determined via sample-and-separate methods are also not ideal, since it is difficult to preserve the physical integrity of oily droplets during the separation process. Release profiles obtained by these methods and shown in most publications on SEDDS look the same as release profiles known from well-established and valid methods used for instance for tablets described in the pharmacopoeia. These profiles, however, are often misdirecting. As the whole scientific community working in this field is obviously aware of these shortcomings and more appropriate alternatives – apart from a few exceptions for certain compounds [6] – are not available, drug release studies from SEDDS are a kind of taboo in the peer-review process. Although our own research group has published numerous articles showing drug release profiles from SEDDS by techniques described above, we were so far never criticised on that. Being aware of on the one hand the key role of drug release from SEDDS for their in vivo performance and on the other hand the lack of appropriate in vitro methods, the whole scientific community is flying blind optimizing formulations on a simple trial and error approach. On closer analysis, however, it seems questionable whether these uncertain and misdirecting in vitro drug release studies from SEDDS do make any sense at all. It is therefore the aim of this article to critically review available data on this topic in order to draw a sound conclusion out of it and to propose a likely more suitable alternative method.

2. State-of-the-art techniques to determine drug release

Various techniques such as membrane diffusion methods, sample-and-separate methods and a very few in situ methods are used to characterize release kinetics from SEDDS. Most of these methods, however, can lead to erroneous results as comprehensively reviewed by

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Shen and Burgess [7].

2.1. Membrane diffusion methods

Membrane diffusion methods are most widely applied for release studies from SEDDS. The oily droplets are thereby separated from the release medium through filters [8,9] or dialysis membranes [10,11] that are permeable to the free drug but impermeable to the oily droplets. Using these methods, however, it is almost impossible to discriminate between the release controlling effect of SEDDS and of the separating membrane. Due to the limited diffusion membrane surface area available for transport from the donor to the acceptor compartment compared with the surface area available for transport from the oily droplets to the release medium, sink conditions are violated in most cases. Control experiments quantifying the increase in drug concentration in the acceptor compartment with just the drug without a formulation in the donor compartment over time are of course contributing to a more meaningful data interpretation (e.g. [12]) but do not satisfyingly improve the validity of results. It is simply impossible to determine the real release profile just based on the difference between the release profiles obtained with and without the SEDDS formulation. Attempts to account for this and other constrains of diffusion membrane methods mathematically [13,14] were of minor success and none of these algorithms could so far be well-established. Sink conditions are additionally violated by an insufficient drug solubility in the release medium. As SEDDS are primarily used for poorly-water soluble drugs such as class II and IV drugs according to the biopharmaceutical classification system, comparatively huge volumes of release medium are needed unless organic solvents and/or surfactants are added. The addition of such auxiliary agents, however, has a great impact on the observed release behaviour. Due to their lipophilic substructure being essential to improve drug solubility both organic solvents and surfactants can penetrate into the oily droplets altering their composition (e.g. [15,16]) and consequently release properties. Furthermore, improving drug solubility in the release medium to a higher extent as it is in vivo the case results in a tremendous shift in the partition coefficient of the drug between the oily phase of SEDDS and the aqueous phase of the release medium representing the intrinsic key parameter for drug release as described in detail herein.

2.2. Sample-and-separate methods

In case of sample-and-separate methods, SEDDS are directly added into the release medium and ultracentrifugation or centrifugal ultrafiltration are used to separate the oily droplets from the release medium in samples having been withdrawn at predetermined time points. In the following, drug content in the supernatant or filtrate is quantified. In most cases, however, it is difficult to separate the oily droplets from the release medium in a rapid and quantitative manner without influencing the release profile. Due to the application of high external energy SEDDS are destabilized and their drug release behavior is altered. Furthermore, sink conditions are often violated.

2.3. In situ methods

In contrast to membrane diffusion methods and sample-and-separate methods, in situ methods can provide fast, direct and reliable drug release profiles from SEDDS. As there is no need for sample separation drug release can be assessed on a real-time basis. Trotta, for instance, determined the release rates of indomethacin from microemulsions by monitoring the change in pH of the release medium caused by this acidic drug [6]. In this way, he could monitor in real time the drug release from microemulsions. Such direct and continuous monitoring of the drug release kinetics from SEDDS holds great promise for in vitro release studies as drawbacks of methods described above can be excluded. In another study, drug-selective electrodes were utilized to monitor the release profiles of electroactive drugs from nanocarriers [17]. In a similar way, release of chemotherapeutics from liposomes was determined by Mora et al. [18]. These in situ methods, however, are no general solution, as they are strongly depending on certain properties of drugs such as acidity or electroactivity. In contrast, spectroscopic techniques might offer a broader applicability. First attempts to utilize spectroscopic techniques, however, were rather disappointing as the scattering from the dispersed droplets causes major background problems. At least for fundamental studies the use of solvatochromic dyes might be helpful [19].

