Self-Emulsifying Drug Delivery Systems

Facing the bioavailability challenge in drug delivery

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■ ABSTRACT

SEDDS are pre-concentrates of excipients with a drug substance that form a thermodynamically stable micro-emulsion upon contact with aqueous media. The drug substance is kept in a solubilized form, thus improving the pharmacokinetic profile of BCS Class 2 drug substances and to optimize efficacy and safety [5].

Self-microemulsion systems are developed by a rational development program taking into account the physicochemical and biopharmaceutical properties of the drug compound. Following careful selection of the right candidate, solubility screening is performed in single excipients and later on in a combination of different excipients. Phase diagrams are established for the excipient combinations in order to identify the right concentration of each component in conjunction with the drug substance. Through the use of innovative software programs (e. g. Lipidex™), the development time of SEDDS can be substantially reduced. The lead formulations are further characterized and tested in vitro before the final formulations are selected for the in vivo trials. The uniqueness of such formulation is the ability to solve not only the poor water solubility problem of API but to also enhance biopharmaceutical performance of the drug product formulation (bioavailability, food effect, transporters, and pre systemic metabolism).

The selected lead formulation needs then be converted into a solid oral dosage form. As these SEDDS are either liquid or semi solid in nature. Their preparation generally starts with a simple blending process resulting in pre-concentrates which can be filled into two piece capsules on laboratory scale equipment (e. g. CFS 1200) for the initial in vivo testing. When larger or commercial quantities are required, the well characterized formulation is filled into two-piece capsules on the standard capsule filling machines online connected with a LEMS capsule sealing machine [24].

■ KEY WORDS

- BCS Class 2 compound
- Bioenhancement
- Drug delivery
- Lipid drug delivery systems
- Self-emulsifying drug delivery systems

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■ ZUSAMMENFASSUNG

Selbstemulgierende Wirkstoffverabreichungssysteme / Das Problem der Bioverfügbarkeit bei der Wirkstofffreigabe

Selbstemulgierende Formulierungen (SEDDS) sind Mischungen aus flüssigen und halbfesten Hilfsstoffen, die einen Wirkstoff in gelöster Form enthalten und in wässrigen Medien thermodynamisch stabile Mikroemulsionen bilden. Da der Arzneistoff in diesen Mikroemulsionen in gelöstem Zustand verbleibt, wird die Absorption und damit das pharmakokinetische Profil eines schwer wasserlöslichen Arzneistoffes erheblich verbessert – und damit auch die Wirksamkeit und Sicherheit.

Die Formulierung von SEDDS erfolgt in einer systematischen Vorgehensweise. Die physikochemischen und biopharmazeutischen Eigenschaften des Arzneistoffes werden betrachtet, um die geeigneten Arzneistoffkandidaten für ein SEDDS zu identifizieren. Anschließend erfolgt ein Screening der Löslichkeit des Arzneistoffes in verschiedenen Hilfsstoffen und Hilfsstoffkombinationen. Mit Hilfe von Phasendiagrammen läßt sich die genaue Zusammensetzung der einzelnen Komponenten ermitteln, die mit der angestrebten Arzneistoffmenge in wässrigen Lösungen eine feine Mikroemulsion bilden. Mittels einer innovativen Software (z. B. Lipidex) kann die Entwicklungszeit eines robusten SEDDS erheblich reduziert werden. Anschließend werden die ausgewählten Formulierungen weiteren in vitro und in vivo Untersuchungen unterzogen, bevor das beste SEDDS ausgewählt wird.

Die ausgewählte Formulierung wird dann in eine feste, orale Darreichungsform überführt. Da die SEDDS zumeist flüssig oder halbfest sind, erfolgt die Vorbereitung der Formulierung durch einen einfachen Mischvorgang. Diese Formulierung kann dann in Hartkapseln abgefüllt werden. Dies geschieht entweder in einem Labormaßstab auf einer einzigen Maschine (z. B. CFS 1200) oder direkt auf einer kommerziellen Abfüllinie, die aus einer Kapselfüllmaschine, einem kurzen Transportband und einer Kapsel-Verschweißmaschiene (z. B. LEMS 70) besteht.

Many of the new chemical entities today display an insufficient bioavailability due to their poor aqueous solubility characteristics. To improve the bioavailability, formulation scientists are often developing and testing different formulation approaches in parallel to achieve their objectives. Self-emulsifying drug delivery systems (SEDDS) aim to maintain the drug in solution during the digestion and absorption phase and offer a potential route for bioenhancement, when developed in a systematic and rational way.

1. Biopharmaceutics classification system

It was in 1997, when Chris Lipinski published a landmark paper, creating awareness of the increasing issue of poor aqueous solubility of the new chemical entities discovered [1]. While many approaches have been taken in the meantime to reduce the 'solubility issue', it remains apparent in drug discovery and development [2]. As a consequence formulation and processing approaches have been developed during the past years to achieve the desired pharmacokinetic profile of the drug substance in vivo [2, 3].

According to the Biopharmaceutics Classification System (BCS) [4], drugs are classified according to their aqueous solubility and membrane permeability. Drugs with a poor solubility but a high permeability are classified as Class II compounds. Some authors estimate that currently 70 % of the small molecules in development belong to the BCS Class II [5]. Their oral bioavailability can be expected to depend on the solubilization kinetics of the drug in the intestinal fluids of the GI tract.

A formulation for a Class II drug will focus on solubility enhancement or solubilization of the drug. Many different technologies have been proposed, especially crystal engineering, particle size reduction and solid dispersions [3]. Recently, lipid formulation approaches such as SEDDS have gained tremendous interest in pharmaceutical sciences as a potential technology to enhance oral bioavailability.

2. Cyclosporin A: From Sandimmun™ to Neoral™

The first marketed pharmaceutical product formulated as a SEDDS has been Cyclosporin A, introduced as Neoral in Europe (1994) and the USA (1995). The challenge for Cyclosporin A was its pre-systemic metabolism and absolute bioavailability of 10 – 60 %. Moreover, Cyclosporin A has very narrow therapeutic range and requires different blood concentrations for each specific organ transplantation (e. g. 250 – 350 µg/L for liver transplant and 80 – 120 µg/L for kidney transplant) [6].

The original market formulation of cyclosporin (Sandimmun), launched in 1981 in Europe, was composed of corn oil, dehydrated ethanol and polyglycolized glycerides (Labrafil 1944 CS), which form a coarse emulsion in water. Even if the achieved bioavailability was acceptable, the major issue remained the high inter- and intra-subject variability of 20 – 60 % of this formulation.

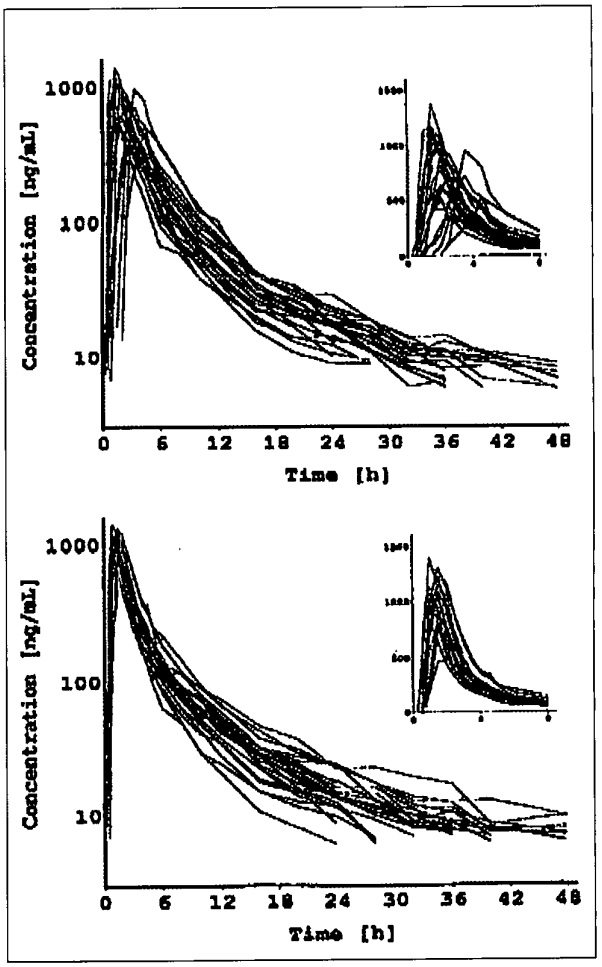

Fig. 1: (A) Interindividual comparison of cyclosporine concentration-time profiles following single oral administration of 300 mg Sandimmun formulation to 24 volunteers. Insert shows the initial portion of the profile on a linear-linear scale. (B) Interindividual comparison of cyclosporine concentration-time profiles following single oral administration of 180 mg Neoral formulation to 24 volunteers. Insert shows the initial portion of the profile on a linear-linear scale [7].