3. The postulates

3.1. Drug release from SEDDS is just a simple diffusion process

The drug release from SEDDS is based on a simple diffusion process from a lipophilic liquid phase into an aqueous liquid phase. Generally, there are no other release controlling mechanisms such as a dissolution process of the drug, a hydration process of a carrier matrix or ionic interactions between the drug and a polymeric network involved. Drug molecules have to diffuse just to the surface of the oily droplets. Once having reached the surface of droplets, drug molecules have to overcome the so-called interfacial barrier to reach the aqueous medium [20,21]. Various studies focusing on this interfacial barrier, however, revealed a very minor impact of it on drug release. Washington and Evans, for instance, determined the release of various fatty acids from submicron emulsions without separating the droplets from the medium by monitoring the change in pH in the acceptor phase. In their study they could show that the interfacial barrier is the rate-limiting step for solute release. However, they had to admit that this effect is very minor and needs to be at least one magnitude higher in order to generate a sustained release or targeted system based on it. In fact the slowest release observed in their study took approximately 3 min to release 90% of its solute load [22]. In another study the release of indomethacin from microemulsions and the impact of the interfacial barrier on it were investigated via the same method. In accordance with Washington and Evans the author came to the conclusion that release rates being controlled just by the interfacial barrier are too rapid to allow a sustained release [6]. Furthermore, it has to be taken into account that rather polar solvents in SEDDS such as DMSO or ethanol exhibiting a higher diffusion coefficient (D_{iff}; (cm^2/s)) than most drugs listed in Table 1 might even accelerate drug diffusion and lower the interfacial barrier via a trigger effect.

According to our knowledge the only effect that has a strong impact on the drug release rate from SEDDS are liquid crystal structures. Trotta, for instance, could show a pronounced sustained release effect

Table 1
Diffusion coefficient values of some selected drugs as a function of their molecular mass.

Drug	Molecular mass (g/mol)	Diffusion coefficient (cm^2/s)	Reference
Paracetamol	151.16	6.21×10^{-6}	[23]
Testosterone	288.43	7.53×10^{-6}	[24]
Prednisone	358.43	7.28×10^{-6}	
Hydrocortisone	362.47	7.05×10^{-6}	
Beclomethasone	408.90	6.70×10^{-6}	
Spironolactone	416.58	6.53×10^{-6}	
Betamethasone valerate	476.59	4.86×10^{-6}	
Piperacillin	517.55	3.60×10^{-6}	[25]
Cefsulodin	533.55	3.60×10^{-6}	
Oxytocin	1007.2	4.34×10^{-6}	[26]
Lys-vasopressin	1056.2	4.25×10^{-6}	
Calcitonin	3417.8	2.55×10^{-6}	
Insulin monomer	5807.6	2.03×10^{-6}	
Insulin hexamer	34845.6	9.33×10^{-7}	

from a microemulsion exhibiting a liquid crystal structure [6]. The appearance of liquid crystal structures in SEDDS, however, is seldom and can be easily excluded under polarized light.

3.2. Equilibrium is reached at least within a few minutes

Generally, most SEDDS are emulsified so fast that this process has a negligible impact on drug release. Because of the submicron size of droplets formed, the incorporated drug can rapidly reach the surface and subsequently the release medium. Diffusion coefficient values listed in Table 1 are based on water as solvent and not on organic solvents or organic solvent/surfactant mixtures as it is the case of SEDDS. In dependence on the association factor, molecular mass and viscosity of solvent(s) these diffusion coefficients are altered following the Wilke-Chang correlation [27]. The diffusion coefficient of spironolactone, for instance, was determined to be 6.5×10^{-6} cm^2/s in water and 1.1×10^{-6} cm^2/s in 1-octanol [24]. This solvent effect on the diffusion coefficient of drugs in SEDDS, however, is in our case too low to be addressed. For a drug moving randomly in three dimensions, the theory of Brownian motion predicts that the mean square distance travelled in time t (s) equals $6\ D_{iff}\ t$. Based on this expression, the mean time for a drug molecule within a spherical oily droplet of a certain radius r (cm) to diffuse to any part of the surface is:

$$t = 4r^2/15D_{iff} \quad (1)$$

as nicely described in more detail by Hey and Al-Sagheer [28]. Taking a simple example illustrates that diffusion out of SEDDS is a comparatively very fast process and equilibrium between SEDDS and an agitated release medium is reached within a second. Assuming a radius of SEDDS of 100 nm corresponding to a mean droplet size of 200 nm results according to Eq. (1) in a drug release depending on the indicated diffusion coefficient within a time listed in Table 2.