The second formulation generation of Cyclosporin A (Neoral) is a composition of a hydrophilic solvent, a hydrophobic solvent and a surfactant, which form a micro-emulsion with a droplet size of < 100 nm in gastric fluid [6]. As reviewed by Friman and Bäckman, several clinical studies confirmed that the Neoral formulation significantly increases the absorption, which was reflected in the increased C_{max} and AUC, while t_{max} decreased. One of the major results of this formulation optimization was the desired dose reduction (Fig. 1 A and B). A dose of 180 mg was found to be bioequivalent to the original dose of 300 mg [7].

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In addition to the dose reduction, the safety profile could be increased substantially. As shown in Fig. 2, the food effect observed with the Sandimmun was negligible with the Neoral product. With the original formulation the high inter- and intrasubject variability led to unpredictable plasma concentration. With its narrow therapeutic range between the minimal effective concentration and the toxic side effect concentration, this improvement was critical to maintain the drug concentration in the therapeutic range and avoid undesirable side effects based on high and low plasma levels [7].

Another important advantage of the new microemulsion formulation Neoral for drug delivery is its bile salt independent absorption. Sandimmun was absorbed after pre-digestion of the coarse emulsion by the bile salts. As demonstrated by Kovarik et al. and Freeman et al. [7, 8] this led to serious issues in freshly liver transplanted patients as their bile salt flow is interrupted after the transplantation. In this patient population the absorption of Cyclosporin A from Sandimmun was insufficient, while the microemulsion formulation (Neoral) is absorbed independently from the bile salts to give the expected plasma concentrations [8].

The introduction of the Neoral formulation has stimulated intensive research in the area of the lipid based drug delivery systems, ranging from simple to sophisticated approaches. Recently, various authors summarized the recent status of self-emulsifying drug delivery systems for oral delivery [5, 9].

3. Self-emulsifying drug delivery systems (SEDDS) in pharmaceutical R & D

Using EMD 50 733 as a poorly water soluble compound (aqueous solubility < 5 µg/ml) a Gelucire 44/14 and Vitamin E TPGS formulation were developed and compared to a standard lactose blend and an i. v. solution formulation [10]. The Gelucire 44/14 and Vitamin E TPGS formulation were prepared by a hot-melt capsule filling process. The formulations were then tested for stability and dissolution in various dissolution media, and for in vivo performance. While the EMD 50 733 showed solubility of 7.8 µg/ml in SGF the solubility in the Gelucire and Vitamin E TPGS formulation was enhanced to 26.1 and 30.9 µg/ml, respectively. After 1 month of storage the dissolution decreases for Vitamin E TPGS formulation while the dissolution profile remained the same for the Gelucre 44/14 formulation for up to 2 years. Furthermore, the drug release from the Gelucire formulation was nearly 100 % resulting in a supersaturation of EMD 50 733 in the media that is stable for more than 3 h. The authors concluded that the drug is dissolved in a micelle structure preventing the drug from nucleation and precipitation over time. In vivo tests performed in beagle dogs confirmed a 10 fold increased bioavailability for the Gelucire formulation compared to the standard lactose blend of EMD 50 733.

Lu et al. investigated the use of a Tween 80 and Cremophor EL emulsifying drug delivery system for the topoisomerase-I inhibitor 9-nitrocamptothecin (9-NC) and compared the performance to a PEG 400/ethanol solution and a suspension [11]. Two self-emulsifying drug delivery systems were developed composed of ethyl oleate, PEG 400, ethanol and Cremophor EL or Tween 80 that led to a stable microemulsion upon dilution for over 12 h with a droplet size of 39.8 and 30.8 nm, respectively. The Cremophor and Tween self-emulsifying formulation were tested in 4 human cancer cell lines. The cytotoxicity expressed as the IC_{50} value increased for both self-emulsifying formulation in all cell lines compared to the 9-NC solution and suspension. Bioavailability studies showed absolute bioavailability of 37.0 and 37.9 % of the Cremophor and Tween formulation compared to 26.7 % for the solution and 16.9 % for the suspension formulation. Antitumor activity was measured using nude mice injected with tumor cells prior to treatment with the different formulation. While all 9-NC formulation were effective, the tumor growth was significantly reduced when treated with the two self-emulsifying formulations. However, no difference could be observed between the Cremophor or Tween self-emulsifying formulation.

Another interesting study incorporating a self-emulsifying pre-concentrate into a solid matrix was recently presented by Li et al. [12]. Li et al. prepared self-emulsi-

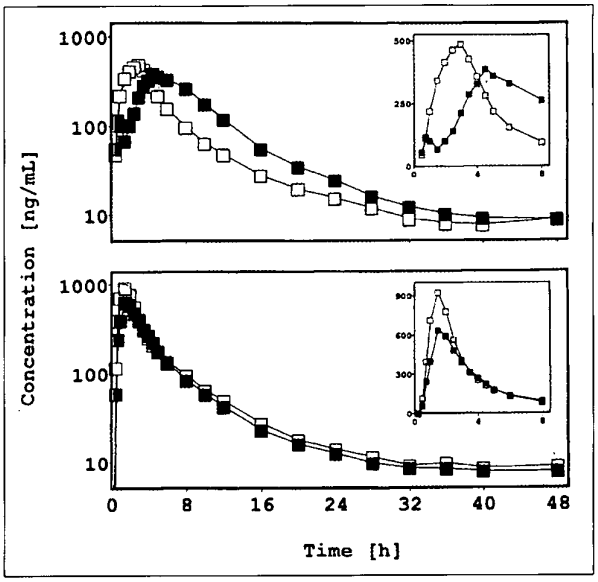

Fig. 2: Concentration-time profiles following single oral administration under fasting conditions (□) and with a fat-rich meal (■) to 24 healthy male volunteers. (A) Sandimmun, (B) Neoral [25].

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fying pre-concentrate using Capmul PG8, Cremophore EL and Tween 80 that was embedded in a PEG 3350 matrix with 4 and 8 % drug load and compared the product performance with a PEG 3350/Tween 80 solid dispersion of the drug. The solid dispersion was prepared by melting PEG 3350, polysorbate 80 (480 mg of a 3 : 1 ratio) and the drug (20 mg) to 65 – 70 °C and filling into a size 0 two-piece capsule where it solidified during cooling [13]. For the solid dispersion it was assumed that the drug is partly dissolved and partly in an amorphous form raising concerns on the long-term stability as crystals were found after 16 months of storage at 40 °C/75 %rh, especially as the clinical dose was increased from 20 mg to 40 mg.

Therefore a self-emulsifying drug delivery system was developed containing Capmul PG8 and Cremophor EL (1/1 ratio) in which the drug was dissolved at 4 % and 8 % drug load. The self-emulsifying pre-concentrate was embedded in a PEG 3350 matrix. The PEG 3350 concentration in the 4 % and 8 % drug load formulation were 38.4 and 36.8 %, respectively. Dissolution and dispersibility testing of the two formulations showed a milky solution after 30 min for the solid dispersion, while the embedded self-emulsifying pre-concentrate formed a translucent microemulsion. Particle size measurements confirmed that the pre-concentrate formed a microemulsion with a particle size of ~ 50 nm and 150 nm compared to the solid dispersion with ~ 250 nm and 800 nm for the 4 % and 8 % drug load respectively. The solid dispersion had an incomplete dissolution and started to crystallize after 120 min, which was not observed for the solid pre-concentrate even after overnight standing in the medium. During long term stability crystals were found in the 4 % drug load solid dispersion after 3 years at 25 °C/60 %rh and after less then 3 weeks for the 8 % drug load solid dispersion. The embedded preconcentrate however, was stable over 3 years ate 25 °C/60 %rh for both, the 4 and 8 % drug load. The difference in stability was suggested to result from the higher solubility of the drug in the pre-concentrate keeping the drug even at 8 % drug load under its saturation solubility.

Self-emulsifying drug delivery systems offer a variety of drug delivery approaches for poorly water soluble drugs. Gao reported the development of supersaturated self-emulsifying drug delivery systems using precipitation inhibitors [14, 15].