Equilibrium between the drug concentration in the oily droplets and the agitated release medium is even in case of comparatively very big molecules such as proteins or plasmids reached within a second by longest. Taking the impact of the interfacial barrier as described above into account, it is still reached at least within a few minutes. According to these considerations, sustained release profiles from SEDDS for > 24 h following an even zero-order release kinetic (e.g. [29]) can only be explained by the release controlling effect of the membrane separating SEDDS from the release medium and/or the release of surfactants and solvents from SEDDS improving drug solubility in the acceptor compartment over time and a violation of sink conditions as described above. Assuming that the drug is 1000-fold more soluble in SEDDS than in the release medium (log $D_{SEDDS/RM}$ = 3) and a maximum payload of 10% can be achieved, for instance, would mean that for release studies from 1 ml of SEDDS pre-concentrate 10–20 l of release medium are needed.

3.3. Drug release is just controlled by the partition coefficient log $D_{SEDDS/RM}$

The consequently only remaining parameter controlling drug release is the partition coefficient (log D) between the lipophilic phase (SEDDS) and the release medium such as the intestinal fluid or saliva

Table 2
Time needed for a drug molecule to reach the surface of SEDDS droplets with a diameter of 200 nm in dependence on the indicated diffusion coefficient.

Diffusion coefficient (cm^2/s)	Time (milliseconds)
10^{-4}	0.000267
10^{-5}	0.00267
10^{-6}	0.0267
10^{-7}	0.267
10^{-8}	2.67
10^{-9}	26.7

Table 3
Correlation between log D and percentage of drug remaining in SEDDS droplets according to the Nernstsches distribution law.

log D $_{SEDDS/RM}$	D $_{SEDDS/RM}$	Ratio SEDDS to release medium	Percentage of drug remaining in SEDDS droplets (C_{SEDDS})
1	10	1 + 5	66.7
2	100		95.2
3	1000		99.5
4	10,000		99.95
1	10	1 + 100	9.1
2	100		50
3	1000		90.9
4	10,000		99

taking pH into account. In Table 3 the correlation between log D and drug release is illustrated in more detail taking the ratio between the volume of SEDDS (V_{SEDDS}) and the volume of the release medium (V_{RM}) according to the Nernstsches distribution law via Eq. (2) into account. Based on this equation the drug concentration remaining in SEDDS (C_{SEDDS}) can be simply calculated.

$$C_{SEDDS}(\%) = \frac{100\%}{1 + \frac{V_{RM}}{V_{SEDDS} \cdot D_{SEDDS/RM}}} \quad (2)$$

When the drug is absorbed from the membrane of course further drug will move out of the oily droplets until equilibrium is reached again. According to this assumption, drug release from SEDDS is to a high extent controlled by the absorption rate from the mucosa and the absorption rate in turn correlates directly with the concentration of drug being available on the membrane [30] as well as its apparent membrane permeability coefficient (Papp). For drugs exhibiting a Papp $> 5 \times 10^{-6}$ (cm/s) being more rapidly taken up by the absorption membrane the entire release process from SEDDS will likely last no longer than a few minutes.

In contrast the release rate of poorly absorbed drugs exhibiting a Papp $< 5 \times 10^{-6}$ cm/s from SEDDS is strongly dependent on their absorption rate. As a steep concentration gradient on the absorption membrane enhances drug uptake, a low log $D_{SEDDS/RM}$ seems favourable. However, when the entire payload is rapidly released, essential properties of the delivery system such as a protective effect towards a presystemic metabolism [31], or towards thiol – disulphide exchange reactions in the intestine [31], enhanced mucus permeation [32] or a permeation enhancing effect [33] cannot become effective. Adjusting the log D $_{SEDDS/RM}$ for class III and IV drugs is consequently a very complex and tricky issue that needs the aid of PK-studies performed with SEDDS containing the drug of different log $D_{SEDDS/RM}$ values. Studies in pigs, for instance, showed that an octreotide – deoxycholate complex exhibiting a log $D_{SEDDS/RM}$ of 1.8 resulted in an oral bioavailability of 5%, whereas an octreotide – docusate complex with log $D_{SEDDS/RM}$ of 2.7 having been incorporated in the same lipase stable SEDDS formulation resulted in an oral bioavailability below 1% [9]. The study provides strong evidence for the substantial impact of log $D_{SEDDS/RM}$ on the in vivo performance of SEDDS.