Paclitaxel with a molecular weight of 853 Da and a water solubility of < 1 µg/ml and is available on the market is an i. v. formulation based on Cremophor EL and ethanol with ~ 6 % drug load. Gao et al. developed an SEDDS formulation containing ethanol, PEG 400, Cremophor EL and Glyceryl dioleate, to which HPMC and HPMC plus Cyclosporin A as an inhibitor of P-glycoprotein and CYP 3A4 was added and compared in vitro and in vivo with the i.v. formulation [16]. The in vitro assessment in rats showed that the pure SEDDS formed a supersaturated solution in SGF that starts precipitating after 10 min with ~ 0.12 mg/ml after 10 min that decreased to ~ 0.03 mg/ml after 30 min. In contrast, the 5 % HPMC containing SEDDS formulation produced a solubility of ~ 0.95 mg/ml after 10 min that gradually decreased over 2 h to ~ 0.12 mg/ml. The supersaturation and suppressed precipitation led to 20 fold increase in C_{max} and a 10 fold increase in oral bioavailability (from 0.9 % to 9.5 %). The study showed that the inhibition of drug precipitation can substantially improve the oral bioavailability of paclitaxel. The addition and co-administration of Cyclosporin A to the SEDDS formulation with HPMC did not alter the initial absorption phase, however, higher plasma concentrations were observed subsequently to t_{max} after 4 h, which suggests the co-administration with potent pre-systemic metabolizing enzyme inhibitors.

4. Development of self-emulsifying drug delivery systems (SEDDS)

SEDDS are isotropic pre-concentrates that spontaneously form fine oil-in-water emulsions in an aqueous environment. With a droplet size of < 200 nm, microemulsions form thermodynamically stable, translucent, clear solutions. These self-emulsifying pre-concentrates normally consist of 3 – 5 components that might be lipophilic, amphiphilic or hydrophilic in nature. Each excipient provides certain functionality to the SEDDS. These excipients can be classified as solvent, surfactant or co-surfactant. Selecting the excipients with the best characteristics for the specific compound as well as for optimal performance in combination with other excipients, is a key challenge in the development of a SEDDS.

As described by Benameur [17] the development of SEDDS follows a systematic and rational development program (Fig. 3). To identify the potential drug candidates for the SEDDS, they are selected according to their physicochemical parameters and their expected dose. Once selected, the drug candidates are screened in a number lipophilic, amphiphilic and hydrophilic excipients for their solubility and stability. The excipients that provide the best solubility and compatibility with the drug are considered for the further formulation development. The aim of combining different excipients is to achieve a thermodynamically stable oil-in-water (O/W) microemulsion in the order of 0.2 µm that solubilizes the required drug concentration. In order to define the right drug combination a series of ternary phase diagrams are constructed with the different excipient combinations.

To speed up the development of self-microemulsifying drug delivery systems, a proprietary software was developed (Lipidex), representing the immiscible, the self-emulsifying and the self-microemulsifying areas

within the phase diagrams of binary and ternary systems. This data base allows for a quick selection of potential excipient combinations for the specific drug candidates that are then evaluated by experiments.

In the next step the formulation is characterized regarding thermodynamic stability, particle size upon dilution in various media, precipitation upon dilution, rheological behavior and other characteristics that are important for the specific drug, e.g. polymorphism. To screen a number of formulation and predict the bio-enhancement an in vitro test using a CaCo2-cell model is used.

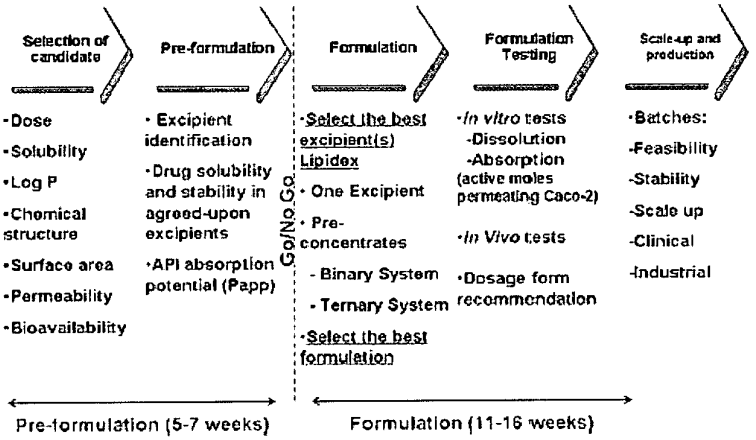

Fig. 3: Systematic and rational development program (5 phase Capsugel model) [17].

Finally, the lead formulations are selected for in vivo testing in animals and where appropriate directly in humans.

This development program and the use of the Lipidex software was applied to a BCS Class II compound with a molecular weight of 420, a log P of 3.5, a high apparent permeability and an aqueous solubility of 1.2 µg/ml and a 50 mg dose in size 0 capsule [18]. Following the solubility screen in single excipients, 20 potential formulations were identified by the Lipidex and tested in vitro in a diluability test. For six out of these 20 formulations a CaCo2 cell permeability test was performed. The results shown in Fig. 4 led to the selection of two formulations (Formulation A and B) for in vivo testing.

Formulation A and B were administered to fasted dogs (n = 3) at a dose of 5 mg/kg in comparison to a standard microsuspension. As shown in Table 1, the pharmacokinetic parameters T_{max}, C_{max} and AUC were improved.

Besides the bioenhancement of the compound by the two SEDDS filled into capsules, the study demonstrates the good correlation of the in vitro data with the in vivo data obtained in dogs.

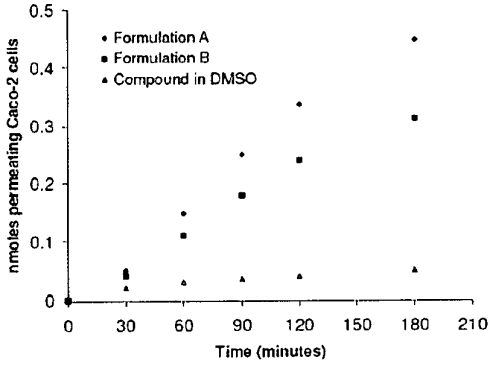

Fig. 4: Permeation of the compound across CaCo2 cells in nmol [18].

5. SEDDS solid oral dosage form development

The solid oral dosage form is known to be the preferred dosage form for patient preference and compliance reasons.

As described above, SEDDS are pre-concentrates of excipients that are liquid or semi-solid in nature. It is obvious that the traditional tablet technologies cannot be used for this type of formulation. In contrast, capsules serve as a drug delivery system that converts the

Table 1

Pharmacokinetic parameters of a microsuspension compared to two SEDDS in capsules (Formulation A and B) [18].

Formulation	T_{max} (h)	C_{max} (µg/ml)	AUC $_{0-32\ h}$ (h µg/ml)	AUC rel. (%)
Microsuspension	2.0 ± 0.0	2.9 ± 0.2	38 ± 2	100
Formulation A	1.7 ± 0.6	3.7 ± 0.1	47 ± 3	123
Formulation B	1.7 ± 0.6	3.7 ± 0.5	49 ± 2	127

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liquid into a solid form and secures an accurate transfer and release of the dosage form in the stomach. Capsules are known as a well recognized dosage form that is easy to swallow, masks taste and odor, and is appealing. Another capsule feature is the possibility of various mono and bi-color options including printing that support the identification of the product. Especially for elderly and multi-drug treated patients, identification and differentiation of the product achieved by coloration is important for their compliance [19, 20]. Even patients with moderate Alzheimer's disease substantially gain from coloration [21]. A recent study also confirmed the patient preference for liquid filled two-piece capsules [22].

In contrast to other drug delivery technologies for bioenhancement, the lipid formulation and filling technology is an easily scalable process. Excipients and drug are mixed in a liquid stage, either at ambient temperature or under gentle heating. These liquid solutions are filled directly into two-piece capsules without any additional processing as recently published by Cole et al. [24].

For the filling, the empty shells are rectified, opened, filled and closed on the common capsule filling machine. The filled capsules are transferred via a standard conveyor belt into a sealing unit where the capsules are sealed by an hydroalcoholic fusion process that refers to the described 'sealing' in the USP 24 'capsules' monograph.

A laboratory scale liquid capsule filling and sealing machine is available and used by all major laboratories today (e.g. CFS 1200). With more than 1 000 capsules per hour, the laboratory scale equipment is sufficient to cover phase I and II clinical supplies until the proof of concept is established. With a minimum recommended batch size of only 20 – 25 ml, the equipment also addresses the need to wisely use the limited drug availability that is common in early development. For commercial scale manufacturing the filling is performed on standard capsule filling machines in conjunction with a commercial scale capsule sealing unit (e.g. LEMS 70).

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