Since SEDDS form spontaneously emulsions, the log D cannot be determined such as for instance in case of the partition coefficient between n-octanol and water. As log D is simply the measure of the difference in solubility of a compound in two phases, however, log $D_{SEDDS/RM}$ can be determined by measuring solubility of drug or drug complex in the SEDDS pre-concentrate and in the release medium in a separate manner. Pinsuwan et al. [34], for instance, determined the solubility of numerous compounds in octanol and water. As illustrated in Fig. 1 the resulting solubility ratio (SR) correlated to a very high extent with the partition coefficient of the corresponding compound [34].

As the drug saturation concentration in SEDDS corresponds with the maximum payload being anyway worth to be determined and drug solubility in aqueous media – at least in water – is in most cases known,

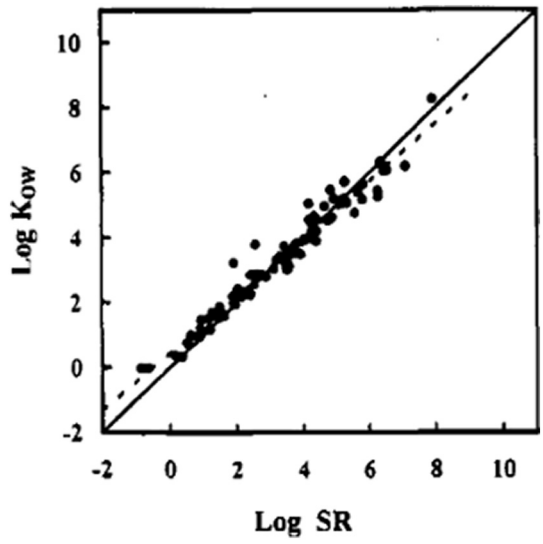

Fig. 1. Relationship between the partition coefficient (Log K_{ow}) and solubility ratio (SR) of various compounds according to Pinsuwan et al. [34].

log $D_{SEDDS/RM}$ can be determined by a minor additional workload. As SEDDS are not static but dynamic delivery systems changing in vivo their composition due to the release of surfactants and solvents as well as due to the digestion of lipids by lipases [35,36], however, the log $D_{SEDDS/RM}$ will also change over time. For more precise calculations this change in log $D_{SEDDS/RM}$ can be addressed by determining drug solubility in the SEDDS pre-concentrate without excipients being likely eliminated from the oily droplets over time. In this way gained results might even improve the design of SEDDS for poorly soluble drugs where supersaturation seems to be the key to success [37]. Furthermore, in case of hydrophobic ion pairs of the drug with oppositely charged surfactants (e.g. [38,39]) the solubility of such ion pairs in the aqueous phase is strongly dependent on their stability in the tested release medium. In case of low stability drug solubility is strongly increased having a huge impact on log $D_{SEDDS/RM}$. In order to improve the validity of log $D_{SEDDS/RM}$, the solubility of hydrophobic ion pairs needs therefore to be determined in various release media.

4. Impact of log $D_{SEDDS/RM}$ on drug release

If log $D_{SEDDS/RM}$ is below 3 a considerable high amount of drug is immediately released from the SEDDS droplets. Assuming an oral soft gelatine capsule containing 1 ml of SEDDS, for instance, and an available intestinal fluid of 50 ml equals to a ratio SEDDS to release medium of 1 + 50. Accordingly, not > 5% of the drug is immediately released when its log D is 3 (D = 1000; Eq. (2)). For the immediately released 5%, however, from a formulators' perspective beneficial properties of SEDDS such as a protective or permeation enhancing effect as discussed above can never become effective. In case of SEDDS aiming to just overcome drug solubility problems by generating a drug supersaturation for instance in the intestinal fluid, such an immediate drug release seems even favourable as long as the drug does not precipitate in the release medium [40]. By a more sustained release kinetic precipitation might be avoided. If SEDDS are supposed to contribute to an improved drug uptake via other properties, however, a log $D_{SEDDS/RM}$ above 3 seems advantageous. In theory a too low log $D_{SEDDS/RM}$ can be raised by lowering the lipophilic character of the composition of SEDDS or raising the lipophilicity of the drug. The leverage of lowering lipophilicity of the SEDDS pre-concentrate, however, is low and as the formulation has to provide also other properties, the needed flexibility is in most cases not provided. In contrast, by raising lipophilicity of the drug demanded log $D_{SEDDS/RM}$ values can be more easily obtained. Morgen et al., for instance, increased the lipophilic character of atazanavir via hydrophobic ion pairing with 2-naphthalene sulfonic acid 6-fold [41]. In another study the log P of vancomycin was increased by a value of 1.37 via hydrophobic ion pairing with linoleic acid [42]. Even the log D of peptides can be strongly raised via hydrophobic ion pairing. Griesser et al., for instance, could strongly increase the log P of the therapeutic peptides leuprorelin, insulin and desmopressin via hydrophobic ion pairing with docusate. The most prominent effect was thereby achieved for leuprorelin with a shift in log P from − 2 to + 3 [38]. In another study the log P of daptomycin was raised from − 5.0 to + 4.8 due to ion pairing with dodecylamine [39]. Apart from peptide drugs even the log P of polysaccharides can be raised sufficiently in order to incorporate them into SEDDS. Zupančič et al. formed hydrophobic ion pairs of enoxaparin with dodecylamine. SEDDS containing this hydrophobic ion pair showed an absolute oral drug bioavailability of 2% [43]. Moreover, Hauptstein et al. could form hydrophobic ion pairs between pDNA and cationic surfactants such as cetrimide or stearalkonium that were subsequently incorporated in SEDDS [2].

On the contrary, highly lipophilic drugs exhibiting a log D > 5 such as fenofibrate, cinnarizine or torcetraqib will likely remain too long in the oily droplets to be sufficiently absorbed from mucosal membranes such as the intestinal mucosa or to reach the lymphatic system [44]. According to the example of the 1 ml soft gelatine capsule given above just < 0.05% of the drug are released when equilibrium is reached (D ≥ 100,000; Eq. (2)). Although a continuous process and not a step-by-step process, in theory equilibrium with the release medium needs to be reached 2000-times in order to achieve entire drug release (0.05% × 2000 = 100%). In this case of course even minor effects such as the interfacial barrier providing a marginal sustained release for a few minutes in maximum as mentioned above have a huge impact. Sustained release over just one minute simply multiplied by 2000 results in a release for even over more than a day. In this case drug release needs to be accelerated by making use of lipases gradually degrading the oily droplets in the intestinal fluid providing in this way a more rapid release. According to these considerations, in vitro drug release studies taking the effect of lipases into account are certainly helpful in case of a log $D_{SEDDS/RM}$ > 3 strongly improving the in vitro-in vivo correlation [4].

5. Future trends

According to theoretical considerations described above, drug release from SEDDS is much more controlled by external factors such as drug solubility in the release medium or drug absorption than by the formulation per se. Drug release from SEDDS is therefore primarily controlled by the body, whereas in case of most other types of formulations it is controlled by the delivery system. The development of SEDDS being capable of providing a sustained release independently from such external factors, however, would of course be advantageous for numerous reasons. For example, PK-profiles might be shaped on demand, an intestinal drug precipitation might be avoided, or the protective effect of SEDDS towards a presystemic metabolism might be improved. Furthermore, the often high variability in the in vivo performance of SEDDS might be narrowed. For orally administered drugs exhibiting a log D > 5 a controlled release can certainly be provided via a controlled degradation of SEDDS by lipases in the small intestine. Leonaviciute et al., could show that SEDDS containing triglycerides are rapidly degraded by lipsases, whereas when they contain mono- and diglycerides the degradation process is comparatively slower and can even be completely avoided by utilizing ester-free compositions [45]. Based on this knowledge, the degradation process and subsequently drug release from SEDDS can be controlled by the combination of more or less biodegradable excipients in the formulation. As intestinal lipase activity is highly variable, however, the concept has its shortcomings. In order to provide a lipase independent controlled release liquid crystalline systems seem to be more promising. Phan et al., for instance,

could demonstrate that the diffusion coefficient of a model compound is in liquid crystalline materials even > 100-times lower [46] and Trotta described SEDDS transforming into lamellar liquid crystals on contact with release medium providing a sustained release for at least several minutes [6]. Furthermore, a controlled release might be achieved by incorporating hydrophobic polymers such as dimethicone or polyethylene into SEDDS providing a sustained drug release based on hydrophobic polymer – drug interactions. Even ionic interactions between lipophilic ionic polymers such as alkyl (C10-30) modified carbomer (e.g. Pemulen; Ultrez) and oppositely charged drugs might be utilized.

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